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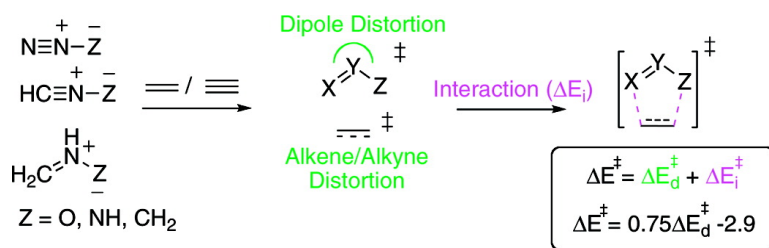
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Distortion/Interaction Energy Control of 1,3-Dipolar Cycloaddition Reactivity

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Huisgen's 1,3-dipolar cycloaddition reactions, extraordinarily versatile methods for heterocycle synthesis, are now used in materials chemistry, drug discovery, and chemical biology.[1,2] The 1,3-dipoles range from the familiar atmospheric components, ozone and nitrous oxide, to the synthetically valuable azides of click chemistry fame.[1] Frontier molecular orbital (FMO) theory has provided a powerful model for the qualitative understanding of reactivity and regioselectivity, based upon electronic properties of isolated reactants.[3] Conceptual density functional theory has also provided a qualitative way to rationalize reactivity patterns.[4]

Chemically accurate theoretical thermochemistries (± 1 kcal/mol) are now available using the CBS-QB3 method.[5] Three of the most important classes of dipoles defined by Huisgen, the diazonium (DB), nitrilium (NB), and azomethine betaines (AB), shown below, were explored.[2] The CBS-QB3 $\Delta H^{\ddagger}$ and ΔH_{rxn} were computed for the reactions of **1−9** with ethylene and acetylene.[6]

Diazonium Betaines

$\overset{+}{N} \equiv N - \overset{-}{Z}$

1 Z = O, Nitrous Oxide
2 Z = NH, Hydrazoic Acid
3 Z = CH₂, Diazomethane

Nitrilium Betaines

$HC \equiv \overset{+}{N} - \overset{-}{Z}$

4 Z = O, Fulminic Acid
5 Z = NH, Formonitrile Imine
6 Z = CH₂, Formonitrile Ylide

Azomethine Betaines

$H_2C \overset{H}{\underset{\underset{Z}{\big|}}{\overset{|}{\overset{+}{N}}}}$

7 Z = O, Methylene Nitrone
8 Z = NH, Formoazomethine Imine
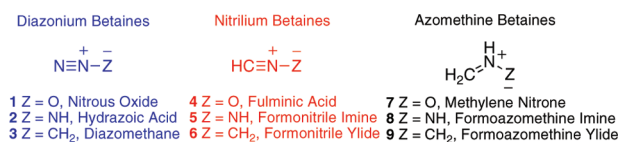**9** Z = CH₂, Formoazomethine Ylide

Figure 1a is a graphical display of the computed CBS-QB3 activation enthalpies of these 9 dipoles with ethylene and acetylene. There is a smooth decrease in barrier height from oxides to imines to ylides, amounting to a 6 ± 1 kcal/mol lowering of the barrier for oxide to imine to ylide, except for the nitrilium ylide. While this is well-known to be the order of reactivity,[3] there is a remarkable consistency in the slope of these lines for different dipoles, with only **6** deviating from the pattern.[7] Second, the NB and AB classes have almost identical barrier heights. Third, ethylene and acetylene barriers are nearly identical for a given type of 1,3-dipole, despite widely different ground state FMO gaps and very different reaction exothermicities (Table S1, Supporting Information). For example, for hydrazoic acid, the $\Delta H^{\ddagger}$ with ethylene and acetylene are both 20 kcal/mol, but the ΔH_{rxn} are −20 and −62 kcal/mol. Huisgen experimentally observed the similar rates of reactions of a few dipoles with related alkene and alkyne dipolarophiles.[2,8]

It might be expected that a graph of this type could be due to differences in ΔH_{rxn}. Marcus theory and earlier empirical relationships going back to Dimroth and Brønsted, have shown that $\Delta \Delta E^{\ddagger} = \frac{1}{2} \Delta \Delta E_{rxn}$ for many reactions.[9] Figure 1b shows a test of this relationship. Some dipoles show the expected trend, but this is not general. Reactions with ethylene and acetylene have identical $\Delta H^{\ddagger}$ but have very different ΔH_{rxn}; formation of aromatic products from acetylene is not accompanied by unusually low barriers for these highly thermodynamically advantageous reactions. Several reaction series show large deviations from this linear relationship.

