DOI: 10.1002/anie.200902263

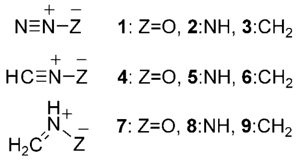
What Controls the Reactivity of 1,3-Dipolar Cycloadditions?**

Bernd Engels* and Manfred Christl*

computational chemistry · cycloaddition · distortion energy · frontier orbital theory · transition states

Intensively investigated and systematically studied by Huisgen,[1] the title reactions have become an important tool for the synthesis of heterocycles.[2] Like Diels–Alder reactions, they are thermal [$_{\pi}4_{s}+{}_{\pi}2_{s}$] cycloadditions. All available criteria indicate that the great majority of these processes proceed concertedly.[1c,3] In spite of the complexity caused by the participating heteroatoms, reaction rates[4] and regioselectivities[4c,5] could be rationalized by means of the frontier orbital theory.

The great success of these quantum chemical studies implies that all essential features are understood. This appears to be contradicted by recent investigations of Houk et al.,[6] who examined the reactions of the prototypical 1,3-dipoles **1–9** (Scheme 1) with the dipolarophiles ethene and ethyne by highly accurate theoretical methods.[7] Similar calculations had been performed previously,[8] but these new studies encompass significantly more systems and seem to be of greater precision. Regardless, the new calculations result in trends not discussed before.



Scheme 1. Structures of the 1,3-dipoles studied by Houk et al.[6] recently.

These new trends are quite remarkable. For example, the activation enthalpies of the ethene and ethyne reactions differ only by less than 2 kcal mol^{-1}. In addition, they decrease within each of the series **1–3**, **4**, **5**, and **7–9** by about 6 kcal mol^{-1}, and the values of the reactions of **4** and **7** as well as those of **5** and **8** hardly deviate from each other. The values of the reactions of the nitrilium ylide **6**, which are too high by about 6 kcal mol^{-1},[9] are the only exceptions to this trend. In particular, the finding that the activation enthalpies of the ethene and ethyne reactions of a given 1,3-dipole are the same is surprising. On the basis of the frontier orbital theory, it would be expected that ethene reacts substantially faster, as its HOMO (−10.5 eV) is higher and its LUMO (1.5 eV) lower in energy than the respective frontier orbitals of ethyne (−11.5 and 2.5 eV, respectively). On the other hand, the similar reaction rates are remarkable also because of the thermodynamics of the ethene and ethyne additions, since the latter are much more exothermic, especially if aromatic products result as in the reactions of **1**, **2**, **4**, and **5**. Kinetic measurements employing numerous 1,3-dipoles had shown previously that ethenes and ethynes with the same substituents add at similar rates, and that either ethyne or ethene may be favored only slightly depending on the nature of the 1,3-dipole.[1c]

Looking for a rationalization of the results, Houk et al. found only a partial correlation of the calculated activation enthalpies with the calculated reaction enthalpies and that other approaches also do not provide an obvious explanation.[10] However, there is an unambiguous correlation between the calculated activation barriers $\Delta E^{\ddagger}$ and the distortion energies $\Delta E_{\mathrm{d}}^{\ddagger}$ ($\Delta E^{\ddagger}=0.75$, $\Delta E_{\mathrm{d}}^{\ddagger}=-2.9$; $R^2=0.97$). The latter is the energy required to distort the 1,3-dipole and the dipolarophile from their equilibrium geometries into the transition-state geometries without allowing any interaction between them.[11] Since the cycloaddends do not interact in this partitioning by definition, the total distortion energy amounts to the sum of the distortion energy of the individual reaction partners. The total activation barrier then is the sum of the total distortion energy and the energy of interaction $\Delta E_{\mathrm{i}}^{\ddagger}$ between the cycloaddends in the transition state. Further computations show that substituted derivatives of **3** and **6** as well as additional 1,3-dipoles such as H_2COO, O_3, and O=NH–O also fit the correlation. About 80 % of $\Delta E_{\mathrm{d}}^{\ddagger}$ is shown result from the distortion of the 1,3-dipoles (see below). The absolute value of the interaction energy $\Delta E_{\mathrm{i}}^{\ddagger}$, which always has a negative sign, generally amounts to 32–46 % of $\Delta E_{\mathrm{d}}^{\ddagger}$, but it has significantly higher values in the cases of **8** and **9**. A linear correlation has also

