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Organic Chemistry

“On Water”: Unique Reactivity of Organic Compounds in Aqueous Suspension**

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Water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns, and the study of organic reactions in aqueous solvents has an intriguing history.[1] Most notably, certain pericyclic reactions such as

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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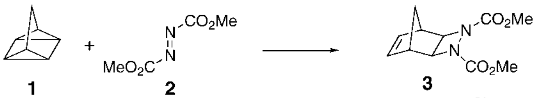
Diels–Alder cycloadditions[2] and Claisen rearrangements[3] of hydrophobic compounds have been found to be accelerated in dilute aqueous solution. Yet, either organic cosolvents and/or substrate modifications are almost always employed in preparative-scale reactions performed in water,[1] as it is assumed that solubility is required for efficient reaction. Not only do these strategies detract from the simplicity and advantages sought from the use of water in the first place, but, as we report here, the venerable assumption "corpora non agunt nisi soluta" (substances do not interact unless dissolved) can be distinctly counterproductive.

In recent years, we have focused on modular synthetic techniques that rely on a few nearly perfect reaction types.[4] In the course of this work, we have noticed that many such reactions often proceed optimally in pure water,[5] and particularly when the organic reactants are insoluble in the aqueous phase.[6] We present here several examples that illustrate a remarkable phenomenon: substantial rate acceleration when insoluble reactants are stirred in aqueous suspension, denoted here as "on water" conditions. Even when the rate acceleration is negligible, the use of water as the only supporting medium has other advantages including ease of product isolation and above all, safety, thanks to its high heat capacity[7] and unique redox stability.

In connection with our studies on the reactivity of strained olefins, we explored the preparation of 1,2-diazetidines from quadricyclane (**1**) by the $2\sigma+2\sigma+2\pi$ cycloaddition with azodicarboxylates, discovered by Lemal and co-workers.[8] The typical reaction conditions involve heating **1** with dimethyl azodicarboxylate (DMAD, **2**) in toluene or benzene at 80°C for 24 h or longer.[8,9] In contrast, when a mixture of DMAD and quadricyclane is vigorously stirred "on water", the reaction is complete within a few minutes at ambient temperature. The corresponding neat (solvent-free) reaction of these two liquids takes nearly two days to reach completion, which shows that the rate acceleration is not the sole consequence of an increase in the effective concentration of reagents (Table 1).

Table 1: Reaction of quadricyclane (**1**) with dimethyl azodicarboxylate (**2**).



1 **2** **3**

(m.p.: 92–94 °C)

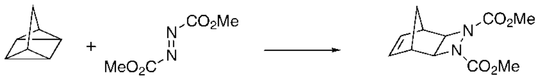
Solvent	Conc. [M]	T [°C]	t	Yield [%][a]
neat	4.53[b]	0	2 h	0[c]
neat	4.53[b]	23	48 h	85
toluene	1	80	24 h	74
on H_2O	**4.53[d]**	**0**	**1.5 h**	**93**
on H_2O	**4.53[d]**	**23**	**10 min**	**82**

[a] Yields are of isolated pure products. [b] Calculated from the measured density of a 1:1 mixture of **1** and **2**. [c] No product discernible after 2 h. [d] The maximum effective concentration "on water" is assumed to be the same as that of the neat reaction.

As the cycloaddition of DMAD with quadricyclane demonstrates, the "on water" method consists simply of stirring the reactant(s) with water to generate an aqueous suspension. Nonpolar liquids that separate from water into a clear organic phase are ideal candidates for these reactions. Solid reactants can also be utilized, provided one reaction partner is a liquid and adequate mixing is ensured. Vigorous stirring promotes the reaction, most likely by increasing the area of surface contact between the organic and aqueous phases. The observed rate acceleration does not depend on the amount of water used, as long as sufficient water is present for clear phase separation to occur.[10] The product is isolated simply by phase separation or filtration. In cases where clear phase separation does not occur, such as in small-scale reactions, liquid–liquid extraction may be necessary.

