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Transition States of Strain-Promoted Metal-Free Click Chemistry: 1,3-Dipolar Cycloadditions of Phenyl Azide and Cyclooctynes

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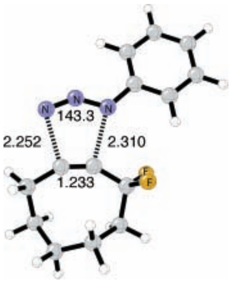
ABSTRACT



Density functional theory (B3LYP) calculations on the transition states for the Huisgen 1,3-dipolar cycloadditions of phenyl azide with acetylene, cyclooctyne, and difluorocyclooctyne are reported. The low activation energy of the cyclooctyne "strain-promoted" cycloaddition ($\Delta E^{\ddagger} = 8.0$) compared to the strain-free acetylene cycloaddition ($\Delta E^{\ddagger} = 16.2$) is due to decreased distortion energy ($\Delta E_d^{\ddagger}$) of cyclooctyne ($\Delta\Delta E_d^{\ddagger} = 4.6$) and phenyl azide ($\Delta\Delta E_d^{\ddagger} = 4.5$) to achieve that cycloaddition transition state. Electronegative fluorine substituents on cyclooctyne further increase the rate of cycloaddition by increasing interaction energies.

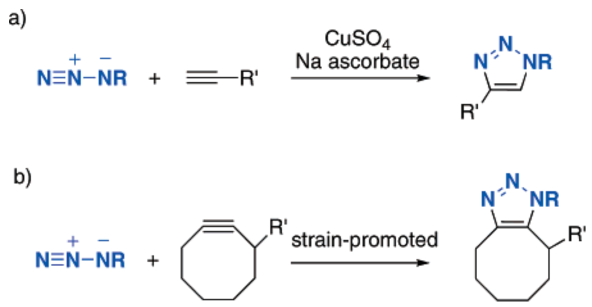


Figure 1. (a) Copper-catalyzed "click" 1,3-dipolar cycloaddition. (b) Strain-promoted 1,3-dipolar cyclaoddition used by Bertozzi and co-workers.

The Huisgen 1,3-dipolar cycloaddition[1] of azides with alkynes has been popularized by Sharpless and co-workers (Figure 1a), who discovered a Cu-catalyzed reaction of azides and terminal acetylenes.[2] This reaction has been exploited in materials chemistry,[3] drug discovery,[4] and chemical biology.[5] The "strain-promoted" 1,3-dipolar cycloaddition of cyclooctyne with azides forms triazoles (Figure 1b) and is a useful alternative to copper-catalyzed reactions of unsaturated terminal acetylenes.[6] Bertozzi and co-workers recently used biotinylated cyclooctyne for selective bioorthogonal chemical modification of living cells without the toxic side effects of

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[1] Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1.

[2] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

[3] (a) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051. (b) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686.

[4] Krasinski, A.; Radic, Z.; Manetsch, R.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 6686.

[5] Seo, T. S.; Bai, X.; Ruparel, H.; Li, Z.; Turro, N. J.; Ju, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5488.

[6] Wittig, G.; Krebs, A. *Chem. Ber.* **1961**, *94*, 3260.

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Cu, making this method an attractive alternative to the Staudinger ligation procedure typically used.[7] Bertozzi has also used fluorocyclooctynes to further enhance reactivity in these strain-promoted cycloadditions.[8]

We recently proposed a general distortion/interaction theory for 1,3-dipolar cycloaddition reactivity.[9] Differences in the energy ($\Delta E_{\mathrm{d}}^{\ddagger}$) required to distort the 1,3-dipole and its dipolarophile counterpart into their transition state (TS) geometries, rather than frontier molecular orbital (FMO) interactions or reaction thermodynamics controls the barrier heights for different 1,3-dipoles. Figure 2 shows the relationship between the activation energy ($\Delta E^{\ddagger}$), distortion energy ($\Delta E_{\mathrm{d}}^{\ddagger}$), and energy of interaction ($\Delta E_{\mathrm{i}}^{\ddagger}$) of the distorted reaction components for the bimolecular reaction of an azide with acetylene. The activation energy is the sum of destabilizing distortions and stabilizing interactions ($\Delta E^{\ddagger} = \Delta E_{\mathrm{d}}^{\ddagger} + \Delta E_{\mathrm{i}}^{\ddagger}$). We report a distortion/interaction energy analysis of the cycloadditions of phenyl azide with acetylene, cyclooctyne, and difluorocyclooctyne to identify the origin of "strain-promoted" rate enhancement and fluorine substituent effects in 1,3-dipolar cycloadditions.

