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Enhanced Hydrogen Bonding of Water to Diels-Alder Transition States. Ab Initio Evidence

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Ab initio molecular orbital calculations reveal enhanced hydrogen bonding of a water molecule to the transition states for the Diels-Alder reactions of cyclopentadiene with methyl vinyl ketone (MVK) and acrylonitrile. The optimal interaction energies are found to be 1.5-2.0 kcal/mol more favorable for hydrogen bonding to the oxygen or nitrogen in the transition states than for the dienophiles. This supports the assertion from a prior simulation study that the observed rate accelerations for Diels-Alder reactions in aqueous solution arise from this hydrogen-bonding effect in addition to a relatively constant hydrophobic term.

Introduction

Diels-Alder reactions with electron-deficient dienophiles are now well-known to be accelerated in water.[1-6] For cyclopentadiene as the diene, rate ratios in aqueous solution over hydrocarbon solvents range from *ca.* 30 with acrylonitrile (AN) as the dienophile to 740 with methyl vinyl ketone (MVK) to 6800 with 2-methoxy-1,6-naphthoquinone.[1,5] In view of the reduction in solvent-accessible surface area during the reactions, a hydrophobic component to the rate increases is expected. However, the loss of exposed surface area should be similar for most Diels-Alder reactions. Thus, the substantial range of rate enhancements suggests that one or more additional factors are involved. A variety of possibilities has been considered.[1-6]

In previous work, we modeled the cyclopentadiene plus MVK reaction in solution with explicit representation of the solvent molecules.[7] Ab initio molecular orbital calculations provided the minimum energy reaction path (MERP) through the preferred endo-cis transition state (TS).[7,8] Partial charges for the atoms of the reacting system were also obtained from the ab initio wave functions (6-31G*) and were used in determining the Coulombic interactions with the solvent molecules. Monte Carlo simulations then yielded the changes in free energy of solvation along the MERP, which showed good accord with the observed rate enhancements in methanol and water.[7] Subsequent analyses revealed that, although there are 2-2.5 hydrogen bonds between water molecules and the oxygen of MVK throughout the reaction, each interaction is 1-2 kcal/mol more favorable for the TS than for the reactants or product. Consistently, the computed partial charges showed greater C^+-O^- polarization of the dienophile's carbonyl bond in the transition state. Consequently, hydrogen bonding was proposed as the key factor controlling the variation of the accelerations for Diels-Alder reactions in water, while the hydrophobic effect was estimated to contribute a relatively constant factor of about 10 to the rates.

A concern in this analysis is that the stronger hydrogen bonding for the TS came from evaluating the solute-solvent potential functions (Coulomb plus Lennard-Jones terms) rather than from actual ab initio calculations for interactions with a solvent molecule. Such calculations have now been performed for the reactions of cyclopentadiene with MVK and acrylonitrile. Striking confirmation of the enhanced hydrogen bonding for the transition states is found.

Computational Procedure

Optimizations were carried out using GAUSSIAN 92 for complexes of the transition states and of the dienophiles with a water molecule.[9] The 6-31G* basis set was chosen for the calculations since it is known to perform particularly well for computing the strengths and geometries of hydrogen bonds.[10,11] The 6-31G* optimized geometries for the dienophiles and the preferred endo transition states were used along with the experimental structure for an

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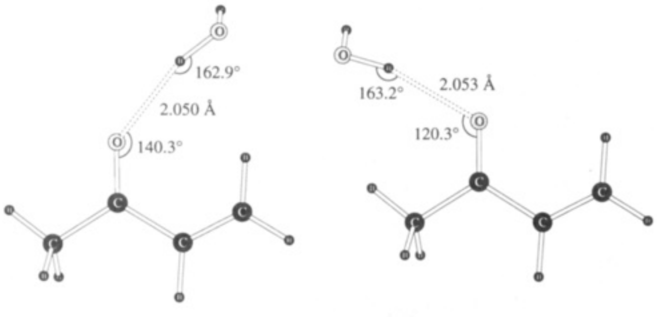
Table 1. Total Energies (au) and Binding Energies (kcal/mol) from the ab Initio 6-31G* Calculations[a]

