QM/MM Simulations for Diels−Alder Reactions in Water: Contribution of Enhanced Hydrogen Bonding at the Transition State to the Solvent Effect†

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Free energy profiles for Diels−Alder reactions of cyclopentadiene with acrylonitrile, methyl vinyl ketone, and 1,4-naphthoquinone have been computed in the gas phase and in aqueous solution using Monte Carlo simulations in a fully automated, mixed quantum and molecular mechanics (QM/MM) approach. The QM/MM calculations in water featured AM1 treatment for the solute in the presence of 500 TIP4P water molecules, and computation of solute−water interactions using scaled CM1A charges for the solute. Free energy perturbation calculations yielded the profiles along a reaction coordinate with all other degrees of freedom sampled. The free energies of activation are reduced on going from the gas phase to water by 1.5, 2.8, and 4.4 kcal/mol for the reactions with acrylonitrile, methyl vinyl ketone, and naphthoquinone, respectively. These values are in good agreement with the corresponding experimental results for transfer from hydrocarbon solvents to water (2.1, 3.8, and 5.0 kcal/mol). The cycloadducts are stabilized less effectively than the transition states by water in all three cases. Therefore, the retro-Diels−Alder reactions are also predicted to be accelerated in water, in accord with related experimental data. These results and consideration of variations in solvent-accessible surface area (SASA) confirm that the rate increases in water arise in part from hydrophobic association of the reactants, but predominantly from enhanced hydrogen bonding between water molecules and the polarized transition states.

Introduction

Rates for organic reactions involving charged species in water can be different by many orders of magnitude than reactions in less polar media.[1] Surprisingly, rates of some Diels−Alder reactions involving neutral substrates, which were traditionally believed to be insensitive to solvent choice,[2] have been found to be accelerated substantially in water.[3,4] While the addition of acrylonitrile to cyclopentadiene (CP) in water vs a hydrocarbon solvent shows a modest rate increase of 31,[3a] larger rate enhancements have been observed with other dienophiles. In addition to CP, methyl vinyl ketone (MVK) has a water-induced rate increase of 741,[3a] and some 1,4-naphthoquinone derivatives show enhancements of over 10 000.[4] The origin of the rate differences produced by aqueous media has been an intriguing problem and has triggered numerous experimental and theoretical investigations.[5]

Several interpretations have been considered, including hydrophobic association of the reactants,[3a] micellar catalysis,[6] solvophobicity,[7] internal solvent pressure,[6c] solvent polarity,[8] Lewis acid-like catalysis by enhanced hydrogen bonding at the transition state,[9] and cohesive energy density.[10] However, most analyses now focus on the hydrophobic effect and enhanced hydrogen bonding. Since the solvent accessible surface area of the reactants is reduced during the cycloaddition process, the hydrophobic effect is expected to accelerate the rate of cycloaddition. The enhanced hydrogen bonding occurs for dienophiles possessing π-electron accepting groups. In Diels−Alder reactions with normal electron demand, π-accepting groups conjugated to the dienophile's π-bond are activating because they lower the energy of the lowest unoccupied molecular orbital (LUMO) and enhance the mixing with the highest occupied MO of the diene. This interaction also results in charge-transfer from the diene to the π-accepting groups. Thus, the transition state is more polarized than the reactants, and the heteroatoms in the π-accepting groups can form stronger hydrogen bonds with hydrogen-bond donating solvent molecules. The preferential stabilization of the transition state causes further reduction in the activation energy.

The two factors are intertwined in all the systems initially examined experimentally.[3,4] Substrates such as naphthoquinones that offer greater reduction in hydrophobic surface area also have additional polar activating groups. It was therefore difficult to dissect the differing contributions to the observed rate changes. Ideally, study of rates of additions involving nonpolar reactants would resolve the question. Unfortunately, low solubility in water reduces the reliability of kinetic measurements in such cases.[3g,7c] Engberts and co-workers obtained valuable insights on the relative importance of hydrophobic association and preferential hydrogen bonding stabilization of the transition state by examining a series of carefully designed substrates. Introduction of alkyl chains revealed that the rate enhancements were sensitive to the precise location of the additional hydrophobic groups.[11] In substrates for which hydrogen bonding interactions are minimized, the acceleration in water was found to be modest.[12] Further, the retro-Diels−Alder reaction leading to the formation of cyclopentadiene and 6-methyl-1,4-naphthoquinone was shown to occur faster in water.[13] The acceleration of both forward and reverse processes in water is well interpreted in terms of stronger hydrogen bonding for the transition state. Recently, fluorous solvents have also been demonstrated to

