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Computational predictions of substituted benzyne and indolyne regioselectivities

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Abstract

A computational study using DFT methods was performed for an array of mono and disubstituted benzynes and indolynes. The inherent distortion present in the geometry-optimized structures predicts the regioselectivity of aryne trapping by nucleophiles or cycloaddition partners. These studies will serve to enable the further use of unsymmetrical arynes in organic synthesis.

Keywords

heterocycles; arynes; computations; regioselectivities; hetarynes

Over the past 10–15 years there has been resurgence in the field of aryne chemistry.[1] Arynes were once avoided because of their high reactivity, but chemists have now demonstrated that arynes can be strategically employed in a host of synthetic applications. Our laboratories have been interested in harnessing substituted arynes and heterocyclic arynes to build complex scaffolds,[2] especially those seen in drugs and natural products. These efforts have led to the aryne distortion/interaction model,[2c,2d,3,4] which explains aryne regioselectivities and can also be used to make reliable regioselectivity predictions. Following our recent regioselectivity studies of 3-substituted benzynes[2p] and substituted indolynes,[2d,2e,2m] we now report regioselectivity predictions for a number of disubstituted benzynes and substituted indolynes. We expect our findings will help propel the further exploitation of unsymmetrical arynes in synthesis.

A brief summary of the predictive powers of the aryne distortion model, as applied to various 3-substituted benzynes, is provided in Table 1. First, the geometry-optimized structure of a given unsymmetrical aryne is obtained using DFT calculations.[5,6,7] These

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Dedicated to Professor Harry H. Wasserman

calculations provide the internal angles of each alkyne terminus. The site with the larger internal angle is the preferred site of attack by nucleophiles.[8] Additionally, the degree of distortion (as measured by the difference in angles) can be used to provide an estimate of regioselectivity. Even a mild degree of distortion (e.g., 4° or greater), typically corresponds to synthetically useful levels of selectivity. As shown for benzynes substituted at C3 with an inductively electron-withdrawing group (entries 1–5), nucleophilic addition is predicted to occur with a preference for attack at C1. Generally speaking, distortion decreases in moving from the most inductively withdrawing groups (entries 1 and 2) to the least withdrawing group (entry 5), which has been validated experimentally.[2p]

We studied benzynes bearing two substituents adjacent to the triple bond, as these have not been assessed previously using the aryne distortion model. An analysis of several 6-substituted 3-fluorobenzynes is shown in Table 2. Fluoride dominates regioselectivity in every case. Nucleophilic addition is predicted to occur at C1 due to the distortion introduced by the electronegative fluoride substituent. Selectivity increases as the C6-substituent becomes less electron-withdrawing.

We also examined the distortion present in 3-substituted 6-methoxybenzynes (Table 3). The inductively withdrawing fluoride group governs regioselectivity in the case of entry 1. However, for the less electronegative halides, Cl, Br, and I, the methoxy group controls aryne distortion (entries 2–4). Accordingly, nucleophilic addition is predicted to occur at C2 in these three cases.

Indolynes are an important class of arynes that have gained recent attention.[9] In addition to serving as building blocks for medicinally-privileged indoles, indolynes and close relatives have been used as intermediates in the total syntheses of several complex alkaloids.[2i–o] Although the effect of N-substituents on indolyne distortion has been previously examined computationally and experimentally,[2d] arene substituent effects on indolyne distortion have been largely neglected.[10]

Table 4 provides a distortion analysis for the 4,5-indolyne and several C6-substituted derivatives. As we have shown previously, the unsubstituted 4,5-indolyne[11] is distorted such that nucleophilic addition occurs at C5 (entry 1). Interestingly, the presence of a 6-methoxy group overturns this distortion, such that nucleophilic addition is expected to occur at C4 (entry 2). A similar prediction is seen for F, Cl, and Br substituents (entries 3–5, respectively). Finally, in the case of the 6-iodo-4,5-indolyne, the aryne distortion model predicts little unsymmetrical distortion and, consequently, low regioselectivities.[12]

As shown in Table 5, we have also studied substituent effects for 5,6-indolynes. The parent 5,6-indolyne shows minor distortion and predicted regioselectivities that favor nucleophilic addition occurring at C5 (entry 1).[2d] The influence of C4 and C7 substituents were examined. C7 substituents generally lead to an increase in distortion and predicted regioselectivities; these results are given in the Supplementary Material. The presence of C4 inductively withdrawing substituents, however, leads to an overturning of the predicted regioselectivity such that C6 attack is expected to be favored (entries 2–6). Distortion is greatest in the case of the most electron-withdrawing substituents (entries 2 and 3) and

becomes less significant in the cases of the Cl, Br, and I substituted analogs (entries 4–6, respectively).

