Pergamon

Tetrahedron 56 (2000) 8239–8243

TETRAHEDRON

Quantitative Predictions of Substituent and Solvent Effects on the Regioselectivities of Nitrile Oxide Cycloadditions to Electron-Deficient Alkynes

Yunfeng Hu and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, USA

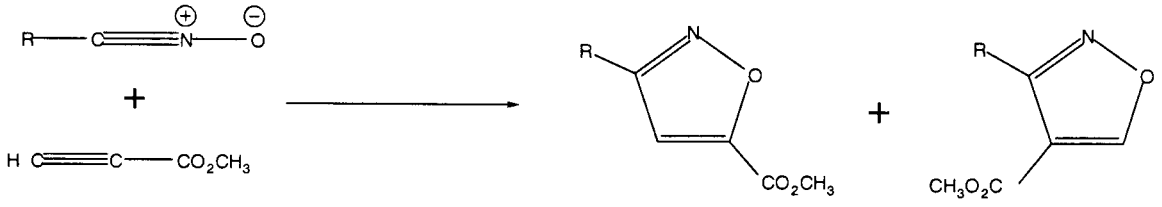
Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

Received 17 July 2000; accepted 22 August 2000

Abstract—Hybrid density functional theory calculations with the B3LYP/6-31G* method were used to calculate the activation barriers of nitrile oxide cycloadditions to the unsymmetrical alkynes cyanoacetylene and methyl propiolate. Inherent electronic effects and solvent polarity both influence regioselectivity.

Rolf Huisgen established the 1,3-dipolar cycloaddition as one of the most general types of organic reactions.[1] These reactions are frequently the methods of choice for five-membered heterocyclic synthesis. Huisgen showed that these reactions have concerted, six-electron pericyclic mechanisms[1] in accordance with the Woodward–Hoffmann rules.[2] He also uncovered a rich bounty of reactivity, regioselectivity, and stereoselectivity puzzles which have led to intense mechanistic and theoretical scrutiny.

One of the intriguing features of 1,3-dipolar cycloadditions involves the reactions of nitrile oxides with unsymmetrical electron-deficient acetylenes.[3] The reactions occur with low and variable regioselectivity which was difficult to understand in terms of a concerted mechanism. Normally, cycloadditions of nitrile oxides to monosubstituted alkenes and alkynes give 5-substituted isoxazolines or isoxazoles. With electron-withdrawing substituents, partial reversal of regioselectivity was observed. Examples of the experimental results for methyl propiolate are shown in Fig. 1.[1,4] We also found that cyanoacetylene, trifluoropropyne, and ethyl propiolate give significant amounts of the 4-substituted



$R=(CH_3)_3C$	91	:	9
H	84	:	16
C_6H_5	72	:	28
CH_3	69	:	31
$2,4,6\text{-}(CH_3)_3C_6H_2$	28	:	72

Figure 1. Regioselectivities of 1,3-dipolar cycloadditions of methyl propiolate with nitrile oxides.

Keywords: density functional theory; nitrile oxide; 1,3-dipolar cycloaddition; regioselectivity; frontier MO theory.
* Corresponding author. Tel.: +1-310-206-0515; fax: +1-310-206-1843; e-mail: houk@chem.ucla.edu

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00747-X

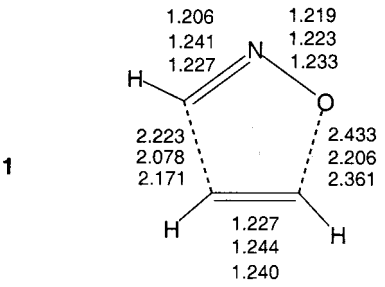


Figure 2. Transition structure for the 1,3-dipolar cycloaddition of fulminic acid to acetylene with (top to bottom) B3LYP/6-31G*, MP2/6-31G*,[16] and CCSD(T)/6-31G*.[16]

adducts, 43, 43, and 66%, respectively, with mesitonitrile oxide in CCl_4.[5] Although a qualitative theory to rationalize these results was presented,[5,6] and an energy partitioning analysis identified the factors involved in regioselectivity control,[7] no quantitative theory to account for the regioselectivity has been reported. Huisgen noted that 'The clouds around the pass are not fully dissipated'.[3] We describe calculations which provide quantitative predictions of regioselectivity and show the influence of inherent electronic effects as well as solvent effects on regioselectivity.

