Activation Energies and Reaction Energetics for 1,3-Dipolar Cycloadditions of Hydrazoic Acid with C−C and C−N Multiple Bonds from High-Accuracy and Density Functional Quantum Mechanical Calculations

by **Gavin O. Jones**, **Daniel H. Ess**, and **Kendall N. Houk***

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, 90024-1569, USA
(e-mail: houk@chem.ucla.edu)

Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

The reactions of hydrazoic acid (HN_3) with ethene, acetylene, formaldimine ($H_2C{=}NH$), and HCN were explored with the high-accuracy CBS-QB3 method, as well as with the B3LYP and mPW1K density functionals. CBS-QB3 predicts that the activation energies for the reactions of hydrazoic acid with ethylene, acetylene, formaldimine, and HCN have remarkably similar activation enthalpies of 19.0, 19.0, 21.6, and 25.2 kcal/mol, respectively. The reactions are calculated to have reaction enthalpies of −21.5 for triazoline formation from ethene, and −63.7 kcal/mol for formation of the aromatic triazole from acetylene. The reaction to form tetrazoline from formaldimine has a reaction enthalpy of −8 kcal/mol ($\Delta G_{rxn} = +5.6$ kcal/mol), and the formation of tetrazole from HCN has a reaction enthalpy of −23.0 kcal/mol. The trends in the energetics of these processes are rationalized by differences in σ-bond energies in the transition states and adducts, and the energy required to distort hydrazoic acid to its transition-state geometry. The density functionals predict activation enthalpies that are in relatively good agreement with CBS-QB3, the results differing from CBS-QB3 results by *ca.* 1–2 kcal/mol. Significant errors are revealed for mPW1K in predicting the reaction enthalpies for all reactions.

1. Introduction. – Cycloadditions of azides are one of the types of reactions that *Rolf Huisgen* and co-workers classified and developed into one of the most important classes of reactions: 1,3-dipolar cycloadditions [1][2]. The 1,3-dipolar cycloaddition reactions of azides with alkynes and nitriles to produce aromatic triazoles and tetrazoles, respectively, were studied by *Huisgen* and co-workers in the 1960s [3][4]. Both reactions have generated renewed interest in the laboratories of *Sharpless* and co-workers, among others, as prototypical ‘Click’ chemistry reactions [5–14]. In particular, the reactions between azides and acetylenes have been demonstrated in a number of interesting biological contexts [9–13] and in materials applications [14]. These reactions can be performed in H_2O over a range of pH values and over a broad temperature range [5]. Moreover, with the addition of catalysts such as Cu [6], Zn [8], and Mg salts [15], these reactions may be completed on a reasonable time scale at ambient temperatures.

The *Scripps* group has investigated the energetics of catalyzed and uncatalyzed versions of both of these reactions with the B3LYP density functional method [16][17]. Their calculations support the catalytic acceleration provided by NH_3, H_2O, Cu^{II} salts, and Zn^{II} salts in these studies. The activation barriers of the catalyzed reactions are typically predicted to be 7–25 kcal/mol lower than the barriers of the uncatalyzed reactions.

Methods that do not rely on catalytic enhancement of the rates of reaction have become an interesting avenue of research, especially in biological applications [9–13][18]. *Sharpless* and co-workers have, in fact, reported catalytic enhancement of the reaction between azides and acetylenes in the active sites of acetylcholine esterase, AChE [9–11], and fucosyltransferase [12]. *Ju* and co-workers have reported uncatalyzed versions of the reactions between azides and alkynes [19]. *Bertozzi* and co-workers have demonstrated the use of 1,3-dipolar cycloaddition of azides with a strained cyclooctyne for *in situ* modification of living cells [18].

The 1,3-dipolar cycloaddition reactions of azides with alkenes, though capable of producing triazolines [4], are more often used to generate aziridines, imines, and enamines on loss of N_2 from a triazoline intermediate [1][20][21]. No reports have been published regarding catalytic versions of the reactions of azides with alkenes or imines. A literature search uncovered only a single report on the reactions of azides with imines to produce tetrazolines [22].

