Hydrophobic and Hydrogen-Bonding Effects on the Rate of Diels−Alder Reactions in Aqueous Solution

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Using a combined quantum mechanical and molecular mechanical (QM/MM) potential, we have carried out Monte Carlo simulations to investigate the hydrophobic and hydrogen-bonding effects on Diels−Alder reactions in aqueous solution. Two prototypical systems were considered, including the reaction of cyclopentadiene (CP) with methyl vinyl ketone (MVK) and the reaction of cyclopentadiene with isoprene. Analysis of the simulation results revealed that the hydrophobic effect is significant in both reactions. Since hydrogen bonding interactions are not involved in the reaction of CP and isoprene, the entire transition-state stabilization (4.6 ± 0.3 kcal/mol) can be attributed to the hydrophobic effect. In the reaction of CP and MVK, enhanced hydrogen-bonding interaction and the hydrophobic effect contribute equally to the transition state stabilization (−3.5 ± 0.4 kcal/mol). These findings are compared with the experimental results and predictions from previous theoretical studies.

In 1980, Rideout and Breslow discovered that the reaction rate of Diels−Alder (DA) reactions can be dramatically accelerated in aqueous solution.[1] The observation was particularly surprising at that time because pericyclic reactions are generally believed to be insensitive to solvent effects. Specifically, the rate constant for the reaction of cyclopentadiene (CP) with methyl vinyl ketone (MVK) was found to increase by a factor of 730 on going from isooctane to water.[1] The rate acceleration is even more striking using the dienophile, 5-methoxy-1,4-naphthoquinone, with a rate that is 12 780 times faster in water than in *n*-hexane.[2] In addition to being theoretically intriguing, the aqueous rate acceleration of Diels−Alder reactions have been successfully utilized in natural product synthesis.[3]

Several explanations have been offered to account for the observed solvent effects, including micellar effects,[4] internal pressure,[5] solvophobicity,[6] and enhanced hydrogen bonding to the transition state.[7] On the basis of kinetic studies of a number of Diels−Alder reactions in water, Breslow suggested that hydrophobic packing of the diene and dienophile is likely to be responsible for the rate enhancement.[8] More recently, Breslow and coworkers established a relationship between reaction rate and the hydrophobic surface area that becomes inaccessible in the transition state.[9] This provides a quantitative assessment of the solvent effect and hydrophobic packing for the Diels−Alder reactions. In addition, Blokzijl and Engberts measured standard Gibbs free energies of transfer from 1-propanol to mixtures of 1-propanol and water, as well as from acetonitrile to several solvents, for the reaction of CP with MVK.[10] These authors conclude that “enforced hydrophobic interaction” due to a decrease in the overall hydrophobic surface area during the activation process is a key factor in determining the rate acceleration in water, consistent with Breslow’s interpretation. Furthermore, hydrogen-bond stabilization of the more polar transition state (TS) also plays an important role, although the hydrogen-bonding effect is unlikely to be the primary factor governing the solvent effect since the largest rate increase is found in water, not in the strong hydrogen bond-donating solvent, trifluoroethanol.[10a]

On the theoretical side, Jorgensen and co-workers found that enhanced hydrogen-bonding interaction at the transition state is the predominant source of the observed rate acceleration for Diels−Alder reactions in water.[7,11,12] Through a series of ab initio molecular orbital and Monte Carlo calculations, Jorgensen et al. observed that the hydrogen-bonding interaction between the transition structure and water is about 1.5−2.0 kcal/mol stronger than that between the dienophile and water for the reaction of cyclopentadiene and MVK. In addition, the hydrophobic effect was estimated to be relatively small, contributing ~1.5 kcal/mol to the change in activation free energy, $\Delta\Delta G^{\ddagger}$, in Diels−Alder reactions.[7,11] The solvent effect on Diels−Alder reactions was also investigated by Ruiz-Lopez et al., using a continuum reaction-field model with a multipole expansion approach up to 6 orders.[13] However, the computed electrostatic solvation effects were found to increase, rather than to decrease, $\Delta\Delta G^{\ddagger}$ by about 2 kcal/mol for the reaction of CP with methyl acrylate in water. Since specific intermolecular interactions are not considered in the continuum model, Ruiz-Lopez et al. attributed the experimental rate increase to enhanced hydrogen-bonding withwater in the transition structure as well as to the hydrophobic com-