species	total energy	binding energy (ΔE)
H_2O (exptl geom)	−76.010530	
MVK (6-31G*//6-31G*)	−229.806306	
MVK–H_2O	−305.827189	−6.50
MVK–H_2O	−305.826852	−6.29
MVK TS (6-31G*//6-31G*)	−422.542194	
MVK TS–H_2O	−498.566297	−8.52
MVK TS–H_2O	−498.565095	−7.76
AN (6-31G*//6-31G*)	−169.768015	
AN–H_2O	−245.786910	−5.25
AN–H_2O	−245.785475	−4.35
AN TS (6-31G*//6-31G*)	−362.502558	
AN TS–H_2O	−438.523842	−6.75
AN TS–H_2O	−438.522638	−5.99
isoprene	−193.951485	
isoprene–H_2O	−269.966803	−3.01
isoprene TS	−386.680167	
isoprene TS–H_2O	−462.695606	−3.08

[a] MVK = methyl vinyl ketone; AN = acrylonitrile. The structures are illustrated in Figures 1–5.



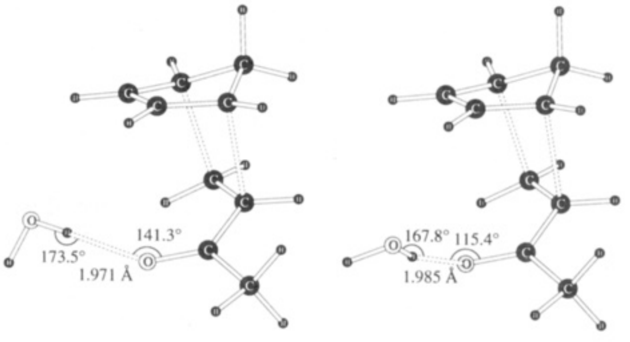
$\Delta E = -6.50$ kcal/mol $\Delta E = -6.29$ kcal/mol

Figure 1. Results of 6-31G* calculations for complexes of methyl vinyl ketone and a water molecule. Six intermolecular degrees of freedom were optimized. The two lowest-energy structures that were found are illustrated. ΔE is the binding energy for the complex relative to the separated molecules.

isolated water molecule (r(OH) = 0.9572 Å, ∠HOH = 104.52°).[8] These structures were not altered, while the six intermolecular degrees of freedom were optimized to position the water molecule in each complex. Starting geometries for the optimizations were selected from the lowest-energy structures obtained from thorough Monte Carlo searches using the prior potential functions with the TIP4P water model.[7,8] Three or more geometries were considered in each case and converged to the two lowest energy structures, shown in Figures 1–4, or to higher-energy alternatives. The total energies obtained for the molecules and complexes considered here are listed in Table 1. It should be noted that reoptimization of the intramolecular geometries is expected to have little effect on the computed interaction energies. For example, the 6-31G* results for the strengths of *N*-methylformamide–water hydrogen bonds change by less than 0.1 kcal/mol for full optimization versus optimization of only the intermolecular variables.[12]

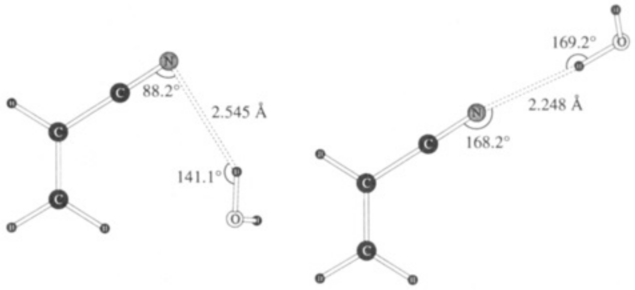
Results and Discussion

For MVK (Figure 1), the lowest energy structure has the water molecule hydrogen-bonded on the vinyl group's side of the oxygen with an interaction energy of −6.5 kcal/mol. The alternate structure with the water syn to the methyl group is only 0.2 kcal/mol higher in energy. The hydrogen bonds have nearly identical lengths, and they are slightly bent with the C=O···H–O fragment nearly coplanar; the other water hydrogen is rotated 14–20° out of plane.