The perturbation MO treatment of cycloaddition reactivity pioneered by Sustmann[8] was applied by our group to explain qualitatively the regioselectivity of 1,3-dipolar cycloadditions.[5,9–13] The 5-substituted products of nitrile oxide cycloadditions to terminal alkynes and alkenes are usually favored because the 1,3-dipolar cycloaddition reaction is controlled by the interaction between the LUMO of the dipole and the HOMO of the dipolarophile.[6] The dipole LUMO has its largest coefficient on carbon, and this becomes united with the unsubstituted dipolarophile carbon, the site of highest HOMO coefficient for a variety of substituents.[6,13] For sufficiently electron-deficient dipolarophiles, however, the major interaction now involves the dipolarophile LUMO and the dipole HOMO.[6–10] This arises because the electron-withdrawing group on the dipolarophile lowers the energy of the HOMO and LUMO. The 4-substituted product is now favored because the nitrile oxide oxygen is most nucleophilic. Consequently, the oxygen becomes bonded to the unsubstituted carbon of the dipolarophile, which in these cases is the site with the largest LUMO coefficient. Based on this rationale, several predictions were made and were verified experimentally.[5,13] The dipole substituent also influences the FMO energies and coefficients and can alter the regioselectivity (Fig. 1).

Many theoretical studies have probed the transition states and mechanisms of 1,3-dipolar cycloadditions.[2,12] Density Functional Theory (DFT)[14] has proven to be a widely applicable method for exploring organic chemistry. For the 1,3-dipolar cycloaddition of fulminic acid to acetylene,[15,16] B3LYP[17] calculations often give comparable or even slightly better results than MP2,[18] CASSCF,[19] or CCSD(T)[20] calculations. The latter is generally considered to be reliably close to experimental values. Morokuma et al.[16] calculated the transition structure for the reaction of nitrile oxide with acetylene at different theoretical levels (Fig. 2). It is clear that B3LYP tends to give an earlier TS than MP2 or coupled cluster methods. Similar energy barriers are predicted by all of these levels of theory (Table 1). All methods predict that the forming CC bond is shorter than the forming CO bond in the transition state, consistent with the electrophilic nature of the carbon terminus of fulminic acid.

Cossío et al. have explored the role of aromaticity in the regioselectivity of nitrile oxide cycloadditions.[21] The transition states are aromatic according to magnetic criteria, but the regioselectivity is not determined by aromaticity. These authors also found that solvent could influence the activation barrier and transition state synchronicity.[21]

We have used hybrid density functional theory calculations (B3LYP/6-31G*) to explore the delicate regiochemical phenomena exhibited by nitrile oxides, and to better understand the role of FMO interactions and electrostatic effects on stereoselectivity. The latter are revealed in the sensitivity of these reactions to solvent effects, which we have also explored theoretically. All the energies were computed with GAUSSIAN 98[22] based on B3LYP/6-31G* optimized transition geometries. A simple polarized continuum model (PCM)[23] was used to estimate solvation energies for CCl_4 and water.

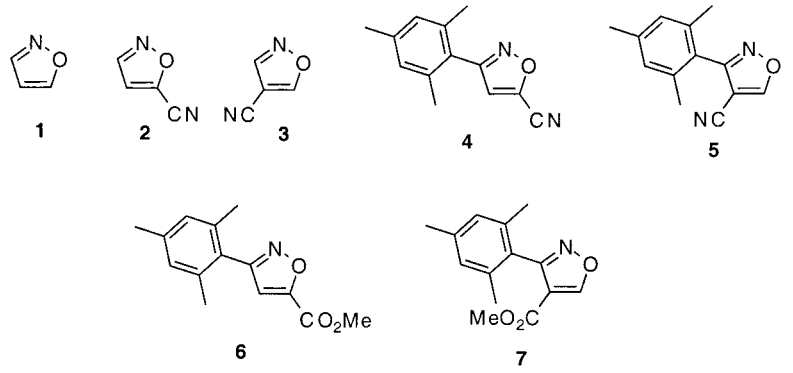
Table 2 shows the computed activation barriers in the gas phase, water, and CCl_4, for formation of regioisomeric products. These results indicate that the energy barriers for the reactions of fulminic acid or mesitonitrile oxide and the electron-deficient acetylenes, cyanoacetylene and methyl propiolate, are generally about 13–14 kcal/mol.[16]