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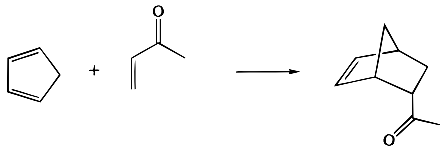
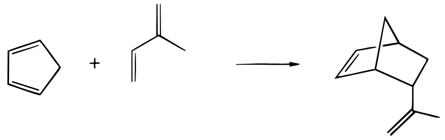
ponent in $\Delta\Delta G^{\ddagger}$.[13] The solvophobicity effect on the rate of Diels−Alder reactions was analyzed by Gajewski, making use of the cohesive energy density of the solvent in a multiparameter equation approach.[14] In this analysis, solvent polarity was also found to have marked effects. Finally, the influence of solvent electron pair-accepting properties on the rate of Diels−Alder reactions has been investigated by Coda et al., and a correlation with the solvent parameters was established.[15] These theoretical studies provided valuable insight into the solvent effect on Diels−Alder reactions. Nevertheless, previous Monte Carlo calculations do not include explicit treatment of the solvent polarization effect on the reactant molecules, whereas the continuum and linear free energy models discussed above suffer from a lack of consideration of specific hydrogen bonding interactions. Both are critical to understanding solvent effects on Diels−Alder reactions.

In an effort to assess the relative contributions of the hydrophobic and specific hydrogen-bonding factors, we have carried out statistical Monte Carlo simulations of two prototypical Diels−Alder reactions in water (eqs 1 and 2), making use of a combined quantum mechanical and molecular mechanical (QM/MM) potential.[16] Reaction 2 was selected because the dienophile, isoprene, does not form hydrogen bonds and its surface area is similar to that of MVK. Consequently, by definition, all components in the computed $\Delta\Delta G^{\ddagger}$ are due to hydrophobic effects.


(1)


(2)

Since the reactants are represented quantum mechanically in the combined QM/MM potential, the effect of solvent polarization on the reactants as well as specific solute−solvent interactions are simultaneously included in the present Monte Carlo calculation. Consequently, our approach has the advantage of overcoming some of the deficiencies of previous computational studies. Furthermore, adjustments of empirical parameters are not involved in our combined QM/MM model, which will lead to less ambiguity concerning the choice of charge models.[11] Results from the present study demonstrate that hydrophobic effects play an important role in determining the rate enhancement of Diels−Alder reactions involving hydrophobic species in water, while both hydrophobic effects and enhanced hydrogen-bonding interactions contribute in the reaction of cyclopentadiene with MVK.

Computational Details

Details of the combined quantum mechanical and molecular mechanical (QM/MM) potential have been given previously; interested readers are referred to ref 17. The key idea in this approach is partition of the condensed phase system into (1) a solute region, which is represented by quantum mechanical molecular orbital theory, and (2) a solvent region, which is approximated by empirical potential functions.[16,17] Thus, the effective Hamiltonian of the system is given as follows:

$$\hat{H}_{\mathrm{eff}} = \hat{H}^{\mathrm{o}}_{\mathrm{qm}} + \hat{H}_{\mathrm{qm/mm}} + \hat{H}_{\mathrm{mm}} \qquad (3)$$

