Published in final edited form as:

J Am Chem Soc. 2010 February 3; 132(4): 1267. doi:10.1021/ja9098643.

Indolyne and Aryne Distortions and Nucleophilic Regioselectivities

Paul H.-Y. Cheong, Robert S. Paton, Sarah M. Bronner, G-Yoon J. Im, Neil K. Garg, and K. N. Houk

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

Abstract

DFT computations reproduce the surprisingly high regioselectivities in nucleophilic additions and cycloadditions to 4,5-indolynes, and the low regioselectivities in reactions of 5,6-indolynes. Transition state distortion energies control regioselectivities, activating the 5 and 6 positions over 4 and 7 positions, leading to high preferences for 5 and 6-substituted product from 4,5- and 6,7-indolynes, respectively. Orbital and electrostatic interactions have only minor effects, producing low regioselectivities in reactions of 5,6-indolynes. The distortion model predicts high regioselectivities with 6,7-indolynes; these are verified experimentally. The regioselectivities found with other benzyne are explained on the basis of distortion energies that are reflected in reactant geometries.

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 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 reported 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 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 energies⁵ and activation barriers has been demonstrated previously in 1,3-dipolar⁶ and Diels-Alder cycloadditions.⁷ After submission of our manuscript, an experimental and computational study of furan cycloadditions to indolynes from Buszek and Cramer came to a related conclusion.⁸

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

The results of density functional computations (B3LYP/6-31G(d))⁹ are shown in the last column. 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 SI for MO6-2X results), and MP2 calculations that will be reported in a full paper. The B3LYP results on the competing transition structures (TSs) reproduce the trends in regioselectivity, while the magnitudes are usually exaggerated. Activation barriers are very low, (in some cases zero), so that variational effects and dynamics may cause 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 C-4 for all bond-forming distances (see supporting information). 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 TSs for nucleophilic addition of aniline. Computed distortion energies, $\Delta E_d^\ddagger$, shown in Fig. 1, are defined as the energies required to distort the indolyne and nucleophile reagent geometries into their transition state (TS) geometries.^{11,12} In each case, we find the favored TS has the lower distortion energy. Internal angles of 4,5-indolyne **1** show that the aryne is distorted, particularly at C-3a ($\theta_{CCC} = 110^\circ$ vs. $\theta_{HCC} = 126^\circ$ in pyrrole). Nucleophilic attack at C-5 relieves some of the strain at C-3a (opening from 110 to 118°) in **TS 2**, but attack at C-4 adds to the unfavorable distortion at C-3a (closing from 110 to 108°) in **TS 3**. Attack at C-4 has 1.4 kcal/mol greater distortion energy than at C-5 due to 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.

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

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

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).

Figure 3 shows the computed structure 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 (charges at C-5 and C-6 are -0.01e and -0.03e respectively). This facilitates attack at C-5 in **TS 10**, albeit to only a small extent.

As shown in Figure 4, internal angles at the C=C termini of 6,7-indolyne are very different from each other ($\theta_{CCC} = 135^\circ$ and 117°). Nucleophilic attack on 6,7-indolyne at C-6 is highly favored due to smaller distortion energies, as the reagent is already distorted into the TS geometry. In fact, the structure of 6,7-indolyne is practically identical to the TS for aniline addition to benzyne (**TS 5**). There is no energetic barrier for the attack at C-6 by aniline (Figure S2), while C-7 attack (**TS 12**) has a $\Delta E_d^\ddagger$ of 8.8 kcal/mol, higher than 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.

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 ring-fusion can also be a powerful directing effect.

This distortion model successfully explains the regioselectivity of nucleophilic additions to substituted benzyne, fused benzyne-cycloalkenes and naphthalynes (Figure 5). Benzyne-cycloalkenes **13-15** display contrasting regioselectivities for reactions with piperidine: **13** favors C-2 addition, **14** reacts unselectively while **15** favors C-1 addition.¹⁴ The unsymmetrically distorted aryne structures and distortion energies reveal why. In **13** C-2 is much flatter than C-1 ($\theta_{CCC} = 130^\circ$ vs. 122°) 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 ($\theta_{CCC} = 130^\circ$ vs. 126° at C-2). Internal angles and distortion energies of naphthalene **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 density functional theory 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 ($\theta = 135^\circ$), again mimicking nearly exactly 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. Computed Mulliken charges shown in Figure 5 show that aryne polarization due to a neighboring methoxy group in **17** makes C-1 (0.01 e) more susceptible to nucleophilic attack than C-2 (-0.10 e). In experiment, 3-methoxybenzyne undergoes C-1 nucleophilic attack exclusively.¹⁶

