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Quantum Mechanical/Molecular Mechanical Modeling Finds Diels−Alder Reactions Are Accelerated Less on the Surface of Water Than in Water

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Abstract: Quantum and molecular mechanics calculations for the Diels−Alder reactions of cyclopentadiene with 1,4-naphthoquinone, methyl vinyl ketone, and acrylonitrile have been carried out at the vacuum−water interface and in the gas phase. In conjunction with previous studies of these cycloadditions in dilute solution, a more complete picture of aqueous environmental effects emerges with implications for the origin of observed rate accelerations using heterogeneous aqueous suspensions, "on water" conditions. The pure TIP4P water slab maintains the bulk density and hydrogen-bonding properties in central water layers. The bulk region merges to vacuum over a ca. 5 Å band with progressive diminution of the density and hydrogen bonding. The relative free energies of activation and transition structures for the reactions at the interface are found to be intermediate between those calculated in the gas phase and in bulk water; i.e., for the reaction with 1,4-naphthoquinone, the $\Delta\Delta G^{\ddagger}$ values relative to the gas phase are −3.6 and −7.3 kcal/mol at the interface and in bulk water, respectively. Thus, the results do not support the notion that a water surface is more effective than bulk water for catalysis of such pericyclic reactions. The trend is in qualitative agreement with expectations based on density considerations and estimates of experimental rate constants for the gas phase, a heterogeneous aqueous suspension, and a dilute aqueous solution for the reaction of cyclopentadiene with methyl vinyl ketone. Computed energy pair distributions reveal a uniform loss of 0.5−1.0 hydrogen bond for the reactants and transition states in progressing from bulk water to the vacuum−water interface. Orientational effects are apparent at the surface; e.g., the carbonyl group in the methyl vinyl ketone transition structure is preferentially oriented into the surface. Also, the transition structure for the 1,4-naphthoquinone case is buried more in the surface, and the free energy of activation for this reaction is most similar to the result in bulk water.

Introduction

The Diels−Alder reaction is an extremely well-characterized and synthetically important cycloaddition. It has also emerged as the benchmark for the study of solvent effects on rates and regio- and stereoselectivities. Since the seminal report by Rideout and Breslow of the large rate accelerations and enhanced *endo* selectivities of Diels−Alder reactions in water,[1] these effects have been attributed in part to the benefit of decreasing hydrophobic surface area.[1−3] Further work specifically pointed to the importance of preferential hydrogen bonding with the polarized transition state, which is consistent with the greater rate increases in water observed for dienophiles that are better hydrogen bond acceptors.[4−8] In addition to possible catalytic value, the use of water as a potential "green" solvent for organic synthesis is appealing.[9]

Of course, the range of concentrations for organic reactions in a homogeneous aqueous medium is often limited by low solubility of the reactants. Indeed, Breslow and co-workers noted that, in the course of studying the concentration dependence of cycloadditions in water, heterogeneous aqueous suspensions were formed at higher concentrations of reactants.[2] Under these conditions, it was observed that the *endo*/*exo* selectivity for the reaction of cyclopentadiene and methyl vinyl ketone was very similar to that found in a dilute aqueous solution (ca. 21) and much higher than the ratio seen using excess diene as the solvent (3.9).[2] No formal rates were reported, but it was noted that an undiluted equimolar mixture of the two reactants went to 50% completion in 35−40 min while a stirred aqueous suspension reached the same point in 10−15 min. Thus, the possibility of significant rate increases under heterogeneous conditions was established. Subsequently, Narayan et al. reported particularly

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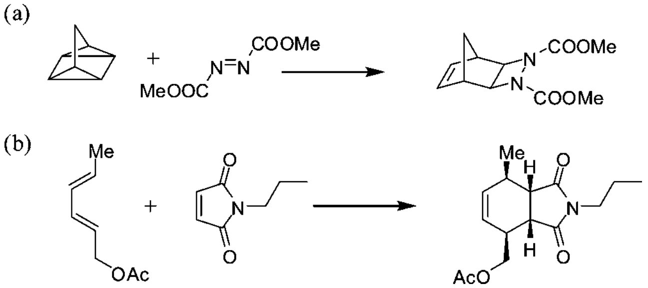
Scheme 1. Reactions Studied by Narayan et al.[10]



remarkable rate enhancements for the $[_{\pi}2 + {}_{\sigma}2 + {}_{\sigma}2]$ cycloaddition of quadricyclane and dimethyl azodicarboxylate (DMAD) to yield a 1,2-diazetidine derivative (Scheme 1a), when carried out in a vigorously stirred aqueous suspension, termed “on water” conditions.[10] While homogeneous solutions of the reactants in polar-protic solvents, including methanol and water−methanol mixtures, did accelerate the reaction in comparison to those in apolar solvents, the most significant increases occurred under the heterogeneous aqueous conditions. For instance, the time to completion for the reaction of quadricyclane and DMAD under neat conditions was 48 h vs 10 min on water at the same temperature and concentration of reactants. An ene reaction with cyclohexene and an azodicarboxylate was also found to be significantly accelerated on water; however, other pericylic reactions do not necessarily respond in the same manner.[10] For example, the time to completion for the Diels−Alder reaction of *trans*,*trans*-2,4-hexadienyl acetate with *N*-propylmaleimide (Scheme 1b) in heterogeneous aqueous solution was similar to that observed under neat conditions (8 vs 10 h).[10]

