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Organic Synthesis “on Water” vs “on Liquids”: A Comparative Analysis

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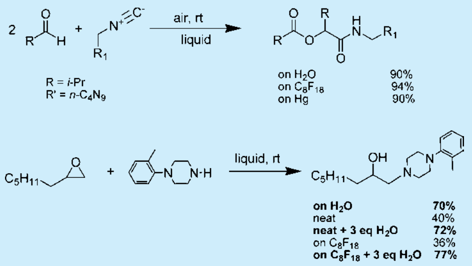
Supporting Information

ABSTRACT: Several organic reactions that are accelerated under the “on water” conditions proceed equally well or better on other “nonsolvents” or in neat conditions. Alternatively, only 1 equiv of water was necessary to obtain the same acceleration effect testifying to the fact that the water−organic compounds boundary might be unnecessary to achieve the “on water”-like reactivity.

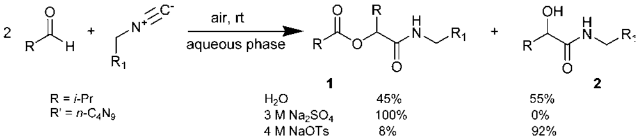


Since its original introduction in 2005,[1] the “on water” term has become ubiquitous in describing organic reactions occurring in aqueous emulsions or suspensions. In many of these reactions, rate acceleration is observed compared with the same reactions performed in organic solutions or neat conditions.[2] The use of water could also lead to selectivity changes.[3] Nevertheless, while hydrophobic interactions that facilitate many organic reactions *in* aqueous solutions have been extensively explored,[4,5] the role of the aqueous phase under the “on water” conditions remains a mystery. Hydrogen bonding at the water/organic compound interface, proposed by computational studies, has perhaps been the most prominent hypothesis to explain the rate acceleration.[6,7] Yet, rarely has the “uniqueness” of water vs other *nonsolvents* as the reaction medium been experimentally established. Herein, we present our results on deciphering the “on water” effect in several organic reactions in the context of the general “on solvent” effect.[8]

In order to separate the genuine “on water” effect associated with the interface boundary from other factors that can potentially contribute to the overall “on water” reactivity, we chose the heterogeneous reactions that are faster “on water” vs organic solvents and (a) involve liquids, (b) proceed at rt, and (c) do not require cosolvents or catalysts. Thus, despite the significant “on water” acceleration, the cycloaddition of quadricyclane and azodicarboxylates[1,7c] was excluded from this study, as complex synthetic protocols, instability of one of the reactants, and/or use of toluene as a cosolvent could all play a role in the observed phenomenon. In all experiments, the formal concentrations were chosen to match the typical on-water experiments.[1,2]

Following the pioneering studies by Pirrung et al.,[9] we recently examined the three-component Passerini reaction that proceeds extremely well “on water” with simple stirring at rt. We have found that the hydrophobicity of the starting materials plays a crucial role in the Passerini reaction “on water”: poorly water-soluble reactants rapidly gave the Passerini reaction products (esters), while water-soluble starting materials reacted slower giving mainly the corresponding amido alcohols, products of the reaction with water.[10] Salting-out additives, such as Na_2SO_4, accelerated the reaction leading to the ester product **1**, while the addition of the salting-in NaOTs resulted in the formation of the alcohol **2** (Scheme 1).[11]

Scheme 1. Salt-Dependent Selectivity in the Passerini Reaction in- and on-Water



Although the importance of the separation between the aqueous and organic phases in increasing the rate and selectivity of the Passerini reaction was clearly established, the origin of this effect remained ambiguous. Thus, we decided to explore this reaction using a series of liquids in place of water. Whereas the reactions were extremely sluggish when performed homogeneously in typical organic solvents (benzene, DMSO, or methanol), using perfluorooctane as a *nonsolvent* gave the Passerini product **1** in a 94% yield after 30 min of stirring at rt (entry 2, Table 1).[12] After 10 min, the reaction on C_8F_{18} gave 72% conversion compared with 42% (7:3 mixture of **1** and **2**) in water.[13] Thus, perfluorooctane appears to be an even better medium for this three-component reaction than water and is comparable with 3 M Na_2SO_4.[11] The acceleration of organic reactions in heterogeneous mixtures with perfluorinated liquids has previously been reported and assigned to the *low* cohesive energy density, c.e.d. (and related Hildebrand parameter) of such liquids.[8,14] As water has a very high c.e.d. value,[15] higher

