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Protruding interfacial OH groups and ‘on-water’ heterogeneous catalysis

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Abstract

The key aspect of the remarkable organic catalysis that is observed to occur at the organic/water phase boundary, the so-called ‘on-water’ catalysis (Narayan *et al* 2005 *Angew. Chem.* **44** 3275), was recently proposed to be the protruding OH groups of water molecules at the interface that interact with the transition state (TS) via hydrogen bonding and lower activation barriers (Jung and Marcus 2007 *J. Am. Chem. Soc.* **129** 5492). In particular, the cycloaddition reaction of quadricyclane (Q) with dimethyl azodicarboxylate (DMAD) on-water was calculated to be more than 100 000 times more efficient in terms of rate constant than the neat reaction. In this paper, we review and consider a related reaction of Q with dimethyl acetylenedicarboxylate, where nitrogen, a good H-bond acceptor, in DMAD is replaced by carbon, a poor H-bond acceptor. A very low rate acceleration of acetylenedicarboxylate on-water relative to the neat reaction is obtained theoretically, as compared to DMAD on-water, due to the relatively low H-bonding ability of acetylenedicarboxylate with water at the TS relative to the reactants. We suggest that there may also be an ‘intrinsic steric effect’ or orientational advantage in the on-water catalysis in general, and both electronic and steric effects may be in operation for the smaller on-water catalysis for the cycloaddition reaction of quadricyclane and acetylenedicarboxylate. A preliminary quantum mechanical/molecular mechanical (QM/MM) simulation including 1264 water molecules for the on-water reaction of DMAD + Q also suggests that there are indeed approximately two–four more H-bonds between the TS and the dangling OH groups than between the reactants and the surface.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Water is a universal medium of biological reactions, since most enzymes, except for those in the cell membranes, reside and function only in the aqueous medium [1]. Yet, water is not a commonly used reaction medium in organic chemistry since most organic compounds do not dissolve in water, and solubility is sometimes considered a prerequisite for reactivity [2]. If one can, however, bypass this solubility dilemma, water has many features that are ideal for organic synthesis. For example, water is arguably the most ‘green’ solvent of low cost, it has a high heat capacity so as to

serve as a heat dissipator for many organic reactions that are highly exothermic, and often provides the convenience of easy product isolation [3].

In a recent experiment where water was also used as a reaction medium, Sharpless *et al* [4] showed that low water-solubility of many organic molecules is not really a problem to be addressed in using water as a reaction medium, but in fact it rather helps reactions be even more accelerated or have better yields. The authors showed that the heterogeneous mixture of neat organic reactants (‘oil’) and water gives a faster reaction and/or a better yield, as compared to the dilute homogeneous system of reactants and water. In a most remarkable example of the on-water rate phenomenon, namely, a cycloaddition reaction between quadricyclane (Q) (**1**) and

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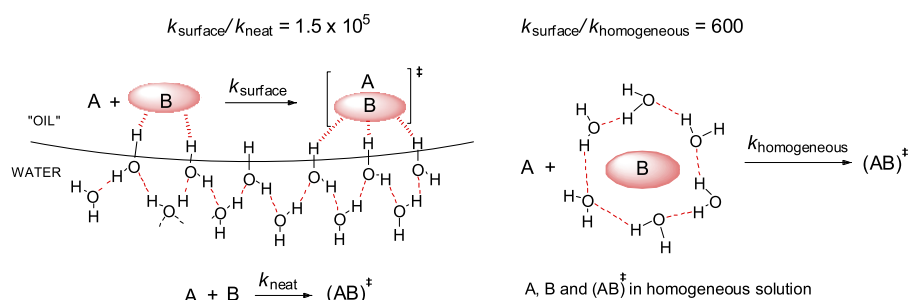


Figure 1. Summarizing cartoon of the on-water catalysis in comparison to the neat and aqueous homogeneous reactions. Reproduced with permission from Jung and Marcus [6]. Copyright 2007 by the American Chemical Society.

Table 1. Cycloaddition reaction of quadricyclane (Q) (1) with DMAD (2). Taken from Narayan *et al* [4].

1	2	3		
Solvent	Conc. (M)	Temp (°C)	Time	Yield (%)
Neat	4.53	0	2 h	0
Neat	4.53	23	48 h	85
Toluene	1	80	24 h	74
On H ₂ O	4.53	0	1.5 h	93
On H ₂ O	4.53	23	10 min	82

dimethyl azodicarboxylate (DMAD) (2) shown in table 1, the reaction time to completion was reduced substantially from two days to 10 min when the reaction condition was changed from neat (water-free) to on-water merely by adding and vigorously stirring with water. Interestingly, the same aqueous reaction that was made homogeneous by adding a co-solvent, methanol, to the on-water system, took 4 h for completion.

