Heterocycles

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An Efficient Computational Model to Predict the Synthetic Utility of Heterocyclic Arynes**

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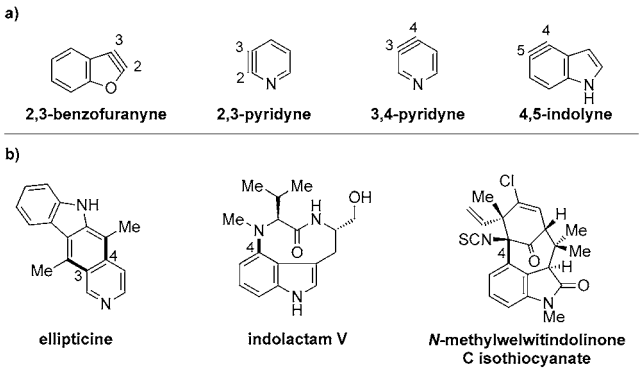
Over the past decade, there has been a rapidly expanding interest in the field of aryne chemistry.[1] The reactivity of benzyne and its derivatives has been well-explored, with numerous trapping methodologies now available for the efficient assembly of functionalized arenes. In contrast, relatively fewer achievements have been made with respect to heterocyclic arynes, or hetarynes.[2] Hetarynes have been a subject of interest and controversy since 1902, when Stoermer and coworkers proposed the intermediacy of a 2,3-benzofuranyne (Scheme 1),[3] which was later called into question.[2a,4] Several reports of hetarynes have appeared over the past fifty years, but only recently have a few hetarynes been deemed useful in synthesis. Pyridynes and indolynes have been the most thoroughly studied from a methodological standpoint, and have also been tested in complex settings.[5,6] For example, 3,4-pyridynes have been employed as key building blocks in syntheses of ellipticine,[5b–g] whereas 4,5-indolynes were recently used to construct key bonds in indolactam V[6g] and *N*-methylwelwitindolinone C isothiocyanate.[6h]



Scheme 1. a) Noteworthy hetarynes and b) hetarynes in total syntheses.

Given the numerous synthetic advantages that arynes possess, along with their recent resurgence in the chemical literature,[7] we sought to evaluate the potential synthetic utility of a variety of heterocyclic arynes. We report a computational approach to predict: a) the likelihood that a given hetaryne can be generated, and b) the degree of regioselectivity one may expect in a reaction involving the hetaryne intermediate. This approach makes the distortion[8] model developed by Cheong et al.[6e,f] generally accessible through routine and rapid calculations. Moreover, we expect these studies will enable synthetic chemists to exploit heterocyclic arynes for the synthesis of natural products, compounds of medicinal value, and other functionalized heterocycles of practical importance.

We first established a computational means to assess if a given hetaryne species should be accessible.[14] Several computational studies of hetaryne energetics have been reported,[9] including energy comparisons for pyridyne isomers.[10] However, to our knowledge, no method has been put forth to predict the accessibility of a hetaryne intermediate. The heat of hydrogenation is a well-established means to explore the strains and relative stabilities of alkynes,[11] and we examined a simple method to estimate hetaryne stability involving the difference between electronic energies of arene and aryne.

Geometry optimization of several known hetarynes[5,6] and the corresponding parent heterocycles was conducted using DFT (B3LYP/6-31G*) and ab initio methods (MP2/6-311 + G**).[12] These results were also checked versus other functionals, as well as literature data. Using these optimized structures, and accounting for the energy of H_2 in the hypothetical dehydrogenation reaction, the energy of dehydrogenation of arene to aryne can be calculated. This straightforward calculation provides a measure of relative stability for the hetarynes that were examined.[13] We found that both B3LYP and MP2 methods gave comparable results for energy of dehydrogenation (Scheme 2). While the MP2 results were typically 4–10 kcal mol^{-1} lower than B3LYP, both methods predicted essentially the same relative stabilities.[14] Given that B3LYP calculations require less computing time,

