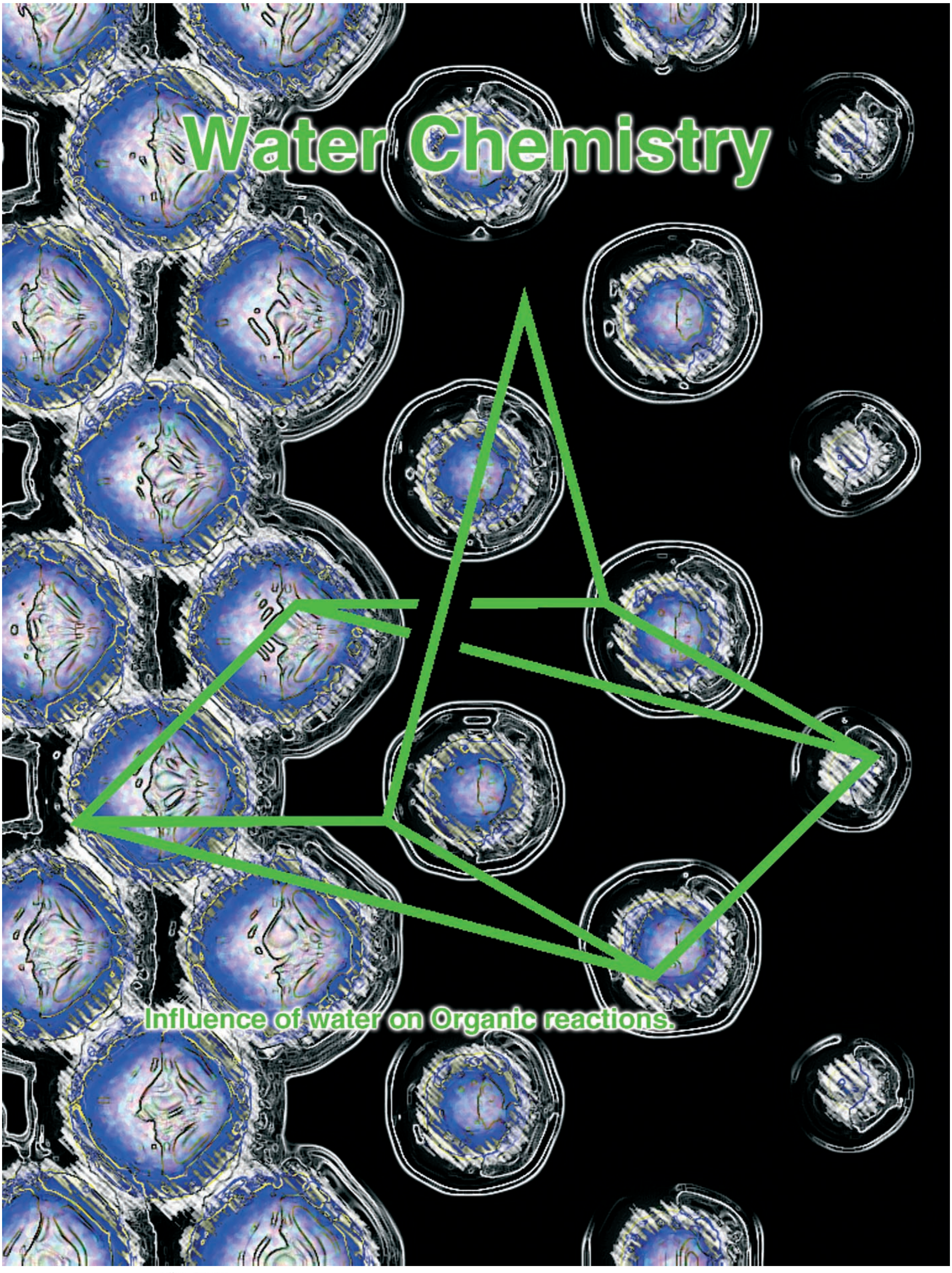
Water Chemistry
Influence of water on Organic reactions.

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Acceleration of Organic Reactions through Aqueous Solvent Effects

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Abstract: The parallels between organic reactions conducted with water as the solvent and reactions conducted under high pressure can be understood in light of theories of aqueous solvation and hydrophobic effects. Such parallels provide powerful tools for promoting reactions of nonpolar compounds.