---

[*] Prof. Dr. B. Engels, Prof. Dr. M. Christl
Institut für Organische Chemie, Universität Würzburg
Am Hubland, 97074 Würzburg (Germany)
Fax: (+49) 931-318-5394
E-mail: bernd@chemie.uni-wuerzburg.de
christl@chemie.uni-wuerzburg.de

[**] B.E. thanks the Sonderforschungsbreich 630, the Graduiertenkolleg 1221, and his research group for valuable support.

been found between $\Delta E_i^{\neq}$ and the activation barrier, which is considerably less pronounced ($R^2 = 0.77$), however.

These new and surprising results raise questions: Why was the meaningful influence of the distortion energy not discovered earlier? How can this finding be reconciled with the tremendously successful frontier orbital theory. As is generally known, the latter explanation rests on the energy differences of the interacting frontier orbitals of the separate cycloaddends, whereas distortion effects are seemingly not taken into consideration at all.[12] It is especially remarkable that the distortion energy of the 1,3-dipole alone appears to be of such importance, although the frontier orbital theory emphasizes only the significance of the interaction between the two cycloaddends.

The answer to the first question is presumably found in the kind of correlations mostly investigated in the 1970s. Thus, the distortion energy discussed above cannot be of any relevance in the parabolic interconnection between the logarithms of the rate constants and the ionization potentials of the dipolarophiles, recognized by Sustmann and Trill,[4b] since the reactions of different dipolarophiles with the same 1,3-dipole, that is, phenyl azide, were considered. The distortion simply was not at the focus of the examination.

To study the trends for a series of different dipolarophiles, Houk et al. also analyzed the additions of five substituted ethenes (C_2H_3R with R = OMe, Me, COOMe, Cl, CN) in comparison with those of unsubstituted ethene to the electrophilic nitrous oxide (**1**), the nucleophilic diazomethane (**3**), and the ambiphilic hydrazoic acid (**2**). Varying images resulted according to the type of 1,3-dipole. For the reactions of **1**, the distortion energy required for the 1,3-dipole is independent of the dipolarophile, since **1** adopts virtually the same geometry in all the six transition states. Hence, the calculated activation barriers contain the constant contribution of the distortion energy of **1** and, as variable quantities, the distortion energy of the alkenes (range of 3 kcal mol^{-1}) as well as the interaction energy (range of 5 kcal mol^{-1}). Consequently, the computed activation barriers exhibit a variation of about 7 kcal mol^{-1}. In these cases, the distortion energy of **1** contributes strongly to the barriers but has no relevance with respect to the trends. Rather, the differences are qualitatively rationalized by well-known orbital concepts. Thus, the large interaction energy calculated for methyl vinyl ether (R = OMe) is explained by the interaction of the low-lying LUMO of **1** with the high-energy HOMO of the dipolarophile. With electron-withdrawing substituents (R = CN), the energy of the HOMO is lowered, which accounts for the decrease in the interaction energy.

As expected, Houk et al. found the well-known parabolic dependence between the electronic nature of the dipolarophile and its reactivity toward the ambiphilic hydrazoic acid (**2**), since both electron-rich and electron-deficient alkenes show barriers decreased by up to 2 kcal mol^{-1} relative to that of ethene. The distortion energy of **2** varies by up to 5 kcal mol^{-1} according to the dipolarophile, because **2** adopts different geometries in the transition states. In contrast, the corresponding geometries of the dipolarophiles are astoundingly remarkable similar to each other, with the consequence that their distortion energies display a range of only 2 kcal mol^{-1}. However, the interaction energy varies by 7 kcal mol^{-1}, since the arrangements of the cycloaddends toward each other are widely different. This divergence results from the action of the unsubstituted carbon atom as the nucleophilic center in the case of electron-rich dipolarophiles (e.g. R = OMe), whereas this role is taken by the NH group of **2** on the approach of an electron-deficient alkene. Thus, the 1,3-dipole **2** acts as either an electrophile or a nucleophile depending on the electronic character of the diploarophile. To achieve sufficient overlap with the orbitals of the substituted ethenes in the transition state, **2** has to bend more (R = OMe) or less (R = CN) than in the reaction with the parent ethene. This causes different distortion energies of **2** and reveals that these quantities are substantially influenced by the interaction with the dipolarophile. Hence, the contours of a bridge between the frontier orbital theory and the new model slowly become evident.