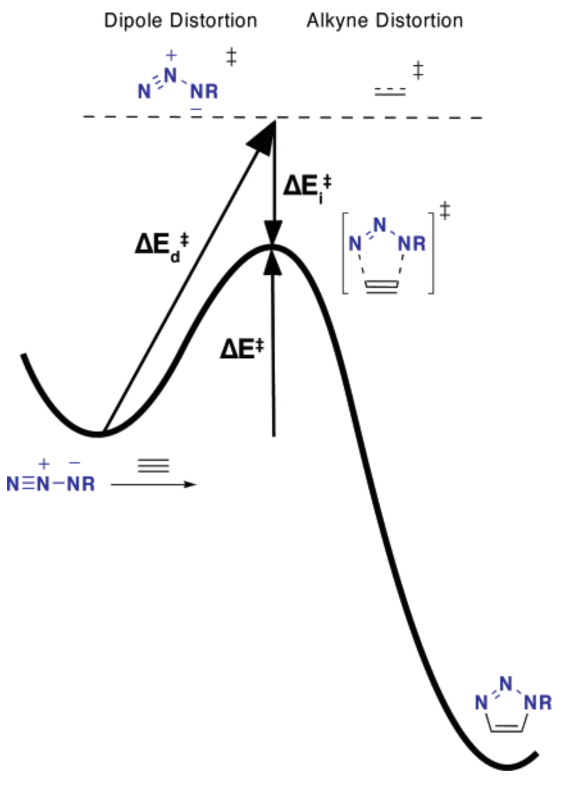

Figure 2. Relationship between activation, distortion, and interaction energies for cycloaddition of an azide with an alkyne.

Alder[10] and Huisgen[11] first noted that strained dipolarophiles, such as norbornene, are much more reactive ($>10^2$) than unstrained olefins toward azides.[12] Houk et al. provided an explanation of "factor X", Huisgen's name for the anomalously high norbornene reactivities.[13] Shea and coworkers have studied substituted mono- and bicyclic alkenes in dipolar cycloadditions with picryl azide and found that reactivity was roughly correlated with strain energy and not ionization potentials.[14]

The transition state for the concerted 1,3-dipolar cycloaddition occurs when orbital overlap between bimolecular fragments is largest and FMO gaps have sufficiently narrowed so that stabilizing interactions overcome destabilizing geometrical distortions. We have shown that to achieve such a transition-state geometry requires significant distortion of the dipole and to a lesser extent dipolarophile distortion.[9] Figure 3 shows the B3LYP/6-31G(d)[15] transition structures for the reaction of phenyl azide with acetylene, cyclooctyne, and difluorocyclooctyne. The B3LYP transition structures are concerted and nearly synchronous, with only minor preference for C−N bond formation with the unsubstituted dipole terminus. Compared to the acetylene transition structure, cyclooctyne transition structures are slightly earlier with longer forming C−N bond lengths and larger N−N−N dipole angles. The transition structure of phenyl azide + acetylene, **TS1** (Figure 3a), has the azide N−N−N angle distorted to 138° from its equilibrium ground state angle of 173°, while for the transition states involving cyclooctyne, **TS2** (Figure 3b), and difluorocyclooctyne, **TS3** (Figure 4c), the N−N−N dipole angle only distorts to 142° and 143°, respectively. The partial bond lengths in **TS1** are 2.119 and 2.252 Å and increase to 2.207 and 2.420 Å for **TS2** and 2.252 and 2.310 Å in **TS3**. For all three transition states there are no differences between the bond lengths of the reacting alkyne.

The barrier for the reaction of phenyl azide and acetylene is 16.2 kcal/mol, leading to the observed sluggish reaction at room temperature. This barrier decreases to 8.0 kcal/mol for the reaction of cyclooctyne and to 6.0 kcal/mol for 3,3-difluorocyclooctyne (see the Supporting Information for enthalpy and free energy corrections). The predicted rate increase of $\sim 10^6$ ($\Delta\Delta E^{\ddagger} = 8.2$ kcal/mol) for the cyclooctyne dipolarophile accounts for the observed strain-promoted click chemistry.

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(7) (a) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046. (b) Lutz, J-F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2182. (c) Ning, X.; Guo, J.; Wolfert, M. A.; Boons, G-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2253.

(8) (a) Agard, N. J.; Baskin, J. M; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *ACS Chem. Biol.* **2006**, *1*, 644. (b) Nguyen, L. T.; De Proft, F.; Dao, V. L.; Ngyuen, M. T.; Geerlings, P. *J. Phys. Org. Chem.* **2003**, *16*, 615.

(9) (a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646. (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, submitted for publication.

(10) (a) Alder, K.; Stein, G. *Liebigs Ann. Chem.* **1931**, *485*, 211. (b) Alder, K.; Stein, G. *Liebigs Ann. Chem.* **1933**, *501*, 1.

