On the Theory of Organic Catalysis “on Water”

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Abstract: A molecular origin of the striking rate increase observed in a reaction on water is studied theoretically. A key aspect of the on-water rate phenomenon is the chemistry between water and reactants that occurs at an oil—water phase boundary. In particular, the structure of water at the oil—water interface of an oil emulsion, in which approximately one in every four interfacial water molecules has a free (“dangling”) OH group that protrudes into the organic phase, plays a key role in catalyzing reactions via the formation of hydrogen bonds. Catalysis is expected when these OH’s form stronger hydrogen bonds with the transition state than with the reactants. In experiments more than a 5 orders of magnitude enhancement in rate constant was found in a chosen reaction. The structural arrangement at the “oil—water” interface is in contrast to the structure of water molecules around a small hydrophobic solute in homogeneous solution, where the water molecules are tangentially oriented. The latter implies that a breaking of an existing hydrogen-bond network in homogeneous solution is needed in order to permit a catalytic effect of hydrogen bonds, but not for the on-water reaction. Thereby, the reaction in homogeneous aqueous solution is intrinsically slower than the surface reaction, as observed experimentally. The proposed mechanism of rate acceleration is discussed in light of other on-water reactions that showed smaller accelerations in rates. To interpret the results in different media, a method is given for comparing the rate constants of different rate processes, homogeneous, neat and on-water, all of which have different units, by introducing models that reduce them to the same units. The observed deuterium kinetic isotope effect is discussed briefly, and some experiments are suggested that can test the present interpretation and increase our understanding of the on-water catalysis.

1. Introduction

A key underlying feature of a critical role of water in biological and other systems1–3 is the hydrogen bond (H bond) that water molecules form among themselves in a largely tetrahedral manner.4–6 This property of water, on the other hand, often makes water of less use for organic synthesis, either because the oxygen of a water molecule is a relatively reactive moiety that can undergo unwanted reactions with some organic reactants, or because most organic compounds that are nonpolar are not easily soluble in water. Traditionally, therefore, most organic reactions have been conducted in polar or nonpolar organic solvents.3

This notion of using organic solvents for organic reactions arising mainly from the reactivity and solubility considerations, however, has been modified by the discovery of the effect of water as a solvent by Rideout and Breslow in 1980.8 They observed significant rate acceleration of Diels—Alder reactions between nonpolar compounds in homogeneous aqueous solutions, when compared with the same solvent-free (or “neat”) or organic solvent-based reactions. Many more experiments have been reported since then for other types of organic reactions that were accelerated in water.9–15 A high endo selectivity of certain Diels—Alder reactions was also obtained using water as a reaction medium.16–19 While most of these aqueous organic reactions were performed in a homogeneous solution, there were also some early reports that rate accelerations could be achieved in the form of aqueous suspensions as well.16,18 Breslow and co-workers observed a moderate decrease by a factor of 3 in reaction time, e.g., 10–15 min versus 35–40 min, for the

Diels–Alder reaction of cyclopentadiene with butenone (Scheme 1) in aqueous suspensions relative to the neat reaction.16

Considerable efforts have been directed at understanding the physical nature of the rate acceleration of homogeneous water-based reactions. Hydrophobic hydration was proposed as a possible acceleration mechanism since that effect often offers more favorable environment for the transition state (TS) relative to the reactants due to increased polarity or decreased molar volume at the TS.8,10,20–24 Also, enhanced H-bonding in the transition state compared to that in the reactants,20–29 the high cohesive energy density of water,15,30 and enforced hydrophobic interactions21,22 were considered as a possible source of rate increase for homogeneous aqueous reactions.13 For example, Jorgensen et al. performed ab initio calculations for the aqueous Diels–Alder reaction in Scheme 1 by using one explicit water molecule.26 They estimated a barrier lowering of 3–5 kcal/mol due to the multiple H-bonds (2–2.5 H-bonds) formed between butenone and water.25,26 This result was in good agreement with experiment where a reduction of activation free energy was determined to be 4 kcal/mol in water relative to isooctane.3 This H-bond-mediated barrier lowering is also similar to the manner in which Lewis acids catalyze Diels–Alder reactions.31–33

Recently, Sharpless and co-workers showed that for a different reaction the direct time for a heterogeneous mixture of reactants and water is dramatically even shorter than that of the same homogeneous solution of reactants in water, by a factor of 300.34 For the [2σ + 2σ + 2σ] cycloaddition reaction of quadricyclane (4) with dimethyl azodicarboxylate (DMAD) (5) to yield 1,2-diazetidines (6) (Scheme 2), they observed a reduction in reaction time from 48 h to 10 min by changing the reactants from solvent-free to emulsion conditions. The aqueous organic emulsions were prepared by vigorously stirring the reaction mixture. They estimated a barrier lowering of 3 kcal/mol in water relative to isooctane.8

It is still unclear and is the topic that we pursue in the present article.

To explain the large acceleration of the heterogeneous on-water reaction for the reaction in Scheme 2, one needs to invoke the interfacial nature of on-water reactions.34,37 Since the molecular composition inside an organic droplet suspended in water can be thought of as being the same as that of the neat reaction, namely pure reactants in the absence of water due to the low solubility (almost zero) of reactants in water, the difference in kinetics for the neat and on-water reactions can be described as follows.

As will be shown later, this factor of 300 reduction in reaction time translates into a catalytic factor of $1.5 \times 10^5$ in terms of rate constants. The reaction in Scheme 2 also took 4 h in a homogeneous solution when a methanol/water mixture was used as solvent.34 The fact that aqueous reactions, both homogeneous and heterogeneous, are faster than the neat reaction suggests that hydrophobic aggregation of reactants is not the most important factor because the reactants under the neat environment are already in their highest local concentrations possible. In addition to the increase in reaction rates and/or yields, high stereo- and regioselectivity were also obtained with high yields for asymmetric aldol15 and cycloaddition36 reactions by performing emulsion reactions on water. One practical advantage of using on-water reactions in terms of synthetic chemistry, it was noted,34 is that high concentration of reactants can be used for preparative purposes, unlike aqueous homogeneous reactions that are usually performed in dilute solutions because of the low solubility of many organic reactants in water. Other advantages of on-water reactions include the safety and almost zero cost of water relative to organic solvents, and the ease of product isolation.34
be attributed to the reactions that occur at the extensive oil—water interfaces of oil (reactants) droplets. In other words, a key to understanding the rate acceleration of on-water reactions may lie in the unique chemistry between water and reactants that occurs at an oil droplet—water phase boundary.