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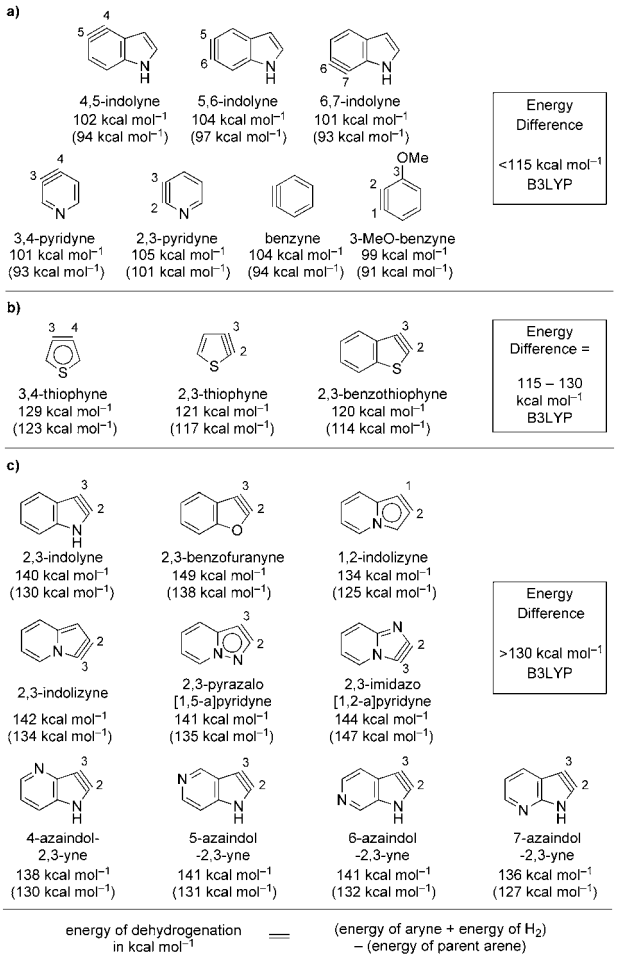


Scheme 2. Various arynes and a model for aryne accessibility. a) Hetarynes and arynes that can be generated (all validated experimentally). b) Hetarynes that can likely be generated (strong experimental evidence). c) Hetarynes that likely cannot be generated. The B3LYP energies are shown and the MP2 energies are given in parentheses.

this method provides a rapid means to assess stabilities. Using B3LYP, the energy of dehydrogenation between an aryne and its parent heterocycle is on the order of 100 kcal mol^{-1}.[14] Benzyne and the frequently studied 3-methoxybenzyne were subjected to the same analysis and gave comparable energy differences. Numerous studies that validate the existence of indolynes,[6] pyridynes,[5] benzyne,[1] and 3-methoxybenzyne[15] are available.

Several 5-membered hetarynes were also evaluated. Interestingly, thiophynes, which have been suggested based on experimental evidence[16] are approximately 120–130 kcal mol^{-1} higher in energy compared to thiophene. The 2,3-indolyne and 2,3-benzofuranyne, neither of which has been conclusively accessed,[2,4a,17] are >140 kcal mol^{-1} higher in energy compared to their parent heterocycle.

Based on these results, an energy difference of approximately 115 kcal mol^{-1} or less suggests that the aryne can be readily generated.[18] An energy difference of roughly 115 to 130 kcal mol^{-1} suggests that an aryne may be accessible, although its preparation is likely to be challenging. Finally, an energy difference greater than approximately 130 kcal mol^{-1} reflects a hetaryne that is predicted to not be accessible experimentally. Several 5-membered hetarynes that fall into the latter two categories are depicted in Scheme 2. In the system studied, 6-membered arynes are accessible, thiophynes are borderline, and most other 5-membered arynes are inaccessible.[19] Importantly, the predictive capabilities of this model are independent of the method used for aryne generation,[20] allowing experimentalists to pursue their method of choice based on precursor availability.[1]

With a general means available to assess the feasibility of hetaryne generation, we evaluated the prospects for a variety of hetarynes to react regioselectively in nucleophilic addition reactions using the aryne distortion model. This predictive model uses routine DFT calculations, but has also been shown to operate comparably well using other functionals or higher level calculations.[6f] A comparison of internal angles of the geometry-optimized hetaryne reveals the preferred site of attack. Specifically, the more linear terminus of the aryne is most electrophilic and is the preferred site of attack by nucleophiles. As shown by Cheong et al.,[6e,f] this is due to less distortion being required to achieve the transition state when the nucleophile attacks the carbon with the larger internal angle. The degree of regioselectivity can be correlated to the difference in angles, with angle differences $\geq 4°$ generally suggesting synthetically useful regioselectivities and lower values giving low and variable levels of selectivity. For arynes with angle differences between the termini being $<4°$, adjacent substituents, such as halides, may be used to modulate regioselectivities.[6g]