$\Delta E = -8.52$ kcal/mol $\Delta E = -7.76$ kcal/mol

Figure 2. 6-31G* results for complexes of the cyclopentadiene–MVK transition state with a water molecule, as in Figure 1.



$\Delta E = -5.25$ kcal/mol $\Delta E = -4.35$ kcal/mol

Figure 3. 6-31G* Results for complexes of acrylonitrile and a water molecule, as in Figure 1.

Figure 2 illustrates the corresponding complexes for the transition state. The lowest energy structure still has the water molecule syn to the vinyl group and, remarkably, the hydrogen bond strength has increased by 2.0 kcal/mol to 8.5 kcal/mol. This is greater than the maximum strength of amide–water (*ca.*−7 kcal/mol) and even urea–water (−8.2 kcal/mol) hydrogen bonds at the 6–31G* level.[11] The alternate structure with the water syn to the methyl group in the TS also shows a notably enhanced attraction, −7.8 kcal/mol. The occurrence of 2–3 such hydrogen bonds to the carbonyl oxygen could certainly provide differential stabilization of the TS by at least 3 kcal/mol. Combined with the hydrophobic effect of 1–1.5 kcal/mol,[7] this is more than enough to account for the 740-fold rate acceleration in water ($\Delta\Delta G^{\ddagger} = -3.85$ kcal/mol).[1] As previously noted, the enhanced polarization for the carbonyl bond is reflected in the 6–31G* Mulliken charges, which are +0.53 and −0.56 for the carbonyl carbon and oxygen in MVK and +0.56 and −0.61 in the transition state.[7]

The results for acrylonitrile in Figures 3 and 4 are analogous with diminished intensity. There is still enhanced polarization for the π-accepting substituent in the transition state. The 6–31G* Mulliken charges are +0.28 and −0.45 for the nitrile carbon and nitrogen in acrylonitrile and +0.32 and −0.49 in the transition state. The strongest hydrogen bond for acrylonitrile with water is highly bent toward the vinyl group with an interaction energy of −5.3 kcal/mol. The strength of the best interaction becomes more favorable by 1.5 kcal/mol for the TS structure. The second minimum found for acrylonitrile has a nearly linear

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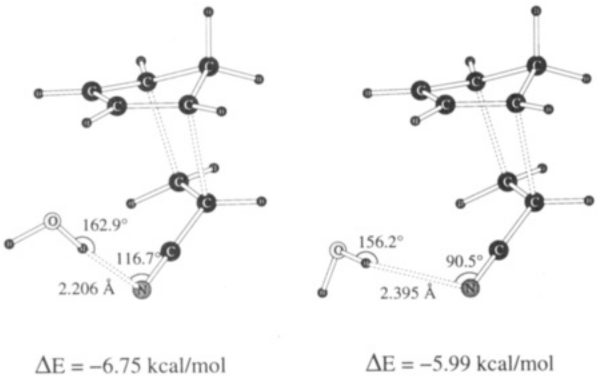

Figure 4. 6-31G* Results for complexes of the cyclopentadiene–acrylonitrile transition state with a water molecule, as in Figure 1.

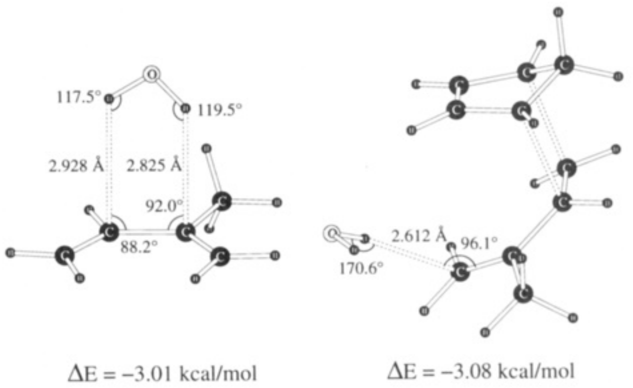

Figure 5. 6-31G* Results for complexes of *s-cis*-isoprene and the cyclopentadiene–isoprene transition state with a water molecule. Six intermolecular degrees of freedom were optimized.

