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Indolyne and Aryne Distortions and Nucleophilic Regioselectivites

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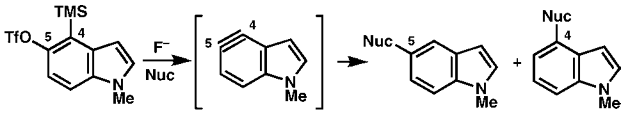
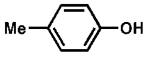
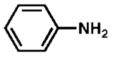
The indole motif is ubiquitous among bioactive natural products and medicinal agents.[1] Indolynes are highly reactive derivatives that have shown promise in the synthesis of indole alkaloids and substituted indole derivatives.[2−4] In contrast to the inherent nucleophilic reactivity of indoles, indolynes are electrophilic. This umpolung of the indole heterocycle, coupled with the high reactivity of arynes, render the indolyne methodology a powerful tool for the preparation of novel and synthetically challenging indole derivatives.[3]

Previous studies have shown that nucleophilic additions to 4,5-indolynes can occur with significant regioselectivity.[3] We now report quantum-mechanical calculations that provide a surprising explanation of the origins of this regioselectivity as well as the regioselectivities for other substituted arynes reported in our laboratories and those of Buszek.[4] We have now predicted and verified experimentally the regioselectivities of nucleophilic additions to 5,6- and 6,7-indolynes. We show that control of the regioselectivity arises from the unsymmetrical bending distortion of arynes and the attendant differential distortion energies required to achieve regioisomeric transition-state geometries. The intimate relationship between distortion energy[5] and activation barrier has been demonstrated previously in 1,3-dipolar[6] and Diels−Alder cycloadditions.[7] After the submission of our manuscript, an experimental and computational study of furan cycloadditions to indolynes from Buszek, Cramer, and co-workers[8] came to a related conclusion.

We previously reported that the generation of 4,5-indolynes from silyl triflates produces aryne intermediates that are trapped to preferentially give 5-substituted adducts (Table 1).[3]

Table 1. Nucleophilic Additions to 4,5-Indolyne[a]



trapping agent (Nuc)	yield (ratio)	*(computed)*
	*80%* (3 : 1)	$\Delta\Delta G^{\ddagger} = 2.8$ *(115 : 1)*
	*91%* (12.5 : 1)	$\Delta\Delta G^{\ddagger} = 3.0$ *(160 : 1)*
N_3−Bn	*86%* (2.4 : 1)	$\Delta\Delta G^{\ddagger} = 0.6$ *(2.5 : 1)*
KCN	*85%* (3.3 : 1)	C-5 preferred[b]

[a] Conditions: see the SI. Computed ratios were obtained from Boltzmann factors using B3LYP/6-31G(d) free energies including CPCM solvation by MeCN. [b] Attack at C-5 is favored (see the SI).

The results of density functional theory (DFT) computations at the B3LYP/6-31G(d) level[9] are shown in the last column of Table 1. Transition states were located for a variety of nucleophilic additions. The results are supported by computations with larger basis sets, other functionals [e.g., see the M06-2X results in the Supporting Information (SI)], and MP2 calculations that will be reported elsewhere. The B3LYP results for the competing transition state (TS) structures reproduce the trends in regioselectivity, while the magnitudes are usually exaggerated. The activation barriers are very low (in some cases zero), so variational effects and dynamics may cause the selectivities to be less than predicted by $\Delta\Delta G^{\ddagger}$. Cyanide addition has no energetic barrier, but approach of the nucleophile at C-5 is favored over that at C-4 for all bond-forming distances (see the SI). The major indolotriazole adduct formed from azide cycloaddition involves attack at C-5 by the nucleophilic internal nitrogen.[10]

Figure 1 shows the calculated structures of 4,5-indolyne and the TSs for nucleophilic addition of aniline. Computed distortion energies, $\Delta E_d^{\ddagger}$, shown in Figure 1, are defined as the energies required to distort the indolyne and nucleophile reagent geometries into their TS geometries.[11,12] In each case, we found that the favored TS has the lower distortion energy. The internal angles of 4,5-indolyne (**1**) show that the aryne is distorted, particularly at C-3a ($\theta_{CCC} = 110°$ vs $\theta_{HCC} = 126°$ in pyrrole). Nucleophilic attack at C-5 relieves some of the strain at C-3a (with θ_{CCC} opening from 110 to 118°) in **TS 2**, but attack at C-4 adds to the unfavorable distortion at C-3a (with θ_{CCC} closing from 110 to 108°) in **TS 3**. Attack at C-4 has 1.4 kcal/mol greater distortion energy than that at C-5 because of the compression at C-3a, leading to a higher activation barrier. Computed distortion energies for amine, alcohol, and azide nucleophilic additions were all lower for C-5 attack, which is favored experimentally.