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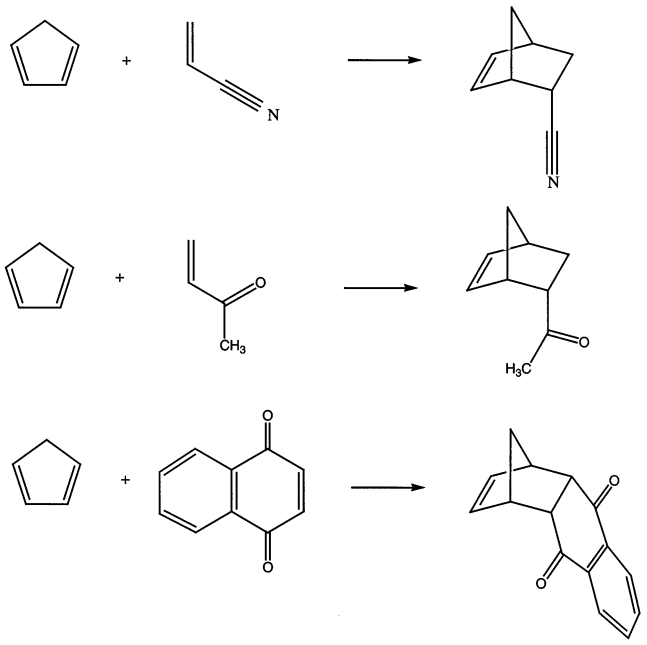
increase the rates of Diels−Alder reactions by factors ranging from 10 to 50.[14] Since the solvents used lacked hydrogen-bond donating ability, the modest rate enhancements relative to those observed in water for the same substrates reflect the rate effects anticipated on the basis of solvophobicity alone.

Theoretical studies have proved to be of considerable interpretive value in the debate.[15−21] Ab initio calculations for stationary points on the Diels−Alder potential energy surface in a number of model systems revealed enhanced polarization at the transition state; transition structures were found to form stronger hydrogen bonds by 1.5−2.0 kcal/mol with a water molecule.[15] Detailed Monte Carlo simulations have also been carried out to determine the solvent effects in propane, methanol, and water for the addition of cyclopentadiene and methyl vinyl ketone.[16] The solute energies and charges were derived from HF/6-31G* calculations on 64 discrete points along the gas-phase reaction pathway. The solvent effects were computed using free energy perturbation (FEP) calculations connecting these points. The calculations reproduced the observed rate variations and highlighted the origin of the rate acceleration in water. While the transition state was found to be stabilized in water by 4.2 kcal/mol, the cycloaddition product was stabilized by only 1.1 kcal/mol. Since a significant change in hydrophobicity between the transition state and the product is unlikely, the aqueous acceleration of the cycloaddition was attributed to a non-hydrophobic component stemming from enhanced polarization of the transition state that leads to stronger hydrogen bonds. The reduction in free energy of activation for the dimerization of cyclopentadiene in water was also computed using MC simulations on a potential surface derived from ab initio calculations.[17] The solvent effect, which can be assigned to hydrophobic association in this case, was found to be 1.8 ± 0.3 kcal/mol. Recently, molecular dynamics and reaction flux simulations have been carried out on the Diels−Alder reaction between cyclopentadiene and MVK in water to include dynamical solvent effects.[19] Dynamical transmission coefficients, accounting for transition state recrossings, have also been computed using reaction path Hamiltonian analysis on the reaction of CP and MVK in the gas phase and in the presence of two explicit water molecules.[20] The solvent effect in supercritical water has also been examined using combined electronic structure and liquid-state RISM theory.[21]

The available experimental and computational studies have resulted in a consensus view on the importance of hydrophobic association and hydrogen bonding effects on the rates of Diels−Alder reactions. However, it is desirable to characterize further the relative contributions of the two effects for both the cycloaddition and the retro-Diels−Alder reaction modes for a set of substrates with widely differing magnitudes of solvent effects and to develop further computational methods for study of reactions in solution. In this paper, we report the free energy profiles (potentials of mean force) for the reactions of cyclopentadiene with three dienophiles in the gas phase and in water (Scheme 1). The systems chosen provide a sensitive test for the reliability of the methods since the experimentally observed aqueous rate enhancements vary from 30 to 4600. A combined quantum mechanical/molecular mechanics (QM/MM) protocol is used. The solutes are treated quantum mechanically, and the effect of the medium is included explicitly by using a large number of water molecules. In significant advances over the earlier work,[16,17] all degrees of freedom are sampled so that the reaction in solution is not constrained to follow the gas-phase reaction path, and three systems are studied to test if the methodology can order correctly the extent of the solvent effects.

SCHEME 1



Methods

The AM1 Hamiltonian[22] was used to obtain the energetics and charges of the Diels−Alder solute systems. The geometries of the isolated reactants, transition state structures, and the cycloadducts were first optimized. The endo addition mode was chosen in all the cases, and for MVK, the s-cis conformation was used. These choices correspond to the preferred transition state structure determined earlier at ab initio levels.[23] A number of geometries connecting the transition structures to the reactants and the cycloaddition product were generated by interpolation for the reactions involving acrylonitrile and MVK. For the addition of naphthoquinone, intermediate geometries were derived by following the intrinsic reaction coordinate. These structures were used as initial-guess geometries for free energy perturbation calculations[24] both in the gas phase and in solution.