(C≡N···H) hydrogen bond with a strength of 4.4 kcal/mol, while the second minimum for the transition state has the water more in the plane of the dienophile and a strength of 6.0 kcal/mol. As a further comparison on an even geometrical footing, optimizations were performed for acrylonitrile and its TS with the C≡N···H–O unit enforced to be collinear. The 6–31G* interaction energies are −4.20 and −5.29 kcal/mol, respectively. It should be noted that nitriles normally form just one hydrogen bond with water in aqueous solutions.[13] Thus, the lessened acceleration for the aqueous Diels–Alder reaction of acrylonitrile than that of MVK results from the reduced polarization of the nitrile group in the TS with concomitant smaller enhancement of the strength for the lone hydrogen bond. The present results suggest the hydrogen-bonding difference amounts to 1–1.5 kcal/mol, which coupled with the hydrophobic effect of 1–1.5 kcal/mol can account for the observed $\Delta\Delta G^{\ddagger}$ of −2.1 kcal/mol.[1]

A recent computational study of the Diels–Alder reaction of cyclopentadiene with methyl acrylate should be noted.[14] A self-consistent reaction field model was used with ab initio MP2/6–31G**//3-21G calculations. Remarkably, the computed electrostatic solvation effects in water are computed to raise the free energy of activation by about 2 kcal/mol. The observed opposite effect is then attributed to a hydrophobic component and specific enhancement of hydrogen bonding with water in the transition state, similar to that elaborated upon here. The authors mention with no structural details that 6–31G**//3–21G calculations for methyl acrylate and the *endo s-trans* transition state (not the lowest energy form) with a water molecule favor the transition state by 1.6 kcal/mol.[14]

The present ab initio results strongly support the notion[7] that the rate accelerations for Diels–Alder reactions in water arise from enhanced hydrogen bonding in the transition state augmented by a relatively constant hydrophobic contribution. The hydrogen-bonding term is variable since it depends on the nature of the substituents in the dienophile. In the absence of hydrogen-bonding sites, as in cyclopentadiene dimerization or the reaction of cyclopentadiene with isoprene, only modest rate accelerations of about a factor of 10 are anticipated from the hydrophobic term. In fact, the optimal interactions with a water molecule that we have found from 6–31G* calculations are −3.0 kcal/mol for isoprene and −3.1 kcal/mol for the isoprene plus cyclopentadiene TS (Figure 5).[8] We have also computed a free energy profile for cyclopentadiene dimerization in water at 25 °C by Monte Carlo simulations; the predicted lowering of the free energy of activation is 1.8 ± 0.3 kcal/mol.[15] Furthermore, in alcohol solvents, smaller rate increases are expected and observed owing to loss of the hydrophobic contribution and to greater steric restrictions for the hydrogen bonding. Deviations from these predictions may warrant consideration of additional effects such as aggregation for poorly water-soluble reactants.

The enhanced polarization for substituents in transition states is expected to be a general feature of reactions between neutral molecules which have some donor/acceptor character. The greater the charge transfer and/or polarization, the greater the potential solvent effects. Thus, for Diels–Alder reactions with cyclopentadiene, the increasing rate enhancements in water along the series of dienophiles, acrylonitrile, MVK, and naphthoquinone are reasonable.[1,5] Of course the rates of dipolar [2 + 2] cycloadditions in polar solvents are also known to increase with increasing charge transfer.[16] Furthermore, it has recently been found that enhanced hydrogen bonding to the ether oxygen is responsible for the acceleration of Claisen rearrangements in water.[17,18] As noted,[7,17] hydrogen bonding is particularly sensitive to small charge variations owing to its predominantly Coulombic nature and the short distances involved. Consequently, the largest solvent effects will be found in hydrogen-bonding solvents; in dipolar aprotic solvents, the partial charge–dipole and dipole–dipole interactions occur at larger separations and are less sensitive to small charge shifts.

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