These results have raised further interest in understanding the role of water as a catalyst and the nature of the interface in aqueous suspensions.[10–27] Pirrung and co-workers discussed the effects of the mixing method on Ugi, Passerini, and ene reactions under heterogeneous aqueous conditions, indicating that different techniques such as stirring, shaking, vortexing, and ultrasonication can have varying impacts on the reaction rate, presumably due to the extent of phase transfer afforded by each.[11] Additional effects proposed earlier to explain the increased reactivity invoke the cohesive energy density of the heterogeneous medium,[14–16] potential pressure influences,[17] and the physical structure of the emulsion, e.g., micellar catalysis.[18] It has been observed by Shen and co-workers[19–21] in vibrational sum frequency generation (SFG) experiments that there is approximately a 25% population of “dangling” OH bonds extending into the bulk hydrophobic or gas-phase boundary. A recent ab initio and classical molecular dynamics study by Buch et al.[22] also suggests that the pH of the water surface is acidic, indicating a preferential attraction of hydronium ions. This result is in agreement with the findings of vibrational spectroscopy of protonated water clusters[23] as well as SFG[24,25] and second harmonic generation[26] experiments on bulk water interfaces, while it is in contrast to observations via ζ potential measurements and titration experiments on dispersed oil droplets in water,[27] underscoring the existing conflict in the literature.[22]

A conceptual model of the organic−aqueous interface with dangling OH bonds was used as the basis for the recent theoretical study of Jung and Marcus,[12] which likened the interface between the droplets in these emulsions to the environment at an oil−water phase boundary, such as that described by Shen. Specifically, they combined energetic results from density functional theory calculations at the UB3LYP/6-31+G* level and semiquantitative hydrogen bond energetics with transition-state theory to produce theoretical rate constants to compare with the corresponding values deduced from the times to completion reported by Sharpless.[10] Their simplified model consisted of the DMAD−quadricyclane complex (Scheme 1a) plus three explicit water molecules representing the surface. Condensed-phase simulations were not performed. It was reasoned that hydrogen bonding at the transition state, enhanced by the higher population of dangling OH bonds available for such interactions at the surface, is responsible for the substantial acceleration. For comparison, the homogeneous aqueous model included energetic penalties for disrupting the water−water interaction network in the bulk phase, and the neat-phase energetics were obtained directly from the gas-phase quantum mechanics (QM) results.[12]

The limited experimental data, coupled with the intrinsic difficulty of separating the potentially superimposed phenomena, promote the desirability of additional computational studies to investigate possible catalysis on a water surface. Thus, we have undertaken the modeling of Diels−Alder reactions at the vacuum−water interface using statistical mechanics simulations. To permit comparison with prior results on the origin of homogeneous solvent effects,[7,8] the reactions of cyclopentadiene with 1,4-naphthoquinone, methyl vinyl ketone (MVK), and acrylonitrile (Scheme 2) have been examined. The same computational approach has been followed featuring quantum and molecular mechanics (QM/MM) calculations using Monte Carlo (MC) simulations and free energy perturbation (FEP) theory. These methods have been shown to perform well in reproducing experimentally observed solvent effects on the kinetics for a wide range of organic reactions in water, pure organic solvents, and aqueous solvent mixtures.[28] Notably, the MC/FEP simulations with explicit solvent representation can provide the medium dependence of the activation barriers and

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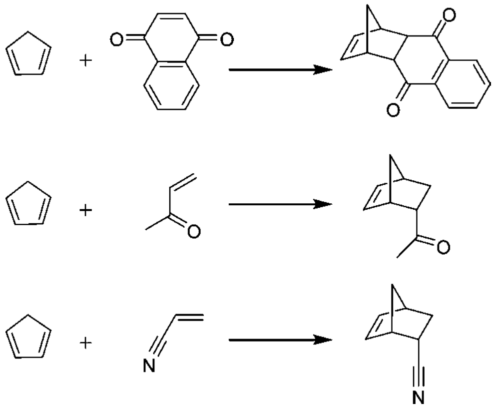
Scheme 2. Modeled Diels–Alder Reactions



atom-level structural detail for characterization of the nature of the vacuum–water interface, the adsorption of the reactants, and the changes in hydration along the reaction paths. Any orientational biases for the reactants at the surface, as has been reported computationally for simple organic solutes,[29,30] should emerge. It is emphasized that the present study is for reactions of an isolated diene and dienophile at the vacuum–water interface. This is an important limit for investigating and understanding possible catalysis on a water surface. Additional studies can certainly be envisioned with detailed representation of an aqueous emulsion or the interface of a biphasic water/hydrocarbon system.

Computational Methods

All calculations were run with the BOSS 4.7 program.[31] The computational methods were the same as in the prior study for the three Diels–Alder reactions in water, methanol, acetonitrile, and hexane.[8] Free energy changes were evaluated using FEP theory with double-wide sampling in Metropolis Monte Carlo simulations.[32] The intramolecular potential energy of the reacting system was computed using semiempirical PDDG/PM3 molecular orbital theory,[33,34] TIP4P was used as the water model,[35] and the solute–water interactions included use of CM3 atomic charges[36] for the solutes scaled by 1.14[37] with OPLS-AA Lennard-Jones parameters.[38] For the cycloadditions, the two forming carbon–carbon bonds were used as the reaction coordinates, R_{C1} and R_{C2}, and independently varied.[8] In the case of asymmetric dienophiles, R_{C2} corresponds to the bond nearest the electron-withdrawing group. All MC simulations were run with $T = 25$ °C.

TIP4P Water Slab. An MC simulation of a pure water slab was carried out to characterize the nature of the TIP4P water surface in the absence of solutes. The initial simulation cell was approximately 27 × 27 × 48 Å containing 1220 TIP4P monomers with periodic boundary conditions in the *x* and *y* directions and no *z* periodicity. While the starting system coordinates ranged from −24 to +24 Å in the *z* direction, a long initial equilibration with variation of the cell limits led to *x* and *y* dimensions near 27.4 Å, while the range of oxygen *z* coordinates extended to ±28 Å, decreasing the density of the surface layers. This equilibrated simulation cell was used as the starting point for the subsequent FEP calculations for the reactions on the water surface. An additional 20×10^6 configuration equilibration and 20×10^6 configuration averaging session with no further variation of the cell dimensions revealed that ca. 2% of the water monomers migrated into the less dense region, while a density near 1.0 g/cm^3 was maintained for inner layers. Intermolecular nonbonded cutoffs of 12 Å were used on the basis of oxygen–oxygen distances for the solvent–solvent interactions with quadratic feathering near the cutoff. Solvent coordinates were stored every 5000 configurations, yielding 4000 snapshots for postprocessing. From these snapshots, the average number density of water molecules in the *z* direction was quantified, with the *z* axis separated into 1 Å bins ranging from −30 to +30. Additionally, a simple geometric hydrogen bond definition of an acceptor–donor, O···H or N···H, distance of 2.5 Å or less was adopted, and the populations of these interactions were also computed as a function of the *z* axis position.

