Cycloaddition

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Experimental Diels–Alder Reactivities of Cycloalkenones and Cyclic Dienes Explained through Transition-State Distortion Energies**

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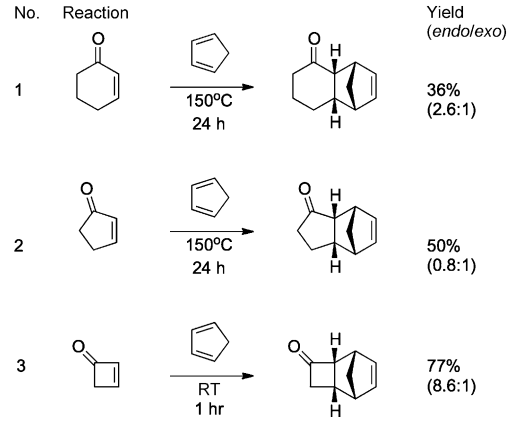
The power of the Diels–Alder reaction was expanded recently through the discovery by Li and Danishefsky that cyclobutenone is an unusually reactive dienophile; importantly, the adducts can be converted to products that are formally the Diels–Alder adducts of unreactive dienophiles.[1] We have determined the origin of the special reactivity of cyclobutenone and quantitate the origins of the unusually high reactivity of strained enones. Cyclopropenones, the Diels–Alder reactions of which were studied earlier by Breslow and co-workers,[2] are also highly reactive dienophiles. We show that the ease of out-of-plane distortion of strained cycloalkenones contributes to their high reactivity.

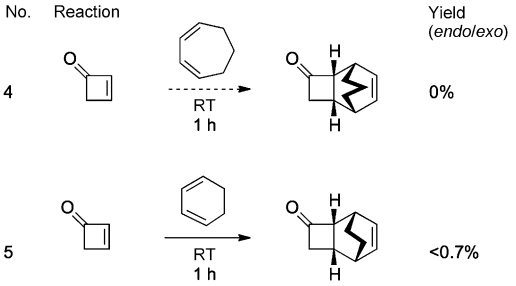
Ross and Danishefsky have compared the reactivity of four-, five-, and six-membered cycloalkenones with cyclopentadiene and other dienes.[3] New experimental results (see the Supporting Information) are summarized in Scheme 1.

The reactivities of different dienes with cyclobutenone have been measured as well. Scheme 2 gives results of standard reaction conditions. Experimental details for these and other conditions are given in the Supporting Information.

The reactions of pent-3-en-2-one, cyclohex-2-enone, cyclopent-2-enone, cyclobutenone, and cyclopropenone with three cyclic dienes have been explored with M06-2X, a density functional that we have shown to give relatively accurate activation and reaction energies for cycloadditions.[4] B3LYP and CBS-QB3,[5] a high-accuracy composite method, were also used (see the Supporting Information for a full comparison) and gave the same trends as discussed here.[6] Herein, we interpret the activation barriers of these reactions by using the distortion/interaction model[7] (or activation strain model).[8] This model relates the activation energy to the energy required for the geometrical deformation to achieve the transition structure, and to the favorable interactions between the two distorted reactants.



Scheme 1. Reactivities of cycloalkenones with cyclopentadiene.



Scheme 2. Reactivities of cyclic dienes with cyclobutenone.

Figure 1 shows the transition structures for reactions of cyclopentadiene with these dienophiles. The *endo* transition states are favored, except with cyclopropenone. The predicted relative rates are given below each structure. Cyclobutenone and cyclopropenone are 1000 to 100000 times more reactive than cyclohexenone at room temperature.[9]

These reactions are asynchronous concerted processes, except that of the symmetrical cyclopropenone. Cyclohexenone and cyclopentenone have high activation barriers and low predicted rate constants, approximately like those of the acyclic analogue. By contrast, cyclobutenone has a considerably lower activation barrier and, accordingly, higher rate constants for reaction. Cyclopropenone is predicted to be even more reactive.

