Organocatalysis

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Water in Organocatalytic Processes: Debunking the Myths

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The past several decades have witnessed a tremendous growth in the application of catalytic routes to the synthesis of complex organic molecules, driven by academic and industrial discoveries of efficient, selective catalysts for a wide variety of liquid- and multiphase organic transformations. These developments coincide with major efforts in the pharmaceutical and chemical industries toward streamlining the costs of manufacture and waste disposal in an evermore economically competitive and ecologically aware market. The area of organocatalysis has received much attention in light of a perception both of its green chemistry advantages and its analogy to eon-perfected enzyme catalysis. Most recently, the challenge of developing efficient aqueous-phase organocatalytic processes has been posed. Water is a beguiling solvent: biological processes are conducted in water; some organic reactions are accelerated by water, while others are inhibited in this medium. Hydrogen bonding, polarity, acidity, entropy, and hydrophobicity all have important roles to play in the ultimate influence that water exerts on organic reactions mediated in its presence. The varied behavior that these properties can impart makes water an interesting candidate as a solvent or cosolvent from an industrial perspective, even before its potential environmental benefits are considered.[1]

We contribute herein to the recent exchange published on the specific issue of enamine-based organocatalysis carried out in systems containing water.[2] Janda and co-workers[2a] began the discussion with important comments about the mechanistic implications of one's choice of reaction conditions, and they noted that development of a truly aqueous version of a reaction catalyzed by a small-molecule catalyst remains a challenge. In response, Hayashi[2b] chose to focus on what he sees as simply "confusion over the terminology", that is, whether we should say that a reaction is carried out "in water", "in the presence of water", or "in the presence of a large excess of water". Indeed, the subject now seems in danger of being mired down in semantics at the expense of science. We would like to address several critical aspects that we feel have been neglected in the discussion to date. We pose two questions that directly challenge our assumptions about aqueous-based organocatalysis: how "green" and how efficient are aqueous-based organocatalytic reactions.

How "Green" Is an Organocatalytic Reaction Carried Out "in the Presence of Water?"

As stated by Hayashi,[2b] "water is environmentally friendly and safe, and the problems of pollution that arise with organic solvents can be avoided." Certainly, pure water is environmentally friendly, but organic reactions carried out in water or in the presence of water add complications to this picture that must be considered. Indeed, what we have in such cases is essentially a water stream contaminated by organics. Strict regulations govern how wastewater-process streams may be released to the environment, including the Water Framework Directive,[3] the most substantial piece of water legislation ever produced by the European Commission. Water is only a truly green solvent if it can be directly discharged to a biological effluent treatment plant (BETP).

Thus, the problem for "water-based" organocatalytic processes is how to get the organics *out* of the water! A neglected point in the discussion to date is that most often we make the problem worse at the end of the reaction by adding further organics in product workup protocols. A quick survey of some of the recently published articles on "water-based" organocatalysis demonstrates that the volume of organic solvent used in the workup exceeds the total volume of water used in the reaction by factors of up to 30-fold. Thus, it is not simply the reaction medium that must be considered when evaluating the "greenness" of a process; the reaction workup must also be factored into the equation.

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A number of organic solvents most commonly used for extractions now have, or will have in the future, such low permitted levels in water that removal is too costly. For example, hexachlorobenzene and trichlorobenzene have environmental quality (EQ) standards of 0.03 and 0.4 $\mu g L^{-1}$, respectively. Solvents such as ethanol and ethyl acetate that are readily biodegradable cannot simply be discharged because high levels are toxic to microorganisms (targets range from less than 0.1% to about 1.5%). Aqueous waste contaminated with organics must either be stripped under vacuum, incinerated, or treated with activated carbon. Stripping requires energy, incineration is problematic because waste streams often have low calorific value, and activated carbon must be burned in its turn.[4] Thus, in many cases, a comparative analysis will conclude that an organic-solvent-based process is cheaper, easier, and ultimately environmentally more sound than a water-based organic reaction is.