Finally, we have analyzed the distortion in several 6,7-indolynes (Table 6). The 6,7-indolyne is known to react with high regioselectivity for nucleophilic addition at C6,[2d] which is consistent with the significant unsymmetrical distortion seen in the geometry-optimized structure (entry 1; ca. 18°). Thus, we were curious if it would be possible to overturn this inherent selectivity using substituents. Although the presence of substituents on 6,7-indolynes partially counters the inherent selectivity, we predict that attack at C6 is still favored in nearly all cases (entries 2–6). For 5-fluoro-6,7- indolyne, selectivity is expected to be poor and may indeed favor nucleophilic attack occurring at C7.

In summary, we have applied the distortion/interaction model to a variety of mono and disubstituted benzynes and substituted indolynes. These studies give regioselectivity predictions using straightforward DFT calculations. We anticipate that our results will help encourage the use of unsymmetrical arynes in the synthesis of complex molecules and drug scaffolds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References and notes

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6. CYLview, 1.0b. Université de Sherbrooke; Québec, Montreal, Canada: 2009. Images of geometry-optimized structures were prepared using CYLview: Legault, C. Y. http://www.cylview.org

7. The distortion present in each unsymmetrical aryne is caused by the proximal inductively withdrawing groups, which deform the triple bond as a result of Bent's rule; Bent H. Chem Rev. 1961; 61:275–311.

8. This pathway is favored because it requires minimal distortion to reach the transition state. For more information regarding the aryne distortion model, see references 2c,d.

9. For a recent review, see reference 1m.

10. We have previously studied the 6-bromo-4,5-indolyne and employed this species in the total synthesis of several indolactam alkaloids; see references 2e and 2m.

11. A stable silyltriflate precursor to the parent 4,5-indolyne is commercially available from Aldrich Chemical Co., Inc. (product #L511625).

12. The predictive capabilities of the aryne distortion model strictly using geometry-optimization does not take into account steric factors. As such, one might expect nucleophilic addition in the case of

6-iodo-4,5-indolyne (Table 4, entry 6) to occur with some selectivity for nucleophilic addition at C4.

Table 1

Distortion analysis of 3-substituted benzynes due to the presence of inductively withdrawing groups.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)	Regioselectivity (N-Me-aniline)[b]
1	OMe (3, 2, 1)		C1 (16°)	C1 addition exclusively
2	F		C1 (17°)	C1 addition exclusively
3	Cl		C1 (12°)	C1 addition favored (>20:1)
4	Br		C1 (10°)	C1 addition favored (13:1)
5	I		C1 (4°)	C1 addition favored (9:1)

Aryne Distortion Model -Predictive Capabilities

- nucleophilic addition occurs at the aryne terminus with the larger internal angle
- degree of distortion correlates with regioselectivity trends (>4° angle difference implies synthetically useful selectivities)

[a]Geometry optimizations were performed using DFT methods (B3LYP/6-31G*; B3LYP/LACVP was used for 3-iodobenzyne (entry 5)).

[b]Known regioselectivities for the addition of *N*-Me-aniline to each aryne (ref 2p).

