Hydrophobic amplification of noncovalent organocatalysis†

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The effects of hydrogen-bonding organocatalysts and water for the acceleration of epoxide openings with a variety of nucleophiles are additive and lead to excellent yields of the catalyzed reactions in water.

Water as Nature's ultimate solvent has been recognized as a key player both as solvent and promoter of organic reactions.[1] Although water does not dissolve organic components well, many organic transformations are significantly accelerated.[2] The simple rationale is that water avoids mixing with organic solutes because this would lead to increased structuring and thus a loss of entropy of the water molecules around the solutes.[3] Water avoids this situation by bringing the solutes together so that this so-called "hydrophobic hydration"[4] can lead to rate enhancements of reactions run with water-insoluble, or only partially soluble, substrates (Fig. 1) through minimization of the solute's volume.[5]

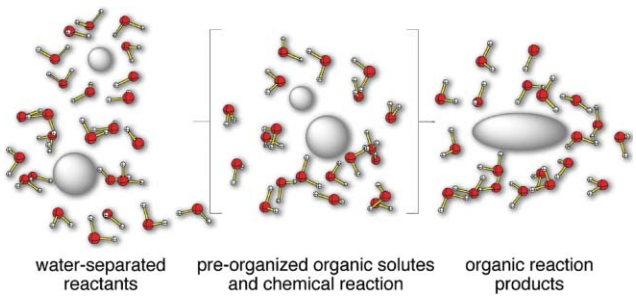
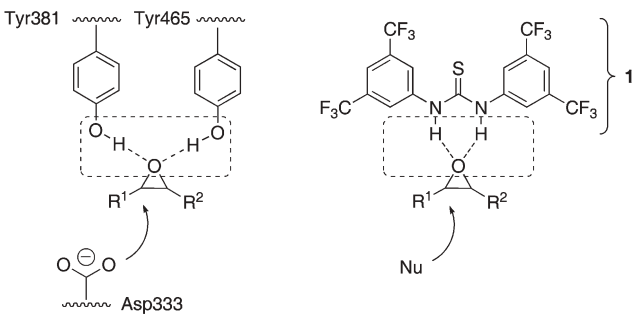


Fig. 1 Hydrophobic hydration: minimization of water ordering.

Catalysis in water depends on the ability of the catalysts to tolerate water on the one hand and to remain active on the other; water-soluble Lewis acids underline this possibility.[6] Organocatalytic reactions have thus far mostly been carried out in organic solvents although some of the key ideas behind organocatalysts derive from enzyme active site motifs that display their activity in their natural aqueous environments. Noncovalent organocatalysis[7] that largely builds on hydrogen-bonding interactions[8] as found in the complexes of organic substrates with heteroatoms and (thio)ureas[9] as well as diols[10,11] is *a priori* not expected to be amenable to aqueous chemistry because water is an excellent hydrogen bond donor/acceptor. However, as water forms the strongest hydrogen bonds with itself, it is not clear how a noncovalent organocatalytic reaction would proceed in water—if hydrophobic hydration were to play a role, the respective reactions should be accelerated (as shown for some Diels–Alder reactions).[12] Here we apply this novel concept to epoxide openings utilizing the noncovalent organocatalyst **1** (Scheme 1) in water. Not only do these reactions proceed best in water,[13] the catalytic activity of **1** is *amplified*.

Epoxide hydrolases detoxify living cells by catalyzing the conversion of epoxides to water-soluble diols.[10] The working model involves the phenolic H's of two tyrosines activating the epoxide for nucleophilic attack. These principles can be translated into an organocatalytic approach whereby a double hydrogen-bonding catalyst activates the epoxide in an analogous fashion (Scheme 1).



Scheme 1 Epoxide recognition for epoxide hydrolase and **1**.