The aim of the present study was to explore the mechanisms and energetics of the uncatalyzed reactions of hydrazoic acid (HN_3) with ethene, acetylene, formaldimine (=methanimine), and hydrogen cyanide (HCN) with several well-known computational methods. We previously reported benchmarking studies on the performance of various density functionals in predicting activation barriers for pericyclic reactions of hydrocarbons [23]. Here we assess how well B3LYP and mPW1K density functionals perform for predictions of activation barriers and thermodynamics for the 1,3-dipolar cycloaddition reactions mentioned above. These functionals performed best in our previous investigations [23]. Since an experimental reaction enthalpy could be determined only for the condensation of hydrazoic acid with HCN, the energetics determined by these density functionals were compared to the high-accuracy CBS-QB3 method for all 1,3-dipolar reactions. This method gives an average error of 1 kcal/mol for a variety of thermodynamic quantities [24].

2. Methodology. – All calculations were performed with the Gaussian 03 suite of programs [25]. The gradient-corrected density functional methods, B3LYP [26] and mPW1K [27], were used in these calculations. The CBS-QB3 [24] method developed by *Petersson* involves optimizations with B3LYP/6-311G(2d,d,p) and computations with this geometry using a series of higher-level calculations. CBS-QB3 gives energies within ± 1 kcal/mol of experimentally determined values for the G2 data set [24], and was used as an indicator of the accuracy of the mPW1K and B3LYP density functionals. The 6-31G(d) basis set was used for B3LYP calculations, and the 6-31+G(d,p) basis set was used for mPW1K calculations. Bonding distances and energies are given in units of Å and kcal/mol, respectively.

3. Results and Discussion. – 3.1. *Transition-State Geometries for the Reactions of Hydrazoic Acid with Ethene, Acetylene, Formaldimine, and Hydrogen Cyanide.* The transition structures for the reactions of hydrazoic acid with the four dipolarophiles ethene, acetylene, formaldimine, and HCN are presented in the *Figure*. Note that the most-favored transition structures are presented for the reactions of hydrazoic acid with formaldimine and HCN, leading to the products where the NH group of the azide attaches to the C-atom of the imide or CN group. Notable bond distances, as determined by the different methods, are also shown.

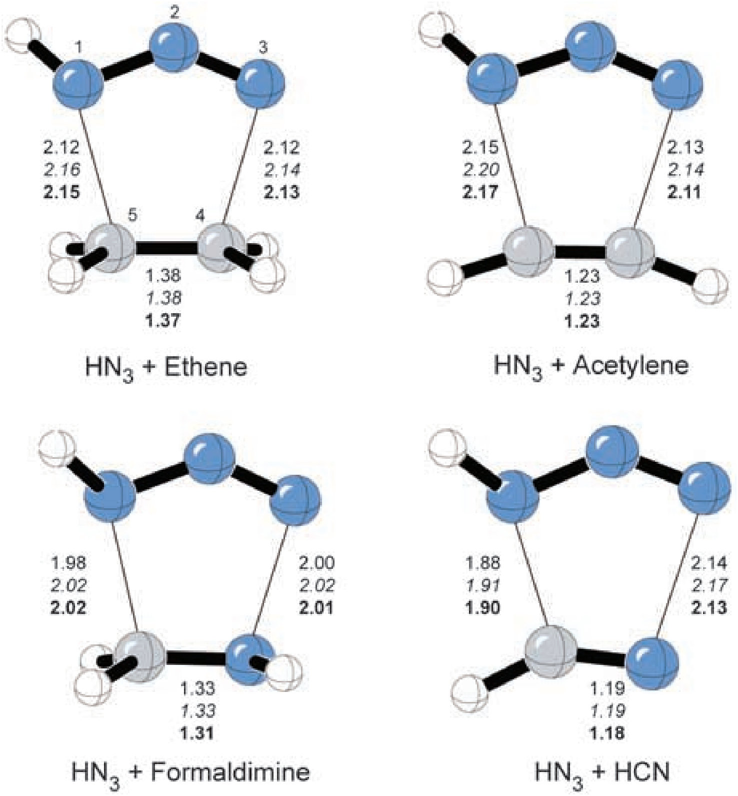

Figure. *Transition-state structures for the reactions of hydrazoic acid with ethene, acetylene, formaldimine, and HCN.* Values refer to B3LYP/6-311G(2d,d,p) (regular type), B3LYP/6-31G(d) (in italics), and mPW1K/6-31+G(d,p) (bold face). Bond distances are given in Å. B3LYP/6-311G(2d,d,p) is the optimization method used in CBS-QB3. N- and C-atoms are shown in blue and gray, resp. Arbitrary atom numbering.

