UNIVERSITY OF CALIFORNIA

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PLASTICIZATION OF PVC: COVALENTLY LINKED PLASTICIZERS USING THERMAL OR COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITIONS

A dissertation submitted in partial satisfaction
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY AND BIOCHEMISTRY

by

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June 2016

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Abstract

PLASTICIZATION OF PVC: COVALENTLY LINKED PLASTICIZERS USING THERMAL OR COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITIONS

Aruna Earla

One of the most effective approaches to avoid migration of plasticizer from PVC material is to covalently attach the plasticizer to the polymer. In this thesis the plasticizers are attached to PVC using (2+3) azide-alkyne cycloaddition reactions. In the first approach, PVC was modified by covalently linking triazole anologue of the most common phthalate plasticizer di(2-ethylhexyl phthalate) (DEHP). Copper-free azide-alkyne (2+3) cycloaddition reaction of PVC-azide with electron-poor acetylene dicarboxylate is utilized to modify PVC. The glass transition temperature of the modified PVC was lower than the glass transition temperature of the unmodified PVC indicating successful plasticization.

The derivatives of DEHP are covalently bonded to PVC using either thermal or copper-catalyzed (2+3) azide-alkyne cycloaddition reaction. Two DEHP derivatives bearing a tether ending with a terminal alkyne were synthesized and covalently

bonded to PVC. The derivative with ether-alkyne undergoes cycloaddition with PVC-azide under copper-catalyzed conditions whereas ester-alkyne derivative undergoes Huisgen thermal cycloaddition. The investigation of glass transition temperatures of these modified PVC samples indicate that the ether-alkyne derivative is more efficient in imparting plasticization to PVC compared to ester-alkyne derivative.

Although bulk of this thesis work is on the plasticization of PVC, a part of this thesis deals with the synthesis and spin-trapping properties of polymer-supported trifluoromethylated cyclic nitrones for the detection of free radicals on the aerosol particles. Polystyrene tethered with fluorinated nitrone spin-trap is used as a solid phase in the continuous flow NMR and EPR study of free radicals.

Three fluorinated alkoxyamine initiators are synthesized and used to study the effect of adding carbon dioxide-philic fluorinated fragment in the nitroxide-mediated precipitation polymerizations of styrene in supercritical carbon dioxide. Two alkoxyamines have fluorinated functional handles built on the nitroxide part of the alkoxyamine whereas the third initiator has fluorinated functional handle on the benzyl-initiating fragment of the alkoxyamine. The partitioning of fluorinated nitroxide derivatives in supercritical carbon dioxide impacts on the controlled/living character and broadening of the molecular weight distributions but does not have any significant effect on the rate of precipitation polymerization in supercritical carbon dioxide.

This dissertation is dedicated to my mother

and the greatest influence on my life

Susheela Earla. It would not exist without her.

Acknowledgments

The work presented in this thesis could not have been done without the support of faculty, colleagues, family, and friends. I wish to thank, first and foremost, my excellent research advisor, Professor Rebecca Braslau for giving me the opportunity to work first as a research technician and then as a graduate student in her lab. In addition to being a terrific chemist, great teacher, and a wonderful person, Rebecca is a keen editor and I really appreciate her taking time in correcting my thesis. I will be grateful for the guidance, advice, and generosity she has provided throughout my time as her student. Thank you very much!

I would also like to thank the members of my research committee for their valuable guidance. I thank Professor Bakthan Singaram for serving as the chair of my committee. His inquiries into my research and valuable guidance helped me develop as a synthetic chemist. Claude F. Bernasconi is one of my wonderful committee. I learned a lot about physical organic chemistry from him. I would like to thank Professor Roger Linington for an enganging class of NMR spectroscopy. Thanks to my collaborators, Dr. Fawaz Aldabbagh, Dr. Eric Walter, and Dr. Phil Costanzo. I got the opportunity to work on many different projects because of their collaboration. I also thank Mitchell Brenner for sitting as the outside committee member on my qualifying exam.

I would like to thank my fellow members of the Braslau lab, past and present. To Dr. Chittreeya Tansakul, thank you for helping me get a start in the Braslau lab. Thank you for being a good friend and helping me even when you were very busy finishing your PhD. To Chad Higa, in addition to being an excellent lab mate he has helped me with every thing. We enjoyed sharing many discussions on chemistry, cars and other things. To Jen Petraitis, we joined the group together and had fun talking about chemistry, food and life in general. Wiley Schultz-Simonton, Jerin Tasnim, and Longbo Li have always been a fun part of the Braslau lab.

Outside of the group, I would like to thank Rachel Snelling, Chris Murphy and Angel Resendez for support of chemicals. I pay my gratitude to the Staff members of the Department of Chemistry and Biochemistry. Janet Jones and Karen Meece have been very generous to me on academic issues. I am grateful for many help from Jack (Hsiau-Wei) regarding nuclear magnetic resonance and Li (Qiangli) Zhang for her help on mass spectrometry.

Finally, I would like to acknowledge with gratitude, the support and love of my family. My brother and sister have always encouraged me to get PhD. Special thanks to my mom and dad, who provided with many of the opportunities that I have had in my life. My husband (Tulasi Meeniga) and my lovely daughters Diya and Riti kept me going and this thesis would not have been possible without them.

1 Plasticization of Polyvinyl chloride: A Review

1.1 Poly(vinyl chloride) (PVC)

Poly(vinyl chloride) is a synthetic resin made from the polymerization of vinyl chloride. It is one of the most widely used and economically relevant thermoplastic materials. Thermoplastic material becomes a homogenized liquid when heated; upon cooling it turns into a solid, which makes it suitable for recycling. Justus von Leibig and his student Henri Victor Regnault first reported vinyl chloride in the 1830s.[1] German scientist Eugen Baumann synthesized PVC from vinyl chloride in the 1870s,[2] but the polymer did not lead to industrial applications until the 1920s,[3] when American chemist Waldo Lonsbury Semon discovered how to plasticize PVC. Pure PVC is a rigid and brittle solid, which limits its applicability. The discovery of plasticization and the development of heat-stabilizing additives for PVC in the 1930s[4] made the processing of PVC compounds possible, leading to the commercial production of PVC. Global demand for PVC has seen a steady increase over the last few decades (2 million tons in 1960 to 38.5 million tons in 2013), and is estimated to reach 53 million tons, worth $US 79 billion in 2020.[5]

PVC is an odorless white solid plastic found in a wide range of consumer products. Properties such as toughness, inertness, chemical stability, high transparency, resistance to chemical stress cracking, flame resistance, and versatility

make PVC common in the construction industry. It is used to make pipes, pipe fittings, pipe conduits, vinyl flooring, and vinyl sliding, packaging materials, wrapping films, downspouts, gaskets, hoses, sealant liners, paper and textile finishes, roof membranes, swimming pool liners, weather stripping, flashing, molding, irrigation systems, containers, automotive parts, and recreational toys. The construction industry is the major industry using PVC products, accounting for more than 65% of the total global PVC consumption in 2014. The inherent flame retardant and excellent electrical insulation properties of PVC make it suitable for wire and cable coatings, and electrical insulation. PVC is used for chemical storage tanks, plastic valves and flanges, drainage and sewage pipes, and plant piping due to its excellent chemical resistance property. PVC is also used in a wide range of medical applications including screening, diagnosis, and treatment, as well as in the creation of a safe healthcare environment. Medical products such as intravenous bags, blood bags, blood and respiratory tubing, feeding tubes, catheters, parts of dialysis devices, and lung and heart bypass tubing are often made of PVC. It is the first choice for medical applications due to its sterilizability, biocompatibility, chemical compatibility with other additives, flexibility, versatility, durability, safety, flame resistance, excellent electrical insulation properties, resistance to chemical stress cracking, low cost, and moldability. PVC possesses the largest share of the polymer medical market, constituting 30% of all dedicated polymeric materials.[6]

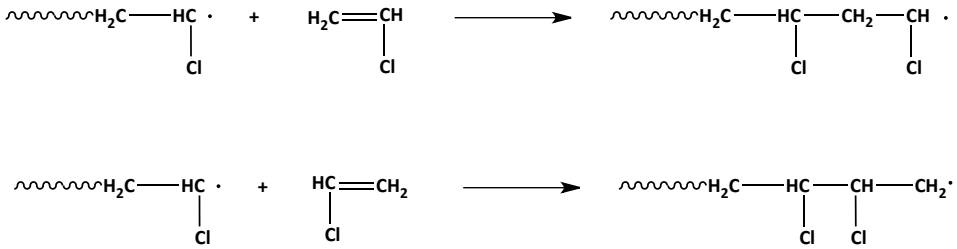
1.1.1 Synthesis of PVC by Radical Polymerization of Vinyl Chloride

Commercial PVC is mainly produced by free radical polymerization of vinyl chloride. Three types of polymerization processes: suspension polymerization, emulsion polymerization, and bulk polymerization are utilized to synthesize PVC. Most PVC is commercially produced by suspension polymerization. In Suspension polymerization, vinyl chloride monomer is added to a mixture of additives (suspending agents and a vinyl chloride soluble free radical initiator) in water under high pressure, and the mixture is stirred with mechanically while heat is applied. The number average molecular weight (M_n) of PVC synthesized by suspension polymerization can range from 30,000 (low-medium) to 60,000 (medium-high) and up to 150,000 atomic mass units for ultra-high M_n PVC. M_n is the statistical average molecular weight of all the polymer chains in the sample and is defined by; $M_n = \frac{\Sigma MiNi}{\Sigma Ni}$, where M_i is the molecular weight of a chain and N_i is the number of chains of that molecular weight. Emulsion polymerization is used to make pastes or plastisols, which are dispersions of PVC resin in plasticizers. The process of emulsion polymerization is similar to suspension polymerization in which vinyl chloride monomer is added to a mixture of free radical initiator and additives in water. However, in emulsion polymerization soaps (often sodium lauryl sulfate) are used instead of dispersants. When the mixture is stirred and heated, vinyl chloride monomer is sequestered within miscelles formed by the soap molecules. Upon

polymerization the polymer particles assume the dimensions of the interior of the miscelles: spherical and roughly one micron in diameter. The difference between suspension and emulsion polymers is mainly the gross morphology of the resins. The microstructure (M_n, crystallinity, number of chain defects, etc) can be virtually the same. The resin produced by bulk polymerization is similar in particle size, porosity, and microstructure to the resin produced by suspension polymerization. In bulk polymerization water is not used as a reaction medium, instead vinyl chloride is used. Bulk polymerization is carried out in two stages. In the first stage, PVC resin seed particles are formed by free radical polymerization process under agitation similar to suspension polymerization. When the polymerization reaches 12% conversion, the reaction mixture is transferred into another vessel with a low-speed mixer more suitable for mixing solids, and heated. The advantage of bulk polymerized PVC is that it does not contain any residual dispersants like suspension-polymerized PVC. However, this method produces a great number of fine particles, which are difficult to separate from the rest of the polymer. More importantly, it is difficult to remove the residual vinyl chloride monomer from the mass resin, making bulk polymerization a less desirable method of polymerization.

1.1.2 Structure and Microstructure of PVC

In the free radical polymerization of vinyl chloride to make PVC, the propagation reaction is an important step in determining the molecular weight and structural defects. The vinyl chloride monomer can add to the growing polymer in two ways: head-to-tail or head-to-head (**Scheme 1.1**). Polymer characterization studies show that polymer produced by suspension polymerization grows predominantly by head-to-tail addition of the monomer, however, some defects are introduced in the molecular structure due to side reactions such as head-to-head addition of monomer, and radical chain transfer. These structural defects include chlorine atoms located on allylic carbon atoms, chlorine atoms located on tertiary carbon atoms, and short and long branches (**Figure 1.1**). These defects negatively impact the heat stability of the polymer and are found to be responsible for thermal- and photo-degradation of PVC. The content of these structural defects can be estimated by NMR spectroscopy, addition reactions of bromine and chlorine to double bonds, and pyrolysis-hydrogenation gas chromatography. These defects can make up to 10% of the polymer.



Scheme 1.1 Head-to-Tail and Head-to-Head Addition of Vinyl Chloride Monomer

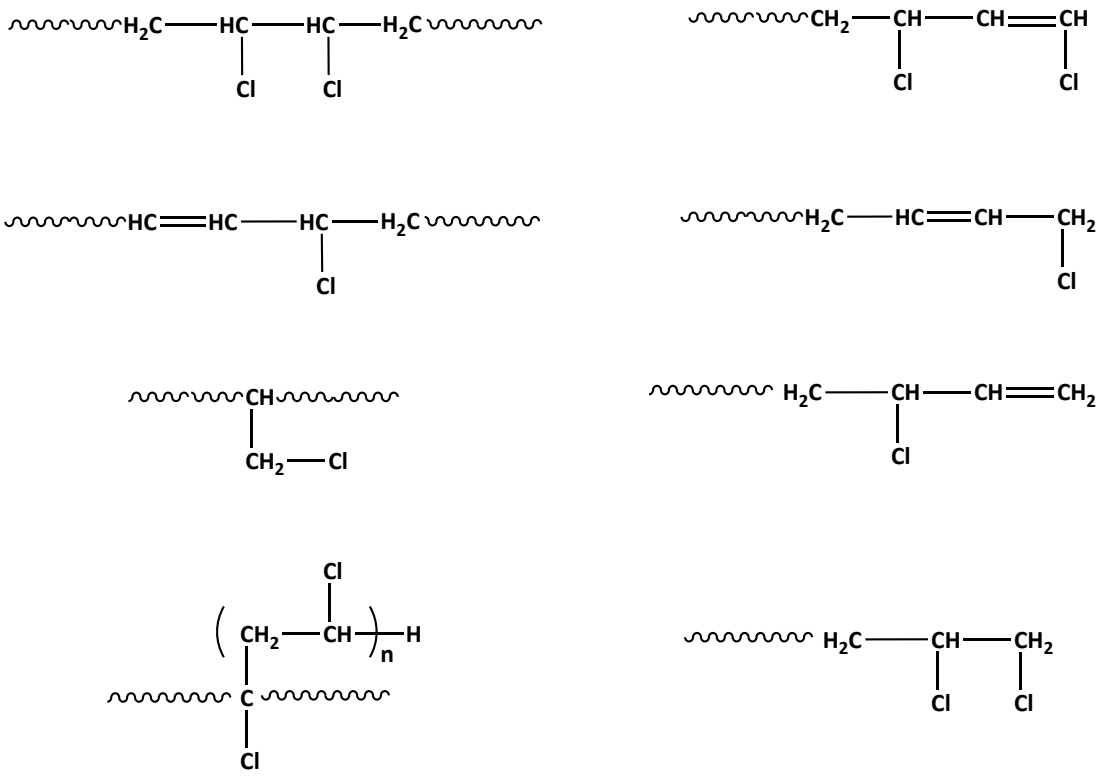


Figure 1.1 Structural Defects in PVC[7]

The microstructure refers to the stereoisomerism or tacticity, which occurs due to the presence of stereogenic carbon atoms in PVC. PVC tacticity can exhibit three basic structures: (a) isotactic, in which all chlorine atoms are on the same side of the PVC chain (b) syndiotactic, in which all chlorine atoms are regularly distributed on both sides of the chain in alternative arrangement, and (c) atactic, in which the chlorine atoms are randomly and irregularly distributed (**Figure 1.2**).

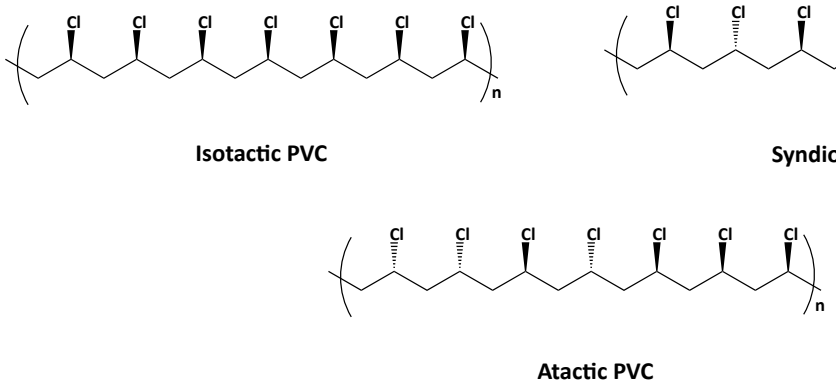


Figure 1.2 Tacticity of PVC

The stereochemistry of the repeating units at the end of the isotactic or syndiotactic sequences further defines the microstructure of PVC. A system of two bonded monomers in a polymer is called a diad. Two identically oriented units make a meso diad (m), whereas two units oriented in opposition make a racemo diad (r). The introduction of triads further defines the streochemical structure of PVC. An isotactic triad (mm) is made up of two adjacent meso diads, a syndiotactic triad (rr) is made up of two adjacent racemo diads, and an atactic diad (rm) consists of a meso diad adjacent to a racemo diad. The definition of tetrads (mmr) and pentads (rrmr) further describe the tacticity of PVC, especially when information on the long range ordering of the polymer is required. The tacticity has a significant influence on the microstructure. Isotacticity induces the TGTG conformation (G and T refer to "gauche" and "trans" conformations of the chain), which is responsible for the helical shape of the chain. Syndiotacticity induces adoption of the TTTT

conformation which gives rise to the "zigzag" shape of the chain (**Figure 1.3**). Syndiotactic segments bring chains closer together due to increased dipolar interactions. Thus, syndiotacticity lowers the free volume and the mobility of chain more than isotacticity.

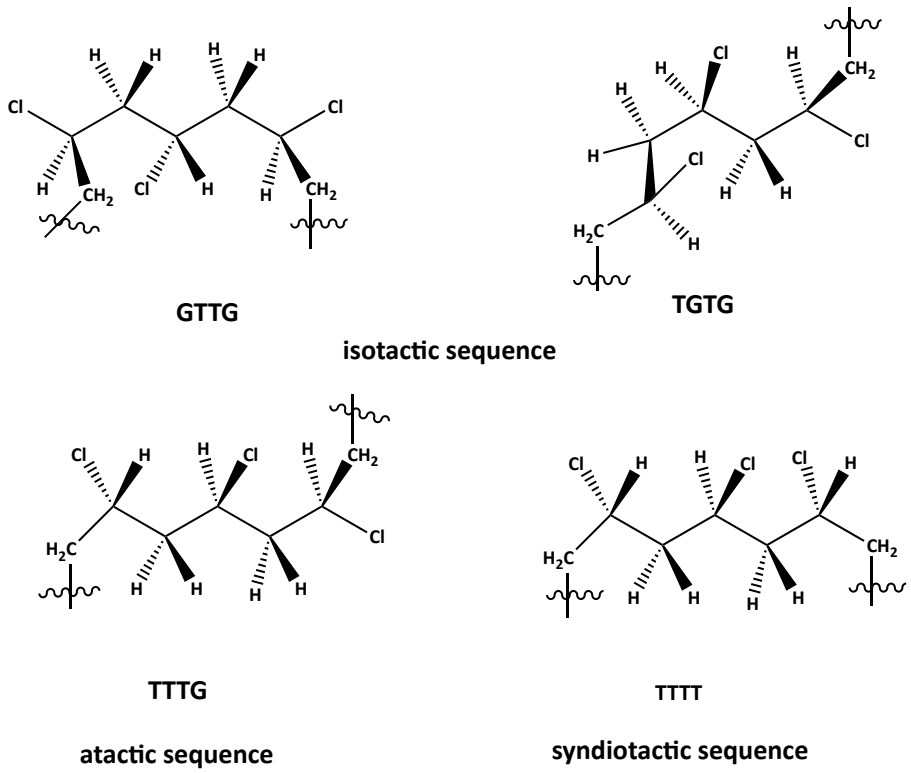


Figure 1.3 Conformations of Isotactic, Atactic and Syndiotactic Sequences

The microstructure of PVC, which refers to the average number and length of the tactic sequences, whether isotactic or syndiotactic, the local configurations located at the end of the isotactic and syndiotactic sequences, and the local conformations relevant to these configurations is responsible in creating the spatial

arrangement of the polymer, thereby influencing the intrachain and interchain interactions, the local free volume, and the local and cooperative motions. The tacticity of PVC strongly affects the crystallinity and the thermal stability of PVC. Crystallinity is associated with syndiotactic sequences. Commercially obtained PVC consists of 7-20% syndiotactic sequences, which impart partial crystallinity to PVC due to strong attractive forces of C-Cl dipoles between chains.[8] Knowledge of the microstructure of the polymer helps determine the physical and mechanical properties of PVC such as strength and elasticity, light absorption, crystallinity, solubility in solvents, melting temperature, and the reactivity of the chlorines. PVC produced by suspension polymerization largely exists in the amorphous form (atactic sequence). However, short and random syndiotactic sequences allow the polymer to form crystal microstructures, which are quite important in the performance of the polymer.

1.1.3 Glass Transition Temperature (T_g)

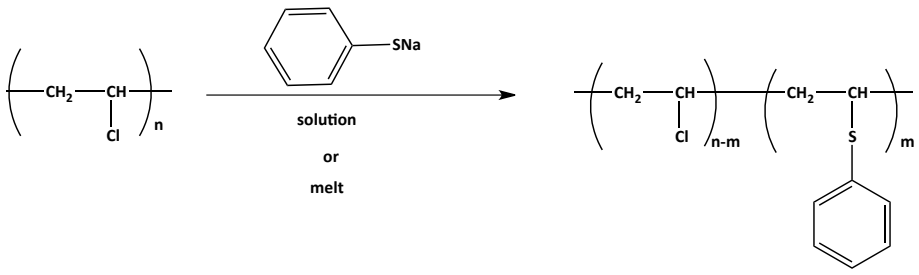
The melting point of perfectly syndiotactic PVC is estimated to be 400 °C, but such a polymer has not yet been synthesized. The melting point (also called the first order transition temperature) of commercial PVC is in the range of 102-120 °C due to imperfections in the structure. Since commercial PVC is mostly amorphous, it is characterized by its second order transition temperature: the glass transition temperature (T_g). T_g defines the temperature at which a polymer goes from its

amorphous rigid state to a more flexible state. In other words, glass transition of a polymeric system defines a temperature below which rubber-like properties are not observed. At low temperatures, the amorphous region of the polymer is in glassy state, in which the polymer molecules are tightly associated as they lack segmental motion in which the portions of the molecule can wiggle around. When the polymer is heated, it gradually reaches its glass transition temperature, where the molecules of the polymer can move: the polymer is now in the rubbery state. Below the glass transition temperature, when the amorphous region of the polymer is in glassy state, it is generally hard, rigid, and brittle. At or above the glass transition temperature, when the amorphous region of the polymer is in the rubbery state, it is soft and flexible. The T_g of PVC depends on the molecular structure of PVC and is usually in the range of 70-82 °C.

1.1.4 Nucleophilic Substitution Reactions of PVC

The tacticity-dependent molecular microstructure governs the chemical transformations of PVC. Substantial research has been devoted to illustrate the presence of labile chlorine atoms by undertaking chemical modifications of PVC by substitution, elimination, reduction, grafting, cross-linking, and degradation reactions. By far, nucleophilic substitution reaction (S_N2) is the most common. In a series of publications, Guarrotxena et al.[9] have extensively shown that the replacement of some chlorine atoms in PVC by chemical groups (e.g. sodium

benzenethiolate, NaSPh) bulkier than chlorine atom proceed in solution through a classic S_N2 mechanism (**Scheme 1.2**), mostly at mmr tetrads, which are located at the end of



Scheme 1.2 Substitution of PVC-Cl with NaSPh

isotactic sequences and at atactic mrr triads sequences adjacent to syndiotactic sequences. The syndiotactic regions of PVC are less vulnerable to nucleophilic substitution reaction. Moreover, of the two most common conformations (GTTG-TT) and GTGTTT) of the mmr structure, it is the GTTG-TT conformation that reacts more quickly. This stereoselective substitution of chlorine by benzenethiolate (PhS^-) changes the physical properties of PVC, including the glass transition temperature.[10,11] Furthermore, studies on the glass transition temperature of modified PVC with sodium benzenethiolate in different solvents and media such as cyclohexanone, tetrahydrofuran, dioxane, and dimethylformamide as well as in the melt have shown that for the same chemical composition, the corresponding T_g of modified PVC depends on the nature of the solvent of the S_N2 reaction. The T_g of the

polymer modified in cyclohexanone is higher than for polymer modified in the melt for the same degree of substitution by the same nucleophile. Differential scanning calorimetry studies showed that the T_g of the polymer modified in the absence of solvent decreased linearly with increasing degree of PhS substitution. However, when the susbtitution reactions were carried out in solvents containing carbonyl groups, such as diethyl malonate, cyclohexanone, and 2-butanone, the change in T_g did not follow that of the melt behavior up to 25% substitution. At substitution higher than 25%, the evolution of T_g was similar to that in the melt.[12,13]

1.2 Plasticization of PVC

Pure PVC is a rigid polymer with a glass transition temperature (T_g) of 70-82 °C, limiting its applicability. In order to obtain the desired durability and flexibility below 82 °C, and to allow for extrusion molding of consumer products, PVC is mixed with a variety of plasticizers. A plasticizer is usually a polar compound, with high boiling point and low vapor pressure, which is added to a synthetic plastic with the purpose of modifying its physical properties. The major function of a plasticizer is to convert the plastic from a hard, brittle, inflexible, high melting substance into a soft, low melting, flexible, resilient, easier to handle material, and to offer good performance properties by lowering its glass transition temperature. For a plasticizer to be effective, it must be thoroughly mixed and incorporated into the PVC polymer matrix. This is typically affected by heating and mixing until either the resin dissolves

in the plasticizer or the plasticizer dissolves in the resin. The plasticized material is then molded or shaped into the desired end product. Different plasticizers exhibit different characteristics in both the ease with which they form the plasticized PVC and in the resulting mechanical and physical properties of the flexible PVC.

1.2.1 Mechanism of Plasticization

Plasticization of PVC is described by three primary theories: lubrication theory, free volume theory, and gel theory. PVC is rigid at temperatures below 82 °C because of the strong intermolecular forces between the molecules. The presence of chlorine atoms in the structure increases the attraction between chains due to C-Cl dipolar interactions, imparting stiffness to the polymer. According to the *Lubrication Theory,* when heat is applied, the energies of the molecular motion become greater than the intermolecular forces: the intermolecular distances between the PVC molecules increase, resulting in the softening of the resin. When plasticizers are added to PVC at this stage, the plasticizer molecules make their way between the polymer chains; reduce interactions between the segments of polymer chains by preventing them from coming close together. Consequently, the polymer chains are kept apart, even at ambient temperature, and flexibility is maintained. In addition, the plasticizer may act as a lubricant, permitting the chains to slide and bend more readily. Thus, a plasticizer imparts increased elasticity at much lower temperatures. The *Gel Theory* considers the plasticizer polymer to be neither solid nor liquid but an

intermediate state (gel), loosely held together by a three dimensional network of weak secondary binding forces. These bonding forces acting between plasticizer and polymer are easily overcome by applied external stresses, allowing the plasticized polymer to flex, elongate, or compress. According to the *Free Volume Theory*, the free volume (empty internal space available for the movement of the chains) of a polymer in the glassy state is low. The molecules are packed closely but not perfectly, which restricts their movement, polymers rigid and hard. When the polymer is heated to or above the glass transition temperature, the thermal and molecular vibrations create additional free volume that allows the polymer molecules to move past each other. Low molecular weight plasticizers occupy significant free volume; when added to the polymer, they lower the glass transition temperature by separating PVC molecules. The free volume of the polymer can also be increased by modifiying the polymer backbone, such as adding side chains or end groups. Hence, the study of plasticization is essentially the study of methods for lowering the glass-transition temperature.

In general, plasticization refers to a change in the thermal and mechanical properties of a polymer, which involves: (a) lowering of rigidity at room temperature by lowering the glass transition temperature; (b) lowering the temperature at which substantial deformations can be effected without the use of excessive force; (c) lowering of tensile strength; (d) lowering of elastic modulus; (e) lowering of density

and melt viscosity; (f) lowering of electrostatic chargeability and volume resistivity; (g) increase of flexibility; (h) increase of the elongation at break at room temperature; (i) increase of the toughness (impact strength); (j) increase of dielectric constant. Plasticizers are generally chosen on the basis of the following criteria: compatibility of the plasticizer with PVC, processing characteristics, desired thermal and mechanical properties of the end product, resistance to water, chemicals, UV radiation, weathering, dirt and microorganisms, effect on rheological properties, toxicity, volume-cost analysis, leaching and migration resistance, and safety. The extent of plasticization depends upon the molecular structure of the plasticizer, which includes chemical composition, molecular weight, and functional groups. Plasticizers are almost invariably esters due to their favorable physical interactions with high molecular weight polymers. Almost every repeating unit of PVC contains a polarized carbon-chlorine bond, which makes it possible to interact with the polar part of the plasticizer (the aromatic ring and the ester linkages) via van der Waals forces and dipole-dipole interactions. The plasticizers in flexible PVC must be closely associated with the amorphous part of the polymer at room temperature. The plasticizer must act as a solvent for the crystalline part of PVC at flexible PVC processing temperatures but not at lower temperatures. Crystalline crosslinks between the polymer molecules are required to provide dimensional stability to the polymer. PVC contains these physical crosslinks (crystallites), which are meltable to

make it a thermoplastic. The crystallites serve the purpose of increasing the elastic modulus of the polymer, thus giving plasticized PVC some memory of its original shape. Therefore, the plasticizer must not be a powerful solvent for all the PVC parts, but must be selective in entering the amorphous PVC sections but must not enter and destroy the crystalline part of PVC. The balance between the polar and nonpolar portions of the plasticizer is critical to control its solubilizing effect: if a plasticizer is too polar, it can destroy PVC crystallites and if it is too nonpolar, compatibility problems can arise.

Several parameters are used to predict the strength of the interactions of plasticizers with PVC, and to understand the performance properties of PVC/plasticizer blends. The *Hildebrand solubility parameter*, which is described as the energy that holds the molecules of a substance together, and the *polarity parameter*, which is determined by multiplying the ratio of apolar carbon atoms to the polar carbon atoms of plasticizer, with the molar mass of the plasticizer, is found useful in comparing the compatibilities of plasticizers with PVC. The *Flory-Huggins interaction* parameter is used to predict the free energy of plasticizer-polymer mixing and *Hansen's Interaction Radius* is a theoretical measure of the interaction forces between the plasticizer and PVC in the absence of other additives. Experimental methods have also been used to determine the strength of the plasticizer-PVC interactions. Fourier Transform Infrared Spectroscopy (FTIR)[14,15] is

used to observe the spectral shift of the carbonyl group of plasticizer and the carbon-chlorine bond of the PVC resin. The absorption frequencies of carbonyl and carbon-chlorine bonds are usually shifted several wavenumbers lower when plasticizer interacts with PVC. Solid state ^{13}C NMR cross-polarization magic angle spinning (CPMAS) spectroscopy has been used to study the PVC-plasticizer interaction: the chemical shifts, line resolutions, spin-lattice and spin-spin relaxation times for the carbonyl carbon of the plasticizer and the alkyl carbons of PVC are measured. Other nonspectroscopic methods for studying plasticizer-PVC interactions include torque rheometer tests (ASTM D 2396, D2538 and ASTM 2383) to test the compatibility under humid conditions, plasticizer-PVC resin clear point and hot bench gelation tests, dynamic mechanical anlaysis (DMA)[16] to study mechanical relaxation temperatures, differential scanning calorimetry (DSC)[16] to study glass transition temperatures, Raman spectroscopy,[16] wide-angle X-ray scattering (WAXS),[17] and inverse gas chromatography.[18,19]

Plasticization can be achieved either internally or externally. Internal plasticization involves the chemical alteration of a polymer or its monomer prior to polymerization. Internal plasticization includes random copolymerization of flexible monomers with vinyl chloride or side chain grafting of PVC. External plasticization involves the addition of plasticizer during compounding, after the polymer has been synthesized. External plasticizers interact with the polymer physically via solvent-like

interactions. The plasticization of PVC by adding external plasticizers is usually done at high temperatures. Since the plasticizer is added after polymerization, plastics of varying degree of flexibility can be produced from one specific polymer formulation. There are two classes of external plasticizers: primary and secondary. Primary plasticizers interact with the polymer to increase its flexibility. On the other hand, secondary plasticizers do not interact with the polymer. Instead they interact with the primary plasticizer to increase its effectiveness. The combination of primary and secondary plasticizers is often used to reduce end product cost or to improve end product properties such as low-temperature flexibility, flame retardance, or processability. Plasticizers can further be grouped into general purpose and specialty plasticizers. General purpose types offer the optimized balance of performance and costs, provide good low temperature properties and acceptable volatility, can be used with variety of processing techniques (injection molding, extrusion, calendaring, etc.) and are usable in almost every market. Specialty plasticizers impart one or more special properties to the polymer but may compromise other properties. Due to the limited availability of speciality plasticizers at competitive pricing, they cannot meet the huge demand for plasticized PVC. Moreover, specialty plasticizers cannot be used with all PVC processing techniques; they are generally confined to applications for which the general-purpose plasticizers do not give the performance required for either the end product or the processing technology. About 50% by

weight of the additives in PVC formulations are plasticizers, thus they greatly influence the properties and behavior of the compounded PVC.

1.2.2 Phthalate Plasticizers

There are more than 30,000 types of plasticizers developed, of which 50-100 are commercially used. The nature of the plasticizer with respect to its molecular structure, size, polarity, glass transition temperature, and its interaction with the polymer control the effectiveness of the plasticizer, both with respect to the flexibility introduced and to the retention of the plasticizer in the polymer. The most common plasticizers are synthetic esters of phthalic acid. These are broadly divided into low molecular weight phthalates which include dimethyl phthalate (DMP) **1.1**, diethyl phthalate (DEP) **1.2**, and di(*n*-butyl phthalate (DBP) **1.3**, and high molecular weight phthalates, which encompass di(2-ethylhexyl) phthalate (DEHP) **1.4**, di(*n*-octyl) phthalate (DNOP) **1.5**, di(*iso*octyl) phthalate (DIOP) **1.6**, di(*iso*nonyl) phthalate (DINP) **1.7**, di(*iso*decyl) phthalate (DIDP) **1.8**, and butylbenzyl phthalate (BBzP) **1.9** (**Figure 1.4)**. Phthalates have good PVC compatibility, a high gelling capacity, good water resistance, and low cost. The polarizable benzene nucleus of phthalates is highly effective with respect to compatibility with PVC, affording great flexibility to the polymer chains. However, compatibility decreases with increasing length of the side chains. Shorter chain phthalates (DMP, DEP, and DBP) are easier to process, as they have faster diffusion rates, but are highly volatile, which limits their application.

Branching increases the plasticization efficiency by introducing free volume. DEHP **1.4** is the ideal phthalate plasticizer with respect to chain length and branching. Moreover, it is a mixture of diastereomers, due to the presence of two stereogenic centers. The diastereomeric mixture creates disorder by breaking the ordered regimes of PVC, thus increase the free volume of the polymer.

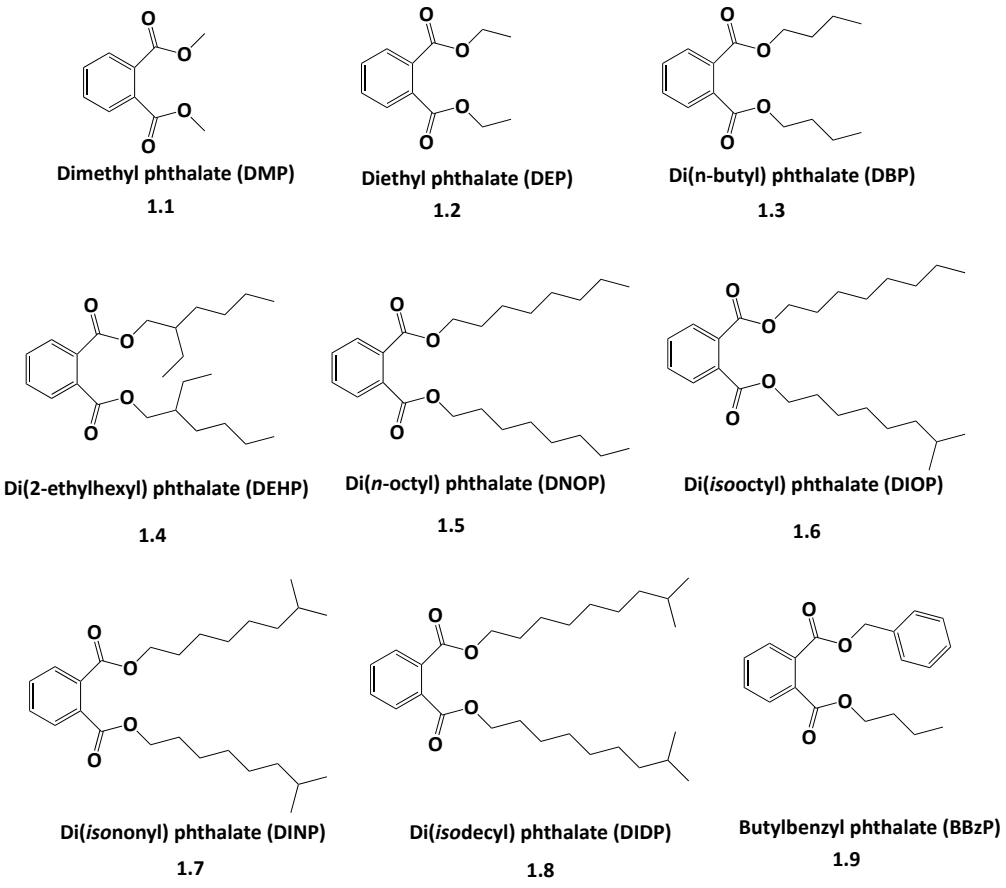


Figure 1.4 Common Commercial Phthalate Plasticizers

Phthalates accounted for 70% of the global plasticizer market in 2014 (**Figure 1.5**).[20] The demand for phthalates was led by DEHP **1.4**, which made up 37% of the

overall plasticizers market in 2014. DINP **1.7** is the second most widely used phthalate plasticizer. Apart from being used as plasticizers for PVC, phthalates are also found in a wide array of other products. In personal care items,[21] they are used in nail polish (to reduce cracking by making the polish coat less brittle), hair sprays (to help avoid stiffness by forming a flexible film), aftershave lotions, soaps, shampoos, perfumes and other fragrance preparations (used as solvent and fixative), and in the coating of some oral medications such as Asacol® used to treat ulcerative colitis.[22] According to FDA's survey conducted in 2010, DBP **1.2** and DMP **1.1** are now rarely used in cosmetics but DEP is still used. DEP prolongs the scent of perfumes, and it functions as a denaturant to render alcohol-based cosmetic products unfit for oral consumption. US Alcohol Tax & Trade Bureau continues to approve DEP as a denaturant in cosmetic products containing alcohol. Phthalates are also used as solvents and plasticizers in making paints and lacquers, varnishes, sealants, detergents, adhesives, printing inks and coatings. According to an analysis conducted by Grand View Research, Inc. in 2015, phthalate consumption is expected to reach 3.3 million tons in 2020.[23]

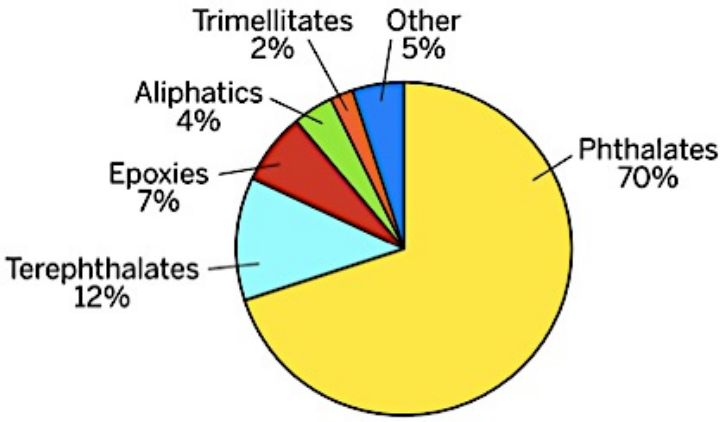


Figure 1.5 Global Plasticizer Consumption in 2014 = 8 Million Metric Tons [20]

PVC plasticized with DEHP is the first choice for plastic blood bags because of the enhancement of red blood cell stability.[24] PVC blood bags are tolerant of the temperatures required for both steam sterilization and freezing plasma, they are clear to allow visual assessment, and strong enough to tolerate centrifugal processing and pressure infusion. The presence of DEHP reduces red cell hemolysis, reduces rates of bacterial contamination,[25] results in better retention of normal morphology,[26] enhances osmotic stability,[7] and improves *in vivo* recovery after transfusion of blood.[27,28] DEHP is the only phthalate plasticizer approved by the FDA for use in medical devices. It is used in intravenous catheters, endotracheal tubes, ventilation devices, infusion or nutrition tubing systems, urinary catheters, occlusive dressing and gloves. DEHP can make up as much as 40% of the weight of these devices.[29] Since its introduction in the 1940s,[30] DEHP has been the favorite

plasticizer of the PVC industry. It is suited for most flexible PVC applications, and is the benchmark for measuring the performance of other plasticizers. It is also the largest-volume plasticizer globally, capturing 37% of the market. Up to 95% of the global production of DEHP is used as a plasticizer.[31]

1.2.3 Leaching of Phthalate Plasticizers

Since phthalate plasticizers are mixed into the pre-formed polymer during the compounding of PVC, they are not covalently linked to the host polymer. These low molecular weight plasticizers can migrate within the material and leach out over time, when the material comes into contact with air,[32] liquid,[11,33,34] or some absorbent solid materials. The most common processes by which a plasticizer is lost from PVC are volatilization, extraction, and migration. The plasticizer is lost from the air/polymer interface by volatilization. The rate of volatilization depends on two factors: rate of diffusion of plasticizer from bulk PVC to the surface, and the rate of evaporation from the surface, which depends on the vapor pressure of the plasticizer. During extraction, plasticizer is lost from liquid/polymer interfaces. Most plasticizers for PVC are hydrophobic and have very low solubility in water (between 0.1-1.0 mg/L).[35] The lipophilicity of phthalate plasticizers enables them to dissolve in most organic solvents and many mineral oils,[36,37] lipids such as milk,[38,39] and some body fluids.[40,41] During migration, plasticizers are removed from PVC by contact with absorbent materials such as food and drug packaging.[42,43] Phthalates are now

ubiquitous and numerous studies have confirmed their presence in household dust,[44] soil, water,[44] indoor and outdoor air,[45] as detectable residues in foods,[46] and in animal and human body fluids.[47] The migration of phthalates is enhanced when exposed to heat and UV light.[48] Although phthalates are generally non-persistent due to their easy photodegradation[49,50] and biodegradation,[51] their contamination in the environment is still significant due to widespread use.[52]

1.2.4 Changes in the Physical Properties of PVC Due to Leaching of Plasticizer

The loss of plasticizer causes changes in the physical properties of PVC, contributing to loss of flexibility with aging, and contamination of the environment. In addition to plasticization, phthalate esters have been found to reduce dehydrochlorination of PVC. Hence, when they leach out from the PVC matrix, discoloration, tackiness, and embrittlement results. Examination of several PVC products suggested that migration, loss and chemical breakdown of plasticizer are the major mechanisms of deterioration.[52,48] The thermal aging of PVC products increases the rate of plasticizer migration and concomitantly decreases flexibility, flame retardance, and the stain resistance properties of the polymer. The exposure of PVC products to UV rays with temperature cycling can also cause the leaching of plasticizer, as observed with automotive dashboards. The new car smell comes largely from the evaporation of phthalate plasticizers. Plasticized PVC degrades faster than unplasticized PVC upon irradiation in the near UV region ($\lambda > 290$ nm).

One good example of PVC deterioration is the space suits that the Apollo astronauts wore on the moon; they returned to earth undamaged. The suits contained PVC tubes plasticized with phthalates. After spending more than 30 years in the museum, they are now falling apart due to the loss of plasticizer. Latini et al[53] observed color changes and rigidness in PVC endotracheal tubes after only a few hours of use during ventilation in high-risk newborns.[54] They analyzed color and spectral changes in the endotracheal tubes after use in the 400- to 700-nm range and compared them to virgin samples. Significant spectrocolorimetric, DSC and TGA changes occurred, indicating *in vivo* PVC degradation and DEHP leakage from these devices.

1.2.5 Exposure to phthalates

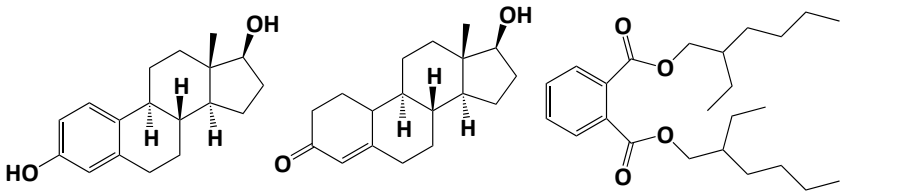
Widespread human exposure to phthalates has been documented by independent studies and representative agencies in US and Europe. People can be exposed to phthalates via water, food, air, soil and dust, and drugs, and can intake of plasticizers via ingestion, inhalation or absorption through the skin. Ingestion of contaminated food is one of the most common routes of exposure to phthalates. Food contamination can occur during the processing of food in facilities using PVC equipment. Another major source of food contamination is the leaching of plasticizer from the food packaging.[55] Cirillo et al[56] measured concentrations of DEHP **1.4** and DBP **1.3** in 22 samples of liquid and 28 samples of powdered baby

formulas. The average DEHP concentration was found to be 0.906 μg/g and that for DBP **1.3** was 0.053 μg/g. Several studies show that the ingestion of DEHP **1.4** from food is much greater than from water. Martine et al.[57] showed that exposure to DEHP from food could be 1000 times higher than from water. The highest degree of exposure to DEHP occurs with hospital patients and with infants in Neonatal Intensive Care Units via multiple treatments, feedings, and transfusions through medical tubing containing phthalates. It is not surprising that greater than 98% of the US population is considered exposed to phthalates, although urinary concentrations of different phthalate metabolites typically span orders of magnitude within a population. The variability in concentrations of phthalates in environmental media and biological samples arises primarily from variation in the sources and concentrations, individual behaviors, and the short biological half-lives of phthalates.

1.2.6 Health Effects of Phthalates

Concerns about phthalates and plasticized PVC are not new, and can be traced back over the last 40 years. The plastic blood bag was first introduced in 1949; by the 1960s it became popular in the medical field. In the 1970s Jaeger et al.[58] first pointed out the possible DEHP contamination of blood stored in PVC bags, and published reports on the migration, extraction, localization, and metabolism of phthalate plasticizers in relation to blood bags and tubing.[59,58] Many reports were published in the following decade, discussing the exposure to phthalates, and raising

concerns about the potential adverse effects.[60,61,62,63,64,65] In the 1990s, phthalates came under strong scrutiny when numerous studies indicated their carcinogenic,[66] mutagenic,[67,68,69] and reprotoxic[70,71,72] properties in rodents. In1999 the European Commission[73] issued an emergency ban (1999/815/EEC) on the use of six phthalate esters in toys and childcare articles that are intended to be placed in the mouths of children under the age of three. These include DBP **1.3**, DEHP **1.4**, DNOP **1.5**, DINP **1.7**, and DIDP **1.8**, and BBzP **1.9**.



Estradiol **1.10** | **Testosterone** **1.11** | **Di(2-ethylhexyl) phthalate (DEHP)** **1.4**

Figure 1.6 Structures of Estradiol, Testosterone and DEHP

Phthalates are now grouped into environmental contaminants called endocrine disrupting chemicals (EDCs). EDCs are exogenous compounds, which can interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological,[74] and immune effects. They can cause endocrine disruption in the body through several mechanisms; they share size, shape or structural features with naturally occurring hormones such as estradiol (a female sex hormone) **1.10**, testosterone (a male sex hormone) **1.11**, (**Figure 1.6**) and thyroid

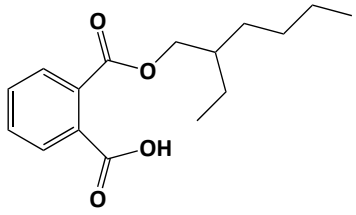
hormones. These hormone mimics and their metabolites can fool the body into overreacting, underreacting, or responding at inappropriate times. EDCs can interact with hormone receptor proteins or enzymes in the cell and block the endogenous hormones from binding. The connections between endocrine disrupting health effects and phthalates led to greater scrutiny of these compounds by scientists, advocacy groups, and consumers, resulting in regulatory agencies banning certain phthalates. In 2005, the European Union permanently banned DEHP, DBP and BBP in all toys and childcare articles.[75] The US Consumer Safety Commission banned DEHP **1.4**, DBP **1.3**, and BBzP **1.9** in toys marketed to children younger than 12 years old, and childcare articles for children up to age 3 in 2009.

Phthalates have been associated with reproductive disorders in humans and animals, with particular focus on reduced sperm viability and declining sperm counts. Consistent laboratory evidence shows that DBP **1.3**, DEHP **1.4**, DINP **1.7**, and BBzP **1.9** are anti-androgenic; they adversely affect the developing male reproductive system through inhibition of testosterone and ins13 synthesis during fetal development in animal models. There are supporting studies that associate these problems with humans. These effects are termed *Phthalate Syndrome* (PS) in animals and *Testicular Dysgenesis Syndrome* (TDS) in human males. PS and TDS include symptoms such as undescended testes, malformations of the penis, reduced anogenital distance, decreased sperm motility and mobility, infertility, and testicular

cancer. The epidemiological studies on humans to phthalate exposure are consistent with the animal models, and implicate phthalates in having the potency to harm the human male reproductive system. The effects of phthalates on the female reproductive system have also been investigated. Rats treated with DBP **1.3** showed a decrease in progesterone levels. Female marmosets (primates) showed effects on ovarian and uterine weight and blood levels of estradiol following 65 weeks of exposure to DEHP **1.4**. Short-term exposure (10 days) of female mice to 0.1mg/kg/day of DBP (which is below its current oral reference dose (0.3 mg/kg/day)) showed that DBP **1.3** is capable of disrupting ovarian function in young female mice.[76]

In addition to developmental and reproductive effects, there is also a growing concern that phthalates can cause other types of toxicity, including epigenetic changes and metabolic disorders. Epigenetic effects are changes to genetic expression, which occur through the changes in the way DNA is packaged, such as histone modification and methylation patterns. New *in vitro*, *in vivo*, and epidemiological studies link human phthalate exposure with obesity,[77,78,79,80,81] metabolic syndrome,[82,83] type II diabetes,[84,85,86,87] cardiovascular disease,[88,89,90] respiratory symptoms,[91,92] decrease in immunity and allergies,[93,91] autism,[94] and learning disabilities.[95] Phthalates that have three to eight carbons in their alkyl side chains possess greater endocrine disrupting properties. To make matters worse,

each phthalate plasticizer has its own toxicity profile, leading to different toxic effects. In some cases, the metabolites and the oxidation products can be more toxic than the parent compound. For example, the toxicity of DEHP is strongly associated with its most toxic metabolite: mono (2-ethylhexyl) phthalate (MEHP) **1.12**, shown in **Figure 1.7**. A number of studies have linked MEHP, the hydrolysis product of DEHP, with endocrine disruption, reproductive dysfuntion, and cytotoxicity to human embryonic stem cells.[96,97,98,99,100,101,102,103] Differences in the structure of phthalates determine how they are metabolized, and thus their toxic effects.



Mono(2-ethylhexyl) phthalate (MEHP)

1.12

Figure 1.7 Structure of the Most Toxic Metabolite of DEHP: MEHP

In 2015, the Chronic Hazard Advisory Panel (CHAP) on phthalates formed by the US Consumer Product Safety Commission (CPSC) studied the health effects of all phthalates and phthalate alternatives found in children's toys, childcare products, and in products used by women of childbearing age. A risk assessment on phthalates was conducted by using the information derived from toxicological experiments,

exposure characterization, and human studies. The CHAP made recommendations to continue to ban DBP **1.3**, BBzP **1.9**, and DEHP **1.4** in children's toys and childcare articles at levels > 0.1%. The panel recommended that the interim ban on DINP **1.7** be made permanent at levels > 0.1% in children's toys and childcare articles. It was recommended that the current ban on DNOP **1.5** and DIDP **1.8** be lifted, as no compelling data was available that justify the ban on these two phthalate plasticizers.[104]

Although DEHP is prohibited in children's products in US and Europe, it is used in medical applications such as intravenous bags and medical tubing. China holds a big share of the PVC market and still uses plenty of DEHP. Therefore, there is a need for alternative plasticizers that migrate to a lesser extent out of PVC and also have low toxicity. Extensive research has been performed to identify alternatives to DEHP and other phthalates, as well as alternatives to PVC. Several approaches have been proposed to circumvent the problems associated with plasticization of PVC. These approaches include (1) replacement of DEHP and other phthalates by alternative monomeric plasticizers, (2) replacement of DEHP and other phthalates by polymeric plasticizers, (3) copolymerization of vinyl chloride, (4) surface modification of PVC, (4) covalent modification of PVC, and (5) replacement of PVC. These approaches are discussed in detail in the following sections.

1.3 Alternatives to Phthalate Plasticizers

Numerous alternatives to DEHP as well as alternatives to the entire class of phthalates have been investigated. Currently, many alternative plasticizers exist: some of them have been used for several decades; some of them have only recently entered the market. Some of them are still in the research phase. Esters of citric acid, succinic acid, adipic acid, maleic acid, trimellitic acid, dibenzoic acid, and some epoxy esters and polymeric plasticizers have been used in the PVC industry for decades. Cyclohexane dicarboxylates have recently entered the market as phthalate substitutes. Plasticizers currently under development include furan dicarboxylates, glucose esters, plant oil based plasticizers, and many polymeric plasticizers.

The performance properties of these alternative plasticizers are compared to those of DEHP as a reference. These properties include color, odor, viscosity, and PVC solvency (the theoretical measure of interaction forces between the plasticizer and PVC). The mechanical properties include tensile strength (modulus at 100% elongation, lower values for tensile strength and modulus are preferred, whereas higher value for elongation is preferred), plasticizer PHR (amount of plasticizer required to provide 70 Durometer A hardness), and substitution factor (ratio of the plasticizer under consideration to that of DEHP required to provide the desired hardness, higher values are preferred). Specific gravity (lower values preferred), volatility (weight % lost due to exposure of 1 mm thick specimens at 100 °C for one

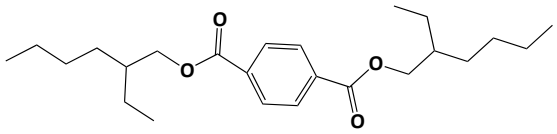
week), diffusibility (extraction of plasticizer from PVC with paraffin oil, lower values preferred), stability to heat, light and hydrolysis, cost/volume analysis, biodegradability, and toxicity are some other important properties that are compared with those of DEHP.

The choice of plasticizer depends on the desired performance properties for specific application. For instance, trimellitates are used as plasticizers when PVC applications require exceptionally good resistance towards volatility. Such applications include high temperature wire and cable insulation, heater pads for waterbeds, etc. The performance properties of common alternative plasticizers are discussed below.

1.3.1 Terephthalate Plasticizers

Terephthalate plasticizers make up approximately 12% of the total worldwide plasticizer consumption.[20] The most common terephthalate plasticizer is di(2-ethylhexyl) terephthalate (DEHTP) **1.13** (**Figure 1.8**), also known as Eastman 168™ from Eastman Chemical Company and Palatinol® from BASF. Terephthalate esters with 10 or more carbons in the alkyl chain show high levels of exudation and are thus poor plasticizers. DEHTP is compatible with both homo- and co-polymers of vinyl chloride. It is used to adjust the characteristics of the polymer, and when improved low temperature flexibility and low volatility of the finished product is required. The viscosity of plastisols and organosols decreases when DEHTP is used

which leads to longer shelf life. Some of the applications where DEHTP is used, include films & sheets, coated fabrics, flooring, wall coverings, and wires and cable. The global demand for DEHTP in 2014 was 500,000 tons.[105] DEHTP is considered a safe alternative to its structural isomer DEHP.



Di(2-ethylhexyl) phthalate (DEHTP)

1.13

Figure 1.8 Structure of the Most Common Terephalate Plasticizer (DEHTP)

Studies have found[106,107] no adverse effects of DEHTP on reproductive tissue, kidney, liver, and peroxisomes in rodents following four weeks of intravenous exposure. No evidence of tetratogenesis or developmental issues were observed in rats following a dietary exposure of up to 12000 ppm.[108] A comprehensive toxicological review and oral risk assessment of DEHTP was presented by Ball et al.[109] This review was based solely on the effects of DEHTP on laboratory animals and *in vitro* test systems. No case reports or epidemiological studies of humans on the exposure to DEHTP were available before 2012. Recently, Silva et al.[110] investigated the metabolism of DEHTP in human liver microsomes to identify exposure biomarkers. The *in vitro* metabolite profiles of DEHTP were compared with

those of DEHP. Terephthalic acid (TPA) **1.14** was identified as the major *in vitro* metabolite of DEHTP; minor metabolites included MEHTP **1.15**, MEOHTP **1.16**, MEHHTP **1.17**, and MECHTP **1.18.**

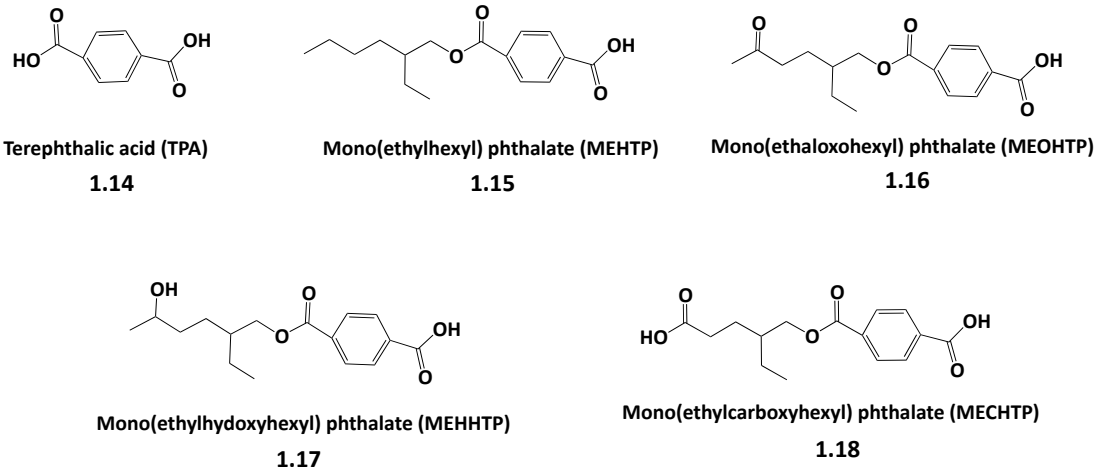
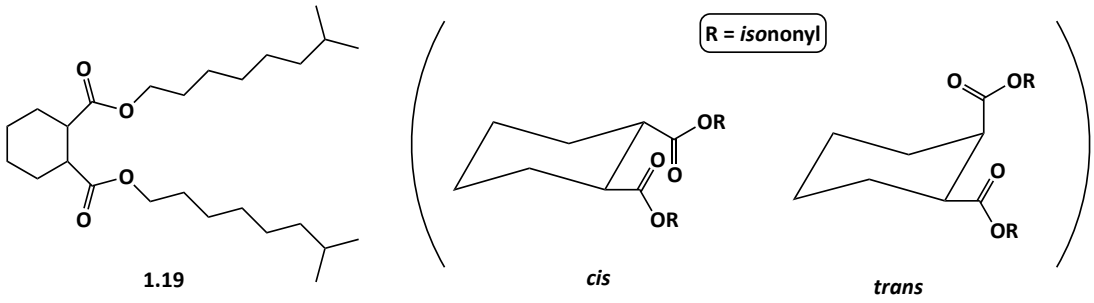


Figure 1.9 Metabolites of DEHTP

1.3.2 Cyclohexane Based Plasticizers

To circumvent the toxicity associated with phthalate plasticizers, some researchers used the hydrogenated benzene ring analogue of phthalates to break the hormone-mimic structure. Di*iso*nonylcyclohexane-1,2-dicarboxylate (DINCH) **1.19** (**Figure 1.10**) also known as Hexamoll DINCH® (BASF SE, Ludwigshafen, Germany), has been recently considered as a potential replacement for DEHP. DINCH is synthesized by the hydrogenation of DINP. Note that DINCH contains two

stereogenic centers. The literature does not specify the relative stereochemistry. Thus it is assumed that DINCH is a mixture of both the *cis* and *trans* isomers. DINCH-PVC shows comparable viscosity and mechanical properties to DEHP-PVC.[111] The high resistance to degradation by steam sterilization makes DINCH a valuable alternative plasticizer for medical device manufacturing. DINCH was introduced to the market in 2002 for use in plastic materials and articles intended to come into contact with food, but it only received final approval from the European Food Safety Authority in 2006.[112]

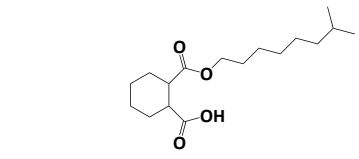


Di-*iso*nonylcyclohexane-1,2-dicarboxylate (DINCH): the relative stereochemistry is unspecified in the literature

Figure 1.10 Structure of Cyclohexane Based Plasticizer (DINCH)

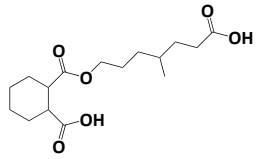
DINCH is also used in toys, cosmetic products, shoes, exercise mats and cushions, textile coatings and printing inks. The production volume of DINCH is high: more than 200,000 tons/year in the European Union. Experiments conducted by Bernard et al.[113] showed that DINCH has a similar migration profile to DEHP: and about one-eighth of the plasticizer is extractedduring the first 24 hour of contact of PVC tubing

with a 50/50 mixture of ethanol/ water. DINCH was found in 44% of the indoor dust samples analyzed by Nagorka et al.[114] Silva et al.[115] investigated the environmental exposure to DINCH in US adults from 2000-2012 by measuring the concentrations of metabolites of DINCH, namely mono*iso*nonylcyclohexane-1,2-dicarboxylate (MINCH) **1.20**, cyclohexane-1,2-dicarboxylic acid-monocarboxy-isooctyl ester (MCOCH) **1.21** , cyclohexane-1,2-dicarboxylic acid-mono-oxo-isononyl ester (MONCH) **1.22**, and cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-isononyl) ester (MHNCH) **1.23** in urine samples (**Figure 1.11**). The solid-phase extraction-high performance liquid chromatography-tandem mass spectrometry of the urines samples collected between 2000 and 2012 showed increased detection of these metabolites from 2007 to 2012.



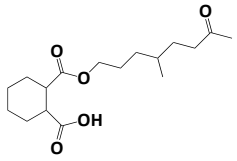
Mono-isononylcyclohexane-1,2-dicarboxylate (MINCH)

1.20



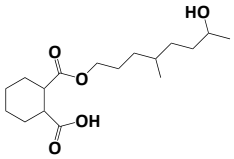
Cyclohexane-1,2-dicarboxylic acid-mono carboxy isooctyl ester (MCOCH)

1.21



Cyclohexane-1,2-dicarboxylic acid- mono(oxo-isononyl) ester (MONCH)

1.22



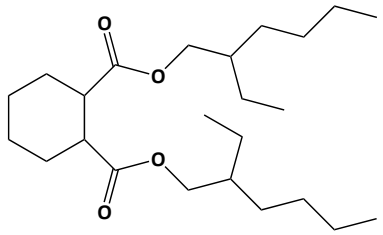
Cyclohexane-1,2-dicarboxylic acid-mono (hydroxy-isononyl) ester (MHNCH)

1.23

Figure 1.11 Structures of Metabolites of DINCH

According to BASF, DINCH has an excellent toxicological profile with no reproductive hazards such as testicular toxicity, fertility impairment, tetratogenecity, endocrine disruption, and no evidence of perixosome proliferation, carcinogenicity, or environmental hazards. However, a recent study by Papadopoulos et al.[116] to evaluate the biological effects of DINCH and its active metabolite cyclohexane-1,2-dicarboxylic acid mono isononyl ester (MINCH) **1.20** suggests that MINCH is a potent PPAR-α antagonist and a metabolic disruptor, capable of inducing stromal vascular fraction preadipocyte differentiation, that may interfere with the endocrine system in mammals. Recently, a toxicogenomic screening of DINCH by Nardelli et al.[117] using the immortalized TM4 sertolli cell line showed that DINCH resulted in altered expression of a large number of genes involved in a major signal transduction pathway.

Another cyclohexane based plasticizer, di(2-ethylhexyl)cyclohexane-1,2-dicarboxylate (DEHHP) **1.24 (Figure 1.12)** was synthesized by nickel catalyzed hydrogenation of DEHP.[118] Xue et al.[**119**] studied the interaction of DEHHP with PVC and compared it with the interaction of DEHP with PVC. Based on low-field ^{1}H NMR results, carbonyl frequency shifts in the FTIR spectra, and theoretical calculations, it appears that the DEHHP-PVC complex interacts mores strongly compared to DEHP-PVC complex. These results support DEHHP as a potential replacement for DEHP. However, further studies on migration and toxicity of this plasticizer are required.



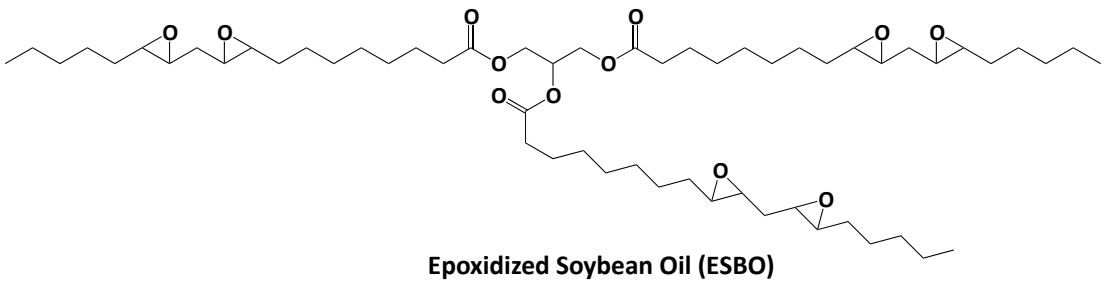
Di(2-ethylhexyl)cyclohexane-1,2-dicarboxylate (DEHHP)

1.24

Figure 1.12 Structure of The Common Terphthalate Plasticizer: DEHHP (Stereoisomers Not Specified)

1.3.3 Epoxy Plasticizers

The plasticizer industry is increasingly interested in replacing phthalates by alternative plasticizers. There is a growing interest in the use of plant-based oils, which are characterized by low toxicity and low migration. Epoxy plasticizers are obtained by the epoxidation of vegetable oils (soybean oil, linseed oil, castor oil, etc.) or fatty acids (oleic acid, butyl-, octyl-, or decyl-esters) with hydrogen peroxide and either acetic or formic acid. A number of epoxy plasticizers are commercially available under the trade name of Vikoflex®. Epoxidzed soybean oil (ESBO) **1.25** (**Figure 1.13)**, also known by the tradename of Virkoflex®7170, is a mixture of organic compounds obtained from the epoxidation of soybean oil. It is one of the most readily available and least expensive vegetable oil plasticizers, which offers compatibility and stability to PVC applications.



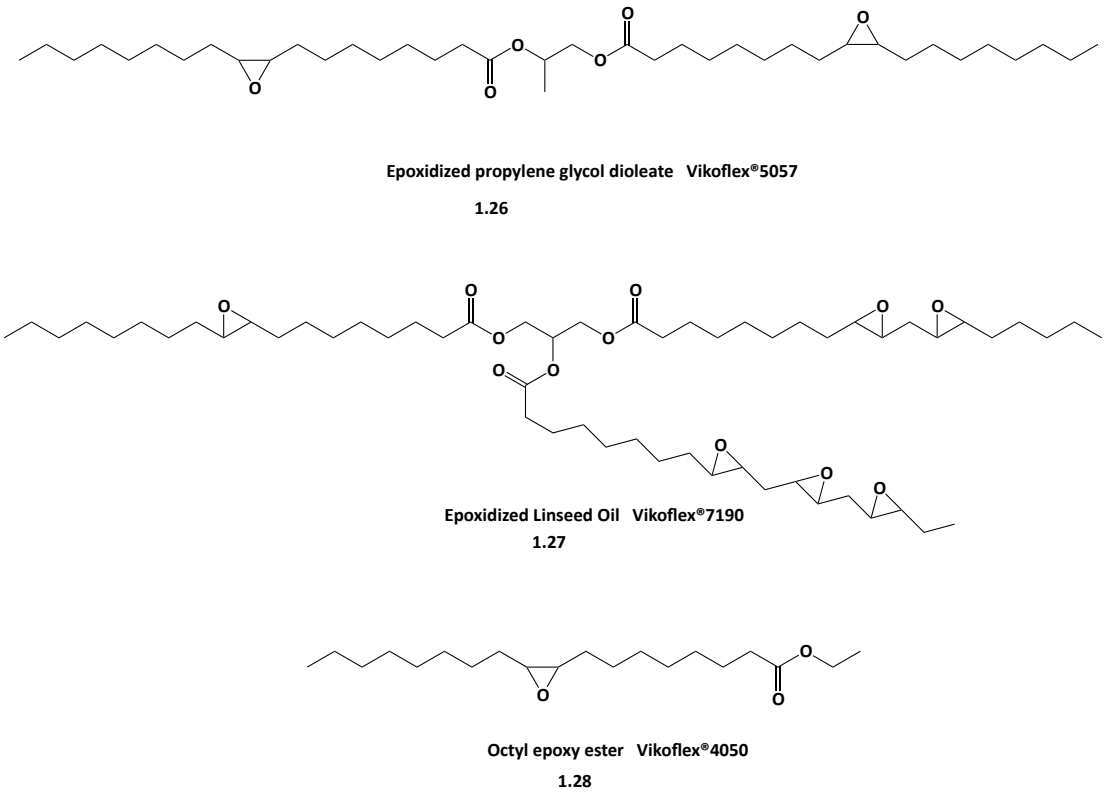
Epoxidized Soybean Oil (ESBO)

1.25

Figure 1.13 Generalized Structure of Epoxy Plasticizer: ESBO

ESBO is a cost efficient and environmentally friendly replacement for phthalate plasticizers, and is replacing DEHP in some applications. Compared to DEHP, it has low volatility, and high water and oil resistance, which make it suitable for applications such as functional fluids, fuel additives, agricultural and pharmaceutical molecules, flavor and fragrances, surfactants, adhesives, sealants, coatings, and special inks. The production volume of ESBO in the EU is 10,000 – 100,000 tons/year. Due to its good acid/ mercaptan-scavenging properties, pigment-dispersing property, antioxidant property, and plasticizing property, ESBO is used in PVC gaskets for glass jars to store acidic foods. However, ESBO shows enhanced migration (1170 mg/kg), exceeding the limit set by the EU, when food with certain amounts of oil are stored for 10 months in glass jars with metal closures with an ESBO-PVC gasket.[120] Recent reports have also raised concerns about the migration of ESBO from PVC gaskets in commercial lids for food storage.[121,122]

The low viscosity of epoxidized propylene glycol dioleate plasticizer, Vikoflex®5057, **1.26** makes it suitable for plastisol and organosol formulations. The high compatibility, and heat and light stability enables epoxidized linseed oil Vikoflex®7190, **1.27** to function as a primary polymeric type plasticizer and stabilizer. The octyl epoxy ester plasticizer Vikoflex®4050, **1.28,** provides improved heat and light stability in PVC formulations (**Figure 1.14**). Epoxy plasticizers are the third



Epoxidized propylene glycol dioleate Vikoflex®5057

1.26

Epoxidized Linseed Oil Vikoflex®7190

1.27

Octyl epoxy ester Vikoflex®4050

1.28

Figure 1.14 Structures of Epoxidized Propyleneglycol Dioleate and Epoxidized Linseed oil and Octyl Epoxy Ester

most widely consumed plasticizer after phthalates and terephthalates.[20] However, it is unlikely that epoxy plasticizers can replace general purpose phthalate plasticizers, as they cannot be used as the sole plasticizer in vinyl formulations.

Acetylated monoglycerides of fully hydrogenated castor oil, (COMGHA) **Figure 1.15**, also known by the trade name of GRINDSTED®SOFT-N-SAFE from Danisco/DuPont, is another plant-based plasticizer derived from fully hydrogenated

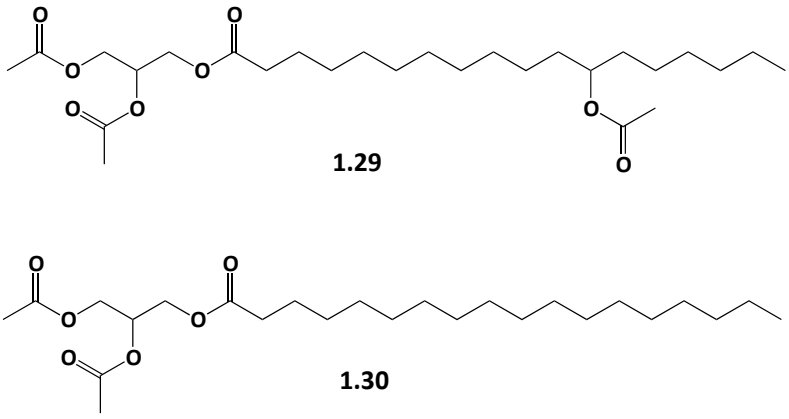


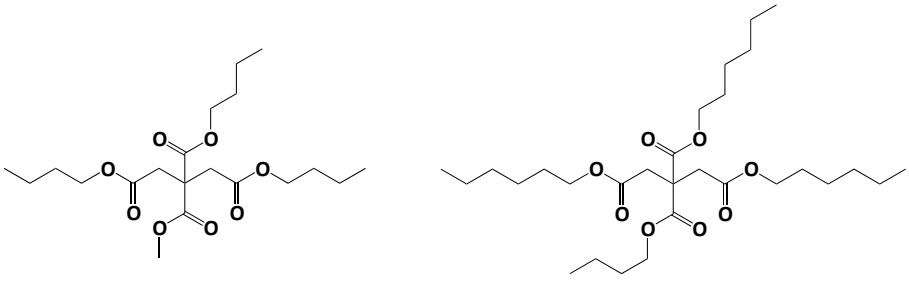
Figure 1.15 Structures of the Main Components of COMGHA

castor oil and acetic acid. It has been approved for use in food contact applications in the US and Europe. COMGHA is considered a safe alternative to phthalates. It offers excellent functionality in applications such as cling films, toys, medical devices. COMGHA is fully biodegradable, is metabolized like vegetable oils, and shows no reproductive and developmental effects. Although not expected, a data gap exists for other toxicities such as carcinogenicity and endrocine activity. The fully aceylated

glycerol monoester on 12-hydroxystearic acid **1.29** is the main component of COMGHA, representing 85% of the plasticizer. Fully acetylated glycerolmonostearate **1.30** is the minor component, representing 10% of the plasticizer composition.

1.3.4 Citrate Plasticizers

Citrates are obtained from citric acid, a common metabolite of plants. They have been available for years as plasticizers in medical devices, especially for blood storage bags. About 4% of the global plasticizer consumption constitutes citrates along with other aliphatic esters. Acetyl tri-*n*-butyl citrate (ATBC) **1.31** known as (Citroflex® A-4, NatureFlexx 509), and *n*-butyl tri-*n*-hexyl citrate (BTHC) **1.32**, known as (Citroflex® B-6), are the most important citrate plasticizers (**Figure 1.16**). ATBC has



Acetyl tri-*n*-butyl citrate (ATBC)

1.31

Butyl tri-*n*-hexyl citrate (BTHC)

1.32

Figure 1.16 Structures of Citrate Plasticizers

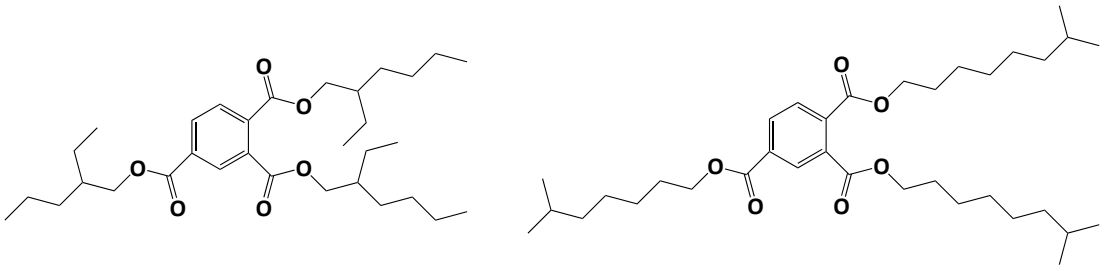
three butyl esters and one methyl ester whereas BTHC has three hexyl esters and one butyl ester. Citrates are biodegradable plasticizers, and are used as alternatives

to DEHP in toys, food contact applications, cosmetic products, pharmaceutical tablet coatings, and medical products. Their low extractability into lipid media enables them to be used as plasticizer in PVC medical articles such as tubing and intravenous bags. Citrates are also used as plasticizers for bio-plastics such as polylactic acid, cellulose acetate and poly(hydroxyalkanoic acid). These plasticizers have low toxicity, good resistance to heat and cold, good resistance to yellowing, good adhesion to metals, and lower volatility compared to phthalates. The volume of ATBC produced in the European Union is 10,000-100,000 tons/year. The safety assessment of ATBC provided by the US Environmental Protection Agency High Production Volume program indicates that ATBC does not induce adverse toxicological effects in rats and mice. Genotoxicity, reprotoxicity and developmental toxicity tests indicated no adverse effects as well.[123] However, compared to DEHP, ATBC migrates ten times faster out of the PVC matrix,[124] thus posing concerns about its use in recurrent long-term applications. Citrate based plasticizers are relatively expensive, and do not display any outstanding technical advantages over phthalate plasticizers.

1.3.5 Mellitate Plasticizers

Trimellitate esters are similar to phthalates with an additional ester functional group, which greatly enhances their high temperature performance, making them the material of choice for applications in which high temperature stability is required.

These esters are prepared by the esterification of trimellitic anhydride with three molar equivalents of alcohol. If linear alcohols are used to synthesize trimellitate esters from trimellitic anhydride, these plasticizers possess good low temperature flexibility, making trimellitate esters versatile. About 2% of the total global consumption of plasticizers constitutes trimellitates. Tris(2-ethylhexyl) trimellitate (TOTM) **1.33** and tris(*iso*nonyl) trimellitate (TINTM) **1.34,** shown in **Figure 1.17** are commercially available mellitate plasticizers. The drawback of these plasticizers is the cost associated with the additional chemistry involved in their synthesis. TOTM



Trioctyl trimellitate (TOTM)

1.33

Triisononyl trimellitate (TINTM)

1.34

Figure 1.17 Structure of Trimellitate Plasticizers

and TINTM are used in plasticized PVC electrical wire insulation applications because of their high temperature resistance, in automotive instrument panels because of their improved resistance to outdoor weathering, packaging, cables, and floor and wall coverings. The unique low leaching and extraction resistance properties of TOTM make it a plasticizer of choice for dishwasher gaskets, medical tubing and photograph storage.

The estimated global production of TOTM is 40,000 – 100,000 tons/year.[125] PVC medical devices that use TOTM have been developed, but are not popular in the medical field because of reduced performance in terms of flexibility compared to traditional PVC products. Veld et al.[126] studied the estrogenic potency of 21 food-packaging associated compounds including TOTM. They used human osteoblast estrogen receptor (ER) alpha and beta cell lines, and found TOTM to be slightly estrogenic in ERα cell lines. TOTM has also been reported to alter the expression of a large number of genes in immortalized TM4 sertolli cells.[117]

1.3.6 Adipate Plasticizers

Adipates are used as secondary plasticizers to provide increased flexibility to plasticized PVC products at low temperatures. They are used in conjunction with other general purpose plasticizers to reduce cost.[127] They provide good technical performance at low temperatures due to their lower viscosity compared to phthalates.[128] The most important plasticizers in this class are: di(2-ethylhexyl) adipate (DEHA) **1.35**, dibutyl adipate (DBA) **1.37**, di(*iso*nonyl) adipate (DINA) **1.36**, and di(*iso*decyl) adipate (DIDA) **1.38**. These plasticizers show similar activity to phthalates, but possess the added benefits of very low viscosity and excellent low temperature flexibility, making them suitable for the plastisol industry. However, adipates are less solvating for PVC than the corresponding general purpose phthalates due to the absence of an aromatic ring. Adipates show two times higher

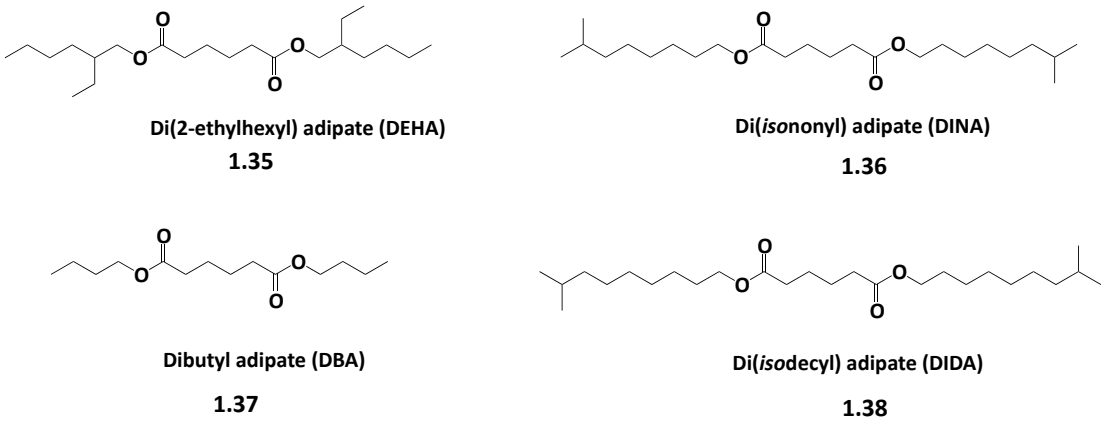


Figure 1.18 Structures of Adipate Plasticizers

loss under diffusion-controlled conditions compared to DEHP. Typically adipates are used as mixtures with phthalates to control compatibility while improving low temperature properties. According to the U.S. Environmental Protection Agency's High Production Volume Information System (HPVIS), the volume of adipate production is 10,000 – 100,000 tons/year in the European Union. DEHA is used in toys, vinyl flooring, wires and cables, stationery, wood veneers, coated fabrics, gloves, tubing, artificial leather, shoes, sealants, and carpet backing. DBA is used in resins and floor wax. DINA and DIDA are used in skin conditioning agents, emollients, and as solvents. Adipates readily penetrate the environment, contaminating biota including humans.[129,130,131] Recent studies have raised concerns over the use of adipates, as their metabolites could interfere with hormone secretions, causing deformities, cancer and mutations.

1.3.7 Benzoate Esters

The general-purpose plasticizers used in flexible PVC applications often require viscosity reduction for efficient plastisol processing. The reduction in viscosity is usually achieved by the addition of specialty plasticizers such as benzoate esters. This class of plasticizer has gained attention as an environmentally friendly green chemical, and was listed as a preferred alternative to phthalates plasticizer by the European Chemical Agency in 2009.[132]

Their primary attribute is strong solvency for PVC. Typically mixtures of benzoate esters with general-purpose phthalates are used to enhance plastisol gelation properties. Benzoate ester plasticizers are known by the tradename of Benzoflex®, by CBC Company Limited. Benzoflex®2888 is the most common benzoate plasticizer used for PVC applications. It is a blend of diethylene **1.39**, dipropylene **1.40**, and triethylene dibenzoate **1.41** esters (**Figure 1.19**).

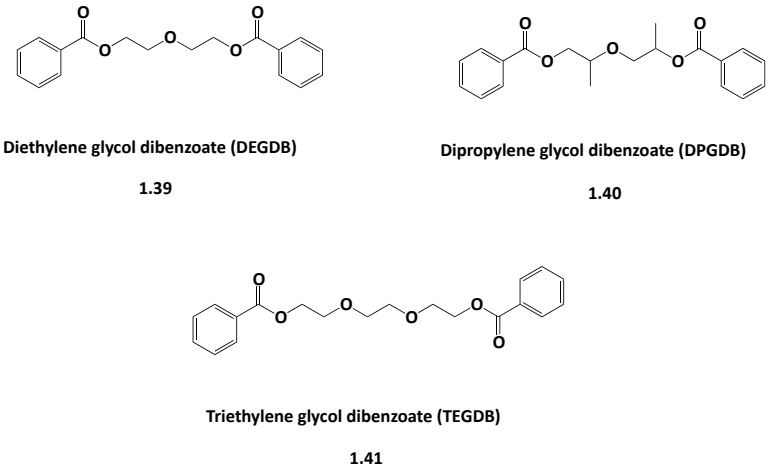
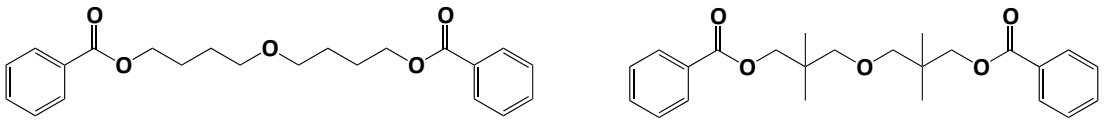


Figure 1.19 Structures of the Main Components of Benzoflex®2888

Benzoflex plasticizers have been in use for more than 40 years in vinyl flooring due to their high solvation, high stain resistance, low viscosity, good processability, and excellent UV stability.[133,134] Wardzinska et al.[135] investigated the influence of glycol content of dibenzoate esters on the plasticizing efficiency of this plasticizer class. Di(*neo*pentyl) benzoate **1.43** showed the highest degree of plasticization, followed by diethylene **1.39**, dipropylene **1.40**, and di(*n*-butylene) glycol benzoate **1.42** (**Figure 1.20**).



Di(*n*-butylene)glycol dibenzoate

1.42

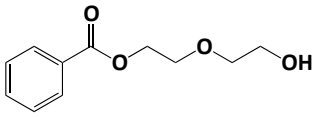
Di(*neo*pentyl) dibenzoate

1.43

Figure 1.20 Structures of Di(*n*-butylene)glycol and Di(*neo*pentyl) dibenzoates

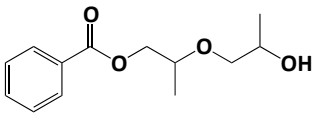
Low toxicity benefits were reported for a blend of dibenzoate plasticizers. However, biodegradation of DEGDB and DPGDB by the common soil organism *Rhodotorula* rubra results in incomplete microbial hydrolysis, and release of the corresponding monoesters; diethylene glycol monobenzoate (DEGMB) **1.44** and Dipropylene glycol monobenzoate (DPGMB) **1.45**, which exhibit significant acute toxicity.[136] Removal of the ether bond significantly enhances the biodegradation rate

of di- and mono-benzoates of 1,3-propanediol **1.46** and 2,2-methylpropyl-1,3-propanediol **1.47** (**Figure 1.21**).[137] Benzoflex plasticizers are harmful to aquatic life, and are skin irritants. Dibenzoate plasticizers have high densities, and reduced low-temperature flexibility, which restricts their use as general-purpose plasticizers.



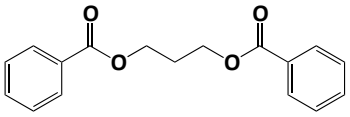
Diethylene glycol monobenzoate (DEGMB)

1.44



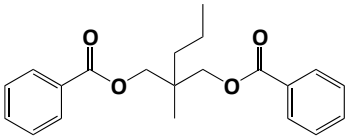
Dipropylene glycol monobenzoate (DPGMB)

1.45



1,3-propanediol dibenzoate

1.46



2,2-methyl-propyl-1,3-propanediol dibenzoate

1.47

Figure 1.21 Structures of Glycol Monobenzoates and 1,3-Propanediol Dibenzoates

1.3.8 Maleate Plasticizers

The biodegradation of DEHP is very slow, and leads to the production of stable metabolites, which are of major concern due to their toxic nature. Di(2-ethylhexyl) maleate (DEHM) **1.48** (trade name, Kanatol-8M®) and di(*n*-butyl) maleate (DBM) **1.49** (trade name, Kanatol-4M®) are commercially available, and are used as secondary plasticizers in coatings and adhesives made of PVC. DEHM was identified

as a possible replacement for DEHP, however the poor biodegradability rates are of concern. A study conducted by Leask et al.[138] on DEHM **1.48** and dihexyl maleate (DHM) **1.50** (**Figure 1.22**) on the reduction of T_g of PVC showed that branching in the maleates has no effect on the plasticization of PVC. Biodegradation experiments with the common soil bacterium *Rhodococcus rhodocrous* showed acceptable hydrolysis rates for linear DHM, while branched DEHM showed no biodegradation. However, DHM was found to be toxic, with $EC_{50} < 1$ mg/L when screened for toxicity by the *Vibrio fischeri* bioluminescence inhibition assay (Microtox).[139]

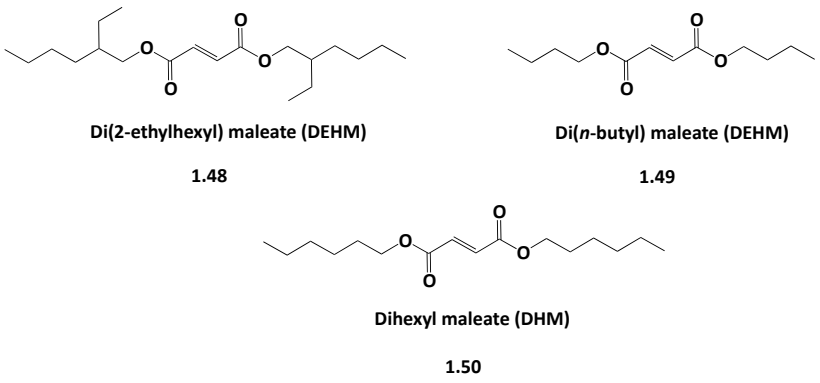


Figure 1.22 Structure of Maleate Plasticizers

1.3.9 Succinate Plasticizers

The bans on certain phthalates spurred interest in the development of bio-based plasticizers. The diesters of succinic acid, a natural molecule involved in the citric acid cycle of mammals, show compatibility with PVC and are proposed as potential nontoxic and sustainable alternative plasticizers.[140] Diethyl succinate (DES)

1.50, di(2-ethylhexyl) succinate (DEHS) **1.51**, dihexyl succinate (DHS) **1.52**, dihexylmethylsuccinate (DHMS) **1.53**, and dihexylcyclohexyl succinate (DHCHS) **1.55** belong to this class of plasticizers (**Figure 1.23**). The T_gs of DEHS and DHS plasticized PVC are significantly lower than DEHP plasticized PVC.[140] DEHS produces flexible PVC with mechanical poperties similar to those produced by the adipate analogue DEHA **1.35**. DEHS is comparable to DEHA in terms of low temperature flexibility, migration, cost and performance, and is useful as a secondary plasticizer with DEHP. DEHS is suitable as a DEHP replcement for applications that do not require high temperature performance. Mohanty et al.[141] reported that mixtures of high molecular weight succinate diesters such as didecyl succinate (DDS) **1.54** and didodecyl succinate (DDoDS) **1.56** with lower molecular weight succinates are more effective at plasticizing PVC compared to the use of a single composition.

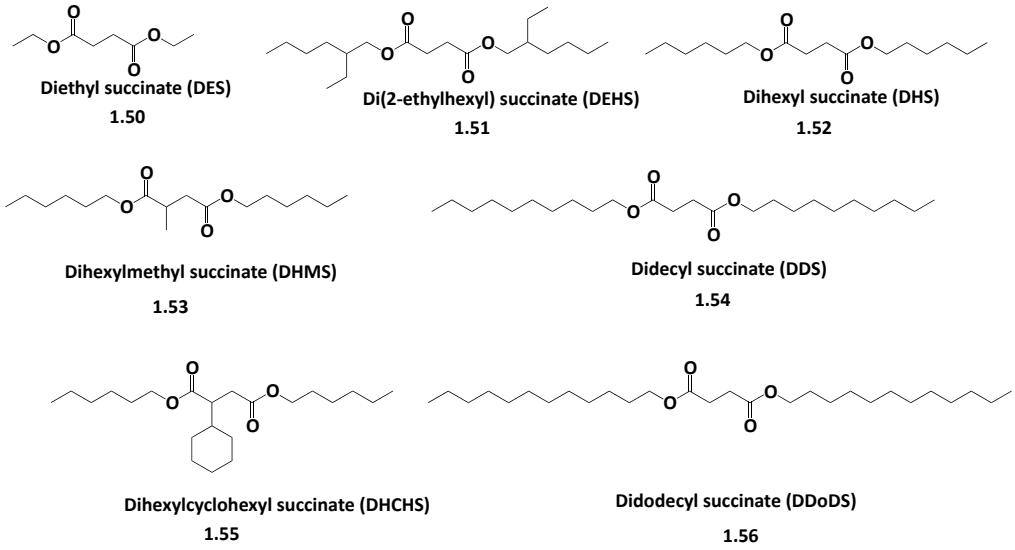
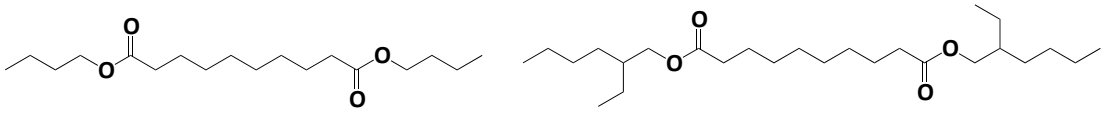


Figure 1.23 Structures of Succinate Plasticizers

1.3.10 Sebacate Plasticizers

Sebacates are commonly used for flexible PVC applications requiring low volatility. The most common sebacate plasticizers are dibutyl sebacate **1.57** and di(2-ethylhexyl) sebacate **1.58** (**Figure 1.24**). They are used as a secondary plasticizer, as a flavoring agent, and as cosmetic and perfume additives. The lopophilicity of sebecates enable them to interact with biomembranes.[142]



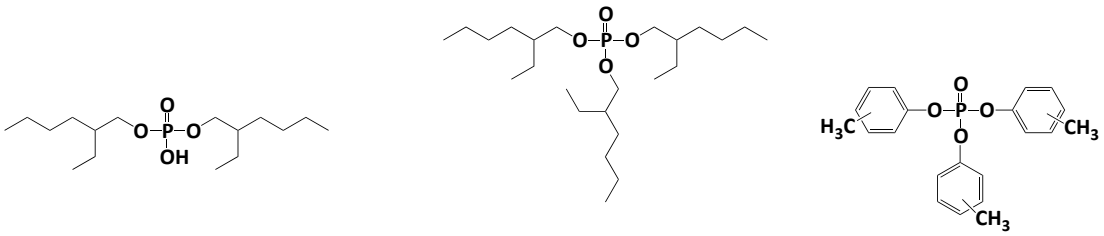
Dibutyl sebacate
1.57

Di(2-ethylhexyl) sebacate
1.58

Figure 1.24 Structures of Sebacate Plasticizers

1.3.11 Phosphate Ester Plasticizers

Phosphate esters were one of the first class of plasticizers proposed for use with PVC. These esters offer both plasticization and flame-retardance. The common phosphate plasticizers are di(ethylhexyl) phosphate (DEHPA) **1.59**, tri(ethylhexyl) phosphate (TEHPA) **1.60**, and tricresyl phosphate (TCP) **1.61**, **Figure 1.25**.



Di(2-ethylhexyl) phosphate (DEHPA)

1.59

Tri(2-ethylhexyl) phosphate (TEHPA)

1.60

Tricresyl phosphate (TCP)

1.61

Figure 1.25 Structures of Phosphate Ester Plasticizers

The majority of phosphate plasticizers are alkyl diaryl phosphates, prepared as mixtures with various phenols and alcohols. Phosphate plasticizers are often used as secondary plasticizers in combination with DINP or DIDP. The flame resistance and smoke suppression properties of phosphate plasticizers make them suitable for PVC applications such as electronics, data and communication cables, and wall coverings. However, color constraints and costs limit the possibility of phosphates to serve as general-purpose plasticizers.

1.3.12 Isosorbide Esters

Isosorbide diesters are bio-based plasticizers produced by the reaction of fatty acids of vegetable origin and isosorbide produced by dehydration of sorbitol, a glucose derivative. Isosorbide diesters are sold under the trade name of

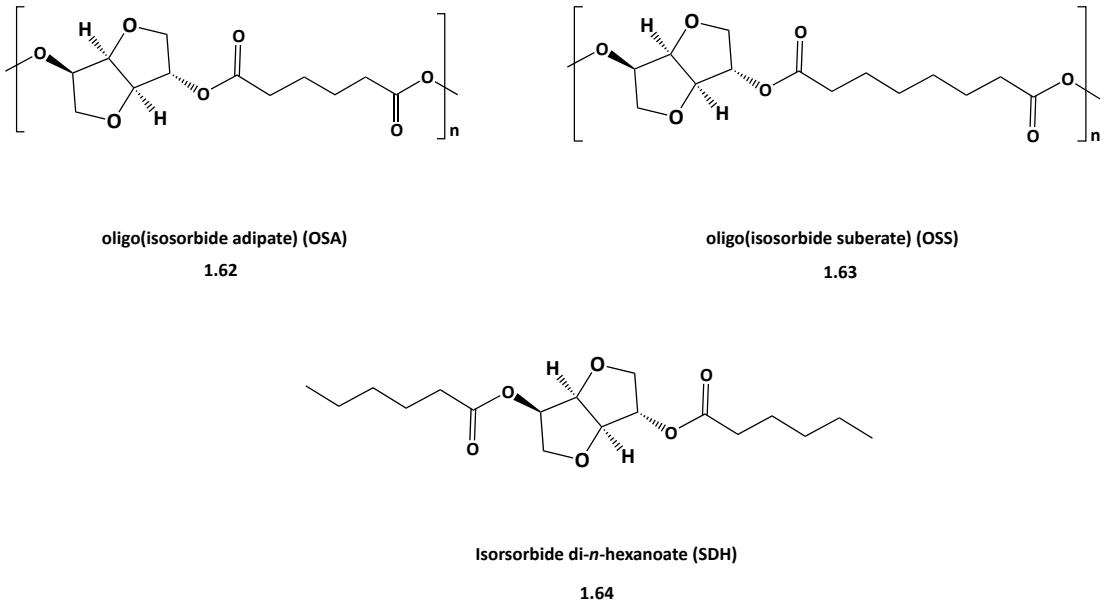


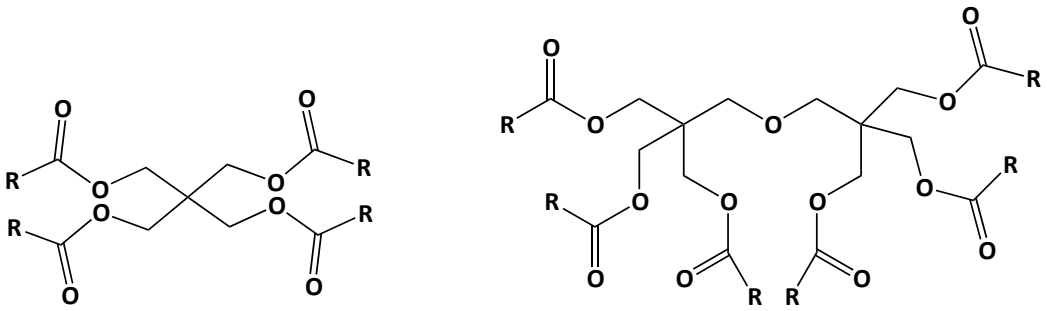
Figure 1.26 Structures of Polymeric and Diester Isosorbide Plasticizers

Polysorb ID37™. Oligomeric isosorbide esters such as oligo(isosorbide adipate) (OSA) **1.62** and oligo(isosorbide suberate) (OSS) **1.63** are possible alternative renewable resource plasticizers for PVC (**Figure 1.26**).[143] Blends of PVC with OSA, OSS and isosorbide di(*n*-hexanoate) (SDH) **1.64** are comparable with blends of PVC with di(*iso*octyl) phthalate (DIOP) in terms of their performance. They are biodegradable PVC plasticizers with good compatibility and low volatility. The main drawback of isosorbide diesters is their sensitivity towards water. Moreover, it has been reported that SDH exhibits estrogenic potency in estrogen receptor (ER) alpha cell lines.[126]

1.3.13 Pentaerythritol esters

Pentaerythritol tetraester (trade name Hercoflex600™) **1.65** and a mixture of pentaerythritol tetraester and dipentaerythritol hexaester **1.66** (Hercoflex707™)

(**Figure 1.27**) are high molecular weight plasticizers with low volatility. These plasticizers are used for low smoke, flame retardant PVC for wire and cable applications. Their use as PVC plasticizers is very limited due to their high cost. Estrogenic potency of these plasticizers in ER alpha cell lines has recently been reported.[126]



Pentaerythritol ester

1.65

Dipentaerythritol ester

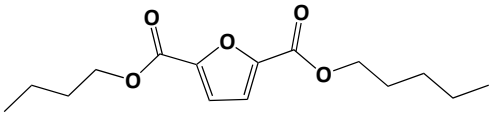
1.66

Figure 1.27 Structures of Pentaerythritol and Dipentaerythritol Esters

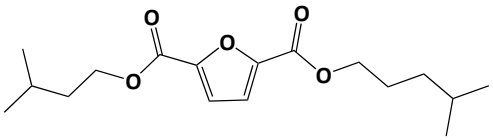
1.3.14 Furandicarboxylate Plasticizers

Dialkyl 2,5-furandicarboxylate esters have recently been investigated as bio-based plasticizers for commercial PVC products. 2,5-Furandicarboxylic acid is a valuable bio-derived product and is considered to be a substitute for phthalic and terephthalic acids. Moreover, furandicarboxylates are metabolized in the citric acid cycle.[144] In the 1990s, Sanderson et al.[145,146] synthesized several types of furancarboxylates from furfural, and characterized their plasticizing abilities toward PVC by evaluating the glass transition temperatures. The efficiency of di(2-

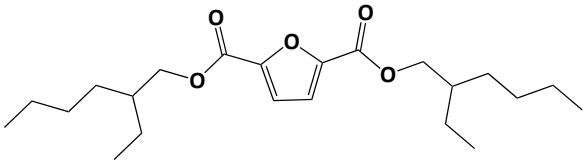
ethylhexyl)furan-2,5-dicarboxylate (DEHF) **1.69** (**Figure 1.28**) in lowering the T_g of PVC is similar to that of the phthalate analog DEHP. Moreoever, DEHF is more miscible with PVC compared to DEHP. However this group did not study other mechanical and thermal properties of PVC blends made with these



Di(*n*-butyl)furan-2,5-dicarboxylate (DBF)
1.67



Di(isopentyl)furan-2,5-dicarboyxlate (DIPF)
1.68



Di(2-ethylhexyl)furan-2,5-dicarboxylate (DEHF)
1.69

Figure 1.28 Structures of furan ester plasticizers

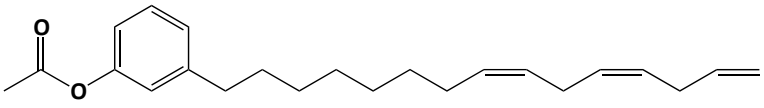
furandicarboxylates. Recently, Yu et al.[147] extended this work, synthesizing three esters: di(*n*-butyl)furan-2,5-dicarboxylate **1.67**, di(*iso*pentyl)furan-2,5-dicarboyxlate **1.68**, and di(2-ethylhexyl)furan-2,5-dicarboxylate **1.69** from furandicarboxylic acid to use as PVC plasticizers. PVC blends with 10-50 parts per hundred (phr) by volume of 2,5-furandicarboxylate esters were prepared, and their thermal and mechanical properties studied. The morphological analysis indicates that all three plasticizers show good miscibility with PVC. The tensile strength and elongation at break of the PVC plasticized with DEHF is similar to PVC plasticized with DEHP. Migration tests

indicate that low-molecular weight furandicarboxylates leach out of PVC blends within 24 hours. Migration is not observed for DEHF up to a concentration of 30 phr. However, when the concentration of DEHF increases to 50 phr, migration is observed within 8 hours.

1.3.15 Plant Oil Based Plasticizers

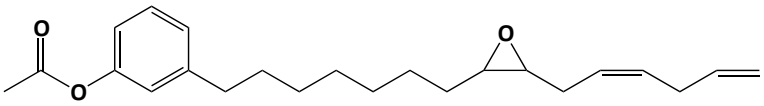
The plasticizer industry is increasingly looking to replace phthalates by alternative plasticizers. There is a growing interest in the use of plant-based oils, which are characterized by low toxicity and low migration. The raw material cardanol is extracted from cashew nut shell liquid. Due to its low cost and versatile chemical structure, cardanol and its derivatives are used in bio-composites, synthetic resins, epoxy curing agents, and coatings. Cardanol has been used as a plasticizer by the polymer and rubber industries, with or without modification. Greco et al.[148] conducted preliminary analysis on the use of cardanol derivatives as renewable plasticizers for PVC. The acetate of cardanol **1.70** (**Figure 1.29**) was synthesized by the esterification of the hydroxyl group. The epoxidation of the side chain of cardanol acetate gave epoxidized cardanol acetate **1.71**. Cardanol acetate is partially miscible with PVC, whereas epoxidized cardanol acetate is completely miscible. Blends of cardanol derivatives as secondary plasticizers with DEHP in PVC show behavior comparable to PVC plasticized with only DEHP. The authors

concluded that the use of biosourced cardanol derivatives could be good secondary plasticizers for soft PVC applications.



Cardanol acetate

1.70

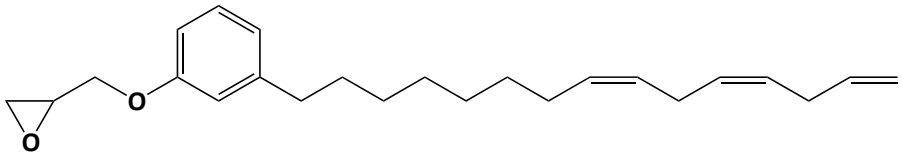


Epoxidized cardanol acetate

1.71

Figure 1.29 Structure of Cardanol Esters

Zhou et al.[149] synthesized cardanol glycidyl ether (CGE) **1.72** and explored its application as a plasticizer for PVC (**Figure 1.30**). Compared to DEHP and DINP, CGE has better mechanical compatibility, thermal properties, processability, exudation resistance, and plasticizing effects on PVC. However, CGE is more volatile than DEHP.

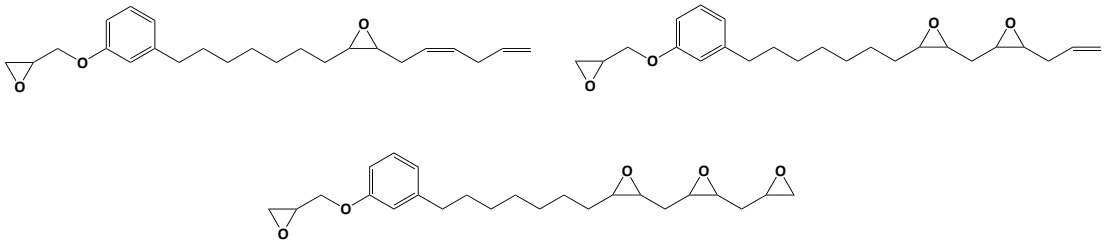


cardanol glycidyl ethers (CGE)

1.72

Figure 1.30 Structure of CGE

In another study, Zhou synthesized mixtures of epoxidized cardanol glycidyl ethers (ECGE)[150] **1.73** and evaluated their performance as a secondary plasticizer for PVC combined with DEHP (**Figure 1.31**). The mechanical properties of the films showed an increase in tensile strength and percent elongation with increasing ECGE content. The thermal stability of the plasticized PVC increased with increasing content of ECGE. The analysis of volatility, extraction, and exudation resistance suggests that ECGE has similar or better performance than DEHP.



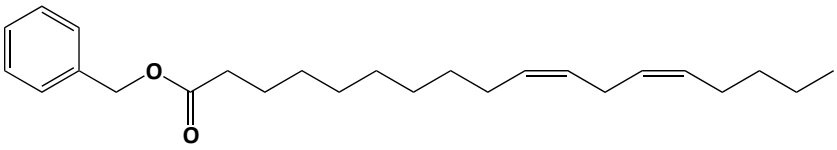
Epoxidized cardanol glycidyl ethers (ECGE)

1.73

Figure 1.31 Structures of ECGE

Sabnis et al.[151] prepared the benzyl ester (BE) of dehydrated castor oil fatty acid **1.74** (**Figure 1.32**) as an environmentally friendly plasticizer for PVC. This plasticizer can be obtained by simple esterification of a renewable resource, dehydrated castor oil fatty acid (DCOFA) with benzyl alcohol in the presence of catalyst. The effectiveness of this ester as a co-plasticizer with DEHP was investigated. The PVC/DEHP/BE blends showed good tensile strength, improved migration stability,

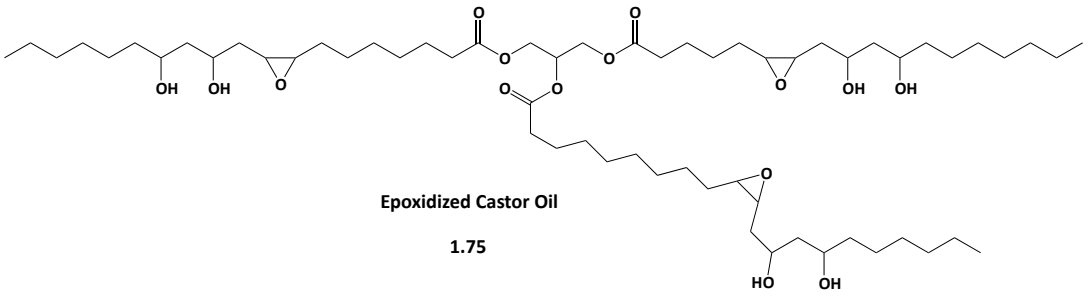
reduced viscosity, improved elongation at break, and improved thermal degradation properties. However, incorporation of BE resulted in the yellowing of the PVC blend.



Benzyl ester of dehydrated castor oil fatty acid

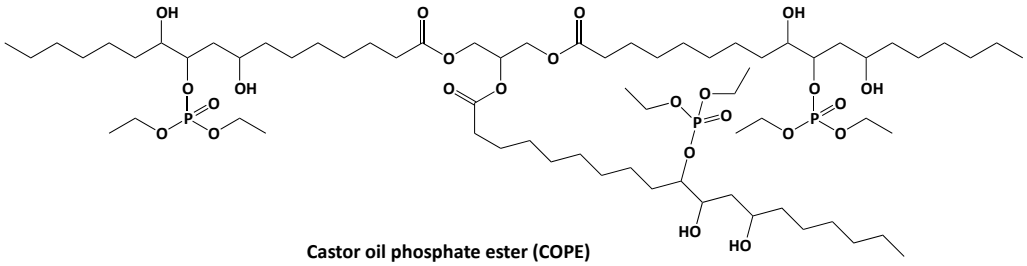
1.74

Figure 1.32 Structure of Benzyl Ester of Dehydrated Castor Oil Fatty Acid



Epoxidized Castor Oil

1.75



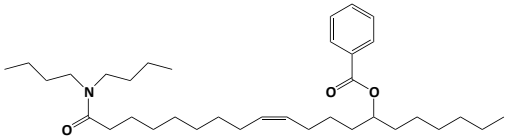
Castor oil phosphate ester (COPE)

1.76

Figure 1.33 Representative Structures of Castor Oil Ester Secondary Plasticizers

In another study, Zhang et al.[152] synthesized castor oil phosphate ester (COPE) **1.75** and epoxidized castor oil (ECO) **1.76** and (**Figure 1.33**), and studied these molecules as secondary plasticizers for PVC. A PVC blend system was prepared using ECO or COPE as an auxiliary plasticizer along with DEHP as the primary plasticizer. As some of the DEHP was replaced by either ECO or COPE, the glass transition temperature of the blend increased indicating poor plasticization.

Savvashe et al.[153] utilized ricinoleic acid: a raw material obtained from the endosperm of the castor bean, to obtain an economically viable plasticizer for PVC. The plasticizer **1.77** was synthesized by esterification and amidation of ricinoleic acid (**Figure 1.34**) and was evaluated for its mechanical and thermal properties. The glass transition temperature of PVC plasticized with this ester amide of ricinoleic acid was found to be -13.9 °C at 40 wt% loading of the plasticizer. The glass transition temperature of PVC with 40 wt% loading of DEHP is -25 °C. The plasticized PVC demonstrated a decrease in the tensile modulus, tensile strength, flexural strength, flexural modulus and crystallinity, and an increase in elongation at break. However, the major drawback is the dark red color of this plasticizer.

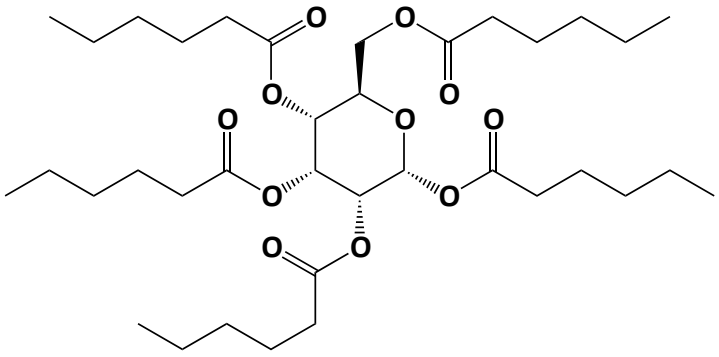


1.77

Figure 1.34 Structure of Ricinoleic Acid Esters

1.3.16 Glucose Based Plasticizers

Hakkarainen et al.[154] synthesized and evaluated three versions of glucose hexanoate (GH) esters as bio-based plasticizers for PVC: a fully esterified structure is shown as **1.78** (**Figure 1.35**). The esterification of glucose with hexanoic acid was carried out using three different time periods (9, 12 and 24 h), to obtain plasticizers with three different degrees of esterification. All of the GHs showed good miscibility and plasticizing efficiency.



1.78

Figure 1.35 Structure of a Glucose Based Plasticizer

1.3.17 Curcumin Based Plasticizer

Curcumin diesters **1.79** (**Figure 1.36**) have been proposed as effective plasticizers for PVC by Raja et al.[155] Curcumin is a commercially available renewable resource isolated from the turmeric plant. It is known for its antioxidant, anti-inflammatory, anitomicrobial, and anticarcinogenic properites. Curcumin diesters look similar to

traditional phthalate plasticizers, with a rigid aromatic core attached to two flexible alkyl ester chains. The glass transition temperatures of PVC-curcumin distearate blends were analyzed and compared to PVC-DBP blends. Curcumin distearate had better efficiency in lowering the glass transition temperature compared to DBP, which may be attributed to the 18-carbon chain of curcumin distearate as opposed to the 4-carbon chain of DBP.

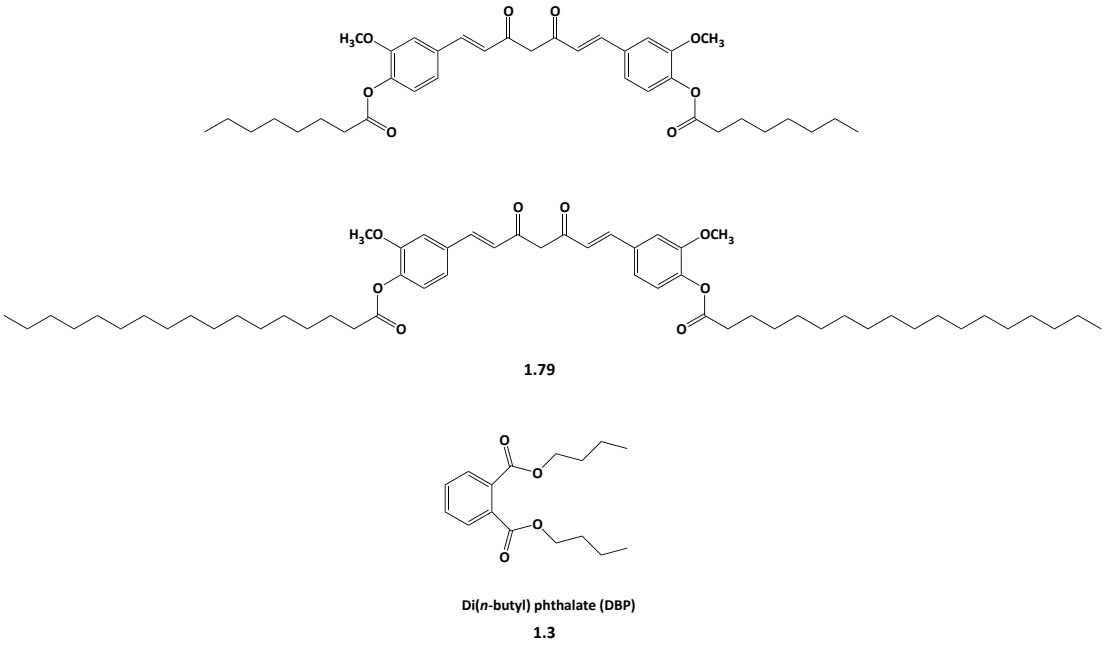


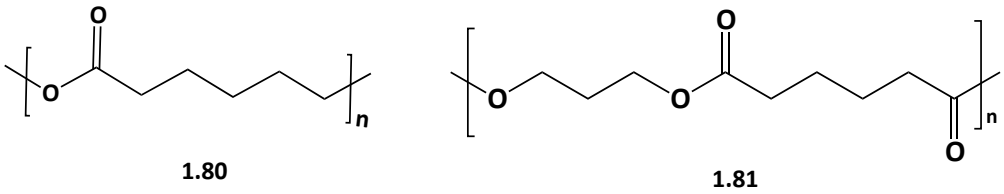
Figure 1.36 Structure of Two Curcumin Based Plasticizers and DBP

1.4 Polymeric Plasticizers

Polymeric plasticizers have been investigated as a substitute for phthalates and other low molecular weight plasticizers. Polymeric plasticizers are characterized as low, medium, or high molecular weight plasticizers, with average molecular weights ranging from 1000 to 10,000. Polymeric plasticizers have a great advantage in that they have negligible volatility due to their high molecular weights. Polymeric plasticizer molecules can have much stronger dipole-dipole interactions with PVC molecules than small molecule plasticizers, accompanied by an entanglement effect, which largely affects the mobility. Moreover, polymeric plasticizers can be designed to make them compatible with the host polymer. Because of these characteristics, polymeric plasticizers have found wide commercial acceptance for applications that require very low plasticizer migration and extended durability. Polymeric plasticizers can be found in PVC applications that are subjected to elevated temperatures by long-term outdoor exposure, food contact, or long-term contact with solvents.

1.4.1 Poly(ε-caprolactone) (PCL)

Polyester plasticizers have been known for a long time. In 1942, investigators at Rohm and Hass Laboratories discovered that linear polymeric esters are excellent plasticizers for PVC.[156] In 1977, Hubbell and Cooper[157] reported the compatibility and plasticizing efficiency of poly(ε-caprolactone) (PCL) **1.80** and poly(butyleneadipate) (PBA) **1.81** (**Figure 1.37**). Good miscibility with PVC makes



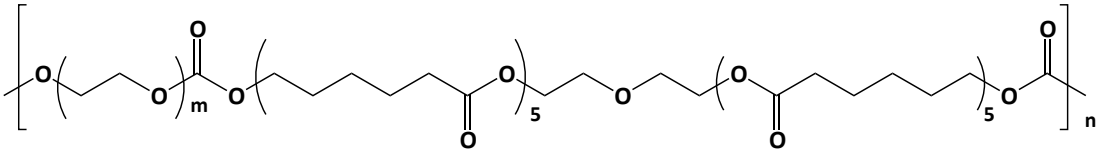
1.80 **1.81**

Figure 1.37 Structure of Poly(ε-caprolactone) and Poly(butylene adipate)

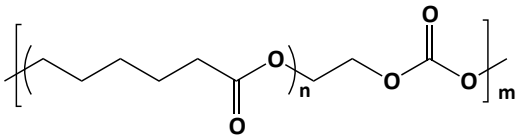
aliphatic polyesters an attaractive alternative for phthalate ester plasticizers. The miscibility of PVC with polyesters is attributed to the multiple dipolar interactions between the carbonyl groups of the polyesters and the methine hydrogens on the PVC chain. Molecular dynamic simulations[158] indicate a ratio of three to four methylene units per ester as a lower limit for miscibility, while ten to twelve methylene units is the upper limit. An optimal ratio of five to six methylene units was determined, which was supported by experimental data. The molecular weight of the polymeric plasticizer affects both the flexibility of the polymeric matrix and the diffusivity of additional incorporated additives.

PCL has five methylene units per carbonyl, and is attractive as an alternative green plasticizer to DEHP due to its well-known biodegradation and non-toxicity, low glass transition temperature (-60 °C) providing low temperature flexibility, miscibility with PVC, low cost and resistance to migration. Ferruti et al.[159] proposed multiblock copolymers of PCL and PEG **1.82** as a potential substitute for DEHP (**Figure 1.38**). The poly(ester-ether)carbonates **1.83** were obtained by polycondensation of commercial

α,ω-dihydroxy-terminated poly-caprolactone oligomers with poly(ethylene glycol) of different lengths using phosgene as a coupling agent. These polymers showed good miscibility: up to 50 wt% with PVC.



1.82

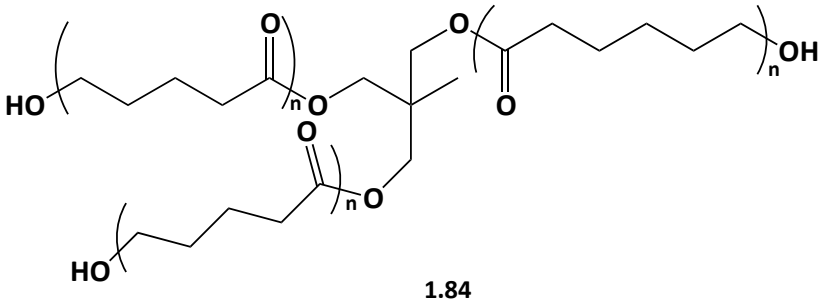


1.83

Figure 1.38 Structure of Poly(caprolactone)/Polyethylene glycol and Poly(caprolactone)/Polycarbonate Copolymer

A series of poly(ε-caprolactone) polymers were synthesized with octanoate or benzoate-terminal groups, and their blends with PVC were tested for biodegradability, tensile strength, elongation at break and migration stability. PVC/PCL-octanoate blends demonstrated similar glass transition temperatures as PVC/DEHP blends at the same plasticizer loading, whereas the glass transition temperature of PVC/PCL-benzoate blends were 20 °C higher.[160] The low molecular weight PCL plasticizers showed similar migration profiles as DEHP. The high molecular weight polymeric plasticizers have less chain-ends per mass of plasticizer

and increased entanglement, which reduces flexibility and elongation at break while increasing the glass transition temperature. One way to overcome this problem is to

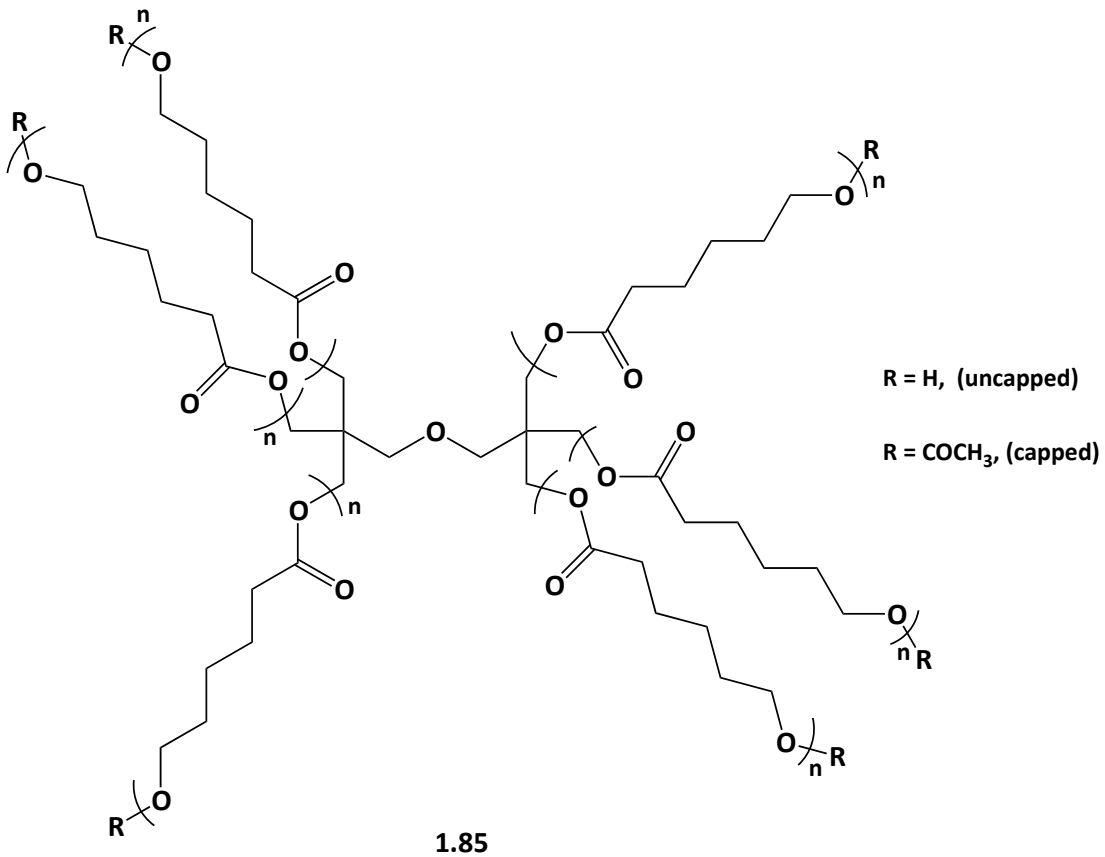


1.84

Figure 1.39 Structure of Branched Polycaprolactone

change the macromolecular structure of polymeric plasticizer from linear to branched **1.84** (**Figure 1.39**). Polymeric branched plasticizers with higher chain-end density induce greater free volume and hence provide more mobility in the PVC blend than a linear polymer of the same molecular weight. Kwak et al.[161] developed unentangled star-shaped hexabranched poly(ε-caprolactone) (UESPCL) **1.85**, **Figure 1.40** by the ring-opening polymerization of ε-caprolactone initiated from a mutlitfunctional core. A higher rate of miscibility of UESPCL with PVC was achieved compared to the miscibility of DEHP with PVC. PVC/UESPCL blends exhibited good flexibility, transparency, and improved migration resistance with a weight loss of 0.6% in the *n*-hexane phase upon extraction compared to 10% weight loss with DEHP/PVC. Major drawbacks of these plasticizers are their low performance in terms

of processing and mixing with the PVC resin, reduced plasticizing efficiency with respect to DEHP and linear PCL, and the possible formation and migration of low molar mass compounds upon hydrolysis of the polyesters.

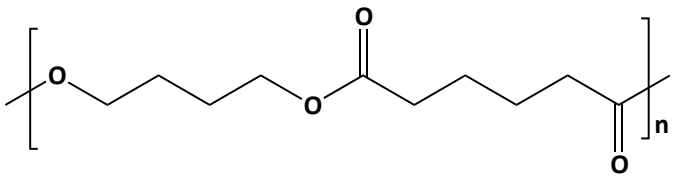


1.85

Figure 1.40 Structure of Unentagled Star-Shaped Hyperbranched Poly(ε-caprolactone) (UESPCL)

1.4.2 Poly(butylene adipate)

Poly(butylene adipate) (PBA) **1.81**, **Figure 1.41** has been evaluated as a polymeric plasticizer for PVC. Oligomers of PBA of up to 11 monomer units have shown significant migration into olive oil. When commercial PVC tubes plasticized



1.81

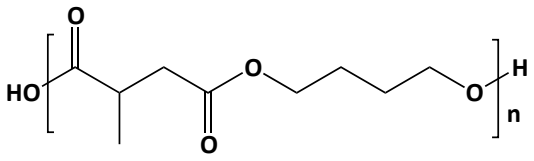
Figure 1.41 Structure of Poly(butylene adipate)

with linear PBA were aged in water at different temperatures, the tubes showed significant loss of plasticizer. Hakkarainen et al.[162] synthesized branched PBA polymers from 1,4-butanediol and adipic acid, the dimethyl ester of adipic acid, or the dimethyl ester of succinic acid with various degrees of branching. Trimethylol propane was used as the branching agent. The analysis of the mechanical properties of solution cast PVC/branched PBA films, evaluated by tensile strength, glass transition temperatures, and miscibility tests, indicated that branching enhanced the plasticizing efficiency of the polyester plasticizer. However, at least 40 wt% of the plasticizer was required to achieve the desirable mechanical properties equivalent to DEHP. In a related study, extraction of the plasticizers DEHP and poly(butylene

adipate) **1.81** from PVC nasogastric tubes through gastric juice and through feeding solutions showed that extraction of polyadipate was 100 times lower than the extraction of DEHP.[163]

1.4.3 Poly(butylene 2-methylsuccinate)

Wu et al.[164] synthesised bio-based and biodegradable polyester poly (butylene 2-methylsuccinate) (PBM) **1.86**, **Figure 1.42** by esterification of 1,4-butanediol and bio-based 2-methylsuccinic acid. PBM was used to plasticize PVC; the tensile properties, plasticization efficiency, and migration stability were investigated. The branching methyl group of PBM should enhance the migration stability of the plasticizer. As expected, the tensile strength, elongation at break, and migration stability of PVC/PBM blends were superior to PVC/DEHP blends. However, there was still signifcant weight loss, when PVC/PBM blends were allowed to undergo aging in 20 °C water for 10 weeks.

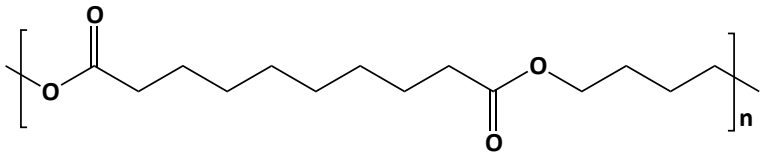


1.86

Figure 1.42 Structure of Poly(butylene 2-methylsuccinate)

1.4.4 Polysebacate

Bachas et al.[165] reported the use of polysebacate (PES) **1.87**, **Figure 1.43**, as a polymeric plasticizer in the preparation of PVC membrane ion-selective electrodes. PVC membrane electrodes plasticized with PES demonstrated potentiometric response characteristics that compared favorably to membranes plasticized with di(2-ethylhexy) sebacate. The enhanced retention of PES in the PVC membrane compared to dioctyl sebacate, resulted in high performance for more than four months, suggesting PES may be a good replacement for conventional plasticizers in preparing PVC membrane electrodes with long lifetimes.



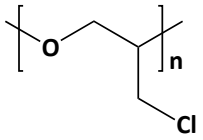
1.87

Figure 1.43 Structure of Polysebacate

1.4.5 Poly(epichlorohydrin)

Ren et al.[166] studied poly(epichlorohydrin) (PECH) **1.88**, as blends with PVC (**Figure 1.44**). PECH is compatible with PVC due to their structural similarities. Like PVC, it has a C-Cl bond in each repeating unit. C-Cl bonds on both PVC and PECH results in strong interactions between the polymeric chains due to hydrogen bonding. The incorporation of low molecular weight PECH into the PVC matrix

lowers the glass transition temperature markedly (-44 °C), and imparts good tensile properties. The glass transition temperatures of the blends increase with an increase in the molecular weight of the PECH. Unlike small molecule phthalate plasticizers, which can be mixed in up to 50 wt % of PVC, but still maintain a strikingly low glass transition temperature, phase separation occurs when the ratio of PECH exceeds 20 wt%. The miscibility of PECH with PVC is solvent dependent. PECH makes uniform blends with PVC in tetrahydrofuran, whereas phase separation occurs in dimethylformamide and methyl ethyl ketone.[167] In addition, PECH exhibits a similar degradation pattern to PVC, undergoing dehydrochlorination at temperatures higher than 100 °C, which making it undesirable as a plasticizer.



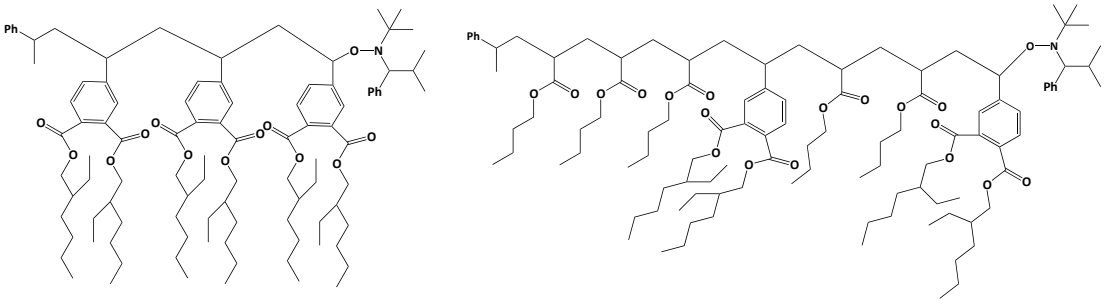
1.88

Figure 1.44 Structure of Poly(epichlorohydrin)

1.4.6 Poly(vinyl phthalates)

The Braslau Group at UCSC developed homopolymer **1.89** and random copolymer **1.90** made from 4-vinyl phthalate esters (VPE) as macromolecular plasticizers for PVC (**Figure 1.45)**.[168] 4-Vinyl phthalate esters bearing various alkyl

chains were synthesized and polymerized using nitroxide mediated polymerization with TIPNO-alkoxyamine as initiator to give poly(vinyl phthalates) (PVP). The random



1.89 1.90

Figure 1.45 Structures of Poly(vinyl phthalates)

copolymerization between VPE and acrylates was carried out to dilute the phthalate ester density in the polymeric plasticizers. Compared to conventional monomeric phthalate plasticizers, phthalates in PVP are linked together by an all-carbon polymer backbone, which reduces migration from PVC matrix. The hydrolysis of PVP release alcohols rather than phthalates, which are not endocrine disrupting chemicals. The glass transition temperatures obtained from differential scanning calorimetry were below -40 °C for all the pure PVP samples, indicating PVP and its copolymer with *n*-butyl acrylate may be promising plasticizers. The only drawback is the complicated synthesis of the 4-vinyl phthalate ester monomers, which requires a palladium catalyzed Suzuki coupling reaction.

1.4.7 Nitrile Rubber

The partial replacement of DEHP in PVC with the polymeric plasticizers acrylonitrile butadiene rubber (NBR) **1.91**, carboxylated nitrile rubber (XNBR) **1.92**, or epoxidized natural rubber (ENR) **1.93** (**Figure 1.46**) reduced the loss of DEHP from plasticized PVC without affecting its performance properties.[169] NBR was found to be the most effective with respect to miscibility, improved mechanical properties and the reduction of plasticizer migration from PVC. NBR is a commercially available elastomer used in biomedical applications because of its low temperature flexibility and resistance to abrasion.

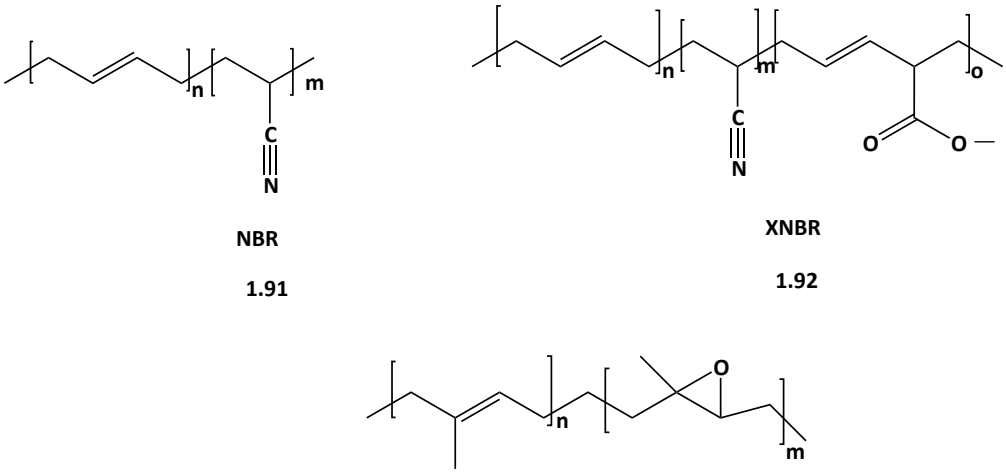


Figure 1.46 Structures of Acrylonitrile butadiene Rubber (NBR), Carboxylated Nitrile Rubber (XNBR), and Epoxidized Natural Rubber (ENR)

The alloys of NBR with plasticized PVC combine the ease of melt processing of PVC with the flexibility and elasticity of rubber. Plasticized PVC/NBR blends show reduction in gas permeability and higher rates of water vapor transmission compared to PVC/DEHP blends. This means that alloys of NBR and plasticized PVC can only be used for medical applications, which require only short term contact with body fluids.[170] Polymer composites of plasticized PVC with vulcanized NBR waste has been proposed as an efficient way of repurposing waste generated from the manufacture of rubber goods.[171] These new polymer composites show low hardness, high elongation at break, good tensile strength, good ozone resistance, good behavior under accelerated aging and upon immersion in water, concentrated acids or bases, animal fat and oils. These composites should be useful for gaskets, hoses, protection equipment, rubber footwear and irrigation pipes for agriculture.

1.5 Other Strategies To Retard Plasticizer Migration

While the PVC industry is still looking for better phthalate substitutes, which can match the all-around performance of DEHP, the scientific community is also working on strategies to retard plasticizer migration from the PVC matrix. These strategies include surface modification of plasticized PVC, covalent modification of PVC, and the use of nanofillers as antimigration agents. Surface modification alters the mesh sizes or pores between the polymer chains of PVC and restricts plasticizers from being released into the environment. Great advances have been made in the

last three decades to fine-tune the surface properties and decrease plasticizer migration. Surface cross-linking, surface coating, surface grafting, and plasma treatments are some of the common modification techniques employed to minimize the leaching of plasticizer. Covalent modification of PVC includes the attachment of plasticizer to the PVC backbone by carbon-carbon bonds, making it impossible for the plasticizer to move out of the matrix. Nanoparticles such as silica and calcium carbonate impact the mechanical and physical properties of PVC. Recent advancements are discussed in detail below.

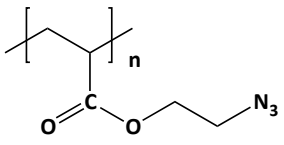
1.5.1 Surface modification of PVC

1.5.1.1 Surface cross-linking

Surface cross-linking is one of the most common modification techniques. Cross-linking of a polymer surface can be achieved through physical treatments such as plasma or UV radiation, or through chemical modification of the polymer surface followed by physical treatment. The surface structure of a PVC sheet changes when irradiated with UV light, resulting in decreased migration of DEHP compared to heat-treated or visible light treated PVC sheets.[172] The use of UV-treated PVC medical devices is a concern, due to increased oxygen content on the surface, which could have a negative impact on the activation of the clotting system. Matsuoka et al.[173] performed a detailed investigation on the chemical, physiochemical, and biological properties of UV irradiated PVC/DEHP sheets. Although suppression of DEHP

migration was observed upon UV irradiation, the PVC sheets exhibited considerable cytotoxicity as well as chromosome aberration due to the generation of oxidation products of DEHP.

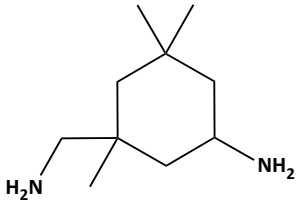
Chemical cross-linking followed by UV irradiation is another option to control plasticizer migration. Plasticized PVC sheets were surface modified by treating with sodium azide, followed by irradiation with UV light. A 30% reduction in the migration of DEHP was observed after modification but was accompanied with discoloration of PVC material due to dehydrochlorination.[174] PVC surfaces modified with thiosulfate were found to reduce DEHP migration in hexanes or oils, but were found to be cytotoxic and cause hemolysis.[175] The migration of plasticizer was prevented to a significant extent when a plasticized PVC sheet was treated with poly(azidoacrylate) **1.94** followed by UV irradiation (**Figure 1.47**). Azido polymers facilitated cross-linking throughout the surface and bulk plasticized PVC, as opposed to just surface cross-linking by thiosulfate, sodium azide, and sodium sulfide. However, prolonged UV irradiation induced color changes in the samples.[176]



1.94

Figure 1.47 Structure of Poly(azidoacrylate)

*Iso*phoron diamine (IPDA) **1.95** (Figure **1.48**) was used as a nucleophilic cross-linking agent for PVC plastisols by Tendero et al.[177] Crosslinking reduces the free volume and segmental mobility, thus minimizing plasticizer diffusion through the matrix. Similar studies performed by Ambrogi et al.[178] demonstrated that chemical cross-linking of PVC with IPDA indeed suppressed plasticizer migration. However, thermal degradation was accelerated as determined by thermogravimetric analysis (TGA) of IPDA cross-linked PVC. For every nucleophilic displacement by an amine group, one equivalent of hydrochloric acid is formed, which then catalyzes dehydrochlorination upon heating.



IPDA

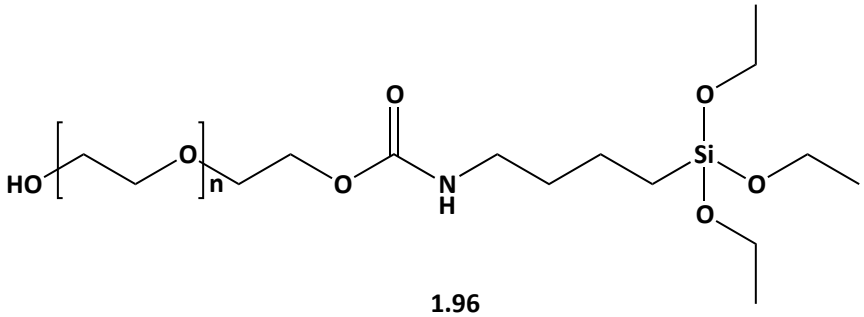
1.95

Figure 1.48 Structure of Isophoron Diamine

1.5.1.2 Surface Coating

Surface coating is another promising approach to reduce plasticizer migration. Earlier examples of surface coating suffered from the drawback of forming a thick coating that reduced the flexibility of PVC. A thin surface coating could be achieved by chemical vapor deposition, which requires high temperatures. Thus chemical

vapor deposition is not suitable for temperature-sensitive materials like PVC. Breme et al.[179,180] developed plasma-activated chemical vapor deposition to form a thin (Ti)-based layers without the need of high temperature processing. PVC and five other commercial polymers were coated with $Ti[N(C_2H_5)_2]_4$. This prevents plasticizer from leaching from the PVC and improves the biological and blood compatibility of the polymer. However, the high cost and loss of transparency limits its application. Surface coating can also be performed by wet chemical processes, as demonstrated by Messori et al.[181] They synthesized α,ω-triethoxysilane terminated poly(ethylene oxide) **1.96**, **Figure 1.49** and used it to produce hybrid coatings for PVC. This coating significantly reduced the leaching of DEHP from PVC, but the authors did not test other parameters. Coating PVC with heparin has also been investigated. The *in vitro* results show a reduced presence of MEHP in blood, which indicates that the heparin coating reduces plasticizer migration, but does not provide an absolute barrier.[182]



1.96

Figure 1.49 Structure of α,ω-Triethoxysilane Terminated Poly(ethylene oxide)

1.5.1.3 Surface Grafting

Surface grafting is another interesting approach used to prevent plasticizer migration. This process involves the formation of stable covalent bonds between the grafted polymeric coating and the PVC surface. The covalent linkage ensures long-term stability of the coating compared to physically bound coatings.[183] Migration resistance and blood compatibility of plasticized PVC (a hydrophobic polymer) was significantly improved by grafting polyethylene glycol (a hydrophilic polymer) to the surface. Williamson ether synthesis was used to covalently link PEG to the PVC surface. PEG 4000 was grafted onto the PVC surface in the presence of metallic sodium at 70 °C. Grafting-from polymerization is another technique by which other hydrophilic polymers, such as poly(acrylic acid) (PAA) **1.97**, poly(dimethyl acrylamide) (PDMA) **1.98**, poly(dimethylaminoethyl acrylate (PDMAEA) **1.99**, poly(2-hydroxyethyl acrylate) (PHEA) **1.100**, poly(2-hydroxyethyl crylate) (PHEA) **1.101**, and poly(4-vinylpyridine) (P4VP) **1.102** (**Figure 1.50**), were covalently linked to the PVC surface.[184] This technique involves physical sorption of a hydrophobic initiator on the PVC surface, followed by radical polymerization of a suitable monomer in a hydrophilic media (**Figure 1.51**).

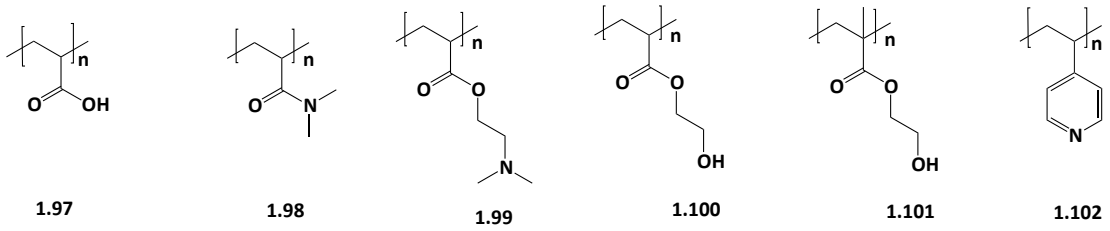


Figure 1.50 Structures of Polymers Grafted Onto the Surface of PVC

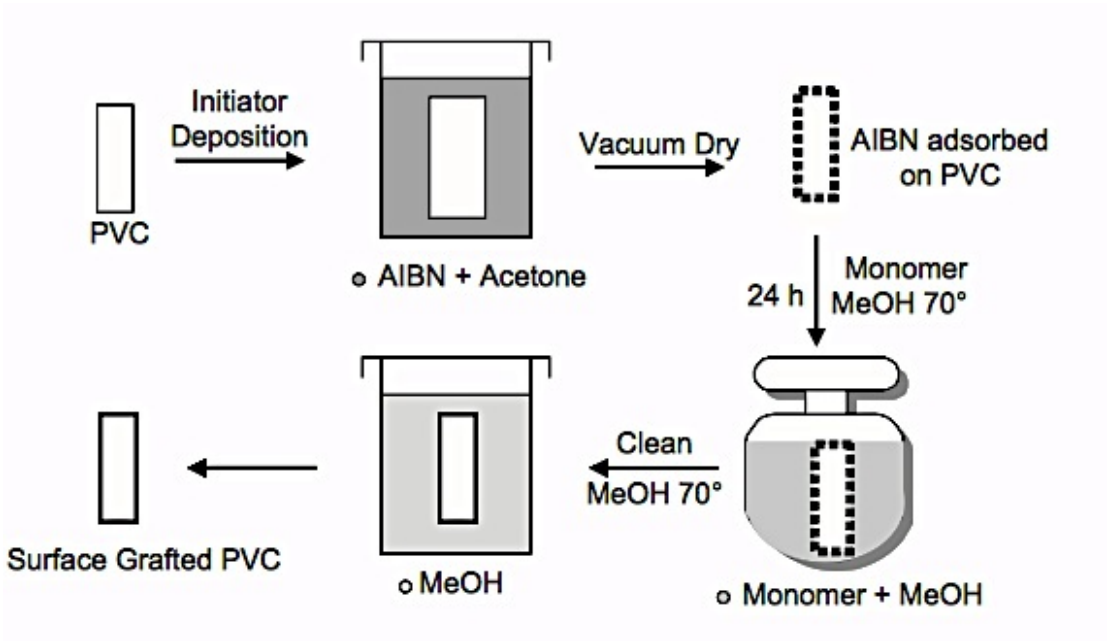


Figure 1.51 Surface Grafting onto PVC via Physisorbed Free Radical Initiation[184]

1.5.1.4 Surface Extraction

Another method to reduce diffusion and leaching of plasticizer from bulk polymers is surface extraction, as proposed by Fugit et al.[185] In this method, plasticized polymer is immersed in a solvent for a short time, and then dried. This leaves the treated polymer with a non-uniform distribution of plasticizer, and a rigid surface which should block interfacial mass transfer of the plasticizer. When PVC containing DEHP system was briefly soaked in *n*-heptane and then dried, plasticizer leaching was reduced significantly, but not completely.

1.5.1.5 Plasma Treatment

Plasma treatment is an elegant technique of enormous potential for surface modification. Plasma is ionized gas containing free electrons, ions, and radicals, as well as neutral particles. PVC containing plasticizer is placed in an active environment where several different interactions between energetic particles and the surface may occur. These interactions include plasma polymerization, plasma functionalization, and plasma etching/ablation. Recently, Chen et al.[186] employed a variety of analytical techniques including sum frequency generation vibrational spectroscopy (SFG), coherent anti-Stokes Raman Spectroscopy (CARS), and X-ray photoelectron spectroscopy (XPS) to investigate the surface and bulk structures of

DEP plasticized PVC and DBP plasticized PVC after oxygen and argon plasma treatment. The results suggest that PVC/DEP is unstable, indicating that plasma etching leads to increased risk of DEP leaching out of the polymer matrix. The PVC/DBP system is more stable; DBP migration can be effectively suppressed by oxygen plasma treatment but not by argon plasma treatment**.** However, treating a PVC surface with plasma can lead to C-C, C-Cl, and C-H bonds scission, since the induced energy exceeds these bond dissociation energies. PVC exposure to inert gas plasma gives rise to metastable carbon radicals.

1.5.2 Nanofillers as Antimigration Agents

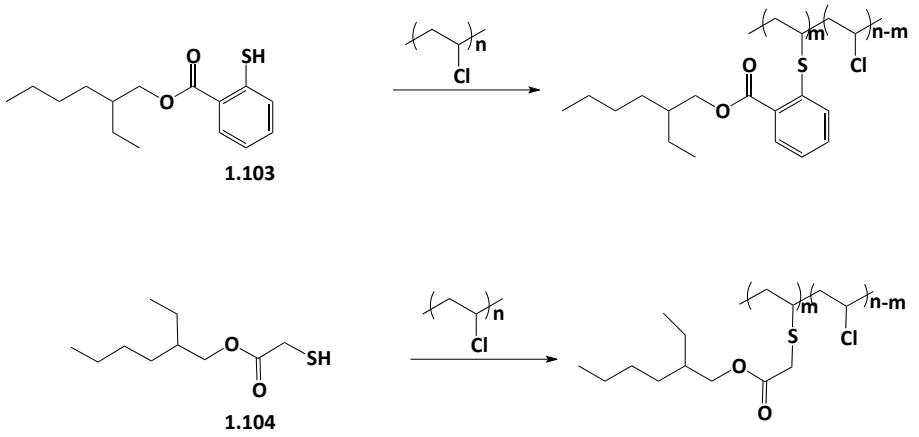
Nanofillers such as calcium carbonate, silica, and zinc oxide nanoparticles have been used to impact the mechanical properties of PVC.[187,188,189,190,191,192] Yang et al.[193] tested the influence of $CaCO_3$ and SiO_2 nanoparticles on the suppression of plasticizer migration from PVC. PVC composites were fabricated by dispersion of nanofillers into PVC powder followed by mixing with DEHP, DINP or TOTM plasticizers. Volatility, migration stability and exudation stability tests indicated that a decrease in plasticizer migration occurs when an appropriate inorganic nanofiller is added to plasticized PVC. Li et al.[194] demonstrated that addition of 5 phr (parts per hundred resin) of SiO_2 decreases the extraction rate of DEHP to 15.6% compared to 20.4% DEHP from neat PVC. The addition of 5 phr of organic modified

montmorillonite reduces the volatilization of DEHP to 0.067% compared to 0.17% from neat PVC. Li et al.[195] also tested the effects of nano-$CaCO_3$ as a nanofiller and poly(1,2-propylene glycol adipate) as a partial replacement for DEHP on the migration of DEHP. Extraction tests and thermogravimetric analysis indicated that the addition of nano-$CaCO_3$ improves the thermal stability of the PVC composite and suppresses plasticizer migration. Recently, Gholami et al.[196] synthesized plasticized PVC nanocomposites with nanofillers such as single-walled carbon nanotubes (SWCNTs), organo clay, titanium oxide, and zinc oxide nanoparticles, and investigated their effects on plasticizer migration. Based on migration and exudation tests, the authors concluded that SWCNTs were the best and most expensive antimigration agent for this plasticized system.

1.5.3 Covalent Bonding of Plasticizers

The most effective approach to avoid migration of plasticizer from the PVC matrix is to covalently attach the plasticizer to the polymer. Historically, PVC has been chemically modified by simple nucleophilic substitution of the chlorine atoms to improve plasticization of PVC.[175,197] In 1986 Michel et al.[198] described the use of thiol compounds as internal plasticizers by attaching 2-ethylhexyl esters of *o*-mercaptobenzoic acid **1.103** and thioglycolic acid **1.104** to the PVC backbone by S_N2 reaction (**Scheme 1.3**). The glass transition temperatures decreased as the degree of

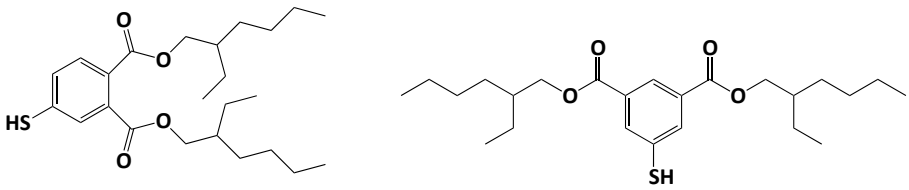
substitution increased. The plasticizing power of thioglycolic ester is greater than that of the ester of *o*-mercaptobenzoic acid.



