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Interfacial Catalysis

Investigation of “On Water” Conditions Using a Biphasic Fluidic Platform**

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Water is the most abundant liquid on the planet and is a unique solvent owing to the internal structure arising from the hydrogen-bond network.[1–3] It is known that water has a strong effect on the reactivity of dissolved hydrophobic organic molecules.[4–9] The rate enhancements in water have been attributed to many factors, including “enforced hydrophobic interactions”,[4–10] enhanced hydrogen bonding of the transition state,[11–14] the unusually high “cohesive energy density” of water,[15] and in more general terms to the decrease of the hydrophobic surface area of the reactants during the activation process, combined with hydrogen-bond stabilization of the polarized activated complex.[16,17] In a landmark paper, Sharpless and co-workers studied a range of reactions accelerated by water despite the non-solubility of the reactants under so-called “on water” conditions.[18] Although a large number of studies have exploited these “on water” conditions and have reported rate enhancements,[19] there is no conclusive agreement on the molecular origin of the effect. One major reason for our limited understanding of “on water” reactions lies in the very nature of the experiment; typically, “on water” reactions are carried out by vigorously stirring two immiscible phases. On a laboratory scale, the water surface area and the surface-to-volume ratio cannot be controlled reproducibly as they are strongly dependent on stirring rates, volumes, ratio of water to organic phase, and the size of both the stirrer bar and the reaction flask. The droplet sizes in the emulsions that are formed during the reaction are unknown, making any estimate of the effect of the water surface on the reaction rate an educated guess. As a result, there have been no systematic studies exploring the “on water” effect and it is still unclear how much the water surface really contributes to the measured reaction rates.

The aim of the present study is to quantify the “on water” effect per unit area of interface for the first time. We present a fluidic approach to generate precisely defined organic–water interfaces, which allows us to systematically probe the influence of the water surface on chemical reactions. Monodisperse water and organic phase plugs (typical frequencies around 0.06 Hz) are generated in polytetrafluoroethylene (PTFE) tubing by connecting an aqueous flow with an organic flow using a chlorotrifluoroethylene (CTFE) cross-junction (Figure 1 a).[20,21] This approach gives excellent control over the water surface area by changing the relative flow rates of the water and organic phase or the internal diameter of the tubing (Figure 1 b).[22,23]

Our study focuses on two model reactions: the cycloaddition of quadricyclane (**1**) and diethyl azodicarboxylate[18] (DEAD; Figure 1 c), and the ene reaction between β-pinene (**2**) and DEAD[19] (Figure 1 d). These reactions were shown by Sharpless and co-workers to be significantly accelerated under “on water” conditions.[18,19,24]

DEAD is shock and light sensitive and commercially available as a 40 wt % solution in toluene; therefore we performed all reactions in toluene and in toluene “on water”, with concentrations in the 1 M to 3 M range. Furthermore, bulk experiments showed (Supporting Information, Figure S1) that the reaction rates vary strongly during the reaction, and therefore we concentrated our studies on reactions with conversions under 10 %, where the percent conversion was linear with time. As shown in Figure 2 a, the “on water” reaction between **1** and DEAD was accelerated to 4.3 ± 0.2 % and 6 ± 0.2 % conversion after 60 min “on water” for water–organic (Q_w/Q_o) flow ratios of 1:1 (Q1) and 2:1 (Q2), respectively, compared to only 1.1 ± 0.2 % conversion in toluene. This result indicated that the reaction takes place because of the introduction of water. It should be noted that when sodium dodecyl sulfate (SDS) was added to the aqueous phase the reaction between **1** and DEAD essentially stopped, with percent conversions closer to those of the reaction in toluene only (Supporting Information, Figure S2). In contrast, we found that the “on water” effect for the reaction of **2** with DEAD is much smaller (Figure 2 b). However, the reaction was sensitive to changes in the water surface area as demonstrated by the 5 ± 0.3 % increase in conversion after doubling the water–organic (Q_w/Q_o) flow ratio, which resulted in a concomitant increase in the water–organic surface area. We determined the order of the reaction by systematically varying the concentration of each reactant between 0.5 M and 3 M (Supporting Information, Figure S3, Table S1, and Table S2). The reactions are close to first order in **1**, **2**, and

