

'ON WATER': A NEW PHASE OF AQUEOUS ORGANIC CHEMISTRY

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INTRODUCTION

Colloquially, water is referred to as “the universal solvent.” And yet, the prevailing notion among today’s chemists is that water is something to be avoided in organic synthesis; great pains are taken to use solvents, reagents, and conditions which are ‘dry’ i.e., free of water. Apart from the obvious concerns surrounding water-sensitive reagents, a primary concern is one of solubility – the notion that solubility is a prerequisite to reactivity is maintained to justify the use of organic solvents at the exclusion of anything else. However, biochemical reactions in living systems largely occur in an aqueous medium. Further, environmental and safety concerns have fueled the push towards so-called “Green Chemistry” – the reduction and eventual elimination of hazardous material and waste. This has prompted investigations into alternatives to traditional organic solvents, including solvent-free conditions, ionic liquids, and water. Of these, water holds great promise as it is cheap, safe, and nonvolatile. Its high heat capacity can allow for safe handling of exothermic reactions. It is easily separated from organics and is a renewable resource. Despite these advantages, the general low water-solubility of organics has prevented the widespread use of water as a standard solvent.

BACKGROUND

Historical role of water

Water did not always play the part of organic pariah. Lindstrom points out that water was the solvent of choice in the early days of organic chemistry beginning with Wöhler’s urea synthesis in 1828, and many early reactions (including the Baeyer-Villiger oxidation and the Wolff-Kishner reduction) were conducted in water.¹ It was in the last century that the development of organometallic compounds necessitated a more strict exclusion of water; meanwhile, technological advances in the petrochemical industry facilitated access to the light organics which comprise traditional solvents.¹

Hydrophobic effect

In 1980 Breslow reported the acceleration of Diels-Alder reactions using water as a solvent.² This came as a surprise given the relative insensitivity of Diels-Alder reactions to solvent polarity. Moreover, polar organic solvents actually *slow* the reaction compared to nonpolar organics, so the polarity of water could not be used to rationalize the reactivity. To explain the increased reaction rate, Breslow invoked a hydrophobic interaction between the reactants and the aqueous medium. This description suggests that the nonpolar species are brought together out of a mutual repulsion to the water, but this is an unfortunate consequence of language. In fact, it is the hydrogen-bond network that

exists in pure water that is disrupted by the presence of nonpolar solutes. This disruption has an entropic cost arising from the formation of clathrates, or cages of water molecules which serve to maintain the polar hydrogen-bond network. When these nonpolar species are brought together to undergo a reaction, as in the Diels-Alder case, the clathrate of the transition state is smaller than the combined clathrates of the reactants. This results in an entropic payoff as water molecules are released into solution (Figure 1) and returned to the intermolecular network.³

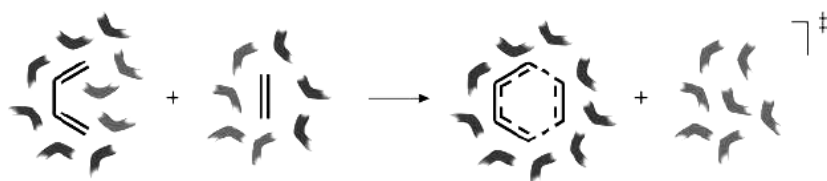
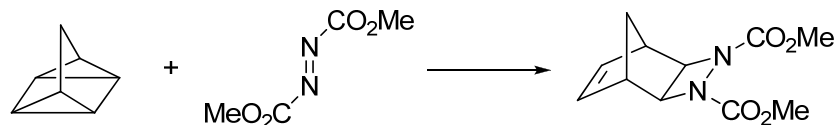


Figure 1. Hydrophobic effect resulting in release of water (From Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809-2820.)