Keywords: green chemistry · high-pressure reactions · solvent effects · water chemistry

Introduction

Solvent effects are among the earliest principles first learnt by students of chemistry. Typically, these effects fall along the polar/nonpolar and protic/nonprotic axes, and their utility is large in both understanding mechanistic detail and efficiently conducting preparative reactions. The solvent effects to be discussed in this Concepts article fall outside of these. For some chemists, solvent effects may have been discussed so long ago during their education and are so unrelated to everyday practice that they are forgotten. A few chemists may use such principles daily. Many aspects of the understanding of solvent properties were topics of active research decades ago, and modern curricula have not allowed time for these principles to be learned by today's chemistry students. Thankfully, much of this information has been captured in monograph form, the foremost being the book of Reichardt, which has recently been updated.[1] This excellent resource can be profitably consulted for useful reminders of relevant considerations of solvent in almost any aspect of organic reactions.

This article is limited to the influence of aqueous solutions on the rates of organic reactions, especially those for which water's polarity is not the only role. Water has been heavily investigated recently as a replacement for more conventional organic solvents, because of its low cost and its avoidance of organic vapors; it has thus been identified as a "green" solvent.[2] As a consequence, conditions under which a wide range of reactions can be conducted in water have been developed,[3] including those ordinarily thought to be intolerant of protic solvents, such as Lewis acid catalyzed[4] and organometallic reactions.[5] Advances in this field have required development of novel, mostly transition-metal reagents that exhibit at least kinetic stability toward water. In these cases, too, water may play a small role in the reaction itself. Because the main aim of such studies was simply to use water as the solvent, there may have been small incentive to directly compare the aqueous reaction with reactions in organic solvents.

Results and Discussion

Water occupies a special place in chemistry, because of its role as the solvent for all of the chemical reactions of life. As such, it is important to consider some of the properties of aqueous solutions. A solution of a polar molecule, such as a soluble salt or a carbohydrate, in water benefits from the formation of hydrogen bonds and dative bonds (enthalpically favorable), but suffers from loss of entropy because of restriction of translational and rotational degrees of freedom of solvent molecules (Scheme 1). Such enthalpy–entropy compensation is a broadly observed phenomenon for a wide variety of the properties of water. Aqueous solutions also experience a change in colligative properties, such as freezing and boiling points. A nonpolar molecule, such as an organic hydrocarbon, is solvated in water differently than ions. A cage or clathrate of water molecules forms around the nonpolar solute, effectively creating a "hole" in the solvent, while benefiting from water–solute van der Waals interactions. To quote Reichardt, "The introduction of apolar molecules (such as hydrocarbons or noble gases), or apolar residues in otherwise polar molecules (such as alkyl side chains in biopolymers) into water leads to a reduction of the de-

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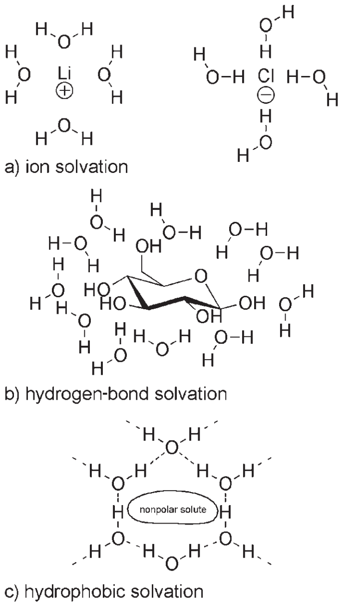

a) ion solvation
b) hydrogen-bond solvation
c) hydrophobic solvation

Scheme 1. Different modes of aqueous solvation.

grees of freedom (spatial, orientational, dynamic) of the neighboring water molecules." While this is in fact his definition[6] of the hydrophobic effect, it is worth emphasizing that, despite decades of research, the origins of this effect and many other aspects of the behavior of water are still not clearly understood.