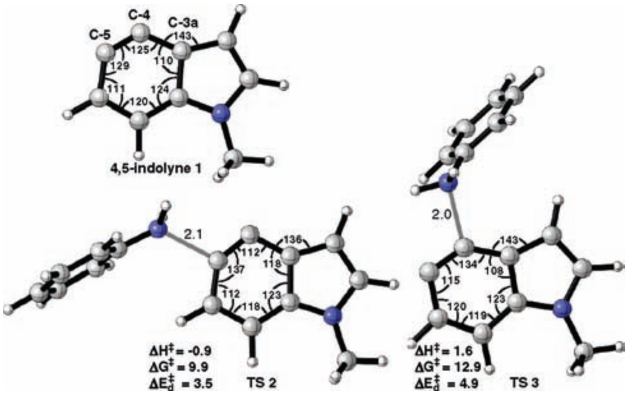


Figure 1. B3LYP/6-31G(d)-optimized structures of 4,5-indolyne and the TSs for aniline addition (energies in kcal/mol).

The distortions in the indolyne TSs can be understood from the geometry for nucleophilic attack on benzyne. As shown in Figure 2, the aryne is flattened at the point of attack of aniline in **TS 5**

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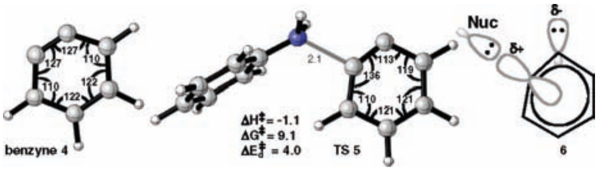


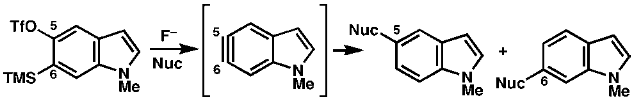
Figure 2. B3LYP/6-31G(d)-optimized structures of benzyne and the TS for aniline addition (energies in kcal/mol).

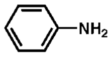
$(\theta_{\mathrm{CCC}} = 136°)$, giving the orbital at the site of attack significant p character and a slight positive charge, while the adjacent angle is compressed $(\theta_{\mathrm{CCC}} = 113°)$, leading to increased s character to stabilize the developing carbanion (see **6**).

Nucleophilic addition to unsymmetrical benzynes is favored for attack at the carbon that requires the minimum geometrical and energetic change in going from the aryne to the TS structure. This is the carbon at which the internal angle is larger, as it is in the nucleophilic-addition TS.

Regioselectivities of nucleophilic attack on 5,6- and 6,7-indolynes were studied computationally prior to experiment. There is uniformly lower unsymmetrical distortion and lower addition selectivity in nucleophilic attack on 5,6-indolyne (Table 2).

Table 2. Nucleophilic Additions to 5,6-Indolyne[a]



trapping agent (Nuc)	yield (ratio)	*(computed)*
	*64%* (2 : 1)	$\Delta\Delta G^{\ddagger}$ = 1.7 *(18 : 1)*
	*73%* (3 : 1)	$\Delta\Delta G^{\ddagger}$ = 0.7 *(3.3 : 1)*
N_3—Bn	*94%* (1.6 : 1)	$\Delta\Delta G^{\ddagger}$ = 0.4 *(1.8 : 1)*
KCN	*84%* (1.7 : 1)	C-5 preferred[b]

[a] Conditions: see the SI. [b] Attack at C-5 is favored.

Figure 3 shows the computed structures of 5,6-indolyne and the TSs for nucleophilic addition. The slightly greater flattening of **7** at C-5 than at C-6 can be attributed to electron withdrawal by N (the charges at C-5 and C-6 are −0.01 and −0.03e, respectively). This facilitates attack at C-5 in **TS 10**, albeit to only a small extent.