Scheme 1.3 Covalent Bonding of 2-Ethylhexyl Esters of *o*-Mercaptobenzoic acid and Thioglycolic acid to PVC

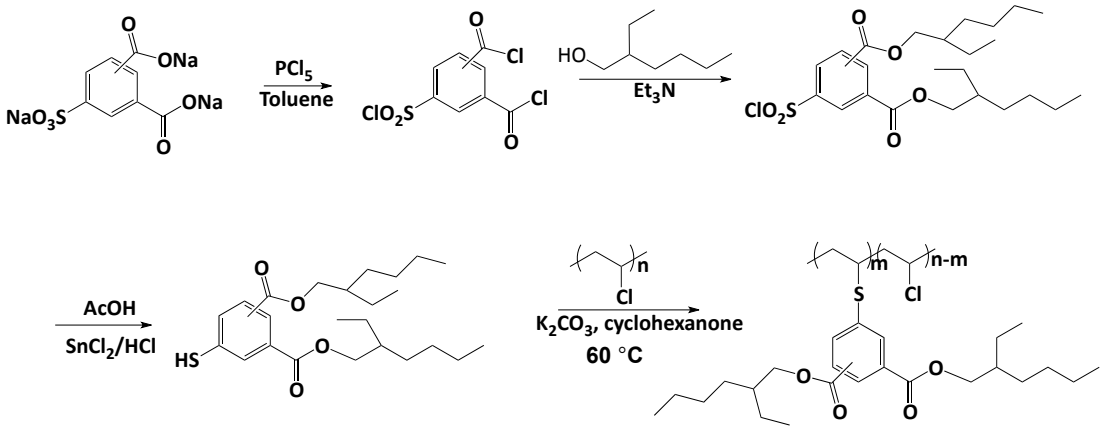
Reinecke et al.[199] demonstrated the internal plasticization of PVC by displacement of some of chlorine atoms of PVC with phthalate-based thiol derivatives. Two thiol derivatized plasticizers: di(2-ethylhexyl) 5-mercaptophthalate (DEHP-SH) **1.105** and di(2-ethylhexyl) 5-mercaptoisophthalate (*iso*DEHP-SH) **1.106** were synthesized and covalently bonded to PVC via thiolate nucleophilic substitution (**Scheme 1.4**). The degree of functionalization obtained was 23 mol% for DEHP-SH and 30 mol% for *iso*DEHP-SH. The glass transition temperatures of the modified PVC-DEHP-SH (0 °C) and PVC-^{iso}DEHP-SH (20 °C) were found to be lower than unmodified PVC (83 °C) but higher than the conventional PVC-DEHP systems (-40 °C for 15 mol%). The migration experiments indicated no loss of plasticizer from the

PVC-DEHP-SH, and PVC-^{iso}DEHP-SH systems, compared to complete loss of DEHP in the PVC-DEHP system after less than 3 h of extraction by *n*-heptane. The absence of



1.105 **1.106**

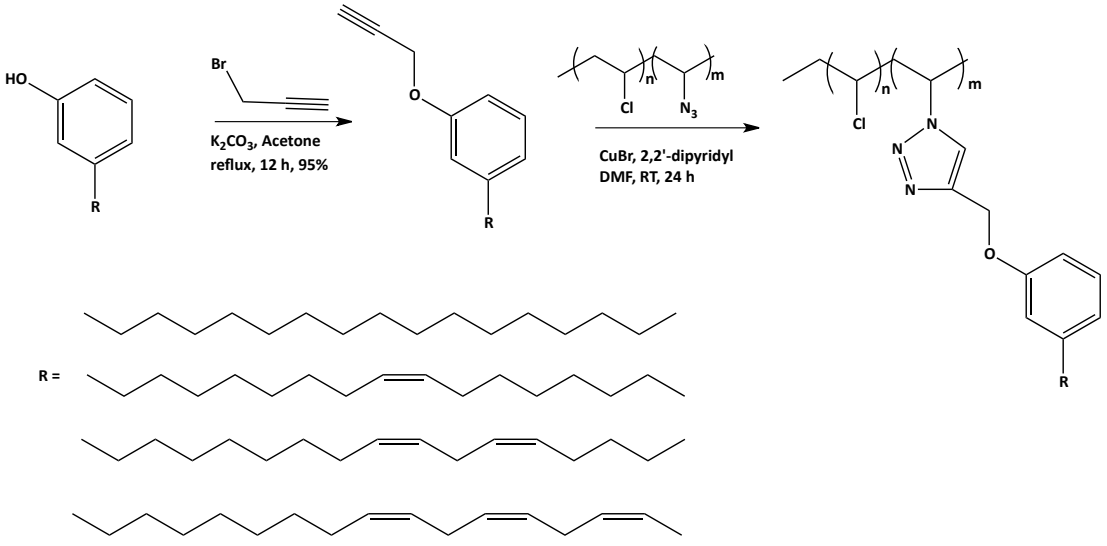
Figure 1.51 Structures of Di(2-ethylhexyl) 5-mercaptophthalate (DEHP-SH) and Di(2-ethylhexyl) 5-mercaptoisophthalate (*iso*DEHP-SH)



Scheme 1.4 Synthesis and Covalent Bonding of 2-Ethylhexyl Esters of Mercaptophthalates to PVC

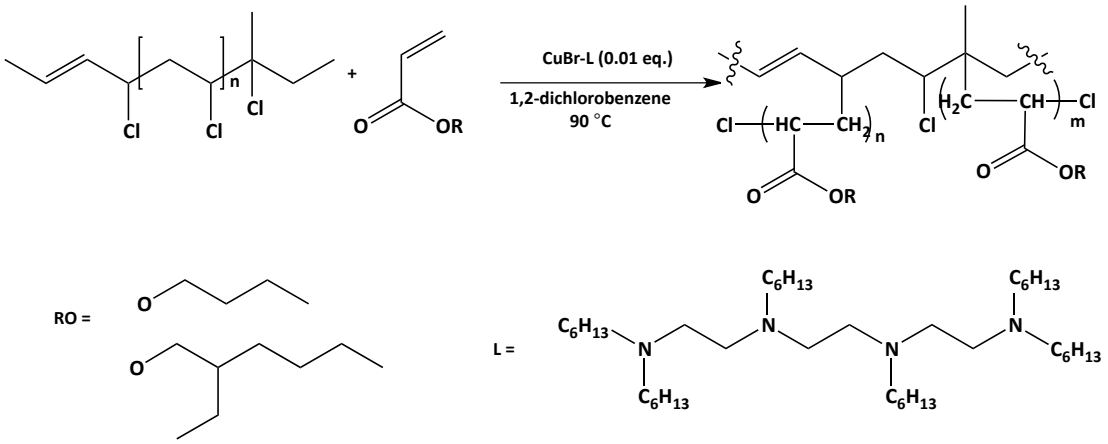
olefinic protons in the ^{1}H NMR indicates that modification was free of undesired side reactions like dehydrochlorination. Although, PVC-DEHP-SH and PVC-^{iso}DEHP-SH showed good plasticization, zero migration and no elimination, the viability of using this approach is restricted by the cost of preparing the thiol phthalate esters, and the requirement of high loading (75 wt% or 30 mol%) of the plasticizer to lower the T_g to 0 °C. The longterm stability of these sulfide derivatives is also a concern; oxidation products are expected as the material ages in air. Elimination could also be a potential concern upon heating.

1,3-Dipolar cycloadditions of azides and alkynes, also known as "click reactions," have become widely popular due to the chemoselectivity and mild reaction conditions. These cycloaddtions to form triazoles have been applied to macromolecular chemistry, offering materials ranging from the block copolymers to the complex macromolecular structures. In 2015, Yang et al.[200] utilized copper catalyzed 1.3-dipolar cycloaddition reactions to synthesize cardanol functionalized PVC as shown in **Scheme 1.5**. As discussed in section 1.3.15, cardanol is a renewable organic byproduct of the cashew industry. The modified polymer exhibits a decreased glass transition temperature (51 °C for 10% displacement) compared to PVC-azide (81 °C) and unmodified PVC (83 °C), but a higher T_g than PVC-DEHP system (47 °C for 8% loading). PVC-cardanol shows excellent thermal stability and no migration.



Scheme 1.5 Covalent Bonding of Cardanol Derivatives to PVC

Bicak et al.[201] demonstrated a relatively simple method to efficiently graft poly(*n*-butyl acrylate) (PBA) or poly(2-ethylhexyl acrylate) (PEHA) onto PVC. They utilized Atom Transfer Radical Polymerization (ATRP) to grow polymers of BA or EHA off of the PVC chain by initiation using labile chlorines at defect points in the polymer (**Scheme 1.6**). Allylic chlorines and tertiary chlorines can take part in this initiation step. Commercial PVC typically contains about 1% of these labile chlorine atoms. Graft copolymerization of BA or EHA by copper-mediate ATRP was carried out in 1,2-dichlorobenzene at 90 °C. After 7.5 h of heating, the graft yields were found to be 162% for *n*-butyl acrylate and 51% for 2-ethyhexyl acrylate.



Scheme 1.6 Covalent Bonding of Poly(*n*-butyl acrylate) and Poly(2-ethylhexyl acrylate) at PVC Defects

In another study,[202] graft copolymerization of EHA in an aqueous medium, again using copper-mediated ATRP was conducted. About 30% of PVC is soluble in aqueous EHA at temperatures of 130° C, which makes graft polymerization possible without the use of additional solvent. The drawbacks of this procedure were loss of chain-growth control at high graft yields, and the resulting greenish color of the graft products, a common problem in copper mediated ATRP.

1.6 Alternative Polymers to PVC

One strategy to reduce global dispersion and health impacts of phthalate additives would be to replace PVC with alternative polymers in consumer products. Candidates include poly(lactic acid) **1.107**, polyethylene **1.108**, polypropylene **1.109**, polyurethane **1.110**, polycarbonate **1.111**, ethylene vinyl acetate **1.112**, and silicone

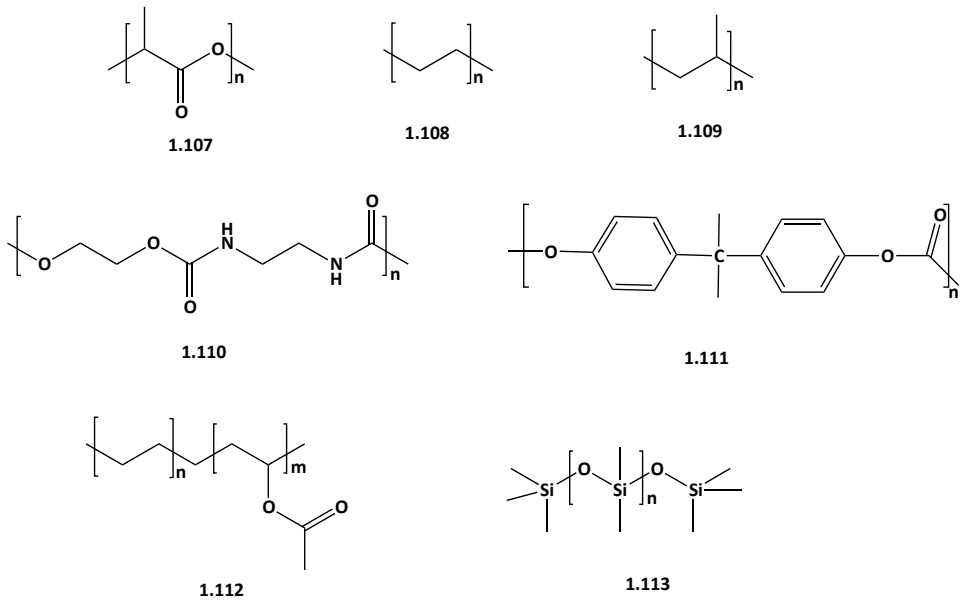


Figure 1.52 Chemical Structures of the Polymers Considered as Possible PVC Replacements

1.113 (**Figure 1.52**). These substitutes would have to compete with PVC in terms of low cost, high-speed production, high mechanical performance, good barrier properties, and good heat stability. In addition, an ideal polymer would also be biodegradable. Even though the performance properties of polyurethane and silicone match with those of flexible PVC, and neither requires added plasticizer, these materials have other limitations. Silicone and polyurethane films are generally three to six times more expensive than PVC films. Ethylene vinyl acetate is not widely accepted as a PVC replacement due to its high material cost, reduced strength and tackiness. Polylactic acid (PLA) is a somewhat compostable, biodegradable thermoplastic aliphatic polyester made from renewable sources, and

has been considered as a possible alternative to PVC. Historically, PLA was used mainly for the biomedical applications, but over the past decade, the discovery of new polymerization routes for the synthesis of high molecular weight PLA and the scrutiny of petroleum based polymers has led to the expanded use of PLA in consumer goods and in packaging applications. PLA has been used in candy wrappers, optically enhanced films, shrink labels, thermoformed cups and containers, and in single serve drink bottles. The limitations of PLA include its high density, high polarity, poor heat resistance, and limited barrier against moisture and gases. Polyolefins have become more prominent alternatives to PVC. Polyolefins have been used to produce medical devices such as feeding tubes, filters, and catheters for decades, and are preferred because of their ease of processing, colorability and cost-effectiveness. Although some polyolefin medical devices are commercially available, problems such as cracks, fractures, solution leakage, and air contamination from loose connectors occur because of the poor flexibility and durability of these materials in comparison with PVC products.

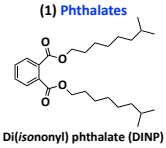
1.7 Conclusion

Phthalate esters, most commonly referred to simply as phthalates, are a group of chemical plasticizers used to impart flexibility and durability to PVC products. Phthalates are ubiquitous chemicals, as demonstrated by their presence in a wide variety of industrial and consumer products, including building materials, clothing,

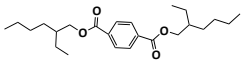
medication coatings, food packaging, toys and recreation products, cosmetics, and medical devices. Phthalates are not covalently bound to PVC, and are released into the environment through volatilization, extraction, and migration. Humans are exposed to phthalates via oral intake, intravenous infusion, dermal contact, and inhalation. Many animal studies, as well as epidemiological and some clinical studies strongly suggest toxicity of phthalates in humans. This risk is even greater for fetuses, pre-term neonates and sick neonates. Due to the economic growth in Asia and other developing countries, the use of PVC is not expected to abate in the near future. The demand for PVC is estimated to be 53 million tons by 2020. In 2014, PVC products accounted for 80% of the plasticizer use; the market continues to be dominated by phthalates. The availability of alternative plasticizers with all-around performance comparable to that of DEHP still represents a major challenge. DEHP serves as the benchmark for new PVC plasticizers. No better low molecular weight plasticizer has yet been found to replace phthalate plasticizers. Likewise, polymeric plasticizers have not been able to match the all-around performance of DEHP. Alternative polymers at competitive costs still need to be developed. Even if the global production of PVC diminishes, other plastics that fill this gap will require plasticizers. Active research continues to develop new plasticizers that will match the general-performance potential and pricing of phthalate plasticizers as well as new strategies to retard plasticizer migration.

Low Molecular Weight Plasticizers Considered as Alternatives to DEHP

(1) Phthalates

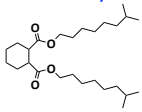


Di(*iso*nonyl) phthalate (DINP)



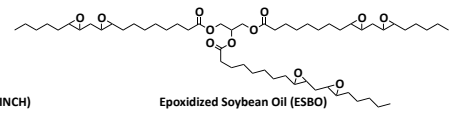
Di(2-ethylhexyl) phthalate (DEHTP)

(2) Cyclohexane dicarboxylates



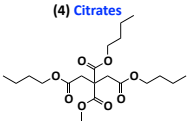
Di-isononylcyclohexane-1,2-dicarboxylate (DINCH)

(3) Epoxy esters



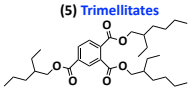
Epoxidized Soybean Oil (ESBO)

(4) Citrates



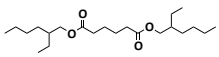
Acetyl tri-*n*-butyl citrate (ATBC)

(5) Trimellitates



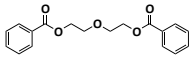
Trioctyl trimellitate (TOTM)

(6) Adipates



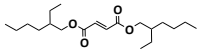
Di(2-ethylhexyl) adipate (DEHA)

(7) Benzoates



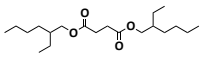
Diethylene glycol dibenzoate (DEGDB)

(8) Maleates



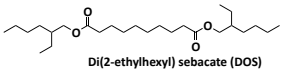
Di(2-ethylhexyl) maleate (DEHM)

(9) Succinates



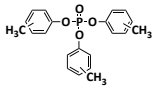
Di(2-ethylhexyl) succinate (DEHS)

(10) Sebacates



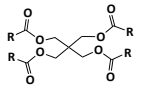
Di(2-ethylhexyl) sebacate (DOS)

(11) Phosphates



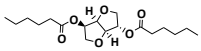
Tricresyl phosphate (TCP)

(12) Pentaertythritols



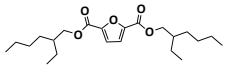
Pentaerythritol ester

(13) Isosorbides



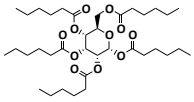
*Iso*sorbide di-*n*-hexanoate (SDH)

(14) Furan dicarboxylates

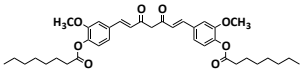


Di(2-ethylhexyl)furan-2,5-dicarboxylate (DEHF)

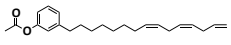
(15) Glucose esters



(16) Curcumin esters



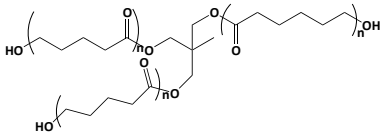
(17) Plant oil based esters



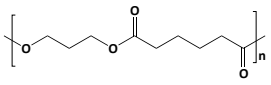
Cardanol acetate

Polymeric Plasticizers Considered as Alternatives to DEHP

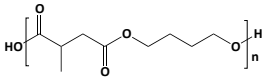
(1) Poly(ε-caprolactone) (PCL)



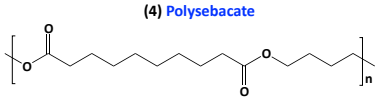
2) Poly(butylene adipate) (PBA)



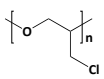
(3) Poly(butylene 2-methylsuccinate) (PBM)



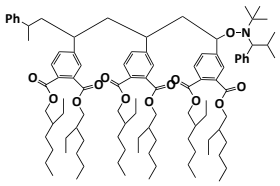
(4) Polysebacate



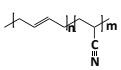
(5) Polyepichlorohydrin



(6) Poly(vinylphthalate) (PVP)



(7) Nitrile Rubber



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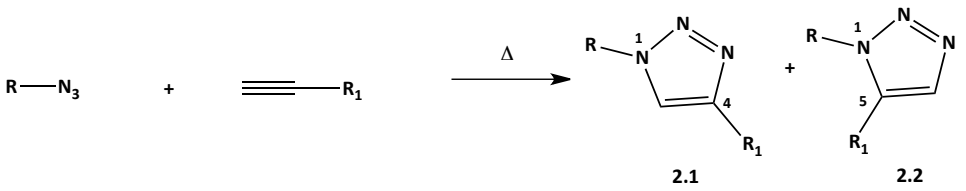
2 Covalently Linked Plasticizers: Triazole Analogues of Phthalate Plasticizers Prepared by Mild Copper-Free "Click" Reactions with Azide-Functionalized PVC

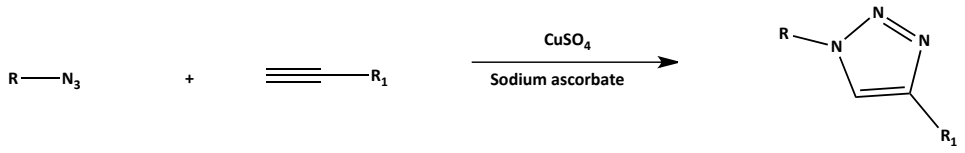
2.1 1,3-Dipolar Cycloadditions of Azides and Alkynes

Among the family of cycloaddition reactions, 1,3-dipolar cycloadditions of azides and alkynes to give 1,2,3-triazoles have found broad applications in organic synthesis,[203] polymer science,[204] biocojugation[205] and peptidomimetic research.[206] The usefulness of this reaction is attributed to extreme chemoselectivity, the ease with which azide and alkynes can be introduced into a molecule, their relative stability, and the stability of the triazole products under a variety of biological and organic conditions. Further interest originates from the biological activity of the 1,2,3-triazoles, perhaps due to their ability to mimic certain aspects of a peptide bond.[207,208] 1,3-Dipolar cycloadditions of azides and alkynes are classified into four groups: thermally activated azide-alkyne cycloadditions (TAAC), copper catalyzed azide-alkyne cycloadditions (CuAAC), ruthenium catalyzed azide-alkyne cycloadditions (RuAAC), and strain promoted azide-alkyne cycloadditions (SPAAC). Thermally activated azide-alkyne cycloaddition (TAAC) was developed first by Michael[209] in the 1890s and then by Huisgen[210] in the 1960s, which involves a thermal reaction of a terminal alkyne or a diester alkyne with an azide to give a mixture of 1,4-disubstituted **2.1** and 1,5-disubstituted **2.2** triazole regioisomers (**Scheme 2.1**).

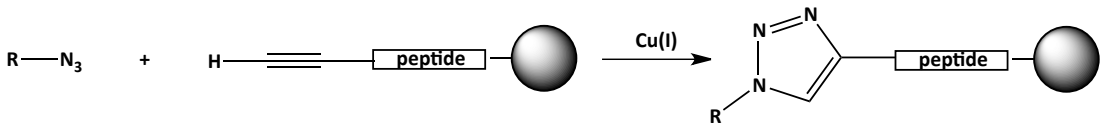


Scheme 2.1 Huisgen's Thermal 1,3-Dipolar Cycloaddition Reaction

This reaction is often referred to as a Huisgen cycloaddition. This reaction did not gain significant synthetic importance, due to poor regioselectivity, low yields, the requirement of elevated temperatures or pressures, prolonged reaction times, and fear of the explosive nature of low molecular weight organic azides.[211] The copper catalyzed azide-alkyne cycloaddition (CuAAC) was developed independently by Sharpless and Meldal in the 2000s. Sharpless'[212] CuAAC involves the regioselective formation of the 1,4-regioisomer using a terminal alkyne and a copper(I) catalyst as shown in **Scheme 2.2**. Simultaneously, Meldal[213] developed a very similar regiospecific copper (I) catalyzed 1,3-dipolar cycloaddition of azides with terminal alkynes bound to a solid support (**Scheme 2.3**).



Scheme 2.2 Sharpless' Copper Catalyzed 1,3-Dipolar Cycloaddition Reaction



Scheme 2.3 Meldal's Copper Catalyzed 1,3-Dipolar Cycloaddition Reaction

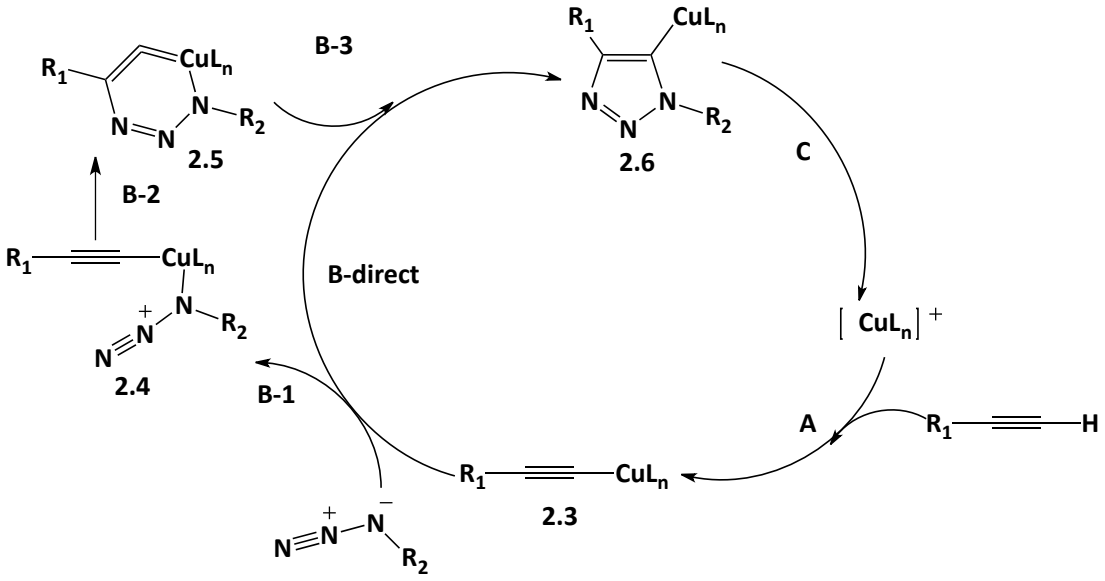
2.2 Proposed Mechanisms of CuAAC

CuAAC has emerged as one of the most important examples of 1,3-dipolar cycloaddition reactions. The relevant features of this reaction are high regioselectivity, insensitivity towards reaction conditions such as solvents, temperature and pH, nearly quantitative yields, wide substrate scope with regards to alkyne and azide, a broad spectrum of Cu(I) source, and significant rate acceleration (by a factor of 10^7) relative to the thermal 1,3-dipolar cycloaddition.[211,212,213] Moreover, this reaction is bioorthogonal: azides and alkynes react only with each other, even in the presence of other functional groups. Neither azide nor alkyne is naturally present in biological molecules. CuAAC has all the properties of a "click reaction" such as simplicity, efficiency, mild reaction conditions, tolerance to a wide range of solvents, chemoselectivity in the presence of other functional groups, the formation of single regioisomeric triazole, and atom economy, as defined by Kolb, Finn, and Sharpless.[211] Hence, CuAAC is commonly referred to as "click chemistry." The great success of the Sharpless' CuAAC is reflected by a number of periodic reviews describing a wealth of applications of this practical chemical approach written over the last thirteen years. A number of reviews of its use are

reported in the fields of biochemical studies and drug discovery[214,215,216] chemical ligation,[217] dendrimer, material science and polymers,[218,219,220,221,204,49,222,223,224,225,226] medicinal sciences,[227,205,228,229] peptidomimetics,[230,206] cycloadditions on solid surfaces,[231] synthesis of biohybrid materials,[232,233,234] chemical biology,[235,236] pharmaceutical science and pharmacores,[237,238] radiochemistry and radiopharmaceuticals,[239,240,241] DNA modification,[242] diagnosis,[243] microwave-assisted cycloaddition reactions,[244] non-classical synthesis of biological molecules,[245] click chemistry generated hydrogen-bonding triazoles,[246] synthesis of catenanes and rotaxanes,[247] electrocatalysis,[248] modification of polysaccharides and carbohydrates,[249,250] decoration of nanotubes and nanoparticles,[251,252] preparation of separation materials for liquid chromatography,[253] synthesis of hydrogels,[254] synthesis of antimicrobial agents,[255] clickable peptides and their applications,[207,256,257] click-chemistry in biocatalysis,[258] overviews of the synthetic utility of click chemistry across many fields,[259,260,261] and mechanistic studies on this copper catalyzed cycloaddition.[262,263,264]

Despite the tremendous popularity of CuAAC, some aspects of the reaction mechanism still remain unclear, such as the role of the solvent in the process, the number of copper atoms involved in catalysis, the influence of ligands, and the distinctive role of copper over other metals. The first mechanistic proposal for the catalytic cycle of copper was outlined by Sharpless, which was supported by Density

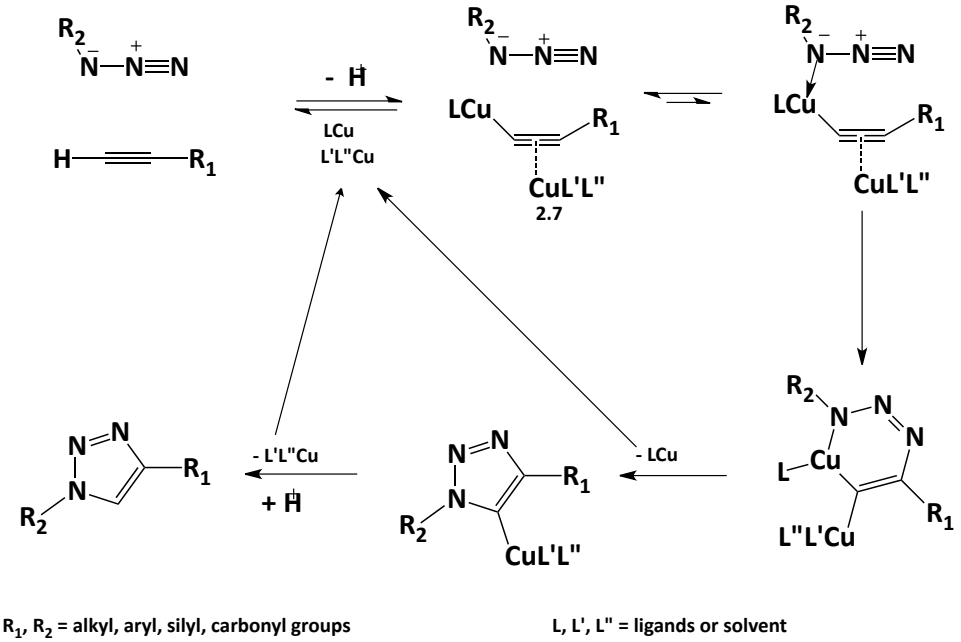
Functional Theory (DFT) calculations.[265] As shown in **Scheme 2.4**, the originally proposed mechanism involved only one Cu atom and was considered to begin with the formation of copper(I) acetylide **2.3** in step **A** followed by the coordination of the azide to Cu(I) to give intermediate **2.4**. This step in the mechanism explains the



Scheme 2.4 Sharpless' Proposed Mononuclear Mechanism of the CuAAC Click Reaction[266]

inactivity of internal alkynes in CuAAC. The density functional theory calculations showed a preference for the stepwise addition (**B-1 to B-2 to B-3**) over the concerted (2+3) cycloaddition (**B-direct**) by about 12-15 kcal/mol to form the six membered metallacycle intermediate **2.5**, which leads to triazole **2.6** with a negligible energy barrier. However, this postulated mononuclear pathway was found incompatible with the results obtained by other studies. The kinetic studies by

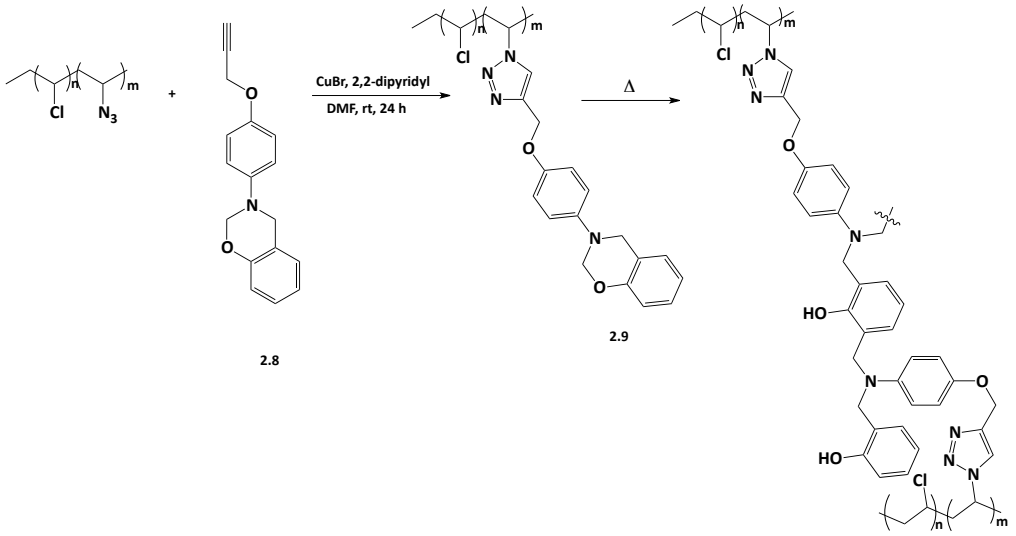
Rodinov et al.[266,267,268] gave a rate law with second-order dependence on the Cu(I) concentration under catalytic conditions, indicating the presence of dinuclear species **2.7** (**Scheme 2.5**). The reaction of an organoazide with mononuclear *N*-heterocyclic carbene copper acetylide was slow and showed a stoichiometric relationship,[269,263] whereas dicopper complexes[270,271] demonstrated superior catalytic activity. The results of copper isotope studies,[272] detection of dicopper intermediates by mass spectrometry,[273] and other theoretical proposals[274,275,271] favor a dinuclear mechanism (**Scheme 2.5**).



Scheme 2.5 Proposed Dinuclear Pathway in the CuAAC Click Reaction[275]

2.3 Application of CuAAC Towards Modification of PVC

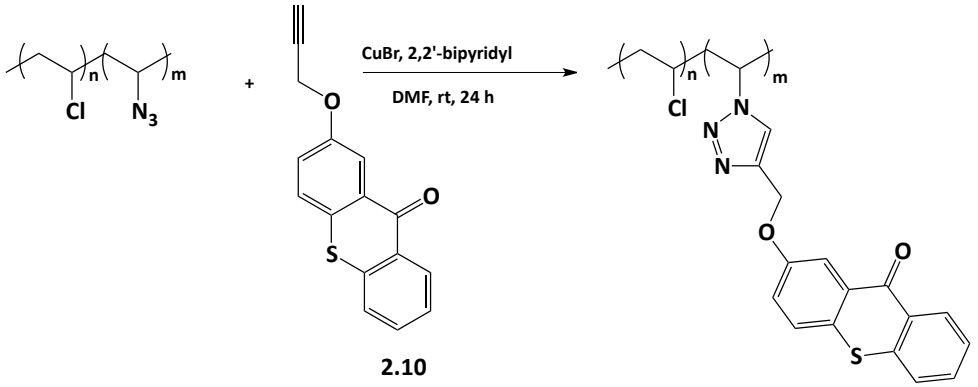
CuAAC has been recognized as a useful synthetic methodology for the covalent modification of PVC. In 2008, Yagci et al.[276] utilized copper catalyzed azide-alkyne cycloaddition to synthesize benzoxazine functionalized PVC **2.9**. This modified PVC undergoes thermally activated curing in the absence of catalyst, forming a PVC thermoset with high thermal stability. The azidation of PVC was carried out in DMF to obtain 10% azide substituted PVC, which was then used for cycloaddition reaction with propargyl benzoxazine **2.8** in the presence of copper bromide and 2,2'-dipyridyl (**Scheme 2.6**).



Scheme 2.6 CuAAC Modification of PVC-Azide Followed by Thermally Activated Benzoxamine Crosslinking

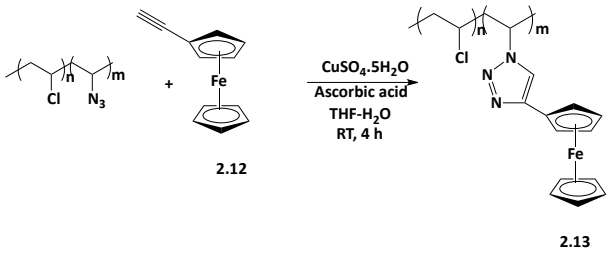
Akat et al.[277] demonstrated that PVC bearing a photoinitiator **2.11** can be successfully synthesized using click chemistry of PVC-azide and propargyl

thioxanthone **2.10** (**Scheme 2.7**). This macroinitiator was investigated for the photopolymerizations of methacrylic acid, methyl methacrylate, *N*-vinyl pyrrolidone, and styrene.



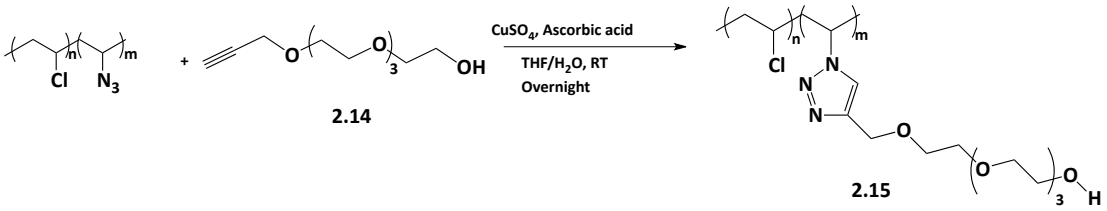
Scheme 2.7 Thioxanthone Functionalized PVC Prepared by CuAAC

Lipophilic ferrocene groups were introduced onto the PVC backbone **2.13** as an alternative to a conducting polymer-based systems.[278,279] The ferrocene groups **2.12** were incorporated by copper-mediated cycloaddition of PVC-azide and ferrocenyl alkyne as shown in **Scheme 2.8**. The electrochemical behavior of the modified PVC membrane was investigated in order to design all solid-state voltametric ion sensors.



Scheme 2.8 Ferrocene Functionalized PVC Prepared by CuAAC

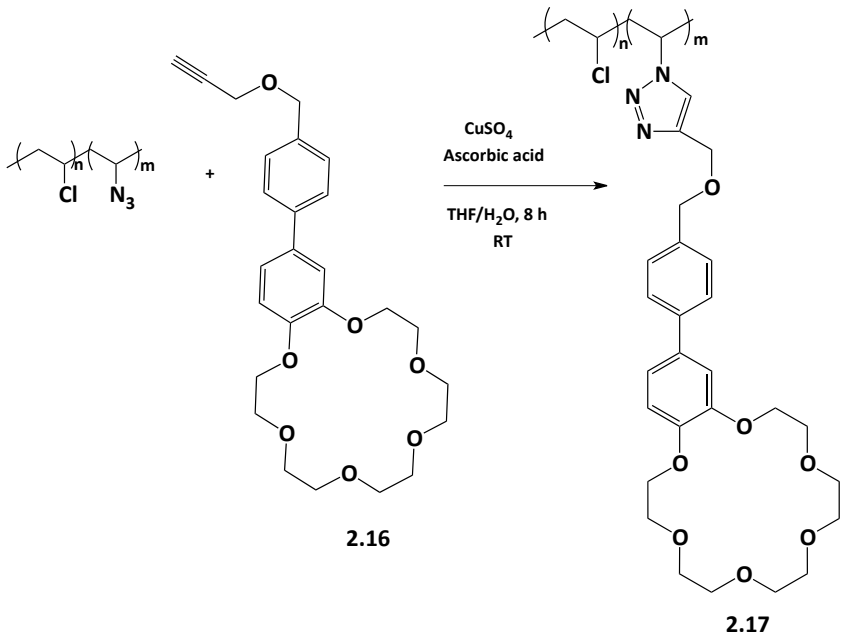
The hydrophilicity and resistance to fouling of PVC surfaces can be improved by attaching tetraethylene glycol to PVC 2.15.[280] The alkyne-terminated tetraethylene glycol was synthesized 2.14 and linked it to PVC using CuAAC as shown in Scheme 2.9. Scanning Electron Microscopy revealed a reduced level of blood cell adsorption on the PVC surface modified with tetraethylene glycol in comparison to unmodified PVC after 18 hours of contact with blood.



Scheme 2.9 Tetraethylene Glycol Functionalized PVC Prepared by CuAAC

Qin et al.[281] developed a potentiometric and optical sensor by grafting ionophores onto PVC 2.17. For this purpose, K^+-selective crown ether tethered to an alkyne was synthesized **2.16** and treated with PVC-azide in the presence of copper

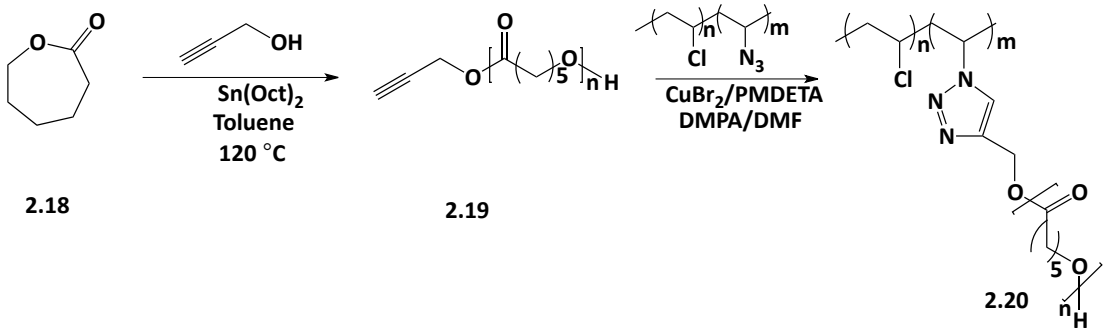
sulfate and ascorbic acid (Scheme 2.10). The modified PVC was used to prepare K^+-selective electrodes and optodes. This solid-state potassium ion sensor showed improved selectivity and lifetime compared to conventional ion sensors with free ionophores.



Scheme 2.10 Crown Ether Functionalized PVC Prepared by CuAAC

Recently, Tasdelen et al.[282] synthesized graft copolymers by photoinduced CuAAC of alkyne terminated poly(ε-caprolactone) (PCL) and PVC. They synthesized terminal alkynes attached to PCL by ring opening polymerization of ε-caprolactone **2.18** using $Sn(Oct)_2$ as a catalyst, and propargyl alcohol as the initiator. The resulting alkyne terminated PCL polymer **2.19** was added to PVC-azide in DMF using $CuBr_2$/N,N,N′,N′,N′′-pentamethyldiethylenetriamine (PMDETA) and 2,2-dimethoxy-2-

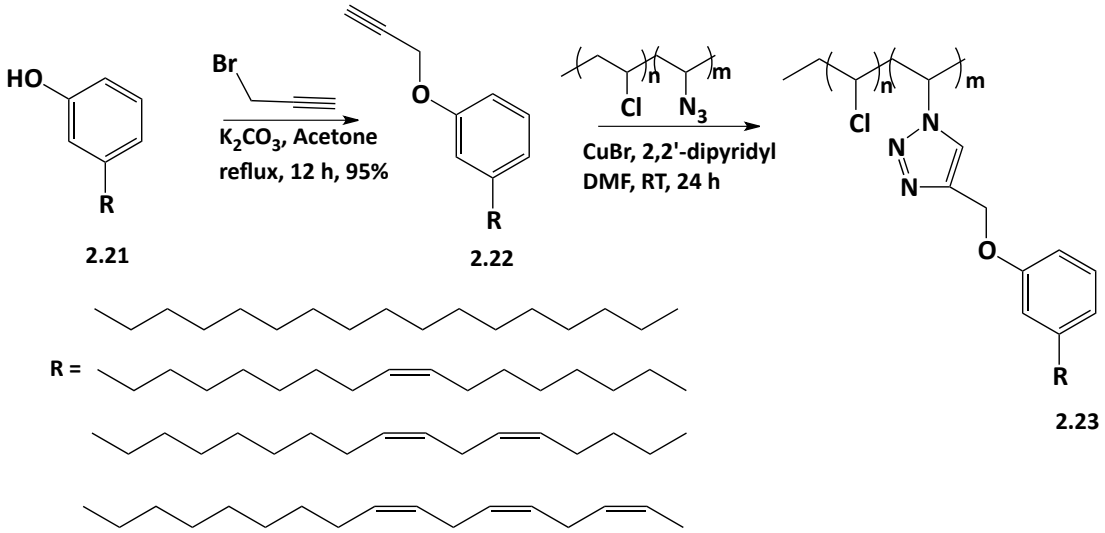
phenyl acetophenone (DMPA) and irradiated with UV light to form the corresponding graft polymer (PVC-g-PCL) **2.20**, as shown in **Scheme 2.11**. The presence of only one glass transition temperature of PVC-g-PCL by DSC curves at 76 °C indicated that PCL is miscible with PVC, and imparts little plasticization.



2.18 2.19 2.20

Scheme 2.11 Synthesis of Graft Polymer PVC-g-PCL

Yang et al.[200] carried out covalent modification of PVC with cardanol **2.21**, a renewable organic resource coming from the cashew industry, using copper catalyzed azide-alkyne cycloaddition. Cardanol was treated with propagyl bromide to give alkyne-substituted cardanol **2.22,** which was then clicked with PVC-azide using a copper catalyst (**Scheme 2.12**). The modified polymer **2.23** exhibited a decreased glass transition temperature of 51 °C, excellent thermal stability and no migration of the cardanol-derived plasticizer.

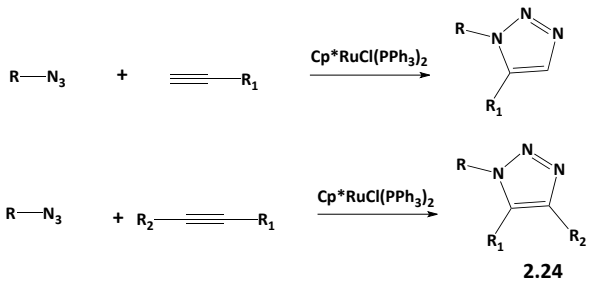


Scheme 2.12 Cardanol Functionalized PVC as an Internal Plasticizer Prepared by CuAAC

Despite the power and versatility of CuAAC, the requirement for the use of toxic Cu(I) metal[283] severely limits its application in both cellular systems and in many materials and applications. Moreover, CuAAC is not effective for internal alkynes, because only terminal alkynes can form the copper-acetylide, an essential intermediate in the CuAAC mechanism. The complete removal of Cu(I) catalyst from the reaction mixture is difficult, as the nucleophilic triazole products formed can act as ligands, binding to the Cu(I) metal. This can futher limit the application of CuAAC in biomedicine and in many consumer products. [284]

2.4 Ruthenium Catalyzed Azide-Alkyne Cycloaddition

Another breakthrough in the application of Huisgen cycloadditions was the ruthenium catalyzed azide-alkyne cycloaddition reaction (RuAAC), developed by Sharpless[285] in 2005. The highlight of this reaction is the complimentary regiospecific synthesis of isomeric 1,5-disubstituted 1,2,3-triazoles. In contrast to the CuAAC reaction, RuAAC can also be applied to internal alkynes to produce fully substituted 1,2,3-triazoles **2.24**, **Scheme 2.13.**[286] RuAAC is used less frequently than CuAAC. It is highly dependent on the nature of the azides: primary azides react faster than secondary, and tertiary azides do not react at all.[287] Moreover, the rate of RuAAC is affected by the choice of the catalyst.[287] To date a limited number of ruthenium catalysts for azide-alkyne cycloadditions have been designed. There are no reports of the use of RuAAC for PVC-azide reactions.

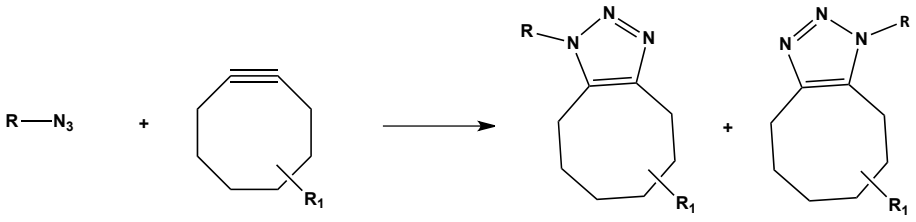


2.24

Scheme 2.13 Sharpless' Ruthenium Catalyzed Azide-Alkyne Cycloadditions

2.5 Strain-Promoted Azide-Alkyne Cycloaddition

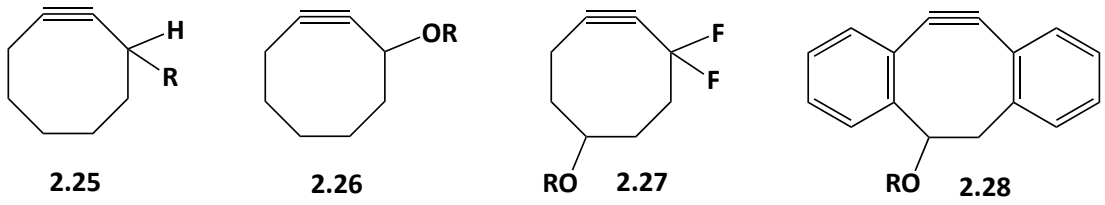
The use of CuAAC is limited in living systems due to the toxicity associated with copper. To improve the biocompatibility of azide-alkyne cycloadditions, the Bertozzi group utilized activated alkynes following a report in 1961 by Wittig and Krebs[288] about a violent reaction between a strained cyclooctyne and phenyl azide to give a triazole product. Bertozzi built upon this strain promoted azide-alkyne cycloaddition (SPAAC) to develop a bioorthogonal reaction, for *in vivo* applications (**Scheme 2.14**)



Scheme 2.14 Bertozzi's Strain Promoted Cycloaddition Reaction of an Azide and Alkyne Incorporated into an Eight-membered Ring

Cyclooctynes are unstable due to a high degree of ring strain, which causes them to react readily with azides.[289,290] Bertozzi demonstrated that biotin conjugated cyclooctyne could be effectively used to label azide-modified human leukemic T cells within the cell-surface glycans with no apparent cytotoxic effects.[291,292] While this method left no side products with cytotoxic effects, the first generation cyclooctyne derivatives **2.25 and 2.26** synthesized by Bertozzi gave slow cycloaddition kinetics in comparison to CuAAC (**Figure 2.1**). However, the rate of cycloaddition was dramatically improved by the introduction of electron-

withdrawing functional groups at one of the propargylic carbons.[293,294,295] The difluorinated cyclooctyne (DIFO) **2.27** demonstrated comparable kinetics to CuAAC in biomolecular labeling experiments.



2.25 **2.26** **2.27** **2.28**

Figure 2.1 Examples of cyclooctyne derivatives studied for SPAAC

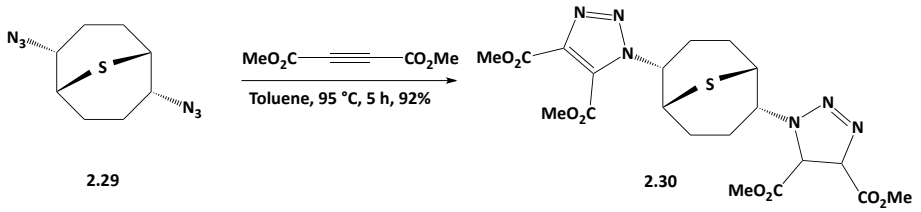
This reaction exhibited "click" features in the sense that it is chemoselective, readily applicable under physiological conditions, and has rapid rates equivalent to CuAAC. For example, the surface of mammalian cells were labelled with fluorescent dyes within minutes using this approach.[296] Bertozzi and other groups have synthesized a number of DIFO-fluorophore conjugates and new cyclooctyne reagents for imaging azide-labelled biomolecules within complex systems. Of the many types of cyclooctynes reported for SPAAC, DIFO is the most reactive and has been extensively utilized to image biomolecules. Boons and coworkers[297] have reported highly reactive dibenzocyclooctyne and dibenzocycloctynol analogs **2.28** for imaging glycoproteins. This cycloaddition is often referred to as "copper-free click" chemistry.[298] Although SPAAC is a valuable azide-labeling technique in living systems,

the synthesis of cyclooctyne conjugates is challenging and much more complicated than attaching a terminal acetylene functional group as in CuAAC.[293] Moreover, like Huisgen's TAAC, 1,3-dipolar cycloaddition of azides to cyclooctynes produce a mixture of regioisomers.[299,296] There are no reports on the use of SPAAC in the modification of PVC.

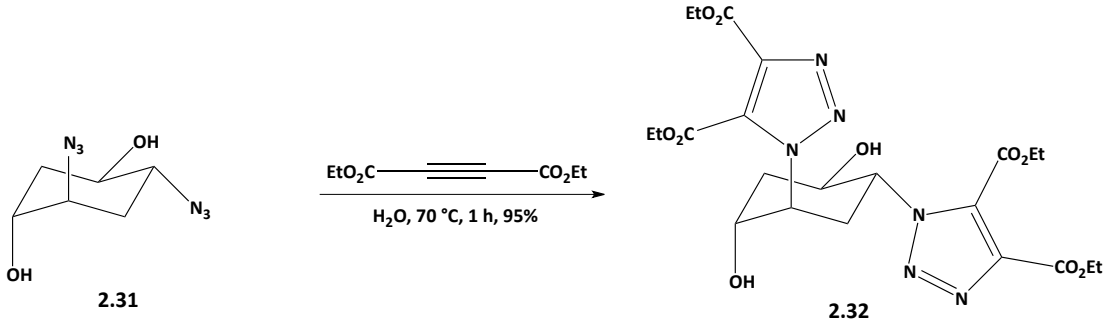
2.6 Thermal Azide-Alkye Cycloaddition

The use of a copper catalyst, even in trace amounts, is not desirable for commodity products with applications in the fabrication of medical devices and food, drink and drug packaging. Trace copper could also be problematic for products used in electronic applications. Strain-promoted copper-free cycloaddition reactions are restricted to the use of very specialized strained 8-membered ring alkynes. The progenitor reaction, the Huisgen cycloaddition, is not attractive at first glance, because of the slow reaction rates, mixture of regioisomers, and high reaction temperatures required. However, the efficiency of the Huisgen cycloaddition can be manipulated by controlling the HOMO-LUMO gap of the reacting molecules.[300] Reduction in the energy gap between the azide HOMO and the alkyne LUMO can be used to enhance the rate of cyclization. One way to do this is to use electron deficient alkynes, electron rich azides, or both. There are several scattered examples of mono- and diester substituted alkynes taking part in Huisgen thermal 1,3-dipolar cycloadditions to form 1,2,3-triazoles in the literature. A review by Sharpless et al.[211]

in 2001 summarized the early applications of TAAC. Michael's work on 1,3-dipolar cycloaddition of phenyl azide with dimethylacetylene dicarboxylate in 1893[209] is the first example. The second reaction is the cycloaddition of bis(azide) **2.29** with two molecules of dimethylacetylene dicarboxylate to give bis(triazole) **2.30** in 92% yield at 95 °C (**Scheme 2.15**). Another example is the 1,3-dipolar addition of bis(azido) cyclohexane **2.31** with diethylacetylene diacrboxylate at 70 °C to give bis(triazole) **2.32** in 95% yield (**Scheme 2.16**).



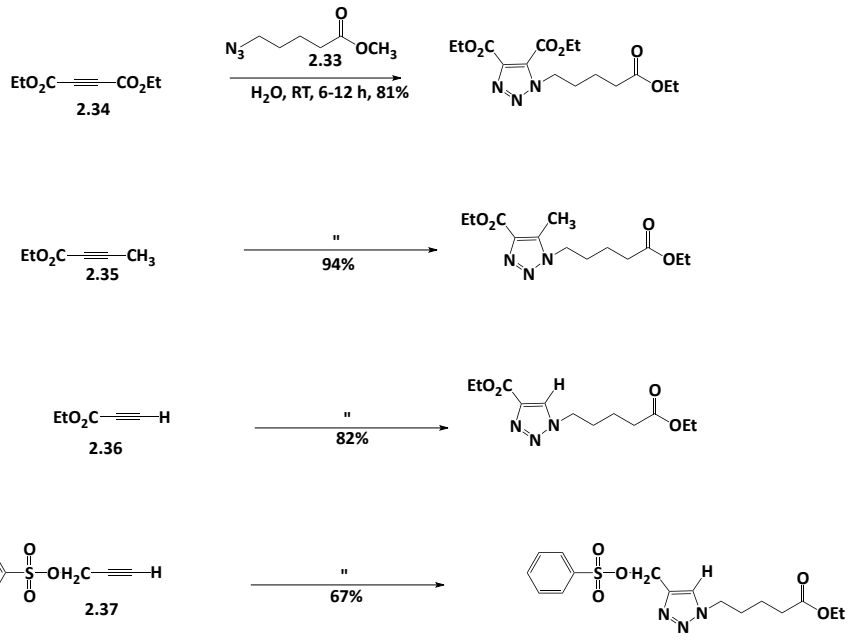
Scheme 2.15 Cycloaddition of Bis(azide) 2.29 with Dimethylacetylene Dicarboxylate



Scheme 2.16 Cycloaddition of Bis(azide)cyclohexane 2.31 with Diethylacetylene Dicarboxylate

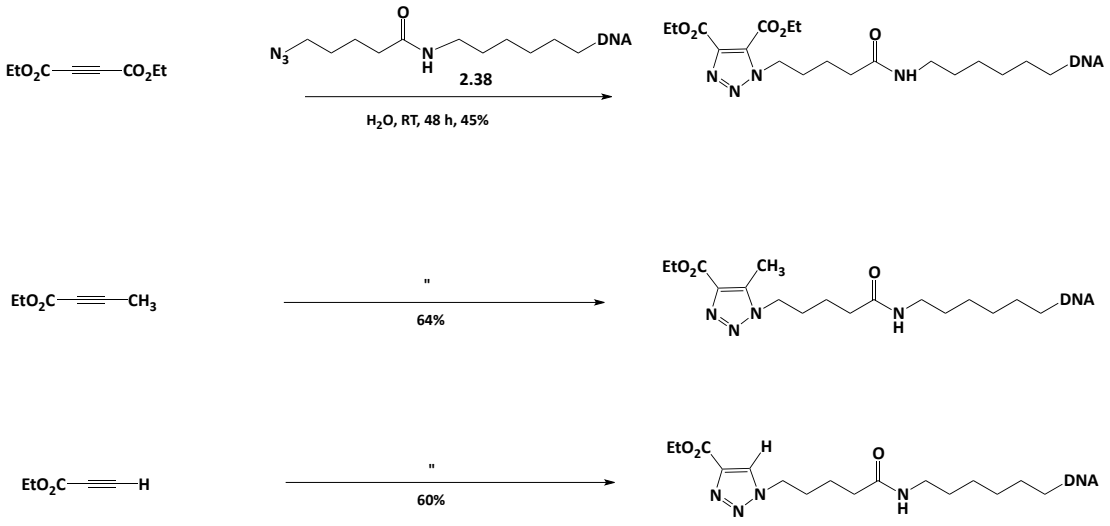
In 2004, Ju et al.[301] explored TAAC for the site-specific fluorescent labeling of an oligonucleotide for DNA sequencing, and found that if an electron-deficient internal

or terminal alkyne was used, the 1,3-dipolar cycloaddition could be carried out at room temperature in water, without the use of catalyst. These conditions are suitable for DNA modification inside a cell. This provides an efficient method for introducing functional groups onto DNA under biological conditions. A number of small molecule models were evaluated. These conditions were extended to the reactions of DNA-azide with electron-deficient alkynes. Methyl 5-azidopentanoate **2.33** was used as a small molecule azide, and was treated it with various alkynes: diethylacetylene dicarboxylate **2.34**, ethyl but-2-ynoate **2.35**, ethyl propiolate **2.36**,



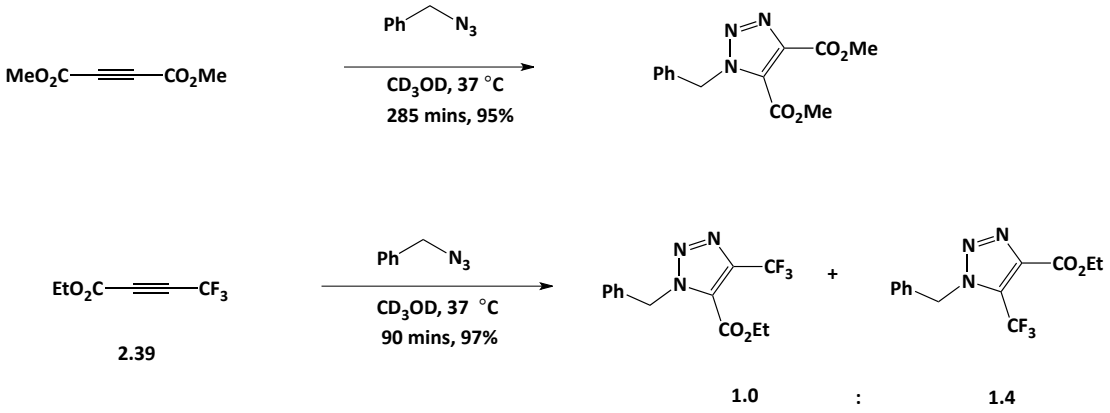
Scheme 2.17 Ju's Small Molecule 1,3-Dipolar Cycloadditions with Electron-poor Alkynes

and prop-2-yn-1-yl benzenesulfonate **2.37** in water at room temperature for 6 to 12 hours to obtain the respective triazoles in 81-94% yields (**Scheme 2.17**). In a similar manner, the azide-substituted oligonucleotide **2.38** underwent cycloaddition with these alkynes in water for 48 hours to give the respective triazole products in 45–60% yields (**Scheme 2.18**).



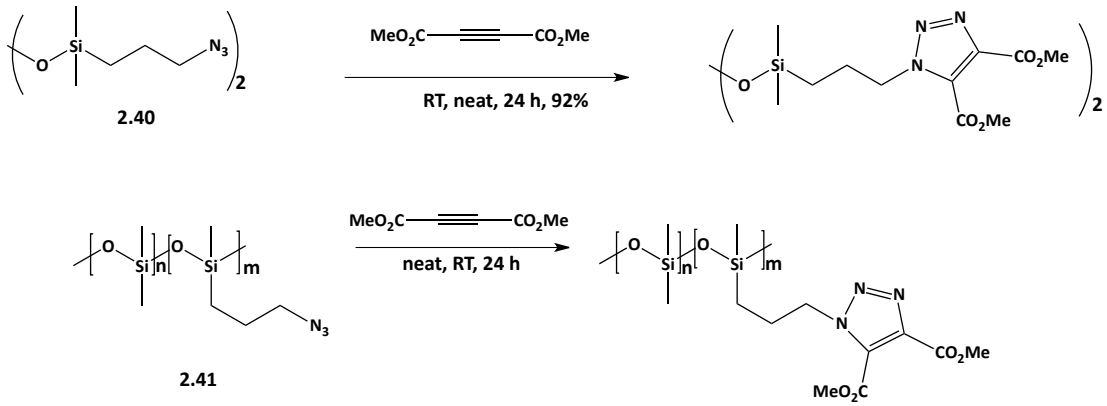
Scheme 2.18 Ju's Cycloadditions of DNA-Azide with Electron-poor Alkynes

The activation of alkynes towards 1,3-dipolar cycloaddition reactions with organic azides by attaching electron-withdrawing groups is further illustrated by the work done by Rutjes.[302] Substitution of one ester group in diethylacetylene dicarboxylate with trifluoromethyl group **2.39** gave a three-fold enhancement in the cycloaddition rate with benzyl azide in deuterated methanol. The regioisomeric triazoles were obtained in a 1.0:1.4 ratio (**Scheme 2.19**).



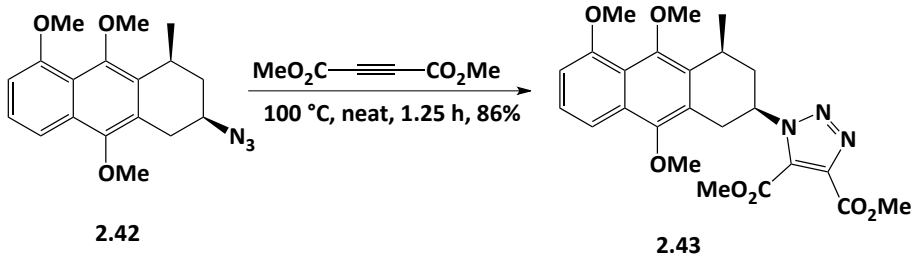
Scheme 2.19 Rutjes' Cycloaddition of Ethyl 4,4,4-Trifluorobut-2-ynoate with Benzyl azide

In order to synthesize polysiloxanes, Brook et al.[303] utilized CuAAC or TAAC of monomeric or polymeric azido-siloxanes with a broad range of alkynes. Polysiloxanes are extremely hydrophobic polymers of significant industrial importance, used as surfactants, liquid crystals, anti-foaming agents, and textile finishing agents. One such example is the use of electron poor alkyne dimethylacetylene dicarboxylate in a thermal cycloaddition with 1,3-azidopropyltetramethyldisiloxane **2.40** and polymeric azido-siloxane **2.41**. The reactions with both azides occurred at room temperature (**Scheme 2.20**).



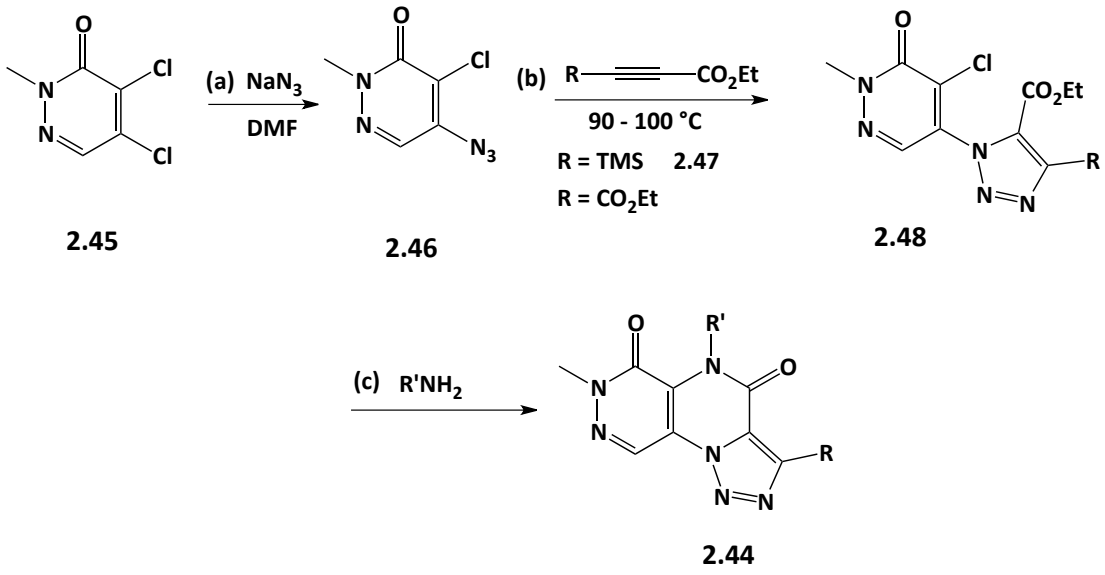
Scheme 2.20 Brook's Cycloaddition of Polysiloxane with Dimethylacetylene Dicarboxylate

Brimble et al.[304] synthesized a series of triazole analogues of the nanomycin antibiotics using thermal 1,3-dipolar cycloaddition of the naphthalene azide derivative **2.42** to dimethylacetylene dicarboxylate. Using 50 equivalents of the alkyne as a solvent, **2.42** underwent cycloaddition in 1.25 hours at 100 °C to afford triazole **2.43** in 86% yield (**Scheme 2.21**).



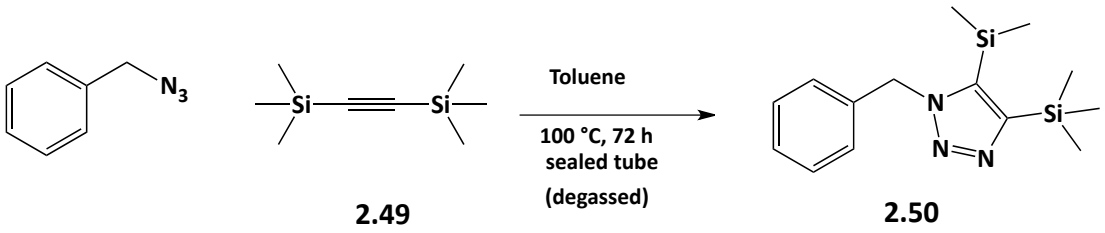
Scheme 2.21 Brimble's Cycloaddition of Naphthalene Azide with Dimethylacetylene Dicarboxylate

A one-pot synthesis of substituted 1,2,3-triazole-fused pyrazinopyridazin dione tricycles **2.44** by TAAC was reported by Qian et al.[305] The reaction of 4,5-dichloro-2-methylpyridazin-3(2H)-one **2.45** with sodium azide in DMF afforded 5-azido-4-chloro-2-methylpyridazin-3(2*H*)-one **2.46** via Michael addition, chlorine expulsion. The addition of ethyl 3-(trimethylsilyl) propiolate **2.47** or diethyl acetylenedicarboxylate to this mixture with heating to 100 °C afforded the corresponding triazoles **2.48** (**Scheme 2.22**).



Scheme 2.22 Qian's Dipolar Cycloaddition of 5-Azido-4-chloro-2-methylpyridazin-3(2*H*)-one with 3-(Trimethylsilyl) Propiolate or Dimethylacetylene Dicarboxylate

Brisbois et al.[306] carried out Huisgen cycloadditions between aliphatic or aromatic azides and bis(trimethylsilyl)acetylene (BMTSA) **2.49** as an electron rich alkyne partner to synthesize a number of click-activated fluorophores. The general protocol using benzyl azide and BMTSA is shown in **Scheme 2.23**. The cycloaddition of benzyl azides with BMTSA in a degassed sealed tube using toluene as solvent at 100 °C for 72 hours afforded 1,2,3-triazole **2.50**.

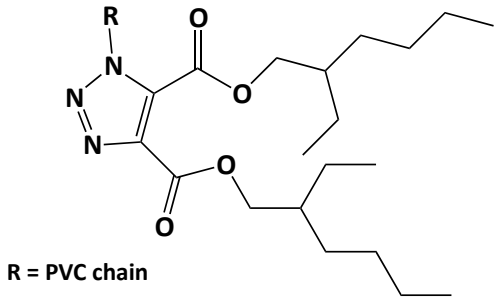


2.49 **2.50**

Scheme 2.23 Brisbois' Cycloaddition of Bis(trimethylsilyl)acetylene (BMTSA) with Benzyl Azide

2.7 Triazole Analogues of Phthalate Plasticizers

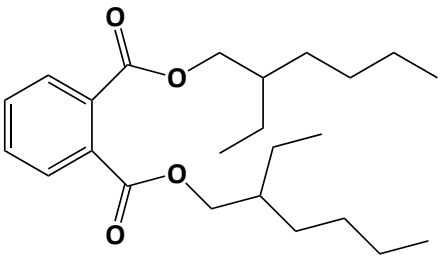
Studies on the metal free 1,3-dipolar cycloaddition of electron-deficient alkynes and azides to form 1,2,3-triazoles under ambient conditions opened up potentially interesting opportunities for the Braslau group. TAAC has not been exploited in the chemical modification of PVC. The goal of this project is to explore a TAAC approach to covalently attach plasticizers to PVC. To install a phthalate plasticizer analogue, Huisgen cycloaddition of PVC-azide with di(2-ethylhexyl) acetylenedicarboxylate would form compound **2.51**, in which R is the PVC chain (**Figure 2.2**). The triazole



R = PVC chain

DEHT: Di(2-ethylhexyl)-1H-triazole-4,5-dicarboxylate

2.51



DEHP: Di(2-ethylhexyl) phthalate

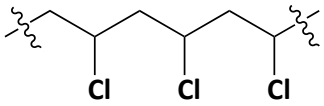
2.52

Figure 2.2 Triazole Analogue of the Most Common Phthalate Plasticizer DEHP

2.51 is expected to mimic the most common phthalate plasticizer: di(2-ethylhexyl)phthalate (DEHP) **2.52**. Moreover, the triazole ring is similar to a benzene ring in terms of its aromaticity, ring shape and size, planarity, and its resistance towards enzymatic degradation, hydrolysis, and redox processes. This work has been published: A. Earla, R. Braslau, *Macromol. Rapid Commun.* **2014**, *35*, 666-671.

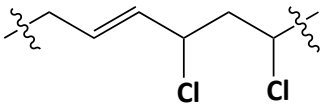
2.7.1 Small Molecule Models

Synthetic modification of polymeric PVC results in polydisperse products, which are not amenable to facile characterization by ^{1}H NMR, ^{13}C NMR, or mass spectroscopy. Therefore, two small molecule models were investigated to confirm the viability of the key Huisgen cycloaddition with dialkylacetylene dicarboxylates using well-defined secondary alkyl azides. The results were then extended to covalently



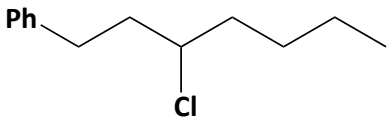
Secondary chlorine of PVC

2.53



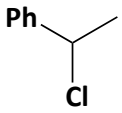
Allylic chlorine of PVC

2.54



(3-chloroheptyl) benzene

2.55



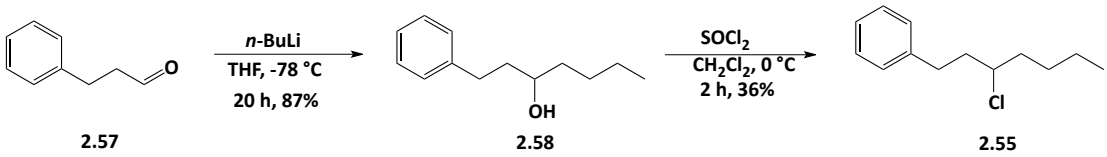
(1-chloroethyl) benzene

2.56

Figure 2.3 Small Molecule Chlorides to Mimic Secondary and Allylic Chlorides of PVC

linking plasticizers to PVC. As discussed in chapter 1, PVC contains three types of chlorines: secondary **2.53**, allylic **2.54** (formed due to thermal dehydrochlorination), and tertiary at branching points. Allylic and tertiary chlorides are labile chlorines. Azide substitution at secondary sites will happen by an S_N2 mechanism, and at allylic sites by an S_N2' mechanism. Therefore, (3-chloroheptyl) benzene **2.55** was selected as a small molecule model for secondary chlorides and (1-chloroethyl) benzene **2.56** was chosen to mimic secondary allylic chlorides of PVC (**Figure 2.3**). The benzylic substrate (1-chloroethyl) benzene **2.56** was obtained commercially. The secondary alkyl substrate (3-chloroheptyl) benzene **2.55** was synthesized.

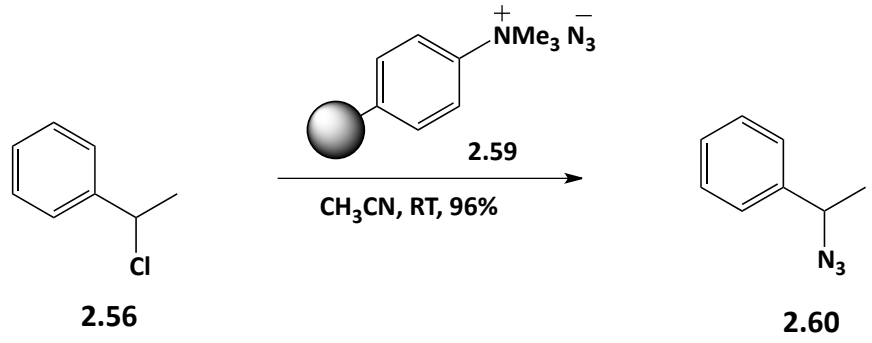
Hydrocinnamaldehyde **2.57** was converted into 1-phenylhept-3-ol **2.58** in 87% yield by nucleophilic addition of *n*-butyllithium in anhydrous THF at -78 °C. The alcohol **2.58** was transformed into (3-chloroheptyl) benzene **2.55** by treating with thionyl chloride in dry dichloromethane (DCM) for 2 hours at 0 °C to afford **2.55** in 36% yield (**Scheme 2.24**).



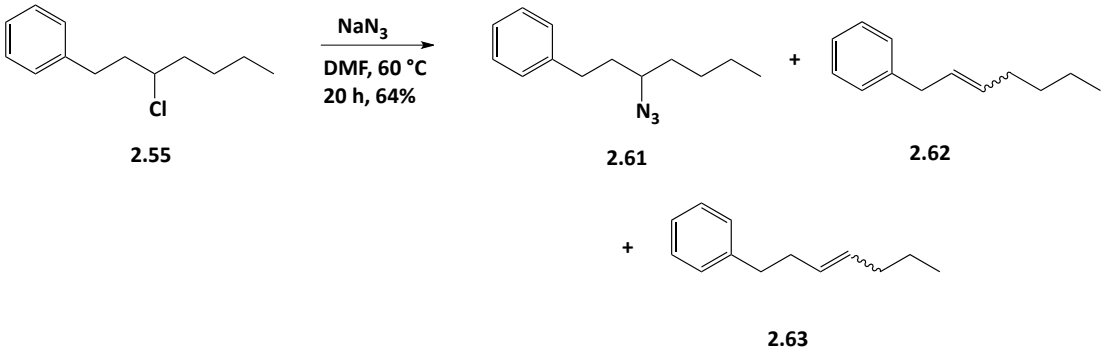
2.57 **2.58** **2.55**

Scheme 2.24 Synthesis of (3-Chloroheptyl) benzene as Secondary Chloride Mimic of PVC

The facile nucleophilic substitution reaction of (1-chloroethyl) benzene **2.56** by azide using Amberlite 400/N_3 resin **2.59** in acetonitrile afforded (1-azidoethyl) benzene **2.60** in 96% yield (**Scheme 2.25**).[307] Amberlite 400/N_3 is a polystyrene supported azide ion exchange resin; it is easily removed from the reaction mixture by simple filtration. The resin can be recovered, recharged with sodium azide in water, and reused without loss of efficiency. Small organic azide molecules are potentially explosive. Therefore, care was taken while evaporating the solvent *in vacuo.* The product was not completely dried; instead it was obtained with traces of acetonitrile.



Scheme 2.25 Azidation of (1-Chloroethyl) benzene 2.56 with Amberlite 400/N_3



Scheme 2.26 Azidation of 3-Chloro-1-phenylheptane 2.55

Since Amberlite 400/N_3 is only useful for small activated benzylic and allylic halides, the secondary alkyl azide (3-azido-1-phenylheptane) **2.61** was obtained by the treatment of 3-chloro-1-phenylheptane **2.55** with sodium azide in DMF at 60 °C for 20 h in 64% yield (**Scheme 2.26**). This product was obtained as an inseperable mixture with a small amount of elimination products (**2.62** and **2.63**) formed by the dehydrochlorination of the starting material. The analysis by ^{1}H NMR, ^{13}C NMR, and DEPT showed the conversion of chloride to azide. The distinctive peak at 2100-2000

cm^{-1} in the FTIR spectra of **2.60** and **2.61** is characteristic of the azide functional group (**Figure 2.4**).

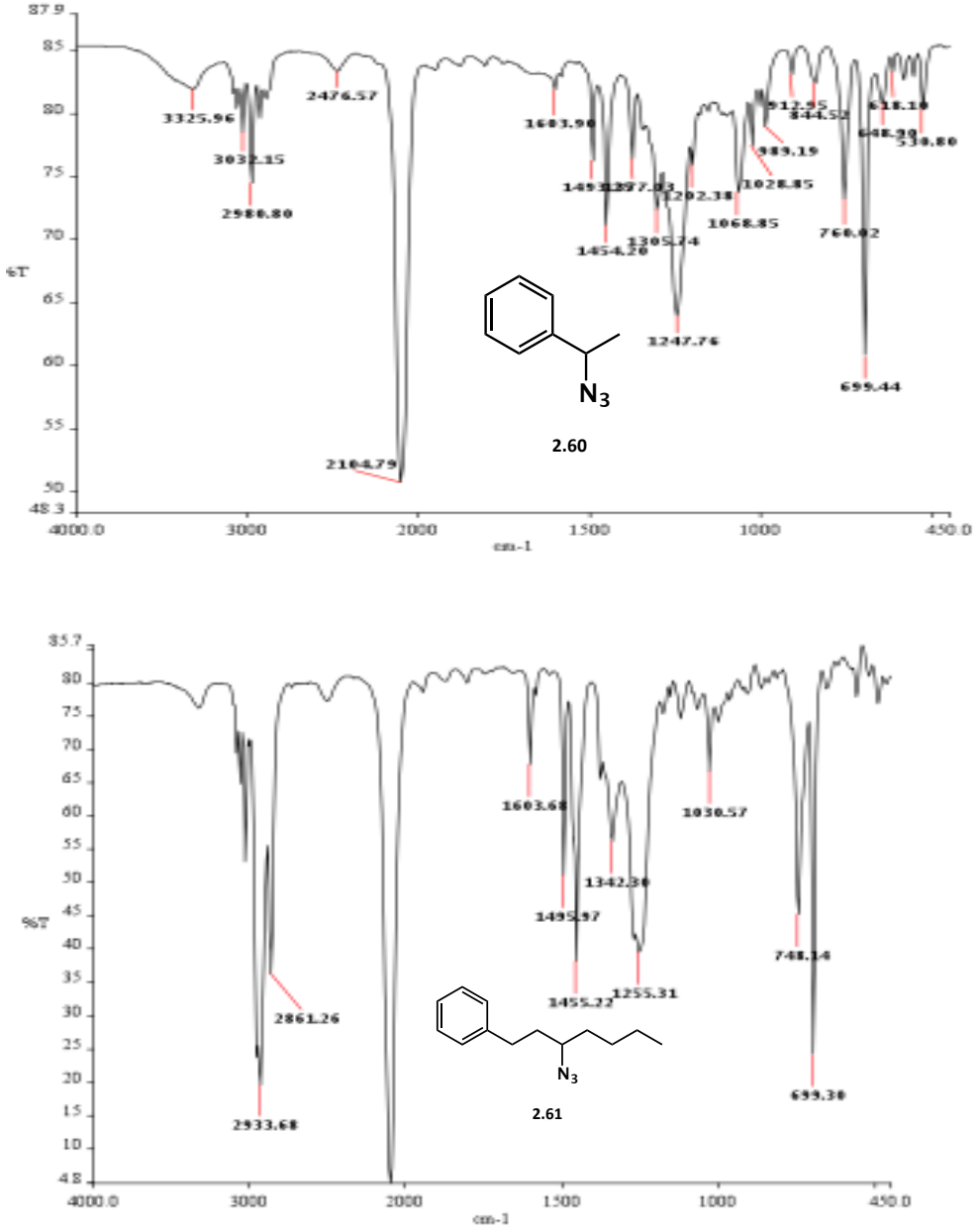
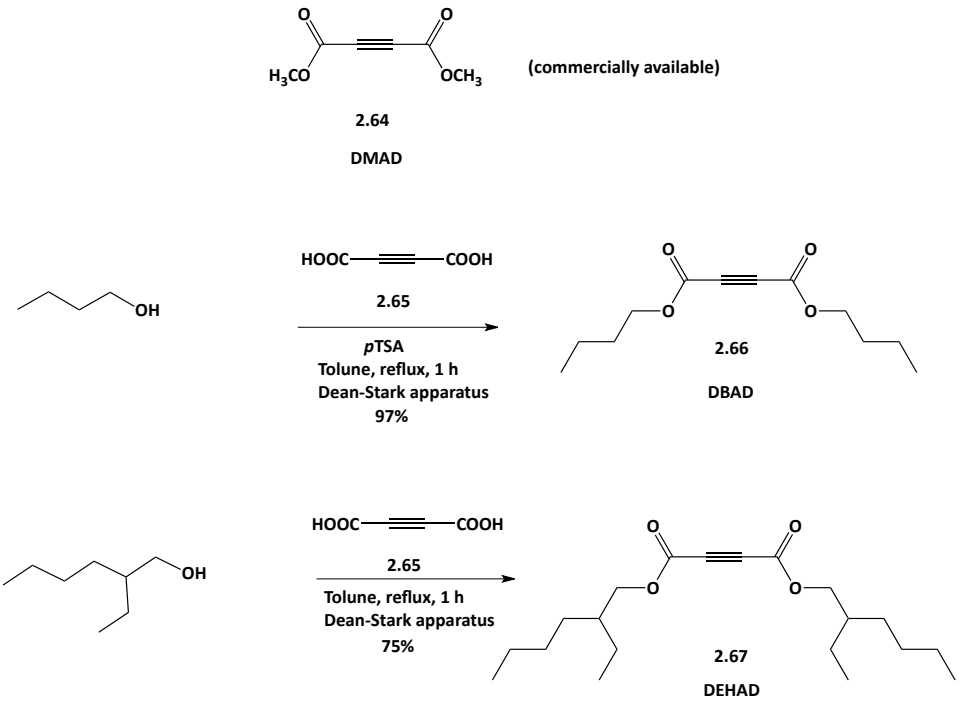


Figure 2.4 FTIR Spectra of Benzylic Azide 2.60 and Secondary Azide 2.61

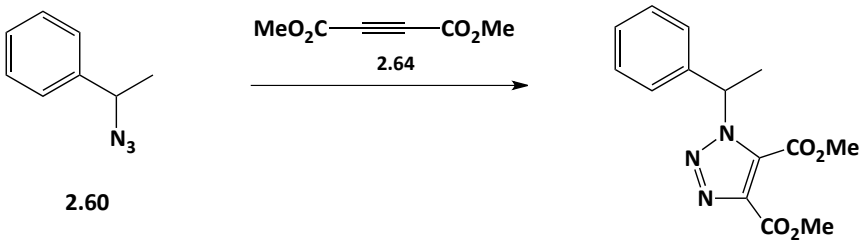
Dimethylacetylene dicarboxylate (DMAD) **2.64** was obtained commercially. Di(*n*-butyl) acetylenedicarboxylate (DBAD) **2.66** was obtained in 97% yield by Fischer esterification of acetylenedicarboxylic acid **2.65** and *n*-butanol with *p*-toluenesulfonic acid as a catalyst in refluxing toluene. A Dean-Stark apparatus was used to remove water formed during esterification. Likewise, Fischer esterification of 2-ethylhexanol with acetylenedicarboxylic acid under similar conditions afforded di(2-ethylhexyl)acetylene dicarboxylate (DEHAD) **2.67** in 75% yield (**Scheme 2.27**).



Scheme 2.27 Synthesis of Electron-poor Alkynes DBAD and DEHAD

With the benzylic azide and several diakylacetylene dicarboxylates in hand, the procedure of Brimble et al.[304] was followed initially to carry out the key thermal Huisgen cycloaddition. DMAD was initially chosen as the alkyne partner to generate

simple NMR spectra. The benzylic azide was mixed with 50 equivalents of DMAD at 100 °C. The reaction went to completion within 40 minutes. The progress of this reaction was monitored by thin layer chromatography. The number of equivalents of DMAD and the temperature were reduced. It was exciting to find that the reaction went to completion with 1.5 equivalents of alkyne at ambient conditions, albeit requiring a reaction time of 22 hours. The reaction proceeded well neat, in chloroform, and in deuterochloroform ($CDCl_3$) as the solvent (**Table 2.1**).



Equivalents alkyne	Solvent	Temperature °C	Time	Yield
50	Neat	100	40 min	91%
5	Neat	50	40 min	ND
5	Neat	RT	40 min	ND
1.5	Neat	RT	22 h	ND
1.5	$CDCl_3$	RT	22 h	89%

ND= not determined

Table 2.1 Preliminary Thermal Cycloadditions of Phenethyl Azide and DMAD

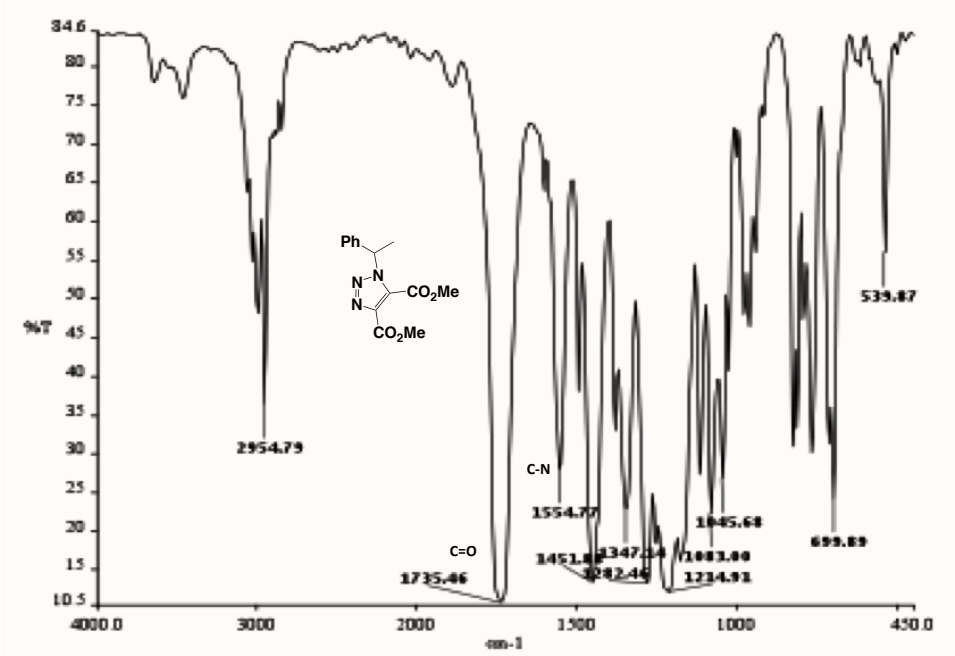
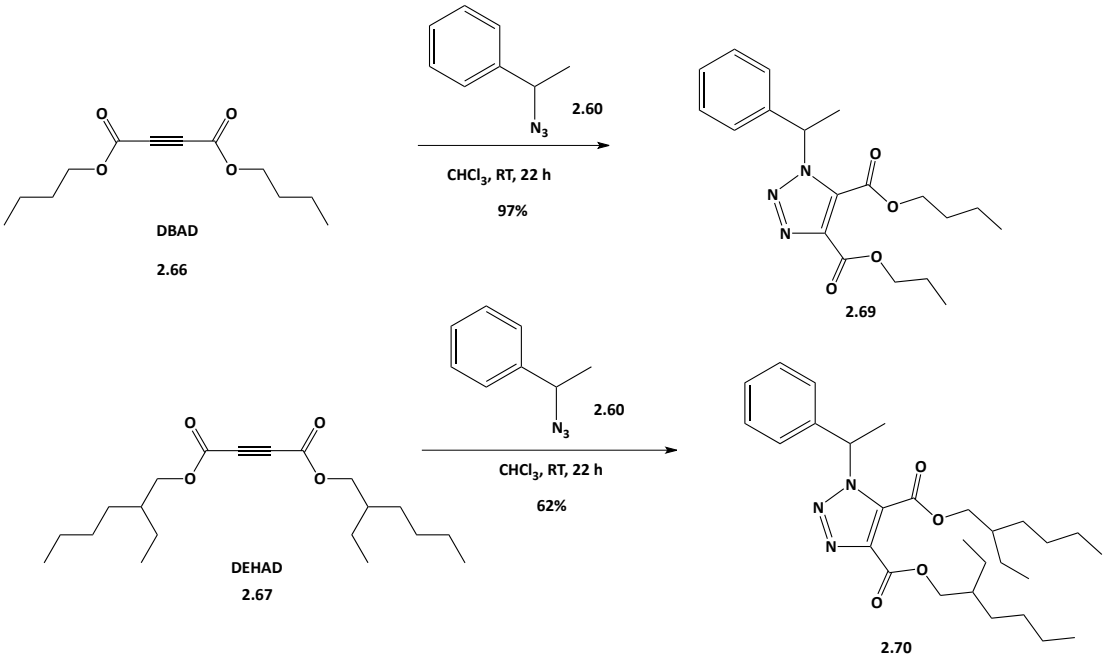


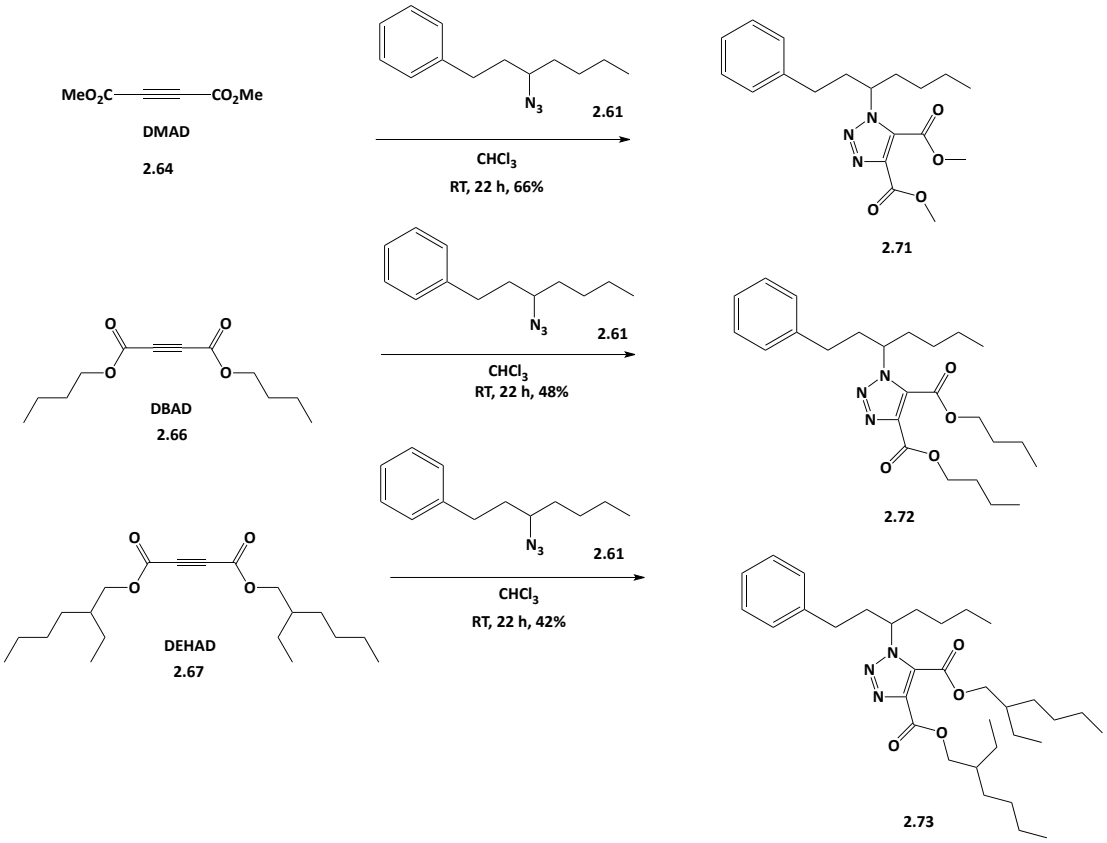
Figure 2.5 FTIR Spectrum of Triazole 2.68 from Benzylic Azide 2.60

The disappearance of the azide peak at 2100 cm^{-1} accompanied by the appearance of a peak at 1725 cm^{-1} attributed to carbonyl (C=O) functional group and a peak at 1554 cm^{-1} attributed to the triazole (C-N) in the FTIR spectra provides a convenient method to follow the formation of these triazoles (**Figure 2.5**). In the ^{1}H NMR spectrum, the benzylic proton of the azide shifts from δ 4.58 to δ 6.12 ppm in the triazole. In the ^{13}C NMR, the benzylic carbon shifts from δ 33.2 to δ 58.1 ppm. The cycloaddition reactions with the benzylic azide were then extended to other dialkylacetylene dicarboxylates. The reactions of phenethyl azide with alkynes DBAD and DHEAD gave the respective triazoles **2.69** and **2.70** in 97% and 62% yields (**Scheme 2.28**). The reactions were conveniently monitored by FTIR.



Scheme 2.28 Thermal Cycloadditions of Phenethyl azide with DMAD, DBAD and DEHAD

After these successful results with phenethyl azide, the cycloadditions of the secondary azide model (3-azido-1-phenylheptane) **2.61** was investigated**.** A 0.3 M solution of 1.5 equivalents of DMAD **2.64**, DBAD **2.66**, or DEHAD **2.67** in chloroform was added to 1.0 equivalent of benzyl azide to give the respective triazoles (**2.71**, **2.72**, and **2.73**) in yields of 66%, 48%, and 42% (**Scheme 2.29**). The formation of these triazoles was followed by TLC and FTIR (**Figure 2.6**), and the products confirmed by NMR.



Scheme 2.29 Thermal Cycloadditions of Secondary Azide with DMAD, DBAD and DEHAD

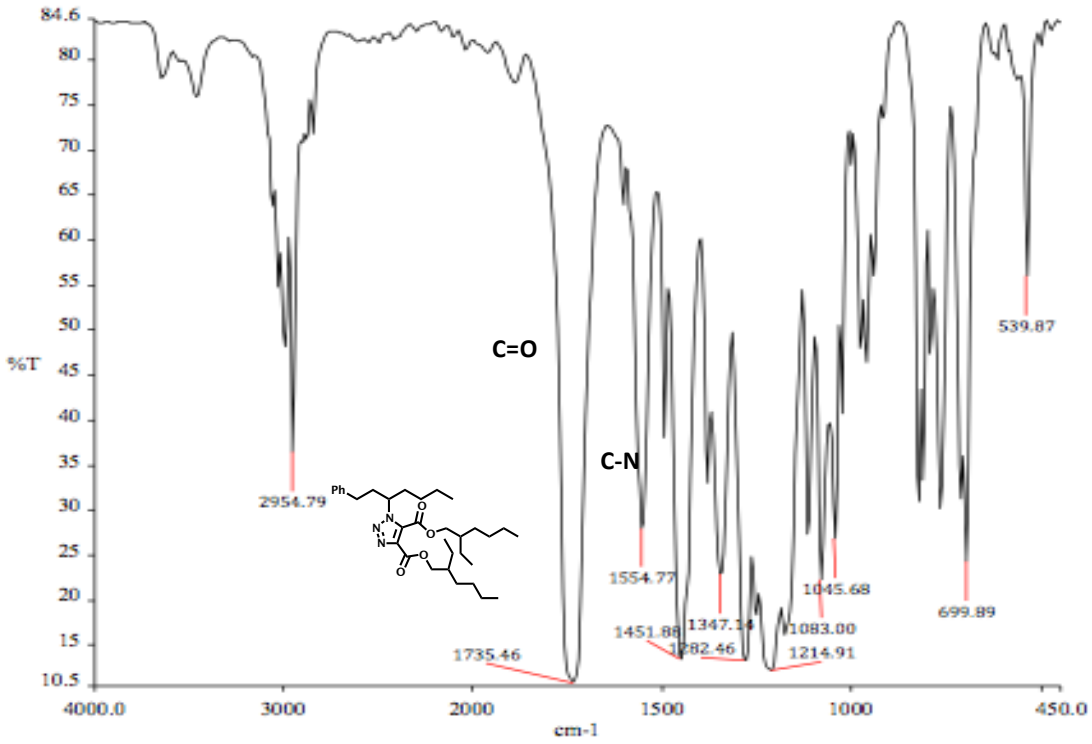
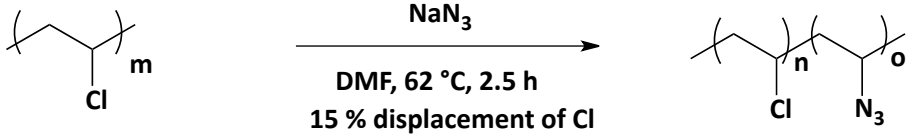


Figure 2.6 FTIR Spectrum of the Bis(2-Ethylhexylcarboxy) Triazole Secondary Azide Model

2.7.2 Modification of PVC

Both secondary and benzylic azides undergo 1,3-dipolar cycloadditions to electron-poor diester substituted alkynes at room temperature to form 1,2,3-triazoles. This methodology was then applied to modify PVC. Azide functional groups were incorporated into PVC by nucleophilic substitution of some of the chlorines. Kameda et al. showed that the efficiency of nucleophilic substitution reaction of Cl in PVC is solvent dependent. The ratio of substitution to elimination of Cl in PVC with nucleophiles I^-, NCS^-, N_3^-, and phthalimide anion was higher in DMF than in ethylene glycol.[308,309] Hence, DMF was chosen as the solvent for nucleophilic substitution of Cl

with azide. Commercial bulk polymerized PVC of molecular weight of 43,000 and PDI of 1.95 was obtained from Sigma-Aldrich, and was purified prior to use. Following Rusen's procedure, 5.003 g of PVC was dissolved in 60 mL of tetrahydrofuran, followed by precipitation with 180 mL of methanol. After filteration and removal of solvent, the purified PVC was treated with sodium azide in DMF at 62 °C for 2.5 h to replace some of the chlorines of PVC with azide functional groups.[310]



2.74

Scheme 2.30 Azidation of PVC

The degree of azidation was determined by elemental analysis: 38.17% C, 4.70% H, 9.81% N, indicating 14.7% displacement of Cl by azide. When the reaction time was reduced to 1 h, or 30 minutes, the degree of azidation was 9.36% and 4.76%, respectively. The characteristic peak of the azide functional group at 2112 cm^{-1} in the FTIR spectrum confirmed the partial azidation of PVC (**Figure 2.7**). In the ^{1}H NMR

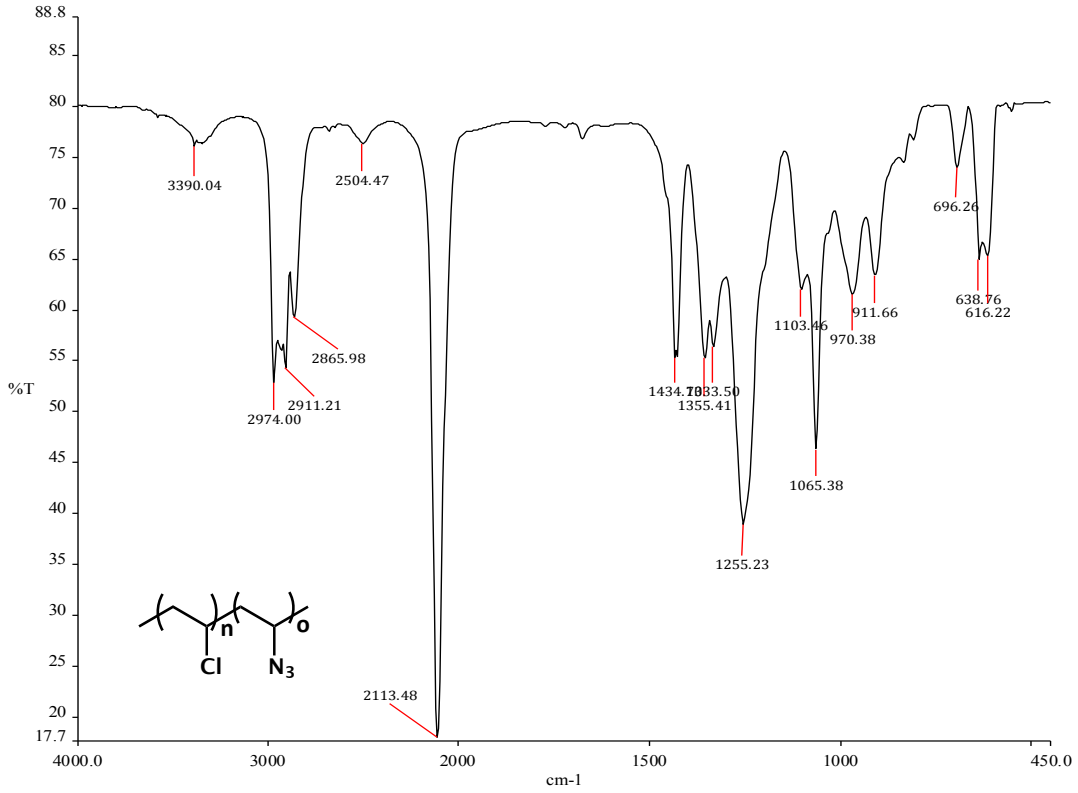


Figure 2.7 FTIR spectrum of 15% PVC-azide

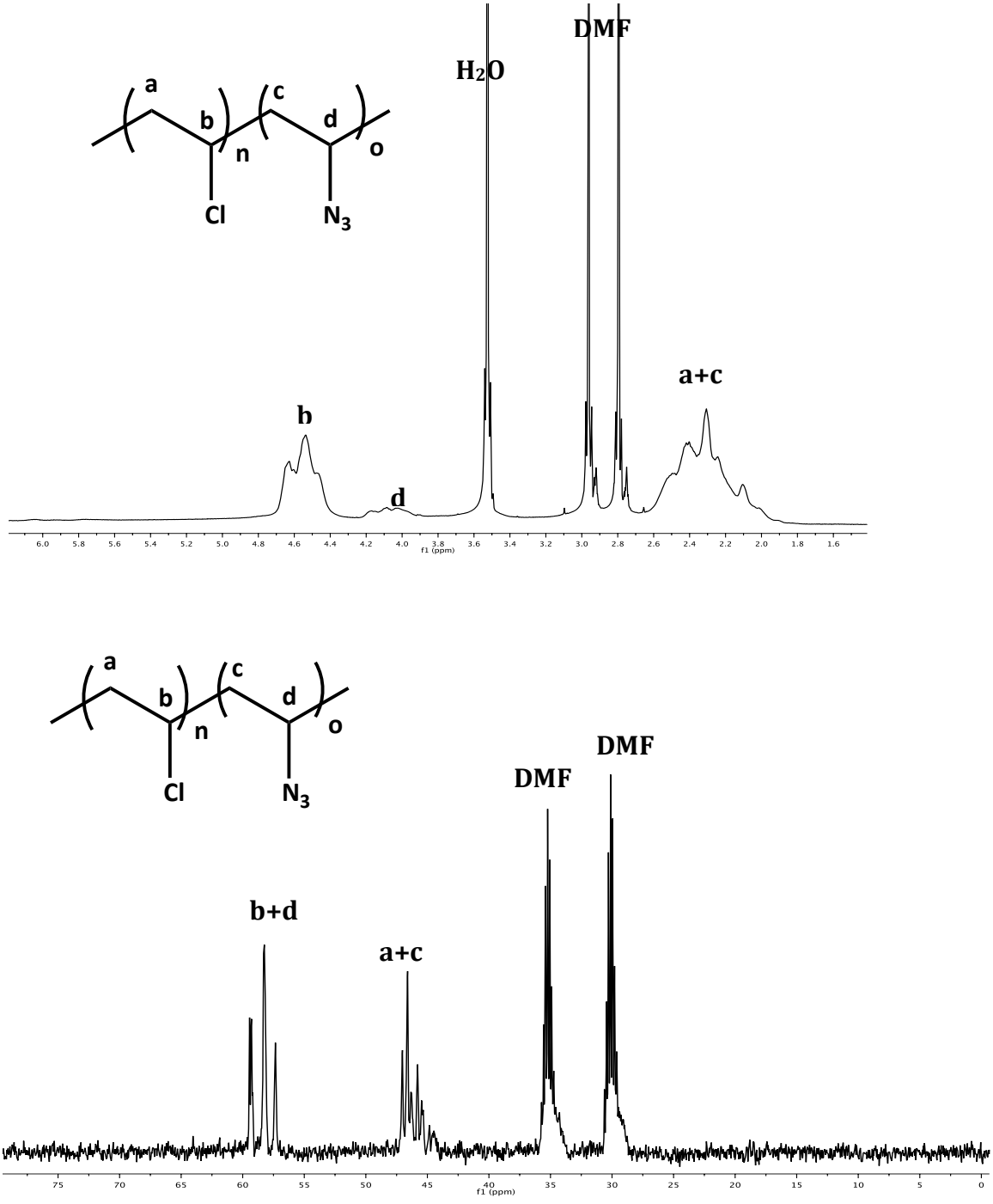
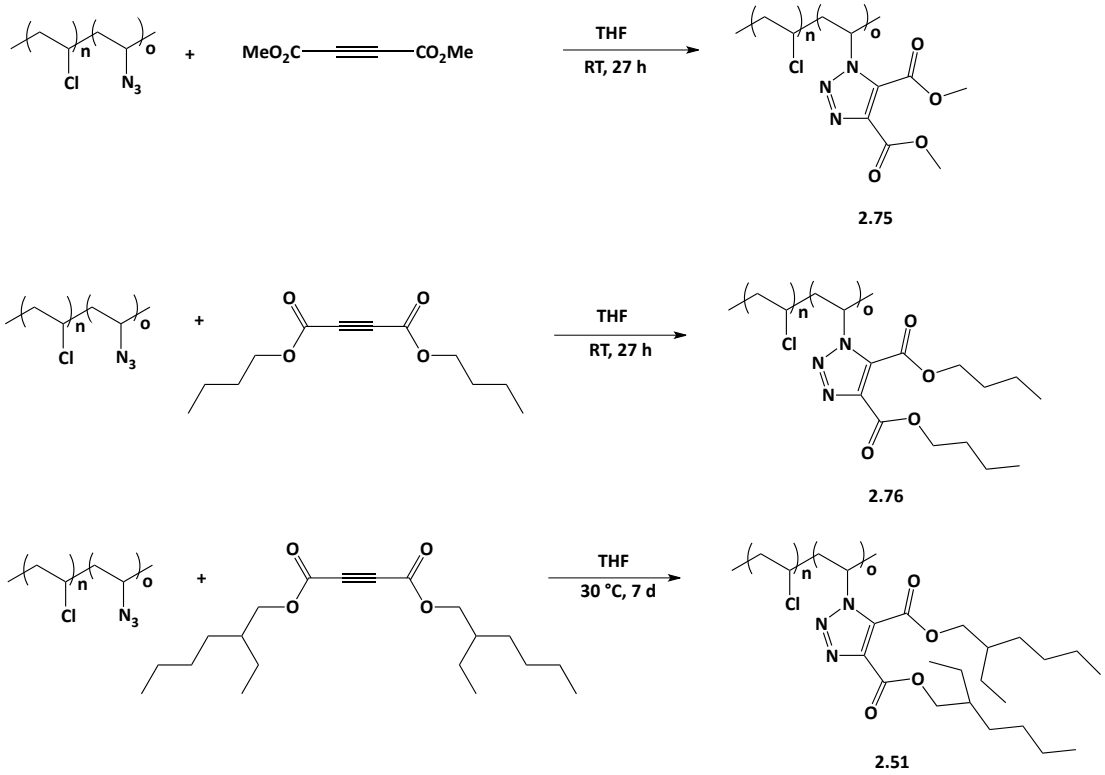


Figure 2.8 ^{1}H NMR and ^{13}C NMR spectra of 15% PVC-Azide in DMF-d_7

spectrum of PVC-N_3, the N_3-C**H**-CH_2- methine is observed as a collection of peaks between δ 4.22-3.85 ppm, the Cl-C**H**-CH_2- methine protons are observed as a family of peaks between δ 4.75-4.39 ppm, and the N_3-CH-C**H**$_2$- and Cl-CH-C**H**$_2$- methylene protons are found at δ 2.00-2.60 ppm. From the ^{13}C NMR spectrum, N_3-**C**H-CH_2- and Cl-**C**H-CH_2- methine carbons are observed as a family of peaks between 57.1-60.1 ppm, Cl-CH-**C**H_2- methylene carbons appear as a family of peaks between δ 45.2-47.1 ppm, and the N_3-CH-**C**H_2- methylene carbons are found between δ 44.1-45.0 ppm (**Figure 2.8**).



Scheme 2.31 Thermal cycloadditions of PVC-azide with DMAD, DBAD, and DEHAD

PVC-N_3 was then subjected to the key Huisgen thermal cycloaddition at room temperature for 27 h to form triazoles PVC-DMT, PVC-DBT, and PVC-DEHT by copper-free "click" reaction using 1.5 equivalents of DMAD, DBAD, and DEHAD to each 1.0 equivalent of azide. This cycloaddition reaction was carried out in tetrahydrofuran rather than chloroform due to lack of solubility of PVC-N_3 in chloroform. The conversion of azides to triazole diester groups pendant to the PVC was again conveniently monitored by FTIR spectroscopy. The shrinking of the diagnostic azide band at 2100-2000 cm^{-1}, with concomitant appearance of the ester C=O band at 1725-1635 cm^{-1} and C-N band at 1550-1500 cm^{-1} was indicative of the formation of triazole diesters (**Figure 2.9**). Experimental elemental analysis of 14.7% PVC-DEHT **2.98** (49.08% C, 6.62% H, 6.54% N) does not agree with the calculated elemental analysis (52.42% C, 7.13% H, 5.46% N). This indicates that this particular sample had about 35% of unreacted azide groups, which is also evident by the FTIR. The reaction condition was later optimized to force 100% conversion of PVC-azide into PVC-DEHT. The elemental analysis of 14.7% PVC-DEHT sample in which all the azide groups were completely consumed is not obtained yet.

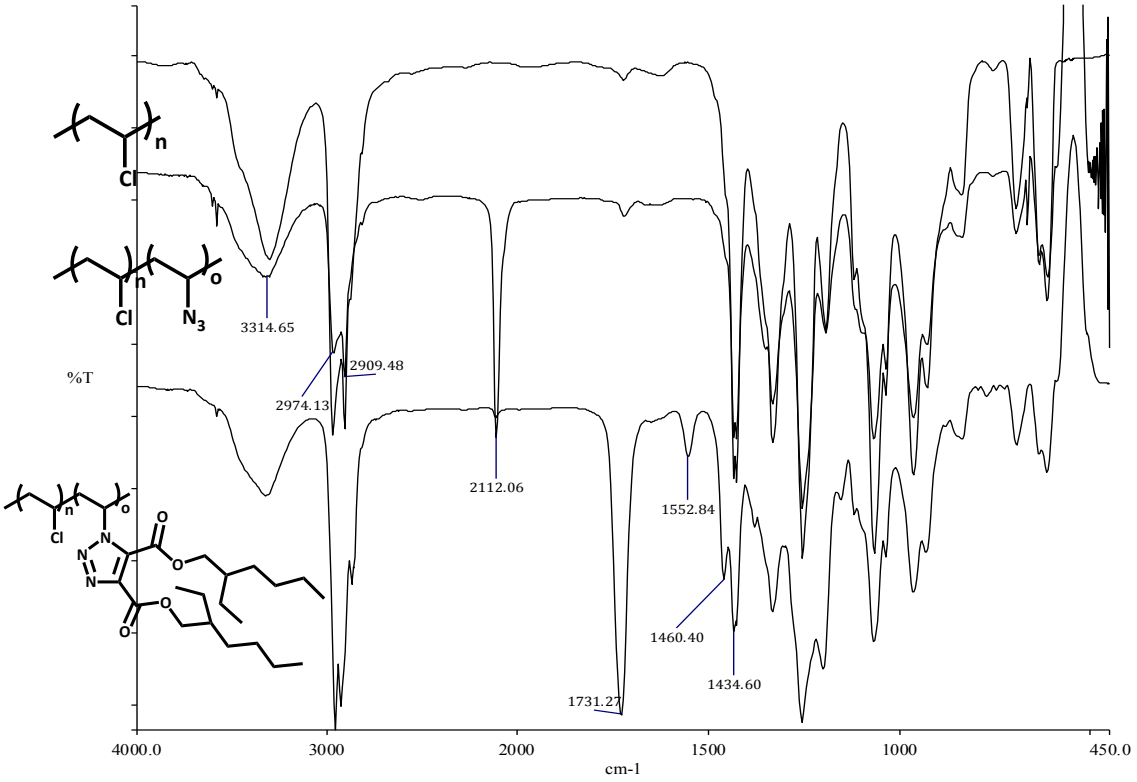


Figure 2.9 FTIR spectra of PVC, 15% PVC-azide and 15% PVC-DEHT

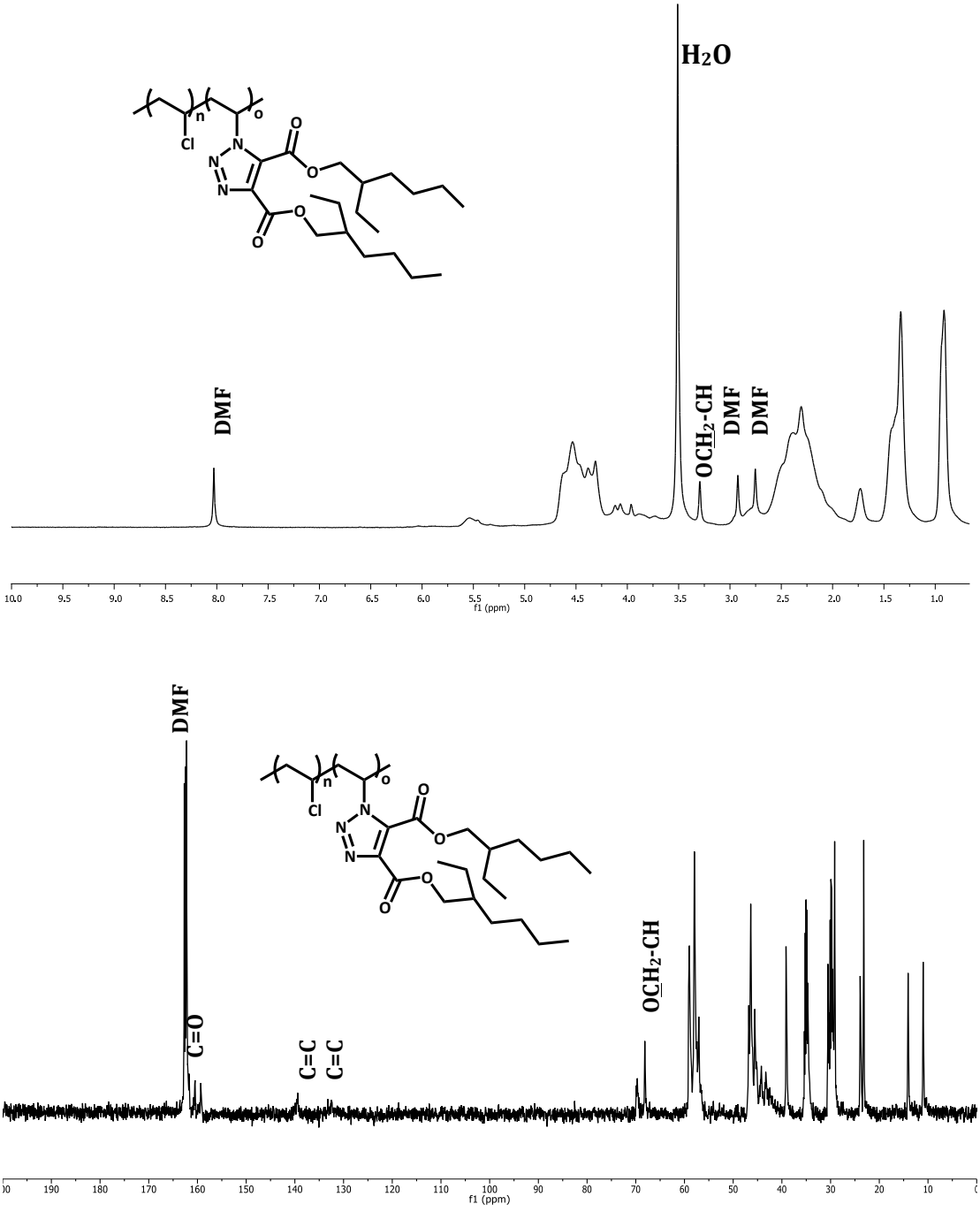


Figure 2.10 ^{1}H NMR and ^{13}C NMR spectra of 15% PVC-DEHT in DMF-d_7

^{1}H NMR in DMF-d_7 shows a characteristic broad peak at δ 3.29 (for the methylene –O**C**$\mathbf{H}_2$-CH of the esters), and ^{13}C NMR (corroborated by DEPT) peaks at δ 160.8 and 159.7 for **C=O**, δ 139.6 and 132.7 for aromatic triazole **C=C**, and δ 69.9 and 68.4 ppm for the –O**C**H_2-CH methylene carbons provide further evidence for the formation of PVC-DEHT (**Figure 2.10**). The attachment to PVC of an aromatic triazole bearing ortho ester substituents occurs under extremely mild conditions. It is noteworthy that FTIR indicates that a small amount of azide remains in the PVC substrate when stirred at room temperature for 22 hours, whereas small alkyl azides were converted entirely to triazoles under the same conditions, presumably due to steric inaccessibility of some azide groups in the polymeric substrate. Subjecting the "click" reaction to sonication did not improve the conversion. However, all the azide groups in 15% PVC-azide were converted into triazoles when the reaction was carried out at 30 °C for seven days in tetrahydrofuran.

Differential Scanning Calorimetry (DSC) was used to measure the glass transition temperatures of the PVC-DEHT samples for plasticization. The measurements were made at the Polymers and Coatings Division at California Polytechnic University in San Luis Obispo as a collaboration with Professor Phil Costanzo's group. The calorimeter was equilibrated at 20 °C, followed by a temperature ramp of 20 °C /min to 150 °C, and then held at isothermal conditions for 5 minutes before ending cycle 1. It was then cooled to 50 °C at a rate of 10 °C/min, and held at isothermal

conditions at 50 °C to end cycle 2. For cycle 3, the calorimeter was heated at the rate of 10 °C/min to 150 °C. Cycles 1 and 2 were carried out to erase the thermal history of the polymer. The glass transition temperatures were determined from cycle 3. As mentioned in chapter 1 of this thesis, the reduction in the glass transition

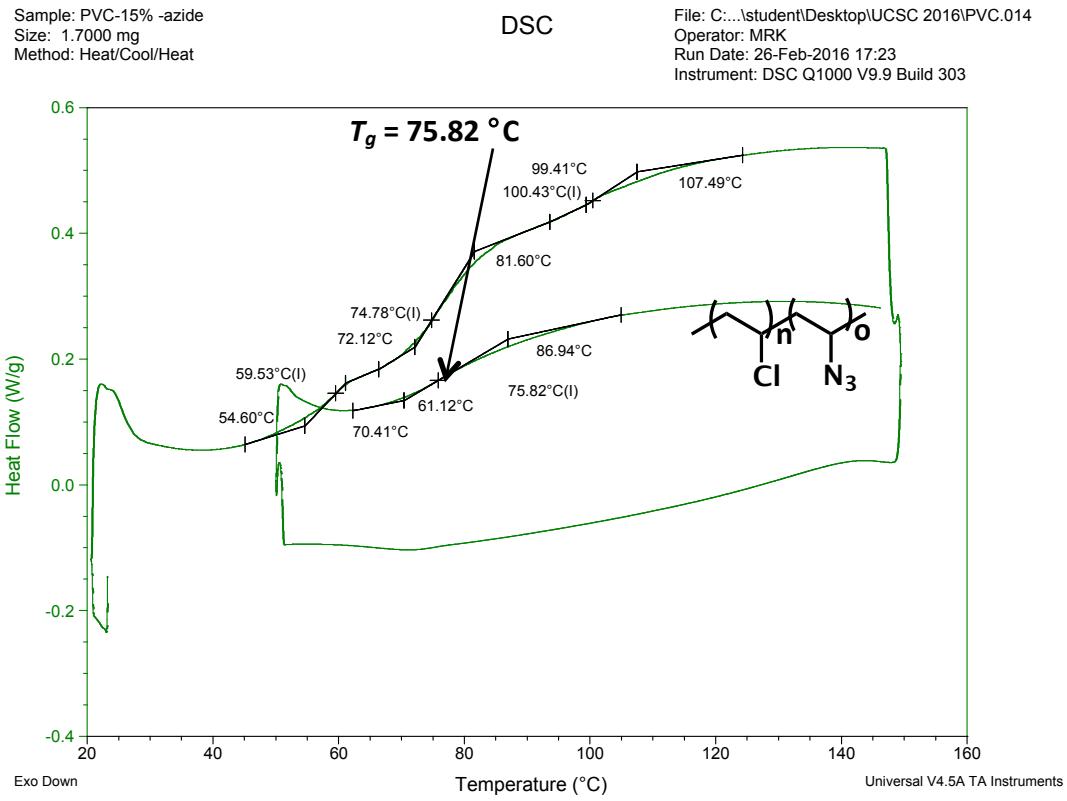


Figure 2.11 DSC analysis of 15% PVC-azide

temperature for our commercial PVC sample (82 °C, measured after purification following Rusen's procedure)[310] is indicative of the degree of plasticization imparted after modification.

Only the internally plasticized PVC with 2-ethylhexyl diesters were measured by DSC. For 5% and 15% displacement of chlorine by azide, the T_g were measured to be 84 °C and 76 °C, respectively (**Figure 2.11**). The T_g, was reduced to 61 °C when the azides underwent cycloaddition with DEHAD to give 5% PVC-DEHT whereas the T_g of 15% PVC-DEHT was 65 °C (**Figure 2.12**). The only moderate reduction in T_g may be due to the restricted rotation of the plasticizer mimic directly attached to the PVC polymer chain.

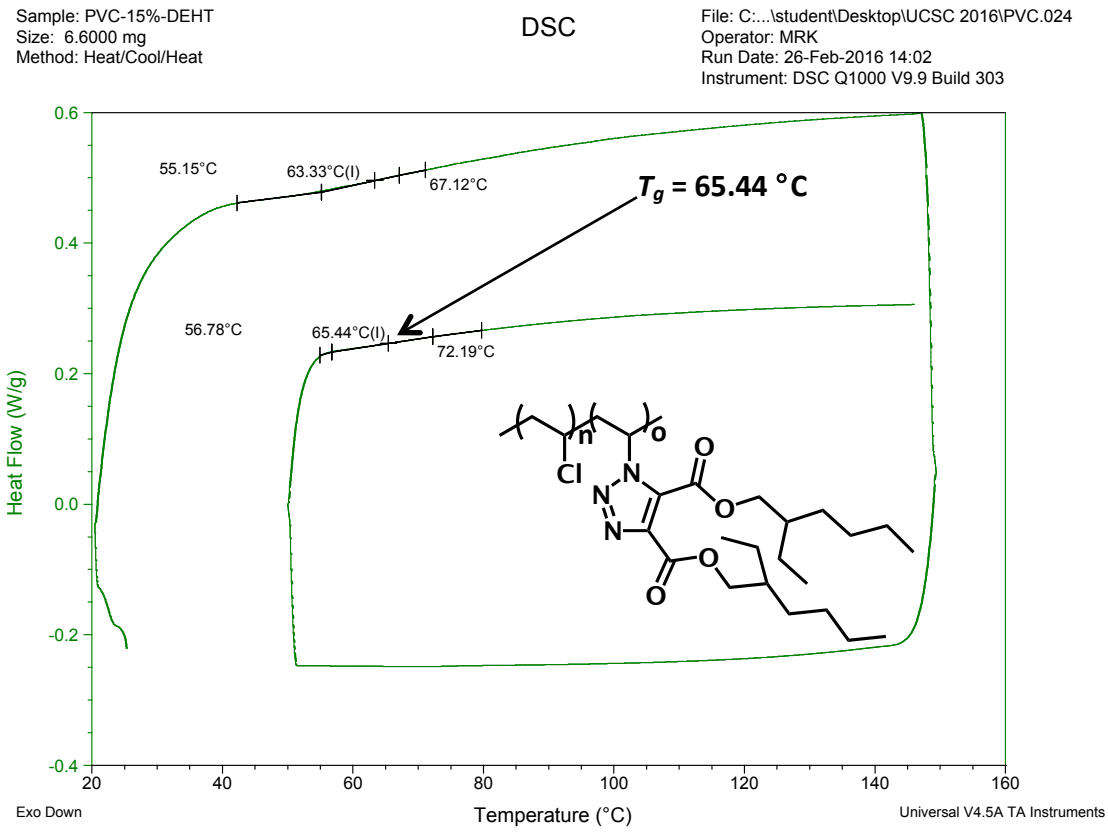


Figure 2.12 DSC analysis of 15% PVC-DEHT

2.8 Conclusion

In summary, PVC was easily modified with pendant triazoles bearing *ortho* ester groups, as covalently bonded mimics of phthalate esters. Three different triazoles: PVC-DEHT, PVC-DBT, and PVC-DMT were prepared using a copper-free thermal "click" reaction with diester-activated internal alkynes, as analogues of traditional phthalate plasticizers DEHP, DBP, and DMP. As the triazole diesters are covalently bound to the PVC chain, no migration of these plasticizer mimics is expected. The reduction in glass transition temperature of PVC, from 82 °C to 61°C for 5% DEHT and to 65 °C at 15% substitution with DEHT, indicates successful plasticization of PVC by covalently linked phthalate mimics.

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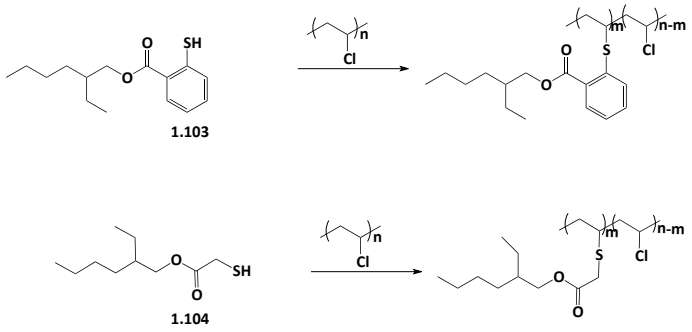
3 Phthalate Plasticizers Covalently Linked to PVC via Copper-Free or Copper-Catalyzed Azide-Alkyne Cycloadditions

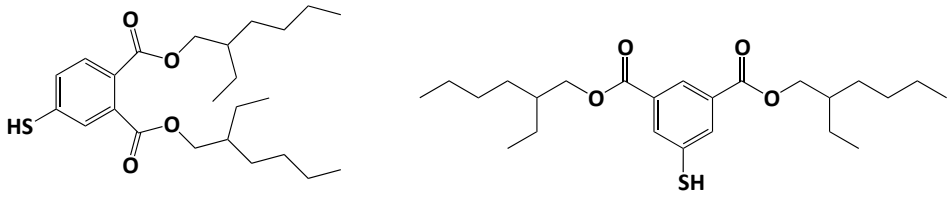
3.1 Introduction

The covalent bonding of plasticizer to PVC is one of the most effective ways to prevent migration. The use of thiol compounds as internal plasticizers was first demonstrated by Michel et al.[198] The covalent bonding of 2-ethylhexyl esters of *o*-mercaptobenzoic acid **1.103** and thioglycolic acid **1.104** to the PVC backbone reduced the glass transition temperature of PVC (**Scheme 3.1**). The plasticizing power of the thioglyolic ester is greater than that of the ester of *o*-mercaptobenzoic acid.



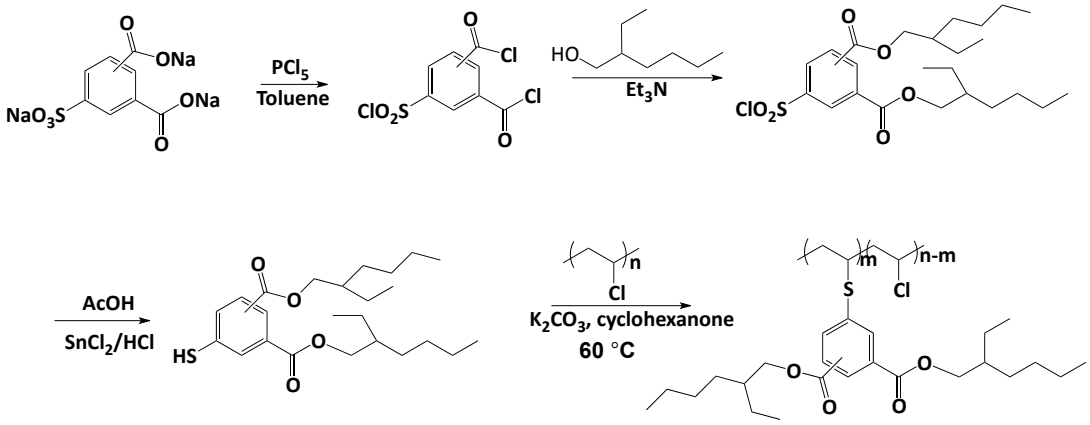
Scheme 3.1 Covalent Bonding of 2-Ethylhexyl Esters of *o*-Mercaptobenzoic Acid and Thioglycolic Acid to PVC

Reinecke et al.[199] demonstrated the internal plasticization of PVC by displacement of some of the chlorine atoms with phthalate-based thiol derivatives. Two thiol derivatized plasticizers: di(2-ethylhexyl) 4-mercaptophthalate (DEHP-SH) **1.105**, and di(2-ethylhexyl) 5-mercapto*iso*phthalate (*iso*DEHP-SH) **1.106** (**Figure 3.1**)



1.105 **1.106**

Figure 3.1 Structures of Di(2-ethylhexyl) 5-mercaptophthalate (DEHP-SH) and Di(2-ethylhexyl) 5-mercaptoisophthalate (*iso*DEHP-SH)



Scheme 3.2 Synthesis and Covalent Bonding of 2-Ethylhexyl esters of Mercaptophthalates to PVC by Reinecke

were synthesized and covalently bonded to PVC via nucleophilic substitution of chlorine atoms (**Scheme 3.2**). Under the reaction conditions, the highest degree of functionalization achieved was to be 23 mol% for DEHP-SH and 31 mol% for *iso*DEHP-SH. The evolution of the glass transition temperatures of PVC-DEHP-SH and PVC-*iso*DEHP-SH was measured as a function of the degree of modification, and compared with the equivalent mixtures of PVC and DEHP. The observed T_gs for 23 mol% PVC-DEHP-SH and 31 mol% PVC-*iso*DEHP-SH are approximately 20 °C and 25 °C. The glass transition temperature of unplasticized PVC (83 °C) is significantly

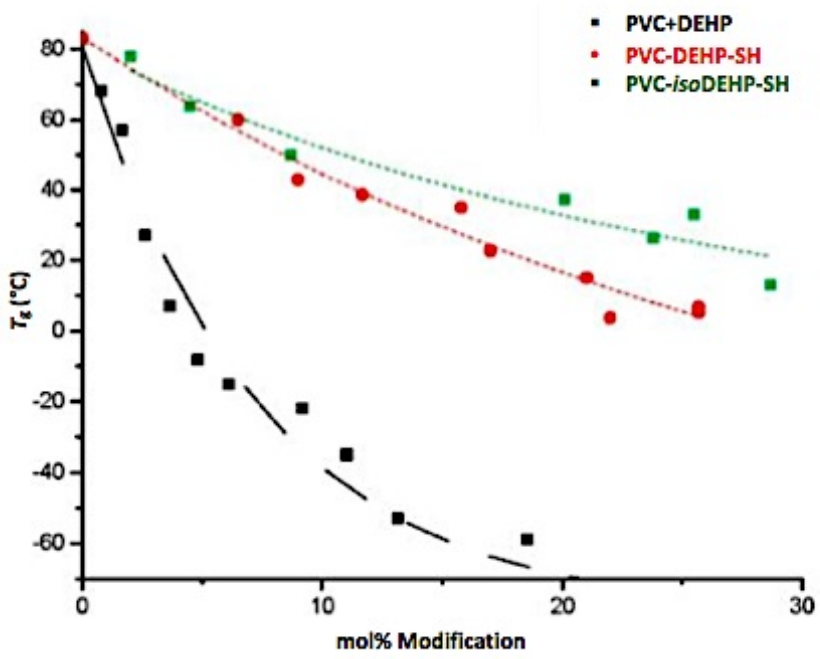


Figure 3.2 Evolution of Glass Transition Temperature with Increasing Content of DEHP, DEHP-SH and *iso*DEHP-SH (adopted from ref. 2)

reduced by covalent bonding of these phthalate derivatives. However, the T_gs of the plasticized PVC are higher than the conventional PVC-DEHP system (-20 °C for 10 mol% loading) (**Figure 3.2**). Migration experiments indicate no loss of plasticizer from the PVC-DEHP-SH and PVC-*iso*DEHP-SH systems, compared to complete loss of DEHP from the PVC-DEHP system after less than 3 h of extraction by *n*-heptane. Although, PVC-DEHP-SH and PVC-*iso*DEHP-SH shows good plasticization, zero migration and no elimination, the viability of using this approach is restricted by the cost of preparing the thiol phthalate esters (**Scheme 3.2**), and the requirement of high loading (75 wt% or 30 mol%) of DEHP-SH to lower the T_g to 0 °C. Another potential drawback is the oxidation fate of the modified PVC due to the presence of sulfide groups.

3.2 Covalent Modification of PVC with Phthalate Plasticizers

As discussed in chapter 2, as part of this thesis work, triazole mimic **2.71** of the common phthalate plasticizer DEHP **2.72** was covalently linked to PVC using Huisgen thermal azide-alkyne cycloaddition (**Figure 3.3**). The glass transition temperatures for PVC-DEHT was determined by differential scanning calorimetry. The T_gs for 5% and 15% DEHT-PVC were found to be 61 °C and 65 °C respectively. These values were lower than the glass transition temperature of pure PVC (83 °C), indicating successful plasticization by this phthalate mimic. However, the glass transition

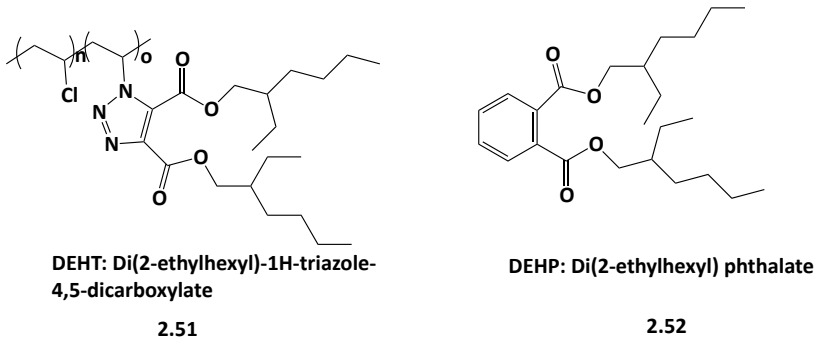
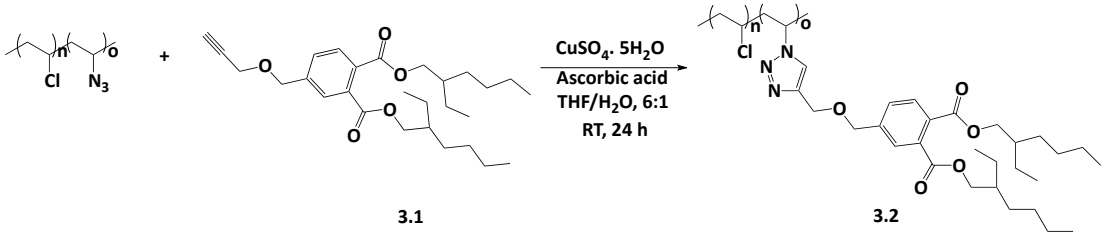


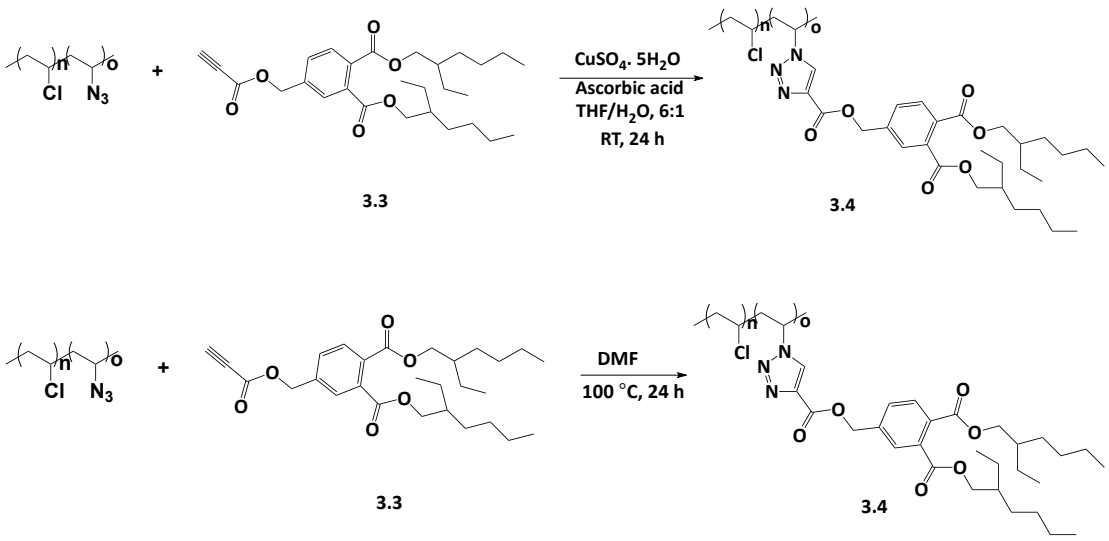
Figure 3.3 DEHT: Triazole Analogue of the Most Common Phthalate Plasticizer DEHP

temperature of the 15% DEHT modified PVC is still considered high. It may be that the only moderate reduction in T_g is due to the restricted rotation of the plasticizer mimic directly attached to the PVC polymer chain. A flexible linker between the triazole ring and the plasticizer should provide additional degrees of rotation. For this purpose, a phthalate plasticizer bearing a tether ending with a terminal alkyne, di(2-ethylhexyl) 4-((prop-2-yn-1-yloxy)methyl)phthalate (DEHP-ether) **3.1** was developed, and was covalently bonded to PVC **3.2** using copper-catalyzed click chemistry (**Scheme 3.3**).



Scheme 3.3 Attachment of DEHP-ether to Form PVC-DEHP-ether Triazole

A similar phthalate plasticizer with an ester linkage, di(2-ethylhexyl) 4-((propioloyloxy)methyl)phthalate (DEHP-ester) **3.3**, was synthesized to covalently link to PVC **3.4**. Two complimentary reaction conditions were employed: copper catalyzed cycloaddition and thermal cycloaddition in dimethylformamide (**Scheme 3.4**).

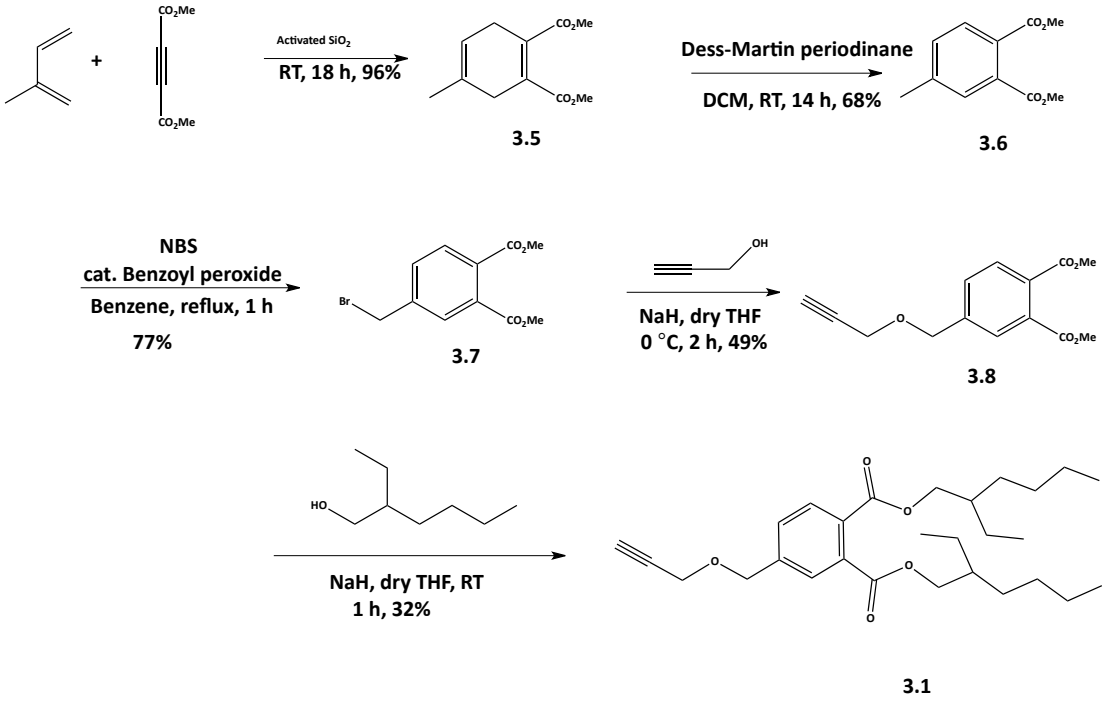


Scheme 3.4 Reaction of DEHP-ester to Obtain PVC-DEHP-ester Triazole

3.3 Synthesis of Phthalate-based Alkynes

For the preparation of DEHP-ether **3.1,** three synthetic routes were explored. The first method involved a Diels-Alder reaction of isoprene and dimethylacetylene dicarboxylate in the presence of activated anhydrous silica gel[311] to give cyclohexadiene dicarboxylate **3.5** in 96% yield (**Scheme 3.5)**. Isoprene is a low boiling liquid (34 °C): a Findensor™ was used to reduce the evaporation of isoprene at room

temperature. Oxidation of **3.5** using Dess-Martin periodinane in dichloromethane at room temperature gave dimethyl-4-methylphthalate **3.6** in 68% yield. The benzylic bromination of **3.6** using *N*-bromosuccinimide (NBS) and a catalytic amount of

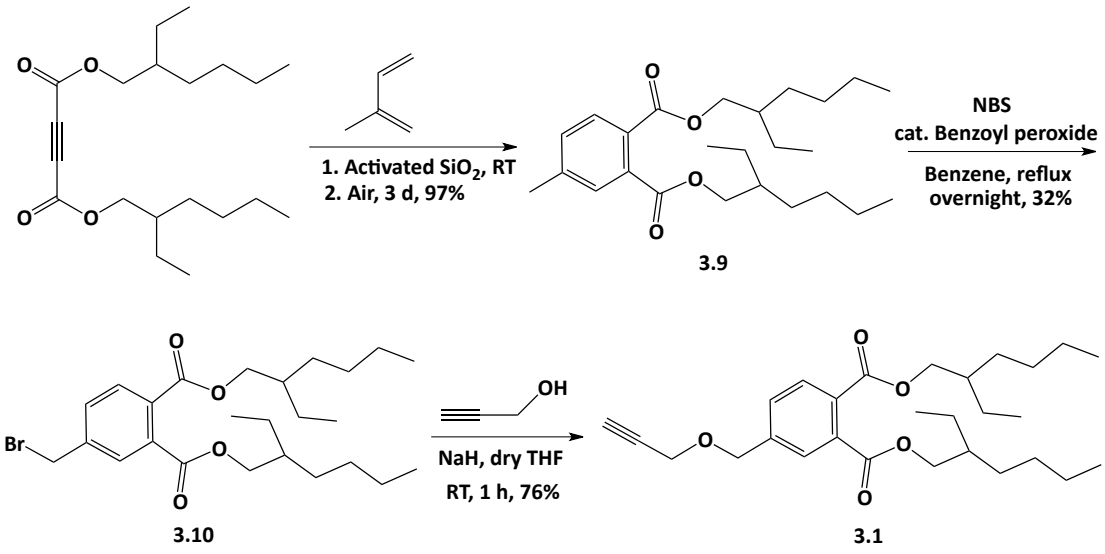


Scheme 3.5 First Synthetic Route to DEHP-ether 3.1

benzoyl peroxide in refluxing benzene for 1 h afforded dimethyl-4-bromomethylphthalate **3.7** in 77% yield. Williamson ether synthesis of benzyl bromide **3.7** with propargyl alcohol in the presence of sodium hydride gave the respective ether **3.8** in 49% yield. Transesterification of dimethylphthalate **3.8** with

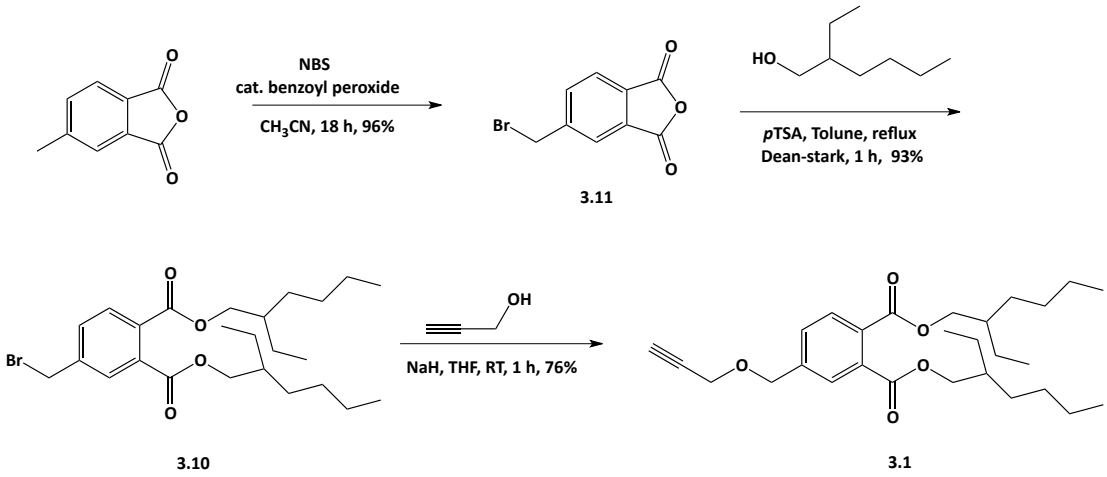
deprotonated 2-ethylhexanol gave the alkyne terminated DEHP derivative **3.1** in 32% yield.

In the second approach, a Diels-Alder reaction of di(2-ethylhexyl) acetylene dicarboxylate and isoprene was carried out in the presence of activated silica gel[311] to give di(2-ethylhexyl) 4-methylphthalate **3.9** (**Scheme 3.6**) in 97% yield. The benzylic bromination of **3.9** using NBS and catalytic benzoyl peroxide in refluxing benzene gave di(2-ethylhexyl) 4-(bromomethyl)phthalate **3.10** in 32% yield. The S_N2 reaction of **3.10** with propargyl alcohol using sodium hydride as a base afforded ether **3.1** in 76% yield.



Scheme 3.6 Second Synthetic Route to DEHP-ether 3.1

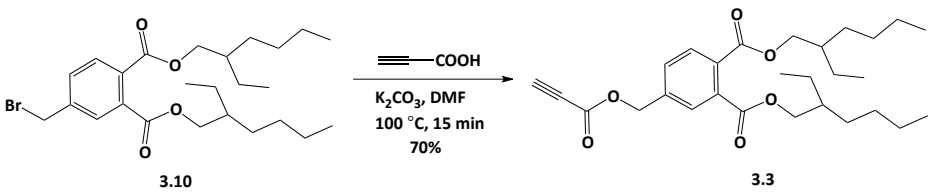
The third and the most facile method to synthesize propargyl ether **3.1** started with commercially available 4-methylphthalic anhydride (**Scheme 3.7**). Bromination using NBS and catalytic benzoyl peroxide in refluxing acetonitrile gave the bromo product **3.11** in 96% yield. The esterification of **3.11** with 2-ethylhexanol using catalytic *p*-toluenesulfonic acid in toluene gave a 93% yield followed by etherification with propargyl alcohol in the presence of sodium hydride gave **3.1** in 76% yield.



Scheme 3.7 Third and Most Efficient Synthetic Route to DEHP-ether 3.1

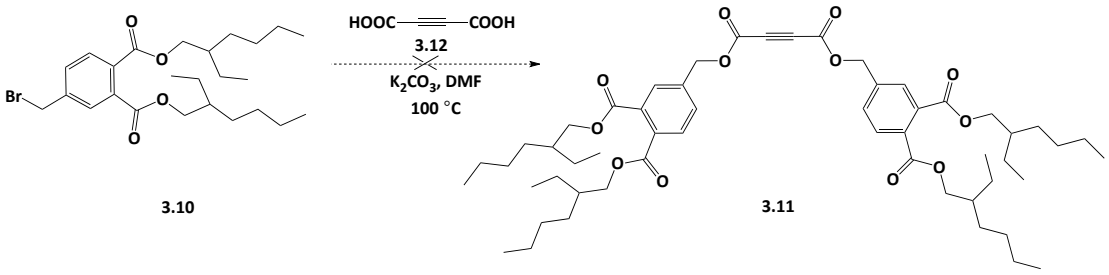
Di(2-ethylhexyl) 4-(bromomethyl)phthalate **3.10** served as a precursor to a second phthalate derivative: DEHP-ester **3.3**. For the preparation of DEHP-ester **3.3**, the bromomethyl phthalate **3.10** was treated with propiolic acid using potassium

carbonate in dimethylformamide for 15 minutes at 100 °C. DEHP-ester was obtained in 70% yield after purification by silica gel column chromatography (**Scheme 3.8**).

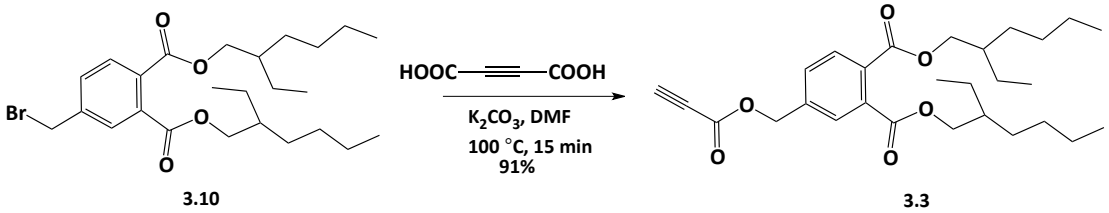


Scheme 3.8 Synthesis of Phthalate Derivative DEHP-ester 3.3

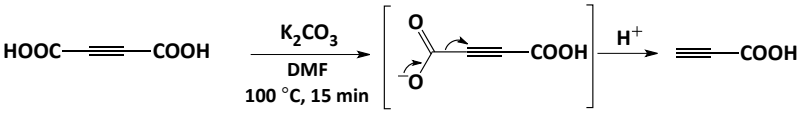
An attempt to prepare DEHP-diester **3.11** by the reaction of **3.10** with acetylenedicarboxylic acid **3.12** using potassium carbonate was not successful in refluxing acetone nor in dimethylformamide at 100 °C (**Scheme 3.9**). Instead, the reaction produced DEHP-ester **3.3** due to monodecarboxylation of acetylenedicarboxylic acid in the presence of potassium carbonate in DMF (**Scheme 3.10**).



Scheme 3.9 Attempted Synthesis of Phthalate Derivative DEHP-diester 3.11



Mechanism:



Scheme 3.10 Unexpected Synthesis of DEHP-ester Via Base-mediated Decarboxylation of Acetylenedicarboxylic acid

The formation of alkyne phthalate derivatives ether **3.1** and ester **3.3** was monitored by thin layer chromatography, and was characterized by ^{1}H NMR, ^{13}C NMR, DEPT, and FTIR. The peak at 2120 cm^{-1} in the FTIR spectra of DEHP-ether and DEHP-ester is characteristic of a terminal alkyne (**Figure 3.4** and **Figure 3.5**).

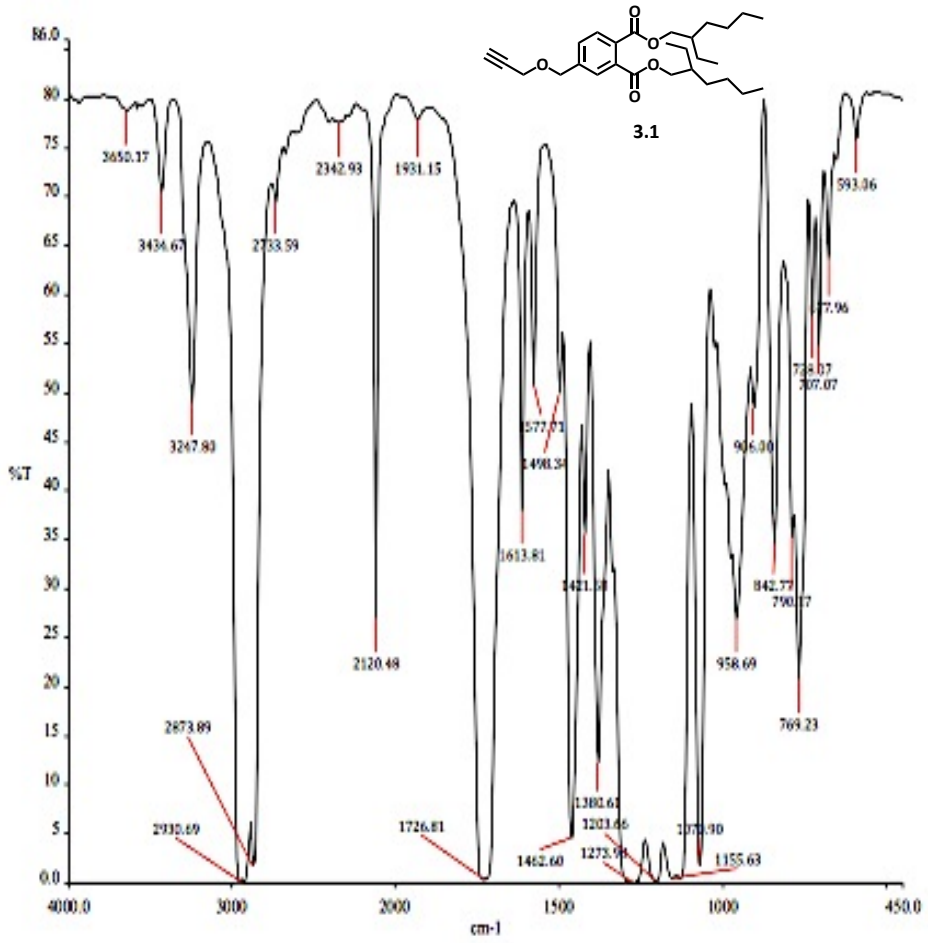


Figure 3.4 FTIR Spectrum of DEHP-Ether 3.1

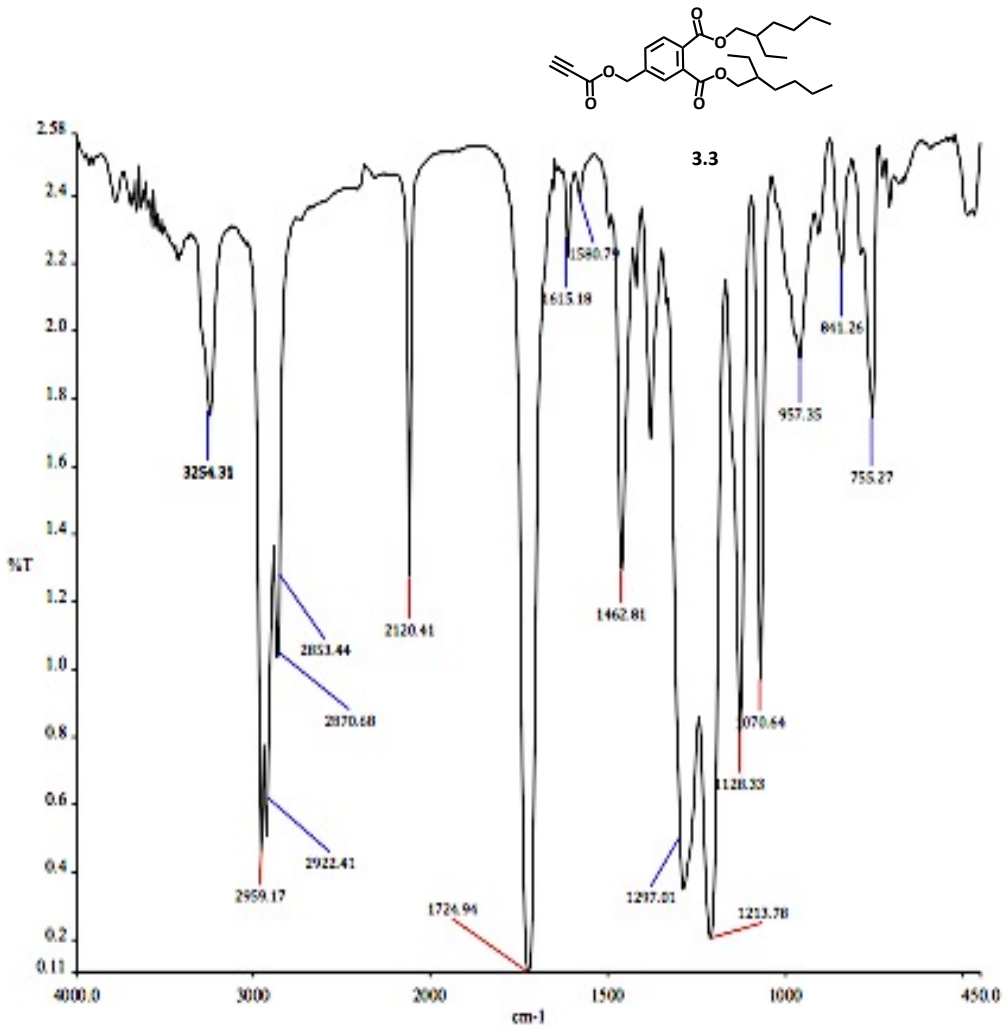
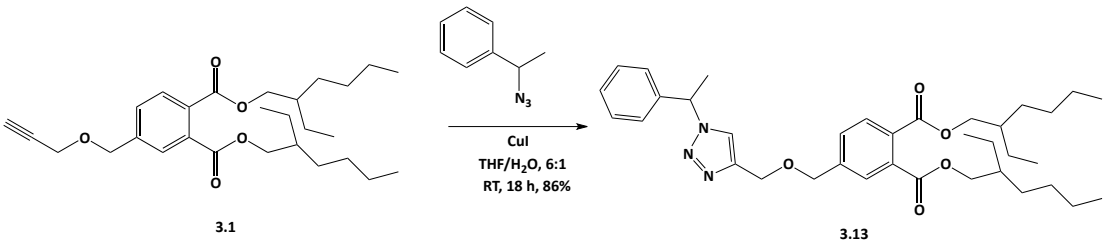


Figure 3.5 FTIR Spectrum of DEHP-Ester 3.3

3.4 Small Molecule Models

Synthetic modification of polymeric PVC results in polydisperse products, which are not amenable to facile characterization by ^{1}H NMR, ^{13}C NMR, or mass spectroscopy. Therefore, (1-azidoethyl) benzene was investigated as a model compound to confirm the viability of azide/alkyne cycloaddition reactions with the newly synthesized phthalate derivatives. The synthesis of (1-azidoethyl) benzene is described in chapter 2. The cycloaddition of DEHP-ether **3.1** with benzyl azide using

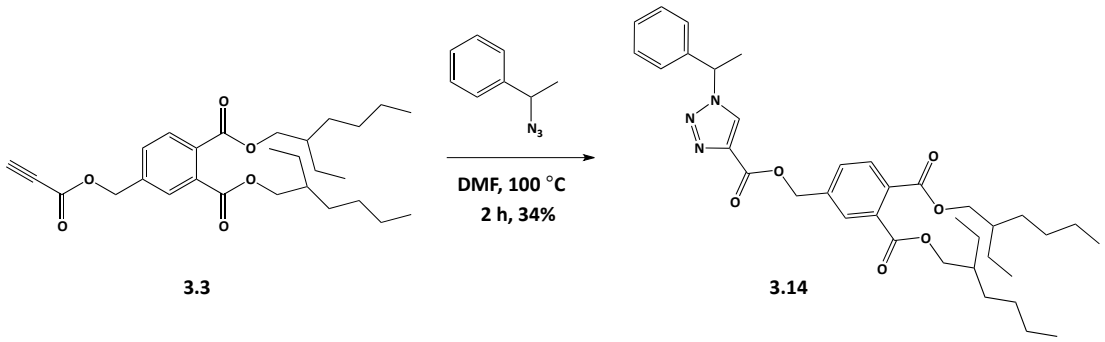


3.1 3.13

Scheme 3.11 Copper Catalyzed Cycloaddition of DEHP-Ether with (1-Azidoethyl) Benzene

copper iodide in a 6:1 mixture of tetrahydrofuran and water gave triazole **3.13** in 86% yield (**Scheme 3.11**). The disappearance of the terminal alkyne peak at 2120 cm^{-1} and the azide peak at 2116 cm^{-1} followed by the appearance of a peak at 1547 cm^{-1} is indicative of the formation of the triazole. In the ^{1}H NMR spectrum, the benzylic proton of (1-azidoethyl) benzene shifted from δ 4.58 to δ 5.81 ppm in the triazole. Using the electron-poor ester substituted alkyne, DEHP-ester **3.3**

underwent thermal 1,3-dipolar cycloaddition with (1-azidoethyl) in benzene at 100 °C for 2 hours to give triazole **3.14** in 34% yield (**Scheme 3.12**).