Another way of viewing the hydrophobic effect involves a consideration of the high cohesive energy density (c.e.d) of water. From this viewpoint, the strong intermolecular forces between and among water molecules drive reactions in which the transition state exists at a smaller volume than the starting materials (i.e. the volume of activation ΔV^\ddagger is negative). Since volume of activation is determined as a measure of the pressure-dependence of reaction rate, water is described as having a high “internal pressure” relative to organic solvents. Breslow makes the point that this internal pressure from water has an upper limit linked to the solubility of the compound; above such a threshold, the compound is squeezed out of the aqueous layer.⁴

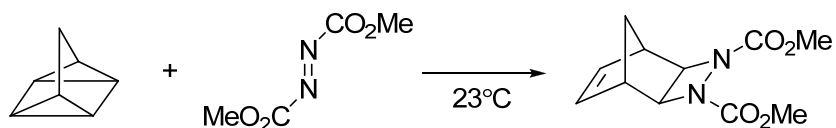
Sharpless ‘On Water’ Effect

In 2005 Sharpless and coworkers noticed an interesting phenomenon while exploring cycloadditions of strained cyclic systems. In a study of the $[2\sigma + 2\sigma + 2\pi]$ cycloaddition of quadricyclane and dimethylazodicarboxylate (DMAD), water was used as the reaction medium instead of toluene as originally reported, despite the relative immiscibility of the starting materials in water.⁵ The result was a remarkable increase in the rate and yield of reaction (Table 1). Performing the reaction without solvent did not accelerate the reaction; thus the effect was due to more than just concentration. Moreover, the conditions were heterogeneous, with the reaction occurring outside of the water, and so the hydrophobic effect seemingly did not apply. Importantly, vigorous mixing to form a suspension seemed to be required for reaction to proceed. Sharpless termed this an “on water” effect.

Table 1. ‘On water’ acceleration in the reaction of quadricyclane and DMAD

<i>Solvent</i>	<i>Conc.</i>	<i>Temp.</i>	<i>Time</i>	<i>Yield</i>
none	4.53 M	0°C	2 h	0%
none	4.53 M	23°C	48 h	85%
Toluene	1 M	80°C	24 h	74%
H ₂ O	4.53 M	0°C	1.5 h	93%
H ₂ O	4.53 M	23°C	10 min	82%

Taking a closer look at solvent dependence, Sharpless and coworkers noted that solvent polarity does play a role (Table 2), as the time to completion diminishes with increasing polarity in the aprotic organic solvents and reaches a nadir with a polar protic solvent. Nevertheless, the dramatic rapidity with which the reaction proceeds ‘on water’ required an explanation beyond solvent polarity. Further, water seemed to be privileged, since heterogeneous conditions conducted ‘on perfluorohexane’ reacted at rates comparable to the homogeneous organic conditions. An isotope effect was also noted, though this was not explained in the original paper. Pirrung suggests that the reduction in reactivity for ‘on D₂O’ conditions arises from the increased viscosity of D₂O which affects mixing.⁶

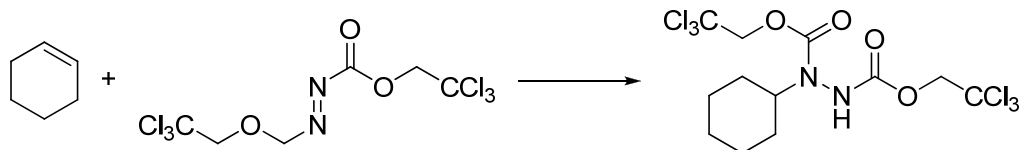
Table 2. Solvent effect in the reaction of quadricyclane and DMAD

<i>Solvent</i>	<i>Conc.</i>	<i>Time</i>	<i>Solvent</i>	<i>Conc.</i>	<i>Time</i>
Toluene	2 M	>120 h	MeOH	2 M	18 h
EtOAc	2 M	>120 h	none	4.53 M	48 h
CH ₃ CN	2 M	84 h	D ₂ O	4.53 M	45 min
CH ₂ Cl ₂	2 M	72 h	C ₆ F ₁₄	4.53 M	36 h
DMSO	2 M	36 h	H ₂ O	4.53 M	10 min