QM/MM Reaction Modeling. The initial configurations were composed of a single *endo* cycloadduct, optimized at the PDDG/PM3 level,[33,34] on the surface of the equilibrated TIP4P water slab. The reacting atoms of the dienophile were initially placed approximately at the top of the surface ($z = +24$ Å) and parallel to the *x* axis in such a way that the remainder of the molecule pointed into the slab. Due to the anisotropic nature of the surface, the starting geometries were chosen such that the hydrogen-bonding moieties of the dienophiles (carbonyl or nitrile groups) were oriented toward the slab. This is commensurate with previous studies which have shown that, for alcohols, hydroxyl groups are preferentially oriented toward the water surface to maximize hydrogen bonding.[29,30] For 1,4-naphthoquinone, which contains two equivalent carbonyl groups, the calculations were started with the dienophile portion of the cycloadduct pointing into the surface. During the course of the simulations, the two reacting carbon–carbon bonds were independently perturbed toward reactants to create two-dimensional free energy maps and to identify the locations of the transition states. Though water molecules were not constrained from evaporation in the ±*z* directions, only temporary excursions occurred; an illustration of a full simulation cell is provided in Figure 1.

Free energies of activation were evaluated in two stages.[8] Initially, approximate locations of the transition states were determined by computing a coarse 2D free energy map that was obtained by perturbing both reaction coordinates from 1.4 to 2.4 Å in 0.05 Å increments, as shown in Figure 2 for the reaction of cyclopentadiene with 1,4-naphthoquinone. The region near the transition state (TS) was then further refined using 0.01 Å perturbations. The free energy change from a point at the edge of this refined map to the reactants, defined as $R_{C1} = R_{C2} = 4.0$ Å,[8] was calculated via the smallest series of sequential one-dimensional perturbations connecting these points.

The intrasolute energy and atomic charges were calculated for each solute move (every 100 configurations), and a 12 Å heavy atom–oxygen solute–solvent nonbonded cutoff was applied; i.e., if any oxygen–heavy atom distance was below 12 Å, the entire solute–water molecule interaction was included in the potential energy. While the overall MC acceptance rates were ca. 40%, the solute move acceptance rates were 3–30%. While lower acceptance rates are usually observed for large solutes, concern regarding the orientational equilibration of the reactants at the water surface led to the use of long MC runs, ranging from 20×10^6 to 120×10^6

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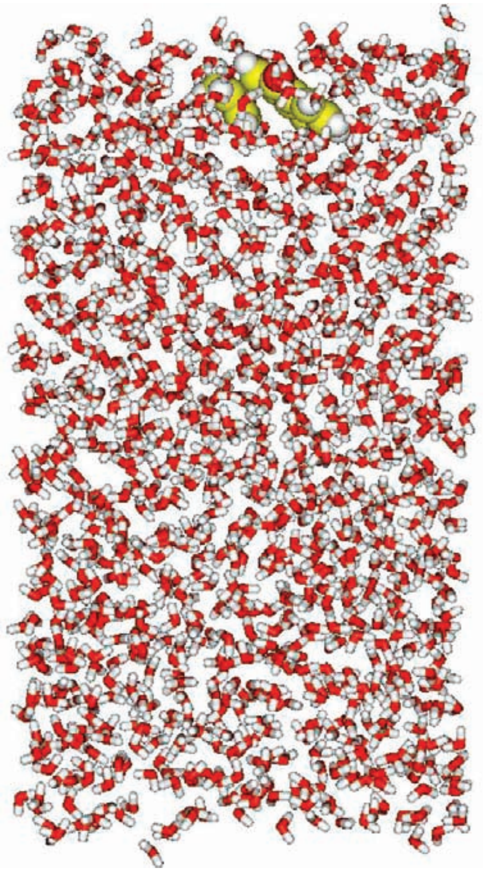

Figure 1. Snaphot of an MC configuration near the transition state for the Diels−Alder reaction of cyclopentadiene with 1,4-naphthoquinone on the water slab. Carbon atoms are in yellow. The system is periodic in the two horizontal directions; the slab is about 55 Å thick.

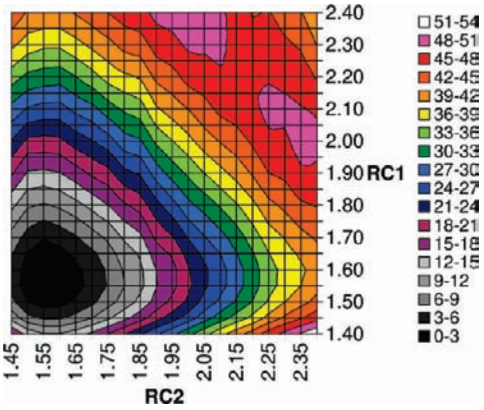

Figure 2. Two-dimensional free energy map for the Diels−Alder reaction of cyclopentadiene with 1,4-naphthoquinone on the surface of a water slab. R_{C1} and R_{C2} are in Angstroms, and the free energies in the legend are relative to the product in kcal/mol.