Solubility has been a key consideration in the development of theories of solvents. It also has practical consequences in the choice of reaction solvents, in which miscibility is important, or solvent partition/extraction solvents, for which immiscibility is key. Quantitation of the "like dissolves like" dictum has been examined by many workers, with one prominent measure being the Hildebrand solubility parameter δ. This parameter is tabulated for several pure liquids commonly used as reaction and/or extraction solvents in Table 1. A guideline is that liquids will be miscible in all proportions when their Hildebrand parameters differ by no more than three. Even beginners at organic chemistry gain experience with questions of miscibility and solubility as they are faced with the task of extracting a water-soluble organic reaction product, say 2-methylcyclohexanone produced by chromic acid oxidation, from an aqueous–organic solvent mixture. The classic means to deal with this problem is the addition of NaCl to the aqueous phase, a so-called "salting-out." The presence of the ionic species reduces the solubility of the organic molecule in the aqueous phase, driving it to the organic extraction solvent. In the context of the theory of aqueous solutions, one can see that this salting tactic has occupied solvent molecules in organizing around and solvating ions, increasing the free energy of hydrophobic molecules when in the aqueous phase and favoring their partition to the organic phase. While not used in solvent extractions, it should be kept in mind that "salting-in" or chaotropic salts are also known, that is, those that enhance the solubility of hydrophobic molecules in aqueous solutions. Guanidinium thiocyanate is one example.

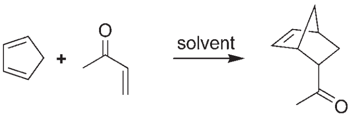
Table 1. Hildebrand parameters, relative permittivities, and cohesive pressures of some pure liquids at 25 °C.

Liquid	Hildebrand solubility parameter (δ [MPa$^{1/2}$])	Permittivity (relative to vacuum, ε_r)	Cohesive pressure [cal cm^{-3}]
water	47.9	78.4	550.2
formamide	39.3	109.5	376.4
methanol	29.6	32.7	208.8
dimethylsulfoxide	26.5	46.4	168.6
ethanol	26.0	24.6	161.3
dimethylformamide	24.7	36.7	139.2
acetone	20.2	20.6	94.3
tetrahydrofuran	18.6	7.6	86.9
diethyl ether	15.4	4.2	59.9

Static permittivity is another solvent parameter tabulated here. It reflects the ability of a solvent to support ion dissociation, and thus is widely used to understand reactions involving charged intermediates. It is often erroneously referred to as the dielectric constant. A third solvent parameter provided in Table 1, one that is far more obscure than it should be, is the cohesive energy density (or c.e.d.). It is also known as cohesive pressure, as the units cal cm^{-3} correspond to a pressure. To convert into more familiar pressure units, 23.8 cal cm^{-3} = 1 kbar = 100 MPa. Thus, the cohesive energy density of water corresponds to a pressure of approximately 23 kbar. The c.e.d. also can be expressed in more familiar energy units; for water, this intermolecular binding energy is 9.9 kcal mol^{-1}. The square root of the cohesive pressure is also the Hildebrand parameter. In formula form [Eq. (1), in which M_r = relative molecular mass and ρ = density], the c.e.d. corresponds to the heat of vaporization of the liquid less an RT term that interconverts enthalpy and energy, divided by the molar volume. In qualitative terms, cohesive pressure is the intermolecular force that gives liquids their cohesion, and is related to the energy needed to separate a molecule from its neighbors, factored by the volume of the molecule removed. In other words, it is related to the energy required to create a cavity in the liquid.[7] One can thus perceive a relationship between the c.e.d. and the hydrophobic effect. The cohesive pressure of water is the highest among many other liquids due to a unique trait, that is, its very high heat of vaporization for its quite low molecular mass. As these terms enter cohesive pressure in the numerator and denominator, respectively, they work in concert to give a very high c.e.d.

$$\text{c.e.d.} = \frac{\Delta H_{\text{vap}} - RT}{M_r/\rho} \tag{1}$$

With these simple properties and theories of solutions secure, we consider some unusual aqueous solvent effects on organic reactions. A classic experiment is Breslow's demonstration that the Diels–Alder cycloaddition of cyclopentadiene and methyl vinyl ketone is accelerated nearly 300-fold in water compared to acetonitrile.[8] This result was provocative because of the presumed absence of charged intermediates in Diels–Alder reactions, meaning this result could not be explained through the polarity of water. A reasonable explanation for this result was enhanced interactions between the reactants through hydrophobic interaction, which Reichardt explains as follows: "it is energetically advantageous for apolar molecules, or apolar groups in otherwise polar molecules, when dissolved in water, to aggregate with expulsion of water molecules from their hydration shells." Another way to view this situation is that the high surface tension of water (72 dyne$\,$cm^{-1}) favors minimal contact between hydrophobic and water molecules. Not considering rate effects, Diels and Alder actually conducted the very first Diels–Alder cycloaddition (furan with maleic acid) in water in 1931. Foreshadowing matters to be discussed later, they reported vigorously shaking the reaction mixture.