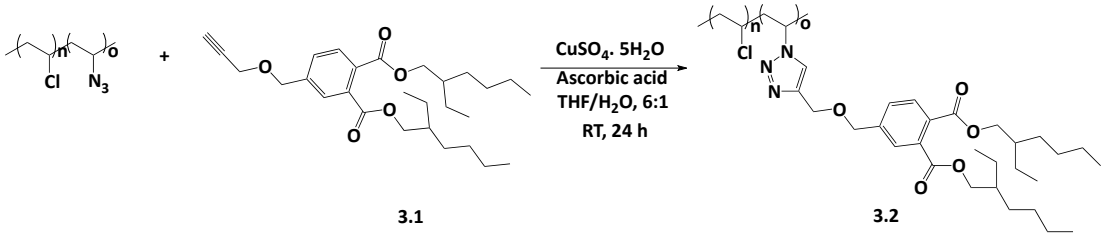


Scheme 3.12 Huisgen Thermal Cycloaddition of DEHP-Ester with (1-Azidoethyl) Benzene

3.5 Modification of PVC

The allylic azide model, benzylic azide underwent copper catalyzed cycloadditions to DEHP-ether **3.1** at room temperature to form 1,2,3-triazole. The cycloaddition of benzylic azide to DEHP-ester **3.3** was successfully achieved under thermal conditions. These conditions were applied to modify PVC. Azide functional groups were incorporated into PVC by nucleophilic substitution of some of the chlorines as described in chapter 2. PVC with 5% or 15% substituted azide was used in the cycloaddition reactions with phthalate derivatives. The degree of azidation was determined by elemental analysis. The cycloaddititon of PVC-azide with DEHP-ether **3.1** using copper iodide in 6:1 mixture of tetrahydrofuran and water gave a blue

colored solid after precipitation in methanol. Therefore, copper iodide was replaced by copper sulfate/ascorbic acid system to catalyze the cycloaddition of PVC-azide with DEHP-ether **3.1**. The reaction went to completion in 24 hours at room temperature, resulting in a white solid after precipitation in methanol (**Scheme 3.13**).



Scheme 3.13 Copper Catalyzed Cycloaddition of PVC-Azide with DEHP-ether 3.1

The progress of the reaction was monitored by FTIR spectroscopy. The disappearance of the azide peak at 2112 cm^{-1} followed by the appearance of the carbonyl peak at 1724 cm^{-1} confirmed the formation of PVC-DEHP-ether triazole (**Figure 3.6**).

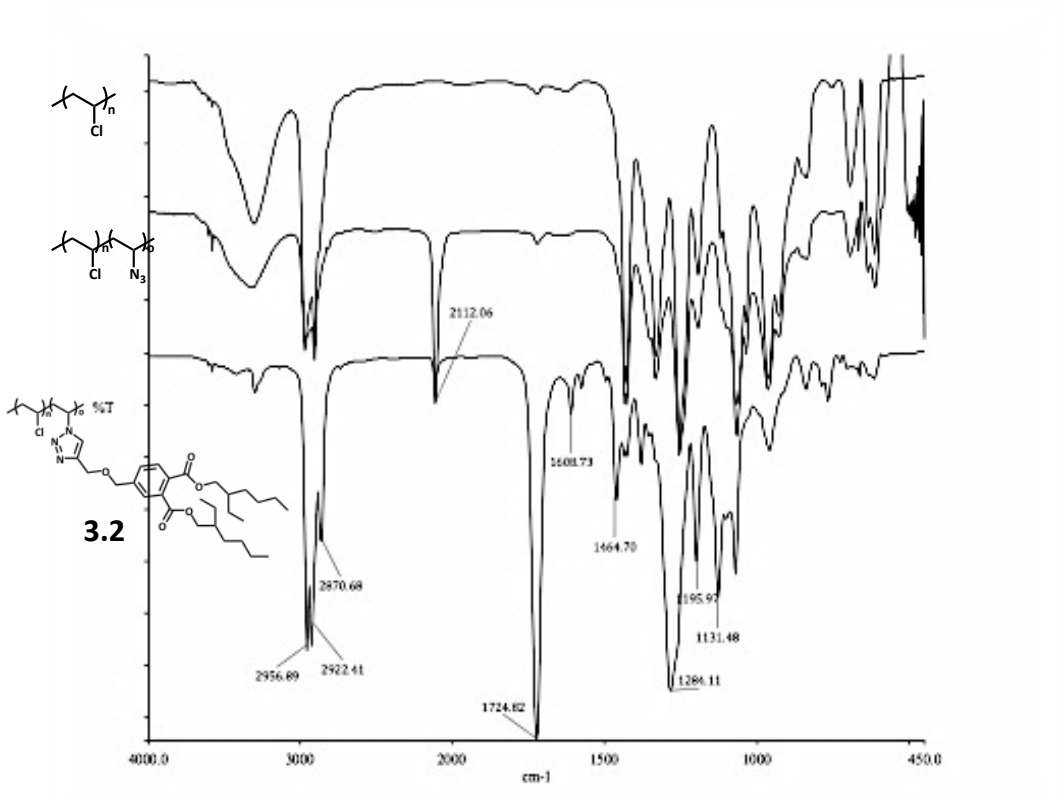
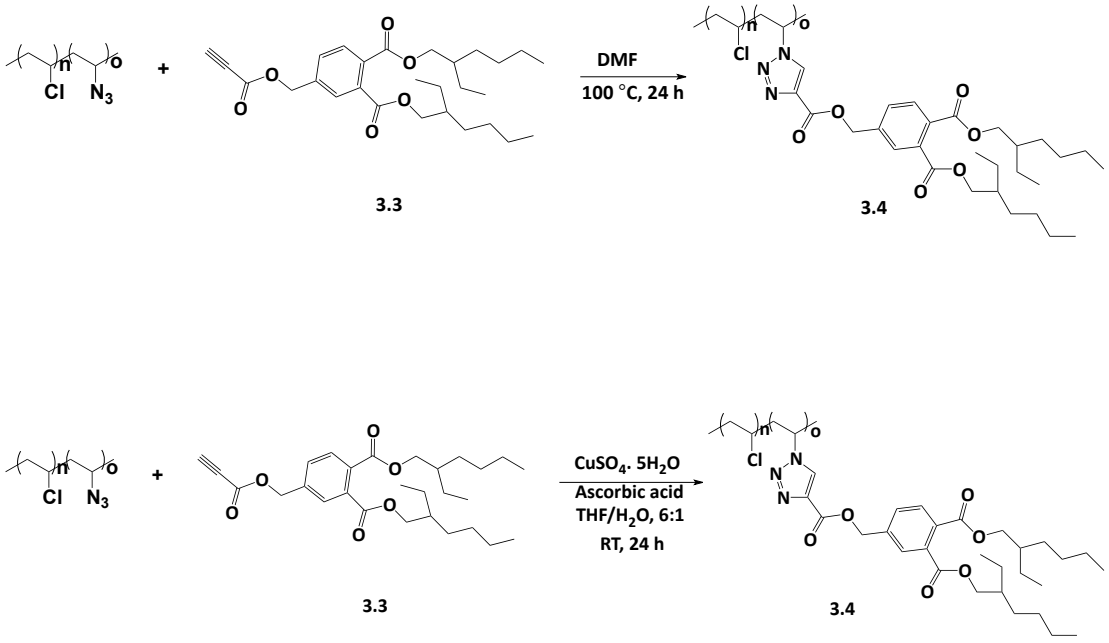


Figure 3.6 FTIR spectra: PVC, 15% PVC-Azide, and 15% PVC-DEHP-ether Triazole

The cycloaddition reaction of DEHP-ester **3.3** with (1-azidoethyl) benzene (**Scheme 3.14**) in dimethylformamide at 100 °C went to completion in 2 h. However, under these same thermal conditions, the reaction of 15% PVC-azide required 24 h, provided an excess of alkyne (6 mol equivalent per azide) was used. Alternatively, 15% PVC-DEHP-ester triazole **3.4** was obtained in 24 h at room temperature when copper sulfate/ascorbic acid was used with 1.5 equivalent of alkyne **3.3** (**Scheme 3.14**).



Scheme 3.14 Thermal Cycloaddition and Copper-Catalyed Cycloaddition of 5% and 15% PVC-Azide with DEHP-ester 3.3

The conversion of azides into triazoles pendant to the PVC was conveniently monitored by FTIR spectroscopy. The shrinking of the diagnostic azide band at 2100-2000 cm^{-1}, with concomitant appearance of the ester C=O band at 1725-1635 cm^{-1} and C-N band at 1550-1500 cm^{-1} is indicative of the formation of the triazole ester **3.4** (**Figures 3.7**).

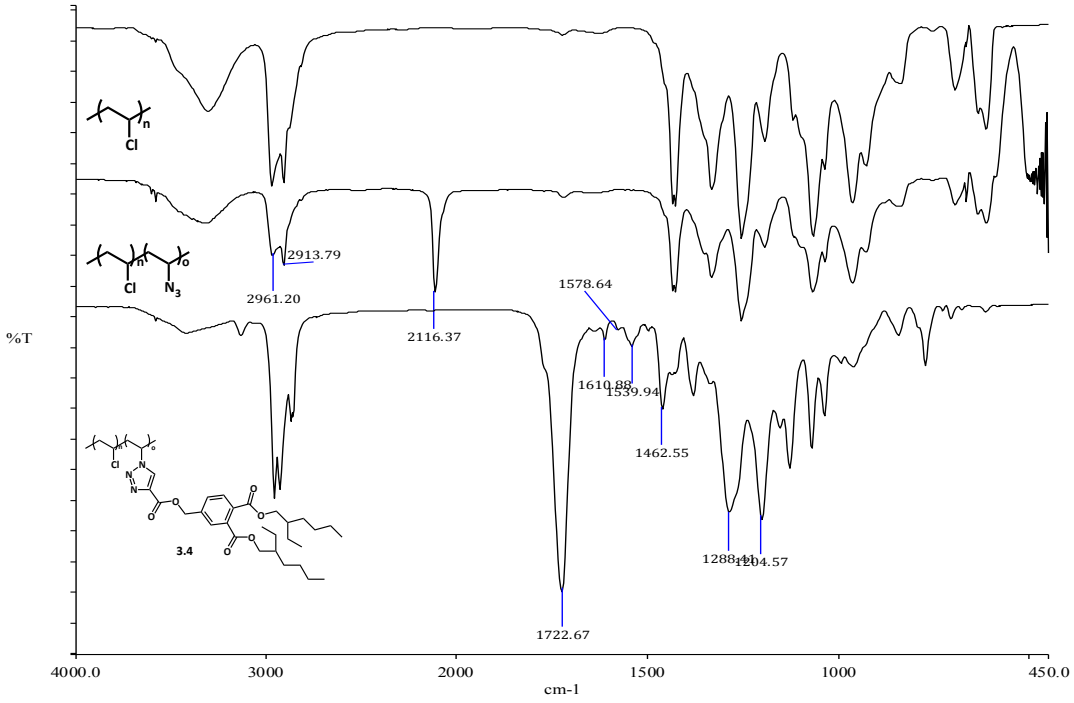


Figure 3.7 FTIR spectra: PVC, 15% PVC-Azide, and 15% PVC-DEHP-ester Triazole

3.6 Glass Transition Temperatures

The glass transition temperatures of unmodified PVC, 5% and 15% PVC-azide and the covalently plasticized PVC samples were determined by using Differential Scanning Calorimetry (DSC) and compared with non-covalent mixtures of 5% PVC-DEHP and 15% PVC-DEHP. To obtain 5% PVC-DEHP and 15% PVC-DEHP, a solution of PVC (purified by the method of Rusen)[310] with 5 mol% DEHP or 15 mol% DEHP was stirred in tetrahydrofuran at room temperature for 24 h, followed by evaporation of solvent *in vacuo*. The mol% of DEHP was calculated per mole of vinyl chloride monomer using a molecular weight of 63 g/mol. The 5 mol% and 15 mol% are equivalent to 24 wt% and 48 wt% of DEHP in PVC.

The extent of T_g reduction in the presence of a plasticizer is used as a parameter to assess the plasticizing efficiency. These measurements were made at the Department of Chemistry and Biochemistry at California Polytechnic State University, San Luis Obispo, as a collaboration with Professor Phil Costanzo's group. DSC is used to measure temperatures and heat flow of thermal transitions in polymers. The calorimeter was equilibrated at 20 °C with a temperature ramp of 20 °C/min to 150 °C and then held at isothermal conditions for 5 minutes before ending cycle 1. It was then cooled to 50 °C with a rate of 10 °C/min and held under isothermal conditions to end cycle 2. For cycle 3, the sample was heated at a rate of 10 °C/min to 150 °C. The first cycle of heating is usually carried out to erase the pre-existing

thermal history of a polymer. Mechanical and thermal properties of a polymer are affected by a number of variables such as chemical composition and molecular weight, as well as thermally induced phenomena such as crystallization and physical aging, which contribute to the microstructure.[312] The covalent modifications of PVC with DEHT, DEHP-ether triazole, DEHP-ester triazole, and with non-covalent DEHP were carried out under different reaction conditions, which would impart different thermal histories to the polymer. In order to compare the plasticizing efficiency of DEHT, DEHP-ether triazole, DEHP-ester triazole, and non-covalently mixed DEHP, it is necessary to analyze the glass transition temperatures of the modified PVC samples under the same conditions. This is achieved by heating and rapid cooling of the PVC samples during cycle 1 and cycle 2 of the DSC analysis.

As shown in **Table 3.1**, for most samples, two T_g values were obtained in cycle 1, as the samples had different thermal histories. Only one T_g value was obtained in cycle 3 following the erasure of the previous thermal histories of the polymers. Moreover, multiple T_gs in cycle 1 and the fact that T_gs in cycle 1 and cycle 3 do not always agree are attributed in part to the polydispersity of PVC samples. The polydispersity index of the commercial PVC used in these experiments was 1.95, which indicates the presence of polymers with different chain lengths. Low molecular weight PVC chains might undergo azidation faster than the high molecular weight polymers and different triads of stereomers should show different

reactivities within the PVC samples, giving rise to multiple T_gs.

Sample	T_g (°C)		
	Cycle 1		Cycle 3
	T_{g1}	T_{g2}	T_g
PVC (purified following Rusen's procedure)[310]	83		82
5% PVC-Azide	84		84
15% PVC-Azide	60	75	75
5% PVC-DEHT **2.51**	61		61
15% PVC-DEHT **2.51**	64		65
5% PVC-DEHP-ether triazole **3.2**	45	68	69
15% PVC-DEHP-ether triazole **3.2**	58		55
5% PVC-DEHP-ester triazole **3.4** (copper catalyzed)	58	71	69
15% PVC-DEHP-ester triazole **3.4** (copper catalyzed)	59	83	60
5% PVC-DEHP-ester-DMF triazole **3.4** (thermal)	67	79	77
15% PVC-DEHP-ester-DMF triazole **3.4** (thermal)	31	61	60
5% PVC-DEHP (non-covalent mixture)	52	67	60
15% PVC-DEHP (non-covalent mixture)	49	72	67

Table 3.1 Glass Transition Temperatures from Cycle 1 and Cycle 3 of DSC

An examination of the DSC thermograms of the internally covalently plasticized PVC samples indicates that the T_g value decrease with increasing substitution of PVC-Cl with azide and subsequently with DEHP derivatives. Although only three data points were taken for each thermogram, the trend clearly indicates plasticizing behavior of these phthalate derivatives. The nucleophilic substitution of 15% of the chlorine atoms of PVC with azide decreased the glass transition temperature of the polymer from 82 °C to 75 °C. The T_gs were further reduced to 69 °C and 55 °C for 5% PVC-DEHP-ether triazole and 15% PVC-DEHP-ether triazole, respectively (**Figure 3.8**). For 5% and 15% PVC-ester triazole, the T_gs were observed at 69 °C and 60 °C, respectively (**Figure 3.9**). In case of PVC-DEHT **2.51**, the glass transition temperature increased from 61 °C for 5% PVC-DEHT to 65 °C for 15% PVC-DEHT. It is possible that DEHT is imparting some crystallinity to PVC because of the close proximity of the aromatic triazole ring to the polymer chain.

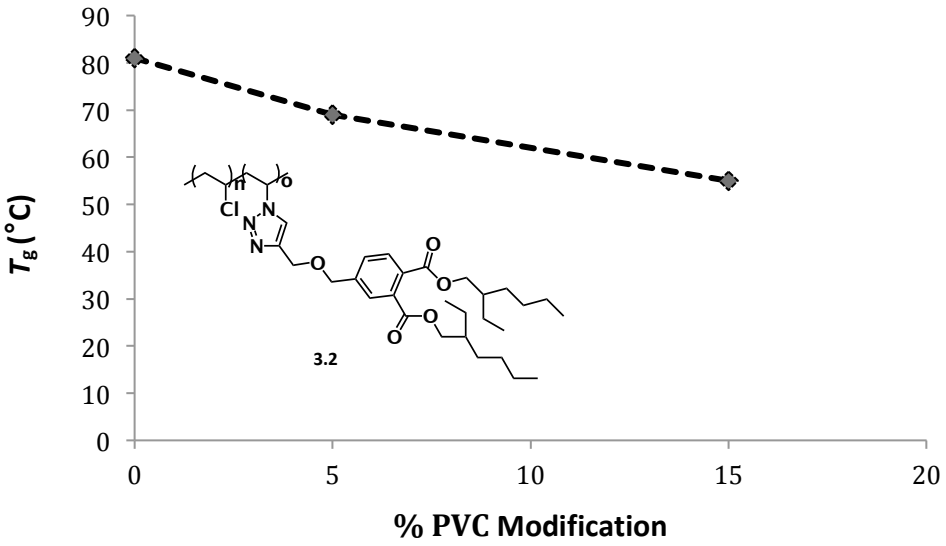


Figure 3.8 Variation of Glass Transition Temperature of PVC-DEHP-ether Triazole 3.2 with Increasing Plasticizer Content

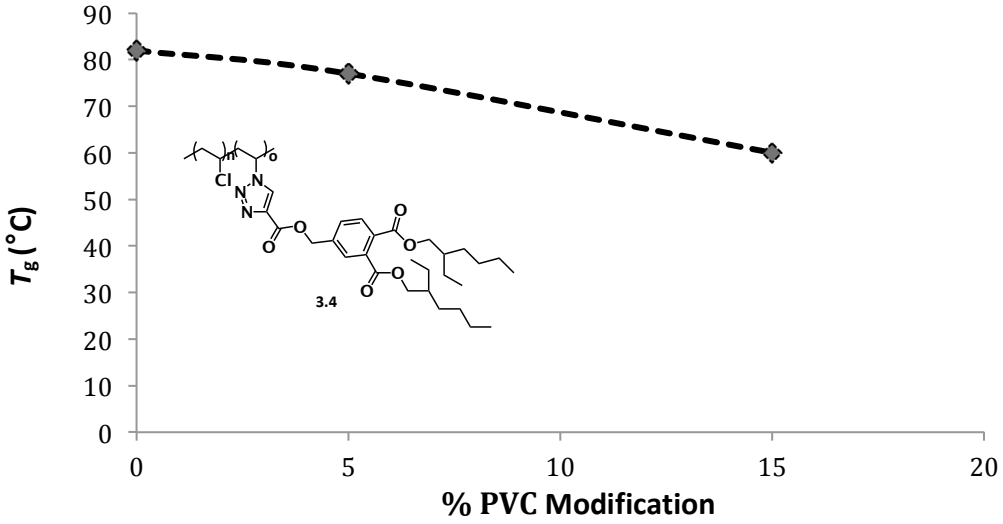


Figure 3.9 Variation of Glass Transition Temperature of PVC-DEHP-ester Triazole 3.4 with Increasing Plasticizer Content

The corresponding T_gs for non-covalent mixtures with 5 mol% and 15 mol% PVC-DEHP were 60 °C and 67 °C, respectively. The glass transition temperature values for PVC-DEHP determined in our hands do not agree with Reinecke's results: they report approximately 10 °C and -50 °C for 5 mol% and 15 mol% of DEHP (**Figure 3.2**). This could be because the commercial sources of PVC were different. Moreover, Reinecke obtained non-covalent PVC-DEHP mixtures commercially, and did not provide details on their formulation. The polydisperse PVC samples used in our study are representative of the type of PVC generally used in commercial applications. The T_gs for 5 mol% and 15 mol% PVC-DEHP obtained by our DSC measurements are the opposite of what was expected. T_g should be decreasing with increasing content of DEHP. It could be that the plasticizer was not completely incorporated in the PVC. In our samples, PVC and DEHP were mixed at room temperature. In conventional PVC formulations, PVC and plasticizer are heated separately to 70 – 80 °C before mixing, and then blended in a specialized heating mixer until the contents reach a temperature of 125 – 130 °C to ensure the uniform distribution of plasticizer in PVC. The blend is then cooled down to 40 °C. At this point the blend achieves good flowability. [313]

The 15% DEHP-ether triazole exhibited better plasticizing efficiency compared to 15% DEHP-ester triazole. This may be due to the larger conformer flexibility of ethers compared to esters. Moreover, the observed glass transition temperatures

for 15% PVC-DEHP-ester triazole obtained by copper catalyzed click reaction and thermal cycloaddition were same, indicating that the T_g of the modified PVC was independent of reaction conditions used to prepare it. Reduction in the T_g of PVC by attaching DEHP-ether triazole or DEHP-ester triazole was in agreement with Reinecke's thiol plasticizers (DEHP-SH, **1.105** and *iso*DEHP-SH, **1.106**). The T_gs for 15% PVC-DEHP-SH and 15% PVC-*iso*DEHP-SH are approximately 50 °C and 60 °C. As observed in their study, a substitution of 20% or higher was required to obtain further reductions in the glass transition temperature of PVC. This might be true in our study, where a displacement of 20% or higher of chlorine atoms with azides, followed by cycloadditions with DEHT, DEHP-ether, and DEHP-ester would be expected to give further reductions in the glass transition temperatures of PVC.

As previously described by Millan[314] certain regions of PVC undergo nucleophilic substitution more readily than other. These regions are associated with the tacticity-dependent microstructure of PVC. PVC tacticity exhibits three basic structures: (a) isotactic, in which all chlorine atoms are on the same side of the PVC chain (b) syndiotactic, in which all chlorine atoms are regularly distributed on both sides of the chain in alternative arrangement, and (c) atactic, in which the chlorine atoms are randomly and irregularly distributed. The stereochemistry of the repeating units at the end of the isotactic or syndiotactic sequences further defines the microstructure

of PVC. A system of two bonded monomers in a polymer is called a diad. Two identically oriented units make a meso diad (m), whereas two units oriented in opposition make a racemo diad (r). An isotactic tetrad (mmr) is made up of two adjacent meso diads and a racemo diad. A syndiotactic tetrad (rrm) is made up of two adjacent racemo diads and a meso diad.

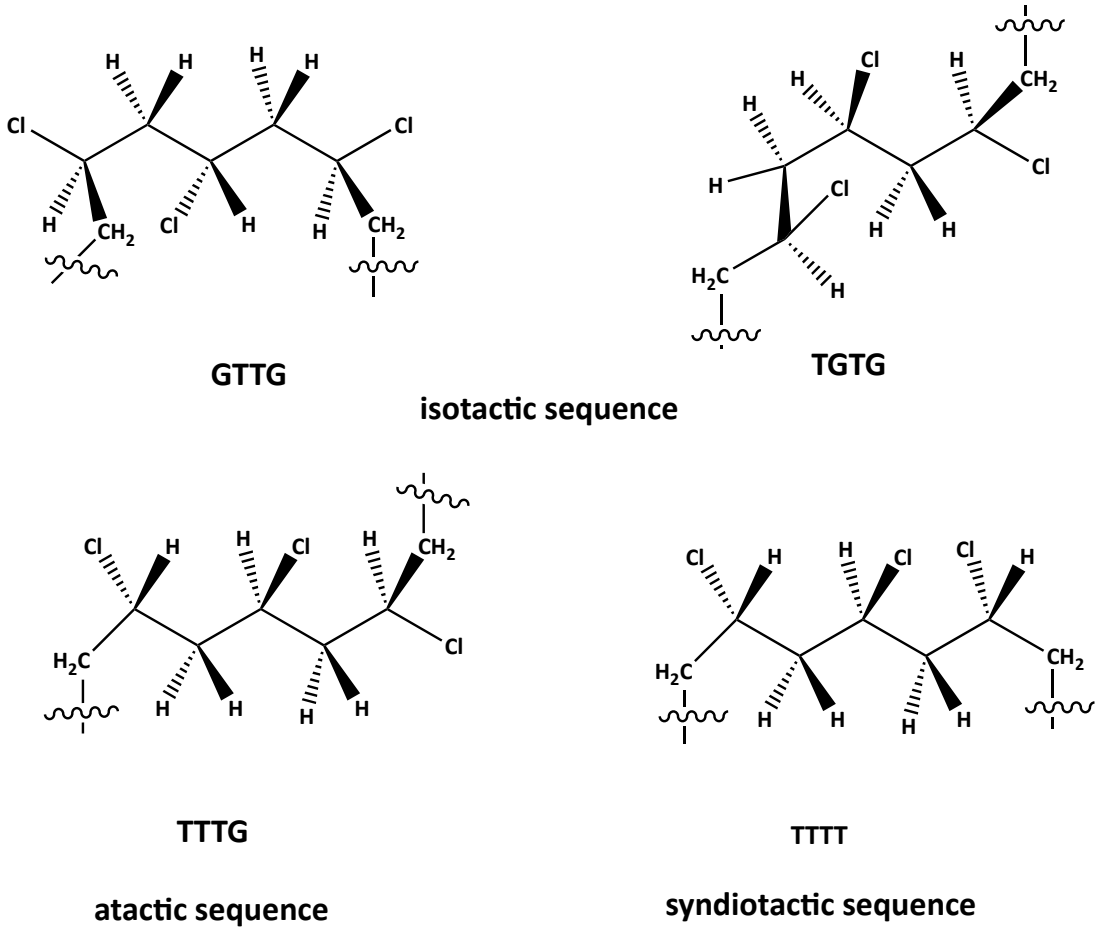


Figure 3.10 Conformations of Two Types of Isotactic, Atactic and Syndiotactic Sequences Within PVC (G = Gaush, and T = Trans)

For the nucleophile, sodium benzenethiolate,[315,316] up to 20% substitution, T_g is related to the mmr terminal of isotactic sequences and the rmr located at the end of syndiotactic sequences (**Figure 3.10**). During the early stages of the nucleophilic substitution, the TGTG or the GTTG conformation of the mmr isotactic tetrads are converted into nucleophile-substituted tetrads with the highly rigid TTTT conformation, thus increasing the glass transition temperature of PVC. When the mmr isotactic tetrads are depleted, the less reactive rrm syndiotactic tetrads then take part in the nucleophilic substitution. This results in the shortening of the syndiotactic sequences by exchanging them for sequences of reduced rigidity, thus decreasing the glass transition temperature. At conversions higher than 20%, neither mmr nor rrm is associated with isotactic or syndiotactic sequences. Therefore no significant change in the tacticity-induced microstructure is expected, and the variation of T_g would be due mainly to the progressive substitution of the nucleophile for chlorine atoms.

3.7 Conclusion

In summary, PVC was successfully modified with pendant triazoles bearing two different flexible linkers to derivatives of the most common phthalate plasticizer, DEHP. Two different triazoles: an ether and an ester linker (PVC-DEHP-ether triazole and PVC-DEHP-ester triazole) were prepared and their glass transition temperatures

were measured to assess the plasticizing efficiency. The reduction in glass transition temperature of PVC, from 83 °C to 55 °C for 15% PVC-DEHP-ether triazole, 60 °C for 15% PVC-DEHP-ester triazole indicates successful plasticization of PVC by covalently linking phthalate derivatives. Comparison of glass transition temperatures of PVC-DEHT, PVC-DEHP-ether triazole, and PVC-DEHP-ester triazole shows that DEHP-ether triazole is most effective in imparting plasticization to PVC. This makes sense because PVC-DEHP-ether triazole has more flexible linker than PVC-DEHP-ester triazole and PVC-DEHT. However, even DEHP-ether triazole showed a moderate decline in T_g of PVC indicating that substitution higher than ≈20% of chlorine atoms of PVC will be required to achieve desirable plasticization for most commercial applications. Substitution of more than 20% of chlorine atoms of PVC may not be a good approach as it may change the inherent properties of PVC. Another efficient approach will be to append multiple plasticizer units to each azide attached to PVC. Strategies to append multiple phthalate mimics to each azide attached to PVC are being pursued in the Braslau Research Group in order to achieve the amount of plasticization required for many consumer products.

3.8 References

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4 Polystyrene Supported Cyclic Fluorinated Nitrones: Spin Traps for Transient Free Radicals in the Atmosphere

4.1 Free Radicals

In recent years, it has become clear that reactive oxygen species (ROS) and reactive nitrogen species (RNS) are critical mediators in cardiovascular dysfunction,[317,318,319] neurodegenerative diseases,[320,321,322] oncogenesis,[323,324] lung damage,[325,326] hypertension,[327] atherosclerosis,[328] rheumatoid arthritis,[329,330,331] diabetes,[332,333,334] and aging,[335,330] as well as degenerative diseases like amyotrophic lateral sclerosis,[336] Alzheimer's disease,[337,338,339] Down's syndrome,[340,341] and Parkison's disease.[342] Many ROS and RNS are free radicals that are either produced in the body by natural biological processes or introduced from outside as pollutants. A free radical is defined as an atom or group of atoms that has at least one unpaired electron: most are short-lived and highly reactive species.

The terms ROS and RNS have been coined in the context of biological chemistry, but these species are also broadly involved in environmental and atmospheric chemistry. ROS are traditionally defined to include superoxide radical anion ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and ozone (O_3). Extended definitions of ROS comprise a wide range of oxygen-centered radicals, ions and molecules, including peroxyl radicals ($ROO^{\bullet}$), alkoxyl radicals ($RO^{\bullet}$), organic peroxides (ROOR), and hypochlorite ions (OCl^-). RNS include nitric oxide radical

($NO^{\bullet}$), nitrate radical ($NO_3^{\bullet}$), nitrite ions (NO^{-}), peroxynitrite ($OONO^{-}$), nitrous acid (HNO_2), and nitric acid (HNO_3). In physiology, ROS are by-products of normal aerobic cell metabolism, and their concentration under physiological conditions is maintained by antioxidant enzymes such as superoxide dismutase and catalase.[343,344,345] Among them, superoxide radical anion ($O_2^{\bullet -}$) is of special interest as it is the origin of other ROS and RNS.[346] ROS is responsible for cell signaling[347] and regulation of physiological processes such as growth and differentiation,[348] proliferation, apoptosis, and defense mechanisms against pathogens.[349] However, the excessive production of ROS can lead to various pathological conditions.[350] For example, excessive production of hydroxyl radical ($HO^{\bullet}$), the most oxidizing species in physiology with an extremely short half-life of 10^{-9} s, can cause oxidation of DNA bases.[351,352] Another ubiquitous free radical in physiology is the nitric oxide radical ($NO^{\bullet}$).[353] Despite lower reactivity with biomolecules compared to $HO^{\bullet}$, $NO^{\bullet}$ is extremely reactive with other free radicals. $NO^{\bullet}$ reacts with $O_2^{\bullet -}$ to give the highly reactive species peroxynitrite ($OONO^{-}$).[354,355] Decomposition of peroxynitrite leads to the formation of $HO^{\bullet}$. Oxidative damage to cell components such as DNA, proteins, carbohydrates and lipids have been witnessed at the onset and evolution of many diseases.[356,357,358,351]

In the atmosphere, ROS and RNS are generated via the interaction of sunlight and photolabile molecules. Most ROS and RNS originate from the photolysis of ozone

and subsequent radical reactions with aerosols.[359,360] Photolysis of ozone by UV light in the presence of water vapor is the main source of $HO^{\bullet}$. Hydroxyl radical plays a central role in the chemistry of the atmosphere, and is known as the "detergent" of the atmosphere. Under most conditions, the removal of pollutants such as volatile organic compounds is governed by reactions with $HO^{\bullet}$.[361] Organic peroxyl radicals ($ROO^{\bullet}$) are intermediates in the oxidation of volatile organic compounds, and are precursors to atmospheric ozone formation.[362] Nitrous oxide emissions[363] are a major source of RNS, and $NO^{\bullet}$ is a key species in the catalytic radical reaction cycle leading to photochemical production or destruction of ozone.[364] Atmospheric concentrations of free radicals are very small, typically one parts per trillion (ppt) in the air. These low concentrations are the consequence of the high reactivity of free radicals. The chemistry and ultimate fate of free radicals affect many aspects of the environment: the control of greenhouse gases (climate change), the formation of atmospheric acids (acid rain), and the production of ozone and secondary organic aerosols (photochemical smog, air quality and air pollution).[365] Atmospheric aerosols include primary biological aerosols (PBA),[366] secondary organic aerosols (SOA), carbonaceous combustion aerosols, polycyclic aromatic hydrocarbons and related compounds. PBA are directly released from the biosphere into the atmosphere and are comprised of cells and fragments of viable and dead organisms (bacteria, fungal spores, viruses, pollen, plant debris, etc.). SOA account for a major fraction of the

fine particulate matter in the atmosphere, and are formed by reactions of O_3, $HO^{\bullet}$, and $NO_3^{\bullet}$ with volatile organic compounds[367] such as isoprene[368] and other terpenes,[369] alkanes and aromatics.[370] Aerosols affect the climate by scattering sunlight and serve as nuclei for cloud droplets and ice crystals.[371] UV irradiation promotes free radical processes on the surface of aerosol particles. These processes contribute to aging of aerosols,[372] which changes their climate influencing properties such as hygroscopicity,[373] light scattering,[374] and absorption of the particles as well as their cloud forming abilities.[375,376,377,378,379]

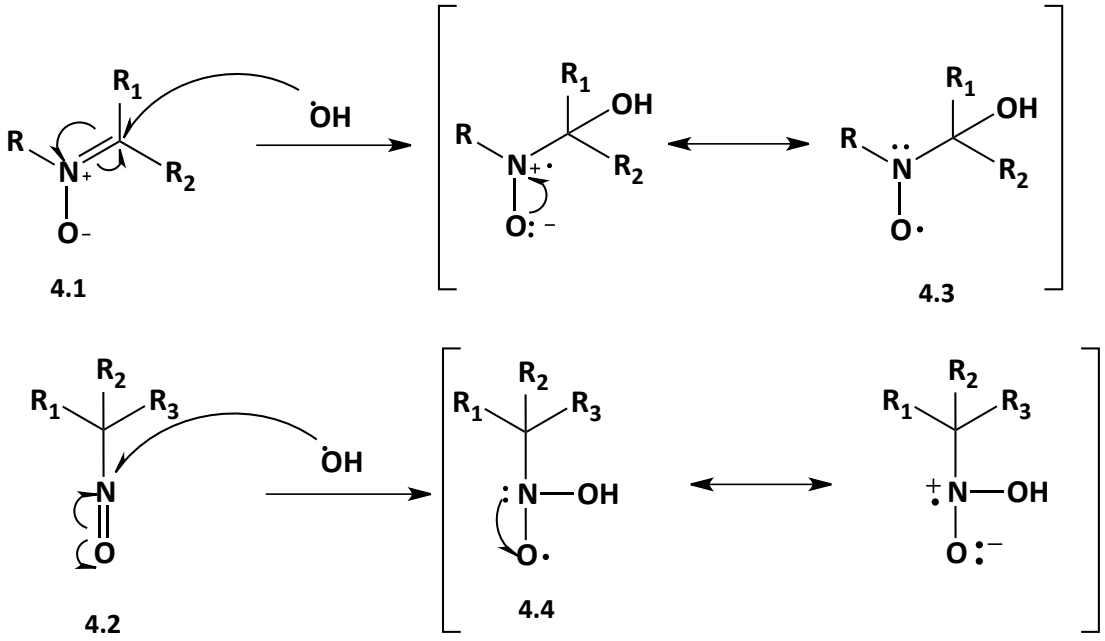
In addition, highly reactive oxygen species are increasingly being used in pollutant abatement as well as in oxidation reactions in wastewater treatment,[380,381] and in natural aquatic systems.[382] Ozonation, peroxone chemistry (reactions of ozone and hydrogen peroxide), and Fenton reactions play important roles in generating sufficient amounts of hydroxyl radicals to purify water. Despite large differences in molecular composition, concentration, and conditions among atmospheric, environmental, and biological systems, the underlying chemistry involving ROS has many similarities. Moreover, the coupling and exchange of atmospheric and physiological ROS and RNS can proceed through various bio-surfaces such as the human respiratory tract, skin, and plant leaves.[383] ROS and RNS in the atmosphere can deposit onto these surfaces, causing oxidative stress and nitrosative stress. Epidemiological studies show a clear correlation between air

pollutants and adverse health effects, including cardiovascular,[384] respiratory, and allergic diseases.[385,386] Hence, specific and sensitive detection of ROS and RNS is an ongoing focus in the field of biomedical research and environmental science.

4.2 Spin-Trapping of Free Radicals

Among a large variety of methods developed for direct detection of free radicals, electron spin resonance spectroscopy (ESR), also called electron paramagnetic resonance (EPR) remains the gold standard. EPR offers direct detection of free radicals due to their unpaired electron. However, the greatest limitation of EPR in the study of free radicals is poor sensitivity in relation to the steady-state concentration of free radicals under physiological and atmospheric conditions. The detection limit of most commonly available EPR spectrometers is in the range of 10^{-7} to 10^{-9} M,[387] which is much higher than the physiological steady-state concentration of free radicals under normal conditions.[388] Within these parameters, only persistent free radicals that accumulate to measurable levels can be identified directly by EPR spectroscopy. Examples of persistent free radicals of biological importance are those derived from vitamin C, vitamin E, flavins including quinones, and some other xenobiotics.[389,390] The limitation of EPR in the direct study of free radicals with extremely short half-lives led to the development of “spin-trapping,” a term coined by Janzen et al. in the 1960s.[391]

The method of spin-trapping depends on the fast reaction of a transient radical (undetectable by EPR) with a diamagnetic molecule; the spin-trap forms a paramagnetic spin-adduct (a persistent radical), whose half-life is significantly longer than that of the parent radical. The greatest advantage of spin-trapping is the increased stability of the spin-adduct, which leads to increased steady-state concentrations, often above the limit of EPR detection. Organic molecules, such as



Scheme 4.1 General Representation of Reactions of a Nitrone or a Nitroso Spin-trap with Hydroxyl Radical (HO$^{\bullet}$) to afford Nitroxide Spin Adducts 4.3 and 4.4

nitrone **4.1** and nitroso **4.2** compounds are used to trap and investigate free radicals (**Scheme 4.1**). The reaction of transient free radicals with nitrone or nitroso compounds (spin-trap)[392,393] form persistent nitroxide radicals **4.3** and **4.4** (spin-adduct) (**Scheme 4.1**), whose EPR signals are strong enough to be recorded and

analyzed. The stability of these nitroxide spin-adducts is due in part to the resonance stabilization of the unpaired electron.

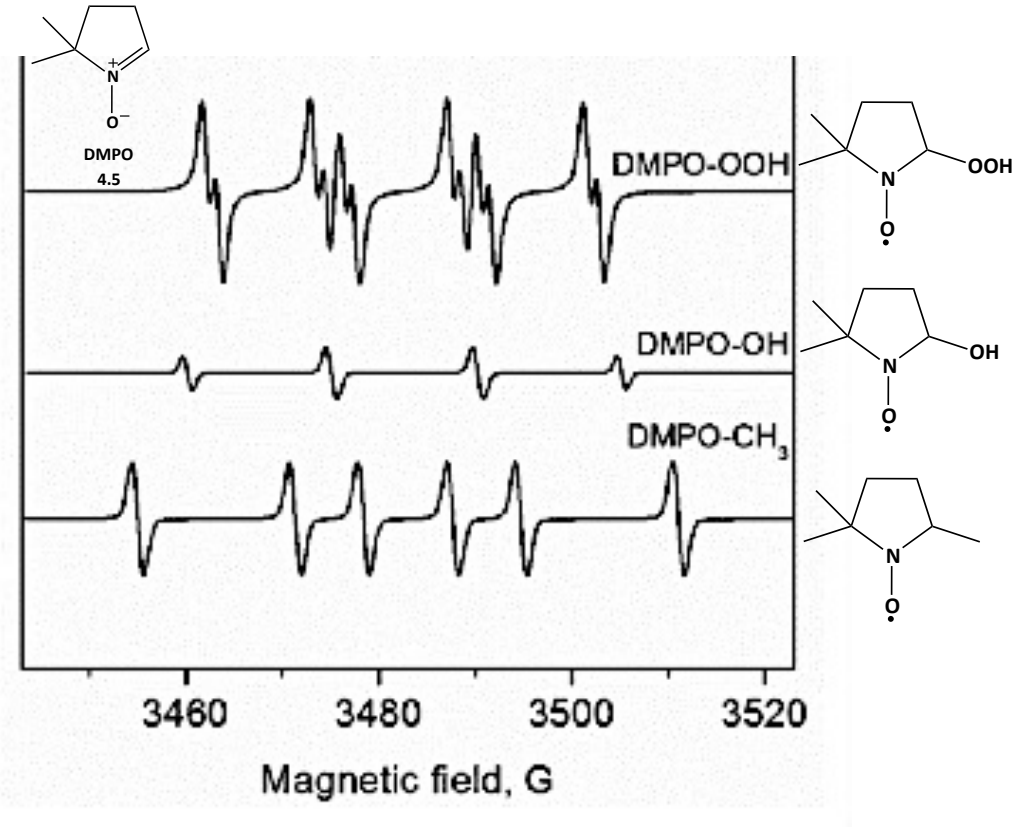


Figure 4.1 EPR Spectra of DMPO Radical Adducts Prepared from $O_2^{\bullet -}$, $HO^{\bullet}$, and $^{\bullet}CH_3$ (adapted from ref. [394])

The specificity of this method lies in the EPR spectra of spin-adducts: the hyperfine coupling constant (hfcc) and *g*-factors are characteristic of the type of the initial radical trapped, allowing its identification. Even small difference between free radicals can result in significant spectral changes. As shown in **Figure 4.1**, spin

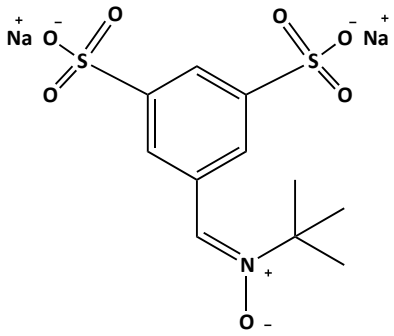
adducts of and $O_2^{\bullet -}$, $HO^{\bullet}$, and $^{\bullet}CH_3$ with cyclic nitrone 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) **4.5** in aqueous solution gives very distinct spectra.[394]

When nitroso compounds are used as spin traps, free radicals attach directly to the nitrogen atom, which gives additional hyperfine coupling that makes identification of the free radical easier than that resulting from nitrone spin traps. However, toxicity,[395,396] thermal and photochemical instability,[397] and extremely short lifetimes of oxygen-centered radical adducts greatly limits the use of nitroso spin-traps to specific free radicals or low temperature.[398] Despite the fact that EPR spectra of spin-adducts of nitrones provide less rich structural information, they have emerged as the most popular spin-traps for biological applications due to their physicochemical properties, membrane permeability, effectiveness at trapping free radicals, and low toxicity.

4.3 Nitrone Spin Traps

Nitrone spin traps are employed both as reagents to detect radicals using EPR and as pharmacological agents against stress-mediated injury. Nitrones have significantly contributed to the understanding of important free radical mediated processes in chemical, and biological systems. The observation of ROS and RNS is achieved by spin trapping in melanosomes,[399] mitochondria,[400,401,402] photosynthetic systems,[403,404] endothelial cells,[405,406,407] human neutrophils,[408,409,410] and reperfused heart tissue,[411,412,413] as well as with enzymes such as nitric oxide synthase.[414,415,416]

Moreover, the ability of nitrones to trap free radicals make them suitable as antioxidants in the treatment of free radical-mediated diseases.[417,418,419,420] An example is "Cerovive," also called OKN-007 **4.6** (**Figure 4.2**), a sulfonated nitrone-containing drug that was



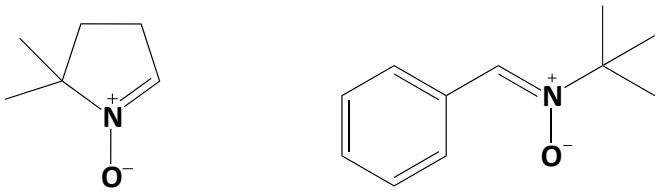
Cerovive (OKN-007)
4.6

Figure 4.2 Structure of OKN-007

discontinued after Phase III trials as it failed to demonstrate benefits in the treatment of acute ischemic stroke.[421,422] Recently, OKN-007 **4.5** is gaining importance due to its efficiency in decreasing free radical levels associated with glioma tumors in a preclinical F98 rat model,[423] and is proposed as a promising drug for treating pediatric glioblastoma.[424] Nitrone derivatives were recently patented for the topical treatment of psoriasis,[425] for the treatment of urinary incontinence,[426] and are shown to protect retinal ganglion cells against *N*-methyl-D-aspartate-induced injury.[427]

Aside from the popularity of EPR spin-trapping of free radicals in biological systems, there is a growing interest of nitrone spin-traps in the fields of fuel cell research,[428,429] nanomaterials,[430] photodynamic therapy,[431] polymerization,[432,433,433a] simple organic transformations,[434] drug metabolism,[435,436] environmental remediation,[437] tobacco smoking,[438] and beverage research.[439,440]

Among the family of nitrones, two classes are widely used: cyclic nitrones derived from 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) **4.6** and linear nitrones derived from α-phenyl-*N*-*tert*-butyl nitrone (PBN) **4.7** (**Figure 4.3**). Both DMPO and PBN are commercially available nitrone spin-traps. PBN reacts efficiently with most short-lived free radicals such as $O_2^{\bullet -}$, $HO^{\bullet}$, and $RO^{\bullet}$, and neutralizes harmful effects by removing free radicals from circulation. At relatively high concentration, PBN has the ability to prevent oxidation of low-density proteins.[441]



DMPO
4.5

PBN
4.7

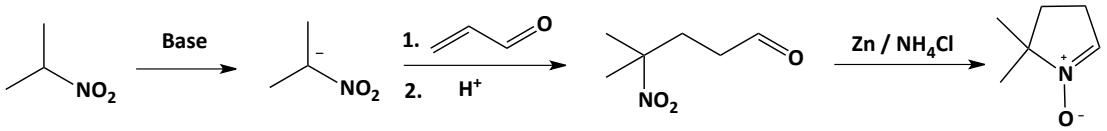
Figure 4.3 Structures of the Commonly Used Nitrone Spin-Traps: DMPO and PBN

Although, PBN has been used widely, it is not without limitations. PBN gives similar EPR spectra for all radical species, generally consisting of a triplet of doublets with a

relatively small variation in the doublet splitting, which makes distinguishing between carbon- and oxygen-centered radicals difficult.[442] The cyclic nitrone DMPO **4.6** has received the most attention due to its lower cytotoxicity and its ability to produce fingerprintable EPR spectra upon reaction with radicals, especially with $O_2^{\bullet -}$ and $HO^{\bullet}$.

4.4 DMPO and its Derivatives

Most cyclic nitrone spin-traps reported in the literature were primarily developed for the detection of superoxide radicals in biological systems. This section is a mini-review on the synthesis and spin trapping properties of DMPO and its derivatives. The preparation of DMPO is carried out in two steps (**Scheme 4.2**).



4.8 4.5

Scheme 4.2 Synthesis of DMPO

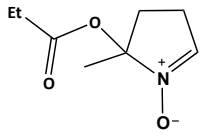
The initial reaction is a simple Michael addition, in which acrolein is carefully added to the anion of 2-nitropropane. In the original experiment, this anion was generated by slowly adding 2-nitropropane to sodium methoxide[443] under ice cooling. Alternative bases such as benzyltrimethylammonium hydroxide,[444] triethylamine or

diazabicyclo[5.4.0]undec-7-ene (DBU) have achieved similar results. The reduction of the γ-nitro-carbonyl compound **4.8** by zinc dust in the presence of acetic acid or ammonium chloride to form the transient hydroxyl amine, followed by condensation with the tethered aldehyde is found to be of general utility in the synthesis of these cyclic nitrones.

Although DMPO exhibits better spin-trapping properties compared to PBN, the use of DMPO as a probe for oxyradicals in a biological milieu is not without limitations. Reaction of DMPO with $O_2^{\bullet -}$ is rather slow, with a second order rate constant ranging from 10 M^{-1} s^{-1} at pH 7.8 to 1.2 M^{-1} s^{-1} at pH 7.4.[445] This makes high concentrations of DMPO mandatory to compete with superoxide disproportionation. The octanol/water partition coefficient for DMPO has been reported to be 0.02 to 0.09, indicating a preference for water over a lipid environment. The stability of DMPO-OOH is very low, with a half-life of 50 seconds in phosphate buffer solutions, and undergoes rapid conversion into DMPO-OH.[446] Moreover, metabolic processes in biological systems further reduce the stability of DMPO-OOH and enhance the conversion of DMPO-OOH into DMPO-OH.[447] Control experiments with SOD are required to distinguish between superoxide and hydroxyl radical trapping. DMPO is sensitive to nucleophilic attack by water in the presence of transition metals, which leads to a false interpretation due to the formation of unwanted DMPO-radical adducts via a non-radical pathway.[448] To overcome the drawbacks of DMPO and the

need for better spin-traps that are less susceptible to oxidation, reduction, hydrolysis, or other degradation processes prevalent in biological systems, resistant to thermal decomposition, and with the desired lipophilicity, development of other nitrone spin-traps has been pursued. Several analogs of DMPO as well as spin-traps with structural motifs different than DMPO have been developed over the last two decades. An efficient spin-trap should fulfill the following criteria: (1) the trapping of free radicals must be fast enough to prevent them from participating in other biological and chemical processes, (2) the resulting spin-adduct must be persistent enough to reach and maintain an EPR-detectable concentration, (3) EPR spectra of spin-adducts must be easy to assign and should provide information on the nature of the radical trapped, and (4) the heterolytic formation of imposter spin-adducts or the fast decay of spin-adducts into other paramagnetic species should be negligible.

Efforts have been directed to increasing the rate of spin-trapping, and increasing the intrinsic stability of the radical adduct by modifying the structure of the spin-trap using theoretical calculations for rational design.[449,450] For example, an

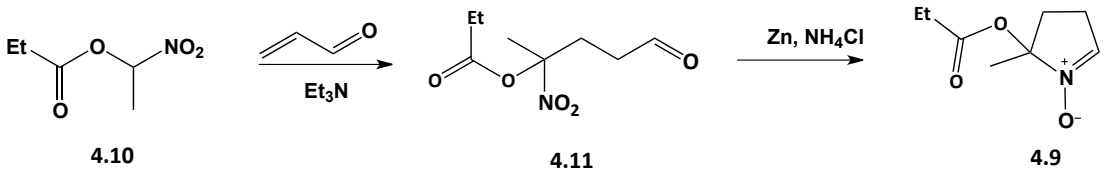


EMPO

4.9

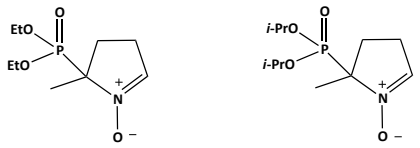
Figure 4.4 Structure of Ethoxycarbonyl Derivative of DMPO: EMPO

ethoxycarbonyl group was introduced to afford a highly hydrophilic nitrone: 2-ethoxycarbonyl-2-methyl-3,4-dihydro-2H-pyrrolidine-1-oxide (EMPO) **4.9** (**Figure 4.4**). EMPO is faster at trapping $O_2^{\bullet -}$ compared to DMPO. The superoxide adduct of EMPO is five times more persistent than that of DMPO, with a half-life of 8.6 minutes in phosphate buffer, and does not decay into EMPO-OH spontaneously.[451] EMPO is prepared by a Michael addition of commercially available ethyl-2-nitropropanoate **4.10** to acrolein using triethylamine in acetonitrile to give



Scheme 4.3 Synthesis of EMPO

the γ-nitrocarbonyl compound **4.11**, followed by reductive cyclization using zinc and ammonium chloride in methanol (**Scheme 4.3**). Although EMPO-OOH is more persistent that DMPO-OOH, its stability is still considered low. Drawbacks such as limited biostability, poor cellular target delivery, and slow reactivity towards superoxide radical limit its application in the detection of superoxide radical in biological systems.



DEPMPO

4.12

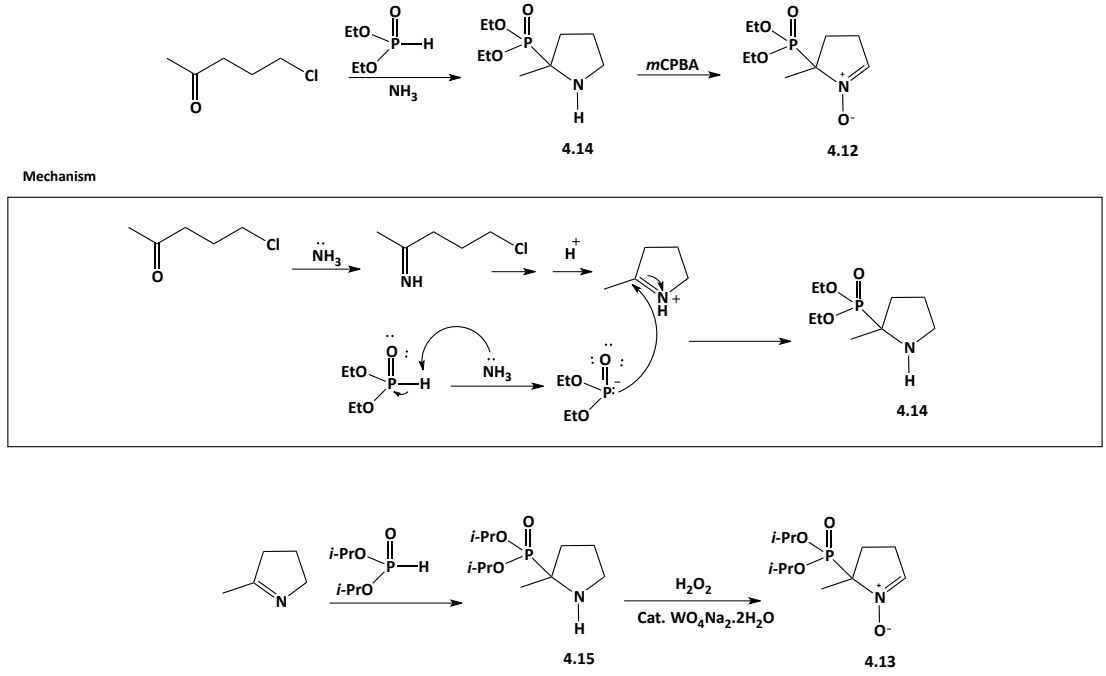
DIPPMPO

4.13

Figure 4.5 Structures of Phosphorylated Derivatives of DMPO: DEMPO and DIPPMPO

Tordo et al. synthesized phosphorous containing analogues of DMPO: 5-diethoxyphosphoryl-5-methyl-1-pyrroline-1-oxide (DEPMPO)[452] **4.12** and 5-di*iso*propoxyphosphoryl-5-methyl-1-pyrroline-1-oxide (DIPPMPO)[453] **4.13** (**Figure 4.5**). The electron withdrawing groups at position 5 led to the formation of very stable spin-adducts. It was demonstrated that DEPMPO/DIPPMPO trap a variety of free radicals including $HO^{\bullet}$ and $O_2^{\bullet -}$, $R^{\bullet}$, $RS^{\bullet}$ and $RO^{\bullet}$. Compared with DMPO, DEPMPO and DIPPMPO offer three major advantages. The first advantage is the presence of phosphorous with a nuclear spin I = ½ that provides additional information, and easier identification of the trapped radical due to large phosphorous hyperfine splittings. The second advantage is that DEPMPO-OOH and DIPPMPO-OOH adducts exhibit long half-lives (15 minutes) in phosphate buffer, and do not spontaneously decompose into the paramagnetic hydroxyl adduct. The third advantage is that $ROO^{\bullet}$ can be trapped in the aqueous phase by DEPMPO and DIPPMPO. The partition coefficients in octanol/water for DEPMPO and DIPPMPO are 2.1 and 0.16 respectively, indicating DIPPMPO to be more lipophilic than DMPO and DEPMPO, and suitable for trapping experiments conducted in subcellular compartments or

lipid rich environments.[454] For the preparation of DEPMPO, diethyl (2-methyl-2-pyrrolidinyl) phosphonate **4.14** was obtained by bubbling ammonia into an ethanolic solution of commercially available 5-chloro-2-pentanone and diethylphosphite

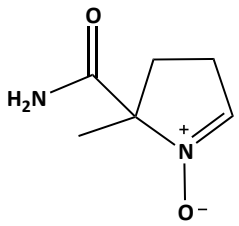


Scheme 4.4 Synthesis of Phosphorylated Analogues of DMPO: DEPPMPO and DIPPMPO

(**Scheme 4.4**). Nucleophilic addition of ammonia to 5-chloro-2-pentanone to form the imine, followed by cyclization gave 2-methylpyrroline. Deprotonation of diethylphosphite by ammonia followed by its reaction with the protonated 2-methylpyrroline imminium gave **4.14**. Oxidation of amine **4.14** using *meta*-chloroperbenzoic acid in chloroform gave the hygroscopic nitrone DEPMPO. The preparation of DIPPMPO started with the addition of di*iso*propylphosphite to

commercially available 2-methylpyrroline to afford di*iso*propyl (2-methyl-2-pyrrolidinyl) phosphonate **4.15.** Oxidation of **4.15** with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate led to the formation of DIPPMPO, which was obtained as a pure solid after recrystallization (**Scheme 4.4**).

Density functional studies performed by Villamena et al.[449] showed that 5-carbamoyl-5-methyl-1-pyrroline-1-oxide (AMPO) **4.16** (**Figure 4.6**) and its spin adduct with hydroxyl radical (AMPO-OH) have similar electronic and thermodynamic properties compared to EMPO and DEPMPO. AMPO was synthesized and investigated for its spin-trapping efficiency in a phosphate buffer. The pseudo first order spin-trapping rate constant with superoxide radical was determined using a stopped flow UV-VIS kinetic method and EPR-based competition kinetics. The



AMPO

4.16

Figure 4.6 Structure of Amide Analogue of DMPO: AMPO

pseudo first order spin-trapping rate constant for AMPO with superoxide radical was found to be the highest (14 ± 1.2) 10^4 s^{-1} at pH 7.2 and 23 °C, followed by EMPO (11.6 ± 0.5) 10^4 s^{-1}, DEPMPO (7.5 ± 0.7) 10^4 s^{-1}, and DMPO (129.0) s^{-1} had the slowest

reactivity. The half-life of AMPO-OOH (8.3 ± 0.7 minutes) is lower than EMPO-OOH (9.9 ± 0.4 minutes) and DEPMPO-OOH (15.5 ± 1.4 minutes), but was higher than DMPO-OOH (0.9 minutes). The octanol/water partition coefficient for AMPO was found to be 0.03, which was comparable to that of DMPO (0.06), indicating the suitability of AMPO as a spin-trap in aqueous solutions. In another study, Stolze et al.[455] synthesized four derivatives of AMPO, 5-carbamoyl-3,5-dimethyl-pyrroline-1-oxide (CADMPO) **4.17**, 3,5-dimethyl-5-methylcarbamoyl-pyrroline-1-oxide (DMMCAPO) **4.18**, 5-carbamoyl-3-ethyl-5-methyl-pyrroline-1-oxide (CAEMPO) **4.19**, and 3-ethyl-5-methyl-5-methylcarbamoyl-pyrroline-1-oxide (EMMCAPO) **4.20**, as shown in **Figure 4.7**. The spin-trapping potential of these AMPO derivatives towards oxygen- and carbon-centered radicals was investigated. These novel derivatives

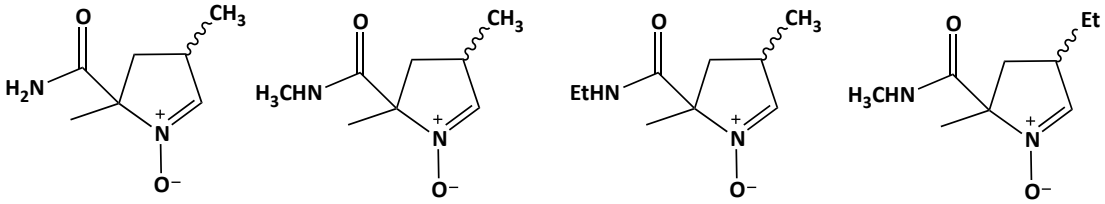
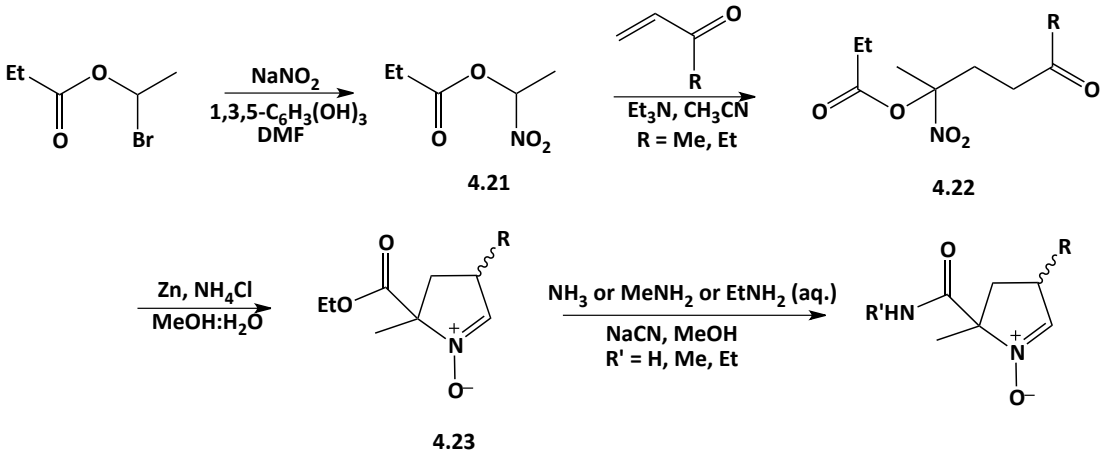


Figure 4.7 Derivatives of AMPO

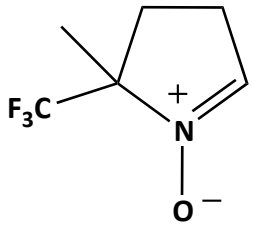
were found to be inferior towards trapping superoxide radical compared to DEPMPO and EMPO due to low spectral intensity, the presence of several diastereomeric isomers, and formation of secondary products leading to complicated spectra.

More amide analogues of DMPO were prepared by the nitration of ethyl 2-bromopropionate using sodium nitrite and phloroglucinol in dry dimethylformamide to give ethyl 2-nitropropionate **4.21**, which was used in Michael additions to acrolein, methacrolein, or ethacrolein in the presence of triethylamine as a base in acetonitrile (**Scheme 4.5**). The reductive cyclization of nitroaldehyde **4.22** was carried out using the zinc/ammonium chloride system. The aminolysis of EMPO derivatives **4.23** by aqueous ammonia, methylamine or ethylamine gave the corresponding carbamoyl derivatives of DMPO. AMPO and its derivatives are useful for the detection of carbon-centered radicals in aqueous solutions, but do not find utility in the detection of superoxide radicals due to low stability of the adducts.



Scheme 4.5 General Synthetic Scheme for Carbamoyl and Methylcarbamoyl Nitrones

The half-life of DEPMPO-OOH is greater than the half-life of DPMO-OOH, because of the electron-withdrawing group on carbon-5. The trifluoromethyl group has electron-withdrawing effects similar to the diethyoxyphosphoryl group. Tordo et al. synthesized a trifluoromethyl analogue of DMPO: 5-TFDMPO **4.24** (**Figure 4.8**), and compared its spin-trapping properties with DEPMPO and DMPO.[456]

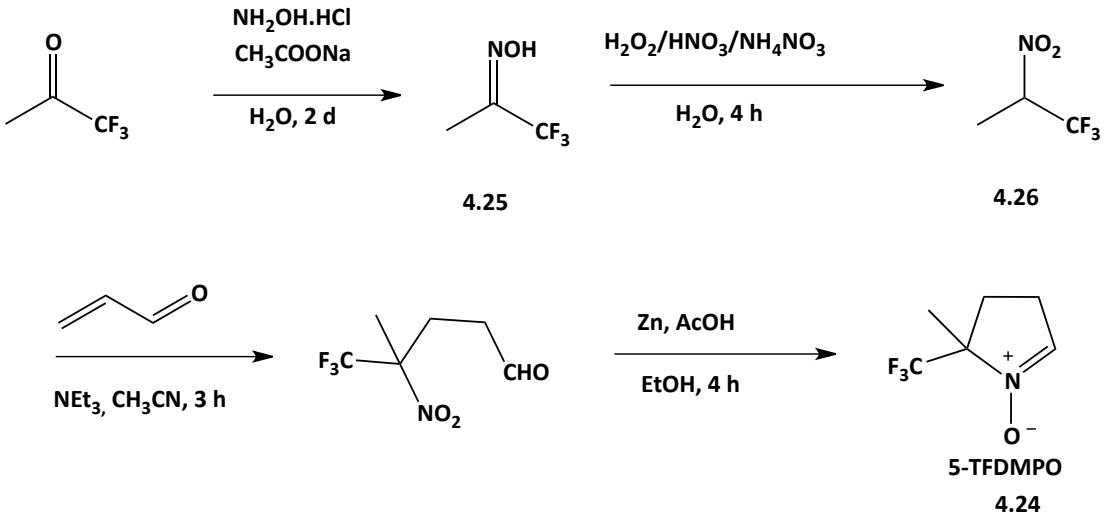


5-TFDMPO
4.24

Figure 4.8 Structure of the Fluorinated Derivative of DMPO: 5-TFDMPO

The spin-trap 5-TFDMPO is stable for several months when stored at low temperature, and like DMPO does not decompose into paramagnetic impurities. It shows efficient trapping of carbon-, sulfur-, and oxygen-centered radicals. The 5-TFDMPO-OOH adduct is more persistent than DMPO-OOH, with a half-life of 4.5 min, compared to 50 s for DMPO-OOH. However, the persistency of 5-FTDMPO-OOH was about three times shorter than DEPMPO-OOH. These results suggest that the stabilization of the superoxide adducts comes with a delicate balance between steric, electronic, and hydrogen-bonding effects that involve the β group, the hydroperoxyl

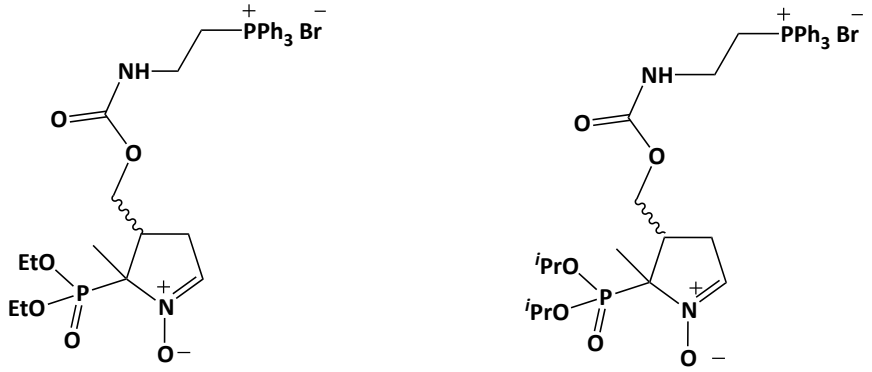
moiety, and the nitroxide.[457] For the synthesis of 5-TFDMPO **4.24** (**Scheme 4.6**), Tordo used the method described by Shepard et al.[458] to synthesize 1,1,1-trifluoroacetone oxime **4.25** by the reaction of commercially available 1,1,1-trifluoroacetone with hydroxylamine hydrochloride in water for two days. The oxidation of the oxime with hydrogen peroxide in the presence of nitric acid and ammonium nitrate gave the nitro compound **4.26**. Treatment of the nitro compound with acrolein in the presence of triethylamine as a base resulted in Michael addition, followed by reductive cyclization using zinc and acetic acid in ethanol to yield 5-TFDMPO **4.24**.



Scheme 4.6 Synthesis of 5-TFDMPO

4.5 Target-Based Spin-Trapping

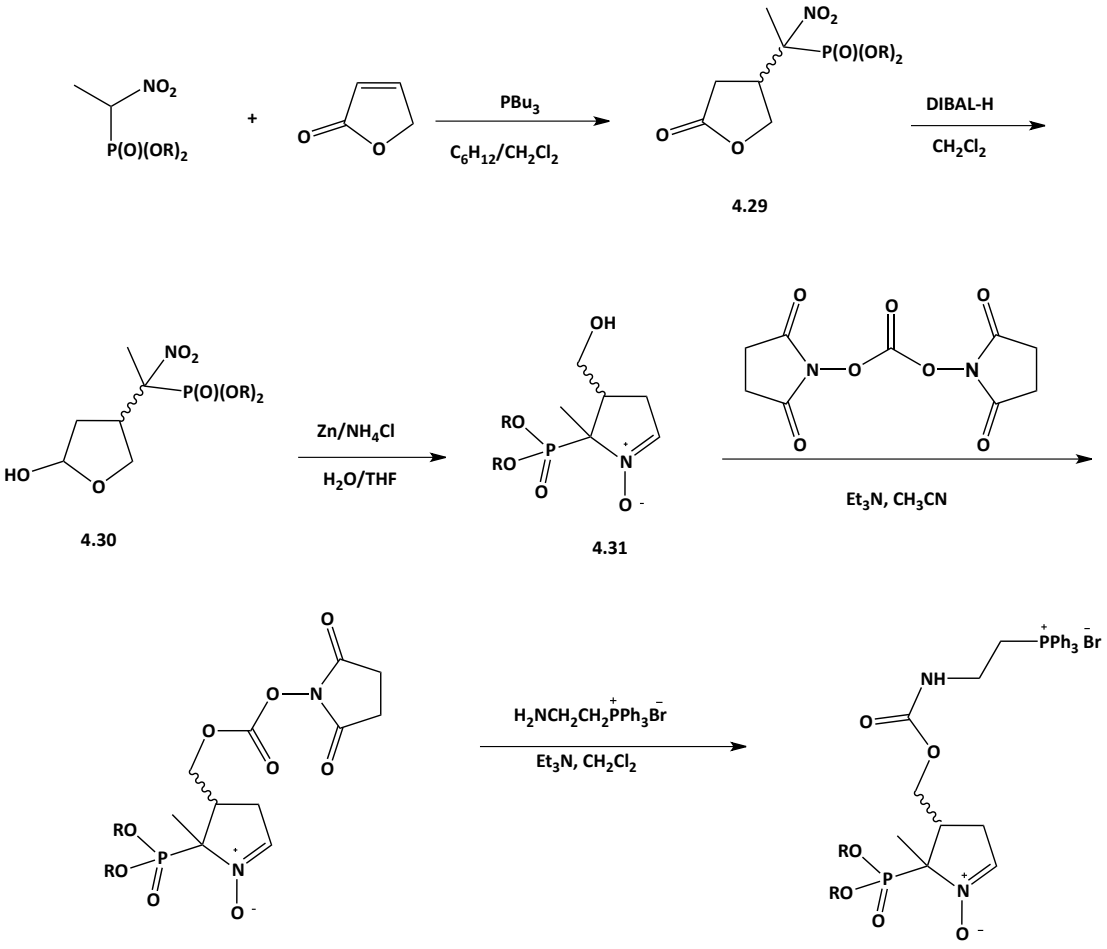
One of the promising strategies in the design of novel nitrone-based spin-traps is to selectively locate these nitrone spin-traps proximal to the sites of radical production, mainly the mitochondrial electron transport chain, the cytosol, and membrane-bound NAD(P)H oxidase. Selective targeting is usually achieved by conjugating the nitrone species to specific target ligands. Nitrones with a hydroxyl tether provide an opportunity to incorporate the spin-trap at sites where cellular metabolism may generate free radicals. Tordo et al.[459,460] demonstrated site-specific detection of free radicals by incorporating a mitochondria targeting lipophilic triphenylphosphonium (TPP^+) cationic moiety on DEPMPO and DIPPMPO. The use of TPP^+-conjugated DEPMPO (Mito-DEPMPO) **4.27** and TPP^+-conjugated DIPPMPO (Mito-DIPPMPO) **4.28** (**Figure 4.9**) demonstrated the feasibility of detecting $O_2^{\bullet -}$,



4.27 **4.28**

Figure 4.9 Mitochondria Targeting Nitrone Spin-Traps by Tordo

generated by partial reduction of oxygen by mitochondrial electron transfer protein complexes, in intact and isolated mitochondria. The rates of spin-trapping of $O_2^{\bullet -}$ by these mitochondria targeted spin-traps are about two times higher than DEPMPO and DIPPMPO. The half-life of the spin adducts of Mito-DEPMPO-OOH (50 ± 4 minutes) and Mito-DIPPMPO-OOH (65 ± 10 minutes) are 2.5 times longer than DEPMPO-OOH and DIPPMPO-OOH. The preparation of Mito-DEPMPO and Mito-DIPPMPO was carried out in five steps starting with Michael addition of



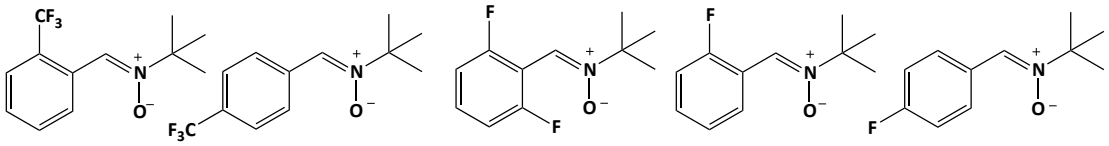
Scheme 4.7 Synthesis of Mitochondria Targeting Spin-Traps by Tordo

nitrophosphonate and 2(*5H*)-furanone in the presence of a catalytic amount of tributylphosphine as base to give nitrofuranone **4.29** (**Scheme 4.7**). Reduction of nitrofuranone by DIBAL-H at -78 °C led to the formation of hemiacetal **4.30**. Reductive cyclization of **4.30** in the presence of zinc and ammonium chloride afforded nitrone **4.31**, which was then treated with *N,N'*-disuccinimidyl carbonate (DSC) in the presence of triethylamine as a base to give NHS-DEPMPO and NHS-DIPPMPO. Mito-DEPMPO **4.27** and Mito-DIPPMPO **4.28** were obtained by treating the respective NHS-nitrone with the amino triphenylphosphonium salt in dichloromethane using triethylamine as base.

4.6 NMR Spin-Trapping (ST-NMR)

The direct detection of spin-adducts (nitroxides) by ^{1}H NMR is difficult due to the broadening of the NMR signal by the unpaired electron, and the instability of most spin-adducts. Therefore, nitroxides are usually reduced using phenyl hydrazine or ascorbic acid to form diamagnetic hydroxylamines. However, the use of ^{1}H NMR or ^{13}C NMR in detection of free radicals is significantly limited by the complexity of multiple signals overlapping. Two alternative stable isotopes: ^{19}F and ^{31}P with comparable sensitivity, when incorporated into the spin-trap should give resolvable spectra of the diamagnetic hydroxylamine adducts. The concept of NMR spin-trapping (ST-NMR) was introduced in the 1980s, when Motten et al.[461] synthesized

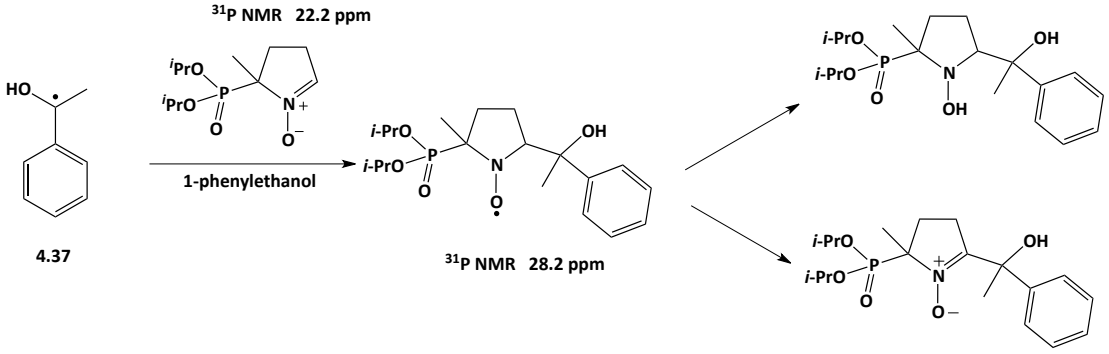
five fluorinated analogues of PBN (**4.32** through **4.36**), **Figure 4.10**, and evaluated detection of free radicals in organic reactions using ^{19}F NMR spectroscopy. The introduction of the NMR-sensitive label ^{19}F into PBN enabled the selective monitoring of chemical reactions associated with phenyl radical after the reduction of spin-adducts with phenylhydrazine.



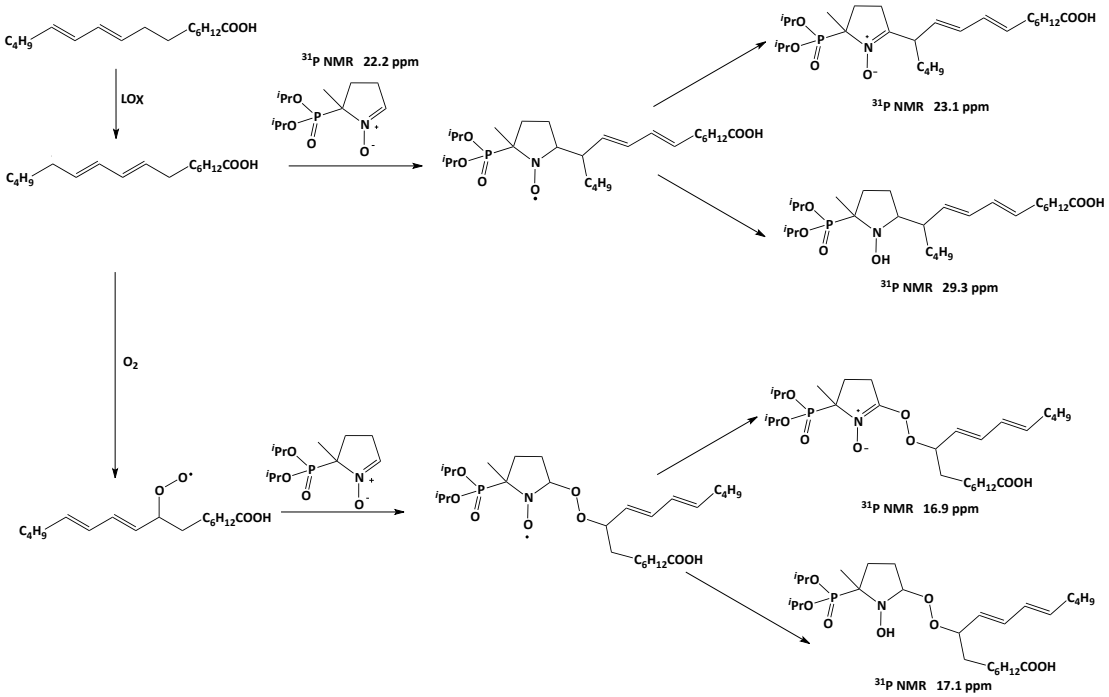
4.32 **4.33** **4.34** **4.35** **4.36**

Figure 4.10 Structures of Fluorinated PBN Analogues Used by Motten et al.

^{31}P NMR was used to study changes in molecular structure arising from the reactions between free radicals and DEPMPO.[462] Detections and quantification of oxygen- and carbon-centered free radicals were carried out using DIPPMPO in conjunction with ^{31}P NMR.[463] In the presence of DIPPMPO, it was possible to trap the UV-generated ketyl radical of acetophenone **4.37** and to characterize the disproportionation adducts by ^{31}P NMR and GC-MS (**Scheme 4.8**).[464]



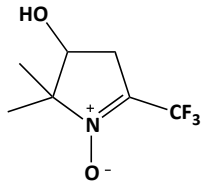
Scheme 4.8 Spin-Trapping Reactions of Ketyl Radical with DIPPMPO and the Disproportionation Reaction of the Nitroxide Adduct to Form the Corresponding Nitrone and Hydroxylamine.



Scheme 4.9 Spin-Trapping Reactions of Lipid-Derived Carbon- and Oxygen-Centered Radicals with DIPPMPO and the Disproportionation Reaction of the Radical Adducts to Form the Corresponding Nitrones and Hydroxylamines

This system was applied to probe the mechanism of the enzymatic oxidation of linoleic acid by soybean lipoxygenases-1, as shown in **Scheme 4.9**.[465] However, this method is limited when detecting radicals *in vivo* due to low concentrations.

Since the use of fluorinated PBN analogues in aqueous solutions is very limited due to poor solubility, resulting in low sensitivity of ^{31}P NMR for *in vivo* systems, the use of fluorinated analogues of DMPO for *in vivo* studies is more suitable. Clanton et al.[466] synthesized a water soluble fluorinated analogue of DMPO: 4-hydroxy-5,5-dimethyl-2-trifluormethylpyrroline-1-oxide (FDMPO) **4.38** (**Figure 4.11**) to study EPR and NMR spin-trapping of free radicals. Comparison of the ^{19}F NMR



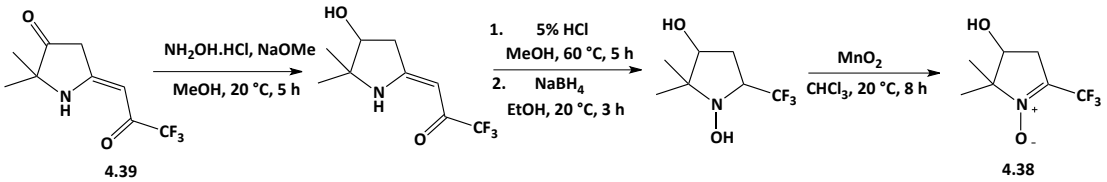
FDMPO
4.38

Figure 4.11 Clanton's Trifluoromethylated Analogue of DMPO Substituted at the α-Carbon: FDMPO

sensitivity of FDMPO to the ^{31}P-NMR sensitivity of DEPMPO showed a 10.4 fold improvement in the signal to noise ratio. The ^{19}F signal for the parent FDMPO nitrone is a single resonance at -66.0 ppm. The ^{19}F peaks for the hydroxylamines of FDMPO-CH_3 and FDMPO-CH_2OH adducts are at -74.6 and -76.7 ppm, respectively.

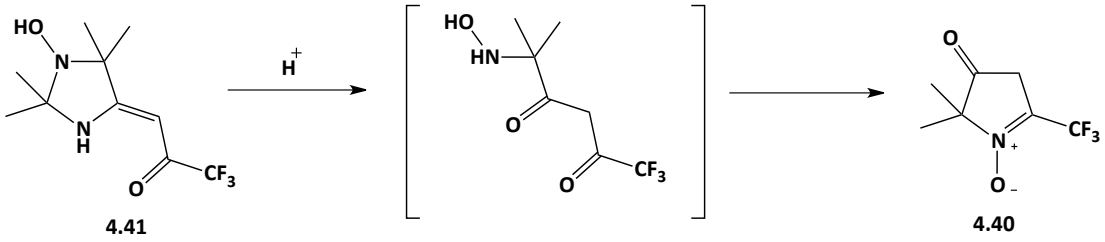
FDMPO shows similar spin-trapping efficiency as DEPMPO. Competitive spin-trapping between FDMPO with DMPO shows similar rates.

The synthesis of FDMPO is unclear as reported by Clanton in 2001.[150] The authors wrote that they treated enaminone **4.39** with hydroxylamine hydrochloride



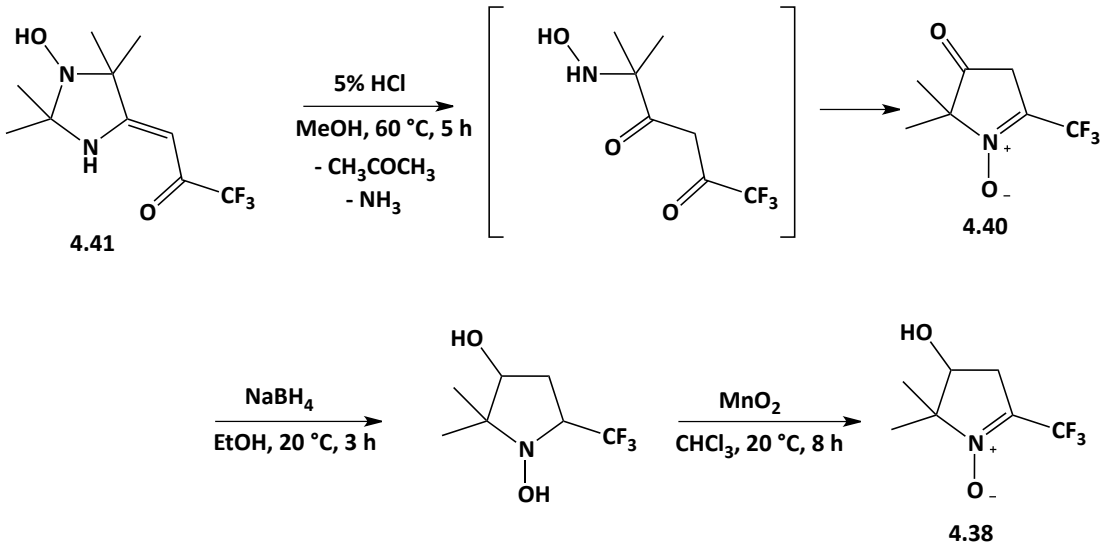
Scheme 4.10 Nonsensical Synthesis of FDMPO, *reported by Clanton et al*.[150]

and sodium methoxide to give the corresponding alcohol reduction product, followed by treatment with 5% hydrochloric acid in methanol and reduction using sodium borohydride to give a rearranged alcohol missing two carbon atoms. Oxidation of the hydroxylamine with manganese oxide gave FDMPO nitrone **4.38** (**Scheme 4.10**). This clearly does not make chemical sense nor does the experimental procedure clarify the preparation. A paper by Volodarsky from 1990[467] provides a clue to this mystery. The Volodarsky paper shows a completely different starting material **4.41** containing an imidazolidine ring: treatment with acid forms a diketo intermediate with loss of acetone, which then condenses to form ketonitrone **4.40** (**Scheme 4.11**).



Scheme 4.11 Hydrolysis of Imidazolidine to form Ketonitrone Intermediate Followed by Condensation to form Nitrone as Reported by Volodarsky[151]

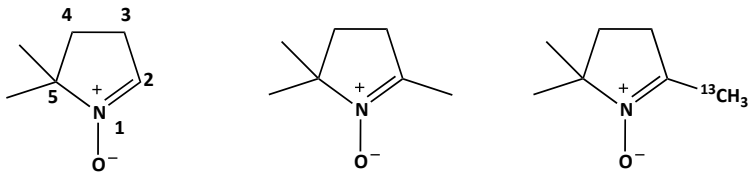
Thus we suggest that Clanton might have started with imidazolidine **4.41** rather than enaminone **4.39** as shown in **Scheme 4.12**. We note that Reznikov is a coauthor on both of these papers, making the imidazolidine starting material **4.41** very likely in Clanton's work.



Scheme 4.12 Proposed Corrected Scheme for Clanton's Synthesis of FDMPO Starting with Imidazolidine 4.41 instead of Enaminone 4.39 as Reported in Ref. 150

4.7 Other DMPO Derivatives With Substitution on the Nitronyl Carbon

Although a large number of substituted DMPO derivatives are known, very few examples exist where DMPO is modified at the sp^2 α-carbon. DMPO and its derivatives possess a hydrogen atom at this α-carbon, making their spin adducts susceptible to decomposition via disproportionation. Janzen et al.[468] synthesized 2,5,5-trimethyl-1-pyrroline *N*-oxide (M_3PO) **4.42**, which has a methyl group at the sp^2 α-carbon (**Figure 4.12**). The nitroxide radicals obtained by the reaction of M_3PO with transient free radicals should be stable. Such adducts were anticipated to survive, and to be detectable inside the cell. Indeed, M_3PO spin adducts of $^{\bullet}CH_3$, $^{\bullet}CO_2$, and $HO^{\bullet}$ were far more stable than those of DMPO. However, without the β-



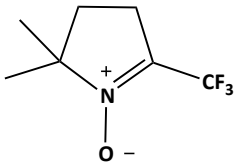
DMPO **4.6** | **M_3PO** **4.42** | **$^{13}CM_3PO$** **4.43**

Figure 4.12 α-Carbon Substituted Derivatives of DMPO: M_3PO and $^{13}CM_3PO$

hydrogen hyperfine splitting, the discrimination between various radical adducts was lost. Therefore, nitrone $^{13}CM_3PO$ **4.43** labelled with a ^{13}C at the sp^2 carbon was synthesized.[469] The spin adducts $^{13}CM_3PO$-CH_3, $^{13}CM_3PO$-CO_2, and $^{13}CM_3PO$-OH

obtained by addition of radiolytically generated radicals persist over days. In human cells, these adducts exhibited half-lives of 2 h and more, in contrast to DMPO-OH adducts that decomposed within a few minutes.[470]

Janzen et al. synthesized a DMPO derivative with a trifluoromethyl group on the nitronyl carbon (2-TFDMPO) **4.44** (**Figure 4.13**),[471] and evaluated its efficiency as a spin-trap. Results obtained from EPR spin-trapping experiments, electron nuclear double resonance (ENDOR) measurements, mass spectrometric tests, and *in vivo* observation in rats as animal model demonstrated 2-TFDMPO as a promising nitrone spin-trap. The hyperfine coupling constants of spin adducts of 2-TFDMPO with many carbon- and oxygen-centered radicals were recorded (**Table 4.1**). The EPR spectra were characteristic of the trapped radical. The oxygen-centered radicals gave EPR



2-TFDMPO

4.44

Figure 4.13 Trifluoromethyl Substituted DMPO: 2-TFDMPO

spectra consisting of three groups of 1:3:3:1 with relatively small N-hfsc's compared to the carbon-centered radicals that showed larger N-hfsc's. Moreover, the rate of reaction of $HOO^{\bullet}$ addition to 2-TFDMPO was found to be greater than that to DMPO.

In addition, the hydroxyl adduct of 2-TFDMPO was more persistent with a half-life time of 75 minutes versus 15 minutes for the hydroxyl adduct of DMPO. The stability of this adduct was attributed to the electron-withdrawing inductive and field effects, the polarizability of the CF_3 group and the hyperconjugation between the CF_3 and the lone pair of electrons on the nitrogen atom in the nitroxide.

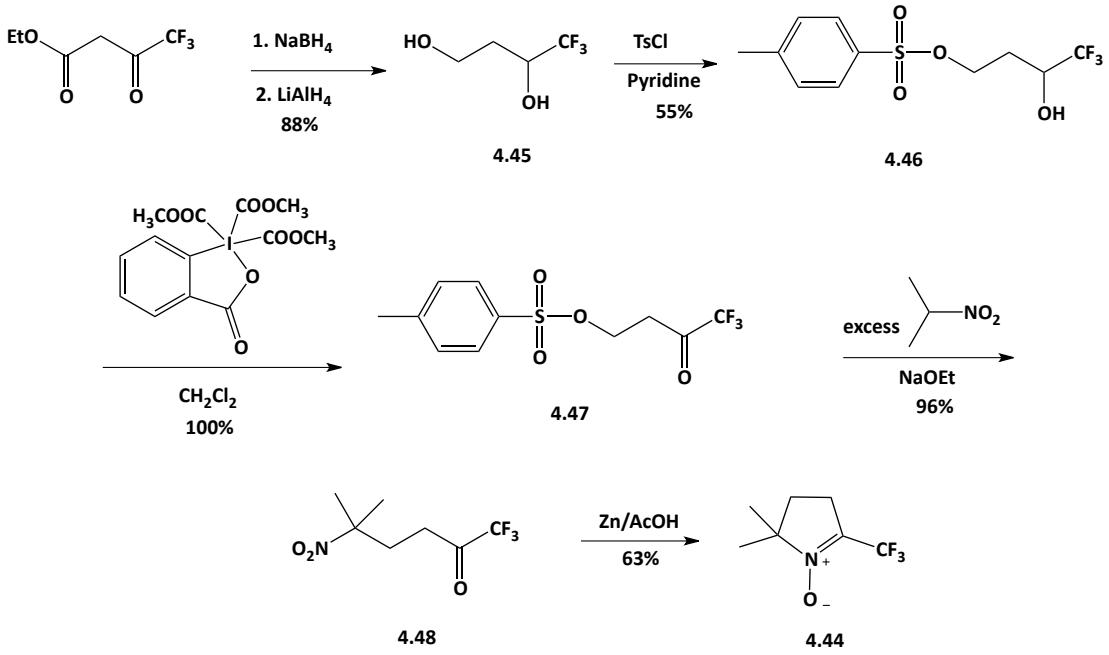
radical	source	solvent	N-hfsc[a]	F-hfsc[a]	H-hfsc[a]
n-BuO•	*n*-BuONO photolysis (*hν*)	C6H6	11.88	2.74	0.79 (2H)
i-BuO•	*i*-BuONO (*hν*)	C_6H_6	11.83	2.69	0.79 (2H)
i-amyl O•	*i*-amylono (*hν*)	C_6H_6	11.83	2.74	0.75 (2H)
HO•	1% H_2O_2 (*hν*)	H_2O	13.98	2.70	–
HO_2•	30% H_2O_2	H_2O	13.14	2.80	0.83 (2H)
^-O_3SO•	$Na_2S_2O_8$	H_2O	12.97	3.21	–
$HOCH_2$	1% H_2O_2, 10% v MeOH (*hν*)	H_2O	14.42	2.33	–
HOCH(Me)	1% H_2O_2, 10% v ETOH (*hν*)	H_2O	14.47	2.87	–
HOCH(Et)	1% H_2O_2, 10% v *n*-PrOH (*hν*)	H_2O	14.52	2.74	–
$HOC(Me)_2$	1% H_2O_2, 10% v *i*-PrOH (*hν*)	H_2O	14.32	2.93	–
$HOCH_2CH(OH)$	1% H_2O_2, $(HOCH_2)_2$ (*hν*)	H_2O	14.37	2.64	–
THF•	1% H_2O_2, THF (*hν*)	H_2O	14.37	2.64	–
Me•	1% H_2O_2, DMSO (*hν*)	H_2O	14.90	2.05	–
Et•	ethyl Grignard	H_2O/C_6H_6	14.66/12.93	2.51/2.64	–
i-Pr•	isopropyl Grignard	H_2O/C_6H_6	14.69/12.95	2.97/3.19	–
Cl_312C•	rat liver/CCl_4	$CHCl_3$	12.26	3.66	–
Cl_313C•	rat liver/CCl_4	$CHCl_3$	12.54	3.41	12.66[b]
HC≡C•	ethynyl Grignard	H_2O/C_6H_6	14.91/13.44	1.76/1.66	–
CH_2=$CHCH_2$•	allyl Grignard	H_2O/C_6H_6	14.59/12.90	2.44/2.53	–
H•	2.5% *n*-Bu_3SnH (*hν*)	C_6H_6	13.20	1.14	15.40
Ph•	phenyl Grignard	C_6H_6	13.05	3.02, 1.41, 0.8	0.3
Ph•	phenyl Grignard	H_2O	14.54	3.05, 1.44, 0.82	0.3
Ph•	phenyl Grignard	$C_6H_5CH_3$ (110 °C)	13.07	1.96	–
Ph•	phenyl Grignard	$C_6H_5CH_3$ (−73 °C)	from ENDOR	4.92, 1.12, 0.81	0.31
CH_2=CH•	vinyl Grignard	H_2O	14.74	2.6, 1.7, 1.3	0.92, 0.69, 0.34
CH_2=CH•	vinyl Grignard	C_6H_6	13.25	2.7, 1.8, 1.4	–
CH_2=CH•	vinyl Grignard	$C_6H_5CH_3$	from ENDOR	4.94, 1.12, 0.81	1.0, 0.51, 0.19
$C_6H_5CH_2$•	benzyl Grignard	H_2O	14.47	2.99, 2.69, 2.39	0.88
$C_6H_5CH_2$•	benzyl Grignard	C_6H_6	12.76	3.15, 2.84, 2.53	0.88
$C_6H_5CH_2$•	benzyl Grignard	$C_6H_5CH_3$ (110 °C)	12.81	2.82	–
$C_6H_5CH_2$•	benzyl Grignard	$C_6H_5CH_3$ (−73 °C)	from ENDOR	not found	0.81, 0.20
$C_5H_{11}C$=O	hexanal, (*t*-BuO)$_2$ (*hν*)	H_2O	13.88	2.65, 2.15, 1.4	–
O=CO^-	1% H_2O_2, sodium formate	H_2O	14.57	3.25, 1.7, 0.76	–

[a] The error is estimated to be ±0.05 G. Units are gauss obtained at *X*-Band. [b] ^{13}C-hfsc.

Table 4.1 Hyperfine Splitting Constants (hfsc's) for Spin Adducts of 2-TFDMPO[471]

For the preparation of 2-TFDMPO, the reduction of ethyl-4,4,4-trifluoroaceto-acetate was carried out with sodium borohydride and lithium aluminium hydride to produce 2,4-dihydroxy-1,1,1-trifluorobutane **4.45** (**Scheme 4.13**). Selective

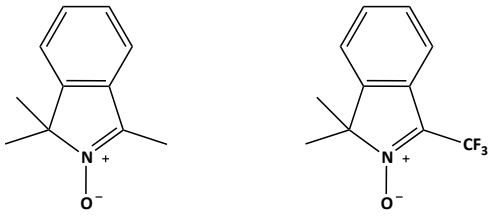
monotosylation of the primary alcohol of **4.45** gave 2-hydroxy-4-(tosyloxy)-1,1,1-trifluorobutane **4.46**. Oxidation of the hydroxyl group of **4.46** by Dess-Martin periodinane afforded 4-(tosyloxy)-1,1,1-trifluoro-2-butanone **4.47**, which was treated with a 10-fold excess of 2-nitropropane in ethanol to generate 5-methyl-5-nitro-1,1,1-trifluoro-2-hexanone **4.48**. Cyclization of nitroketone with zinc and acetic acid in ethanol provided 2-TFDMPO.



Scheme 4.13 Synthesis of 2-TFDMPO

Bottle et al. synthesized and evaluated isoindole-based nitrone 1,1,3-trimethylisoindole N-oxide (TMINO) **4.49** as a spin-trap (**Figure 4.14**).[472] The fused isoindole ring structure was expected to inhibit decomposition by ring-opening reactions and the absence of hydrogen atoms at the α-carbon was expected to

minimize the formation of artifactual nitroxide species via non-radical pathways. TMINO was stable for many months without significant decomposition when stored



TMINO 4.49 2-TFTMINO 4.50

Figure 4.14 Isoindole Based Cyclic Spin-Traps: TMINO and 2-TFTMINO

at -18 °C under argon atmosphere compared to DMPO, which developed significant paramagnetic impurities when stored under the same conditions. TMINO was capable of trapping both carbon- and oxygen-centered radicals, and the spin adducts were very stable. In a related study, Bottle et al. demonstrated selective spin-trapping of $HO^{\bullet}$ by TMINO in the presence of $O_2^{\bullet -}$.[473] Hatano et al. synthesized a derivative of TMINO bearing a trifluoromethyl group, 1,1-dimethyl-3-(trifluoromethyl)-1H-isoindole N-oxide (2-TFTMINO) **4.50** and evaluated spin-trapping ability for *i*-amyloxy radical.[474] The spin-trapping ability of TMINO and 2-TFTMINO was studied by irradiating the nitrones and *i*-amyl nitrite with UV light for 35 seconds at room temperature. The EPR spectrum of the TMINO adduct of *i*-amyloxy radical showed a strong signal exhibiting nitrogen hyperfine interactions of 13.2 G. The EPR spectrum of 2-TFTMINO adduct showed three groups of intensities

with the ratio of 1:3:3:1 (**Figure 4.15**). The EPR absorption profiles of 2-TFTMINO adduct with *n*-butyl nitrite, *i*-butyl nitrite, and *i*-amyl nitrite were similar to those of

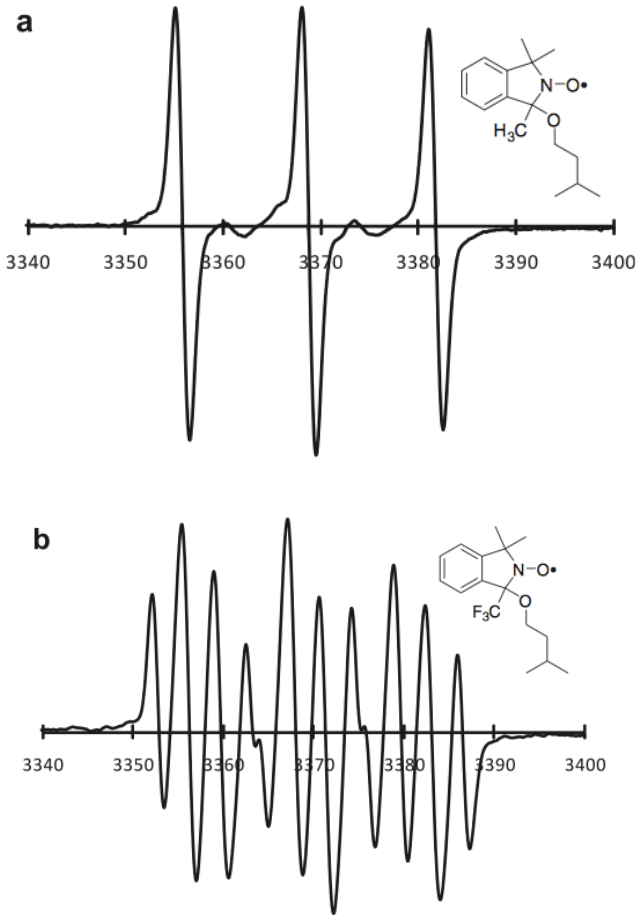
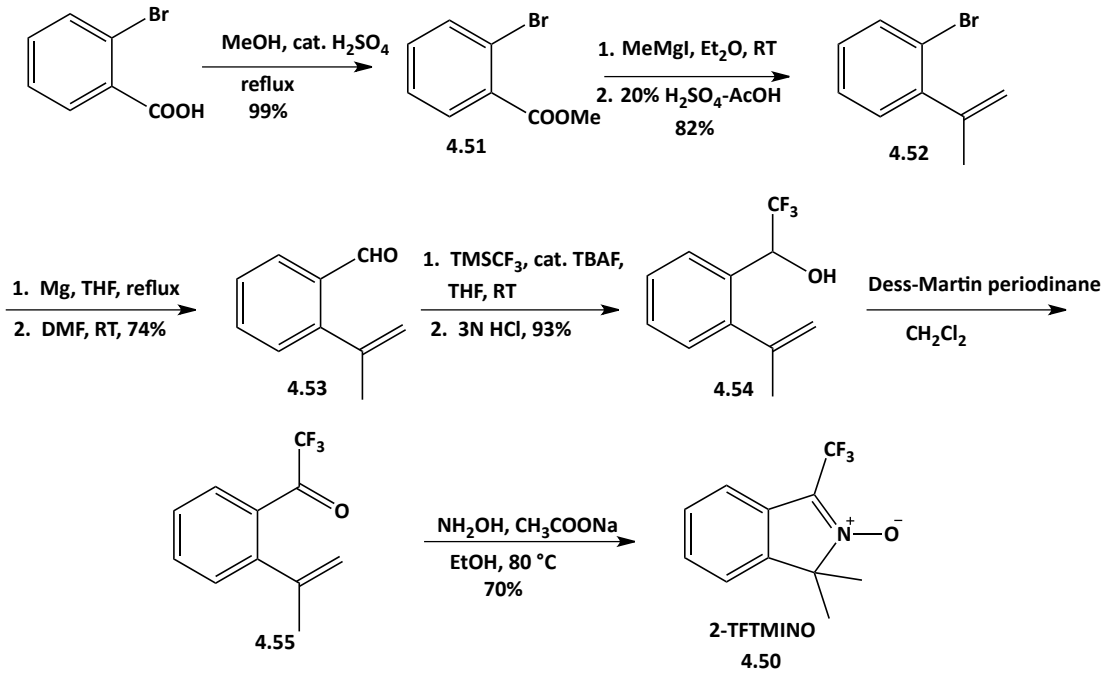


Figure 4.15 ESR spectra of Spin Adducts of TMINO 4.49 and 2-TFTMINO 4.50 in the Presence of *i*-Amyloxy Radical: Obtained by UV Photolysis in Benzene

radical adducts generated by 2-TFDMPO. Moreover, the radical adduct of 2-TFTMINO had a half-life of three days when stored in the dark, which was much longer than the radical adduct of TMINO with *i*-amyloxy radical.



Scheme 4.14 Synthesis of 2-TFTMINO

The synthesis of 2-TFTMINO started with esterification of 2-bromobenzoic acid with methanol in the presence of concentrated sulfuric acid as a catalyst to give ester **4.51** (**Scheme 4.14**). Methylation of **4.51** with methylmagnesium iodide and subsequent dehydration using a sulfuric acid-acetic acid system afforded the olefin **4.52**. The olefin was treated with magnesium metal to give the Grignard reagent, followed by the addition of dimethylformamide to give the aldehyde **4.53**. The trifluoromethyl group was incorporated into the aldehyde by using $TMSCF_3$ in the presence of a catalytic amount of tetrabutylammonium fluoride, followed by

oxidation using Dess-Martin periodinane to give ketone **4.55**. The final cyclization step to afford nitrone 2-TFTMINO **4.50** was carried out using hydroxylamine hydrochloride under buffered acidic conditions.

4.8 Detection of Free Radicals in the Atmosphere

Several sampling and analytical methods have been developed to identify and quantify ROS in air samples. The most common methods include matrix isolation and electron spin-resonance (MI-ESR),[475] peroxyl radical chemical amplification (PERCA),[476] chemical ionization mass spectrometry (CIMS),[477] and laser-induced fluorescence (LIF).[478] The MI-ESR technique traps peroxyl radicals by cryogenic solid inert gas matrix isolation followed by the analysis using EPR. This method requires a long sampling time (~ 30 minutes) to achieve a sensitivity of ~5 ppt. LIF has been used for the direct measurement of $HO^{\bullet}$. The reaction of $HOO^{\bullet}$ with NO generates $HO^{\bullet}$, which allows indirect determination of $HOO^{\bullet}$ possible using LIF (**Reaction (1)** in **Table 4.2**).[479,480] Although, LIF has high sensitivity to $HOO^{\bullet}$, it requires low pressure that results in the decomposition of some radicals. PERCA is an indirect method for *in situ* detection of peroxyl radicals. This technique uses chemiluminescence reaction of NO_2 with luminol.[481,476] The $HOO^{\bullet}$ is converted to NO_2 and $HO^{\bullet}$ in reactions with

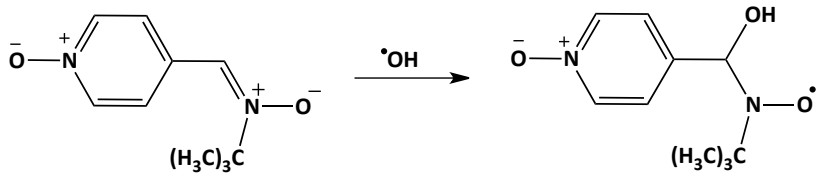
excess NO. The $HO^{\bullet}$ is converted back to $HOO^{\bullet}$ through the addition of CO,[482] which again reacts with NO to produce NO_2 and $HO^{\bullet}$ (**Reactions 1, 2,** and **3** in **Table 4.2**).

$HOO^{\bullet} + NO \longrightarrow HO^{\bullet} + NO_2$	**(1)**
$HO^{\bullet} + CO \longrightarrow H + CO_2$	**(2)**
$H + O_2 \longrightarrow HOO^{\bullet}$	**(3)**

Table 4.2 Indirect Determination of $HOO^{\bullet}$ Using LIF by Reaction (1) and PERCA by Reactions (1), (2) and(3)

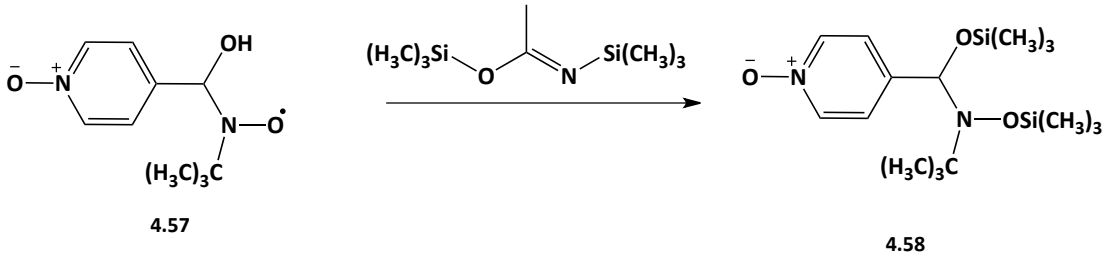
This chain reaction produces amplified level of NO_2, which is then detected using PERCA. However, luminol detection of NO_2 is subject to interference by ozone and other oxidants. These methods have been applied to various outdoor and indoor air samples, laboratory-generated tobacco smoke and secondary organic aerosol particles from ozone chemistry. However, accurate analytical determination of ROS is still challenging, due to the high reactivity of the radicals, instability of probes and potential interference with other atmospheric species. Furthermore, methods used successfully to determine high ROS concentrations (such as those present in tobacco smoke and other combustion sources) may not be directly applicable to lower levels found in the atmosphere.

While spin-trapping of short-lived free radicals using nitrones coupled with EPR has been widely used in biomedical research, employment of this method for the detection of free radicals in the atmosphere is less common. Watanabe et al. succeeded in trapping HO$^{\bullet}$ from the atmosphere using the nitrone alpha-(4-pyridyl-1-oxide)-*N*-tert-butylnitrone (4-POBN) **4.56**, **Scheme 4.15**.[483] An airborne sampler,



Scheme 4.15 Trapping of Atmospheric HO$^{\bullet}$ with 4-POBN

mounted with a filter paper impregnated with 4-POBN was used in this study. The air was collected at 10 km above Japan, and the resulting 4-POBN-OH **4.57** adduct was isolated after washing the filter paper with acetone. The acetone was evaporated and the residue was dissolved in benzene and analyzed by EPR. For the GC-MS measurements, radical adduct **4.57** was transformed into a volatile derivative **4.58** by trimethysilylation using *N*,*O*-bis(trimethylsilyl)acetamide (**Scheme 4.16**). The results indicated that the concentration of HO$^{\bullet}$ ranges from 10^5 to 10^6 molecules/cm^3 at an altitude of 10 km.



4.57 4.58

Scheme 4.16 Trimethylsilylation of Hydroxyl Adduct of 4-POBN

Sakakibara et al. reported the use of poly[*N*-(*p*-vinylbenzylidene)-*tert*-butylamine oxide] (polyPBN) **4.59** and copolymers of PBN and styrene (copolyPBN) **4.60** (**Figure 4.16**) in reactions with alkyl radicals in the gas phase.[484] The spin-trap containing polymers were deposited on glass wool or on solid foam filled in a spin-trapping reactor tube. Alkyl radicals were generated via photolysis of the corresponding alkyl chloride. The spin-adducts were characterized and quantitatively determined by EPR. The peaks of polyPBN adducts were considerably broader than those of the monomeric PBN. The significant broadening of peaks is attributed to the restricted motion of the nitroxide moiety in the solid polymer. The broadening was decreased to some extent in the spectrum of copolyPBN adducts, probably due to the decrease in the steric congestion around the nitroxide moiety.

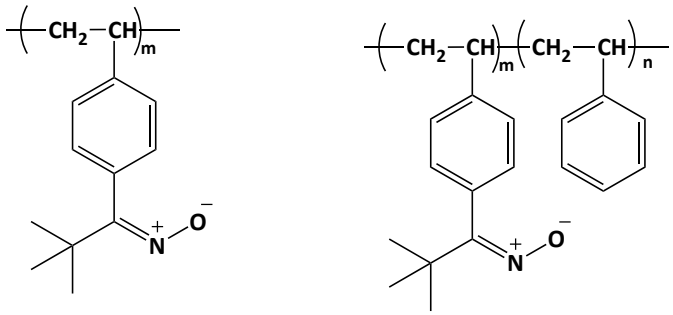


Figure 4.16 Sakakibara's Polymer and Copolymer of PBN and Styrene

4.9 Preparation of a Polystyrene Supported Cyclic Trifluoromethylated Nitrone Spin-Trap

The goal of this project was to develop a trifluoromethylated cyclic nitrone spin-trap tethered to a polystyrene support for the detection of free radicals in the atmosphere, to study reactions on aerosol particles. This project is a collaboration with Dr. Eric Walter from the Environmental Molecular Sciences Laboratory (EMSL) at the Pacific Northwest National Laboratory. Continuous flow NMR and EPR capabilities have been developed at EMSL, which allows the monitoring of chemistry on a solid phase while a gas or liquid mobile phase flows through the sample cell. This technique has been used primarily in the fields of biochemistry and catalysis. This project aims to apply this technique to study the reactive species on aerosol particles using polymer-supported fluorinated cyclic nitrone spin-traps as a solid phase. As shown in **Figure 4.17**, particulates from air flow will be collected in a non-

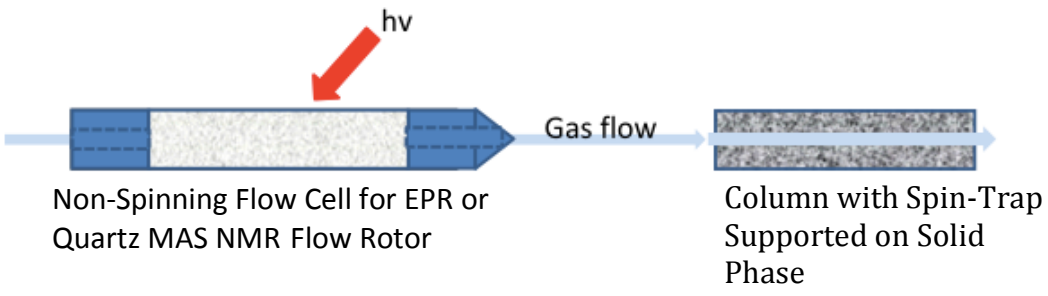


Figure 4.17 Generalized Flow Scheme For Spin-Trapping Experiments (This figure is adapted from a grant proposal by Dr. Eric Walter)

spinning flow cell for EPR or in a quartz Magic Angle Spinning (MAS) rotor for NMR (left). Particulates will be irradiated with UV light. The immobile products of these UV reactions will be studied in a time dependent manner with EPR or NMR. The gas outflow will carry mobile radicals, which will be trapped by the fluorinated nitrone column (right). The contents of the spin-trap column will be analyzed by ^{19}F NMR and EPR. This work is expected to enhance the field of aerosol chemistry by combining continuous flow NMR and EPR techniques using the polymer-supported fluorinated spin-trap methodology.

FDMPO **4.38** is the only fluorinated cyclic nitrone spin-trap commercially available that can be tethered to a solid support. FDMPO is very expensive (10 mg for $83) and the synthesis is not straightforward. An attempt in our lab to replicate Janzen's synthesis of 2-TFDMPO **4.44** failed. Tosylate **4.47**, **Scheme 4.13** undergoes

elimination to form the intermediate trifluoromethylvinyl ketone. In our hands, this unsaturated ketone underwent polymerization prior to nitroalkane addition. Therefore, a new synthetic strategy to prepare 2-TFDMPO **4.44** was developed, and was modified to develop two hydroxyl analogues: 2-HFDMPO **4.61** and 2-PFDMPO **4.62**, **Figure 4.18**. These hydroxyl substituted analogues of 2-TFDMPO were then attached to a polystyrene resin to form **4.63** and **4.64**. The spin-trapping chemistry of these newly synthesized nitrones were studied by EPR and ^{19}F NMR.

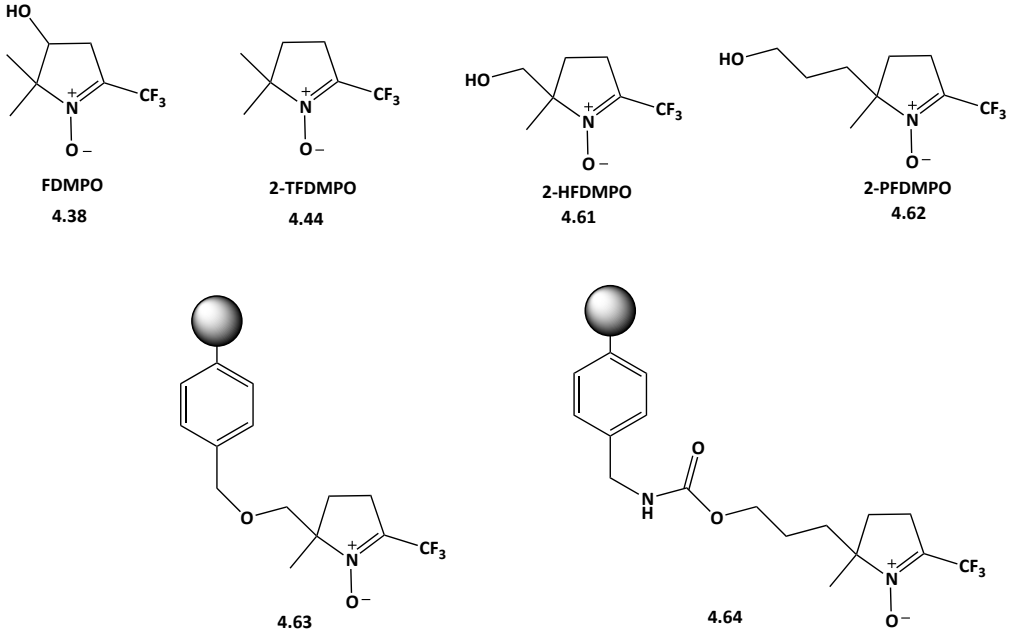
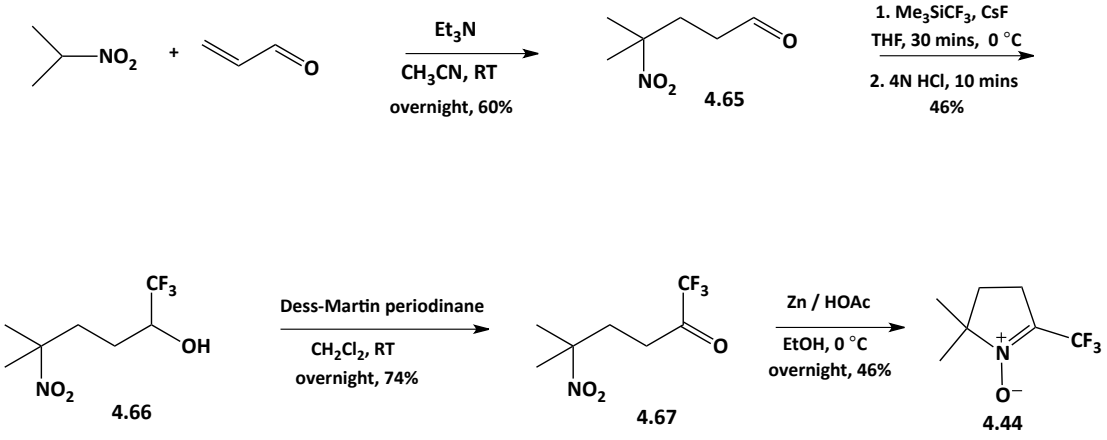


Figure 4.18 FDMPO, 2-TFDMPO and Derivatives Studied in this Work

4.10 Alternate Synthesis of 2-TFDMPO

Our alternate synthesis of 2-TFDMPO **4.44** started with a Michael reaction of commercially available 2-nitropropane to acrolein in the presence of a catalytic amount of triethylamine to give nitroaldehyde **4.65**, **Scheme 4.17**. The nucelophilic addition of trifluormethyltrimethyl silane ($TMSCF_3$) with cesium fluoride as a catalyst in dry tetrahydrofuran gave the trifluoromethylated alcohol **4.66**. Trifluoromethylation of carbonyl derivatives is a valuable tool for carbon-CF_3 bond construction. The trifluoromethylating agent trifluoromethyltrimethylsilane



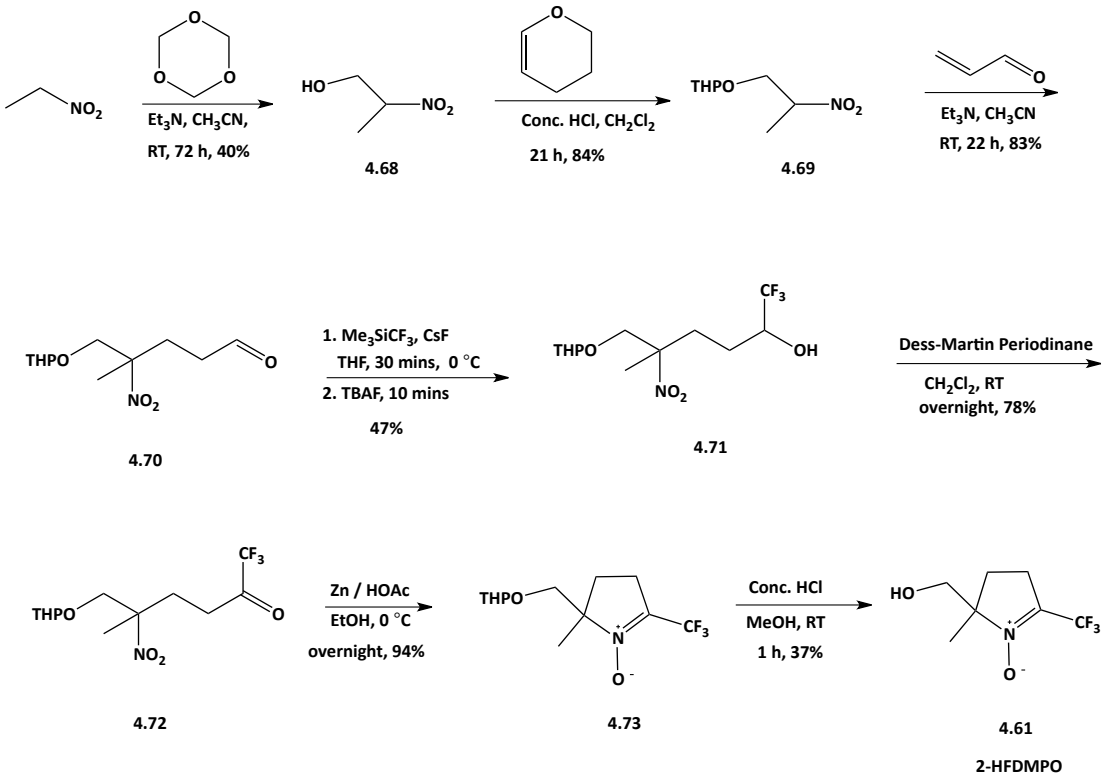
Scheme 4.17 Our Alternate Synthesis of 2-TFDMPO

($TMSCF_3$), also known as the Ruppert-Prakash reagent, has been used extensively to incorporate the trifluoromethyl group into organic compounds by nucleophilic addition.[485] $TMSCF_3$ itself does not react with carbonyl compounds, but needs to be

activated by an initiator to liberate the trifluoromethide anion. Usually sources of fluoride anion such as tetrabutylammonium fluoride, tetramethylammonium fluoride, or cesium fluoride are used as this initiator. However, TBAF gave poor results in our case. The CF_3 addition step was followed by oxygen desilylation using aqueous acid to give the desired trifluoromethylated alcohol **4.66**. The oxidation of **4.66** with Dess-Martin periodinane in dichloromethane afforded the ketone in 74% yield **4.67**. Finally, the reductive cyclization of the nitroketone using zinc and acetic acid in ethanol gave the desired nitrone 2-TFDMPO **4.44**. Our alternate synthesis of 2-TFDMPO involved four steps with an overall yield of 9.4% compared to five steps of Janzen's synthesis with an overall yield of 29.3% (**Scheme 4.13**). A major advantage of our route is the avoidance of pyrophoric lithium borohydride and sodium borohydride from the synthesis, making potential scale-up attractive. Our route also made the synthesis of functionalized analogues viable, as described in the next few sections.

4.11 Synthesis of 2-HFDMPO

For the preparation of 2-HFDMPO, a similar route was utilized using a protected hydroxyl substituted analogue of 2-nitropropane. Thus, 2-nitropropanol **4.68** was synthesized by the reaction of nitroethane and paraformaldehyde in acetonitrile using triethylamine as a base. The hydroxyl group of 2-nitroethanol was protected using 3,4-dihydropyran in the presence of hydrochloric acid to give **4.69**, which was



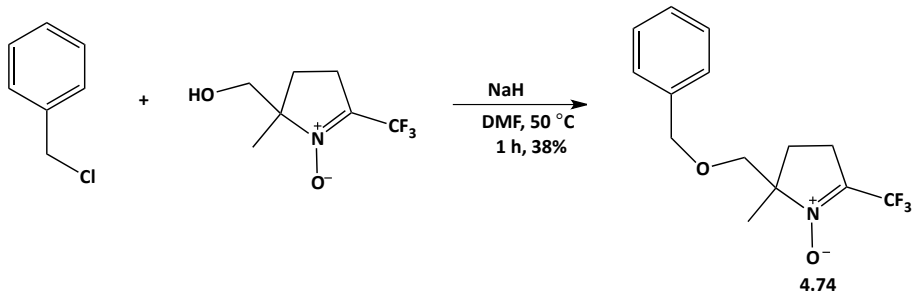
Scheme 4.18 Synthetic Scheme for the Preparation of 2-HFDMPO

then used in a Michael addition to acrolein to afford the THP-protected nitroaldehyde **4.70** in 70% yield over two steps (**Scheme 4.18**). Trifluoromethylation of the aldehyde with $TMSCF_3$ afforded the alcohol **4.71** in 47% yield. Dess-Martin periodinane oxidation of the alcohol gave the ketone **4.72** in 78% yield. Reductive cyclization of the nitroketone using Zn and acetic acid in ethanol afforded the nitrone **4.73** in excellent yield. Final deprotection of the THP group was carried out with hydrochloric acid in methanol in a disappointing yield to give 2-HFDMPO **4.61** as a white solid with a melting point of 70 – 72 °C. The hydroxyl substituted nitrone

2-HFDMPO is soluble in water as well as in most organic solvents, making it suitable for experiments in aqueous as well as in lipophilic environments.

4.12 Preparation of Polystyrene Supported 2-HFDMPO (Resin-2-HFDMPO)

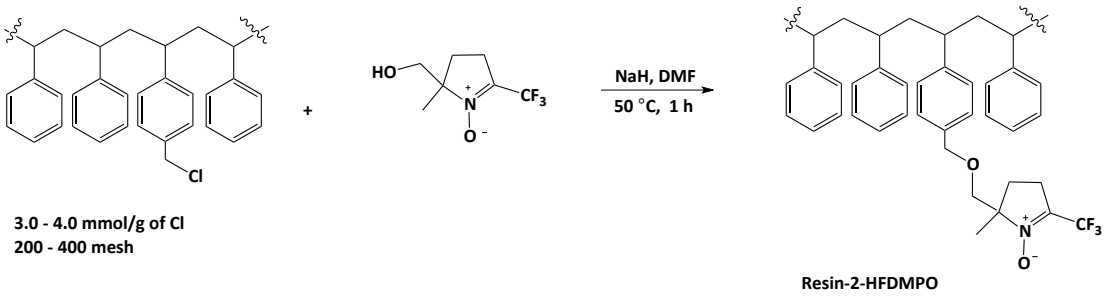
Benzyl chloride was selected as a model compound to test the viability of the nucleophilic substitution of the benzylic chloride in Merrifield resin by the alcohol of 2-HFDMPO, **Scheme 4.19**. The reaction of benzyl chloride with 2-HFDMPO in DMF using sodium hydride at 50 °C afforded the desired ether **4.74** in 38% yield.



4.74

Scheme 4.19 Model Reaction of Benzyl Chloride With 2-HFDMPO

To append 2-HFDMPO to Merrifield resin, a mixture of resin, 2-HFDMPO, and sodium hydride was stirred in anhydrous dimethylformamide at 50 °C for 1 h. The progress of the reaction was monitored by thin layer chromatography to observe the disappearance of 2-HFDMPO (**Scheme 4.20**). The presence of the nitrone spin-trap on the resin was confirmed by EPR of the $HO^{\bullet}$ trapped adduct.



Scheme 4.20 Preparation of 2-HFDMPO Tethered to Merrifield Resin

4.13 Spin-Trapping Experiments Using Polystyrene Supported 2-HFDMPO

As shown in **Figure 4.19**, Resin-2-HFDMPO was immobilized in teflon tubing, which was connected to an EPR instrument. EPR spectra were recorded continously (**Figure 4.20**) by flowing a mobile phase over Resin-2-HFDMPO via a programmable double syringe pump with a mixer and a divert valve (not shown in the **Figure 4.19**).

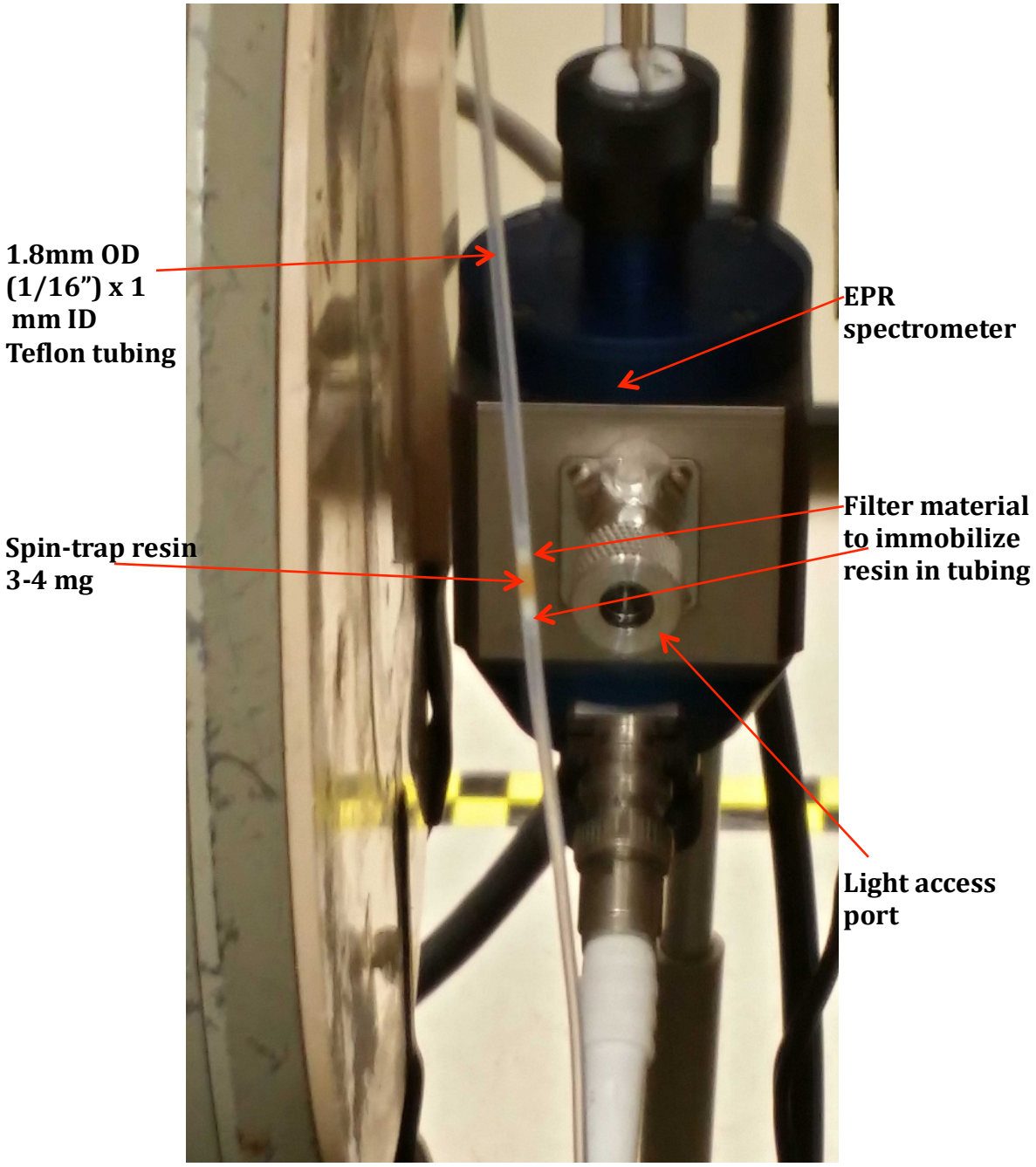


Figure 4.19 Flow-cell for Immobilized Spin-Trap Experiments, Shown Outside of the EPR Spectrometer (Image from Dr. Eric Walter)

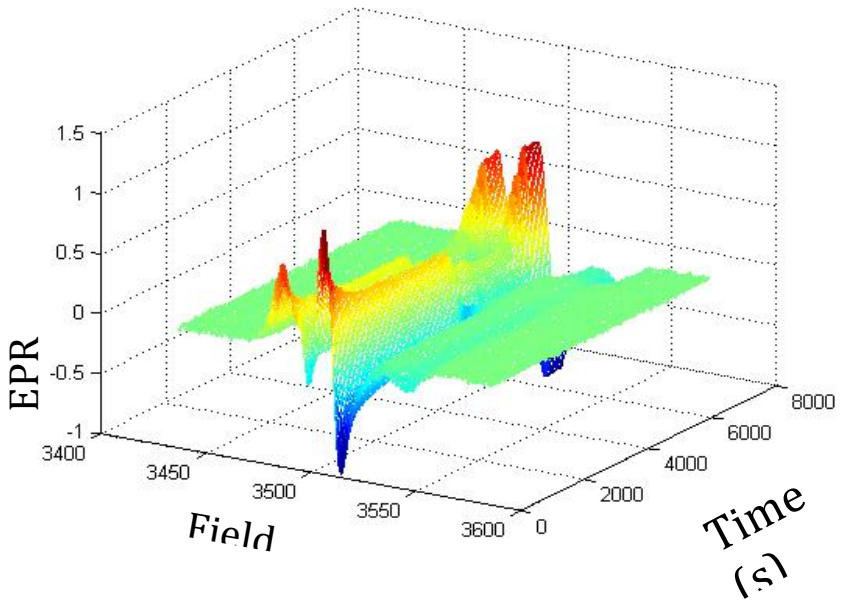
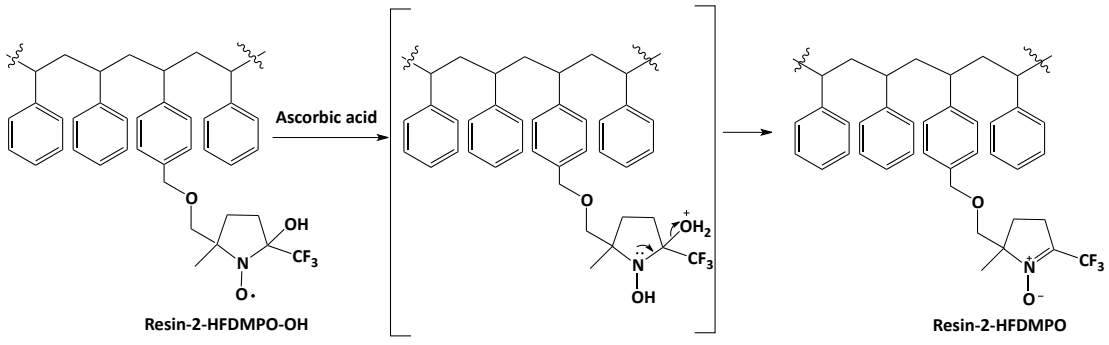


Figure 4.20 Three Dimensional Plot of Time Resolved HO• Spin-Trap Experiment

Hydroxyl radicals were generated by photolysis of 3% hydrogen peroxide solution in water using a UV lamp, and were trapped by the Merrifield resin supported 2-HFDMPO. The spin-trap resin was rejunevated by reducing it with ascorbic acid for the next experiment (**Scheme 4.21**).



Scheme 4.21 Rejunevation of Resin-2-HFDMPO

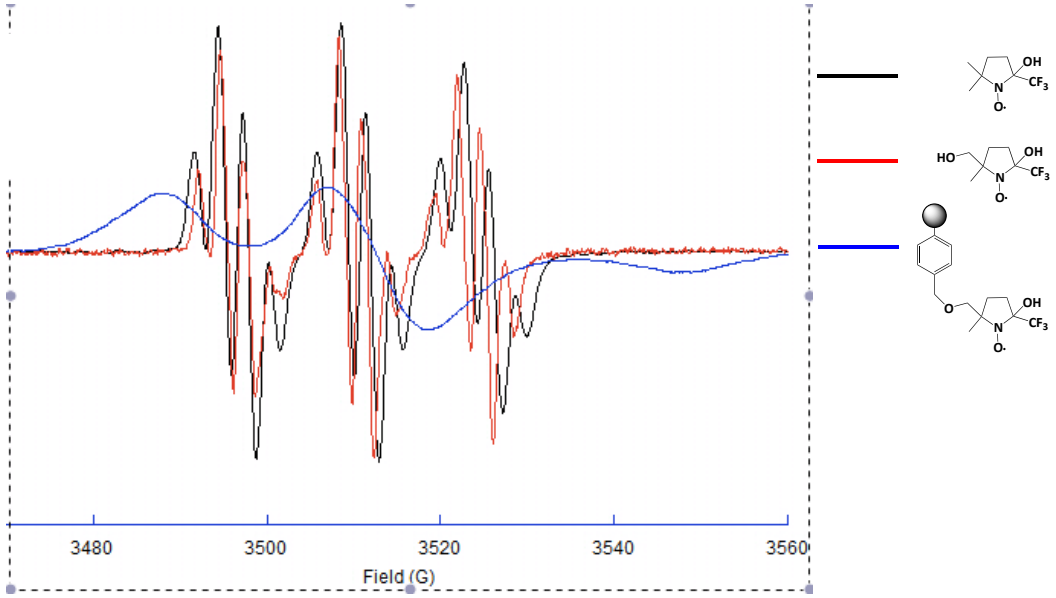
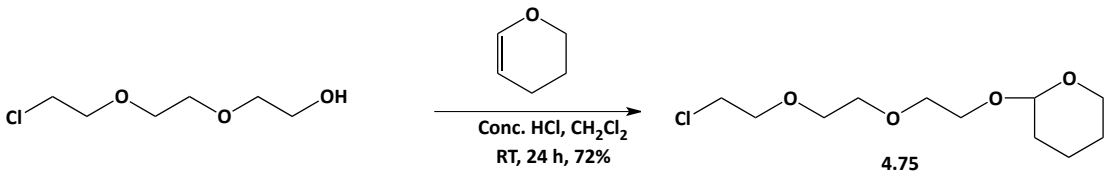


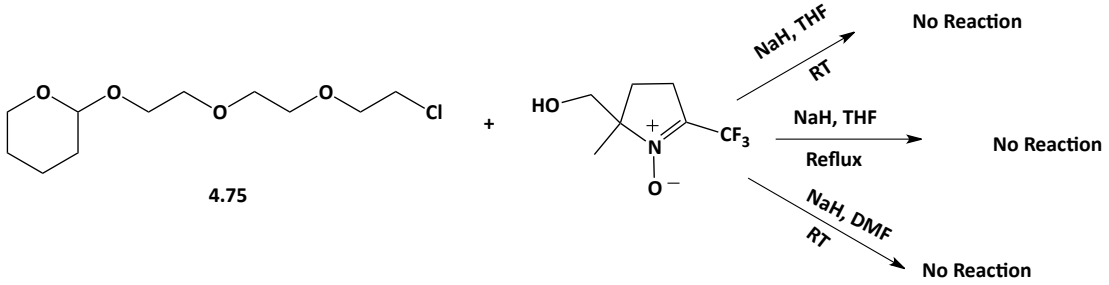
Figure 4.21 EPR spectra of 2-TFDMPO-OH (black), 2-HFDMPO-OH (red), and Resin-2-HFDMPO-OH (**blue**) in water

The EPR spectrum of the hydroxyl adduct of Resin-2-HFDMPO gave broad peaks compared to the EPR spectra of hydroxyl adducts of 2-TFDMPO and 2-HFDMPO (**Figure 4.21**). The absence of hyperfine splitting makes the identification of the original radical difficult. The significant broadening of the peaks is likely due to the close proximity of the spin-trap to the polymer, which results in restricted motion of the nitroxide adduct. A longer linker between the nitrone and resin would provide more freedom of rotation, and should give spectra with narrow peaks. This would make it possible to distinguish the identity of the radical adducts. It was decided to use triethylene glycol as a linker. For this purpose, commerically available chloroethoxyethoxy ethanol was protected with 3,4-dihydropyran to give the

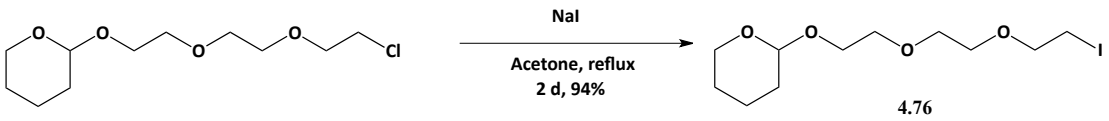
corresponding THP-protected chloro ether **4.75** (**Scheme 4.22**). Attempts to displace the chlorine atom with the neopentyl hydroxyl group of 2-HFDMPO failed (**Scheme 4.23**). Thus the chlorine atom was substituted with iodine atom using a Finkelstein reaction to give the iodo ether **4.76** (**Scheme 4.24**).



Scheme 4.22 Monoprotection of Chloroethoxyethoxy ethanol

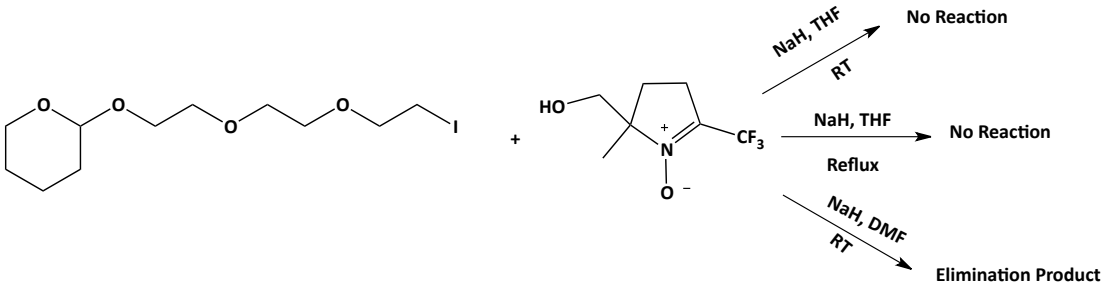


Scheme 4.23 Attempted Nucleophilic Substitution Reaction of 4.75 with 2-HFDMPO



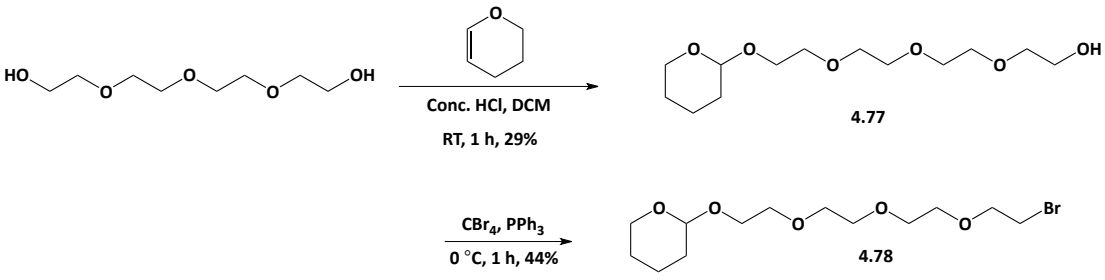
Scheme 4.24 Synthesis of Iodo-Ether Via Finkelstein Reaction

The reactions of iodo ether **4.76** with the anion of 2-HFDMPO did not work in tetrahydrofuran at room temperature nor under reflux. The elimination product was obtained in dimethylformamide (**Scheme 4.25**).

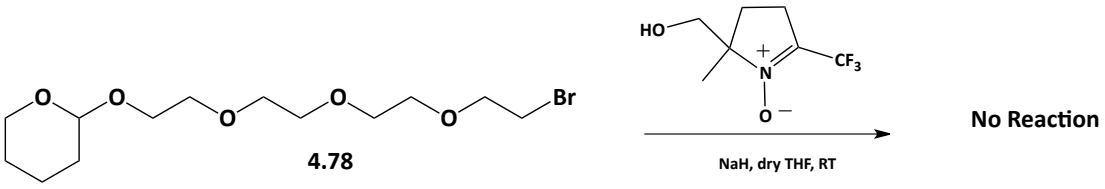


Scheme 4.25 Attempted Substitution Reactions of iodide 4.76 with 2-HFDMPO

The THP-protected chloroethoxyethanol **4.75** did not undergo reaction with 2-HFDMPO, and the THP-protected iodoethoxyethanol **4.76** gave only elimination product. It was decided to synthesize a bromo derivative. For this purpose, the mono-protection of commerically available tetraethylene glycol was carried out using 3,4-dihydropyran. The mono-protected alcohol **4.77** was converted into bromide **4.78** using carbon tetrabromide and triphenylphosphine in dichloromethane (**Scheme 4.26**). The bromide also failed to react with the hydroxy nitrone in dry tetrahydrofuran using sodium hydride (**Scheme 4.27**).

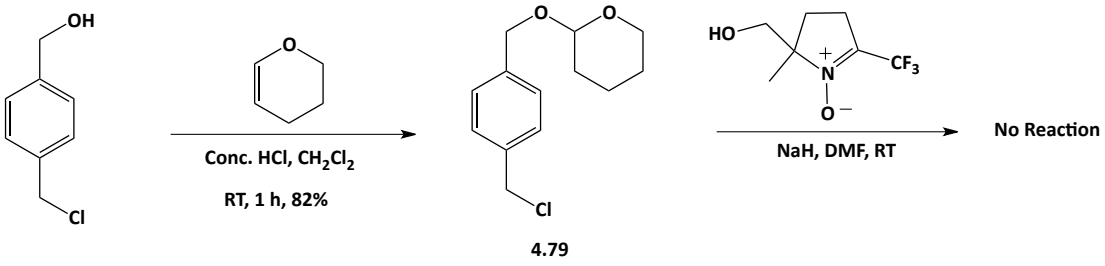


Scheme 4.26 Synthesis of Bromo-Derivative of Tetraethylene Glycol



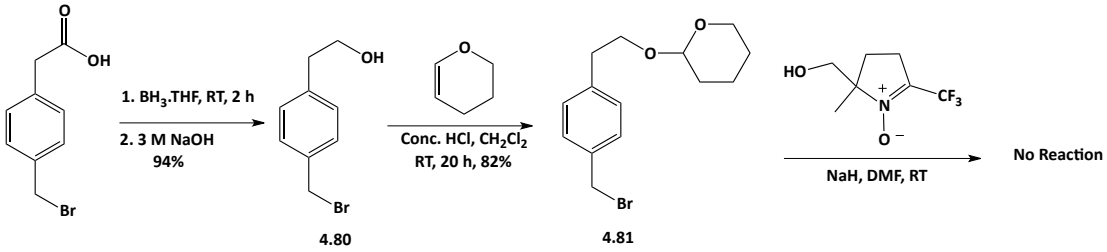
Scheme 4.27 Attempted Nucleophilic Substitution Reaction of 4.78 with 2-HFDMPO

The primary halides showed no reactivity with the neopentyl alcohol of 2-HFDMPO. A benzyl halide would be more reactive in the Williamson ether synthesis. Hence, it was decided to use 4-chloromethylbenzyl alcohol to link 2-HFDMPO to the Merrifield resin. The 4-chloromethylbenzyl alcohol was obtained commercially, and protected using 3,4-dihyropyran and a catalytic amount of concentrated hydrochloric acid in dichloromethane to give protected alcohol **4.79** in 82% yield, **Scheme 4.28**. The reactions of THP protected benzyl alcohol with 4-HFTDMPO using sodium hydride also did not work.



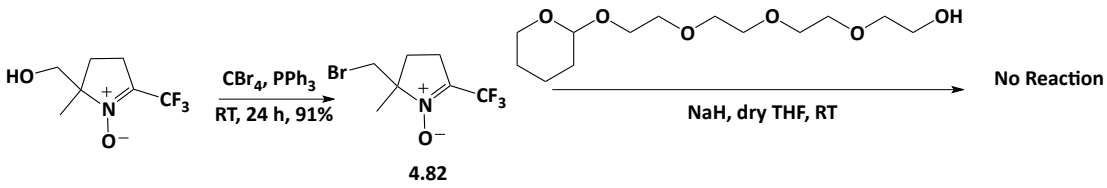
Scheme 4.28 Protection of 4-Chloromethylbenzyl Alcohol and Attempted Reaction with 2-HFDMPO

Benzyl bromide would be more reactive than benzyl chloride. Therefore, methyl 4-(bromomethyl)phenylacetic acid was reduced to the respective alcohol **4.80** using hydroborane in THF followed by the protection of the alcohol with 3,4-dihydropyran in dichlormethane to give **4.81**. This bromide also failed to react with the neopentyl alcohol 2-HFDMPO (**Scheme 4.29**).



Scheme 4.29 Synthesis of THP-protected Bromomethyl Benzyl Alcohol and Attempted Reaction with 2-HFDMPO

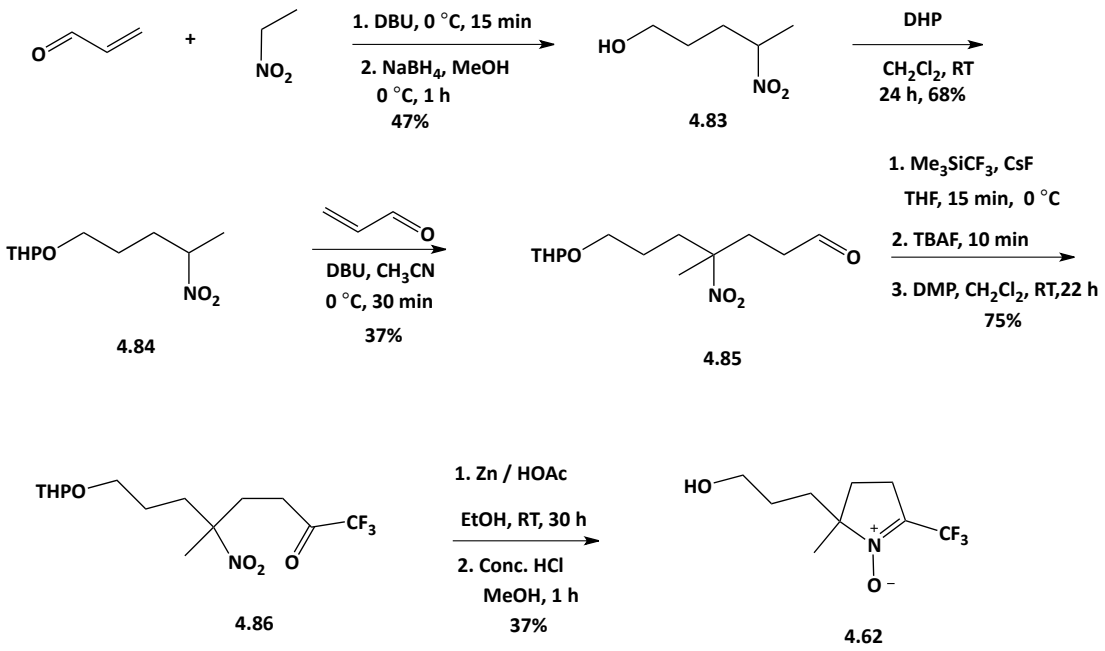
A reverse strategy was applied: the neopently alcohol of 2-HFDMPO was converted into the corresponding bromide **4.82** using carbon tetrabromide and triphenyl phosphine in dichloromethane (**Scheme 4.30**). The reaction of neopentyl bromide with monoprotected tetraethylene glycol using sodium hydride in THF did not work.



Scheme 4.30 Synthesis of Bromo-Derivative of 2-HFDMPO and Attempted Reaction with Mono-Protected Tetraethylene Glycol

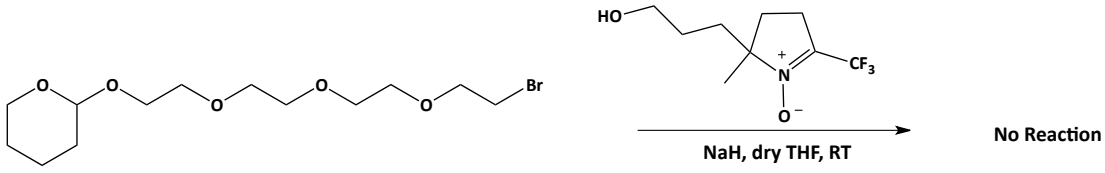
4.14 Synthesis of 2-PFDMPO

The lack of reactivity of the alkoxide of 2-HFDMPO with alkyl halides and benzyl halides is probably due to the steric hindrance of this neopentyl alcohol. Therefore, a nitrone with a primary alcohol tether, 2-PFDMPO **4.62**, was developed. For the preparation of 2-PFDMPO, Michael reaction of the anion of nitroethane with acrolein was carried out using catalytic 1,8-diazabicycloundec-7-ene (DBU) as a base in acetonitrile to give the corresponding nitroaldehyde, which was reduced using sodium borohydride in methanol to yield the alcohol **4.83** (**Scheme 4.31**) in 47% yield. The alcohol **4.83** was protected using 3,4-dihydropyran to give the product **4.84** in 68% yield. The THP-protected nitro compound was again allowed to react with acrolein in the presence of DBU in acetonitrile to give the aldehyde **4.85** in 37% yield. Trifluoromethylation of this nitroaldehyde was carried out using the Ruppert-Prakash reagent ($TMSCF_3$) followed by desilylation with tetrabutylammonium fluoride to give the corresponding alcohol, which was oxidized using Dess-Martin periodinane to give trifluoromethyl ketone **4.86** in 75% yield. Zinc and acetic acid in ethanol was used for the reductive cyclization of ketone, followed by deprotection to give 2-PFDMPO in 37% yield. The nitrone 2-PFDMPO is an amphiphilic molecules with solubilities in water as well as in most organic solvents.