Table 2

Distortion analysis of 3-fluorobenzynes bearing a C6 inductively-withdrawing substituent.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)
1	F, 3, 2, 1, 6, OMe	125∞, 128∞	C1 (3°)
2	F, Cl	122∞, 130∞	C1 (8°)
3	F, Br	121∞, 131∞	C1 (10°)
4	F, I	121∞, 131∞	C1 (10°)

[a]Geometry optimizations were performed using DFT methods (B3LYP/6-31G*; B3LYP/LACVP was used for 3-fluoro-6-iodobenzyne (entry 4)).
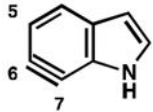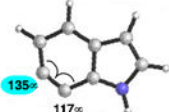
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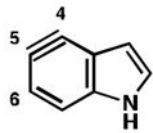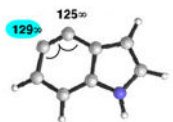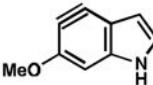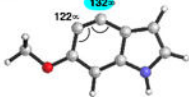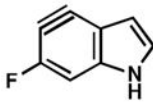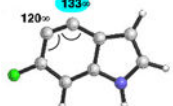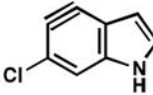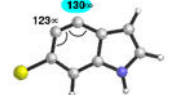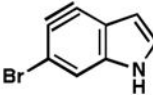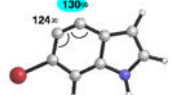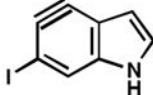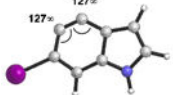
Distortion analysis of 6-methoxybenzynes bearing a C3 inductively withdrawing substituent.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)
1			C1 (3°)
2			C2 (5°)
3			C2 (7°)
4			C2 (7°)

[a]Geometry optimizations were performed using DFT methods (B3LYP/6-31G*; B3LYP/LACVP was used for 6-methoxy-3-iodobenzyne (entry 4)).

Table 4
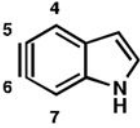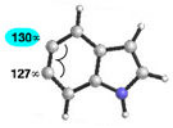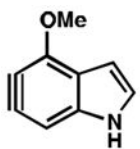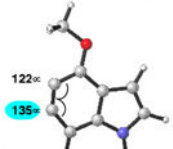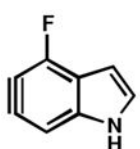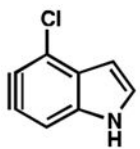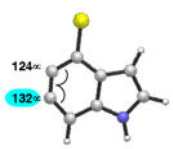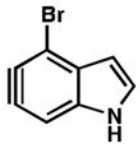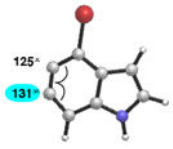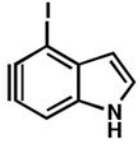
Distortion analysis of 4,5-indolynes.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)
1			C5 (4°)
2			C4 (10°)
3			C4 (13°)
4			C4 (7°)
5			C4 (6°)
6			N/A (0°)

[a]Geometry optimizations were performed using DFT methods (B3LYP/6-31G*; B3LYP/LACVP was used for 6-iodo-4,5-indolyne (entry 6)).
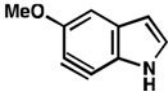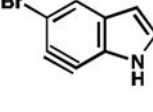
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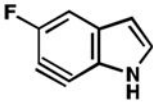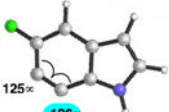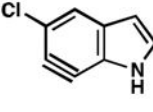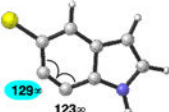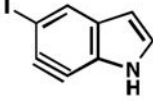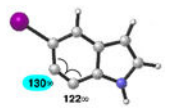
Distortion analysis of 5,6-indolynes.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)
1			C5 (3°)
2			C6 (13°)
3			C6 (15°)
4			C6 (8°)
5			C6 (6°)
6			C6 (2°)

[a]Geometry optimizations were performed using DFT methods (B3LYP/6- 31G*; B3LYP/LACVP was used for 4-iodo-5,6-indolyne (entry 6)).

Table 6

Distortion analysis of 6,7-indolynes.

Entry	Aryne	Geometry-optimized structure[a]	Site of attack (angle difference)
1			C6 (18°)
2			C6 (6°)
3			C7 (1°)
4			C6 (6°)
5			C6 (8°)
6			C6 (8°)

[a] Geometry optimizations were performed using DFT methods (B3LYP/6-31G*; B3LYP/LACVP was used for 5-iodo-6,7-indolyne (entry 6)).