where $\hat{H}^{\mathrm{o}}_{\mathrm{qm}}$ is the Hamiltonian for the QM solute, $\hat{H}_{\mathrm{mm}}$ is the MM energy of the solvent, and $\hat{H}_{\mathrm{qm/mm}}$ is the Hamiltonian describing solute−solvent interactions. In the present study, the semiempirical Austin model 1 (AM1) method developed by Dewar et al. is used to describe the reacting system.[18] The solvent molecules are represented by the three-point charge model, TIP3P, for water.[19] The combined AM1/TIP3P model has been used to study several organic reactions and has been shown to provide a good description of the solute-solvent interaction.[17,20] The $\hat{H}_{\mathrm{qm/mm}}$ term is comprised of an electronic and a van der Waals component (eq 4):

$$\hat{H}_{\mathrm{qm/mm}} = \hat{H}^{\mathrm{el}}_{\mathrm{qm/mm}} + \hat{H}^{\mathrm{vdW}}_{\mathrm{qm/mm}} \qquad (4)$$

The van der Waals term contains empirical parameters; however, these parameters are not specifically derived for any particular chemical reaction such as the Diels−Alder reactions investigated here. Rather, these parameters are determined from previous studies of bimolecular complexes of organic compounds with water and have been given in ref 17. It should be mentioned that the parameters depend only on atomic numbers and hybridization in the combined AM1/TIP3P potential.[17]

The initial step in our calculation is to determine the minimum energy path for each reaction in the gas phase at the HF/6-31G(d) level using Gaussian 92.[21] This is followed by Monte Carlo simulations with the combined QM/MM AM1/TIP3P potential to evaluate the solvent effects in water. In principle, four transition structures are possible for each reaction (eqs 1 and 2), corresponding to the dienophile being s-cis or s-trans and the approach being exo or endo. Previous calculations by Blake and Jorgensen and by Houk and co-workers have shown that the endo-s-cis transition structure is the lowest energy form in several Diels−Alder reactions.[7,12,22] We note that Assfeld et al. have shown in a recent calculation that the endo-s-trans TS of the reaction of cyclopentadiene and methyl acrylate becomes the more stable form in aqueous

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solution.[23] Without further analyzing all other transition structures, the endo-s-cis transition structure was chosen in this study, as in the work by Blake and Jorgensen,[7] to determine the intrinsic reaction coordinate (IRC) as well as structures along the reaction path for reactions 1 and 2. In our calculation, a total of 121 geometrical frames along each IRC were generated with adjacent points separated by less than 0.1 Å. Thus, the reaction coordinate R_c, which is defined as the average distance of the two forming C−C bonds, varies from 1.5 to 9.3 Å for eq 1, and from 1.5 to 8.6 Å for eq 2. Only relative free energies of hydration $\Delta\Delta G_{hyd}$ with respect to the largest separations between the two reactants are computed in these simulations.

Combined QM/MM Monte Carlo simulations were carried out in an isothermal-isobaric (NPT) ensemble at 25 °C and 1 atm with Metropolis sampling and periodic boundary conditions. A cubic box of roughly 24.8 × 24.8 × 24.8 Å^3, consisting of 500 water molecules plus the reactants, was employed. The semiempirical AM1 theory was utilized to describe the reactants,[18] cyclopentadiene and methyl vinyl ketone or isoprene, along with the TIP3P model for water. To evaluate the interaction energies, a cutoff distance of 9 Å was used for both solute−solvent and solvent−solvent interactions. Effectively, the Monte Carlo simulations step along adjacent frames to yield changes in free energy of hydration via statistical perturbation theory.[24]

All simulations were performed using the MCQUB (Monte Carlo QM/MM at University of Buffalo) program developed in our laboratory.[25] The program incorporates semiempirical and ab initio molecular orbital methods into statistical Monte Carlo calculations. In the present study, the quantum mechanical energies were determined using the MOPAC package,[26] while the BOSS program was used to generate the Monte Carlo trajectory.[27] For both reactions, a total of 60 simulations were performed to span the entire reaction coordinate. For each simulation, 2.5 × 10^6 configurations were sampled (10^6 for equilibration and 1.5 × 10^6 for averaging), which takes about 75 h on an SGI 4000 or Sun Sparc 10/Model 41 workstation. The entire calculation would have required about 1 yr CPU time on a single machine. Fortunately, six workstations were made available to the project.