Both homogeneous and heterogeneous aqueous reactions in the above example are catalyzed by water molecules, in particular by OH groups of water that act like a Lewis acid catalyst in particular Diels–Alder reactions [5]. The activation barrier of the reaction in table 1 is lowered by the electrophilic DMAD forming H-bonds with water which stabilizes the transition state (TS) more than the reactants. An apparent puzzle was then, why the heterogeneous on-water catalysis is so much more efficient than the homogeneous counterpart by many orders of magnitude in the rate constant, when they both have the same catalyst, water. This intrinsic difference between homogeneous and heterogeneous catalysis arises, we proposed [6], from the different structural arrangements of water around a small hydrophobic solute (homogeneous) and at the oil–water extended interface (on-water).

In particular, for an on-water reaction, approximately 25% of the interfacial water molecules at the oil–water interface have a *free* OH group (H-bond already broken) [7] that protrudes into the organic phase that is *ready* to catalyze reactions. In contrast, in a homogeneous solution, for example for a methane molecule in water, water molecules are twisted around a small nonpolar organic solute, without perturbing

its existing H-bond network significantly, by employing a tangential orientation around the solute [8, 9]. If we extrapolated the latter structure of water molecules around a methane molecule to the small organic compounds we are treating in the present study, then a breaking of an existing H-bond network in homogeneous solution is needed in order to permit a catalytic effect of water. This ‘free’ (on-water) versus ‘non-free’ (homogeneous) utilization of the catalyst, i.e. the free dangling OH groups that are not H-bonded, is what makes on-water catalysis extremely efficient and fast as compared to the homogeneous catalysis [6]. The most dramatic example was the reaction of DMAD that accelerated by a factor of 1000 for on-water as compared with in-water. A cartoon that summarized these molecular interpretations is reproduced in figure 1.

We note in passing that it is not clear to us whether many of the arguments suggested for the limited rate acceleration of aqueous homogeneous reactions earlier in the literature [10–17] apply directly to the on-water catalysis. For example, since the reactants in an emulsion are already in their highest local concentration due to the organic phase in the emulsion itself being essentially a neat system, the hydrophobic aggregation effect [14] would not appear to contribute much to the catalysis at the oil–water interface. Also, since organic molecules at the oil–water interface are already largely desolvated, enforced hydrophobic interaction [15] due to a decreased solvent-accessible surface area during the activation process seems to be relatively unimportant on-water. The high cohesive energy density character of water [10, 18] is not expected to strongly affect the on-water catalysis rate for the same reason.

In this paper, we also consider a different reaction, a cycloaddition reaction between Q and dimethyl acetylenedicarboxylate (4). As a guiding principle, we suggested in the previous paper [6] and also above, that an on-water acceleration can be anticipated whenever the TS is more H-bonded to the surface water molecules than are the reactants. According to this rule, reaction of acetylenedicarboxylate was then suggested to be only marginally accelerated because of the replacement of the nitrogen in DMAD of table 1 (a good H-bond acceptor) by carbon in acetylenedicarboxylate (a poor H-bond acceptor) in table 3. Herein we present a detailed analysis and calculated results for that reaction in comparison with the reaction of DMAD. Some general comments on the on-water catalysis will be given in the last section.

Table 2. Experimental and theoretical rate constants for the cycloaddition reaction of quadricyclane (**1**) with DMAD (**2**) at 23 °C. Reproduced with permission from Jung and Marcus [6] (see also table 1). Copyright 2007 by the American Chemical Society.

	Neat	Homogeneous	Surface
Reaction time	48 h	4 h	10 min
k (experiments) (s^{-1})	4×10^{-6}	9×10^{-4} ^a	0.5 ^b
k (theory) (s^{-1})	5×10^{-7}	2×10^{-4}	0.2

^a 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 a first-order one. The unconverted second-order rate constant is $2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$.

^b A droplet radius of $1 \mu\text{m}$ was assumed on the basis of a typical size of n -alkane emulsions ($n = 6\text{--}16$).