The B3LYP/6-311G(2d,d,p) bond distances for the developing bonds in the transition structure for the addition of hydrazoic acid to ethene are both approximately 2.1 Å. These geometric parameters compare favorably with results found by *Su et al.* [28] using B3LYP/6-31G(d), and *Geerlings* and co-workers [29] using B3LYP with the doubly polarized 6-311++G(d,p) basis set. B3LYP/6-311G(2d,d,p) predicts that the N(1)–C(5) bond distance in the corresponding reaction of hydrazoic acid with acetylene is 2.2 Å, while the N(3)–C(4) forming bond distance is 2.1 Å.

For the reactions of hydrazoic acid with acetylene, ethene, and formaldimine, B3LYP/6-311G(2d,d,p) determines that there is little difference between the forming bonds in the transition structure, with bond differences varying from 0 Å (HN_3 + ethene) to 0.02 Å (HN_3 + acetylene or formaldimine). However, the transition structure for hydrazoic acid with HCN is the most asynchronous, with the difference between forming bonds being 0.23 Å. *Chen* has explored the reaction of hydrazoic acid with HCN with the B3LYP and CBS-QB3 methods, among others, and has observed similar geometric parameters [30].

B3LYP, with the smaller 6-31G(d) basis set, and MPW1K/6-31+G(d,p) predict geometric parameters for the transition structures in the *Figure* that are consistent with values determined by B3LYP/6-311G(2d,d,p).

3.2. *Activation Barriers and Reaction Energies. Table 1* gives activation enthalpies, free energies of activation, and reaction energies for the reactions of hydrazoic acid with ethene, acetylene, formaldimine, and HCN. The CBS-QB3 activation enthalpy for the reaction of hydrazoic acid with acetylene is 19.0 kcal/mol. B3LYP predicts that the activation enthalpy for this reaction is *ca.* 17 kcal/mol, which is 2 kcal/mol lower than the CBS-QB3 prediction. mPW1K overestimates the CBS-QB3 value by 1 kcal/mol, an activation enthalpy of *ca.* 20 kcal/mol being predicted for this reaction.

Table 1. *Activation Enthalpies* ($\Delta H^{\ddagger}$), *Free Energies of Activation* ($\Delta G^{\ddagger}$)*, and Heats and Free Energies of Reaction* (ΔH_{rxn} and ΔG_{rxn}, resp.) *for 1,3-Dipolar Cycloaddition Reactions of Hydrazoic Acid with Different Dipolarophiles.* Prediction methods: mPW1K/6-31+G(d,p); B3LYP/6-31G(d); CBS-QB3. All values are expressed in kcal/mol.

Dipolarophile	Method	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}
Ethene	mPW1K	20.0	31.3	−33.7	−21.1
	B3LYP	18.3	29.5	−22.0	−9.6
	CBS-QB3	19.0	30.3	−21.5	−9.1
Acetylene	mPW1K	19.9	29.9	−80.0	−67.9
	B3LYP	17.4	27.5	−67.0	−54.9
	CBS-QB3	19.0	29.1	−63.7	−51.7
Formaldimine	mPW1K	21.2	33.3	−20.8	−7.4
	B3LYP	20.5	32.8	−8.2	5.1
	CBS-QB3	21.6	33.8	−7.6	5.6
HCN[a])	mPW1K	24.0	34.6	−38.9	−26.6
	B3LYP	22.9	33.6	−25.2	−13.0
	CBS-QB3	25.2	35.9	−23.0	−10.8

[a]) The experimental ΔH_{rxn} value is -26.6 ± 1.2 kcal/mol (see text).

CBS-QB3 predicts that the reaction of hydrazoic acid with ethene has an activation enthalpy identical to the one with acetylene. In this case, B3LYP underestimates the activation barrier of the reaction by *ca.* 1 kcal/mol. mPW1K overestimates the barrier for the reaction of the azide with ethene by 1 kcal/mol, consistent with the result found previously for the reaction of the azide with acetylene.