The Sharpless group next demonstrated an ‘on water’ ene reaction of cyclohexene with bis(trichloroethyl) azodicarboxylate (Table 3). The reaction was sluggish in neat conditions but proceeded readily in aqueous conditions. This showed that reactions involving solids could also be

carried out, and further that water could be employed as a “mixing agent” without the dilution cost of a true solvent.⁵

Table 3. Ene reaction of cyclohexene with bis(trichloroethyl) azodicarboxylate



<i>Solvent</i>	<i>Temp.</i>	<i>Time</i>	<i>Yield</i>
Benzene	80°C	24 h	70%
none	50°C	36 h	62%
H ₂ O	50°C	8 h	91%

Sharpless also went on to demonstrate his ‘on water’ effect for the Diels-Alder reaction and an aromatic Claisen rearrangement (Figures 3 and 4), both reactions previously known to be accelerated by water.^{4,7} In both cases, the reactions proceeded faster than in neat conditions, though the acceleration was minor.

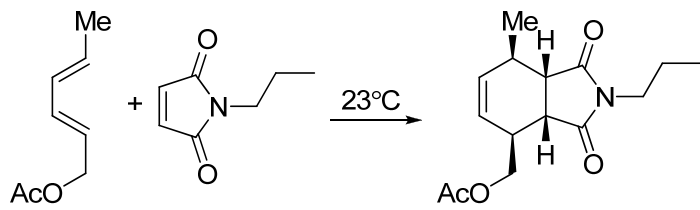


Figure 3. Diels-Alder reaction of 2,4-hexadienyl acetate and *N*-propylmaleimide

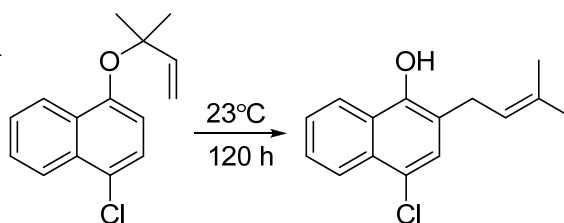


Figure 4. Aromatic Claisen rearrangement

PROPOSED MODEL

In 2006 Marcus and Jung proposed a model to describe Sharpless’ ‘on water’ reactivity.⁸ Citing previous work by Shen,⁹ they note that water at an aqueous-organic interface extends into the organic layer with approximately 1 in 4 surface hydroxyls protruding. At this interface, they posit that an organic compound with sufficient hydrogen-bonding capabilities would interact with the hydroxyls as on a catalytic surface (Figure 5). The rapid mixing required for these reactions serves to maximize the reactive surface. Though compelling, this model fails to address reactivity in unimolecular cases such as the Claisen rearrangement, in which increased reactivity had already been demonstrated using the hydrophobic interaction model.