With the reactions of the nucleophilic diazomethane (**3**), mainly the distortion energy of the 1,3-dipole changes (range of about 5 kcal mol^{-1}), while that of the dipolarophile and the interaction energy vary much less (by 1 and 2 kcal mol^{-1}, respectively). In the case of **3**, therefore, the alterations of the activation barrier first and foremost result from the variations of the distortion energy of the 1,3-dipole. Here, a relation with the frontier orbital theory is also apparent, though, since the changes emerge from the optimization of the interaction between the cycloaddends in the transition state. As a consequence, the distortion and, thus, the associated energy is rather an effect than a cause. Now, the bridge between the new model of explanation and the frontier orbital model is completely apparent.

The connection between the HOMO–LUMO energy gap of a 1,3-dipole and its distortion energy provides the last detail of that bridge. At this point, Houk et al. argue consistently that molecules having a large HOMO–LUMO energy gap are more stable and, therefore, can in general be distorted less easily than those with a small energy gap. This becomes particularly noticeable when the transition from the oxides (**1**, **4**, **7**) via the imines (**2**, **5**, **8**) to the ylides (**3**, **6**, **9**) is considered. As the calculations prove, the HOMO–LUMO energy gap decreases significantly in this order, which qualitatively rationalizes the lowering of the barrier to reaction by improved interactions of the frontier orbitals as well as the substantial decrease of the distortion energy. In fact, direct correlations are observed between the newly computed activation and distortion energies and the HOMO energies already estimated in the 1970s.

Essentially, the distortion energy of the 1,3-dipoles is caused by the bending toward the attacking dipolarophile. This suggests that the reaction should proceed more readily if the corresponding deformation vibration is excited. Dynamics calculations indeed confirm this anticipation.[6d] However, it is surprising that most of the energy necessary to overcome the activation barrier still is supplied by translation.

Admittedly, the detailed examination of these cycloadditions appears to be quite theoretical. However, the proximity to practical application is demonstrated by the industrial oxidation of cyclododecatriene to cyclododecadienone with nitrous oxide (**1**); startup of a plant based on this conversion is projected for this year.[13] This industrial procedure[13] not only provides a precursor for Polyamide 12 but also it consumes **1**, which is formed as a by-product in a number of processes and is a known greenhouse gas and the dominant ozone–depleting substance.[14] Known for a long time,[1a] this reaction type starts with the 1,3-dipolar cycloaddition of **1** to an ethene subunit and requires heating at almost 300 °C in the case mentioned. If the above predictions are valid, the selective excitation of the bending vibration of **1** will considerably boost the reaction. But this brings up the question whether the selective and efficient excitation of bending vibrations is indeed possible. If a rapid redistribution of the excitation energy to all other degrees of freedom of the nuclei occurs as in most pertinent cases, the efficacy will be severely diminished.

Received: April 28, 2009

---

[1] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; b) R. Huisgen, *Angew. Chem.* **1963**, *75*, 742–754; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633–645; c) R. Huisgen in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 1–176.

[2] a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2809; c) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235–3285.

[3] a) R. Huisgen, *J. Org. Chem.* **1968**, *33*, 2291–2297; b) J. J. W. McDouall, M. A. Robb, U. Niazi, F. Bernardi, H. B. Schlegel, *J. Am. Chem. Soc.* **1987**, *109*, 4642–4648.