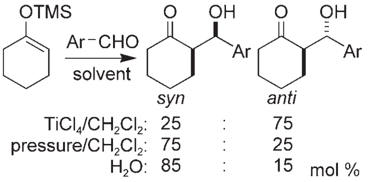
$k_{H2O}/k_{MeCN} = 290$

Scheme 2. Acceleration of a Diels–Alder reaction in an aqueous medium compared to organic solvent.

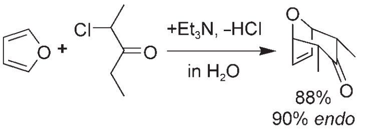
Certainly, another well-known method for promoting the Diels–Alder reaction is the application of pressure. This tactic is effective for *any* reaction that has a significant, negative volume of activation. The volume of activation is defined as the molar volume of the transition state less the molar volumes of the reactants. While chemists are accustomed to understanding the impact of energy on reactions in units of kcal$\,$mol^{-1}, an intuitive sense about activation volumes is uncommon. The Diels–Alder reaction between cyclohexadiene and maleic anhydride has $\Delta V^{\neq}$ of $-37\,cm^3\,mol^{-1}$, which would be considered fairly large and which makes the reaction significantly pressure sensitive. Activation volumes as large as $-70\,cm^3\,mol^{-1}$ are known.[9]

Following on the heels of these studies, Grieco attempted to connect reaction promotion by high external static pressures to the high internal pressure in solvents like water.[10] He reported significant rate accelerations for Diels–Alder reactions in 5$\,$M $LiClO_4$/diethyl ether, initially implying that such solutions compress reactants in a manner analogous to external pressure. Subsequent studies have instead attributed the rate acceleration to Lewis acid catalysis.[1,11]

In 1986, in studies of the Mukaiyama aldol reaction in aqueous solution, Lubineau hypothesized that "a reaction under kinetic control between two nonpolar molecules for which $\Delta V^{\neq}$ is negative must be accelerated in water *as it is under pressure*."[12] Support for this idea came from his studies of the reaction of the silyl enolate of cyclohexanone with aldehydes (Scheme 3). As shown by Yamamoto,[13] when conducted under high pressure this reaction shows a reversal in stereoselectivity (75:25 *syn*:*anti*) with respect to the Lewis acid promoted version at standard temperature and pressure (25:75 *syn*:*anti*). Yamamoto explained his observation by asserting that the transition state leading to the *syn* isomer is more compact; in other words, competition between the diastereomeric pathways is controlled by the magnitude of $\Delta V^{\neq}$; the pathway with the smaller $\Delta V^{\neq}$ value is favored. When Lubineau conducted the same reaction in water, the stereochemistry he observed was 85:15 *syn*:*anti*, drawing a direct correlation between the Mukaiyama aldol reaction in water and that under high pressure. Similar correlations with other reactions, such as the Michael reaction and oxyallyl cation cycloaddition (Scheme 4), have been observed many times since and are discussed Lubineau's reviews on the subject.[14] As in Breslow's work on the aqueous Diels–Alder reaction, Lubineau has shown that in the presence of structure-making solutes like carbohydrates or salts, rates of reactions are accelerated, and with structure-breaking solutes, like methanol, rates are slowed. These observations point to the hydrophobic interaction as a key element of the rate acceleration in aqueous solution, as well as make these reactions even more practical.



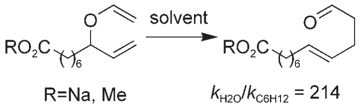
Scheme 3. The outcome of a Mukaiyama aldol reaction in an aqueous medium is similar to a corresponding high pressure reaction.



Scheme 4. An oxyallyl cation cycloaddition is conducted very effectively in an aqueous medium.