All methods confirm the expectation that hydrazoic acid reacts exothermically with acetylene to form the aromatic triazole. Examination of the energetic parameters predicted by the three methods reveals some significant differences in the values of the reaction enthalpies and free energies. On the one hand, CBS-QB3 predicts that the formation of triazole is exothermic by 64 kcal/mol, and B3LYP predicts a reaction enthalpy of 67 kcal/mol. mPW1K, on the other hand, predicts that the reaction is exothermic by 80 kcal/mol, 16 kcal/mol greater than predicted by the more-accurate CBS-QB3 method.

Triazoline is predicted to be more stable than hydrazoic acid and ethene, by all methods. Both CBS-QB3 and B3LYP predict that the reaction is exothermic by *ca.* 22 kcal/mol. mPW1K overestimates exothermicity by 12 kcal/mol.

The CBS-QB3 enthalpic barrier for the reaction of hydrazoic acid with HCN is 25.2 kcal/mol, consistent with the observation that this reaction requires heating for several days at 100° to produce tetrazole [4]. Of the density functionals, mPW1K predicts an activation enthalpy of 24.0 kcal/mol, the value in best agreement with CBS-QB3. B3LYP predicts a barrier of 22.9 kcal/mol, a value 2.3 kcal/mol lower than the CBS-QB3 value.

The 1,3-dipolar cycloaddition of hydrazoic acid with formaldimine is predicted to have an activation enthalpy of 20.5 kcal/mol by B3LYP, and 21.2 kcal/mol by mPW1K. The mPW1K activation enthalpy agrees best with the value calculated by CBS-QB3 (21.6 kcal/mol). This activation enthalpy is *ca.* 4 kcal/mol lower than the value for the reaction of the azide with HCN. These results differ from results found for the corresponding reactions of hydrazoic acid with ethene and acetylene, which have identical activation barriers and similar distances between the forming bonds.

The experimental reaction enthalpy for the reaction of HCN with hydrazoic acid can be determined from experimental gas-phase heats of formation for hydrazoic acid ($\Delta H_f^{298} = 71.7 \pm 0.2$ kcal/mol) [31], HCN (31.5 ± 1.0 kcal/mol) [32], and tetrazole (76.6 ± 0.7 kcal/mol) [33], and is -26.6 ± 1.2 kcal/mol. CBS-QB3 predicts a reaction enthalpy of -23.0 kcal/mol, which is an overestimation of the experimental value by *ca.* 3 kcal/mol. The B3LYP reaction enthalpy of -25.2 kcal/mol is similar to the CBS-QB3 value. mPW1K predicts that the reaction enthalpy for the reaction between hydrazoic acid and HCN is -38.9 kcal/mol, an overestimation of the CBS-QB3 value by *ca.* 16 kcal/mol. This error is similar to the roughly 16 kcal/mol overestimation of ΔH_{rxn} found by mPW1K for the reaction of hydrazoic acid with acetylene to afford the aromatic triazole.

The predicted reaction enthalpy for the cycloaddition of hydrazoic acid with formaldimine is consistent with previous results: B3LYP agrees closely with CBS-QB3. The reaction is predicted to be only slightly exothermic ($\Delta H_{rxn} \approx -8$ kcal/mol) and to have an unfavorable free energy of 5.6 kcal/mol by B3LYP; and 5.1 kcal/mol by CBS-QB3. As noted, reactions of imines are mostly unknown [4]. mPW1K predicts a reaction enthalpy of -7.4 kcal/mol. The mPW1K reaction enthalpy is overestimated by *ca.* 12 kcal/mol, the same error as obtained for the formation of triazoline from ethene and hydrazoic acid.

3.3. *Charge Separation at the Transition State.* The amount of charge transferred between the dipolarophile and the azide was evaluated with both *Mulliken* charges and CHelpG charges derived from electrostatic potentials. *Table 2* indicates that the sum of charges on the atoms of hydrazoic acid is greater when *Mulliken* population analysis is used to assess the amount of charge transferred in the transition states of the 1,3-dipolar cycloadditions studied. However, both methods predict very little charge transfer in any case.

The amount of charge transferred by ethene to the dipole is $-0.10e$ for the CBS-QB3 transition state, and this reaction has the lowest barrier. The least charge transfer occurs in the transition state for HCN and hydrazoic acid, where $0.01e$ is transferred to the dipolarophile; this reaction has the greatest barrier. Essentially, there is little or no charge transferred in any of these cases.