$\Delta H^{\ddagger}$ is not a simple function of ΔH_{rxn}; there is a tendency toward early and late transition states (TS), but it is related only to the barrier height, not to ΔH_{rxn}.[9] Figure 2 shows overlays of the TSs
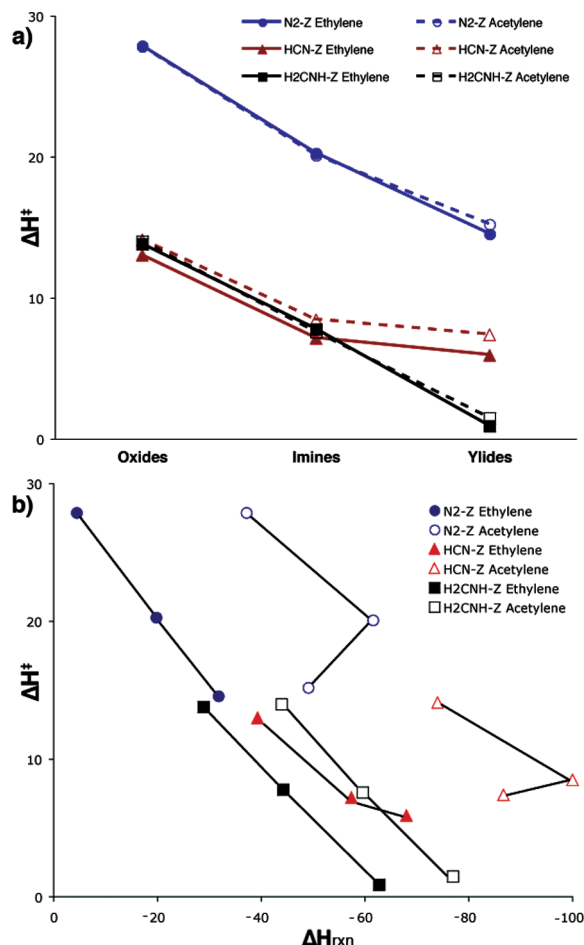

Figure 1. (a) Graphical display of CBS-QB3 $\Delta H^{\ddagger}$ at 0 K for 1,3-dipolar cycloadditions; (b) CBS-QB3 $\Delta H^{\ddagger}$ vs ΔH_{rxn}. Solid lines connect (left to right) O, NH, and CH₂ in each series. Values are in kcal/mol.

for reactions of **1−9** with ethylene and acetylene. Only the positions of the hydrogen atoms reveal that each picture actually represents a superposition of two TSs. The shift from late to early, as the activation barrier drops, is barely perceptible in the TS drawings. The average forming bond length increases by 0.2−0.3 Å, but the C−C bond lengths of the dipolarophiles change by <0.1 Å over each series. Each TS involves 26−45° bending of the dipole from a linear or planar to a product-like pentagonal geometry.

Figure 3 shows a remarkable correlation between the activation barriers and the total TS distortion energies ($\Delta E_d^{\ddagger}$).[10] The $\Delta E_d^{\ddagger}$ is the energy required to distort the dipole and the dipolarophile into the TS geometries without allowing interaction. This is different from Marcus's reorganization energy, λ.[9] A number of studies have shown that the distortion energies influence the barrier heights of cycloadditions and related reactions.[11] Table S2 gives the B3LYP (1.5 kcal/mol mean absolute deviation from CBS-QB3 values)[12] $\Delta H^{\ddagger}$, ΔH_{rxn}, $\Delta E_d^{\ddagger}$, and TS interaction energies, $\Delta E_i^{\ddagger}$. Figure 3 is a
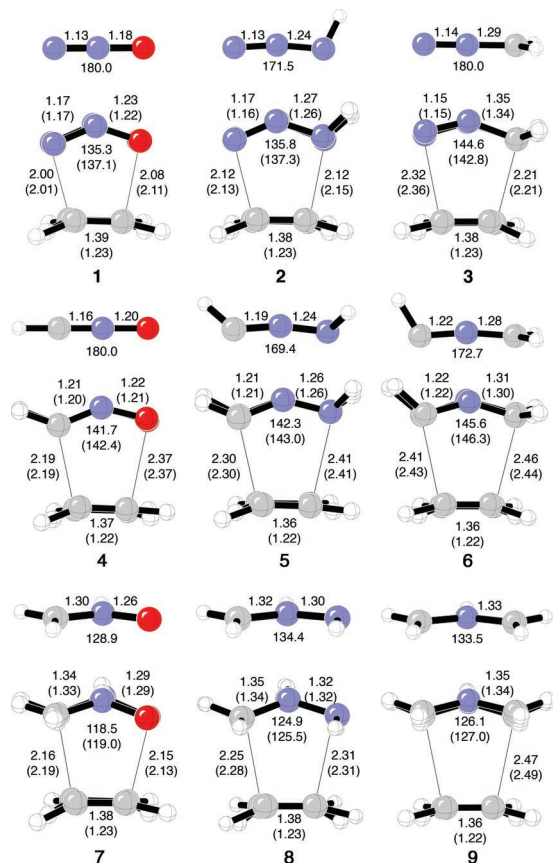
Figure 2. Overlay of CBS-QB3 TSs for 1,3-dipolar cycloadditions with ethylene and acetylene.
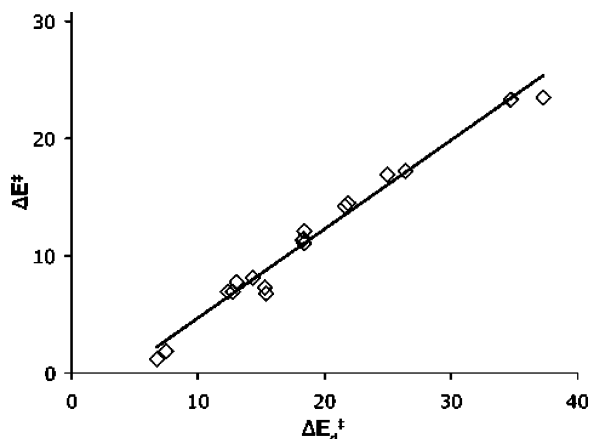
Figure 3. Plot of B3LYP distortion energy versus activation energy for reactions of dipoles **1**−**9** with ethylene and acetylene (also see Figure S3).