Results and Discussion

The key results are plotted in Figure 1, which shows the profiles of hydration free energy for the reactions of cyclopentadiene with MVK (eq 1) and cyclopentadiene with isoprene (eq 2) in aqueous solution. Since the gas-phase activation energies are much greater than the solvent effects,[22] the overall reaction profiles are not shown. The transition states for both reactions are located at an R_c of about 2.2 Å. The solvent effects on these two reactions show some interesting similarities and differences. Both transition structures are strongly stabilized in water, which results in a predicted $\Delta\Delta G^{\ddagger}$ of −3.5 ± 0.4 and −4.6 ± 0.3 kcal/mol for reactions 1 and 2, respectively (Table 1). The predicted transition-state stabilization for CP + MVK in water is in good agreement with a value of −3.2 kcal/mol obtained by Jorgensen et al. using 6-31G(d) CHELPG charges in Monte Carlo simulations.[11] Experimentally, transition-state stabilization is found to be −3.8 ± 0.1 kcal/mol at 20 °C in water over that in isooctane according to the rate data reported by Rideout and Breslow.[1] There appears to be no direct experimental measurement for reaction 2, although results from a related study have been reported by Blake and Jorgensen.[7] In their calculation, Monte Carlo simulations were carried out for a model system in which all partial atomic charges were set to zero in the reaction of CP + MVK, effectively creating a “hydrophobic” analogue for the reaction. The computed $\Delta\Delta G_{hyd}$ was found to decline monotonically, as in the case of CP + isoprene shown in Figure 1, from reactants to product by −4.4 ± 0.4 kcal/mol. This is in excellent accord with our results for reaction 2.

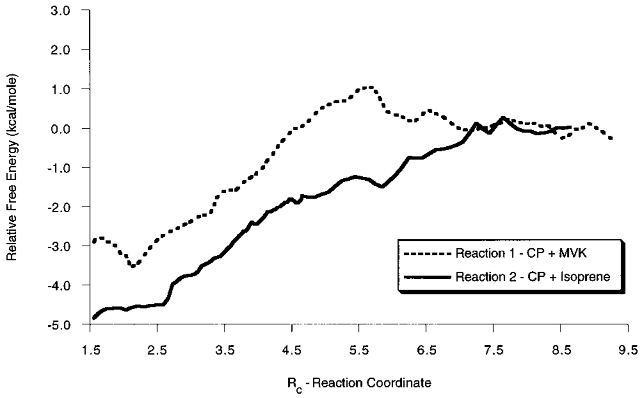

Figure 1. Relative free energy of hydration profiles for reactions 1 and 2. The reaction coordinate is given in angstroms.

Table 1. Computed Transition-State Stabilization ($\Delta\Delta G^{\ddagger}$) in Aqueous Solution Relative to the Gas-Phase Reaction for Diels−Alder Reactions (kcal/mol)

		transition state		
	reactant	QM/MM	OPLS[a]	expt[b]
CP + MVK	0.0	−3.5 ± 0.4	−3.2 ± 0.4	−3.9 ± 0.1
CP+ isoprene	0.0	−4.6 ± 0.3	−4.4 ± 0.4	

[a] References 7 and 11. [b] Reference 1. Experimental free energy was determined on the basis of the measured reaction rates in water and in isooctane.