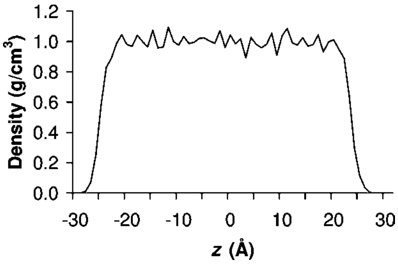

Figure 3. Computed density profile for the TIP4P water slab constructed from 4000 configurations saved during the MC simulation.

configurations during equilibration and averaging, to obtain thorough convergence of the free energies of activation. Similarly, the corresponding gas-phase systems were equilibrated for 0.5 × 10^6 configurations and averaged for 1 × 10^6 configurations, wherein solute moves and reevaluation of the QM energy took place at every step. Additional simulations near the transition states and reactants were carried out once these points were located to collect configurations for postprocessing. In these runs, coordinates were saved every 10000−20000 configurations, providing 4000 snapshots. The calculations were technically novel as QM/MM calculations for reactions at an interface are rare, and appropriate coding was required in BOSS.

The orientational preferences for the solutes on the water surface were monitored by calculating the angle between relevant intramolecular vectors and the normal to the surface (the *z* axis); histograms of population vs orientation were separated into 10° bins ranging from 0° to 180°. For instance, the angle between the CO carbonyl vector of MVK and the *z* axis was monitored to characterize the orientation of this hydrogen-bonding group. Due to the fact that angles around 90° have an inherently higher probability of being sampled as a result of the spherical nature of the angle distribution, the histogram populations were subsequently weighted by a factor of 1/sin(bin midpoint). These weighted probabilities were then normalized by dividing each by the sum of their total. Others have carried out similar analyses.[29] Additionally, the average *z* coordinates of selected solute atoms were calculated to characterize their positions with respect to the surface. As in the pure water slab, the number of solvent molecules as a function of the *z* height was monitored to serve as a reference for the solute atom locations.

Results and Discussion

TIP4P Water Surface. The inner layers of the water slab were found to be bulklike. The average number density of water molecules for the *z* axis bins ranging from −15 to +15 Å was calculated to be ~25 monomers per 27.5 × 27.3 × 1.0 Å layer, yielding a density of 1.0 g/mL, which agrees with previous studies of pure TIP4P water[35] and a TIP4P water slab.[39] The outermost "bulk" layer was defined by the bin whose water population deviates from the inner average by 2 standard deviations. This corresponds to the first layers with approximately 23 water monomers, which were identified as the −22 and +21 *z* bins. There are then several less dense "surface" layers with *z* coordinates ranging from −23 to −29 Å and from +22 to +28 Å. In particular, the layers with approximately half of the bulk water population have *z* coordinates of −25 and +23 Å. The TIP4P slab progresses from bulk water to vacuum over a ca. 5 Å thick band (Figure 3). It may also be noted that a recent result for the surface tension of TIP4P water is 59.0 ± 0.9 mN/m, while the experimental value is 71.7 mN/m at 300 K.[40] That study also found that the water density at the interface declines from 90% to 10% of the bulk value over 3.7 Å, which is again consistent with the present and earlier results.[39] The thickness of the transition zone is expected to shrink by only ca. 0.5 Å for water models that match the experimental surface tension.[40]

Analyses of the hydrogen bonding find that, in the bulk layers, water oxygen atoms engage in an average of 1.75 hydrogen bonds per monomer, while each hydrogen participates in an

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Table 1. Computed Bond Lengths and Asynchronicity ($\Delta r = R_{C2} - R_{C1}$) for the Transition Structures of Diels−Alder Reactions with Cyclopentadiene at 25 °C[a,b]

	gas phase	water surface	water[c]
	Dienophile = 1,4-Naphthoquinone		
R_{C1} (Å)	2.23 (2.15−2.23)	2.22 (2.21−2.26)	2.22
R_{C2} (Å)	2.16 (2.16−2.19)	2.14 (2.13−2.15)	2.25
Δr (Å)	−0.07	−0.08	0.03
	Dienophile = Methyl Vinyl Ketone		
R_{C1} (Å)	2.11 (2.09−2.11)	2.06 (2.01−2.09)	2.01
R_{C2} (Å)	2.14 (2.14−2.16)	2.20 (2.16−2.26)	2.34
Δr (Å)	0.03	0.14	0.33
	Dienophile = Acrylonitrile		
R_{C1} (Å)	2.09 (2.05−2.12)	2.08 (2.05−2.10)	2.00
R_{C2} (Å)	2.18 (2.15−2.21)	2.20 (2.18−2.22)	2.28
Δr (Å)	0.09	0.12	0.28

[a] From 2D QM/MM free energy maps. [b] Values in parentheses indicate the range for structures with free energies within ~0.5 kcal/mol. [c] Reference 8.

average of 0.90 hydrogen bond, for a total of ca. 3.5 hydrogen bonds per water monomer. This is in agreement with previous studies.[35,39,41] However, in the surface layers, these averages are significantly lower, with values of 1.2 per oxygen and 0.4 per hydrogen, for an average of only 2.0 hydrogen bonds per monomer.[39] Hence, the TIP4P water slab consists of a bulklike core that melds into a 5 Å thick, less structured surface region. Density and hydrogen bonding for both oxygen and hydrogen atoms decline. All aspects of the present results for the pure TIP4P water slab are essentially the same as reported by Wilson et al.,[39] though their system size of 342 molecules was smaller than the present one with 1220 molecules. Very similar results have been obtained using other water models.[30] It should be noted that, in the present TIP4P-based model, there is no occurrence of hydronium or hydroxide ions.

Transition Structures. Table 1 lists the computed values of the reaction coordinates for the transition structures and the asynchronicities (Δr) from the MC/FEP calculations in the gas phase, on the water surface, and in bulk water. Transition structures on the water surface are illustrated in Figure 4. For all three reactions, the saddle point at the transition-state geometry in bulk water was sharply defined. However, in the gas-phase and surface simulations, the regions near the TS were flatter. The entries in Table 1 for the gas-phase and surface simulations give the geometry of the lowest free energy saddle point and include in parentheses the range of surrounding reaction coordinate values with free energies within ~0.5 kcal/mol.