The structures of approximately 150 plausible hetarynes were optimized using rapid DFT (B3LYP/6-31G*) calculations. Selected results are depicted in Tables 1 and 2 with MP2 results for comparison, while the remaining data are available in the Supporting Information. Table 1 features a sampling of hetarynes where the triple bond is in the non-heterocyclic ring. For both indolynes and benzofuranynes, significant regioselectivities are predicted for most isomers, with the exception of the 5,6-arynes (entries 1 and 2). Replacing C2, C3, or both with N or O causes minimal perturbation of these trends, except additions to 4,5-hetarynes are expected to occur with improved regioselectivities. This is likely because of an inductive effect caused by the proximal heteroatoms. An example of this trend is shown in entry 3 for benzotriazolynes, although similar results were found for benzimidazolynes, benzoxazolynes, indazolynes, and other derivatives.[14] Finally, for 6,6-bicyclic hetarynes, regioselectivities are generally predicted to be less controlled, likely because of decreased ring strain present in the 6-membered ring, compared to the 5-membered ring.[21] For example, the aryne termini internal angles for each of the quinolyne isomers are nearly identical, suggesting modest regioselectivity in all cases (entry 4). Analogous trends were seen for an array of related hetarynes, including isoquinolynes, phthalazynes, and quinazolynes.[14]

The 2,3-pyridyne and related compounds in Table 2 show enormous angular distortions, which have been noted previously.[22] In 2,3-pyridyne, resonance involving the in-plane lone pair on N causes even greater distortions than the inductive effects and angle restrictions from ring fusion that were noted earlier.[6e–g] However, the B3LYP calculations

Table 1: Predicted heterocyclic aryne regioselectivities.

Entry	Site of Attack[a] (angle difference) B3LYP	MP2	Hetaryne
1: indolynes	C5 (4°)	C5 (1°)	
	C5 (3°)	C5 (<1°)	
	C6 (17°)	C6 (7°)	
2: benzofuranynes	C5 (7°)	C5 (3°)	
	C5 (2°)	N/A (0°)	
	C6 (20°)	C6 (9°)	
3: benzotriazolynes	C5 (11°)	C5 (4°)	
	C5 (2°)	C5 (1°)	
	C6 (20°)	C6 (9°)	
4: quinolynes	C6 (2°)	C6 (<1°)	
	C7 (1°)	C7 (1°)	
	C7 (2°)	C7 (3°)	

[a] Predicted site of attack based on the aryne distortion model.

Table 2: Predicted heterocyclic aryne regioselectivities.

Entry	Site of Attack[a] (angle difference) B3LYP	MP2	Hetaryne
1: pyridynes	C4 (1°)	C4 (3°)	
	C2 (47°)	C2 (34°)	
2: pyridizyne and pyrimidyne	C3 (42°)	C3 (23°)	
	C4 (44°)	C4 (31°)	
3: triazyne	C5 (51°)	C5 (9°)	
4: isoquinolyne	C3 (45°)	C3 (25°)	
5: quinolynes	C2 (49°)	C2 (43°)	
	C4 (3°)	C4 (3°)	
6: 4-azaindolynes	C5 (45°)	C5 (36°)	
	C6 (13°)	C6 (2°)	
7: 5- and 6-azaindolynes	C6 (53°)	C6 (49°)	
	C5 (48°)	C5 (47°)	
8: 7-azaindolynes	N/A (0°)	C4 (2°)	
	C6 (41°)	C6 (25°)	

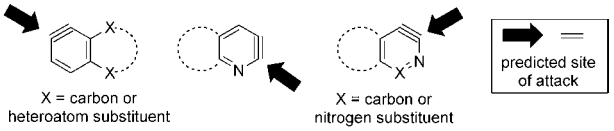
[a] Predicted site of attack based on the aryne distortion model.

(and calculations with other density functionals, such as M06-2X) exaggerate the difference in angles for 2,3-pyridyne and 3,4-pyridizyne. Computational studies of 2,3-pyridine with SF-CCSD predict angles at C2 and C3 of 143° and 114°, respectively, while B3LYP predicts 151° and 104°, respectively, leading to an angle difference of 29° with SF-CCSD and 47° with B3LYP. Table 2 also contains results for geometry optimizations with MP2/6-311+G**; this method gives angles closer to the accurate SF-CCSD values in addition to energies of dehydrogenation (ΔE_D) that are 3–8 kcal mol^{-1} lower. While B3LYP exaggerates the angular distortions, the qualitative model proposed here gives rapid and important predictions about the magnitudes of regioselectivities of nucleophilic additions.