We chose cyanoacetylene and methyl propiolate to study the effects of the electron-withdrawing substituents on regioselectivity. Fig. 3 gives the structures of transition states for cycloadditions of fulminic acid with cyanoacetylene at different levels of theory: B3LYP and two lower levels were utilized to test whether more economical methods might be used for larger systems. Each method leads to early asynchronous TSs. For the 5-substituted cases, the differences in forming bond lengths are large. It is largest, 0.4 Å, with B3LYP. The TS leading to the 4-substituted product is much less asynchronous. The TS for the 5-substituted isoxazole product is lower in energy and also much more polar, so that the preference for the 5-substituted product increases in water. Although these reactions are not usually carried out in water, recent

Table 1. Activation energy of the 1,3-dipolar cycloaddition of fulminic acid and acetylene at different theoretical levels

Energy evaluation	Geometry optimization	Activation energy (kcal/mol)
B3LYP/6-31G*	B3LYP/6-31G*	13.4
CCSD(T)/6-31G*	B3LYP/6-31G*	13.4
CCSD(T)/6-31G*	MP2/6-31G*	13.3
CCSD(T)/6-31G*	CCSD(T)/6-31G*	13.8

Table 2. (B3LYP/6-31G*) Activation energies (kcal/mol) for 4- and 5-substituted products in the gas phase, CCl_4, and water using a PCM solvation model



	Gas phase		CCl_4		Water	
Reaction	ΔE_a (kcal/mol)	Dipole moment (D)	ΔE_a (kcal/mol)	Dipole moment (D)	ΔE_a (kcal/mol)	Dipole moment (D)
1	14.0	2.4	13.2	2.6	13.9	3.2
2	13.5	6.4	12.6	7.1	12.2	8.6
3	14.7	2.4	14.4	2.6	15.2	2.9
4	13.5	8.7	14.1	9.6	14.2	11.7
5	13.0	3.2	14.6	3.5	15.7	4.1
6	13.4	5.1	14.6	5.7	15.0	7.3
7	12.1	4.1	15.2	4.6	20.6	5.6

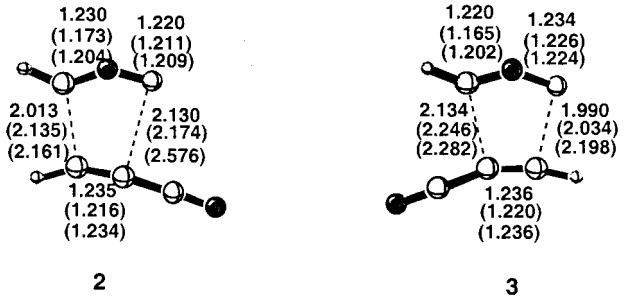


Figure 3. Transition structures of 1,3-dipolar cycloaddition of fulminic acid and cyanoacetylene by (top to bottom) PM3, HF/6-31G*, and B3LYP/6-31G*.

examples of antibody catalysis of related reactions caused us to probe the influence of polar solvents on regioselectivity.[24] This also provides an extreme in solvent polarity. We showed earlier that the bending of fulminic acid in the transition state causes the C to increase in nucleophilicity.[10] The 5-substituted transition state benefits from both HOMO–LUMO and LUMO–HOMO interactions.

The B3LYP geometries for transition states of cycloadditions of mesitonitrile oxide and cyanoacetylene are shown in Fig. 4. The mesityl substituent is a good electron donor. It increases the nucleophilicity of the nitrile oxide by raising the HOMO and LUMO energies, and enhances the HOMO coefficient on oxygen. The 4-substituted regioisomer is now favored. This transition state is quite asynchronous, reflecting the high nucleophilicity of oxygen. The forming isoxazole is planar in this and the remaining transition states. The reaction is now under dipole HOMO and dipolarophile LUMO control. The difference in energy is quite small, in line with the experimental ratio of 72:28 in favor of the 4-isomer. However, the disfavored 5-substituted transition state is more polar and may become the lowest energy transition state in polar solvents. In CCl_4, the regioselectivity is in the same direction as in the gas phase.