The computed lengths for the forming bonds at the transition states for the Diels−Alder reactions, 2.2 ± 0.2 Å, are typical of results from high-end QM calculations.[8,42] As noted previously, gas-phase CBS-QB3 results for the present reactions yield greater asynchronicities, i.e., 0.4 and 0.6 Å for the reactions with acrylonitrile and MVK.[8] For the symmetrical dienophile, 1,4-naphthoquinone, the transition structure remains synchronous with $R_{C1} \approx R_{C2}$ in all three environments, while for the unsymmetrical dienophiles the asynchronicity increases in progressing from the gas phase to the water surface to bulk water. R_{C2} increases, and R_{C1} decreases. This is qualitatively reasonable, as more negative charge is then placed on the carbonyl or cyano group at the TS, which should enhance hydrogen bond acceptance with water molecules.[4–8] The asynchronicity is somewhat greater for MVK since its carbonyl group is a better hydrogen bond acceptor than the cyano group of acrylonitrile. For these cases, the TS geometry on the water surface is intermediate between the gas-phase and bulk-water results. Furthermore, it is clear from Figure 4 that at the transition states the carbonyl and cyano groups of the dienophiles lie beneath the water surface in the slab simulations and are participating in hydrogen bonds; detailed results are provided below.

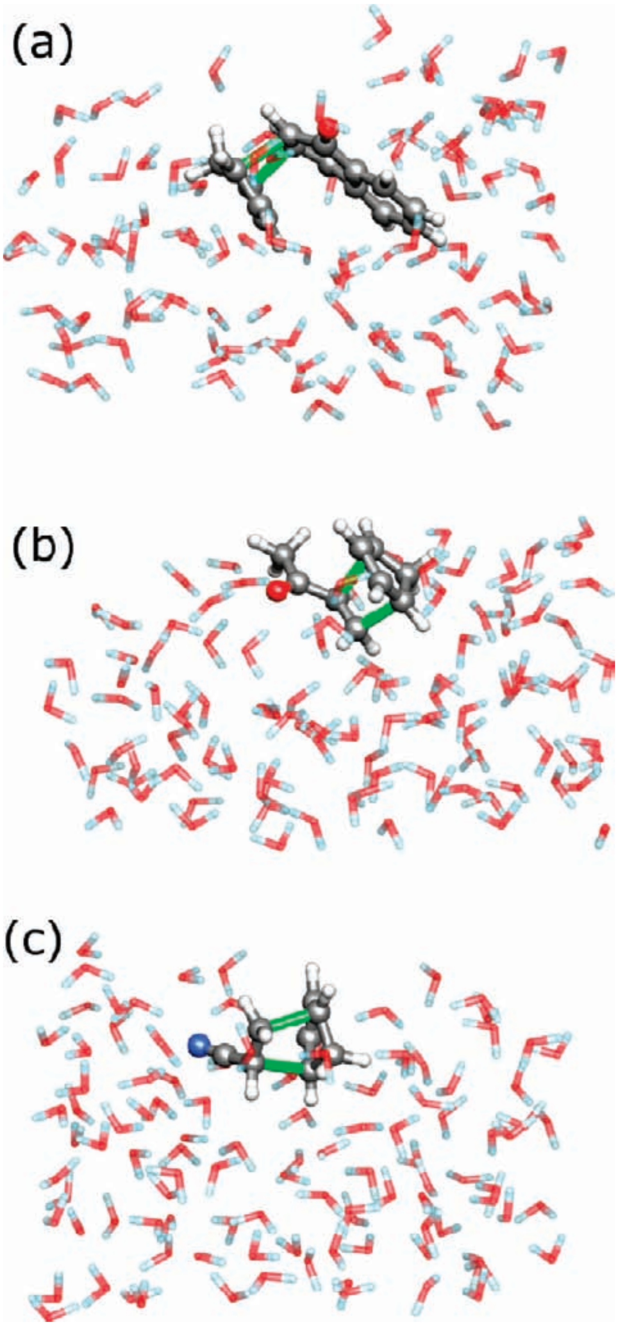

Figure 4. Illustrative MC configurations for the transition structures on the water surface for the reactions of cyclopentadiene with (a) 1,4-naphthoquinone, (b) MVK, and (c) acrylonitrile. The reaction coordinates R_{C1} and R_{C2} are highlighted in green. Water molecules with oxygen atoms beyond 6 Å in any Cartesian direction of any solute atom have been omitted. The z axis is vertical.

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(42) (a) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445–11459. (b) Pieniazek, S. N.; Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 7746–7749.

Table 2. Computed Free Energies of Activation (kcal/mol) for the Diels–Alder Reactions with Cyclopentadiene at 25 °C[a]

	gas	water surface[b]	methanol[c,d]	water[c,d]
		Dienophile = 1,4-Naphthoquinone		
$\Delta G^{\ddagger}$	33.3	29.7	29.2 (20.0)	26.0 (16.6)
$\Delta\Delta G^{\ddagger}$	7.3	3.7	3.2 (3.4)	0 (0)
		Dienophile = Methyl Vinyl Ketone		
$\Delta G^{\ddagger}$	40.3	39.0	36.4 (21.6)	32.2 (19.2)
$\Delta\Delta G^{\ddagger}$	8.1	6.8	4.2 (2.4)	0 (0)
		Dienophile = Acrylonitrile		
$\Delta G^{\ddagger}$	40.2	38.0	35.2 (23.8)	34.0 (22.2)[e]
$\Delta\Delta G^{\ddagger}$	6.2	4.0	1.2 (1.6)	0 (0)

[a] Experimental values in parentheses. Computed values have uncertainties of ca. ±0.5 kcal/mol. [b] Values are Helmholtz free energies, $\Delta A^{\ddagger}$, as the system volume was not varied after equilibration of the slab. [c] Reference 8. [d] Reference 6a. [e] Reference 1, 30 °C.