[4] a) R. Sustmann, *Tetrahedron Lett.* **1971**, *12*, 2717–2720; b) R. Sustmann, H. Trill, *Angew. Chem.* **1972**, *84*, 887–888; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 838–840; c) K. N. Houk, K. Yamaguchi in *1,3-Dipolar Cycloaddition Chemistry, Vol. 2* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 407–450.

[5] K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315.

[6] a) D. H. Ess, K. N. Houk, *J. Phys. Chem. A* **2005**, *109*, 9542–9553; b) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647; c) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198; d) L. Xu, C. E. Doubleday, K. N. Houk, *Angew. Chem.* **2009**, *121*, 2784–2786; *Angew. Chem. Int. Ed.* **2009**, *48*, 2746–2748.

[7] A precise description of the methods applied is presented in references [6a–d]. Activation and reaction enthalpies were determined by using the CBS-QB3 procedure. Its largest error amounts to 2.8 kcal mol^{-1} in the G2 test set; the average and the absolute average error amount to 0.2 kcal mol^{-1} and 0.98 kcal mol^{-1}, respectively. Additional calculations were performed with the B3LYP/6-31G(d) standard method. In this case, larger absolute errors are to be expected. However, the majority of the results arise by the examination of trends, which are reproduced quite reliably for the most part. Methods are compared in reference [8] as well.

[8] a) P. B. Karadakov, D. L. Cooper, J. Gerratt, *Theor. Chem. Acc.* **1998**, *100*, 222–229; b) M. T. Nguyen, A. K. Chandra, S. Sakai, K. Morokuma, *J. Org. Chem.* **1999**, *64*, 65–69; c) M.-D. Su, H.-Y. Liao, W.-S. Chung, S.-Y. Chu, *J. Org. Chem.* **1999**, *64*, 6710–6716.

[9] These deviations are attributed to the small HOMO–LUMO energy gap of **6** with a linear HCNC arrangement. Consequently, the interaction between the π HOMO and the σ* orbital of the C–H bond causes a pseudo Jahn–Teller effect, giving rise to a significant stabilization and a nonlinear HCNC geometry: P. Caramella, K. N. Houk, *J. Am. Chem. Soc.* **1976**, *98*, 6397–6399.

[10] Based on different singlet–triplet energy gaps of ethene and ethyne, Houk et al. assume that the curve-crossing model of Pross and Shaik (A. Pross, S. S. Shaik, *Acc. Chem. Res.* **1983**, *16*, 363–370) also cannot explain why the reactions of ethene and ethyne have activation barriers of similar height. However, here they leave out of consideration that the ethyne reactions are clearly more exothermic than those of ethene because aromatic compounds are formed. Thereby, different slopes of the curves result within the curve-crossing model (A. Pross, *Theoretical and Physical Principles of Organic Reactivity*, Wiley, New York, **1995**, pp. 113–114), which is why an explanation could nevertheless be possible. An unconstrained explanation could also be offered by additional repulsive interactions, which increase the activation barrier by the second electron-rich π system in the case of ethyne: I. V. Alabugin, M. J. Manoharan, *J. Chem. Phys. A* **2003**, *107*, 3363–3371.

[11] a) K. Kitaura, K. Morokuma, *Int. J. Quantum Chem.* **1976**, *10*, 325–340; b) S. Nagase, K. Morokuma, *J. Am. Chem. Soc.* **1978**, *100*, 1666–1672; c) A. P. Bento, F. M. Bickelhaupt, *J. Org. Chem.* **2008**, *73*, 7290–7299; d) G. T. de Jong, F. M. Bickelhaupt, *ChemPhysChem* **2007**, *8*, 1170–1181.

[12] There was already a very early discussion on the significance of the bending of azides for their 1,3-dipolar cycloaddition, but these studies were not pursued further: J. D. Roberts, *Chem. Ber.* **1961**, *94*, 273–278.

[13] http://www.basf.com/group/corporate/de/innovations/research-verbund/research-projects/processes/cdon.

[14] A. R. Ravishankara, J. S. Daniel, R. W. Portmann, *Science* **2009**, DOI: 10.1126/science.1176985.