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Table 1. Passerini Reactions (Schemes 1 and 2) in- and on-Liquids

entry	liquid	yield of **1**,[a] %	yield of **3**,[b] %
1	water	90[c] (42)[d]	44[e]
2	C_8F_{18}	94 (72)[d]	89
3	neat		85
4	Hg	90	91
5	C_6D_6	1[f]	5
6	CD_3OD		0[f]
7	*n*-$C_{16}H_{34}$		17

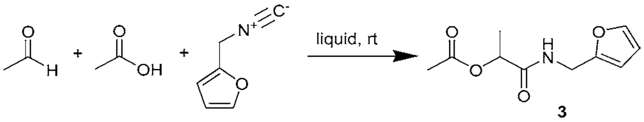
[a] 30 min. [b] 5 min. [c] Mixture of **1** and **2**. [d] After 10 min. [e] D_2O was used; yield of the mixture of **3** and free alcohol. [f] After 1 h.

than most solvents, it was proposed that liquids with very high or low c.e.d. accelerate organic reactions.[14] To verify this, we used mercury as the medium for the Passerini reaction (*Caution*: mercury is very toxic and must be handled in a fume-hood using proper protecting gear). Mercury has the highest c.e.d. values (951 cal/cm^3) among the liquids.[16,17] We found that the yield of the Passerini reaction "on mercury" was similar to those obtained on water, saturated sodium sulfate,[11] or perfluoroalkanes. The yields were likely to increase if efficient stirring was ensured, a challenging task for mercury. Similarly, the conventional stirring was complicated for the neat reactions, albeit the yields were only insignificantly lower than those in the reactions on perfluoroalkanes or mercury. As we maintained the same stirring rate throughout the experiments, no effort was invested to further improve the yields under the "on mercury" or neat conditions. In any event, it appears that the observed acceleration of the Passerini reaction "on water" is unrelated to the chemical interactions between the substrates and water surface; efficient phase separation leading to bulking the neat reaction played a major role in the observed effect.

Next, we reversed the situation to establish whether substrate *hydrophilicity* plays a role in the observed enhanced kinetics. To this end, we performed the Passerini reactions between the hydrophilic water-soluble acetic acid, acetaldehyde, and 2-furfuryl isocyanide. The reactions proceeded extremely fast and selectively when performed on perfluoroalkanes or mercury, but sluggishly in organic solvents or in water.

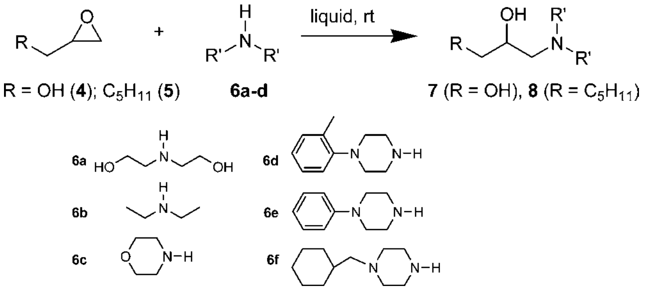
In the latter case, mainly the analogue to **2** amido alcohol was observed (Scheme 2, Table 1). Overall, these data demonstrate that, in the truly "on solvent" Passerini reactions, water has no distinct beneficial effect on the selectivity and yields when compared with other nonsolvents.