The methyl ester exhibits similar behavior. Fig. 5 shows the relevant transition states obtained in the gas phase. The trends in bond lengths are the same as for the cyano substituent. The calculations predict that the ester favors the

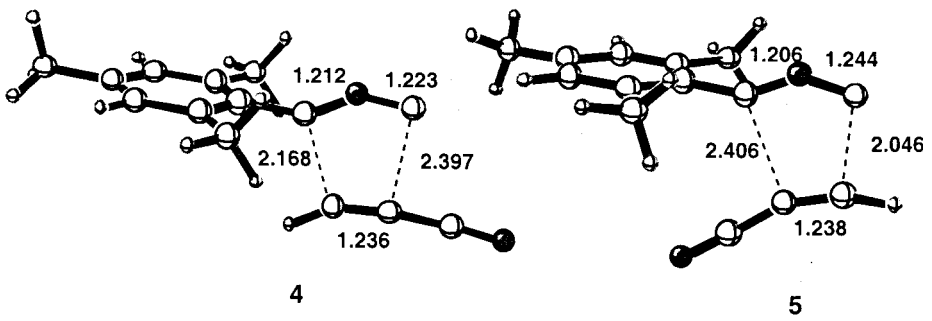
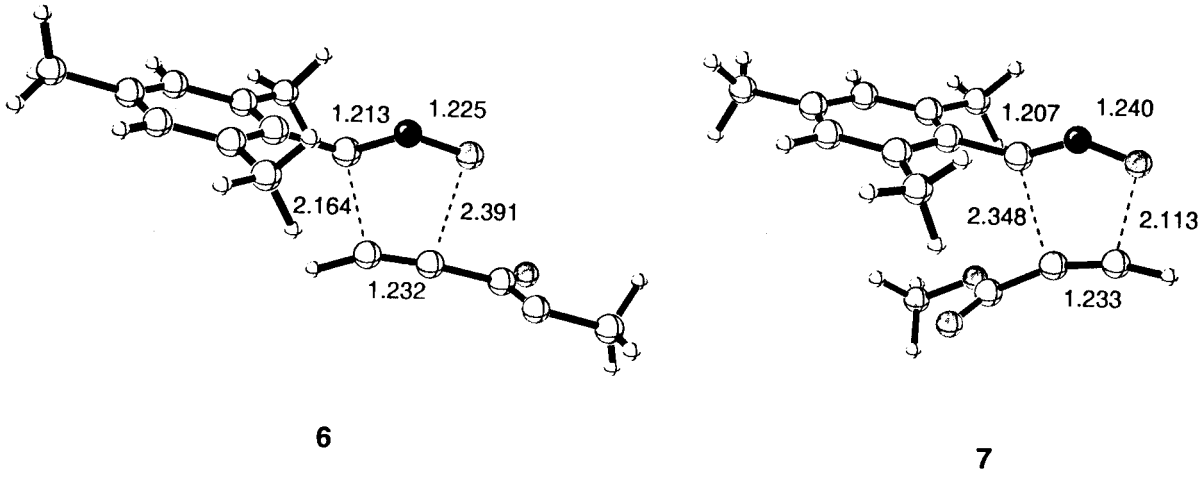


Figure 4. The B3LYP/6-31G* optimized transition structures for the 1,3-dipolar cycloaddition of mesitonitrile oxide and cyanoacetylene.



6 7

Figure 5. The B3LYP/6-31G* optimized transition structures for the 1,3-dipolar cycloaddition of mesitonitrile oxide and methyl propiolate.