We conducted our experiments in water as well as in CH_2Cl_2 and obtained the highest yields in water with 10 mol% **1**, irrespective of the epoxide and the nucleophile. The relative accelerations are as large as 200-fold. This effect, which may be larger for other systems, is taken as a proof-of-principle that hydrogen bonding catalysis and water are not mutually exclusive. While the yields are scattered in DCM and highly substrate-dependent, it is safe to say that the catalyzed epoxide openings in water proceed in good to excellent yields. The effect of the catalyst is most pronounced for sterically hindered nucleophiles (*e.g.*, *t*-$BuNH_2$). With propene oxide (**2**, Table 1) only the sterically less hindered regioisomer forms, while the opposite is true for styrene oxide (**4**); ratios of regioisomers (by NMR) are given in Table 2. The latter finding is likely to be due to benzyl conjugation that outweighs the steric effect. This is also in line with the structures of the transition structures for the simple model system discussed below.

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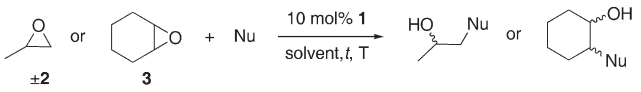
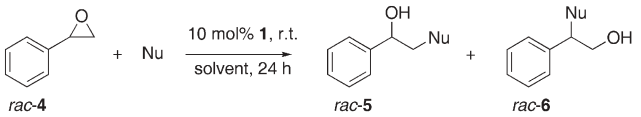
Table 1 Organocatalytic nucleophilic ring opening of oxiranes in water: reactions of ±**2** run at rt; of **3** at 40 °C. Nu = nucleophile



±**2** **3**

		Yield (%)			
Oxirane	Nu	DCM no cat.	DCM cat.	H_2O no cat.	H_2O cat.
±**2**	*t*-$BuNH_2$	<0.5	37	29	**94**
±**2**	*n*-Bu_2NH	17	70	73	**90**
±**2**	*n*-Pr_2NH	36	48	30	**91**
±**2**	*i*-Pr_2NH	<1	47	30	**64**
±**2**	$(C_3H_5)_2NH$	63	85	78	**87**
±**2**	Morpholine	52	62	25	**83**
±**2**	Piperidine	45	57	83	**87**
±**2**	Pyrrolidine	63	85	82	**90**
3	*n*-$BuNH_2$	9	27	89	**95**
3	*t*-$BuNH_2$	<0.5	14	59	**68**
3	*i*-Pr_2NH	<1	10	11	**62**
3	$(C_3H_5)_2NH$	4	11	54	**60**
3	Morpholine	24	37	84	**85**
3	Piperidine	15	47	72	**94**
3	Pyrrolidine	63	70	75	**97**

Table 2 Organocatalytic ring opening of styrene oxide in water



rac-**4** *rac*-**5** *rac*-**6**

Nu[a]	DCM no cat.	DCM cat.	H_2O no cat.	H_2O cat.	Ratio[b] **5** : **6**
t-$BuNH_2$	2	17	61	71	1 : 2
PhSH	19	32	45	76	1 : 4
PhOH	11	30	30	74	1 : 1
C_3H_5OH	<1	6	30	74	1 : 2

[a] Yields and ratios for the catalyzed reaction in water for: *n*-$BuNH_2$ = 96% (3 : 17); *n*-Bu_2NH = 80% (1 : 1); morpholine = 85% (1 : 1); $(C_3H_5)_2NH$ = 92% (1 : 1). [b] For the catalyzed reaction in water.

The formally observed "hydrophobic amplification" is a key element in enzyme catalysis, but is, to the best of our knowledge, a novel concept in organocatalytic reactions with neutral molecules. Similar effects were recently reported by Sharpless *et al.* for "on-water chemistry"[15] that may perhaps be rationalized by similar interactions.

To probe this concept further, we utilized DFT computations and discuss the complexes as well as the transition structures (TSs) for the opening of ethylene oxide (**7**) with NH_3 with and without thiourea (**8**) in the gas phase, CH_2Cl_2, and water as model clusters (Fig. 2 and 3†). We find that the interactions of an individual water molecule with **7** is more favorable than the water dimer (D_0 = 1.1 kcal mol^{-1} at our reference level) but less favorable than with **8** (*cf.* dissociation energies in Fig. 2). Note that the symmetric (C_{2v}) complex of a water molecule with **7** is not a minimum. Higher (*e.g.*, ternary) complexes are less likely to be involved.