Additional evidence in support of our findings for reaction 2 can be found in related experiments on the dimerization of cyclopentadiene, a “hydrophobic” Diels−Alder reaction in water.[6] Sangwan and Schneider estimated a rate ratio of over 8700 in water relative to ethanol, which corresponds to a $\Delta\Delta G^{\ddagger}$ of −5.3 kcal/mol at 20 °C.[6] Steffan and Gajewski obtained a smaller yet still appreciable rate change, 153 ± 30 times faster in water than in benzene at 25 °C, or a $\Delta\Delta G^{\ddagger}$ of −3.0 ± 0.2 kcal/mol.[28] Recently, Breslow and Zhu reported a rate constant that is 46 times smaller than Sangwan and Schneider’s data for the cyclopentadiene dimerization in water.[9a] This leads to an estimate of −3.1 kcal/mol in $\Delta\Delta G^{\ddagger}$. These experimental observations are consistent with the magnitude of hydrophobic effects for the reaction of cyclopentadiene and isoprene in water obtained in the present study and that from Blake and Jorgensen’s

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chargeless model system.[7] Thus, the hydrophobic effect on the rate acceleration is significant in these systems. Jorgensen et al., employing 6-31G(d) CHELPG charges in Monte Carlo free-energy perturbation calculations, obtained a $\Delta\Delta G^{\ddagger}$ of −1.7 kcal/mol for the dimerization of cyclopentadiene in water relative to that in the gas phase.[11] These authors argued that the low solubility of cyclopentadiene in water makes it difficult to accurately measure the rate acceleration.[11] However, in view of the latest experimental results by Breslow and Zhu,[9] which are in agreement with Gajewski's value,[28] the computed hydrophobic effect by Jorgensen et al. in the CP dimerization appears to be too small.

Returning to Figure 1, it is informative to examine the difference in the computed changes in free energy of hydration for the two reactions. For CP + MVK, the free energy of hydration shows a maximum at $R_c = 5.6$ Å which is about 1 kcal/mol higher in free energy than the separated species. From the maximum to the location of the transition structure ($R_c = 2.2$ Å), the computed ΔG_{hyd} gradually decreases to yield a net stabilization of the transition state by −3.5 ± 0.4 kcal/mol. Although the profile of free energy of hydration in Figure 1 is very similar to that obtained by Blake and Jorgensen, the solvent-separated minimum observed in their study is not reproduced here.[7] Nevertheless, the maximum at $R_c = 5.6$ Å reflects the free-energy cost to remove the solvent water molecules bridging the two reactant molecules as the two reactants get closer. The origin of the computed decrease in ΔG_{hyd} is much more complex and will be further examined below. A small maximum occurs in the region between the transition state and product (Figure 1). In this region, bond formation takes place rapidly, which is followed by a rotation of the carbonyl group away from the ring. We obtained a much smaller increase in the relative free energy in going from the transition state to product than did Blake and Jorgensen (0.6 vs 3.1 kcal/mol).[7] This translates to a much greater relative free energy of hydration for the reaction in our calculation, −2.9 vs −1.1 kcal/mol in ref 7. In a subsequent calculation by Jorgensen et al. which employed 6-31G(d) CHELPG charges, the transition state stabilization was found to be 1 kcal/mol smaller than when Mulliken charges were used.[11]

The profile for the reaction of CP and isoprene exhibits fewer structural features than the reaction of CP + MVK: ΔG_{hyd} smoothly declines from reactants to the final product. The solvent-separated complex is again not observed in our simulation using a combined AM1/TIP3P potential. This seems to be in accord with the description of the chargeless model for CP + MVK by Blake and Jorgensen.[7] In comparison with reaction 1, a notable difference in reaction 2 is that the free energy continuously decreases as the reactants approach each other, reflecting enforced hydrophobic effects in the activation process due to reduction in hydrophobic surface area. Furthermore, unlike reaction 1, there is no need to pay a free energy cost for removing hydrogen bonds in the solvent-separated complex region. Consequently, the hydrophobic Diels−Alder reaction shows a greater transition-state stabilization (4.6 kcal/mol) in water.