The free energy profiles at 25 °C in the gas phase were determined using Monte Carlo simulations with Metropolis sampling. In a second series of FEP calculations, the effect of the aqueous medium was treated by including 500 TIP4P water molecules[25] and imposing periodic boundary conditions. The NPT ensemble was used at 25 °C and 1 atm. Solvent−solvent and solute−solvent interactions were computed using pairwise additive Coulombic and van der Waals terms with standard Lennard-Jones parameters from the OPLS-AA force field.[26] For the electrostatic contributions to the solute−solvent energy, CM1A charges[27a] obtained for the solute in the AM1 calculations were used with a scale factor of 1.20.[27b] This combined AM1-OPLS−CM1A (AOC) approach was validated previously in studies of solvent effects on conformational equilibria,[27b] a Claisen rearrangement,[27b] and acidities of carboxylic acids.[27c] Presently, water−solute interaction energies were included if any intermolecular pair of heavy atoms was within 9 Å. The water−water cutoff was also 9 Å and was based on the OO separation. The distance between the midpoint of the terminal carbon atoms of the diene and the midpoint of the C═C bond of the dienophile was chosen as the reaction coordinate (RC). This choice ensured that the synchronous region of the potential energy surface was effectively, though not exclusively, sampled. The solute was represented in internal coordinates using a Z-matrix. All internal degrees of freedom for the solute were

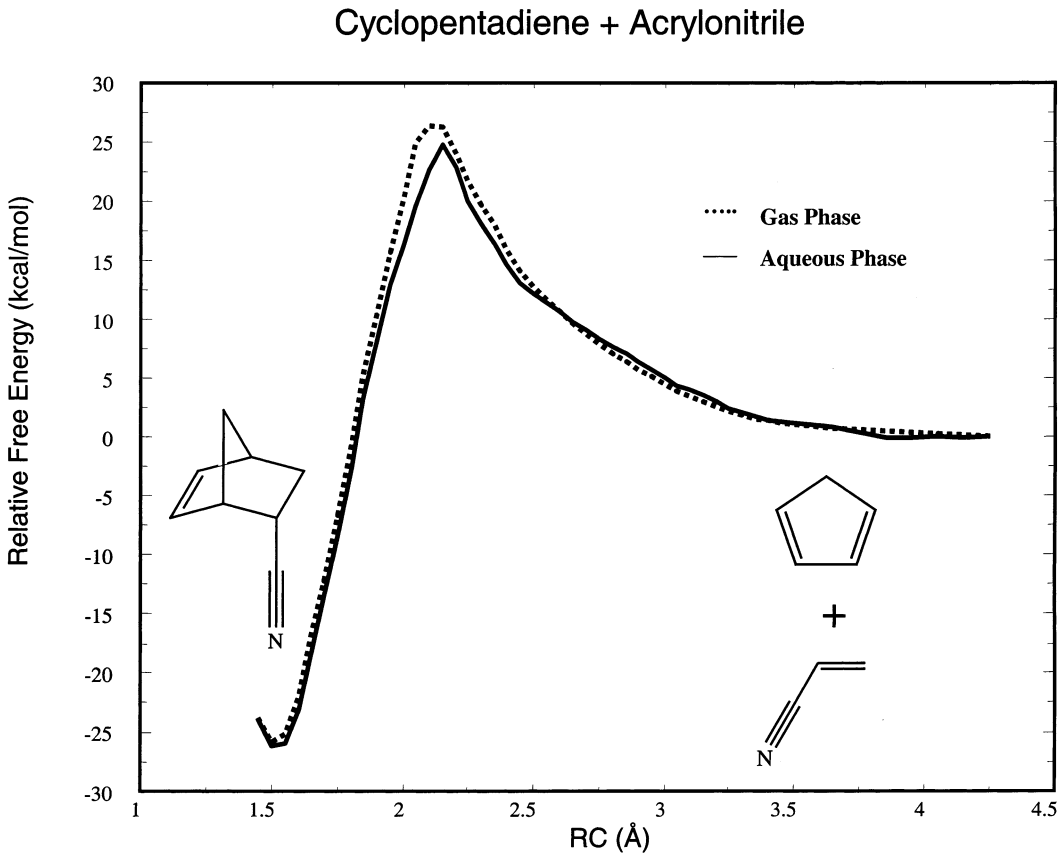


Figure 1. Computed free energy profiles in the gas phase and in water for the cycloaddition reaction between cyclopentadiene and acrylonitrile.

sampled in the MC simulations, except for the one degree of freedom defining RC. Total translations and rotations for the solute and the water molecules were also sampled in ranges that led to overall acceptance rates of ca. 40% for new configurations.

The value of RC was varied from 1.40 to 4.25 Å. Double-wide sampling with increments of 0.05 Å was employed. For each perturbation step, in the solution phase simulations, the system was equilibrated over 4−5 million steps and averaged over a subsequent 6−10 million configurations. An attempted move of the solute was made every 120 configurations and requires a new QM calculation. The small increments and long averaging periods were needed to yield very smooth free energy profiles with uncertainties of less than ca. 0.3 kcal/mol for the computed free energies of activation. In all, computation of each free energy profile required ca. 3.5 million single-point AM1 calculations. Averages for the solvent accessible surface area (SASA) of the solute using a probe with a 1.4-Å radius for water, number of hydrogen bonds formed by the solute, and solute−solvent and solvent−solvent interaction energies were also computed. All calculations were carried out with the BOSS program.[28] The calculations have been automated such that an entire free energy profile can be obtained from one job submission by running the FEP windows sequentially. However, in the present case, individual windows were run simultaneously using multiple processors on a Pentium-based cluster.