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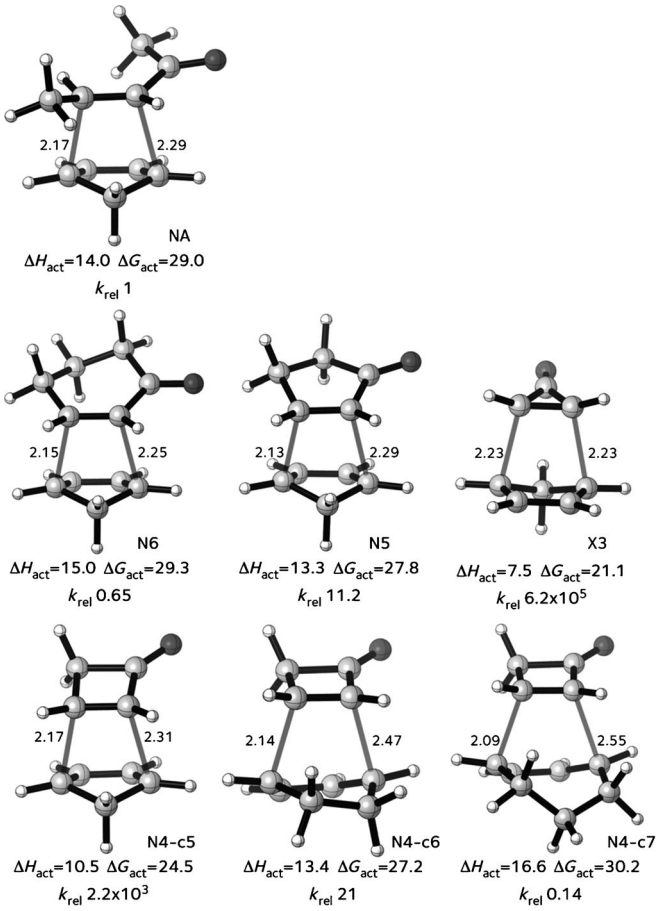

Figure 1. M06-2X/6-31G(d) optimized transition states for Diels–Alder reactions of (*Z*)-2-pentene-3-one (A), cyclopropenone (3), cyclobutenone (4), cyclopentenone (5), and cyclohexenone (6), reacting via *endo* (N) or *exo* (X) transition structures. For cyclobutenone different dienes were considered: cyclopentadiene (c5), 1,3-cyclohexadiene (c6), and 1,3-cycloheptadiene (c7). Predicted energetics (kcal mol^{-1}) and relative rates (applying transition-state theory at 298 K) are shown.

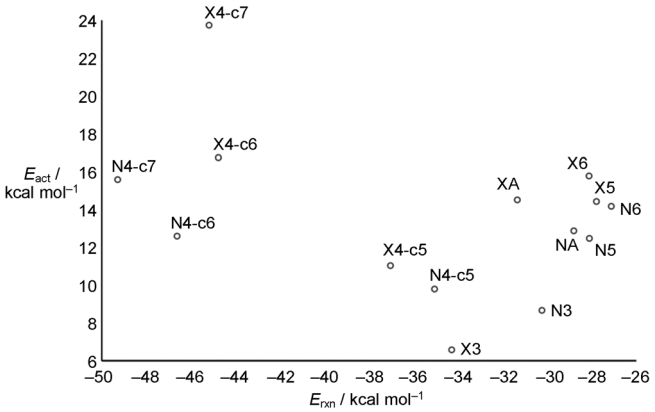

Figure 2. Plot of activation energy E_{act} versus reaction energy E_{rxn}: M06-2X/6-31G(d) results for cycloadditions of cyclopentadiene. See Figure 1 for meaning of symbols ($E_{act} = -0.19\,E_{rxn} + 6.75$, $r^2 = 0.14$).

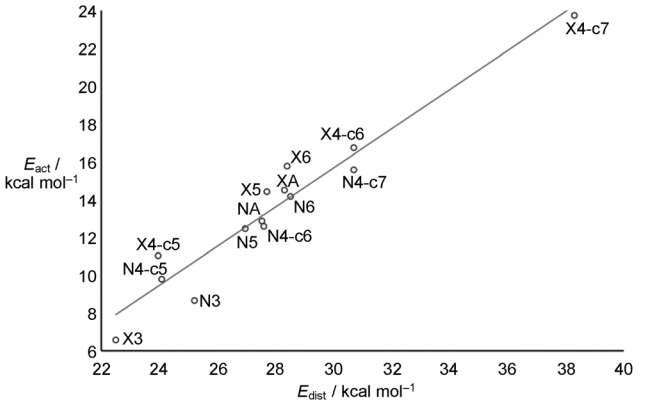

Figure 3. Plot of E_{act} versus distortion energy E_{dist}: M06-2X/6-31G(d) results. See Figure 1 for meaning of symbols ($E_{act} = 1.03\,E_{dist} - 15.4$, $r^2 = 0.93$).

The trends in activation energies are often described in terms of relative energies of reaction, or "strain release." This factor is related to that discovered empirically by Dimroth and Brønsted, gained theoretical justification in discussions by Evans, Polanyi, and Hammond, and culminated in the thermodynamic factor in Marcus theory.[10] However, the role of this factor is controversial: according to Hammett, "The idea that there is some sort of relationship between the rate of a reaction and the equilibrium constant (or energy of reaction) is one of the most persistently held and at the same time most emphatically denied concepts in chemical theory [*sic*]."[11]

Figure 2 shows a plot of the activation energies of these reactions versus their reaction energies. There is a weak correlation ($r^2 = 0.13$) at best, and a Hammond effect with the more exothermic reactions having earlier transition states. Figure 3 shows a much tighter correlation ($r^2 = 0.93$) between activation energies and reactant distortion energies, which are the energies required to distort the reactants into transition-state geometries without interaction.