The oscillatory behavior of reaction 1 is reflected by the radial distribution functions (rdfs) between the carbonyl oxygen and water oxygen, which are displayed in Figure 2 for several key points along the reaction coordinate. The striking first peaks in Figure 2 are undoubtedly due to hydrogen-bonding interactions. Integration of the rdfs to the first minima gives a rough estimate of the coordination number around the carbonyl oxygen. Figure 3 depicts the computed average number of water molecules participating in hydrogen-bonding interactions with the carbonyl oxygen as a function of the reaction coordinate for CP + MVK, and is compared with the hydration profile to show the correlation. Although the computed coordination numbers exhibit large statistical fluctuations, a "rough" trend is reflected. Figure 3 indicates that about 2.5−3 water molecules form hydrogen bonds to the carbonyl group at longer Rc values (except for a spurious point at $R_c = 8.3$ Å), while the estimated number of nearest neighbors gradually decreases to below two in the region between $R_c = 7$ and 3.5 Å. The cause of the occurrence of the large spike in the computed coordination number at $R_c = 4.1$ Å is not clear, although it did not seem to affect the hydration profile. As the reaction coordinate approaches the transition state, the carbonyl oxygen seems to regain some hydrogen bonds, perhaps due to an enhanced hydrogen-bonding interaction, with an average coordination of about 2.5 water molecules at the transition state.

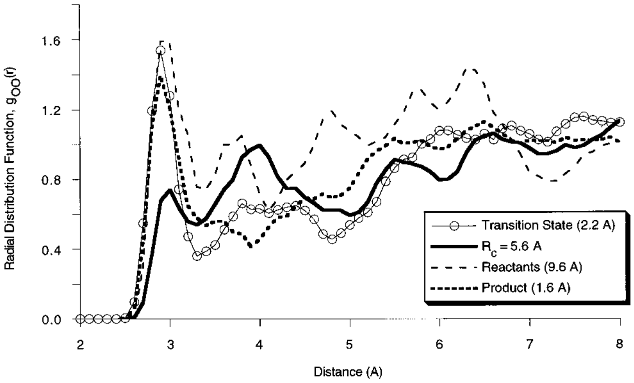

Figure 2. $O-O_w$ radial distribution functions for the reaction of cyclopentadiene and methyl vinyl ketone.

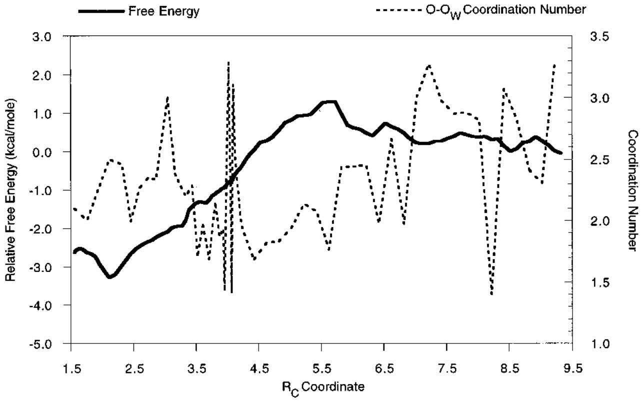

Figure 3. Computed coordination number as a function of the reaction coordinate for the reaction of cyclopentadiene and methyl vinyl ketone. The reaction coordinate is given in angstroms.

The decrease in coordination number in the reaction of CP + MVK in water is accompanied by an increase in the strength of hydrogen bonding. This is demonstrated by the energy pair distribution functions of the reactants, transition state, and product shown in Figure 4. The low-energy bands for CP + MVK are indicative of hydrogen-bonding interactions, whereas similar structural features are not found for CP + isoprene in water. In both cases, the spike at 0 kcal/mol is due to distant, bulk interactions.