The computed competition reaction for the thiourea (**8**) hydrogen bonds (eqn (1)) reveals that the various complexes are comparable in energy. However, this only takes one water molecule into account (not water) that would otherwise be very

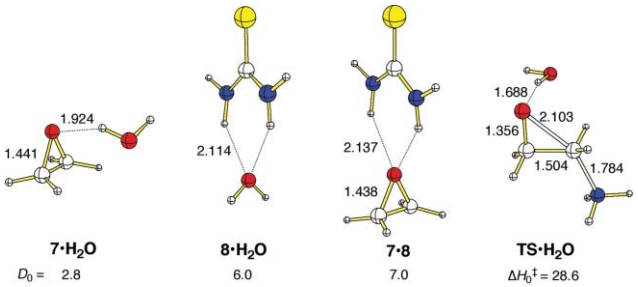


Fig. 2 Hydrogen bonded complexes of the reactants with dissociation energies (D_0) and the TS for the water-catalyzed opening of **7** at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d).

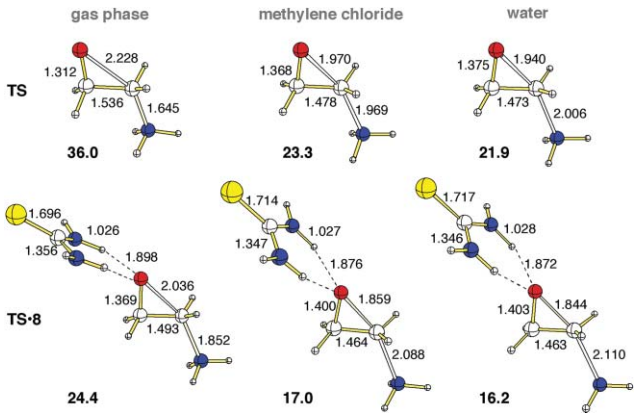


Fig. 3 TSs for uncatalyzed and thiourea-catalyzed epoxide openings in the gas phase, CH_2Cl_2, and water at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) (SCRF solvent inclusion). Selected bond distances in Å. Activation barriers (bold) in kcal mol^{-1}. Red = O, white = C/H, blue = N, yellow = S.

strongly bonded to other water molecules in bulk water. Hence, the small thermodynamic preference for the complex of thiourea with the epoxide (**7**·**8**) is likely to be a lower limit. This is especially true for our highly electron deficient thiourea catalyst that will bind more strongly to the substrate.

$$\mathbf{7} + \mathbf{8}\cdot\mathbf{H_2O} \xrightarrow{\Delta H_0 = -0.6} \mathbf{7}\cdot\mathbf{8} + H_2O \qquad (1)$$

The uncomplexed zwitterionic transition structures display large solvent effects that follow rational geometric patterns (Fig. 3, top). The TS in the gas phase is far along the reaction path (highest barrier) as evident from the short C–N and the long C–O distances. As the solvation power increases from CH_2Cl_2 to water the barriers are lowered and the TSs occur earlier along the reaction path (longer C–N and shorter C–O distances). These findings are paralleled when the TSs are complexed with thiourea.

Table 3 Aminolysis of propene oxide (conditions as in Table 1)

Nu	Time/h	Yield % (H_2O)	Yield % (D_2O)
t-$BuNH_2$	21	94	76
Morpholine	36	83	62
i-Pr_2NH	21	64	38
$(C_3H_5)_2NH$	36	87	41

Remarkably, the bond distances between the TS moieties and the thiourea hydrogen bond donor also decrease with increasing solvation power (this is also true for the complexes of thiourea and epoxide†). That is, the interactions are indeed amplified in water and the corresponding barrier is the lowest overall. While water stabilizes polar transition states, the additional rate enhancement with **1** is likely to be due to its inclusion into the hydrophobic hydration cavity (Fig. 1). The stabilization of the TS with an individual water molecule is also significant (**TS·H_2O**, Fig. 3, right) but considerably less than the bulk water effect. Dynamic modeling of the hydrophobic effect would be highly desirable.

Further evidence for this effect is provided by the 20–40% decrease in the yields (Table 3) when the reactions are carried out in D_2O instead of H_2O. D_2O has a *ca.* 20% higher viscosity that makes mixing more difficult and reduces the hydrophobic effect.[14]

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