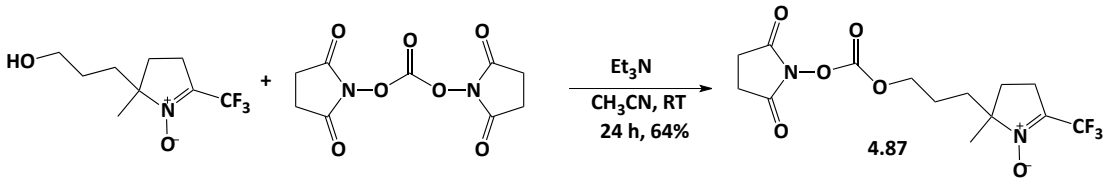
Scheme 4.31 Synthetic Scheme For 2-PFDMPO

The alkoxide of 2-PFDMPO was generated in dry tetrahydrofuran using sodium hydride at room temperature, with the intention to take part in a nucelophilic substitution reaction with bromo-derivative of THP-protected tetraethylene glycol. This reaction failed under these conditions (**Scheme 4.32**).



Scheme 4.32 Attempted Nucleophilic Substitution of THP-protected Bromo Ether 4.78 with 2-PFDMPO Alkoxide

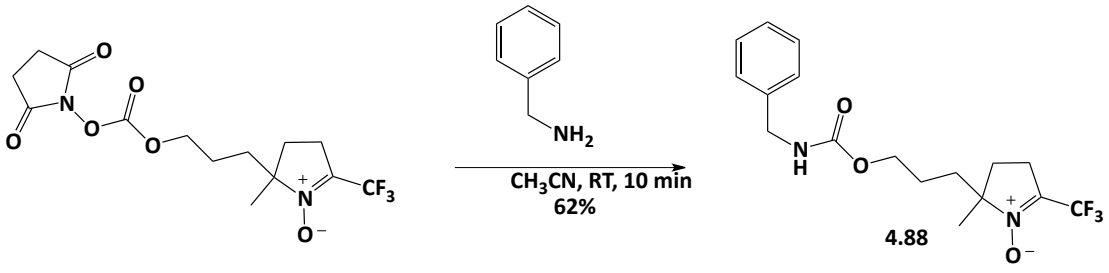
The nucleophilic substitution reactions of 2-HFDMPO and 2-PFDMPO were not successful, and even a benzylic halide failed to react with 2-HFDMPO. S_N2 reactions of alcohols with an sp^3 carbon atom bearing a leaving group is much more sterically demanding than acylation at a flat sp^2 carbon atom. Thus another approach was investigated in which the hydroxyl group of 2-PFDMPO was activated by addition of *N,N*'-disuccinimidyl carbonate (DSC), followed by subsequent coupling with a primary amine to form a carbamate. This coupling chemistry has been used extensively for the PEGylation of proteins and drugs, and for solid phase synthesis of peptide carbamates. This reaction is chemospecific in reactions with primary amines. Moreover, the resulting carbamate linkage is known to have good stability againsts hydrolysis. Thus nitrone 2-PFDMPO was activated with DSC in acetonitrile using triethylamine as a base to afford the desired activated alcohol acyl succinate of 2-PFDMPO **4.87** in 64% yield (**Scheme 4.33**).



Scheme 4.33 Conversion of the Primary Alcohol of 2-PFDMPO into an Acyl Succinate

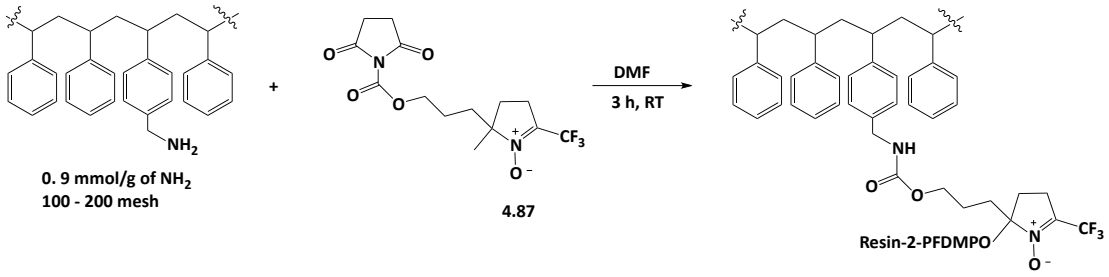
4.15 Polystyrene Supported 2-PFDMPO (Resin-2-PFDMPO)

As a model reaction, the activated acyl succinate of 2-PFDMPO was treated with benzyl amine in acetonitrile at room temperature to give the respective carbamate **4.88** in 62% yield (**Scheme 4.34**).



Scheme 4.34 Model Reaction of Acyl Succinate of 2-PFDMPO with Benzyl Amine

To append 2-PFDMPO onto an aminomethylated polystyrene resin, a mixture of resin and acyl succinate nitrone **4.88** was stirred in dimethylformamide for 3 h (**Scheme 4.35**). The polystyrene resin beads exhibit better swelling in dimethylformamide than in acetonitrile. The progress of the reaction was monitored by thin layer chromatography to observe the disappearance of the activated nitrone **4.88**. The presence of nitrone on the resin was confirmed by EPR as the $ClH_2C^{\bullet}$ addition product.



Scheme 4.35 Preparation of Polystyrene Supported 2-PFDMPO: Resin-2-PFDMPO

4.16 Spin-Trapping Experiments of the Polystyrene Supported 2-PFDMPO

For spin-trapping experiments using Resin-2-PFDMPO as the solid phase, the alkyl radical $ClH_2C^{\bullet}$ was generated by the photolysis of dichloromethane. The EPR spectrum of the adduct was compared to the EPR spectrum of 2-HFDMPO-CH_2Cl. As expected, the braodending of peaks was significantly reduced in the EPR spectrum of the adduct Resin-2-PFDMPO-CH_2Cl with a longer, more flexible linker than Resin-2-HFDMPO-CH_2Cl (**Figure 4.22**). Although the spectrum of the spin-adduct Resin-2-PFDMPO-CH_2Cl is not as narrow as that of free small molecule 2-HFDMPO, it is narrow enough to distinguish between different radical adducts. The next step is to investigate other gas-phase radicals such as $O_2^{\bullet-}$, $HO^{\bullet}$, $CH_3O^{\bullet}$, and to extend this technique towards the study of free radical reactions on aerosol particulates.

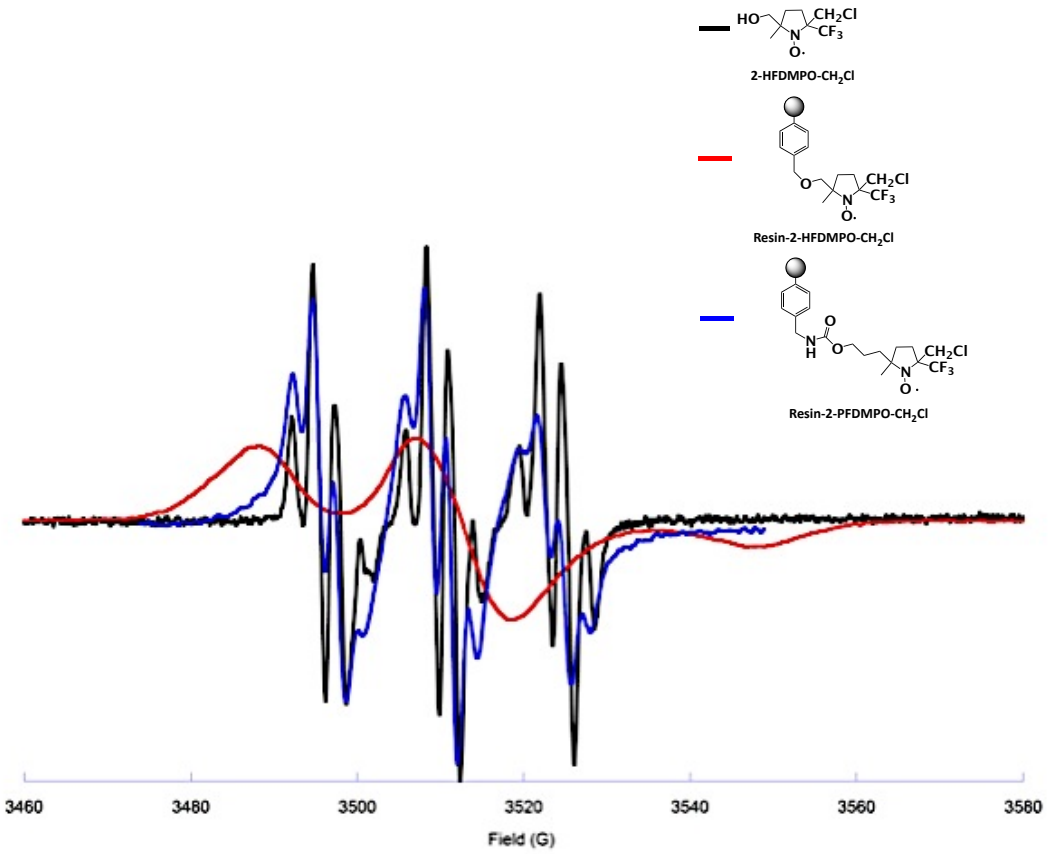


Figure 4.22 EPR spectra of 2-HFDMPO-CH_2Cl (black), Resin-2-HFDMPO-CH_2Cl (red), and Resin-2-PFDMPO-CH_2Cl (**blue**)

4.17 Conclusion

A comprehensive understanding of free radical behavior in the atmosphere and reactions with organic and inorganic compounds is of paramount importance from an environmental perspective. Investigators need atmospheric models with high accuracy and resolution to study free radical reactions on aerosol particulates to

determine the effects of increased pollution on climate change. The instrumentation developed at EMSL, which uses continuous flow EPR and NMR spectroscopy coupled with polymer-supported spin-trap was successfully utilized to detect free radicals in the solution as well as in the gas-phase. This technique will enable the detection of ROS and RNS in the atmosphere and enhance advances in the field of aerosol chemistry. An improved synthesis of 2-TFDMPO was developed and two new amphiphilic nitrones (2-TFDMPO, 2-HFDMPO, and 2-PFDMPO) were prepared for this project. These fluorinated spin-traps may also facilitate biological studies of free radicals in aqueous as well as in subcellular lipophilic environments. Moreover, the hydroxyl functional groups on 2-HFDMPO and 2-PFDMPO provide a functional handle to enable the tethering of spin-traps to macromolecules such as peptides and cyclodextrins for site-specific detection of free radicals in the cell.

4.18 References

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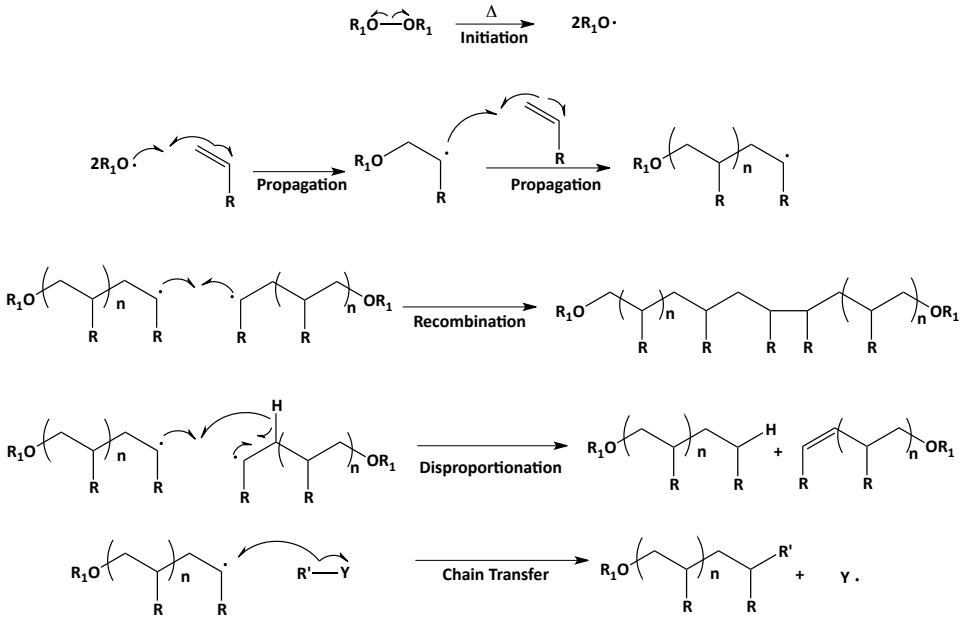
5 Synthesis of Fluorinated Alkoxyamines and Alkoxyamine-Initiated Nitroxide-Mediated Precipitation Polymerizations of Styrene in Supercritical Carbon Dioxide

5.1 Controlled/Living Radical Polymerization (CLRP)

Free radical polymerization (FRP) is one of the most widely used processes for the commercial production of high molecular weight polymers. Conventional FRP is an uncontrolled chain reaction initiated by free radicals formed from an initiator. The chain propagation occurs by the sequential addition of monomer units to form propagating radicals. The chains are terminated when these propagating radicals react with one another by recombination or disproportionation (**Scheme 5.1**). Due to significant termination or chain transfer, the resulting polymer displays poor molecular weight control and undefined chain ends with a polydispersity index (PDI) of > 1.5. PDI is the ratio of weight average molecular weight (M_w) and the number average molecular weight (M_n) of the polymer (**equation 5.1**). M_w, M_n, and PDI are obtained by gel permeation chromatography (GPC) or size exclusion chromatography, which use a series of columns packed with materials of different pore sizes. High molecular weight polymers pass through the column faster than the low molecular weight polymers as they are trapped in the porous material. The detector (UV-visible or refractive index) measures the signal of the polymers as they

are eluted and the affiliated software compares the data with polymer standards of known molecular weight to provide M_w, M_n, and PDI.

$$\boldsymbol{PDI = \frac{M_w}{M_n}} \qquad \textbf{equation 5.1}$$



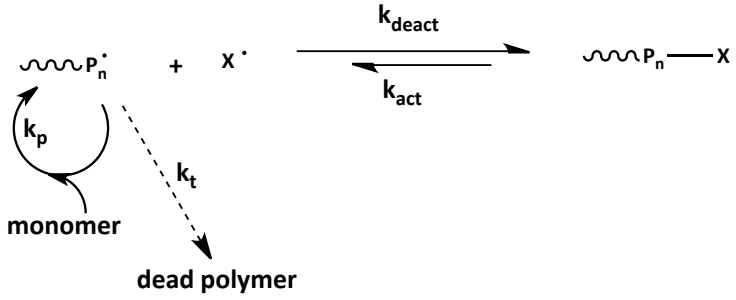
Scheme 5.1 Reactions Involved in Conventional Free Radical Polymerization: Initiation, Propagation, and Termination Through Recombination, Disproportionation, or Chain transfer.

The drawbacks of conventional FRP have been addressed with the advent of controlled/living radical polymerization (CLRP).[486] In an ideal controlled/living polymerization, all chains are initiated at the beginning of the process, grow at a similar rate, and survive the polymerization without being terminated due to

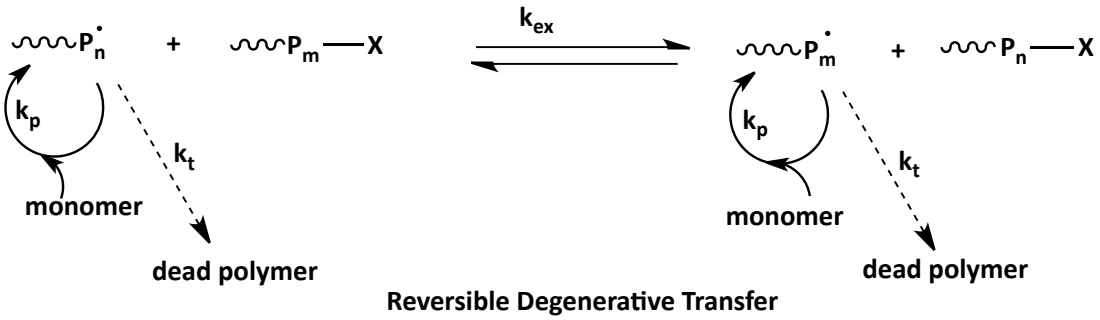
irreversible chain transfer or recombination. This results in a narrow molecular-weight distribution (PDI<1.5). The term "living" is used to describe a class of chain-growth polymerizations that react in a controlled manner until manually terminated. IUPAC recommends the use of "reversible-deactivation radical polymerization" (RDRP) instead of the more widely used "living/controlled free radical polymerization" (LFRP), since termination by radical-radical reactions or chain transfer reactions will always occur, no matter how minimal the termination might be within radical polymerization systems.[487] However, the predominant and common usage of "living" will be utilized in this thesis. CLRP was developed in the 1980s,[488,489] and has revolutionized the field of free radical polymerization. The control over free radical polymerization has allowed the synthesis of well-defined polymers,[490] block copolymers,[491] complex structures (star, comb, and dendritic topologies),[492,493,494,495] bio-conjugates,[496,497] organic/inorganic composites,[498,499] and surface tethered copolymers.[500,501] The potential of developing functional polymers with predetermined, well-defined structure has allowed manufacturers to improve the properties of currently existing materials and to create new ones.

The key feature of CLRP is the establishment of a dynamic equilibrium between a low concentration of active chains/propagating radicals ($\mathbf{P_n^{\bullet}}$) and a predominant amount of dormant species ($\mathbf{P_n}$-**X**). The CLRP systems follow one of the two basic mechanisms: (1) the persistent radical effect (PRE)[502,503] (**Scheme 5.2**) and (2)

reversible degenerative transfer[504] (**Scheme 5.3**). In PRE, the propagating radicals ($\mathbf{P_n^{\bullet}}$) are reversibly trapped in the deactivation process (with a rate constant $\mathbf{k_{deact}}$) by species **X**, which is typically a free radical. The dormant species are activated (with a rate constant of $\mathbf{k_{act}}$) thermally, photolytically, or with an appropriate catalyst to reform the propagating radicals ($\mathbf{P_n^{\bullet}}$). The radical ($\mathbf{P_n^{\bullet}}$) can propagate with a rate constant of $\mathbf{k_p}$. It can also terminate with a rate constant of $\mathbf{k_t}$. However, the persistent radical X cannot couple with itself. It can couple only with the propagating species (**Scheme 5.2**). The propagating radicals ($\mathbf{P_n^{\bullet}}$) can also be involved in a "reversible transfer", degenerative exchange process with $\mathbf{P_m}$-**X** as shown in **Scheme 5.3.** Thus in CLRP, the steady state of growing radicals is established through the activation-deactivation process rather than initiation-termination process as in conventional FRP. The end-capped dormant species in CLRP are unable to propagate or terminate throughout the polymerization process, which results in uniform growth of chains.

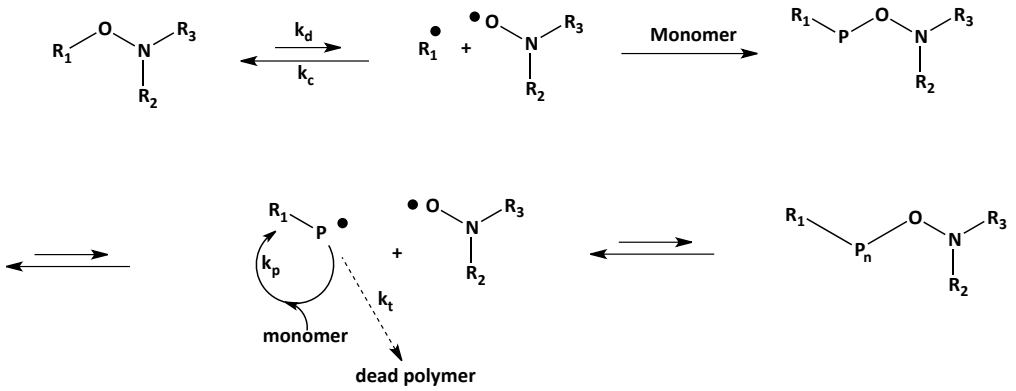


Scheme 5.2 Persistent Radical Mechanism for Inducing a CLRP

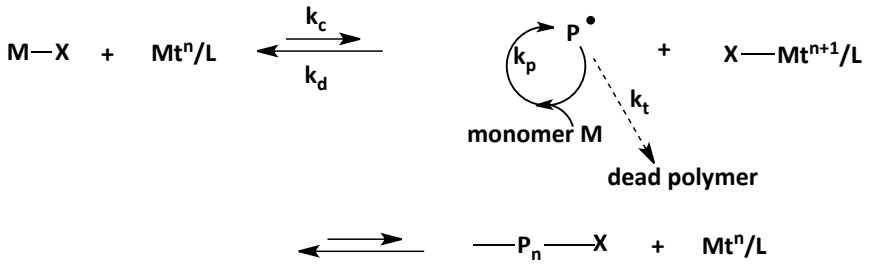


Scheme 5.3 Reversible Degenerative Transfer Mechanism For Inducing a CLRP

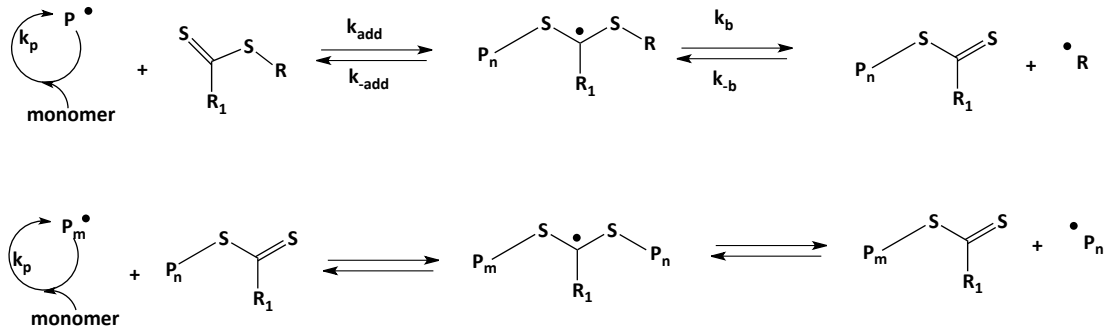
The most common CLRP techniques are nitroxide-mediated polymerization (NMP),[490] atom transfer radical polymerization (ATRP),[505] and reversible addition-fragmentation chain transfer (RAFT) polymerization.[504] Other less popular CLRP techniques include iodine-,[506] tellurium-,[507] antimony-,[508] bismuth-,[509] and cobalt-mediated polymerization.[510] NMP and ATRP are based on the PRE mechanism, whereas RAFT proceeds via a reversible degenerative transfer. The term "nitroxide" is also discouraged in IUPAC nomenclature. Thus "nitroxide-mediated radical polymerization" (NMP) should be called "aminoxyl-mediated radical polymerization" (AMRP) following IUPAC conventions. However, the term NMP will be used in this thesis. In NMP, the dormant species is a polymeric alkoxyamine (**Scheme 5.4**), in ATRP it is a polymeric alkyl halide **(Scheme 5.5)**, and in RAFT it is a polymer chain with a dithioester end group (**Scheme 5.6**).



Scheme 5.4 General Mechanism of Nitroxide Mediated Polymerization (NMP) with Alkoxyamine as Initiator and as the End-Capping Group



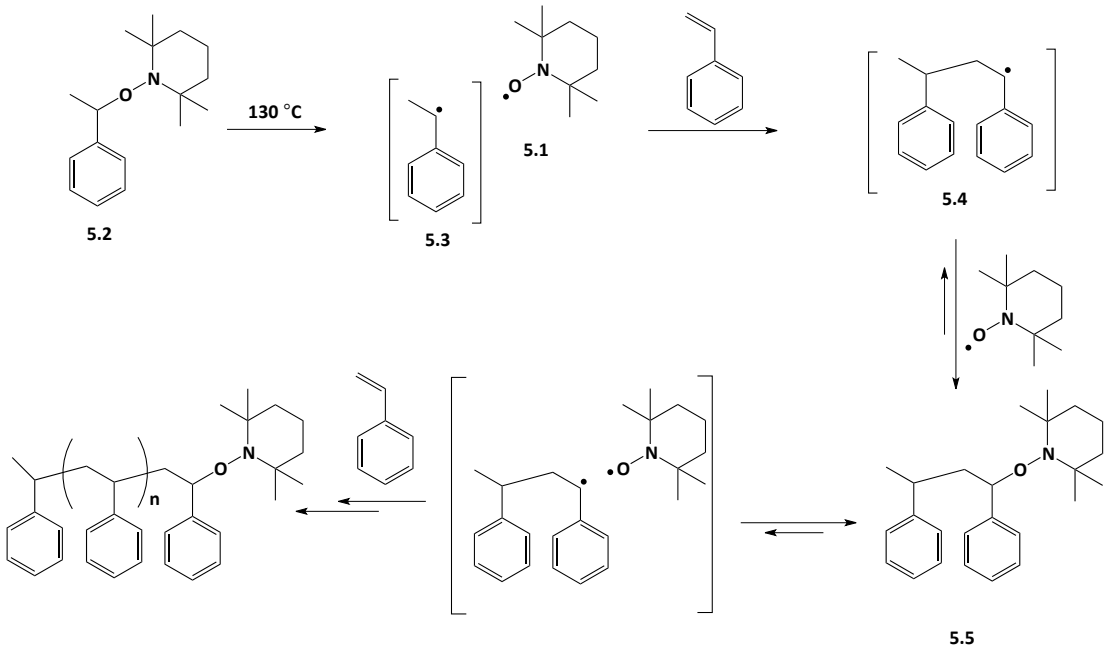
Scheme 5.5 General Mechanism of Atom Transfer Radical Polymerization (ATRP)



Scheme 5.6 General Mechanism of Reversible Addition-Fragmentation Transfer (RAFT)

5.2 Nitroxide-Mediated Polymerization

Nitroxide-mediated radical polymerization is historically the first method developed for CLRP. NMP was devised in the 1980s, and has been extensively exploited for the synthesis of styrenic and acrylic polymers. The first nitroxide mediated living polymerization was described in a patent filed by Rizzardo et al. at CSIRO in 1986.[511] However, NMP received significant renewed attention in the 1990s, when Georges et al.[512] demonstrated that 2,2,6,6-tetramethyl-1-piperidinyloxy TEMPO **5.1** can be used as the control agent in combination with AIBN or benzoyl peroxide (BPO) for the preparation of polystyrene with narrow molecular-weight distribution. A series of publications[513,514,515,516,517,518,519,520] by this group in the following decade established the significance of nitroxide mediated controlled/living free radical polymerization. This work was based on a bicomponent system of a nitroxide and a conventional initiator (BPO). The alkoxyamine was formed "*in situ*" from the reaction of the nitroxide and the radical generated from BPO. Simultaneously, work from other groups, Fakuda,[521,522,523,524] Hawker,[525,526,527,528,529,530] and Matyajaszewski[531] suggested alkoxyamines (monocomponent) to be an efficient way to initiate NMP.[532] Alkoxyamines can function both as initiators and generate the nitroxide end-capping groups as outlined in **Scheme 5.7**. Thermolysis of the C-ON bond of the alkoxyamine **5.2** at elevated temperatures results in the formation of a carbon-centered radical



Scheme 5.7 Mechanism of Nitroxide Mediate Radical Polymerization (NMP) of Styrene using TEMPO-Alkoxyamine Initiator

5.3, that follows one of two major reaction pathways to enable controlled polymerization: (1) recombination with a nitroxide radical to regenerate alkoxyamine **5.2** or (2) addition to the alkene group of a monomer molecule to extend the reactive chain by one repeat unit, which forms a new polymer radical **5.4**. The polymer radical **5.4** can either react with nitroxide **5.1** to form macroalkoxyamine **5.5** or add to another monomer to form another carbon polymer radical. Termination of polymerization by combination of polymer radicals is disfavored by the low concentration of polymeric carbon radicals compared to persistent nitroxide radicals. Thus, polymers are obtained with well-controlled structure and low polydispersity index.

5.3 Nitroxides in NMP

Nitroxides (aminoxyl radicals) are *N,N*-disubstituted *N-O* radicals with a delocalized unpaired electron shared between the nitrogen and oxygen atoms, which is indicated by two resonance structures (**Figure 5.1)**. The electron density can be further delocalized, depending on the nature of the substituents R_1 and R_2. Nitroxides are paramagnetic compounds that can be readily analyzed by EPR spectroscopy, which provides information on the spin density at the nitrogen atom.[533]

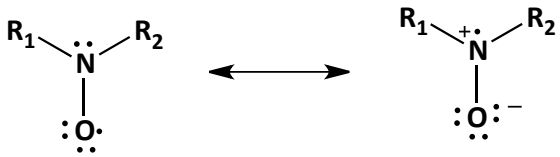
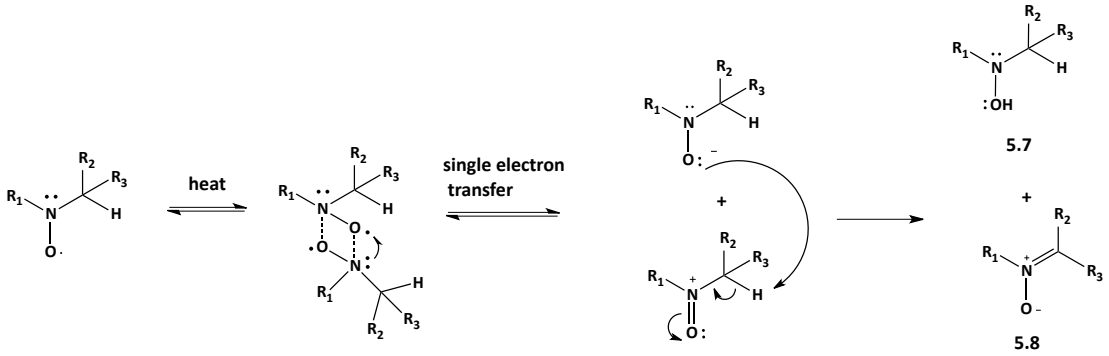


Figure 5.1 Resonance Stabilization of a Nitroxide

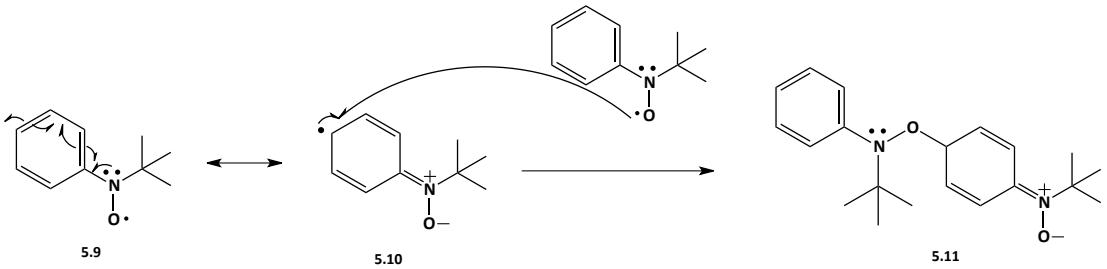
The *N-O* bond can be described as a three-electron bond with a bond order of 1.5. X-ray scattering and electron diffraction have revealed *N-O* bond lengths of 1.23 to 1.29 Å. This is less than a single *N-O* bond length of 1.44 Å, and more than an N=O bond length of 1.20 Å, suggesting a partial double bond character for the N-O bond in the nitroxide.[534] Many nitroxides are bench stable. The stability of nitroxide radicals originates from the high delocalization energy of the strong $\pi_{N\text{-}O}$ three-electron bond (23-30 kcal/mol).[534] The gain in energy by dimerization (35 kcal/mol)

is lower than the loss of the resonance energy of two aminoxyl groups. The stability of nitroxide is a crucial parameter with respect to its application in NMP. The substituents, R_1 and R_2 strongly affect the stability of a nitroxide. For most isolable nitroxides, R_1 and R_2 are sp^3 carbon atoms with no hydrogen atom directly attached to them. The presence of a hydrogen atom on the vicinal carbon atom can lead to disproportionation of two nitroxides into the corresponding hydroxylamine **5.7** and nitrone **5.8**, **Scheme 5.8**.[535]



Scheme 5.8 Disproportionation of a Nitroxide Bearing α-H

While the presence of a phenyl group can increase the stability of a nitroxide, it can lead to side reactions. For instance, the phenyl group in *tert*butylphenyl nitroxide **5.9** leads to extra stabilization of the nitroxide due to delocalization of the unpaired electron on the aromatic ring (**Scheme 5.9**). However, a high electron density on the carbon atom at the *para* position **5.10** gives rise to unwanted combination reaction products **5.11**, which then participate in undesired side reactions during polymerization.[536]



Scheme 5.9 Dimerization of *t*-Butylphenyl Nitroxide

An important contribution to the field of nitroxide chemistry was made in 1959, when Lebedev and Kazarnovsky introduced 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (4-oxo-TEMPO or TEMPONE) **5.12** as a readily prepared nitroxide. TEMPONE served as a precursor for highly useful nitroxides TEMPO **5.1** and 4-*N*-acetylamino-TEMPO **5.13** (**Figure 5.2**), which opened the door for nitroxide-mediated polymerization in 1986.[511] The nitroxides TEMPONE, 4-NHAc-TEMPO, and TEMPO are commercially available, and have been utilized extensively in nitroxide mediated polymerization.[537] While the polymerizations of styrene and derivatives using TEMPO are straight forward, the polymerizations of acrylates and methacrylates have proven to be more difficult. One problem is the low value of

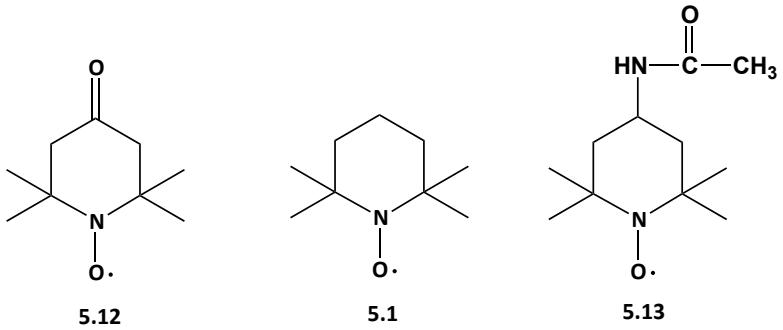
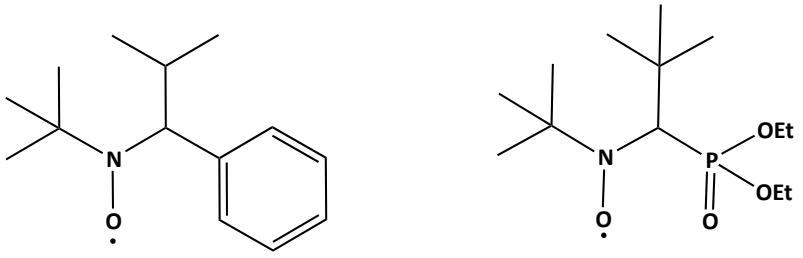


Figure 5.2 TEMPONE, TEMPO, 4-NHAc-TEMPO

the activation rate constant (k_{act}) of the corresponding macroalkoxyamine.[538] The rate constant for trapping a carbon-centered radical (k_{deact}) with a nitroxide radical strongly depends on the structure of both the nitroxide and the carbon-centered radical.[539,540] The rate constant for the reverse reaction, which is thermal C-O bond homolysis (k_{act}) depends on the structure of the alkoxyamine.[541,542] The equilibrium constant K (k_{deact}/k_{act}) for the reversible C-O bond homolysis of an initiator alkoxyamine or a polymeric alkoxyamine is a key parameter for the success of NMP.[543] In this context, a number of TEMPO based and other nitroxides have been designed with appropriate K values for the corresponding alkoxyamines. The other problem with TEMPO-based NMP is the persistence of the TEMPO free nitroxide under the thermal conditions of the polymerization. When a few polymer chains do self-couple, the concentration of nitroxide builds up to a level at which trapping of the polymer carbon radical out-competes addition to olefin monomer, effectively stopping chain growth.

The fact that TEMPO is limited to the NMP of styrene and its derivatives along with the requirement of high temperatures (125 – 140 °C**)** and long polymerization times (24 – 72 h) led to the development of nitroxides with structural motifs different than TEMPO. Moreover, for non-styrenenic monomers, nitroxide bearing a hydrogen atom α to the nitrogen atom is required that decomposes to keep the concentration of nitroxide low. The higher rates of polymerization of non-styrenic polymers such as acrylates, acrylamides, acrylonitriles, and dienes were made possible with the development of acyclic nitroxides such as 2,2,5-trimethyl-4-phenyl-3-azahexane nitroxide (TIPNO)[544] **5.14**, and *N*-tert-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (DEPN), also called SG1,[545,546] **5.15** (**Figure 5.3**) These nitroxides bear a hydrogen atom α to the nitrogen atom, which provides a decomposition pathway not possible to TEMPO, resulting in a low concentration of free nitroxide during the polymerization process, faster polymerization rates, and improves the "livingness" of the polymerization.[547]



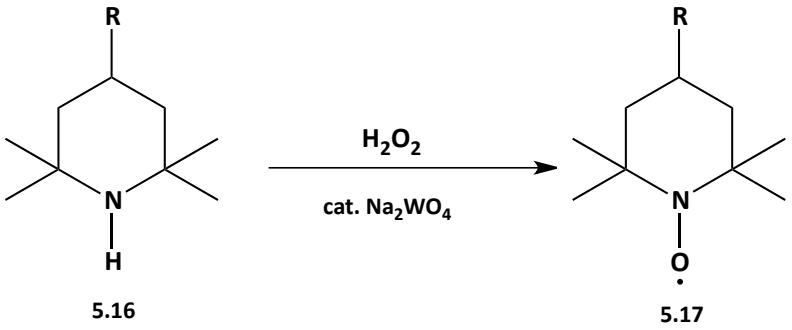
5.14 **5.15**

Figure 5.3 Stable α-H Bearing Nitroxides (TIPNO and SG1)

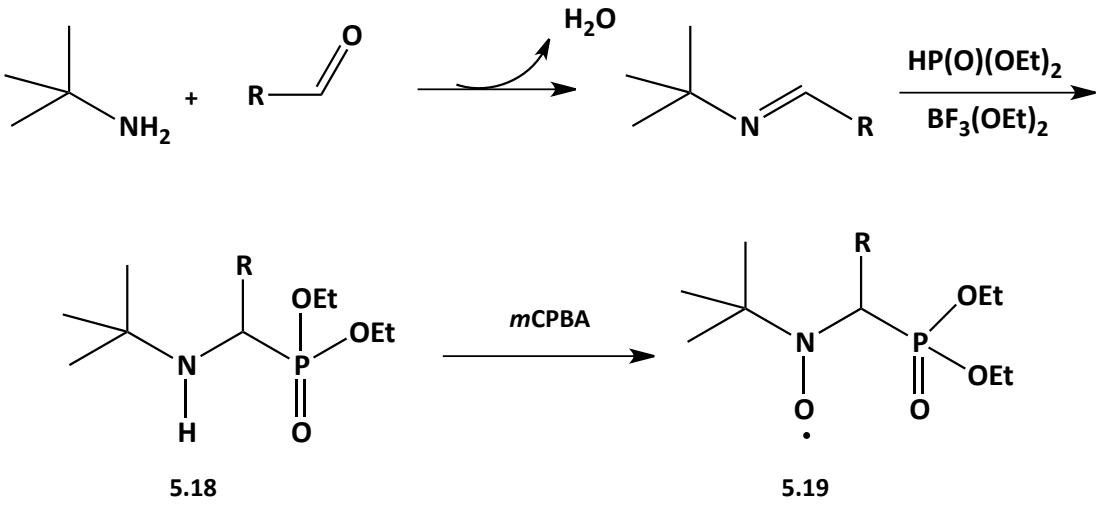
Most nitroxides that are used for NMP are functional modifications of TEMPO, TIPNO or SG1. The other structural motifs include 5-, 7-, and 8-membered ring cyclic nitroxides, cyclic nitroxides bearing a heteroatom, acyclic nitroxides with a heteroatom, aromatic nitroxides, and bis-nitroxides. These sophisticated nitroxides have allowed the controlled/living polymerization of styrenes, acrylates, acrylic acid, dienes, acrylamides, and other vinyl monomers.[548]

5.4 Synthesis of Nitroxides and Alkoxyamines

Some of the synthetic routes applied for the preparation of nitroxides are discussed in this section. Nitroxides can be prepared via oxidation of secondary amines directly to the corresponding nitroxides using tungstate-, molybdate-, or vandate-based catalysts in combination with stoichiometric amount of oxidants such as hydrogen peroxide or meta-chloroperbenzoic acid (*m*CPBA).[549,550] For example, the synthesis of TEMPO derivatives **5.17** is carried out by the oxidation of the corresponding piperidine **5.16** by using a combination of hydrogen peroxide/catalytic sodium tungstate (**Scheme 5.10)**.[551] Derivatives of SG1 nitroxide **5.19** are prepared by oxidation of the corresponding secondary amines **5.18** using *m*CPBA as the oxidant without metal catalyst (**Scheme 5.11**).[552]



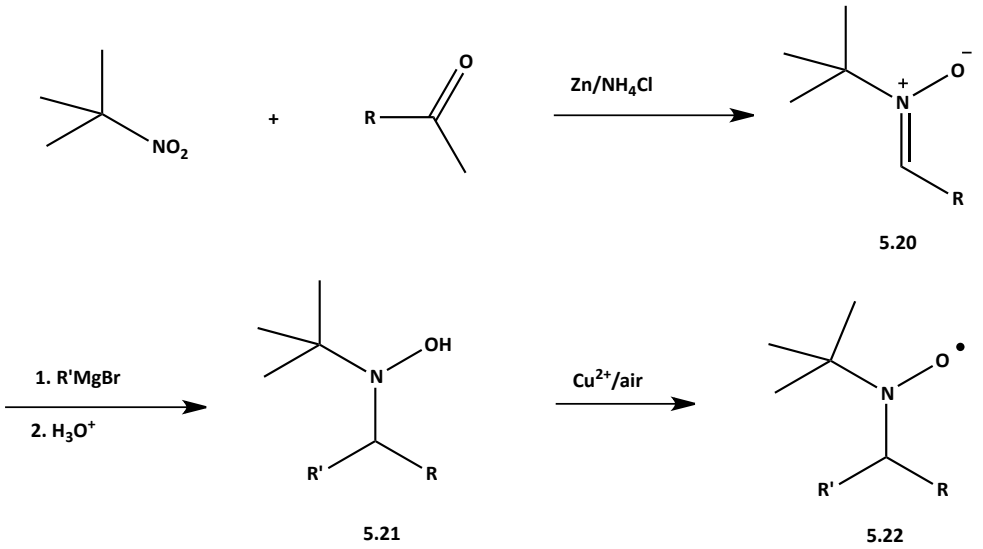
Scheme 5.10 Common Synthetic Pathway for TEMPO Based Nitroxides[551]



Scheme 5.11 Common Synthetic Pathway for SG1 Based Nitroxides[552]

The oxidation of hydroxylamines using milder oxidants such as nickel peroxide, manganese oxide, sodium periodate, or catalytic amounts of copper (II) salts in combination with oxygen afford nitroxides.[553,554] For instance, the synthesis of TIPNO derivatives **5.22** is carried out by the oxidation of the corresponding hydroxylamines **5.21** using copper (II) salts in the presence of air (**Scheme 5.12**).

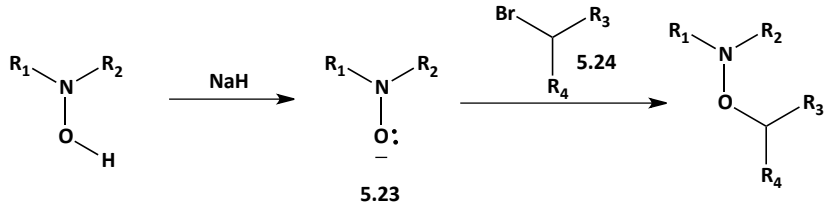
Other less common routes of nitroxide synthesis include spin trapping of alkyl radicals by nitrone[433b] or nitroso compounds[555] and reduction of nitro compounds.[556]



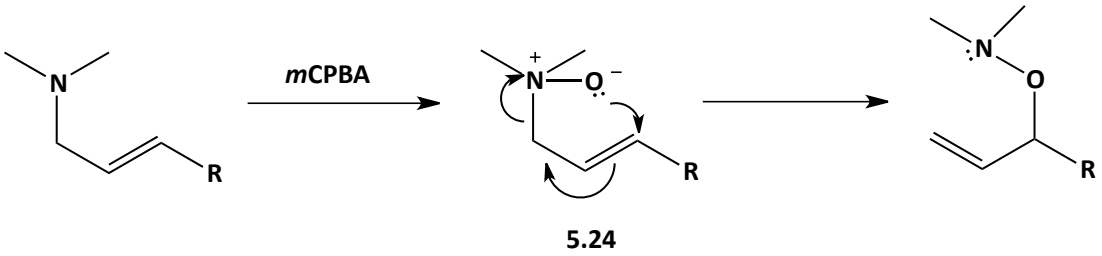
Scheme 5.12 Common Synthetic Pathway for TIPNO Based Nitroxides[553]

Several approaches have been applied towards the synthesis of alkoxyamines. The first approach includes nucleophilic substitution by the hydroxylaminate anion **5.23** with an activated alkyl bromide (**Scheme 5.13**).[532,557,558] Preparation of alkyl and benzyl alkoxyamines can be carried out by the Meisenheimer rearrangement of allyl (or benzyl) amine oxides **5.24**, **Scheme 5.14**.[559,560,561] The reaction of oxoammonium

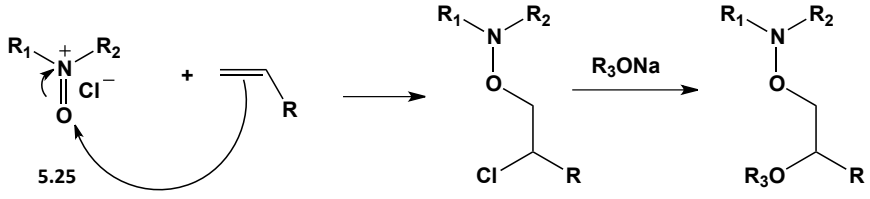
salts **5.25** (derived from nitroxides) with olefins or enolates afford alkoxyamines (**Scheme 5.15**).[562,563] The fourth and the most common route to prepare alkoxyamines is the scavenging of "*in situ*" generated carbon-centered alkyl radicals **5.26** by an organic nitroxide (**Scheme 5.16**).[564] The C-O bond-forming process is very fast, and the rate constants are strongly influenced by the structure of the alkyl radical.



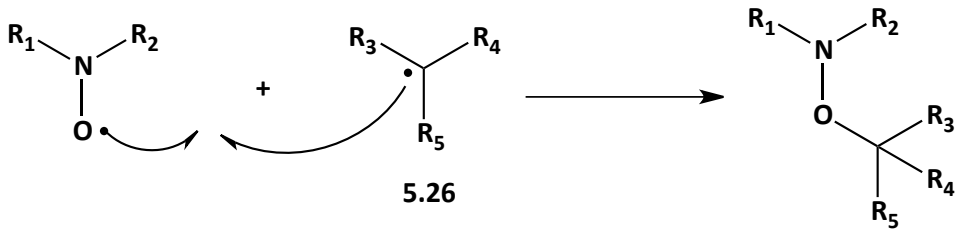
Scheme 5.13 Nucleophilic Substitution by Hydroxyaminate Anion with an Activated Alkyl Halide



Scheme 5.14 Meisenheimer Rearrangement of Allyl (or Benzyl) Amine Oxides



Scheme 5.15 Reaction of an Oxoammonium Salt with an Olefin



Scheme 5.16 Trapping of a Carbon-Centered Radical by a Nitroxide

Various styrene derivatives are readily transformed into alkoxyamines by reaction with nitroxide (TEMPO, TIPNO, and SG1) in the presence of Mn(salen)Cl **5.27** and sodium borohydride. Schmidt-Nakke et al.[565] demonstrated the use of the parent Mn(salen)Cl as a low cost alternative to the use of Jacobsen's catalyst **5.28**, **Figure 5.4**, which was developed first by Takeuchi [566] and then Hawker.[567]

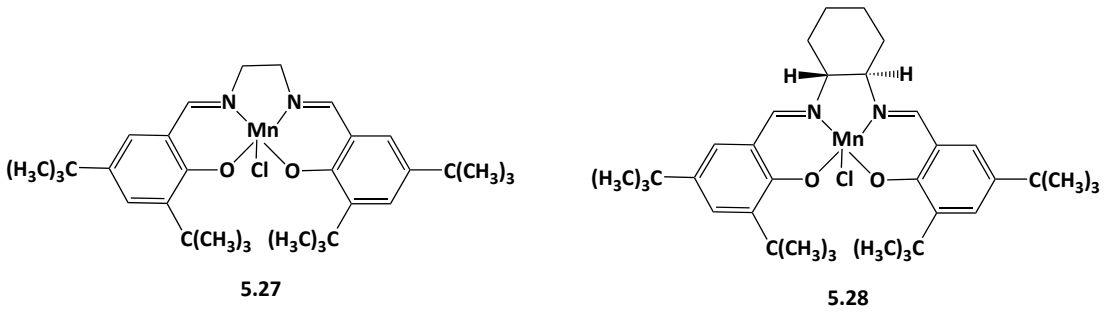
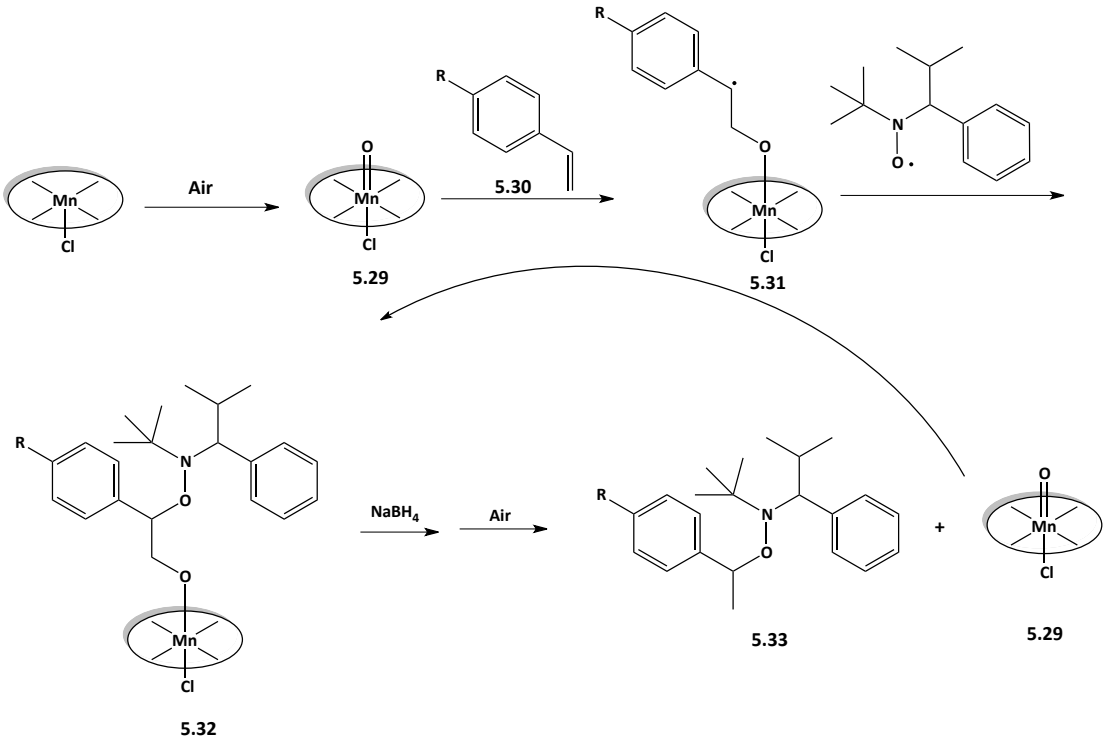


Figure 5.4 Structures of the Parent Mn(salen)Cl complex and Jacobsen's Asymmetric Catalyst

The mechanism occurs via the oxidation of the manganese complex to the manganese-oxo-species (Mn=O) **5.29**, which reacts with an activated olefin **5.30** to afford radical intermediate **5.31**. Trapping of this radical intermediate by a nitroxide leads to the desired alkoxyamine **5.33** after reductive deoxygenation of the Mn-O-C bond in **5.32** using sodium borohydride, followed by reformation of the Mn=O species **5.29** by air (**Scheme 5.17**).



Scheme 5.17 Mechanism of the Catalytic Mn(salen)Cl Complex Mediated Synthesis of TIPNO-Alkoxyamine

5.5 Classification of NMP

NMP can be classified as either homogenous or heterogenous.[568] In a homogenous polymerization, all components, including monomer, initiator, and polymer, are soluble in the solvent throughout the duration of the reaction. A heterogenous polymerization contains at least one insoluble component at some point during the reaction. Precipitation, suspension, dispersion, and emulsion are the four most widely studied heterogenous processes.[569,570,571,572,573,574] These processes are distinguished on the basis of the initial state of the polymerization mixture, the kinetics of polymerization, the mechanism of particle formation, and the shape and size of the final polymer particles. In precipitation polymerization,[575] an initially homogenous mixture of monomer, initiator, and solvent becomes heterogenous during the reaction as growing polymer chains become insoluble and aggregate to form a separate phase. In suspension polymerization,[576] the monomer, initiator, and the resulting polymer are insoluble in the solvent throughout polymerization. The solvent acts as a dispersant and heat dissipating agent during the reaction. Dispersion polymerization[577] is a modification of precipitation polymerization. The monomer and the initiator are initially soluble in the reaction medium; when the growing oligomeric radicals reach a critical molecular weight (degree of polymerization, J_{crit}), the chains are no longer soluble and phase separation occurs. Surface-active stabilizing molecules are used to coat the polymer

particles to prevent their coagulation or aggregation. Polymerization persists both in the reaction medium and in the growing polymer particles. The estimation of J_{crit} is possible by visual observation: the reaction mixture changes from clear to opaque (**Figure 5.5**).[578] In conventional free radical polymerization, the value of J_{crit} changes with the conversion as the composition of the continuous phase changes over time.

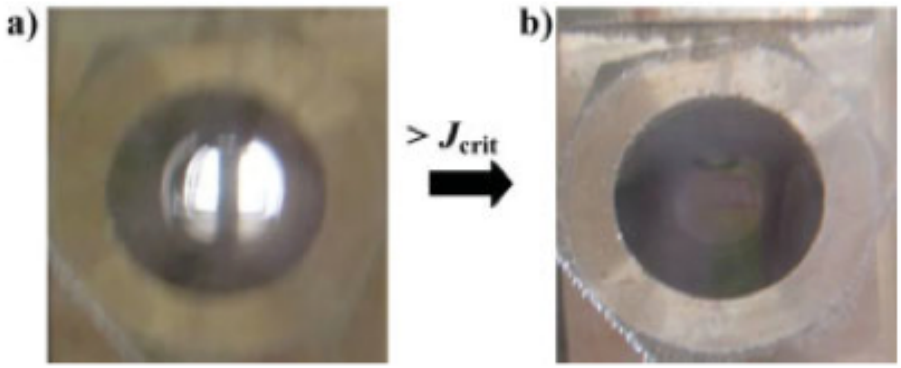


Figure 5.5 Sapphire Viewing Window of 90 mL Stainless Reactor Showing [578] (a) Transparent Polymerization Solution Before J_{crit} (stirrer visible) and (b) Opaque Mixture After J_{crit}

In controlled/living polymerization, a single value of J_{crit} can be obtained, since the conversion at J_{crit} is dictated by the initial stoichiometry of the monomer and the initiator. Aldabbagh et al.[579] developed a graphical approach to predict J_{crit} as a function of the target molar mass ($[monomer]_0/[initiator]_0$) and the initial monomer loading (**Figure 5.6**).

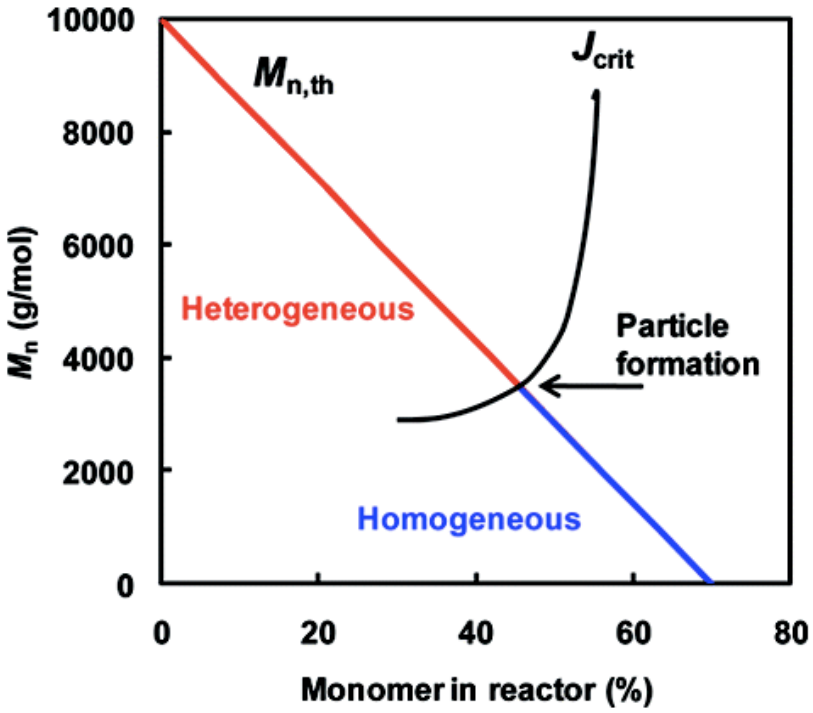


Figure 5.6 Graphical Approach for the Predictions of J_{crit} as a Function of Both the Target Molar Mass and the Initial Monomer Loading.[579]

5.6 Supercritical Carbon Dioxide ($scCO_2$) as a Polymerization Medium

The ongoing search for environmentally friendly alternatives to organic solvents in chemical processes has led to the development of technologies based on supercritical fluids. Significant effort has been devoted to the replacement of conventional solvents by supercritical carbon dioxide ($scCO_2$), as it is environmentally benign, non-flammable, non-toxic, relatively inert, odorless, inexpensive, easily removed after a chemical transformation, can be recycled, and avoids chain transfer to solvent during free radical polymerization.[580,581]

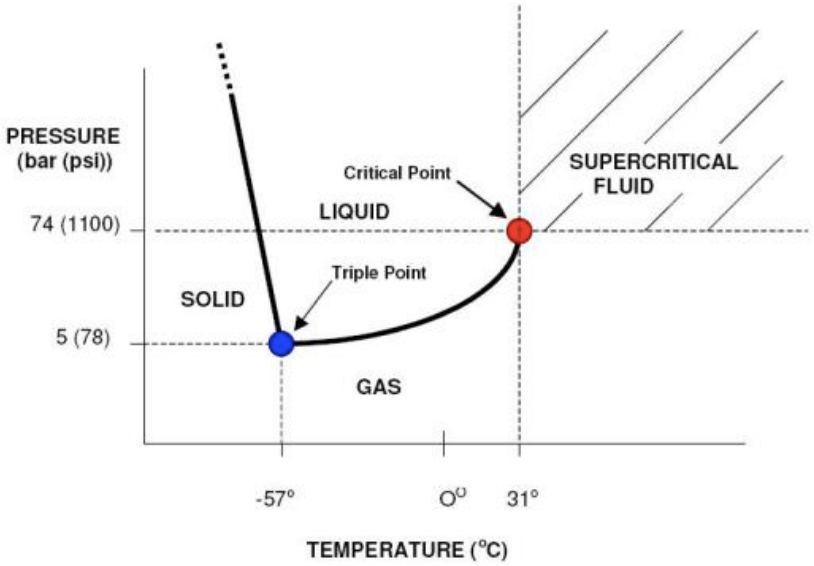


Figure 5.7 Pressure-Temperature Phase Diagram for CO_2[582]

Carbon dioxide usually behaves as a gas at standard temperature and pressure (STP), or as a solid when frozen. The supercritical state of carbon dioxide is achieved when the temperature and pressure are both increased from STP to reach beyond the critical point of temperature (T_c = 31.17 °C) and pressure (P_c = 73.8 bar). At the critical point, CO_2 exhibits both gas-like and liquid-like properties. In the supercritical state it is characterized by a viscosity close to a gas and a density similar to a liquid (**Figure 5.7**).[583] Moreover, these properties can be easily tuned by adjusting the pressure and/or temperature. For example, $scCO_2$ exhibits changes in solvent density with small changes in pressure or temperature without changing the solvent composition (**Figure 5.8**).[584]

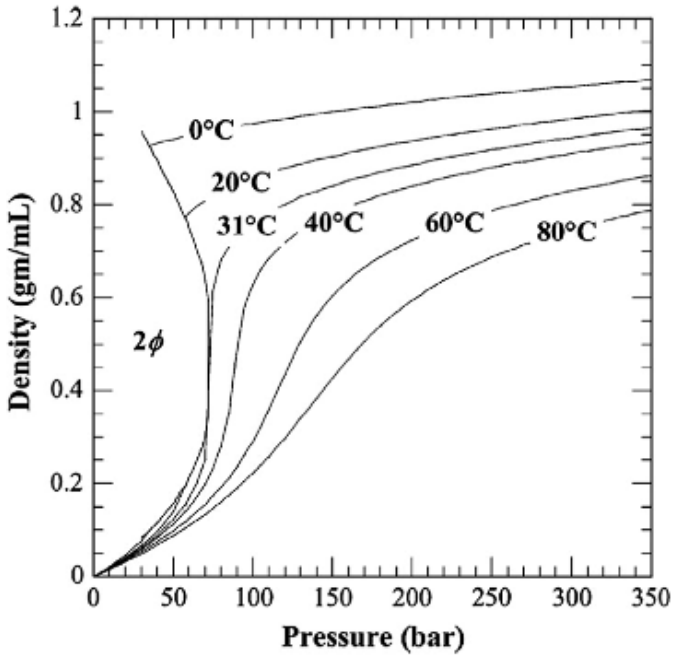


Figure 5.8 Changes in the Density of CO_2 with Changes in the Pressure at Various Temperatures [582]

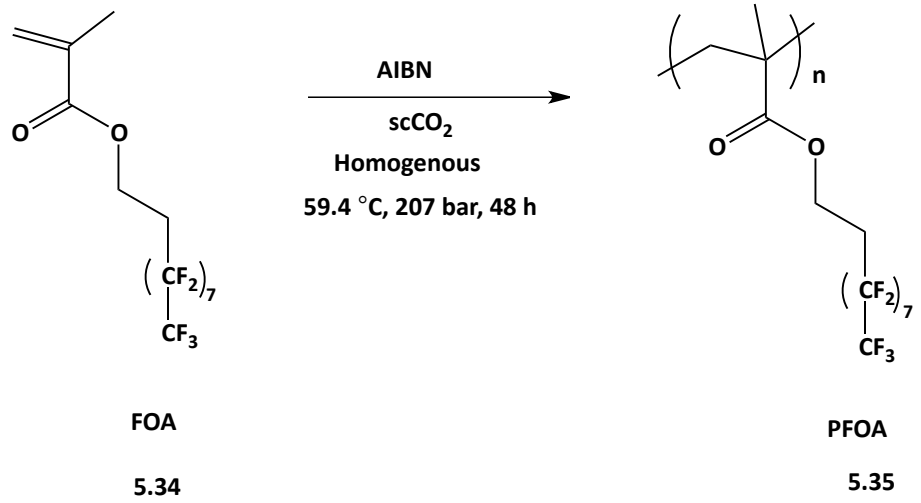
Typical examples of processes that have been studied in $scCO_2$ include polymerization,[585] particle generation,[586] coating,[587] extraction,[588,589] impregnation in controlled-release drugs,[590] dyeing,[591] dry cleaning,[592] photolithography,[593] food,[594] pharmaceutical,[595] biopesticides,[596] electronics,[597] soil decontamination,[598] and applications in the paints and coating industry.[587] Supercritical CO_2 is the most extensively studied supercritical fluid in polymerization reactions. DeSimone et al[580, 599] pioneered the use of scCO2 as an alternative medium for radical and condensation polymerization. The gas-like diffusivity and liquid-like density of $scCO_2$ have important implications for reaction kinetics. Scientists have taken advantage of

the adjustable solubilizing power of $scCO_2$ in designing heterogenous precipitation and dispersion radical polymerizations. Reagents such as monomer, initiator, and controlling agent are generally soluble in $scCO_2$, but the resulting polymer is often insoluble. Isolation of the dry polymer product is carried out by simple depressurization.[600] This feature eliminates energy-intensive drying procedures required in polymer manufacturing to remove the solvent, and represents a potential cost and energy savings for $scCO_2$-based systems. Moreover, residual CO_2 is a good plasticizing agent for a host of polymeric materials including polystyrene, polyethylene, polyisoprene, polypropylene, polyvinyl chloride, polymethacrylates, polycarbonates, polyurethanes, and nylon.[601,602,603,604]

5.7 Polymerizations in $scCO_2$

Although the solvent strength of $scCO_2$ can be tuned by varying the pressure and temperature, $scCO_2$ is a poor solvent for most polar molecules and high molecular weight polymers under the readily achievable conditions of 100 °C and 1000 bar.[605] Polymers that display good solubility in $scCO_2$ include amorphous fluoropolymers,[605,606,607] siloxanes,[599, 608] and poly(ether-carbonates).[609] The unusual solubility of fluorinated materials allows the synthesis of high molecular weight fluoropolymers by homogeneous solution polymerization in $scCO_2$. In a seminal paper, DeSimmone et al.[599,610] reported the first case of radical polymerization of

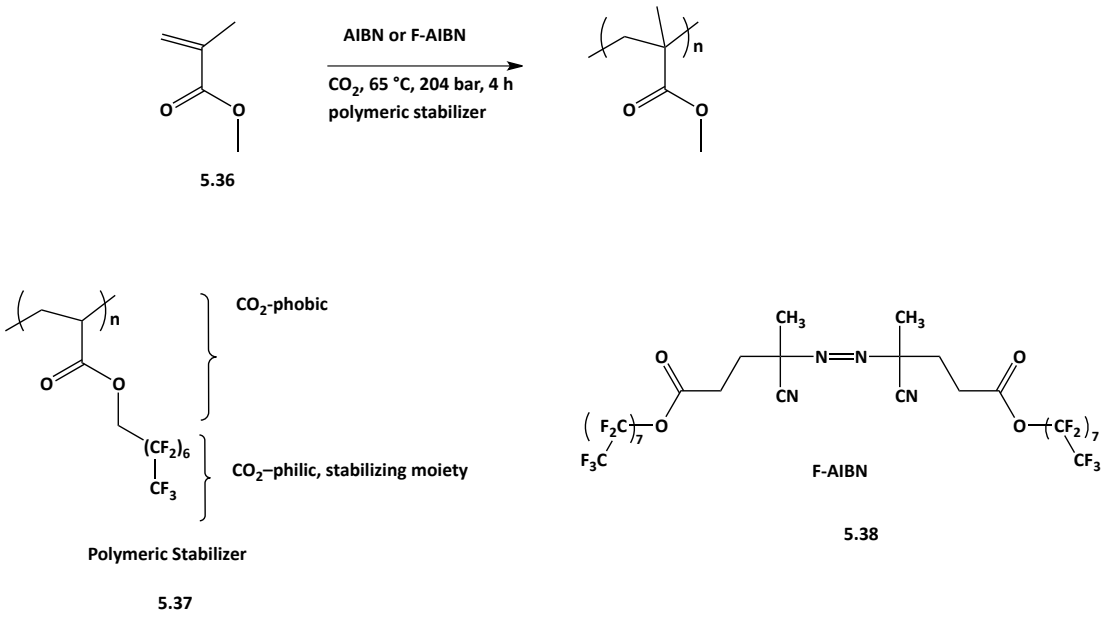
1H,1H,2H,2H-perfluorooctyl methacrylate (FOA) **5.34** in $scCO_2$ using 2,2'-azobis(isobutyronitrile) (AIBN) as an initiator (**Scheme 5.18**). The solution properties of poly(fluoromethacrylates) PFOA **5.35** synthesized in $scCO_2$ were compared with those synthesized in chlorofluorocarbons (CFCs), showing $scCO_2$ to be a good solvent for poly(fluoromethacrylates), and thus a good replacement for toxic CFCs. Other fluorinated acrylates and styrenes with fluoroalkyl sidechains are polymerized or copolymerized in $scCO_2$ via homogenous methods, confirming $scCO_2$ to be an excellent solvent medium for the synthesis and solution processing of fluoropolymers.[611]



Scheme 5.18 First Case of Homogenous Polymerization of a Fluorous Monomer in $scCO_2$

The negligible solubility of common hydrocarbon polymers in $scCO_2$ drastically limits the application of homogenous polymerization in $scCO_2$. The syntheses of these polymers involve heterogenous polymerization techniques. A variety of industrially important polymers have been prepared in $scCO_2$ by free radical precipitation polymerization. DeSimone et al.[612] carried out the free radical precipitation polymerization of acrylic acid, styrene and methyl methacrylate in $scCO_2$ using ethanediol as a chain transfer agent. High performance fluoropolymers and copolymers are synthesized by precipitation polymerization leading to high molecular weight polymers (>10^6). Thermoresponsive polymers based on *N-iso*propylacrylamide, 2-hydroxyethylmethacrylate, and vinylidene fluoride have been synthesized using precipitation polymerization in $scCO_2$.[613,614,615] Highly cross-linked polymers with a range of surface-active functional groups are synthesized with or without stabilizer using AIBN as initiator. However, in the absence of stabilizers, the particles showed agglomeration and broad molecular weight distributions.

Free radical dispersion polymerization techniques have been developed using $scCO_2$ as the continuous phase. The first free radical dispersion polymerization of methyl methacrylate (MMA) **5.36** was investigated by DeSimone et al.[580] A fluorinated polymeric surfactant/stabilizer **5.37** was used to form a stable polymer colloid dispersion in the $scCO_2$ continuous phase. A derivative of AIBN with a



Scheme 5.19 The First example of Heterogenous Dispersion Polymerization of MMA in scCO_2

fluorinated alkyl chain (F-AIBN) **5.38** was used as the initiator (**Scheme 5.19**). A stabilizer requires an intramolecular combination of CO_2–philic and CO_2–phobic segments. The CO_2–philic segments are either fluoropolymers or siloxanes, whereas the CO_2–phobic segments are hydrophilic or hydrophobic chains, depending on the nature of the dispersed phase. The CO_2–philic fluorocarbon chain prevents the agglomeration of polymer particles through a solubility stabilization mechanism by extending the poly(fluoromethacrylates) (PFOA) chain into the continuous phase. The CO_2–phobic/lipophilic backbone adsorbs onto the surface of the acrylic colloidal particles, providing a surface anchor for the CO_2–philic fluoropolymer stabilizer. The

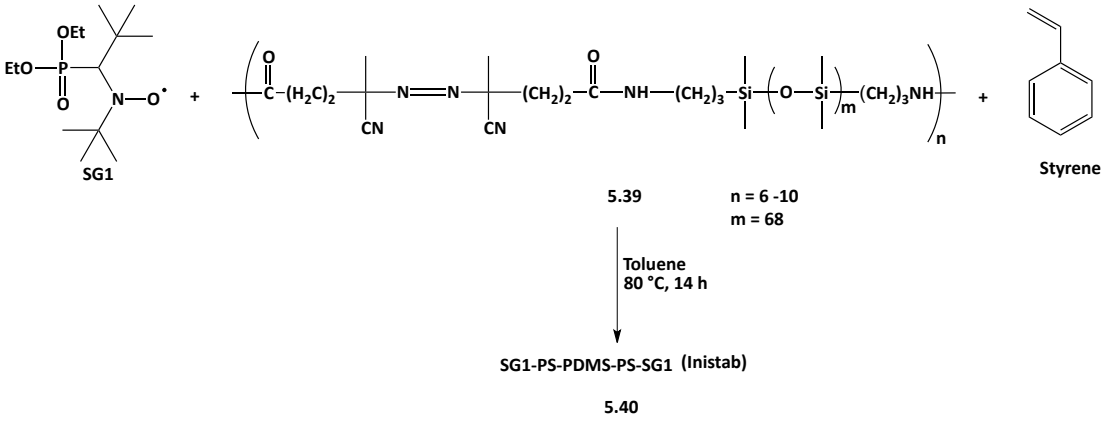
fluorinated initiator (F-AIBN) is highly soluble in $scCO_2$, and can partition away into the $scCO_2$ continuous phase from either a lipophilic dispersed phase or a hydrophobic dispersed phase. These results suggest PFOA to be an effective stabilizer for dispersion polymerization. The successful formation of a stable colloid in $scCO_2$ results in higher rates of polymerization and higher molecular weights than with no added stabilizer. After the successful dispersion polymerization of MMA in $scCO_2$, other hydrophilic and hydrophobic polymers have been prepared as substrates. Successful monomers include styrene, vinyl actetate, glycidyl methacrylate, 2-hydroxyethyl acrylate, 1-vinyl-2-pyrrolidone, and sugar containing amphiphiles.[616,617,618,619]

5.8 Nitroxide Mediated Polymerizations in $scCO_2$

5.8.1 Dispersion NMP in $scCO_2$

Aldabbagh et al.[620] demonstrated the first nitroxide-mediated dispersion polymerizations of styrene in $scCO_2$ using SG1 nitroxide. Stabilization of the growing polymer was achieved by using the inistab (initiator + stabilizer) concept. The bifunctional polymeric alkoxyamine macroinitiator (SG1-PS-PDMS-PS-SG1) "inistab" **5.40** with dual function of initiator and stabilizer was synthesized. A solution of 1.5 M styrene, 0.04 M of a polydimethylsiloxane (PDMS) based azoinitiator **5.39**, and 0.048 M SG1 in toluene was heated for 14 h at 80 °C to prepare **5.40** (**Scheme 5.20**).

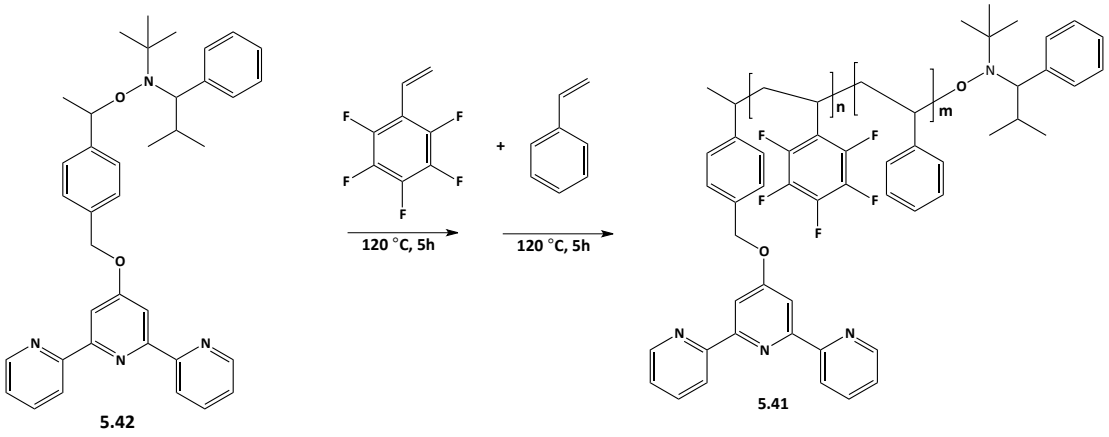
The controlled/living polymerization of styrene in $scCO_2$ at 110 °C using inistab **5.40** proceeded to high conversion and with a high degree of livingness. However, stabilization resulting in a high conversion and isolation of the polymer as a dry powder was possible only when an excessive amount (0.0008 equivalent per styrene monomer) of insitab **5.40** was added. The use of a large amount of inistab resulted in a broad molecular weight distributions.



Scheme 5.20 First Example of Dispersion NMP in $scCO_2$

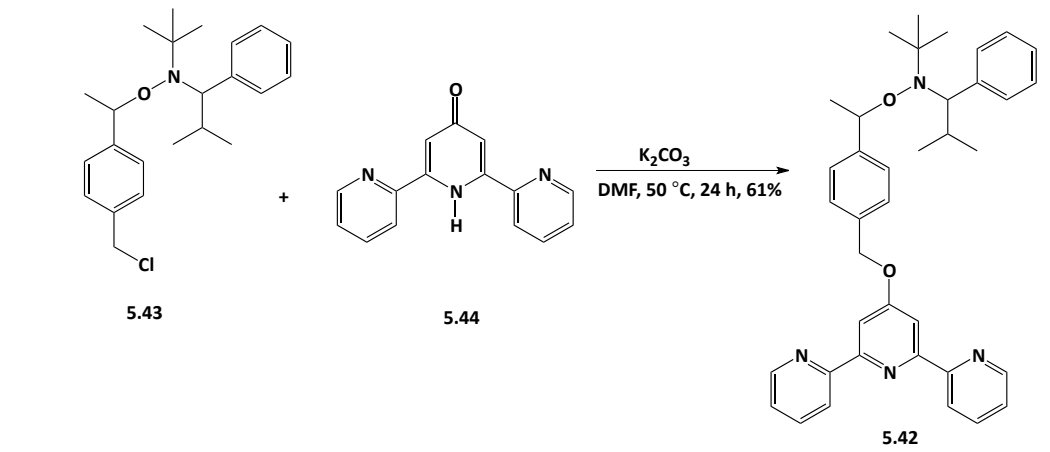
Good control over the living character in dispersion polymerization of styrene in $scCO_2$ (PDI = 1.43) was achieved when PDMS-b-PS-SG1 block copolymer was used as an inistab with 100% excess of SG1 (0.02 equivalent per styrene monomer).[621] In a related study, AIBN with a PDMS-b-PMMA stabilizer produced polystyrene as a dry powder with 85% conversion and a PDI of 1.12 - 1.43, provided a large excess of

free SG1 (0.005 equivalent per styrene monomer) was initially introduced into the reaction medium.[622]



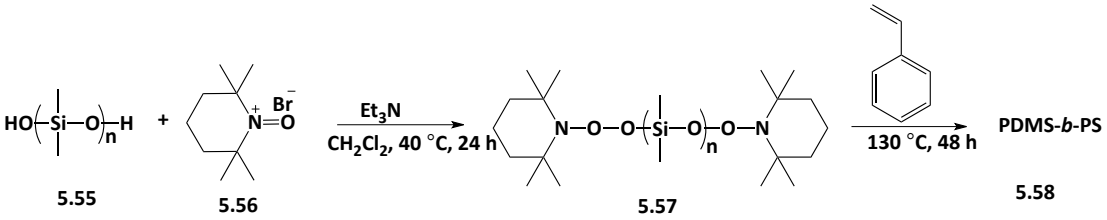
Scheme 5.21 Synthesis of PPFS-b-PS stabilizer 5.41

Guerra et al.[623] tested fluorinated block copolymer **5.41** as a stabilizer for dispersion NMP of styrene in $scCO_2$. NMP of pentafluorostyrene followed by styrene gave fluorinated block copolymer poly(2,3,4,5,6-pentafluorostyrene)-block-poly(styrene) (PPFS-b-PS) stabilizer **5.41**, **Scheme 5.21**, using terpyridine-functionalized alkoxyamine **5.42**. The alkoxyamine initiator **5.42** was prepared by the reaction of TIPNO-alkoxyamine derivative **5.43** and terpyridine derivative **5.44** (**Scheme 5.22**).[624]



Scheme 5.22 Synthesis of Terpyridine Alkoxyamine Initiator 5.42

The silicon-based poly(dimethylsiloxane-block-styrene) **5.58** stabilizer was synthesized by allowing the oxammonium bromide salt of TEMPO **5.56** to react with a hydroxyl functionalized siloxane **5.55**, followed by NMP with styrene (**Scheme 5.23)**.

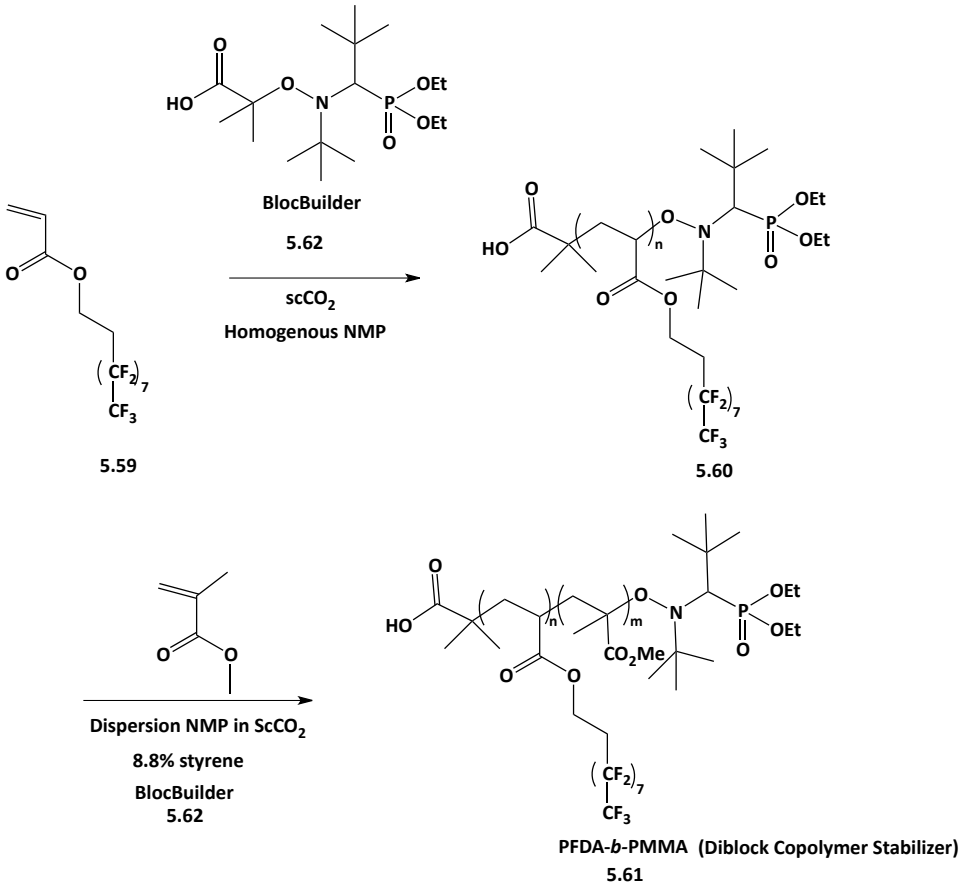


Scheme 5.23 Synthesis of PDMS-*b*-PS Stabilizer and Use in Dispersion NMP of Styrene

The fluorinated solubilizer **5.41** and silicon-based **5.58** stabilizers in combination with TEMPO were used in the dispersion NMP of styrene and copolymerization of

styrene with butyl acrylate in $scCO_2$. The resulting polymers revealed conversions of up to 35% with PDIs in the range on 1.2-1.4.

Detrembleur et al.[625] reported the first dispersion NMP of methylmethacrylate in $scCO_2$ using a diblock copolymer stabilizer composed of a CO_2-philic block (poly(heptadecafluoroacrylate)) (PFDA) **5.59** and a CO_2-phobic block (polymethylmethacrylate)(PMMA). PFDA-*b*-PMMA diblock copolymer **5.61** was generated "*in situ*" from SG1-terminated PFDA macroinitiatora (PFDA-SG1) **5.60** during dispersion NMP of MMA with 8.8% styrene initiated by BlocBuilder® **5.62**,



Scheme 5.24 Synthesis of PFDA-*b*-PMMA Diblock Copolymer Stabilizer 5.61

Scheme 5.24. Using the PFDA-*b*-PMMA diblock copolymer **5.61** as a stabilizer, poly(methyl methaacrylate) was obtained as a white free flowing powder consisting of small sized microspheres, quasi spherical particles or microspheres/elongated particles with PDIs in the range of 1.22 to 1.30 in up to 98% conversion. When dispersion NMP of methyl methacrylate was conducted in the absence of the PFDA-*b*-PMMA **5.61** stabilizer, the resulting polymer was obtained with a broad PDI.

5.8.2 Precipitation NMP in $scCO_2$

Aldabbagh et al.[575] used a bimolecular nitroxide/AIBN system to perform nitroxide-mediated precipitation polymerization of styrene in supercritical carbon dioxide. This system was superior at high monomer loadings (70% w/v) with respect to MWD and rate (1.58 times faster) in comparison to solution polymerization in toluene under analogous conditions. Polystyrene becomes insoluble at a certain degree of polymerization (J_{crit}): precipitation occurs. This can be steered towards the target molecular weight by adjusting the initial loading of the monomer compared to loadings of nitroxide and AIBN, and the pressure. The level of control over MWD was superior for the SG1/AIBN compared to the TIPNO/AIBN system. They speculated that extensive partitioning of TIPNO between the continuous solution phase and the monomer rich phase after precipitation is responsible for the poor control in the case of the TIPNO/AIBN system. However, using the bimolecular

nitroxide/AIBN system leads to uncertainty due to the unknown amounts of alkoxyamine generated *in situ*. Therefore, a large excess of free nitroxide (3.3 equivalents per AIBN) was used to achieve both a controlled /living polymerization as well as high conversion. A large excess of nitroxide relative to AIBN was required to negate the loss of nitroxide via partitioning from the locus of polymerization, as well as carbon radical dimerization and nitroxide disproportionation at the initial stages of alkoxyamine formation and during polymerization.

5.9 Unimolecular Fluorinated Alkoxyamine Initiators For NMP in $scCO_2$

The goal of this project was (1) to study the precipitation NMP of styrene in $scCO_2$ in the absence of excess free nitroxide by using unimolecular alkoxyamine initiators and (2) to study the effect of adding CO_2-philic fluorinated fragments to either the nitroxide or the benzyl-initiating fragment (foot part of alkoxyamine) **5.63** by using three new fluorous-labelled TIPNO-alkoxyamine initiators. Two alkoxyamines **5.64** and **5.65** were synthesized by incorporating fluorinated functional handles built onto the nitroxide, either on the phenyl position or on the

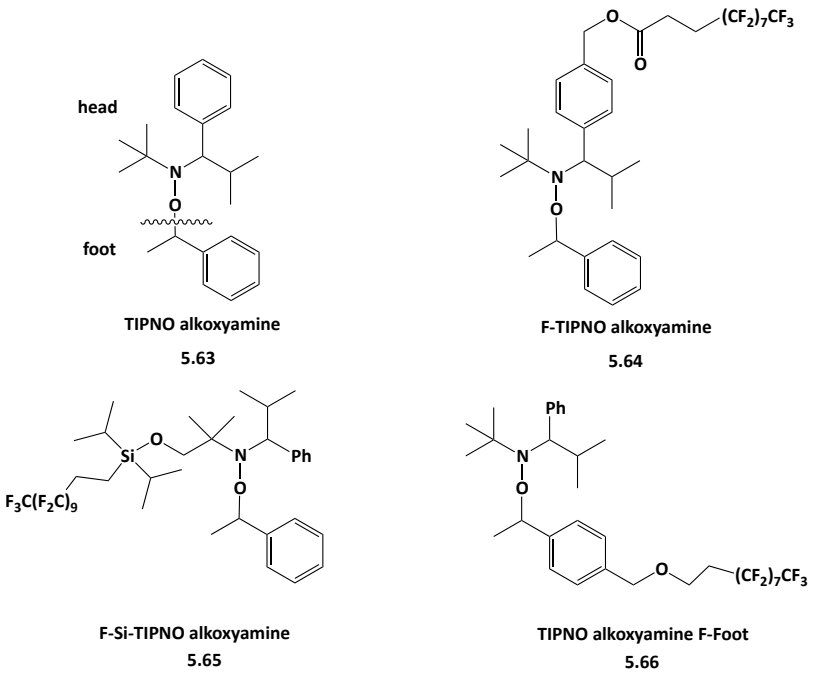
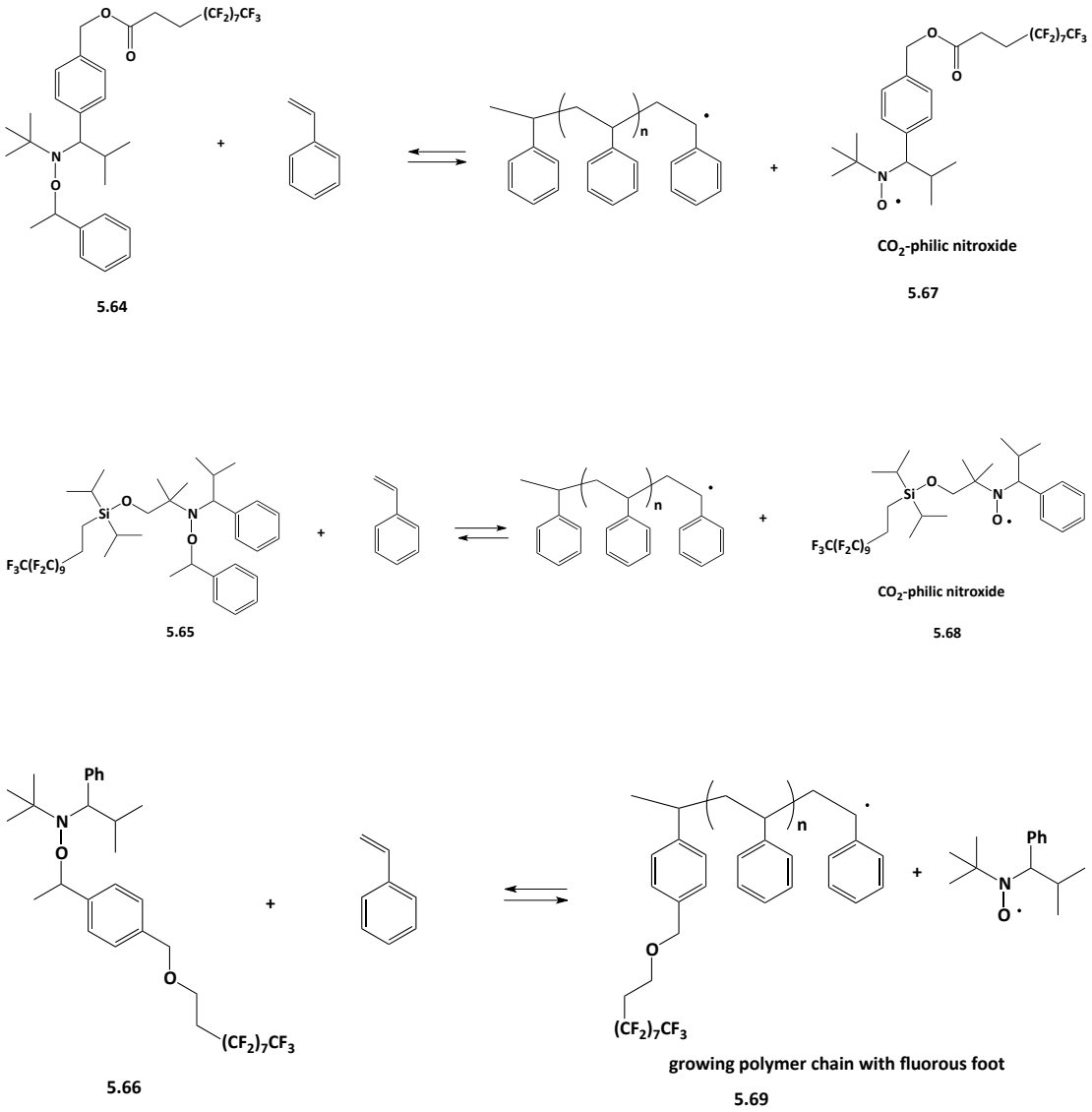


Figure 5.9 TIPNO-Alkoxyamine and Fluorous-Labelled TIPNO-Alkoxyamines Investigated in This Work

t-butyl fragment of the alkoxymine head. The third alkoxyamine **5.66** was prepared by modifying the foot part of the TIPNO-alkoxyamine (**Figure 5.9**). This project was a collaboration with the Aldabbagh group in Ireland. Alkoxyamine initiators were synthesized in the Braslau lab at the University of California, Santa Cruz. The corresponding polymerization work was conducted in the Aldabbagh lab at the National University of Ireland, Galway. This work has been published: C. Magee, A. Earla, J. Petraitis, C. Higa, R. Braslau, Per B. Zetterlund, and F. Aldabbagh, *Macromol. Polym. Chem.* **2014**, *5*, 5723 - 5733.

The alkoxyamines **5.64** and **5.65** dissociate into the CO_2-philic fluorinated TIPNO-nitroxide derivatives **5.67** and **5.68**, while alkoxyamine **5.66** contains a similar sized fluorinated foot, which remains attached to the growing polymer chain **5.69** (**Scheme 5.25**). The performance of these fluorinated alkoxyamines in the



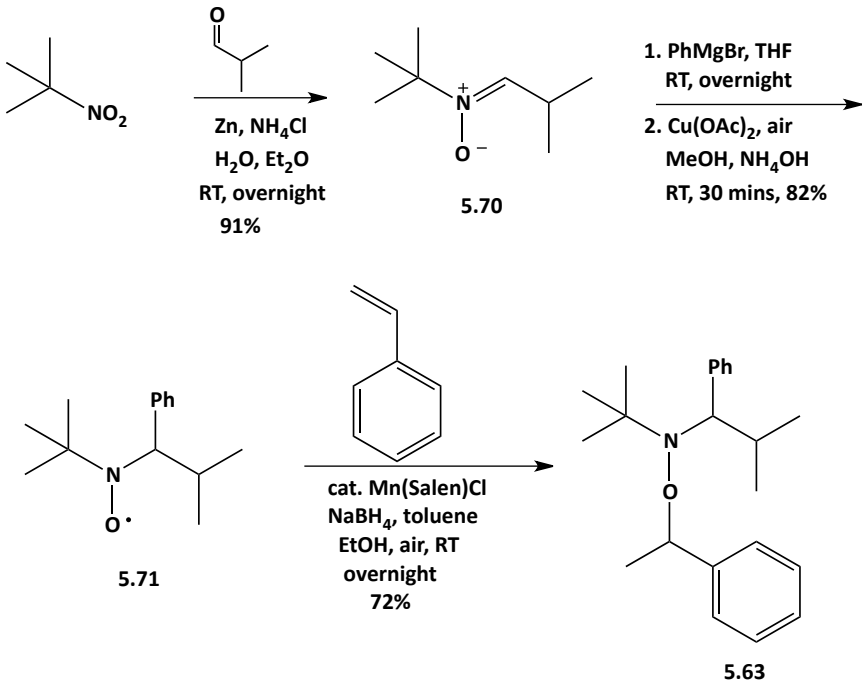
Scheme 5.25 Dissociation of Fluorous-Labelled Alkoxyamines

precipitation NMP of styrene in $scCO_2$ was evaluated and compared with TIPNO- and SG1-alkoxyamine based precipitation polymerizations. These polymerizations were also compared with solution polymerizations in toluene.

5.10 Synthesis of TIPNO-Alkoxyamine and Fluorous-Labelled TIPNO-Alkoxyamine Initiators

5.10.1 Preparation of TIPNO-Alkoxyamine Initiator

The synthesis of 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (TIPNO initiator) **5.63** begins with the preparation of *N*-tert-butyl-α-isopropylnitrone **5.70** as per **Scheme 5.26.** The nitrone **5.70** was obtained by the reductive

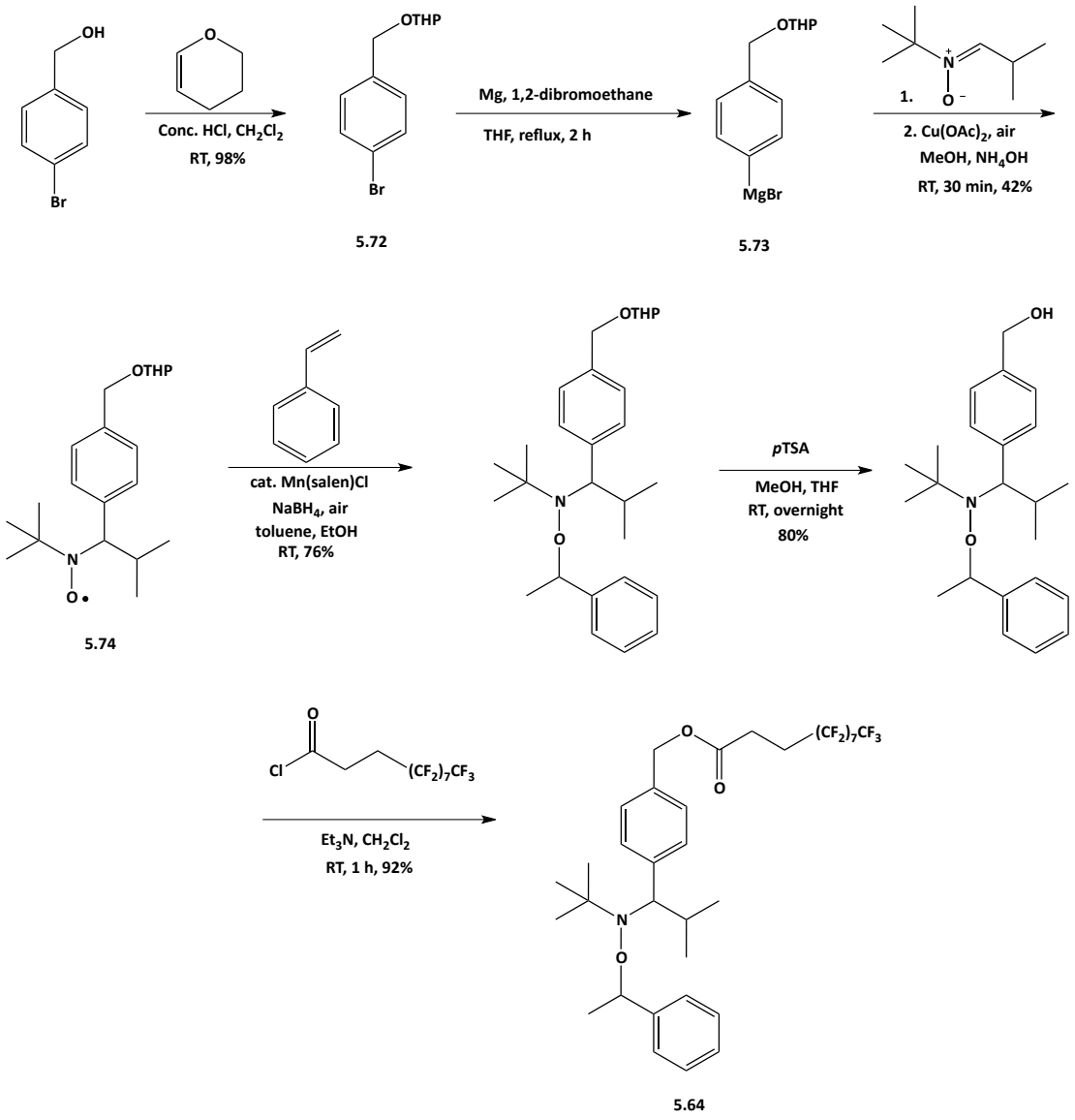


Scheme 5.26 Synthesis of TIPNO-Alkoxyamine Initiator 5.63

condensation of 2-methyl-2-nitropropane with *iso*butyraldehyde in the presence of ammonium chloride and zinc, using a mixture of water and diethyl ether as a solvent in 91% yield. The nucleophilic addition of phenylmagnesium bromide followed by oxidation using 5% copper acetate in the presence of air gave the nitroxide 2,2,5-trimethyl-4-phenyl-3-azahexane-nitroxide (TIPNO) **5.71** in 82% yield after purification by silica gel column chromatography. Following the modified procedure of Hawker et al.[567] the nitroxide **5.71** was trapped by the carbon radical generated from styrene in the presence of a catalytic amount of an achiral manganese salen catalyst and stoichiometric sodium borohydride in a mixture of toluene and methanol, while bubbling with air to give TIPNO-alkoxyamine **5.63** in 72% yield after silica gel column chromatography.

5.10.2 Preparation of F-TIPNO-Alkoxyamine Initiator

For the preparation of F-TIPNO-alkoxyamine **5.64**, the commercially available 4-bromobenzyl alcohol was protected using 3,4-dihyro-2H-pyran (DHP) in the presence of concentrated hydrochloric acid as a catalyst at room temperature for 18 h to yield product **5.72** in 98% yield (**Scheme 5.27**). The Grignard reagent formed from THP protected 4-bromobenzyl alcohol **5.73** was prepared. This was a challenging reaction: the key to success was the use of 1,2-dibromoethane to enhance the formation of the Grignard species. Other methods for activating Mg such as iodine and acid failed. The Grignard species **5.73** was added to the nitrone



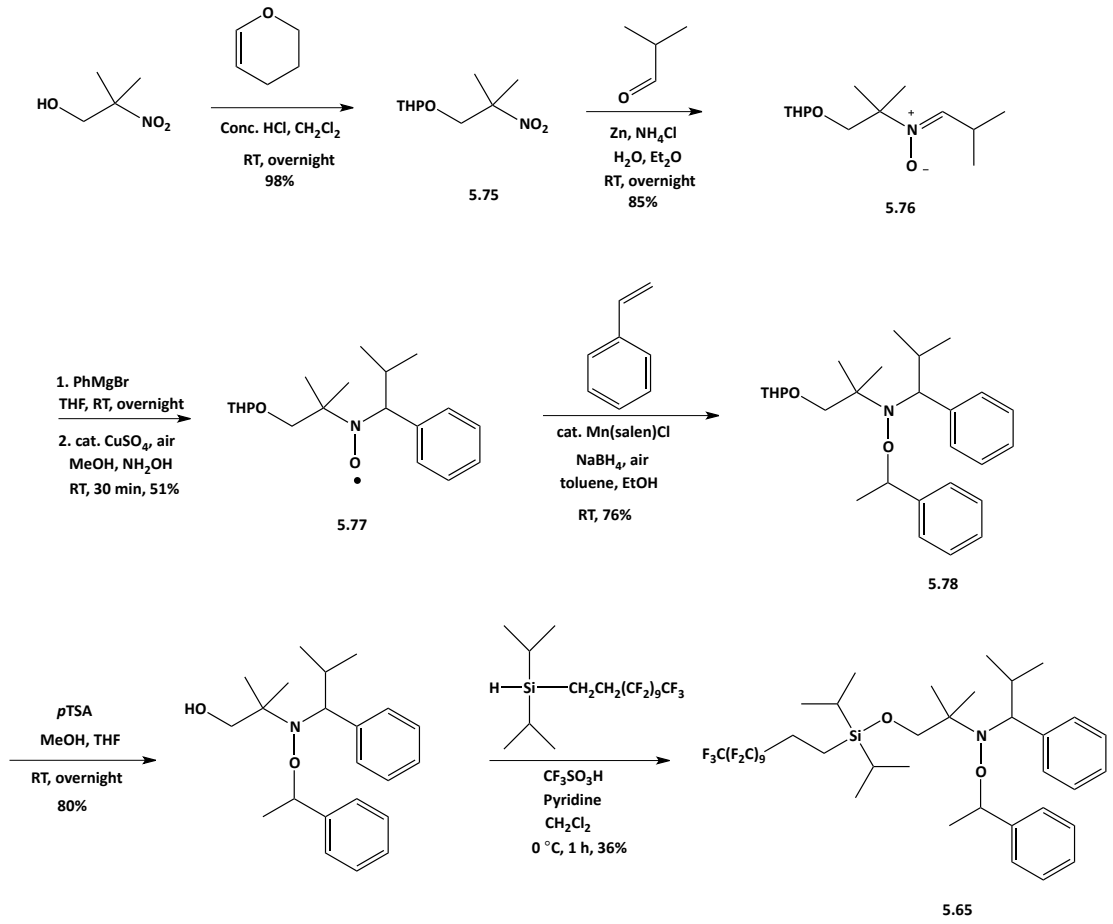
Scheme 5.27 Synthesis of F-TIPNO-Alkoxyamine Initiator 5.64

5.70, followed by oxidation using a copper catalyst, while bubbling with air to afford the nitroxide **5.74** in 41% yield. The alkoxyamine synthesis was carried out by the treatment of nitroxide **5.74** with styrene in the presence of air, sodium borohydride, and Mn(salen) catalyst. *p*Toluenesulfonic acid mediated deprotection of the THP

group, followed by esterification with the fluoroalkane acid chloride provided F-TIPNO alkoxyamine **5.64** bearing a tag containing 17 fluorine atoms.

5.10.3 Preparation of F-Si-TIPNO-Alkoxyamine Initiator

For the preparation of F-Si-TIPNO-alkoxyamine **5.65**, THP protection of commercially available 2-methyl-2-nitropropan-1-ol was carried out using DHP with concentrated hydrochloric acid as a catalyst in dichloromethane to yield the desired product **5.75** in 98% yield (**Scheme 5.28**). The THP protected 2-methyl-2-nitropropanol **5.75** was reductively condensed with *iso*butyraldehyde to give THP-protected nitrone **5.76** in 85% yield. The reaction of the nitrone **5.76** with phenylmagnesium bromide, followed by oxidation using a copper catalyst, while bubbling with air afforded the nitroxide **5.77** in 51% yield. The coupling of nitroxide **5.77** with styrene in the presence of sodium borohydride, air and Mn(salen) catalyst afforded THP-protected alkoxyamine **5.78** in 76% yield. Deprotection of the alcohol using *p*TSA, followed by silylation using the procedure of Crich et al.[626] gave F-Si-TIPNO-alkoxyamine bearing 21 fluorine atoms on the fluorous unit **5.65** in 36% yield.

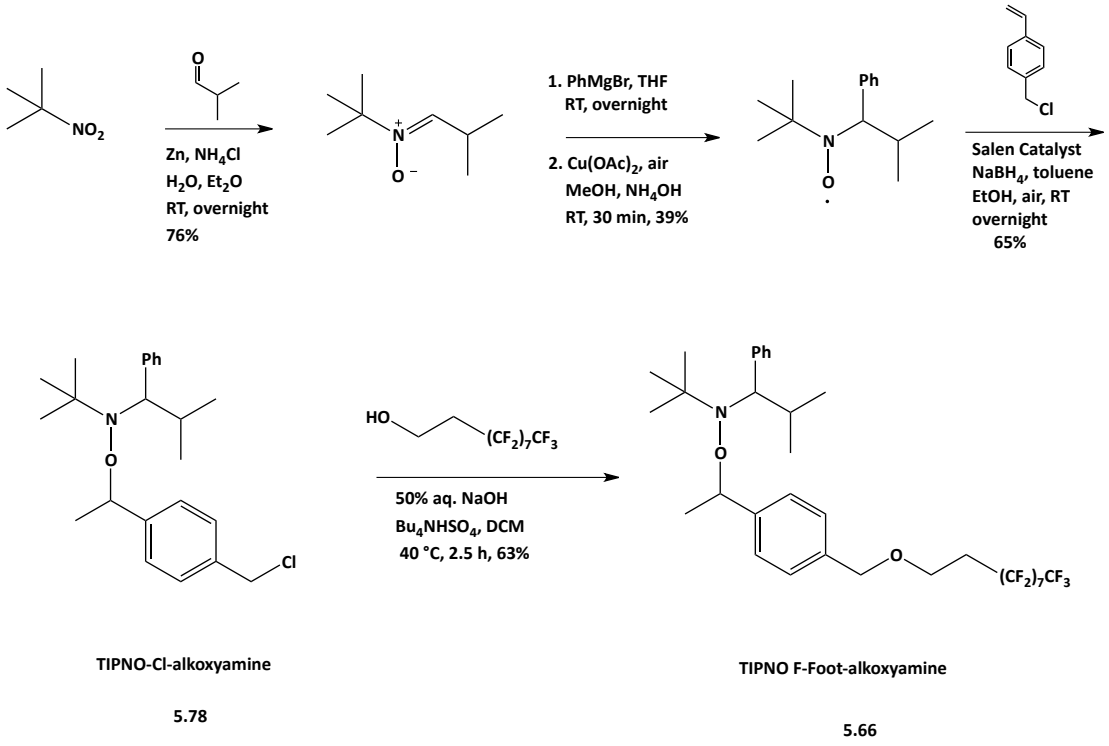


Scheme 5.28 Synthesis of F-Si-TIPNO-Alkoxyamine Initiator 5.65

5.10.4 Preparation of TIPNO-F-Foot-Alkoxyamine Initiator

The synthesis of TIPNO-F-foot-alkoxyamine **5.66** proceeded with the formation of TIPNO by carrying out reductive condensation of 2-methyl-2-nitropropane with *iso*butyraldehyde in the presence of zinc and ammonium chloride (**Scheme 5.29**). Grignard addition of phenylmagnesium bromide followed by oxidation gave TIPNO. TIPNO was coupled with styrene benzyl chloride using the Mn(salen) protocol to give the alkoxyamine **5.78** in 65% yield. Williamson ether synthesis of TIPNO-benzyl

chloride with fluorous alcohol afforded TIPNO F-Foot-alkoxyamine **5.66** in 63% yield bearing a 17-fluorine atom segment on the "foot" portion of the initiator, which dissociates to become the first carbon radical in the polymerization sequence.



Scheme 5.29 Synthesis of TIPNO F-Foot-Alkoxyamine Initiator 5.66

5.11 Solution Polymerizations in Toluene

Solution polymerizations of styrene (50% w/v) were conducted at 110 °C in toluene by our collaborators in the Aldabbagh lab in Ireland. SG1 **5.13** alkoxyamine was examined as well as TIPNO alkoxyamine **5.63**, and three new fluorinated TIPNO-derivatives **5.64**, **5.65**, and **5.66**. TIPNO and derivatives gave very similar rates of

polymerization, indicating that structural modification to the nitroxide and the benzyl "foot" part of the alkoxyamine have no significant effect on the equilibrium constant (K) for trapping and dissociation in organic solution. All polymerizations proceeded in a controlled/living manner with molecular weights close to theoretical values (**Figures 5.10-5.14**).

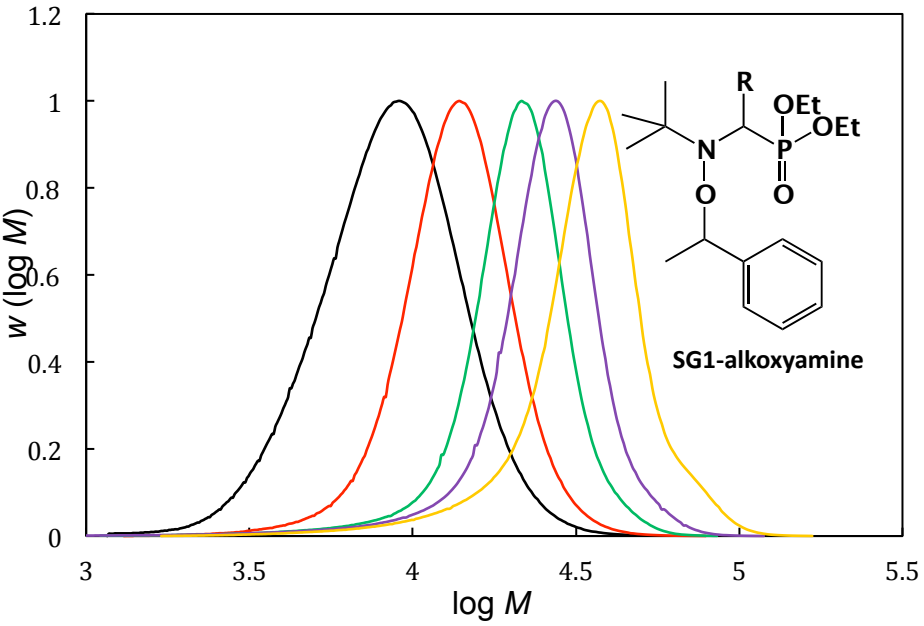


Figure 5.10 MWDs for the SG1-Alkoxyamine Initiated Solution NMP of Styrene (50% w/v) at 110 °C in Toluene using [Styrene]/[SG1-alkoxyamine] = 384: Conversions are 17 (**Black**), 31 (**Red**), 51 (**Green**), 62 (**Purple**) and 82% (**Yellow**)

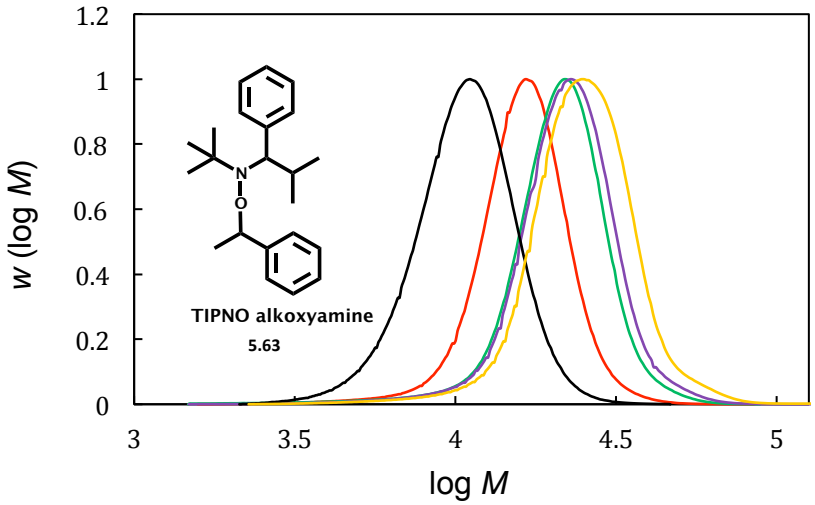


Figure 5.11 MWDs for the TIPNO-Alkoxyamine **5.63** Initiated Solution NMP of Styrene (50% w/v) at 110 °C in Toluene using [Styrene]/[**5.63**] = 384: Conversions are 27 (Black), 33 (Red), 55 (Green), 63 (Purple) and 72% (Yellow)

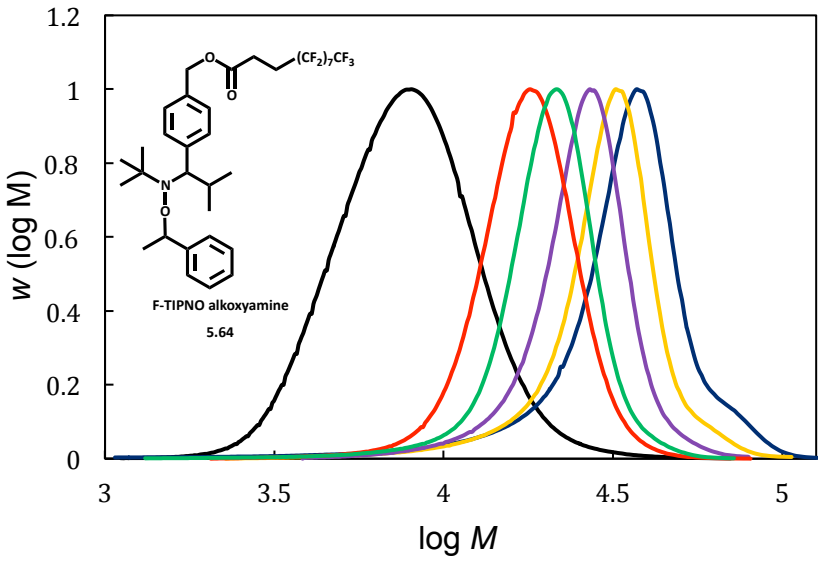


Figure 5.12 MWDs for F-TIPNO-Alkoxyamine **5.64** Initiated Solution NMP of Styrene (50% w/v) at 110 °C in Toluene using [monomer]/[**5.64**] = 384: Conversions are 13 (**Black**), 33 (**Red**), 51 (**Green**), 63 (**Purple**) and 74% (**Yellow**) and 80 % (**Blue**)

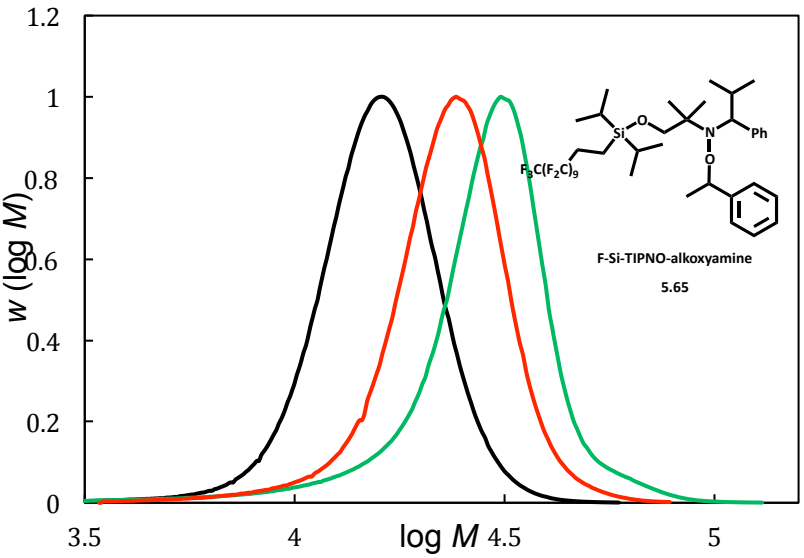


Figure 5.13 MWDs for F-Si-TIPNO-Alkoxyamine **5.65** Initiated Solution NMP of Styrene (50% w/v) at 110 °C in Toluene using [Styrene]/[**5.65**] = 384: Solution Polymerizations in Toluene. Conversions are 38 (**Black**), 61 (**Red**) and 78% (**Green**)

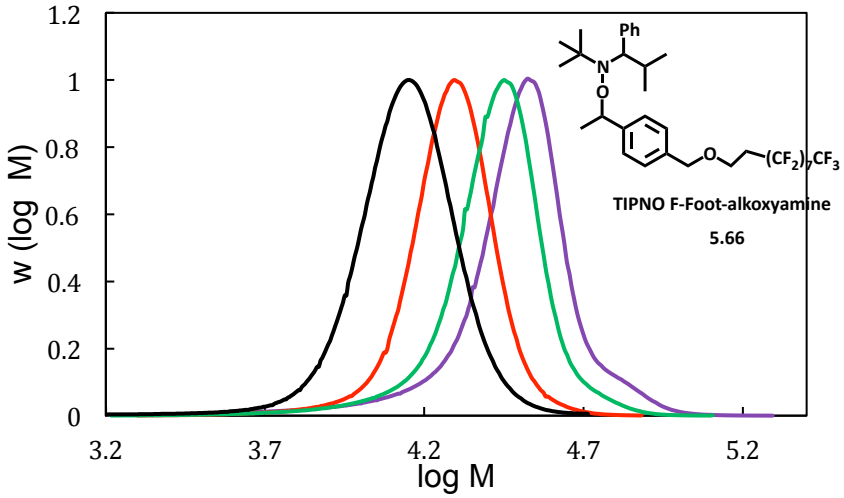


Figure 5.14 MWDs for TIPNO F-Foot-Alkoxyamine **5.66** Initiated Solution NMP of Styrene (50% w/v) at 110 °C in Toluene using [Styrene]/[**5.66**] = 384: Conversions are 24 (**Black**), 44 (red), 65 (**Green**) and 75 % (**Purple**)

The theoretical values of the number-average molecular weight $\mathbf{M}_n$ were calculated by using **equation 5.2**, where α is a fractional conversion of monomer, $[\mathbf{M}]_0$ is the initial monomer concentration, $[\text{alkoxyamine}]_0$ is the initial concentration of the alkoxyamine, $\mathbf{MW}_{mon}$ and $\mathbf{MW}_{alk}$ are the molecular weights of monomer and alkoxyamine. For example, the calculated M_n for polystyrene, where α = 0.3, $\mathbf{MW}_{mon}$ =104.1520 g/mol for styrene, $\mathbf{MW}_{alk}$ = 325.4960 for TIPNO-alkoxyamine, and $[M]_0/[\text{alkoxyamine}]_0$ = 384 is approximately 11,123 g/mol. The experimental value

$$\mathbf{M}_{n,th} = \frac{\alpha[\mathbf{M}]_0\mathbf{MW}_{\text{mon}}}{[\text{alkoxyamine}]_0} + \mathbf{MW}_{\text{alk}} \qquad \textbf{equation 5.2}$$

of M_n as determined by gel permeation chromatography (GPC) system at 30% conversion of styrene was 9,910 g/mol (**Figure 5.15**). The experimental $\mathbf{M}_n$ values for conversions over 55% were less than the predicted theoretical values. SG1-alkoxyamine mediated polymerizations proceeded at higher rates compared to TIPNO-alkoxyamine and its fluorinated derivatives (**Figure 5.16**). The polydispersity index (M_w/M_n) in most cases was less than 1.3, indicating a controlled/living polymerization of styrene by SG1, TIPNO-alkoxyamine and its fluorinated derivatives in solution (**Figure 5.17**).

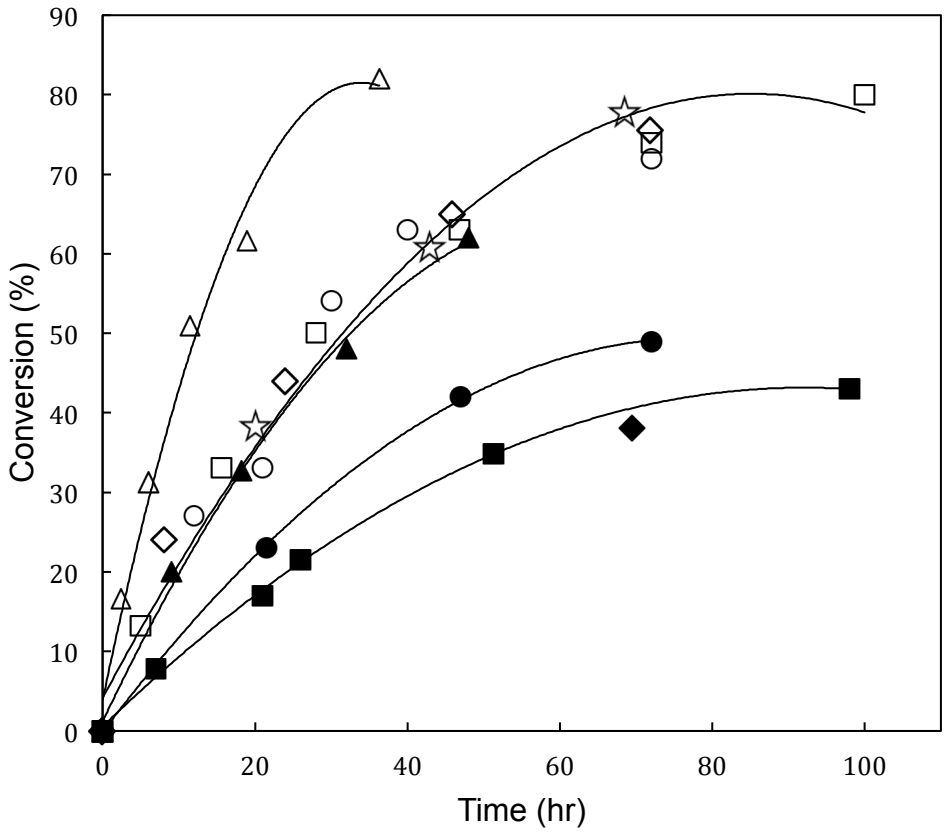


Figure 5.15 Conversion Versus Time Plots for TIPNO **5.63** (circles), F-TIPNO **5.64** (Squares), F-Si-TIPNO **5.65** (Stars), TIPNO-F-Foot **5.66** (Siamonds) and SG1 (Triangles), Styryl-Alkoxyamine Initiated NMP of Styrene (50% w/v) at 110 °C using [styrene]/[alkoxyamine] = 384. Closed and Open Symbols are Respectively Precipitation (in $scCO_2$ at 30 MPa) and Solution (in toluene) Polymerizations

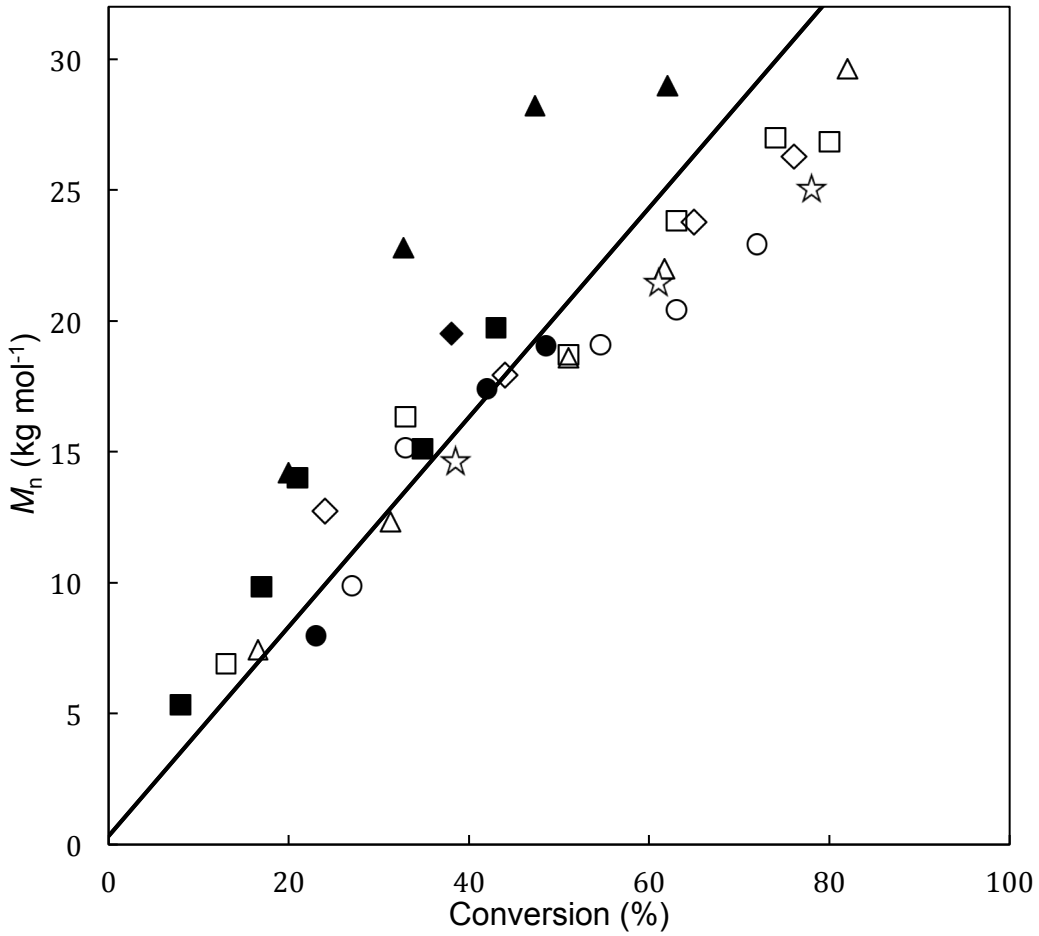


Figure 5.16 Number-Average Molecular Weights (M_n) Versus Conversion for TIPNO **5.63** (Circles), F-TIPNO **5.64** (Squares), TIPNO-F-Foot **5.66** (Diamonds), F-Si-TIPNO **5.65** (Stars) and SG1 (Triangles), Styryl-Alkoxyamine Initiated NMP of Styrene (50% w/v) at 110 °C using [styrene]/[alkoxyamine] = 384. Closed and Open Symbols are Respectively Precipitation (in $scCO_2$ at 30 MPa) and Solution (in toluene) Polymerizations. The Line Represents Theoretical MW ($M_{n,th}$) based on **Equation 5.2**

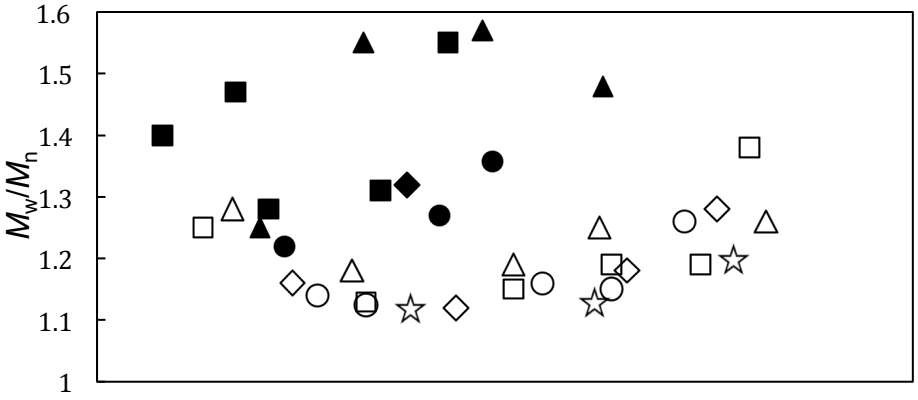


Figure 5.17 (a) Polydispersities (M_w/M_n) TIPNO **5.63** (Circles), F-TIPNO 5.64 (Squares), TIPNO-F-Foot **5.66** (Diamonds), F-Si-TIPNO **5.65** (Stars) and SG1 (Triangles), Styryl-Alkoxyamine Initiated NMP of Styrene (50% w/v) at 110 °C using [styrene]/[alkoxyamine] = 384. Closed and Open Symbols are Respectively Precipitation (in $scCO_2$ at 30 MPa) and Solution (in toluene)

5.12 Precipitation Polymerizations in Supercritical Carbon Dioxide

All NMP in $scCO_2$ were conducted in the Aldabbagh lab in a 25 mL stainless steel Parr reactor with a maximum operating pressure of 40 MPa and 130 °C. The pressure was achieved using a Tharr P-50 series high-pressure pump, and the temperature was monitored by a Thar CN6 controller. The reactor was loaded with styrene (50% w/v loading), the respective alkoxyamine and a magnetic stir bar and sealed. Carbon dioxide gas was bubbled through the reaction mixture for 20 minutes. Liquid CO_2 was then added and the reactor was heated to 110 °C in an oil bath, followed by the raise in the pressure of the reactor to 30 MPa by adding more CO_2. The reactions were quenched by submersion of the reactor into an ice-water bath. As mentioned earlier in this chapter, the degree of polymerization can be

estimated by using the model developed by Aldabbagh et al.[579] This model is based on the estimation of J_{crit} as a function of initial monomer loading and targeted molecular weight. Based on this model, NMP of styrene at (50% w/v loading) in $scCO_2$ at 110 °C and 30 MPa was expected to reach J_{crit} at approximately M_n = 3,450 (8.5% conversion). In this work, conversions higher than 8.5% were obtained for all the alkoxyamine initiators. Therefore, these systems are considered heterogenous.

5.12.1 Model Precipitation NMP of Styrene in $scCO_2$ with TIPNO

The model precipitation NMP of styrene in $scCO_2$ was conducted using TIPNO-alkoxyamine **5.63**. Two polymerization systems were developed: (1) TIPNO-alkoxyamine with 5% excess of TIPNO nitroxide and (2) TIPNO-alkoxyamine with no added TIPNO nitroxide. Both polymerizations proceeded at a similar rate as shown in **Figure 5.18.** However, the system containing an initial excess of free TIPNO reached a limiting conversion sooner than the one with no free nitroxide. The M_n and M_w/M_n for 0% TIPNO were 7960 and 1.22 respectively, and for 5% excess TIPNO were 9000 and 1.14 respectively (**Figure 5.19**). This shows that the controlled/living character for alkoxyamine-initiated precipitation polymerizations in $scCO_2$ can be estabilished without the requirement of free nitroxide (**Figure 5.20**). Therefore, all subsequent NMPs of styrene in $scCO_2$ were initiated by alkoxyamines without the addition of free nitroxide.

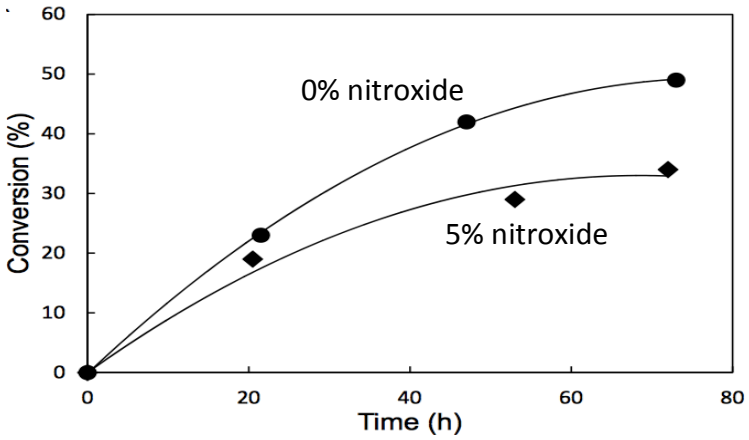


Figure 5.18 The effect of free TIPNO on NMP in $scCO_2$ at 110 °C. Conversion Versus Time for TIPNO-Alkoxyamine **5.63** Initiated Precipitation NMP of Styrene (50% w/v) using $[Monomer]_0/[Alkoxyamine]_0$ = 384 with $[Free\ TIPNO]_0$ = 5% (Diamonds) and $[Free\ TIPNO]_0$ = 0% (Circles)

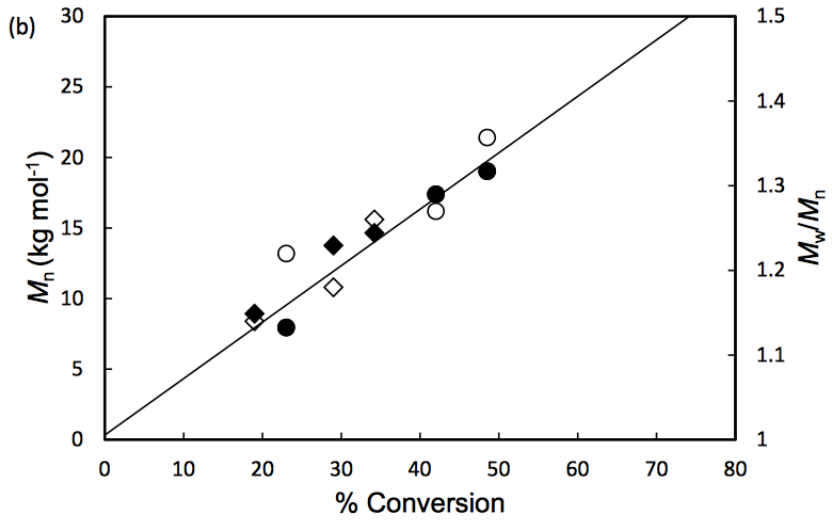


Figure 5.19 The Effect of Free TIPNO on NMP in $scCO_2$ at 110 °C. Conversion Versus Mn (Closed symbols) and Mw/Mn (Open symbols) plot for TIPNO-Alkoxyamine Initiated Precipitation NMP of Styrene (50% w/v) using $[Monomer]_0/[Alkoxyamine]_0$ = 384 with $[Free\ TIPNO]_0$ = 0.05 (Diamonds) and $[Free\ TIPNO]_0$ = 0 (Circles)

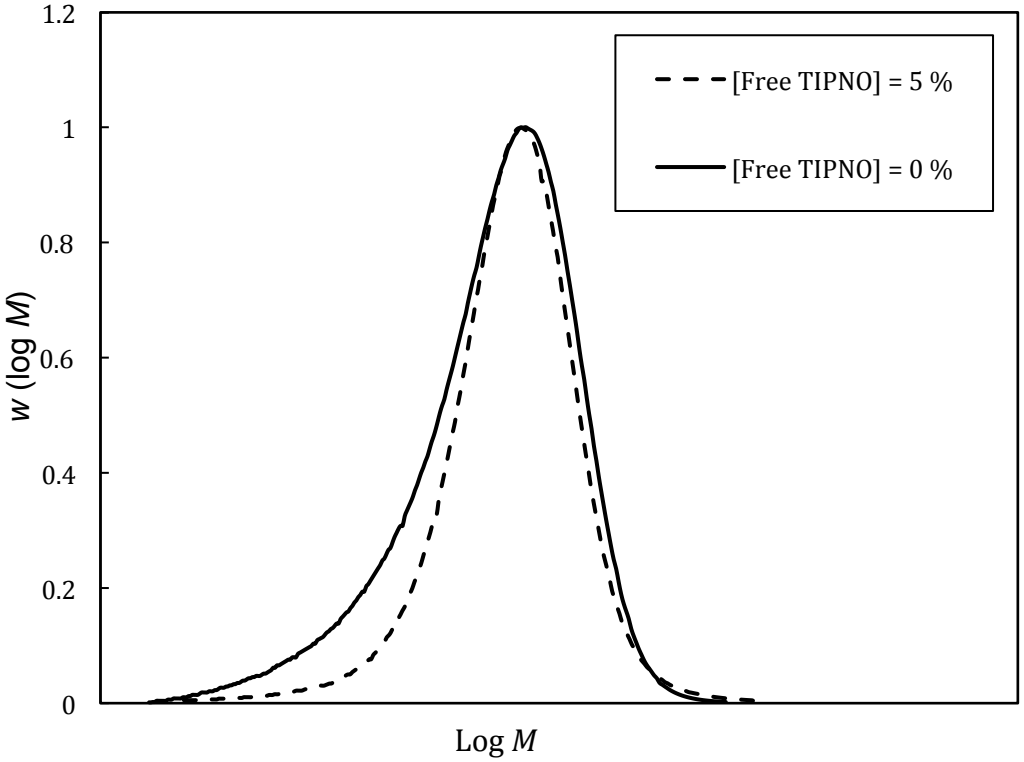


Figure 5.20 Comparisons of MWDs for the Precipitation NMP of Styrene at 30 MPa and 110 °C using [styrene]/[**5.63**] = 384. Effect of Free Nitroxide at Styrene 50% (w/v): $[\text{Free TIPNO}]_0/[\mathbf{5.63}]_0 = 0.05$, dashed line is 19% conv. after 21 h, $M_n = 9000$ and $M_w/M_n = 1.14$ and for 0% free TIPNO, the solid line is 23% Conv. after 22 h, $M_n = 7960$ and $M_w/M_n = 1.22$

5.12.2 Comparison of TIPNO 5.63 and SG1 in Precipitation NMP in $scCO_2$

As mentioned earlier in this chapter, Aldabbagh et al. observed lower rates of polymerization of styrene for bimolecular nitroxide/AIBN systems in $scCO_2$ compared to the analogous solution polymerizations in toluene. This effect was attributed to monomer partitioning: some styrene resides in the continuous $scCO_2$ phase after particle formation, leading to low monomer concentration in the particle

(the main locus of polymerization). Moreover, significant differences in polymerization rate and control were observed between SG1- and TIPNO-alkoxyamine mediated polymerizations with respect to M_n and M_w/M_n. The SG1-mediated polymerization gave higher M_n but poor control (M_w/M_n = 1.25 – 1.57) compared to TIPNO-mediated polymerization (M_w/Mn = 1.22 – 1.36). The higher rate and inferior control for SG1 in $scCO_2$ is due to a combination of higher K,[541-542,540] and a higher solubility of SG1 in $scCO_2$, leading to greater nitroxide partitioning away from the locus of polymerization after particle formation. Poor control for SG1-mediated polymerization was not observed when an excess of free SG1 radical was used. It is expected that TIPNO will have better solubility in the organic phase (particles) due to TIPNO's non-polar nature compared to SG1, which contains a phophonate ester. Poor control for SG1-mediated polymerizations in $scCO_2$ was not previously observed in bimolecular nitroxide/AIBN systems because of the use of a higher ratio of $[SG1]_0/[AIBN]_0$.[575, 621-622,627]

5.12.3 Comparison of TIPNO-Alkoxyamine 5.63 and Fluorous-Labelled TIPNO-Alkoxyamines in Precipitation NMP in $scCO_2$

TIPNO-alkoxyamine **5.63** and F-TIPNO-alkoxyamine **5.64** initiated NMP show similar rates of polymerization in solution. A higher rate of polymerization for F-TIPNO **5.64** initiated NMP in $scCO_2$ was expected compared to TIPNO **5.63**. The

fluorinated TIPNO-aloxyamine **5.64** is expected to have better solubility in $scCO_2$ compared to TIPNO-alkoxyamine **5.63**. The fluorinated nitroxide will be more CO_2-philic than TIPNO, and is thus expected to partition away from the locus of polymerization upon particle formation, which should lead to a higher rate of polymerization. Contradictory to this, F-TIPNO-alkoxyamine **5.64** initiated NMP was slower in $scCO_2$ compared to TIPNO-alkoxyamine **5.63**.

To understand the effects of nitroxide partitioning on rates of polymerization and molecular weight distribution, modeling and simulations were conducted by Per Zetturland using the PREDICI software for the styrene/TIPNO systems at 110 °C. The polymerization was simulated for three values of nitroxide partition coefficients of I' = $[nitroxide]_{org}/[nitroxide]_{CO2}$ = ∞(no partitioning), 1 and 0.25. I' = 1 and 0.25 correspond to situations where 50% and 80% of free nitroxide, respectively, is located in the continuous phase (**Figure 5.21** and **Figure 5.22**). It is clear from the simulations that even if extensive nitroxide partitioning occurs, the increase in the rate of polymerization is relatively small. As expected there is a broadening of MWDs with increasing nitroxide partitioning, with the livingness (number fraction of chains with alkoxyamine-terminated α-ends at 48% conversion) decreasing: 97.5, 96.8, and 95.3% (**Figure 5.22**). Indeed the alkoxyamine-initiated polymerizations using fluorinated TIPNO derivative **5.64** (M_w/M_n = 1.25 – 1.55) proceeded with

inferior control relative to TIPNO **5.63**, as demonstrated by M_ns higher than theoretical values and high polydispersities (**Figures 5.16 and 5.17**).

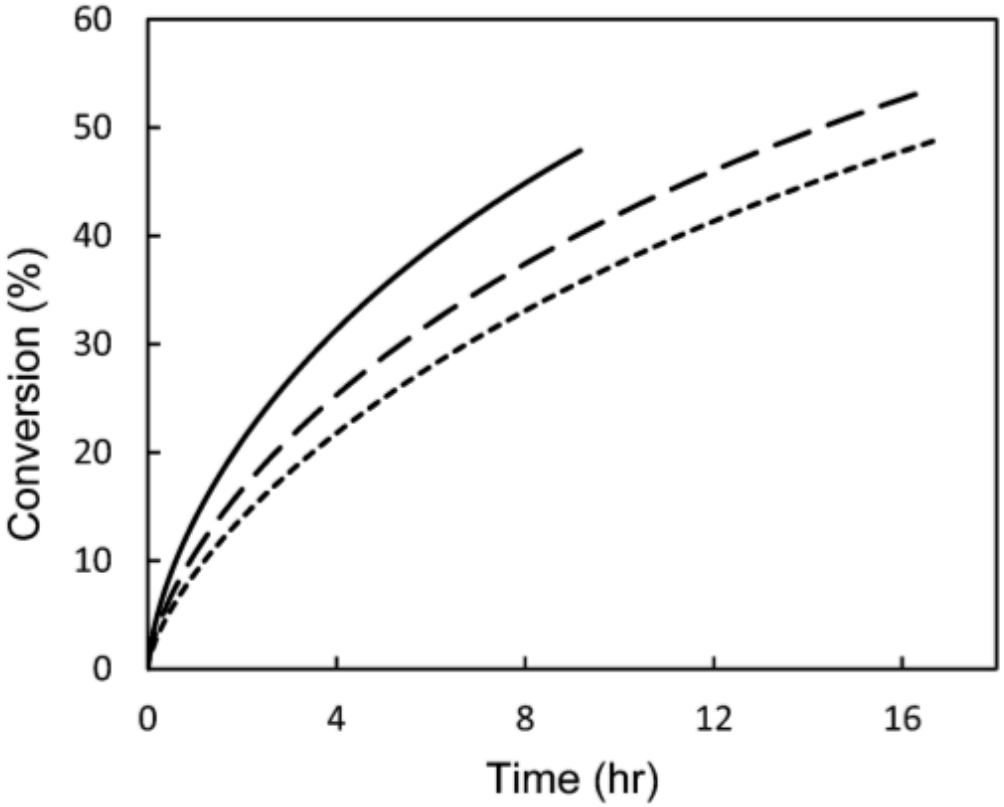


Figure 5.21 Simulated Conversion vs. Time Data of the Styrene/TIPNO system at 110 °C. $[Nitroxide]_{org}$ /$[nitroxide]_{CO2}$ = ∞ (dotted line), 1 (dashed line), and 0.25 (solid line). I^{-} = ∞, 1 and 0.25 Correspond to Situations where 0, 50 and 80% of Free Nitroxide, Respectively, is Located in the Continuous Phase

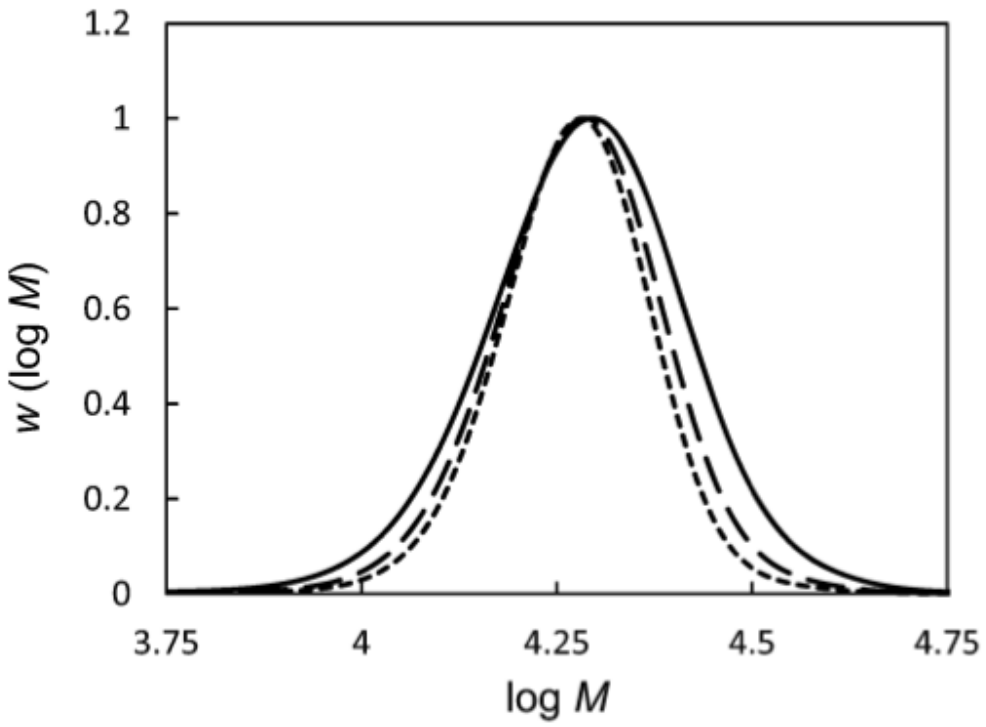


Figure 5.22 Simulated MWDs (at 48% conv.) of the Styrene/TIPNO system at 110 °C. $[Nitroxide]_{org}$ /$[nitroxide]_{CO2}$ = ∞ (dotted line), 1 (dashed line), and 0.25 (solid line). I^- = ∞, 1 and 0.25 Correspond to Situations where 0, 50 and 80% of Free Nitroxide, Respectively, is Located in the Continuous Phase.

If nitroxide partitioning is the main cause of inferior control for alkoxyamine **5.64** in $scCO_2$, it follows that the polymerization rate is quite insensitive to the degree of nitroxide partitioning. The relatively small difference in the rate of polymerization between TIPNO **5.63** and F-TIPNO **5.64** in $scCO_2$ is not necessarily inconsistent with the F-TIPNO nitroxide partitioning away from the locus of polymerization resulting in wider MWDs. Moreover similar to the simulated MWD

overlays, nitroxide partitioning seems to give marginal broadening experimentally when comparing MWDs for TIPNO **5.63** and F-TIPNO **5.64** initiated polymerization at similar intermediate conversions (**Figures 5.23 and 5.24**).

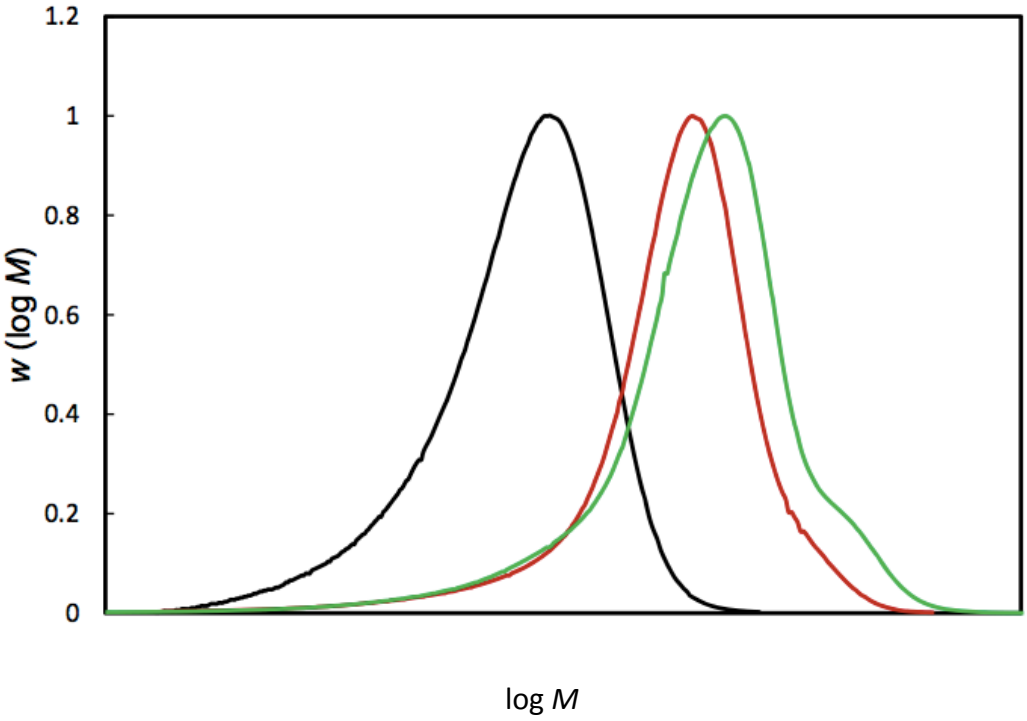


Figure 5.23 MWDs for the TIPNO-Alkoxyamine **5.63** Initiated NMP of Styrene (50% w/v) at 110 °C using [styrene]/[**1a**] = 384: (a) Precipitation Polymerizations in $scCO_2$ at 30 MPa. Conversions are 23 (**Black**), 42 (**Red**) and 49% (**Green**)

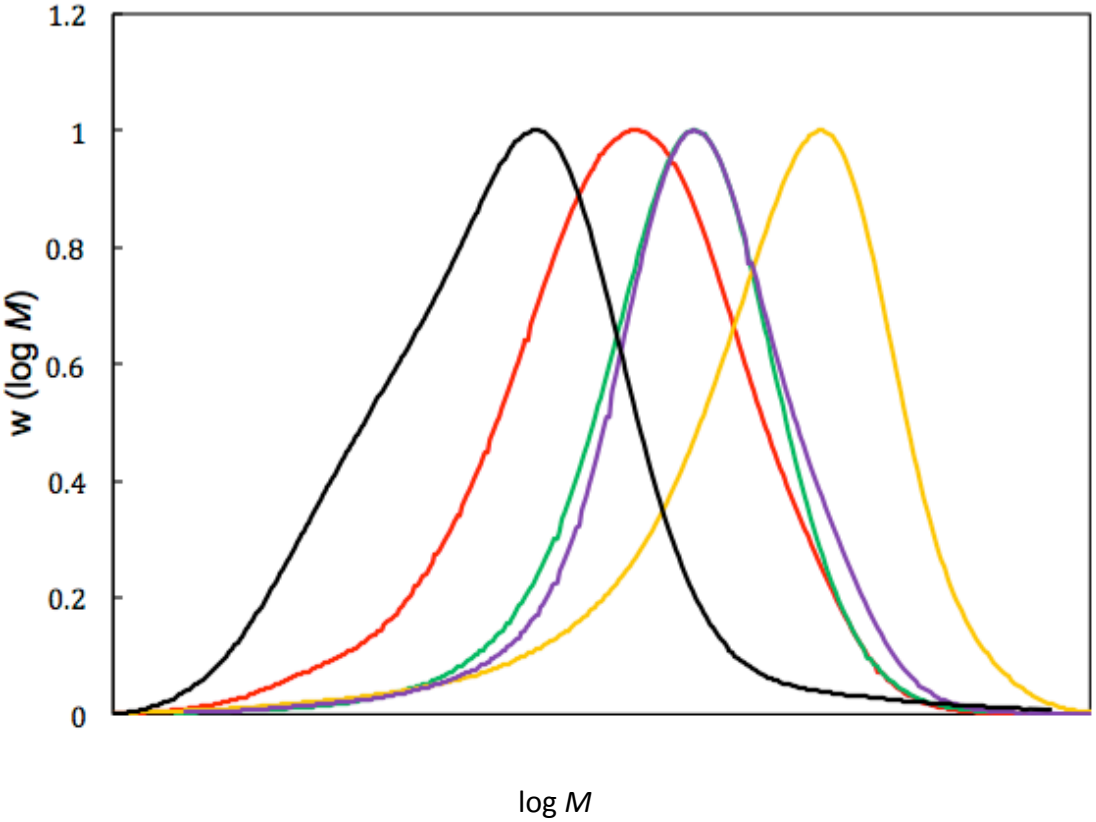


Figure 5.24 MWDs for F-TIPNO-Alkoxyamine **5.64** Initiated NMP of Styrene (50% w/v) at 110 °C using $[Monomer]_0$ /$[Alkoxyamine]_0$ = 384: Precipitation Polymerizations in $scCO_2$ at 30 MPa; Conversions are 8 (**Black**), 17 (**Red**), 21 (**Green**), 35 (**Purple**) and 43% (**Yellow**)

The precipitation polymerization of styrene in $scCO_2$ using F-Si-TIPNO **5.65** gave broadening of MWDs compared to TIPNO-alkoxyamine **5.63** presumably due to nitroxide partitioning as discussed for **5.64 (Figure 5.25)**. Again, contrary to expectations, the polymerization rate for **5.65** was somewhat lower than for **5.63**.

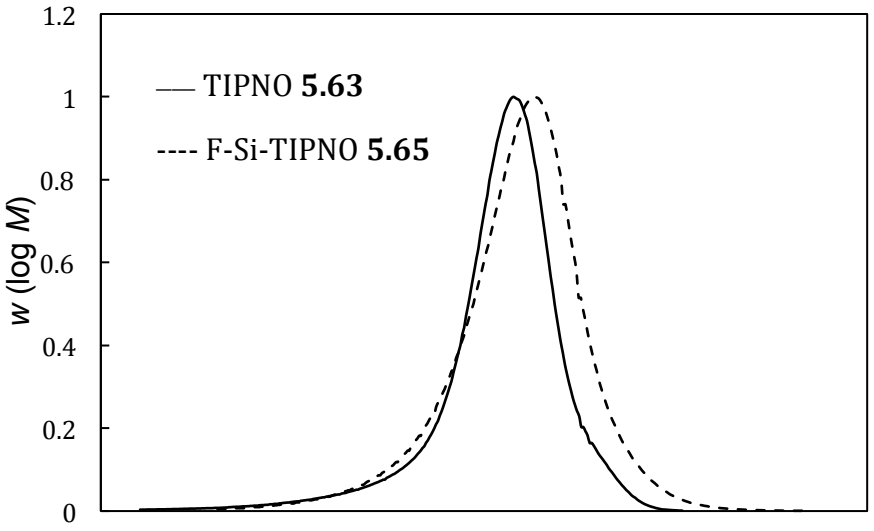


Figure 5.25 Comparing the Performance of F-Si-TIPNO-Alkoxyamine **5.65** with the TIPNO-Alkoxyamine **5.63** in the Precipitation NMP of Styrene (50% w/v) at 110 °C using $[Monomer]_0/[Alkoxyamine]_0 = 384$. (a) F-Si-TIPNO **5.65**, 39% Conversion After 61 h, M_n = 20,000 and M_w/M_n = 1.29 Compared with the TIPNO **5.63**, 42% Conversion After 47 h, M_n = 17,400 and M_w/M_n = 1.27

The precipitation polymerization of styrene in $scCO_2$ using TIPNO-F-Foot **5.66** alkoxyamine gave a high M_w shoulder. Alkoxyamine **5.66** differs from the other fluorinated alkoxyamines **5.64** and **5.65** in that (non-fluorinated) TIPNO is the mediating nitroxide and a fluorinated initiating benzyl "foot" radical is produced upon dissociation. The extent of nitroxide partitioning would be expected to be the same as TIPNO **5.63**. It can be speculated that the F-content in the propagating radical part of the alkoxyamine leads to an increase in J_{crit} (due to increased solubility in the continuous phase), and thus later nucleation; it is possible that this is related to the partial loss of control. It is unlikely that a higher k_d for TIPNO-F-foot

5.66 causes the observed MWD broadening in comparison to TIPNO-alkoxyamine **5.63** (**Figure 5.26**), because rates and control are very similar in solution (toluene).