Interfacial structures of water, in particular those of hydrophobic water surfaces, have been studied extensively, both experimentally and theoretically. Pioneering sum-frequency generation (SFG) studies by Shen and co-workers provided the first experimental molecular picture of the hydrophobic surface structure of water. The authors showed that about 25% of surface water molecules at the hydrophilic interface have one dangling OH group, i.e., an OH group of water that is not H-bonded, protruding into the hydrophobic phase while the other OH group of the same water molecule is still H-bonded to other water molecules.

We also note that this interfacial structure of liquid water is similar to the (0001) basal plane of hexagonal ice Ih surface that has 0.25 monolayer of dangling OH groups, perhaps not surprisingly because the hexagonal basal plane is the surface configuration that maximizes the number of water—water H-bonds given that molecules at the topmost surface layer cannot complete tetrahedral structure. The resulting surface density of free OH groups is roughly $2.8 \times 10^{14}$ cm$^{-2}$, similar to the dangling OH density at the aqueous hydrophobic interface ($2.5 \times 10^{14}$ cm$^{-2}$) estimated by Shen et al. In fact, such an ice surface is believed to catalyze some important atmospheric reactions through its surface dangling OH groups in stratospheric cloud particles. One example is a reaction thought to be an important step for the ozone depletion, the adsorption of chlorofluorocarbons (CFCs) or HCl on ice via H-bond formation with dangling OH groups, which produce molecular chlorines that eventually decompose the ozone molecules.

In the present paper, we explore the possibility that the hydrophobic-mediated barrier lowering as in the ice catalysis might be the key to understanding the fast kinetics of on-water organic reactions. As a starting point to understand more complicated on-water reactions under various conditions, we focus mainly on the cycloaddition reaction in Scheme 2, since it showed the most impressive rate acceleration in the original paper. We also comment briefly on some other experimental observations where the rate enhancements were moderate.

This paper is organized as follows. We first describe a kinetic model and set up rate equations for the neat, surface, and aqueous homogeneous reactions to compare with experimental systems and with each other (Figure 1). We treat also the difference in units of all three rate constants by reducing them to rate constants which have the same units, thus permitting them to be compared straightforwardly with each other. Transition state theory estimates of the rate constants are then made for comparison with experiment. The results suggest the nature of rate acceleration for the chosen on-water reaction. Implications of the proposed rate acceleration mechanism are then discussed in light of aqueous homogeneous and other on-water reactions that showed smaller accelerations in rate. We close with some concluding remarks, in which we also propose some experiments that would test the present theoretical model and interpretation, and increase our understanding of the on-water catalysis. Computational details are described in a final section.

2. Theory

2.1. Models. We first obtain expressions for the rate equations for the neat, aqueous homogeneous, and surface reactions by reducing them to the same units using simple models. Since these reactions under different conditions have very different units, it is important to define new rate constants that have the same units.

2.1.1. Neat Reaction. For the purpose of comparing the rates for neat solution and emulsion conditions, instead of employing the standard bimolecular second-order rate constant, we define a new rate constant for the neat reaction that is cognizant of the fact that in neat solution the two reactants are already almost always nearby with respect to each other. Therefore, we define the rate constant, $k_N$, for the neat reaction as

$$\frac{d[A]}{dt} = k_N[A]Z_n n_B(t)$$

where, $[A]$ is the instantaneous concentration of A at time $t$, $Z_n$ is a bulk coordination number, e.g., $Z_n \approx 6$ for a cubic lattice model, and $n_B(t)$ is a “mole fraction” of B at time $t$.

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(42) Considering the liquidlike disordered film structure of the surface of ice, this prescribed density should be interpreted as a statistical estimate.
in terms of \([A]\) is given as

\[
n_{\text{H}}(t) = 1 - \frac{a}{b + [A]} \tag{2}
\]

where \(a = [A]_0\) and \(b = [B]_0\), initial concentrations of \(A\) and \(B\), respectively. The product \(Z_{\text{H}}n_{\text{H}}(t)\) is essentially the probability that a \(B\) is next to an \(A\) at time \(t\). Integrating eq 1 leads to an expression for \(k_{\text{H}}\) in terms of experimentally measurable quantities, namely the reaction yield as a function of \(t\).

\[
k_{\text{H}} = \frac{1}{Z_{\text{H}}t} \frac{1}{a - b} \left( b \ln \frac{[A]}{a} - a \ln \frac{[A] - a + b}{b} \right) \tag{3}
\]

In the particular condition where \(a = b\), a condition used in the cited experiments for Scheme 2,\(^{34}\) the rate constant can be simplified to be

\[
k_{\text{H}} = \frac{1}{Z_{\text{H}}t} \left( \frac{a}{[A]} - \ln \frac{[A]}{a} - 1 \right) \tag{4}
\]

If we further assume that the products \(6\) are separated from the organic phase as a viscous liquid as soon as they are formed which eventually solidify, that is if \(n_{\text{H}}(t) = 0.5\) at all times, then we have

\[
k_{\text{H}} = -\frac{2}{Z_{\text{H}}t} \ln \frac{[A]}{a} \tag{5}
\]

2.1.2. Aqueous Homogeneous Reaction. For the aqueous homogeneous reaction, we use the analogous equation that defines \(k_{\text{H}}\)

\[
-\frac{d[A]}{dt} = k_{\text{H}}[A]Z_{\text{H}}n_{\text{H}}(t) \tag{6}
\]

where \(Z_{\text{H}}\) is again the coordination number for the homogeneous reaction, \(Z_{\text{H}} \approx 6\), and \(n_{\text{H}}(t) \approx ([B]/([A] + [B] + M_0))\), in which \(M_0\) is the initial molar concentration of the solvent. For a 3:1 mixture of methanol and water, which was the solvent composition used in the homogeneous reaction,\(^{28}\) \(M_0 = 32\) M. Since 32 M \(\gg 2\) M, which is the initial concentration of \(A\), we further approximate \([A] + [B] + M_0 \approx M_0\) and we then obtain

\[
-\frac{d[A]}{dt} = k_{\text{H}} \frac{Z_{\text{H}}}{M_0} [A][B] \equiv k_{\text{H}}^\text{bi}[A][B] \tag{7a}
\]

where \(k_{\text{H}}^\text{bi}\) is the standard second-order rate constant, and is reduced to \(k_{\text{H}}\) by

\[
k_{\text{H}} = k_{\text{H}}^\text{bi} \frac{Z_{\text{H}}}{M_0} \tag{7b}
\]

Integrating eq 7 for \([A] = [B]\) yields the expression for \(k_{\text{H}}\).

\[
k_{\text{H}} = \frac{M_0}{Z_{\text{H}} t} \left( \frac{1}{[A]} - \frac{1}{a} \right) \tag{8}
\]

While an experimentally measurable constant for the aqueous homogeneous reaction is typically \(k_{\text{H}}^\text{bi}\) in \(\text{M}^{-1} \text{s}^{-1}\), the present derivation yields a \(k_{\text{H}}\) with a unit of \(\text{s}^{-1}\), the same unit derived for the neat reaction in eq 5, and for the surface reaction given below. It permits a straightforward comparison of catalytic effects of different reactions.