Seeking insight into the origin of rate acceleration in the DMAD–quadricyclane cycloaddition, the reaction between **1** and **2** was carried out under a variety of conditions and the time to completion was monitored (Table 2). Under homogenous conditions, polar protic solvents accelerate the reaction, with observed reaction rates in the following order: $\mathrm{MeOH/H_2O}$ (3:1) > MeOH > DMSO > $CH_3CN \approx CH_2Cl_2$ > EtOAc ≈ toluene.[11] This trend suggests that hydrogen bonding, charge stabilization, and dipolar effects may each be important for rate acceleration.[12] While water contributes to such properties in homogeneous mixtures, heterogeneity was crucial for observing large rate accelerations. Thus, the presence or absence of methanol in a heterogeneous reaction made little difference, but the rate slowed considerably when enough methanol was used to make the reaction homogeneous. However, heterogeneity in itself is not responsible for rate acceleration as the reaction "on" perfluorohexane was only slightly faster than the neat reaction. Interestingly, a significant solvent isotope effect was also observed: the reaction slowed noticeably when D_2O was used in place of water.

Table 2: Reaction of quadricyclane (**1**) with dimethyl azodicarboxylate in various solvents.[a]



1 **2** **3**

Solvent	Conc. [M][b]	Time to completion
toluene	2	> 120 h
EtOAc	2	> 120 h
CH_3CN	2	84 h
CH_2Cl_2	2	72 h
DMSO	2	36 h
MeOH	2	18 h
neat	4.53	48 h
on D_2O	4.53	45 min
on C_6F_{14}	4.53	36 h
on H_2O	**4.53**	**10 min**
$\mathrm{MeOH/H_2O}$ (3:1, homogeneous)	2	4 h
$\mathrm{MeOH/H_2O}$ (1:1, heterogeneous)	4.53	10 min
$\mathrm{MeOH/H_2O}$ (1:3, heterogeneous)	4.53	10 min

[a] Compound **3** was the only product observed in each case. [b] Concentrations of the neat and heterogeneous reactions are calculated from the measured density of a 1:1 mixture of **1** and **2**. DMSO = dimethylsulfoxide.

Acceleration of reactions “on water” is evident even when a nonpolar solvent comprises a part or most of the organic phase as shown in Table 3. Thus, the reaction of quadricyclane (**1**) with diethyl azodicarboxylate (DEAD, **4**), carried out simply by stirring a toluene solution of DEAD with **1** “on water”, proceeds at a considerably higher rate than when the reaction is carried out in toluene alone.

Table 3: Cycloaddition of quadricyclane (**1**) performed with DEAD (commercial reagent in toluene) “on water”.[a]

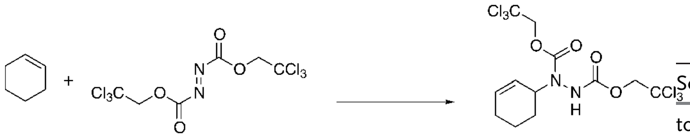
1 **4** **5**

t [h]	Conversion [%][b]	
	toluene[c]	**toluene on H_2O[d]**
3	4	**42**
6	8	**56**
17	18	**69**

[a] Isolated yield after 24 h at 23 °C: toluene, 24 %; toluene “on water”, 72 %. [b] Determined by ^1H NMR spectroscopy using acetophenone as internal standard. [c] Commercial DEAD in toluene used (49 %, 2.86 M). [d] As [c], except for the presence of an equal volume of water to toluene.

We have found that the high reactivity of azodicarboxylates “on water” is not limited to their cycloaddition reactions: the ene reactions of these compounds respond similarly to conditions of aqueous suspension relative to organic solution. Leblanc et al. have used the ene reaction of bis(trichloroethyl) azodicarboxylate (**7**) to achieve the allylic amination of olefins under thermal conditions.[13] In nonpolar solvents such as benzene, prolonged heating at 80 °C was reportedly required to attain useful levels of reactivity with simple olefins such as cyclohexene (**6**). In the absence of solvent, the reaction of liquid **6** and solid **7** was found to proceed at 50 °C, but still required 36 h for completion as well as the presence of excess cyclohexene. In contrast, the reaction performed “on water” was complete within eight hours at 50 °C and afforded the product in 91 % yield (see Table 4). The neat reaction between **6** and **7** not only appeared to be slower, but the reaction mixture was also considerably harder to mix uniformly. In contrast, when heated to 50 °C “on water” the reaction mixture initially formed a molten organic phase, which gave way to the product as a white precipitate. In practical terms, reactions of solid components in aqueous suspension are more reproducible and convenient than in the absence of solvent, as water provides for efficient “mixing” of the reactants without the dilution cost of a true solvent. Furthermore, the effective melting point of solid reaction mixtures is noticeably lowered in the presence of water, such that a fused organic phase is often formed.

Table 4: Ene reaction of cyclohexene (**6**) with bis(trichloroethyl) azodicarboxylate (**7**) “on water”.