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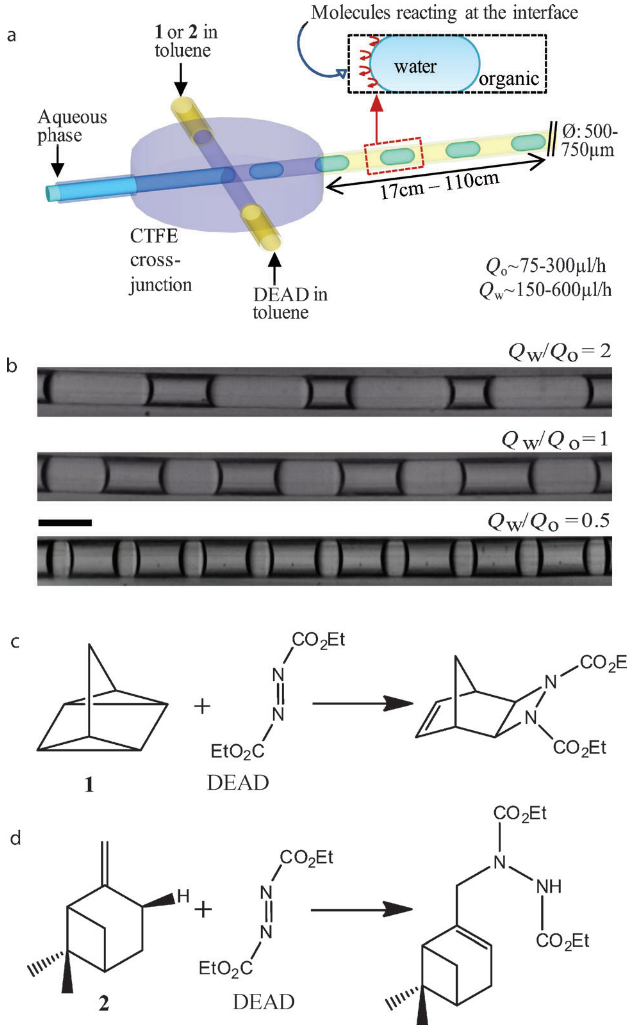

Figure 1. Experimental set up. a) Plugs form at the junction between a toluene solution containing the reagents ("organic phase") and an aqueous phase, and travel down PTFE tubing where the reaction occurs. b) Plug size and water surface area can be controlled by varying the relative flow rates of the two phases. Images taken from a fast camera were analyzed with Matlab software to calculate plug lengths, volumes, and surface areas. Model reactions selected for this study: c) the cycloaddition of quadricyclane (**1**) with DEAD and d) the ene reaction between β-pinene (**2**) and DEAD. Scale bar = 250 μm.

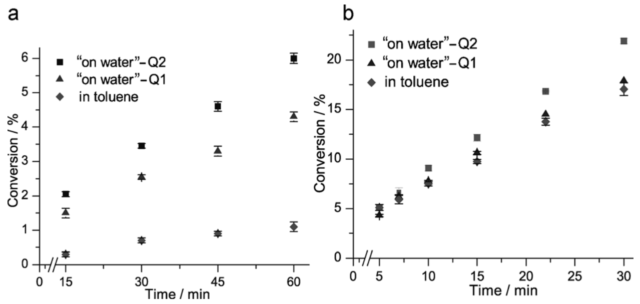

Figure 2. Influence of water on the percent conversion for model reactions in toluene and "on water". a) The reaction between **1** and DEAD under different water–organic flow ratios ($Q_w/Q_o = 1 = Q1$, $Q_w/Q_o = 2 = Q2$). b) The reaction between **2** and DEAD under the same water–organic flow ratios. Note: fits of these data would not pass through the origin because there is a lag between sampling and ^{1}H NMR acquisition.

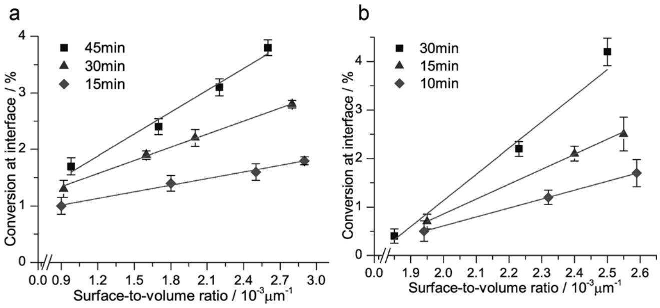

Figure 3. Influence of the surface-to-volume ratio on the percent conversion of a) **1** or b) **2**. Note: "Conversion at interface" indicates that the "on water" percent conversions have been corrected for the conversion that takes place in the toluene phase.