The trends in activation enthalpies for these reactions may be related to their transition-state geometries and charge separations. As noted, the transition structures

Table 2. *Sum of* Mulliken *Charges* (*Q*, in units of *e*) *on the Atoms of the 1,3-Dipole at the Transition States for 1,3-Dipolar Cycloadditions of Hydrazoic Acid with Different Dipolarophiles.* CHelpG Charges are given in parentheses.

Dipolarophile	mPW1K[a])	B3LYP[b])	CBS-QB3
Ethene	– 0.07	– 0.09	– 0.09
	(– 0.08)	(– 0.10)	(– 0.11)
Acetylene	– 0.05	– 0.06	– 0.06
	(– 0.04)	(– 0.05)	(– 0.05)
Formaldimine	– 0.04	– 0.05	– 0.05
	(– 0.05)	(– 0.07)	(– 0.07)
HCN	0.01	– 0.00	0.01
	(– 0.00)	(– 0.02)	(– 0.02)

[a]) 6-31 + G(d,p). [b]) 6-31G(d).

for the reactions of hydrazoic acid with acetylene and ethene have similar N(1)–C(5) and N(3)–C(4) bond distances. Charge transfer at these transition states is minor, and does not differentiate between various reactions.

The cycloaddition of hydrazoic acid with formaldimine has a synchronous transition structure, quite similar to the transition-state geometries of hydrazoic acid with acetylene and ethene. The activation enthalpy for cycloaddition is only 2 kcal/mol higher than that of ethene, in spite of the reaction being *ca.* 14 kcal/mol less exothermic. The reaction of hydrazoic acid with HCN is somewhat asynchronous, but both CHelpG and *Mulliken* population analysis indicate that the amount of charge transfer is negligible. Compared to the reaction of acetylene, the reaction of HCN is 41 kcal/mol less exothermic and has a 6 kcal/mol higher activation barrier.

3.4. *Distortion Energies of Hydrazoic Acid.* The distortion energy is the difference in energy between a reactant in its ground- and transition state geometries. We have found that the distortion energies for a series of 1,3-dipoles with ethene and acetylene is similar, and makes the greatest contribution to the activation barriers [34].

The energy required to distort hydrazoic acid to its transition state geometry for the reaction with ethene is 19.6 kcal/mol, and the activation enthalpy for this reaction is 20.0 kcal/mol. Similarly, the distortion energy for hydrazoic acid in its reaction with acetylene is 18.1 kcal/mol, and the activation enthalpy is 19.9 kcal/mol – giving an interaction energy of +1.8 kcal/mol. In both cases, the interaction energies are destabilizing, but they increase the activation barrier to a small degree. More significantly, the activation enthalpy is almost entirely composed of the distortion energy. The similarity between the distortion energies for the reactions of hydrazoic acid with ethene and acetylene account for the similarity of their activation enthalpies.

Hydrazoic acid requires 22.4 kcal/mol to distort to its transition-state geometry with formaldimine, and 21.2 kcal/mol for the HCN reaction. The activation enthalpies for these reactions are 21.2 and 24.0 kcal/mol, respectively. Here, the distortion energies are 1.2 kcal/mol above and 2.8 kcal/mol below the activation enthalpies, respectively.

As seen before for ethene and acetylene, the distortion energies for reactions of hydrazoic acid with formaldimine and HCN make the greatest contribution to the activation enthalpy, as seen previously for ethene and acetylene. The distortion energies for hydrazoic acid in transition states with formaldimine and HCN are larger than the corresponding ones for ethene and acetylene, accounting for their higher activation enthalpies.

3.5. *Dependence of the Trend in Activation Barriers and Reaction Energies on σ-Bond Energy.* Trends in activation enthalpies and reaction enthalpies for 1,3-dipolar reactions have been rationalized by *Huisgen* as involving differences in gain of σ-bond energy on cycloaddition [1][20]. The bond energy of the C−N σ-bond is greater than that of the N−N σ-bond [35]. C−N Bond formation in the cycloadditions of hydrazoic acid with ethene and acetylene is, therefore, energetically more favorable than formation of N−N bonds in cycloadditions of hydrazoic acid with formaldimine and HCN.