(11) (a) Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951. (b) Huisgen, R. *Pure Appl. Chem.* **1981**, *53*, 171.

(12) (a) Huisgen, R. *Angew. Chem. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (c) Huisgen, R. *Angew. Chem. Chem., Int. Ed. Engl.* **1968**, *7*, 321.

(13) Rondan, N. G.; Paddon-Row, M. N.; Caramalla, P.; Mareda, J.; Mueller, P. H.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4974.

(14) Shea, K. J.; Kim, J-S. *J. Am. Chem. Soc.* **1992**, *114*, 4846.

(15) (a) Gaussian 03, Revision C.02, Frisch, M. J. et al. See the Supporting Information for the full reference and computational details. (b) For 1,3-dipolar cycloadditions, B3LYP/6-31G* has a mean absolute deviation of 1.5 kcal/mol compared to the multicomponent ab initio CBS-QB3 method for activation barriers. See: Ess, D. H.; Houk, K. N. *J. Phys. Chem. A* **2005**, *109*, 9542. (c) Ess, D. H.; Jones, G. O.; Houk. K. H. *Adv. Synth. Catal.* **2006**, *348*, 2337. (d) Jones, G. O.; Ess, D. H.; Houk, K. N. *Helv. Chim. Acta* **2005**, *88*, 1702.

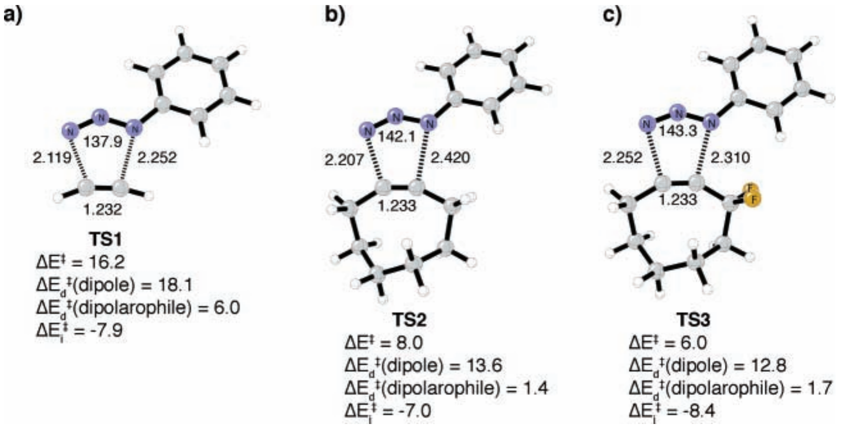

Figure 3. B3LYP/6-31G(d) $\Delta E^{\ddagger}$, $\Delta E_{d}^{\ddagger}$(dipole), $\Delta E_{d}^{\ddagger}$(alkyne), and $\Delta E_{i}^{\ddagger}$ for the concerted transition structures of phenyl azide cycloaddition with (a) acetylene, (b) cyclooctyne, and (c) difluorocyclooctyne (kcal/mol). **TS3** is the lowest energy regioisomer; see the Supporting Information.

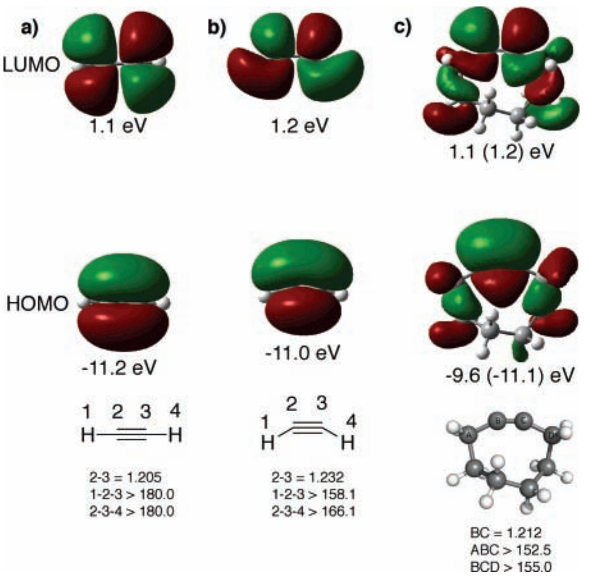

Figure 4. Geometries and frontier orbitals of (a) acetylene, (b) distorted actylene, and (c) cyclooctyne (orbital energies in eV). Values in parentheses use hydrogen in place of the cyclooctyne ring fragment.