2.1.3. Surface Reaction. For a surface reaction occurring at an oil—water interface, we consider a case where water, in particular the dangling OH groups, participates in the reaction as a catalyst. It does so by forming H-bonds with the transition state and, in the cited example, as with a reactant such as DMAD. We consider \(A + [B\text{-water}] \rightarrow [C\text{-water}]\) as a surface reaction (assumption v below),\(^{45}\) where \(A\) and \(B\) denote, for example, quinidine (4) and DMAD (5), respectively. The molecular effect of water is included in the rate constant, \(k_s\). We then write a rate equation for the surface reaction as

\[
\frac{d[A]}{dr} = k_sN_0 \tilde{A}_s(t)Z_{\text{H}}n_{\text{H}}(t) \tag{9}
\]

where \(A(t)\) is the total number of molecules (not a concentration) of species \(A\) contained in all of the oil droplets at time \(t\), \(\tilde{A}_s(t)\) is the average number of molecules of species \(A\) on the surface of one droplet at time \(t\), \(N_0\) is the total number of droplets in the system, and \(Z_s\) is the surface coordination number. In applying eq 9, we assume for simplicity that (i) the oil droplets are composed purely of organic molecules containing no water, since the water solubility of reactants is close to zero, as in the neat condition; (ii) these droplets are spherical and have the same size with a radius of \(r\); (iii) reaction products are removed from the droplets as soon as they are formed either in the form of precipitate or as a viscous liquid, which means that the droplets shrink as a function of time; (iv) the surface coordination number, \(Z_s\), is taken as 4 by considering a simple twodimensional surface lattice; (v) the H-bond formation between the reactants (DMAD) and the surface dangling OH groups of water upon droplet formation are taken to be sufficiently rapid relative to the subsequent chemical reaction, such that the appropriate starting state is taken to be the H-bonded form of reactants, rather than a transient state that proceeds, namely the separated reactants and free OH groups. Initially we also have an assumption (vi) that the reaction on the surface of a droplet is so much faster than the neat reaction occurring inside the droplet that, to a first approximation, the disappearance rate of \(A\) depends only on the number of molecules on the surface, but later we give in eq 12 the formula to be used when this approximation is not used, e.g. when the acceleration is very modest.

For integrating eq 9, we express \(\tilde{A}_s(t)\) in terms of \(A(t)\). The \(\tilde{A}_s(t)\) and \(A(t)\) are related by the radius of a droplet at time \(t\), \(r(t)\), approximately as

\[
\frac{N_0 \tilde{A}_s(t)}{A(t)} \approx \frac{N_0^\text{bi}4\pi r(t)^2 \rho_A^{2/3}}{N_0^\text{bi}4\pi r(t)^2 \rho_A^{2/3}} = \frac{3}{r(t)\rho_A^{1/3}} \approx \frac{3}{0.8\rho_A^{1/3}} \tag{10}
\]

where \(\rho_A\) is a molar concentration of \(A\) in a droplet. We approximated the surface concentration of \(A\) to be \(\rho_A^{2/3}\). The radius \(r(t)\) is a monotonically decreasing function of time since droplets shrink. In the last approximate equality of eq 10, we have an approximation \(r(t) \approx 0.8\rho_0\), a radius of a droplet when

\[(45)\text{ We assume for the surface reaction that DMAD is always multiply H bonded to water since the free OH bonds are always available at the interface with almost zero cost. The stabilizing energy of DMAD at the water interface as a result of H bond formation with three water molecules is estimated to be } -4.4 \text{ kcal/mol at B3LYP/6-31G}^\text{**}.\]
Table 1. Experimental and Theoretical Rate Constants for the Cycloaddition Reaction of Quadricyclane with Dimethyl Azodicarboxylate (DMAD), Shown in Scheme 2, at 298 K under the Neat, Aqueous Homogeneous, and On-Water Conditions.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Neat reaction</th>
<th>Homogeneous reaction</th>
<th>Surface reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td>48 h</td>
<td>4 h</td>
<td>10 min</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>85</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Concentration (M)</td>
<td>4.5</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>k (experiments)</td>
<td>$4 \times 10^{-6}$ s$^{-1}$</td>
<td>$2 \times 10^{-4}$ M$^{-1}$ s$^{-1}$</td>
<td>0.5 s$^{-1}$</td>
</tr>
<tr>
<td>k (theory)</td>
<td>$5 \times 10^{-7}$ s$^{-1}$</td>
<td>(or $9 \times 10^{-3}$ s$^{-1}$)$^{1/3}$</td>
<td>0.2 s$^{-1}$</td>
</tr>
</tbody>
</table>

The yield was reported as “completion”, so we instead used the same yield as the on-water reaction. For a direct comparison with $k_N$ and $k_S$, the unit of the second-order rate constant for the homogeneous reaction is converted to that of the first order. See section 2.1. in Theory for details.

50% of reaction was completed, thus simplifying the integration, where $r_0$ is the radius of a droplet at time zero. According to the assumption (iii), the mole fraction of B is assumed to remain at all times as the initial mole fraction of B, $n_B(0) = (B_0)/(A_0 + B_0)$, where $A_0$ and $B_0$ are the total number of A and B molecules, respectively, at $t = 0$. Substituting eqs 9 and 10 and integrating over time yields the rate constant for the surface reaction in terms of $A(t)$:

$$k_S = \frac{1}{Z_S^d n_B(0)} \frac{0.8 r_0 p_A^{1/3}}{3} \ln \left( \frac{A(t)}{A_0} \right) \quad (11)$$

For the cited example,$^{34} A_0 = B_0$, and thus $n_B(0) = 0.5$ is then introduced into eq 11. We note that for a given total amount of reactants, the rate of surface reaction is inversely proportional to the size of droplets, since the smaller the droplet size is, the larger is the total surface area-to-volume ratio. Thereby, the first-order rate constant in eq 11 is directly proportional to the mean droplet radius.