DEAD, confirming that both reactions are simple bimolecular reactions. As expected for a non-acid–base-catalyzed reaction, we measured small kinetic solvent isotope effects in the range of $k_H/k_D \approx 1.1$ to 1.2 for both reactions, independent of the flow ratios (Supporting Information, Figure S4).

Our fluidics platform allows a systematic variation of the surface area available to the reacting molecules while keeping all other parameters constant. To probe directly the effect of the water surface, we measured percent conversions at three different reaction times, while varying the surface-to-volume ratio by changing the water- and organic-phase flow rates and using 500 or 750 μm internal diameter (Ø) tubing (Figure 3). The water surface area was calculated as the hemispherical cap of the water meniscus (Supporting Information, Figure S5).[25–29] As shown in Figure 3, there was a linear relation between surface area and percent conversion, which implies that the contact between the organic and the water phases was directly involved in the measured rate enhancements. For a constant initial concentration of DEAD (2 M), we increased the concentration of **1** and **2** from 2 M to 10.5 M and 6.4 M, respectively (close to neat conditions). As expected, the increase in concentration led to an increase in reaction rates for the reactions in toluene (Supporting Information, Figure S6). Unexpectedly, the "on water" reaction did not show a similar dependence of rate enhancement on starting material concentration. The "on water" reaction of DEAD with **1** (10.5 M) was accelerated almost threefold, whereas the reaction of DEAD with **2** (6.4 M) was slowed down threefold, both compared to the reaction rates at 2 M starting concentration (as estimated from initial reaction rates). These results strongly suggest that the reaction with **1** was limited by diffusion of reagent molecules to the surface. For the reaction with **2**, we think that the reaction products remain at the interface, preventing the water surface from catalyzing further reactions. This accumulation of product results in a decreased reaction rate at higher concentrations of reactants or prolonged reaction times.

Because we knew the percent conversion at a certain reaction time and the total area of interface associated with

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this reaction, we could calculate the number of molecules reacted per unit surface area per unit time (i.e. a turnover number; see Supporting Information, Table S3). Surprisingly, for both reactions the turnover number decreased 11–14% over the course of 15 minutes. This result indicates that the interfacial activity decreases over time and could explain why it is sometimes difficult to reproduce "on water" conditions in stirred bulk emulsions, where fresh water–organic interface is continuously generated. We used Arrhenius plots to determine the temperature dependence of the reaction rates for both reactions "on water" and in toluene (Supporting Information, Figure S7). Equation (1), where k is the rate

$$\ln k = \ln A - \frac{E_a}{R}\left(\frac{1}{T}\right) \qquad (1)$$

constant, A the pre-exponential factor, and R the gas constant, was used to determine the activation energy E_a.

Table 1: Activation energies and rate constants for the reaction between DEAD and **1** or **2**.

Reaction	E_{aS}[a,b] [kcal mol^{-1}]	E_{aT}[b] [kcal mol^{-1}]	ΔE_a [kcal mol^{-1}]	$k_{s,cal}$[b] [L mol^{-1} s^{-1}]	$k_{T,cal}$[b] [L mol^{-1} s^{-1}]	$k_{s,obs}$[b] [L mol^{-1} s^{-1}]
1 + DEAD	3.9 ± 0.4	9.3 ± 1.3	5.4	1.3×10^{-5}	1.6×10^{-6}	$1.1 \pm 0.9 \times 10^{-6}$
2 + DEAD	5.4 ± 1.0	7.8 ± 0.3	2.4	5.2×10^{-5}	7.5×10^{-5}	$5.8 \pm 0.5 \times 10^{-5}$

[a] The experiments were performed at a flow rate ratio of $Q_w/Q_o = 2$. [b] S = "on water" reaction at the surface. T = reaction in toluene.