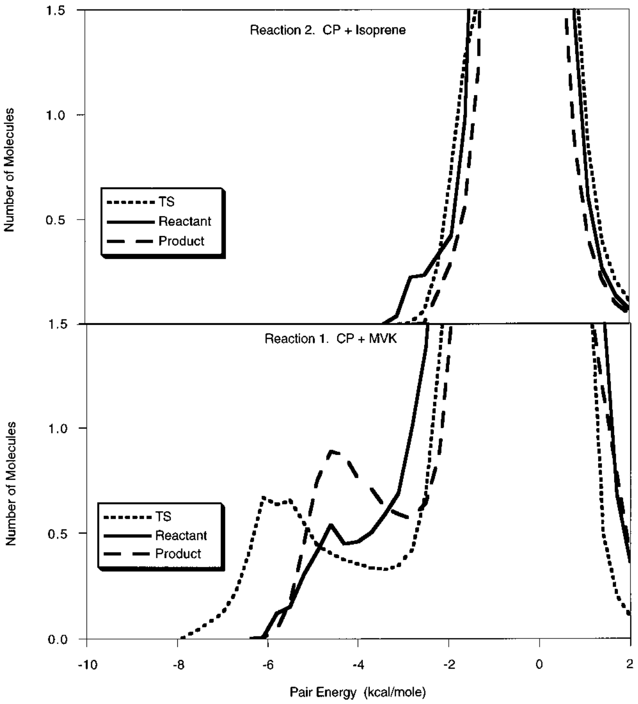

Figure 4. Pair energy distribution functions for the reactions of cyclopentadiene and isoprene (top) and cyclopentadiene and methyl vinyl ketone (bottom). Units for the ordinate are number of molecules per kcal/mol.

For the reaction of CP + MVK, the lowest interaction energy between water and the reactant as well as the product is ∼−6 kcal/mol, while the two distributions peak at about −4.5 kcal/mol. This may be assigned to hydrogen-bonding interactions between water and the carbonyl oxygen. On the other hand, for the transition state, the strongest interaction occurs at −8.0 kcal/mol, with the maximum of the low-energy band occurring at an interaction energy of −6 kcal/mol. This represents an increase of 1.5−2.0 kcal/mol in hydrogen-bond strength in the transition state relative to the reactant, in excellent accord with the ab initio results on bimolecular complexes by Blake et al.[12] It should be pointed out that the observed enhanced hydrogen bonding at the transition state comes naturally from hybrid QM/MM calculations without complications of parameter fitting as in the case of empirical potentials.

If these observations are combined, the origin of the aqueous rate acceleration of Diels−Alder reactions may be unraveled. First, hydrophobic effects are significant, particularly in the reaction of CP and isoprene. In this case, there is little ambiguity that the entire computed $\Delta\Delta G^{\ddagger}$ of −4.6 kcal/mol can be attributed to the enforced hydrophobic interaction due to reduction of the hydrophobic surface area. This is about 1.5 kcal/mol greater than experimental results on the dimerization of cyclopentadiene in water.[9a,28] The effect may be assigned as ground state (reactant) destabilization according to Engberts' transfer free-energy data.[10] Second, hydrogen-bonding interactions are undoubtedly important in the reaction of CP + MVK. Jorgensen's ab initio calculations and our simulation results (Figure 4) clearly demonstrate that enhanced hydrogen bonding leads to transition-state stabilization.[7,11,12] The difficulty, however, is to separate the contribution of the hydrophobic effect from that of hydrogen-bonding interactions in **1**.

Table 2. Computed Electrostatic Components of the Free Energies of Hydration for the Reactants and Transition State (kcal/mol)[a]

	ΔG_{elec}(reactant)	ΔG_{elec}(TS)	$\Delta\Delta G^{\ddagger}_{\mathrm{elec}}$
CP + isoprene	3.20 ± 0.09	2.46 ± 0.11	−0.74 ± 0.14
CP + MVK	−0.79 ± 0.16	−2.39 ± 0.15	−1.60 ± 0.22

[a] Computational details follow the same procedure described in ref 17 through a series of five Monte Carlo simulations for each species. The total free energy of solvation consists of electrostatic (ΔG_{elec}) and van der Waals (ΔG_{vdW}) components as a result of the two terms in eq 4. The decomposition scheme used here can provide a reasonable estimate of the electrostatic interactions in the present discussion, although free energy decomposition calculations depend on specific paths used in the free-energy perturbation calculation. Comparisons are made on the basis of results obtained without changing the van der Waals parameters for both reactions.