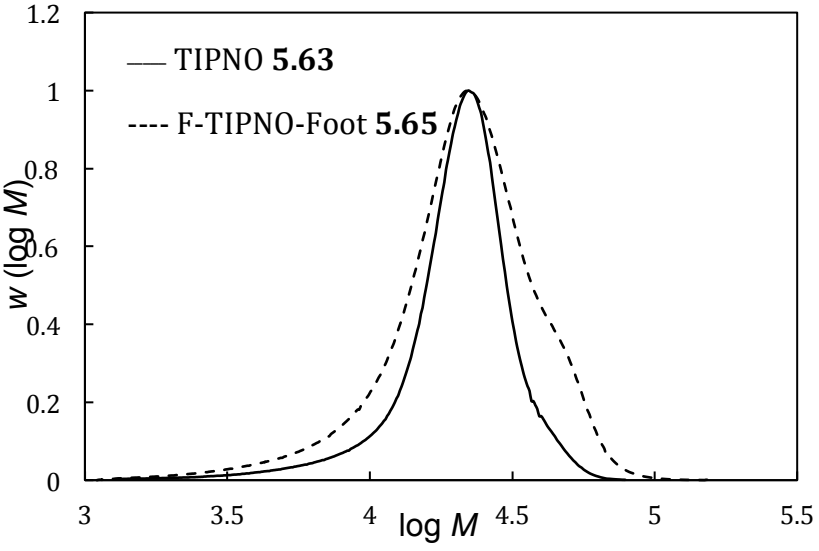


Figure 5.26 Comparing the Performance of TIPNO-F-Foot-Alkoxyamine **5.66** with the TIPNO-Alkoxyamine **5.63** in the Precipitation NMP of Sytrene (50%w/v) at 110 °C using$[Monomer]_0/[Alkoxyamine]_0$ = 384. TIPNO-F-Foot **5.66**, 38% Conversion after 69 h, M_n = 19,500 and M_w/M_n = 1.32 Compared with the TIPNO **5.63** , 42% conversion After 47 h, M_n = 17,400 and M_w/M_n = 1.27

5.13 Conclusion

In the absence of excess free $[nitroxide]_0$, TiPNO-alkoxyamine gave superior controlled/living character in precipitation NMP of styrene in $scCO_2$ compared to the SG1 analogue. In solution (toluene), SG1 resulted in slightly less control and a higher rate of polymerization. Differences between TIPNO- and SG1-alkoxyamines can be

rationalized in terms of higher dissociation constant for SG1-alkoxyamine and a greater level of nitroxide partitioning for SG1 in the heterogenous system. Despite increased steric congestion about the (N-O bond) in novel fluorinated TIPNO-alkoxyamine initiators, a similar equilibrium constant to TIPNO for activation/deactivation in organic solution (toluene) can be inferred. The greater partitioning of fluorinated TIPNO nitroxide derivatives in $scCO_2$ impacts on the controlled/living character and broadening of the molecular weight distributions but does not have any significant effect on the rate of precipitation polymerization in supercritical carbon dioxide.

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6 Experimental Section

6.1 General Considerations

6.1.1 General Materials

Commercial bulk polymerized PVC (Mw = 43,000) was purchased from Sigma-Aldrich and was purified by dissolving 5.003 g in 60 mL of tetrahydrofuran (THF) at room temperature, followed by precipitation with 180 mL of methanol. Acrolein (96%, stabilized with hydroquinone, Alfa Aesar) was distilled at ambient pressure. Tetrahydrofuran (Fischer Scientific) and diethyl ether (Fischer Scientific, 99.1%) were dried over sodium and benzophenone when anhydrous conditions were required. Acetonitrile (Fisher Scientific) and toluene (Fisher Scientific) were obtained from a Puresolv solvent purification system manufactured by Innovative Technologies, Inc. when anhydrous conditions were required. Silica gel (grade 60, 40 - 75 mesh, Sorbent Technologies) was activated by heating at 200 °C for 24 h under nitrogen and stored in a dessicator upon cooling. All other chemicals were used as received. Water was deionized. Manganese salen catalyst was prepared following the procedure of Choudary et al.[628]

The following chemicals were purchased from Sigma-Aldrich: sodium azide (99.5%), 2-ethylhexanol (99%), 1-butanol (99.4%), *n*-butyllithium (1.6 M in hexanes), anhydrous *N,N*-dimethylformamide (99.8%), triethylamine (99%), triphenylphosphine (99%), benzylamine (99%), paraformaldehyde (95%), Merrifield

resin (3.0-4.0 mmol/g of chloride), sodium hydride (60% in mineral oil), *N*-bromosuccinamide (NBS), benzoyl peroxide, concentrated ammonium hydroxide (7.4 N), glacial acetic acid (17.4 N), and propiolic acid (95%). The following chemicals were purchased from Acros Organics: dimethyl acetylenedicarboxylate (98%), pyridine (99%), 4-methylphthalic anhydride (96%), Dess-Martin periodinane (97%), *p*-toluenesulfonic acid monohydrate (99%), 3,4-dihydro(2H)pyran (99%), 4-vinylbenzyl chloride (90%), tetrabutylammonium fluoride (1 M in THF), and cesium fluoride (99%). The following chemicals were purchased from Alfa Aesar: phenyl hydrazine (97%), phenylmagnesium bromide (3.0 M in diethyl ether), *iso*butyraldehyde (98%), acetylenedicarboxylic acid (97%), isoprene (99%, stabilized with 4-tert-butylcatechol), dimethylacetylene dicarboxylate (95%), 2-nitropropanol (98%), L-ascorbic acid, sodium salt (99%). The following reagents were purchased from Fischer Scientific: ammonium chloride (99.7%), sodium hydroxide (98.7%), magnesium sulfate (98%), sodium chloride (98%), sodium bicarbonate (98%), chloroform, methanol, benzene, acetone, ethanol, magnesium turnings, zinc (99%), sodium borohydride (98%), and concentrated hydrochloric acid (12M). Propargyl alcohol (98%) and 2-nitroethane (96%) were purchased from Lancaster. Trifluoromethyltrimethyl-

silane (99%) was purchased from Oakwood Chemicals. 2-Nitropropane (98%) was purchased from Spectrum Chemicals. *1H, 1H, 2H, 2H*-Perfluorodecanol (97%) was

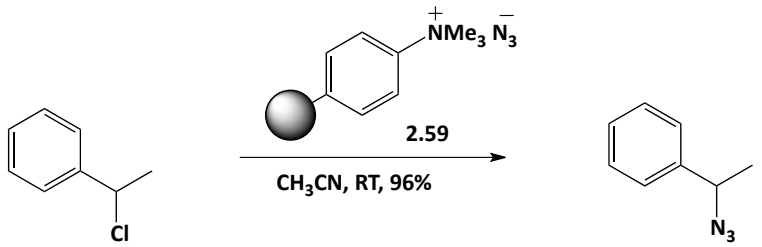
purchased from Matrix Scientific. Trifluoromethanesulfonic acid (98%), tetrabutylammoniumhydrogen sulfate (98%), (1-chloroethyl) benzene (97%) was purchased from TCI America. 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecanoyl chloride was obtained from Santa Cruz Biotechnology. Copper sulfate (98%) was purchased from Strem Chemicals. (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosafluorododecyl) di*iso*propylsilane (97%) was purchased from Fluorous Technologies Inc. 4-Bromo-benzylalcohol (98%) was purchased from Combi-Blocks. Flash chromatography was performed using premium grade 60, 40 - 75 mesh silica gel from Sorbent Technologies. Analytical thin layer chromatography (TLC) was carried out on Whatman silica gel plates (0.25 mm thick). Findenser™ was purchased from Radleys.

6.1.2 Instrumentation

NMR spectra were recorded at ambient temperature on a Varian 500 MHz spectrometer or INOVO 500 MHz in $CDCl_3$ as solvent unless otherwise noted. The spectra were recorded with the $CHCl_3$ peak (δ 7.27 ppm) as internal standard for ^{1}H-NMR and $CDCl_3$ triplet (δ 77.27 ppm) for ^{13}C-NMR. C_6F_6 (δ -164.9 ppm) was used as reference for ^{19}F NMR. FTIR spectra were recorded on a Perkin-Elmer spectrometer as a neat film on a KBr cell. High resolution mass spectra (HRMS) were recorded

either on a benchtop Mariner electrospray ionization time-of-flight (ESITOF) mass spectrometer or on an LTQ Orbitrap.

6.2 Experimental Section for Chapter 2



2.56 2.60

Preparation of (1-azidoethyl) benzene) (2.60). Following the procedure of Castrica et al.[307] 1-chloroethyl)benzene (0.5037 g, 3.575 mmol) was added to a mixture of amberlite-400/N_3 resin **2.59** (4.562 g) in 10 mL of acetonitrile under nitrogen. The reaction mixture was stirred at room temperature for 22 h. Thin layer chromatography indicated unreacted chloride, so an additional 2.054 g of amberlite-400/N_3 was added and the reaction mixture was stirred for 48 h. After filtration, the Amberlite resin was washed with 50 mL of acetonitrile. The filtrate was concentrated *in vacuo* to give the product as a pale yellow oil (0.5031 g, 95.68% yield). ^{1}H NMR showed complete conversion of chloride into azide, with traces of acetonitrile.

TLC: 98:2 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.42.

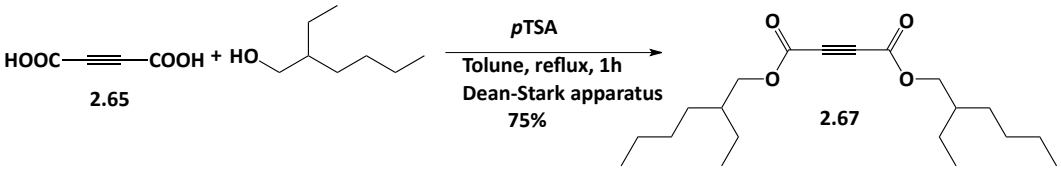
1H NMR (500MHz, $CDCl_3$): δ 7.45-7.25 (m, 5H), 4.66-4.58 (q, *J* = 7.0 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 148.1 (4°), 128.4 (CH), 126.1 (CH), 125.9 (CH), 33.2 (CH), 23.2 (CH_3).

IR (neat): 2980 (C-H aliphatic stretch), 2104 (N=N=N stretch), 1454 (aromatic C=C stretch) cm^{-1}.

Preparation of di(alkyl) acetylenedicarboxylates.

The following procedure using 2-ethylhexyl alcohol is representative:



Preparation of di(2-ethylhexyl) acetylenedicarboxylate (2.67). *p*Toluenesulfonic acid (0.2044 g, 1.074 mmol) was added to a solution of acetylenedicarboxylic acid **2.65** (2.043 g, 17.91 mmol) and 2-ethylhexyl alcohol (5.132 g, 39.41 mmol) in 28 mL of toluene. The reaction mixture was refluxed at 110 °C for 1 h in a Dean Stark apparatus to remove the water by-product. Upon cooling, the reaction mixture was poured into 20 mL of sodium chloride solution, the layers were separated, and the aqueous layer was extracted two times with 20 mL of hexanes. The combined organic layer was washed sequentially with 20 mL of saturated $NaHCO_3$ solution, 20

mL of water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo.* The resulting crude yellow oil (6.323 g) was purified by silica gel chromatography with 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (4.568 g, 75.35% yield).

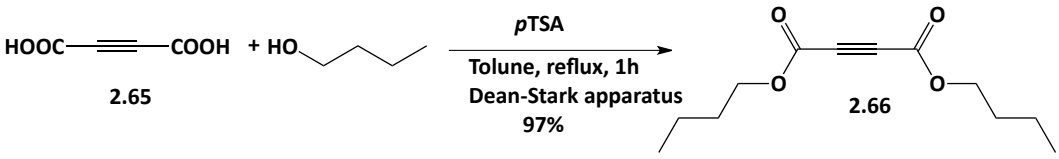
TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.81.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18-4.11 (m, 4H), 1.62-1.58 (m, 2H), 1.38-1.22 (m, 4H), 1.48-1.35 (m, 12H), 0.88 (t, *J* = 8.0 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 152.3 (C=O), 74.8 (OCH_2), 69.3 (4°), 38.6 (CH), 30.2 (CH_2), 28.8(CH_2), 23.5 (CH_2), 22.9 (CH_2), 14.0 (CH_3), 10.9 (CH_3).

IR (neat): 2960 (aliphatic C-H stretch), 1731 (C=O stretch), 1212 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{20}H_{34}O_4$ $[M+Na]^+$ 361.23548: found 361.23605**.**



Preparation of di(*n*-butyl) acetylenedicarboxylate (2.66).

1.0261 g (96.91% yield) was obtained as a colorless oil.

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.43.

IR (neat): 2931 (aliphatic C-H stretch), 1731(C=O stretch), 1212 (C-O stretch) cm^{-1}.

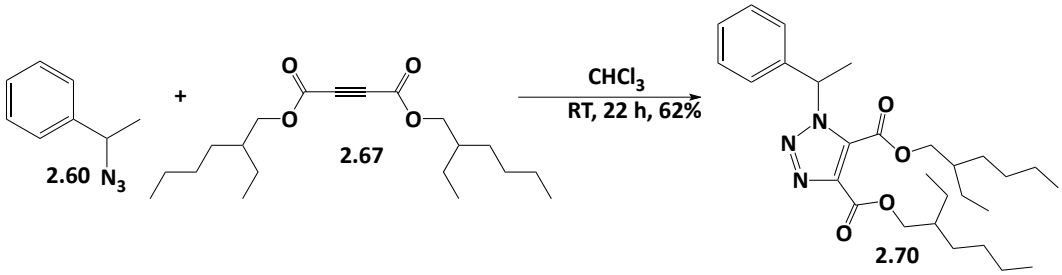
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (t, *J* = 6.5 Hz, 4H), 1.68 (tt, *J* = 7.8, 6.5 Hz, 4H), 1.45-1.39 (tq, *J* = 7.8, 7.2 Hz, 4H), 0.94 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 152.1 (C=O), 74.8 (4°), 66.8 (O-CH_2), 30.2 (CH_2), 18.9 (CH_2), 13.5 (CH_3).

HRMS: calcd. for $C_{12}H_{18}O_4$ $[M+Na]^+$ 249.11028: found 249.11287.

Preparation of triazoles with copper-free "click" reaction to form 2.68 - 2.70.

The following procedure using di(2-ethylhexyl) acetylenedicarboxylate is representative:



Preparation of bis(2-ethylhexyl) 1-(1-phenylethyl)-1*H*-1,2,3-triazole-4,5-dicarb-Oxylate (2.70). To a solution of di(2-ethylhexyl) acetylenedicarboxylate **2.67** (0.1893 g, 0.5594 mmol) in 5 mL of chloroform was added (1-azidoethyl) benzene **2.60** (0.5490 g, 0.3729 mmol). The reaction mixture was stirred at room temperature for 22 h and then concentrated *in vacuo*. The resulting crude yellow oil (0.2442 g) was purified by silica gel column chromatography using 95:5 hexanes/ethyl acetate as eluent to give the product as a pale yellow oil (0.1121 g, 61.89% yield).

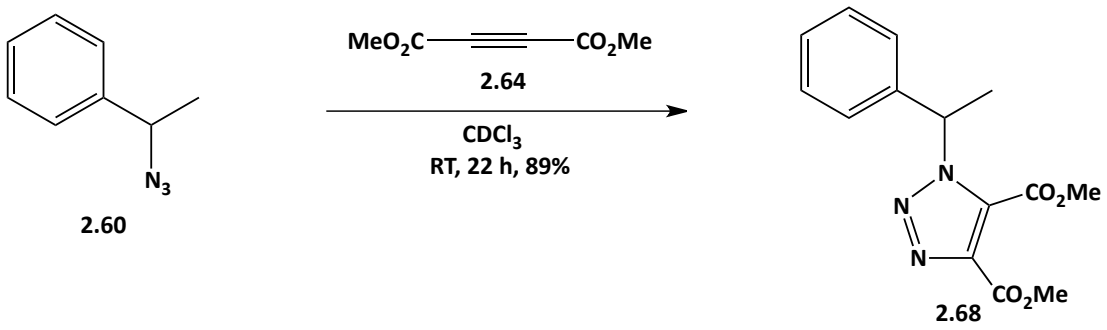
TLC: 95:5 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.36.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.35-7.25 (m, 5H), 6.12 (br q, *J* = 6.5 Hz, 1H), 4.30-4.20 (m, 2H), 4.18-4.08 (m, 2H), 2.09-2.07 (d, *J* = 7.0 Hz, 3H), 1.74-1.70 (m, 1H), 1.58-1.21(m, 17H), 0.93-0.82 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 160.7 (C=O), 159.4 (C=O), 140.3 (4°), 139.7 (4°), 130.4 (4°), 128.9 (CH), 128.6 (CH), 126.7 (CH), 69.2 (CH), 68.3 (CH), 60.6 (CH), 38.8 (CH), 38.6 (CH), 30.2 (CH_2), 30.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 23.6 (CH_2), 22.9 (CH_2), 21.7 (CH_3), 14.1 (CH_3), 10.9 (CH_3), 10.8 (CH_3).

IR (neat): 2931 (aliphatic C-H stretch), 1738 (C=O stretch), 1551 (C-N stretch), 1462 (aromatic C=C stretch), 1210 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{28}H_{43}N_3O_4$ $[M+H]^+$ 486.33318: found 486.33277.



Preparation of dimethyl 1-(1-phenylethyl)- 1*H*-1,2,3-triazole-4,5-dicarboxylate (2.68). Using dimethyl acetylenedicarboxylate **2.64**, 0.1141 g (89.57% yield) of triazole product was obtained as a colorless oil.

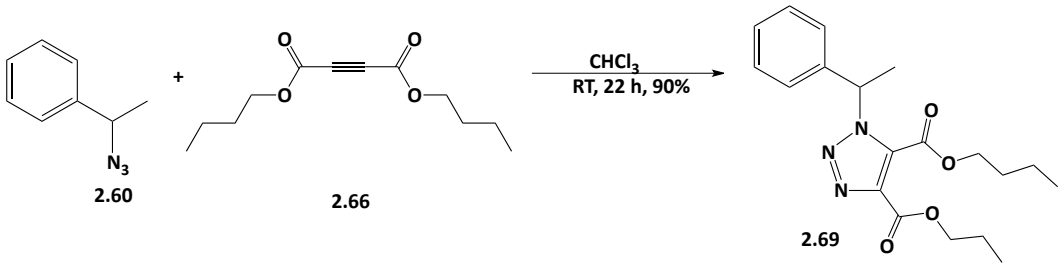
TLC: 75:25 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.33.

^{1}H NMR (500 MHz, $CDCl_3$,): δ 7.35-7.24 (m, 5H), 6.12 (q, *J* = 7.0 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 2.07 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 158.1 (C=O), 156.7 (C=O), 137.2 (4°), 136.9 (4°), 127.8 (4°), 126.3 (CH), 126.0 (CH), 124.0 (CH), 58.1 (CH), 50.7 (O-CH_3), 49.9 (O-CH_3), 18.9 (CH_3).

IR (neat): 2954 (aliphatic C-H stretch), 1735 (C=O stretch), 1554 (C-N stretch), 1452 (aromatic C=C stretch), 1214 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{14}H_{15}N_3O_4$ $[M+H]^+$ 290.11408: found 290.11283.



Preparation of di*(n*-butyl) 1-(1-phenylethyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (2.69). Using di*(n*-butyl) acetylenedicarboxylate **2.66**, 0.0844 g (89.57% yield) of product was obtained as a colorless oil.

TLC: 75:25 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.10.

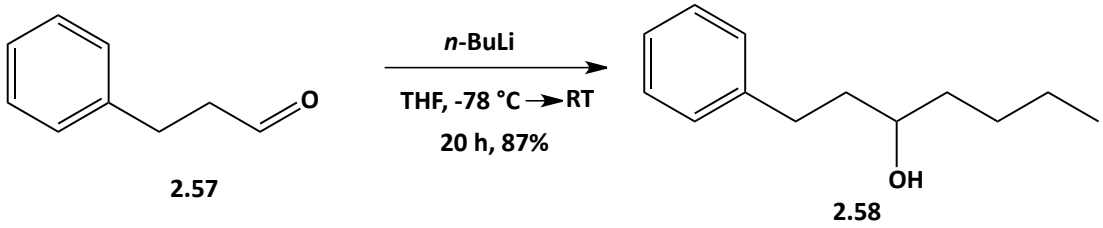
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 - 7.23 (m, 5H), 6.10 (q, *J* = 7.5 Hz, 1H), 4.33 (t, *J* = 6.8 Hz, 2H), 4.22-4.14 (m, 2H), 2.06 (d, *J* = 7.5 Hz, 3H), 1.74-1.69 (m, 2H), 1.68-1.53

(m, 2H), 1.45-1.37 (m, 2H), 1.31-1.23 (m, 2H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 160.6 (C=O), 159.3 (C=O), 140.2 (4°), 139.7 (4°), 130.4 (4°), 128.9 (CH), 128.6 (CH), 126.7 (CH), 66.7 (O-CH_2), 65.7 (O-CH_2), 60.6 (N-CH) 30.6 (CH_2), 30.2 (CH_2), 21.6 (CH_3), 19.1 (CH_2), 18.9 (CH_2), 13.7 (CH_3), 13.6 (CH_3).

IR (neat): 2961 (aliphatic C-H stretch), 1732 (C=O stretch), 1552 (C-N stretch), 1449 (aromatic C=C stretch), 1210 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{20}H_{27}N_3O_4$ $[M+H]^+$ 374.20798: found 374.21172.



2.57 2.58

Preparation of 1-phenylhept-3-ol (2.58). To a solution of 40 mL of anhydrous tetrahydrofuran at -78° C containing 3-phenyl propionaldehyde **2.57** (2.133 g, 15.89 mmol) was added *n*-BuLi (1.6 M in hexanes, 12.91 mL, 20.66 mmol) under nitrogen, and stirred for 10 minutes. The reaction mixture was allowed to warm to room temperature, and left stirring for 20 h. The reaction mixture was cooled in an ice bath, quenched with 3 mL of saturated ammonium chloride solution followed by 50 mL of water. The organic layer was separated and the aqueous layer was extracted three times with 25 mL of dichloromethane. The combined organic layer was

washed with 20 mL of water, 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The resulting pale yellow oil (2.661 g, 87.06% yield) was used without purification in the next step.

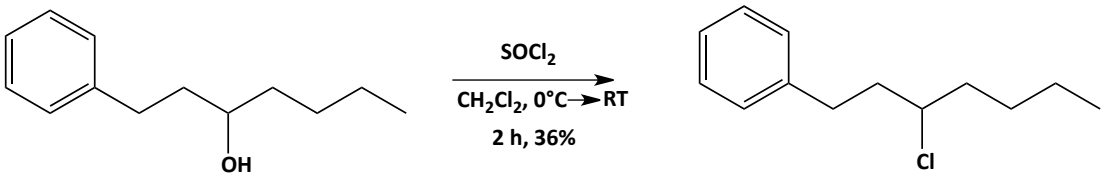
TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.25.

^{1}H NMR (500 MHz, $CDCl_3$,): δ 7.31-7.18(m, 5H), 3.68-3.63 (m, 1H), 2.84-2.78 (m, 1H), 2.71-2.65 (m, 1H), 1.88-1.71 (m, 2H), 1.48-1.35 (m, 6H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 142.4, 128.6 (CH), 127.8 (CH), 125.9 (CH), 71.5 (CH), 39.2 (CH_2), 37.4 (CH_2), 32.1 (CH_2), 27.8 (CH_2), 22.8 (CH_2), 14.1 (CH_3).

IR (neat): 3426 (O-H, stretch), 2932 (alkane C-H stretch), 1454 (aromatic C=C stretch) cm^{-1}.

HRMS: calcd. for $C_{13}H_{20}O$ $[M+Na]^+$ 215.14118: found 215.14257.



2.58 **2.55**

Preparation of (3-chloroheptyl) benzene (2.55). Thionyl chloride (50.0 mL, 68.5 mmol) was added dropwise to a solution of 1-phenyl-3-heptanol **2.58** (4.583 g, 23.83 mmol) in 5 mL of anhydrous dichloromethane at 0° C over 10 minutes. The reaction mixture was allowed to come to room temperature, stirred for 2 h, and then poured

into 20 mL of ice-cold water. The organic layer was separated and the aqueous layer was extracted two times with 15 mL of hexanes. The combined organic layer was washed three times with 15 mL of saturated $NaHCO_3$ solution, one time with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography using hexanes as eluent to give (0.2053 g, 36.41% yield) of pure alkyl chloride and 0.2133 g of an inseperable mixture of chloride plus alkene elimination products.

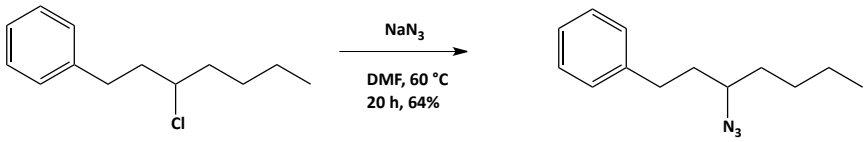
TLC: 95:5 hexanes, UV, *p*-anisaldehyde stain,R_f: 0.51.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H), 3.91-3.88 (tt, *J* = 6.5, 6.5 Hz, 1H), 2.95-2.89 (m, 1H), 2.81-2.76 (m, 1H), 2.07-2.02 (m, 2H), 1.77 (q, *J* = 7.0 Hz, 2H), 1.55-1.51 (m, 1H), 1.43-1.31 (m, 3H), 0.95-0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 141.4, 128.7 (CH), 128.6 (CH), 126.2 (CH), 63.4 (CH), 40.2 (CH_2), 38.4 (CH_2), 32.8 (CH_2), 28.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

IR (neat): 3028 (aromatic C-H stretch), 2861, 2931 (alkane C-H, stretch), 1446 (aromatic C=C, stretch), 796 (C-Cl, stretch) cm^{-1}.

HRMS: calcd. for $C_{13}H_{19}Cl$ $[M-Cl]^+$ 175.14922: found 175.15264.



2.55 2.61

Preparation of (3-azidoheptyl) benzene (2.61). To a mixture of sodium azide (0.1232 g, 3.359 mmol) in 2 mL of dimethylformamide was added (3-chloroheptyl) benzene **2.55** (0.1533 g, 0.7289 mmol). The reaction mixture was heated to 60 °C and stirred for 22 h. Upon cooling to room temperature, the reaction mixture was filtered. The filtrate was diluted with 10 mL of water and 15 mL of hexanes. The organic layer was separated and the aqueous layer was extracted two times with 10 mL of hexanes. The combined organic layer was washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give (0.1017g, 64.25% yield) of the title compound as a colorless oil. This product was obtained as an inseparable mixture with a small amount of elimination product formed by the loss of hydrochloric acid from the starting material.

TLC: 95:5 hexanes/ethyl acetate, UV, *p*-anisaldehyde, R_f: 0.62.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.21 (m, 5H), 3.28-2.35 (m, 1H), 2.83-2.77 (m, 1H), 2.72-2.66 (m, 1H), 1.85-1.81(m, 2H), 1.59-1.56 (m, 2H), 1.44-1.31 (m, 4H), 0.94-0.90 (m, 3H).

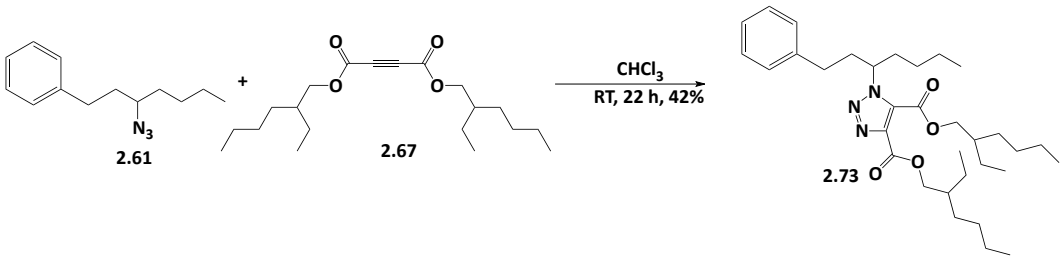
^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 132.2 (4°), 128.7 (CH), 128.6 (CH), 126.2 (CH), 62.4 (CH), 36.2 (CH_2), 34.2 (CH_2), 32.5 (CH_2), 28.3 (CH_2), 22.6 (CH_2), 14.06 (CH_3).

IR (neat): 3027 (aromatic C-H stretch), 2956, 2932 (alkane C-H, stretch), 2096 (N=N=N stretch), 1454 (aromatic C=C, stretch) cm^{-1}

HRMS: calcd. for $C_{13}H_{19}N_3$ $[M+H]^+$ 218.16572: found 218.16547.

Preparation of triazoles with copper-free "click" reaction 2.71-2.73.

The following procedure using di(2-ethylhexyl) acetylenedicarboxylate is representative:



Preparation of bis(2-ethylhexyl) 1-(1-phenylheptan-3-yl)-1*H*-1,2,3-triazole-4,5-Dicarboxylate (2.73). To a solution of di(2-ethylhexyl)acetylene dicarboxylate **2.67** (1.033g, 6.994 mmol) in 10 mL of chloroform was added (3-azidoheptyl) benzene **2.61** (0.6621 g, 5.829 mmol) and the reaction mixture was stirred at room temperature. After 22 h, the reaction mixture was concentrated *in vacuo*. The resulting yellow crude oil (1.6762 g) was purified by silica gel chromatography with 95:5 hexanes/ethyl acetate as eluent to give the title compound (0.7032 g, 41.49% yield) as a colorless oil.

TLC: 95:5 hexanes/ethyl acetate, UV, *p*-anisaldehyde, R_f: 0.15.

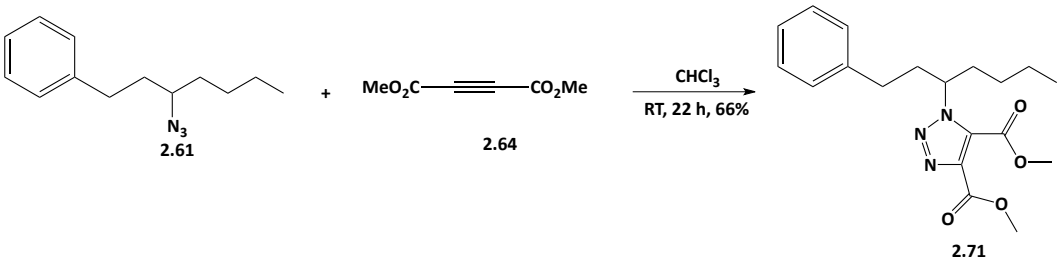
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ 7.28-7.09 (m, 5H), 4.78-4.32 (m, 1H), 4.31-4.23 (m, 5H), 4.17-4.15 (m, 1H), 2.54-2.41(m, 3H), 2.20-2.09 (m, 2H),

1.93-1.89 (m, 1H), 1.76-1.68 (tt, *J* = 6.5, 6.5 Hz, 1H), 1.65 (m, 2H), 1.50-1.19 (m, 17H), 1.19-1.04 (m, 1H), 0.97-0.88 (m, 11H), 0.84 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, mixture of diastereomers): δ 160.7 (4°), 159.6 (4°), 140.5 (4°), 139.4 (4°), 131.8 (4°), 128.6 (CH), 128.4 (CH), 126.3 (CH), 69.4 (O-CH_2), 69.3 (O-CH_2), 68.3 (O-CH_2) 62.0 (N-CH), 38.8 (CH), 38.7 (CH), 38.6 (CH), 36.7 (CH_2), 35.28 (CH_2), 32.17 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 27.9 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 22.27 (CH_2), 14.08 (CH_3), 13.8 (CH_3), 10.9 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 1728 (C=O stretch), 1552 (C-N stretch), 1456 (aromatic C=C, stretch), 1214 (C-O stretch) cm^{-1}

HRMS: calcd. for $C_{33}H_{53}N_3O_4$ $[M+H]^+$ 556.41143: found 556.41442.



Preparation of dimethyl 1-(1-phenylheptan-3-yl)-1*H*-1,2,3-triazole-4,5-dicarbox-Ylate (2.71). Using dimethylacetylene dicarboxylate **2.64**, 0.763 g (65.97% yield) of the product was obtained as a colorless oil.

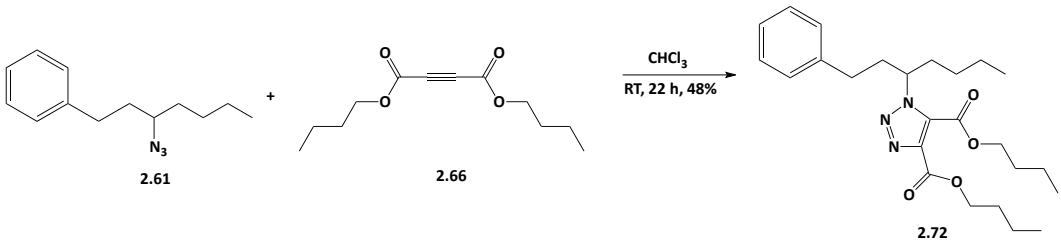
TLC: 95:5 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.03.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.05 (m, 5H), 4.72 (tt, *J* = 5.0, 5.0 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.50-2.42 (m, 3H), 2.22-2.18 (m, 2H), 2.10-2.06 (m, 1H), 1.89-1.85 (m, p, 1H), 1.26-1.15 (m, 1H), 0.81 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 160.7, 159.6, 140.5, 139.4, 131.8, 128.6 (CH), 128.4 (CH), 126.3 (CH), 59.4 (N-CH), 51.1 (O-CH_3), 50.2 (O-CH_3), 34.1 (CH_2), 32.8 (CH_2), 29.5 (CH_2), 25.4 (CH_2), 19.7 (CH_2), 11.3 (CH_3).

IR (neat): 2956 (aliphatic C-H stretch), 1735 C=O stretch), 1552 (C-N stretch), 1455 (aromatic C=C, stretch), 1224 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{19}H_{25}N_3O_4$ $[M+H]^+$ 360.19233: found 360.19515.



Preparation of di(*n*-butyl 1-(1-phenylheptan-3-yl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (2.72). Using di(*n*-butyl) acetylenedicarboxylate **2.66**, 0.0853 g (48.01% yield) of product was obtained as a colorless oil.

TLC: 95:5 hexanes/ethyl acetate, UV, R_f: 0.06.

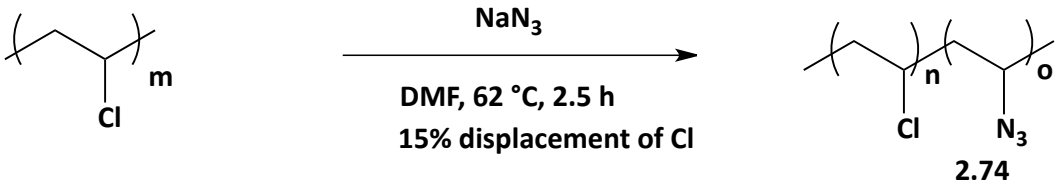
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.09 (m, 5H), 4.75 (tt, *J* = 5.0, 5.0 Hz, 1H), 4.39-4.31(m, 4H), 2.54-2.43(m, 3H), 2.24-2.19 (m, 1H), 2.15-2.07 (m, 1H), 1.93-1.89 (m,

1H), 1.82-1.65 (m, 5H), 1.50-1.38 (m, 5H), 1.31-1.17 (m, 3H), 0.98-0.95 (m, 5H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 158.2 (4°), 157.1 (4°), 138.1 (4°), 136.9 (4°), 129.5 (4°), 126.3 (CH), 126.0 (CH), 123.9 (CH), 64.5 (O-CH_2), 63.2 (O-CH_2), 59.6 (N-CH), 34.3 (CH_2), 32.9 (CH_2), 30.1 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 25.6 (CH_2), 19.9 (CH_2), 16.8 (CH_2), 16.7 (CH_2), 11.4 (CH_3), 11.4 (CH_3), 11.3 (CH_3).

IR (neat): 2960 (aliphatic C-H stretch), 1732 (C=O stretch), 1550 (C-N stretch), 1455 (aromatic C=C, stretch), 1224 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{25}H_{37}N_3O_4$ $[M+H]^+$ 444.28623: found 444.28667.



2.74

Preparation of 15% PVC-Azide. PVC (1.004 g, 10.84 mmol, based on M_w = 43,000) was dissolved in 20 mL of dimethylformamide and sodium azide (1.033 g, 15.87 mmol) was added. The reaction mixture was heated at 62°C for 2.5 h. The reaction mixture was allowed to cool to room temperature, and poured into 100 mL of methanol. A pale yellow solid precipitate formed, was filtered, washed with 50 mL of methanol and vacuum dried to give 0.7233 g of PVC-azide as a white solid. Elemental analysis indicated 14.7% displacement of chlorides with azide groups. To obtain 5% substitution, the reaction mixture was heated at 62°C for 30 minutes.

^{1}H NMR (500 MHz, DMF-d_7): δ 4.75 - 4.39 (br m, IH *Cl-C-H*), 4.22 - 3.85 (m, 0.15H *N-C-H*), 2.00-2.60 (br m, 2H CH_2).

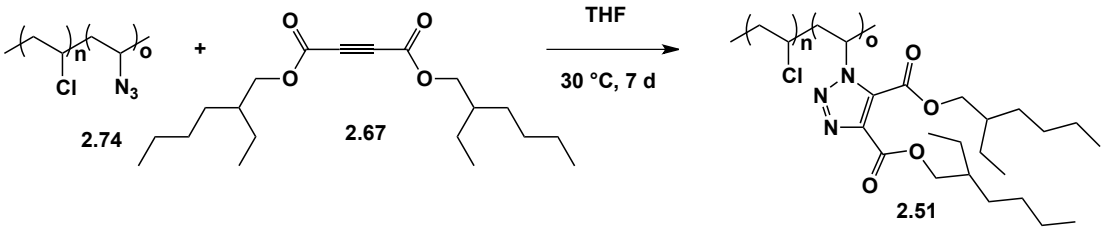
^{13}C NMR (125 MHz, DMF-d_7, DEPT): δ 57.1 - 60.1 (family of CH peaks), 45.2 - 47.1 (family of CH_2 peaks), 44.1 - 45.0 (family of CH_2 peaks).

IR (neat): 2973 (aliphatic C-H stretch), 2112 (N=N=N stretch), 1434 (C-H aliphatic bending), 1255 (C-C aliphatic bending), 616 (C-Cl stretch) cm^{-1}

Elemental analysis: 38.17% C, 4.70% H, and 9.81% N.

Preparation of PVC-bearing triazoles with copper-free "click" reaction.

The following procedure using di(2-ethylhexyl) acetylenedicarboxylate **2.67** is representative:



Preparation of 15% PVC-DEHT (2.51). 15% PVC-azide **2.74** (0.1333 g, 1.961 mmol) and di(2-ethylhexyl) acetylenedicarboxylate **2.67** (0.4760 g, 0.9801 mmol) were dissolved in 5 mL of tetrahydrofuran and the reaction mixture was stirred at room temperature for 27 h. The mixture was poured into 20 mL of methanol. The precipitated white solid was filtered, dissolved in 1 mL of tetrahydrofuran followed by precipitation by addition of 20 mL of methanol. The solid was collected by filtration and dried *in vacuo* to give 0.1288 g of 15% PVC-DEHT. Preparation of 5%

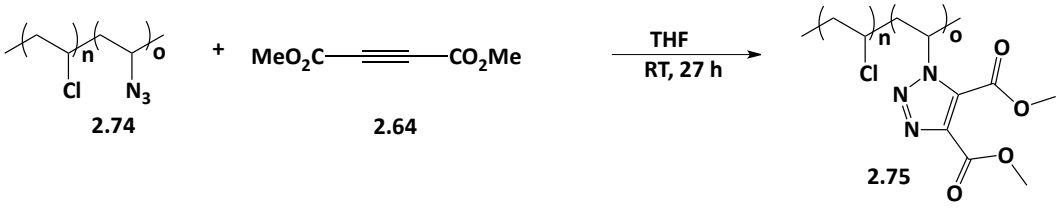
PVC-DEHT was carried out in a similar fashion using 5% PVC-azide (0.4337 g, 6.377 mmol) and di(2-ethylhexyl) acetylenedicarboxylate **2.67** (0.4397 g, 0.4783 mmol).

^{1}H NMR (500 MHz, DMF-d_7): δ 5.6-5.4 (br m), 4.63-4.31 (br m), 3.30-3.29 (d, J = 5.5 Hz), 2.49-2.31 (br m), 1.73 (br m), 1.43-1.34 (br m), 0.94-0.92 (br m).

^{13}C NMR (125 MHz, DMF-d_7, DEPT): δ 160.8 (family of C=O peaks), 159.7 (family of peaks), 139.6 (family of peaks), 132.7 (family of peaks), 69.9 (O-CH_2), 68.4 (O-CH_2), 59.7-55.8 (family of CH peaks), 46.6-42.0 (family of CH_2 peaks), 39.5 (CH), 30.0 (CH_2), 23.8 (CH_2), 14.7 (CH_3), 11.0 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 1731 (C=O stretch), 1553 (C-N stretch), 1258 (C-O stretch), 615 (C-Cl stretch) cm^{-1}

Elemental analysis: 49.08% C, 6.62% H, and 6.54% N.



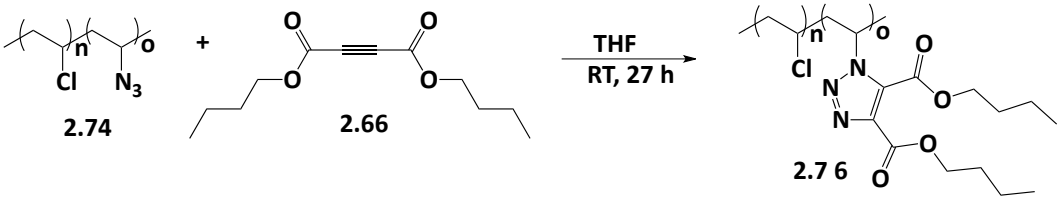
Preparation of 15% PVC-DMT. Using dimethyl acetylenedicarboxylate **2.64**, (0.1976 g, 1.3905 mmol), and 15% PVC-N_3 **2.74** (0.1895 g, 2.786 mmol) in 5 mL of THF, 0.0732 g of the polymer product was obtained as a white solid. The sample was only somewhat soluble in DMSO-d_6.

IR (neat): 2954 (aliphatic C-H stretch), 1732 (C=O stretch), 1554 (C-N stretch), 1454 (aliphatic C-H bending), 1280 (C-O stretch), 1223 (aliphatic C-C bending) 614 (C-Cl stretch) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ 5.25-5.42 (br m), 4.16-4.49 (br m), 3.95 (s, OMe (minor triad)), 3.87 (s, OMe, major triad), 3.32 (br s, OMe), 2.27 (br s).

^{13}C NMR (125 MHz, DMSO-d_6, DEPT): δ 58.6-56.6 (family of CH peaks), 53.9 (O-CH_3), 52.6 (O-CH_3), 45.2 - 44.4 (family of CH_2 peaks).

Elemental analysis: 41.36% C, 4.57% H, and 7.29% N.



Preparation of 15% PVC-DBT. Using di(*n*-butyl) acetylenedicarboxylate **2.66**, (0.4842 g, 2.139 mmol) and 15% PVC-N_3 **2.74** (0.1455 g, 2.139 mmol) of in 4 mL of THF, 0.1767 g of the polymer product was obtained as a white solid. The sample was only somewhat soluble in DMSO-d_6.

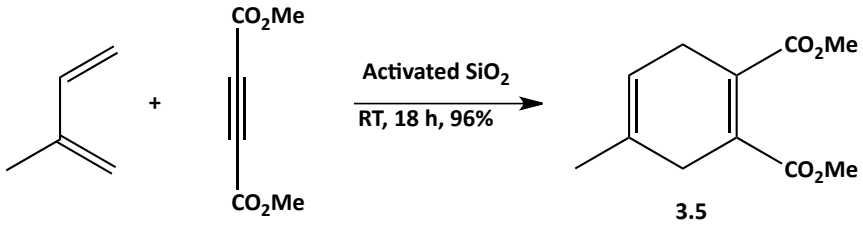
^1H NMR (500 MHz, DMSO-d_6): δ 5.25-5.42 (br m), 4.58-4.27 (br m), 2.80-2.06 (br m), 1.72 (br s), 1.55 (br s), 1.42-1.29 (br br m), 0.98-0.68 (br s).

^{13}C NMR (125 MHz, DMSO-d_6, DEPT): δ 159.8, 158.6, 1.39.6 (family of 4°C peaks), 131.8 (family of 4°C peaks), 67.3 (O-CH_2), 65.7 (O-CH_2), 58.9-55.9 (family of CH peaks), 47.3-44.8 (family of CH_2 peaks), 19.1 (CH_2), 18.5 (CH_2), 13.7 (CH_3).

Elemental analysis: 47.01% C, 5.89% H, and 6.98% N.

IR (neat): 2954 (aliphatic C-H stretch), 1732 (C=O stretch), 1554 (C-N stretch) 1455 (aliphatic C-H bending), 1223 (C-O stretch), 615 (C-Cl stretch) cm^{-1}

6.3 Experimental Section For Chapter 3



3.5

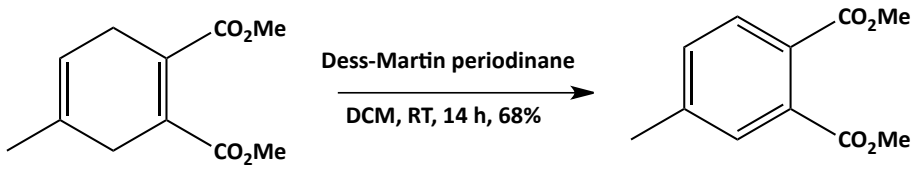
Preparation of dimethyl 4-methylcyclohexa-1,4-diene-1,2-dicarboxylate (3.5).[629] Following the procedure of Smit et al.[311] a mixture of dimethylacetylene dicarboxylate (3.468 g, 24.40 mmol), isoprene (14.7 mL, 146 mmol), and activated silica gel (40.13 g) was stirred at room temperature for 18 h. The reaction flask was equipped with a Findenser™ to minimize the evaporation of isoprene. Diethyl ether (100 mL) was added to the reaction mixture, and then filtered. The filterate was concentrated *in vacuo* to give the title compound as a yellow oil (4.932 g, 96.14% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.50.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 – 5.34 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.98 – 2.92 (m, 2H), 2.87 – 2.82 (m, 2H), 1.67 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 168.7 (C=O), 168.5 (C=O), 132.9 (4°), 132.4 (4°), 129.7 (4°), 116.7 (CH), 52.15 ($O\underline{C}H_3$), 32.1 (CH_2), 28.6 (CH_2), 22.5 (CH_3).

FTIR: 2953 (C-H stretch), 1727 (C=O stretch), 1655 (C=C stretch), 1435 (C-H scissoring), 1250 (C-O stretch) cm^{-1}.



3.5 **3.6**

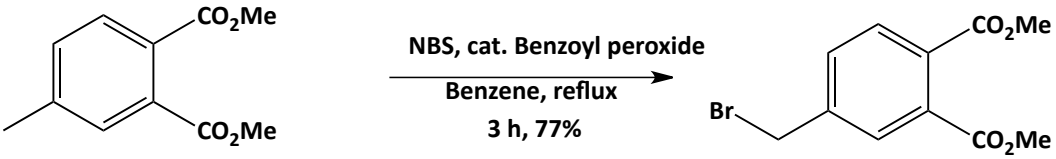
Preparation of dimethyl 4-methylphthalate (3.6).[630] To a stirred solution of dimethyl 4-methylcyclohexa-1,4-diene-1,2-dicarboxylate **3.5** (2.816 g, 13.39 mmol) in 50 mL of dichloromethane was added Dess-Martin periodinane (5.682 g, 13.39 mmol) and stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo*, diluted with 100 mL of hexanes, and then filtered. The filterate was concentrated *in vacuo* to give the title compound as a yellow oil (1.891 g, 67.76% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.47.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 7.33 (dd, d, *J* = 8.0, 1.7 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 168.8 (C=O), 167.9 (C=O), 142.2 (4°), 132.8 (4°), 131.5 (CH), 129.4 (CH), 129.3 (CH), 128.5 (4°), 52.7 (CH_3), 52.5 (CH_3), 21.3 (CH_3).

FTIR: 2959 (C-H stretch), 1728 (C=O stretch), 1463 (C-H scissoring), 1288 (C-O stretch) cm^{-1}.



3.6 **3.7**

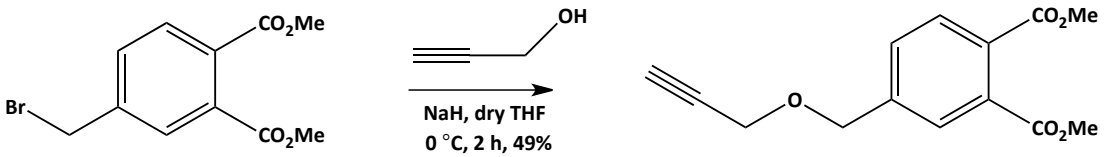
Preparation of dimethyl 4-(bromomethyl)phthalate (3.7).[630] To a stirred solution of dimethyl 4-methylphthalate **3.6** (1.891 g, 9.082 mmol) and *N*-bromosuccinimide (1.617 g, 9.082 mmol) in 20 mL of benzene was added benzoyl peroxide (0.0391 g, 0.2738 mmol) and the reaction mixture was refluxed for 3 h. The reaction was allowed to cool to room temperature, diluted with 100 mL of hexanes, and then filtered. The filterate was concentrated *in vacuo.* The resulting crude yellow oil (3.124 g) was purified by Biotage gradient chromatography using hexanes/ethyl acetate as eluent to give the title compound as a pale yellow oil (1.995 g, 76.78% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.42.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 1.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 4.48 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 167.7 (C=O), 167.6 (C=O), 141.2 (4°), 132.7 (4°), 131.7 (4°), 131.7 (CH), 129.7 (CH), 129.5 (CH), 52.8 (CH_3), 52.7 (CH_3), 31.3 (CH_2).

FTIR: 2953 (C-H stretch), 1728 (C=O stretch), 1435 (C-H scissoring), 1294 (C-O stretch) cm^{-1}.



3.7 **3.8**

Preparation of dimethyl 4-((prop-2-yn-1-yloxy)methyl)phthalate (3.8). To a stirred solution of dimethyl 4-(bromomethyl)phthalate **3.7** (1.228 g, 4.294 mmol) and propargyl alcohol (0.4798 g, 8.564 mmol) in 20 mL of dry tetrahydrofuran was added sodium hydride (0.0961 g, 1.713 mmol, 60% suspension in mineral oil) in portions over 10 minutes at 0 °C. The reaction mixture was stirred for 2 h and then quenched with 10 mL of saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted three times with 50 mL of ethyl

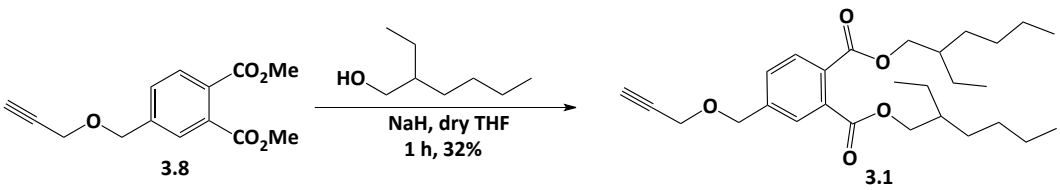
acetate. The combined organic layer was washed two times with 20 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting red oil (2.325 g) was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent to give the title compound as a pale yellow oil (0.5515 g, 48.97% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.33.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.67 (s, 2H), 4.21 (d, *J* = 2.5 Hz, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 2.76 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 168.2 (C=O), 167.8 (C=O), 141.1 (4°), 132.5 (4°), 131.1 (4°), 130.0 (CH), 129.3 (CH), 127.9 (CH), 79.2 (CH), 75.3 (4°), 70.4 (CH_2), 57.7 (CH_2), 52.8 (CH_3), 52.7 (CH_3).

IR (neat): 2931 (aliphatic C-H stretch), 2120 (alkyne C-C stretch), 1727 (C=O stretch), 1462 (aromatic C=C stretch), 1287 (C-O stretch) cm^{-1}.



3.8 3.1

Preparation of bis(2-ethylhexyl) 4-((prop-2-yn-1-yloxy)methyl)phthalate (3.1). To a stirred solution of 2-ethylhexanol (0.4398 g, 3.377 mmol) in 5 mL of anhydrous tetrahydrofuran was added sodium hydride (0.3402 g, 7.091 mmol, 60% suspension

in mineral oil) at room temperature and stirred for 5 minutes. A solution of dimethyl 4-((prop-2-yn-1-yloxy)methyl) phthalate **3.8** (0.4428 g, 1.688 mmol) in 5 mL of anhydrous tetrahydrofuran was added at room temperature, and stirred for 1 h. The reaction mixture was cooled to 0 °C, and then quenched with 3 mL of saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted three times with 10 mL of chloroform. The combined organic layer was washed two times with 10 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting red oil (0.8178 g) was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (0.2414 g, 31.18% yield).

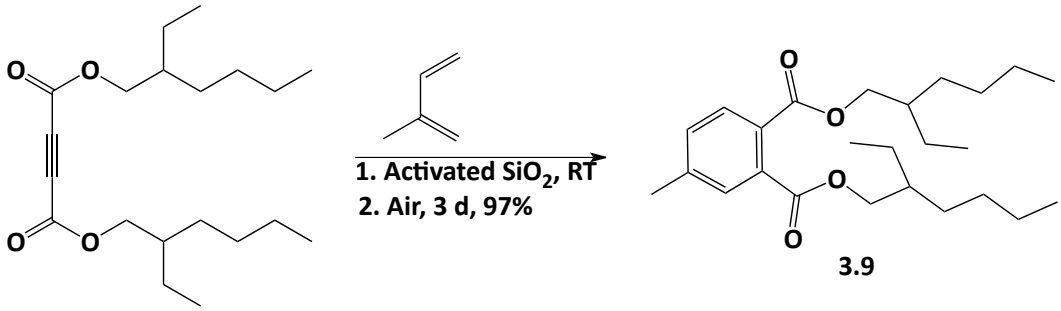
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde, R_f: 0.77.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.67 (s, 2H), 4.31 - 4.11 (m, 6H), 2.49 (t, *J* = 2.5 Hz, 1H), 1.68 (m, 2H), 1.47 - 1.20 (m, 16H), 0.99 - 0.81 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.9 (C=O), 167.5 (C=O), 141.1 (4°), 133.1 (4°), 131.6 (4°), 129.9 (CH), 129.3 (CH), 127.9 (CH), 79.2 (CH), 75.2 (4°), 70.4 (CH_2), 68.3 (CH_2), 68.2 (CH_2), 57.6 (CH_2), 38.8 (CH), 31.9 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 23.7 (CH_2), 23.0 (CH_2), 14.08 (CH_3), 10.99 (CH_3).

IR (neat): 2931 (aliphatic C-H stretch), 2120 (alkyne C-C stretch), 1727 (C=O stretch), 1462 (aromatic C=C stretch), 1287 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{28}H_{42}O_5$ $[M+H]^+$: 459.3105: found 459.3075.



2.67 3.9

Preparation of bis(2-ethylhexyl) 4-methylphthalate (3.9). Following the procedure of Swit et al.[311] a mixture of 2-ethylhexylacetylene dicarboxylate (1.739 g, 4.746 mmol), activated silica gel (20.13 g), and isoprene (5.8 mL, 58 mmol) was stirred at room temperature for 18 h. The reaction flask was equipped with a Findenser™ to minimize evaporation of isoprene. Dichloromethane (200 mL) was added to the reaction mixture, and then filtered. The filterate was concentrated *in vacuo* and bubbled with air for 3 d to give the title compound as a yellow oil (2.011, 96.14% yield).

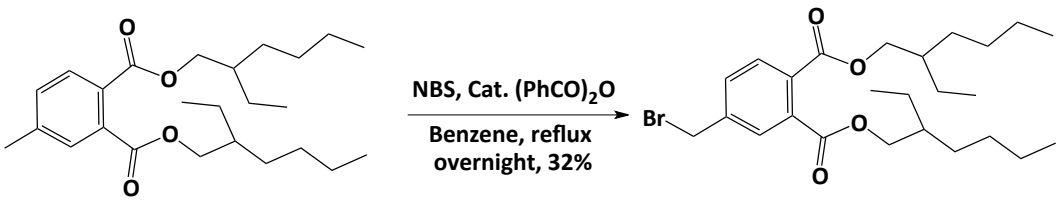
TLC: 90:10 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.66.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.31 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.25 – 4.11 (m, 4H), 2.42 (s, 3H), 1.75 – 1.49 (m, 2H), 1.51 – 1.18 (m, 16H), 1.02 – 0.77 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 168.5 (C=O), 167.5 (C=O), 141.9 (4°), 133.3 (4°), 131.3 (CH), 129.91 (CH), 129.3 (4°), 67.9 (CH_2), 67.6 (CH_2), 38.8

(CH), 38.7 (CH), 30.4 (CH_2), 30.2 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 23.7 (CH_2), 23.5 (CH_2), 21.3 (CH_3), 14.05 (CH_3), 10.98 (CH_3).

FTIR: 2953 (C-H stretch), 1728 (C=O stretch), 1435 (C-H scissoring), 1294 (C-O stretch) cm^{-1}.



3.9 **3.10**

Preparation of bis(2-ethylhexyl) 4-(bromomethyl)phthalate (3.10). To a stirred solution of bis(2-ethylhexyl) 4-methylphthalate **3.9** (0.3681 g, 0.9098 mmol) and *N*-bromosucinimide (0.1943 g, 0.0273 mmol) in 10 mL of benzene was added benzoyl peroxide (0.0039 g, 1.991 mmol) at room temperature. The reaction mixture was refluxed for 3 d using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo* to evaporate benzene. The resulting yellow oil (0.2221 g) was purified by biotage gradient chromatography using hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (0.1511 g, 32.29% yield).

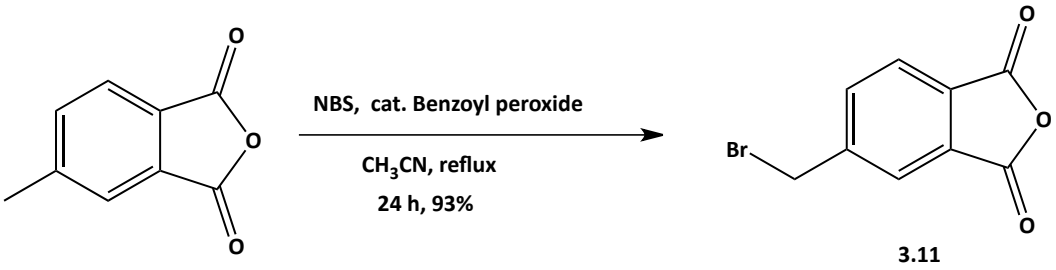
TLC: 90:10 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.40.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.8 Hz, 1H), 4.49 (s, 2H), 4.29 - 4.12 (m, 4H), 1.68 (m, 2H), 1.48 - 1.18 (m, 16H), 0.81 - 0.91 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.8 (C=O), 167.7 (C=O), 141.4 (4°), 133.7 (4°), 132.6 (4°), 131.9 (CH), 129.9 (CH), 129.8 (CH), 68.9 (CH_2), 68.7 (CH_2), 39.12 (CH), 31.9 (CH_2), 30.76 (CH_2), 29.33 (CH_2), 24.15 (CH_2), 23.41 (CH_2), 14.50 (CH_3), 11.38 (CH_3).

FTIR: 2930 (C-H stretch), 1728 (C=O stretch), 1463 (C-H scissoring), 1288 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{29}H_{35}BrO_4$ [M-H] : 481.1958: found 481.1955.



3.11

Preparation of 4-bromomethylphthalic anhydride. To a stirred solution of 4-methylphthalic anhydride (5.103 g, 31.47 mmol) and *N*-bromosuccinimide (5.601 g, 31.47 mmol) in 100 mL of acetonitrile was added dibenzoyl peroxide (0.1345 g, 0.9441 mmol) at room temperature. The reaction mixture was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature and 20 mL of saturated sodium bisulfite solution was added. The reaction mixture was concentrated *in vacuo* to evaporate acetonitrile. The aqueous layer was extracted three times with 100 mL of diethyl ether. The combined organic layer was washed with 100 mL of

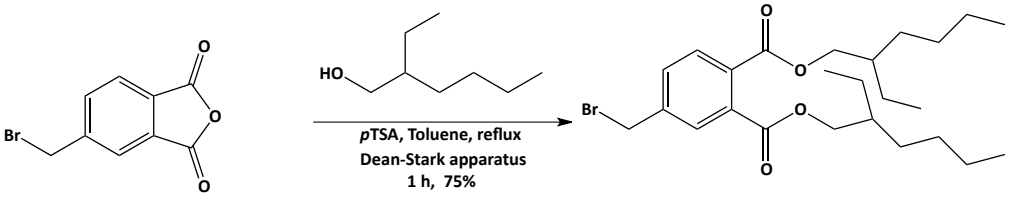
brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting yellow viscous oil (7.027 g, 92.64%) was used in the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 1.5 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.59 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 162.2 (C=O), 162.1 (C=O), 146.9 (4°), 136.9 (4°), 136.8 (CH), 126.2 (CH), 125.9 (CH), 125.5 (4°), 30.5 (CH_2).

FTIR: 2953 (C-H stretch), 1701 (C=O stretch, anhydride), 1423 (C-H scissoring), 1289 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_9H_5BrO_2$ $[M+H]^+$: 240.9495: found 240.9476.



3.10

Preparation of bis(2-ethylhexyl) 4-(bromomethyl)phthalate (3.10). To a stirred solution of 4-bromomethylphthalic anhydride **3.11** (7.997 g, 33.18 mmol) and 2-ethylhexanol (8.641 g, 66.35 mmol) in 50 mL of toluene was added *p*-toluene-sulfonic acid (0.3786 g, 1.991 mmol) at room temperature. The reaction mixture was refluxed for 2 h using a Dean-Stark apparatus, then cooled and concentrated *in vacuo* to evaporate toluene. The resulting yellow oil (0.2221 g) was purified by silica

gel column chromatography using 90:10 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (12.12 g, 75.17% yield).

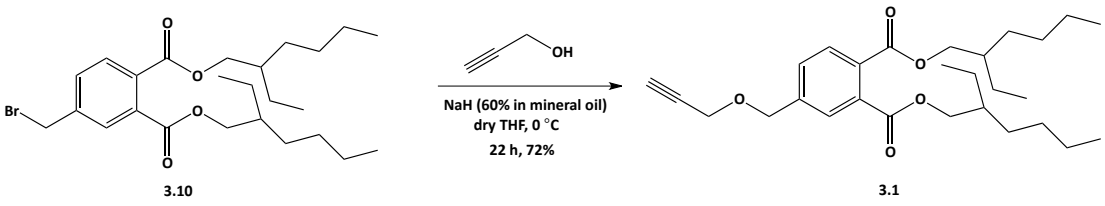
TLC: 90:10 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.49.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.8 Hz, 1H), 4.49 (s, 2H), 4.29 - 4.12 (m, 4H), 1.68 (m, 2H), 1.48 - 1.18 (m, 16H), 0.91 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.7 (C=O), 167.5 (C=O), 141.4 (4°), 133.7 (4°), 132.6 (4°), 131.9 (CH), 129.9 (CH), 129.8 (CH), 68.9 (CH_2), 68.8 (CH_2), 39.12 (CH), 31.9 (CH_2), 30.76 (CH_2), 29.33 (CH_2), 24.15 (CH_2), 23.41 (CH_2), 14.50 (CH_3), 11.38 (CH_3).

FTIR: 2930 (C-H stretch), 1728 (C=O stretch), 1463 (C-H scissoring), 1288 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{25}H_{39}BrO_4$ [M-H] : 481.1958: found 481.1955.



3.10 3.1

Preparation of bis(2-ethylhexyl) 4-((prop-2-yn-1-yloxy)methyl)phthalate (3.1). To a stirred solution of bis(2-ethylhexyl) 4-(bromomethyl)phthalate **3.10** (3.084 g, 6.391 mmol) and propargyl alcohol (0.4297 g, 7.669 mmol) in 60 mL of dry tetrahydrofuran

was added sodium hydride (0.6282 g, 26.18 mmol, 60% suspension in mineral oil) in portions over 10 minutes at 0 °C. The reaction mixture was warmed to room temperature and stirred for 22 h, then cooled to 0 °C and quenched with 10 mL of saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic layer was washed two times with 20 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting red oil (3.325 g) was purified by silica gel column chromatography with 90:10 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (2.111 g, 72.03% yield).

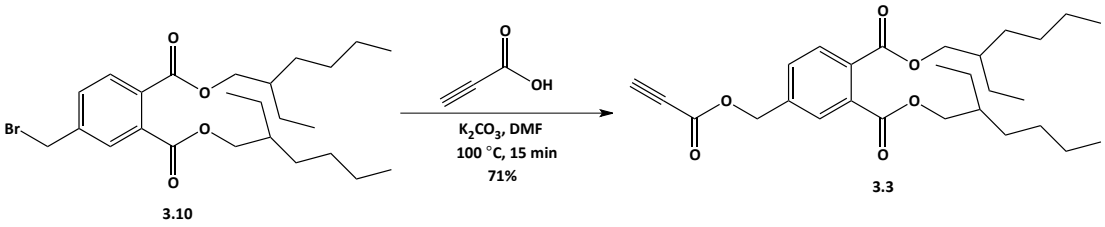
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.77.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.67 (s, 2H), 4.31 - 4.11 (m, 6H), 2.49 (t, *J* = 2.5 Hz, 1H), 1.68 (m, 2H), 1.47 - 1.20 (m, 16H), 0.99 - 0.81 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.9 (C=O), 167.5 (C=O), 141.1 (4°), 133.1 (4°), 131.6 (4°), 129.9 (CH), 129.3 (CH), 127.9 (CH), 79.2 (CH), 75.2 (4°), 70.4 (CH_2), 68.3 (CH_2), 68.2 (CH_2), 57.6 (CH_2), 38.74 (CH), 31.9 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 23.7 (CH_2), 23.0 (CH_2), 14.08 (CH_3), 10.99 (CH_3).

IR (neat): 2931 (aliphatic C-H stretch), 2120 (alkyne C-C stretch), 1727 (C=O stretch), 1462 (aromatic C=C stretch), 1287 (C-O stretch), 1203 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{28}H_{42}O_5$ [M+1] : 459.3105: found 459.3075.



Preparation of bis(2-ethylhexyl) 4-((propioloyloxy)methyl)phthalate (3.3). To a stirred solution of bis(2-ethylhexyl) 4-(bromomethyl)phthalate **3.10** (4.311 g, 8.935 mmol) and propiolic acid (0.6706 g, 8.935 mmol) in 10 mL of dry dimethylformamide was added potassium carbonate (3.705 g, 26.81 mmol) at room temperature. The reaction mixture was heated to 100 °C and stirred for 15 minutes, then allowed allowed to come to room temperature and diluted with 100 mL of water. The aqueous layer was extracted three times with 100 mL of chloroform. The combined organic layer was washed three times with 100 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting red oil (4.123 g) was purified by silica gel column chromatography using 90:10 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (2.985 g, 70.63% yield).

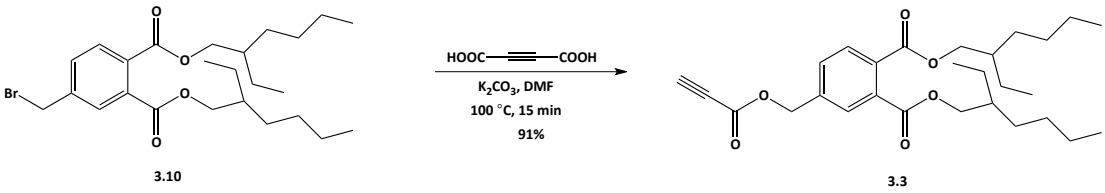
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.24.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.53 (m, 1H), 5.26 (s, 2H), 4.21 (m, 4H), 2.94 (s, 1H), 1.75 – 1.60 (m, 2H), 1.36 (m, 16H), 1.02 – 0.79 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.3 (C=O), 167.1 (C=O), 152.2 (C=O), 137.7 (4°), 132.9 (4°), 132.4 (4°), 130.3 (CH), 129.3 (CH), 128.3 (CH), 75.7 (CH), 74.1 (4°), 68.3 (CH_2), 68.2 (CH_2), 66.4 (CH_2), 38.7 (CH), 38.6 (CH), 30.4 (CH_2), 30.3 (CH_2), 28.87 (CH_2), 23.70 (CH_2), 22.94 (CH_2), 14.02 (CH_3), 10.93 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 2020 (alkyne C-C stretch), 1725 (C=O stretch), 1461 (aromatic C=C stretch), 1286 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{28}H_{41}O_6$ $[M+H]^+$: 473.2898: found 473.2875.



3.10 3.3

Preparation of bis(2-ethylhexyl) 4-((propioloyloxy)methyl)phthalate. To a stirred solution of bis(2-ethylhexyl) 4-(bromomethyl)phthalate **3.10** (4.403 g, 9.125 mmol) and acetylenedicarboxylic acid (0.5204 g, 4.563 mmol) in 10 mL of dry dimethylformamide was added potassium carbonate (1.8918 g, 13.69 mmol) at room temperature. The reaction mixture was heated to 100 °C and stirred for 15 minutes. The reaction mixture was allowed to come to room temperature and then diluted with 100 mL of water. The aqueous layer was extracted three times with 100 mL of ethyl acetate. The combined organic layer was washed three times with 100 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting red oil

(4.123 g) was purified by silica gel column chromatography with 90:10 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (1.026 g, 91.44% yield).

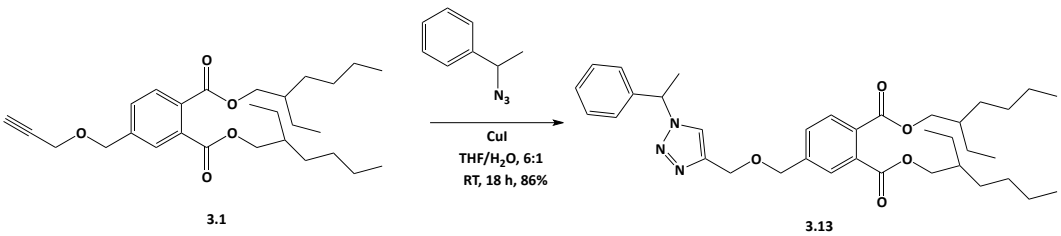
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.24.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.53 (m, 1H), 5.26 (s, 2H), 4.21 (m, 4H), 2.94 (s, 1H), 1.75 – 1.60 (m, 2H), 1.36 (m, 16H), 1.02 – 0.79 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 167.3 (C=O), 167.1 (C=O), 152.2 (C=O), 137.7 (4°), 132.9 (4°), 132.4 (4°), 130.3 (CH), 129.3 (CH), 128.3 (CH), 75.7 (CH), 74.1 (4°), 68.3 (CH_2), 68.2 (CH_2), 66.4 (CH_2), 38.7 (CH), 38.6 (CH), 30.4 (CH_2), 30.3 (CH_2), 28.87 (CH_2), 23.70 (CH_2), 22.94 (CH_2), 14.02 (CH_3), 10.93 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 2020 (alkyne C-C stretch), 1725 (C=O stretch), 1461 (aromatic C=C stretch), 1286 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{28}H_{41}O_6$ $[M+H]^+$: 473.2898: found 473.2875.



3.1 3.13

Preparation of bis(2-ethylhexyl) 4-(((1-(1-phenylethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)methyl)phthalate (3.13). To a stirred solution of bis(2-ethylhexyl) 4-((prop-2-yn-1-yloxy)methyl)phthalate **3.1** (0.0876 g, 0.1910 mmol) and 1-phenylethyl azide

(0.0637 g, 0.4331 mmol) in 10 mL of 6:1 THF:H_2O was added copper iodide (0.0521 g, 0.2736 mmol) at room temperature and stirred for 18 h. The reaction mixture was diluted with 50 mL of diethyl ether. The organic layer was separated and washed three times with 10 mL of saturated sodium carbonate solution, one time with 10 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (0.1041 g, 86.03% yield).

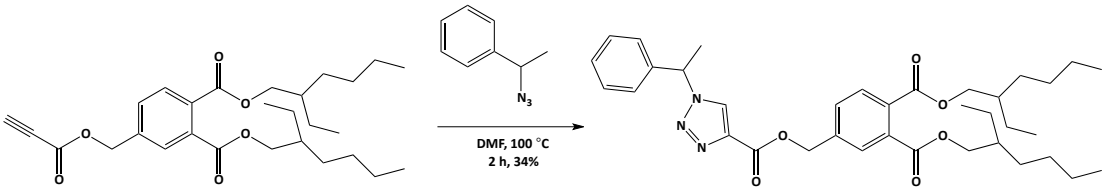
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.19.

^{1}H NMR (500 MHz, $CDCl_3$, diastereomers): δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.38 – 7.10 (m, 3H), 7.29 – 7.26 (m, 2H), 5.80 (q, *J* = 7.0 Hz, 1H), 4.68 (s, 2H), 4.64 (s, 2H), 4.30 – 4.09 (m, 4H), 1.97 (d, *J* = 7.0 Hz, 3H), 1.67 (m, 2H), 1.47 – 1.20 (m, 16H), 0.90 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, diastereomers): δ 168.1 (C=O), 167.5 (C=O), 144.8 (4°), 141.6 (4°), 139.6 (4°), 133.2 (4°), 131.4 (4°), 129.8 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 127.7 (CH), 126.7 (CH), 121.5 (CH), 71.5 (CH_2), 68.3 (CH_2), 68.2 (CH_2), 64.2 (CH_2), 60.4 (CH), 38.8 (CH), 38.7 (CH), 30.4 (CH_2), 30.3 (CH_2), 28.96 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 23.02 (CH_2), 21.6 (CH_3), 14.08 (CH_3), 10.99 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 1726 (C=O stretch), 1576 (C-N stretch), 1458 (aromatic C=C stretch), 1286 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{36}H_{51}N_3O_5$ $[M+H]^+$: 606.3902: found 606.3848.



3.3 3.14

Preparation of bis(2-ethylhexyl) 4-(((1-(1-phenylethyl)-1*H*-1,2,3-triazole-4-carbonyl)oxy)methyl)phthalate (3.14). A solution of bis(2-ethylhexyl) 4-((propioloyloxy)methyl)phthalate **3.3** (0.4865 g, 0.1029 mmol) and 1-phenylethyl azide (0.1514 g, 0.1029 mmol) in 3 mL of dimethylformamide was stirred at 100 °C for 2 h. The reaction mixture was allowed to come to room temperature, and then diluted with 20 mL of dichloromethane. The organic layer was washed three times with 10 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting yellow oil (0.5432 g) was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (0.2155 g, 33.78% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.24.

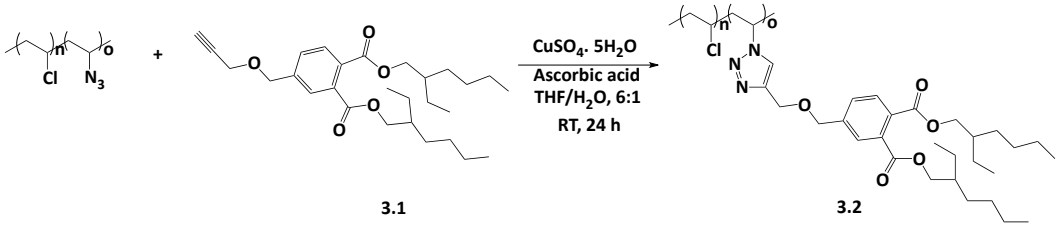
^{1}H NMR (500 MHz, $CDCl_3$, multiple diastereomers): δ 7.96 (s, 1H), 7.75 – 7.62 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.28-7.17 (m, 2H), 5.84 (q, *J* = 7.1 Hz, 1H), 5.37 (s, 2H), 4.22 - 4.10 (m, 4H), 1.96 (d, *J* = 7.1 Hz, 3H), 1.65 - 1.58 (m, 2H), 1.45 – 1.15 (m, 16H), 0.94 - 0.76 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, multiple diastereomers): δ 167.5 (C=O), 167.2 (C=O), 160.3 (C=O), 139.4 (4°), 138.8 (4°), 138.7 (4°), 132.9 (4°), 132.1 (4°),

130.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 126.6 (CH), 126.5 (CH), 68.3 (CH_2), 68.1 (CH_2), 65.4 (CH_2), 60.8 (CH), 38.7 (CH), 38.6 (CH), 30.3 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 22.9 (CH_2), 21.2 (CH_3), 14.06 (CH_3), 10.97 (CH_3).

IR (neat): 2959 (aliphatic C-H stretch), 1726 (C=O stretch), 1541 (C-N stretch), 1458 (aromatic C=C stretch), 1286 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{36}H_{49}N_3O_6$ $[M+H]^+$: 620.3695: found 620.3644.

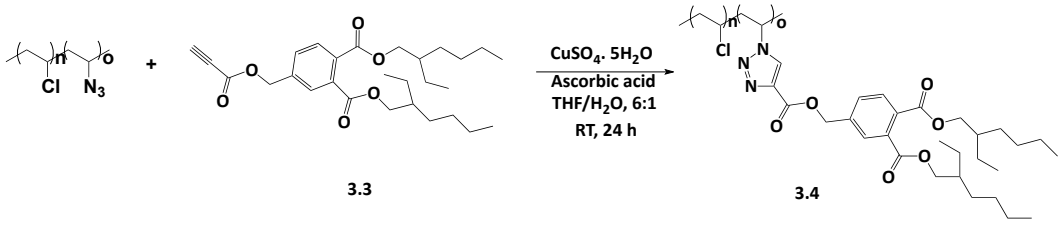


3.1 3.2

Preparation of 5% PVC-DEHP-ether (3.2). To a stirred solution of 5% PVC-azide (1.511 g, 22.22 mmol) and DEHP-ether **3.1** (0.7642 g, 1.667 mmol) in 70 mL of 6:1, THF:H_2O was added $CuSO_4.5H_2O$ (0.5548 g, 2.272 mmol) and ascorbic acid (0.6783 g, 5.677 mmol). The reaction mixture was stirred at room temperature for 24 h, and then filtered. The filterate was poured into 200 mL of methanol. The precipitated solid was filtered, washed one time with 25 mL of water, one time with 25 mL of methanol and dried to give yellow solid (1.236 g). The cycloaddition of 15% PVC-

azide sample was carried out in a similar fashion with three times more of DEHP-ether.

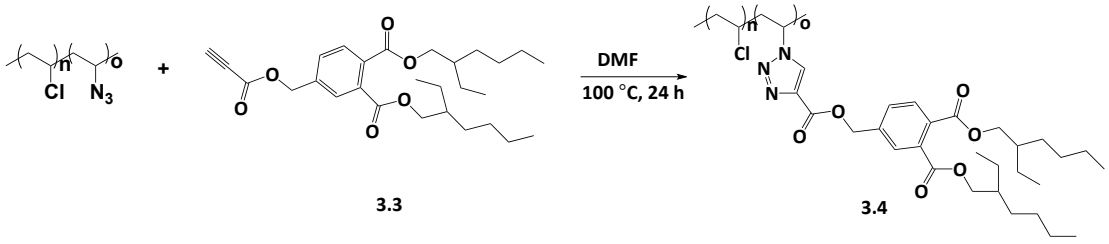
IR (neat): 2959 (aliphatic C-H stretch), 1723 (C=O stretch), 1541 (C-N stretch), 1462 (aromatic C=C stretch), 1284 (C-O stretch) cm^{-1}.



3.3 3.4

Preparation of 5% PVC-DEHP-ester (3.4). To a stirred solution of 5% PVC-azide (1.031 g, 15.16 mmol) and DEHP-ester **3.3** (0.5338 g, 1.129 mmol) in 70 mL of 6:1, THF:H_2O was added $CuSO_4.5H_2O$ (0.5673 g, 2.272 mmol) and ascorbic acid (0.6783 g, 3.851 mmol). The reaction mixture was stirred at room temperature for 24 h, and then filtered. The filterate was poured into 200 mL of methanol and filtered. The cake was washed one time with 25 mL of water, one time with 25 mL of methanol and dried to give yellow solid (1.012 g). The cycloaddition of 15% PVC-azide sample was carried out in a similar fashion with three times more of DEHP-ester.

IR (neat): 2959 (aliphatic C-H stretch), 1725 (C=O stretch), 1578 (C-N stretch), 1459 (aromatic C=C stretch), 1287 (C-O stretch) cm^{-1}.

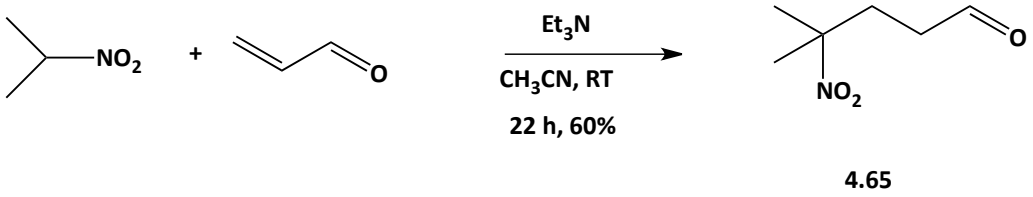


3.3 3.4

Preparation of 5% PVC-DEHP-ester (3.4). To a stirred solution of 5% PVC-azide (0.3479 g, 5.116 mmol) in 10 mL of dimethylformamide was added DEHP-ester **3.3** (0.7254 g, 1.535 mmol) and stirred at 100 °C for 24 h. The reaction mixture was allowed to cool to room temperature and then poured into 100 mL of methanol, and filtered. The cake was washed three times with 20 mL of methanol and dried to give white solid (0.3256 g). The cycloaddition of 15% PVC-azide sample was carried out in a similar fashion with three times more of DEHP-ester.

IR (neat): 2959 (aliphatic C-H stretch), 1725 (C=O stretch), 1577 (C-N stretch), 1461 (aromatic C=C stretch), 1286 (C-O stretch) cm^{-1}.

6.4 Experimental Section For Chapter 4



4.65

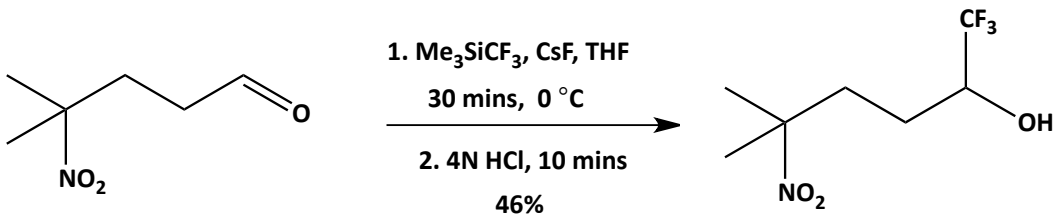
Preparation of 4-methyl-4-nitropentanal (4.65).[631] To a solution of freshly distilled acrolein (14.6 mL, 219 mmol) under ambient pressure and 2-nitropropane (15.9 mL, 175 mmol) in 60 mL of acetonitrile was added triethylamine (4.5 mL , 50 mmol) at room temperature. The reaction mixture was stirred for 22 h and then concentrated *in vacuo*. The resulting crude yellow oil (20.03 g) was purified by silica gel column chromatography with 85:15 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (15.33 g, 60.19% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.46.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.59 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 199.9 (C=O), 87.3 (4°), 38.9 (CH_2), 32.3 (CH_2), 25.9 (CH_3).

FTIR: 1721 (C=O stretch), 1536 (N-O stretch), 1349 (N=O stretch), 1278 (C-N stretch) cm^{-1}.



4.65 **4.66**

Preparation of 1,1,1-trifluoro-5-methyl-5-nitrohexan-2-ol (4.66). Following the procedure of Shreeve et al.[632] to a stirred mixture of 4-methyl-4-nitropentanal **4.65** (3.898 g, 26.85 mmol) and cesium fluoride (1.273 g, 0.8381 mmol) in 30 mL of anhydrous tetrahydrofuran was added trifluoromethyltrimethylsilane (4.3 mL, 29 mmol) dropwise over 10 minutes at 0 °C. The reaction mixture was stirred for 30 minutes, and then 20 mL of 4 N hydrochloric acid was added. The layers were separated and the aqueous layer was extracted three times with 30 mL of dichloromethane. The combined organic layer was washed with 30 mL of saturated $NaHCO_3$ solution, 20 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude yellow oil (4.023 g) was purified by silica gel column chromatography with 85:15 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (2.633 g, 46.17% yield).

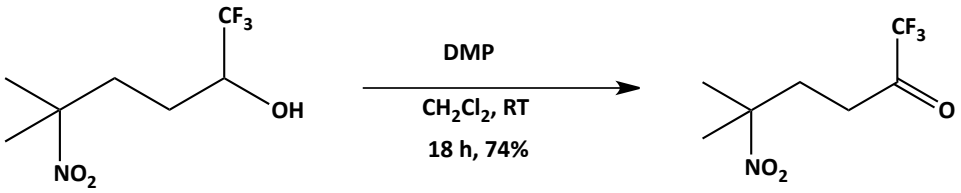
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.48.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.44 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 2.28 (m, 2H), 2.23 (m, 2H), 1.64 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 105.4 (q, J_{CF} = 290 Hz, CF_3), 87.8 (4°), 82.6 (q, J_{CF} = 35.0 Hz, C̲H-CF_3), 37.2 (CH_2), 26.3 (CH_3), 26.2 (CH_2), 25.3 (CH_3).

FTIR: 3468 (O-H stretch), 1536 (N-O stretch), 1349 (N=O stretch), 1278 (C-N stretch), 1127 (C-F stretch) cm^{-1}.

HRMS: calcd. for $C_7H_{12}F_3NO_3$ [M-H] : 214.0696: found 214.0607.



4.66 **4.67**

Preparation of 1,1,1-trifluoro-5-methyl-5-nitrohexan-2-one (4.67). Following the procedure of Janzen et al.[471] To a stirred solution of 1,1,1-trifluoro-5-methyl-5-nitrohexan-2-ol **4.66** (3.764 g, 17.49 mmol) in 50 mL of dichloromethane was added Dess-Martin periodinane (8.903 g, 20.99 mmol) at room temperature. The reaction mixture was stirred for 18 h, concentrated *in vacuo*, diluted with 150 mL of hexanes, and filtered. The filterate was concentrated *in vacuo* to give the title compound as a pale yellow oil (2.761 g, 74.07% yield).

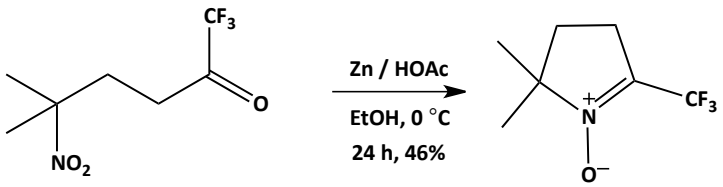
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.40.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.64 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 189.9 (q, J_{CF} = 35.5 Hz, CF_3-C=O), 115.4 (q, J_{CF} = 290 Hz, CF_3), 86.7 (4°), 32.8 (CH_2), 31.6 (CH_2), 25.9 (CH_3).

FTIR: 1761 (C=O stretch), 1541 (N-O stretch), 1351 (N=O stretch), 1271 (C-N stretch), 1154 (C-F stretch) cm^{-1}.

HRMS: calcd. for $C_7H_{10}F_3NO_3$ [M-H] : 212.0540: found 212.0534.



4.67 **4.44**

Preparation of 2,2-dimethyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide 4.44.[471] To a stirred mixture of 1,1,1-trifluoro-5-methyl-5-nitrohexan-2-one **4.67** (2.761 g, 12.95 mmol) and zinc (2.424 g, 38.87 mmol) in 70 mL of ethanol was added acetic acid (4.5 mL, 78 mmol) in an ice bath to keep the temperature below 10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h, filtered over Celite, concentrated *in vacuo*, and 150 mL of dichloromethane was added. The organic layer was washed sequentially with 20 mL of water, 20 mL of saturated $NaHCO_3$, and 20 mL of brine. The organic layer was concentrated *in vacuo* to give the title compound as a pale yellow oil (1.082 g, 46.14% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.25.

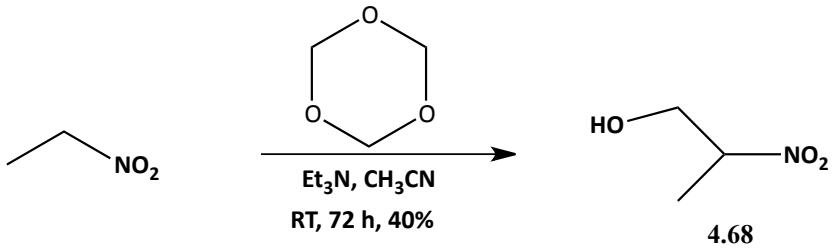
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.82 (t, *J* = 7.0 Hz, 2H), 2.16 (t, *J* = 7.0 Hz, 2H), 1.45 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 129.3 (q, J_{CF} = 35.1 Hz, C-CF_3), 119.7 (q, J_{CF} = 271 Hz, CF_3), 77.7 (4°), 32.1 (CH_2), 25.1 (CH_3), 23.9 (CH_2).

^{19}F NMR (470 MHz, C_6F_6): δ -68.6 (s, CF_3)

FTIR: 1581 (N-O stretch), 1424 (C=N stretch), 1258 (C-N stretch), 1144 (C-F stretch) cm^{-1}.

HRMS: calcd. for $C_7H_{10}F_3NO$ [M-H] : 181.0641: found 181.0480.

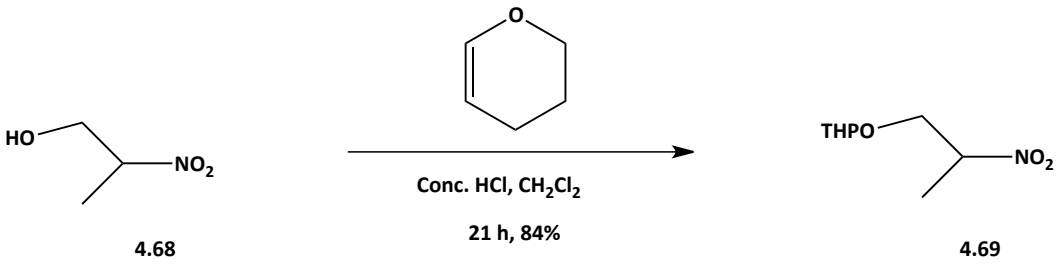


4.68

Preparation of 2-nitropropan-1-ol (4.68).[633] To a stirred mixture of nitroethane (10.26 g, 136.7 mmol) and paraformaldehyde (4.105 g, 136.7 mmol) in 100 mL of acetonitrile was added 0.2 mL of triethylamine at room temperature. The reaction mixture was stirred for 72 h and the solvent was evaporated *in vacuo*. The resulting yellow oil was diluted with 100 mL of chloroform and filtered. The filterate was concentrated *in vacuo* to give the title compound as a red oil (5.805 g, 40.42% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 (ddq, *J* = 7.2, 7.0, 3.3 Hz, 1H), 4.00 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.92 (dd, *J* = 12.4, 3.3 Hz, 1H), 2.22 (bs, 1H, OH), 1.55 (d, *J* = 7.0, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 84.6 (CH), 64.2 (CH_2) 15.3 (CH_3).

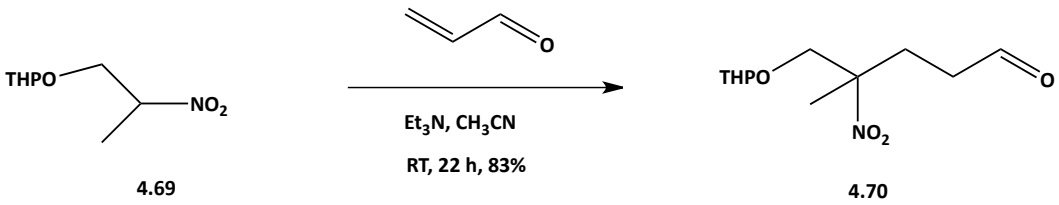


4.68 **4.69**

Preparation of 2-(2-nitropropoxy)tetrahydro-2H-pyran (4.69).[634] To a stirred solution of 2-nitropropan-1-ol **4.68** (10.08 g, 95.87 mmol) and 3,4-dihydro-2H-pyran (8.871 g, 10.55 mmol) in 100 mL of dichloromethane was added 1 mL of concentrated hydrochloric acid at room temperature. The reaction mixture was stirred for 21 h and then washed sequentially with 30 mL of water, 30 mL of saturated $NaHCO_3$ solution, and 20 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude orange oil (17.24 g) was purified by silica gel column chromatography with 50:50 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (15.18 g, 83.66% yield).

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 4.84 – 4.72 (m, 1H), 4.66 (m, 1H), 4.60 (m, 1H), 4.17 – 4.09 (m, 1H), 3.95 – 3.83 (m, 1H), 3.82 – 3.77 (m, 1H), 3.76 – 3.70 (m, 1H), 3.69 – 3.64 (m, 1H), 3.56 – 3.49 (m, 2H), 1.83 – 1.56 (m, 2H), 1.56 – 1.45 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 99.4 (CH), 98.0 (CH), 82.8 (4°), 82.2 (4°), 68.9 (CH_2), 68.0 (CH_2), 62.2 (CH_2), 61.7 (CH_2), 30.2 (CH), 30.1 (CH), 25.3 (CH_2), 19.1 (CH_2), 18.7 (CH_2), 15.8 (CH_3), 15.7 (CH_3).

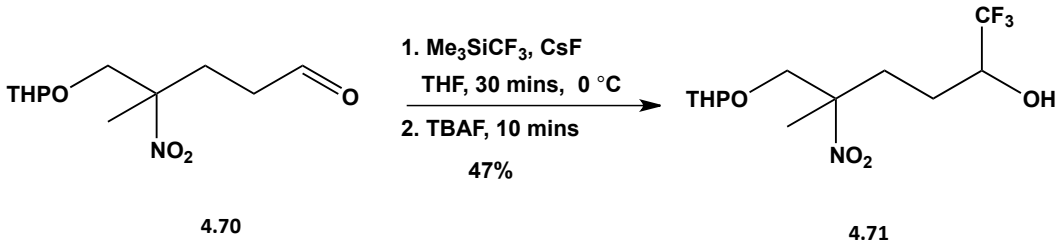


4.69 4.70

Preparation of 4-methyl-4-nitro-5-((tetrahydro-2H-pyran-2-yl)oxy)pentanal (4.70).[634] To a stirred solution of 2-(2-nitropropoxy)tetrahydro-2H-pyran **4.69** (10.63 g, 56.19 mmol) and acrolein (6.6 mL, 98 mmol) in 50 mL of acetonitrile was added 2 mL of triethylamine at room temperature. The reaction mixture was stirred for 22 h and concentrated *in vacuo*. The resulting crude oil was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (11.39 g, 82.69% yield).

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 9.77 (s, 1H), 9.75 (s, 1H), 4.84 – 4.72 (m, 2H), 4.59 (dt, *J* = 10.5, 3.4 Hz, 2H), 4.06 (d, *J* = 10.5 Hz, 1H), 3.95 (d, *J* = 10.5 Hz, 1H), 3.77 – 3.66 (m, 3H), 3.63 (d, *J* = 10.5 Hz, 1H), 3.51 (dt, *J* = 11.0, 4.4 Hz, 2H), 2.54 (dt, *J* = 11.1, 7.7 Hz, 3H), 2.35 (ddt, *J* = 23.0, 15.2, 7.5 Hz, 2H), 2.17 (ddt, *J* = 23.0, 15.2, 7.5 Hz, 2H), 1.77 – 1.61 (m, 2H), 1.61 (s, 4H), 1.59 – 1.55 (m, 3H), 1.53 – 1.44 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 199.9 (CHO), δ 199.8 (CHO), 98.9 (CH), 89.7 (4°), 71.7 (CH_2), 71.6 (CH_2), 62.2 (CH_2), 62.0 (CH_2), 38.5 (CH_2), 38.3 (CH_2), 30.2 (CH), 30.1 (CH), 28.3 (CH_2), 28.1 (CH_2), 25.2 (CH_2), 20.8 (CH_3), 20.5 (CH_3), 18.9 (CH_2), 18.8 (CH_2).



4.70 4.71

Preparation of 1,1,1-trifluoro-5-methyl-5-nitro-6-((tetrahydro-2H-pyran-2-yl)oxy)hexan-2-ol (4.71). Following a modified procedure by Shreeve et al.[632] to a stirred mixture of 4-methyl-4-nitro-5-((tetrahydro-2H-pyran-2-yl)oxy)pentanal **4.70** (7.068 g, 28.82 mmol) and cesium fluoride (0.6566 g, 4.323 mmol) in 50 mL of dry tetrahydrofuran was added trifluomethyltrimethylsilane (5.1 mL, 34 mmol) dropwise for 10 minutes at 0 °C. The reaction mixture was stirred for 1 h and tetrabutylammonium fluoride (28 mL, 1M in THF) was added. The reaction mixture was stirred for 10 minutes and diluted with 100 mL of dichloromethane. The organic layer was washed with 50 mL of water and 50 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude yellow oil (6.238 g) was purified by

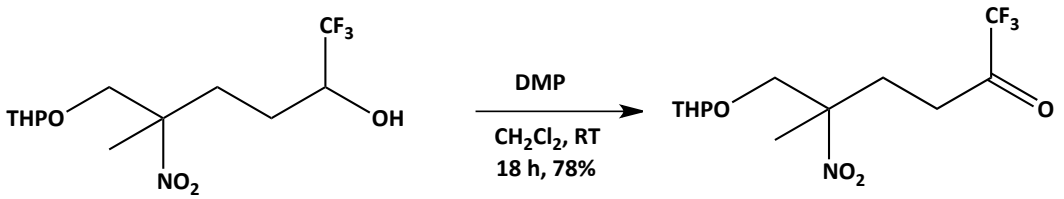
silica gel column chromatography with 60:40 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (4.295 g, 47.27% yield).

TLC: 60:40 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.62.

^{1}H NMR (500 MHz, $CDCl_3$, multiple diastereomers): δ 4.69 – 4.56 (m, 1H), 4.16 – 3.99 (m, 1H), 3.83 – 3.67 (m, 2H), 3.60 – 3.47 (m, 1H), 3.22 – 3.05 (m, 1H), 2.95 – 2.80 (m, 1H), 2.57 – 2.38 (m, 1H), 2.38 – 2.18 (m, 1H), 1.82 – 1.45 (m, 10H), 1.29 (d, *J* = 24.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, multiple diastereomers): δ 127.1- 120.3 (m, CF_3), 98.10 (CH), 97.12 (CH), 97.8 (CH), 97.8 (CH), 89.0 (4°), 88.8 (4°), 88.76 (4°), 70.8 (CH_2), 70.4 (CH_2), 70.1 (CH_2), 69.9 (CH_2), 69.2 - 68.3 (m, C<u>H</u>-CF_3), 61.5 (CH_2), 61.3 (CH_2), 61.0 (CH_2), 60.9 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 29.0 (CH_2), 28.95 (CH_2), 28.91 (CH_2), 23.9 (CH_2), 23.00 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 19.6 (CH_3), 19.5 (CH_3), 18.9 (CH_3), 18.6 (CH_3), 17.9 (CH_2), 17.8 (CH_2), 17.7 (CH_2), 17.6 (CH_2).

FTIR: 3393 (O-H stretch), 1544 (N-O stretch), 1352 (N=O stretch), 1278 (C-N stretch), 1121 (C-F stretch), 1074 (C-O stretch), 1005 (C-O stretch) cm^{-1}.



4.71 4.72

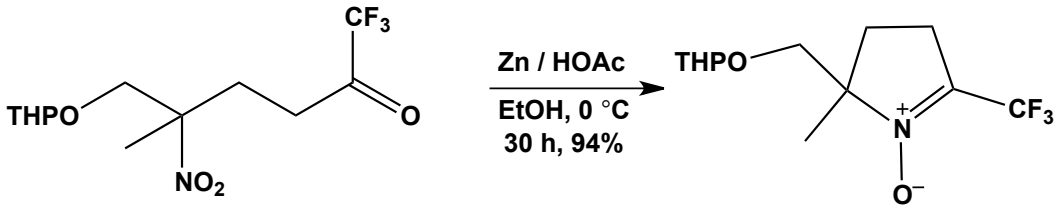
Preparation of 1,1,1-trifluoro-5-methyl-5-nitro-6-((tetrahydro-2H-pyran-2-yl)oxy)hexan-2-one (4.72). Following the procedure of Kelly et al.[485] to a stirred solution of 1,1,1-trifluoro-5-methyl-5-nitro-6-((tetrahydro-2H-pyran-2-yl)oxy) hexan-2-ol **4.71** (10.41 g, 33.02 mmol) in 150 mL of dichloromethane was added Dess-Martin periodinane (16.83 g, 39.22 mmol) at room temperature. The reaction mixture was stirred overnight, concentrated *in vacuo*, diluted with 300 mL of hexanes, and filtered. The filterate was concentrated *in vacuo* to give the title compound as a pale yellow oil (8.064 g, 77.96% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.40.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 4.69 – 4.56 (m, 1H), 4.16 – 3.99 (m, 1H), 3.83 – 3.67 (m, 2H), 3.60 – 3.47 (m, 1H), 3.22 – 3.05 (m, 1H), 2.95 – 2.80 (m, 1H), 2.57 – 2.38 (m, 1H), 2.38 – 2.18 (m, 1H), 1.82 – 1.45 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 191.7 - 186.04 (m, CF_3-C=O), 116.6 - 114.3 (m, CF_3), 98.9 (CH), 98.8 (CH), 89.4 (4°), 89.2 (4°), 71.7 (CH_2), 71.6 (CH_2), 62.1 (CH_2), 62.0 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 30.09 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.20 (CH_2), 21.2 (CH_3), 21.0 (CH_3), 18.9 (CH_2), 18.8 (CH_2).

FTIR: 1716 (C=O stretch), 1546 (N-O stretch), 1348 (N=O stretch), 1241 (C-N stretch), 1183 (C-F stretch) cm^{-1}.



4.72 **4.73**

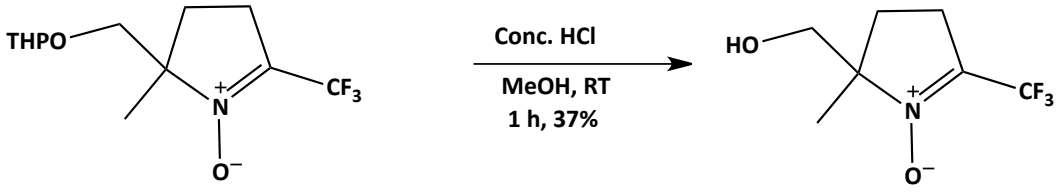
Preparation of 2-methyl-2(((tetrahydro-2H-pyran-2yl)oxy)methyl)-5-(trifluoro-methyl)-3,4-dihydro-2H-pyrrole 1-oxide (4.73). Following the procedure of Tordo et al.[635] to a stirred mixture of 1,1,1-trifluoro-5-methyl-5-nitro-6-((tetrahydro-2H-pyran-2-yl)oxy)hexan-2-one **4.72** (8.064 g, 25.74 mmol) and zinc (5.049 g, 77.23 mmol) in 150 mL of ethanol was added acetic acid (8.8 mL, 15 mmol) in an ice bath to keep the temperature below 10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 30 h, filtered over Celite, and washed three times with 20 mL of methanol. The filterate was concentrated *in vacuo*, to give the title compound as a yellow oil (6.811 g, 94.07% yield).

TLC: 60:40 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.33.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 4.98 – 4.78 (m, 2H), 4.11 - 3.98 (m, 2H), 3.82 – 3.66 (m, 4H), 3.58 – 3.46 (m, 2H), 3.17 – 3.05 (m, 1H), 2.92 – 2.79 (m, 2H), 2.53 – 2.36 (m, 2H), 2.35 – 2.16 (m, 2H), 1.79-1.42 (m, 18H), 1.27 – 1.12 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 131.4 - 129.7 (m, C-CF_3), 121.7- 116.6 (m, CF_3), 98.5 (CH), 96.1 (CH), 79.1 (4°), 78.7 (4°), 73.1 (CH_2), 72.0 (CH_2), 70.3 (CH_2), 68.9 (CH_2), 61.6 (CH_2), 61.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 20.2 (CH_3), 19.9 (CH_3), 18.5 (CH_2), 18.3 (CH_2).

FTIR: 1589 (N-O stretch), 1421 (C=N stretch), 1245 (C-N stretch), 1135 (C-F stretch) cm^{-1}.



4.73 **4.61**

Preparation of 2-hydroxymethyl-2methyl-5-(trifluoromethyl)-3,4-dihydro-2H-pyrrole 1-oxide (4.61). To a stirred solution of 2-methyl-2(((tetrahydro-2H-pyran-2yl)oxy)methyl)-5-(trifluoromethyl)-3,4-dihydro-2H-pyrrole 1-oxide **4.73** (6.811 g, 24.22 mmol) in 70 mL of methanol was added 3 mL of concentrated hydrochloric acid at room temperature. The reaction mixture was stirred for 1 h and then solid sodium bicarbonate (3.089 g, 36.77 mmol) was carefully added. The reaction mixture was filtered and the filterate was concentrated *in vacuo*. The resulting crude brown oil was purified by silica gel column chromatography using 50:50

hexanes/ethyl acetate as eluent, to give the title compound as a white solid (1.719 g, 37.33% yield, m.p: 70 – 72 °C).

TLC: 50:50 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.22.

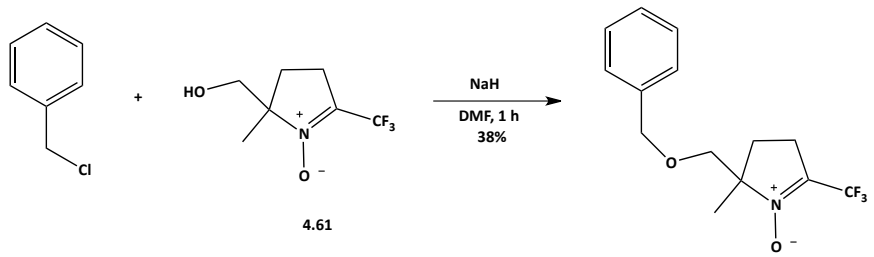
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.94 (d, *J* = 12.1 Hz, 1H), 3.56 (d, *J* = 12.1 Hz, 1H), 2.96 - 2.97 (m, 2H), 2.43 (m, 1H), 2.04 (m, 1H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 133.2 (q, J_{CF} = 36.1 Hz, C=N), 119.3 (q, J_{CF} = 271 Hz, CF_3), 81.2 (4°), 66.1 (CH_2), 26.7 (CH_2), 24.9 (CH_2), 20.6 (CH_3).

^{19}F NMR (470 MHz, C_6F_6): δ -68.7 (s, CF_3).

FTIR: 3392 (O-H stretch), 1610 (N-O stretch), 1417 (C=N stretch), 1238 (C-N stretch), 1135 (C-F stretch) cm^{-1}.

HRMS: calcd. for $C_7H_{10}F_3NO_2$ [M-H] : 196.0590: found 196.0580.



Preparation of 2-((benzyloxy)methyl)-2-methyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (4.74). To a stirred solution of 2-hydroxymethyl-2methyl-5-(trifluoromethyl)-3,4-dihydro-2H-pyrrole 1-oxide **4.61** (0.511 g, 0.2587 mmol) in 3 mL of dimethylformamide was added sodium hydride (0.0093 g, 0.3881 mmol) at room temperature. The reaction mixture was stirred for 1 h and then quenched with

1 mL of saturated ammonium chloride solution. The reaction mixture was diluted with 5 mL of dichloromethane. The organic layer was separated and washed one time with 3 mL of brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude brown oil was purified by silica gel column chromatography using 50:50 hexanes/ethyl acetate as eluent, to give the title compound as a yellow oil (0.0236 g, 37.57% yield).

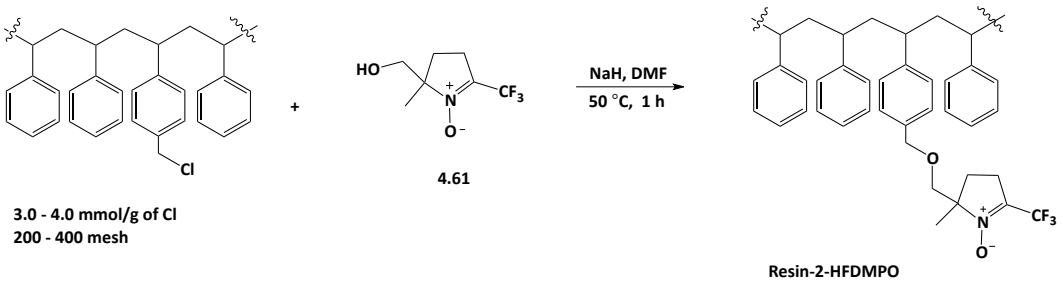
TLC: 50:50 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.64.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 2H), 7.32 – 7.20 (m, 3H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.87 (d, *J* = 10.1 Hz, 1H), 3.36 (d, *J* = 10.1 Hz, 1H), 2.95 – 2.81 (m, 1H), 2.73 (m, 1H), 2.57 (m, 1H), 2.01 (m, 1H), 1.38 (s, 3H).

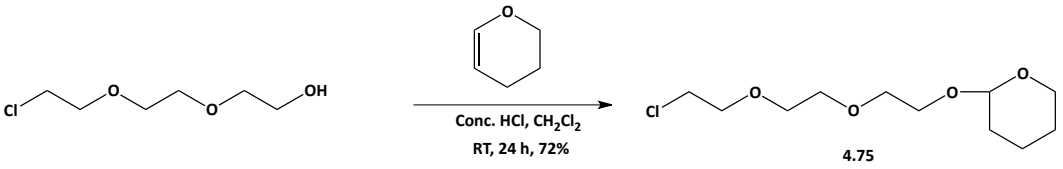
^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 137.9 (4°), 131.8 (q, J_{CF} = 36.1 Hz, C=N), 128.6 (2CH), 127.9 (CH), 127.6 (2CH), 119.5 (q, J_{CF} = 275 Hz, CF_3), 80.3 (4°), 73.6 (CH_2), 73.4 (CH_2), 27.6 (CH_2), 25.1 (CH_2), 21.4 (CH_3).

FTIR: 1610 (N-O stretch), 1417 (C=N stretch), 1238 (C-N stretch), 1135 (C-F stretch) cm^{-1}.

HRMS: calcd. for $C_{14}H_{16}F_3NO_2$ $[M+H]^+$: 288.1167: found 288.1198.



Merrifield resin supported nitrone (Resin-2HFDMPO). To a stirred solution of 2-hydroxymethyl-2methyl-5-(trifluoromethyl)-3,4-dihydro-2H-pyrrole 1-oxide **4.61** (0.3879 g, 1.969 mmol) was added sodium hydride (0.1889 g, 10.23 mmol) at room temperature and stirred for 30 minutes. Merrifield resin (0.7501 g) was added and the reaction mixture was stirred at 50 °C for 1h. The reaction was cooled to room temperature and then filtered. The resulting cake was washed three times with 10 mL of dimethylformamide, one time with 20 mL of water, followed by 20 mL of methanol, 20 mL of chloroform, and 20 mL of hexanes. The resulting cake was dried *in vacuo* to yield 0.8121 g of a brown solid. This material was used in EPR spin-trapping experiment of $HO^{\bullet}$ without further purification.



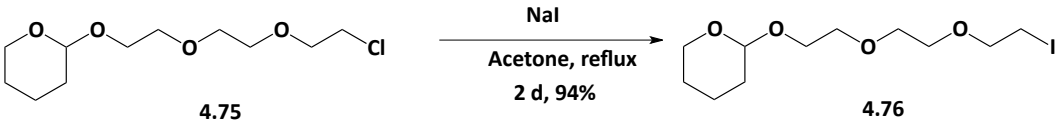
Preparation of 2-(2-(2-(2-chloroethoxy)ethoxy)ethoxy)tetrahydro-2*H*-pyran (4.75).[636] To a stirred solution of 2-(2-(2-chloroethoxy)ethoxy)ethanol (1.084 g, 0.6431 mmol) and 3,4-dihydro-2*H*-pyran (0.5951 g, 0.7073 mmol) in 10 mL of

chloroform was added 2 drops of concentrated hydrochloric acid and stirred at room temperature for 24 h. The reaction mixture was diluted with 50 mL of chloroform, washed with 20 mL of water, 20 mL of saturated sodium bircarbonate solution, 20 mL of brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil (1.523 g) was purified by silica gel column chromatography with 40:60 hexanes/ethyl acetate as eluent, to give the title compound as a clear oil (1.178 g, 72.49 % yield).

TLC: 40:60 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.40.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.66 – 4.62 (t, *J* = 3.5 Hz, 1H), 3.90 – 3.84 (m, 2H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.71 – 3.68 (m, 6H), 3.65 – 3.59 (m, 3H), 3.54 – 3.48 (m, 1H), 1.87 – 1.79 (m, 1H), 1.76 – 1.68 (m, 1H), 1.65 – 1.50 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 99.0 (CH), 71.4 (CH_2), 70.8 (CH_2), 70.7 ($2CH_2$), 66.7 (CH_2), 62.3 (CH_2), 42.8 (CH_2), 30.6 (CH_2), 25.5 (CH_2), 19.5 (CH_2).



4.75 4.76

Preparation of 2-(2-(2-(2-iodoethoxy)ethoxy)ethoxy)tetrahydro-2*H*-pyran (4.75).[637]

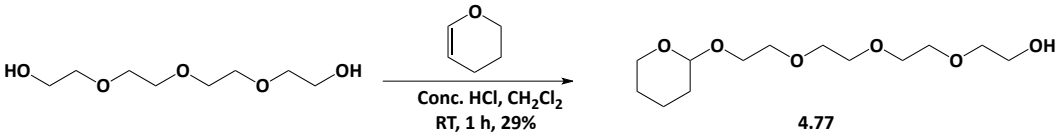
To a stirred solution of 2-(2-(2-(2-chloroethoxy)ethoxy)ethoxy)tetra-

hydro-2*H*-pyran **4.75** (0.2191 g, 0.8691 mmol) in 10 mL of acetone was added sodium iodide (0.4723 g, 3.151 mmol) and refluxed for 2 days. The reaction mixture was allowed to cool to room temperature, diluted with 25 mL of diethyl ether, filtered, and concentrated *in vacuo* to give the title compound as a red oil (0.2814 g, 94.05% yield).

TLC: 50:50 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.78.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.62 – 4.58 (t, *J* = 3.5 Hz, 1H), 3.89 – 3.81 (m, 2H), 3.79 – 3.71 (t, *J* = 5.5 Hz, 2H), 3.69 – 3.61 (m, 6H), 3.62 – 3.55 (m, 1H), 3.51 – 3.45 (m, 1H), 3.38 – 3.21 (t, *J* = 5.5 Hz, 2H), 1.87 – 1.79 (m, 1H), 1.76 – 1.68 (m, 1H), 1.65 – 1.50 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 99.1 (CH), 72.1 (CH_2), 70.7 ($2CH_2$), 70.4 (CH_2), 66.8 (CH_2), 62.3 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 19.5 (CH_2), 3.0 (CH_2).



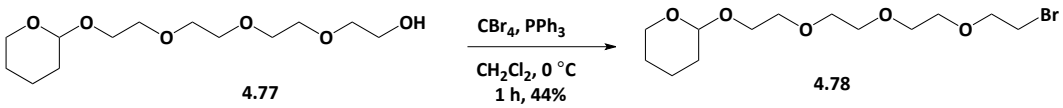
Preparation of 2-(2-(2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)ethoxy)-ethoxy)ethanol 4.77.[638] To a stirred solution of tetraethylene glycol (5.056 g, 26.03 mmol) in 200 mL of dichloromethane was added *p*-toluenesulfonic acid (0.1485 g, 0.7807 mmol) at room temperature and stirred for 1h. The reaction mixture was washed one time with 50 mL of saturated sodium bicarbonate solution, two times

with 50 mL of water, one time with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by silica gel column chromatography with 10:90 methanol/ethyl acetate as eluent to give the title compound as a colorless oil (2.114 g, 29.18% yield).

TLC: 10:90 methanol/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.26.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.53 (t, *J* = 3.6 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.64 – 3.58 (m, 2H), 3.56 – 3.53 (m, 12H), 3.29 (bs, 1H), 1.72 (m, 2H), 1.61 (m, 2H), 1.55 – 1.37 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 98.9 (CH), 72.6 (CH_2), 70.5 ($3CH_2$), 70.4 (CH_2), 70.2 (CH_2), 66.6 (CH_2), 62.2 (CH_2), 61.5 (CH_2), 30.4 (CH_2), 25.4 (CH_2), 19.4 (CH_2).



4.77 4.78

Preparation of 2-(2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethoxy)tetrahydro-2*H*-pyran (4.78). Following the procedure of Ishow et al.[639] to a stirred solution of 2-(2-(2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)ethoxy)ethoxy)ethanol **4.77** (2.286 g, 8.213 mmol) and carbon tetrabromide (2.723 g, 8.213 mmol) in 100 mL of dichloromethane was added triphenyl phosphine (2.154 g, 8.213 mmol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated *in vacuo*. The resulting crude

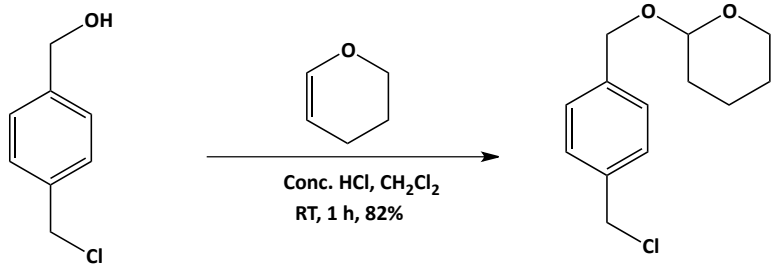
oil was purified by Biotage gradient column chromatography with hexanes/ethyl acetate as eluent to give the title compound as a pale yellow oil (1.236 g, 44.11% yield).

TLC: 50:50 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.51.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.62 (t, *J* = 3.7 Hz, 1H), 3.90 – 3.83 (m, 2H), 3.75 (t, *J* = 6.4 Hz, 2H), 3.71 – 3.64 (m, 10H), 3.63 – 3.55 (m, 2H), 3.62 – 3.55 (m, 1H), 3.51 – 3.45 (m, 1H), 1.82 (dd, *J* = 9.4, 3.7 Hz, 1H), 1.71 (dd, *J* = 13.0, 9.4 Hz, 1H), 1.64 – 1.44 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 98.9 (CH), 71.2 (CH_2), 70.7 (CH_2), 70.6 ($2CH_2$), 70.5 ($2CH_2$), 66.7 (CH_2), 62.2 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 25.5 (CH_2), 19.5 (CH_2).

HRMS: calcd. for $C_{13}H_{25}BrO_5$ $[M+Na]^+$: 363.0767: found 363.0777.



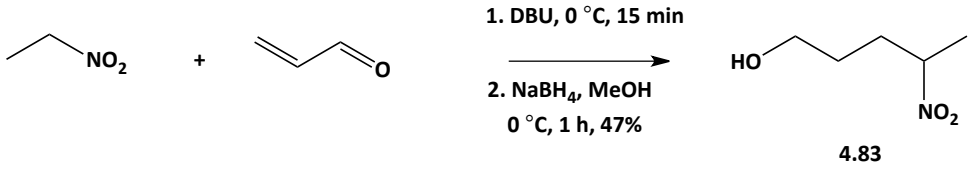
4.79

Preparation of 2-((4-(chloromethyl)benzyl)oxy)tetrahydro-2*H*-pyran 4.79.[640] To a stirred solution of 4-chloromethylbenzyl alcohol (0.8592 g, 5.410 mmol) and 3,4-dihydro-2*H*-pyran (0.6817 g, 8.115 mmol) in 25 mL of dichloromethane was added one drop of concentrated hydrochloric acid at room temperature and stirred for 2 h.

The reaction mixture was diluted with 25 mL of dichloromethane and washed sequentially with 20 mL of saturated sodium bicarbonate solution, 20 mL of water, 10 mL of brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil was purified by silica gel column chromatography with 80:20, hexanes/ethyl acetate as eluent to give the title compound as a colorless oil (1.131 g, 82.08% yield).

TLC: 80:20 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.55.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 4H), 4.81 (d, *J* = 12.2 Hz, 1H) 4.73 (t, *J* = 3.5 Hz, 1H, OC<u>H</u>O), 4.61 (s, 2H, Cl-C<u>H</u>$_2$), 4.53 (d, *J* = 12.2 Hz, 1H), 3.97 – 3.92 (m, 1H), 3.59 – 3.57 (m, 1H), 1.90 – 1.87 (m, 1H), 1.80 – 1.75 (m, 1H), 1.69 – 1.55 (m, 4H).



4.83

Preparation of 4-nitropentan-1-ol (4.83).[641] To a stirred solution of nitroethane (21.08 g, 280.8 mmol) and acrolein (18.8 mL, 280 mmol) in 300 mL of acetonitrile was added of DBU (0.1 mL, 0.001 mmol) at 0 **°**C. The reaction mixture was stirred for 15 minutes and then 2 mL of acetic acid was added to quench the reaction. The reaction mixture was concentrated *in vacuo* to give 15.12 g of a crude orange oil. Methanol (350 mL) was added and the reaction mixture was cooled to 0 **°**C. Sodium borohydride (4.172 g, 110.3 mmol) was added in portions over 20 minutes. The

reaction mixture was stirred for 1 h and the solvent was evaporated *in vacuo*. The resulting orange oil was dissolved in 500 mL of dichloromethane, washed with 100 mL of water, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a pale yellow oil (16.82 g, 46.99% yield).

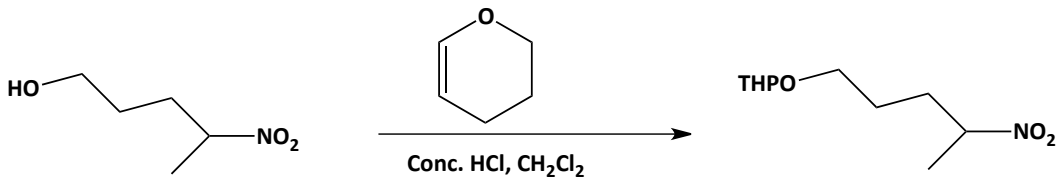
TLC: 50:50 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.51.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.65 – 4.58 (m, 1H), 3.71 – 3.63 (m, 2H), 2.11 – 2.03 (m, 1H), 1.90 – 1.82 (m, 1H), 1.66 (bs, 1H), 1.61 – 1.56 (m, 2H), 1.54 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 80.3 (CH), 60.2 (CH_2), 30.2 (CH_2), 28.1 (CH_2), 19.8 (CH_3).

FTIR: 3369 (O-H stretch), 1547 (N-O stretch), 1391 (N=O stretch), 1278 (C-N stretch), 1064 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_5H_{11}NO_3$ [M-H] : 132.0666: found 132.0666.



4.83 **4.84**

Preparation of 2-((4-nitropentyl)oxy)tetrahydro-2*H*-pyran (4.84). To a stirred solution of 4-nitropentan-1-ol **4.83** (5.326 g, 40.01 mmol) and 3,4-dihydro-2H-pyran (4.035 g, 48.01 mmol) in 100 mL of dichloromethane was added 1 mL of concentrated hydrochloric acid at room temperature. The reaction mixture was

stirred for 24 h and then washed sequentially with 30 mL of water, 30 mL of saturated $NaHCO_3$ solution, 20 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude orange oil (8.326 g) was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent, to give the title compound as a clear oil (6.065 g, 67.78% yield).

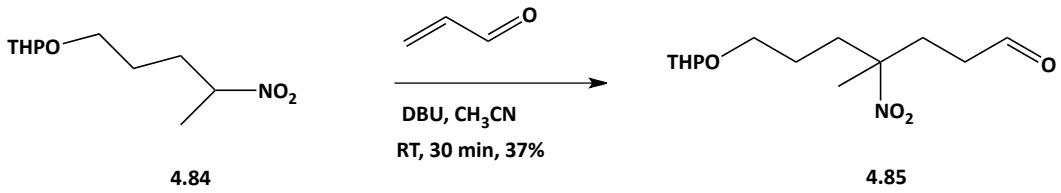
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.64.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 4.62 (dddd, *J* = 8.2, 6.8, 5.5, 1.4 Hz, 1H), 4.46 (dt, *J* = 5.5, 2.1 Hz, 1H), 3.86 – 3.70 (m, 1H), 3.70 – 3.61 (m, 1H), 3.40 (dt, *J* = 10.0, 6.0 Hz, 1H), 3.31 (dt, *J* = 10.0, 6.0 Hz, 1H), 1.98 (dddd, *J* = 16.7, 14.2, 8.2, 4.1 Hz, 1H), 1.82 – 1.66 (m, 2H), 1.65 – 1.56 (m, 1H), 1.56 – 1.50 (m, 2H), 1.45 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 98.9 (CH), 83.4 (CH), 83.3 (CH), 66.4 (CH_2), 66.3 (CH_2), 62.2 (CH_2),62.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 30.6 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 19.5 (CH_2), 19.2 (CH_3).

FTIR: 1548 (N-O stretch), 1391 (N=O stretch), 1278 (C-N stretch), stretch), 1064 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{10}H_{19}NO_4$ [M-H] : 216.1214: found 216.1237.



4.84 4.85

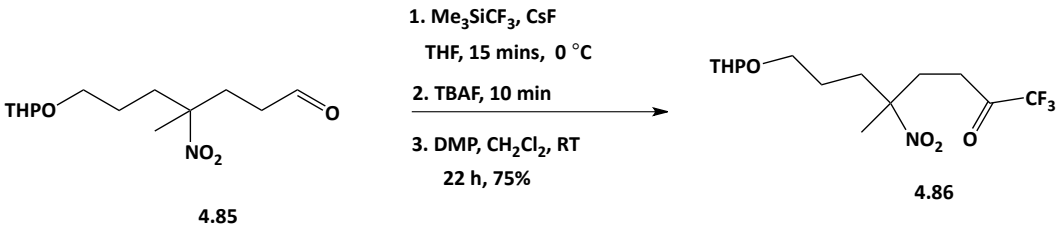
Preparation of 4-methyl-4-nitro-7-((tetrahydro-2*H*-pyran-2-yl)oxy)heptanal (4.85). To a stirred solution of 2-((4-nitropentyl)oxy)tetrahydro-2*H*-pyran **4.84** (3.755 g, 17.28 mmol) and acrolein (1.2 mL, 17.0 mmol) in 50 mL of acetonitrile was added catalytic amount of DBU (0.1 mL) at 0 °C. The reaction mixture was stirred for 30 minutes, and then 1 mL of acetic acid was added. The reaction mixture was concentrated *in vacuo*. The resulting crude red oil (4.742 g) was purified by silica gel column chromatography with 75:25 hexanes/ethyl acetate as eluent, to give the title compound as a clear oil (1.754 g, 37.16% yield).

TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.26.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 9.77 (s, 1H), 4.54 (m, 1H), 3.84 - 3.81 (m, 1H), 3.79 - 3.71 (m, 1H), 3.49 – 3.47 (m, 1H), 3.39 – 3.36 (m, 1H), 2.52 – 2.46 (m, 2H), 2.37 – 2.32 (m, 1H), 2.16 – 2.08 (m, 2H), 1.94 – 1.91 (m, 1H), 1.80 – 1.78 (m, 1H), 1.73 – 1.24 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 199.2 (HC=O) 99.0 (CH), 98.9 (CH), 90.0 (4°), 66.7 (CH_2), 62.5 (CH_2), 62.4 (CH_2), 38.6 (CH_2), 36.6 (CH_2), 36.5 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 25.4 (CH_2), 24.4 (CH_2), 22.0 (CH_3), 19.5 (CH_2).

FTIR: 1725 (C=O stretch), 1537 (N-O stretch), 1391 (N=O stretch), 1033 (C-O stretch) cm^{-1}.



4.85 **4.86**

Preparation of 1,1,1-trifluoro-5-methyl-5-nitro-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octan-2-one (4.86). Following a modified procedure by Shreeve at al.[632] to a stirred mixture of 4-methyl-4-nitro-7-((tetrahydro-2*H*-pyran-2-yl)oxy)heptanal **4.85** (1.731 g, 6.334 mmol) and CsF (0.1443 g, 0.9501 mmol) in 20 mL of dry tetrahydrofuran was added trifluoromethyltrimethylsilane (1.1 mL, 7.0 mmol) dropwise for 2 minutes at 0 °C. The reaction mixture was stirred for 15 mins and then tetrabutylammonium fluoride (3.2 mL, 3.2 mmol, 1M in THF) was added. The reaction mixture was stirred for 10 minutes and then diluted with 50 mL of ether. The organic layer was washed with 20 mL of water, 20 mL of brine, dried over $MgSO_4$ and concentrated *in* vacuo. The resulting yellow oil (2.061 g) was dissolved in 50 mL of dichloromethane and Dess-Martin periodinane (3.064 g, 7.224 mmol) was added at room temperature. The reaction mixture was stirred for 22 h, concentrated *in vacuo*, diluted with 100 mL of 95:5 hexanes/dichloromethane, and filtered. The filterate was concentrated *in vacuo* to give the title compound as a pale yellow oil (1.545 g, 74.96% yield).

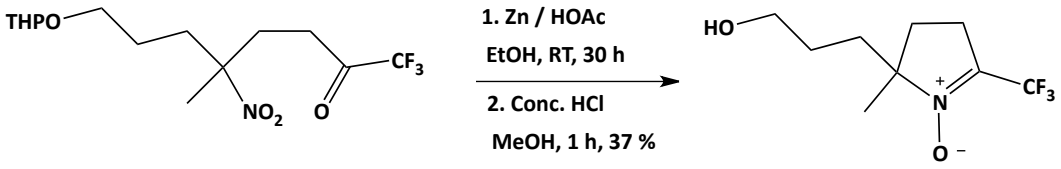
TLC: 75:25 hexanes/ethyl acetate, *p*-anisaldehyde stain, R_f: 0.25.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 4.51 (m, 1H), 3.82 – 3.79 (m, 1H), 3.73 – 3.70 (m, 1H), 3.48 – 3.47 (m, 1H), 3.39 – 3.36 (m, 1H), 2.76 – 2.75 (m, 2H), 2.45 – 2.35 (m, 1H), 2.19 – 2.15 (m, 2H), 2.09 – 2.04 (m, 2H), 1.96 – 1.93 (m, 1H) 1.79 – 1.77 (m, 1H), 1.70 – 1.68 (m, 1H), 1.67 – 1.49 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 190.0 (q, J_{CF} = 30 Hz, C-CF_3), 115.2 (q, J_{CF} = 240 Hz, CF_3), 99.1 (CH), 99.0 (CH), 89.9 (4°), 66.8 (CH_2), 66.5 (CH_2), 62.8 (CH_2), 62.5 (CH_2), 36.5 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 30.5 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 24.2 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 19.6 (CH_3).

FTIR: 1766 (C=O stretch), 1539 (N-O stretch), 1351 (N=O stretch), 1278 (C-N stretch), 1175(C-F stretch), 1024 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{14}H_{22}F_3NO_5$ [M-H] : 340.1377: found 340.1364.



4.86 **4.62**

Preparation of 2-(3-hydroxypropyl)-2-methyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (4.62). To a stirred mixture of 1,1,1-trifluoro-5-methyl-5-nitro-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octan-2-one **4.86** (1.545 g, 4.513 mmol) and zinc (0.8852 g, 13.54 mmol) in 30 mL of ethanol was added acetic acid (1.6 mL, 27 mmol)

at room temperature. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was filtered over Celite, rinsed three times with 10 mL of methanol and the filtrate was concentrated *in vacuo*. The resulting red oil was dissolved in 20 mL of methanol and 1 mL of concentrated hydrochloric acid was added at room temperature. The reaction mixture was stirred for 1 h and then concentrated *in vacuo*. The resulting red oil was purified by silica gel column chromatography with ethyl acetate as eluent, to give the title compound as a pale yellow oil (0.3733 g, 36.76% yield).

TLC: ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.37.

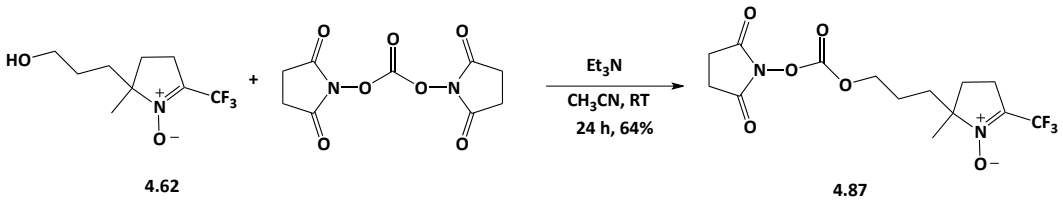
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.59 (t, *J* = 6.0 Hz, 2H), 2.85 – 2.70 (m, 2H), 2.60 (br s, 1H), 2.25 (m, 1H), 2.04 (m, 1H), 1.88 – 1.74 (m, 2H), 1.70- 1.59 (m, 1H), 1.58 (m, 1H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 131.9 (q, J_{CF} = 36 Hz, C-CF_3), 119.5 (q, J_{CF} = 270 Hz, CF_3), 80.6 (4°), 62.5 (CH_2), 34.0 (CH_2), 28.8 (CH_2), 26.3 (CH_2), 24.6 (CH_3), 24.5 (CH_2).

^{19}F NMR (470 MHz, C_6F_6): δ -68.4 (s, CF_3).

FTIR: 3401 (O-H stretch), 1590 (N-O stretch), 1278 (C-N stretch), 1146 (C-F stretch), 1058 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_9H_{14}F_3NO_2$ [M-H] : 224.0903: found 224.0900.



4.62 4.87

Preparation of 2-(3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)propyl)-2-methyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (4.87). To a stirred solution of 2-(3-hydroxypropyl)-2-methyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide **4.62** (0.6085 g, 2.702 mmol) and *N,N*'-disuccinimidyl carbonate (0.6922 g, 2.702 mmol) in 15 mL of acetonitrile was added triethylamine (0.38 mL, 2.7 mmol) at room temperature. The reaction mixture was stirred for 24 h and then concentrated *in vacuo*. The resulting red oil (1.235 g) was purified by silica gel column chromatography with 50:50 hexanes/ethyl acetate as eluent, to give the title compound as a pale yellow oil (0.6341 g, 64.10% yield).

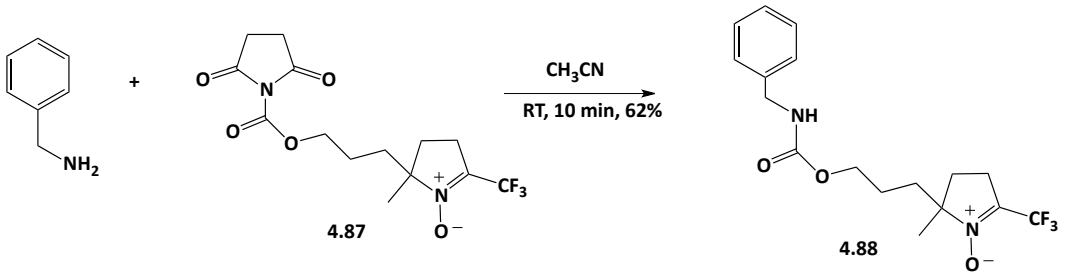
TLC: ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.73.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37 – 4.32 (m, 1H), 4.32 – 4.36 (m, 1H), 2.81 (s, 4H), 2.25 – 2.17 (m, 1H), 2.11 – 2.05 (m, 1H), 1.95 – 1.86 (m, 1H), 1.86 – 1.74 (m, 2H), 1.70 – 1.59 (m, 1H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 168.6 (C=O), 151.4 (C=O), 130.0 (q, J_{CF} = 35 Hz, C-CF_3), 119.5 (q, J_{CF} = 270 Hz, CF_3), 79.7 (4°), 70.7 (CH_2), 33.9 (CH_2), 28.9 (CH_2), 25.4 (CH_2), 24.4 (CH_3), 24.2 (CH_2), 22.8 (CH_2).

FTIR: 1788 (C=O stretch), 1740 (C=O stretch), 1587 (N-O stretch), 1144 (C-F stretch), 1095 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{14}H_{17}F_3N_2O_6$ [M-H] : 365.0965: found 365.0934.



Synthesis of 2-(3-((benzylcarbamoyl)oxy)propyl)-2-methyl-5-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (4.88). To a stirred solution of nitrone (0.0512 g, 0.1398 mmol) in 5 mL of acetonitrile was added benzyl amine (0.0149 g, 0.1398 mmol) at room temperature and stirred for 10 minutes. The reaction mixture was concentrated *in vacuo*. The resulting yellow oil (0.0632 g) was purified by silica gel column chromatography with 50:50, ethylacetate/hexanes as eluent to give the title compound as a colorless oil (0.0313 g, 62.47% yield).

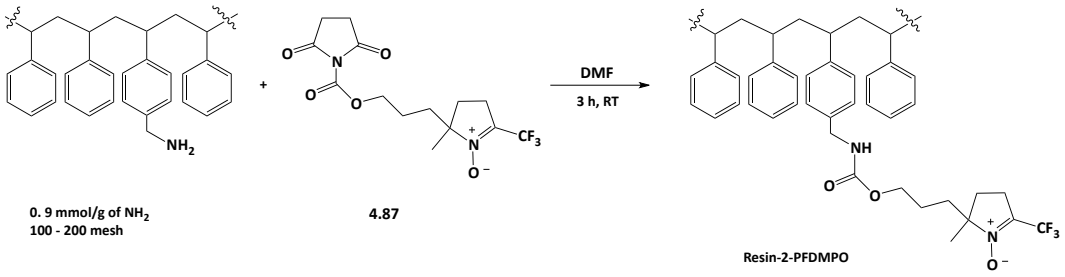
TLC: 50:50 ethyl acetate/hexanes, UV, *p*-anisaldehyde stain, R_f: 0.73.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.24 (m, 3H), 5.09 (bs, 1H, NH), 4.35 (t, *J* = 5.8 Hz, 2H), 4.10 (m, 2H), 2.88 – 2.67 (m, 4H), 2.27 – 2.15 (m, 2H), 1.92 -1.58 (m, 2H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ 156.5 (C=O), 138.5 (4°), 128.69 (CH), 127.54 (CH) 130.0 (q, J_{CF} = 35 Hz, C-CF_3), 119.5 (q, J_{CF} = 270 Hz, CF_3), 80.1 (4°), 64.4 (CH_2), 45.1 (CH_2), 34.4 (CH_2), 29.0 (CH_2), 24.5 (CH_3), 24.3 (CH_2), 23.5 (CH_2).

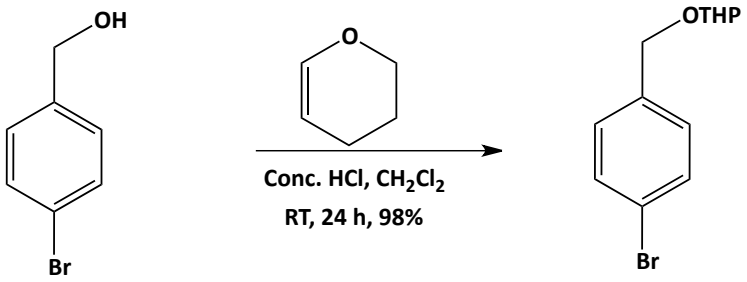
FTIR: 1788 (C=O stretch), 1587 (N-O stretch), 1144 (C-F stretch), 1095 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{17}H_{21}F_3N_2O_3$ $[M+H]^+$: 359.1538: found 359.1567.



Polystyrene supported 2-PFDMPO (Resin-2-PFDMPO). To a stirred solution of aminomethylated polystyrene (0.4063 g, 0.3657 mmol) in 5 mL of dimethylformamide was added nitrone **4.87** (0.1339 g, 0.3657 mmol) at room temperature, stirred for 3 h, and then filtered. The resulting cake was washed three times with 10 mL of methanol, one time with 10 mL of hexanes, and dried to give 0.6013 g of Resin-2-PFDMPO as a pale yellow solid. This material was used in EPR spin-trapping experiments of $ClCH_2^{\bullet}$ without further purification.

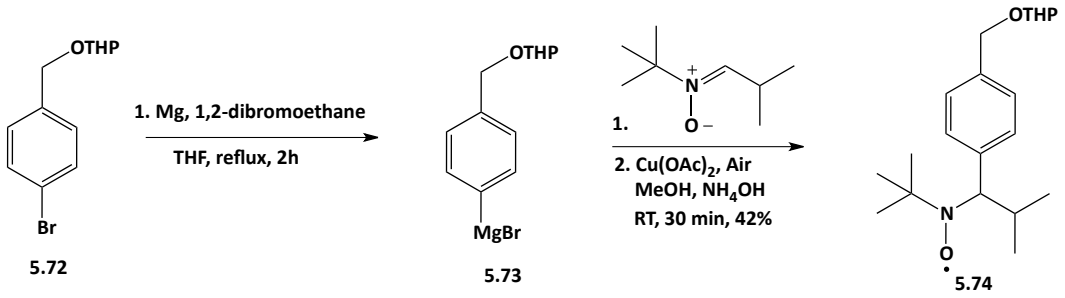
6.5 Experimental Section for Chapter 5



5.72

2-((4-bromobenzyl)oxy)tetrahydro-2*H*-pyran.[642] To a solution of 4-bromobenzyl alcohol (15.03 g, 80.37 mmol) and 3,4-dihydro-2H-pyran (7.426 g, 88.41 mmol) in 75 mL of dichloromethane was added 20 drops of concentrated hydrochloric acid and the reaction mixture was stirred under nitrogen at room temperature for 18 h. The reaction mixture was washed two times with 50 mL of water and one time with 20 mL of saturated $NaHCO_3$ solution. The layers were separated; the organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The resulting crude yellow oil (23.34 g) was purified by silica gel chromatography with 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (20.82 g, 97.55% yield). TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.62.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 4.72 (d, *J* = 12.5 Hz, 1H), 4.69 (dd, *J* = 7.0, 3.0 Hz, 1H) 4.45 (d, *J* = 12.5 Hz, 1H), 3.89-3.75 (m, 1H), 3.59-3.46 (m, 1H), 1.92 -1.45 (m, 6H).

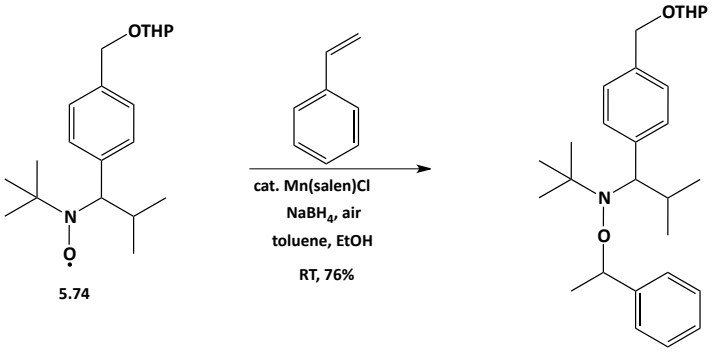


***N*-(*tert*-butyl)-*N*-(2-methyl-1-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl) propyl) nitroxide (5.74).**[643] Magnesium turnings (0.6161 g, 0.0254 mmol) were taken in 20 mL of tetrhydrofuran dried over sodium and benzophenone under nitrogen. 1,2-dibromoethane (0.15 mL, 0.0017 mmol) was added at 40 °C. The reaction mixture was stirred at 40 °C for 30 minutes and then a solution of 2-((4-bromobenzyl)oxy) tetrahydro-2*H*-pyran **5.72** (5.501 g, 0.0202 mmol) in 30 mL of tetrahydrofuran was added dropwise. The reaction mixture was refluxed for 2 h. The reaction mixture was allowed to cool to room temperature and then transferred to a flask containing a solution of (*Z*)-2-methyl-*N*-(2-methylpropylidene)propan -2-amine oxide (2.421 g, 0.0169 mmol) in 30 mL of dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to 0 °C and 10 mL of saturated NH_4Cl was added followed by the addition of 30 mL of water to quench the excess Grignard reagent. The layers were separated; the aqueous layer was extracted three times with 25 mL of dichloromethane, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* Methanol (60 mL), NH_4OH (5.0 mL), and $Cu(OAc)_2$ (0.3334 g, 0.0018 mmol) were added and the reaction mixture was

bubbled with air for 30 minutes. The reaction mixture turned from orange to green. The reaction mixture was concentrated *in vacuo,* dissolved in 60 mL of chloroform and 60 mL of water was added. The layers were separated and the aqueous layer was extracted three times with 30 mL of chloroform, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The resulting crude orange oil (6.326 g) was purified by silica gel column chromatography using 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (2.626 g, 42.32% yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.24.

^{1}H NMR (500 MHz, $CDCl_3$ + $PhNHNH_2$, two diastereomers): δ 6.88-7.44 (m, 4H), 4.55-4.85 (m, 2H), 3.53 - 4.01 (m, 9H), 3.46 (m, 1H), 2.34 (m, 1H), 1.95-0.43 (m, 15H).

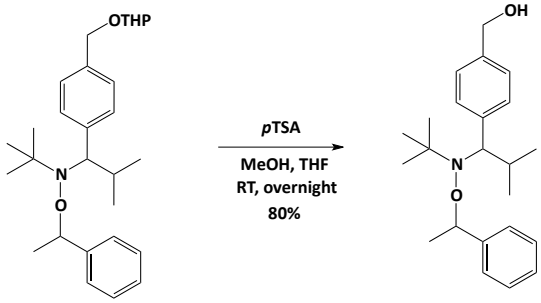


***N*-(*tert*-butyl)-*N*-(2-methyl-1-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl) phenyl)propyl)-*O*-(1-phenylethyl)hydroxylamine.**[643] A mixture of 130 mL of toluene and 130 mL of ethanol was bubbled with air for 1 h. Styrene (2.011g, 14.32 mmol), *N*-(*tert*-butyl)-*N*-(2-methyl-1-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl) phenyl)propyl)nitroxide (3.225 g, 9.655 mmol), salen catalyst (0.7921 g, 2.221 mmol),

and sodium borohydride (1.096 g, 28.97 mmol) were added. The reaction mixture was bubbled with air overnight. The reaction mixture was filtered over Celite; the residue was washed with 50 mL of ethanol, and the filterate was concentrated *in vacuo*. The resulting crude yellow oil (3.576 g) was purified by silica gel chromatography with 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (2.809 g, 76.31% yield).

TLC: 1:1 chloroform/hexanes, UV, *p*-anisaldehyde stain, R_f: 0.51.

^{1}H NMR (500 MHz, $CDCl_3$, multiple diastereomers): δ 7.4-7.9 (m, 18H), 4.53-4.98 (m, 2H), 4.50 (dd, *J* = 12.5 Hz, 4H), 4.03 (m, 4H), 3.63 (m, 4H), 3.36 (d, *J* = 10.8 Hz, 1H,), 3.08 (d, *J* = 10.8 Hz, 1H), 2.35 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H,), 1.56 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 6H), 1.05 (s, 9H), 0.93 (d, 3H), 0.77 (s, 9H), 0.56 (d, 3H), 0.22 (d, 3H).

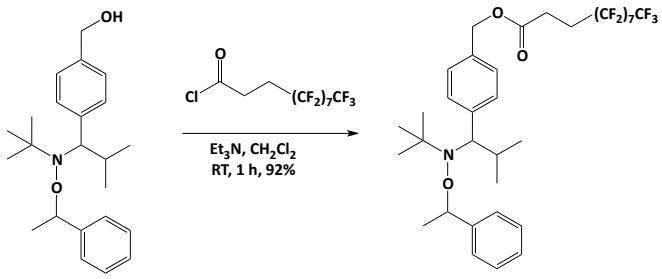


4-(1-(*tert*-butyl(1-phenylethoxy)amino)-2-methylpropyl)phenyl)methanol.[643] To a solution of *N*-(*tert*-butyl)-*N*-(2-methyl-1-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy) methyl) phenyl)propyl)-*O*-(1-phenylethyl)hydroxylamine (2.809 g, 6.399 mmol) in 110 mL of methanol and 60 mL of tetrahydrofuran was added *p*TSA (0.1194 g,

0.6398 mmol) and the reaction mixture was stirred at room temperature for 20 h. Sodium bicarbonate (2.146 g, 25.55 mmol) was added, the reaction mixture was stirred for 10 minutes, filtered through sintered funnel and concentrated *in vacuo*. The resulting crude oil (5.322 g) was purified by silica gel column chromatography using 90:10, hexanes/ethyl acetate as eluent to give the title compound as a colorless oil (1.711 g, 80.35% yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.27.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.56-6.97 (m, 9H), 4.92 (q, *J* = 6.6 Hz, 2H), 4.70 (s, 2H), 4.64 (s, 2H), 3.59 (s, 1H, OH), 3.47 - 3.38 (m, 1H), 3.37 - 3.26 (m, 1H), 2.33 (m, 1H), 1.64 (d, *J* = 6.6 Hz, 3H), 1.55 (d, *J* = 6.6 Hz, 1H), 1.44 -1.34 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 1H), 1.06 (s, 9H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.79 (s, 9H), 0.54 (d, *J* = 6.6 Hz, 3H), 0.22 (d, *J* = 6.6 Hz, 3H).



F-TIPNO-Alkoxyamine

5.64

4-(1-(*tert*-butyl(1-phenylethoxy)amino)-2-methylpropyl)benzyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate (5.64). To a

solution of 4-(1-(*tert*-butyl(1-phenylethoxy)amino)-2-methylpropyl)phenyl)methanol (0.6962 g, 1.961 mmol) and 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11 heptadecafluoro-undecanoyl chloride (1.001 g, 1.961 mmol) in 30 mL of anhydrous dichloromethane was added triethylamine (0.1997 g, 1.961 mmol) at room temperature and the reaction mixture was stirred for 1 h. A mixture of 50 mL of dichloromethane and 50 mL of water was added. The layers were separated, the organic layer was washed two times with 30 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude oil (2.136 g) was purified by silica gel column chromatography with 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (1.445 g, 92.29% yield).

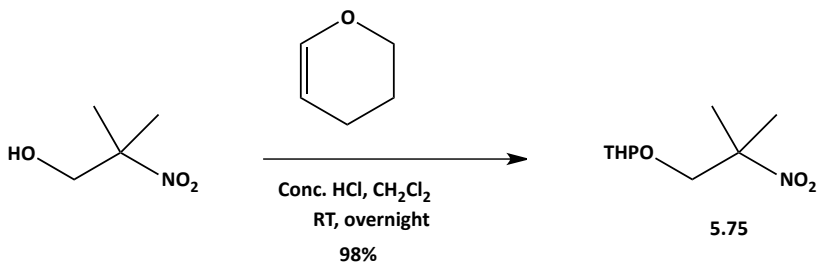
TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.62.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.54 - 7.15 (m, 18H), 5.18 (s, 2H), 5.11 (s, 2H), 4.95 - 4.90 (m, 2H), 3.45 (d, *J* = 10.6 Hz, 1H), 3.33 (d, *J* = 10.6 Hz, 1H), 2.73 – 2.67 (m, 4H), 2.55 - 2.45 (m, 4H), 2.36 - 2.31 (m, 2H), 1.64 (d, *J* = 6.6 Hz, 3H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.43 – 1.35 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.79 (s, 9H), 0.55 (d, *J* = 6.6 Hz, 3H), 0.22 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, two diastereomers): δ 171.2 (C=O), 148.3 (4°), 145.8 (4°), 143.0 (4°), 142.8 (4°), 133.3 (4°), 133.2 (4°), 131.3 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.3 (CH), 83.7 (CH), 83.0 (CH), 72.0 (CH), 71.9 (CH), 67.1

(CH_2), 60.6 (4°), 60.5 (4°), 32.1 (CH), 31.7 (CH), 28.4 (CH_3), 28.3 (CH_3) 26.8 (CH_2), 26.7 (CH_2), 25.7 (CH), 24.59 (CH_3), 23.1 (CH_3), 22.1 (CH_3), 21.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3). ^{19}F NMR (470 MHz, C_6F_6, two diastereomers): δ -82.9 (t, *J* = 9.9 Hz, 4H), -116.9 to -116.7 (m, 4H), -123.7 to - 123.8 (m, 4H), 123.8 to - 123.9 (m, 4H), -124.0 to -124.1 (m, 4H), -124.8 to -124.9 (m, 4H), -125.6 (t, *J* = 14.6 Hz, 6H), -128.2 to - 128.3 (m, 4F). FTIR: 2973 (benzylic C-H stretch), 1744 (C=O stretch), 1449 and 1365 (N-O stretch), 1204 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{34}H_{36}F_{17}NO_3$ $[M+H]^+$: 830.2496: found 830.2502 **.**

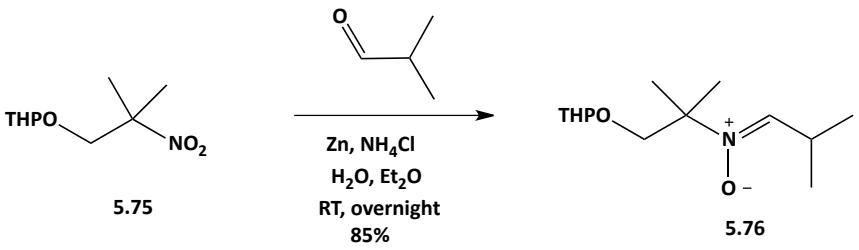


2-(2-methyl-2-nitropropoxy)tetrahydro-2*H*-pyran (5.75).[644] To a solution of 2-methyl-2-nitropropanol (5.063 g, 42.52 mmol) and 3,4-dihyropyran (4.292 g, 51.02 mmol) in 35 mL of dichloromethane was added 12 drops of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 18 h, washed with 20 mL of saturated sodium bicarbonate solution followed by 20 mL of water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude oil (10.31 g) was purified by silica gel column chromatography with

95:5, hexanes/ethyl acetate as eluent to yield the title compound as a colorless oil (8.571 g, 98.22% yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.47.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.63 (t, *J* = 3.0 Hz, 1H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.71 (d, *J* = 10.0 Hz, 1H), 3.79 – 3.52 (m, 2H), 1.77 – 1.49 (m, 6H), 1.64 (s, 3H), 1.60 (s, 3H).

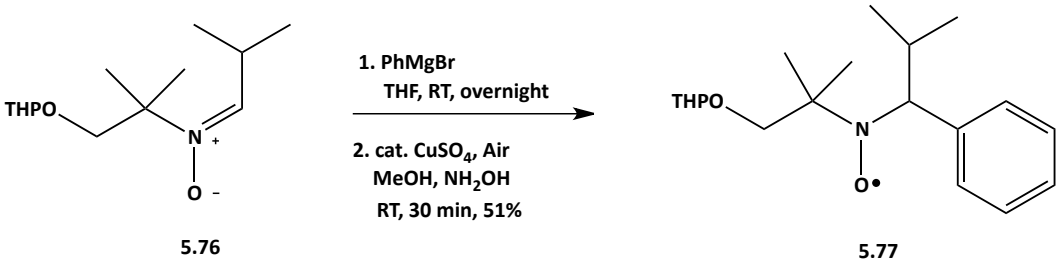


2-methyl-*N*-(propan-2-ylidene)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-amine oxide (5.76).[3] To a stirred mixture of 2-(2-methyl-2-nitropropoxy)-tetrahydro-2*H*-pyran **5.75** (5.451 g, 26.85 mmol), *iso*butyraldehyde (3.891 g, 53.96 mmol), ether (25 mL), water (62 mL), and ammonium chloride (1.594 g, 29.81 mmol) was added zinc (7.022 g, 107.4 mmol) in portions over 10 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h while open to air. The mixture was filtered through Celite and rinsed two times with 10 mL of methanol. The organic layer was separated, and the aqueous layer was extracted three times with 50 mL of dichloromethane. The organic layers were combined, washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

The resulting yellow oil (5.513 g, 84.55% yield) was used as in the next experiment without purification.

TLC: 75:25, hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.70.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (d, *J* = 7.0 Hz, 1H), 4.63 (t, *J* = 3.0 Hz, 1H), 3.74 (d, *J* = 11.0 Hz, 1H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.59 – 3.43 (m, 4H), 3.20 (h, *J* = 7.0 Hz, 1H), 1.91 – 1.56 (m, 4H), 1.49 (s, 3H), 1.44 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 6H).



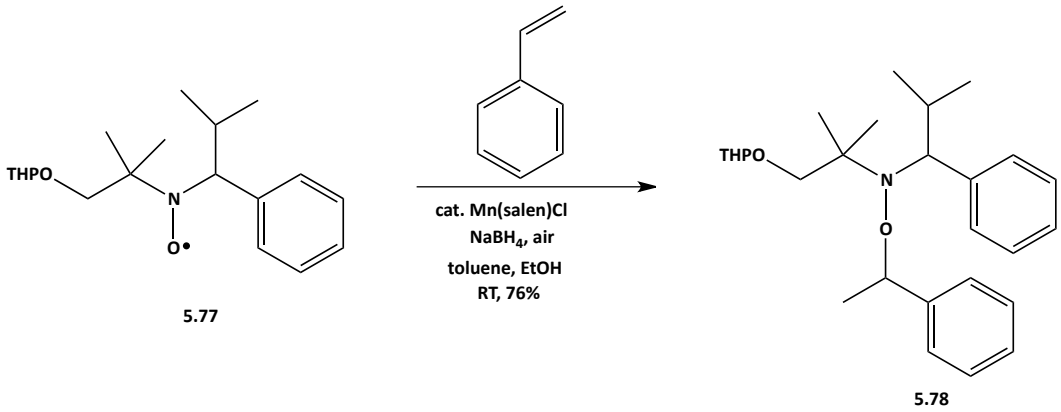
5.76 **5.77**

***N*-(2-methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-yl)-*N*-(2-methyl-1-phenylpropyl)nitroxide (5.77).**[3] To a solution of 2-methyl-*N*-(propan-2-ylidene)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-amine oxide **5.76** (5.513 g, 22.68 mmol) in 37 mL of tetrahydrofuran dried over sodium and benzophenone under nitrogen was added phenylmagnesium bromide (45.37 mL, 45.37 mmol, 1 M in THF) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C, and 30 mL of saturated NH_4Cl and 30 mL of water were added to quench the excess Grignard reagent. The layers were separated; the aqueous layer was extracted three times with 30 mL of

dichloromethane, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* Methanol (127 mL), NH_4OH (3.3 mL), and $Cu(OAc)_2$ (0.226 g, 0.0011 mmol) were added and the reaction mixture was bubbled with air for 30 minutes. The reaction mixture turned from orange to green. The reaction mixture was concentrated *in vacuo,* dissolved in a mixture of 75 mL of chloroform and 75 mL of H_2O. The layers were separated; the aqueous layer was extracted three times with 50 mL of chloroform, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The resulting crude orange oil (7.536 g) was purified by silica gel column chromatography using 90:10 hexanes/ethyl acetate as eluent, to give the title compound as an orange oil (3.683, 50.74% yield).