The computed activation and reaction enthalpies confirm this theory. The cycloadditions of hydrazoic acid with ethene and acetylene have smaller activation enthalpies than cycloadditions of hydrazoic acid with formaldimine and HCN, while triazole and tetrazole are more stable than tetrazole and tetrazoline, respectively. For the latter cycloadditions, N−C and N−N σ-bonds are being formed, and differences in σ-bond energy become significant as a result.

The formation of tetrazole from hydrazoic acid and HCN is favored by a ΔG_{rxn} value of only -10.8 kcal/mol. The stability of tetrazole is derived from its aromaticity, a factor that is lacking in tetrazoline. Consequently, formation of tetrazoline from hydrazoic acid and formaldimine is an endergonic process. An interesting result of this is seen in cycloadditions of azides with ketimines and aldimines, in which it is more-often observed that products are formed from addition of the 1,3-dipole to the thermodynamically unfavorable enamine tautomer of the imine [36][37].

4. Conclusions. – The data presented here suggest that the uncatalyzed reactions of hydrazoic acid, or other azides, with alkenes will have activation barriers similar to those of azides with alkynes. The major difference between the cycloaddition reactions of azides with alkenes and alkynes is thermodynamic in nature, in which a non-aromatic adduct is made from reaction of the 1,3-dipole with alkenes, and a stabilized aromatic adduct from reaction with alkynes.

In contrast, the 1,3-dipolar reactions of hydrazoic acid with formaldimine and HCN have very different activation characteristics. The activation energy for the reaction of azide and formaldimine is *ca.* 4 kcal/mol lower than that of the reaction between azide and HCN. The thermodynamic parameters of the two reactions are also very different. As expected, the reaction between hydrazoic acid and HCN is quite exothermic; the reaction between the azide and formaldimine is endothermic.

These reactions are characterized by negligible charge separations at the transition states. The distortion energy of hydrazoic acid in the transition states for these reactions makes the largest contribution to activation enthalpies, rather than charge-transfer stabilization.

The B3LYP and mPW1K density functionals both predict the activation enthalpies within *ca.* 2 kcal/mol of the CBS-QB3 values. Some significant errors in predictions of reaction enthalpies by the mPW1K method are identified that seem to be systematic in nature. mPW1K predicts the reaction enthalpies for the reactions of hydrazoic acid with acetylene and HCN to be *ca.* 16 kcal/mol more negative than found by CBS-QB3; reaction enthalpies for the cycloadditions of hydrazoic acid with ethene and formaldimine are predicted to be *ca.* 12 kcal/mol more negative than CBS-QB3 results.

This research was facilitated through the *Partnerships for Advanced Computational Infrastructure* (*PACI*) through the support of the *National Science Foundation.* The computations were performed on the *National Science Foundation Terascale Computing System* at the *Pittsburgh Supercomputing Center* (*PSC*) and on the *UCLA Academic Technology Services* (*ATS*) *Hoffman Beowulf* cluster.

REFERENCES

[1] R. Huisgen, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, John Wiley & Sons, New York, 1984, Vol. 1, p. 1.

[2] R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 565; R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 633; R. Huisgen, *Angew. Chem.* **1963**, *75*, 741.

[3] R. Huisgen, H. Blaschke, *Chem. Ber.* **1965**, *98*, 2985; R. Huisgen, R. Knorr, L. Moebius, G. Szeimies, *Chem. Ber.* **1965**, 98, 4014; R. Huisgen, H. Blaschke. *Liebigs Ann. Chem.* **1965**, *686*, 145; R. Huisgen, G. Szeimies, L. Moebius, *Chem. Ber.* **1967**, *100*, 2494; R. Huisgen, G. Szeimies, L. Moebius, *Chem. Ber.* **1966**, *99*, 475; R. Huisgen, K. von Fraunberg, H. J. Sturm, *Tetrahedron Lett.* **1969**, 2589; R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613.

[4] W. Lwowski, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, John Wiley & Sons, New York, 1984, Vol. 1, Chapt. 5.

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

[6] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

[7] F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2002**, *124*, 12210.

[8] Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945.

[9] K. B. Sharpless, V. V. Fokin, V. Vsevolod, L. G. Green, *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.