Results and Discussion

Solvent Effects on the Diels−Alder Reactions. The computed free energy profiles in the gas phase and in water for the reactions of cyclopentadiene with acrylonitrile, methyl vinyl ketone, and 1,4-naphthoquinone are shown in Figures 1−3, respectively. The cycloadduct minima are found when RC is close to 1.5 Å and the transition states occur near 2.1−2.2 Å. The energies remain quite constant for RC beyond 4 Å. Solvation does not significantly affect the location of the minima or transition states in these cases, but it does modify the relative free energies. The effect of solvation on the relative free energy is seen primarily near the transition state region for the reactions of acrylonitrile (Figure 1) and methyl vinyl ketone (Figure 2). In the case of the reaction with naphthoquinone, the cycloadduct is also stabilized in water, although the solvent effect is still greater near the transition state (Figure 3).

The principal point of interest is the ability of the present QM/MM AOC approach to reproduce the observed rate accelerations of these Diels−Alder reactions upon transfer from the gas phase to water. Since the same computational approach is used both for the gas phase and in water, most errors including deficiencies of the AM1 method are expected to largely cancel. Solvation by water reduces the activation free energy in all three cases (Figures 1−3). As observed, the magnitude of the solvent effect shows considerable variation with the nature of the dienophile. The activation free energy for the reaction of acrylonitrile is reduced by only 1.5 kcal/mol (Table 1). The reaction of methyl vinyl ketone is computed to show a greater solvent effect, 2.8 kcal/mol. The previous simulation with Mulliken charges at the HF/6-31G(d) level yielded an aqueous solvent effect of 4.2 kcal/mol.[23] The corresponding value including dynamical solvent effects with B3LYP energies and 215 SPC water molecules was computed to be 2.2 kcal/mol.[19] In the present study, the free energy of activation for the cycloaddition of CP and 1,4-naphthoquinone is reduced by 4.4 kcal/mol by water. The computed variations slightly underestimate but exactly parallel the observed rate enhancements in water. The experimental rate changes for the three dienophiles on going from hexane or isooctane to water translate to

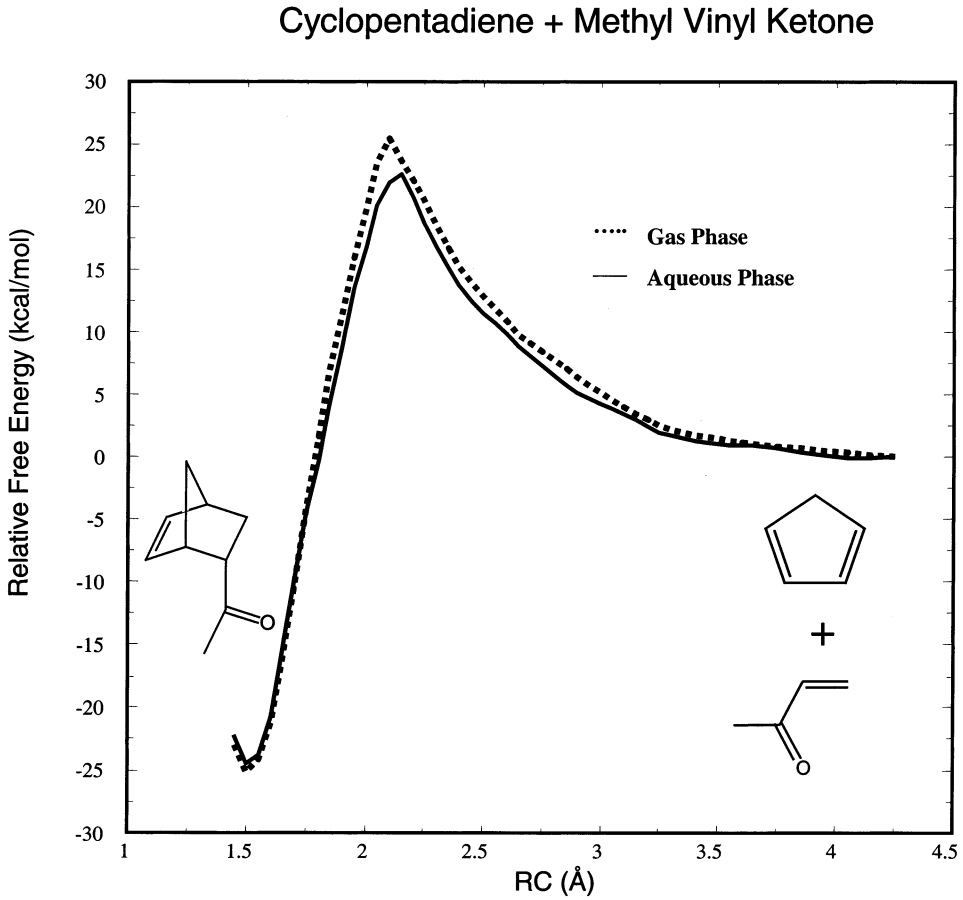


Figure 2. Computed free energy profiles in the gas phase and in water for the cycloaddition reaction between cyclopentadiene and methyl vinyl ketone.

reductions in the free energy of activation by 2.1, 3.8, and 5.0 kcal/mol, respectively.[3a,4e] Thus, the prior success[27b,c] of this semiempirical QM/MM protocol has been extended to reproduction of the magnitudes of changes in free energies of activation for Diels−Alder reactions in different media. The accuracy of the method is notable considering the relatively low magnitude of the solvent effects on the free energies of activation for these systems in contrast to reactions involving ionic species.