TLC: 80:20 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.46.

^{1}H NMR (500 MHz, $CDCl_3$ + $PhNHNH_2$, two diastereomers): δ 7.57 – 7.15 (m, 5H), 4.51 - 4.07 (m, 1H), 3.76 (m, 1H), 3.66 (d, *J* = 8.0 Hz, 1H), 3.46 (d, *J* = 8.0 Hz, 1H), 3.45 (m, 1H), 3.30 (d, *J* = 10.0 Hz, 1H), 3.16 (d, *J* = 10.0 Hz, 1H), 2.36 – 1.31 (m, 7H), 1.27 – 0.59 (m, 12H).



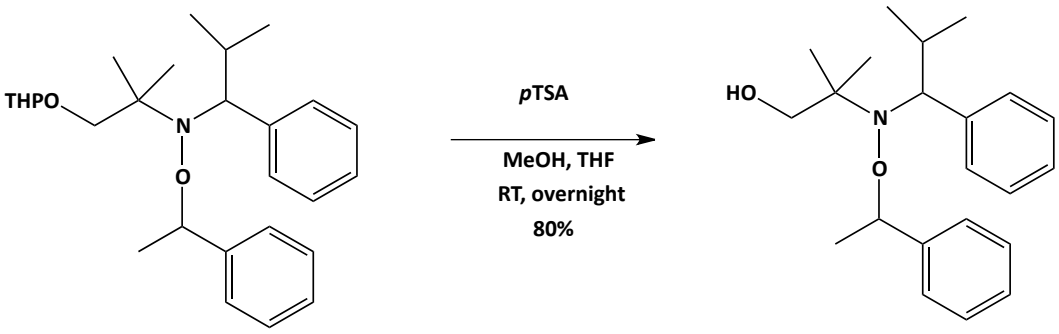
5.77 5.78

***N*-(2-methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-yl)-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl)hydroxylamine (5.78).**[3] A solution of 10 mL of toluene and 15 mL of ethanol was bubbled with air for 1 h. Styrene (0.6626 g, 6.362 mmol), *N*-(2-methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-yl)-*N*-(2-methyl-1-phenylpropyl)nitroxide **5.77** (1.018g, 3.181 mmol), manganese salen catalyst (0.4538 g, 1.272 mmol), and $NaBH_4$ (0.1444 g, 3.817 mmol) were added. The reaction mixture was bubbled with air overnight. The reaction mixture was filtered over Celite; the residue was washed with 25 mL of ethanol, and the filtrate was concentrated *in vacuo*. The resulting crude yellow oil (3.576 g) was purified by silica gel chromatography with 95:5 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (1.053 g, 75.88% yield).

TLC: 80:20 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.71.

^{1}H NMR (500 MHz, $CDCl_3$, multiple diastereomers): δ 7.53 - 7.14 (m, 10H), 5.01 – 4.87 (m, 1H), 4.59 (t, *J* = 3.4 Hz, 1H), 4.57 (t, *J* = 3.4 Hz, 1H), 4.23 (t, *J* = 3.4 Hz, 1H),

4.09 (t, *J* = 3.5 Hz, 1H), 3.92 - 3.28 (m, 4H), 3.24 (d, *J* = 9.5 Hz, 1H), 3.17 (d, *J* = 9.5 Hz, 1H), 2.87 (d, *J* = 9.5 Hz, 1H), 2.78 (d, *J* = 9.5 Hz, 1H), 2.44 -2.29 (m, 1H), 1.94 -1.56 (m, 6H), 1.45 - 1.39 (m, 1H), 1.38 - 0.23 (m, 15H).



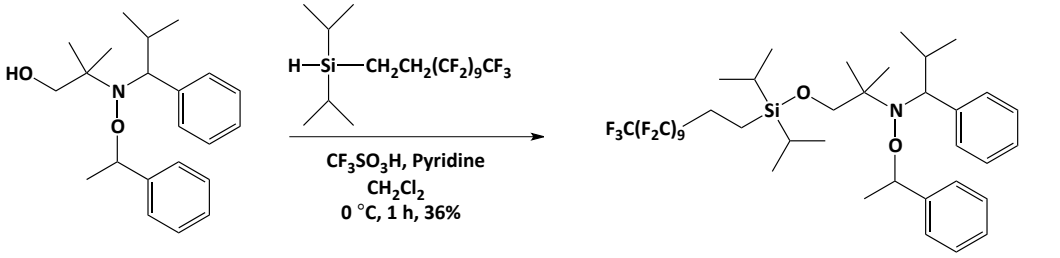
5.78

2-methyl-2-((2-methyl-1-phenylpropyl)(1-phenylethoxy)amino)propan-1-ol.[3]

To a solution of *N*-(2-methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)propan-2-yl)-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl)hydroxylamine **5.78** (6.286 g, 14.79 mmol) in 245 mL of methanol and 137 mL of tetrahydrofuran was added *p*TSA (0.2536 g, 1.479 mmol) and the reaction mixture was stirred at room temperature for 20 h. Sodium bicarbonate (4.851 g, 48.51 mmol) was added, the reaction mixture was stirred for 10 mins, filtered through sintered funnel and concentrated *in vacuo*. The resulting crude oil (7.832 g) was purified by silica gel column chromatography using 95:5, hexanes/ethyl acetate as eluent to give the title compound as a colorless oil (4.007 g, 79.78% yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.33.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.59 - 7.08 (m, 10H), 4.92 (q, *J* = 7.0 Hz, 1H), 4.88 (q, *J* = 7.0 Hz, 1H), 3.67 (d, *J* = 10.6 Hz, 1H), 3.39 (d, *J* = 10.6 Hz, 1H), 3.23 (d, *J* = 10.6 Hz, 1H), 3.14 (t, *J* = 10.6 Hz, 1H), 2.95 (d, *J* = 10.6 Hz, 1H), 2.86 (d, *J* = 9.0 Hz, 1H), 2.65 (t, *J* = 9.0 Hz, 1H), 2.44 (m, 1H), 2.30 (d, *J* = 9.0 Hz, 1H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.52 - 1.40 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.30 (s, 3H), 1.13 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.71 (s, 3H), 0.60 (d, *J* = 6.5 Hz, 3H), 0.44 (s, 3H), 0.25 (d, *J* = 6.5 Hz, 3H).



F-Si-TIPNO-alkoxyamine

5.65

Preparation of F-Si-TIPNO-alkoxyamine (5.65). Following the procedure of Crich et al.[626] A mixture of (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosa-fluorododecyl) di*iso*propylsilane (0.3012 g, 0.4549 mmol) and trifluoromethane-sulfonic acid (0.6827 g, 0.4549 mmol) was added to a flame dried round bottom flask and was stirred under nitrogen for 48 h. The reaction mixture was diluted with 1 mL of dichloromethane and a solution of 2-methyl-2-((2-methyl-1-phenylpropyl)

(1-phenylethoxy)amino)propan-1-ol (0.1032 g, 0.3026 mmol) in 1 mL of dichloromethane was added at 0 °C. The reaction mixture was stirred for 1 h and then diluted with 15 mL of dichloromethane, washed sequentially with 10 mL of water, 10 mL of saturated NH_4Cl solution and 10 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude oil (0.3503 g) was purified by silica gel column chromatography with 90:10 hexanes/ethyl acetate as eluent to give the title product as a colorless viscous oil (0.1081 g, 35.79 % yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.70.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.62 - 7.12 (m, 20H), 4.88 (m, 2H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.48 (d, *J* = 10.5 Hz, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 3.08 (d, *J* = 9.0 Hz, 1H), 3.00 (d, *J* = 9.0 Hz, 1H), 2.39 - 2.36 (m, 2H), 2.25 -2.12 (m, 2H), 2.01 - 1.80 (m, 2H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.53 (s, 3H), 1.41 - 1.35 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.17 (s, 3H), 1.20 - 0.99 (m, 12H), 0.96 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 - 0.80 (m,16H), 0.77 - 0.66 (m, 4H), 0.63 (s, 3H), 0.56 (d, *J* = 6.6 Hz, 3H), 0.23 (d, *J* = 6.6 Hz, 3H).

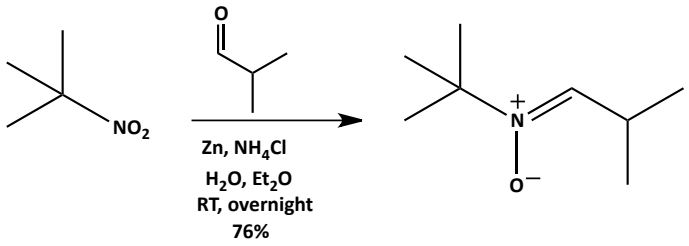
^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 145.7 (4°), 142.7 (4°), 130.8 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.6 CH), 126.5 (CH), 126.1 (CH), 83.8 (CH), 83.0 (CH), 72.3 (CH), 72.2 (CH), 70.1 (CH_2), 69.8 (CH_2), 64.8 (4°), 64.6 (4°), 31.9 (CH), 31.5 (CH), 25.4 (CH_2), 24.8 (CH_2), 24.1 (CH_3),

23.7 (CH_3), 23.3 (CH_3), 21.9 (CH_3), 21.6 (CH_3), 21.2 (CH_3), 20.4 (CH_3), 17.6 (CH_3), 17.5 (CH_3), 17.4 (CH_3), 12.4 (CH_3), 12.1 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$, both diastereomers): δ -83.0 (t, *J* = 9.9 Hz, 2F), -83.2 (t, *J* = 9.9 Hz, 2F), -118.6 to -118.9 (m, 2F), -119.1 to -119.2 (m, 2F), -124.0 to -124.1 (m, 10F), -124.1 to -124.3 (m, 10F), -124.9 to -125.0 (m, 2F), -125.1 to - 125.2 (m, 2F), -125.4 to -125.6 (m, 2F), -125.8 to -125.9 (m, 2F), -128.4 (t, *J* = 13.8 Hz, 3F), -128.5 (t, *J* = 13.8 Hz, 3F).

FTIR: 3056 (aromatic C-H stretch), 2969 (benzylic C-H stretch), 1453 and 1363 (N-O stretch), 1428 (aromatic C=C stretch), 1211 (Si-O stretch), 1150 (C-O stretch), 815 (*p*-substituted benzene), 699 (mono substituted benzene) cm^{-1}.

HRMS: calcd. for $C_{40}H_{48}F_{21}NO_2Si$ $[M+H]^+$: 1002.3192: found 1002.3162

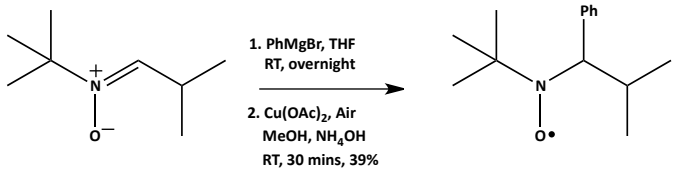


2-methyl-*N*-(2-methylpropylidene)propan-2-amine oxide.[544] A mixture of 2-methyl-2- nitropropane (14.33g, 138.9 mmol), *iso*butyraldehyde (15.03 g, 208.50 mmol), ammonium chloride (8.178 g, 152.9 mmol), and 275 mL of water were cooled to 0 °C in an ice-bath, and 115 mL of diethyl ether was then added to partially dissolve the crystallized 2-methyl-2-nitropropane. Zinc powder (36.37 g, 555.9 mmol) was added

in small portions over 15 minutes with stirring. After 18 h, the mixture was filtered over Celite and the residue was washed three times with 100 mL of methanol. The product was extracted three times with 150 mL of dichloromethane. The organic layers were combined and washed with 100 mL of brine, dried over magnesium sulfate, and concentrated in vacuo to give crude nitrone as a colorless oil (15.66 g, 76.11% yield).

TLC: 90:10 ethyl acetate/methanol, UV, R_f: 0.45.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 7.0 Hz, 1H), 3.16 (dq, *J* = 7.0, 6.9 Hz, 1H), 1.47 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 6H).

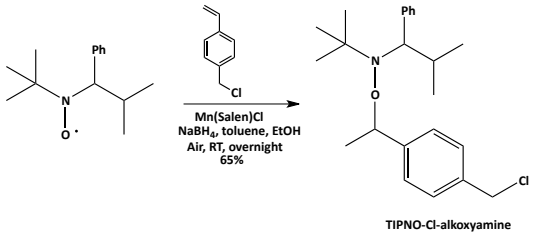


***N*-(*tert*-butyl)-*N*-(2-methyl-1-phenylpropyl)nitroxide.**[544] To a solution of 2-methyl-*N*-(2-methylpropylidene)propan-2-amine oxide (7.137 g, 49.82 mmole) were taken in 50 mL of tetrahydrofuran dried over sodium and benzophenone under nitrogen was added phenylmagnesium bromide (100.3 mL, 100.3 mmol, 1 M in THF) under ice cooling. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Upon cooling to 0 °C, 30 mL of saturated NH_4Cl solution was added followed by 30 mL of water to quench the excess Grignard reagent. The layers were separated; the aqueous layer was extracted four times with 50 mL of dichloromethane, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.*

Methanol (193 mL), NH_4OH (15 mL), and $Cu(OAc)_2$ (5.439 g, 27.24 mmol) were added and the reaction mixture was bubbled with air for 30 minutes. The reaction mixture turned from orange to green. The reaction mixture was concentrated *in vacuo,* dissolved in 75 mL of chloroform, and then 75 mL of H_2O was added. The layers were separated; the aqueous layer was extracted three times with 50 mL of chloroform, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The resulting crude orange oil (14.432 g) was purified by silica gel column chromatography using 90:10 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (4.231 g, 38.55 % yield).

TLC: 90:10 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.63.

^{1}H NMR (500 MHz, $CDCl_3$ + $PhNHNH_2$): δ 7.60 - 7.25 (m, 5H), 3.41 (d, J = 6.5 Hz, 1H), 2.28 (m, 1H), 1.44 (s, 9H), 1.20 (d, J = 6.5 Hz, 3H), 0.97 (s, 9H), 0.58 (d, J = 6.5 Hz, 3H).



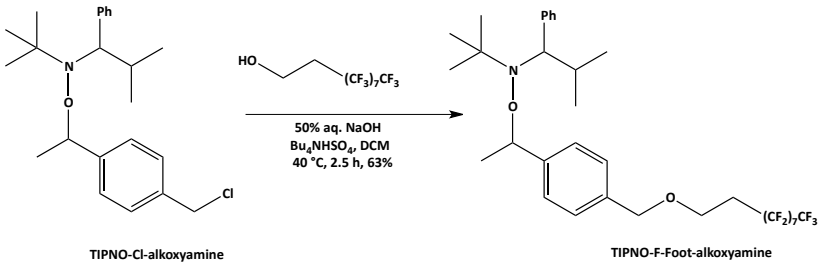
TIPNO-Cl-alkoxyamine

***N*-(*tert*-butyl)-*O*-(1-(4-(chloromethyl)phenyl)ethyl)-*N*-(2-methyl-1-phenyl propyl) hydroxylamine (TIPNO-Cl-alkoxyamine).** A mixture of 80 mL of toluene and 112 mL of ethanol was bubbled with air for 1 h. 4-vinylbenzyl chloride (5.861 g, 38.46 mmol), *N*-(*tert*-butyl)-*N*-(2-methyl-1-phenylpropyl)nitroxide (4.231 g, 19.23 mmol), salen catalyst (2.055 g, 5.761 mmol), and sodium borohydride (2.179 g, 5.761

mmol) were added. The reaction mixture was bubbled with air overnight. The reaction mixture was filtered over Celite; the residue was washed with 50 mL of ethanol, and the filterate was concentrated *in vacuo*. Dichloromethane (200 mL) and water (200 mL) were added. The layers were separated; the aqueous layer was extracted three times with 150 mL of dichloromethane, dried over $MgSO_4$ and concentrated in vacuo. The resulting crude brown oil (10.31 g) was purified by silica gel chromatography with 98:2 hexanes/ethyl acetate as eluent, to give the title compound as a colorless oil (4.401 g, 65.42% yield).

TLC: 80:20 hexanes/ethyl acetate, UV, *p*-anisaldehyde stain, R_f: 0.71.

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.50 - 7.14 (m, 9H), 4.92 (m, 1H), 4.59 (d, *J* = 16 Hz, 2H), 3.42 (d, *J* = 10.0 Hz, 1H), 3.31 (d, *J* = 10.0 Hz, 1H), 2.42 - 2.23 (m, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.78 (s, 9H), 0.54 (d, *J* = 7.0 Hz, 3H), 0.21 (d, *J* = 6.3 Hz, 3H).



TIPNO-Cl-alkoxyamine

TIPNO-F-Foot-alkoxyamine

5.66

Preparation of F-TIPNO-Foot-alkoxyamine (5.66). To a solution of *1H, 1H, 2H, 2H*-perfluorodecanol (8.715 g, 18.77 mmol) in 44 mL of 50% aqueous NaOH and 45 mL of dichloromethane was added tetrabutylammoniumhydrogen sulfate (1.912 g, 5.633 mmol) and the reaction mixture was stirred vigorously for 10 minutes. TIPNO-Cl-alkoxyamine (1.752 g, 4.694 mmol) in 45 mL of dichloromethane was added and the reaction mixture was refluxed for 2.5 h. The layers were separated; the aqueous layer was extracted three times with 50 mL of dichloromethane. The organic layers were combined, washed three times with 50 mL of 0.1 M hydrochloric acid, dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting crude oil (3.527 g) was purified by silica gel column chromatography with 98:2 hexanes/ethyl acetate as eluent to give the title compound as a pale yellow oil (2.353 g, 62.57% yield).

^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.55 -7.09 (m, 18H), 4.93 (m, 2H), 4.55 (s, 2H), 4.51 (s, 2H), 3.75 (m, 4H), 3.43 (d, *J* = 10.4 Hz, 1H), 3.31 (d, *J* = 10.4 Hz, 1H), 2.43 - 2.38 (m, 4H), 2.36 - 2.28 (m, 1H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H), 1.02 – 0.96 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.78 (s, 9H), 0.54 (d, *J* = 6.6 Hz, 3H), 0.21 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT, two diastereomers): δ 145.7 (4°), 144.9 (4°), 136.6 (4°), 135.6 (4°), 131.1 (CH), 131.0 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 126.3 (CH), 83.4 (CH), 82.3 (CH), 73.3 (CH_2), 73.2 (CH_2), 72.2 (CH), 72.1 (CH), 62.1 (CH_2), 61.2 (CH_2), 59.7 (4°), 59.6 (4°), 32.0 (CH), 31.7 ($\underline{C}H_2$-CF_2), 31.6 ($\underline{C}H_2$-CF_2), 28.4 (CH_3), 28.2 (CH_3), 24.7 (CH_2), 23.2 (CH_3), 22.1 (CH_3), 21.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3).

^{19}F NMR (470 MHz, C_6F_6, two diastereomers): δ -82.9 (t, *J* = 10.0 Hz, 2F), -83.1 (t, *J* = 10.0 Hz, 2F), -115.5 to - 115.7 (m, 2F), 115.7 to - 115.8 (m, 2F), -123.8 to - 124.0 (m, 4F), -125.8 to -125.9 (m, 4F), -128.3 to - 128.4 (m, 6F).

FTIR: 3034 (aromatic C-H stretch), 2943 (benzylic C-H stretch), 1492 and 1365 (N-O stretch), 1466 (aromatic C=C stretch), 1211 (Si-O stretch), 1150 (C-O stretch) cm^{-1}.

HRMS: calcd. for $C_{33}H_{36}F_{17}NO_2$ $[M+H]^+$: 802.2547: found 802.2307.

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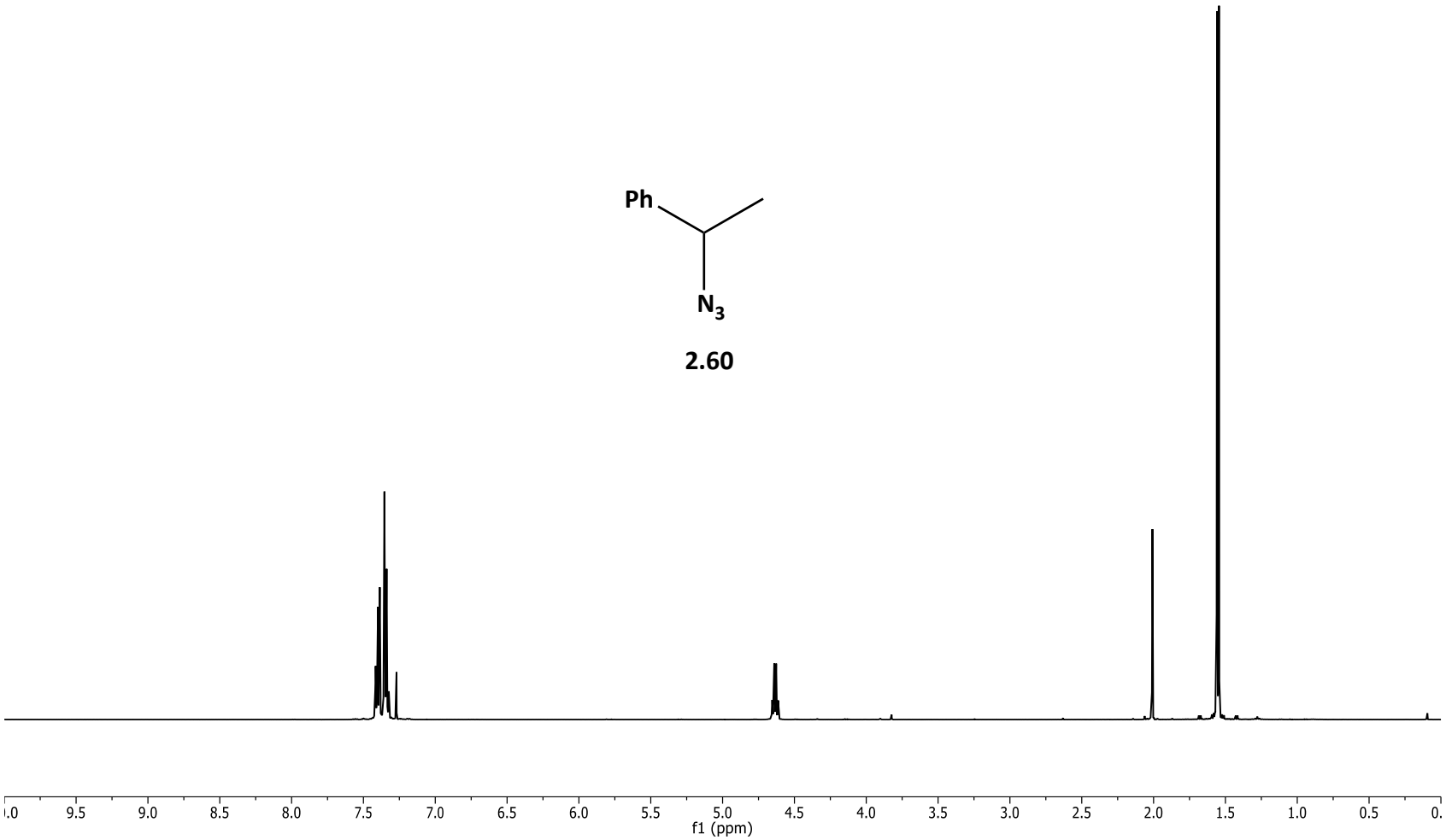
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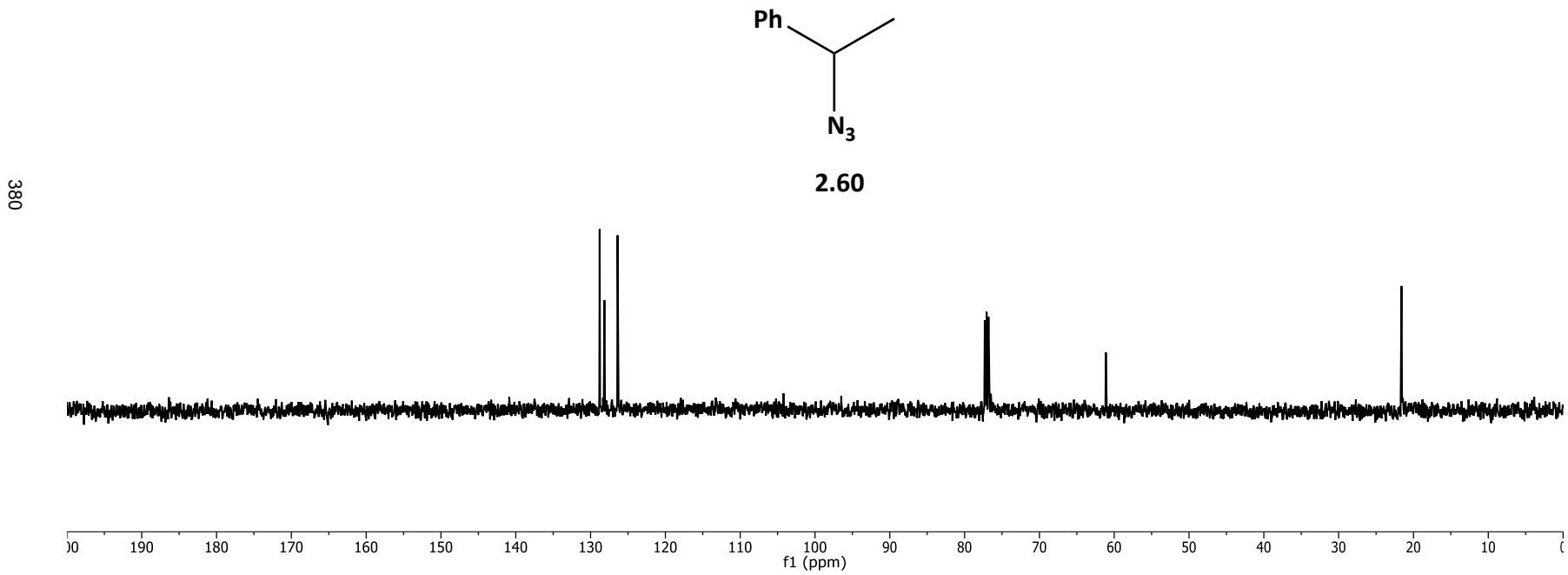
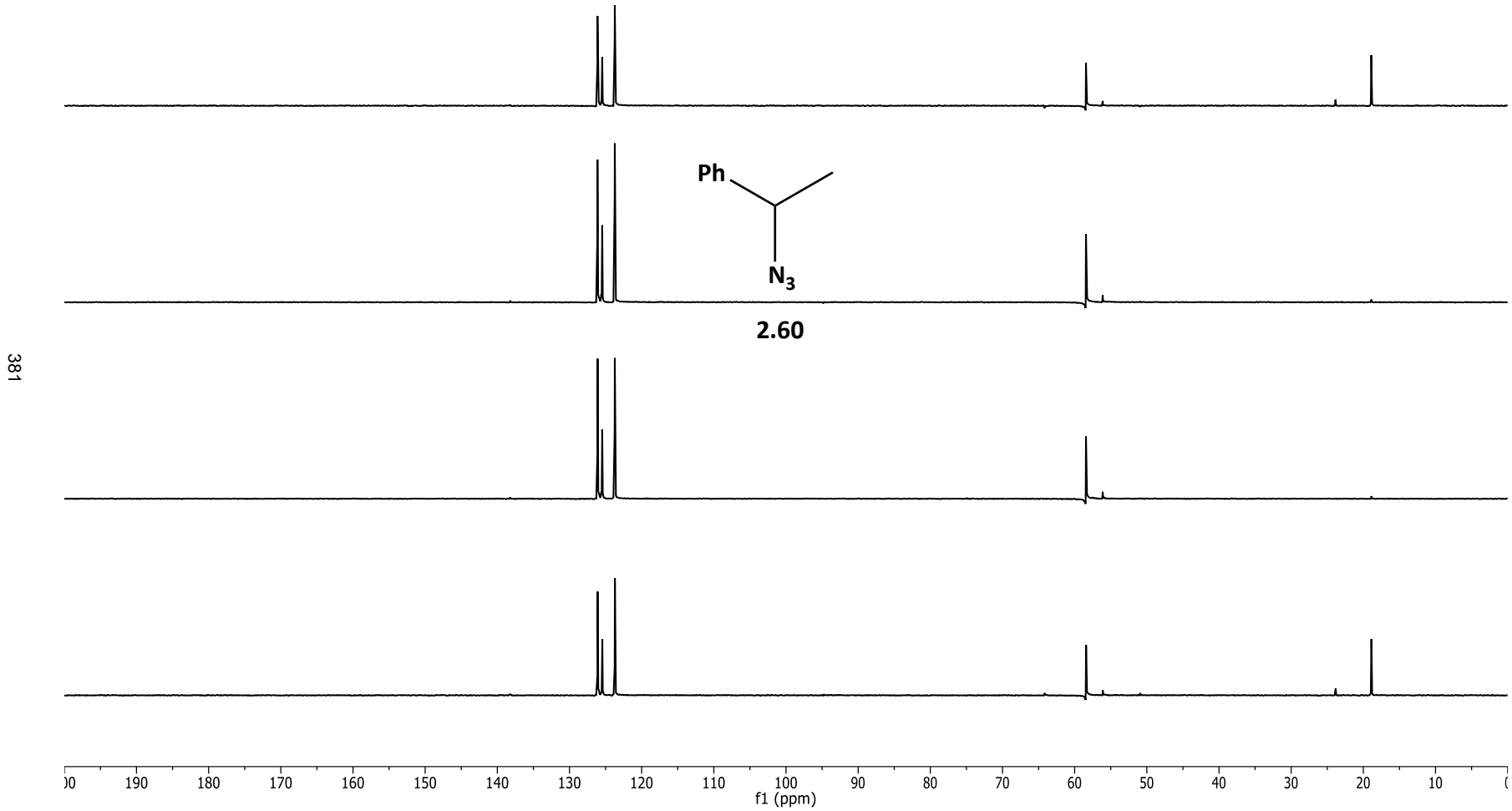
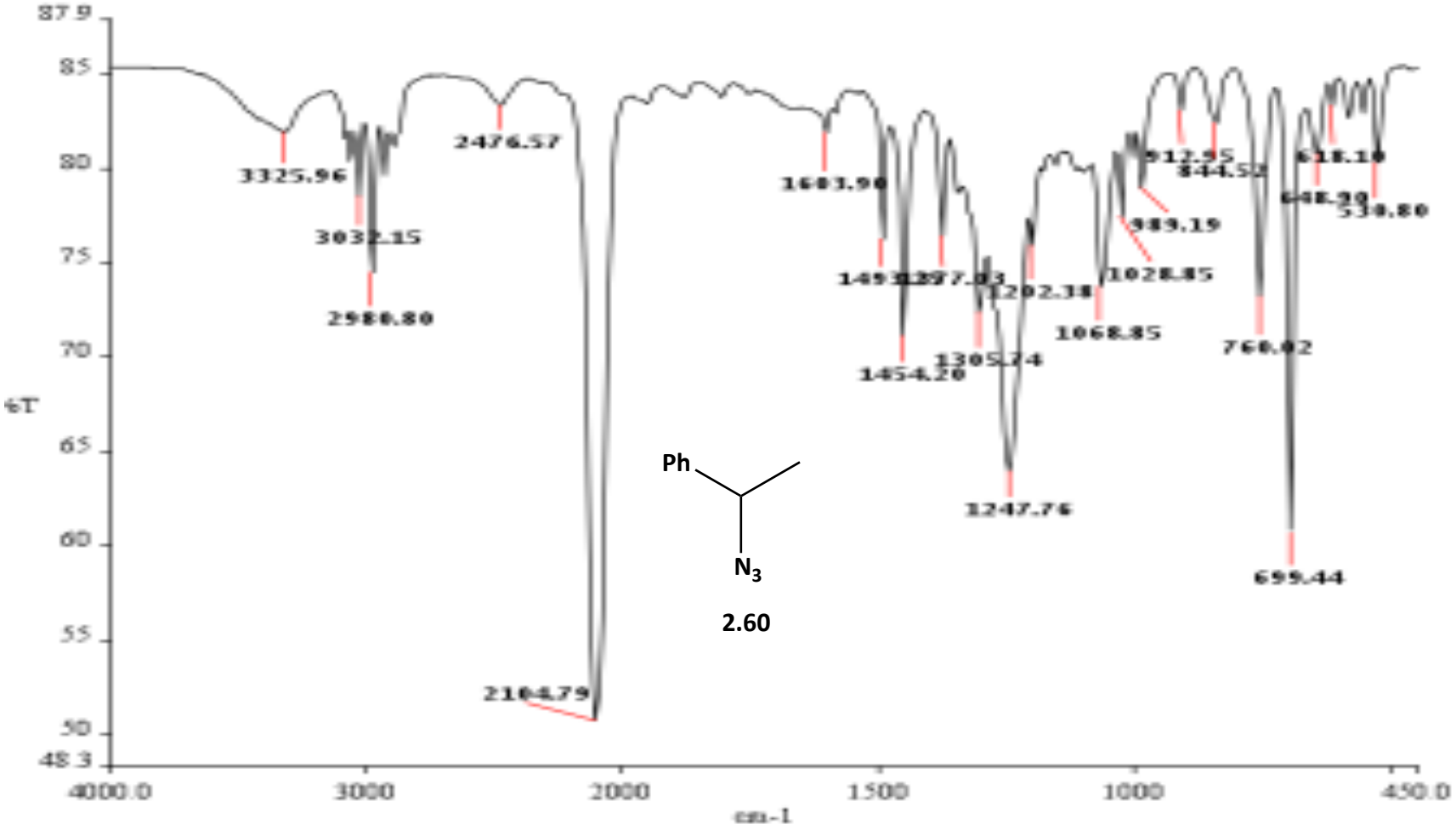
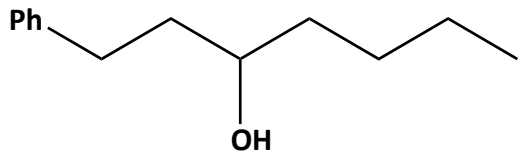
N3
2.60
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Ph
N3
2.60
380
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

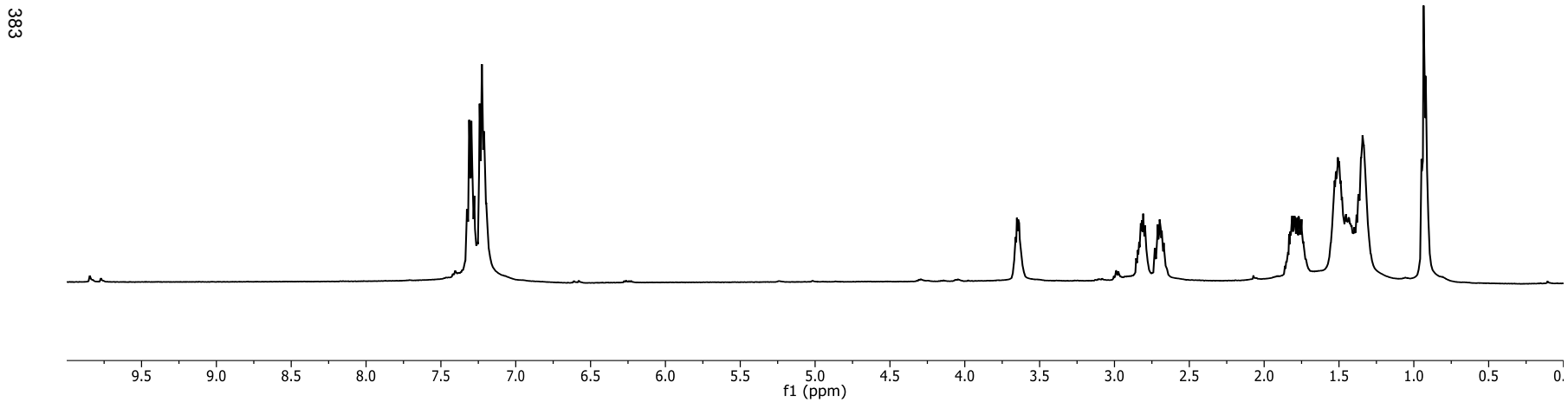

Ph
N3
2.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


87.9
85
80
75
70
65
60
55
50
48.3
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
3325.96
3032.15
2986.80
2476.57
2164.79
1683.90
1454.20
1305.74
1247.76
1202.38
1068.85
1028.85
989.19
912.95
844.52
760.02
699.44
618.10
548.20
530.80
Ph
N_3

2.60


Ph
OH

2.58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9.5
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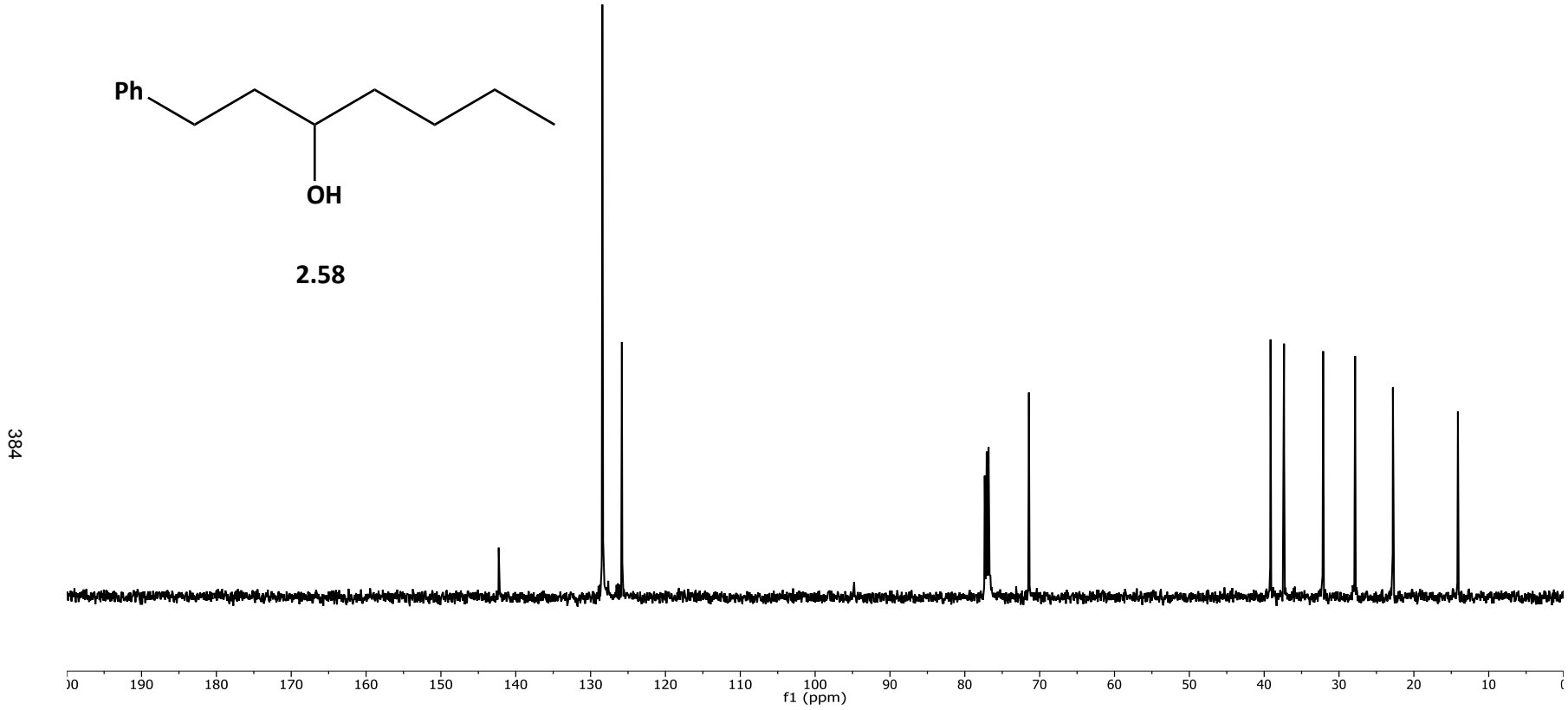
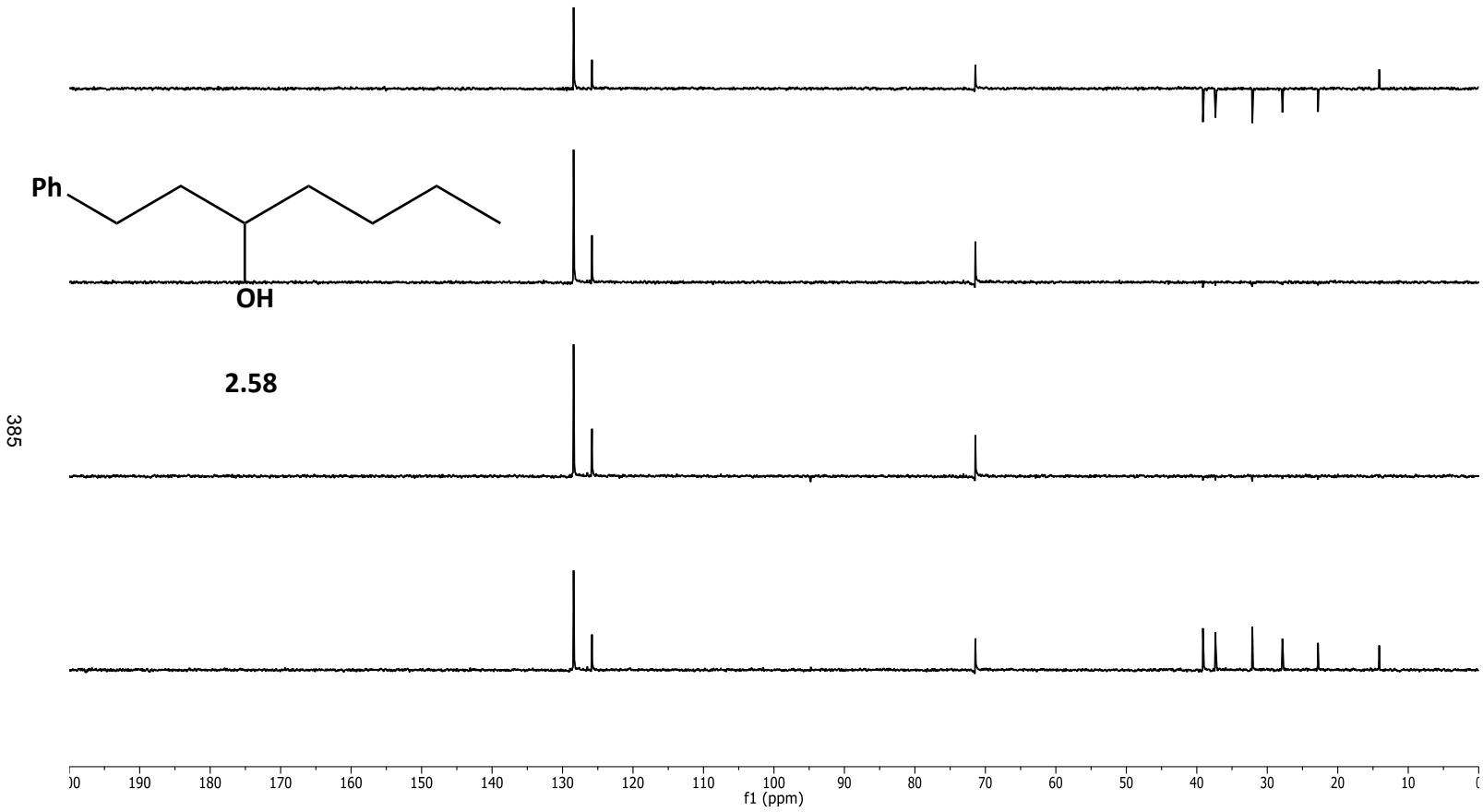
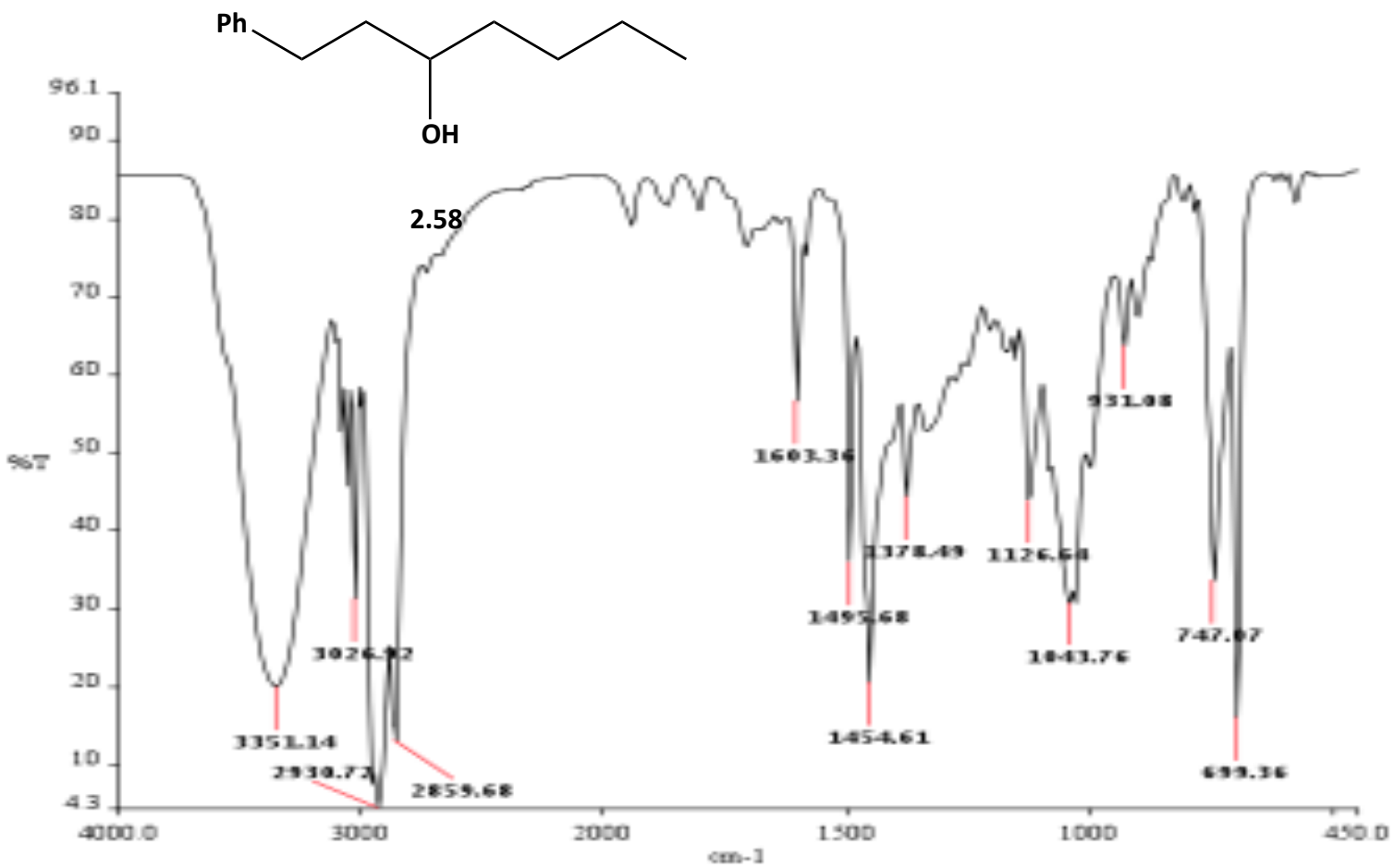
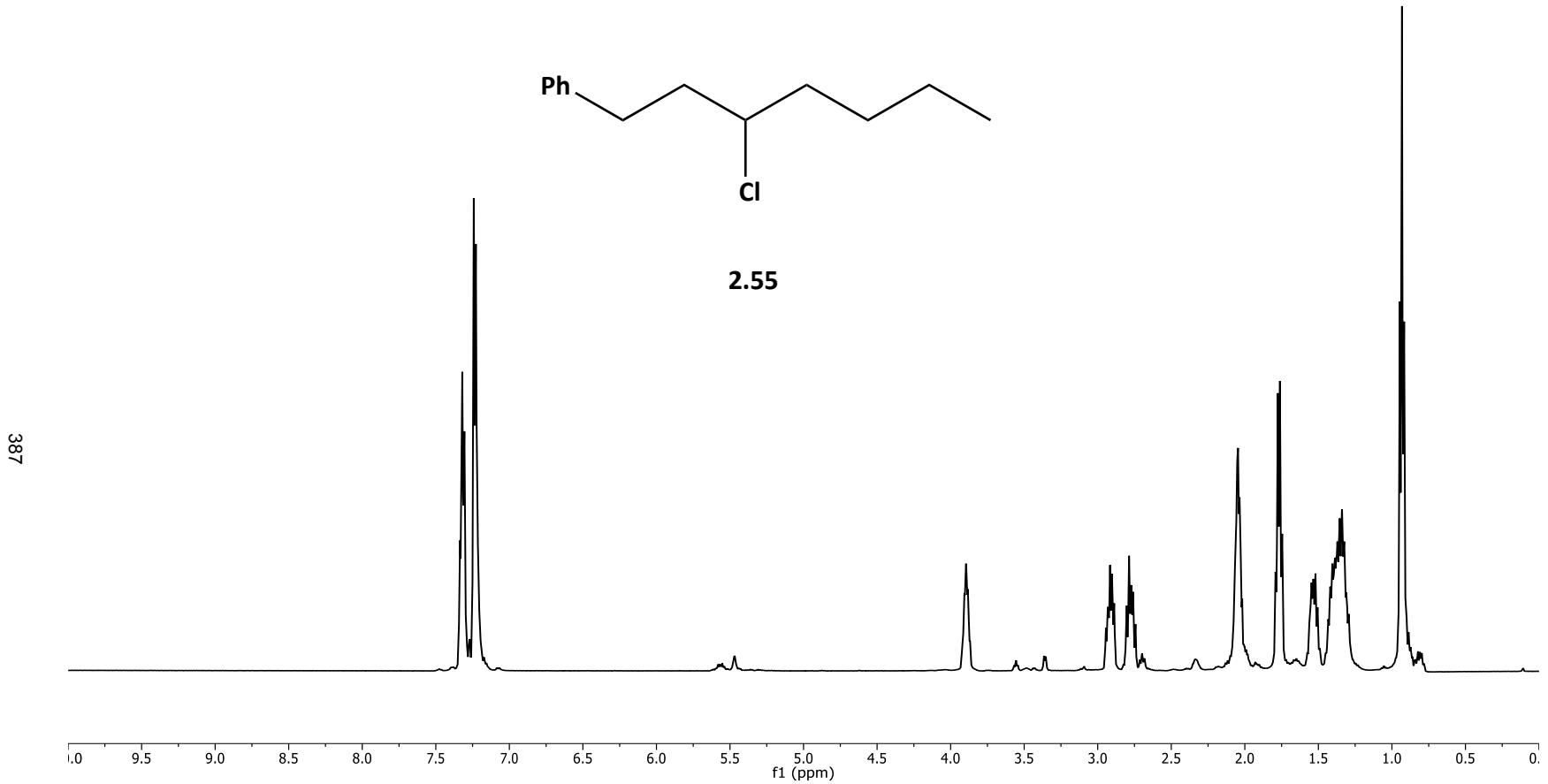
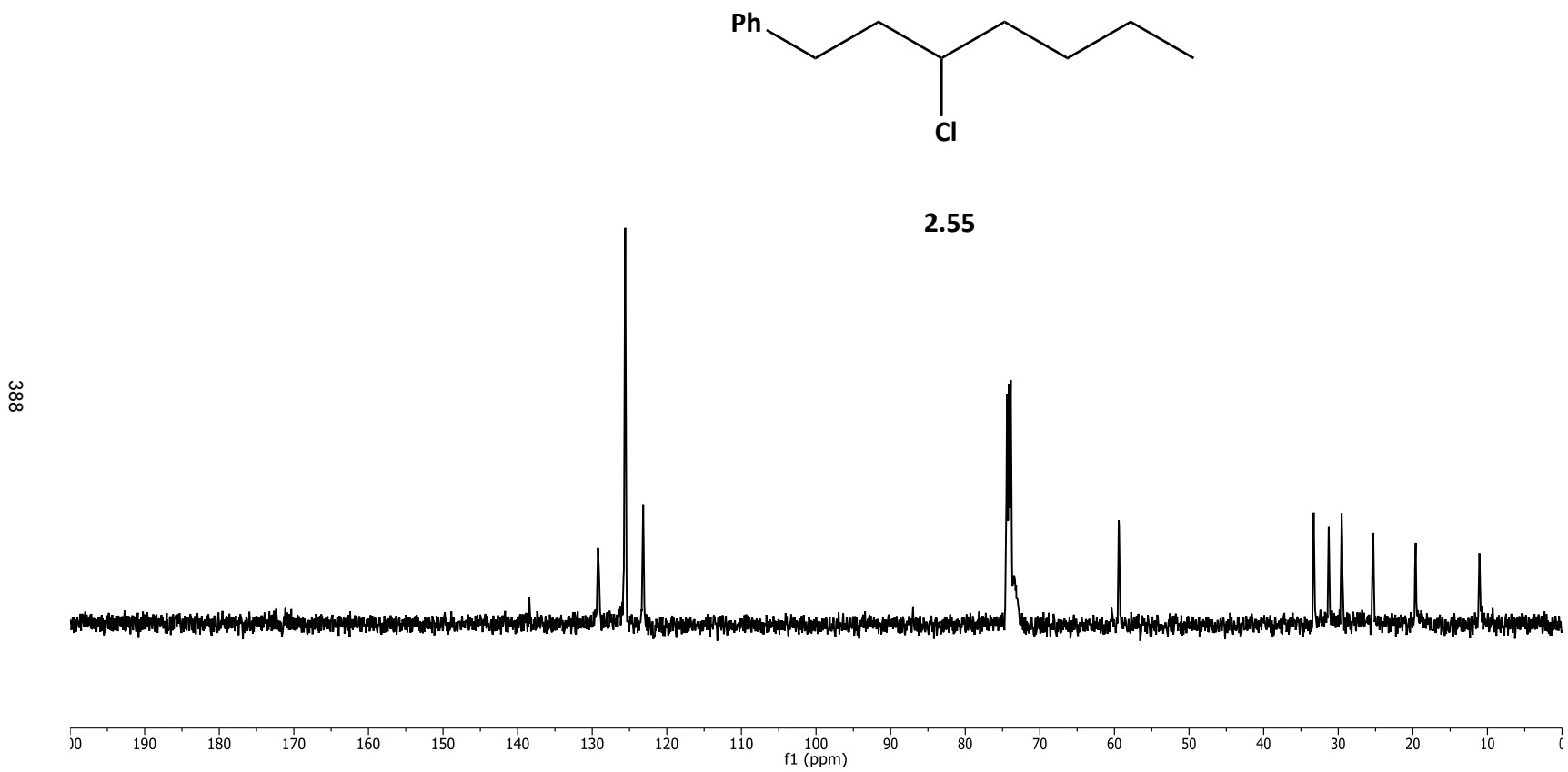
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

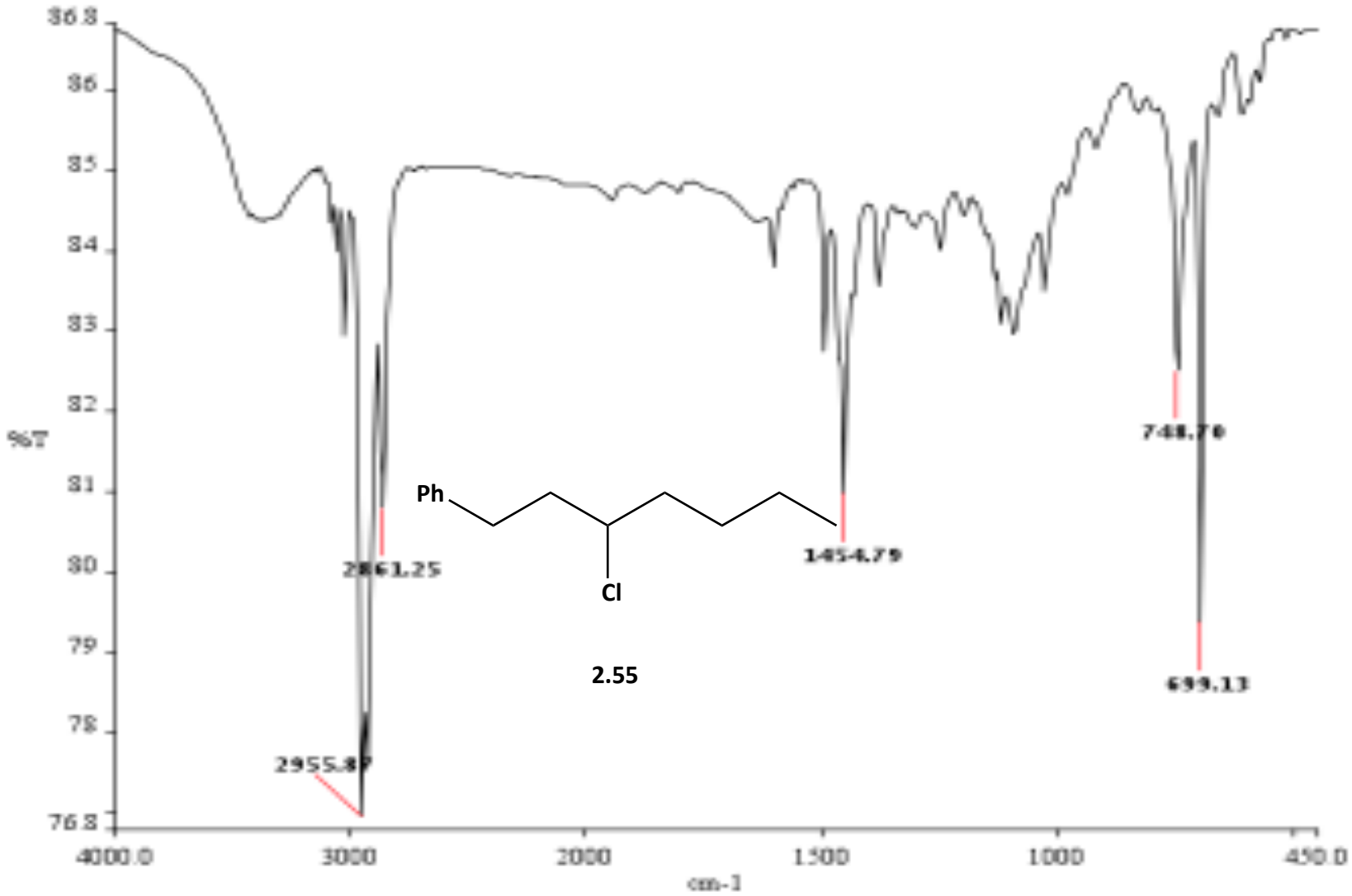

Ph
OH
2.58
384
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Ph
OH
2.58
385
f1 (ppm)


Ph
OH
2.58
96.1
90
80
70
60
50
40
30
20
10
4.3
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
3351.14
3026.92
2930.73
2859.68
1603.36
1495.68
1454.61
1378.49
1126.68
1043.76
931.08
747.07
699.36


Ph
Cl
2.55
387
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Ph
Cl
2.55
388
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


%T
cm-1
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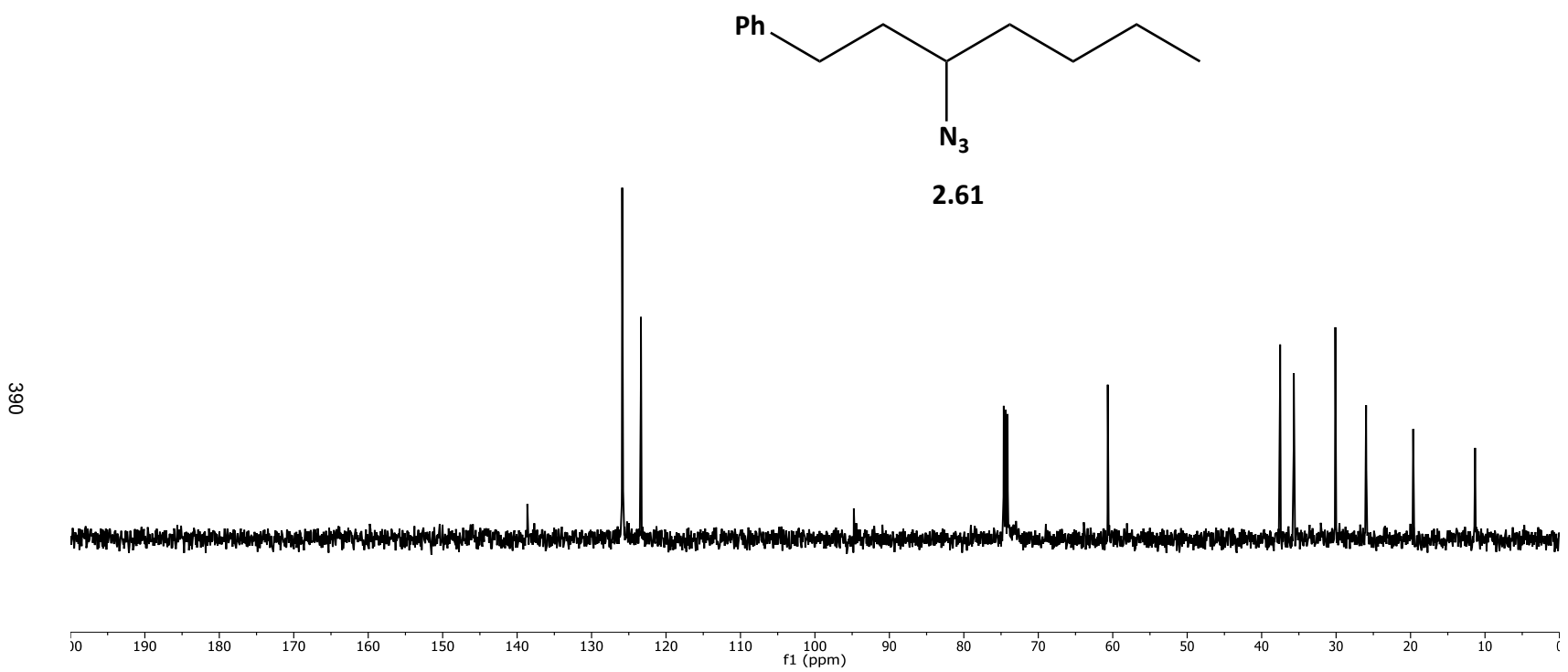
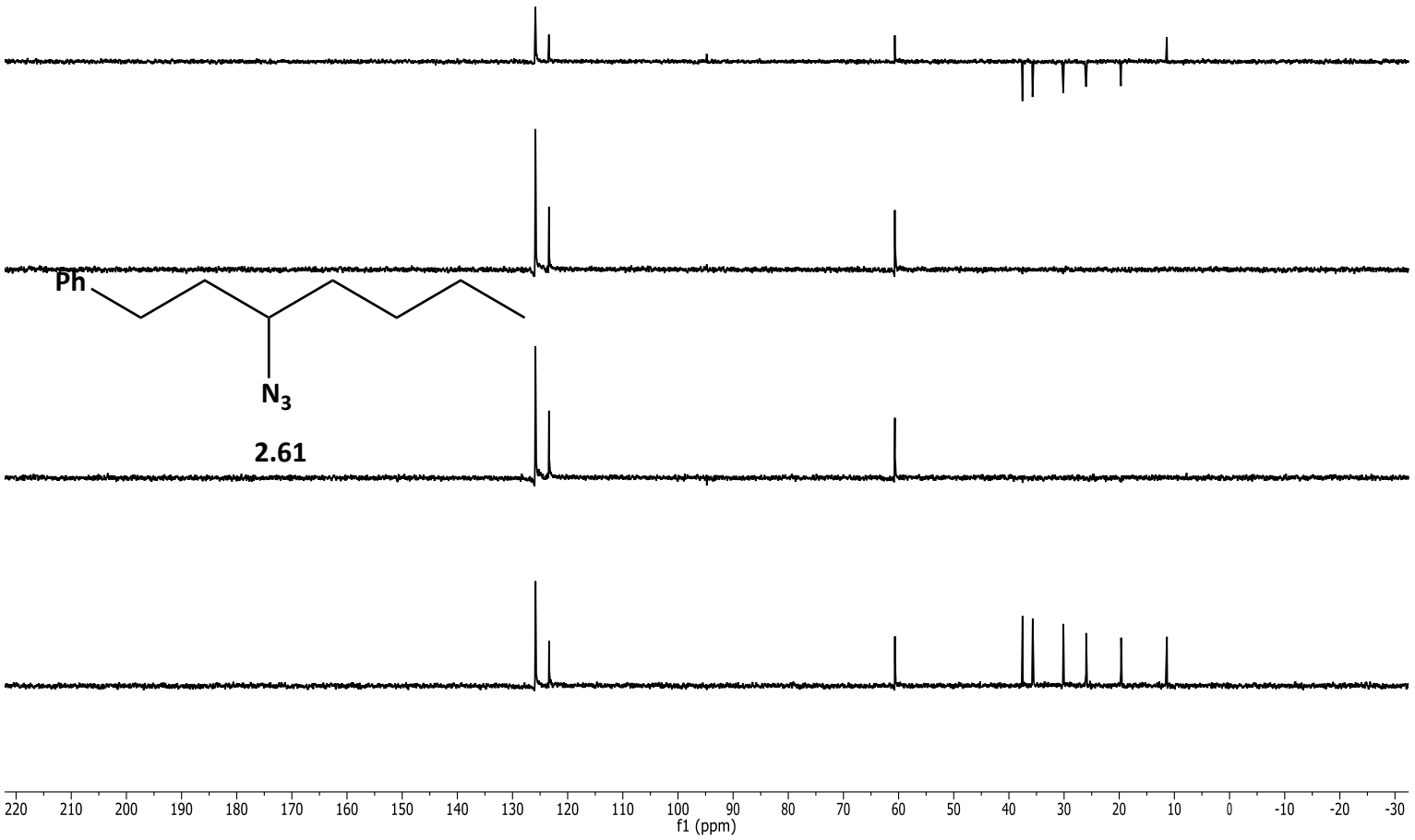
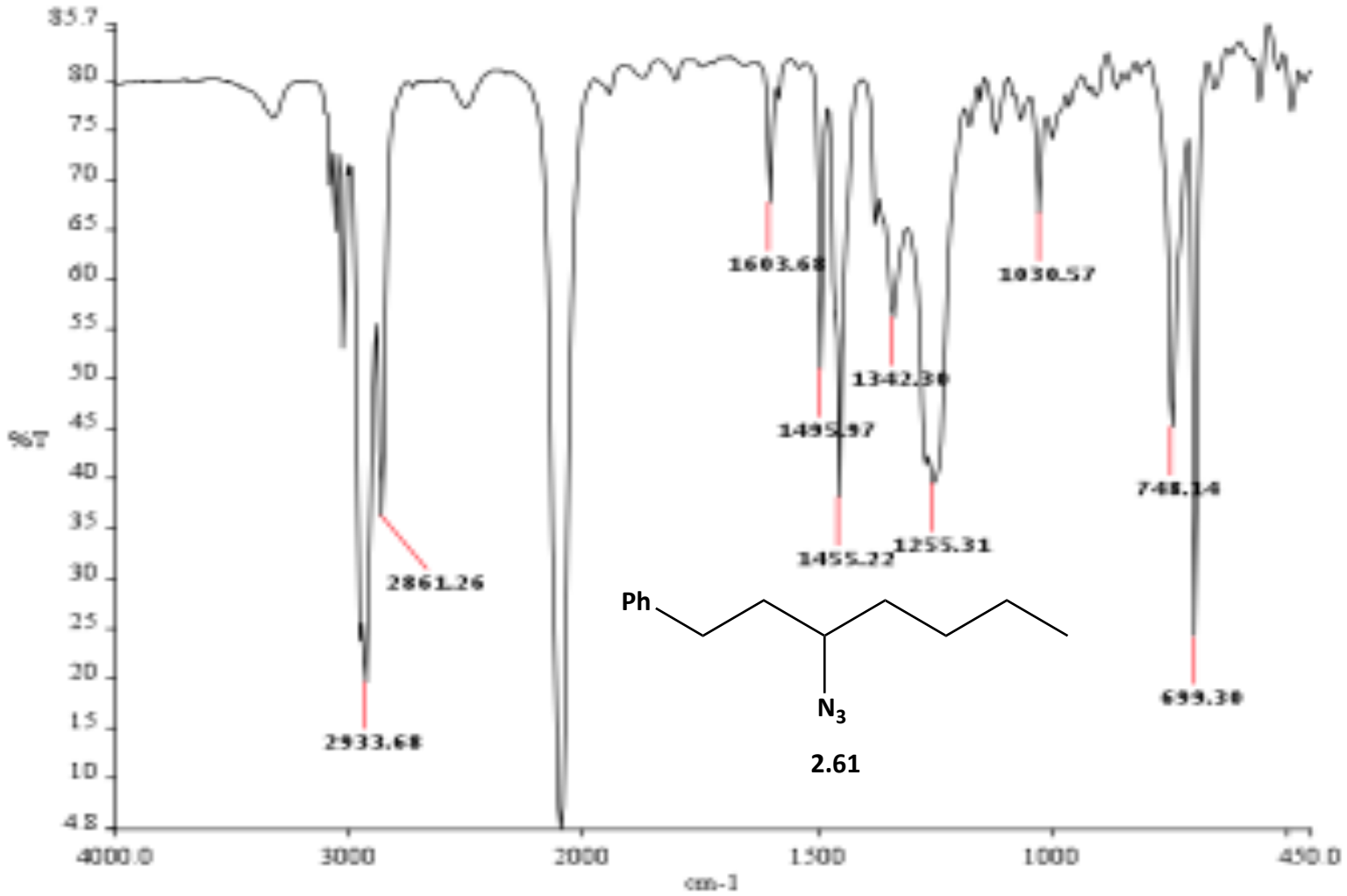
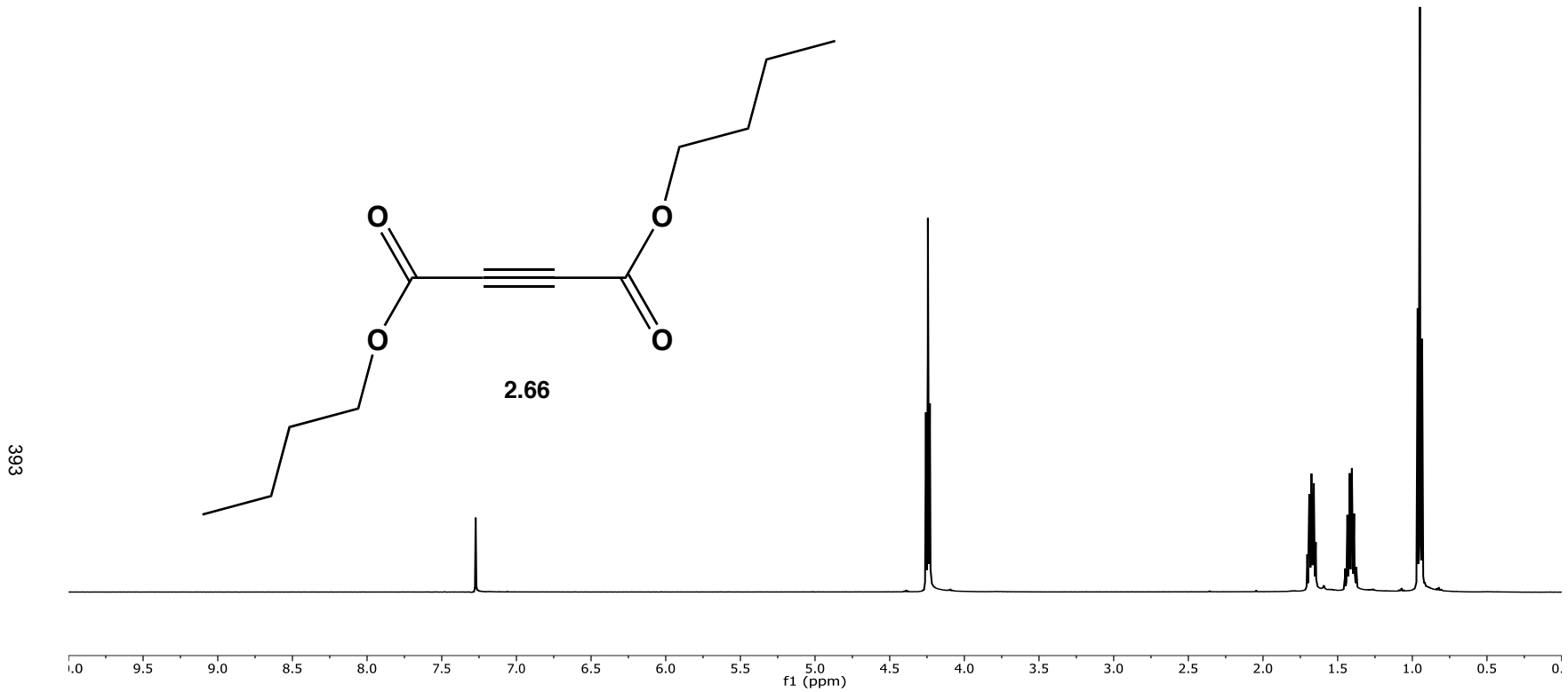
2861.25
1454.79
748.76
699.13
Ph
Cl
2.55

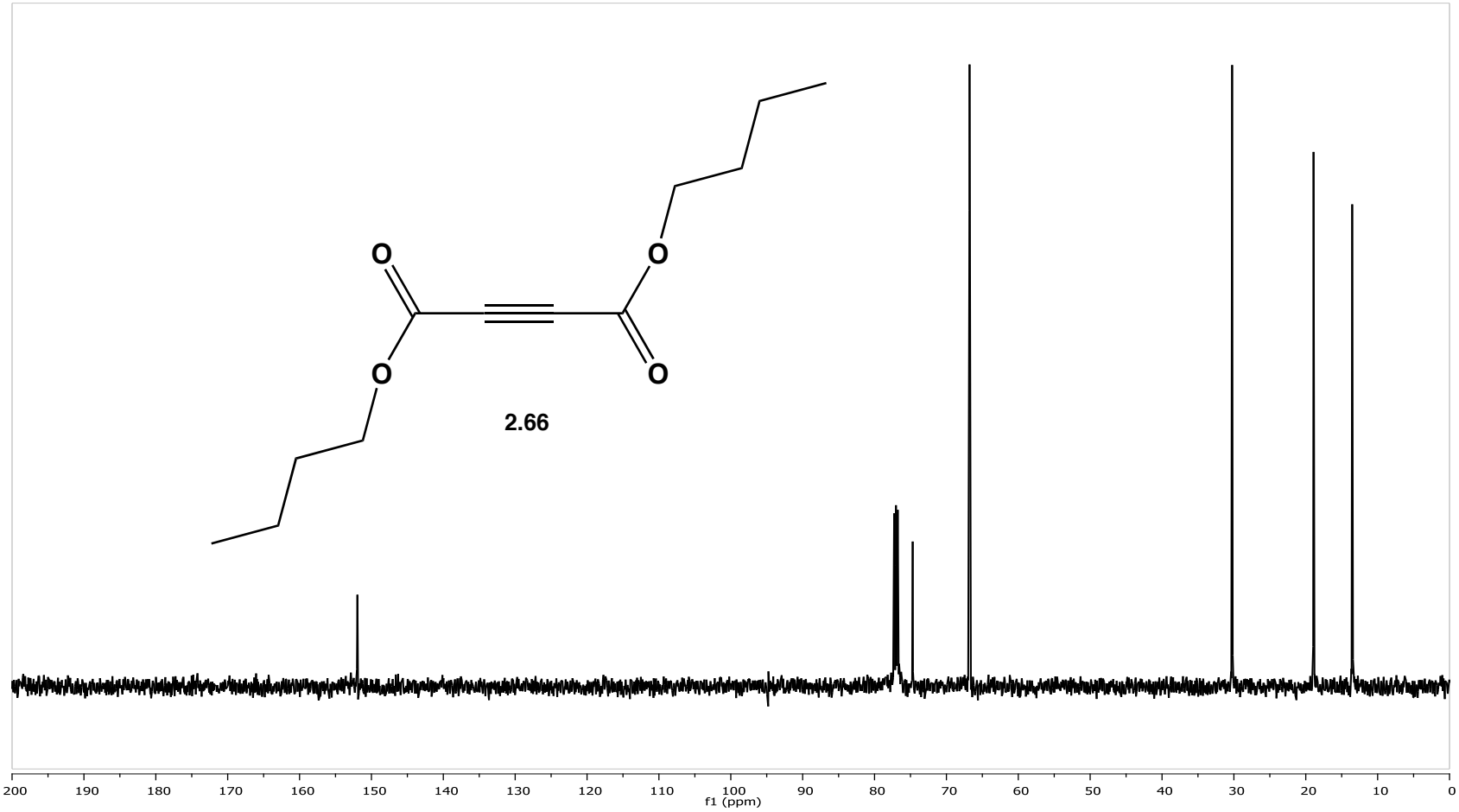

Ph
N3
2.61
390
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

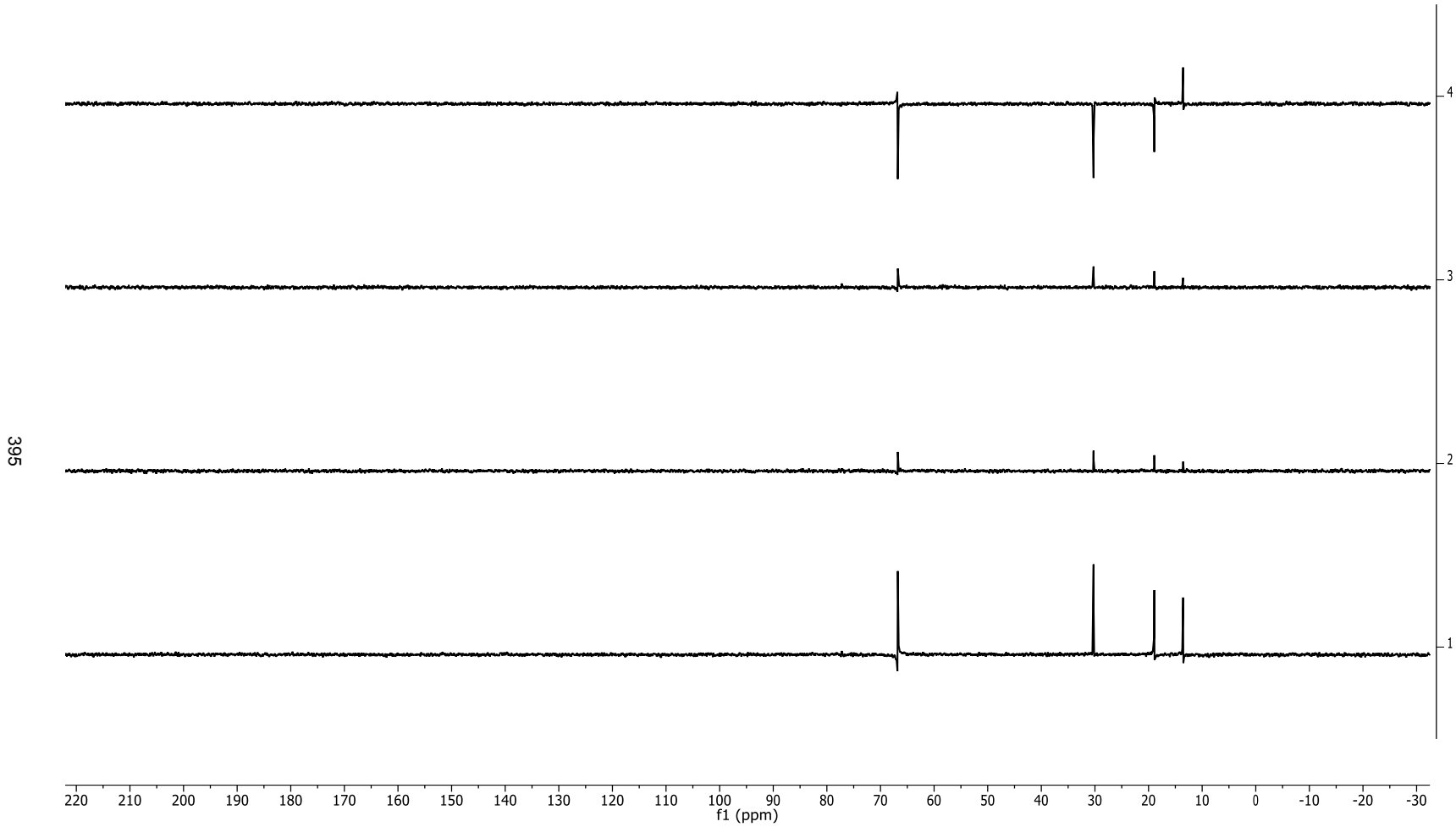

Ph
N3
2.61
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


85.7
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4.8
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
2933.68
2861.26
1603.68
1495.97
1455.22
1342.30
1255.31
1030.57
748.14
699.30
Ph
N3

2.61


O
O
O
O
2.66
393
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
O
O
O
2.66
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


4
3
2
1
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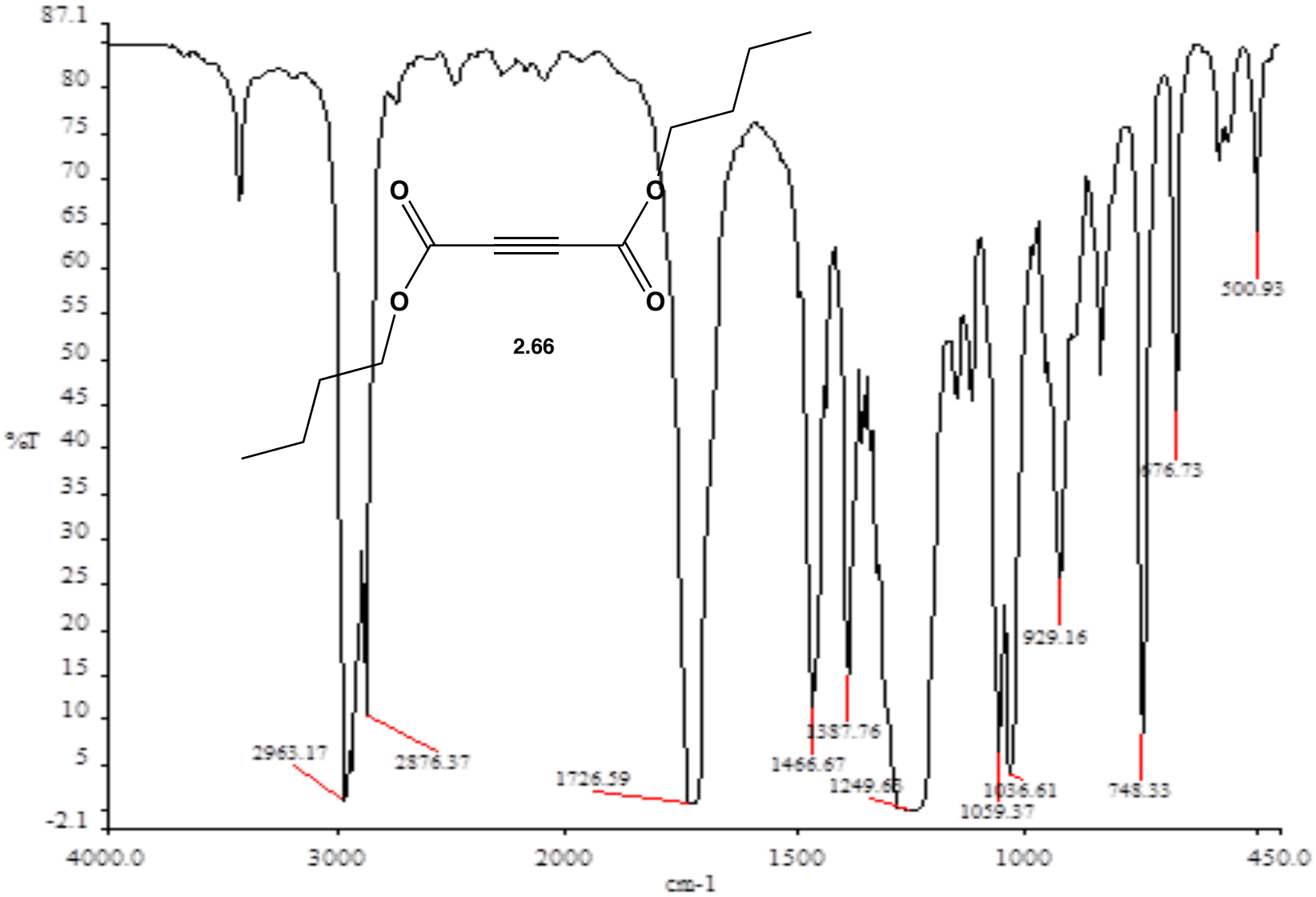
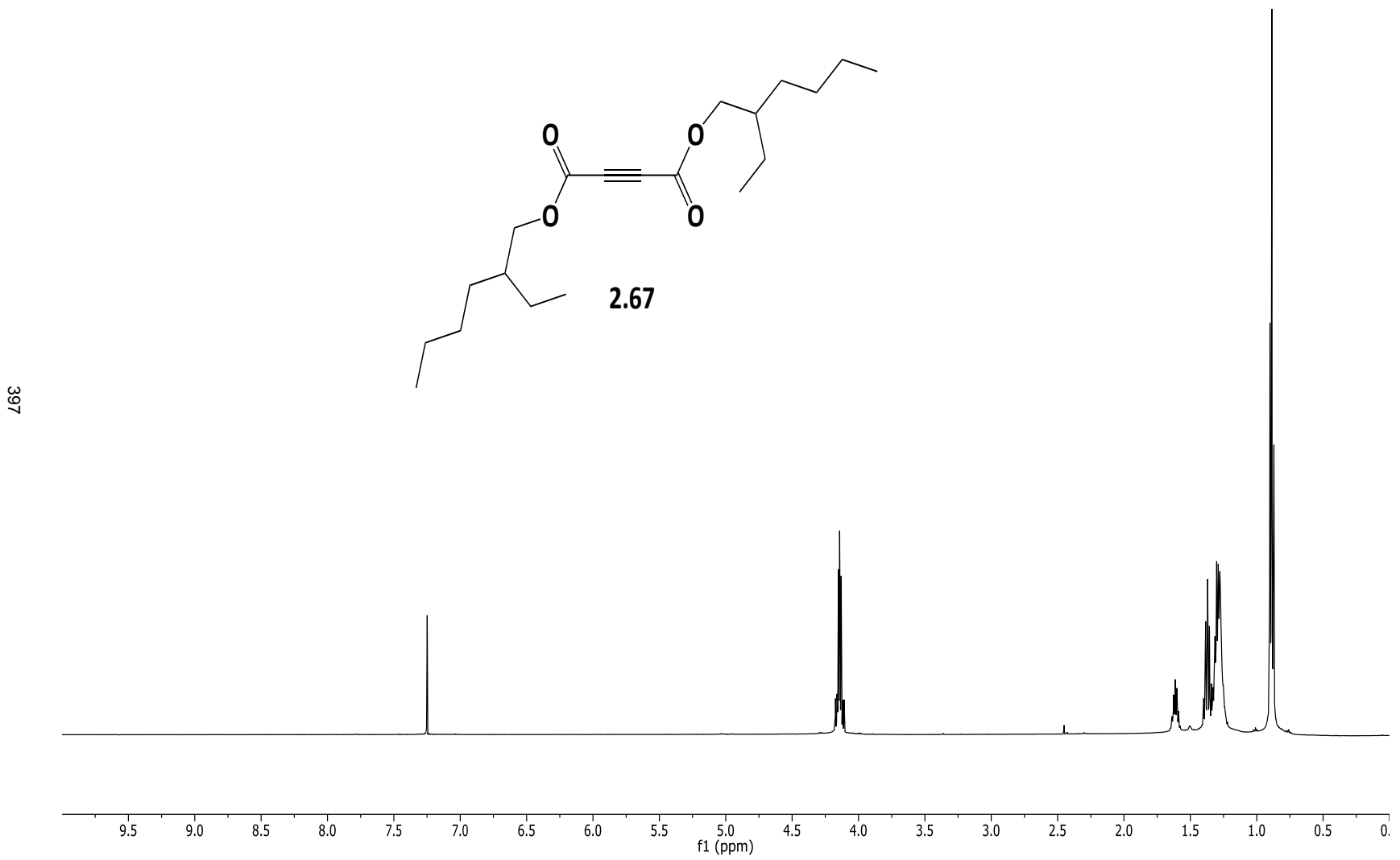
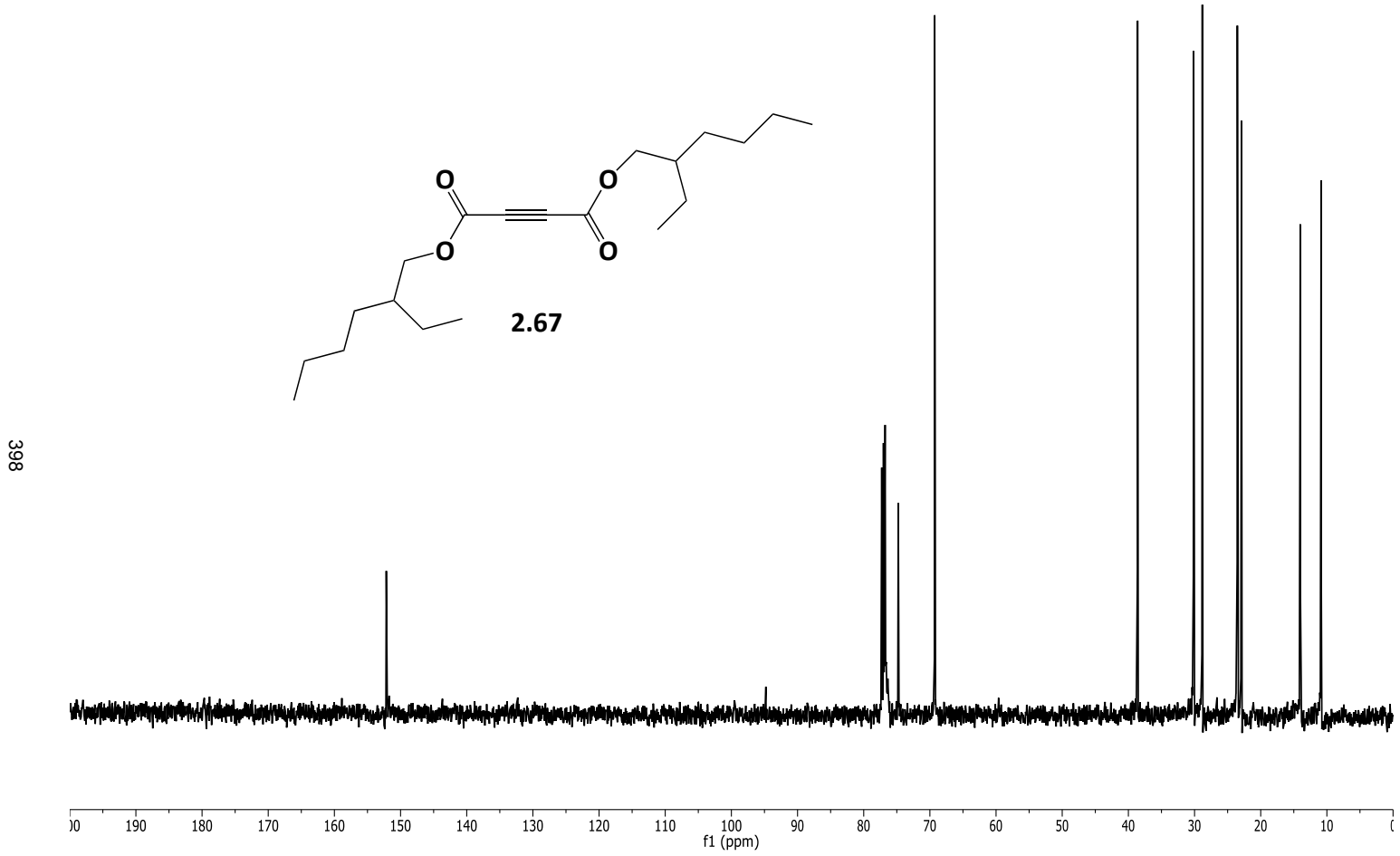
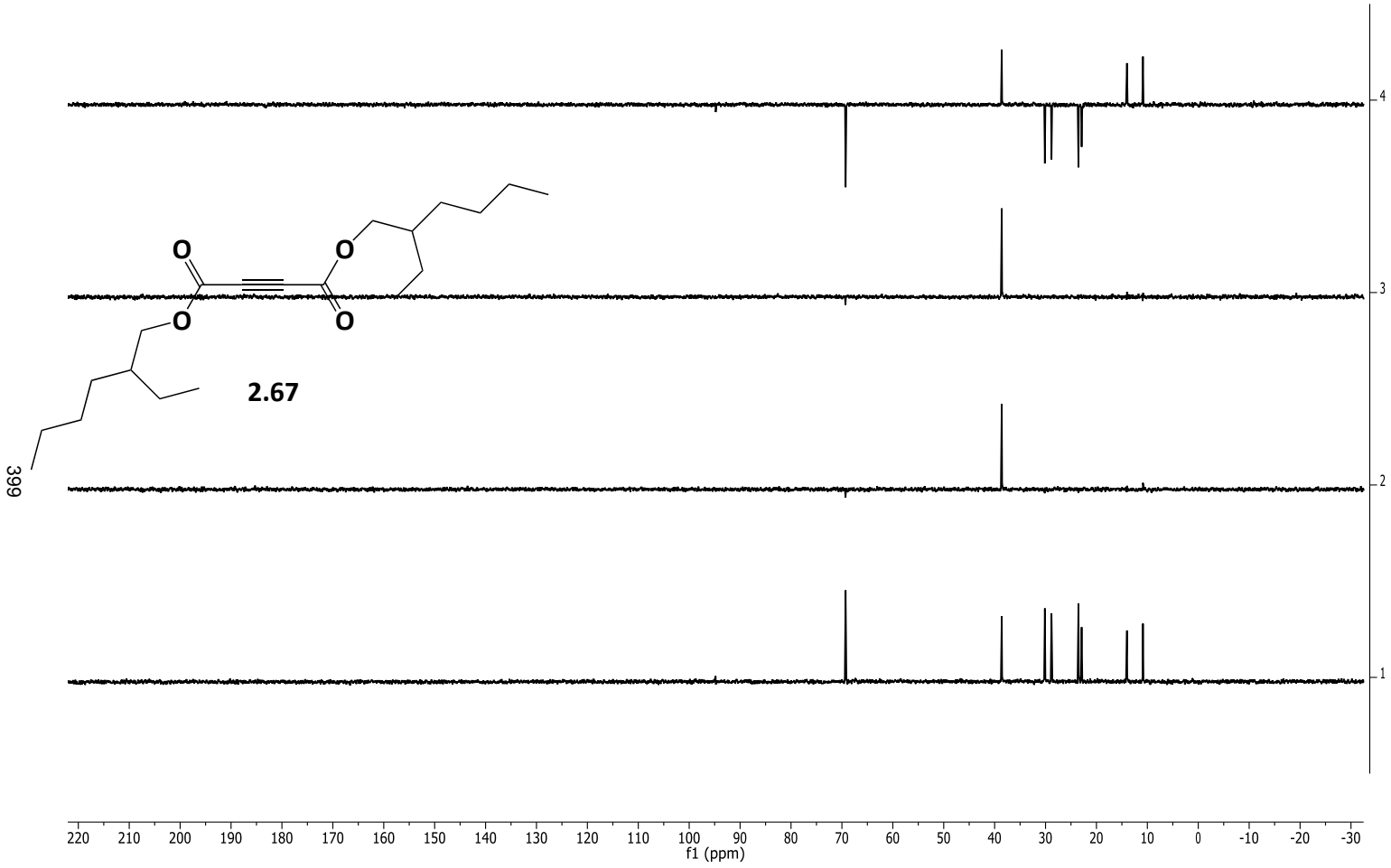
f1 (ppm)

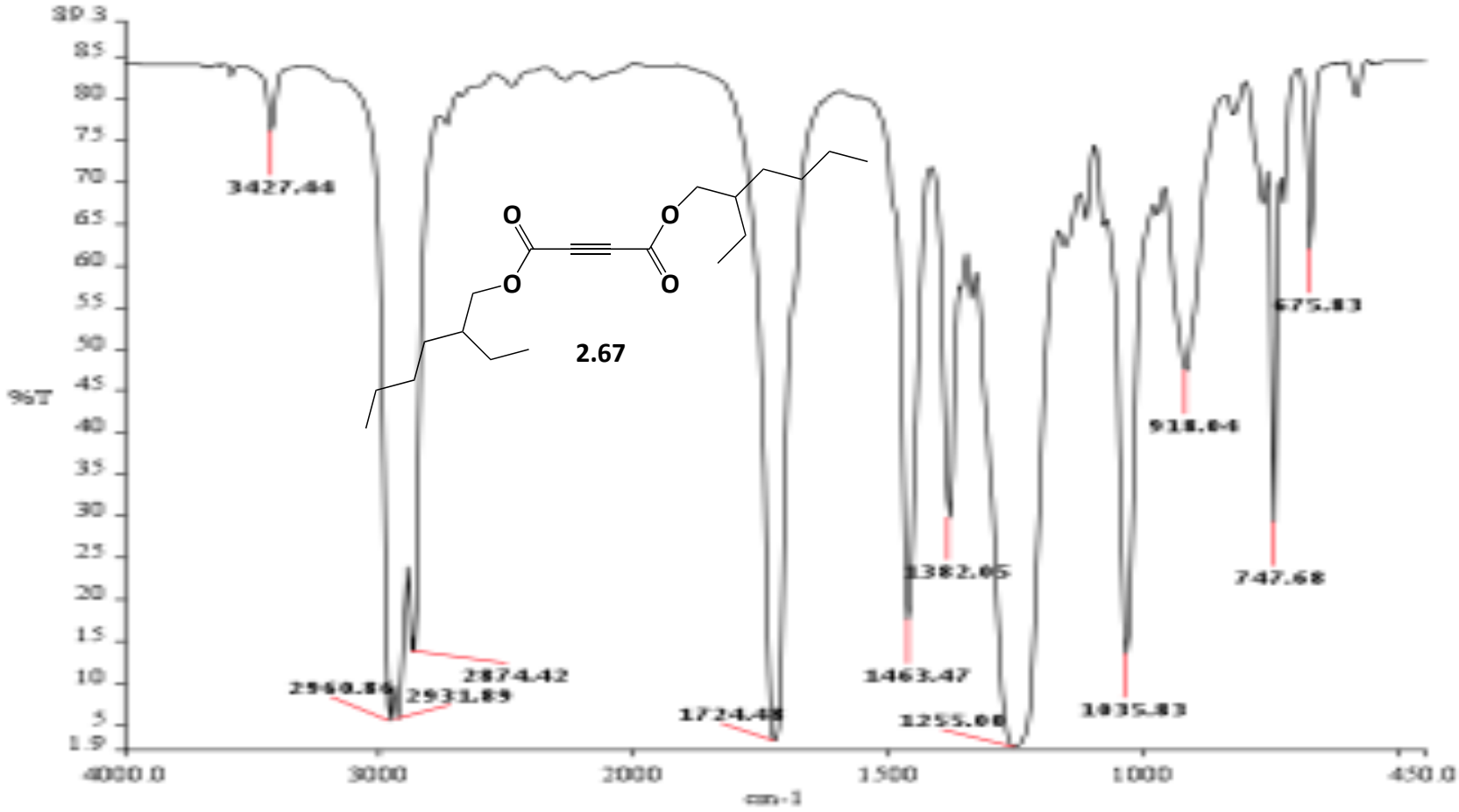

87.1
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
-2.1
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
O
O
O
O
2.66
2963.17
2876.37
1726.59
1466.67
1387.76
1249.66
1059.37
1036.61
929.16
748.33
676.73
500.93


O
O
O
O
2.67
397
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
O
O
O
2.67
398
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
O
O
O
2.67
399
4
3
2
1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

400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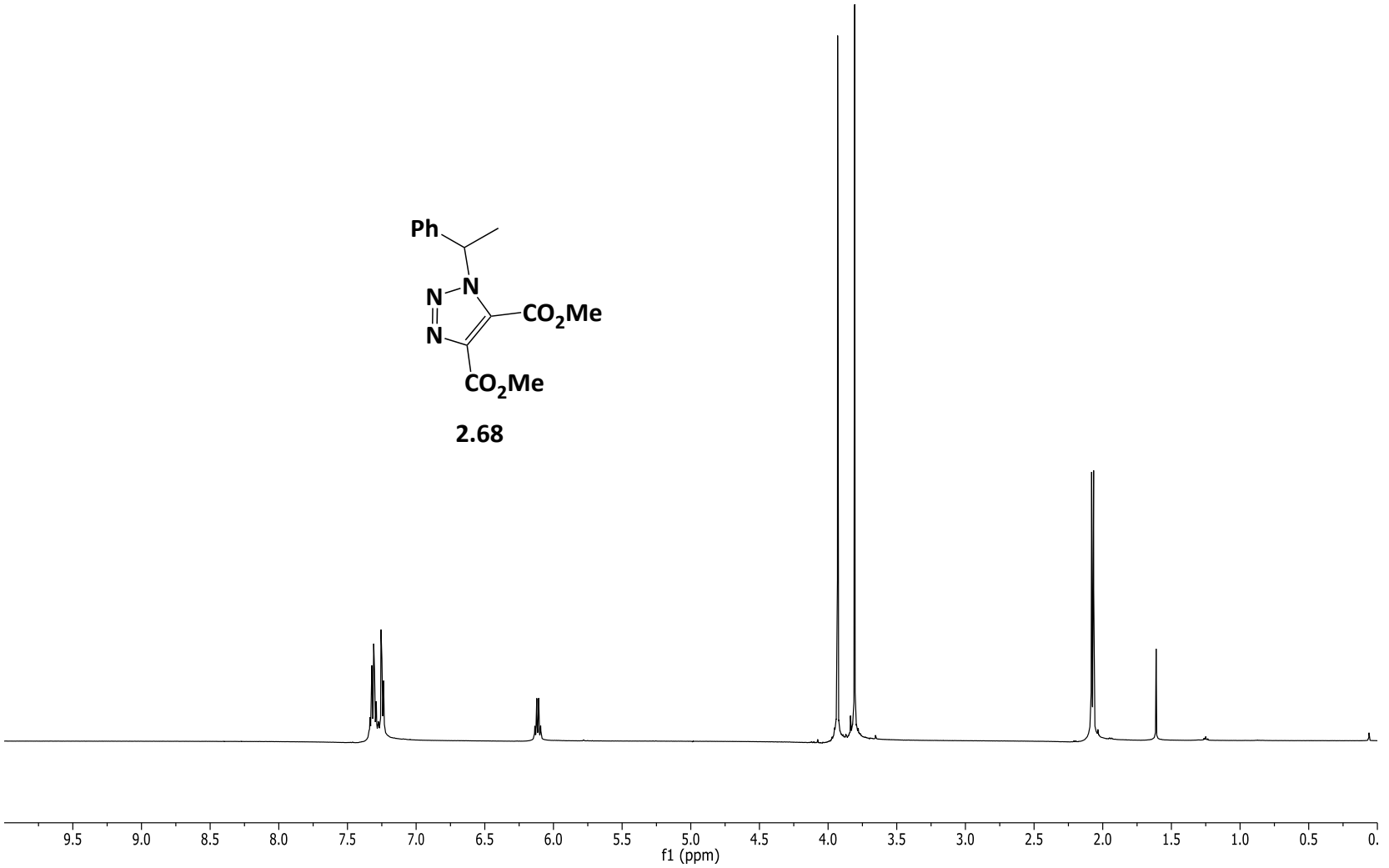
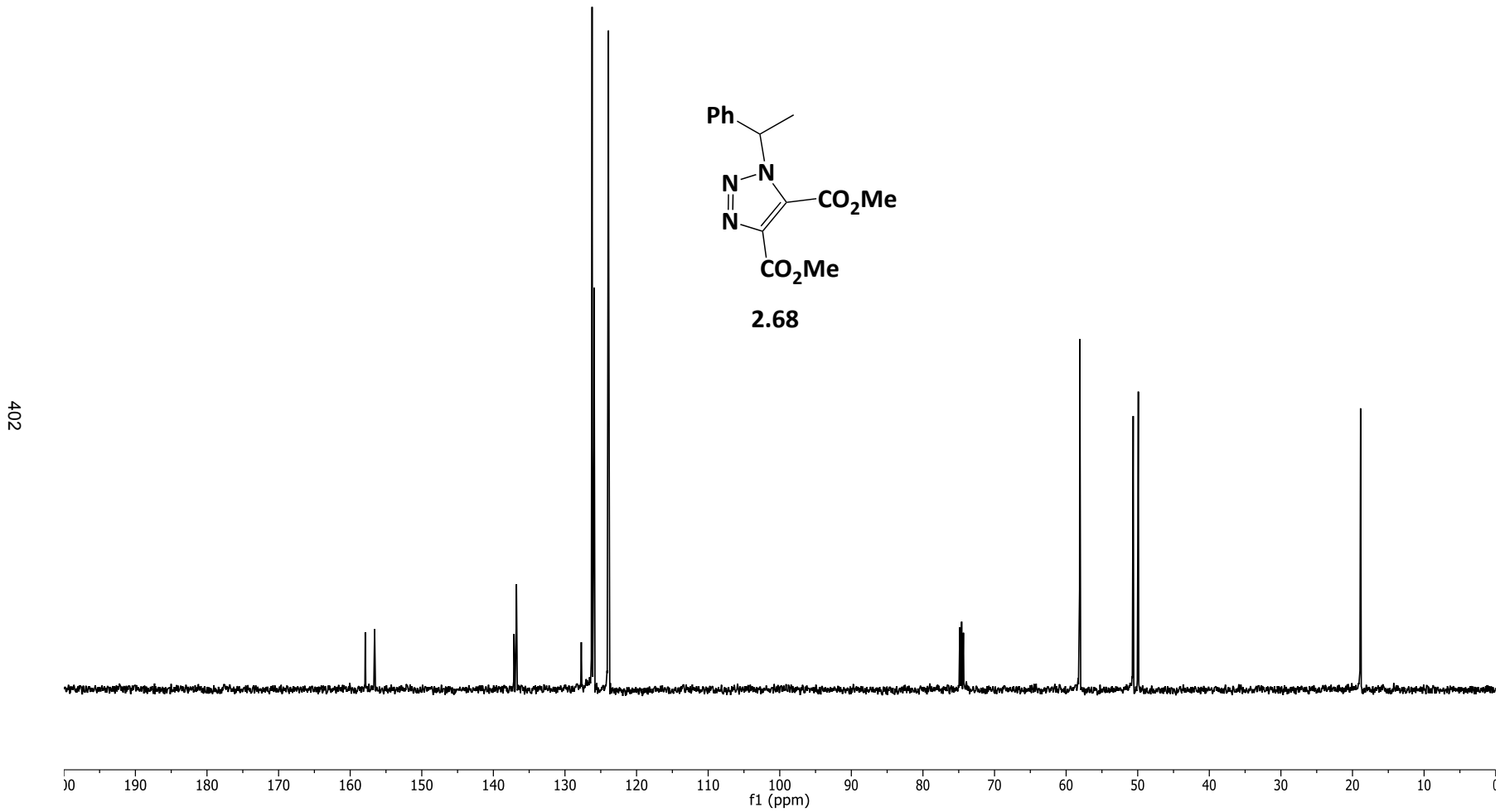
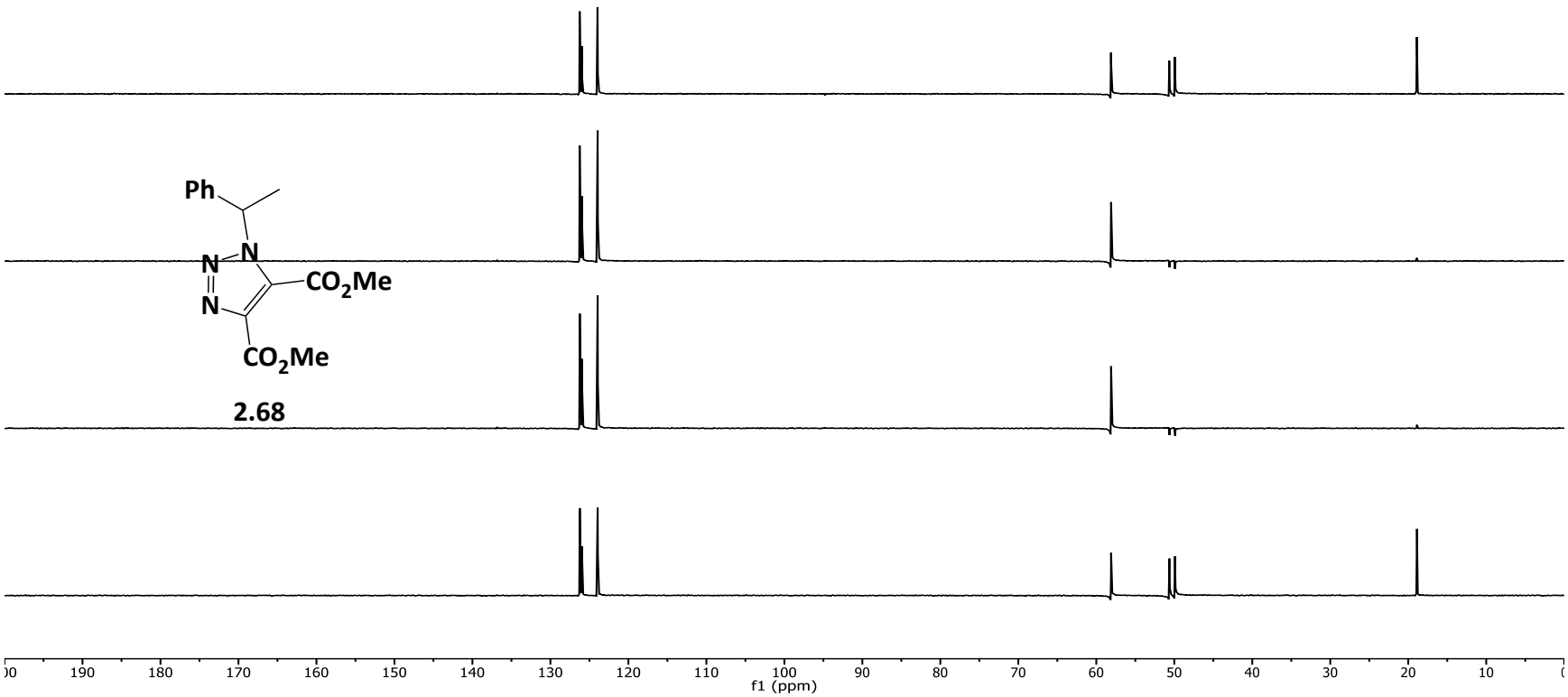
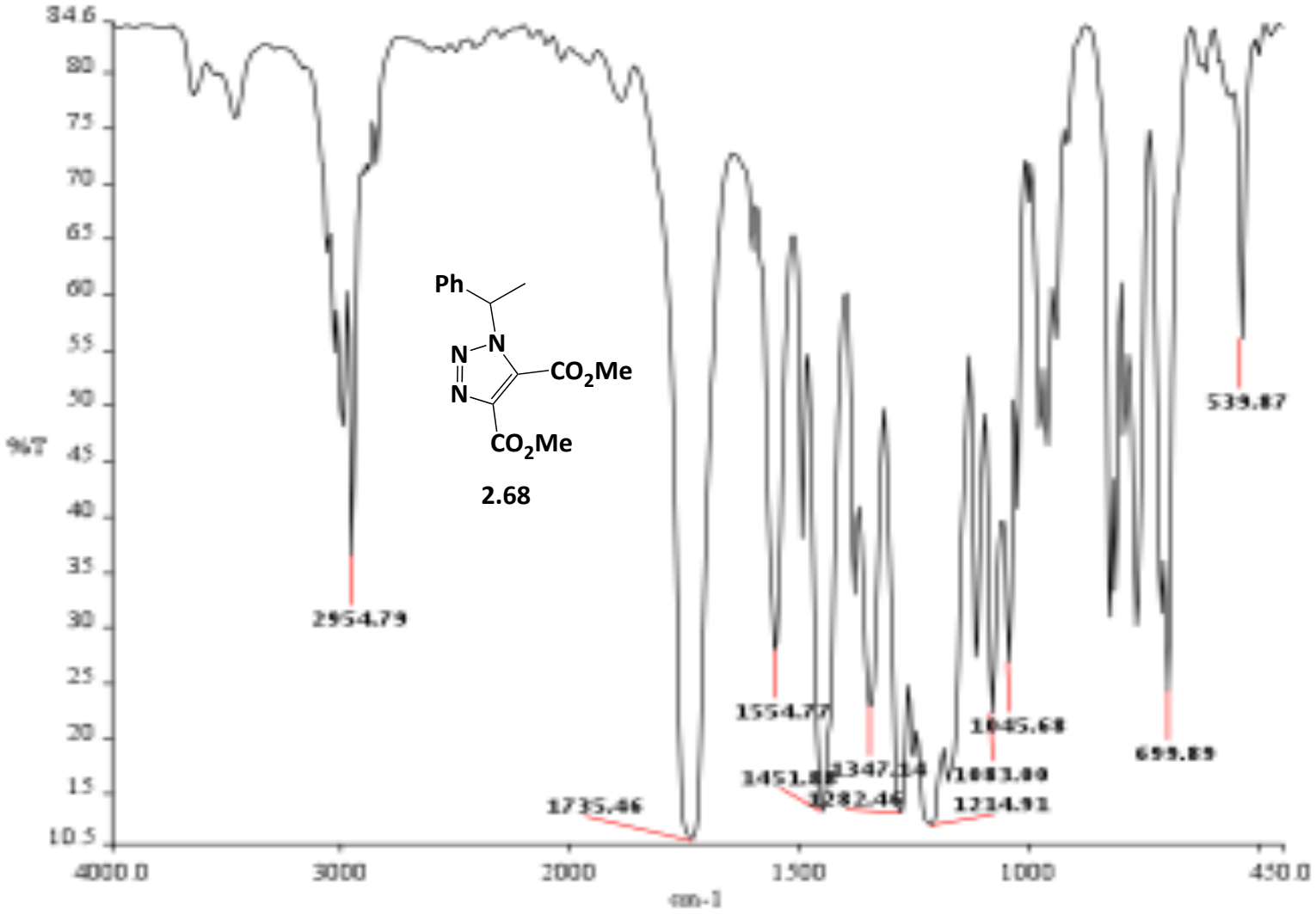
2960.86
2931.89
2874.42
1724.48
1463.47
1382.65
1255.68
1035.83
918.64
747.68
675.83
2.67
%T
cm-1
4000.0
3000
2000
1500
1000
450.0

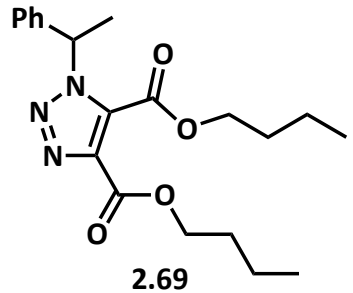

Ph
N
N
N
CO2Me
CO2Me
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

2.68

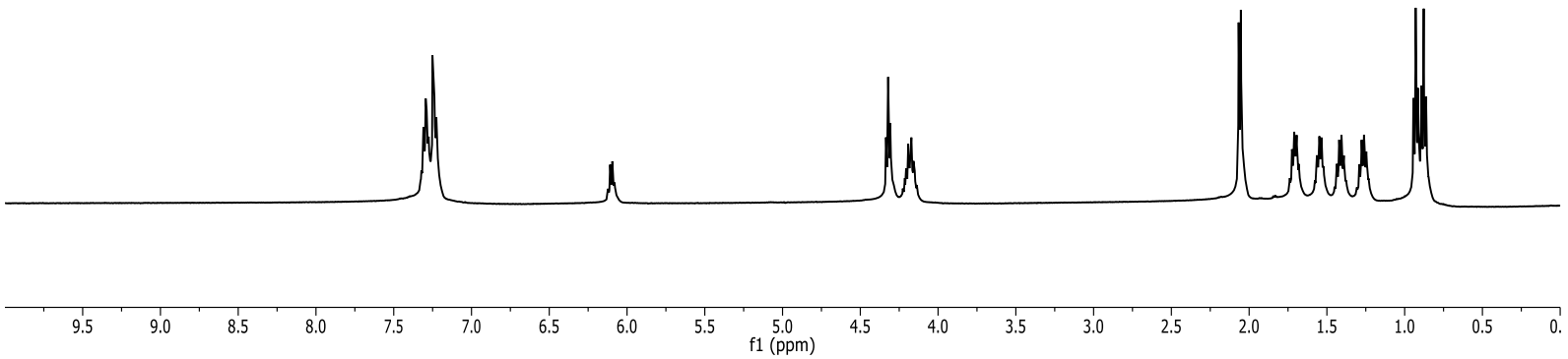

Ph
N
N
N
CO2Me
CO2Me
2.68
402
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

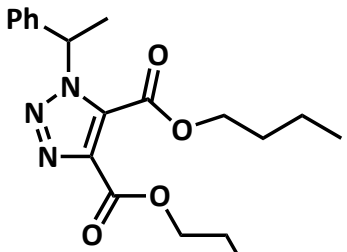

Ph
N
N
N
CO2Me
CO2Me
2.68
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Ph
N
N
N
CO2Me
CO2Me
2.68
%T
2954.79
1735.46
1554.77
1451.88
1347.14
1282.46
1214.91
1083.80
1045.68
699.89
539.87
4000.0
3000
2000
1500
1000
450.0
cm-1

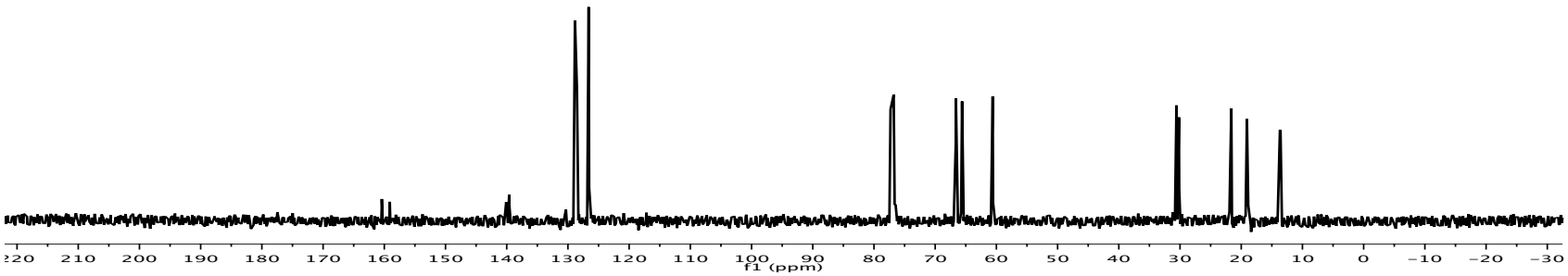

Ph
N
N
N
O
O
O
O

2.69

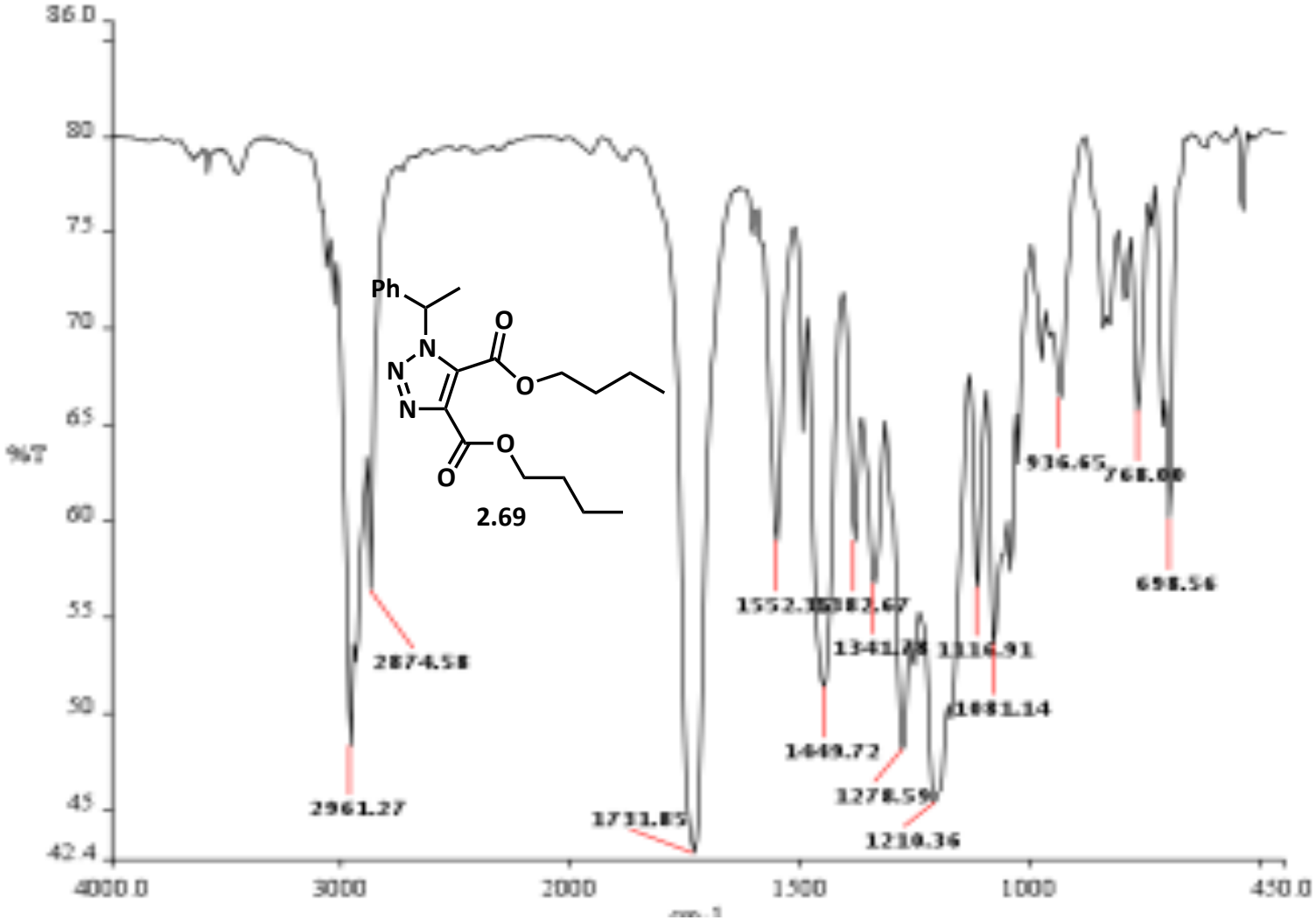

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

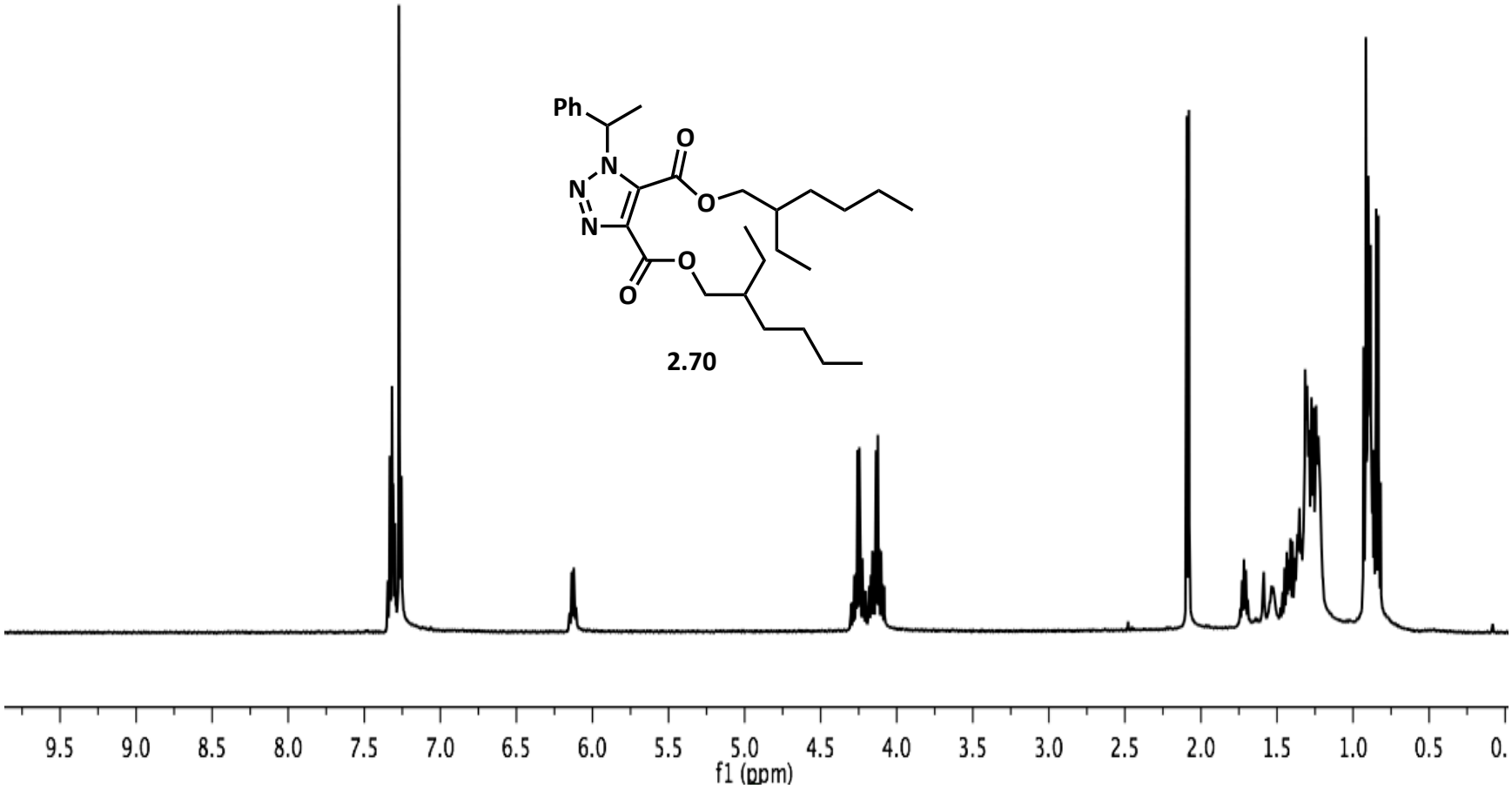

Ph
N
N
N
O
O
O
O

2.69

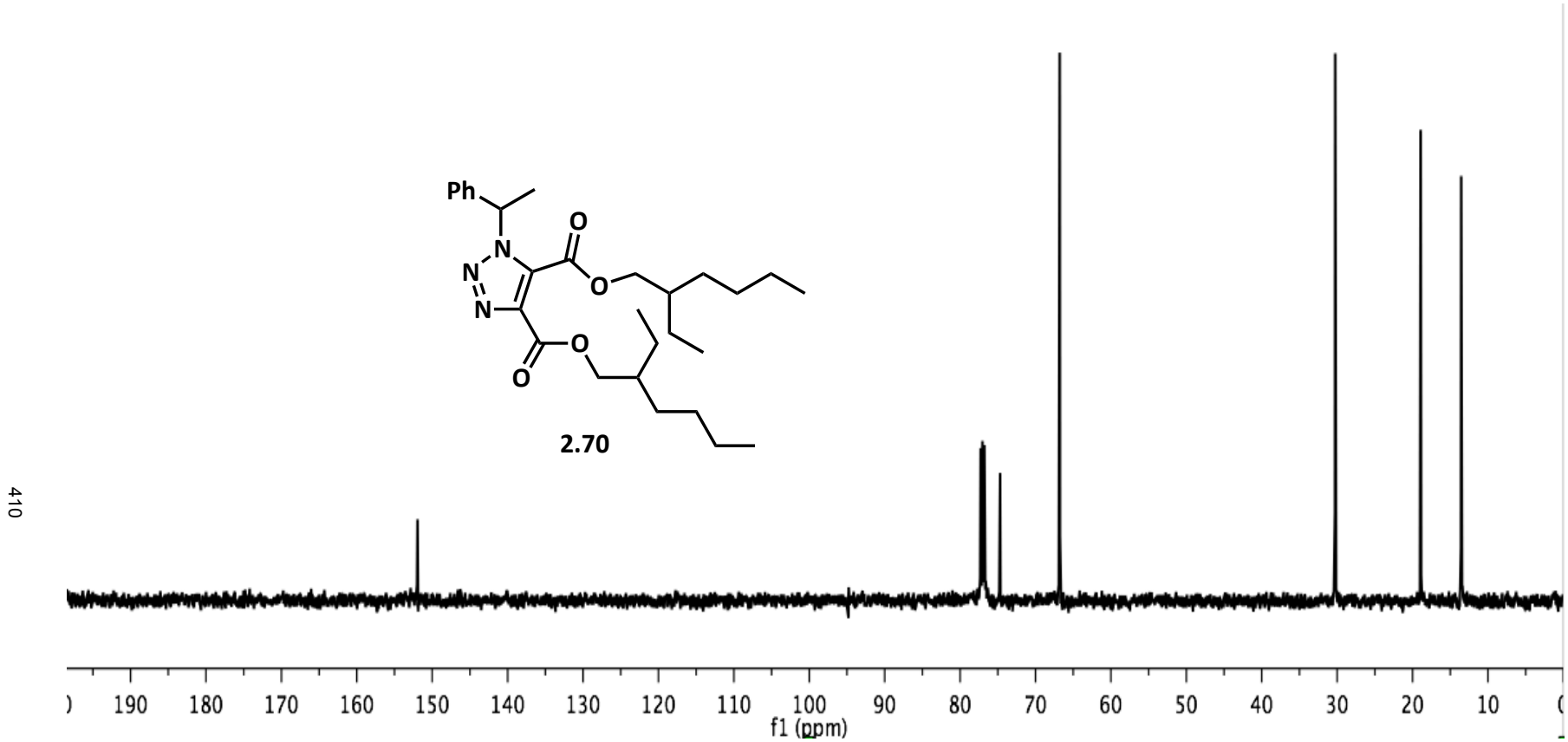

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

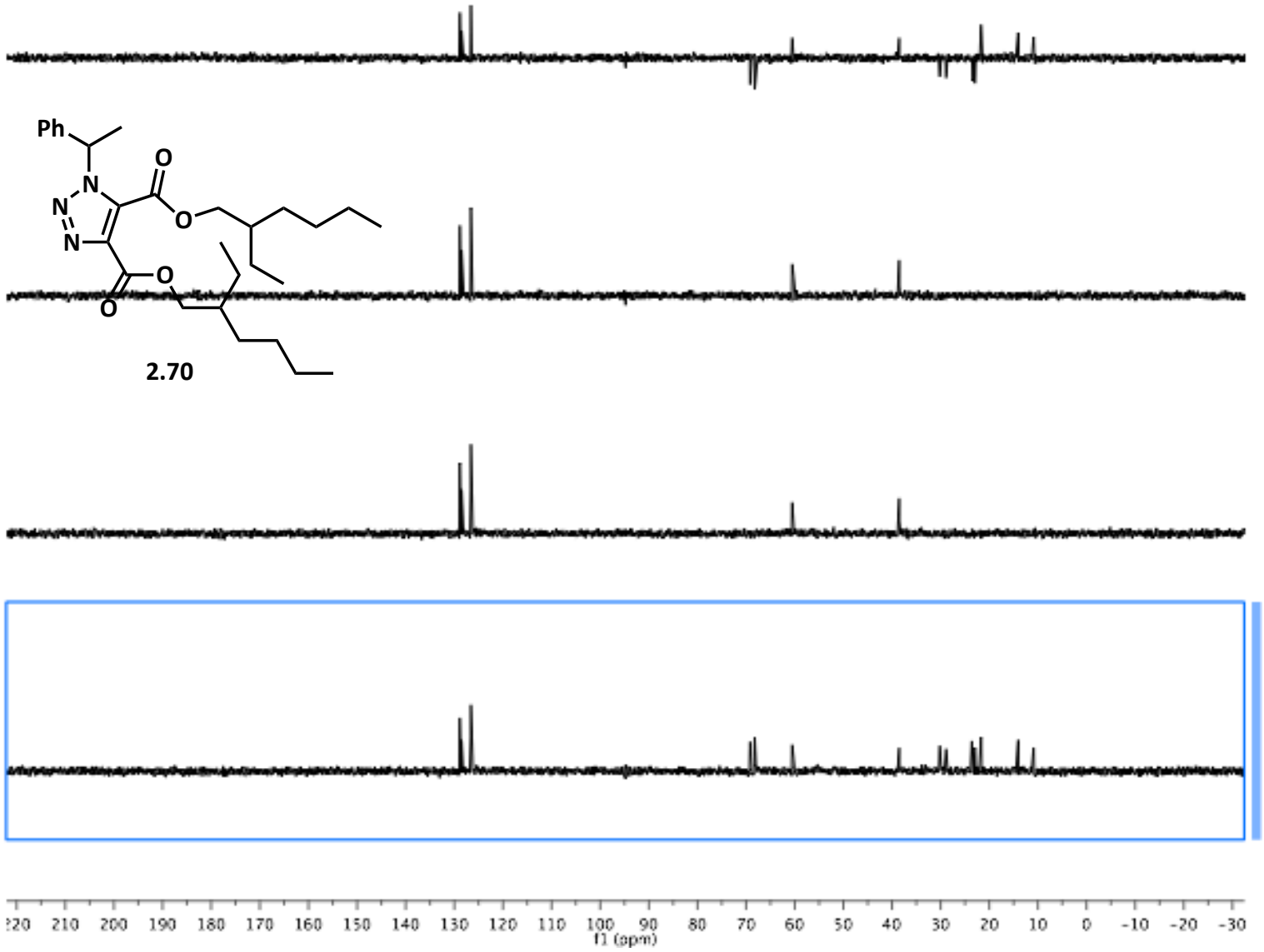
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

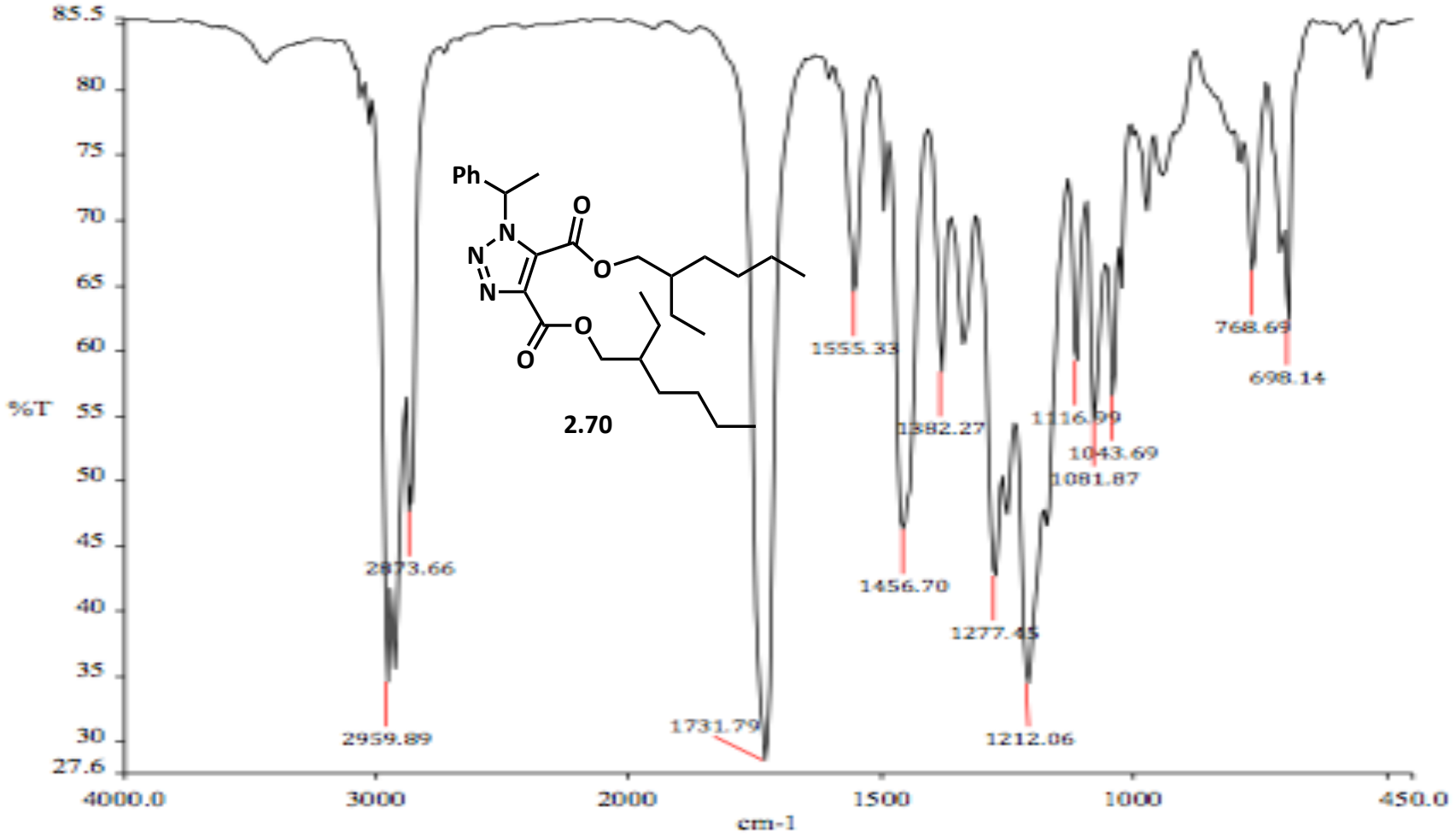

86.0
80
75
70
65
60
55
50
45
42.4
%T
4000.0
3000
2000
1500
1000
450.0
Ph
N
N
N
O
O
O
O
2.69
2961.27
2874.58
1731.85
1552.35
1497.67
1449.72
1341.28
1316.91
1278.59
1210.36
1081.14
936.65
768.00
698.56

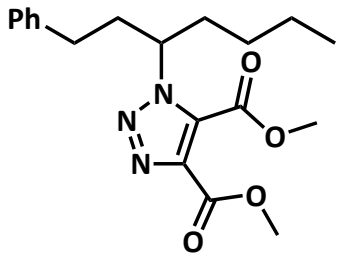

Ph
N
N
N
O
O
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

2.70


Ph
N
N
N
O
O
O
O
2.70
410
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

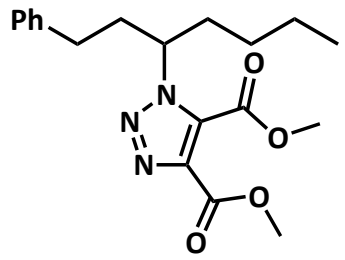

Ph
N
N
N
O
O
O
O
2.70
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


85.5
80
75
70
65
60
55
50
45
40
35
30
27.6
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
Ph
N
N
N
O
O
O
O
2.70
2873.66
2959.89
1731.79
1555.33
1382.27
1456.70
1277.45
1212.06
1116.99
1081.87
1043.69
768.69
698.14

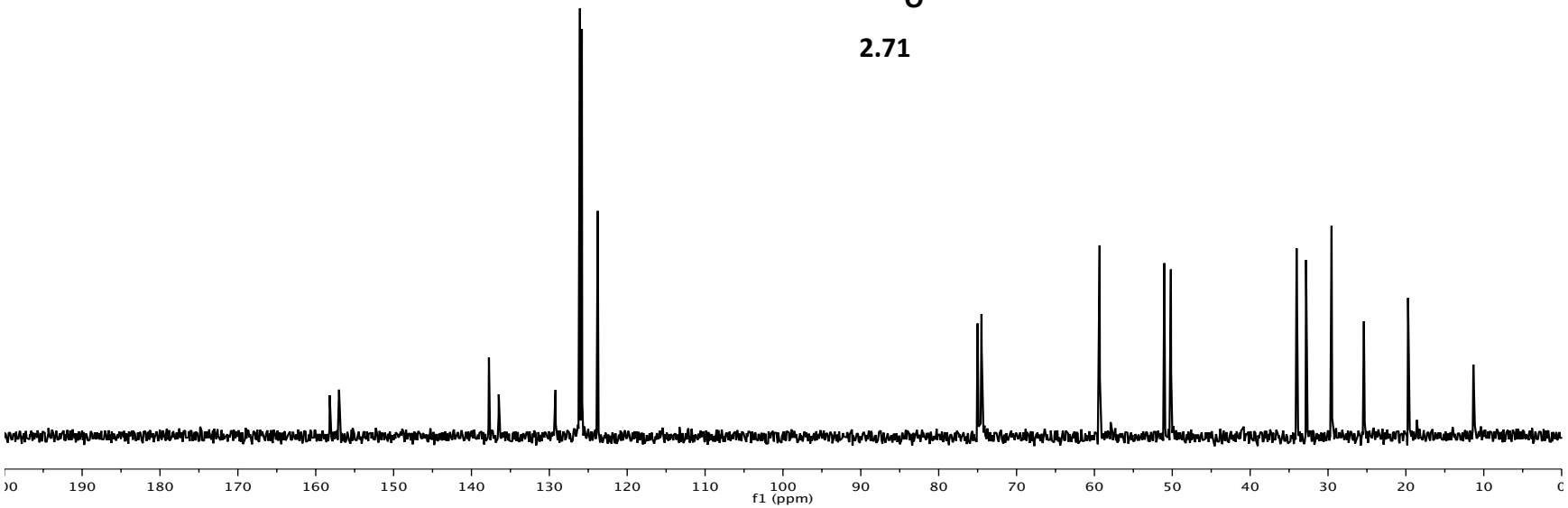

Ph
N
N
N
O
O
O
O

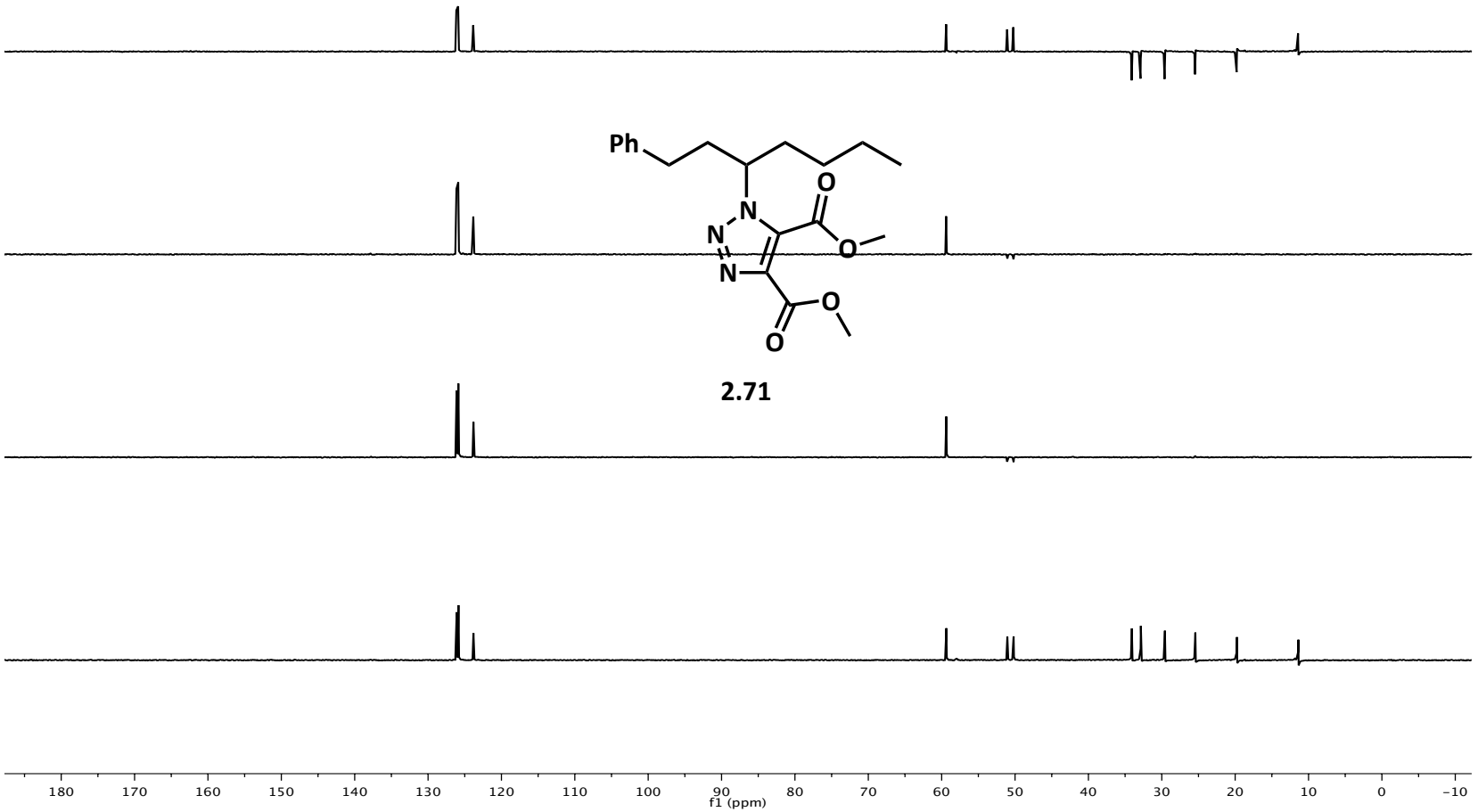
2.71

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

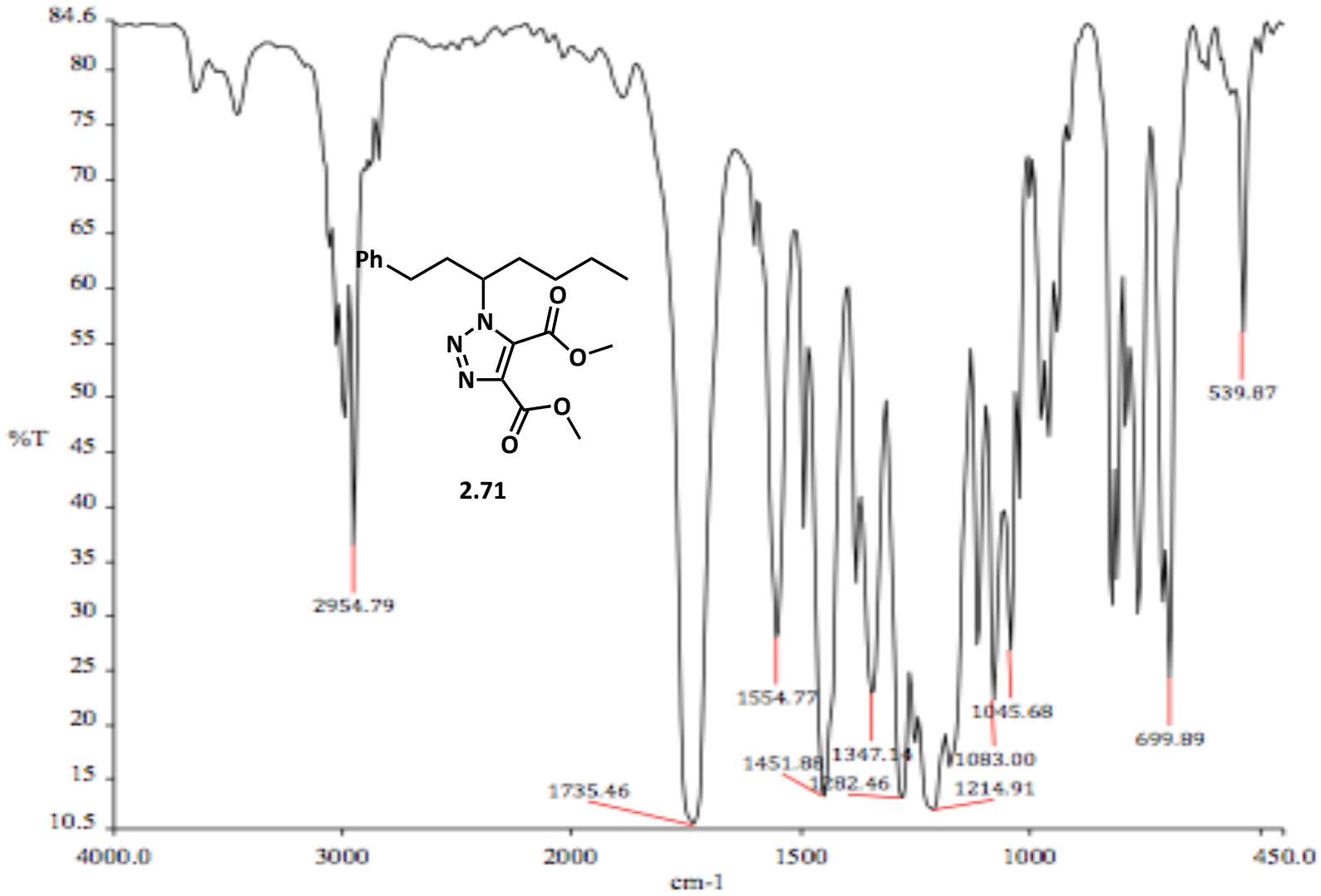

Ph
N
N
N
O
O
O
O

2.71

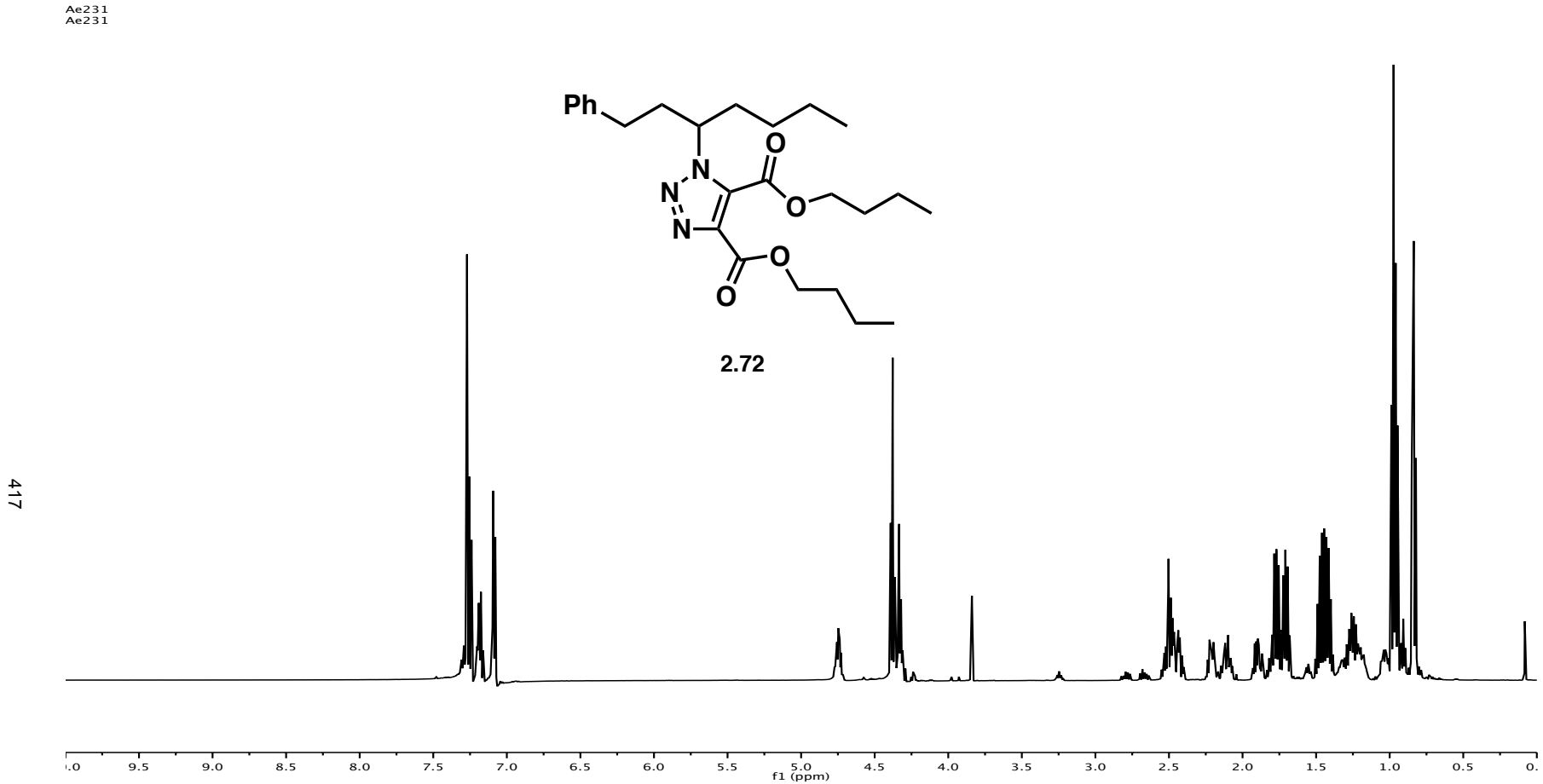

190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10

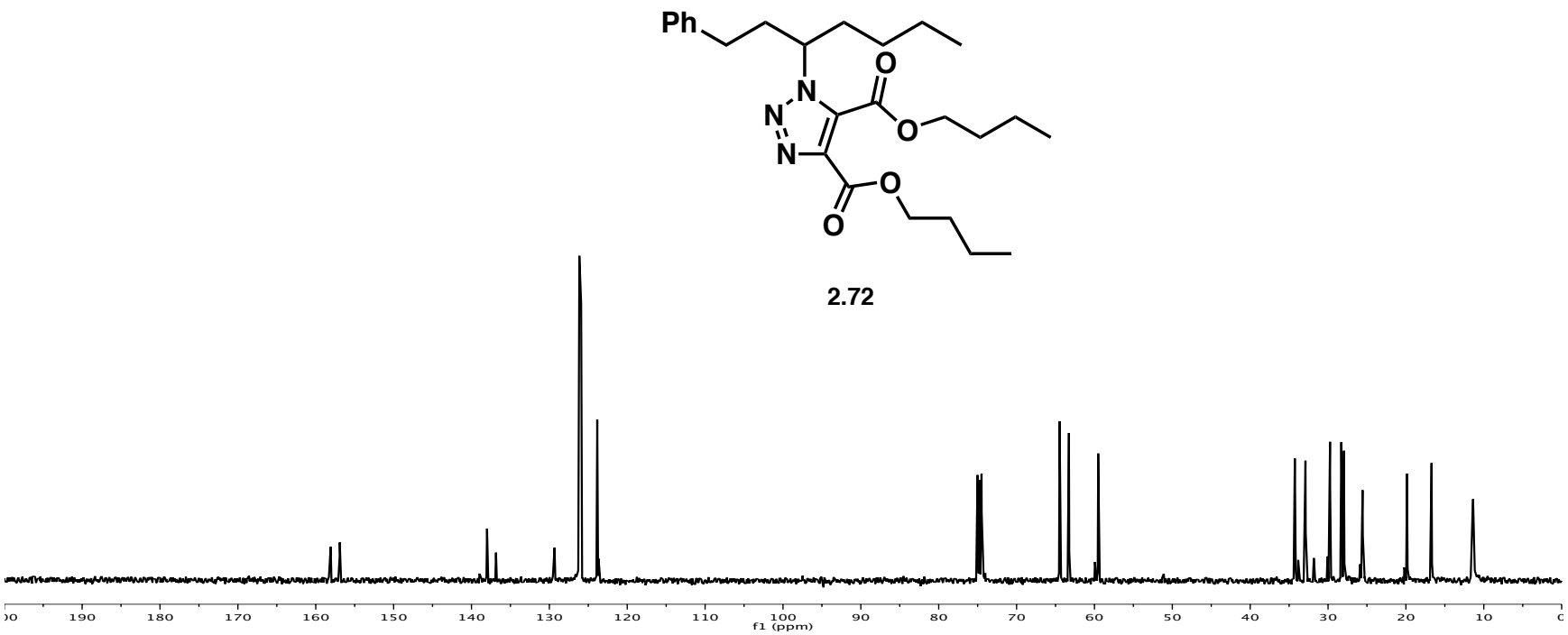

Ph
N
N
N
O
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

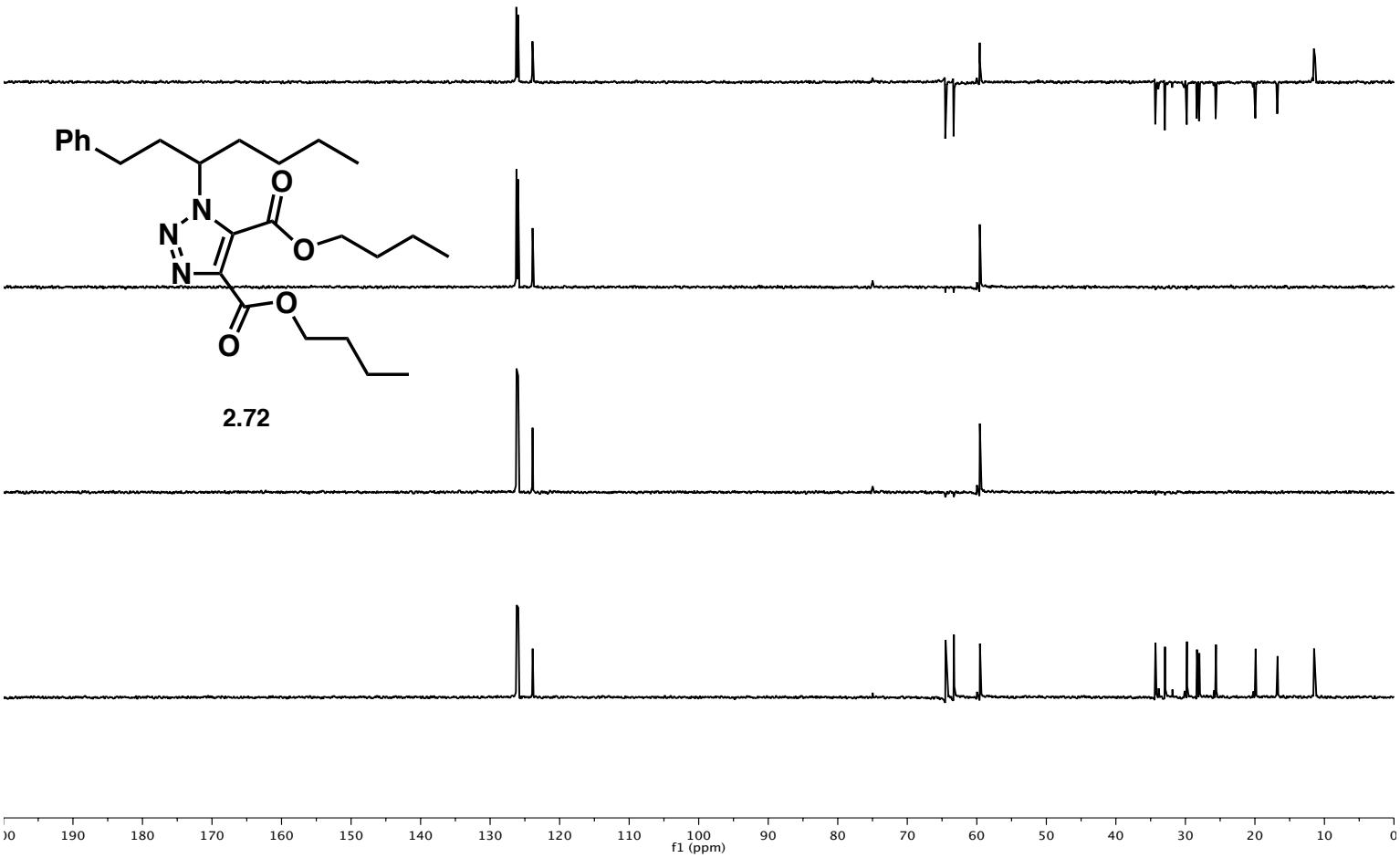
2.71

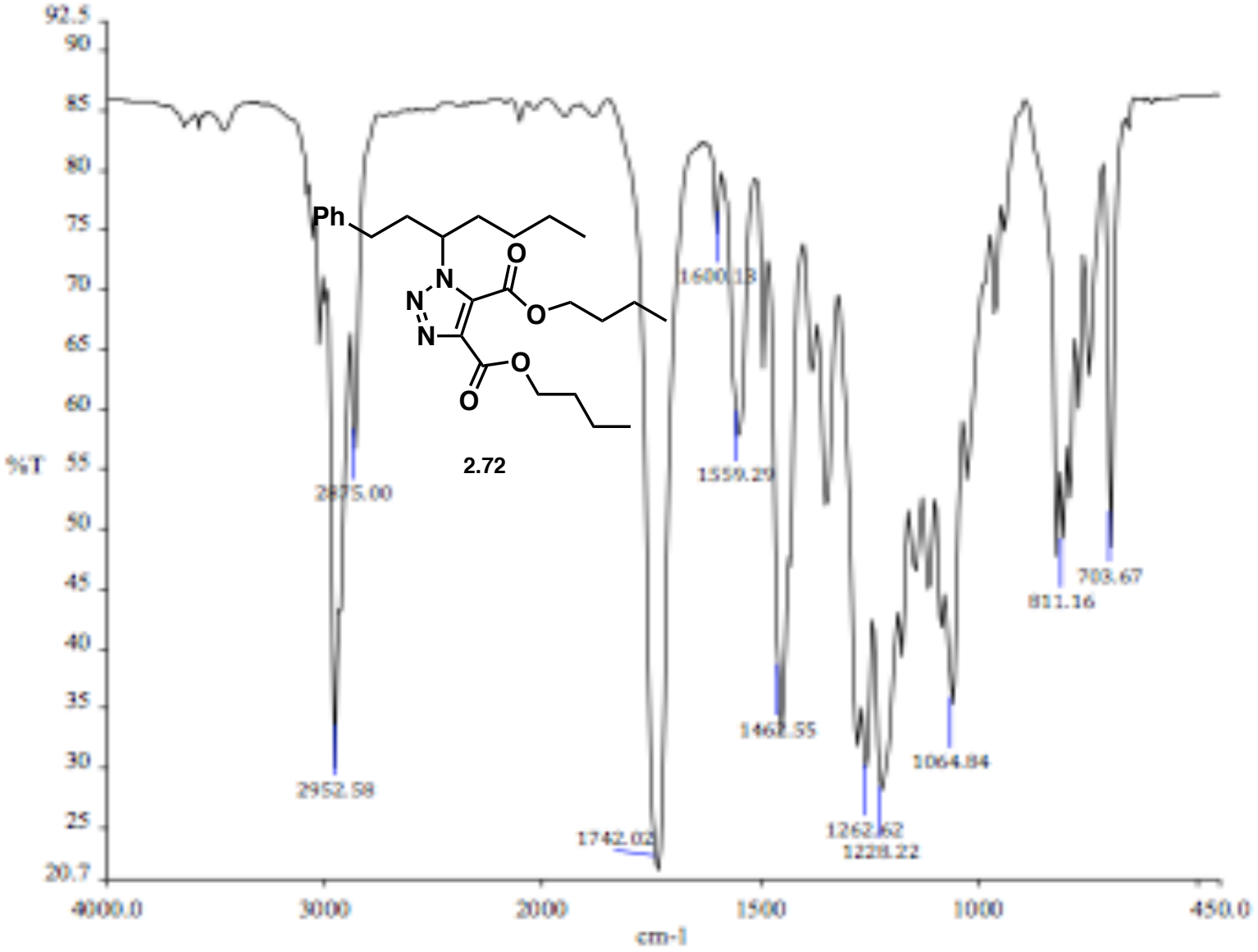

84.6
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.5
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
Ph
N
N
N
O
O
O
O
2954.79
1735.46
1554.77
1451.88
1347.14
1282.46
1214.91
1083.00
1045.68
699.89
539.87