As shown in Figure 4, the internal angles at the C≡C termini of 6,7-indolyne are very different from each other $(\theta_{\mathrm{CCC}} = 135$ and $117°)$. Nucleophilic attack on 6,7-indolyne at C-6 is highly favored because of the smaller distortion energy, as the reagent is already distorted into the TS geometry. In fact, the structure of 6,7-indolyne is practically identical to that of the TS for aniline addition to benzyne (**TS 5**). There is no energetic barrier for the attack at C-6 by aniline (Figure S2 in the SI), while C-7 attack (**TS 12**) has a $\Delta E_{\mathrm{d}}^{\ddagger}$ of 8.8 kcal/mol, which is higher than that for any other position of the indolyne heterocycle. Extremely high levels of regioselectivity are observed experimentally (Table 3), and even azide cycloaddition gives very high selectivity. The 6,7-indolynes also display remarkably high regioselectivity in cycloadditions with 2-substituted furans, unlike 4,5- and 5,6-indolynes.[8] Additions of electron-rich furans behave in a similar fashion to the nucleophiles studied here.

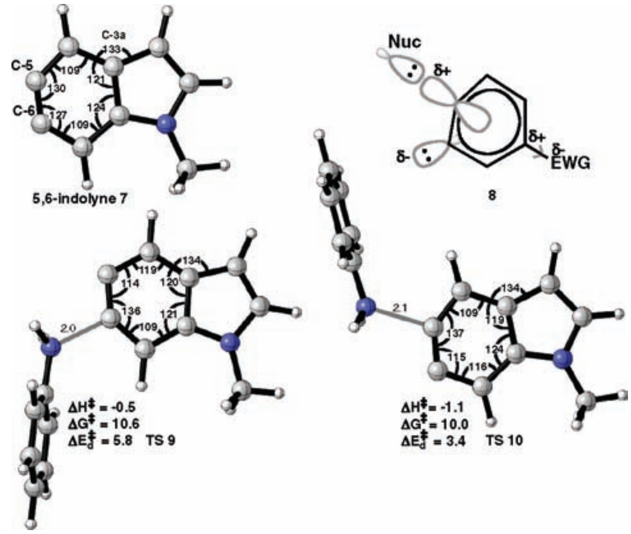


Figure 3. B3LYP/6-31G(d)-optimized structures of 5,6-indolyne and the TSs for aniline addition (energies in kcal/mol).

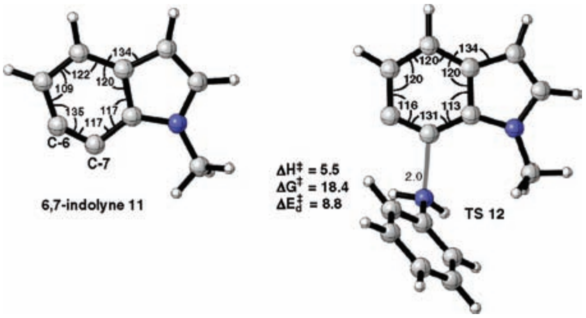
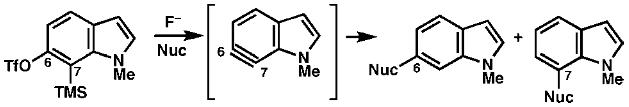
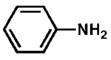


Figure 4. B3LYP/6-31G(d)-optimized structures of 6,7-indolyne and the TS for aniline addition. Energies in kcal/mol.

The regioselectivity of addition to unsymmetrical arynes has often been rationalized in the literature by considering the differing degrees of electronic stabilization in the zwitterionic intermediates formed upon nucleophilic attack.[13] Our calculations show that polar effects can influence the distortion of an aryne and the TS but that ring-fusion can also be a powerful directing effect.

Table 3. Nucleophilic Additions to 6,7-Indolyne[a]



trapping agent (Nuc)	yield (ratio)	*(computed)*
	*53%* (C7 not observed)	$\Delta\Delta G^{\ddagger}$ = 11.4 *(solely C6)*
	*91%* (C7 not observed)	$\Delta\Delta G^{\ddagger} > 5.5^{b}$ *(solely C6)*
N_3—Bn	*77%* (C7 not observed)	$\Delta\Delta G^{\ddagger}$ = 2.7 *(63 : 1)*
KCN	*70%* (C7 not observed)	C6 preferred[c]

[a] Conditions: see the SI. [b] C-6 attack has no energetic barrier; C-5 attack has $\Delta\Delta H^{\ddagger} = 5.5$ kcal/mol. [c] Attack at C-6 is favored (Figure S1).

