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The Mechanism of On-Water Catalysis

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Sharpless and co-workers[1] used the term on-water to describe the substantial rate acceleration that is observed when some insoluble organic reactants are stirred in aqueous suspension. We now propose a mechanism that accounts for the phenomenon of on-water catalysis. Three of the observations of Sharpless and co-workers are directly pertinent to the mechanism we propose below. Firstly, the reaction mixture must be heterogeneous, that is, there must be an interface between the organic reactants and water. The presence of some methanol in the aqueous phase made little difference to the rate of the reaction, "but the rate slowed considerably when enough methanol was used to make the reaction homogeneous." Secondly, the interface must be with an aqueous phase. An emulsion formed with the organic reactants in perfluorohexane gave an only slightly enhanced rate. Thirdly, there was a significant solvent isotope effect, with a noticeably slower rate in D_2O.

Our proposed mechanism is supported by two additional considerations. One is that all of the reactions that have been described as accelerated by the on-water effect (with the possible exception of those of metal complexes) are also known to be subject to acid catalysis.[1,2] This suggests that acid–base chemistry at the interface is responsible. Hence the second consideration is our recently developed model that explains the intrinsic charge that develops at the interface of water with low relative permittivity (low dielectric constant) materials.[3] This model accounts for the numerous observations made over many decades that the surface of water at these interfaces, whether they are with gas, liquid or solid, becomes negatively charged by the strong adsorption of hydroxide ions.[4,5] The adsorption equilibrium constant can be estimated from the pH dependence of the zeta potentials of oil drops in water to be at least 10^8.[6]

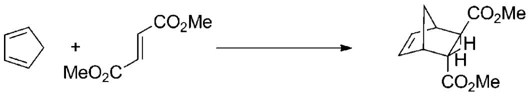
At first this seems unlikely to account for acid catalysis at the same interface, but a little reflection reveals that this counterintuitive result is to be expected. Consider a substrate that is activated by protonation. Reaction with water at the interface results in the protonated activated substrate and a hydroxide ion that is stabilised by its strong adsorption at the interface. This drives the protonation equilibrium of the substrate [Eq. (1)] strongly to the right and accounts for acid catalysis even in neutral solution.

$$\mathrm{S} + \mathrm{H_2O} \rightleftharpoons \mathrm{SH^+} + \mathrm{OH^-}_{\mathrm{ads}} \quad (1)$$

$$\mathrm{SH^+} \rightarrow \text{products} \quad (2)$$

This mechanism accounts for all of the available evidence described above. It requires water, at the interface with the organic reactants, which provides the conditions for the protonation of the substrate, driven by the adsorption of the hydroxide ion product, with the associated deuterium isotope effect, leading to acid catalysis and the enhanced rate.

We now describe additional experimental evidence consistent with this mechanism. We chose to examine another Diels–Alder reaction, that between cyclopentadiene and dimethylfumarate (Scheme 1). In addition to having a rate that is convenient to measure, this reaction possesses other advantages: 1) the use of symmetric reagents removes any *endo, exo* stereochemical ambiguities; 2) the ester units of the dienophile do not react with water itself, so no background rate correction is required; and 3) the volatile diene can be easily evaporated allowing the relative proportions of the non-volatile fumarate and product to be measured directly by NMR spectroscopy.



Scheme 1. Diels–Alder [4+2] cycloaddition.

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Following the approaches adopted by previous authors,[1,2] we first compared the rates of reaction in different solvents by monitoring the conversion of fumarate to product using identical amounts of reactants for a fixed reaction time of thirty minutes (Table 1). Because of the generally low solubility of the organic reactants in water, it is often difficult to measure the very slow reactions of the substances fully dissolved in-water. We have adopted a pragmatic approach by comparing the on-water rate of the reaction performed with vigorous stirring to create an emulsion to what we will term the at-water rate of the reaction performed with gentle stirring so that the organic phase is not mixed with the aqueous phase and the area of the interface between the phases is minimised. This should approximate the rate of the neat reactants mixed together, a supposition supported by the data in Table 1, with 45 % conversion for the neat reaction and 40 % conversion for the at-water conditions. By this means we observed that the reaction was indeed accelerated by rapid stirring to form an emulsion, with a higher yield than under at-water conditions of gentle stirring, or dissolved in THF, or neat. The same high conversion was found on-water and on-water containing 1 mM, or 10 mM NaCl (see the Supporting Information).

Table 1. Solvent effect on the yield of the [4+2] cycloaddition of cyclopentadiene and dimethylfumarate at room temperature after a reaction time of 30 min.