Scheme 2. Passerini Reaction with the Hydrophilic Reactants



The nucleophilic ring opening of epoxides with secondary amines is another reaction that was reported to proceed very efficiently under the heterogeneous "on water" conditions and relatively slowly in the organic media.[1,18,19] We sought to compare this reaction in solutions vs "on liquids" at rt using liquid substrates. We found that when both substrates were fully miscible with water, the nucleophilic ring opening was very slow while the same reactions performed on perfluoroalkanes or mercury were significantly faster. For example, the reaction between *N*,*N*-diethanolamine (**6a**) and glycidol (**4**) gave the aminoalcohol **7a** in 85% yield after 2 h when stirred on perfluorooctane, while only a 45% conversion was obtained after 2 h of stirring in D_2O (Scheme 3, Table 2).[20]

Scheme 3. Epoxide Ring Opening with Secondary Amines



Furthermore, using hexadecane as a nonsolvent gave significantly better yields than the reactions in water despite the low density of the former and ensuing difficulties in efficient stirring under these "*under liquid*" conditions.[21] With the less reactive hydrophobic 1-octene oxide (**5**), the reactions required several days to reach significant conversion; however, stirring on perfluoroalkanes was much more efficient than on water or D_2O (Table 2). Organic solvents (chloroform, DMSO, or CH_3CN) were the least efficient media. With the more nucleophilic diethylamine (**6b**) and morpholine (**6c**),[22] the epoxide opening became significantly faster when water or D_2O was used but still slower than on perfluoroalkanes or neat. Finally, when the hydrophobic *solid N*-(*o*-tolyl)piperazine was used (**6d**), *the "on water" reaction was noticeably faster* than on perfluoroalkanes or in neat. These starting materials are the most similar to the originally reported system,[1] thus confirming the observed "on water" acceleration with the hydrophobic substrates. The "on water" acceleration was also observed for the *liquid N*-(phenyl)piperazine (**6e**) and *nonaromatic N*-(cyclohexylmethyl)piperazine (**6f**).

When performed under the highly dilute *homogeneous* conditions *in* a D_2O solution (4 mmol/L for the limiting 1-octene oxide),[23] the reaction was extremely slow not allowing for the kinetic studies. The results indicate that the reaction does not proceed in the aqueous solution. Still, performing the reaction in the moderately kosmotropic NaCl (4 M) led to some *decrease* in conversion. Conversely, the reaction can be accelerated (79% vs 69% on water) by the addition of the surfactant sodium dodecyl sulfate (SDS),[21] at concentrations above its critical micelle concentration. As the product **8d** can be considered amphiphilic and potentially form micelles, we also verified the possibility of the product acceleration mechanism. When 0.5 equiv of **8d** was added at the beginning of the reaction, the conversion was lower (48% vs 69% on water) testifying against this mechanism. Unfortunately, the obtained information did not explain the apparent "on water" acceleration leading us to investigate the reaction "in the presence of water".[24,25] Surprisingly, in the presence of 1 equiv of water, the reaction between 1-octene oxide and *N*-(*o*-tolyl)piperazine "on perfluorooctane" gave a 67% conversion, comparable with that obtained "on water". Adding 3 equiv of water further increased the conversion (77% after 17 h, Table 2).

Table 2. Epoxide Ring Opening with Secondary Amines in- and on-Liquids[a]

entry	liquid	yield of **7**, %	yield of **8**, %
1	D_2O	**7a** 45, **7b** 67, **7c** 84	**8a** 65 (53),[b] **8b** 48 (33),[b] **8c** 47 (35)[b]
2	C_8F_{18}	**7a** 85, **7b** 75, **7c** 95	**8a** 98, **8b** 31, **8c** 58, **8d** 36, **8e** 28, **8f** 50
3	Hg	**7a** 95, **7b**, 50, **7c** 94	
4	Neat	**7a** 95, **7b** 70, **7c** 94	**8a** 99, **8b** 15, **8c** 47, **8d** 40, **8e** 24, **8f** 37
5	H_2O		**8d** 69 (65),[b] **8e** 50, **8f** 69
6	neat + H_2O[c]		**8d** 72 (73)[d]
7	C_8F_{18} + H_2O[c]		**8d** 67 (77),[d] **8f** 77[d]

[a] Reaction times, h: **7a−c** 2, **8a** 66, **8b** 42, **8c** 42, **8d** 17 or 23, **8e,f** 17. [b] In 4 M NaCl. [c] 1 equiv of H_2O. [d] 3 equiv of H_2O.