Absolute Energetics. There are multiple issues that compromise the accuracy of QM/MM computations of absolute free energies of activation for bimolecular reactions; this problem has not be solved by the current approach. Presentation of some of the complicating details is made here to emphasize the remaining challenges. First, there is the choice of QM method. AM1 calculations overestimate activation energies of cycloaddition reactions, and substituent effects are often not in the correct order.[29] Indeed, the present AM1 calculations yield activation energies of 29.8, 30.1, and 31.0 kcal/mol for the reactions of CP with acrylonitrile, MVK, and naphthoquinone. Prior MP3/6-31G* results for the former two reactions are 18.5 and 15.9 kcal/mol.[23] In fact, for the MVK + CP reaction, the activation energy in the gas phase has been computed at many levels of ab initio theory with a wide range of outcomes (HF/6-31G*, 35.0;[23] MP2/6-31G*, 2.2;[23] MP3/6-31G*, 15.9;[23] B3LYP/6-31G**, 17.0;[20] MP4SDQ/6-31+G*, 17.7;[19] CCSD(T)/6-31+G*, 12.1 kcal/mol[19]). Thus, for reasonable quantitative accuracy on absolute activation parameters, it is apparent that MP3/6-31G*, B3LYP/6-31G*, or higher levels are required. There would be no quantitative benefit in switching from AM1 to ab initio HF/6-31G* or MP2/6-31G* calculations. As noted above, computation of each free energy profile entailed ca. 3.5 million single-point QM calculations, which would make the present QM/MM approach prohibitive from a practical standpoint at the necessary ab initio levels.

The second issue is the treatment of entropy effects in typical QM/MM simulations with either MC or MD sampling. In principle, since all degrees of freedom are sampled in the present FEP approach, the entropy changes as a function of the reaction coordinate are fully accounted for in the classical limit. However, this assumes complete sampling, including full tumbling of the reactants at larger separations, which does not occur even in the present lengthy MC runs. More serious is the fact that although QM calculations were used to evaluate the energy of the solute at each MC step, the vibrational energy has not been quantized and is treated classically. For a bimolecular reaction this is particularly problematic since six translational and total rotational degrees of freedom are converted into vibrations. The associated, significant entropy penalty is underestimated since the transition state and product are effectively too soft relative to the reactants.

Some smaller points can also be noted. In computations of free energy profiles for a bimolecular reaction as in Figures 1−3, the reactants are not infinitely separated but begin at some "noninteracting" distance, 4.25 Å in the present case. This necessitates a cratic entropy adjustment for constraining the reactants to be within the sphere of this radius; for a 1 M standard state, the cratic correction can be estimated to decrease the entropy of activation by about 3 cal/mol-K.[30] A final point is further rate reduction through dynamical effects or solvent friction, as reflected in the transmission coefficient of transition state theory, κ. For the cyclopentadiene plus MVK cycloaddition,