Solvent[a]	Conversion [%][b]
on-water	75
on-D_2O	56
at-water	40
neat	45
THF (0.1 M)	16
THF (0.2 M)	32
DCM (0.1 M)	16
DCM (0.2 M)	40
on 10 mM aq. NaCl	69

[a] For standard reaction conditions see the Supporting Information. [b] Measured by ^1H NMR analysis of the reaction mixture after evaporation of the diene.

Subsequently we observed the first-order kinetics of the reaction by measuring the disappearance of the fumarate from replicate samples quenched at regular intervals (Figure 1).

The same technique was used to determine the influence of D_2O on the reaction rate. As shown in Figure 2, the rate is clearly faster on-water than at-water, and faster on-water than on-D_2O, with a kinetic isotope effect of 1.4. A value of 1.2 was reported for another cycloaddition reaction according to unpublished results cited in reference [7]. According to our mechanism the deuterium isotope effect will be a complex product of the effect on the autolysis of water, any effect on the adsorption of hydroxide ion at the interface, as well as the effect on the protonation and reaction of the substrate.[8]

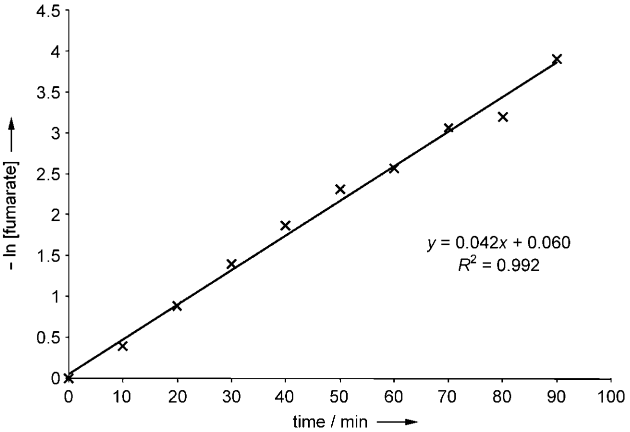

Figure 1. Plot of −ln [furmarate] versus time, showing first-order kinetics.

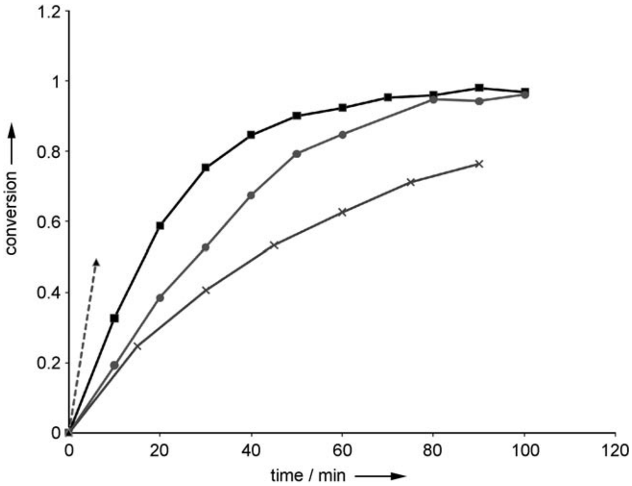

Figure 2. Comparison of reaction rates at-water (×), on-water (■), on-D_2O (●) and on-water using a piston homogeniser (▲).

When the reaction mixture was passed through a four-stage piston homogenizer[9] to reduce the droplet size the rate was increased significantly (Figure 3) reaching 49 % conversion in the six minutes required to homogenize the solution. (It will be necessary to study a slower reaction to make a quantitative determination of the effect of droplet size on the rate.)

Up to this point, the reactions were performed in water at its natural pH of 5.6 with no protection from air. To exclude the possibility that the observed rate enhancements resulted from partial dissolution of the reactants into the acidic bulk solvent, the reactions were conducted at pH 9. As shown in Figure 3, the rate of the on-water reaction was independent of the pH of the aqueous medium. Indeed, the on-water reaction was faster than the at-water reaction conducted in 1 mM, 10 mM, or 1 M aqueous HCl (see the Supporting Information). In no case was any ester hydrolysis observed.