An increase to 10 equiv did not lead to a further increase of the product yield. Similarly, a high yield was obtained when 1 equiv of water was added to the neat reaction between **5** and **6d**. Thus, only 1−3 equiv of water are sufficient to observe a substantial increase in the product's yield. While such stoichiometric interactions between the organic compounds and water molecules may involve hydrogen bonding, there was clearly no need for the water−organic layer interface to obtain the "on water"-like acceleration. The lack of a positive effect of additional water, beyond the stoichiometric amounts, also argues against such a need.

Ene-reactions between unactivated alkenes and azodicarboxylates were reported to be accelerated "on water".[1,9b] Although, in our hands, the reactions between β-pinene (**9**) and isopropyl azodicarboxylate (**10**) were faster than reported earlier,[9b] a clear preference for water vs CH_2Cl_2 or chloroform was observed at rt (Scheme 4, Table 3). However, the reactions on perfluorohexane or in neat were even slightly more efficient. The addition of water to the heterogeneous mixture on C_6F_{14}, neat, or in solution in $CDCl_3$ did not lead to an increase of the reaction yield. Thus, it is likely that the acceleration observed for the reaction between cyclohexene and *solid* bis(trichloroethyl) azodicarboxylate on water was due to the more efficient formation of a molten organic phase, as was proposed in ref 1. When only *liquid* components are used, the ene-reaction proceeds equally efficiently on water, neat, or on a nonsolvent, such as perfluoroalkane. Interestingly, while clearly separable organic liquids are considered ideal candidates for the "on water" transformations, the majority of reported "on water" accelerated reactions involved solid reactant(s).[2]

Scheme 4. Azodicarboxylate Addition to β-Pinene

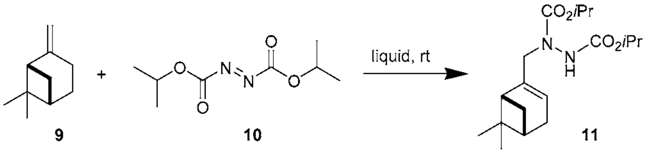


Table 3. Isopropyl Azodicarboxylate Addition to β-Pinene

entry	liquid	yield of **11**,[a] %
1	H_2O	60 (41)
2	4 M NaCl in H_2O	58 (42)
3	$CDCl_3$	43 (30)
4	$CDCl_3$ + 3 H_2O	46 (32)
5	C_6F_{14}	67 (50)
6	C_6F_{14} + 3 H_2O	71 (54)
7	neat	67 (50)
8	neat +3 H_2O	66 (49)

[a] Yields are after 1 h at rt; those in parentheses are after 30 min.

Although not comprehensive, our studies suggest that the presence of a defined water surface is not a prerequisite for obtaining the "on water"-like acceleration. In three different reactions, similar or better results were obtained by mixing neat substrates or adding nonsolvents, e.g. perfluoroalkane. The observed behavior is consistent with high concentrations (neat or bulked neat reactions) and, in one case, stoichiometric interactions between some organic compounds and water molecules responsible for the enhanced reactivity. Certainly, more studies are necessary to better assess the generality of our findings. Nevertheless, from the practical point of view, the "on water" reaction protocols may have a significant advantage over other conditions that provide similar yields. We are presently investigating potential applications of these findings in affecting the reactivity of organic compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental protocols and products characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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