These reactions have energies of reaction of −71.0, −74.8, and −75.6 kcal/mol. The distortion energies for each bimolecular component along with the total interaction energy are shown in Figure 3. In **TS1**, the barrier height is large because there is a 24.1 kcal/mol distortion energy penalty to deform phenyl azide and acetylene into their transition state geometries. The majority of the distortion energy (18.1 kcal/mol) results from deforming phenyl azide (mostly bending of the N−N−N angle), while 6.0 kcal/mol of the total distortion energy is due to deforming acetylene (5.4 kcal/mol from bending the H−C−C angles and 0.6 from $C_{sp}-C_{sp}$ bond length increase). The interaction energy of −7.9 kcal/mol (a sum of all electrostatic, charge-transfer, and repulsion interactions) lowers the barrier height to 16.2 kcal/mol.

In the transition state for cycloocytne (**TS2**) only 1.4 kcal/mol of alkyne distortion energy is required; 4.6 kcal/mol less distortion energy than observed for acetylene. The distortion energy of phenyl azide in the TS involving cyclooctyne decreases by 4.5 kcal/mol compared to acetylene; this is due to the earlier transition state of this reaction. The decrease in dipole distortion energy is nearly equal to the decrease in required alkyne distortion energy, and therefore, the large rate enhancement for strain-promoted cycloaddition of cyclooctyne is due to the decreased distortion energies for the 1,3-dipole and the alkyne. Rate enhancement is not due to interaction (orbital) effects. The interaction energy, $\Delta E_{i}^{\ddagger}$, in **TS2** is actually smaller than that for **TS1** by 0.9 kcal/mol (see the Supporting Information for a schematic comparison).

Figure 4 shows the geometries and frontier orbitals (HF/6-311++G(2d,p)//B3LYP/6-31G(d) HOMO and LUMO) of the ground-state linear acetylene, distorted acetylene in the **TS1** geometry, and the ground state of cyclootyne. The linear H−C−C angles of acetylene bends to 158° and 166° in the transition state (**TS1**). Cyclooctyne in the ground state is even more bent with C−C−C angles of 153° and 155°. Although the frontier orbitals of cyclooctyne and distorted acetylene are polarized in the direction of bond formation, the HOMO energy is only 0.2 and 0.1 eV higher for distorted acetylene and cyclooctyne (using hydrogens instead of the carbon ring system) compared to ground-state acetylene.[16] The LUMO energies for distorted acetylene and cyclooctyne both increase by 0.1 eV. Upon distortion to the transition state (**TS2**), the HOMO of cyclooctyne increases by only 0.1 eV and there is no change in the LUMO energy.

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(16) (a) Maier, W. F.; Lau, G. C.; McEwen, A. B. *J. Am. Chem. Soc.* **1985**, *107*, 4724. (b) Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340. (c) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N. *Tetrahedron Lett.* **1979**, *35*, 3237.

Bertozzi and co-workers have recently reported that the rate for cycloaddition with cyclooctyne can be further increased by substitution with fluorine.[8] Our calculations confirm Bertozzi's speculation; difluoro substitution lowers the LUMO from 1.1 eV in cyclooctyne to 0.9 eV in difluororcyclooctyne.[17,18] The HOMO energy is more significantly affected, increasing to −10.5 eV; both charge-transfer directions are typically important for so-called ambiphilic 1,3-dipoles such as azide.[19,20] Difluoro substitution lowers the barrier for **TS3** by 2.0 kcal/mol compared to **TS2**. The interaction energy increases from −7.0 kcal/mol to −8.4 kcal/mol, and the distortion energy decreases only slightly (0.6 kcal/mol), due to offsetting effects; the dipole distortion energy decreases by 0.8 kcal/mol, but the difluororcyclooctyne distortion energy increases by 0.3 kcal/mol. Therefore, the reactivity enhancement caused by fluorination is primarily due to charge-transfer interaction effects.

The distortion/interaction theory provides significant insight into the rate enhancement of strain-promoted Huisgen cycloadditions. The high reactivity of cyclooctyne with azides is due to the lower energy required to distort the 1,3-dipole and alkyne into the transition-state geometry. FMO interaction energies are increased upon fluorine substitution.

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Supporting Information Available: Absolute energies and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] (a) Baskin, J. M; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci. U.S.A.* **2007**, *104*, 16793.

[18] (a) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[19] Absolutely localized molecular orbital decomposition calculations show that charge transfer from acetylene to azide (HN_3) is nearly twice the amount from azide to acetylene. Ess, D. H.; Khaliullin, R. Z.; Head-Gordon, M.; Houk, K. N. Unpublished results.

[20] (a) Houk, K. N. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2. (b) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717. (e) Sustmann, R.; Trill, H. *Angew. Chem. Chem., Int. Ed. Engl.* **1972**, *11*, 838.