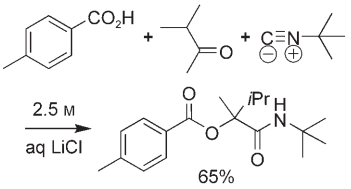
The observation of slower reactions in the presence of organic co-solvents raises a common concern with reactions of organic molecules in water, that their solubility limits reaction efficiency. A conceivable consequence would be that rate acceleration applies only to water-soluble reactants. This may be a fallacy, however, and just the opposite is more likely. Fully water-miscible molecules should not experience the hydrophobic solvation that is essential for the rate acceleration. Heterogeneous reactions need not be intrinsically inefficient, though the highest possible rate of phase transfer is crucial for maximum efficiency. Indeed, efficient methods of mixing have been an important element of the reactions of organic substances in water, from Diels and Alder to Lubineau, who used violent shaking and ultrasound-promoted reactions in even his earliest report.

While it is readily understandable that reactions such as cycloadditions and condensations may have negative reaction volumes and negative $\Delta V^{\ddagger}$, other concerted reactions, such as the Claisen rearrangement, also have negative activation volumes[15] and are accelerated both by pressure and by aqueous media. Careful analysis by Gajewski has demonstrated that a Claisen rearrangement in water (Scheme 5) is accelerated about equally by hydrophobic interactions (the c.e.d. effect) and the hydrogen-bond donating ability of water.[16]



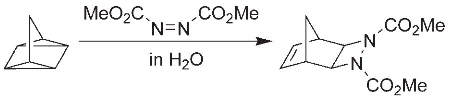
Scheme 5. The Claisen rearrangement is accelerated in an aqueous medium as compared to organic solvent.

While it seems that the physical organic world had a strong grip on understanding of the main factors involved in reaction acceleration in water, as evidenced in recent reviews,[17] this information has not been widely enough known in the synthetic community. In our study of multi-component reactions in aqueous solutions,[18] we have shown that reactions that are accelerated by high pressure can also be accelerated in water (Scheme 6). The increase in rate over organic solvent approaches 300-fold in some cases. Furthermore, direct comparison to reactions in methanol and formamide provides support for the idea that the cohesive pressure of water, rather than its protic nature or polarity, plays a dominant role in the rate enhancement. We also showed an inverse dependence of reaction rate on temperature, which clearly identifies the entropy term (which includes $\Delta V^{\ddagger}$) as an important contributor to the reduced free energy of activation. Inverse temperature dependence of the rate is seen in other multi-component and water-accelerated reactions.[19,20] These observations are also consistent with the dominant role of e.d, as water's cohesive pressure decreases with increasing temperature. This is in contrast with water's internal solvent pressure,[1,7] which increases with temperature until its maximum at 150 °C. One factor that has not been given enough attention in earlier studies of reactions in water is the effect of mixing. With organic molecules that are clearly not water-miscible, reactions in water may have significant heterogeneous character. This is not an intrinsic difficulty, as chemists have dealt with heterogeneous reactions for decades, but requires attention to experimental detail, particularly regarding mixing.[21]



Scheme 6. A Passerini reaction in aqueous salt solution that does not occur at all in organic solvent.

Workers at the Scripps Research Institute have recently reported a number of reactions that are accelerated "on water",[22] which they define as insoluble reactants stirred in aqueous suspension. The main distinction between this work and previous studies was the very high (up to 4.5 M!) concentrations of reactants used. One of their most extensively studied examples was the cycloaddition of quadricyclane with dimethylazodicarboxylate (Scheme 7). This is an interesting choice, as *many* cycloaddition reactions of quadricyclane have been shown by Jenner to be accelerated by high pressure.[23] Thus, this reaction has features in common with many earlier reactions accelerated in aqueous solution: a heterogeneous component, which can be overcome by mixing, and a high pressure analogue. An interesting aspect of this reaction is a reduced rate in D_2O. While D_2O has a 3 % higher cohesive pressure than H_2O, it also has a 23 % higher viscosity, which may make mixing more difficult, and is a better solvent for nonpolar solutes; this must reduce the hydrophobic effect.[24]



Scheme 7. Quadricyclane cycloaddition with an azodicarboxylate occurs at high concentration in an aqueous medium.

Conclusion

The main concept to be drawn from this article is that reactions with negative activation volumes, as indicated by their pressure dependence, should be accelerated in aqueous solution over organic solvent when conducted with nonpolar reactants, provided that efficient mixing is assured. Immiscibility of hydrophobic reactants with water is not only *not* a deficit when conducting reactions in water, it may contribute to the rate acceleration observed in water with respect to organic solvents. Water should be considered a "green" solvent for organic reactions not only because of its environmental benefits, but because it signals to a reaction what a driver sees at a traffic signal: green means GO!

Acknowledgements

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