Both reactions showed a considerable drop in activation energy ($\Delta E_a = 5.4$ and 2.4 kcal mol^{-1} for reaction of DEAD with **1** and **2**, respectively) upon introduction of water plugs as summarized in Table 1. A drop in the energy barrier by 5.4 kcal mol^{-1} was seen, which was in good agreement with a theoretically predicted value of around 7.5 kcal mol^{-1} for a hydrogen-bond-stabilized transition state for the reaction of **1** with dimethyl azodicarboxylate (instead of DEAD), reported by Jung and Marcus[17] (Figure 4a). Using the Eyring equation, we determined the values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for both "on water" and toluene reactions (Supporting Information, Table S4). A large change in $\Delta H^{\neq}$ was accompanied by a more negative value for $\Delta S^{\neq}$ for reactions with **1** and **2** (-59 and -38 J mol^{-1}K^{-1}, respectively), which indicates that the interfacial nature of the "on water" reaction may put constraints on the reactivity of molecules at the interfaces (Figure 4b).

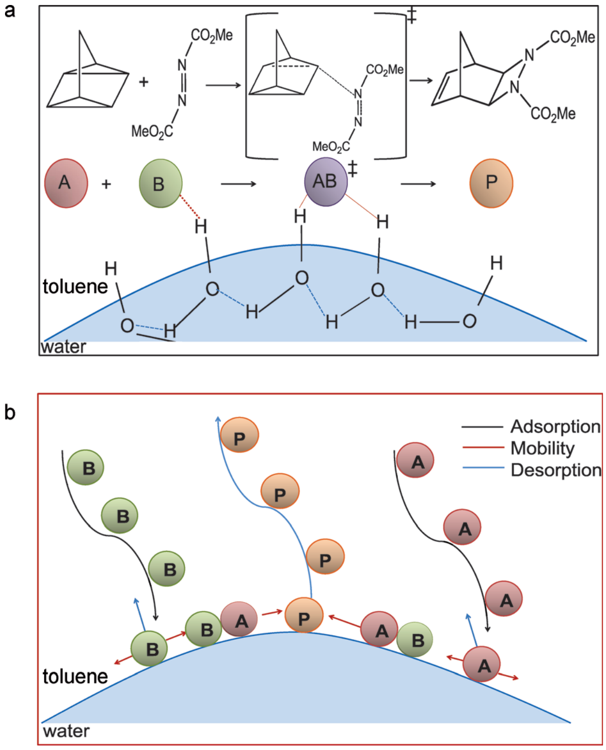

Figure 4. Cartoon of "on water" catalysis. a) Mechanistic hypothesis proposed by Jung and Marcus.[17] The hydroxy groups at the interface stabilize the reactants and the transition state. b) The reactivity of molecules at the interface is affected by adsorption and desorption processes, as well as by their mobility on the surface.

Finally, we calculated the rate constants $k_{s,cal}$ (obtained from the activation energy plots) and compared these with experimentally determined values $k_{s,obs}$ from Figure 2 at the same flow rate (Table 1). The striking agreement between the calculated and observed values for the "on water" rate constants demonstrates that the biphasic-flow approach has provided us with an insight into "on water" reactions.

In conclusion, we have demonstrated how biphasic flow can be used to study interfacial reactions on a macroscopic scale. Total flow rate, residence times, and most importantly, the interfacial area between the water and the organic phase can be precisely known and controlled in a (micro)fluidic system, which is not possible in bulk emulsions. We have used this technique to quantify the "on water" effect for the first time. We suggest as a possible mechanism the model based on the stabilization of the transition state by hydrogen bonding proposed by Jung and Marcus.[17] But it is also quite apparent that the magnitude of the "on water" effect can be rather modest (as seen in the reaction with **2**) and even if the reaction is accelerated initially, the effect becomes less pronounced with longer reaction times. As shown in Figure 4b, the interfacial nature of the reaction can greatly influence the overall reaction rates as product molecules might become pinned at the interface. These factors strongly counteract the favorable reduction in activation energy. In bulk emulsion studies, where the emphasis has been on increasing the percent conversion, these effects are not measurable because droplets are formed and merged continuously, thereby exposing "fresh" water–organic interfaces. Our method allows for rapid examination of the key features of "on water" conditions, which could reduce the use of organic solvents.

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