2. On-water reactivity of azodicarboxylate and acetylenedicarboxylate

Dimethyl azodicarboxylate (**2**) and dimethyl acetylenedicarboxylate (**4**) are both abbreviated as DMAD in the literature. To avoid confusion, we use DMAD only to denote dimethyl azodicarboxylate (**2**), and use the full name for dimethyl acetylenedicarboxylate (**4**).

The cycloaddition reaction between DMAD (**2**) and Q (**1**) showed the most impressive rate acceleration on-water among many reactions performed on-water [4]. Experimental data due to Narayan *et al* are shown in table 1. By calculating ‘intrinsic’ rate constants in different reaction conditions [6], so reducing all rate constants in different environments (neat, surface, and homogeneous) to the same units, we deduced that the surface reaction is more efficient than the neat reaction by more than a factor of 10^5 , although the reaction time was reduced by a factor of 300 (48 h versus 10 min) by changing the reaction condition from neat to on-water. Since the amount of reactants at an interface in the typical emulsion is almost negligible in comparison to the total number of reactant molecules in an organic droplet and the interfacial reaction is so much faster than the neat reaction inside a droplet, the rate acceleration factor in the reaction time needs to be corrected for this factor. A quick rough correction is given by the surface area to volume ratio (≈ 0.0027 using equation (3), assuming a droplet size of $1 \mu\text{m}$ in radius). It yielded $48 \text{ h} / (10 \text{ min} \times 0.0027) = 1.1 \times 10^5$, which is similar to the ratio of intrinsic rate constants estimated in our more elaborate calculations (table 2). In estimating the experimental rate constants in table 2, the rate of on-water surface reaction was defined [6] as

$$R(t) = -\frac{dA(t)}{dt} = kN_d(t)\bar{A}_S(t)z_S n_B(t), \quad (1)$$

where $\bar{A}_S(t)$ is the average number of A molecules (DMAD in the present case) on the surface of one droplet at time t , $N_d(t)$ is the total number of droplets at time t , and $n_B(t)$ is the mole fraction of B (quadricyclane in the present case) in organic droplets at time t .

Such a unique reactivity of azodicarboxylate on-water, an acceleration by a factor of 10^5 , was ascribed in our publication to the enhanced H-bond interactions in the TS between tertiary nitrogens and carbonyl oxygens of DMAD with the dangling

Table 3. Calculated theoretical rate constants for the cycloaddition reaction of quadricyclane (**1**) with dimethyl acetylenedicarboxylate (**4**).

1	4	5
		Neat Surface
Activation barrier (DFT) ^a (kJ mol^{-1})		94.6 92.9
k (theory) ^b (s^{-1})		2×10^{-9} 5×10^{-7} ^c

^a Computed at UB3LYP/6-31 + $G(d)$ after the zero-point energy correction.

^b An approximate TS theory is used. See section 3 for details.

^c Depending on the surface area to volume ratio of the emulsions used in experiments, the actual reduction in reaction time for the surface reaction can be comparable to that of the neat reaction.

OH groups of water at the interface [6]. Spin-polarized density functional calculations using three water molecules confirmed this idea. In other words, due to a partially broken C–N bond at the TS, the TS is more polarized than the reactant DMAD, that is, nitrogens and carbonyl oxygens become more electronegative at the TS than in the reactants. Because H-bonding is predominantly electrostatic [1], the latter charge separation means a stronger H-bond interaction at the TS than in the reactants, overall lowering the reaction barrier.

As an extension of our previous work using three water molecules, we have performed an initial study of the same reaction using 1264 water molecules to mimic the realistic water surface. Indeed, this preliminary quantum mechanical/molecular mechanical (QM/MM) simulation including 1264 water molecules for the on-water reaction of DMAD + Q suggests that there are approximately two–four more H-bonds between the TS and the dangling OH groups than between the reactants and the surface. A more detailed free energy calculation for the latter reaction that showed the most dramatic rate acceleration is under investigation using QM/MM methods and 1264 water molecules.

One simple test of the above analysis and interpretation, namely, interfacial H-bonding of DMAD with the free OH groups of water being the key mechanism, would be to slightly modify DMAD such that it has now fewer functional groups capable of H-bonding, and see if that indeed reduces the rate acceleration on water. In this work, we examine theoretically the on-water reactivity of dimethyl acetylenedicarboxylate, in which nitrogens in DMAD are replaced by carbons. Both in the reactants and in the TS, carbons do not form H-bonds with water, and thus the on-water rate acceleration is expected to be relatively small, if the remaining effects are small or similar.