To provide some quantitative estimates, we have carried out additional Monte Carlo simulations for the transition state and reactants, where the electrostatic component of the solute−solvent or QM/MM interaction Hamiltonian is gradually annihilated in a series of free-energy perturbation calculations. This procedure is analogous to Kollman's charge annihilation approach,[29] yielding effectively the electrostatic component of free energy of hydration (Table 2). The results listed in Table 2 reveal that the TS for the reaction of CP and MVK is better solvated by electrostatic interactions ($\Delta\Delta G_{\mathrm{elec}}^{\ddagger}$) than the reactants by −1.6 kcal/mol. This may be regarded as an upper limit for the hydrogen-bonding stabilization in this reaction since such interactions are electrostatic in nature. On the other hand, the hydrophobic stabilization for the reaction of CP and isoprene also contains electrostatic contributions in hybrid QM/MM simulations, and a difference of −0.7 kcal/mol in favor of the TS over the reactant for reaction **2** is obtained. Thus, the lower limit of hydrogen-bonding stabilization for reaction **1** can be estimated by removing the electrostatic component of the hydrophobic interactions predicted for reaction **2** (−0.9 kcal/mol). Thus, it appears that, following this analysis, enhanced hydrogen-bonding interaction contributes about −1 to −1.6 kcal/mol to the TS stabilization, and it plays an equally important role as that of hydrophobic effects in the rate acceleration of CP + MVK in water.

Experimentally, factors governing the solvent effects on Diels−Alder reactions have been thoroughly analyzed by Blokzijl and Engberts.[10] In particular, the initial-state (reactants) and transition-state effects were determined on the basis of free energies of transfer for the reactions of CP with alkyl vinyl ketones. It was shown that the diene and dienophile are strongly destabilized in water relative to 1-propanol and other organic solvents, while the standard chemical potential of the transition state changes only slightly in the entire concentration range in a mixture of 1-propanol and water.[10] Consequently, the rate acceleration of Diels−Alder reactions in water was attributed to the substantial reduction in the hydrophobic molecular surface area during the activation process. Blokzijl and Engberts also suggested that the insensitivity of the standard chemical potential of the transition state to solvent polarity is due to enhanced hydrogen-bonding interactions of water; however, it is

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(29) Bash, P. A.; Singh, U. C.; Langridge, R.; Kollman, P. A. *Science* **1987**, *236*, 564.

not of primary importance to the overall medium effect because the reaction rate is smaller in the strong hydrogen bond-donating solvent, trifluroethanol.[10] Recent experiments and correlation of reaction rates with hydrophobic effects, which lead to an estimate of buried hydrophobic surface area at the transition state, provide convincing support of the importance of hydrophobic effects on the rate acceleration of Diels−Alder reaction by aqueous solution.[9]

Conclusions

Monte Carlo statistical simulations employing a combined semiempirical AM1/TIP3P potential were carried out to investigate the relative contributions of hydrophobic and hydrogen-bonding effects to the rate acceleration of Diels−Alder reactions in water. Two prototypical systems were considered in this study; the reaction of cyclopentadiene + methyl vinyl ketone, and cyclopentadiene + isoprene in aqueous solution. In the latter reaction, hydrogen bonding between the reactants and solvent does not occur. Consequently, the computed transition-state stabilization can be attributed entirely to the hydrophobic effect. Enforced hydrophobic interaction due to reduction of the hydrophobic surface area during the activation process was found to provide 4.6 kcal/mol stabilization of the transition state in CP + isoprene. On the other hand, hydrophobic effects and enhanced hydrogen bonding at the transition state in the reaction of CP + MVK were found to contribute equally to the aqueous rate acceleration. The present study is in agreement with Jorgensen et al.'s finding of a significant increase in hydrogen-bond strength of the solvent with the transition state for the reaction of CP and MVK.[11,12] However, our calculations suggest that the magnitude of the hydrophobic effect on Diels−Alder reactions in aqueous solution depends on the nature of the diene and dienophile.

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