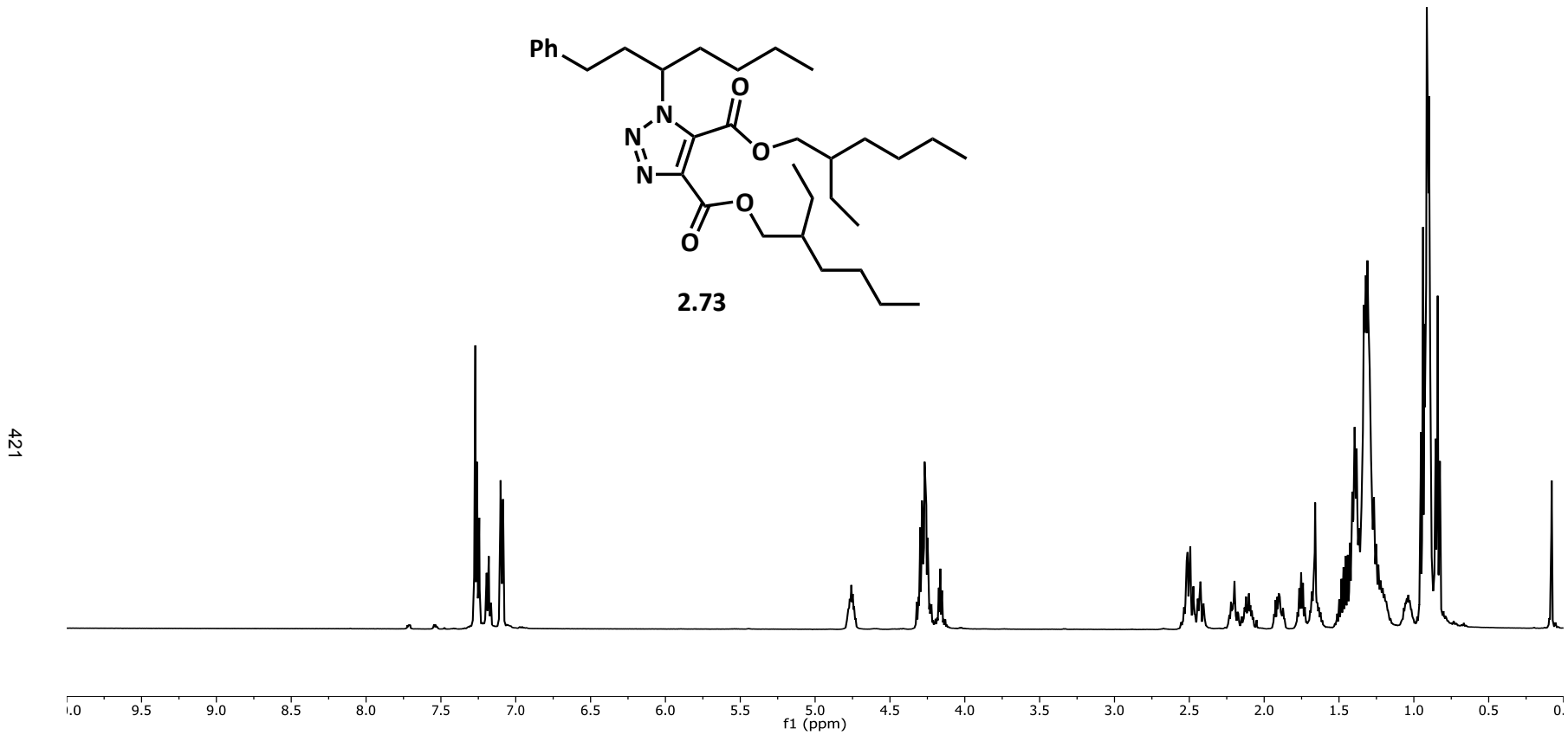
2.71

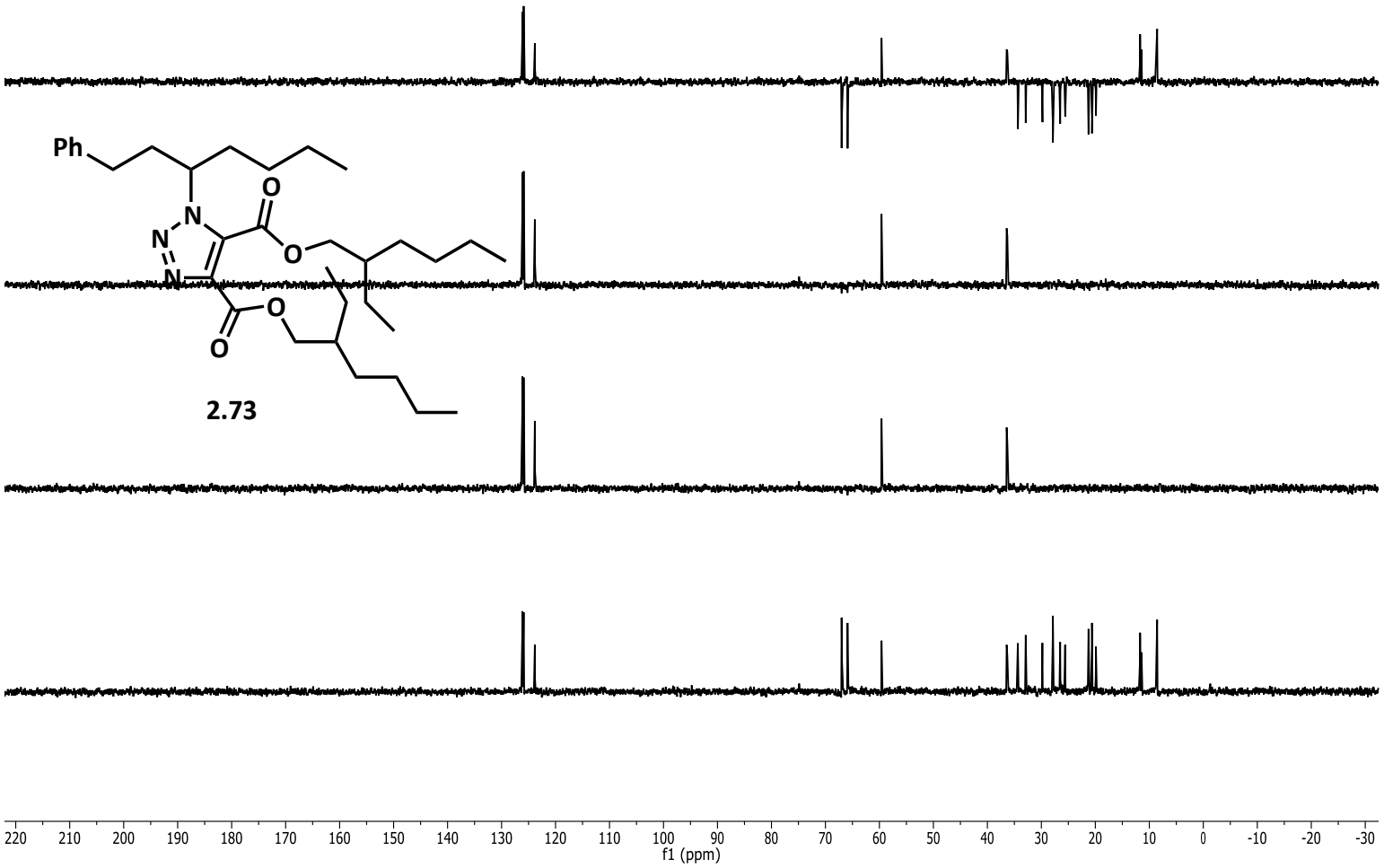

Ae231
Ae231
Ph
N
N
N
O
O
O
O
2.72
417
f1 (ppm)

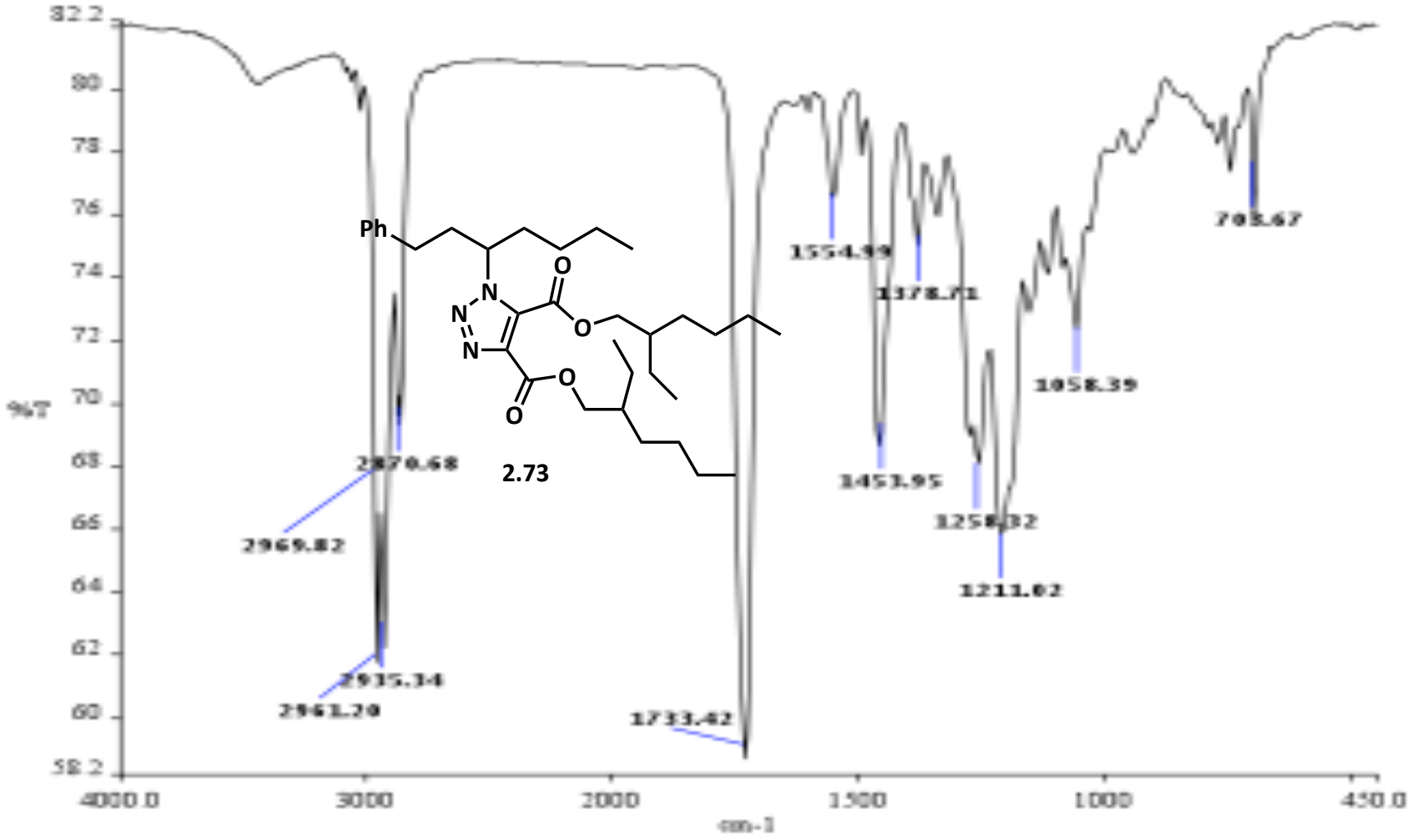

Ph
N
N
N
O
O
O
O
2.72
418
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

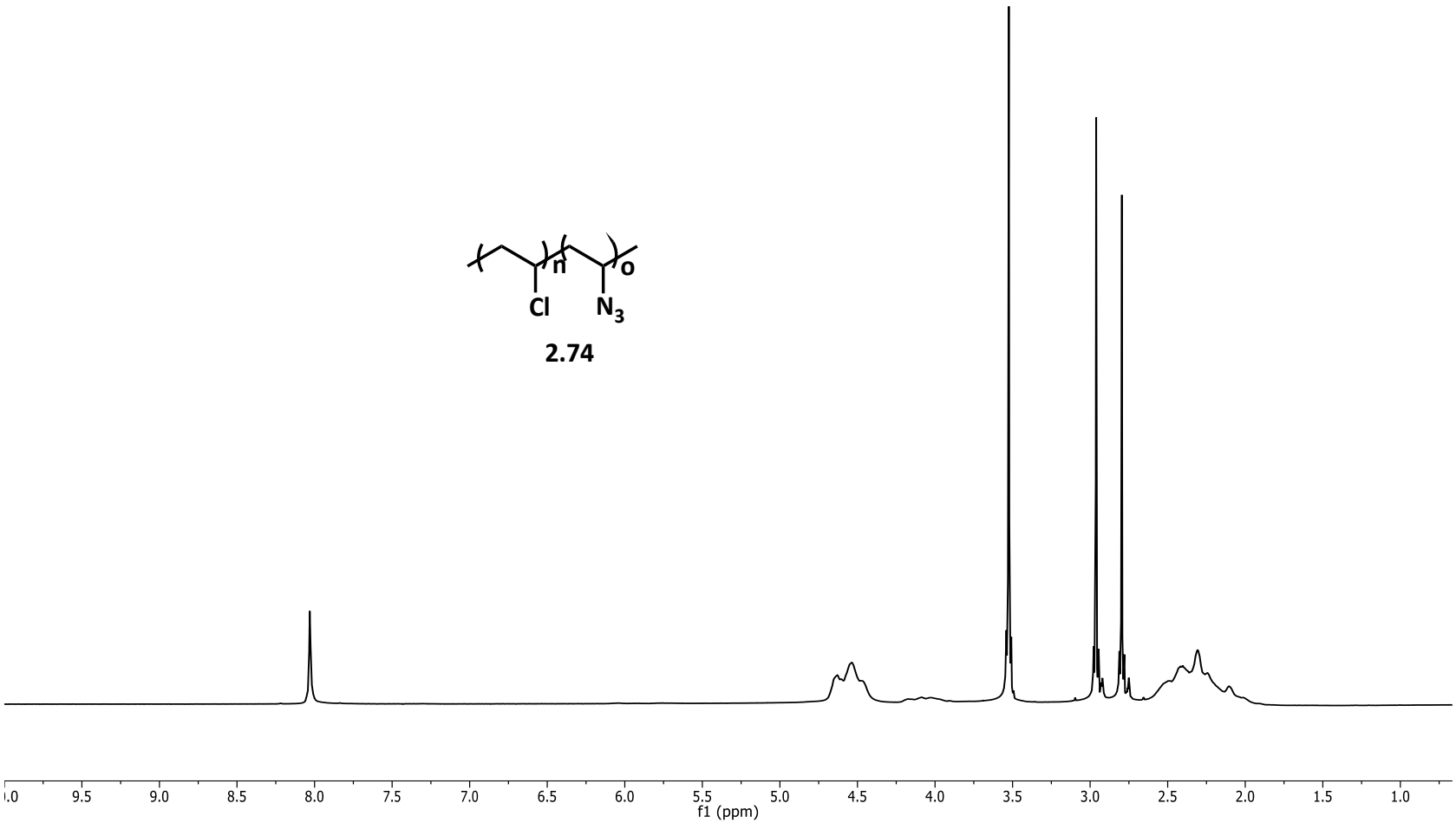

Ph
N
N
N
O
O
O
O
2.72
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

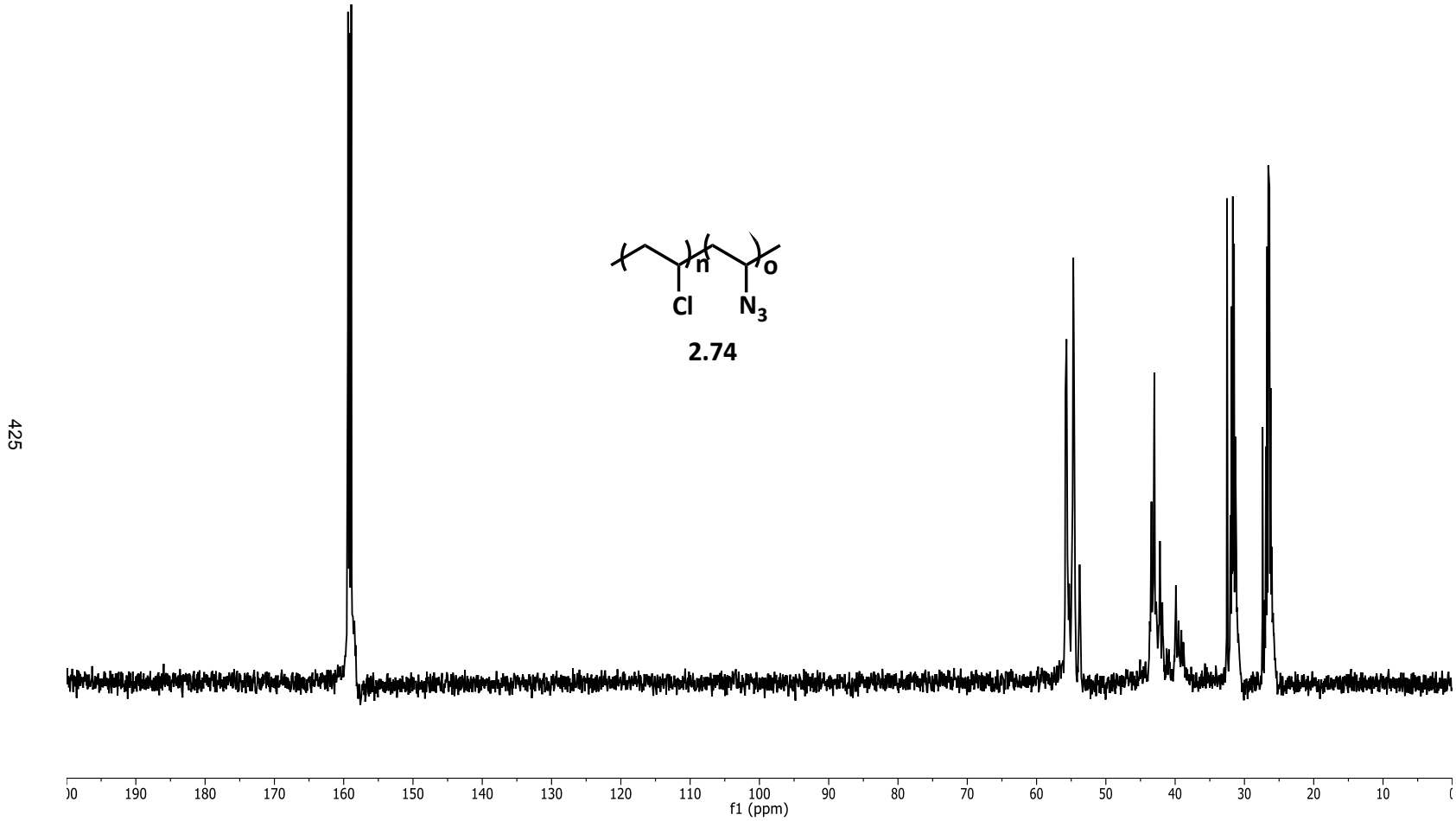

92.5
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20.7
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
Ph
N
N
N
O
O
O
O
2.72
2875.00
2952.58
1742.02
1600.13
1559.29
1462.55
1262.62
1228.22
1064.84
811.16
703.67

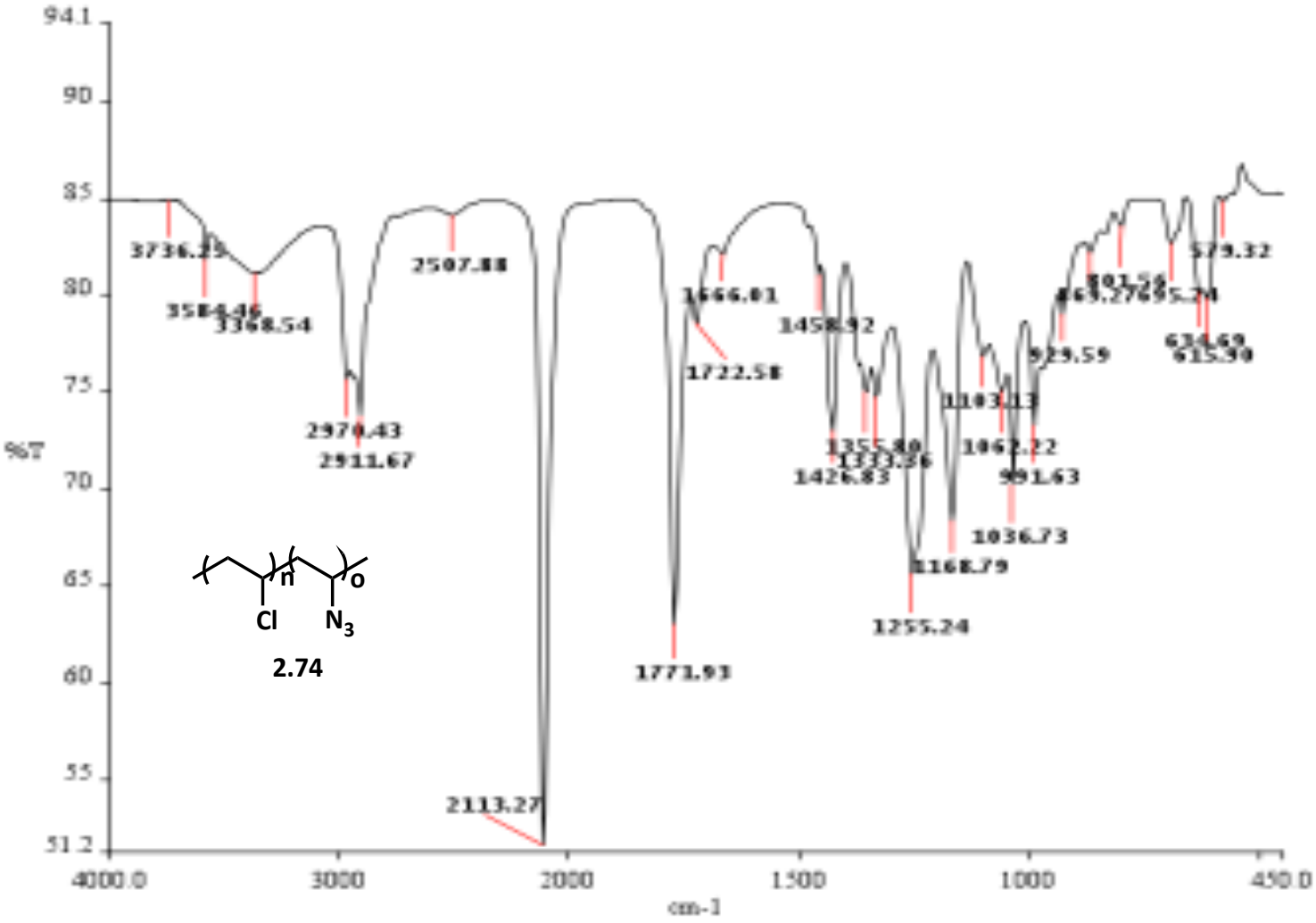

Ph
N
N
N
O
O
O
O
2.73
421
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Ph
N
N
N
O
O
O
O
2.73
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

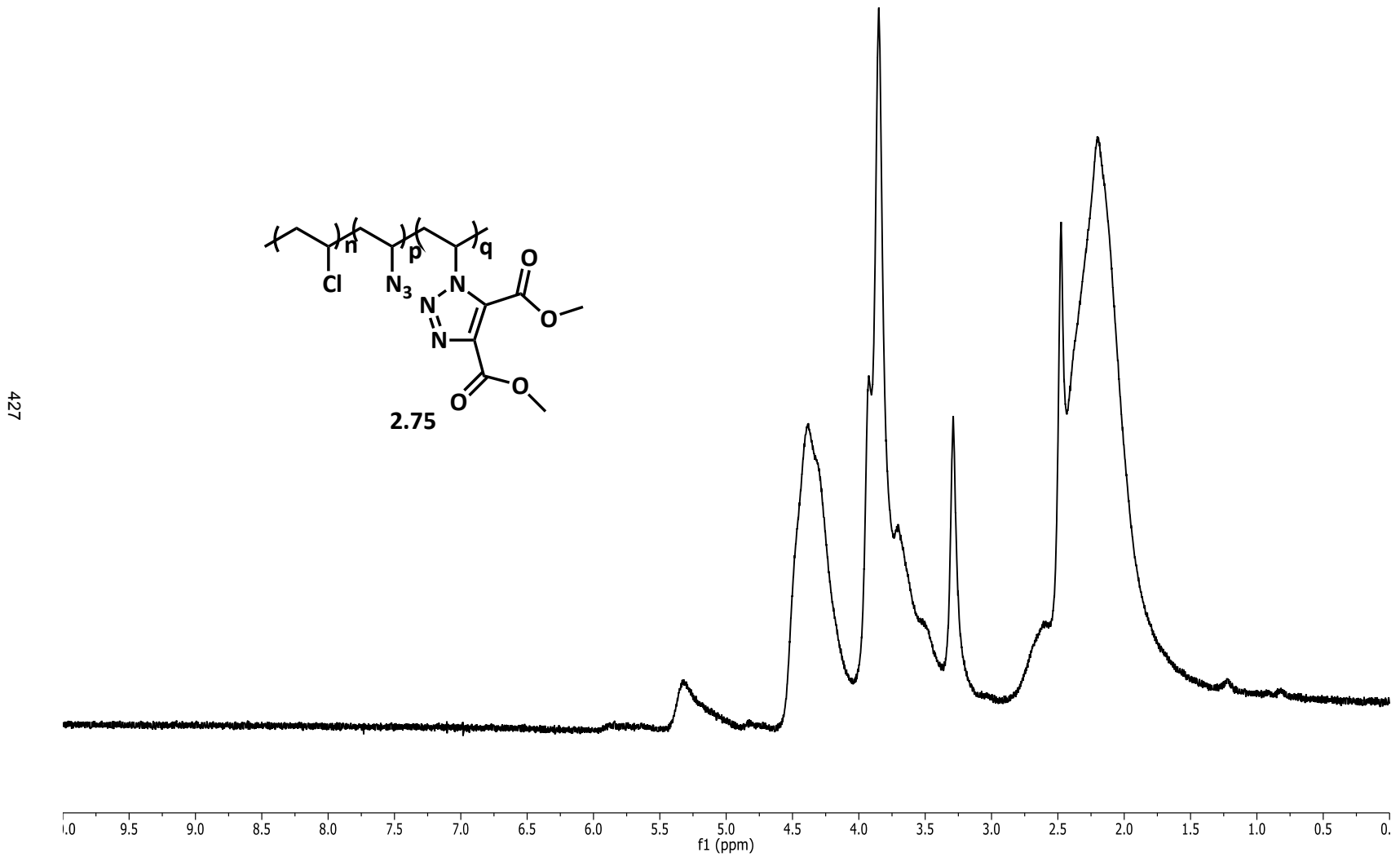

82.2
80
78
76
74
72
70
68
66
64
62
60
58.2
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
Ph
N
N
N
O
O
O
O
2.73
2870.68
2969.82
2935.34
2961.20
1733.42
1554.99
1378.71
1451.95
1258.32
1211.02
1058.39
705.67

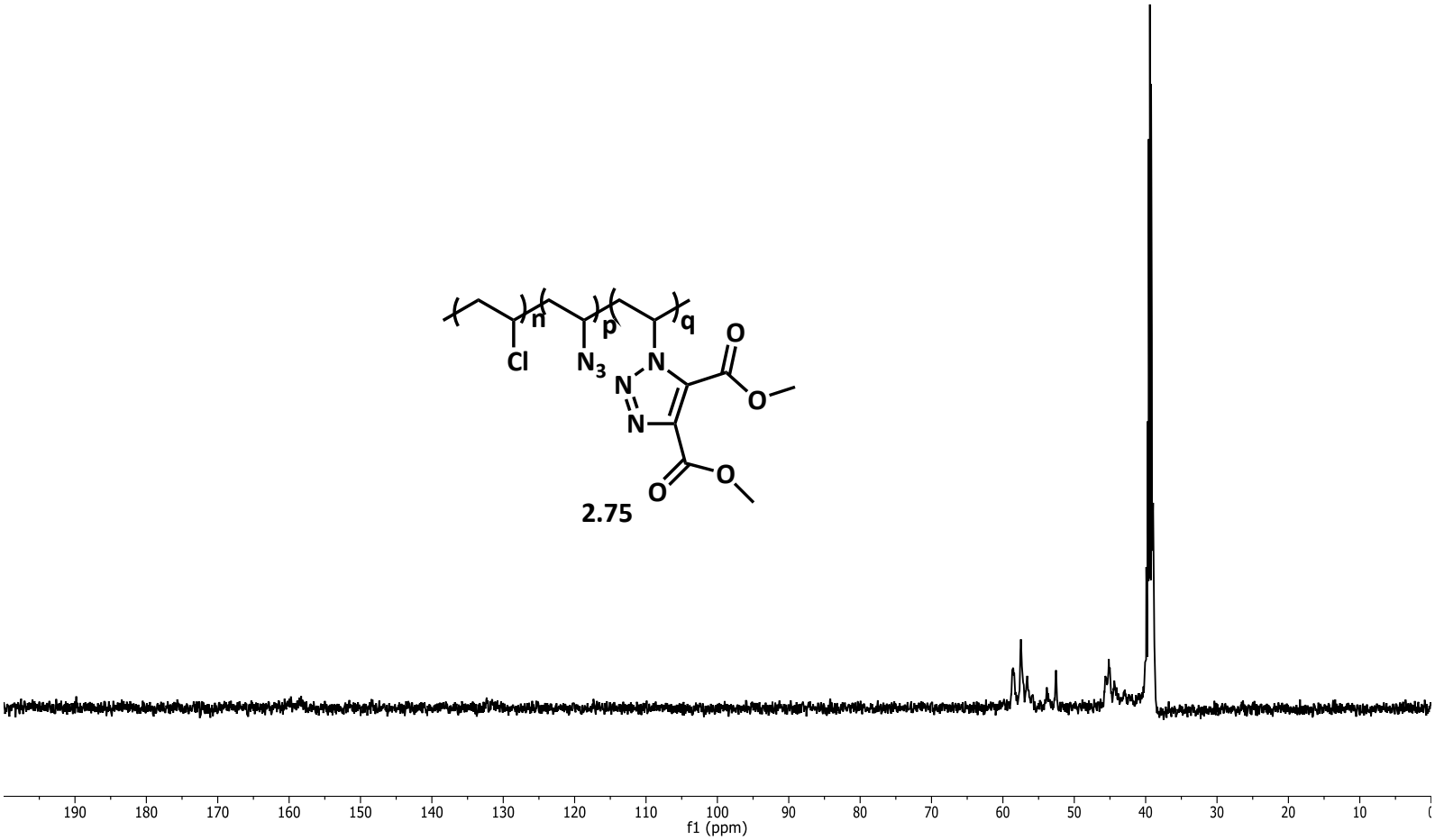

n
o
Cl
N3
2.74
424
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

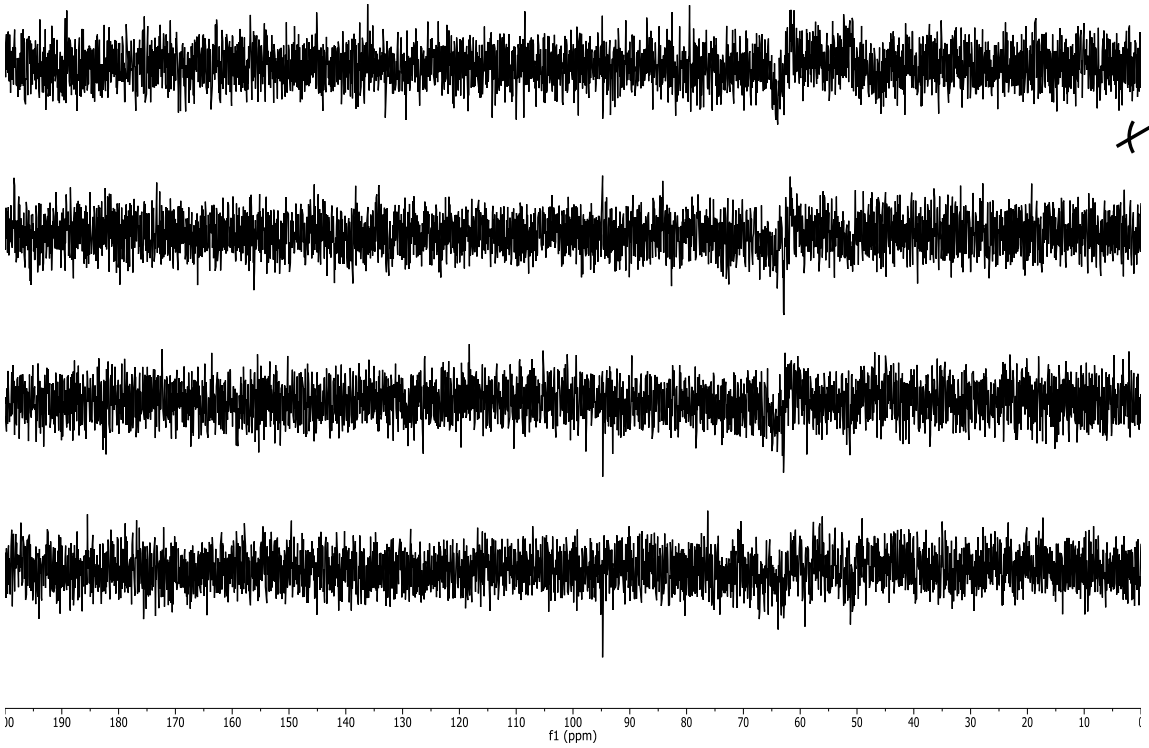

n
o
Cl
N3
2.74
425
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

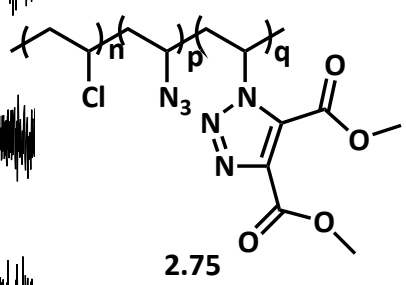

94.1
90
85
80
75
70
65
60
55
51.2
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
3736.25
3584.46
3368.54
2970.43
2911.67
2507.88
2113.27
1773.93
1722.58
1666.81
1458.92
1426.83
1355.80
1333.56
1255.24
1168.79
1103.13
1062.22
1036.73
991.63
929.59
879.32
634.69
615.30
n
o
Cl
N3

2.74

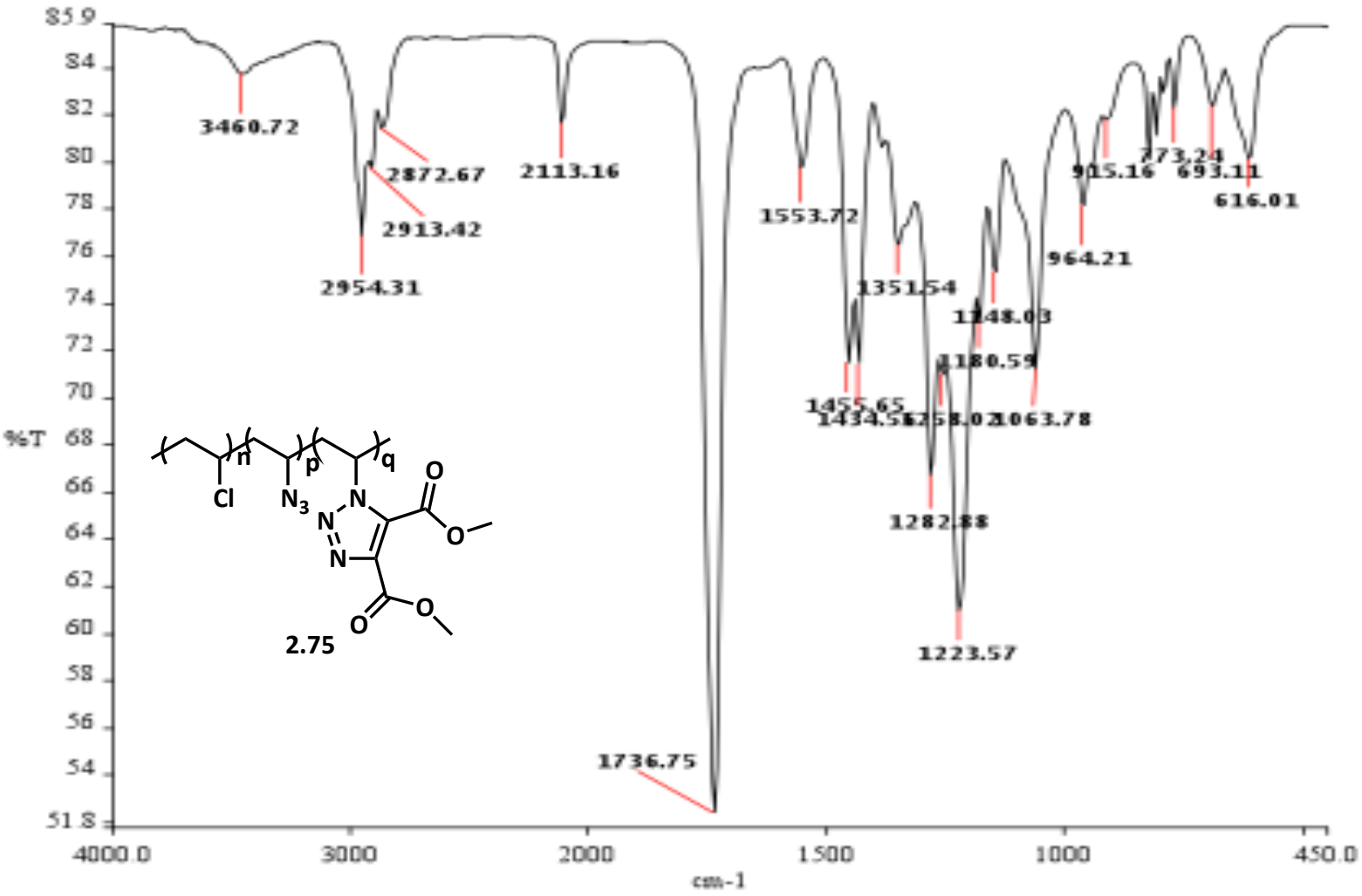

Cl
n
N3
p
q
N
N
N
O
O
O
O
2.75
427
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

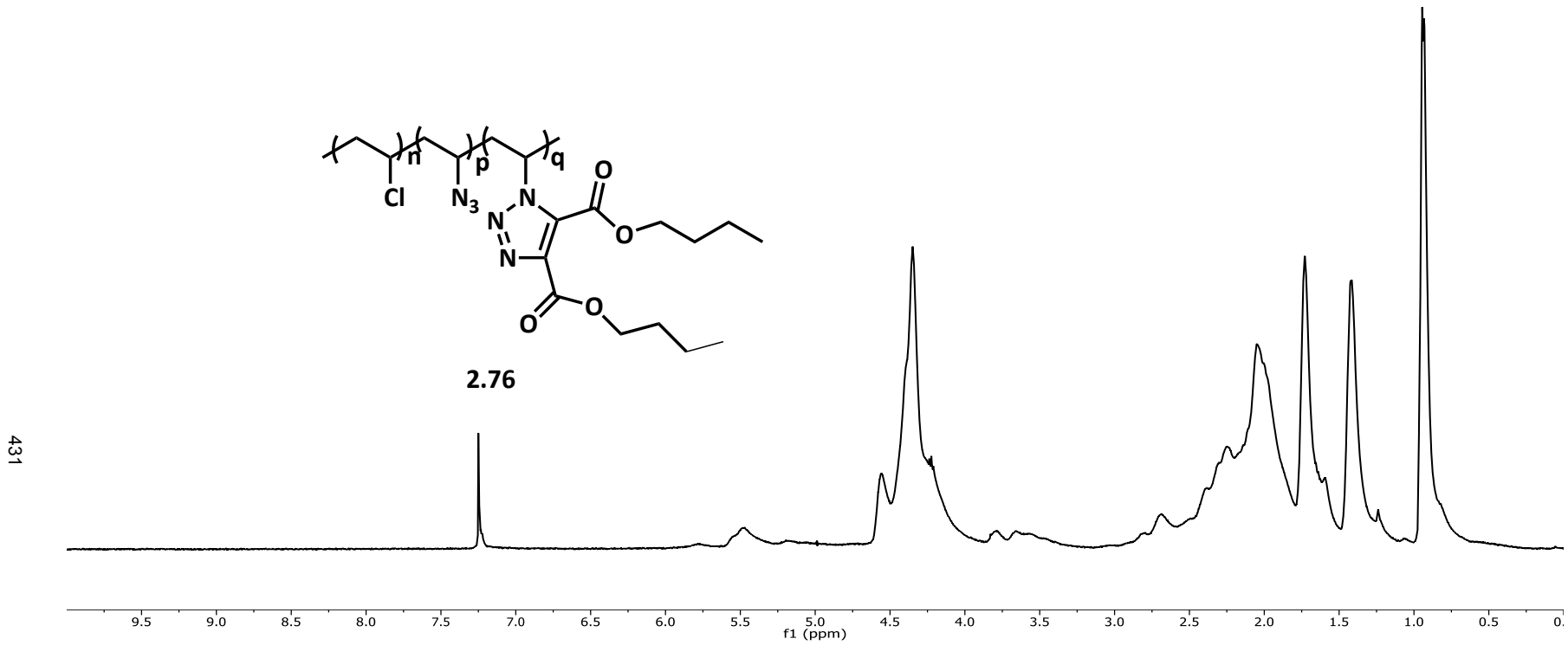

n
p
q
Cl
N3
N
N
N
O
O
O
O
2.75
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

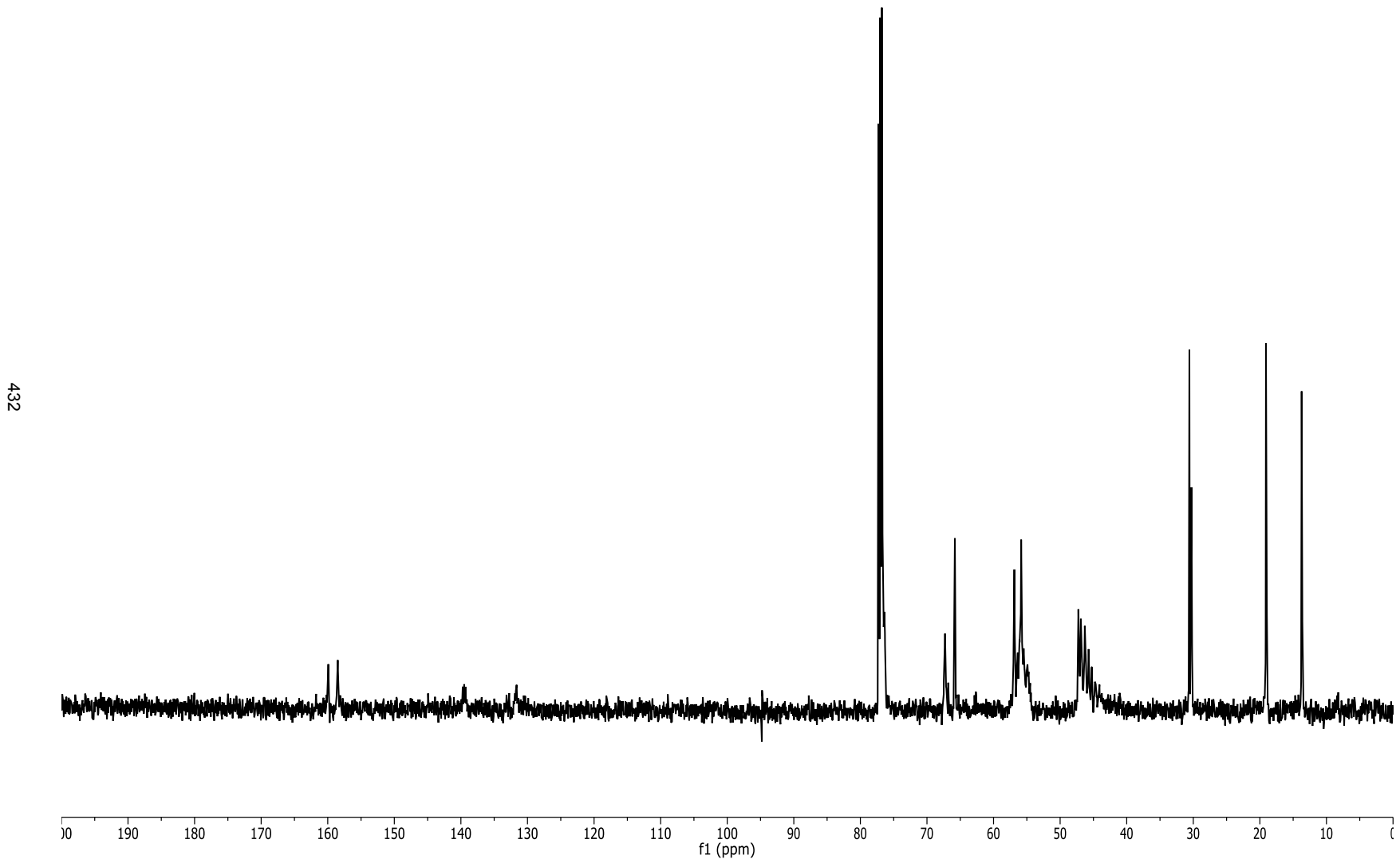


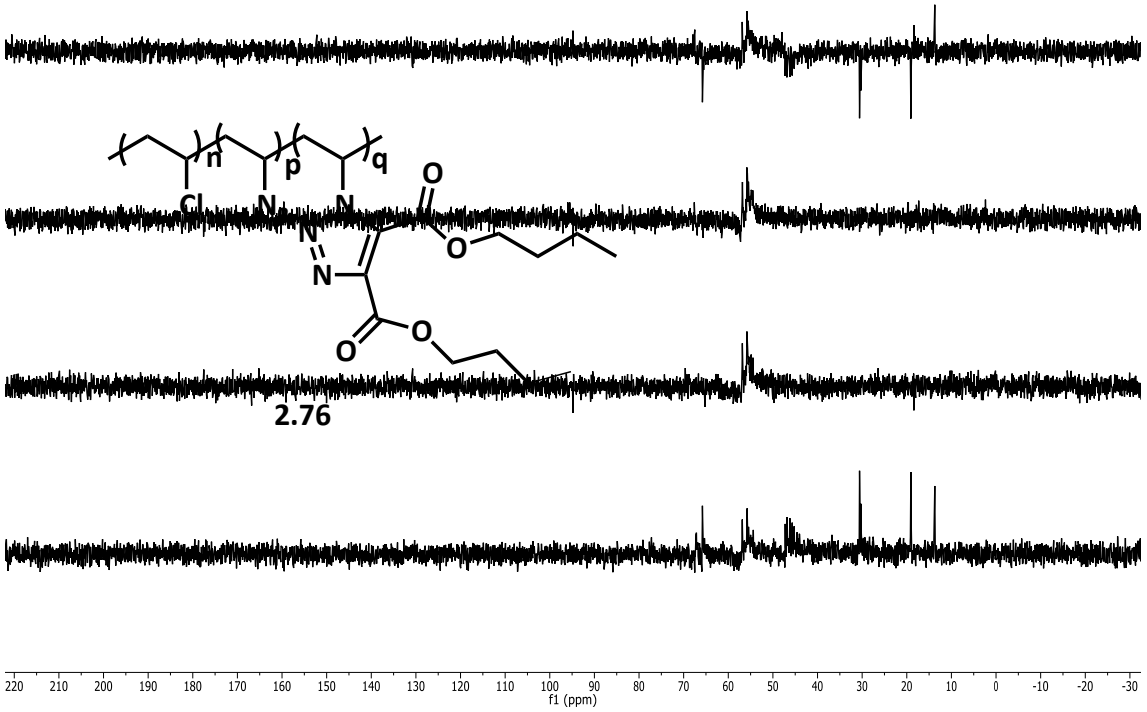


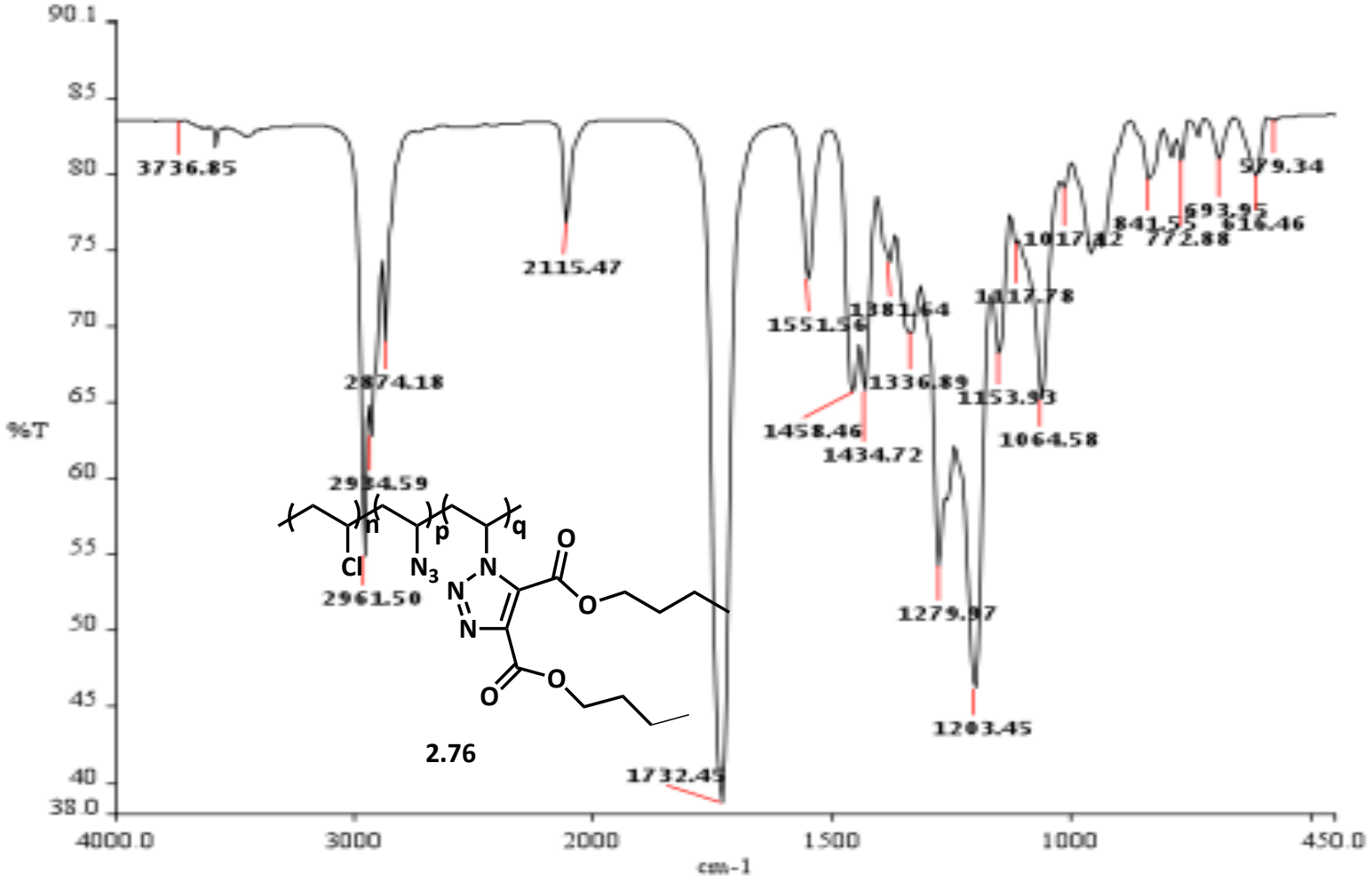
2.75

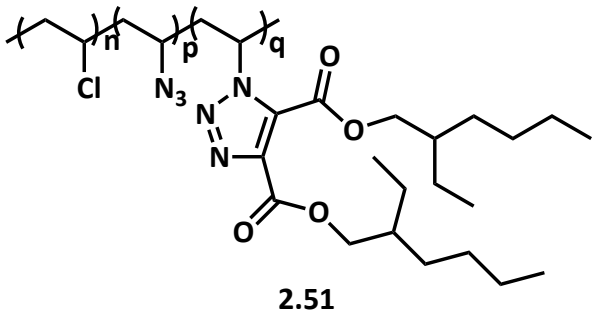

%T
85.9
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
51.8
4000.0
3000
2000
1500
1000
450.0
cm-1
3460.72
2872.67
2913.42
2954.31
2113.16
1736.75
1553.72
1455.65
1434.58
1351.54
1282.88
1258.02
1223.57
1180.59
1148.03
1063.78
964.21
915.16
773.24
693.11
616.01
Cl
N3
n
p
q
O
N
2.75


n
p
q
Cl
N3
N
N
N
O
O
O
O
2.76
431
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


432
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

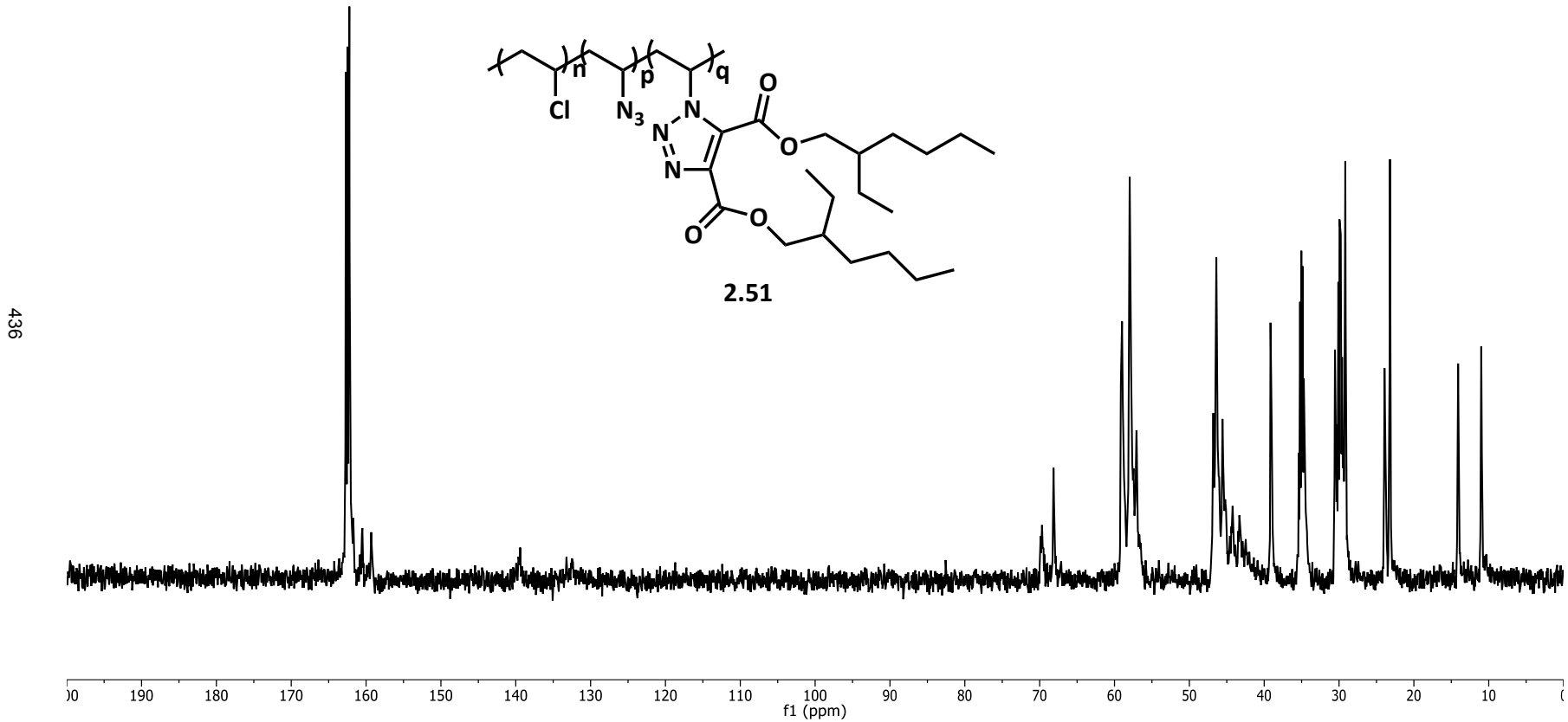

n
p
q
Cl
N
N
N
N
O
O
O
O
2.76
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

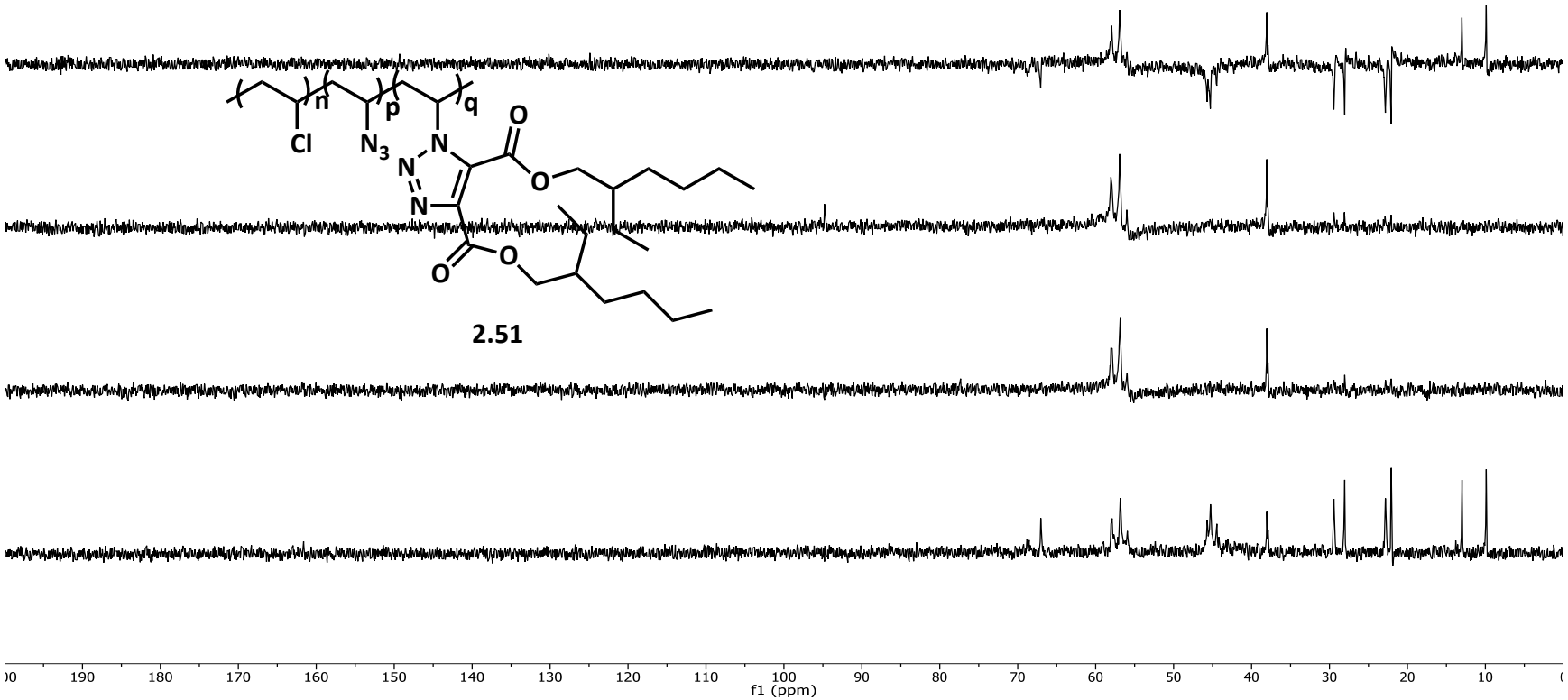

90.1
85
80
75
70
65
60
55
50
45
40
38.0
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
3736.85
2874.18
2934.59
2961.50
2115.47
1732.45
1551.56
1458.46
1434.72
1381.64
1336.89
1279.87
1203.45
1153.93
1117.78
1064.58
1017.42
841.55
772.88
693.95
616.46
579.34
n
p
q
Cl
N3
O
2.76

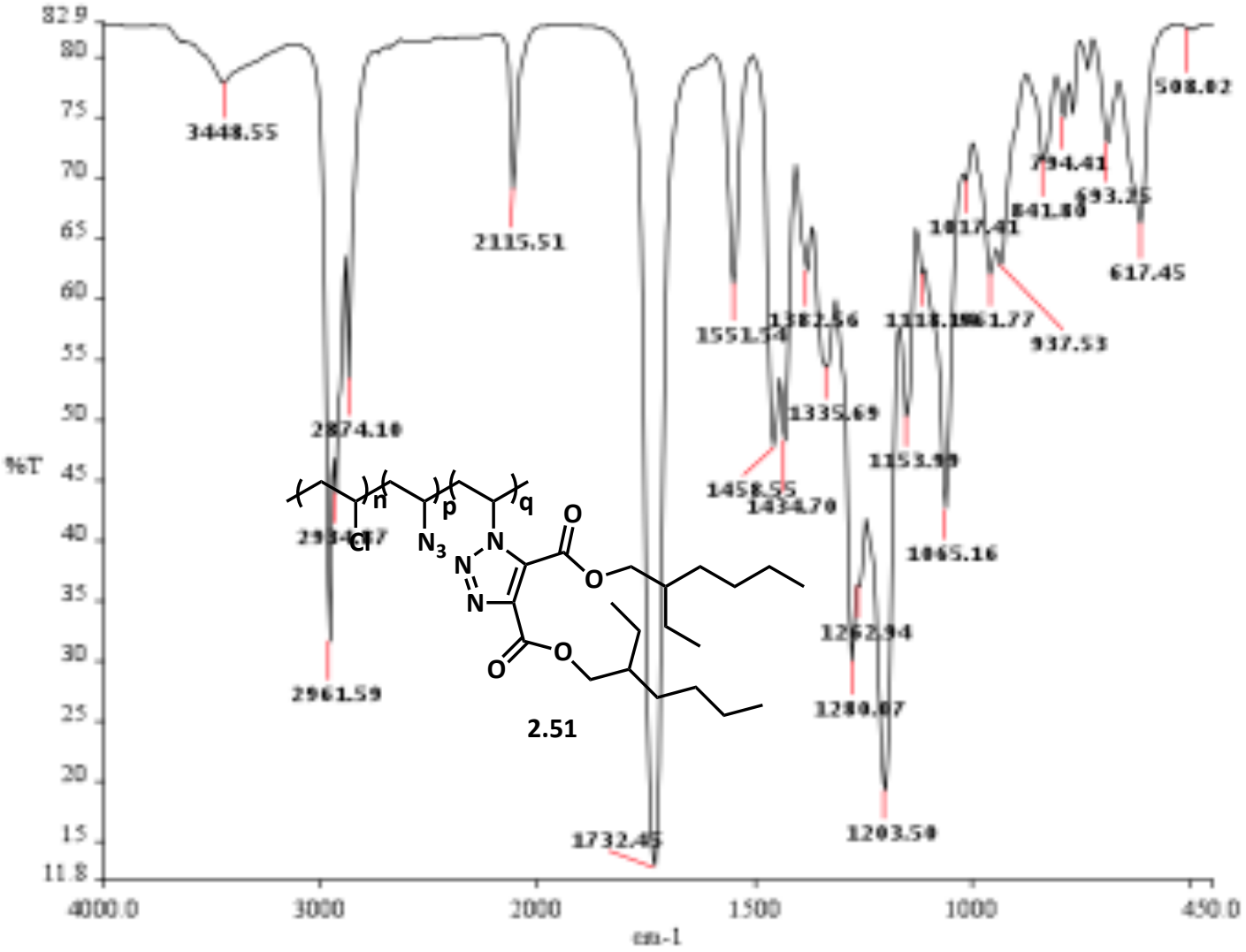

n
p
q
Cl
N3
N
N
N
O
O
O
O

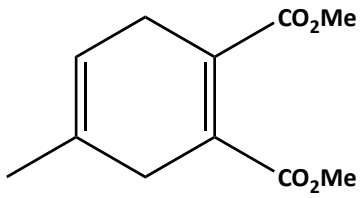
2.51

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


n
p
q
Cl
N3
N
N
N
O
O
O
O
2.51
436
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

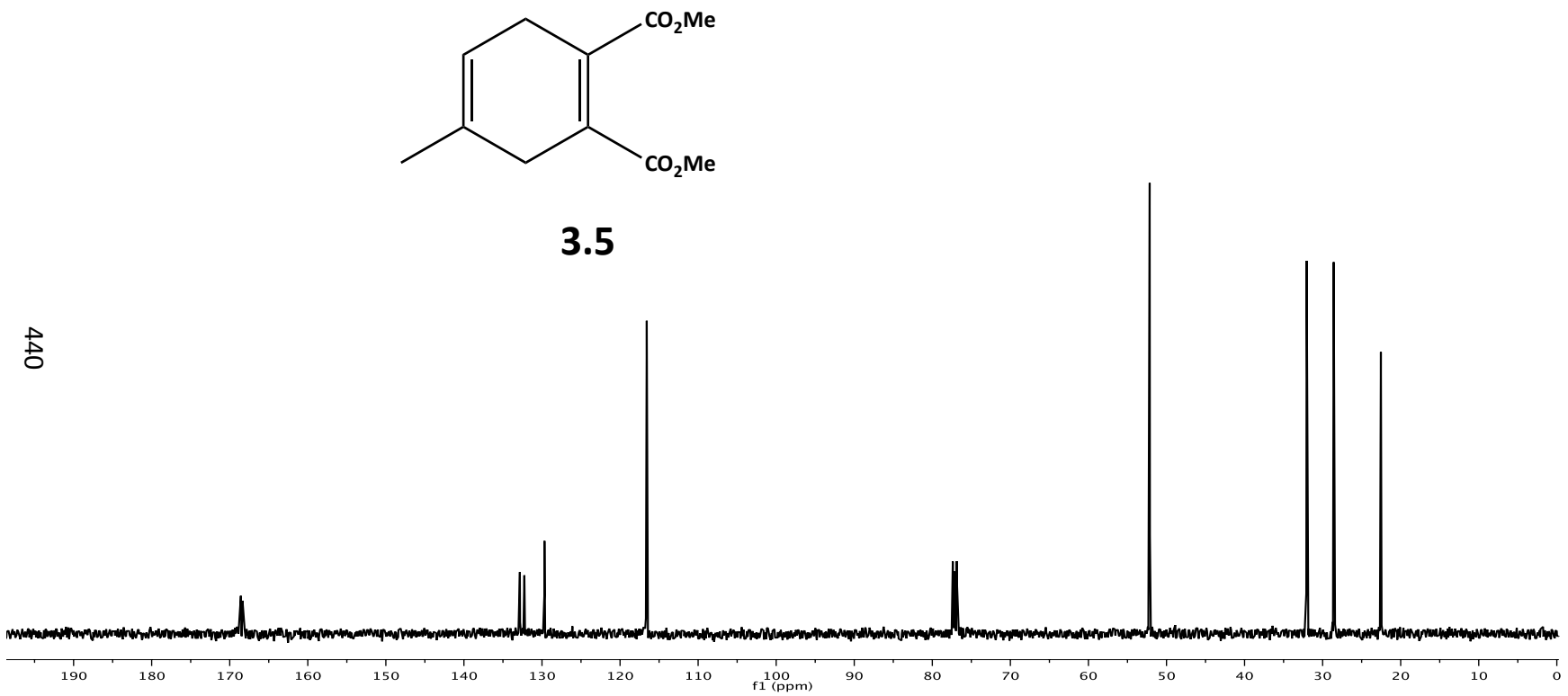

n
p
q
Cl
N3
N
N
N
O
O
O
O
2.51
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

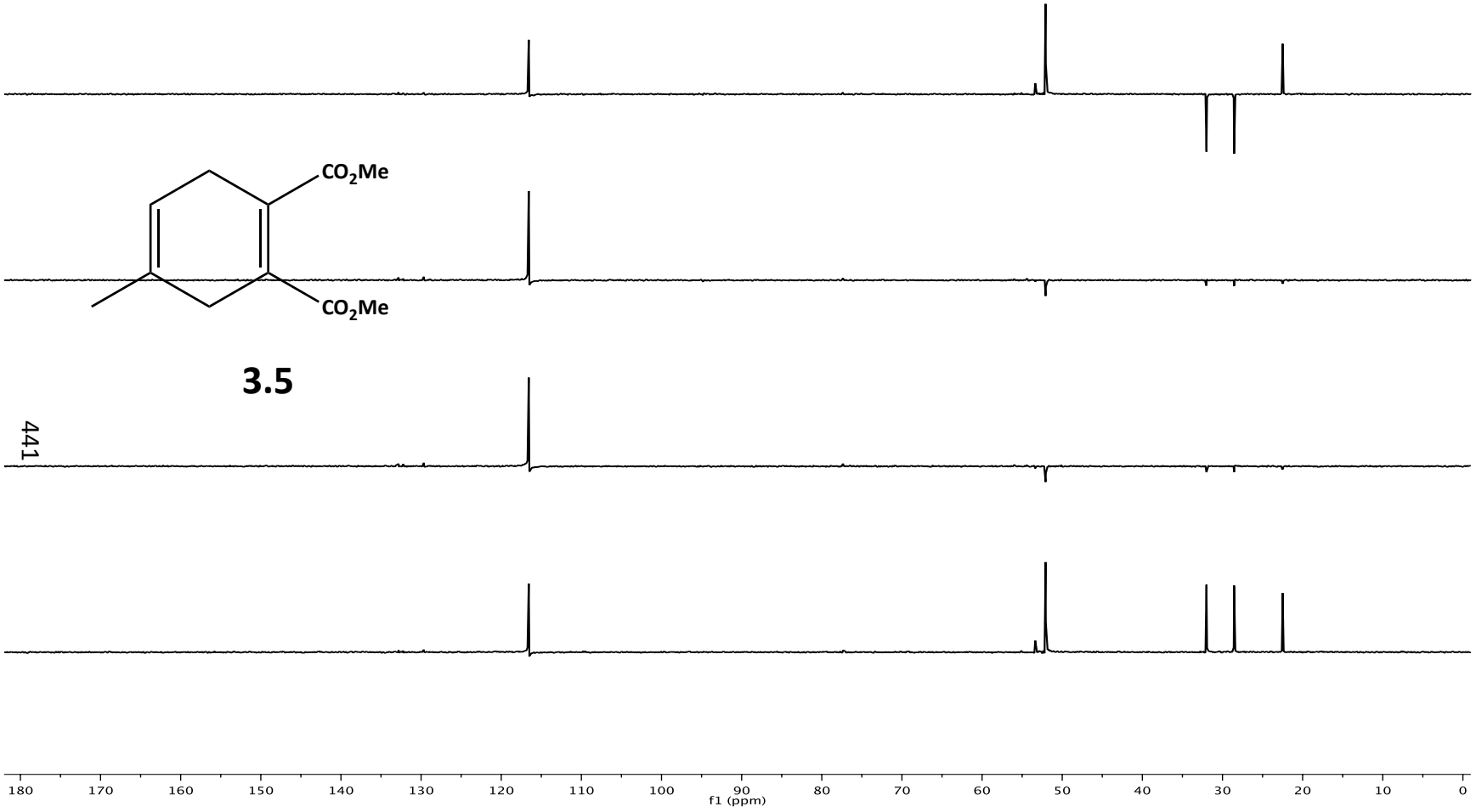

%T
cm-1
4000.0
3000
2000
1500
1000
450.0
3448.55
2115.51
2874.10
2961.59
1732.45
1551.54
1458.55
1434.70
1335.69
1153.99
1065.16
1262.94
1280.87
1203.50
937.53
617.45
508.82
Cl
n
p
q
N3
N
O
2.51

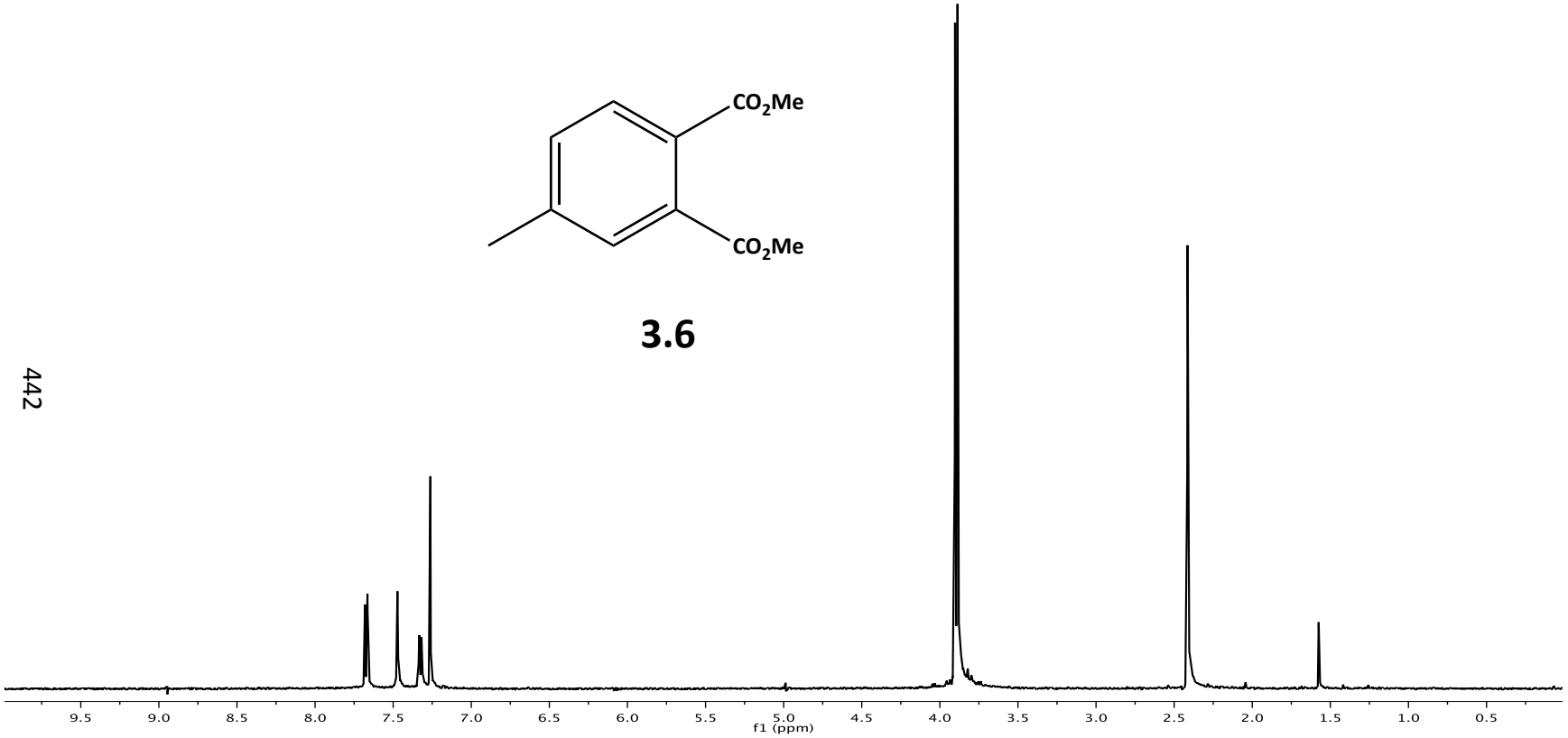

CO2Me
CO2Me

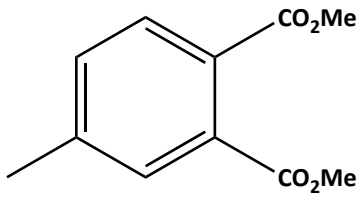
3.5

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CO2Me
CO2Me
3.5
440
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

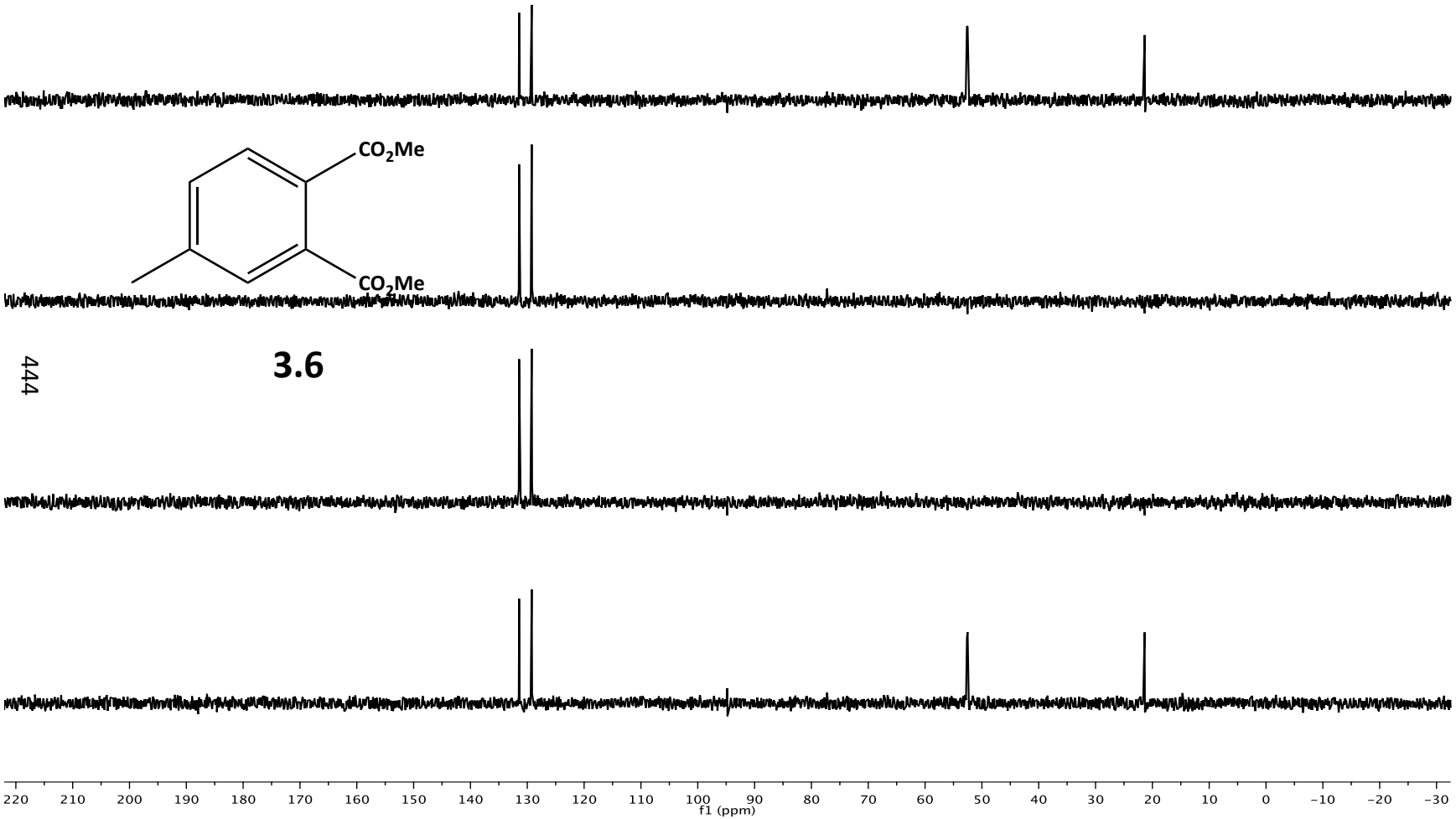

CO2Me
CO2Me
3.5
441
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

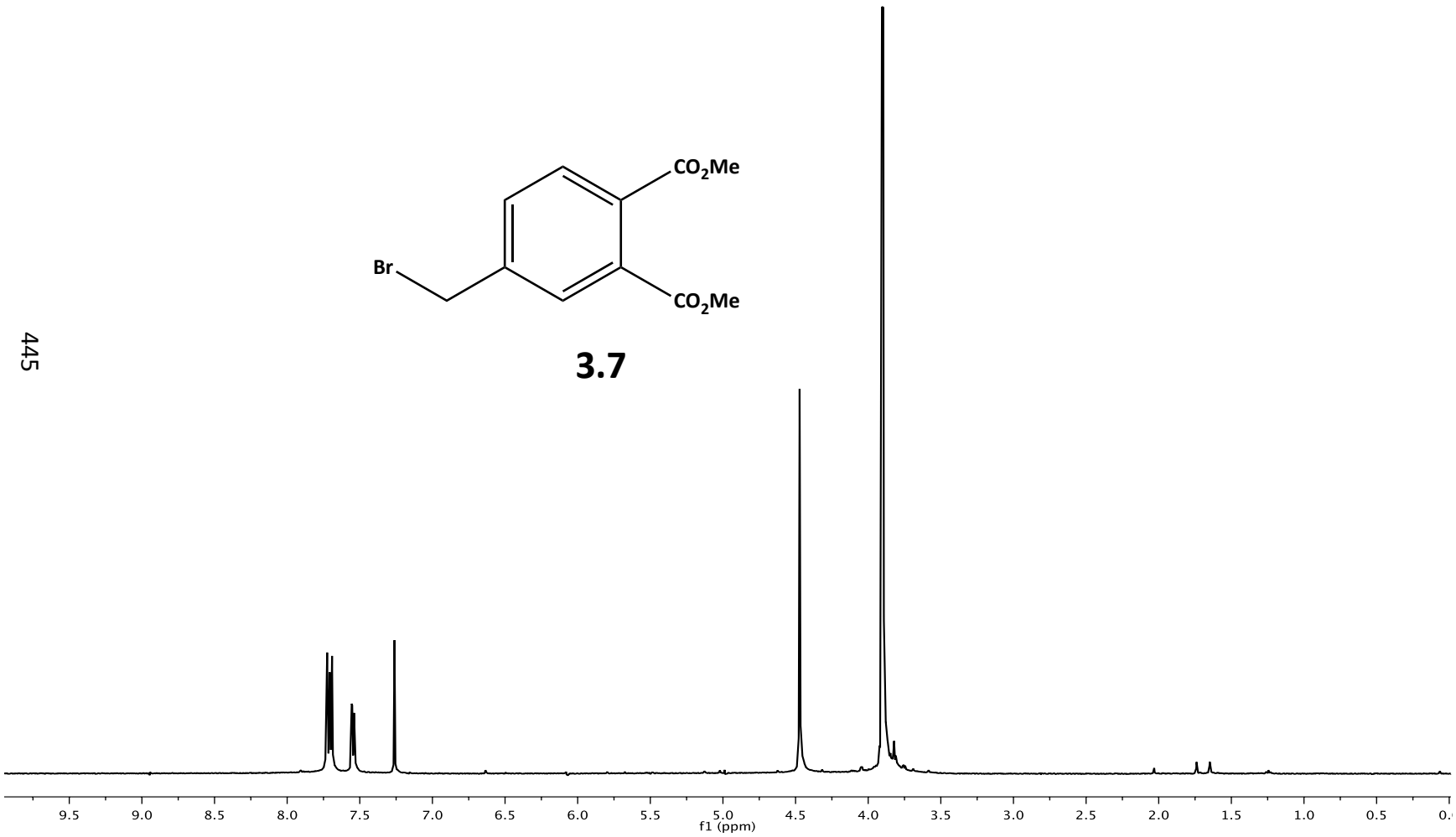

CO2Me
CO2Me
3.6
442
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

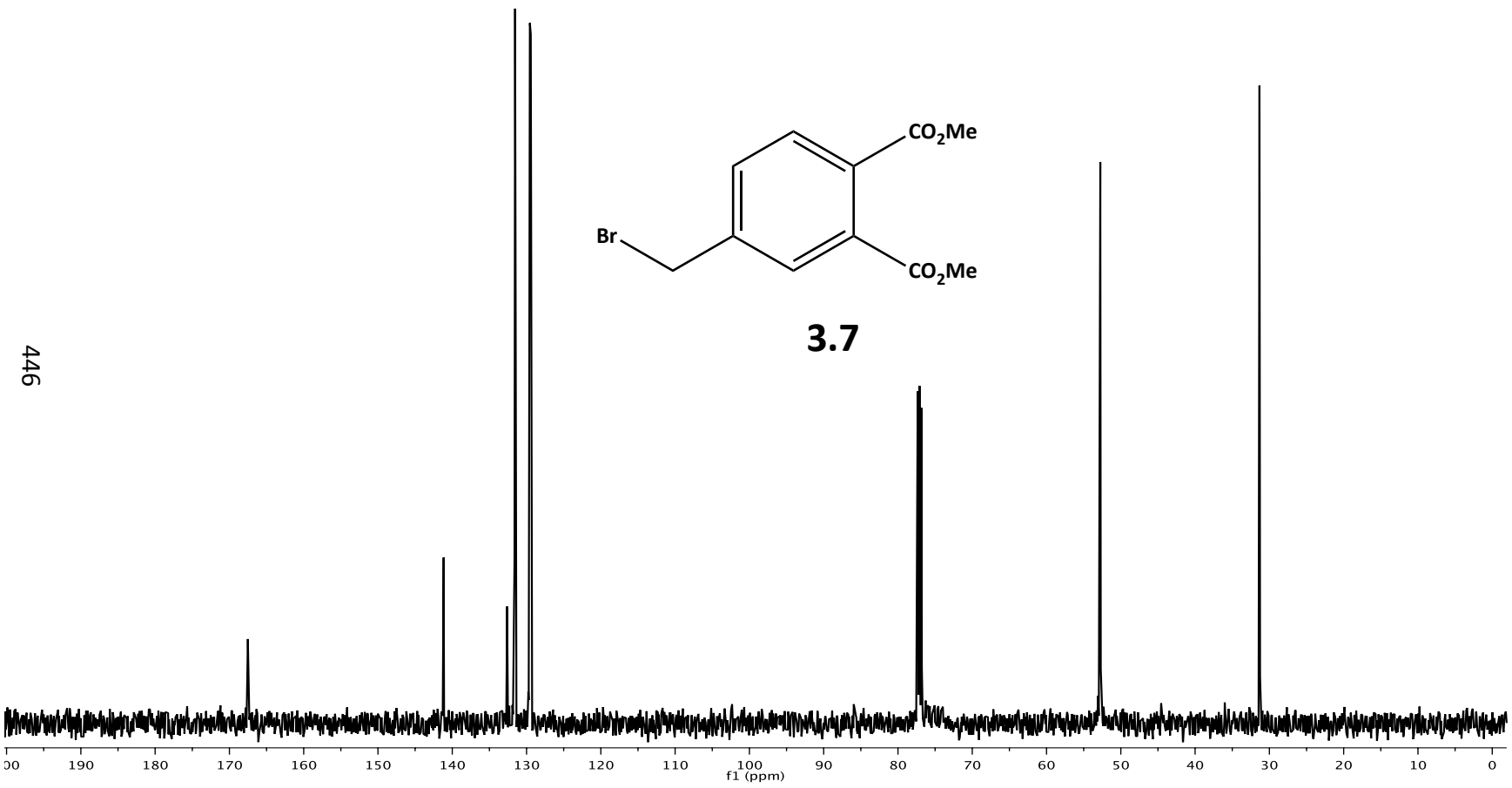

CO2Me
CO2Me

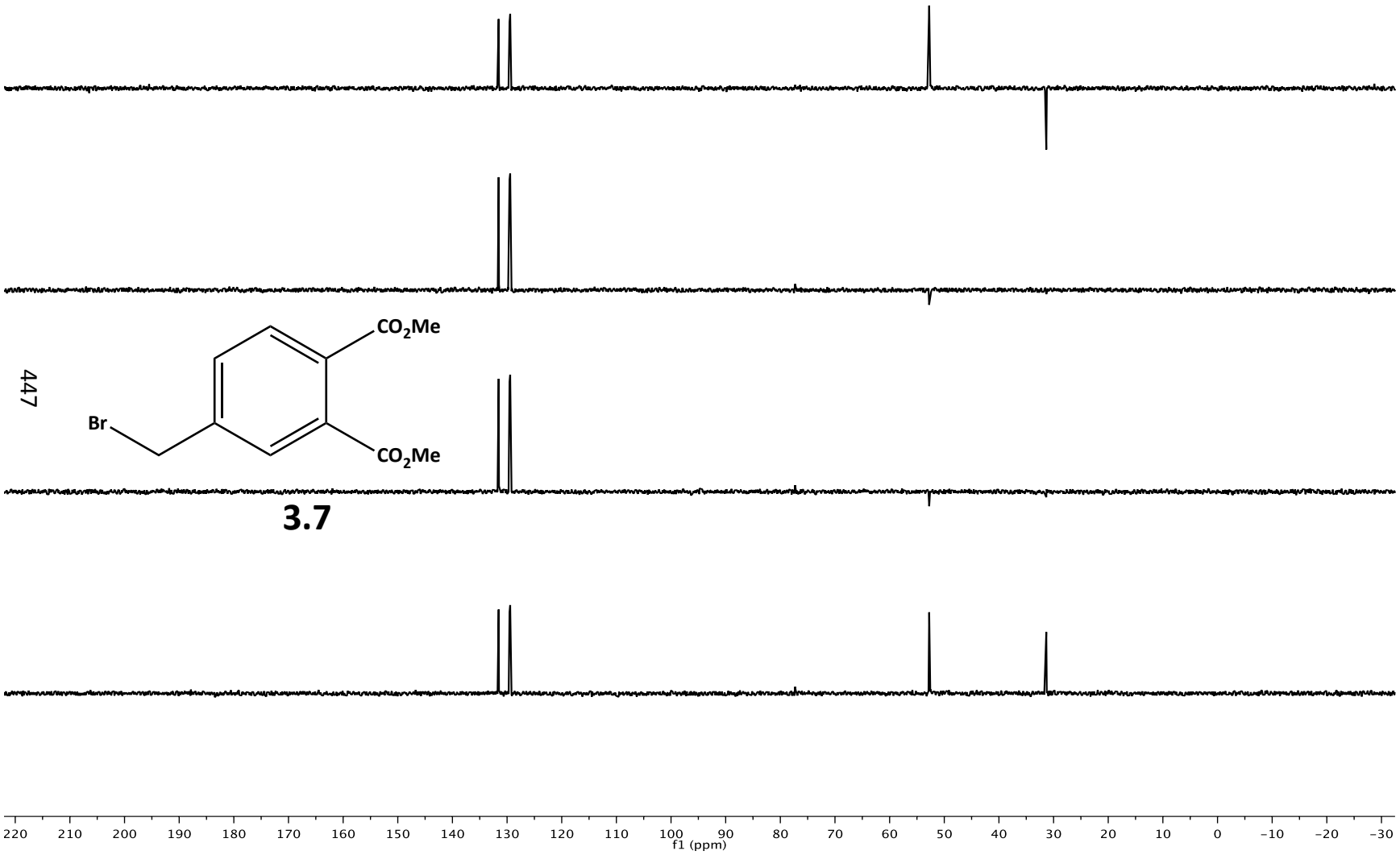
3.6

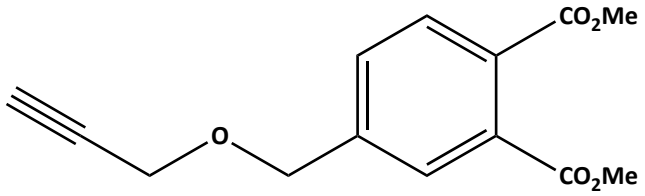
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CO2Me
CO2Me
3.6
444
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)


CO2Me
Br
CO2Me
3.7
445
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

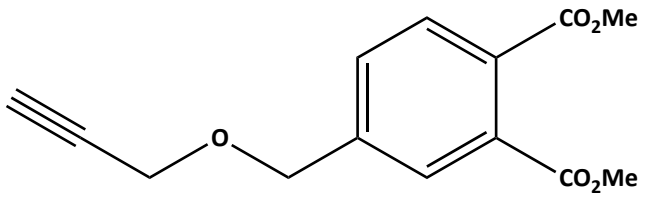

CO2Me
Br
CO2Me
3.7
446
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CO2Me
Br
CO2Me
447
3.7
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

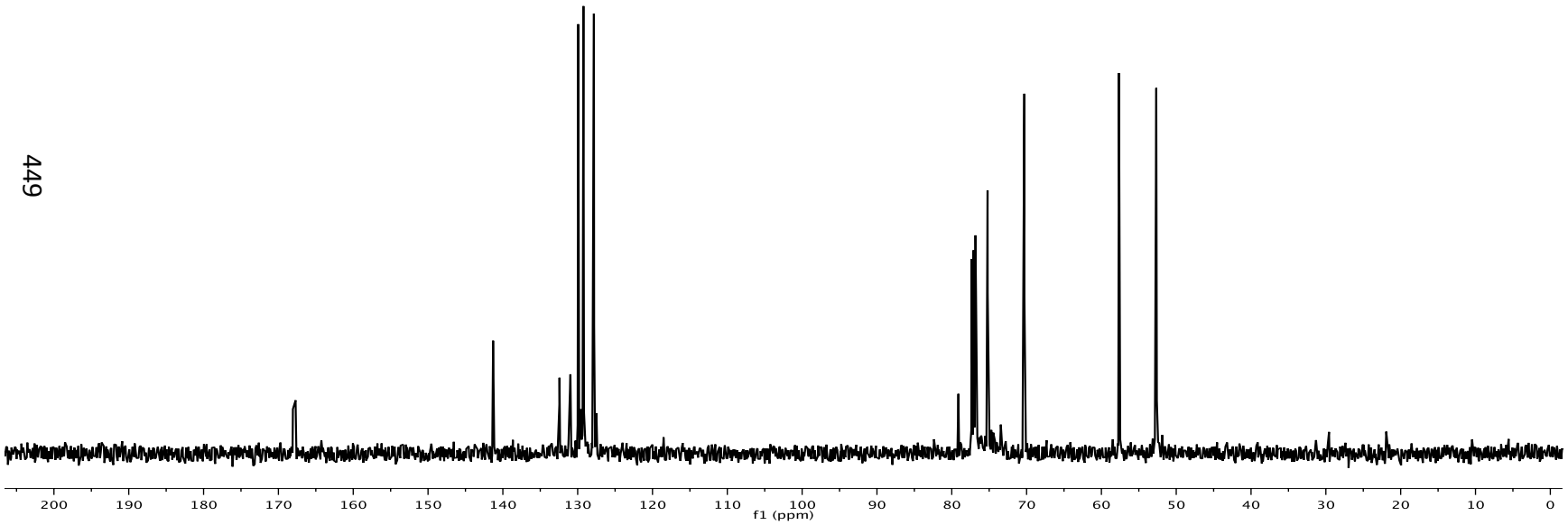


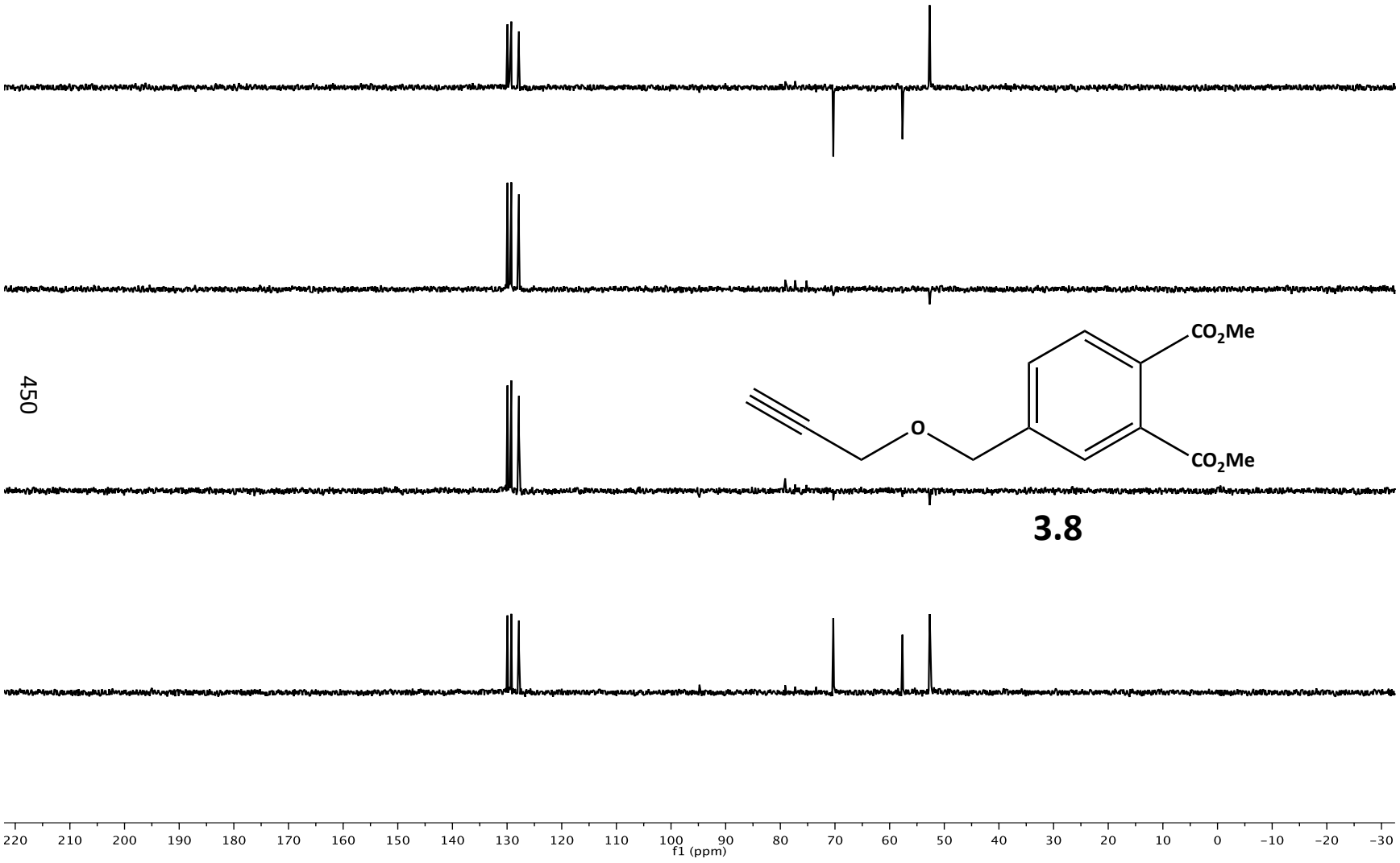
3.8

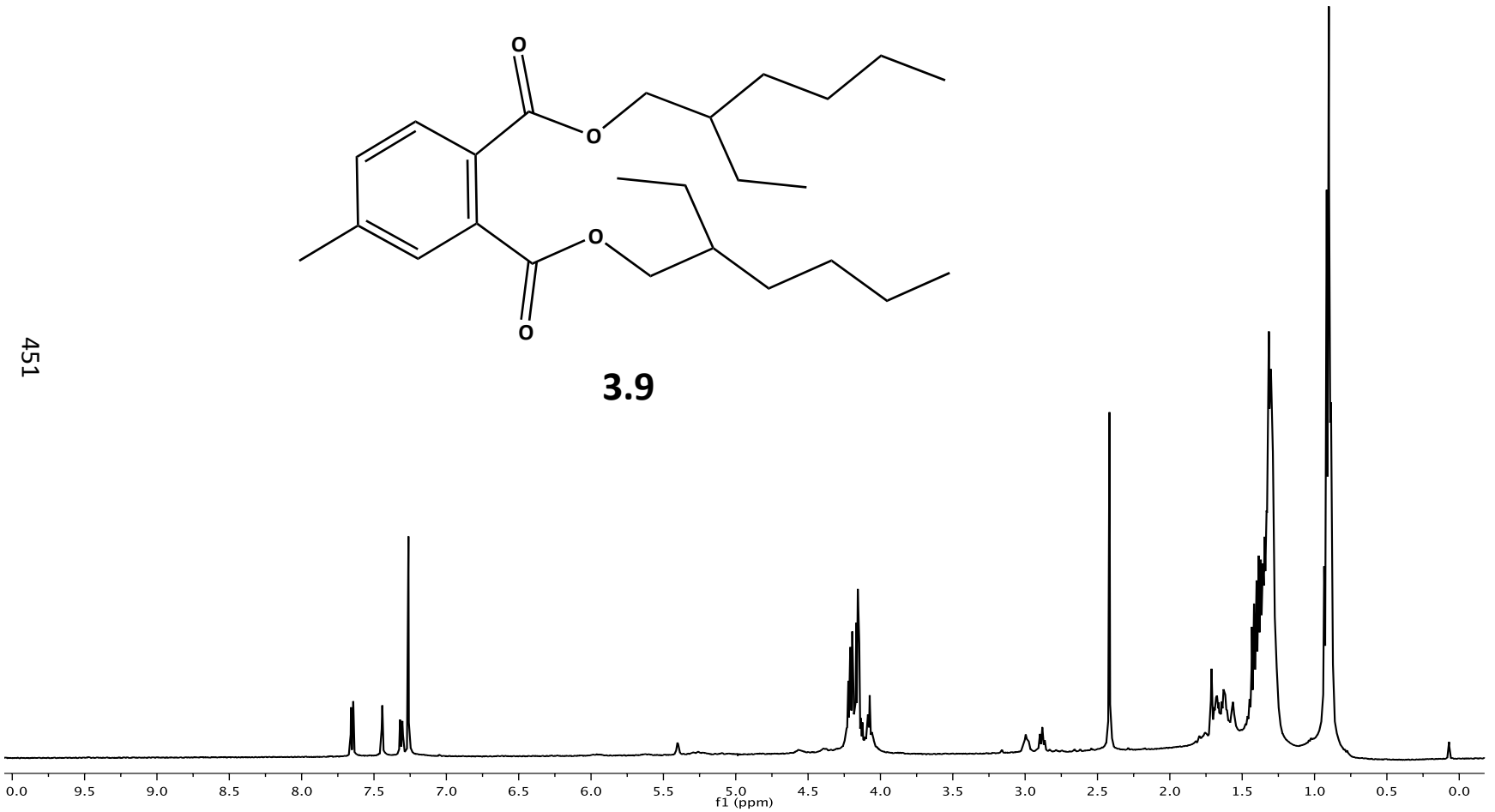
448

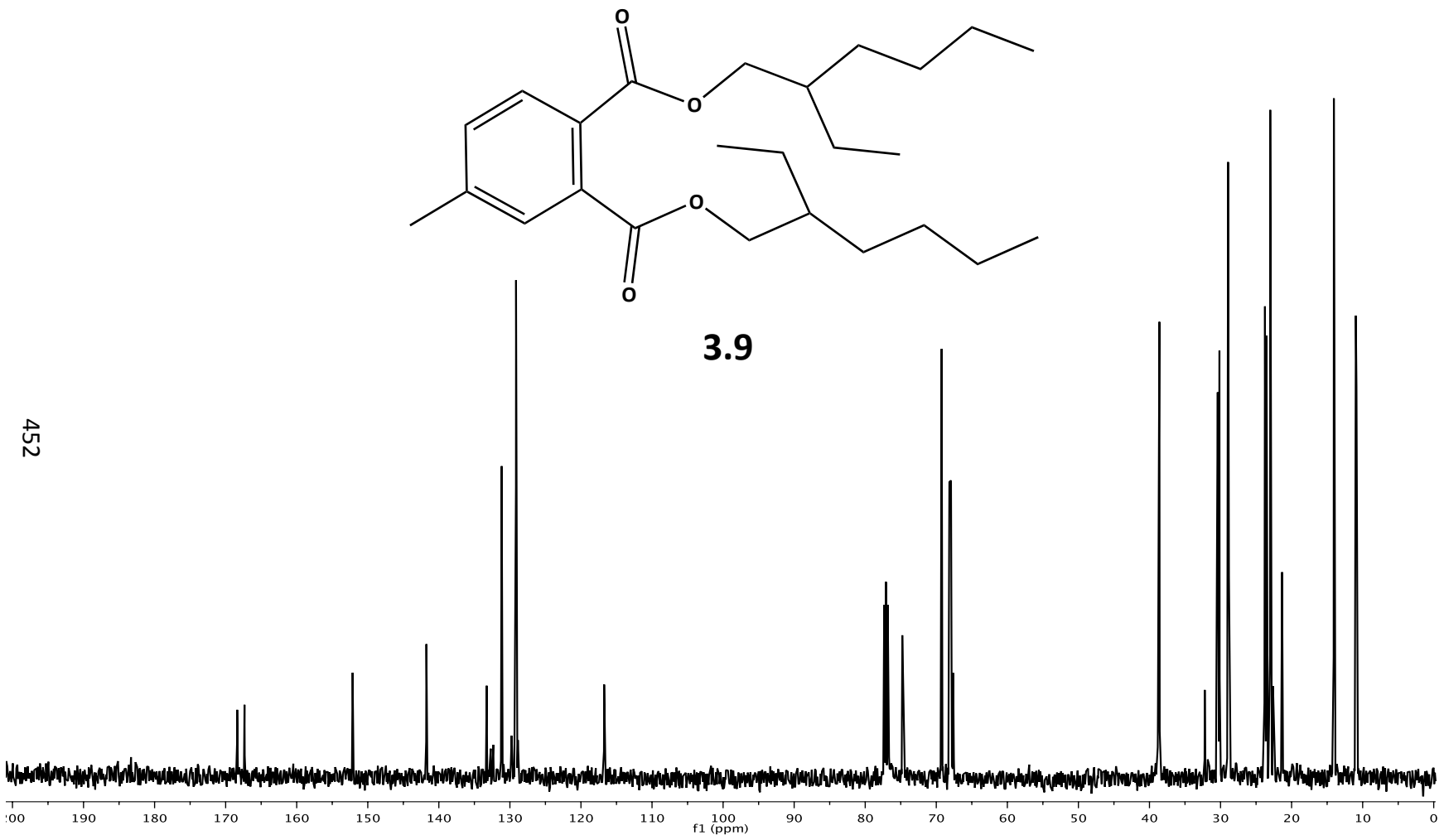

CO2Me
O
CO2Me

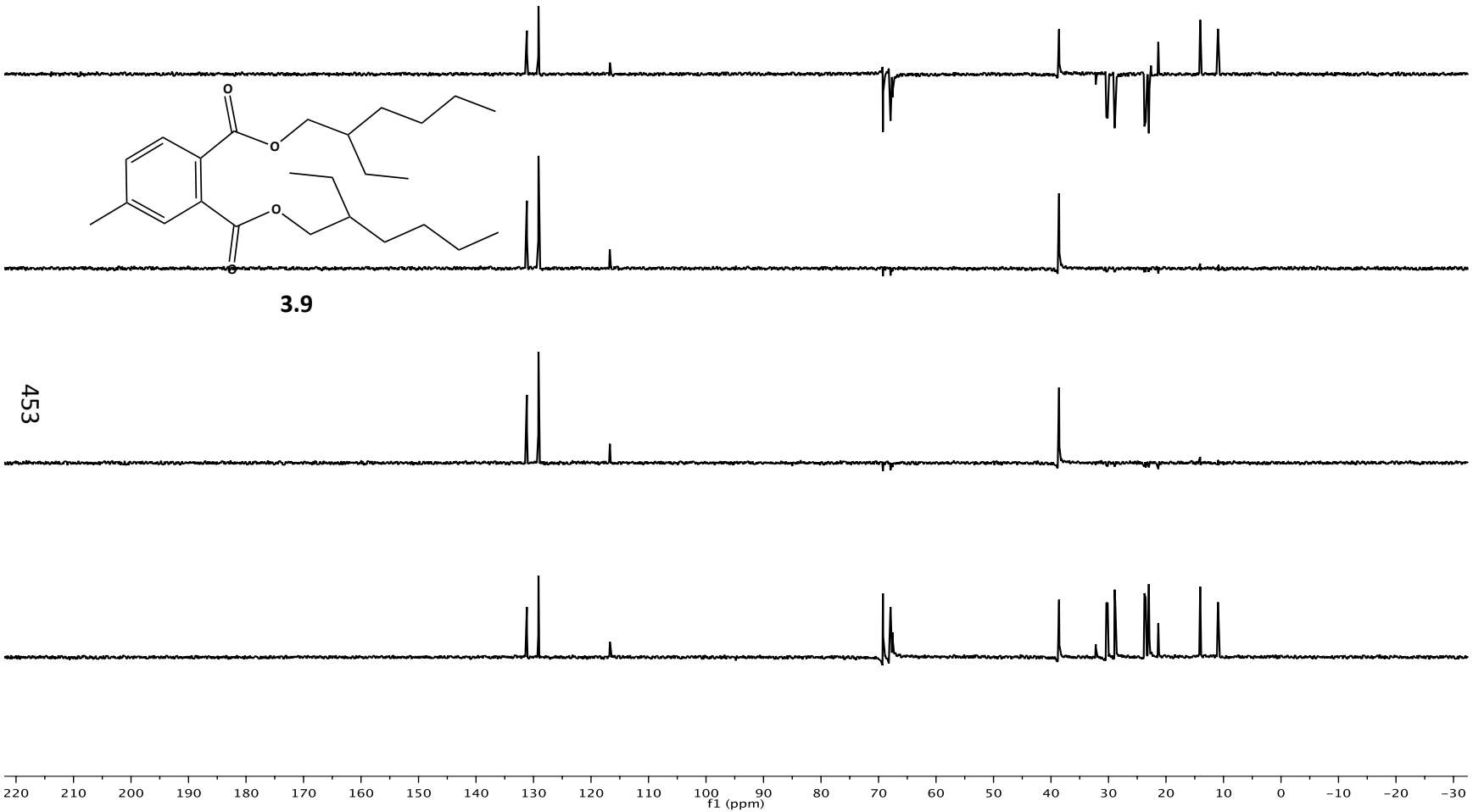
3.8

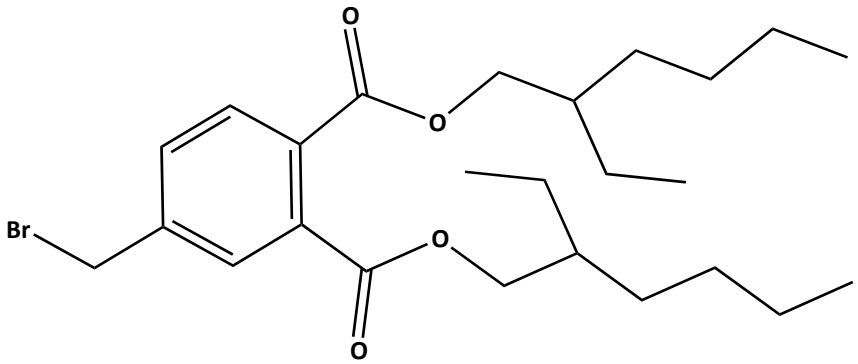

449
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


450
O
CO2Me
CO2Me
3.8
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)


O
O
O
O
O
3.9
451
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

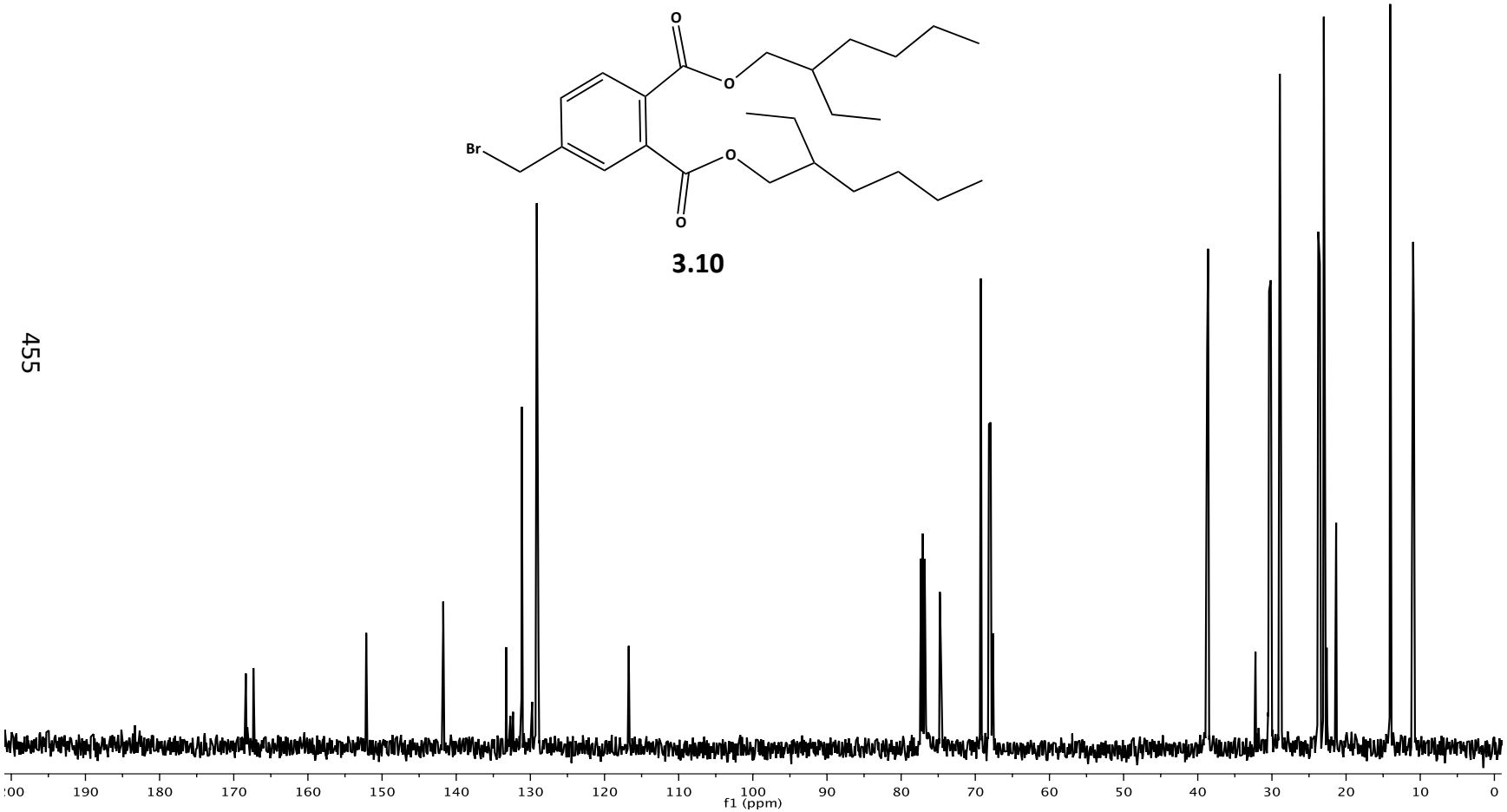

O
O
O
O
O
3.9
452
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

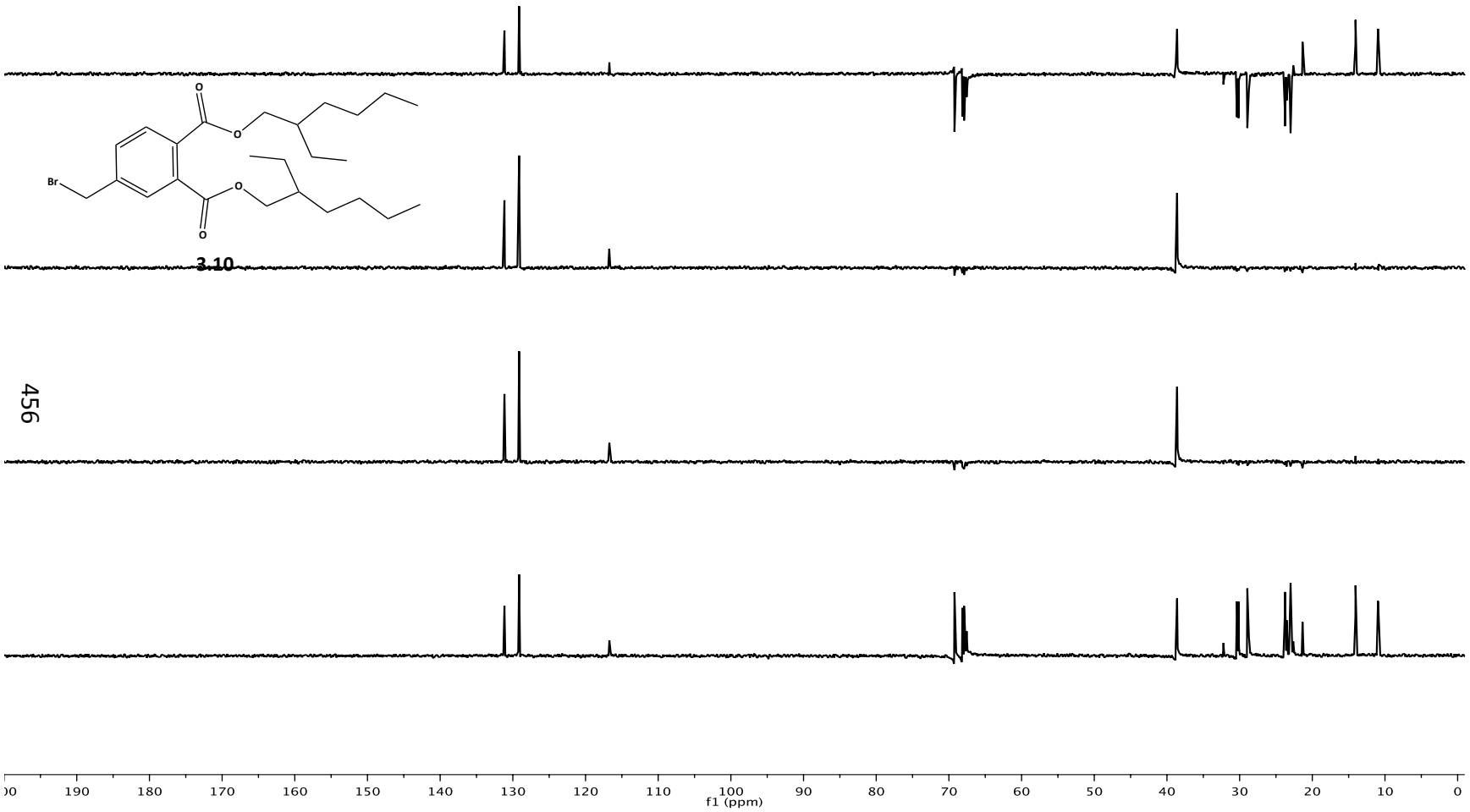

O
O
O
O
3.9
453
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

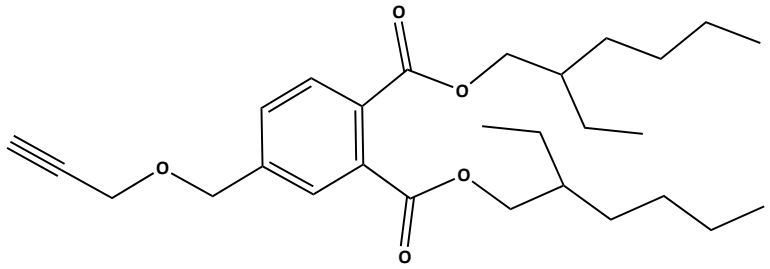

O
O
Br
O
O

3.10

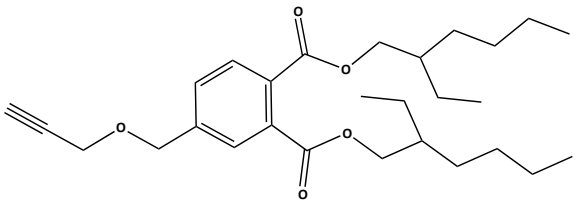
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Br
O
O
O
O
3.10
455
f1 (ppm)


Br
O
O
O
O
3.10
456
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

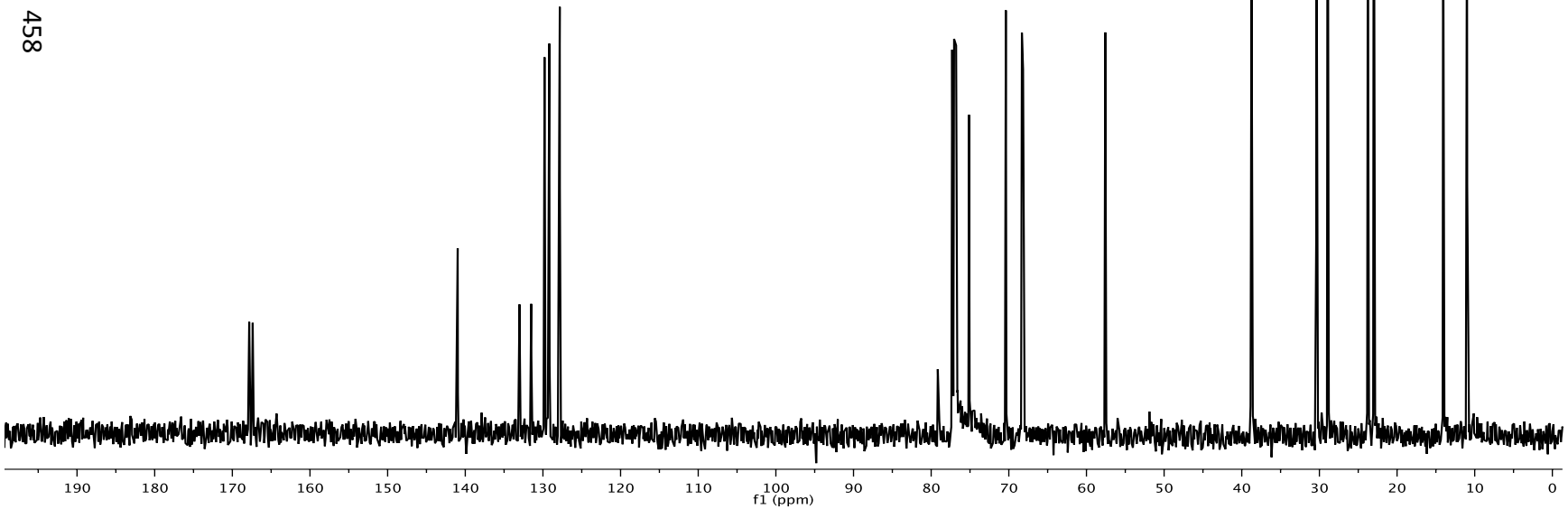


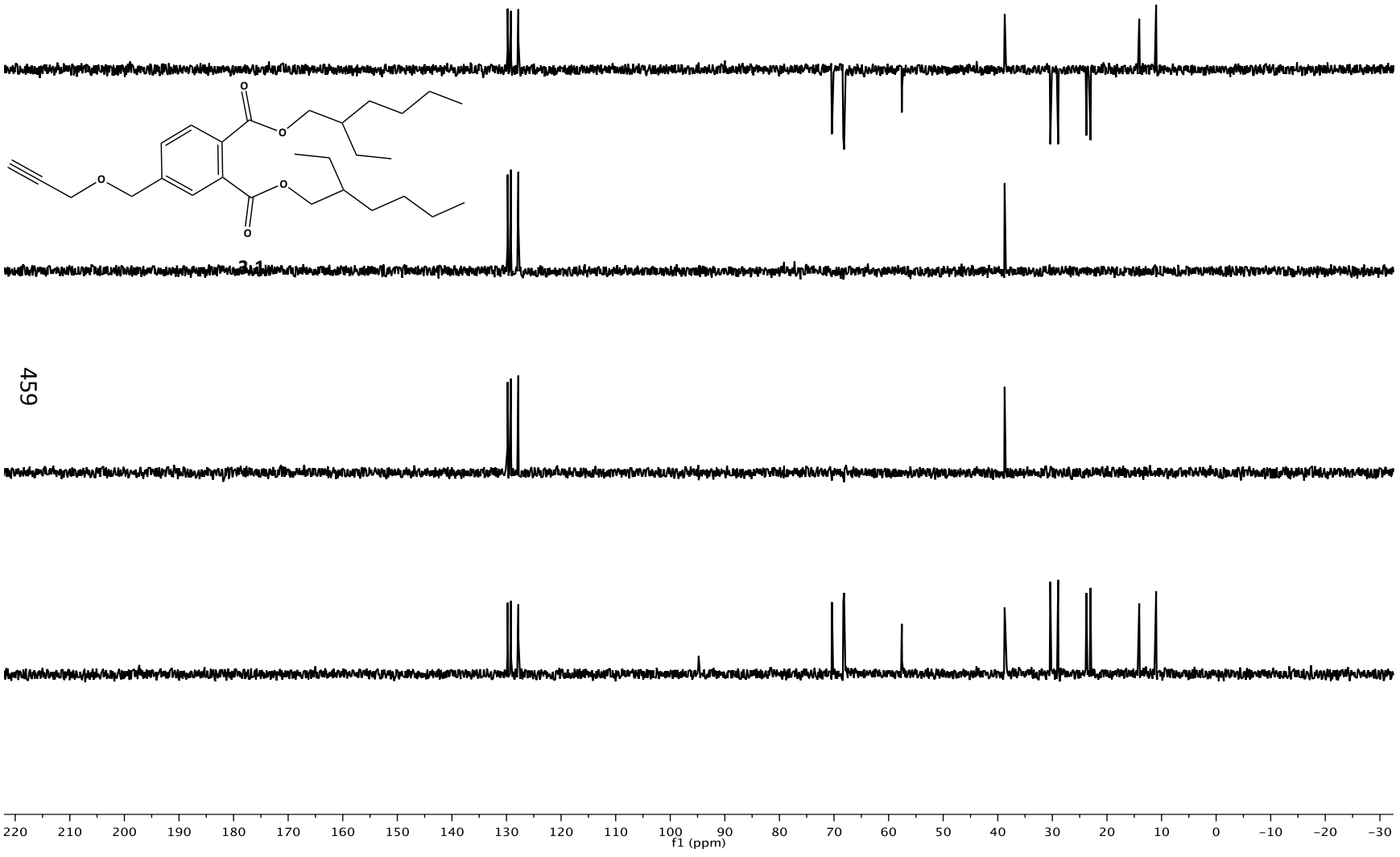
3.1

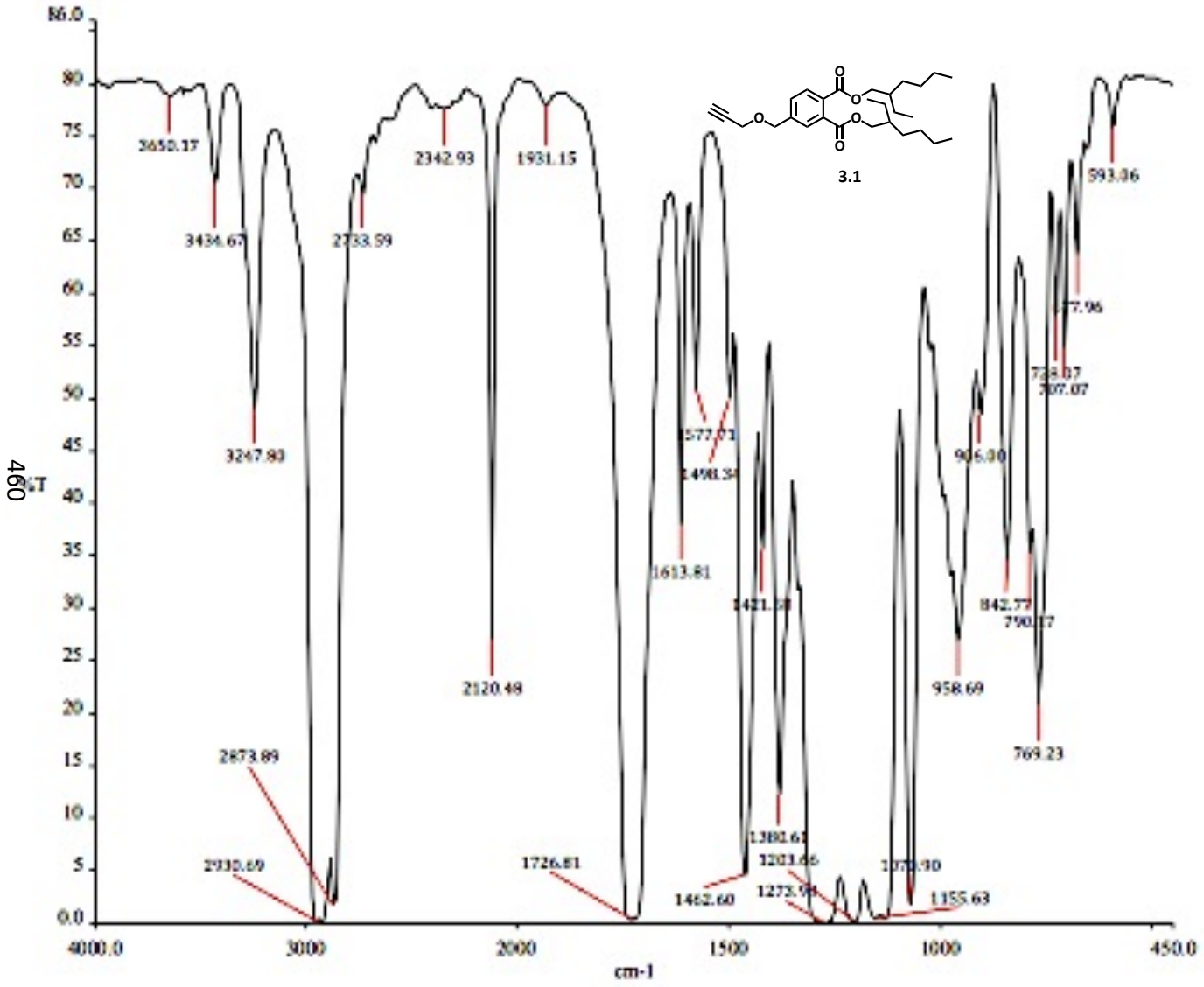


3.1

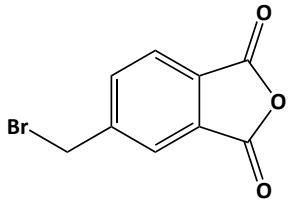
458


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
O
O
O
31
459
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

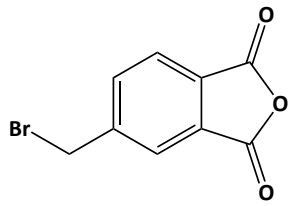

3650.17
3434.67
3247.80
2933.59
2342.93
2120.48
1931.15
1613.81
1498.34
1577.71
1462.60
1421.58
1380.61
1203.66
1273.98
1726.81
2930.69
2873.89
1155.63
958.69
906.30
842.77
790.17
769.23
707.07
593.06
%T
cm-1
4000.0
3000
2000
1500
1000
450.0
3.1

460

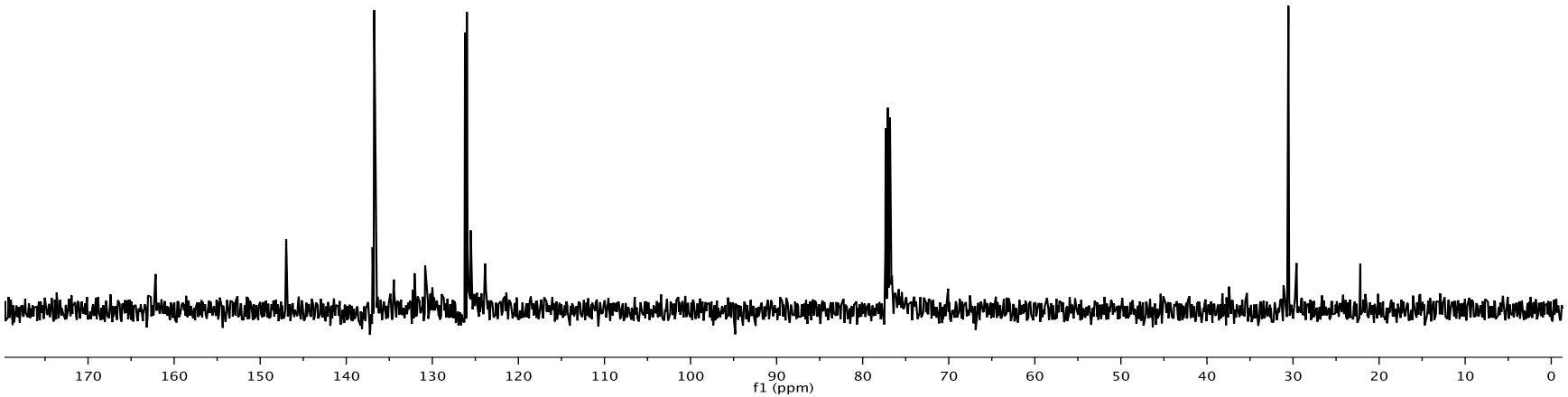

O
O
Br
O

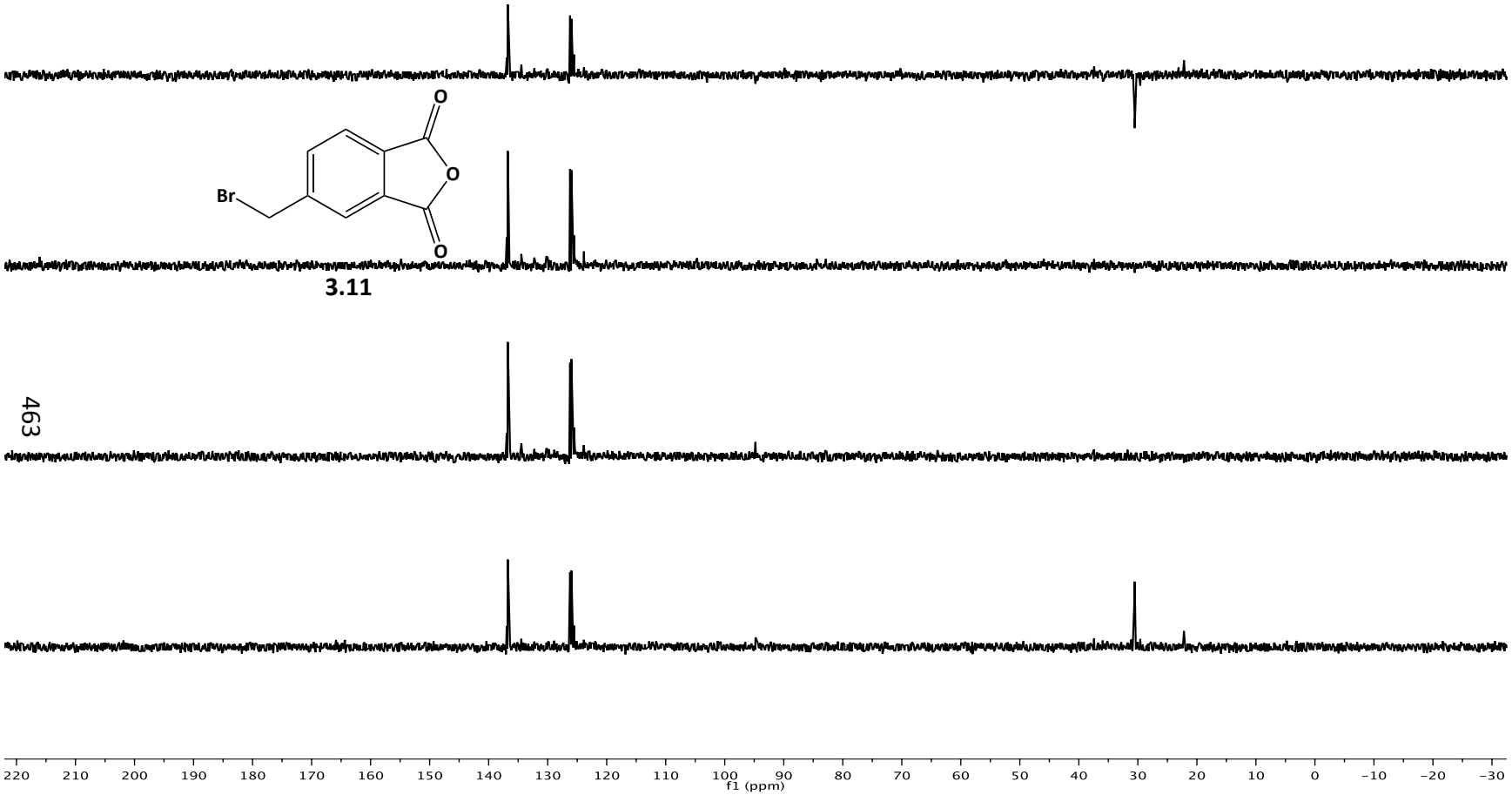
3.11

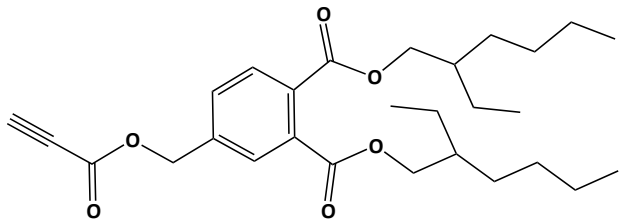
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Br
O
O
O