4-substituted product more than the nitrile does in the gas phase. There appears to be no significant steric effect here since the larger ester forms the 4-position even more than the small cyano group. This is also consistent with the experimental result in CCl_4, where CN gives 43% of the 4-substituted isomer and CO_2Et gives 66% of the 4-substituted isomer. The PCM model for CCl_4 overestimates the relative destabilization of the 4-substituted isomer, predicting that the 5-isomer should be favored by 0.5–0.6 kcal/mol with mesitonitrile oxide, whereas the 4-isomer makes up 66% of the mixture of isomers with CO_2Et and 43% with CN experimentally. The amount of 4-isomer obtained with CO_2Me in ether (72%) is about the same as with CO_2Et in CCl_4 (66%).

In all cases studied here, the 5-substituted transition structure is more polar than the 4-substituted one. The trends in predicted effects of solvent on reaction rates are in qualitative accordance with the magnitude of the transition state dipole moments relative to those of reactants. Table 2 gives the dipole moments calculated for the various transition states in each solvent. In the gas phase, the computed dipole moments of HCNO, MesCNO, HCCCN, and $HCCCO_2Me$ are 3.2, 4.4, 3.8 and 1.8 D, respectively. The low effect of solvent polarity on the rate of reaction **3** arises because the polarities of reactants (3.2 and 3.8 D) and transition state (2.4 D) are similar. By contrast, the formation of the 5-substituted isomer from reaction **5** is accelerated substantially by polar solvents, since the transition state dipole moment is high (6.4 D). The trend is followed in all cases: the transition state leading to the 4-substituted product is relatively nonpolar; consequently, the reactions are unaffected or even slowed down by polar solvents. The formation of the 5-substituted product is accelerated to varying degrees by an increase in solvent polarity.

In reactions **3**–**7**, the activation barriers are higher in water than in the gas phase. The transition states are less polar than the reactants. The computed dipole moments of the reactants in the gas phase are: fulminic acid (3.2 D), misitonitrile oxide (4.4 D), cyenoacetylene (3.8 D), methyl propiolate (1.8 D). The 5-substituted transition state is more polar than the 4-substituted. Consequently, in these cases, a polar solvent reverses the regioselectivity preference from the 4- to the 5-substituted product. Experimental data on such solvent effects are not yet available but may provide a useful way to control regioselectivity.

Our studies confirm the regioselectivity model described earlier, but also show that solvent effects can influence regioselectivity. The more polar 5-substituted transition states are favored in more polar solvents. We anticipate explorations of these solvent effects in the future.

Acknowledgements

We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support, and to Dr Andrew Leach for helpful comments.

References

1. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633–645.
2. (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395. (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
3. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1–176.
4. Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345–3367 (see also Ref. 3, Table II, p 339).
5. Houk, K. N.; Chang, Y.-M.; Strozier, R. W.; Caramella, P. *Heterocycles* **1977**, *7*, 793.
6. (a) Houk, K. N.; Sims, J.; Duke, R. E.; 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.
7. Caramella, P.; Houk, K. N. Results cited in Ref. 3, p. 343.
8. (a) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838.
9. Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.
10. Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 6397–6399.
11. Houk, K. N.; Caramella, P.; Munchausen, L. L.; Chang, Y.-M.;

Battaglia, A.; Sims, J.; Kaufman, D. C. *J. Electron Spectrosc. Related Phenom.* **1977**, *10*, 441.
12. Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A. Ed.; Wiley: New York, 1984; Vol. 2, pp 407–450.
13. Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798.
14. Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*, Oxford University Press: New York, 1989.
15. Morao, I.; Lecea, B.; Cossío, P. *J. Org. Chem.* **1997**, *62*, 7033–7036.
16. Nguyen, M. T.; Chandra, A. K.; Sakai, S.; Morokuma, K. *J. Org. Chem.* **1999**, *64*, 65–69.
17. B3LYP is the designation of a hybrid functional: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1980**, *37*, 785.
18. Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229; Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1.
19. Roos, B. O. *Adv. Chem. Phys.* **1987**, *69*, 399.
20. Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.
21. Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737–6746.
22. *GAUSSIAN 98*, Revision A.7, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; Gaussian Inc., Pittsburgh, PA, 1998.
23. Miertus, S.; Tomasi, J. *J. Chem. Phys.* **1982**, *65*, 239–245.
24. Toker, J. D.; Wentworth Jr., P.; Hu, Y.; Houk, K. N.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 3244.