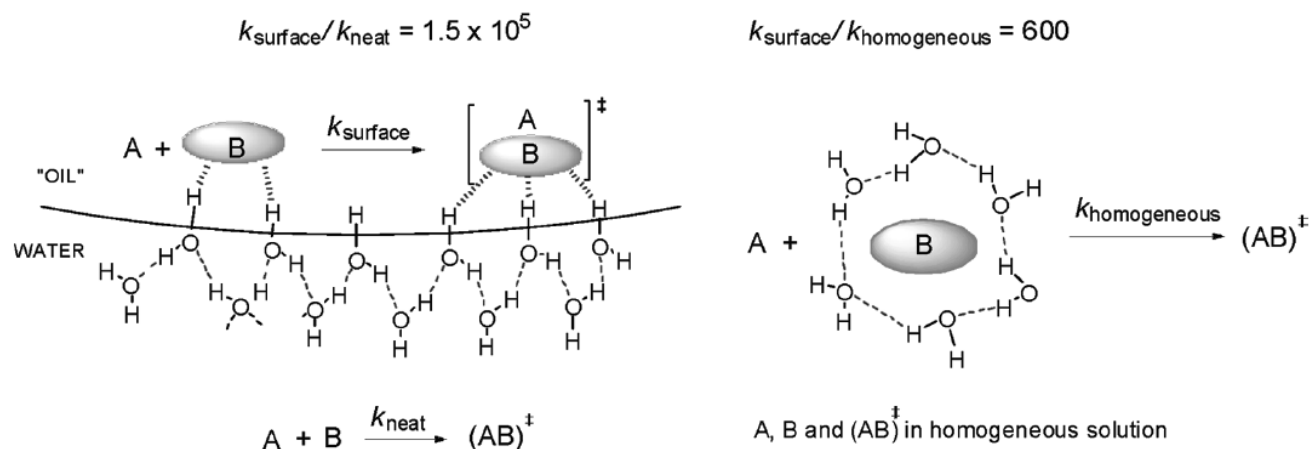


Figure 5. Cartoon summary of ‘on water’ catalysis compared to neat and homogeneous conditions (from Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502)

Sharpless and coworkers present a persuasive argument for the unique nature of water in their reaction system. Nevertheless, the presentation of ‘on water’ conditions as a new class of reactivity is not without controversy. Indeed, it has been suggested that the new conditions are merely an extension of Breslow’s work with the Diels-Alder reaction. Pirrung notes that cycloaddition of azodicarboxylates are accelerated by pressure, and thus should be expected to show increased reactivity due to the hydrophobic effect.⁶

APPLICATIONS

There have been several demonstrations of ‘on water’ reactivity in the years since Sharpless coined the term. In 2005 Kobayashi demonstrated a catalytic asymmetric epoxide opening using a scandium tris(dodecylsulfate) catalyst (Figure 6). This catalyst, which he terms a lewis acid surfactant catalyst (LASC) was developed as a water-tolerant species to allow a range of Mukayama-type aldol in homogeneous organic/aqueous system. The epoxide opening functioned on pure water, however. Enantioselectivity arises from the use of a chiral pyridine dimer by a mechanism as-yet unknown.¹⁰

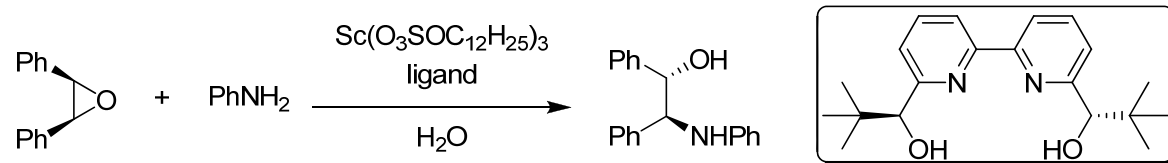


Figure 6. Catalytic asymmetric opening of aryl epoxide

Efforts at performing organocatalyzed aldol reactions using “green” methods preceded Sharpless’ report. Barbas and Hayashi independently arrived at modified proline catalysts which would allow for reactions to be performed using water instead of DMSO.^{11,12} In both reports the reactions are said to occur ‘in water’ in order to distinguish themselves from other reports which claimed to

demonstrate ‘green chemistry’ despite extensive use of organic cosolvent. Subsequent commentary redubbed these reactions as being ‘on water’.

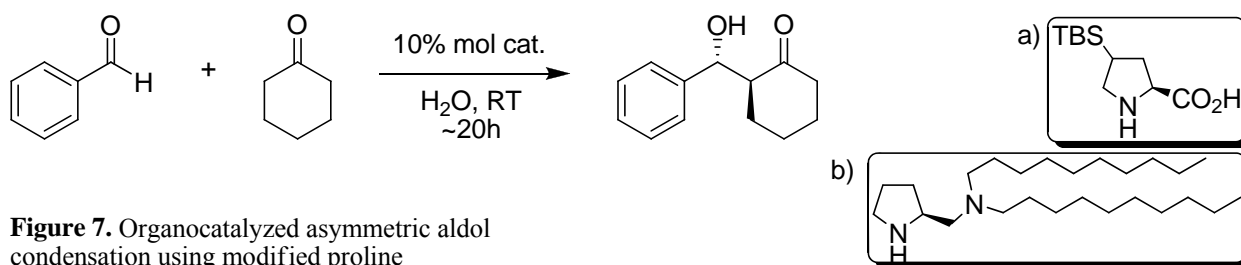


Figure 7. Organocatalyzed asymmetric aldol condensation using modified proline

Bergdahl reports a water-stable Wittig reaction employing stabilized ylides (Figure 8). E/Z ratio of the resulting α,β -unsaturated esters are good, though not as high as when performed in organic solvent. On the other hand, on water conditions gave the highest yield.¹³