We will term the derived rate constants $k_N$, $k_H$, and $k_S$ the intrinsic rate constants. They all have the same units, s$^{-1}$, and can be directly compared with each other.

2.2. Experimental Rate Constants. We evaluate rate constants, $k_N$, $k_H$, and $k_S$, using the reaction time data given in Table 1 taken from ref 34. To this end, we use eqs 5, 8, and 11. The results are summarized in Table 1.

In comparing the neat and the surface reactions, the water-catalyzed surface reaction is seen to be about $1.5 \times 10^5$ times faster than the neat reaction, where $r_0$ is the average initial radius of an organic droplet expressed in micrometers. The size of organic emulsions of quadricyclane and DMAD in water has not been measured experimentally. We use instead available data for a typical size of n-alkane ($n = 6$–10) oil droplets in water whose molecular dimensions are similar to those of quadricyclane and DMAD, $r_0 \approx 1 \mu m$. With this approximation, the intrinsic rate constant of the surface reaction is seen to be approximately $1.5 \times 10^5$ times that of the neat reaction. Since reducing the radius of the droplets will increase the rate of reaction by increasing the total surface area for a given amount of reactants, increasing the speed of stirring, at least up to some point, will also increase the rate of reaction by reducing the mean size of droplets. This issue can be tested experimentally by measuring the droplet size and the reaction time as a function of the stirring rate.

This 5 orders of magnitude difference in rate constants is, at first, surprisingly high, considering that the actual reaction times of the surface and neat reactions differed only by a factor of 300, namely, 48 h versus 10 min. The difference being $1.5 \times 10^5$, contrasted with 300, is understandable, however, if one considers that the amount of reactants at an interface is almost negligible in comparison to the total number of reactant molecules in a droplet. In particular, that ratio is roughly $(3)/(0.8 r_0 p_A^{1/3})$ according to eq 10, i.e., about $0.0027$ if one assumes $r_0 \approx 1 \mu m$ as above, and $p_A \approx 4.5 M$. Therefore, the reaction time of 10 min for the surface reaction needs to be corrected by this dilution factor, 0.0027, in order to yield rate of a surface reaction that is higher than that of the neat reaction by a factor of $48 h/(10 min \times 0.0027) = 1.1 \times 10^5$. The latter is close to $1.5 \times 10^5$ obtained from the kinetic model described above. The small difference is due to approximating $r(t)$ as an “average” radius $0.8 r_0$ in eq 10 for simpler integration that yielded $1.5 \times 10^5$, and also the volume to surface ratio estimated using the same “average” radius that yielded $1.1 \times 10^5$.

Since $k_S$ is larger than $k_N$ by a large factor, $1.5 \times 10^5$, it is a good assumption that any reaction occurring inside the droplets that is essentially a neat reaction does not contribute to the overall rate of reaction for emulsions. Removing that approximation, in fact, changes the value of $k_S$ by less than 0.2%, when one uses a more complete expression

$$- \frac{dA(t)}{dt} = k_S N_d A_S(t) Z_A n_B + k_N [A(t) - N_d A_S] Z_N n_B \quad (12)$$

The term “surface reaction” for the on-water reaction is thus quite appropriate. For on-water reactions where the rate acceleration is minor, reactions inside a droplet become important, and eq 12 is thus more appropriate to use than eq 9.

The rate constant of the aqueous homogeneous reaction is also increased substantially compared to that of the neat reaction, by approximately a factor of 200 (Table 1). This result is close to what Rideout and Breslow observed for the reaction of cyclopentadiene with butanone (Scheme 1), in which they measured the rate constants: The rate constants for the reaction in water was about 700-fold faster in a dilute aqueous homogeneous solution than in isooctane. This aqueous homogeneous reaction rate constant, however, is still far less than that for the surface reaction, by a factor of 600, when compared on the same basis according to eq 8. This large difference between $k_S$ and $k_N$, both of which contain catalytic water molecules, suggests that the particular nature of neighboring water (OH protruding versus lying flat) plays an important role in the observed acceleration of an on-water reaction at the interface.

2.3. Transition State Theory. We calculate theoretical rate constants using an approximate transition state (TS) theory. In eqs 1 and 9, $k_N$ and $k_S$ were defined as the first-order constant of reaction since the two reactants are always nearby ready to form a transition state. In applying a TS-type theory description,

(49) If emulsifiers such as surfactants are used, smaller droplets can be obtained with a radius of ~0.1 µm. Without emulsifiers, the size of n-alkane droplets, $n = 6$–16, is on the order of micrometers.
where \( k \) corresponds to the vibrational frequency of the mode that becomes a translation in the TS and leads to the reaction, \( \nu \) is the ratio of partition functions of vibrations of the TS that were originally rotational partition functions of the reactants (\( \rho \) is thereby the TS form of a steric factor), and \( \Delta E^a \) is the activation barrier at zero temperature. For an aqueous homogeneous reaction that has a second-order rate constant as defined in eq 7a, a method is given below to reduce it to the first-order TST expression.

### 2.3.1. Neat Reaction

We consider first the neat reaction. We use a typical frequency \( 10^{13} \text{ s}^{-1} \) for \( \nu \). For a steric factor, \( \rho \), we approximate it by taking the typical values of vibrational and rotational partition functions, namely 1 for each vibrational mode and 10 for each rotational degree of freedom. It gives a steric factor \( p = \frac{10^3}{10^1 \times 10^3} = 10^{-3} \), given the three rotations of each reactant, a total of six coordinates, go over to three rotations and three vibrations of the TS. The activation barrier, \( \Delta E^a \), is determined using ab initio quantum chemistry calculations as 22 kcal/mol, where the reaction goes by a stepwise biradical mechanism (see the Computational Details section). Combining these values, we obtain the TST estimate of rate constant for the neat reaction as \( k_{TST}^{\text{neat}} \approx 5 \times 10^{-3} \text{ s}^{-1} \).