[10] K. B. Sharpless, Y. Bourne, H. C. Kolb, Z. Radić, P. Taylor, P. Marchot, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 1449.

[11] K. B. Sharpless, H. C. Kolb, P. Taylor, Z. Radić, R. Manetsch, A. Krasiński, J. Raushel, *J. Am. Chem. Soc.* **2004**, *126*, 12809.

[12] K. B. Sharpless, L. V. Lee, M. L. Mitchell, S.-J. Huang, V. V. Fokin, C.-H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588.

[13] H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128.

[14] K. B. Sharpless, V. V. Fokin, C. G. Hawker, P. Wu, A. K. Feldman, A. K. Nugent, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, *Angew. Chem., Int. Ed.* **2004**, *43*, 3928.

[15] A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237.

[16] F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2002**, *124*, 12210.

[17] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2004**, *127*, 210.

[18] N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046.

[19] Z. Li, T. S. Seo, J. Ju, *Tetrahedron Lett.* **2004**, *45*, 3143.

[20] G. L'Abbé, *Chem. Rev.* **1969**, *69*, 345.

[21] C. K. Sha, A. K. Mohanakrishnan, in 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Eds. A. Padwa, W. H. Pearson, John Wiley & Sons, Hoboken, 2003, p. 649.

[22] W. Lwowski, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, John Wiley & Sons, New York, 1984, Vol. 1, p. 636.

[23] V. A. Guner, K. S. Khuong, A. G. Leach, P. S. Lee, M. D. Bartberger, K. N. Houk, *J. Phys. Chem. A* **2003**, *107*, 11445; V. A. Guner, K. S. Khuong, K. N. Houk, A. Chuma, P. Pulay, *J. Phys. Chem. A* **2004**, *108*, 2959.

[24] J. A. Montgomery Jr., M. J. Frisch, J. W. Ochterski, G. A. Petersson, *J. Chem. Phys.* **2000**, *112*, 6532; J. A. Montgomery Jr., M. J. Frisch, J. W. Ochterski, G. A. Petersson, *J. Chem. Phys.* **1999**, *110*, 2822.

[25] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D.

Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian 03, Revision C.02, *Gaussian, Inc.*, Wallingford CT, 2004.

[26] D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.

[27] J. Lynch, L. F. Patton, M. Harris, D. G. Truhlar, *J. Phys. Chem. A* **2000**, *104*, 4811; Y. Zhao, J. Pu, B. J. Lynch, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **2004**, *6*, 673.

[28] M.-D. Su, H.-Y. Liao, W.-S. Chung, S.-Y. Chu, *J. Org. Chem.* **1999**, *64*, 6710.

[29] L. T. Nguyen, F. De Proft, V. L. Dao, M. T. Nguyen, P. Geerlings, *J. Phys. Org. Chem.* **2003**, *16*, 615.

[30] C. Chen, *Int. J. Quant. Chem.* **2000**, *80*, 27.

[31] P. Gray, *Proc. R. Soc. London, Ser. A.* **1956**, *235*, 106.

[32] J. Berkowitz, G. B. Ellison, D. Gutman, *J. Phys. Chem.* **1994**, *98*, 2744.

[33] A. A. Balepin, V. P. Lebedev, E. A. Miroshnichenko, G. I. Koldobskii, V. A. Ostovskii, B. P. Larionov, B. V. Gidaspov, Y. A. Lebedev, *Svoistva Veshchestv Str. Mol.* **1977**, 93.

[34] D. H. Ess, G. O. Jones, K. N. Houk, in preparation.

[35] P. W. Atkins, 'Physical Chemistry', 5th edn., Oxford University Press, Oxford, 1994, p. C7.

[36] K. Alder, G. Stein, W. Friedrichsen, K. A. Hornung, *Ann. Chem.* **1935**, *515*, 165.

[37] G. Bianchetti, P. D. Croce, D. Pocar, *Tetrahedron Lett.* **1965**, 2043; G. Bianchetti, P. D. Croce, D. Pocar, A. Vigevani, *Gazz. Chim. Ital.* **1967**, *97*, 289; G. Bianchetti, D. Pocar, P. D. Croce, R. Stradi, *Gazz. Chim. Ital.* **1967**, *97*, 304.

Received March 9, 2005