Reaction Energetics. Table 2 summarizes the results for the absolute and relative free energies of activation from the QM/MM/MC calculations. As discussed previously, the absolute free energy barriers for Diels–Alder reactions are too large from semiempirical QM calculations; the results from ab initio and DFT calculations are also sensitive to the treatment of electron correlation.[7,8] However, the medium effects on the barrier heights are well represented with the present QM/MM approach.[28] For example, the observed increases in $\Delta G^{\ddagger}$ for the reaction of cyclopentadiene and 1,4-napthoquinone upon transfer from aqueous solution to ethanol, acetonitrile, and hexane (3.4, 4.0, and 5.0 kcal/mol) are reproduced within ±0.2 kcal/mol by PDDG/PM3-based MC/FEP calculations.[8] From Table 2, it is clear that the results for the computed free energies of activation for the reactions on the water surface lie between those for the gas phase and bulk water. In fact, catalysis of the Diels–Alder reactions by the water surface is somewhat less effective than what was computed previously for pure methanol (Table 2). No unusual rate acceleration for the surface reactions is apparent. In retrospect, this seems reasonable. Since the density of water is less near the surface, the situation is analogous to a condition of higher temperature or lower pressure, which would be expected to diminish the solvent effects. The importance of the density of hydrogen bond donating groups is also apparent in the results for pure water vs methanol. About 1.0–1.5 kcal/mol of the $\Delta\Delta G^{\ddagger}$ values can be attributed to the hydrophobic effect in water,[4,6b,7] but the remainder can be ascribed to the differences in hydrogen-bonding capacity for water and methanol.

For an additional quantitative point, the experimentally determined second-order rate constant for the cycloaddition of cyclopentadiene and MVK in bulk water can be compared to values derivable from the heterogeneous and neat half-lives.[2] The relationship between the half-life and second-order rate constant for equimolar components (eq 1)[43] comes from integration of the second-order rate law. In the present cases,[1,2] $[\mathrm{A}]_0$ for the suspension was 0.15 M for both reactants, and for the equimolar neat reaction, the average of the liquid densities[44] was used to estimate the concentrations. This analysis yields approximate rate constants for the MVK reaction under the neat and heterogeneous conditions of 7.2×10^{-5} and 8.8×10^{-3} $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$, respectively. Considering the reported rate constant in bulk water (4.4×10^{-2} $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$),[1] the rate under the heterogeneous conditions is indicated to be intermediate between those for the neat mixture and bulk water.

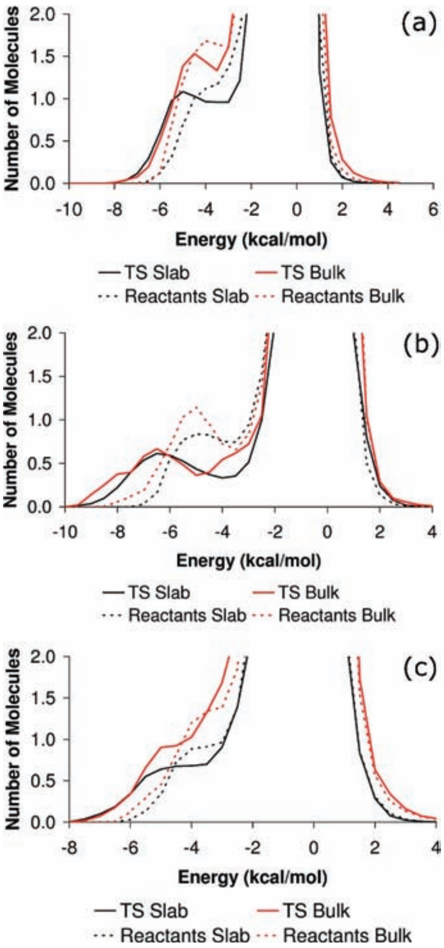

Figure 5. Solute–water energy pair distributions for windows for the transition structures and reactants of the Diels–Alder cycloadditions of cyclopentadiene and (a) 1,4-naphthoquinone, (b) MVK, and (c) acrylonitrile at the surface of a water slab and in bulk water. Units for the *y* axis are the number of water molecules per kcal/mol.

$$k_2 = ([\mathrm{A}]_0 t_{1/2})^{-1} \tag{1}$$

Energy Pair Distributions and Hydrogen Bonding. The interactions between the reacting systems and water were further analyzed via energy pair distributions, which record the average number of water molecules interacting with the solutes with a given solute–water potential energy (Figure 5). Hydrogen-bonding interactions are reflected in the bands at lowest energy, while the large peaks centered near 0 kcal/mol are due to the many weak interactions with distant water molecules. Table 3 lists the average number of solute–water hydrogen bonds and average interaction energy per hydrogen bond as obtained from energy pair distributions for the transition structures and reactants. The numbers of hydrogen bonds are obtained by integrating the curves to −3.5 kcal/mol, a standard limit for hydrogen bonding that often corresponds to the position of a minimum in the distributions.[4,7,8] There is negligible statistical uncertainty in the results in Table 3 as the distributions are averaged over the entire simulations.

In pure water, the number of solute–water hydrogen bonds is greatest for the naphthoquinone system and declines in progressing to MVK and acrylonitrile, as expected in view of

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(43) Maron, S. H. L., J. B. *Fundamentals of Physical Chemistry*; Macmillan Publishing Co., Inc.: New York, 1974; pp 681–683.

(44) *CRC Handbook of Chemistry and Physics*; CRC Press, Inc.: Boca Raton, FL, 1989; Tables C-233 and C-354.