This distortion model successfully explains the regioselectivity of nucleophilic additions to substituted benzynes, fused benzynocycloalkenes, and naphthalynes (Figure 5). Benzynocycloalkenes **13**−**15** display contrasting regioselectivities for reactions with piperidine: **13** favors C-2 addition, **14** reacts unselectively, and **15**

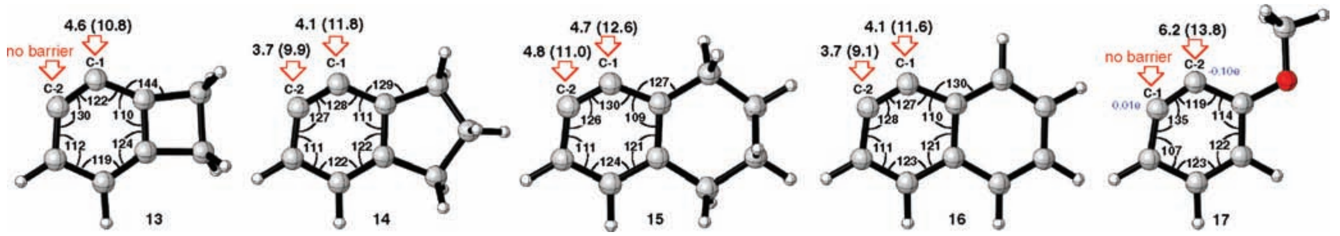


Figure 5. B3LYP/6-31G(d)-optimized structures of benzynocyclo-*n*-alkenes ($n = 4-6$), naphthalyne, and 3-methoxybenzyne. The TS (with aniline) distortion energies (activation energies) are given in kcal/mol.

favors C-1 addition.[14] The unsymmetrically distorted aryne structures and distortion energies reveal the reason for this. In **13**, C-2 is much flatter than C-1 ($\theta_{\mathrm{CCC}} = 130°$ at C-2 vs 122° at C-1), and C-2 attack is calculated to be barrierless. In **14**, the two angles are almost identical, whereas in **15**, C-1 is the flatter of the two positions ($\theta_{\mathrm{CCC}} = 130°$ at C-1 vs 126° at C-2). The internal angles and distortion energies of naphthalyne (**16**) are also in accord with the observed preference for nucleophilic attack at C-2.[15] As noted earlier, these trends are reproduced at a variety of DFT and ab initio levels.

Polar effects can cause significant distortion of the benzyne. The structure of 3-methoxybenzyne (**17**) is significantly flattened at C-1 ($\theta = 135°$), again nearly exactly mimicking the angle of the carbon attacked by the nucleophile in **TS 5**. Indeed, aniline attack at C-1 is barrierless, while attack at C-2 requires significant distortion and has a significant barrier. The computed Mulliken charges shown in Figure 5 indicate that aryne polarization due to the neighboring methoxy group in **17** makes C-1 (0.01*e*) more susceptible to nucleophilic attack than C-2 (−0.10*e*). Experimentally, **17** undergoes C-1 nucleophilic attack exclusively.[13,16]

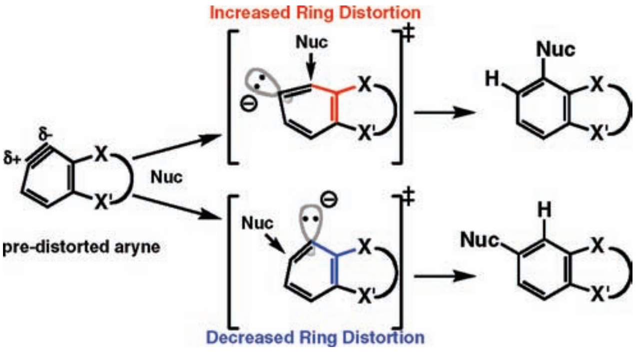


Figure 6. Distortion model for regioselective nucleophilic addition to fused benzynes (X = electron-withdrawing group). The effect of X is larger than the more remote X′.

The regioselectivity in nucleophilic addition to ring-fused benzynes is controlled by the relative ease of distorting the aryne into the two TS structures, as summarized in Figure 6. The unsymmetrical distortion present in ring-fused benzynes biases nucleophilic attack to the flatter end of the aryne. Electron-withdrawing groups (X) polarize benzynes and also cause unsymmetrical distortion. Attack is favored at the flatter, more electropositive terminus of the aryne.

Our combined experimental and computational studies demonstrate that the fundamental reactivity of indolynes and other substituted benzynes toward nucleophilic attack may be understood in terms of a distortion/interaction model and that the regioselectivity is directed by TS distortion energies.

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Supporting Information Available: Full experimental details and compound characterization data, absolute energies, Cartesian coordinates, M06-2X results, and complete ref 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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