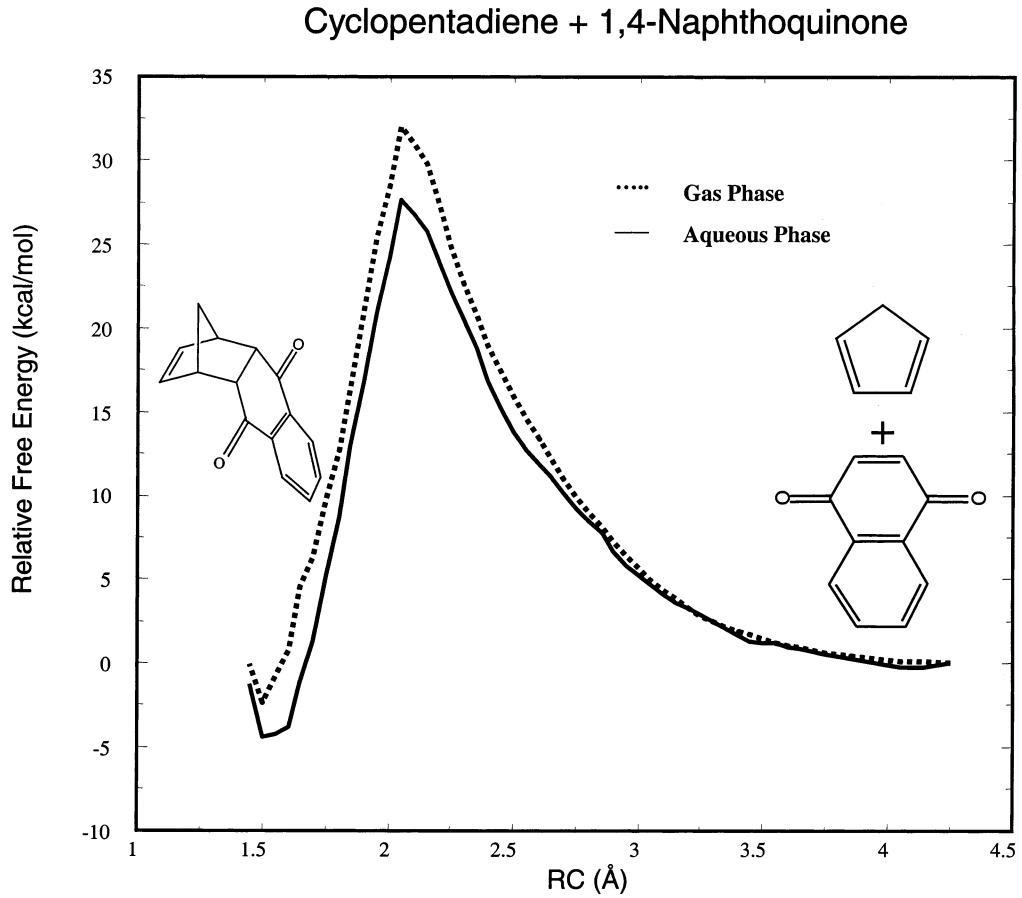


Figure 3. Computed free energy profiles in the gas phase and in water for the cycloaddition reaction between cyclopentadiene and 1,4-naphthoquinone.

TABLE 1: Free Energy Changes (kcal/mol) in the Gas Phase and in Water for Diels−Alder Reactions of Cyclopentadiene with Acrylonitrile, Methyl Vinyl Ketone, and 1,4-Naphthoquinone

dienophile	gas phase	aqueous phase	solvent effect (experiment)
ΔG activation for Diels−Alder addition			
acrylonitrile	26.3	24.7	−1.5 (−2.1)[a]
methyl vinyl ketone	25.4	22.6	−2.8 (−3.8)[a]
1,4-naphthoquinone	32.0	27.6	−4.4 (−5.0)[b]
ΔG reaction for Diels−Alder addition			
acrylonitrile	−25.8	−26.2	−0.4
methyl vinyl ketone	−25.1	−24.6	0.6
1,4-naphthoquinone	−2.4	−4.4	−2.1
ΔG activation for retro-Diels−Alder reaction			
acrylonitrile	52.1	50.9	−1.1
methyl vinyl ketone	50.5	47.2	−3.3
1,4-naphthoquinone	34.3	32.0	−2.3

[a] Reference 3a. [b] Reference 4e.

activated-trajectory MD simulations have indicated that this is a small effect with a computed κ of 0.67 in water[19] and 0.95 in the gas phase.[20]

In the event, the computed free energies of activation for the Diels−Alder reactions with CP in the gas phase are 26.3 kcal/mol for acrylonitrile and 25.4 kcal/mol for MVK (Table 1). The fact that these values are close to the experimental values in isooctane, 24.3 and 22.8 kcal/mol,[3a] respectively, results from a cancellation of overestimation of both the energy and entropy of activation. In the case of addition of cyclopentadiene and 1,4-naphthoquinone, the free energy of activation at the AM1 level in the gas phase from the MC simulations (32.0 kcal/mol) is substantially greater than the experimental value in hexane (21.6 kcal/mol).[4e] This reflects further overestimation of the energy of activation.

Solvent Effects on the Retro-Diels−Alder Reactions. The results of the MC simulations also predict the solvent effects on free energies of reaction and activation for the retro-Diels−Alder processes (Table 1). The cycloadditions of cyclopentadiene with acrylonitrile and MVK are computed to be exoergic by ca. 25 kcal/mol and to have free energies of activation for the cycloreversions near 50 kcal/mol. In contrast, the reaction with 1,4-naphthoquinone is computed to have a free energy change of only −2.4 kcal/mol. The difference may be attributed to some loss of aromaticity for the naphthoquinone and increased steric strain for the elaborated endo product. Thus, the free energy of activation for the retroreaction is much reduced to 34.3 kcal/mol in the gas phase. This result is qualitatively correct; a retro-Diels−Alder reaction under ambient conditions has been observed experimentally only for naphthoquinone derivatives.[13] Upon transfer to water, the free energy change for the cycloaddition of cyclopentadiene with acrylonitrile becomes more exoergic by 0.4 kcal/mol, while the reaction with MVK becomes more endoergic by 0.6 kcal/mol. In view of the large number of perturbation steps required to reach the products, these results have statistical uncertainties that are similar to the predicted solvent effects. However, for the cycloaddition with naphthoquinone, the solvent effect of −2.1 kcal/mol is statistically significant and smaller in magnitude than the stabilization of the transition state.

Combination of the computed solvent effects on the transition states and products finds that on transfer to water the free energies of activation for the three retro-Diels−Alder are all decreased. The magnitude is smallest for the cycloreversion of 5-*endo*-cyanonorbornene, −1.1 kcal/mol. Larger effects are