We use three water molecules to represent the water surface in the simplest model, as was also used in the previous study [6]. Spin-polarized density functional calculations (B3LYP/6-31 + G^*) were performed to determine activation barriers and the results are shown in table 3.

The reaction barrier height for the surface reaction is lowered by 1.7 kJ mol^{-1} as compared to the neat reaction, as a result of H-bond interactions of acetylenedicarboxylate

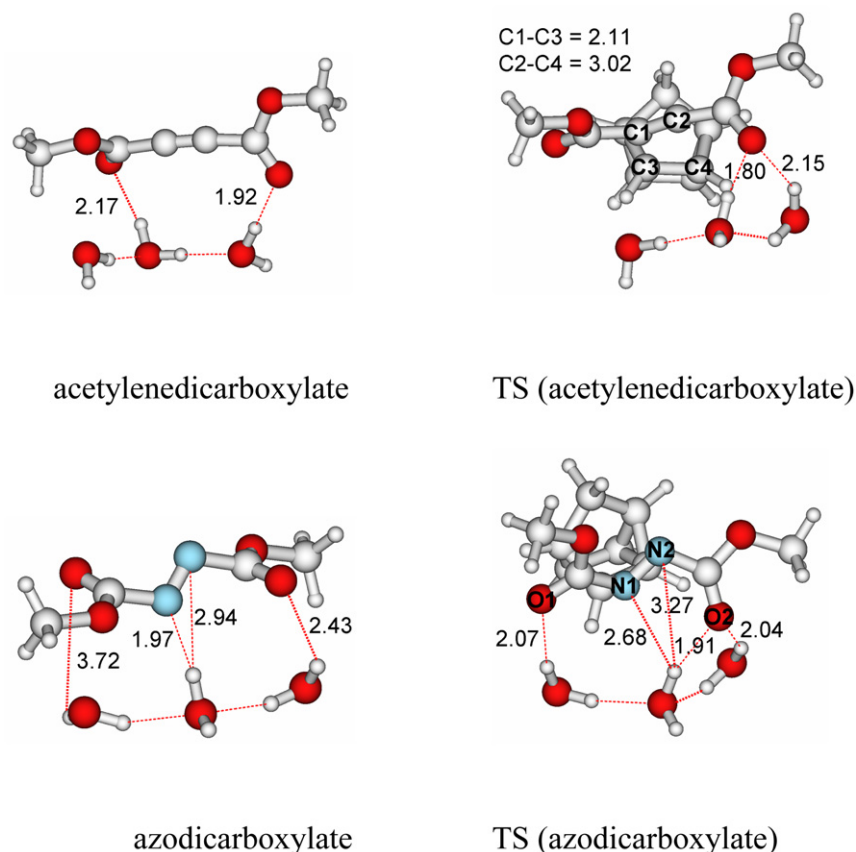


Figure 2. Lowest energy structures of the reactant and TSs for acetylenedicarboxylate (top) and azodicarboxylate (bottom). Nitrogen and oxygen are colored in blue and red, respectively, and carbon and hydrogen all in gray. Results for the azo compound are reproduced from Jung and Marcus [6].

with water. This lowered barrier then amounts to a factor of $e^{0.4/k_B T} \approx 2$ in favor of the surface reaction, in terms of the relative ‘intrinsic rate’ (rate of a neighboring pair of reactants) at room temperature, if all the remaining statistical effects are similar both in the neat and surface reactions. The latter was and is assumed in the previous and present studies. For comparison, the activation barrier for the reaction of DMAD with Q was reduced on-water by 31.4 kJ mol^{-1} as compared to the neat reaction, giving a factor of $e^{7.5/k_B T} \approx 10^5$ in relative intrinsic rates at room temperature.

H-bonded structures of acetylenedicarboxylate in the reactants and the TS are shown in figure 2. For comparison, those for DMAD are also shown in the same figure. Unlike DMAD which has roughly one more H-bond with water in the TS than in the reactants, acetylenedicarboxylate forms approximately the same number of H-bonds with water in the reactants and in the TS although more detailed calculations with additional water molecules might be helpful to determine the more realistic number of H-bonds⁵. This qualitative picture means that stabilization of the TS relative to the reactants due to water is more favorable for DMAD than for

acetylenedicarboxylate, and is consistent with the activation barriers and rates computed in tables 2 and 3.