Table 3. Average Number of Hydrogen Bonds (HBs) and Energy per Hydrogen Bond (kcal/mol) for Diels−Alder Reactions with Cyclopentadiene at 25 °C[a]

	water surface		water	
	TS	reactants	TS	reactants
	1,4-Naphthoquinone			
no. of HBs	3.0	2.2	3.7	3.4
energy/HB	−4.8	−4.3	−4.6	−4.4
	Methyl Vinyl Ketone			
no. of HBs	2.3	2.3	3.0	2.8
energy/HB	−5.9	−4.8	−5.5	−4.9
	Acrylonitrile			
no. of HBs	2.0	1.5	2.7	2.1
energy/HB	−4.8	−4.2	−4.6	−4.2

[a] From integration of energy pair distributions to −3.5 kcal/mol.

the hydrogen-bonding capacity of the dienophiles. In all three cases, the numbers of hydrogen bonds to both the reactants and transition structures are lower for the slab than for bulk water. The reduction in the number of hydrogen bonds is mostly between 0.5 and 1.0. Simply, there is a smaller number of solute−water hydrogen bonds formed in the lower density medium. More hydrogen bonds do not form in the interfacial region because it is entropically unfavorable. This applies to both water−water and water−solute hydrogen bonding. The average hydrogen bond strengths are similar in both media. Catalysis arises in all cases since the numbers and strengths of the hydrogen bonds are greater for the transition structures than for the reactants, reflecting the enhanced polarization of the transition structures.[4–8] Again, hydrophobic effects contribute some in pure water, but their impact is expected to decline in the less structured surface milieu. Finally, it may be noted that, looking more closely at Figure 5, the distributions for the water surface and bulk water generally coincide at the lowest energies. The loss of hydrogen bonds for the surface case is mostly in the weaker range from −5.5 to −3.5 kcal/mol.

Surface Orientation. The counts of hydrogen bonds and their energetics are affected by the orientations and positions of the adsorbates on the surface. To help characterize this, the orientational distributions were computed for the carbonyl vectors of 1,4-naphthoquinone and MVK at the water surface. Figure 6 depicts the normalized histograms for the reactants and transition structures; the orientation angle is relative to the *z* axis, which is perpendicular to the surface of the slab. Orientations at high angles indicate structures where the carbonyl oxygen is pointing into the surface, a 90° angle corresponds to a carbonyl vector parallel to the surface, and low angles signify that the oxygen is pointing away from the surface.

The two carbonyl vectors for the 1,4-naphthoquinone TS take on intermediate values, with the highest preference of the carbonyl near R_{C1} peaking below 90° and that for the carbonyl near R_{C2} peaking just above 90° (Figure 6a). The TS adopts a relatively flat orientation on the surface, presumably to maximize formation of hydrogen bonds simultaneously to both carbonyl groups. However, for the reactants, the preference favors having only one carbonyl group pointing into the surface, while the other populates lower orientation angles. This is consistent with the hydrogen-bonding results in Table 3, where 3.0 hydrogen bonds were found for the TS and 2.2 for the reactants. As the TS is more polarized (more negative charge on the oxygen atoms) than the reactants,[6–8] more enthalpic gain is possible to offset any entropic costs by maximizing the number of hydrogen bonds. For MVK, the preference in Figure 6b is for pointing the sole carbonyl group into the surface for the TS, while the carbonyl group is generally parallel to the surface for the reactants. This is consistent with formation of about two hydrogen bonds in both cases (Table 3). For acrylonitrile, the C−N distributions for both the reactants and TS (not shown) favor angles near 90°, so there is little orientational bias into the surface for this weaker hydrogen bond accepting group.

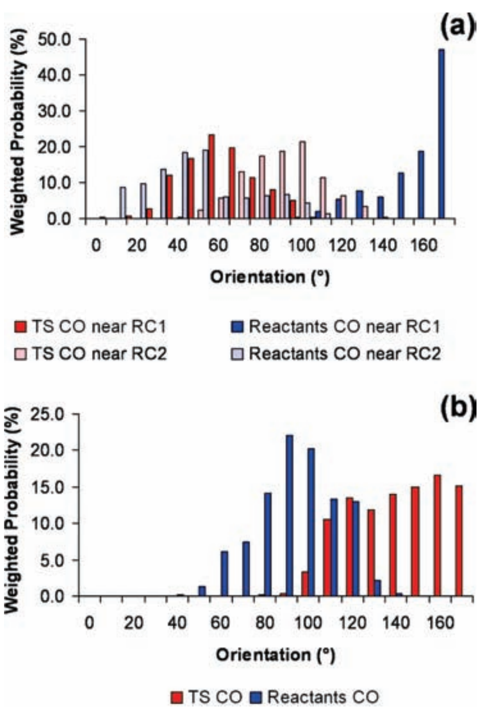

Figure 6. Distributions for the orientation of carbonyl vectors for the Diels−Alder reactions of (a) 1,4-naphthoquinone and (b) MVK on the water surface. High and low angles correspond to the carbonyl oxygen atoms pointing toward or away from the surface.

For additional clarification, the average *z* coordinates of solute atoms were computed for the surface simulations. The same definition of bulklike layers for the pure water slab was applied here. The outermost 1 Å thick bulk layer has approximately 23 water monomers and occurs at a $+z$ coordinate of 20 ± 1 Å. In all cases, the water density reaches about half the bulk value in the slices at $z = 22-23$ Å. Figure 7 depicts the three transition structures with atoms labeled with their average *z* coordinate value. The transition structures mostly reside at the edge of the bulklike region with *z* coordinates of 19−22 Å.

For the 1,4-naphthoquinone TS (Figure 7a), the diene fragment ended up below (lower *z*) the dienophile portion with the oxygen atoms oriented parallel to the surface, which is consistent with the results in Figure 6a. Similar averaging for the reactants finds higher *z* values, 22−26 Å, than for the transition structure, which partially reflects the elongation of the reaction coordinate bonds by 2.5 Å. Notably, the average *z* coordinate of one of the carbonyl oxygen atoms is ca. +22 Å, while the other oxygen is in the +25 Å bin, where the water population is only about 10% of the bulk value. This is also consistent with the interpretation of the results from the energy pair and orientation distributions. The smaller, more polarized transition structure resides deeper in the water surface than the more hydrophobic reactants.