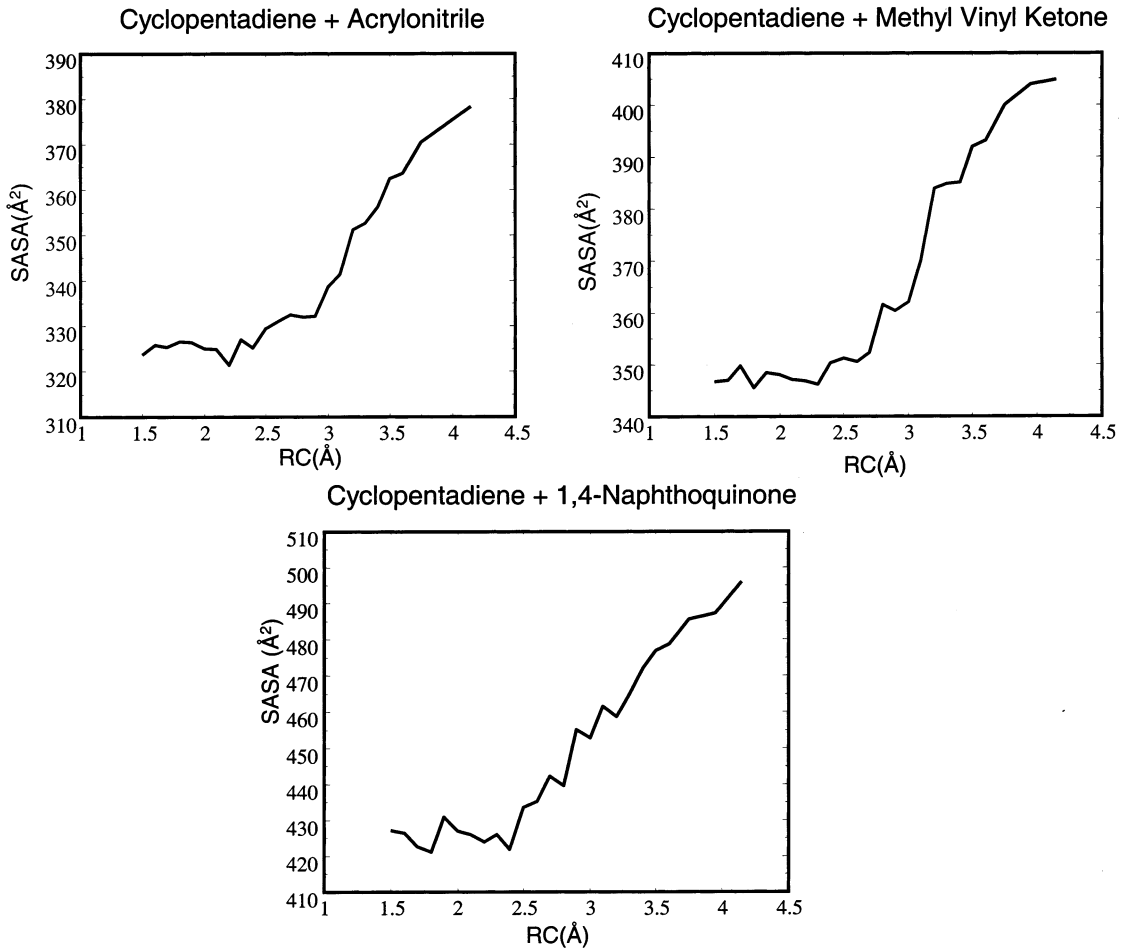
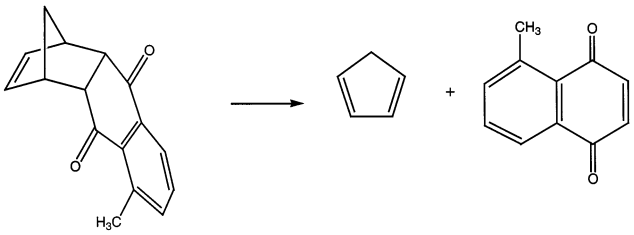


Figure 4. Variations in SASA along the reaction coordinate for Diels−Alder reactions of cyclopentadiene with acrylonitrile, methyl vinyl ketone, and 1,4-naphthoquinone.

noted in the remaining two cases. The activation free energy of the retro-Diels−Alder reaction leading to the formation of cyclopentadiene and 1,4-naphthoquinone is reduced by 2.3 kcal/mol in water. This value is the same within the statistical limits of the calculations to that obtained experimentally in a closely related system. Specifically, the free energy of activation for the retro-Diels−Alder reaction leading to the formation of cyclopentadiene and 6-methyl-1,4-naphthoquinone (Scheme 2) is observed to be reduced by 2.1 kcal/mol on going from hexane to water.[13]

SCHEME 2



Origin of the Solvent Effects on Diels−Alder Reactions. The good agreement between the computed magnitudes of solvent-induced changes in activation free energies and the observed rate enhancements suggests that the simulations capture the key contributions of the medium effects. To focus on the role of hydrophobic effects, the variation of the solute's SASA along the reaction coordinate was examined. The same pattern is observed for all three reactions (Figure 4). The separated reactants clearly have the maximum SASA. The cycloaddition process results in a rapid reduction in the exposed surface area. The SASA drops by 50−80 Å^2 on reaching the transition state region (RC of around 2.2 Å), but remains fairly constant beyond that leading up to the formation of the cycloadduct. It is known that the change in SASA and free energy of hydration for hydrocarbon systems show a linear correlation with a proportionality constant of about 0.01 kcal/mol/Å^2.[31] This suggests that the hydrophobic effect should not contribute more than 1 kcal/mol to the reduced free energies of activation for these reactions in water, which is also not far from the 1.8 ± 0.3 kcal/mol computed for cyclopentadiene dimerization.[17] The larger changes that are observed, especially for the naphthoquinone derivatives, imply the participation of other factors. The rate enhancements predicted and observed for retro-Diels−Alder reactions leading to cyclopentadiene and naphthoquinones also cannot be interpreted on the basis of hydrophobicity effects, since there is little change in SASA on going from the cycloadduct to the transition state.