Regioselectivity in the nucleophilic addition to ring-fused benzyne is controlled by the relative ease of distorting the aryne into the two transition structures, as summarized in Figure 6. Unsymmetrical distortion present in ring-fused benzyne biases nucleophilic attack to the flatter end of the aryne. Electron-withdrawing groups (X) polarize benzyne and also causes 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 benzyne towards nucleophilic attack may be understood in terms of a distortion/interaction model, and that regioselectivity is directed by TS distortion energies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Science Foundation and the National Institute of General Medical Sciences, National Institutes of Health Grant GM-36700 (K.N.H.), University of California Cancer Research Coordinating Committee, Boehringer Ingelheim (N.K.G.), the Fulbright Commission and AstraZeneca (R.S.P) for financial support.

References

1. Bandini M, Eichholzer A. *Angew. Chem. Int. Ed* 2009;48:9608–9644.
2. Tian X, Hutters AD, Douglas CJ, Garg NK. *Org. Lett* 2009;11:2349–2351. [PubMed: 19432408]
3. Bronner SM, Bahnck KB, Garg NK. *Org. Lett* 2009;11:1007–1010. [PubMed: 19178159]

4. (a) Buszek KR, Brown N, Luo D. *Org. Lett* 2009;11:201–204. [PubMed: 19055375] (b) Brown N, Luo D, Decapo JA, Buszek KR. *Tetrahedron Lett* 2009;50:7113–7115. (c) Buszek KR, Luo D, Kondrashov M, Brown N, VanderVelde D. *Org. Lett* 2007;9:4135–4137. [PubMed: 17880092] (d) Brown N, Luo D, VanderVelde D, Yang S, Brassfield A, Buszek KR. *Tetrahedron Lett* 2009;50:63–65.
5. Also known as deformation energy: Nagase S, Morokuma K. *J. Am. Chem. Soc* 1978;100:1666–1672.
6. (a) Ess DH, Houk KN. *J. Am. Chem. Soc* 2007;129:10646–10647. [PubMed: 17685614] (b) Ess DH, Houk KN. *J. Am. Chem. Soc* 2008;130:10187–10198. [PubMed: 18613669]
7. Xidos JD, Poirier RA, Pye CC, Burnell DJ. *J. Org. Chem* 1998;63:105–112. [PubMed: 11674049]
8. Garr AN, Luo D, Brown N, Cramer CJ, Buszek KR, VanderVelde D. *Org. Lett.* 2009 *article ASAP* 10.1021/ol902415s.
9. Frisch, MJ., et al. *Gaussian 03*, revision C.02. Gaussian, Inc.; Wallingford, CT: 2004. Optimizations at B3LYP/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels of theory (SI) give very similar aryne geometries and also predict the same sense of regioselectivity in each case studied.
10. Houk KN, Sims J, Watts CR, Luskus LJ. *J. Am. Chem. Soc* 1973;95:7301–7315.
11. Hayden AE, Houk KN. *J. Am. Chem. Soc* 2009;131:4084–4089. [PubMed: 19256544]
12. Schoenebeck F, Ess DH, Jones GO, Houk KN. *J. Am. Chem. Soc* 2009;131:8121–8133. [PubMed: 19459632]
13. Liu Z, Larock RC. *J. Org. Chem* 2006;71:3198–3209. [PubMed: 16599619]
14. Hamura T, Ibusuki Y, Sato K, Matsumoto T, Osamura Y, Suzuki K. *Org. Lett* 2003;5:3551–3554. [PubMed: 14507170]
15. (a) Kauffmann K, Fischer H, Nürnberg R, Withwein R. *Justus Liebigs Ann. Chem* 1970;731:23–26. (b) Kolomeitsev AA, Vorobyev M, Gillandt H. *Tetrahedron Lett* 2008;49:449–454.
16. Yoshida H, Fukushima H, Ohshita J, Kunai A. *J. Am. Chem. Soc* 2006;128:11040–11041. [PubMed: 16925418]

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

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

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

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

Figure 5. B3LYP/6-31G(d) optimized structures of benzynocyclo-n-alkenes (n=4,5,6), naphthalene and 3-methoxybenzene. TS (with aniline) distortion energies (activation energies) in kcal/mol.

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

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 supporting information. Computed ratios obtained from Boltzmann factors using B3LYP/6-31G(d) free energies including CPCM solvation by MeCN.

^b Attack at C-5 favored (see SI).

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 supporting information.^b Attack at C-5 favored.

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 supporting information.^b C-6 attack has no energetic barrier; C-5 attack has $\Delta\Delta H^\ddagger = 5.5$.^c Attack at C-6 favored (Figure S1).