For the MVK TS (Figure 7b), the most notable, additional feature is that the carbonyl group points into the surface, as also indicated in Figure 6b. The reactants again sit higher on the surface with an average value of 22.5 Å for the atoms

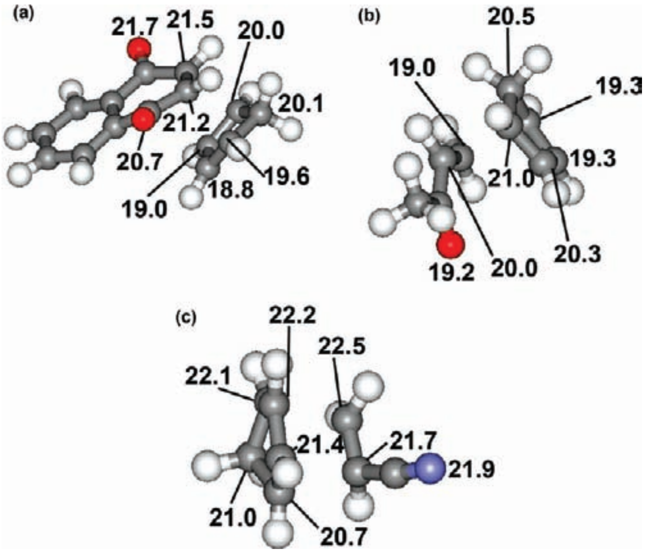

Figure 7. Transition structures for the Diels−Alder reactions with (a) 1,4-naphthoquinone, (b) MVK, and (c) acrylonitrile on the water surface. The labels give the average computed z coordinate value for the atoms from the QM/MM/MC simulations. The outermost bulklike layer of the slab is located near $z = 20$ Å, and the water density is reduced to about half the bulk value near $z = 23$ Å.

making up R_{C1} and R_{C2}, while the corresponding value for the TS is 19.8 Å. For the acrylonitrile TS (Figure 7c), the nitrile group lies more parallel to the water surface. It seems to be less effective at anchoring the TS in the surface than the carbonyl group of MVK. Analogously, the TS for the 1,4-naphthoquinone reaction is the most buried in the surface, as reflected in Figures 4 and 7. This can be attributed to the solubilizing effects of the two carbonyl groups. A related consequence is that the water surface is computed to be more catalytic for the Diels−Alder reaction with 1,4-naphthoquinone than for the other dienophiles (Table 2).

Conclusion

The present results provide a consistent picture. For the three Diels−Alder reactions at the vacuum−water interface, the transition structures are found to reside at the fringe of the bulk region (Figures 1, 4, and 7), while the more hydrophobic reactants favor being somewhat more elevated into the less dense regime. The hydrogen bond accepting groups of the reacting systems favor being oriented either into the water surface or parallel to it. The QM/MM simulations for the Diels−Alder reactions also find that the transition structures and activation barriers at a vacuum−water interface are intermediate between those for the gas phase and bulk aqueous solution. The results agree qualitatively with estimates of rates for the reaction of cyclopentadiene and MVK under neat, dilute aqueous, and heterogeneous aqueous conditions. For the reactions in pure water or on the water surface, preferential stabilization of the transition states through enhanced hydrogen bonding does provide rate increases in comparison to the gas phase or aprotic media. Water can be viewed as acting as a weak Brønsted acid catalyst in analogy to the well-known Lewis acid catalysis of Diels−Alder reactions. However, the stabilization is less on the water surface owing to the formation of a smaller number of solute−water hydrogen bonds in the lower density surface environment (Table 3). In the limit of zero density, there would clearly be no hydrogen bonds, hydrophobic effects, or catalysis. Thus, the present results do not support the notion that dangling OH bonds at the water surface lead to enhanced catalysis. The surface of water is not atomically sharp. It is a region ca. 5 Å thick with decreasing density and hydrogen bonding in progressing to vacuum (Figure 3). In this layer, most water oxygens and hydrogens do not have their full complement of hydrogen-bonding partners. More hydrogen bonds are not formed because it would be entropically unfavorable. Similarly, hydrogen bonding to a solute in the surface layer is less probable than hydrogen bonding to it in bulk water. These issues cannot be confidently addressed in the absence of proper configurational averaging, which is accessible through statistical mechanics simulations. An interesting corollary for the present results is the expectation that at higher protic solvent densities, e.g., under high-pressure conditions, there could be enhanced catalysis beyond that arising from the smaller volume of Diels−Alder transition states than reactants.

In summary, the present results do not ascribe the striking rate accelerations that are sometimes observed for cycloaddition reactions under heterogeneous conditions to unusual participation of water molecules on a water surface. The present model of two isolated reactants on a water surface is found here to result in a lower degree of catalysis than would occur for the fully hydrated reactants. Additional computational and experimental studies are certainly warranted to obtain further insights. On the computational side, for example, to better represent an aqueous emulsion, similar QM/MM calculations could be executed for reactions at the interface of a biphasic water/hydrocarbon system. Also, inclusion of explicit polarization effects in the MM part of the calculations could lead to modified interactions in the asymmetric environment of an interface, though the dipole moment of water molecules is computed to decrease in approaching the surface of water.[45] Examination of the pressure dependence of catalysis in, for example, liquid water, methanol, and hexane would be interesting, and further consideration of the possible role of interfacial hydronium ions is also warranted.

Acknowledgment. Gratitude is expressed to the National Science Foundation (Grant CHE-0446920) and National Institutes of Health (Grant GM32136) for financial support and to Profs. R. Breslow, R. A. Marcus, and K. B. Sharpless for helpful discussions. Receipt of a preprint on related studies for an aromatic Claisen rearrangement is also appreciated.[46]

JA909740Y

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