### 2.3.2. Surface Reaction

We next use an analogous TST expression for the surface reaction, but taking into account that the surface reaction involves a catalyst, namely the unbounded OH groups of interfacial water molecules protruding into the organic phase. The effect of these water molecules is reflected in value of the rate constant \( k_8 \), as defined in eq 9. To use eq 13, we need to take into account the water involvement via the H bond formation to the TS. To this end, we make the following assumptions to simplify the treatment in this initial study.

For simplicity, we assume that the structure of interfacial water molecules does not change significantly during the reaction between reactants and TS, so that the net effect of water is mainly energetic. Thereby, it is assumed that the catalysis does not involve significant surface reconstruction. We consider the case where the reactant B (DMAD) and the transition state A\( ^* \) are H-bonded to the surface water molecules. Three rotational degrees of freedom of A are then lost in forming the TS. On the basis of this assumption, the steric factor is approximately \( p \approx 10^{-3} \). An activation energy is estimated using three water molecules as a simple model to account for the energy effects of water, and the quantum chemistry calculations yield a barrier 15 kcal/mol (see Computational Details). In the presence of water, a shallow well representing the biradical intermediate disappears, unlike the calculated case of the neat reaction, making the reaction mechanism concerted. However, whether the on-water reaction goes by a shallow biradical intermediate or by a concerted pathway is not essential for our analysis, since the second step, even if it exists, is not rate determining as shown in Figure 2; thus, the acceleration on water applies to both mechanisms. Similarly, kinetic derivations and approximations presented in the previous sections do not assume any such details of the reaction mechanism. Introducing these quantities into eq 13, theoretical rate constant for the surface reaction, \( k_{TST}^{\text{surf}} \approx 0.2 \text{ s}^{-1} \), is estimated.

### 2.3.3. Aqueous Homogeneous Reaction

In the case of the homogeneous reaction where the reactant concentrations are relatively low compared to those in the neat or surface reactions, second-order rate constants, \( k_{H}^{\text{HOM}} \), are typically measured experimentally for bimolecular reactions. For comparing with the neat and surface reaction rate constants, we reduce it to the first-order TST expression, \( k_{H}^{\text{TST}} \), using the following treatment:

\[
k_{H}^{\text{HOM}} = K_{H}^{\text{HOM}} = K_{H}^{\text{TST}}
\]

where, \( l = \mu \sigma \) is the moment of inertia of the TS complex, \( \sigma \) being the approximate center-to-center distance between the two reactants in the TS. The \( K_{H}^{\text{HOM}} \) is an “equilibrium constant” to form a “neighboring complex” from the separated reactants, and \( K_{H}^{\text{TST}} \) is a “unimolecular” rate constant that yields the products from the nearby reactants. In eq 15 for \( K_{H}^{\text{HOM}} \), three translations in the center of mass system of coordinates have become two rotations of the collision complex and one vibration of that complex. The \( K_{H}^{\text{TST}} \) can then be evaluated using eq 13 in an analogous way to the neat and surface reactions. The \( K_{H}^{\text{TST}} \) is seen in eq 15 to equal a bimolecular collision frequency, \( (\sqrt{8\pi k_{B} T/\mu}) \sigma^{2} \), divided by the vibration frequency \( \nu \) in the complex. In an approximate expression of \( K_{H}^{\text{TST}} \) in eq 15, we focused only on the reactants that are approaching and neglected the solvent degrees of freedom. If, as before, three rotations are lost in forming the TS from the neighboring reactants, the rate expression yields a steric factor \( p \approx 10^{-3} \). An activation barrier for the homogeneous reaction is approximated as 19 kcal/mol, which is based on the surface reaction barrier and a semiquantitative argument for the H-bond energy of water given in the next section. A theoretical estimate of the homogeneous reaction

\[
K_{H}^{\text{TST}} \approx \frac{k_{B} T}{h} \frac{1}{(2\pi k_{B} T)^{3/2}} \left( \frac{2\pi k_{B} T}{h^2} \right)^{1/2}
\]

quantities into eq 13, theoretical rate constant for the surface reaction, \( k_{TST}^{\text{surf}} \approx 0.2 \text{ s}^{-1} \), is estimated.
of interfacial water molecules than does the reactant DMAD. While there are two H-bonds between DMAD and three water molecules, there are approximately three H-bonds in TSw (Figure 3). Therefore, it is the difference in extent of the H-bonding for reactants and TS that reduces the barrier and accelerates the surface reaction, according to the present model.

The theoretical estimate of the $3 \times 10^5$-fold increase in rate due to the H-bond-mediated reduction in barrier height is close to the experimental result, $1.5 \times 10^5$ in Table 1. We note again that, depending on the actual size of organic droplets used in experiments, the difference between theory and experiments can also change. It is, nonetheless, interesting that the calculated surface activation barrier using a three-water model, 15 kcal/mol, is close to the empirical Arrhenius activation parameter, 12 kcal/mol, determined from the kinetic measurements at two different temperatures. 34

In experiments, adding methanol to the on-water reaction up to a 1:1 composition of methanol/water did not change the reaction time of on-water reactions, completing the reaction for Scheme 2 also in 10 min. This result suggests that the structure of dangling OH groups of interfacial water and their surface coverage may not be perturbed significantly by methanol.

### 3.2. Aqueous Homogeneous Reaction

The H-bond-mediated barrier lowering is a key aspect of the on-water acceleration, relative to the neat reaction. It suggests that the same mechanism may be in operation in the homogeneous reaction because it also contains water. In fact, previous studies indicated that the H-bond is one of the key factors responsible for the rate acceleration of some organic reactions in aqueous solution. 20–23,26–28 As such, our results that the rate constant for the reaction in Scheme 2 is about 200-fold higher in water compared with that of the neat reaction can also be interpreted in terms of the H-bond with water.

This qualitative interpretation, however, requires some explanation as to why the surface reaction is still considerably more efficient than the aqueous homogeneous reaction when both reactions contain the same catalyst, water molecules. To address this question, we focus on how water molecules are arranged or structured around hydrophobic molecules in homogeneous solution and in emulsions.