3. Theoretical rate constants

An approximate TS theory is used to estimate rate constants. Due to the high local reactant concentrations implied in both the neat and on-water conditions, two reactants **1** and **4** in a 1:1 reaction system can be assumed to be always nearest neighbors and ready to form a TS. We then use an approximate unimolecular TS theory to describe the neat and on-water reactions.

$$k^{\text{TST}} = \frac{k_B T}{h} \frac{1}{\left(\frac{k_B T}{h\nu}\right)} p e^{-\Delta E^\ddagger/k_B T}. \quad (2)$$

In equation (2), ν is a frequency of the vibration in the reactants that becomes a translation along the reaction coordinate in the TS, p is the ratio of partition functions of vibrations of the TS to those of the rotations in the reactants that were originally rotations of the reactants (p is thereby the TS form of a steric factor), and $\Delta E^\ddagger$ is the activation barrier at zero temperature. We use $\nu \approx 10^{13} \text{ s}^{-1}$, a typical low-frequency vibration of relative motion of the reactants, and without detailed calculations, we also use approximately the typical values of vibrational and rotational partition functions, that is, 1 for each vibrational mode and 10 for each rotational degree of freedom.

⁵ Our preliminary QM/MM calculations with about 1000 water molecules for the surface reaction suggest that there are about two–three H-bonds between DMAD and the surface water molecules while there are about five–six H-bonds between the TS with interfacial water molecules. Similar calculations for acetylenedicarboxylate are in progress.

For the neat reaction, since three rotations of each reactant, a total of six coordinates, become five bending vibrations of the TS plus one rotation about the line of centers between the two reactants, an approximate steric factor p is $10/(10^3 \times 10^3) = 10^{-5}$. So, it is due to the loss of five rotational degrees of freedom during the activation process.

For the surface reaction, one of the reactants (acetylenedicarboxylate) forms approximately two H-bonds with water (figure 2) and can thus be considered as energetically anchored to the surface with all three rotational motions of the latter reactant described now as bending vibrations. The other reactant (Q) does not form H-bonds with water and can rotate freely in the reactant state. The TS of the acetylenedicarboxylate/Q complex forms about the same number of H-bonds to the surface as in the reactant, and so three rotations of this TS can also be considered as bending vibrations. Considering these rotational motions of reactants and TS, an approximate orientational steric factor p would then be $1/10^3 = 10^{-3}$. More detailed calculations with additional water molecules would be helpful to determine a more accurate number of H-bonds that acetylenedicarboxylate and TS form with the interfacial water molecules, and so provide a more refined steric factor.

Assuming the in-water reaction also has a similar number of H-bonds with the reactant acetylenedicarboxylate and the TS, rotations of both acetylenedicarboxylate and the TS are hindered rotations due to H-bonding to the water molecules and can be considered as bending vibrations. An approximate orientational steric factor p for the in-water reaction of acetylenedicarboxylate with Q would thus be $1/10^3 = 10^{-3}$, as in the on-water reaction. Here also, more detailed calculations with additional water molecules would be helpful for estimating the steric factor more accurately in a future study.

Comparing the steric factors for the neat, in-water, and on-water reactions described above, therefore, we suggest that the orientational ordering or the anchoring of the reactant and TS via multiple H-bonds with water contributes to making the in-water and on-water catalysis intrinsically more efficient than the neat reaction by approximately a factor of 100. With the latter estimate, the calculated rate acceleration of the on-water cycloaddition reaction of Q with DMAD reported in [6] can be as large as 10^7 as compared to the same solvent-free reaction, instead of 10^5 that was estimated originally.

Activation barriers, $\Delta E^\ddagger$, are determined by density functional calculations to be 94.6 and 92.9 kJ mol⁻¹ for the neat and on-water surface reactions, respectively, as mentioned in the previous section. This difference of 1.7 kJ mol⁻¹ may change if one uses more accurate electronic structure methods. Using the latter $\Delta E^\ddagger$, we obtain the TS theory estimates of the rate constants as 2×10^{-9} and 5×10^{-7} s⁻¹ for the neat and surface reactions, respectively, for DMAD (table 3). However, since the total surface area is small compared to the total number of reactants in the system, as in equation (3), the calculated intrinsic rate enhancement of the on-water reaction as compared to the neat reaction by a factor of 250 will be translated into only a modest decrease in reaction time depending on the size of emulsions. For example, if the average emulsion size were larger than 2 μ m in radius, the

surface area to volume ratio correction shown in equation (3) would suggest that essentially there is no decrease in reaction time. If the emulsion radius was smaller than 2 μ m, one might get some reduction in reaction time that is inversely proportional to r_0 , an average initial radius of emulsions.

$$\frac{4\pi r(t)^2 \rho_A^{2/3}}{\frac{4\pi}{3} r(t)^3 \rho_A} = \frac{3}{r(t) \rho_A^{1/3}} \approx \frac{3}{0.8r_0 \rho_A^{1/3}}. \quad (3)$$

In equation (3) derived in [6], ρ_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 equation (3), we have an approximation $r(t) \sim 0.8r_0$, a radius of a droplet when 50% of the reaction was completed.