A further environmental "red herring" that was also noted by Janda and co-workers,[2a] albeit for different reasons, concerns the relative amounts of water and organic reactants employed in many of these studies. In most cases that boast environmentally friendly water-based reactions, water makes up only about 10% of the total reaction volume, even when it is in large excess of the limiting reagent. Most often, an even greater excess of one of the reactants is employed, effectively making it serve as both reactant and organic solvent. Indeed, most claims of "solventless" reactions turn out to fall in this category.[5] While an academic approach may be unconcerned with the fate of the nine leftover equivalents of a reagent used in tenfold excess, the environmental problem posed in such a case would not escape the notice of an industrial process chemist. Even more to the point, however, is that a process that effectively utilizes only one molecule out of ten is not atom-economical; in a pharmaceutical process, this excess component may itself be the costly product of a multistep synthesis, and employing it in excess in lieu of a much cheaper organic solvent makes neither economic nor environmental sense.

How Efficient is an Organocatalytic Reaction Carried Out "in the Presence of Water?"

Discussions lauding the advantages of water-based organocatalysis invariably cite the striking results of Breslow,[6] who reported strong rate acceleration for Diels–Alder reactions carried out in water. We note that in the context of most of the organocatalytic examples under discussion, this comparison is misleading. Breslow's group carried out detailed and exhaustive studies to understand the effect of water in their reactions, with the conclusion that the accelerating effect is due to the bringing together of nonpolar segments of the reactants in the transition state. None of the water-based organocatalytic reactions have been studied extensively enough to claim mechanistic analogies to that work, and, indeed, the experimentally observed influence of water on the rate of organocatalytic reactions is not straightforward. As noted by Janda and co-workers,[2a] acceleration of an enamine-based mechanism in water is counterintuitive. The best studies of the role of water in organocatalytic reactions are those conducted by Pihko and co-workers,[7] who were the first to note that the presence of water enhanced the yield in proline-mediated aldol reactions, allowing smaller excesses (even stoichiometric amounts) of the donor reactant to be employed. Their careful work showed that water suppresses the formation of proline oxazolidinones; it has been suggested that the role of water is primarily to prevent deactivation rather than promote activity.[8] Similar arguments have been used to rationalize the effect of silica surfaces on the activity of homogeneous metal complexes used as catalysts in olefin metathesis.[9] However, the intrinsic effect of water in proline-mediated aldol reactions has not yet been deconvoluted from its role in suppressing catalyst deactivation. Citing the work of Breslow in the context of water in these organocatalytic reactions is not justified without the benefit of careful kinetic and mechanistic studies.

The tacit assumption that combining the words "aqueous" and "organocatalytic" necessarily provides an environmentally and economically sound process may distract us from focusing on the basic chemistry research needed for future breakthroughs in the discovery and development of new catalysts and new reactions. As a case in which the details belie the buzzwords, we consider the (salen)Co-catalyzed hydrolytic kinetic resolution of epoxides (HKR) by Jacobsen and co-workers.[10] This truly solventless reaction uses catalyst loadings as low as 0.0001 mol% Co, starts out with 1 equivalent of racemic epoxide to 0.55 equivalents of water, and yields approximately 0.5 equivalents of enantiopure epoxide and about 0.5 equivalents of nearly enantiopure diol.[11] Yet as a kinetic resolution, where by definition only 50% of the substrate is turned into the desired product, and as a metal-catalyzed reaction, the HKR has not received the level of green attention—either scientific or semantic—that has been devoted to the environmentally and economically unproven organocatalytic reactions carried out in the presence of water. The success of the HKR arises from a creative discovery and the marriage of sound fundamental science with innovative process research. By contrast, as of yet neither synthetic and mechanistic advances nor process considerations support the theme of "just add water" as the key to future general advances in organocatalysis.

In conclusion, the environmental and economic assessment of an aqueous-based organocatalytic process is shown to involve a complex set of parameters. A holistic approach[12] that considers not only the reaction step but also the economics and environmental impact of product workup and reagent preparation provides the key to making an informed decision on the benefits of water on a case-by-case basis. A fundamental mechanistic understanding of the role of water in any reaction is necessary before its general use in organocatalytic reactions may be advocated.

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[3] For a comprehensive discussion of this directive, see the following website: http://www.euwfd.com/.

[4] Interestingly, note that many "green" solvent alternatives such as ionic liquids and fluorous-phase compounds exhibit one or more of the three properties of most environmental concern: toxicity, bioaccumulation, and persistence.

[5] Thermal process safety considerations is another neglected aspect of most truly solventless reactions, although a full discussion of this is beyond the scope of this Essay.

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