Organic emulsions in water can be viewed as exhibiting an extreme case of hydrophobic hydration of organic compounds with the interface formed in addition, to minimize the overall free energy. The structure of water molecules surrounding an emulsion droplet is very different from the hydration structure of water in the immediate vicinity of simple hydrophobic solutes: In aqueous methanol solution, water molecules around a methane molecule in the first hydration shell are tangentially oriented with respect to the methane hydrophobic sphere, inferred from neutron diffraction data. 54–56 The same behavior occurs for aqueous ethane and n-butane solutions. 56,57 Simulations have been made for small-to-medium-sized hydrocarbons up to octane, and indicate that the structure of water around the solute is perturbed only in a minor way from the structure in the absence of the solute. 58 That is, H-bonding

---

### Table 2. Atomic Charges, in Units of e−, Determined from the Natural Population Analyses

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>N2</th>
<th>O1</th>
<th>O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>reactant DMAD (S)</td>
<td>−0.17</td>
<td>−0.17</td>
<td>−0.58</td>
<td>−0.58</td>
</tr>
<tr>
<td>transition state (TS1)</td>
<td>−0.23</td>
<td>−0.31</td>
<td>−0.64</td>
<td>−0.63</td>
</tr>
</tbody>
</table>

* a At the UB3LYP/6-31+G* level. b See Figure 3 for atomic notations.

---

### Figure 3.

Structures for the reactants, transition states, and intermediates with and without water molecules, shown at the bottom and top panels, respectively. Distances are in Å. See also Figure 2. Red spheres denote oxygen atoms, blue spheres denote nitrogens, and gray spheres denote carbons.

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patterns can twist around those small hydrocarbon solutes without losing much H-bonding at the expense of entropy, maintaining overall their usual hydrogen-bonding network.\(^{(66)}\)

This finding is in sharp contrast to the structure of water at the extended hydrophobic surface, as in emulsions. There, for example, at the water/hexane interface, about 25% of interfacial water molecules lose one H-bond on average. These free, dangling OH groups at the interface are then preferentially oriented toward the oil phase (Figure 1).\(^{(38)}\)

Because the free OH group of water is essentially a catalyst of the reaction, the above structural difference of water molecules around a solvated hydrophobic solute and an extended hydrophobic interface can have significant consequences. At the emulsion interface, some OH groups are always protruding into the organic phase ready to catalyze reactions, while in the homogeneous solution, the existing H-bond network surrounding the reactant has to be broken in order for the OH bonds to become free and available for catalysis. Stronger H-bond energy of water, 5–6 kcal/mol,\(^{(5,60)}\) compared with that estimated between the reactant (DMAD) and water, 2–4 kcal/mol,\(^{(61)}\) supports that the breaking of the water–water H bond is an additional step for the homogeneous catalysis as compared with the surface reaction.

Saykally and co-workers, using the “total electron yield near-edge X-ray absorption fine structure” (TEY-NEXAFS) spectroscopy, recently suggested that the average thermal (activation) energy required to break a hydrogen bond in a strongly H-bonded domain in ice or liquid water is about 1.5 ± 0.5 kcal/mol.\(^{(62)}\) The hydrogen bonds around the hydrophobic surface are weaker than those in the bulk water,\(^{(63)}\) and we will assume ~1 kcal/mol as an average energy to break a hydrogen bond of water around a hydrophobic solute.\(^{(64,65)}\)

From the analysis of the three-water molecule model we used, there is approximately one more H-bond in the TS than in the reactants for the surface reaction (Figure 3). We then assume that, for the homogeneous reaction, there are about four additional H-bonds forming in the TS relative to the reactants, because along the DMAD backbone chain, there are four sides of nitrogens and carbonyl oxygens that are accessible to water molecules, top, bottom, left, and right.\(^{(66)}\) If the catalytic effects of water were similar for both the homogeneous and surface reactions in lowering the barrier,\(^{(67)}\) very crudely, 4 kcal/mol would be the extra energy that the aqueous homogeneous reaction would pay in order to make use of that catalytic ability of water, by breaking four existing H-bonds. This additional energy amounts to a factor of \(e^{4/k_B T} \approx 900\) in terms of relative kinetics at room temperature. This crude estimate is close to the experimental difference in intrinsic \(k_s\) between the homogeneous and surface reactions, a factor of 600 in favor of the surface reaction, assuming roughly similar entropic effects of water for the homogeneous and surface reactions.

Cartoons that summarize the on-water catalysis as compared to the neat and aqueous homogeneous reactions are given in Figure 1.

3.3. On-Water Reactions That Are Less Accelerated. The reduction in reaction time for a case of the most accelerated on-water reaction, the cycloaddition reaction in Scheme 2, by Sharpless and co-workers was 300-fold relative to that of the neat reaction. All other on-water reactions studied by Breslow et al.\(^{(68)}\) and Narayan et al.\(^{(69)}\) typically showed a 1- to 5-fold decrease in reaction time relative to that of the neat reaction. Those reactions that are less accelerated include the Diels–Alder (Schemes 1 and 3) reactions, and the H-transferring reactions, ene (Scheme 4), and nucleophilic opening of an epoxide (Scheme 5) reactions.

In understanding the relatively slower (but still faster than the neat reaction) on-water kinetics for the reactions in Schemes 1 and 3–5 in comparison with those of the reaction in Scheme 2, our analyses in the preceding sections suggest that the relative interfacial H-bonding ability of the TS and the reactants is a key factor. Every reaction in Schemes 1 and 3–5, however, is a special case, electronically or mechanistically, which requires detailed calculations for individual reactions. In particular, the reactions in Schemes 4 and 5 involve an H-atom transfer, and

\(\text{Scheme 3. Diels–Alder Reaction of trans,trans-2,4-Hexadienyl Acetate (7) with N-Propylmaleimide (8)}\)

\[\begin{align*}
\text{Me} & + \begin{array}{c}
\text{N} \\
\text{OAc}
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{Me}
\end{array}
\end{align*}\]

\(\text{Scheme 4. Ene Reaction of Cyclohexene (10) with Bis(trichloroethyl) Azodicarboxylate (11) with an H-Transfer Involved}\)

\[\begin{align*}
\text{Cl}_2\text{C} & + \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{Cl}_2\text{C} \\
\text{O}
\end{array} \begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\end{align*}\]