All of these observations are consistent with the mechanism proposed above. The rate-determining step of the reaction occurs at the interface and increases with the surface

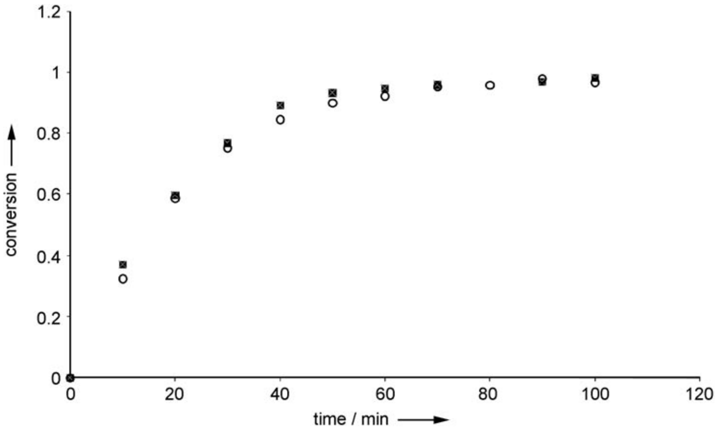

Figure 3. Rate dependence on pH. (■) on pH 9 water, (○) on-water.

area of the interface. It does not involve dissolution of the dieneophile into the aqueous medium, as the rate is independent of the aqueous pH. It is not affected by the addition of mM NaCl to the water, which has the effect of releasing the protons in the double layer by replacing them with sodium ions, but these released protons are not catalytically active. Neither are the strongly adsorbed hydroxide ions, for they lie in a deep thermodynamic well; hence no on-water accelerated reactions are base-catalysed. The rate-determining step is the protonation of the fumarate ester by interfacial water, which accounts for the deuterium isotope effect, and the first-order kinetics.

Jung and Marcus have proffered an alternative mechanism that, however, they recognised was not consistent with all of the evidence available at the time. It involves the stabilisation of the activated complex by hydrogen bonding to the interfacial water.[7] This was consistent with the acceleration involving an interface with water, but did not account for the deuterium isotope effect, which they recognised, nor the acid catalysis, which they did not address. They predicted that, if the azodicarboxylate dieneophile used in the original Sharpless study were replaced by an olefin or acetylene group with less hydrogen bonding ability, the effect would be almost eliminated. Our results indicate that this is not the case.[10]

Acevedo and Armacost recently used simulations to examine the on-water reactivity of a Claisen rearrangement,[11] and others have used quantum and mechanical modelling of the Diels–Alder reaction,[12] but neither group considered the acid catalysis. Cozzi and Zoli[13] reported the on-water catalysed nucleophilic substitution of a series of benzylic alcohols (a reaction known to be acid catalysed) and invoked a carbocation intermediate, which is in perfect agreement with our proposed mechanism. In the Supporting Information we briefly describe how other reactions that do or do not display on-water catalysis are consistent with the proposed mechanism.

In summary, the on-water effect can be explained by a simple acid-catalysis mechanism facilitated by the strong adsorption of the hydroxide ion by-product at the oil–water interface. With this understanding, the effect can be exploited in a rational way for new synthetic pathways.

Acknowledgements

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Keywords: biphasic catalysis · cycloaddition · green chemistry · interfaces · water chemistry

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[1] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
[2] A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725.
[3] A. Gray-Weale, J. K. Beattie, *Phys. Chem. Chem. Phys.* **2009**, *11*, 10994.
[4] J. K. Beattie in *Colloid Stability—The Role of Surface Forces—Part II, Vol. 2* (Ed.: T. Tadros), Wiley-VCH, Weinheim, **2007**, p. 153.
[5] J. K. Beattie, A. M. Djerdjev, G. G. Warr, *Faraday Discuss.* **2009**, *141*, 31.
[6] P. Creux, J. Lachaise, A. Graciaa, J. K. Beattie, A. Djerdjev, *J. Phys. Chem. B* **2009**, *113*, 14146.
[7] Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492.
[8] While specific acid catalysis is generally faster in D_2O, the autolysis of water is an order of magnitude smaller in D_2O. These two opposing effects, together with any isotope effect on the adsorption of OH^-, as yet unknown, lead to the small observed kinetic isotope effect.
[9] L. Kong, J. K. Beattie, R. J. Hunter, *Chem. Eng. Process.* **2001**, *40*, 421.
[10] We are aware of a report (in ref. [2]) of unpublished observations that an acetylenedicarboxylate does not show any rate enhancement, in accord with the Jung and Marcus prediction. Acetylenedicarboxylates have long been considered the most activated dieneophiles, rendering it unlikely that a Diels–Alder reaction involving this species could be accurately monitored. We must await more evidence to resolve this contradiction.
[11] O. Acevedo, K. Armacost, *J. Am. Chem. Soc.* **2010**, *132*, 1966.
[12] L. L. Thomas, J. Tirado-Rives, W. L. Jorgensen, *J. Am. Chem. Soc.* **2010**, *132*, 3097.
[13] P. G. Cozzi, L. Zoli, *Angew. Chem.* **2008**, *120*, 4230; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162.

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