These data are summarized in Table 1, and data from B3LYP and CBS-QB3 are given in the Supporting Information. Figure 4 provides a graphical representation of the relationship between activation energies and distortion energies for these cases.

For a variety of cycloadditions, we have shown that there is a linear relationship between activation energies and the energy required to distort the reactants into transition-state geometries.[6] Here, this distortion is associated with the bending of C–H bonds out of the plane of the C=C bonds to which they are attached, as new C–C bonds are formed. The force constants for bending of the alkene groups out of plane are reduced significantly by angle strain in cyclobutenone and cyclopropenone. These force constants were evaluated computationally by performing constrained energy scans in which the dihedral angle of the β-C–H bond (chosen because the bond formation is more advanced at this position in the transition state) was held fixed relative to the plane of the C= C bond and incremented from 0 to 15°. The difficulty of out-of-plane distortion is found to parallel increased ring size (see the Supporting Information). This behavior arises from the

Table 1: M062X/6-31G(d) energetics for Diels–Alder cycloadditions of various dienophiles in kcal mol^{-1}.

	E_{act}	H_{act}	G_{act}	E_{dist}	E_{rxn}
cyclopropenone + cyclopentadiene					
endo	8.7	9.5	23.0	25.2	−30.2
exo	6.6	7.5	21.1	22.5	−34.3
cyclobutenone + cyclopentadiene					
endo	9.8	10.5	24.5	24.1	−35.1
exo	11.0	11.8	25.7	24.0	−37.0
cyclobutenone + 1,3-cyclohexadiene					
endo	12.6	13.4	27.2	27.6	−46.6
exo	16.7	17.7	31.3	30.7	−44.8
cyclobutenone + 1,3-cycloheptadiene					
endo	15.6	16.6	30.2	30.7	−49.3
exo	23.7	25.2	38.5	38.3	−45.2
cyclopentenone + cyclopentadiene					
endo	12.5	13.3	27.8	27.0	−28.1
exo	14.4	15.4	29.8	27.7	−27.8
cyclohexenone + cyclopentadiene					
endo	14.2	15.0	29.3	28.5	−27.1
exo	15.8	16.8	31.3	28.4	−28.1
(*Z*)-2-pentene-3-one + cyclopentadiene					
endo	12.9	14.0	29.0	27.5	−28.8
exo	14.5	15.5	29.7	28.3	−31.3

larger degree of s character in the C–H bond and the fact that the smaller internal angle in the small rings is more appropriate for the pyramidal transition structure.

For all cases in Figure 4, the interaction energies are nearly constant (14.1–15.9 kcal mol^{-1}), consistent with the fact that all these enones and dienes have essentially constant interacting frontier molecular orbitals. Nevertheless, the reactivities at 25 °C are predicted to span over a million-fold range in rate. The differences arise in changes in distortion energies of both dienophile and diene, the former directly related to the ease of out-of-place distortion, and the latter to the energy of bringing the diene termini into a geometry that maximizes overlap with the dienophile termini. The detailed analysis of these factors, as well as the reactivities of cycloalkenes as dienophiles, are the subjects of ongoing investigations.

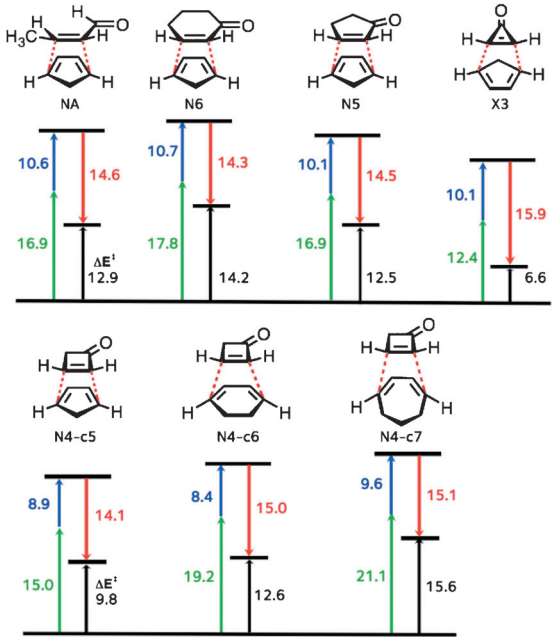

Figure 4. Activation, distortion, and interaction energies: green: diene distortion energy, blue: dienophile distortion energy, red: interaction energy, and black: activation energy (kcal mol^{-1}).

Experimental Section

General procedure for thermal Diels–Alder reactions: Diene (4 equiv) was added to a solution of the appropriate dienophile (1 equiv) at ambient temperature, and the mixture was sealed in a microwave tube. The reactions were stirred at set temperatures for the indicated number of hours, then directly purified by flash column chromatography on silica gel. Characterization and spectra are included in the Supporting Information.

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