Aza and diaza analogues of the 2,3-pyridyne all possess similar properties and presumably would undergo attack by nucleophiles with excellent regioselectivity (entries 2 and 3). Quinolyne and isoquinolynes were also examined. Although the 3,4-quinolyne is predicted to display modest regioselectivity, the other isomers appear more promising (entries 4 and 5). Finally, a series of azaindolynes were surveyed (entries 6–8). With the exception of the 7-aza-4,5-indolyne, these species are likely to undergo attack by nucleophiles with excellent regioselectivity. Promising data regarding even more exotic hetarynes is presented in the Supporting Information.

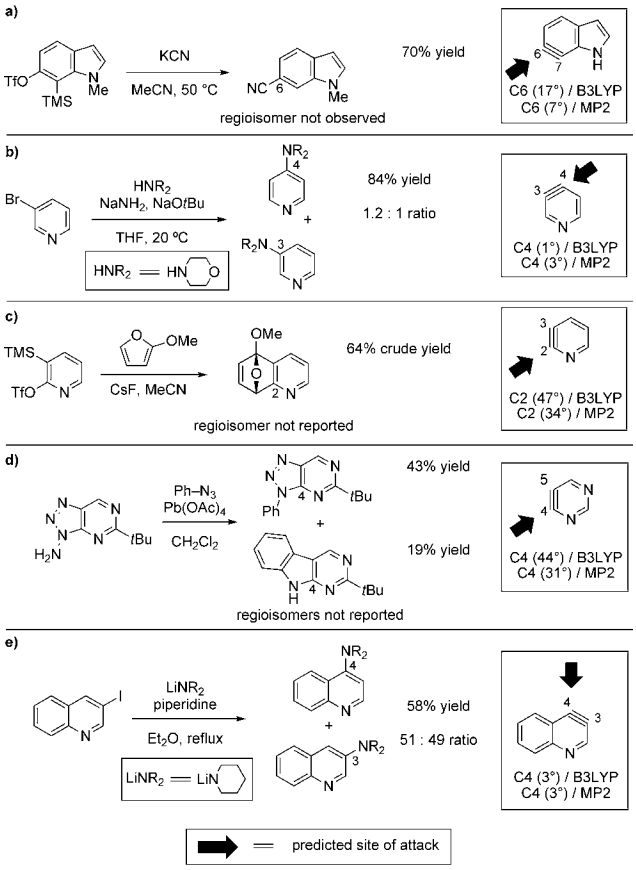
Even though the model for predicting regioselectivities in nucleophilic additions to hetarynes is exceptionally efficient using routine computations, in some cases, computations are not necessary. Three general classes of hetarynes and their preferred site of attack by nucleophiles are shown in Scheme 3. While not encompassing every hetaryne discussed in this manuscript, we expect these general guidelines will enable synthetic applications of hetaryne intermediates.

Although relatively few unsymmetrical hetarynes have been prepared, regioselectivity data is available for comparison to the computational predictions. In all cases where significant yields of product are obtained,[23] the predictions



Scheme 3. General predictions for hetaryne regioselectivity.

and experimental results are in agreement (Scheme 4). Indolynes have recently been studied by our laboratories, and each of the > 20 examples that have been reported are in accord with the aryne distortion model.[6e–g] An example pertaining to a 6,7-indolyne is depicted. The remaining literature examples predominantly involve pyridynes and their derivatives. As shown, our findings for the 3,4-pyridyne[5h,i] and 2,3-pyridyne[5j] are also consistent with experimental data regarding the preferred site of attack and the degree of regioselectivity in each case.[5b–g] Comparisons of computational and experimental data for a 4,5-pyrimidyne[9b] and a 3,4-quinolyne[24] were also found to be in good accord. Several additional examples are depicted in the Supporting Information pertaining to 2,3-pyridyne-*N*-oxide, 4,5-benzofurazanyne, and 1,2-dibenzofuranyne.



Scheme 4. Known examples of a) 6,7-indolyne (C6 attack favored), b) 3,4-pyridyne (C4 attack favored), c) 2,3-pyridyne (C2 attack favored), d) 4,5-pyrimidyne (C4 attack favored), and e) 3,4-quinolyne (C4 attack favored).

In summary, we have developed an efficient computational approach for evaluating the synthetic potential of heterocyclic arynes. DFT or ab initio calculations can be used to predict the likelihood that a given hetaryne can be generated, in addition to the degree of regioselectivity one may expect in a reaction between a given hetaryne and a nucleophilic trapping agent. Although both methods give comparable predictions, DFT requires less computing time. Our predictive tool requires only routine and rapid calculations, and further validates the aryne distortion model as a means to gauge regioselectivities. We expect that these findings will enable synthetic chemists to judiciously design syntheses of functionalized heterocycles using hetarynes as versatile intermediates.

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