6 **7** **8**

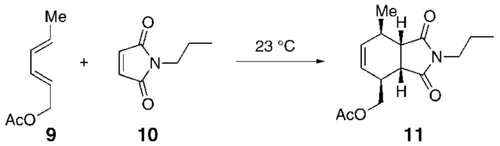
Solvent	*T* [°C]	*t* [h]	Yield [%]
benzene	80	24	70[a]
neat	50	36[b]	62
on H_2O	**50**	**8**	**91**

[a] Data from Ref. [13]. [b] Additional **6** added after 24 h.

The notion of the special nature of water as a solvent for organic reactions began with examples of Diels–Alder reactions more than fifty years ago.[14] The first quantitative data were reported by Rideout and Breslow, who showed that Diels–Alder reactions between nonpolar compounds proceeded at much higher rates in water (dilute homogeneous solution) than in organic solvents.[15] Rate accelerations as high as 200-fold were noted in certain cases. Breslow et al. also noted the high *endo* selectivity of certain Diels–Alder reactions carried out in water, under both homogeneous and heterogeneous conditions.[16] Although rate acceleration and selectivity were ascribed primarily to hydrophobic effects, it has since been appreciated that hydrogen bonding plays an important role.[17] Ironically, much of the careful quantitative work on the process does not directly apply to synthetic chemistry, as the experiments reported by Breslow, Engberts, and others were conducted at low concentrations (mM or less) to maintain homogeneity in water, while preparative reactions usually require much higher concentrations. In a rare example of a heterogeneous process, Grieco et al. reported the Diels–Alder reaction of an acyclic diene bearing a carboxylic acid group to occur in aqueous suspension faster than in organic solution.[18] The best results were obtained in the reactions of diene carboxylate salts with various dienophiles in water, and the rate accelerations due to water were ascribed to micellar catalysis.[19] As some of these reactions were carried out under conditions similar to ours, we evaluated the effectiveness of the “on water” protocol for Diels–Alder reactions.

We performed the cycloaddition of the water-insoluble *trans,trans*-2,4-hexadienyl acetate (**9**) and *N*-propylmaleimide (**10**) under various conditions (Table 5). As before, a protic solvent (methanol) was better than nonprotic solvents, and

Table 5: Comparison of water versus organic solvents for a typical Diels–Alder reaction.



9 **10** **11**

Solvent	Conc. [M]	Time to completion [h]	Yield [%]
toluene	1	144	79
CH_3CN	1	> 144	43[a]
MeOH	1	48	82
neat	3.69[b]	10	82
H_2O	**3.69[b]**	**8**	**81**

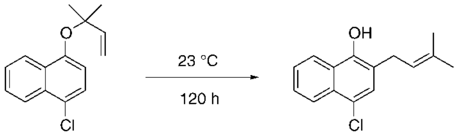
[a] Yield after chromatographic purification. Other yields are of crude products, which were > 95 % pure by ^1H NMR spectroscopy. [b] Calculated from the measured density of a 1:1 mixture of **9** and **10**.

the reaction in aqueous suspension showed substantial rate acceleration over homogeneous solution. Consistent with the results of Grieco et al.[18] and in contrast to the reaction of **1** + **2** described above, the neat Diels–Alder addition of **9** to **10** (both liquids) was approximately as fast as in water suspension.[20]

Claisen rearrangements are another significant class of reactions for which the accelerating effect of water is well-recognized.[21] The initial discovery appears to have been made during mechanistic studies of the chorismate–prephenate rearrangement, a key step in the biosynthesis of shikimic acid.[22] Brandes, Grieco, and Gajewski then performed a kinetic study on the rearrangement of an allyl vinyl ether substrate with an attached carboxylate functionality.[23] The rate of rearrangement of the carboxylate salt in water was found to be about two orders of magnitude higher than that of the methyl ester in nonpolar solvents.[24] These findings were exploited further by Grieco et al., who used the accelerating influence of water to promote difficult rearrangements.[25]

In contrast to the aliphatic Claisen rearrangements, the effect of water on the analogous aromatic Claisen rearrangement is little known.[26] We have made preliminary measurements on naphthyl ether **12**, which undergoes rearrangement at an appreciable rate even at room temperature. Table 6 shows the effect of various solvents on this process. After five days at 23 °C, the sample of **12** in aqueous suspension had completely rearranged to **13**, while the rearrangement was considerably slower in organic solvents. The neat reaction was again closest in rate to water and required one further day to reach completion. As with Diels–Alder reactions, the "on water" protocol provides the best set of conditions in terms of efficiency, convenience, and safety, even when rate accelerations are not large.