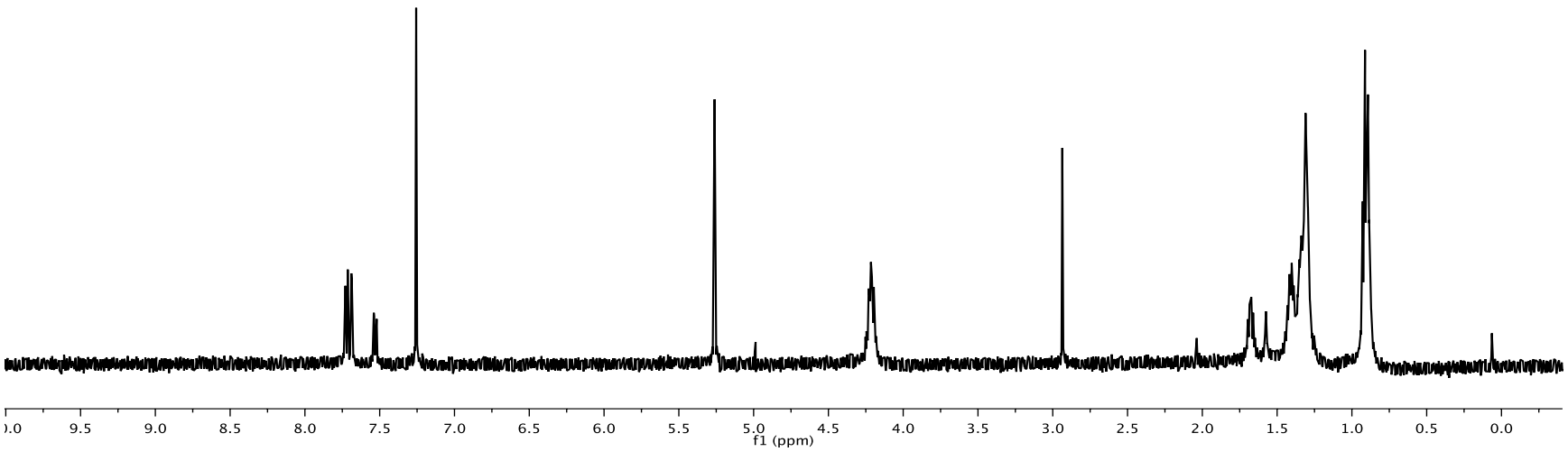
3.11

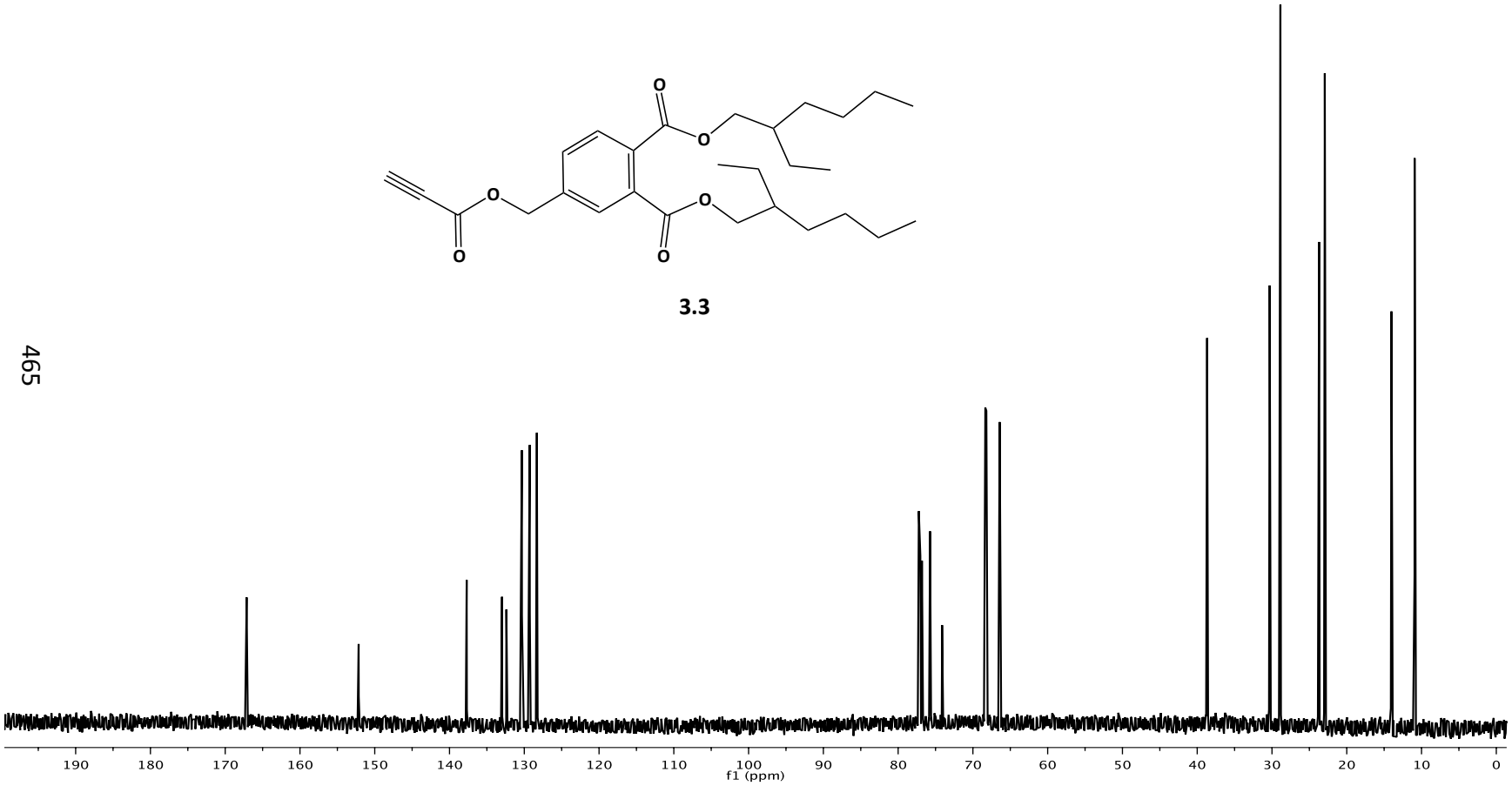

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

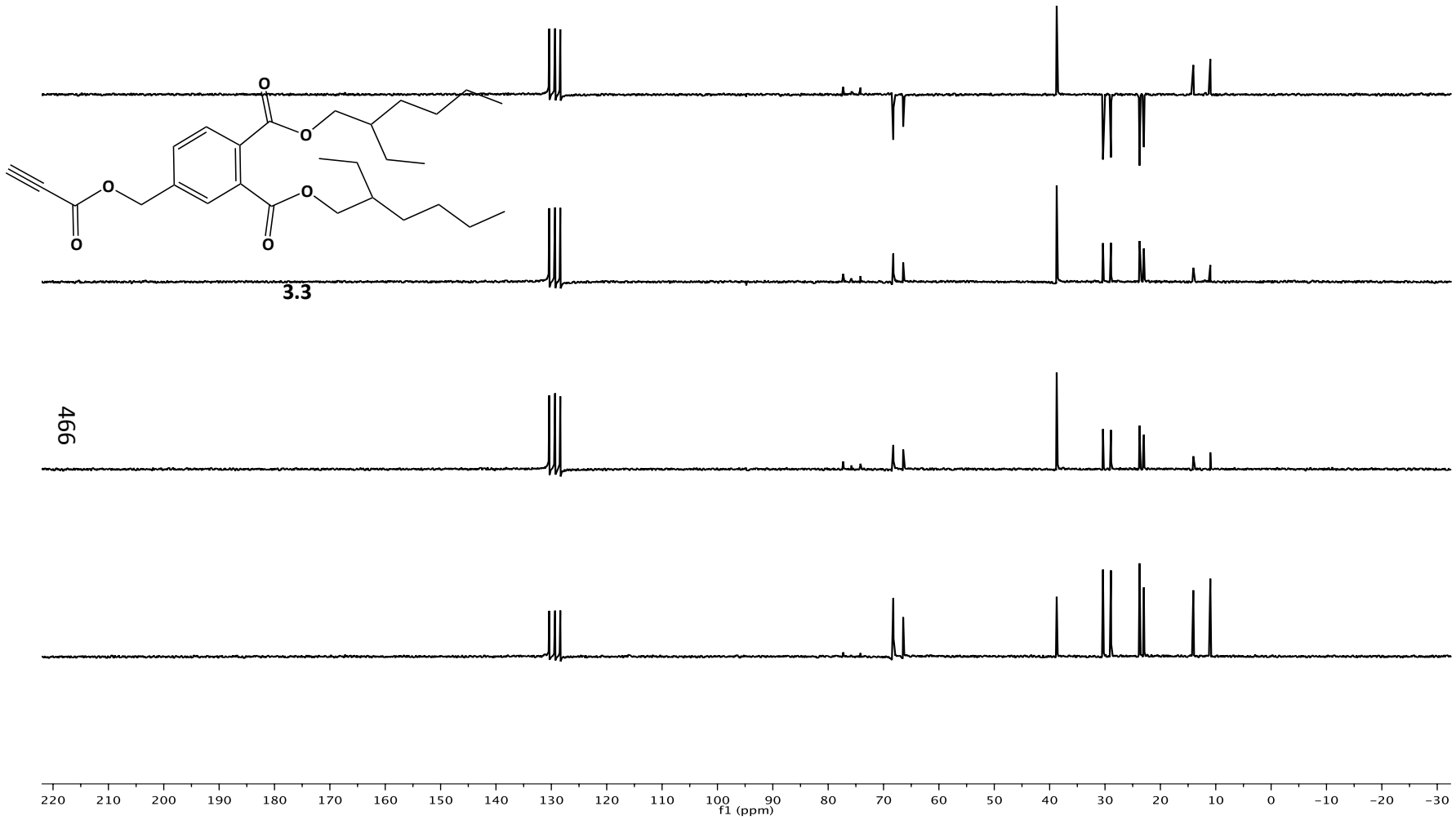

O
O
O
Br
3.11
463
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

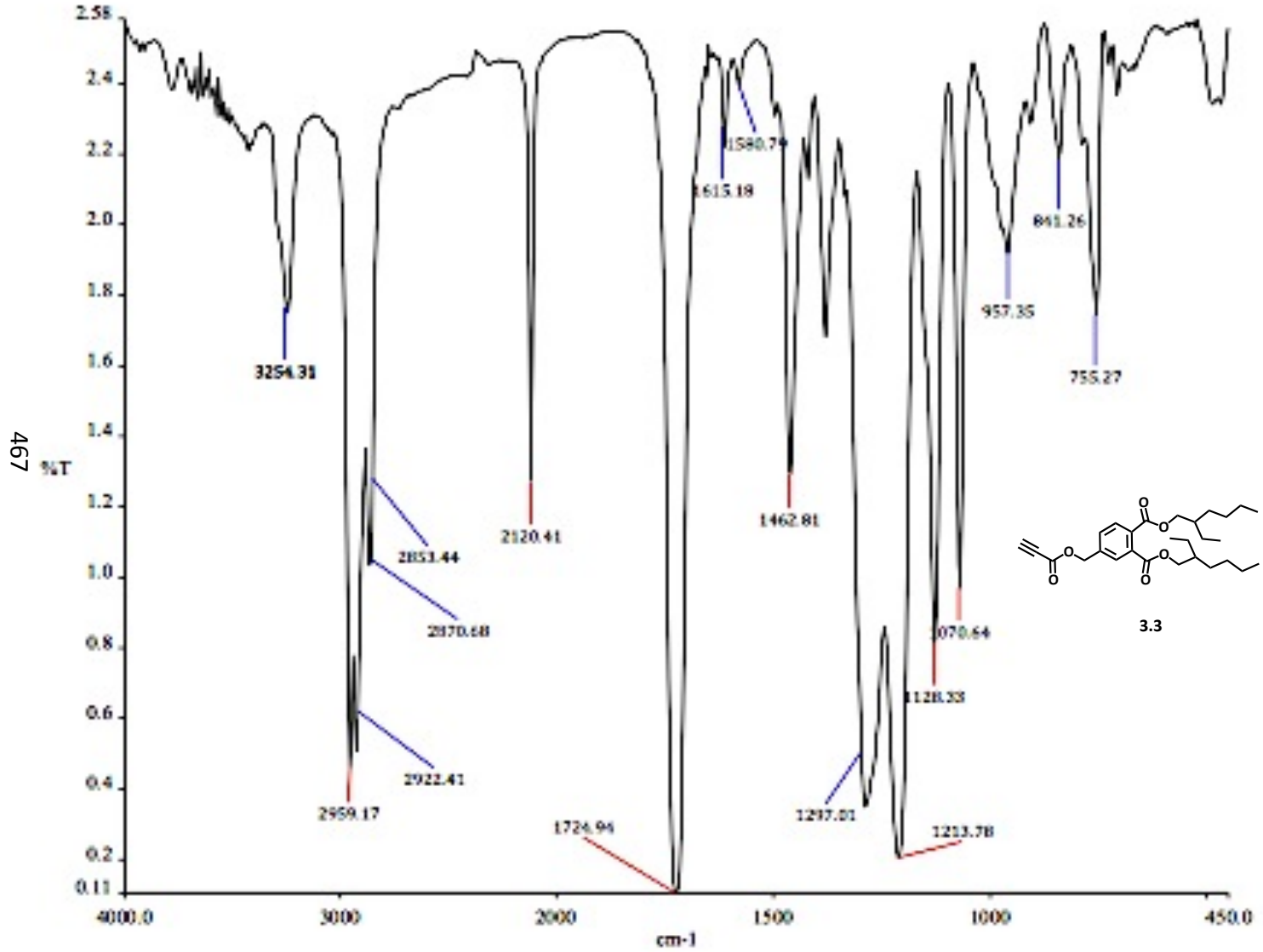


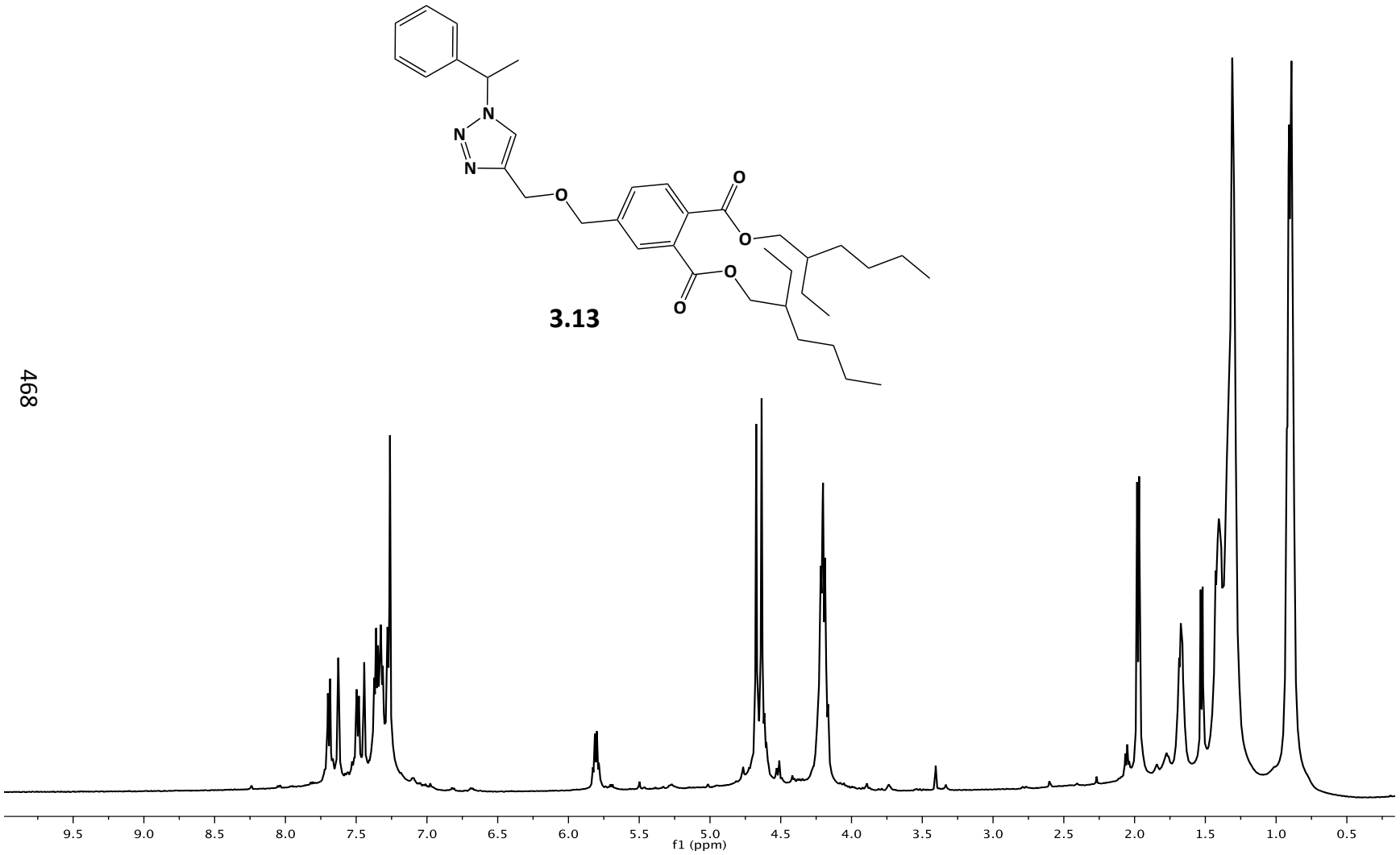
3.3

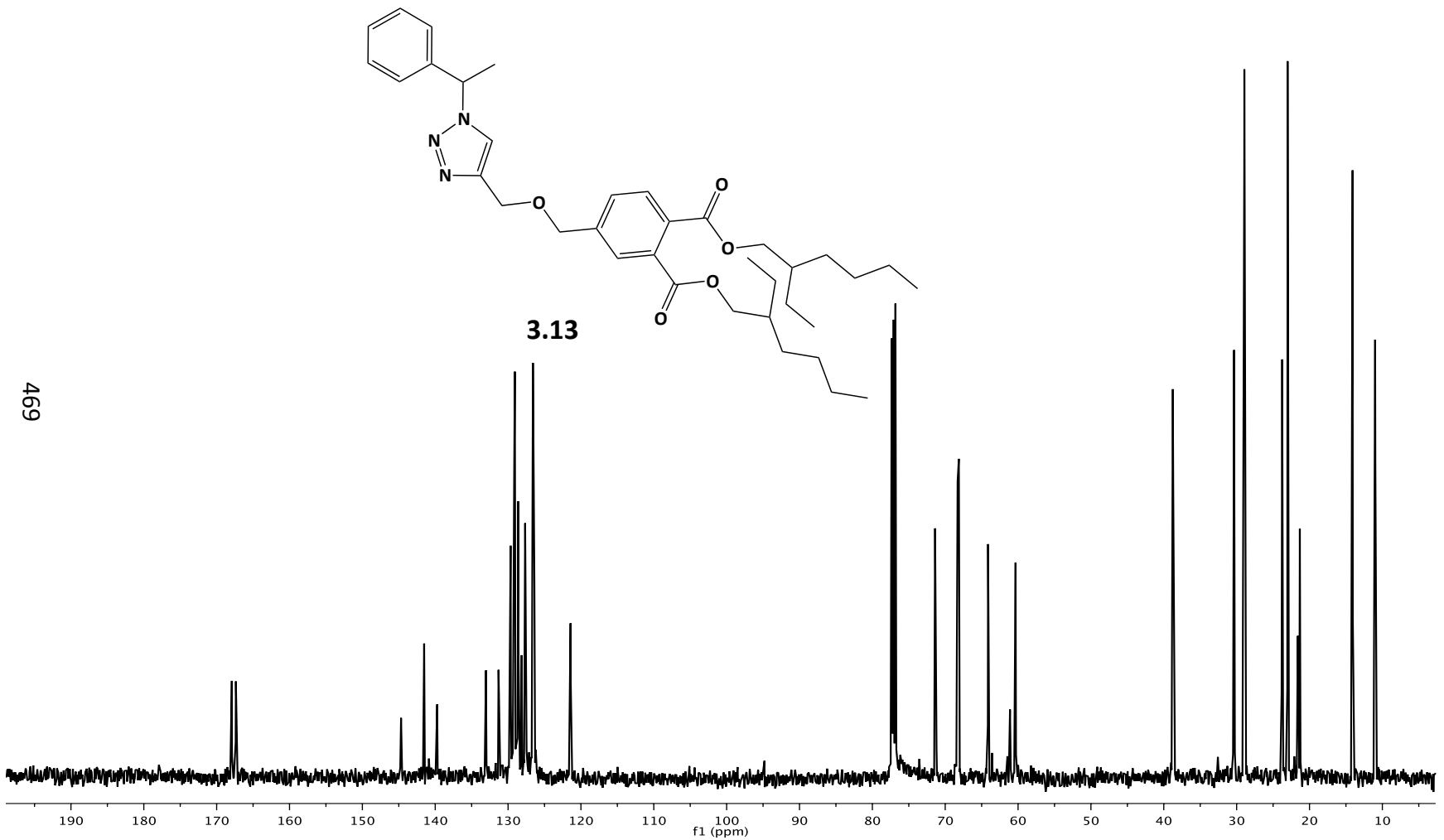


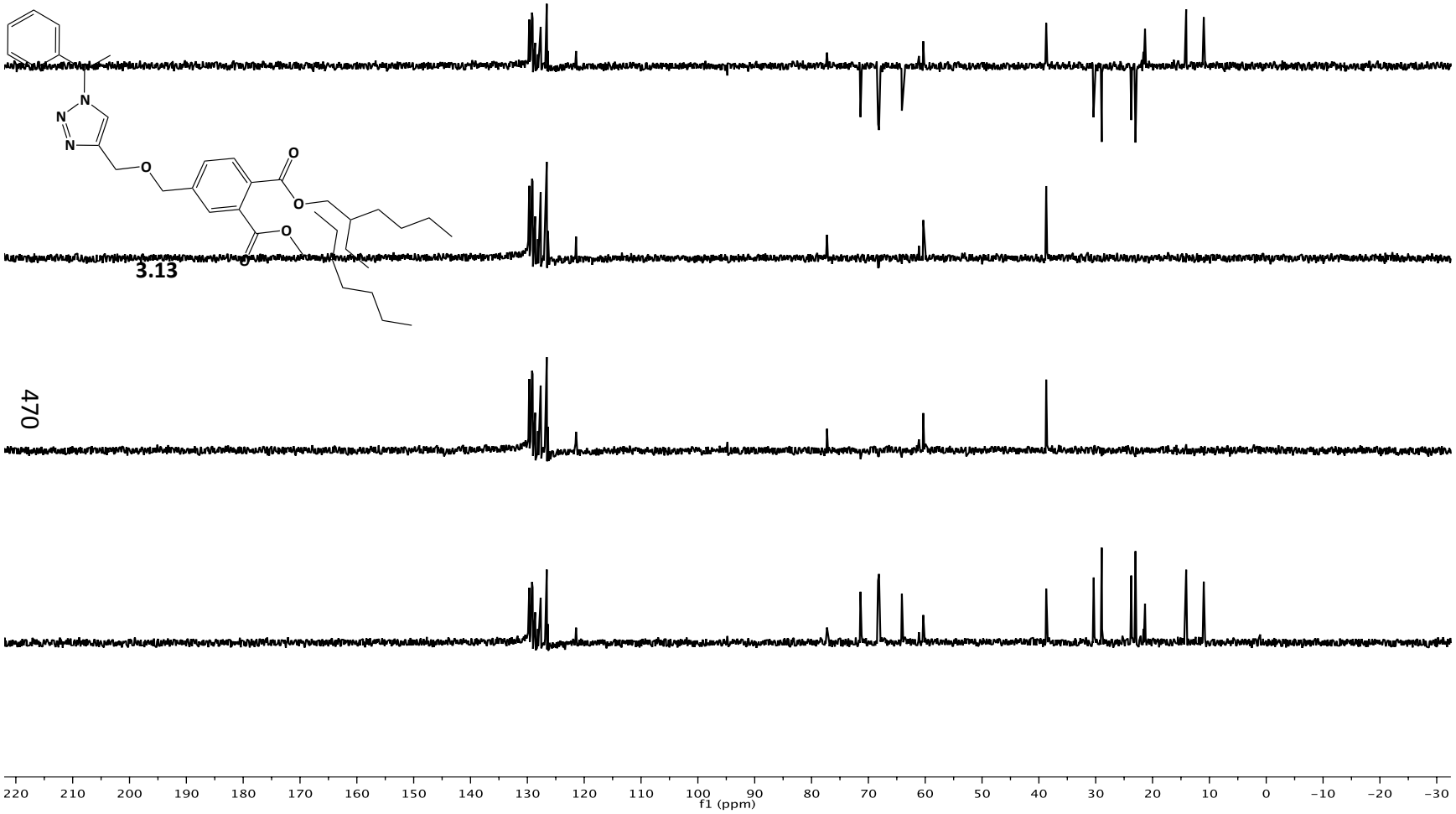

O
O
O
O
O
O
3.3
465
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

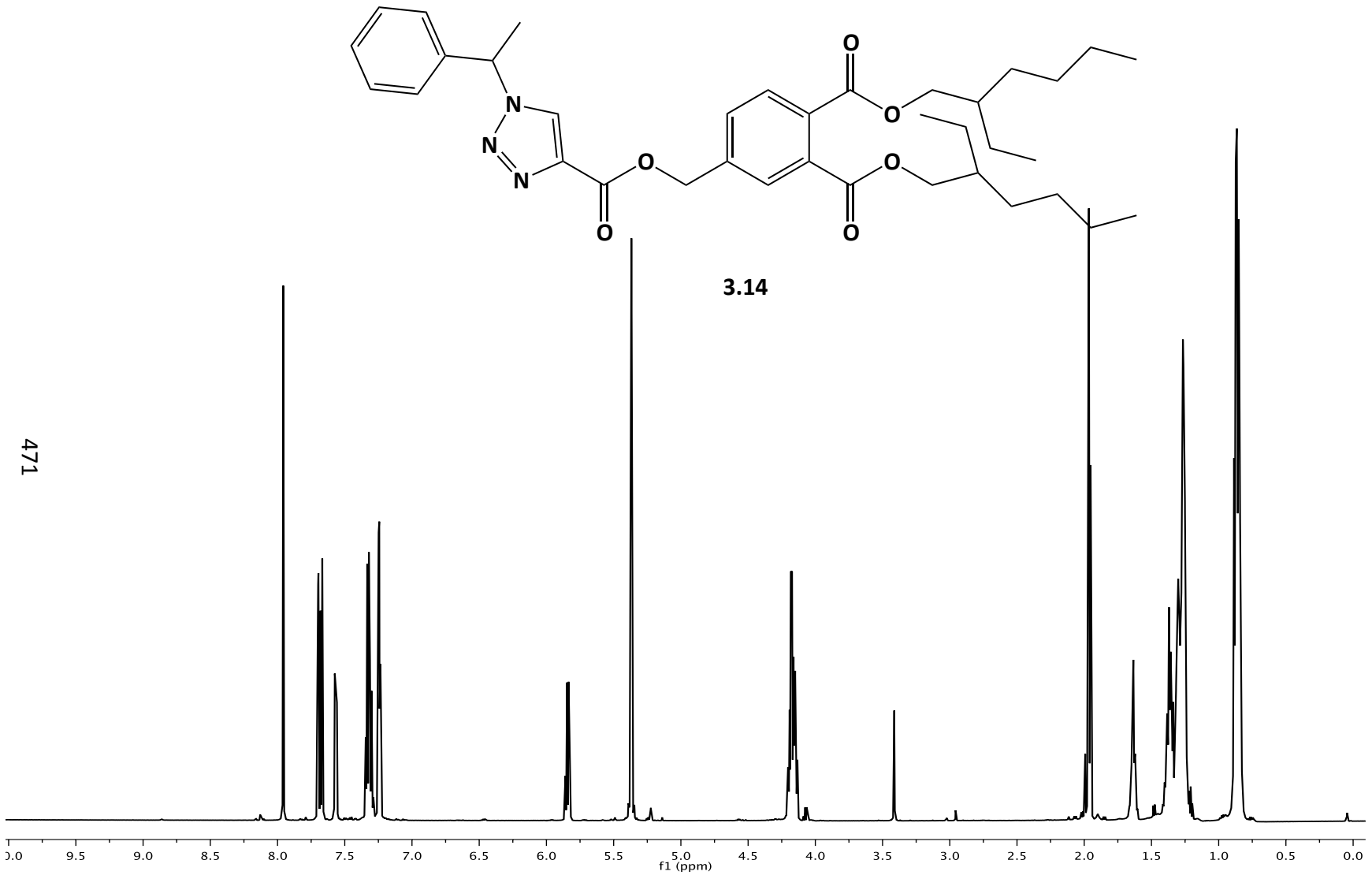

O
O
O
O
O
O
3.3
466
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

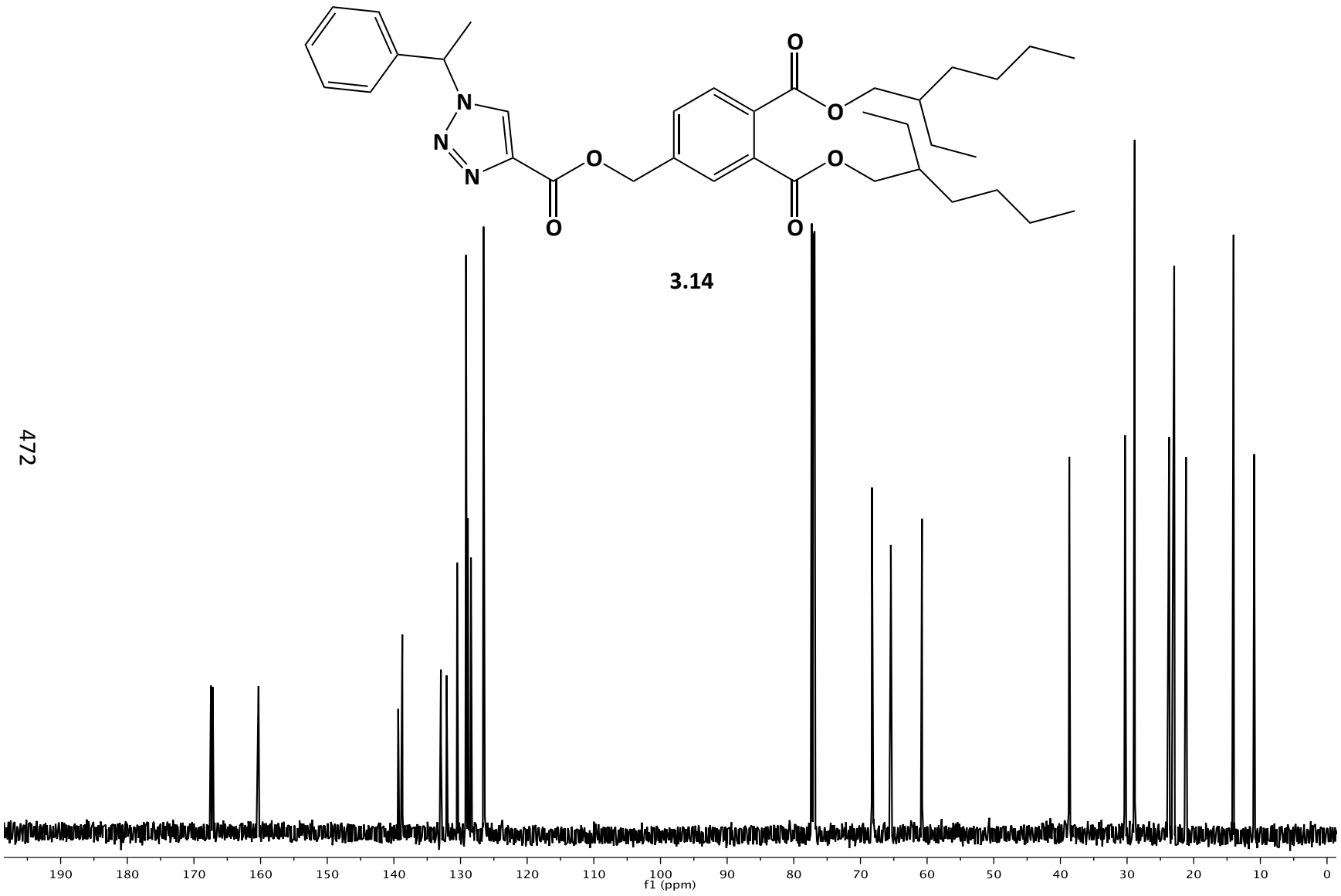

467
%T
cm-1
3254.31
2959.17
2922.41
2870.68
2853.44
2120.41
1724.96
1615.18
1580.74
1462.81
1297.01
1213.78
1128.33
1070.64
957.35
841.26
755.27
3.3

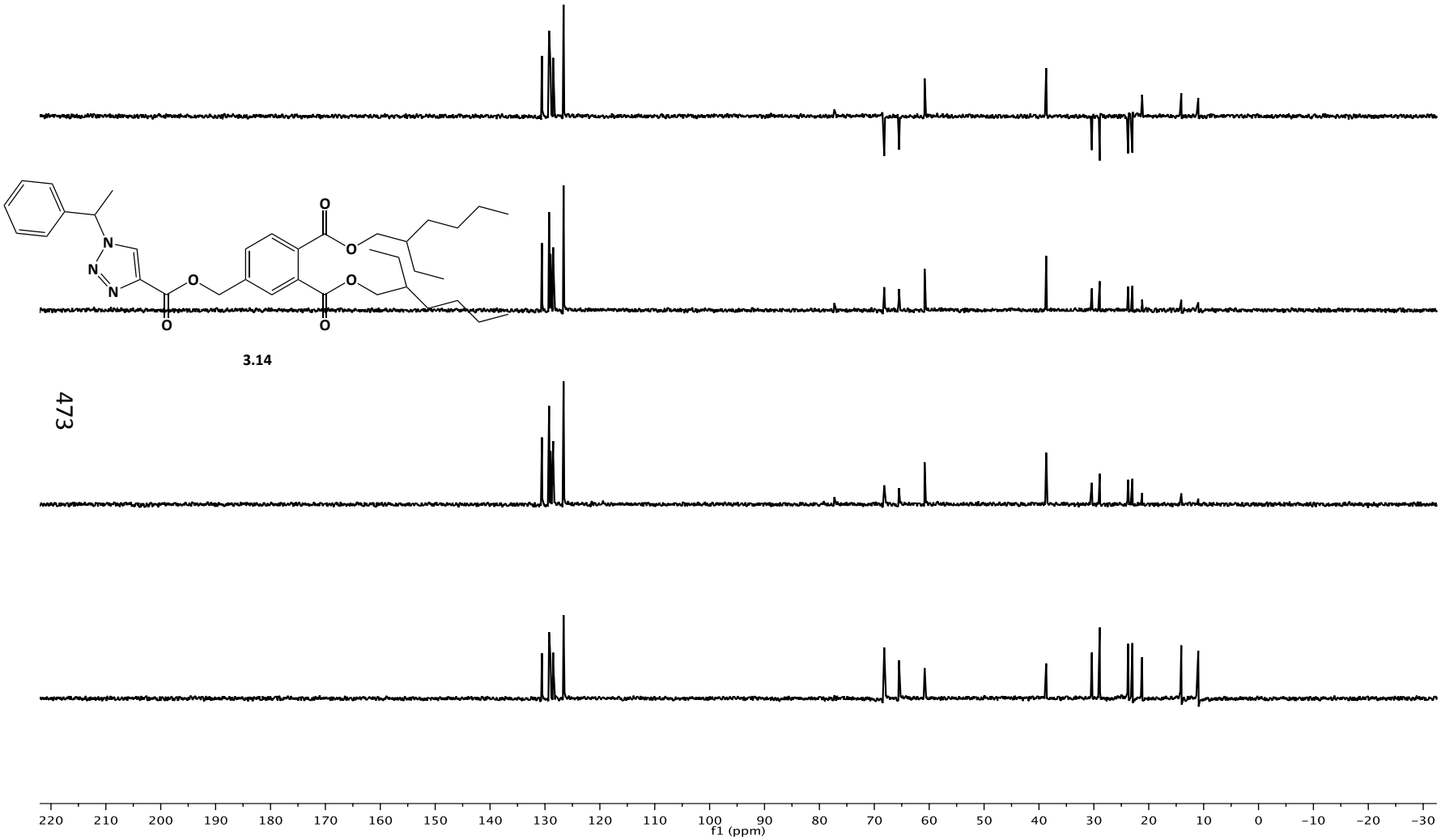

3.13
468
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

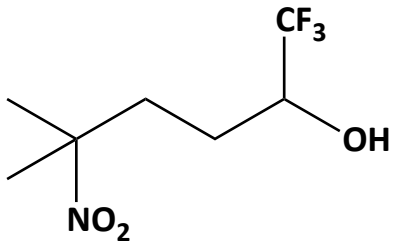

3.13
469
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


3.13
470
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)


N
N
N
O
O
O
O
O
O
3.14
471
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
N
N
N
O
O
O
O
O
3.14
472
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

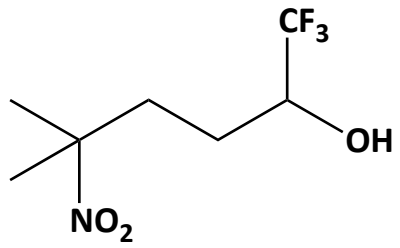

3.14
473
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)


CF3
OH
NO2

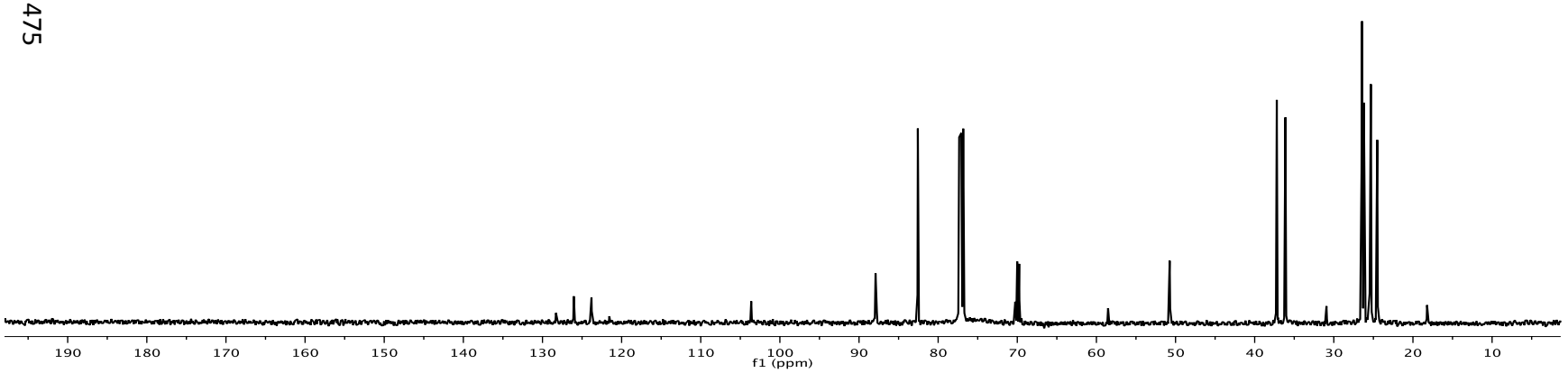
4.66

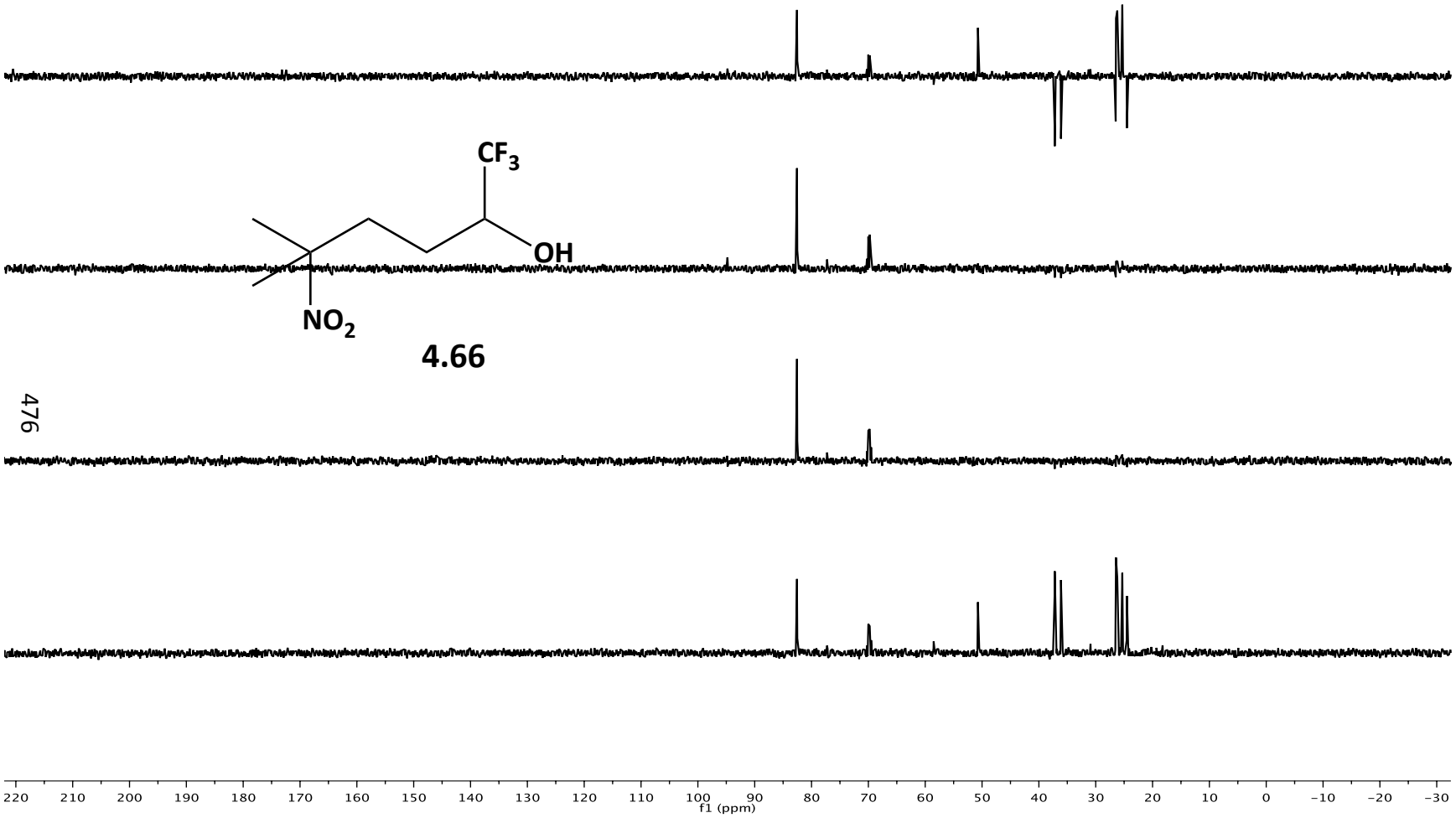
474

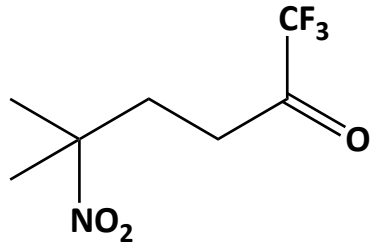
.0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CF3
OH
NO2

4.66

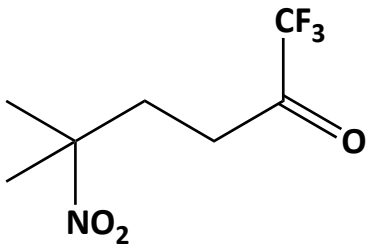

475
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


CF3
OH
NO2
4.66
476
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)


CF3
O
NO2

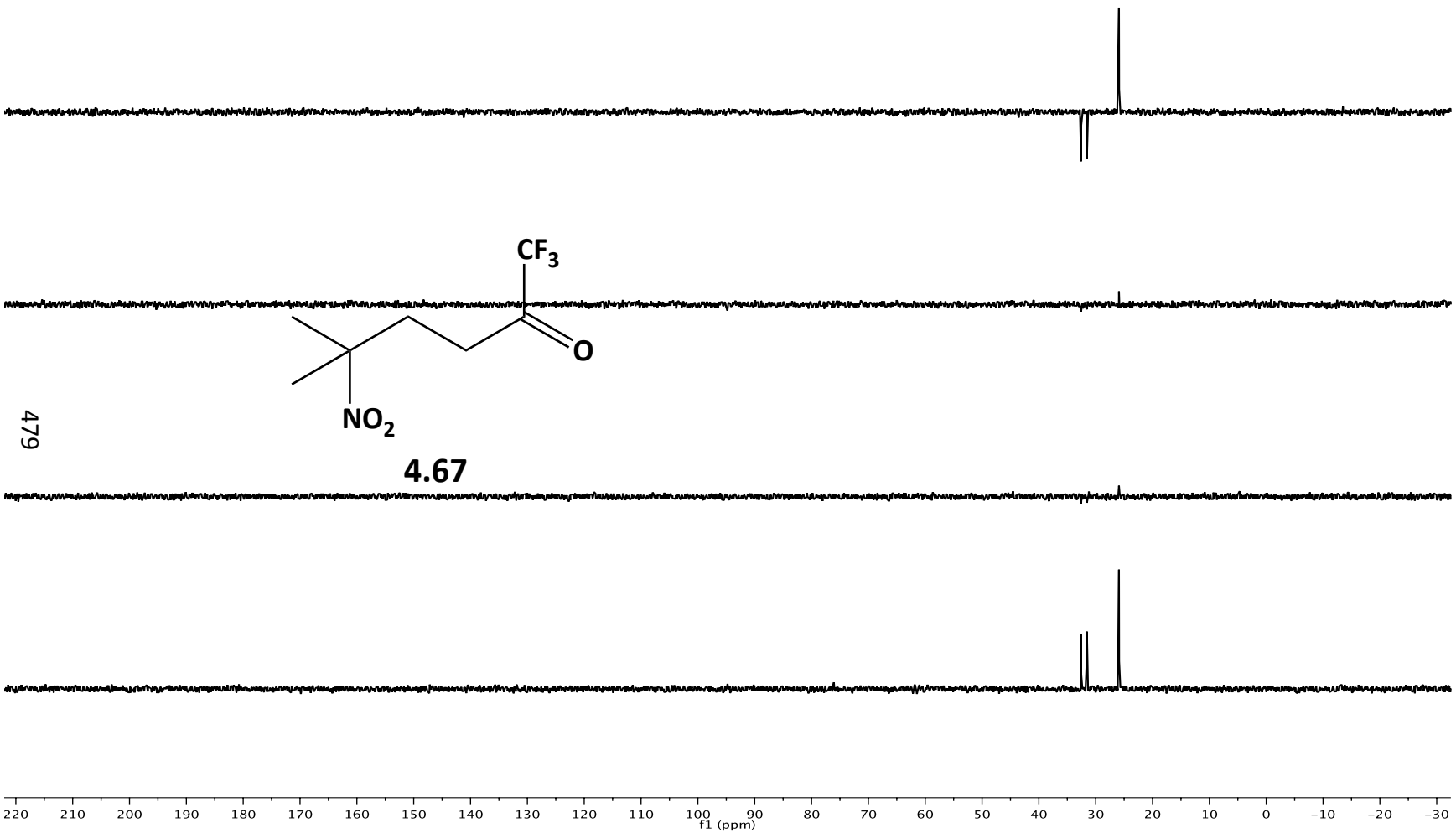
4.67

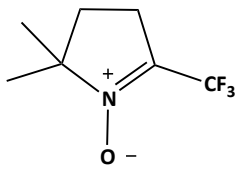
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CF3
O
NO2

4.67

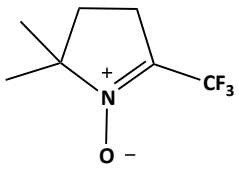
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CF3
O
NO2
479
4.67
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)



2-TFDMPO

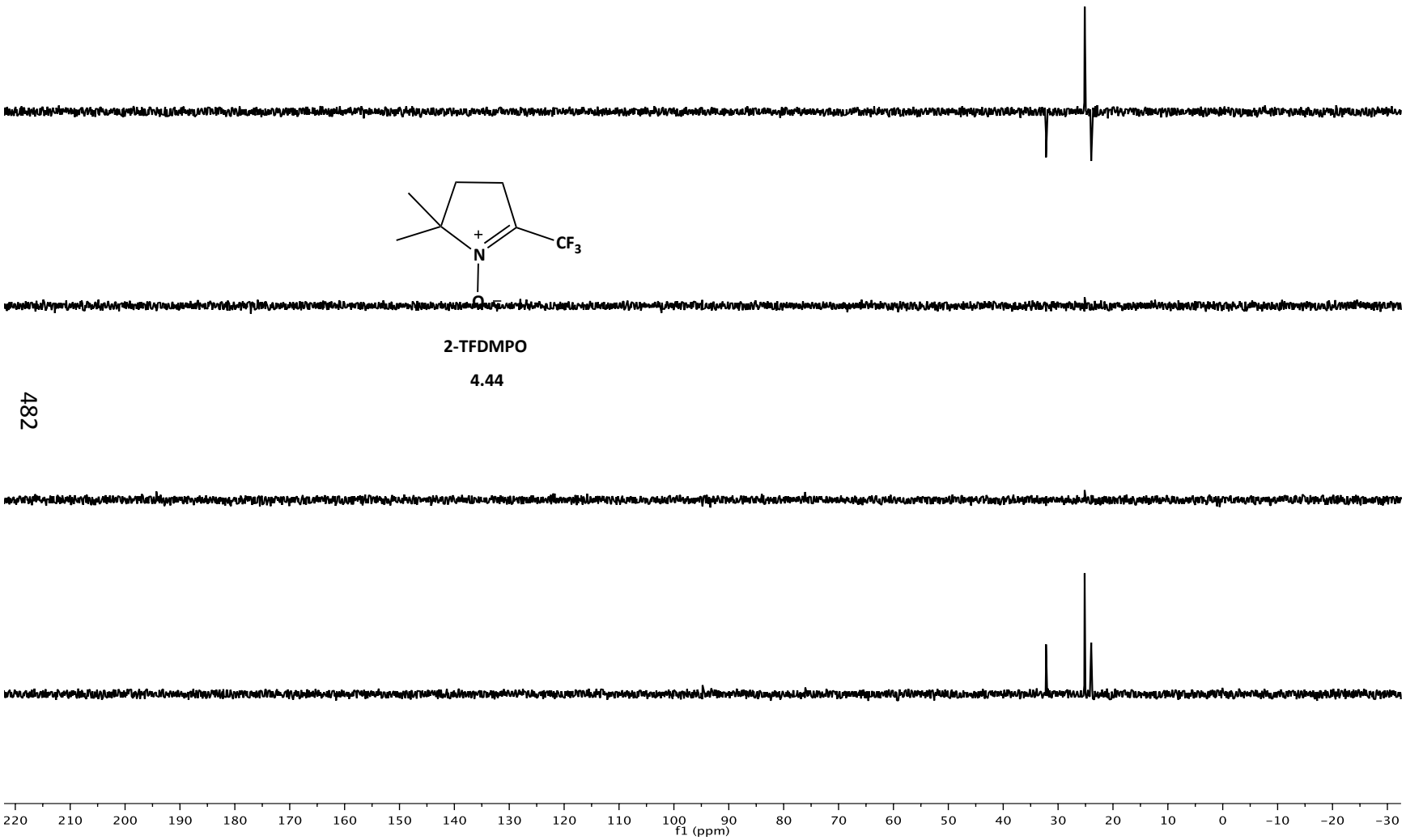
4.44


+
N
O −
CF3

2-TFDMPO

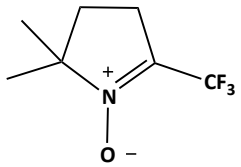
4.44

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)


CF3
N
+
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

2-TFDMPO

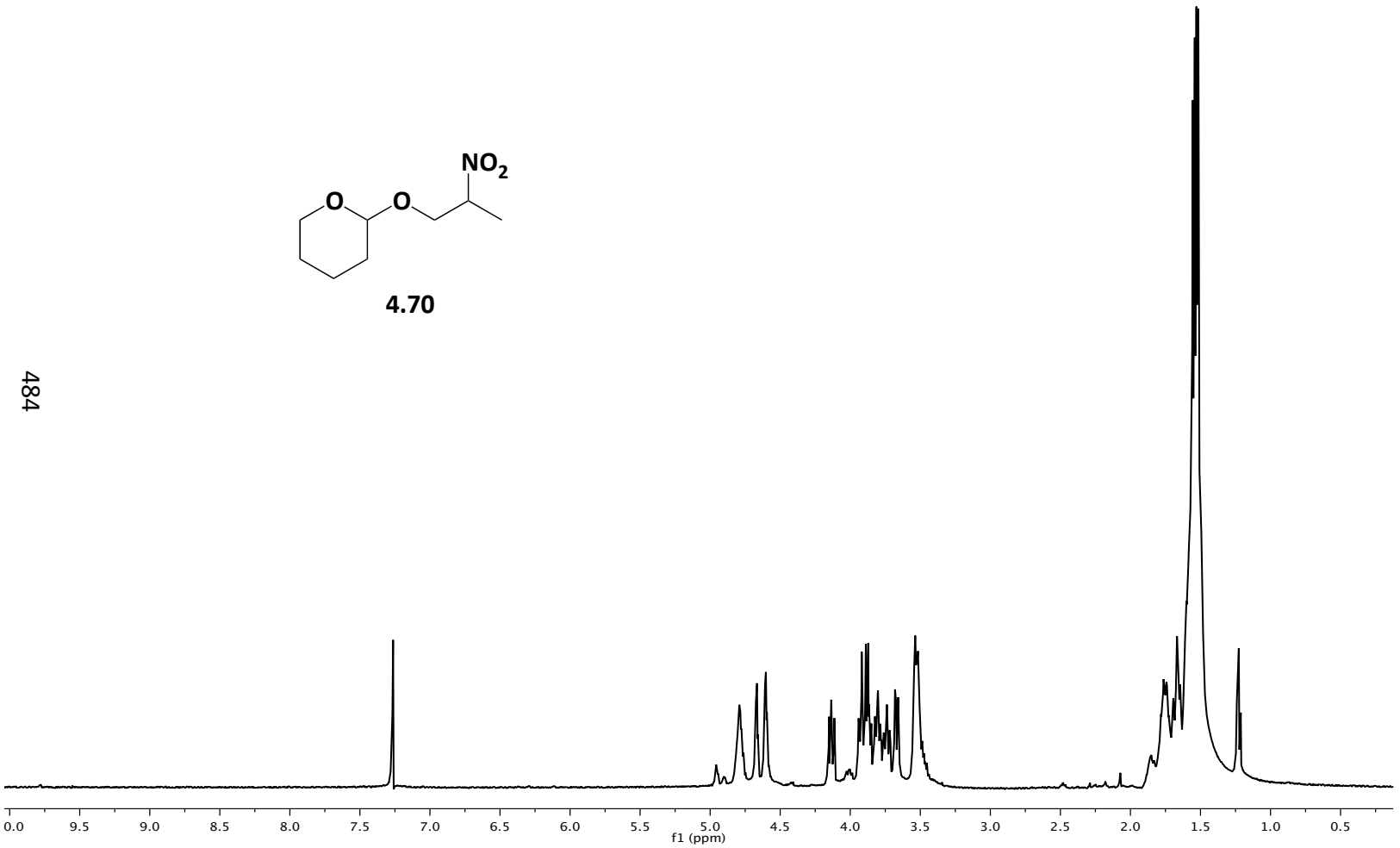
4.44

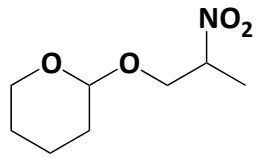

+
N
O −
CF3

2-TFDMPO

4.44

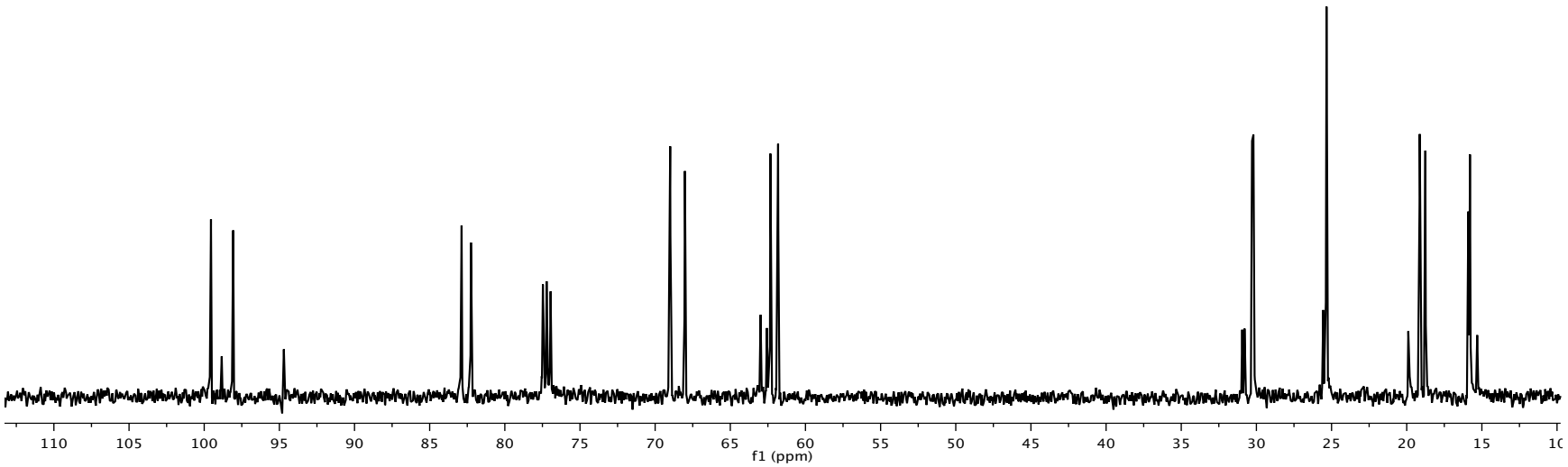
40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
−230
−240
−250
f1 (ppm)

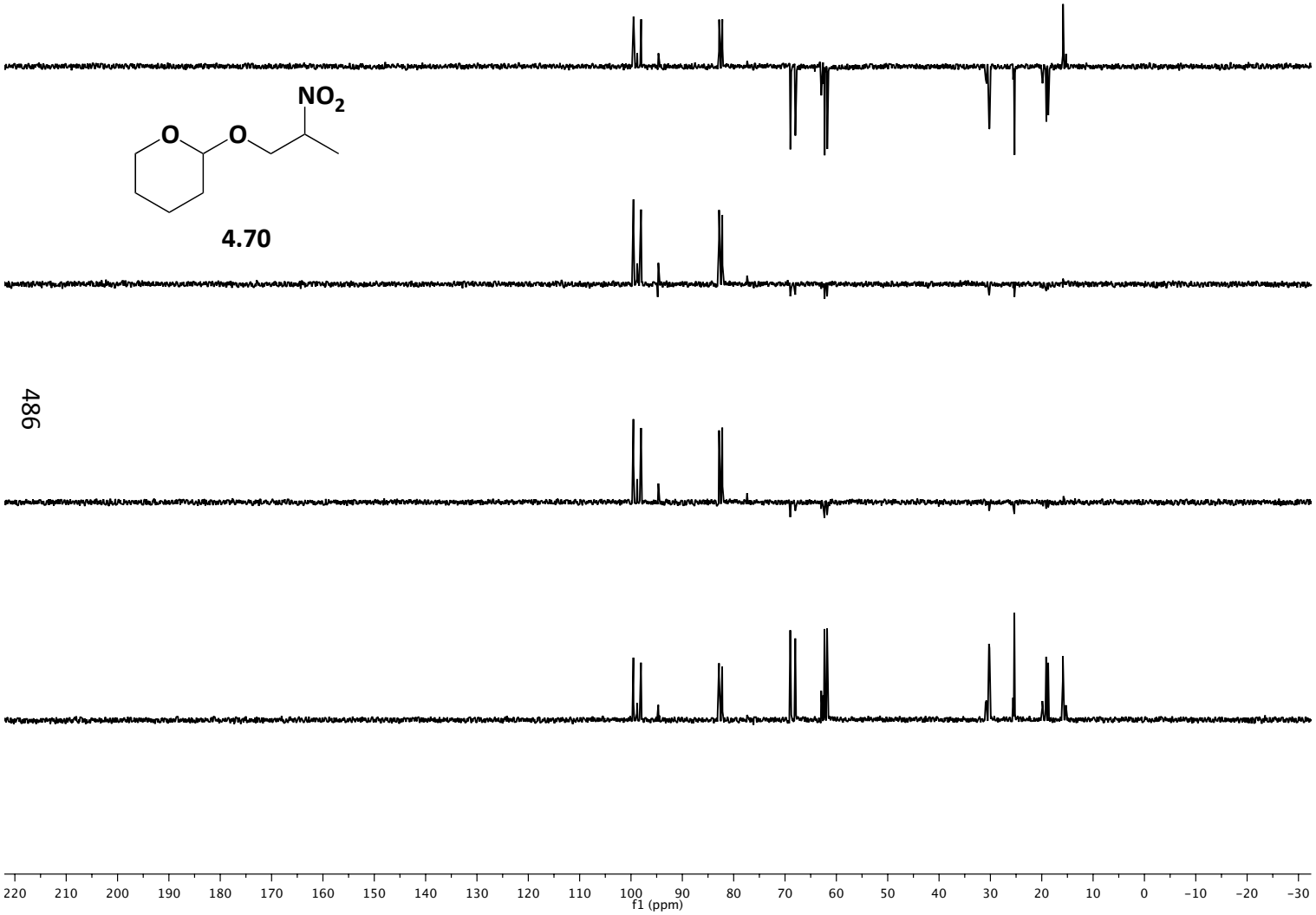

NO2
O
O
4.70
484
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

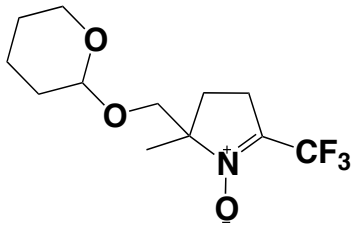

NO2
O
O

4.70

485

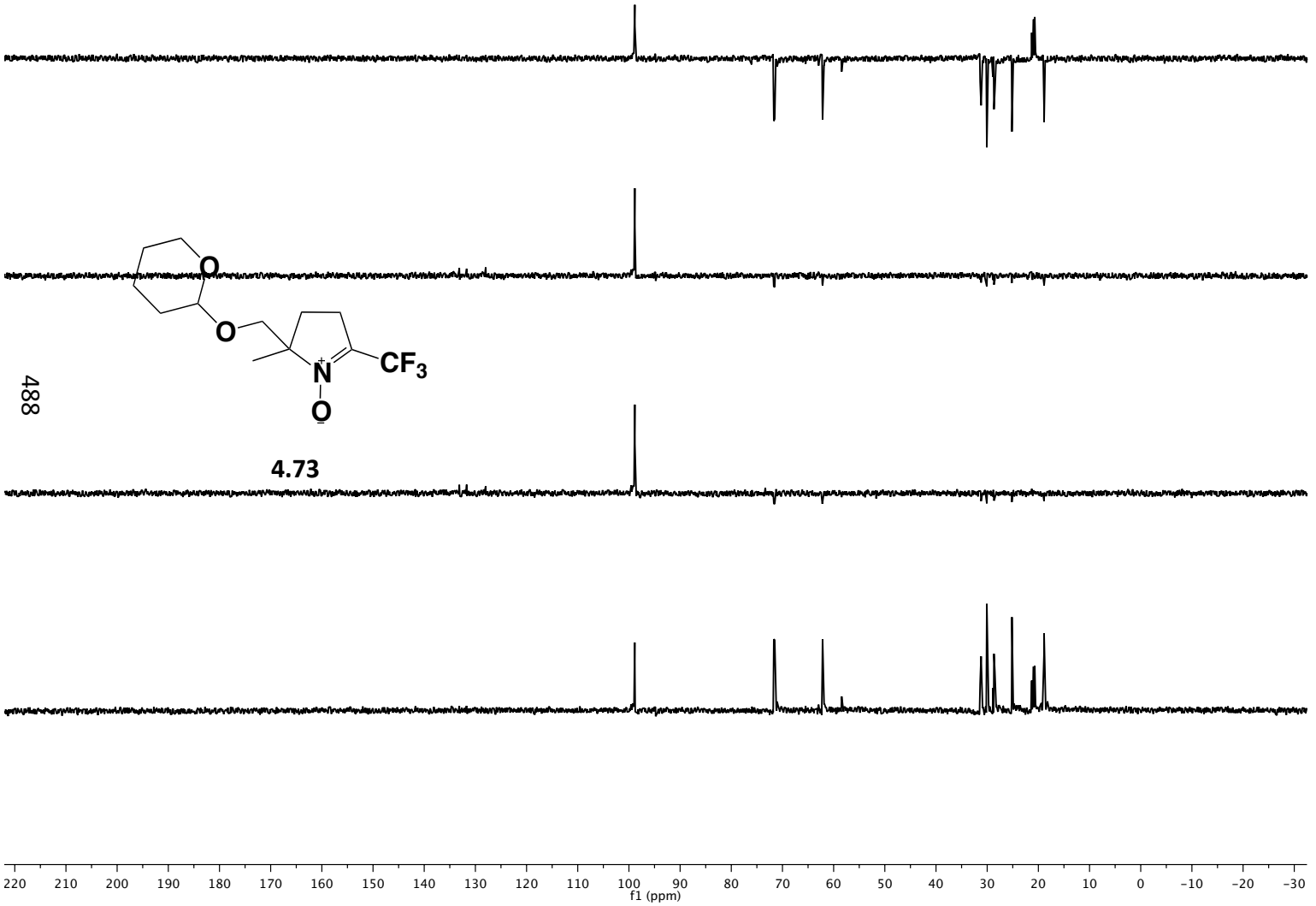

110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)

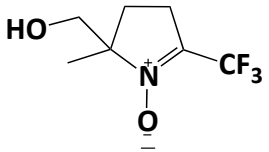

NO2
O
O
4.70
486
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


O
O
N
O
CF3

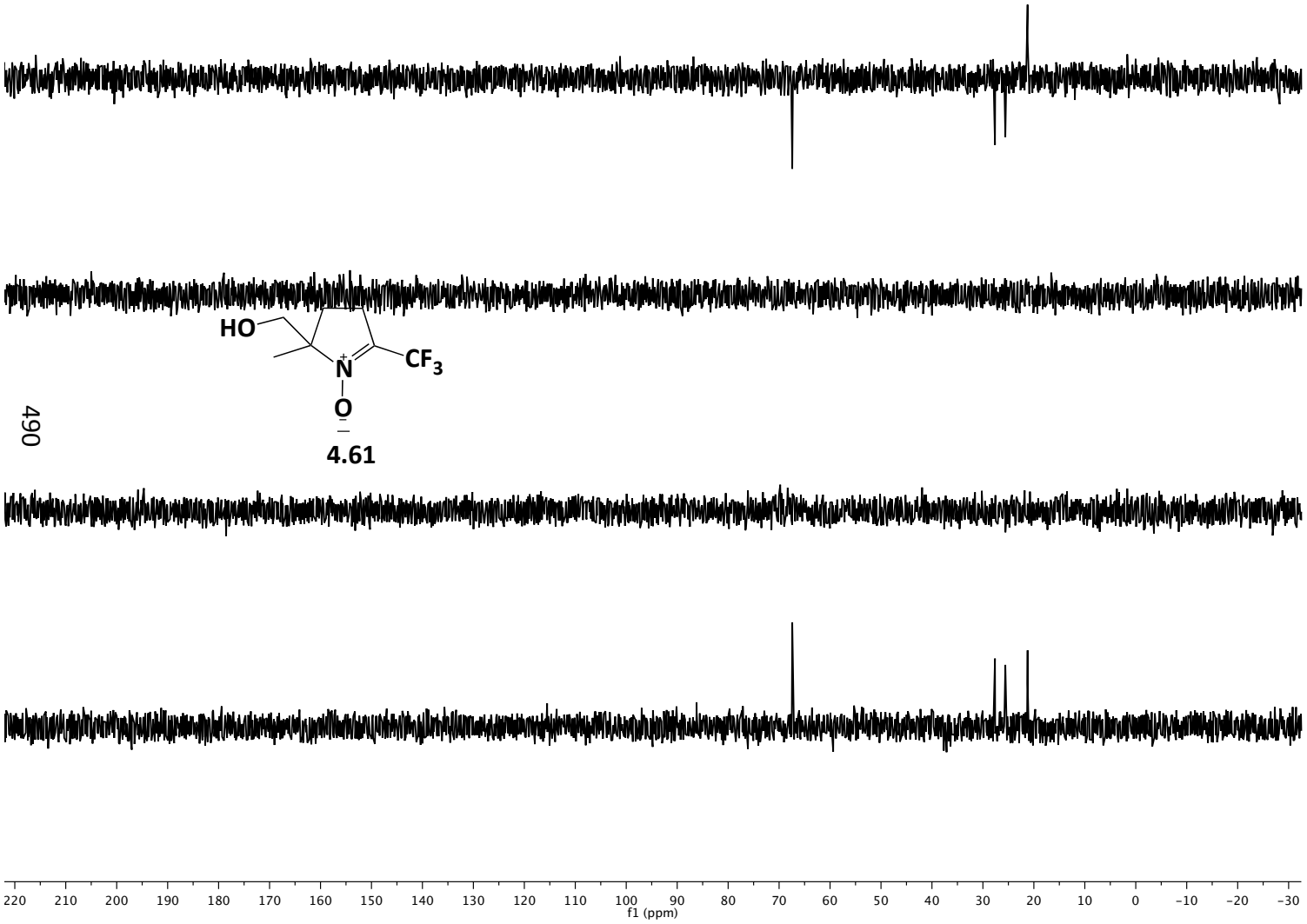
4.73

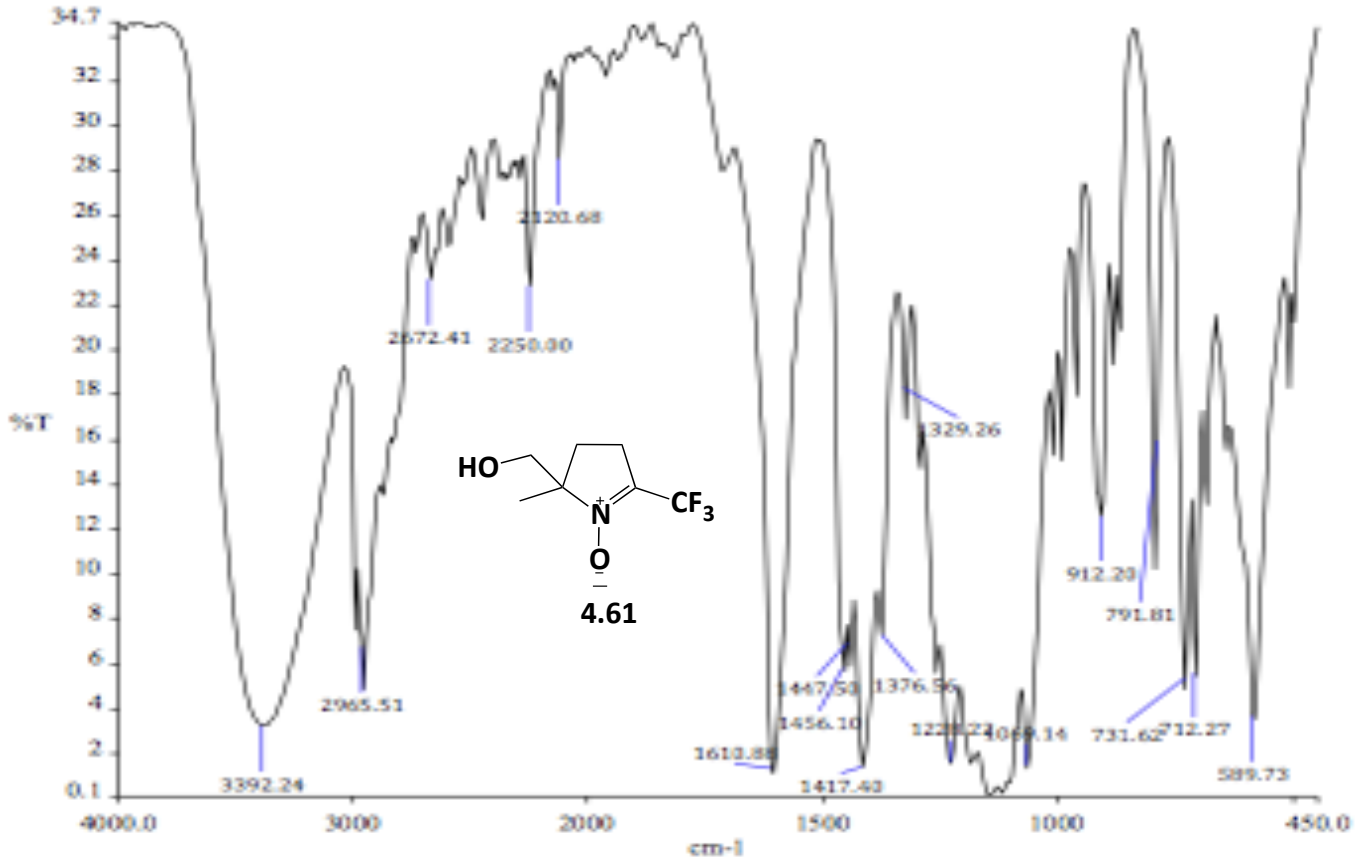
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
O
N
O
CF3
488
4.73
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

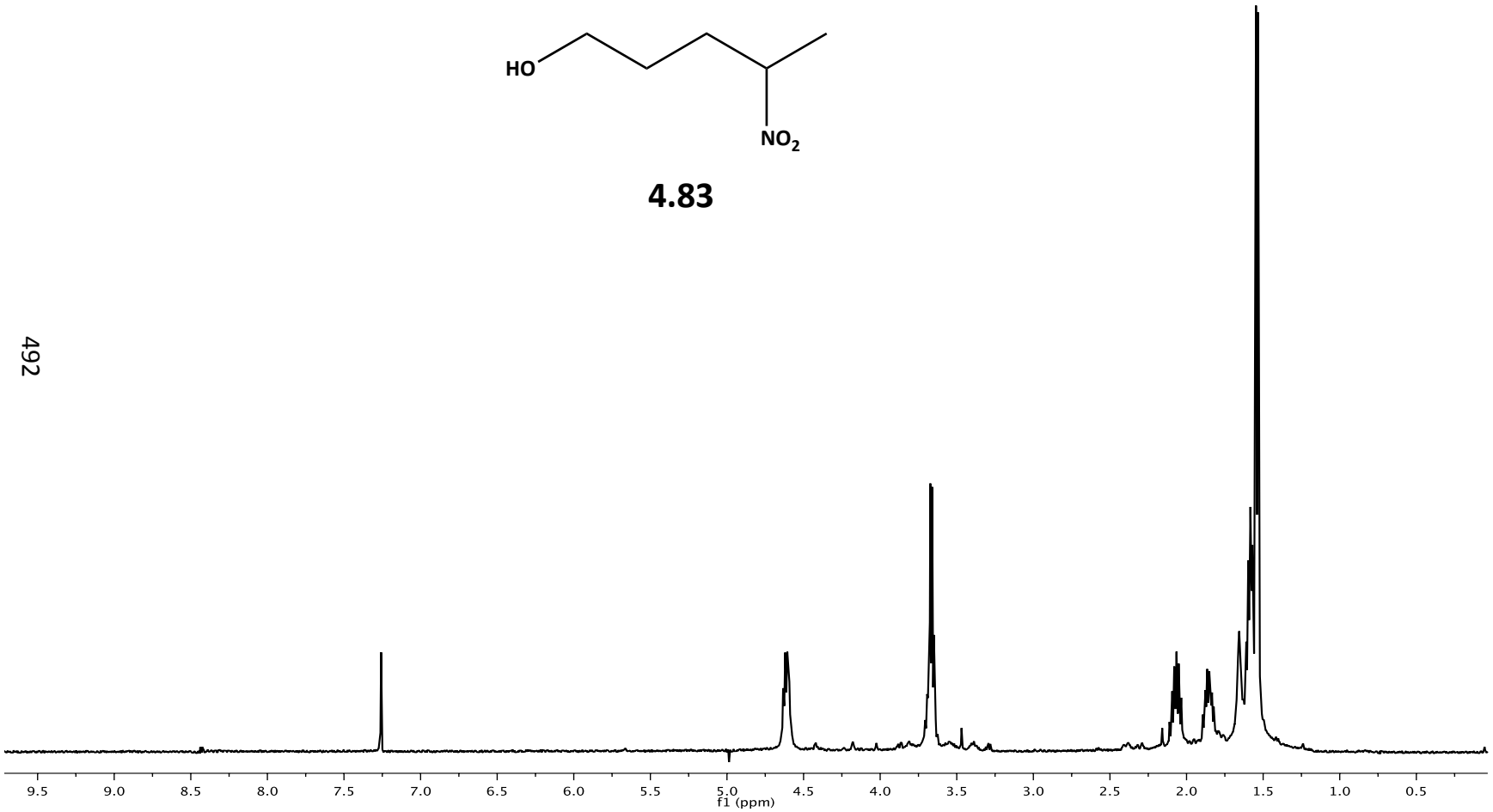


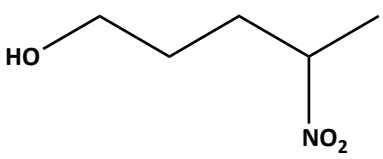
4.61


HO
N
+
O
−
CF3
490
4.61
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

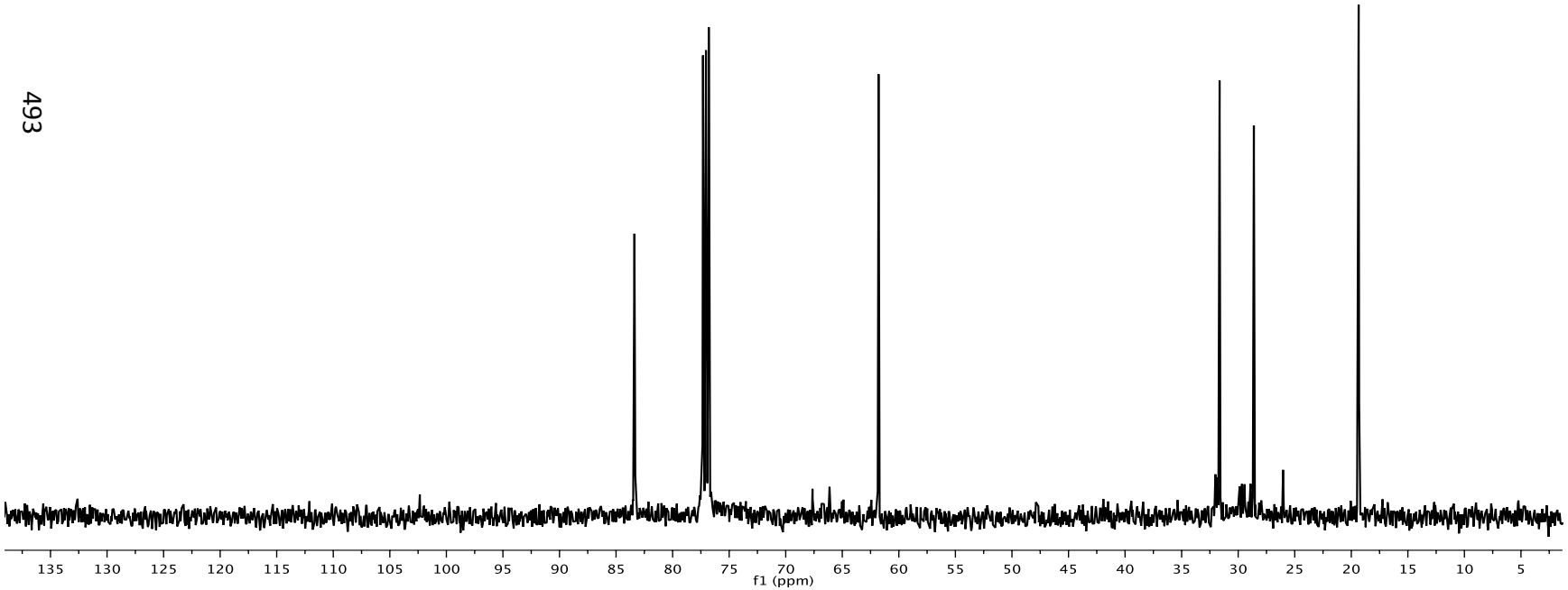

%T
cm-1
4000.0
3000
2000
1500
1000
450.0
3392.24
2965.51
2672.41
2250.00
2320.68
1613.88
1456.10
1417.43
1329.26
912.20
791.81
731.62
712.27
589.73
HO
CF3
N
O

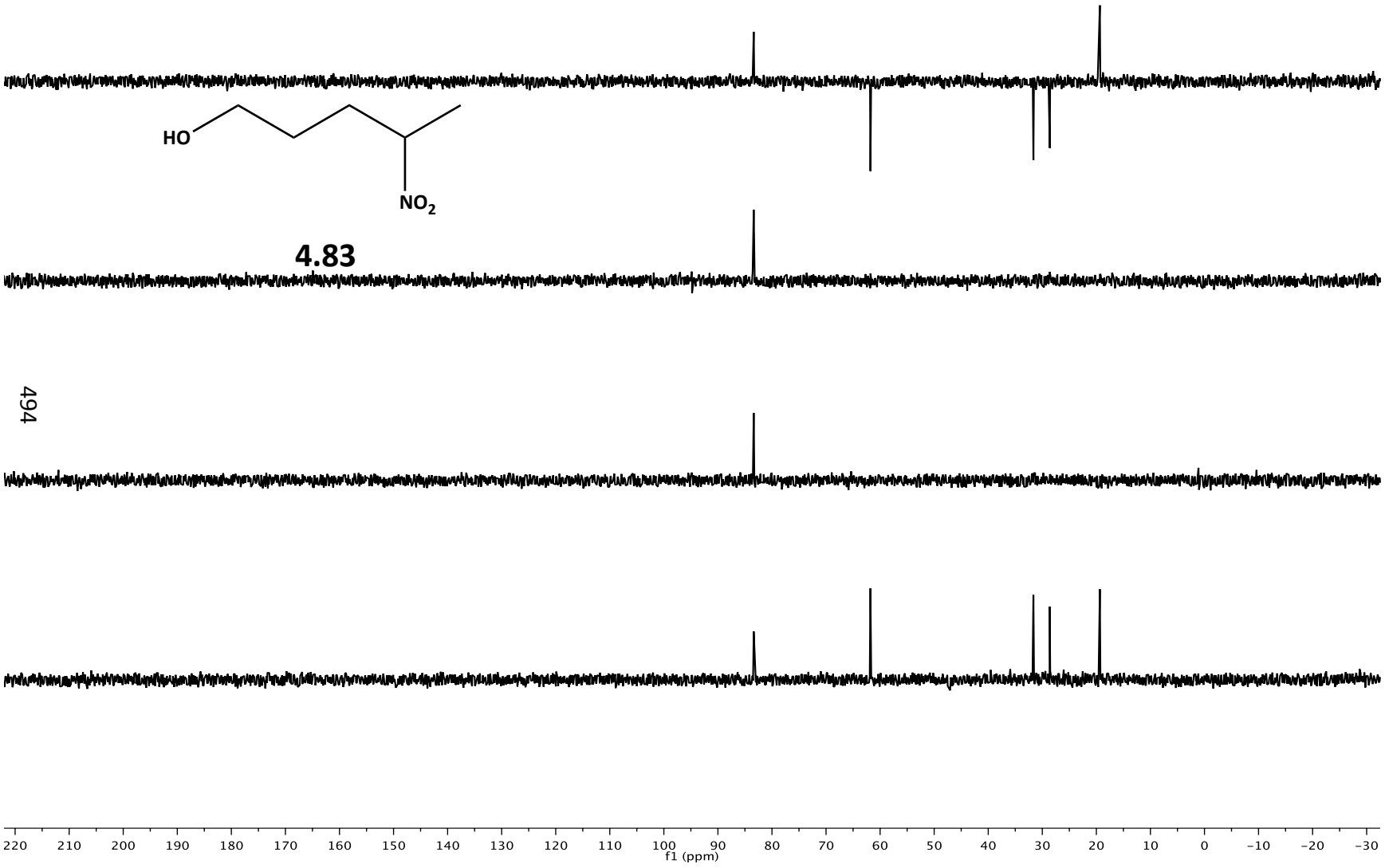
4.61

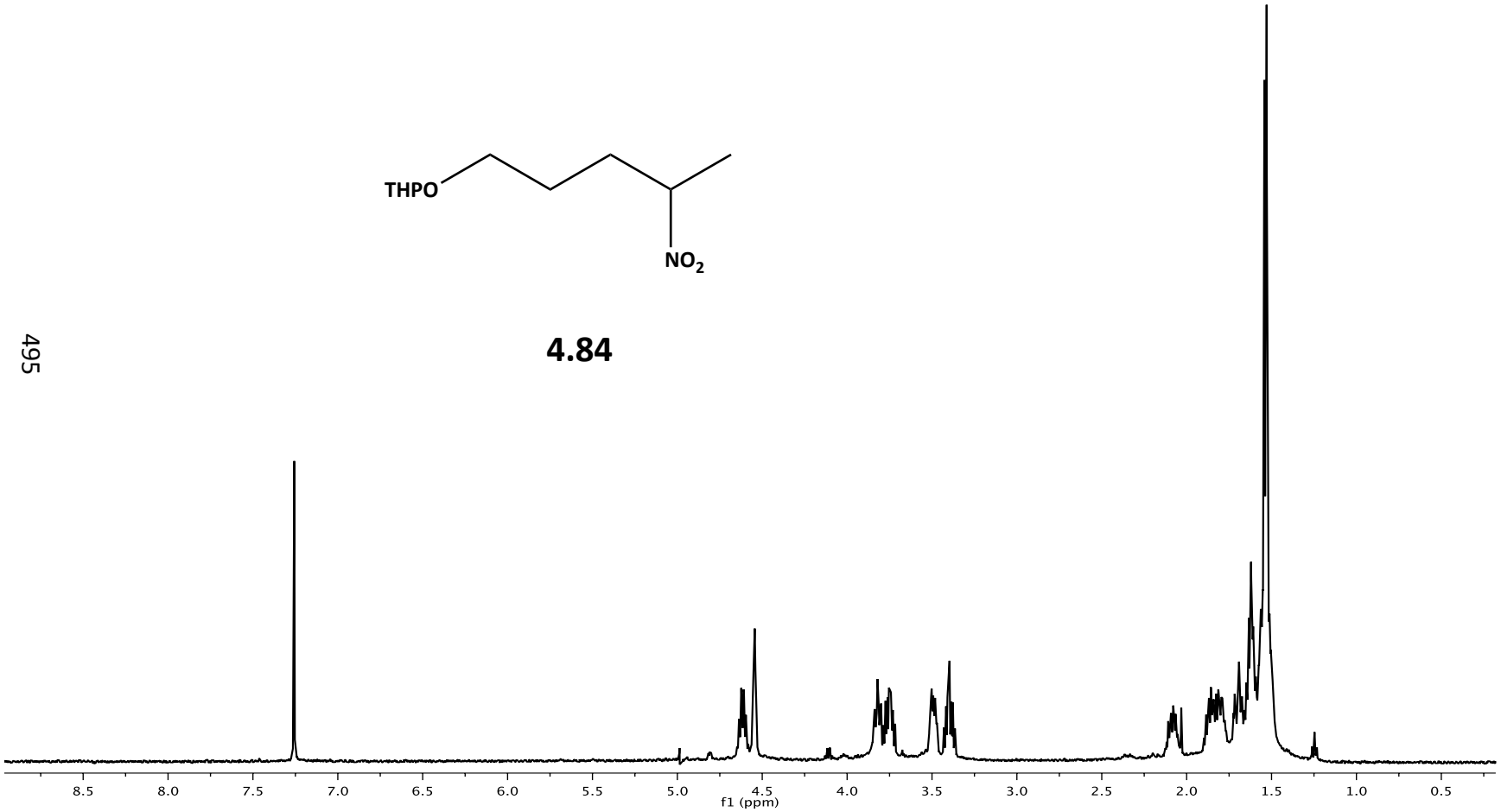

HO
NO2
4.83
492
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

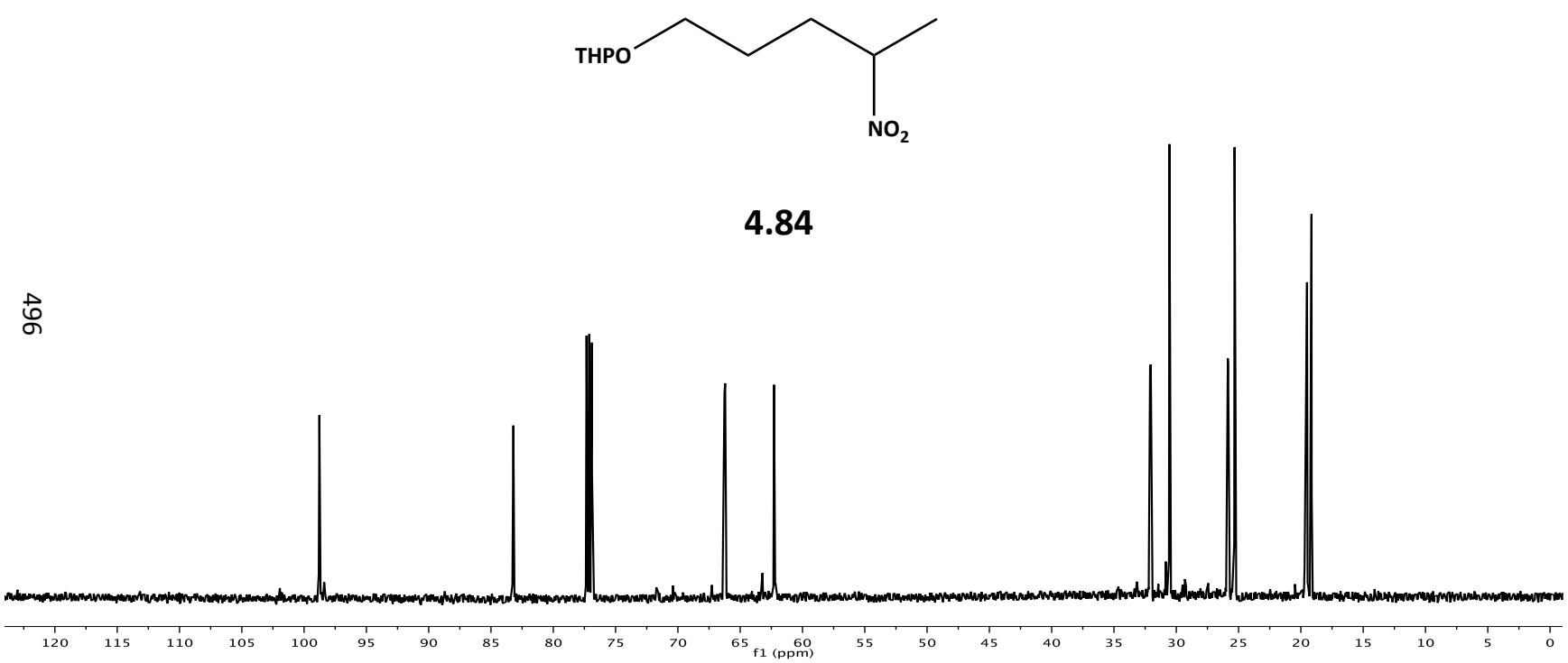

HO
NO2

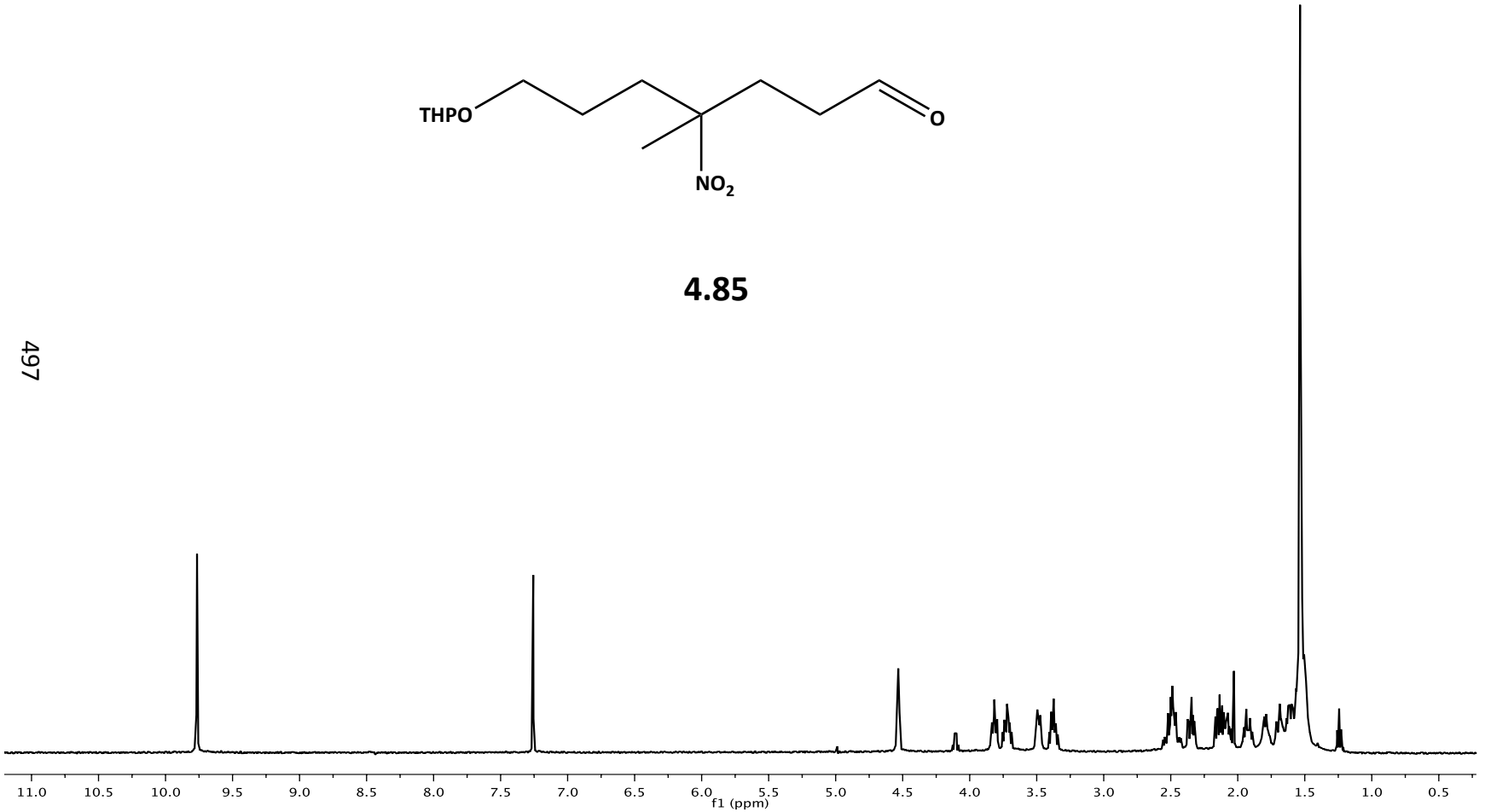
4.83

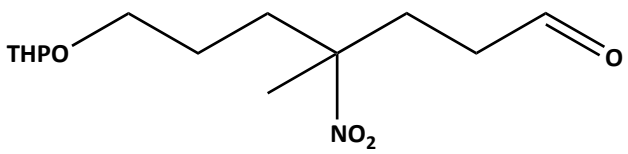

493
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5
f1 (ppm)


HO
NO2
4.83
494
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

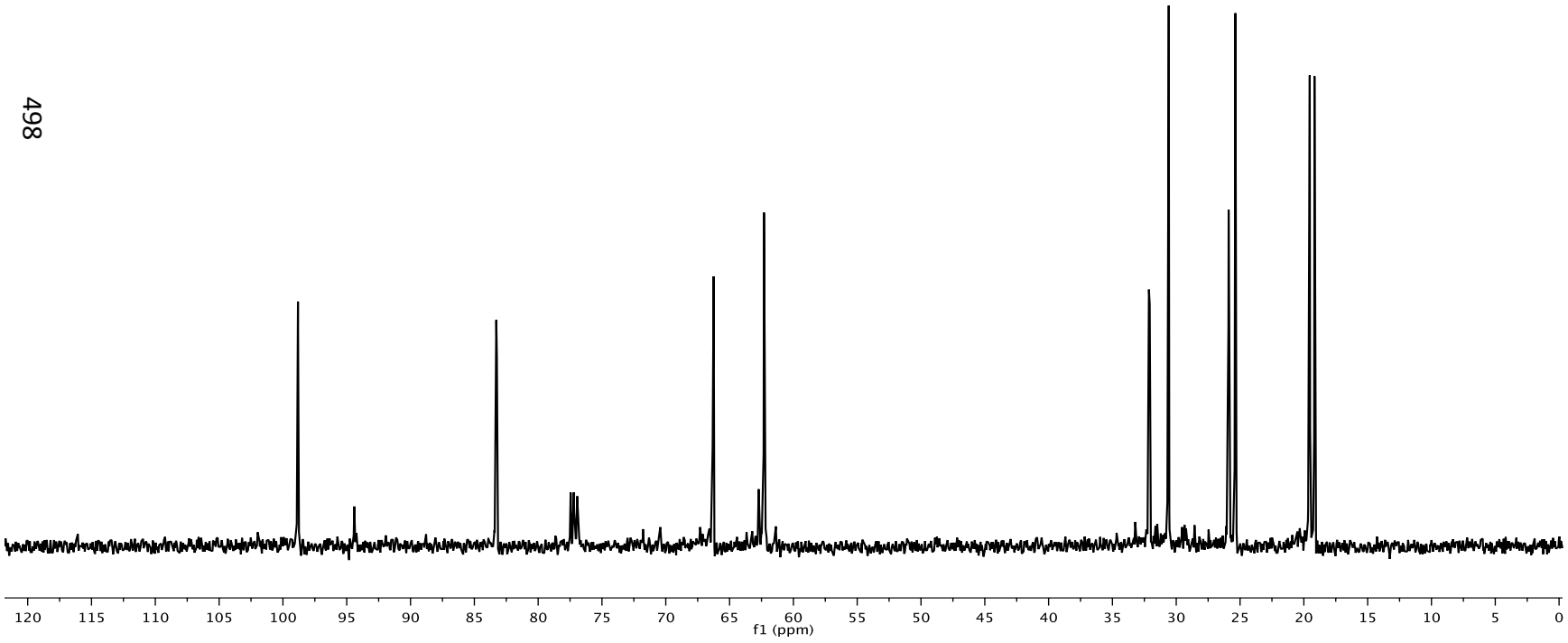

THPO
NO2
4.84
495
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

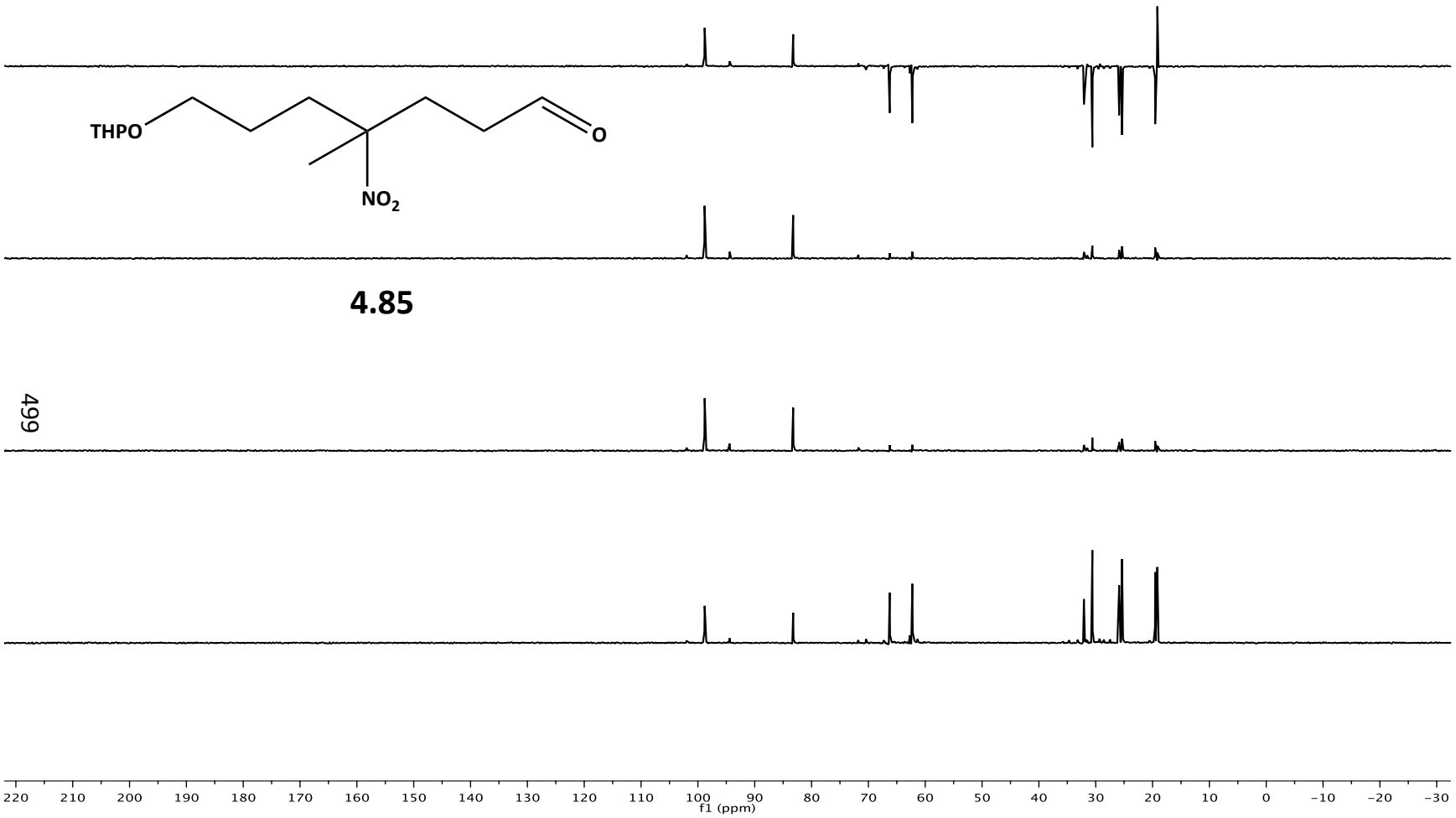

THPO
NO2
4.84
496
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

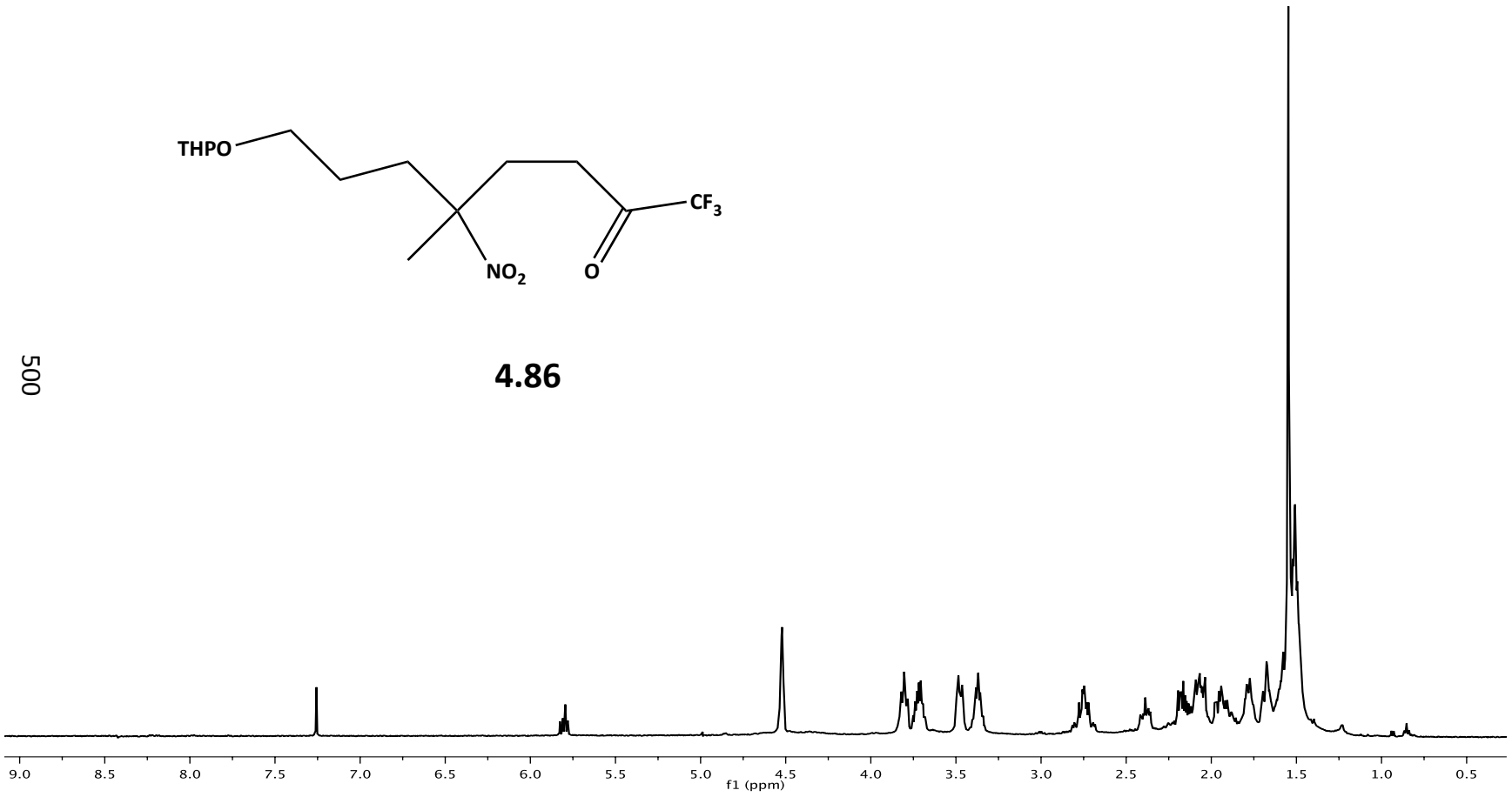

THPO
O
NO2
4.85
497
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

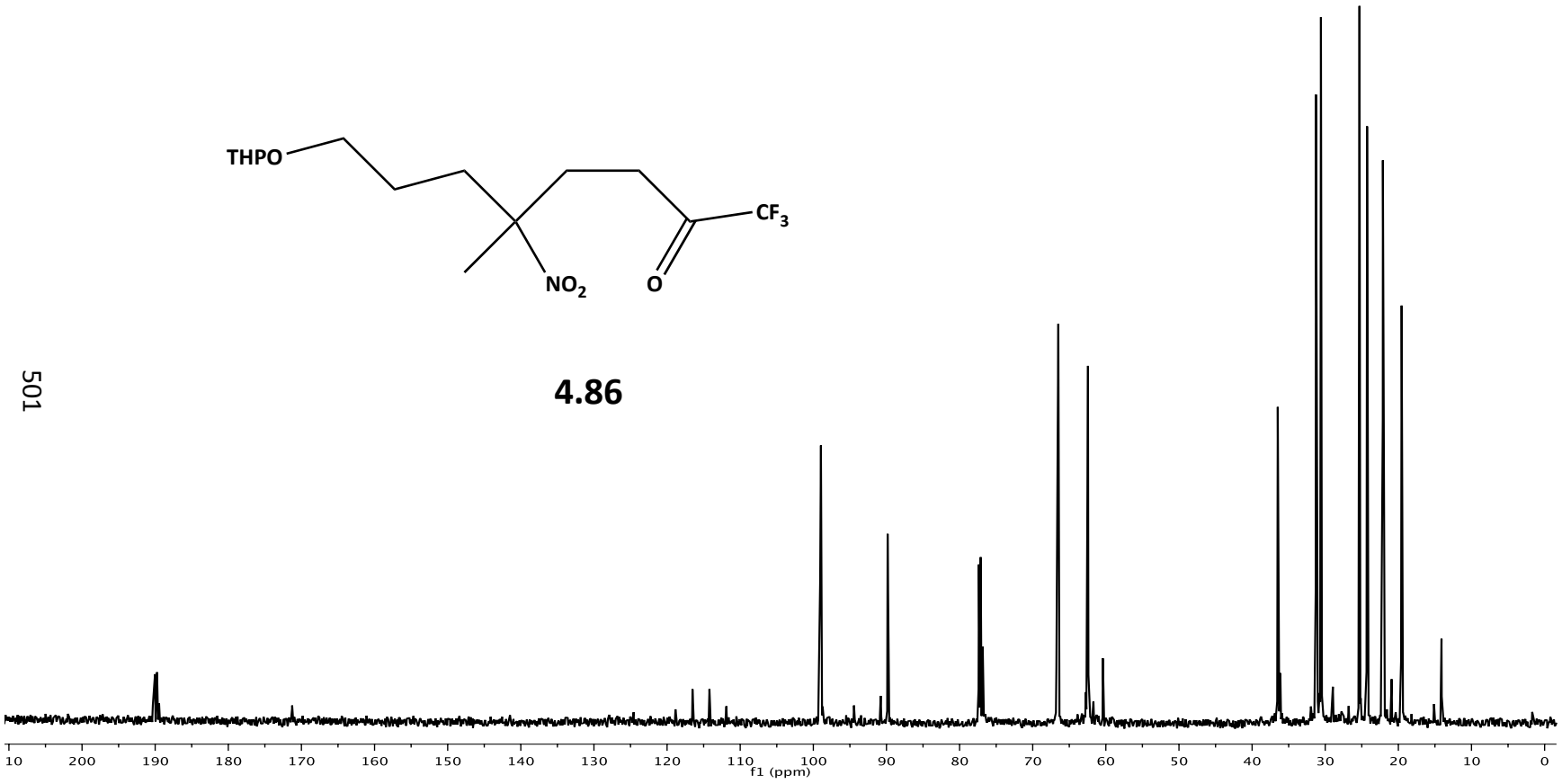

THPO
O
NO2

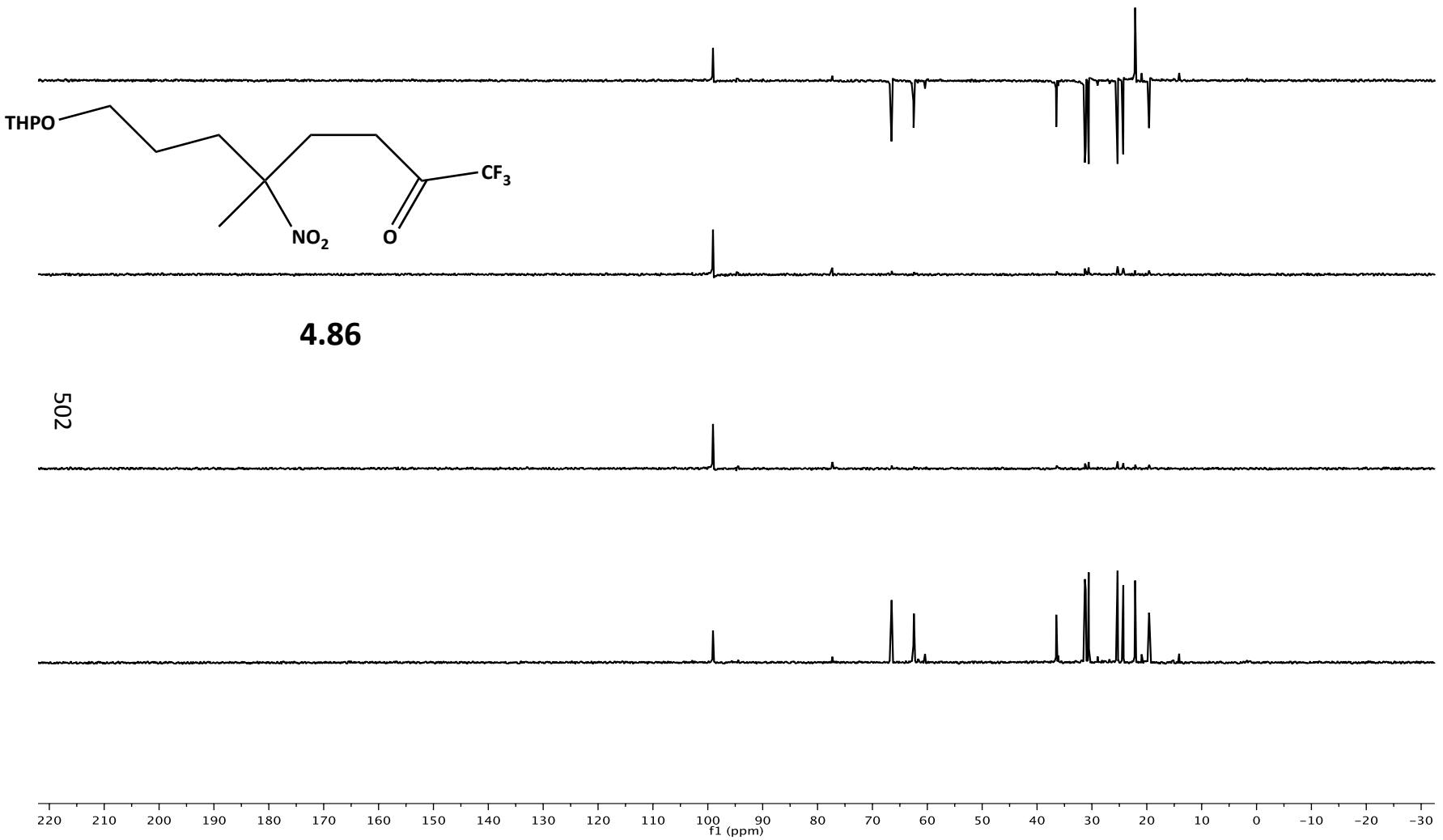
4.85


498
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

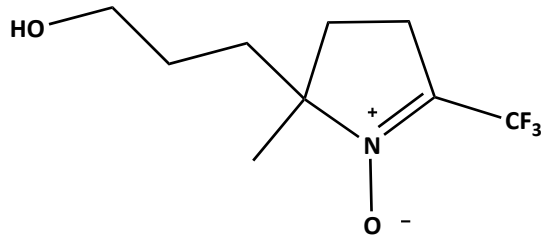

THPO
O
NO2
4.85
499
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)


THPO
CF3
NO2
O
4.86
500
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

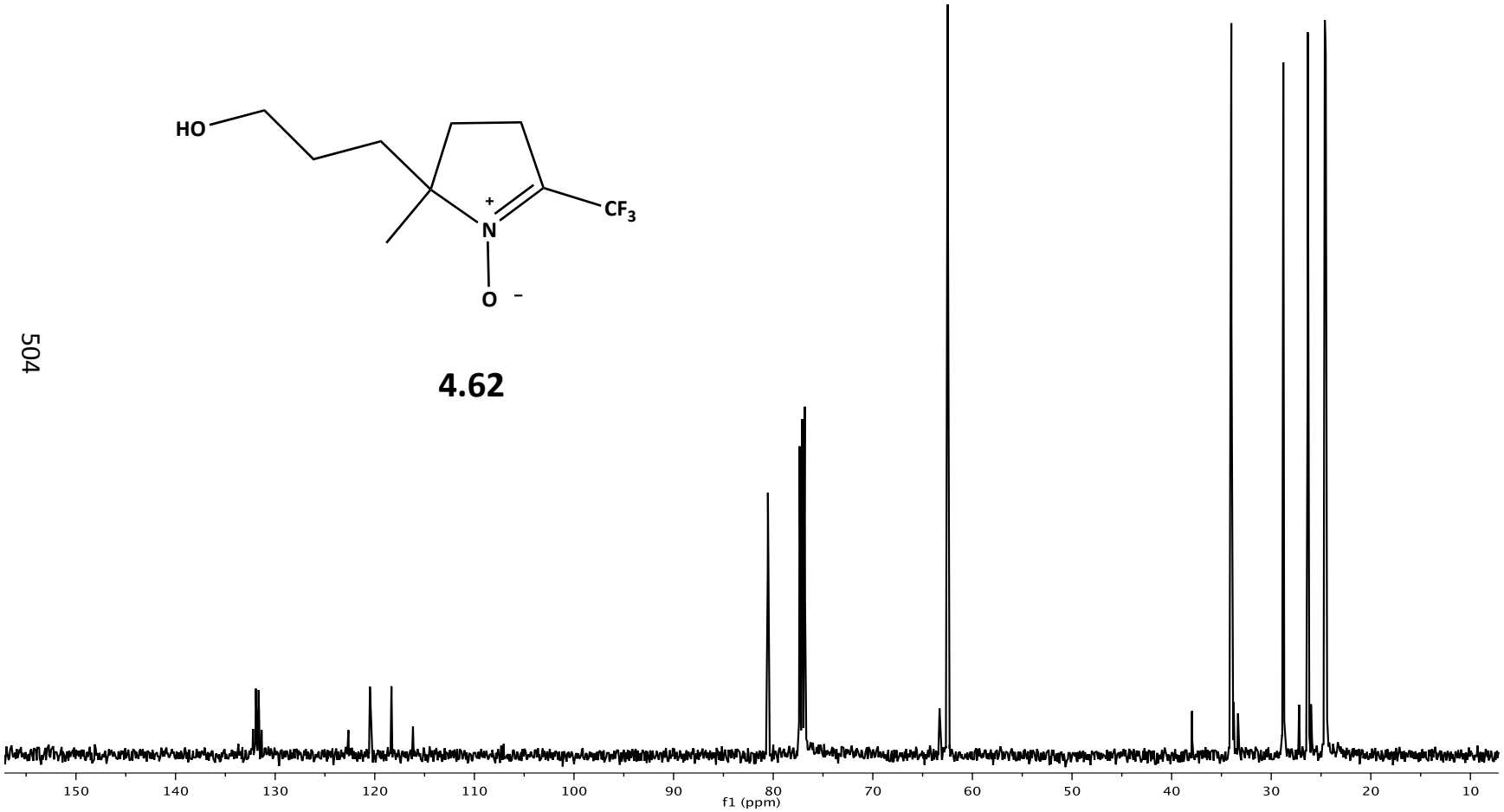

THPO
CF3
NO2
O
4.86
501
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

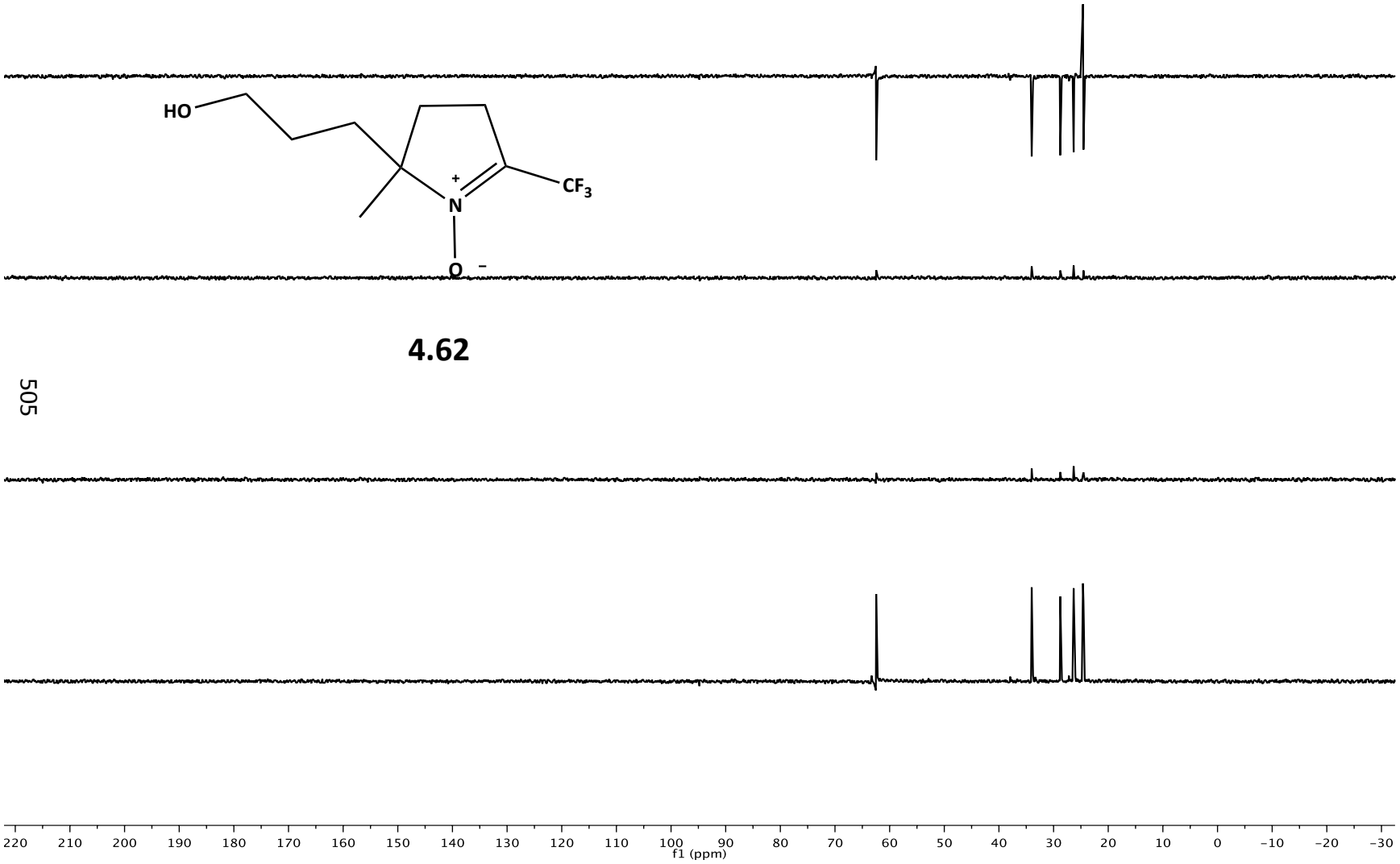

THPO
CF3
NO2
O
4.86
502
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30
f1 (ppm)

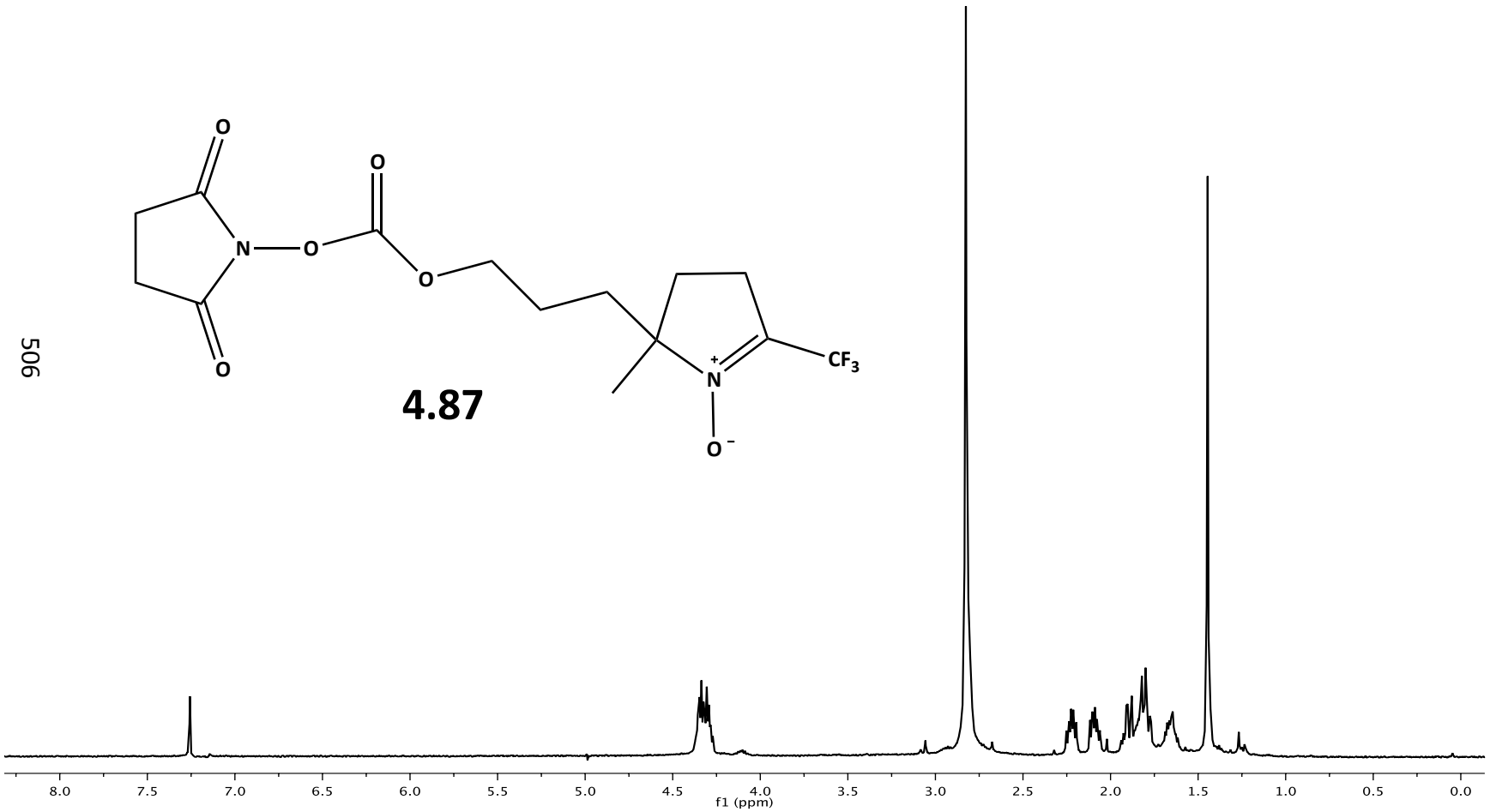
503

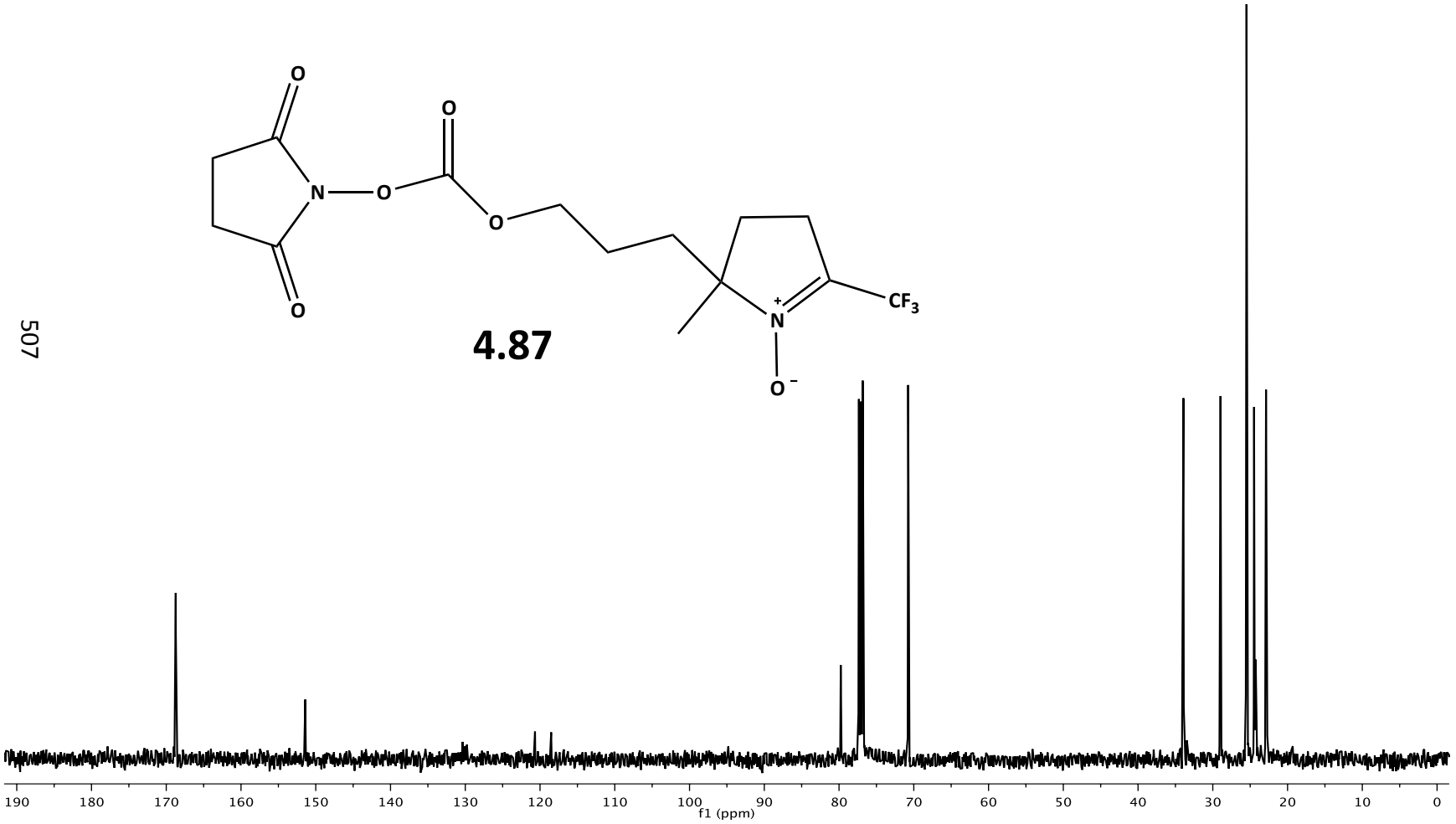


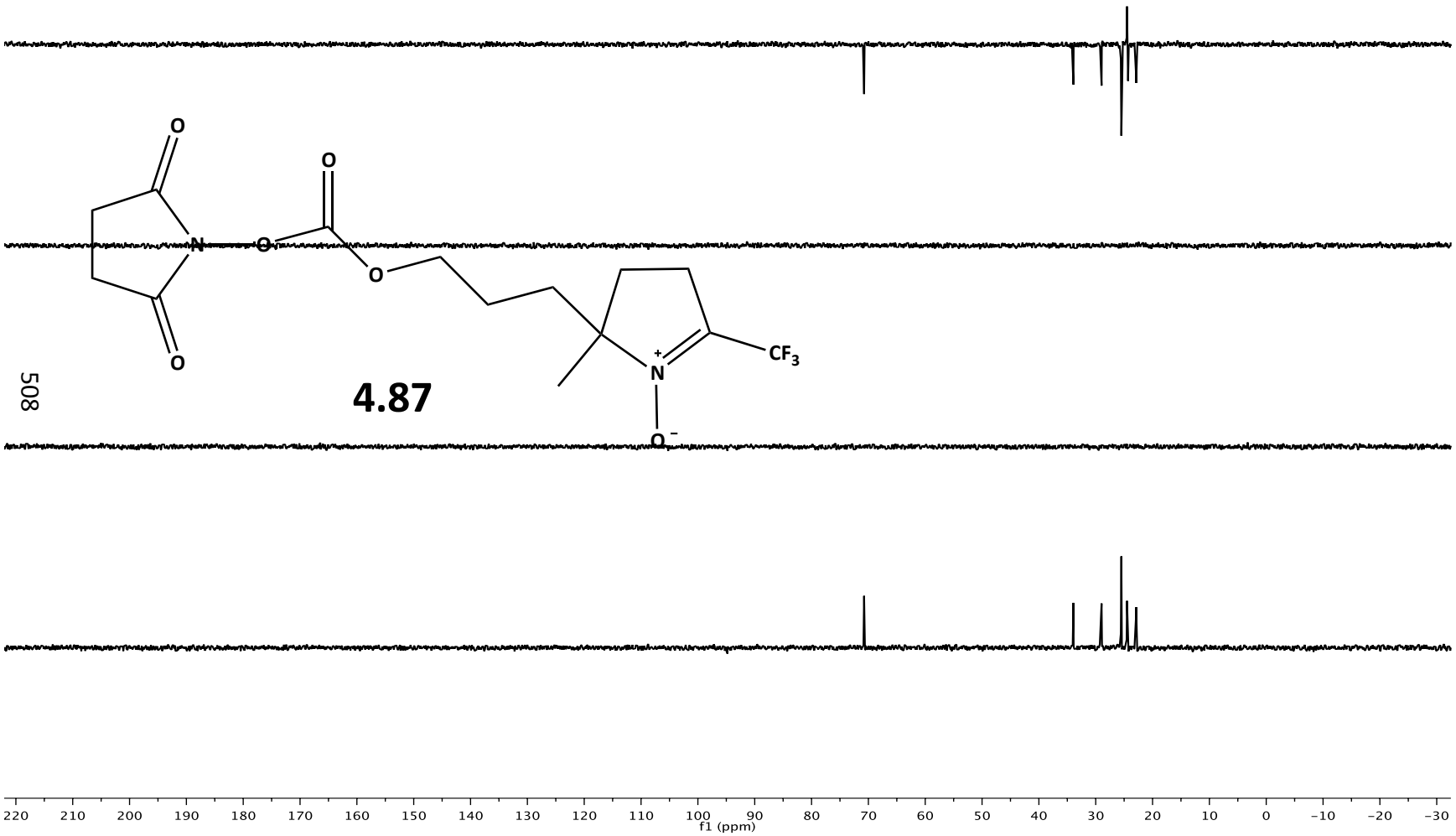
4.62

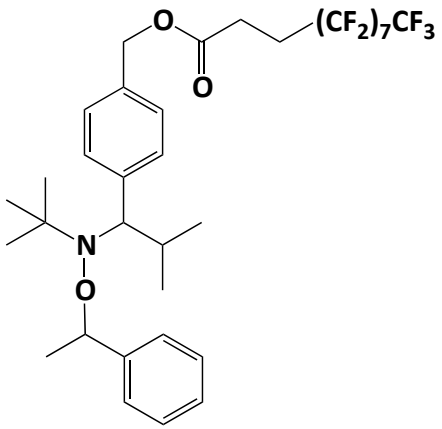

HO
CF3
N
+
O
–
504
4.62
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


HO
CF3
N
+
O
–
4.62
505
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
–20
–30
f1 (ppm)

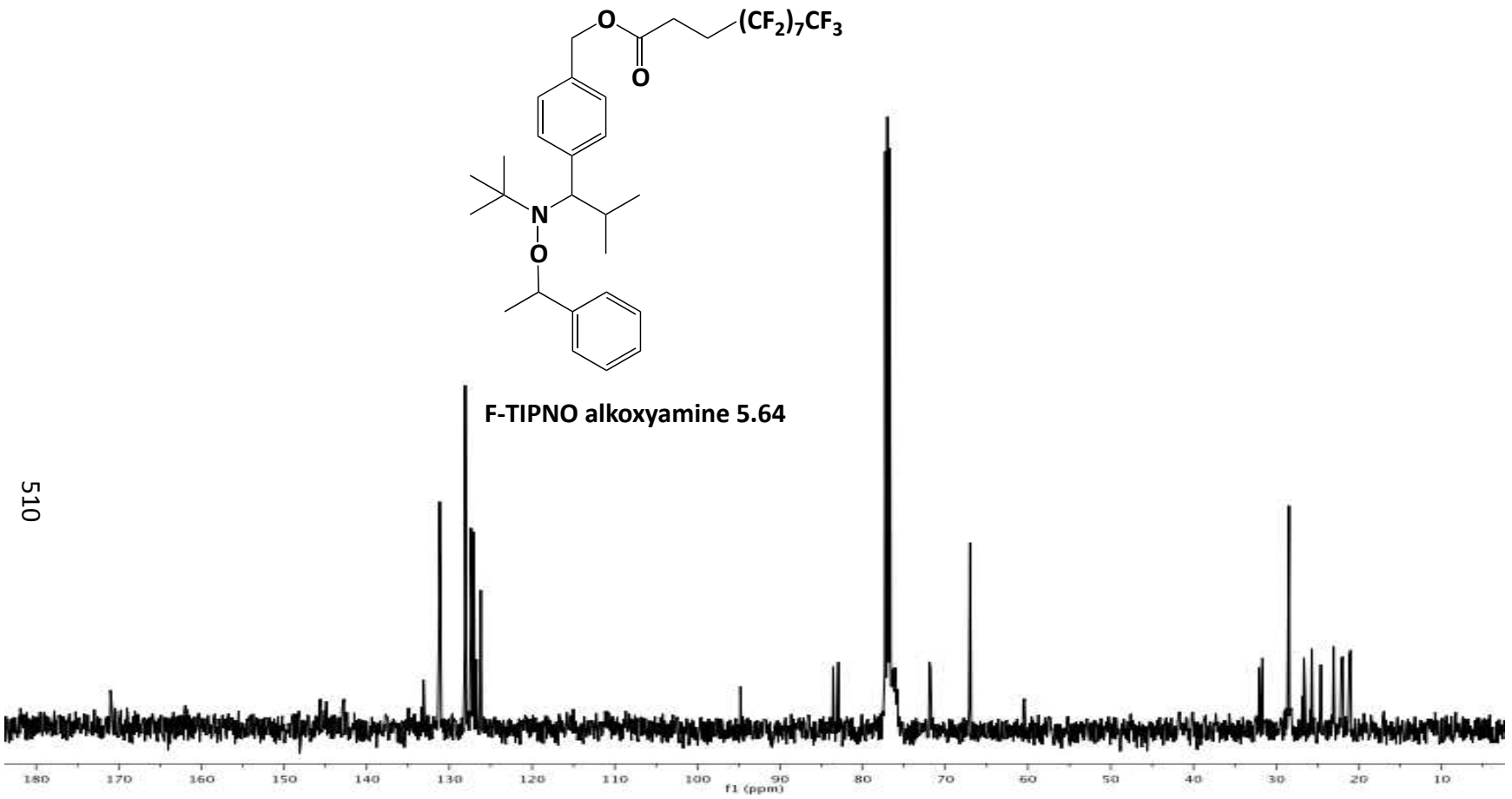

506
O
O
N
O
O
O
4.87
+
N
O
–
CF3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

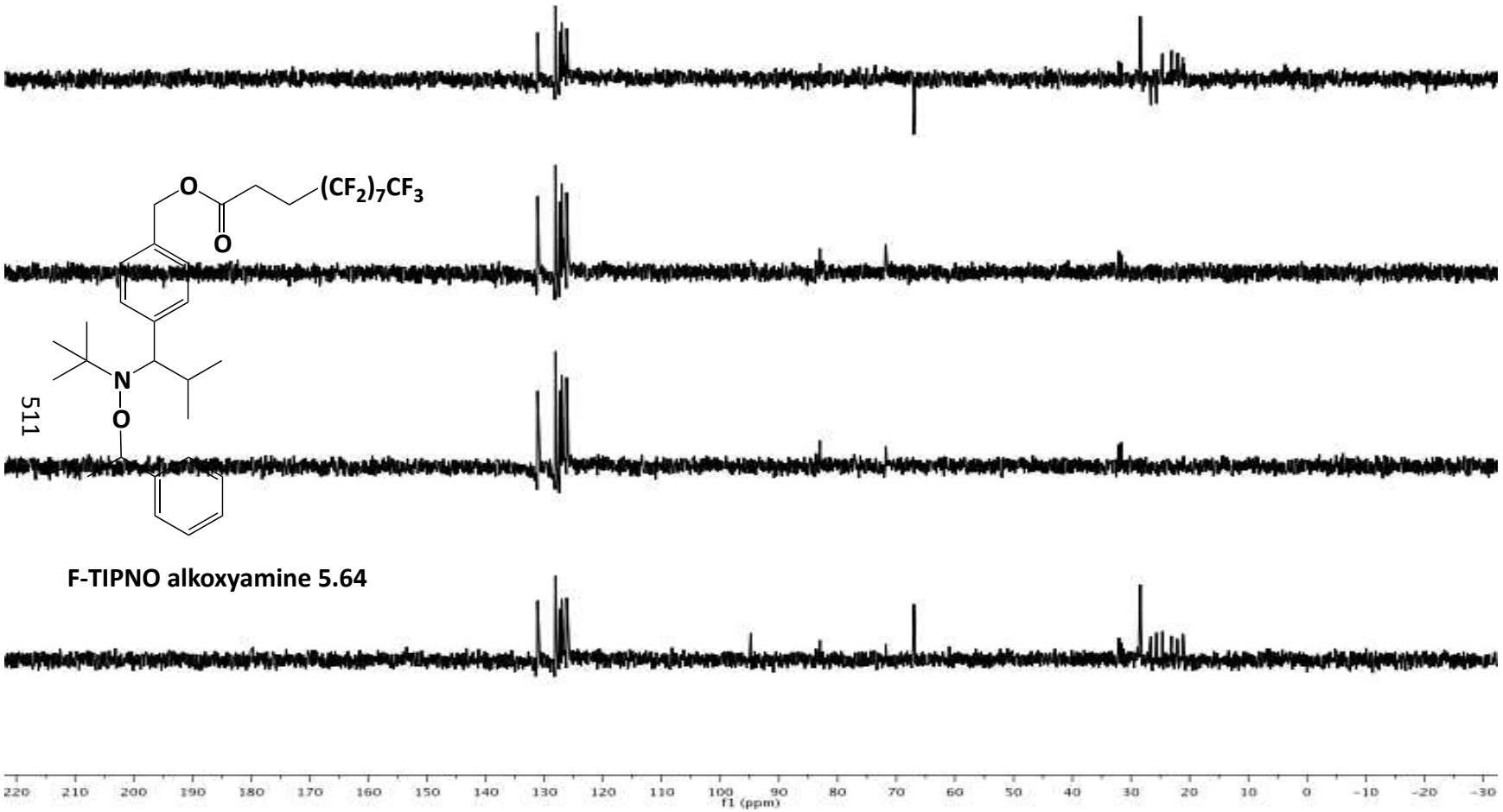

O
O
N
O
O
O
O
CF3
N
+
O
-
4.87
507
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
N
O
O
O
O
CF3
N
O
508
4.87
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
f1 (ppm)

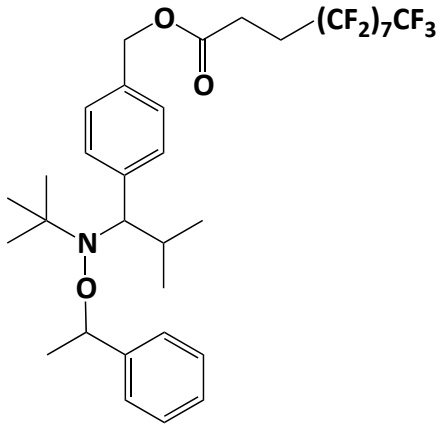


F-TIPNO alkoxyamine 5.64


O
O
(CF2)7CF3
N
O
F-TIPNO alkoxyamine 5.64
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

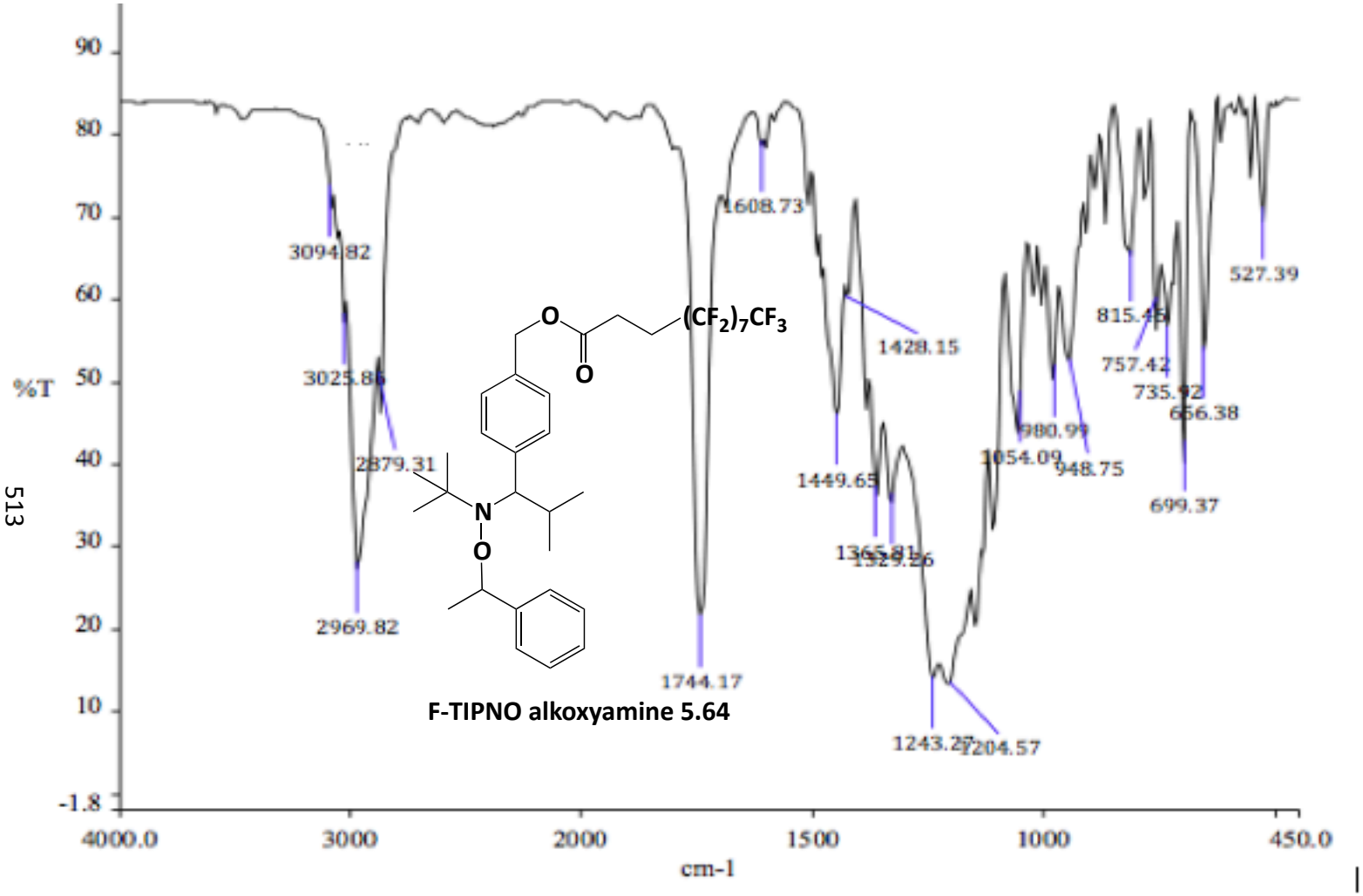


F-TIPNO alkoxyamine 5.64

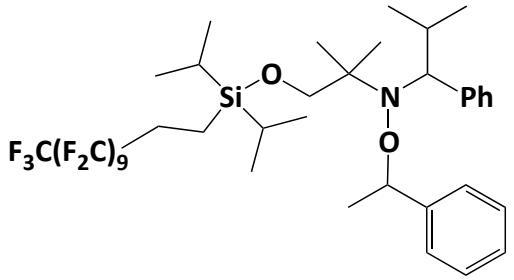


F-TIPNO alkoxyamine 5.64

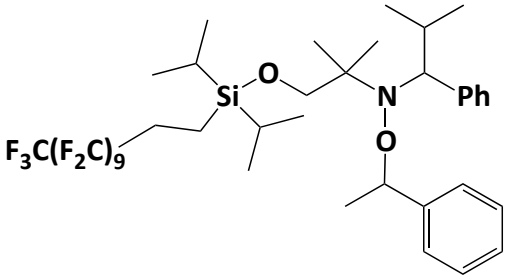
512



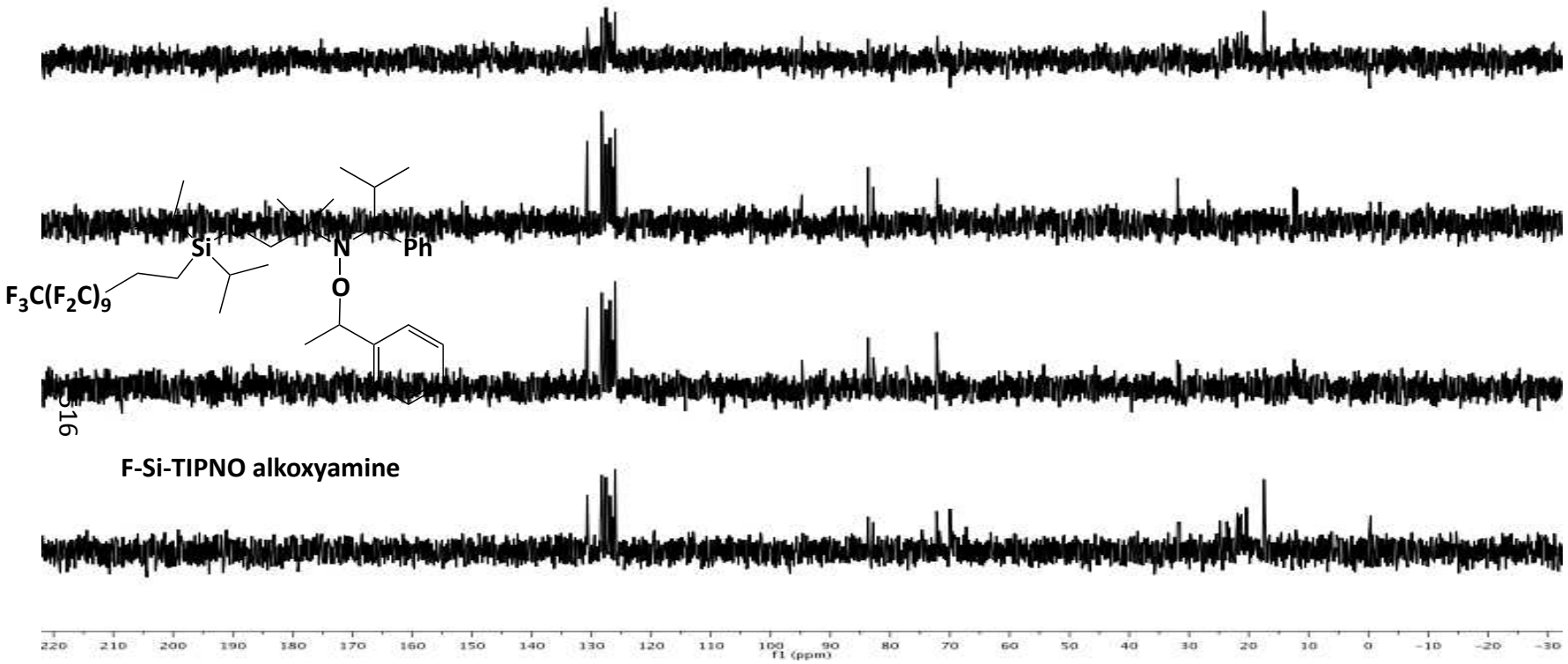
F-TIPNO alkoxyamine 5.64

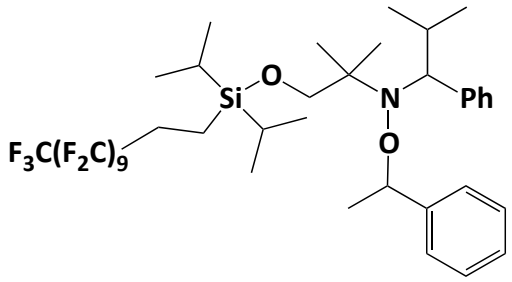


F-Si-TIPNO alkoxyamine

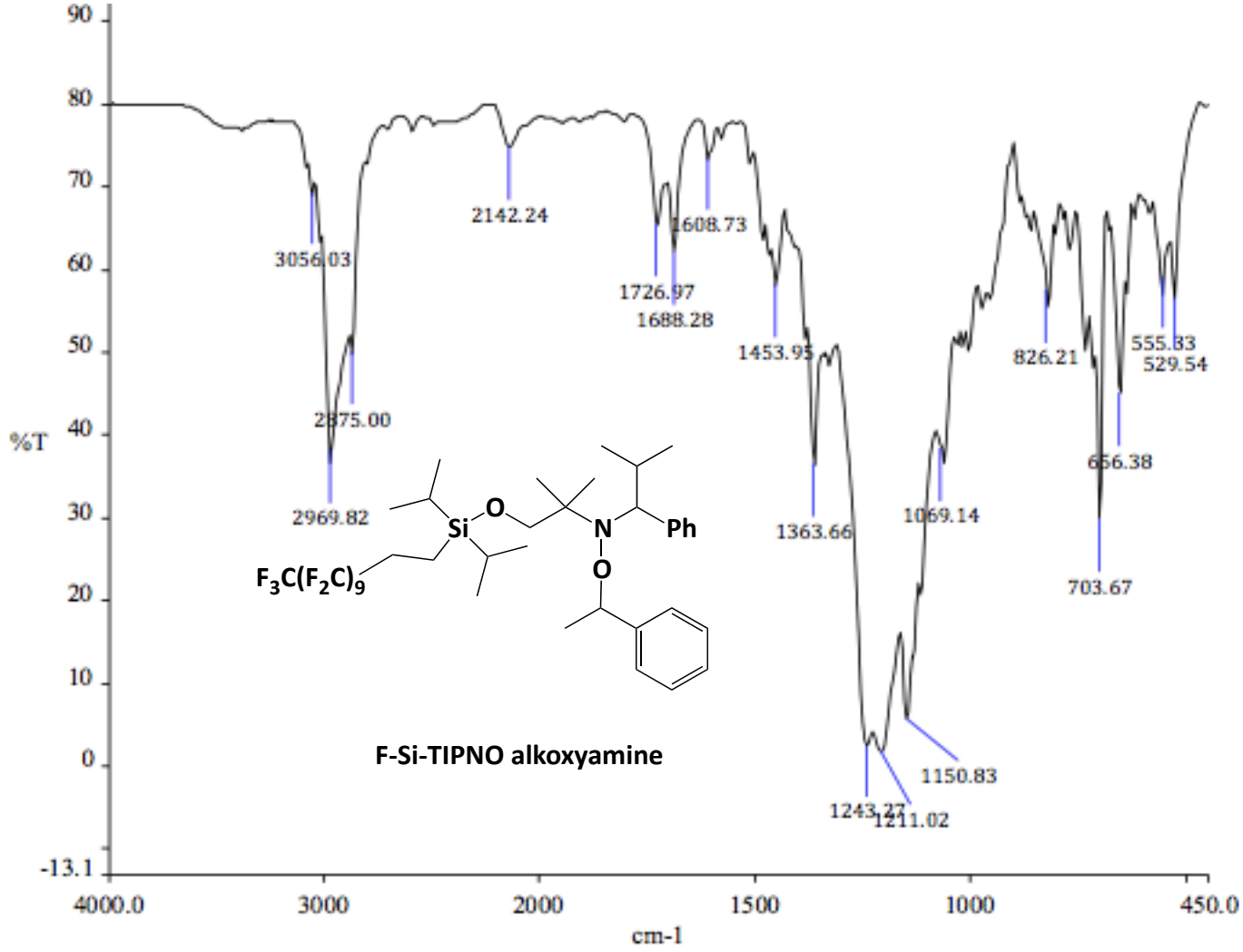


F-Si-TIPNO alkoxyamine

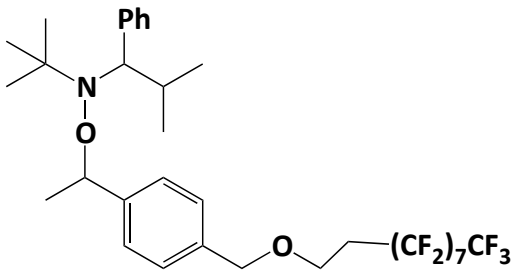

Si
N
Ph
O
F3C(F2C)9
516
F-Si-TIPNO alkoxyamine
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)



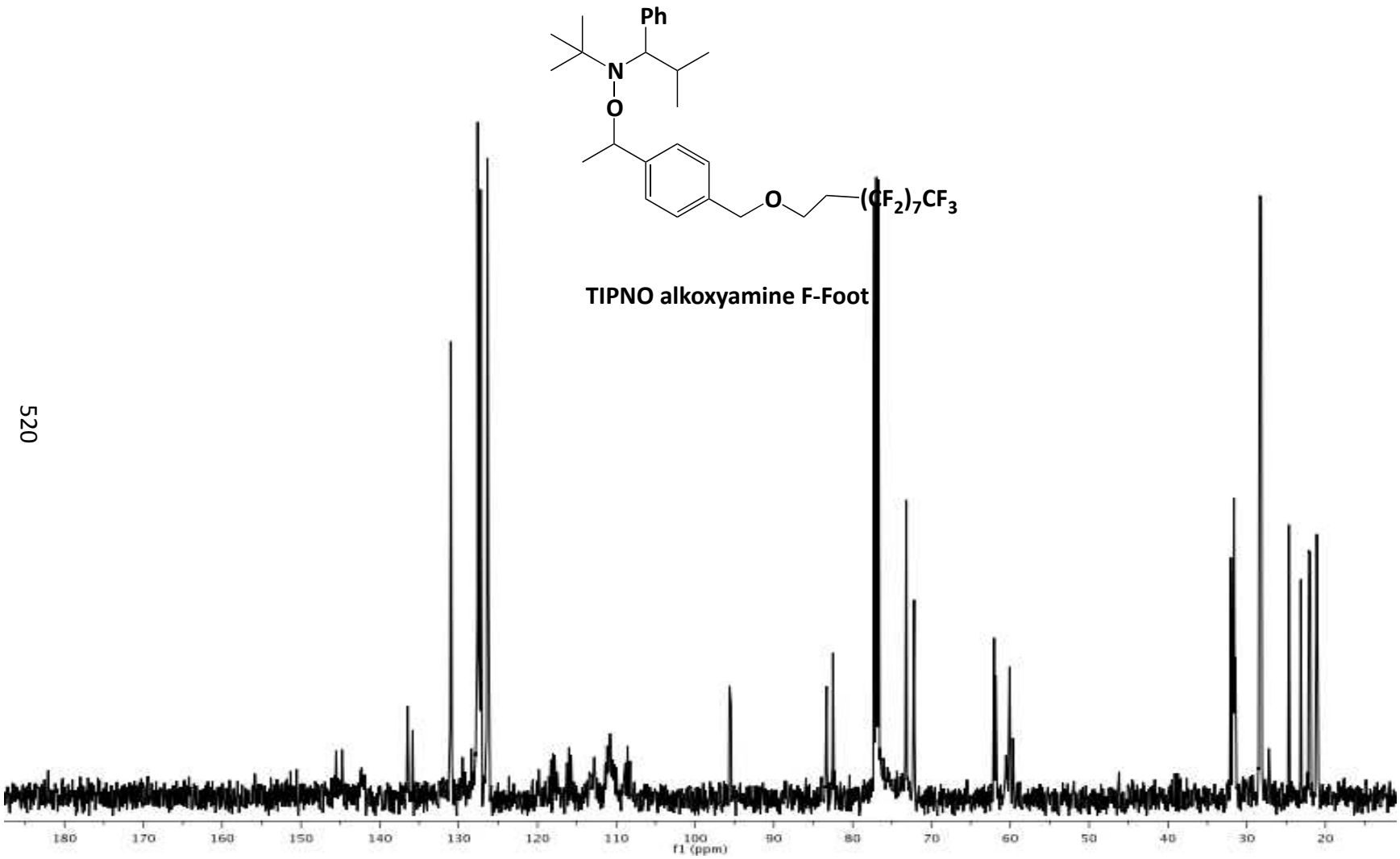
F-Si-TIPNO alkoxyamine



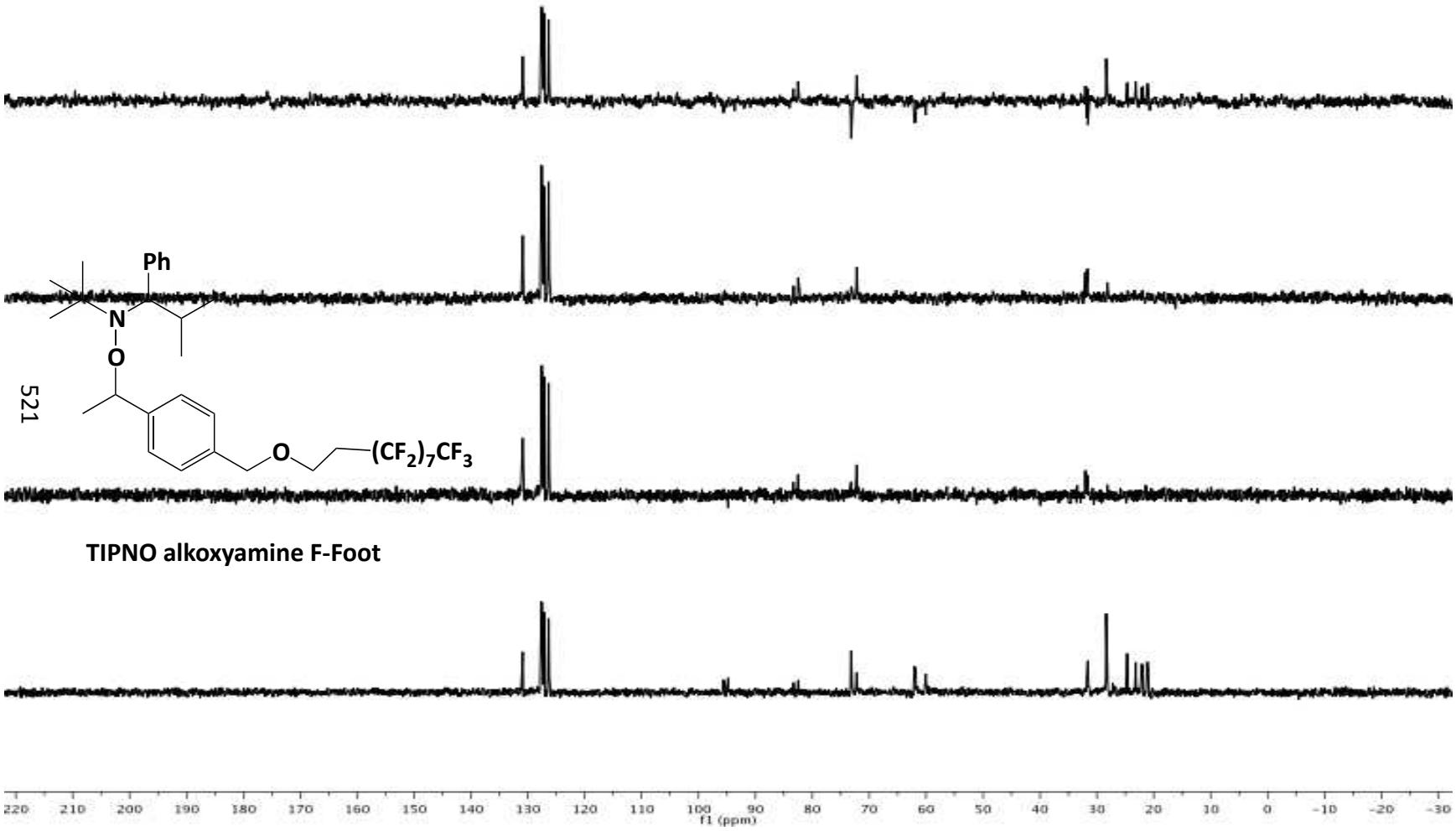
F-Si-TIPNO alkoxyamine



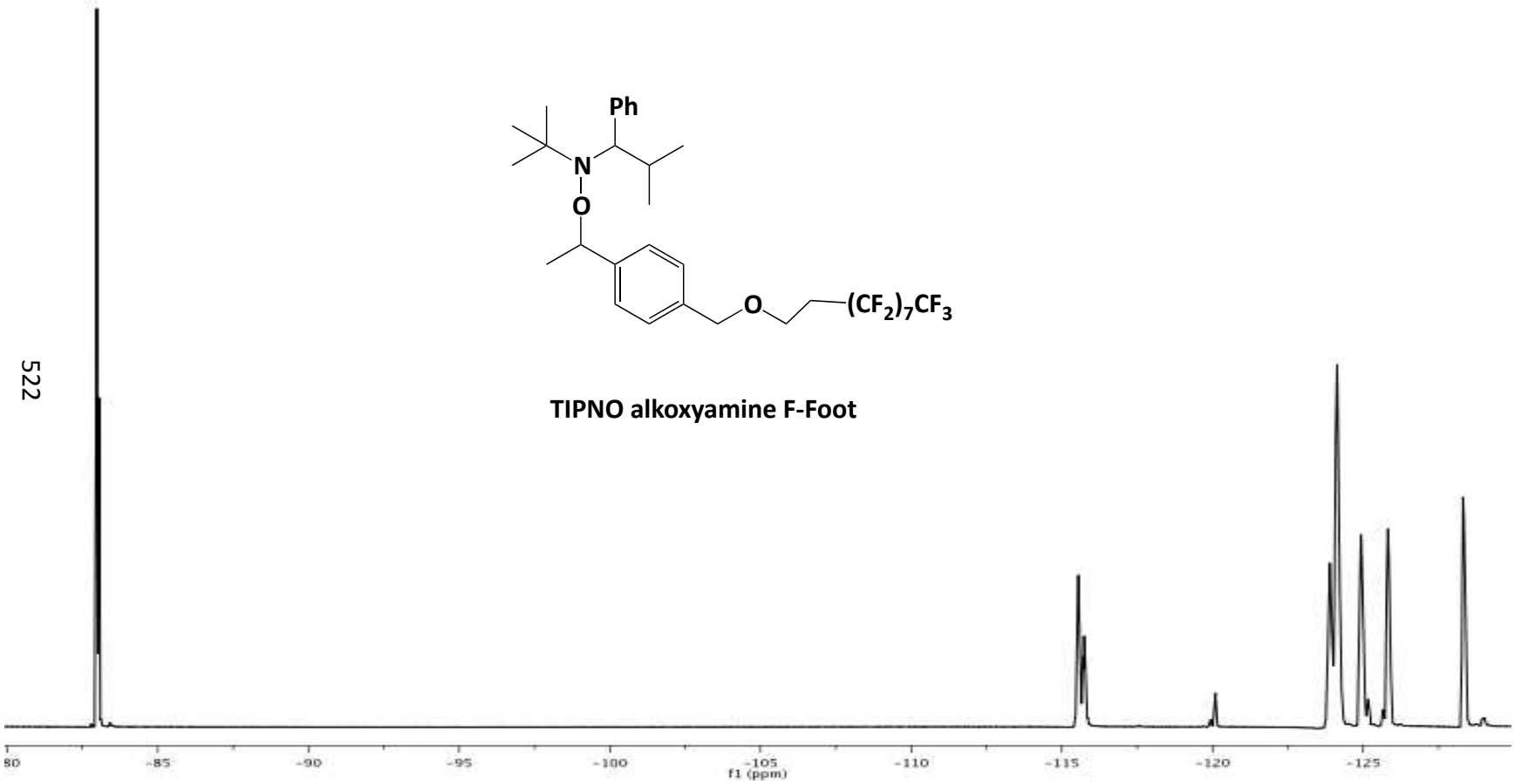
TIPNO alkoxyamine F-Foot



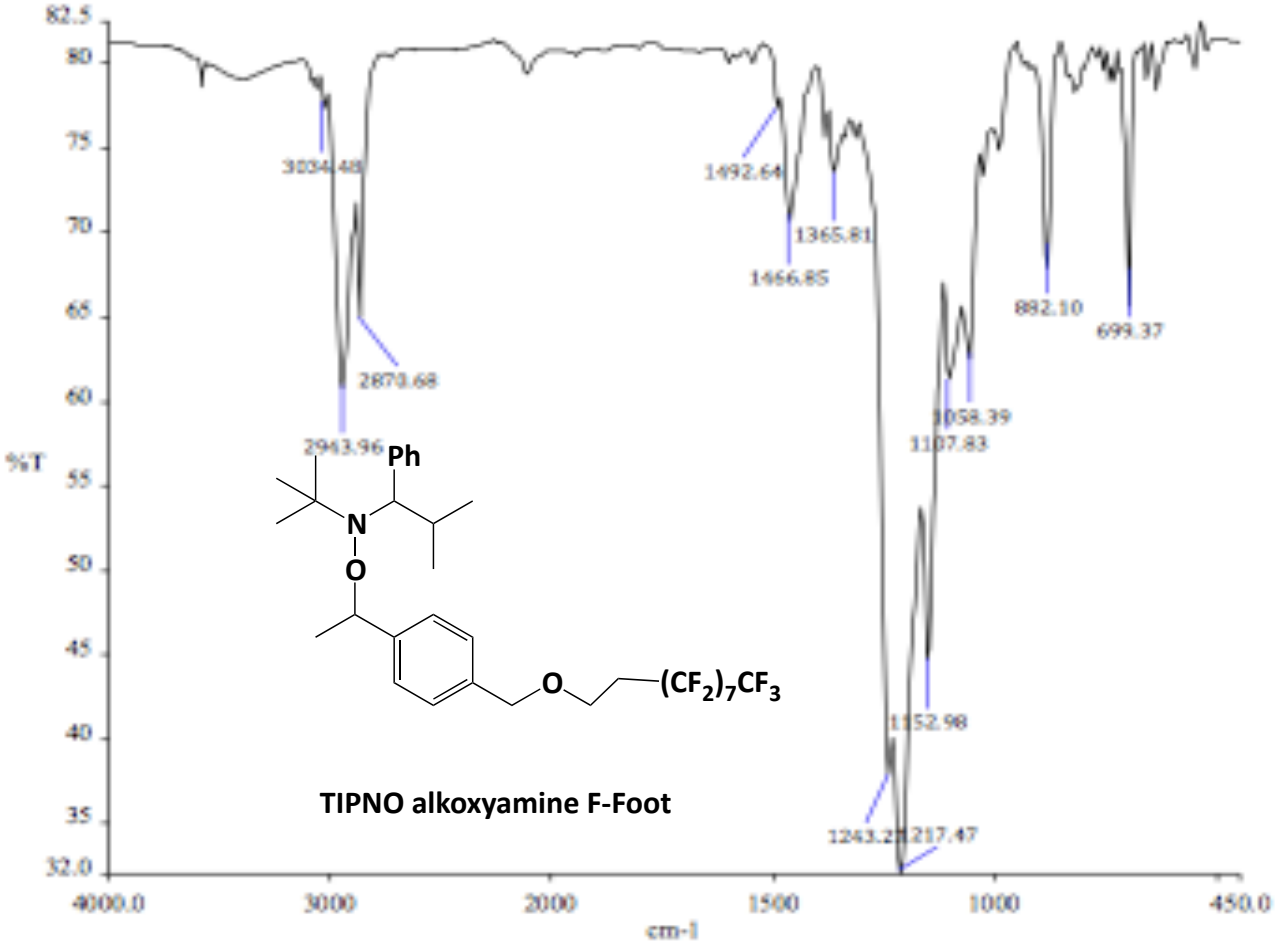
TIPNO alkoxyamine F-Foot



TIPNO alkoxyamine F-Foot



TIPNO alkoxyamine F-Foot



TIPNO alkoxyamine F-Foot

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