The nature of the free energy profiles in the gas phase and in water (Figures 1−3) and the computed reaction energetics (Table 1) imply that differential stabilization of the transition state is the principal effect of hydration. To quantify the interaction energies, solute−solvent energy pair distributions were analyzed in three representative windows: near the reactants, transition state, and product. The distributions record the average number of water molecules that interact with the solute with the interaction energy shown on the abscissa. Hydrogen bonding between the solute and water molecules is reflected in the left-

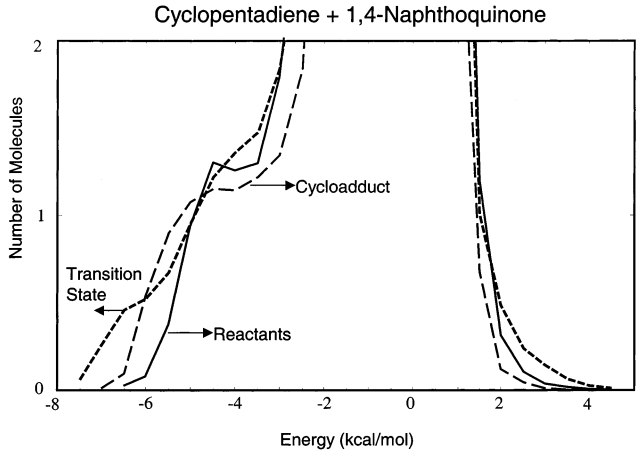


Figure 5. Solute−solvent energy pair distributions for the addition of cyclopentadiene with 1,4-naphthoquinone for structures near the reactants, transition state, and product. The plots show the number of water molecules on the ordinate that interact with the solutes with the interaction energy shown on the abscissa. Units for the ordinate are number of water molecules per kcal/mol.

most region with interaction energies more attractive than ca. −3 kcal/mol. The results for the naphthoquinone + CP reaction are shown in Figure 5; the results for the other reactions are qualitatively similar and consistent with earlier findings.[16,17] The numbers of solute−solvent interactions for the reactants, transition state and product are 0.2, 1.0, and 0.4 for integration from −∞ to −5.25 kcal/mol, 1.3, 2.1, and 1.9 for integration to −4.25 kcal/mol, and 2.6, 3.5, and 3.1 for integration to −3.25 kcal/mol. Thus, for naphthoquinone as dienophile, there is an increase in number of hydrogen bonds with water by about one in going from reactant to transition state, and there is also a shift in the average hydrogen-bond strength to lower energy. The greater polarization of the Diels−Alder transition state induced by the activating substituents in the dienophile leads to the enhanced hydrogen bonding. Consistently, the maximum differential stabilization is found for naphthoquinone with two carbonyl units adjacent to the reactive sites. As noted previously,[15−17] hydrogen bonding is sensitive to small charge shifts. In the present case, the computed charges on oxygens in the naphthoquinone only decline from −0.414 e for the reactant to −0.444 e for the transition state and product, and the charges on the carbonyl carbons average +0.379, +0.406, and +0.382 e for the reactant, transition state, and product. Thus, the transition state has the greatest $C^{+}-O^{-}$ polarization, as expected.

The above interpretations have significance for predicting the effect of water on other cycloaddition reactions. In reactions involving nonpolar substrates, the role of the solvent is restricted to the hydrophobic effect favoring the reduction of exposed surface area of the reactants near the transition state region. In the absence of differential hydrogen bonding stabilization of the transition state, the rate enhancements are expected to be limited. It must also be noted that the effect of hydrogen bonding is not expected to be always in favor of the cycloaddition transition state. In dipolar cycloadditions, the reactants themselves form strong hydrogen bonds. For example, 1,3-dipoles have considerable zwitterionic character and the change in hydrogen bonding strength on reaching the transition state is relatively low. Therefore, the corresponding cycloaddition processes are accelerated to a lesser extent in water.[32,33]

Conclusions

Monte Carlo simulations using the free energy perturbation method in conjunction with the AOC QM/MM protocol were used to study the effects of hydration on the rates of Diels−Alder reactions for a variety of substrates. For cyclopentadiene as the diene, the increasing enhancements of the cycloaddition rates as the dienophile is varied from acrylonitrile to methyl vinyl ketone to 1,4-naphthoquinone are quantitatively well reproduced. The calculated results are also consistent with the observed acceleration of the retro-Diels−Alder reaction leading to cyclopentadiene and naphthoquinone derivatives. The computational methodology has been highly automated and can be readily employed to study other solution-phase reactions. A strength of the approach is the complete sampling of the solutes' internal degrees of freedom; however, improvements in the QM calculations are desirable, though challenging for computer resources. The present simulations confirmed that the observed rate increases for the Diels−Alder reactions in water are primarily due to enhanced hydrogen bonding between the solvent and the polarized transition states. The contribution from enforced hydrophobic association is estimated to be ca. 1 kcal/mol in these systems.

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