\(\text{Scheme 5. Reduction of 2,4-Dinitrophenylhydrazines (12)}\)

\[\begin{align*}
\text{Cl}_2\text{C} & + \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{Cl}_2\text{C} \\
\text{O}
\end{array} \begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\end{align*}\]
so have an aspect which makes their interpretation more complicated. We consider here only the other reactions (Schemes 1 and 3) that do not involve H-atom transfer. We focus on their relative ability to form interfacial H-bonds in the TS and in the reactants, as compared to the reaction in Scheme 2. All three reactions in Schemes 1–3 have carbonyl groups, but a key difference is that, in Schemes 1 and 3, a C–C bond is formed, while in Scheme 2, a N=N bond is activated. This comparison suggests that a more polar tertiary nitrogen that appears at the TS in Scheme 2 is an important player in the on-water kinetics because it can form stronger H-bonds with water relative to the reactants at the interface. In contrast, carbons do not form H-bonds with water both in the reactants and in the TS, and thereby the on-water rate acceleration is expected to be relatively small, if the remaining effects are small or similar. Our preliminary calculations using the same computational methods and the same water surface model on a reaction similar to that in Scheme 2, in which the N=N bond in DMAD is replaced by a C≡C bond, as in Jones et al.,68 indeed suggest that a reaction with the latter compound exhibits only a minor barrier lowering as a result of the surface H-bond interactions, 0.4 kcal/mol, instead of the 7 kcal/mol calculated for DMAD. An experimental study of the cycloaddition reaction of quadiycyclene with dimethyl acetylenedicarboxylate on water would be a useful test of this prediction. Thus far, the reaction has been studied in organic solvents,69 but not on water.

We note in passing that, although the decrease in reaction times on water for the four reactions in Schemes 1 and 3–5 was only a factor of 1 to 5 relative to that of the neat reaction, rate acceleration in terms of rate constant is a factor of ~1000 for the given droplet sizes. For example, applying the same experimental kinetic model developed here to the ene reaction in Scheme 4, i.e., using eqs 5 and 12 as a first approximation, yields an intrinsic rate constant of surface reaction of about 6000 M\(^{-1}\)s\(^{-1}\) for the given droplet sizes. It lowers the activation barrier and so enhances the reaction time recently observed for an aqueous emulsion reaction,34 it is suggested that the dramatic on-water acceleration is due mainly to the ease of free OH groups of interfacial water molecules to form H bonds with the H-bond-accepting groups in the TS compared with that in the reactants. It lowers the activation barrier and so enhances the rate. A rate constant increase of roughly 1.5 \(\times 10^3\)-fold was estimated for the on-water cycloaddition reaction shown in Scheme 2.

In contrast to the heterogeneous on-water reaction, a moderate decrease in reaction time was observed experimentally for the aqueous homogeneous reaction.34 It is suggested that the Alder reaction between the reactants that do not have H-bond capability is only modestly accelerated in water compared to that in organic solvents, approximately by a factor of 5 in terms of rate constants.\(^{70}\)

3.4. Comments on a Deuterium Isotope Effect. An apparent puzzle for the reported on-water reaction of Scheme 2 is a major deuterium isotope effect, where time for the DMAD + quadracyclic reaction to “completion” on-D\(_2\)O appeared to be about 4.5 times longer than the same reaction time on-H\(_2\)O.\(^{34}\) In general, a deuterium kinetic isotope effect (KIE) when a bond is broken typically yields \(kD/kH \approx 5\) to 7, and larger when there is large H-tunneling. Since the rate acceleration mechanism suggested here does not involve the breaking of any chemical bond of water, explaining such a large deuterium isotope effect remains a challenge. In a similar but slower reaction between DEAD (diethyl azodicarboxylate) and quadracyclene, rate constants were measured and showed only a minor isotope effect for on-H\(_2\)O versus on-D\(_2\)O reactions, yielding \(kD/kH \approx 1.2.\)\(^{71}\)

The latter reaction is slower and so permitted a more accurate comparison of the H/D reaction rate constants. Accordingly, further kinetic experiments on these reactions are desirable.

The above discussion of the deuterium KIE focuses on the chemical aspects. There are also potential physical factors that could differ for H\(_2\)O and D\(_2\)O that affect the droplet size and thus reaction times: the viscosity of H\(_2\)O is lower than D\(_2\)O by 25%.\(^{72}\) The higher viscosity would mean more “friction” on the formation of organic droplets in D\(_2\)O and could change the mean droplet size as compared to those in H\(_2\)O. Measurements of the mean droplet size in the two media would address this issue. Surface tension, on the other hand, seems to be not important for the observed deuterium KIE, since H\(_2\)O and D\(_2\)O have an almost identical surface tension within the experimental error.\(^{73}\)

4. Conclusions

A molecular origin of the factor of hundreds in decrease in reaction time recently observed for an aqueous emulsion reaction, the “on-water” reaction by Sharpless and co-workers,\(^{34}\) can be understood by combining structural information for a water surface and electronic structure calculations. Approximate kinetic models and transition state theory suggest that the dramatic on-water acceleration is due mainly to the ease of free OH groups of interfacial water molecules to form H bonds with the H-bond-accepting groups in the TS compared with that in the reactants. It lowers the activation barrier and so enhances the rate. A rate constant increase of roughly \(1.5 \times 10^3\)-fold was estimated for the on-water cycloaddition reaction shown in Scheme 2.

In contrast to the heterogeneous on-water reaction, a moderate decrease in reaction time was observed experimentally for the aqueous homogeneous reaction.\(^{34}\) It is suggested that the


\(^{(71)}\) Rate constants for the cycloaddition reaction of DEAD with quadracyclene on H\(_2\)O versus on D\(_2\)O were measured to be 5.5 \(\times 10^{-3}\) and 4.5 \(\times 10^{-3}\) M\(^{+1}\)s\(^{-1}\), respectively, yielding \(kD/kH \approx 1.2\) These unpublished experimental data were kindly provided by Drs. Narayan and Sharpless from a private communication.


\(^{(73)}\) The recommended values of surface tension for H\(_2\)O and D\(_2\)O by the International Association for the Properties of Water and Steam (IAPWS) are 71.98 \(\pm\) 0.36 and 71.87 \(\pm\) 0.50, respectively (1997).
structure of water, the catalyst, near the reactants is again a key difference between the on-water and aqueous homogeneous reactions responsible for the difference in catalytic effects. While there are always some catalytic, free OH-bonds protruding into the organic phase ready to catalyze reactions in the on-water reaction, in homogeneous solution, the existing H-bond network of water surrounding the reactants has to be broken first before any significant number of OH groups become free and available for catalysis.