plot of the $\Delta E_d{}^\ddagger$ versus $\Delta E^\ddagger$ for the eighteen reactions, $\Delta E^\ddagger = 0.75\Delta E_d{}^\ddagger - 2.9$ kcal/mol; $R^2 = 0.97$. This linear correlation was unexpected, since many other reactions give no general correlation between rates and $\Delta E_d{}^\ddagger$.[11] This relationship is general for substituted dipoles, including methyl, trifluoromethyl, dicyano, and amido as shown in Figures S2 and S3.

These observations have led us to propose a new 1,3-dipolar cycloaddition distortion/interaction reactivity model. The concerted TS occurs at the geometry at which the overlap between the orbitals of the termini of the cycloaddends are aligned to lead directly to the cycloadduct without further distortion. To achieve this TS geometry requires distortion of the dipole, and the energy of distortion is related to the dipole stability.

The principal resonance structure of a dipole, $X=Y^+-Z^-$, is stabilized by electronegative Z atoms, so that the stability order of the dipoles is oxide > imine > ylide. In molecular orbital terms, the HOMO−LUMO gap of the dipole is largest for oxides (Table S3). Consequently, it is difficult to distort oxides through a second-order Jahn−Teller effect.[13] The narrow HOMO−LUMO gap of the ylides results in a very low $\Delta E_d{}^\ddagger$. The only exception found for the decrease in $\Delta H^\ddagger$ along each series of dipoles was for **6**, which has a barrier ∼6 kcal/mol too high. This dipole has an unexpectedly large $\Delta E_d{}^\ddagger$, because the narrow HOMO−LUMO gap in the dipole causes it to bend, resulting in HOMO stabilization.[7] The stabilized nonplanar ylide is thus more difficult to distort to the TS. Carbonyl ylides (SI) are very easy to distort and have no barriers to reaction.

When there is a nitrogen at the terminus, X of $X=Y^+-Z^-$, the dipole is stabilized compared to those with terminal carbons. This causes the dipoles to have larger HOMO−LUMO gaps and larger barriers than with NB and AB.[13] Again, this is due to the difference in $\Delta E_d{}^\ddagger$, and it is unrelated to ΔE_{rxn}.

Finally, when the cycloaddends collide in the appropriate distorted geometries, the TS energy depends upon $\Delta E_d{}^\ddagger$ and $\Delta E_i{}^\ddagger$. By definition, $\Delta E^\ddagger = \Delta E_d{}^\ddagger + \Delta E_i{}^\ddagger$; therefore, when $\Delta E_d{}^\ddagger$ are approximately the same, as in a series of substituted alkenes, interaction energies that are differentiated by the extent of HOMO−LUMO interactions can become the determining factor.[3]

These discoveries build on previous views of 1,3-dipolar cycloaddition reactivity theory based on FMO interactions and are related to recent discussions of the failures of the reactivity−selectivity principle.[14] The generalization of this distortion/interaction model to all types of cycloadditions is the subject of ongoing studies.

Supporting Information Available: Complete ref 5, Tables S1−S3, Figures S1 and S2, absolute energies, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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