Table 6: Comparison of solvents for an aromatic Claisen rearrangement (0.28–0.46 M), performed at room temperature.[a]



12

13
(m.p.: 54–56 °C)

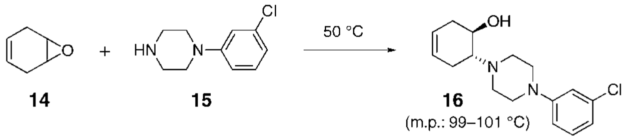
Solvent	Yield [%][b]
toluene	16
DMF	21
CH_3CN	27
MeOH	56[c]
neat	73
on H_2O	**100**

[a] Conversion was monitored by ^1H NMR analysis of aliquots. [b] Except in the case of MeOH, no other products were detected by ^1H NMR spectroscopy. [c] 14% of 4-chloro-1-naphthol was also observed.

Non-pericyclic reactions such as the opening of epoxides and aziridines with heteroatom nucleophiles also derive unique benefits from the "on water" environment. Hydrogen bonding is crucial for the activation of such electrophiles, making these ring-opening processes autocatalytic and difficult to control under neat conditions. Instead, protic solvents such as alcohols and especially alcohol/water mixtures provide good homogeneous media for these transformations.[4] Here too, we find that water alone is the medium of choice. The reactions are completed in shorter times than in other protic solvents, and the pure product often precipitates, to be isolated by simple filtration.

The reaction of cyclohexadiene monoepoxide (**14**) with *N*-(3-chlorophenyl)piperazine (**15**) is illustrative (Table 7). When heated at 50 °C, the reaction "on water" was completed overnight, while the reactions in solution in ethanol or without solvent required approximately three days to reach completion. In toluene, less than 10% conversion occurred after five days at the same temperature. Thus, taking into account the concentrations of the reagents, the rates of reactions "on water" and in ethanol appeared to be approximately the same, and greater than that for the reaction performed in the absence of solvent.

Table 7: Application of the "on water" method to the nucleophilic opening of an epoxide.



14

15

16
(m.p.: 99–101 °C)

Solvent	Conc. [M]	*t* [h]	Yield [%]
toluene	1	120	< 10[a]
neat	3.88[b]	72	76
EtOH	1	60	89
on H_2O	**3.88[b]**	**12**	**88**

[a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [b] Calculated from the measured density of a 1:1 mixture of **14** and **15**.

Thus, a variety of reactions can be efficiently carried out in aqueous suspension, with the most dramatic effects observed for the addition of azodicarboxylates to unsaturated hydrocarbons. To the best of our knowledge, these examples represent some of the largest rate accelerations due to water observed under preparative conditions, that is, at molar concentrations. A central theme in the field of aqueous organic chemistry has been the need to promote solubility in these reactions. Clearly, solubility is not essential.

Although the reactivity phenomenon described here has immediate practical implications, its origins are presently unclear; nevertheless, a few preliminary remarks are in order. For example, it is possible that reactions "on water" actually proceed through small amounts of dissolved solutes. Rate acceleration in homogeneous aqueous solution has been attributed to a variety of effects such as hydrophobic aggregation,[2,15] cohesive energy density,[27] or ground-state destabilization.[28,29] Breslow et al. have invoked solution-phase hydrophobic effects to explain the high *endo* selectivity of certain Diels–Alder reactions in aqueous suspension and solution.[2a,16] Engberts and co-workers made a fundamental point by providing evidence that, in cycloaddition reactions, hydrophobic destabilization will have a considerably greater impact on the ground state than on the transition state.[29,30] The importance of hydrogen bonding in the acceleration of Diels–Alder reactions in aqueous solution is supported by both experimental[31] and theoretical[32] studies.

However, it seems that many of the reactions described above are simply too fast for the acceleration to be solely due to solution-phase phenomena. In this regard, the observed requirement for heterogeneity and the finding that the rates of reactions "on water" often exceed those of the same reactions performed in the absence of solvent demand attention. Perhaps the unique properties of molecules at the macroscopic phase boundary between water and insoluble hydrophobic oils play a role.[33] The same principles that contribute to solution-phase effects may be amplified at such phase boundaries, but other factors, such as the redistribution of surface species driven by surface-tension energetics,[34] may also be relevant. We plan to keep exploring the "on water" phenomenon both for practical applications and mechanistic understanding.

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