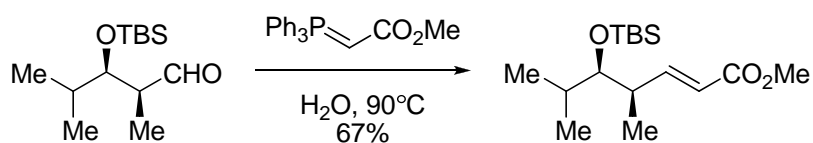


Figure 8. Wittig reactions of stabilized ylides in aqueous medium

Chakraborti, recognizing the wide range of application for benzothiazoles demonstrated the synthesis of aryl-benzothiazoles on water (Figure 9). Previous methods required extremely harsh conditions which would have been potentially detrimental to the a natural product. In a survey of organic and solvent-free conditions, the on-water technique was demonstrated to give the fastest reactivity. Moreover, formation of a benzothiazoline as a side product was shut down in water, as water seemed to facilitate dehydrogenation from the benzothiazoline to the benzothiazole.¹⁴

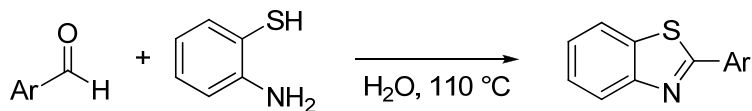


Figure 9. Formation of 2-aryl-benzothiazoles

In 2005 Nicolaou reported a new synthesis of gambogin which employed a biomimetic Claisen/Diels-Alder cascade (Figure 10) and demonstrated increased reaction rate upon addition of water.¹⁵ Strictly speaking, this did not constitute an ‘on water’ effect as there was always organic co-solvent present. In fact, the low concentration of material suggests that hydrophobic effect considerations were at work. Nicolaou explicitly states that the water addition reached an upper limit when starting material began to crash out of solution. In this case the reaction was sufficiently rapid (full conversion in 30 minutes) as to obviate further optimization. Nevertheless, this example highlights a shortcoming in ‘on-water’ chemistry in that there is no allowance for reactions purely in the solid state.

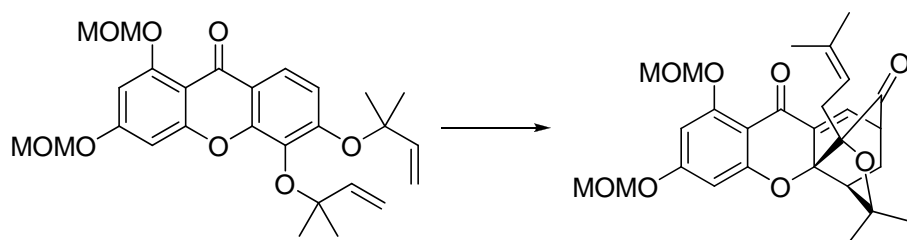


Figure 10. Claisen/Diels-Alder cascade accelerated by addition of water

CONCLUSION

Sharpless' 'on water' conditions have been demonstrated in several reaction types. The working model proposed by Marcus seems to indicate that the conditions should accelerate reactions involving insoluble compounds provided there is sufficient opportunity for hydrogen-bonding to allow for "docking" on the catalytic water/oil interface. However, there remains work to be done to better elucidate the underpinnings of this increased reactivity. As more examples of this reactivity are reported, general trends will become even more apparent. Nevertheless, the demonstration that solubility is not a requisite to reactivity is a strong step towards cleaner chemistry.

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