4. Concluding remarks

Performing organic reactions on-water is as simple as mixing the concentrated nonpolar reactants and water (without adding any organic solvent), and stirring them until the completion, yet it has many intriguing consequences. The main focus of the present study, amongst others, was the rate-accelerating effect of water by forming emulsion with the organic reactants. In particular, in the process of forming the large ‘oil’–water interfacial areas during the vigorous stirring, the catalyst, the OH groups of water that act like a Lewis acid catalyst and form H-bonds with reactants, is arranged such that the OH groups protrude into the organic phase and are free and ready for the catalysis. These H-bonds then stabilize the TS more than the reactants, lower the activation barrier, and thus enhance the rate of reaction. A preliminary QM/MM simulation including 1264 water molecules also suggests that there are approximately two–four more H-bonds between the TS and the dangling OH groups than between the reactants and the surface. On the basis of the latter mechanism of on-water catalysis, we suggested that the cycloaddition reaction of Q with azodicarboxylate is accelerated on-water by a lowering of activation energy by 31.4 kJ mol⁻¹ as compared to the neat reaction. The latter electronic activation energy reduction corresponds to an increase in intrinsic rate constant by a factor of 10^5 [6]. By contrast, a similar cycloaddition reaction of Q with acetylenedicarboxylate treated in the present study shows virtually no activation barrier lowering due to a replacement of nitrogen, a good H-bond acceptor, by carbon, a poor H-bond acceptor.

In addition to this electronic effect of the on-water catalysis (nitrogen versus carbon), we suggest in the above analysis that there may also be an ‘intrinsic steric effect’ or orientational advantage in the on-water catalysis. Due to an anchoring of a reactant and the TS to the surface via interfacial H-bonds, formation of a TS that has a correct relative orientation of reactants becomes more facile than in the case of the neat reaction. Without the interfacial anchoring, two reactants simultaneously have to be reoriented to form a TS, but with anchoring only one of the reactants that is not anchored need to be reoriented to form a TS. If one uses 1

for each mode of the vibrational partition function and 10 for rotations, this steric effect can give a rate enhancement up to a factor of 100 in favor of the on-water reactions as compared to the neat reaction.

Additional steric effects not included above may also play a role. For example, the linear geometry of the acetylene backbone may make it harder for its ester oxygens to form favorable H-bonds with the dangling hydrogens of interfacial water than for the DMAD which is in equilibrium between *cis*- and *trans*-forms. In this regard, it would be interesting to compare the cycloaddition reaction of dimethylmaleate and dimethylfumarate, *cis*- and *trans*-olefin analogs of carbon-based DMAD, respectively, for a study of the steric effects of the on-water catalysis. This work is in progress. The cycloaddition reaction of acetylene (triple bond) is generally less reactive than that of olefin (double bond) due to a different electrocyclic chemistry.

This heterogeneous catalysis is different in a major respect from the homogeneous catalysis of water. In the latter case, that also contains the same catalyst, water, the OH groups are not free (since H-bonded to other water molecules) and they have to be ruptured before the catalysis, as judged from an extrapolation of the methane study [8, 9]. In other words, a price has to be paid for breaking the existing H-bond network of water in the homogeneous catalysis, and that price or energy is added to the activation barrier of reaction, thereby slowing down the homogeneous reaction as compared to the heterogeneous reaction. This clear distinction between the aqueous homogeneous and heterogeneous reactions has often not been made explicitly in recent literature, but appears to be a major origin of their intrinsic difference in catalytic efficiency.

This exciting on-water rate phenomenon [4], or the concept of using water such as in 'click chemistry' [19], is being explored very rapidly and found successful in organic synthesis [3], and additional detailed kinetic measurements and analysis will undoubtedly help us understand the phenomenon better and make it even more useful for industrial applications.

Acknowledgments

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