Since many organic reactions of different types have been performed and tested “on water” as emulsions to achieve faster kinetics, higher yields, or higher stereoselectivity since the work of Sharpless and co-workers, the details for different reactions may vary. However, the present study suggests that a key aspect of the on-water reaction that distinguishes it from aqueous homogeneous or neat reactions is the interfacial nature of on-water reactions, such as facilitated hydrogen-bonding interactions that utilize free OH groups of interfacial water molecules.

Several experiments suggested in the text can further test the present theoretical model and so increase our understanding of the on-water catalysis. We summarize the proposed experiments and the underlying principle of the catalysis here:

1. Cycloaddition reaction of quadricyclane with dimethyl acetylenedicarboxylate on water is predicted to show very little or no catalysis, and so experiments on this system would be desirable. Thus far, this reaction has been studied in organic solvents, but not on water.

2. In the paper by Sharpless and co-workers, several representative reactions on water for different classes were examined. A systematic kinetic investigation of the reactions would be useful to test further the acceleration mechanism proposed here.

3. Measurements of the mean size of organic droplets in water as a function of stirring speed will define more sharply the relationship between the rate of reaction and the size of droplet, given in eq 11. The same measurements of the droplet size in D_2O will further test the present interpretation of the observed KIE.

4. As a guiding principle, it is suggested that an on-water acceleration can be anticipated whenever the transition state is more H-bonded to the surface water than are the reactants. The presence of the “dangling OH group”, i.e. OH-bonds that protrude from the water surface toward the organic droplet, means that no OH-bonds have to be ruptured to form H-bonds with the transition state and/or the reactants.

5. Computational Details

We describe the potential energy profiles, and thereby the reaction mechanisms, for a cycloaddition reaction of quadricyclane (4) with DMAD (5) in Scheme 2, for the neat and aqueous surface conditions. Activation barriers determined here are used in calculated estimate of the rate constants for both processes using an approximate transition state theory.

Cycloaddition of DMAD to quadricyclane (Scheme 2) is formally a Woodward–Hoffmann symmetry-allowed [2σ + 2σ + 2τ] reaction. Thereby, the reaction normally would follow a concerted pathway where all the newly forming bonds are created simultaneously in a concerted way. Previous stereochemical studies of similar types of reactions between quadricyclane and alkenes supported a concerted mechanism, by showing that the cycloaddition reaction products preserved the original alkene stereochemistry. A recent computational and experimental kinetic isotopic study, however, suggested an alternative mechanism for the same systems, namely nonconcerted biradical mechanism. The authors suggested that the reaction proceeds via the formation of biradical intermediate that is rate determining, followed by relatively low-barrier fast subsequent steps. If the rate of conversion of biradical intermediates to product is faster than rotation about the newly formed single bonds in the biradicals, the nonconcerted process can also be consistent with earlier stereochemical results that led to the concerted mechanism. Our calculations also support a nonconcerted mechanism for Scheme 2 for the neat reaction, but not for the reaction in the presence of water. In the latter, a concerted mechanism is calculated.

In the present calculations, we use the spin-unrestricted DFT formalism with B3LYP functional with a moderate size basis, 6-31+G*. The theoretical method, UB3LYP/6-31G*, was shown to yield good geometries and energies for Diels–Alder cycloaddition reactions in comparison to experiments perhaps due to a fortuitous cancellation of errors between the approximate functional and a medium-sized basis set. We then added a set of diffuse functions to heavy atoms to improve the description of the H-bonding interactions. The B3LYP hybrid functional that we are using was also shown to describe H-bond interactions well in good agreement with experiments. All stationary points were characterized, whether they are minima or transition states, by computing the Hessian. A transition state yields one negative eigenvalue for the Hessian matrix, while a minimum yields only positive eigenvalues. Intrinsic reaction coordinate (IRC) calculations were performed to connect the two stationary geometries from the transition states. Energies reported are all zero-point vibration corrected using harmonic approximation. The Q-CHEM quantum chemistry package was used for all calculations.

Reaction profiles are summarized in Figure 2. In this calculation for the unsolvated reactants, the reaction occurs via the nonconcerted two-step biradical mechanism. The overall kinetic barrier for Scheme 2 is 22.2 kcal/mol, in agreement with the previous results for similar reactions with carbon analogues instead of an azo compound. We also note that this biradical mechanism has been proposed as a possible mechanism for similar cycloaddition reactions with quadricyclane from the gas phase ab initio calculations. It is notable that the reaction intermediate is a biradical species in the neat system but still quite stable, ~9.4 kcal/mol relative to the reactants. This fact that it is a biradical and is stable, the calculations can inferred from the 〈S^2⟩ = 0.92 at the M1 structure, since 〈S^2⟩ values from UB3LYP “wave functions” have been empirically related to the extent of biradical character. This observation means that, once the biradical intermediati:

ate is formed in this rate-determining step, the reverse reaction is unlikely to occur due to a high barrier (31.6 kcal/mol), and the intermediate will stabilize quickly to the product with a low barrier of 3.8 kcal/mol.

For the surface reaction, as a simple description before any more elaborate treatment is introduced, we have chosen to use a small cluster of water molecules that can span the dimension of reactants. We added three water molecules to one side of a system that can H-bond to water, i.e., near DMAD, where the water molecules are connected among themselves via H-bonds. The results are summarized in Figure 2 with solid lines. The water-involving cycloaddition reaction, unlike the neat reaction, follows a one-step concerted pathway without a biradical intermediate. In other words, about 4 kcal/mol of shallow second barrier (TS2) for the neat reaction disappears as a result of H-bonds in the presence of water. The overall activation barrier, i.e., TS1 versus TSw, is reduced by 7.5 kcal/mol in the presence of interfacial water molecules compared with the reaction in the absence of water. This result suggests that, although both the transition state (TS1) and reactant DMAD (5) are stabilized through H-bonds to surface water molecules, the transition state is a better hydrogen-bond acceptor than the isolated DMAD, whose net effect is the lowering of the transition barrier. It is supported by the atomic charge analysis described in the main text and Table 2.

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**Note Added after ASAP Publication:** The errors in Figure 1 and in the caption to Figure 3 in the version published on the Internet March 28, 2007, have been corrected in the version published March 29, 2007. The title was changed in the version published April 2, 2007.

**Supporting Information Available:** Derivation of bimolecular rate constants for the dilute and neat reactions (S1); a full list of authors for ref 83 (S2); energies and structures of the stationary geometries for the neat and surface reactions (S3,S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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