Organic Process Research & Development **2007**, *11*, 114–120

Reaction Solvent Selection: The Potential of Water as a Solvent for Organic Transformations

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Abstract:

The increasing need for more sustainable strategies in organic synthesis has led to a growing interest in the use of water and other nonclassical solvents. This short review focuses on the potential use of water as a reaction solvent, highlighting advantages and the range of reactions that can be carried out in water.

Introduction

With an increasing awareness of the need for more sustainable strategies for synthetic chemistry across academic and industrial communities, most notably for the manufacture of chemicals at scale, several environmentally friendly strategies have been recognized: to carry out reactions neat without the use of solvent; to replace the use of stoichiometric reagents with catalysts; to use biocatalytic processes, and finally to perform reactions in aqueous media or other nonclassical reaction solvents.[1−11] With this emphasis on the use of cleaner green chemistry processes and concerns over the environmental impact of using volatile organic solvents (VOCs), the potential of water or other nonclassical solvents has become highly relevant when designing organic syntheses.[1] Indeed, alternative solvents including water, natural products such as limonene, or other readily available solvents such as polyethylene glycol (PEG) have been shown to be promising in some systems: also supercritical fluids and ionic liquids, or combinations of the systems described above.[1] The use of these alternative reactions solvents can have inherent advantages such as enhanced rates of reaction or fewer or more readily isolated side products as well as facilitating product recovery.

In selecting a solvent for an organic transformation, the reaction must proceed in the solvent selected and consideration must be given to the ease of isolation of the product. Other factors include solvent cost, disposal, toxicity, and hazards arising such as solvent flammability. Typically, most solvents are removed by evaporation, and being volatile, exposure by workers to VOCs and atmospheric pollution is of concern. Others such as polar aprotic solvents have high boiling points and are therefore not readily removed by distillation. Organic solvents are also used for their extraction properties and for overall usage, recovery efficiencies are between 50−80%, they make up approximately 85% of the total mass of chemicals in the manufacture of pharmaceuticals, and usage is at £4 billion per annum.[1,12,13] This short review will highlight the use of water as a reaction medium, covering carbon−carbon bond formation, oxidations and reductions, and briefly organometallic reactions.

Reactions in Water

If a solvent is to be used for a reaction, water is the cheapest, most abundant solvent available. It is nonflammable and nontoxic, and if a biphasic reaction system is used organic substrates can be isolated by a simple phase separation. Water also has the highest value for specific heat capacity, enabling the more facile control of an exothermic reaction, and has a network of hydrogen bonds which can influence the reactivity of substrates.[9] Other interesting features of water are that additives such as salts can be used, inducing salting-in or salting-out effects, or surfactants and cyclodextrins can be added, the pH can be varied, and cosolvents or biphasic reaction systems can be utilised. Importantly, products can be isolated by filtration and also many biocatalytic reactions are also performed in water, and therefore chemoenzymatic strategies can be considered.

Although water has these unique properties, it has not traditionally been the solvent of choice in which to perform organic reactions. One reason has been that organic synthetic techniques often involve the use of water sensitive reagents, catalysts, or intermediates and that the nonpolar nature of organic molecules results in low or no solubility in water. Also problems can be encountered in isolating water soluble products. However, in the past 20−30 years the potential benefits of using aqueous media have been recognized, and reactions including pericyclic reactions, Michael additions, and organometallic reactions have been reported and in some cases water has increased the selectivity and reaction rate.[5−11]

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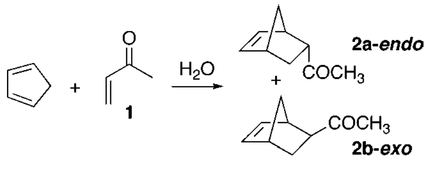
(1) Sheldon R. A. *Green Chem.* **2005**, *7*, 267−268.
(2) *Organometallics in Synthesis. A Manual;* Schlosser, M., Ed.; Wiley: New York, 1996.
(3) Sheldon, R.A.; van Rantwijk, F. *Aust. J. Chem.* **2004**, *57*, 281−289.
(4) Schoemaker, H. E.; Mink, D.; Wubbolts, M. G. *Science* **2003**, *299*, 1694−1697.
(5) Li, C.-J.; Chan, T.-K. *Organic. Reactions in Aqueous Media*; Wiley: New York, 1997.
(6) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Acad. Professional Pb.: London, 1998.
(7) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035.
(8) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68−82.
(9) Engberts, J. B. F. N.; Blandamer, M. J. *Chem. Commun.* **2001**, 1701−1708.
(10) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221−237.
(11) Manabe, K.; Kobayashi, S. *Chem.*−*Eur. J.* **2002**, *8*, 4095−4101.
(12) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521−527.
(13) Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commum.* **1998**, 1765−1766.

10.1021/op060157x CCC: $37.00

Scheme 1. **Diels−Alder reaction between cyclopentadiene and butan-2-one in solvents including water**



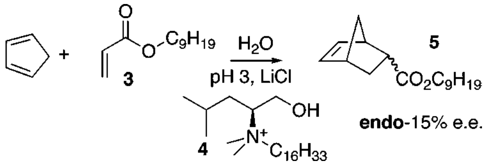
	N (2a)/*X* (2b)
Cyclopentadiene	3.9
Ethanol	8.5
H_2O	21.4

Below, some key reactions that can be performed successfully in water are highlighted, together with recent progress in this area.

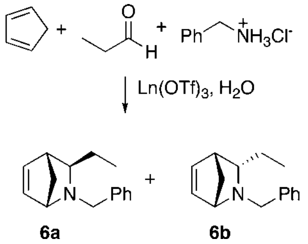
One of the most widely studied reactions in water is the Diels−Alder reaction, which generates several defined stereocentres in one step.[5−9,14] Although Diels−Alder reactions were reported in the 1930s in aqueous media,[15] it was in the 1980s that Breslow highlighted the rate enhancements observed in water for the reaction between cyclopentadiene and butanone (**1**).[16] Interestingly, the reaction rate in methanol was similar to other organic solvents, and the unusual acceleration in water was attributed to enforced hydrophobic interactions and hydrogen bonding interactions.[16,17] Further studies highlighted the enhanced endo/exo (*N*/*X*, **2a**/**2b**) product ratios that can be achieved when using water as a solvent: using cyclopentadiene as the solvent, the *N*/*X* ratio was approximately 4, but this was increased to over 21 in water (Scheme 1).[17]

Since this report, many other Diels−Alder reactions have been described using a range of substrates,[5−9,14] including the use of acid[18] or glycohydrophilic[19] moieties to enhance diene or dieneophile water solubilities. An alternative approach to enhance solubilisation effects, and the preorientation of reacting species is the use of additives ranging from cyclodextrins, to form inclusion complexes,[16] to surfactants, to generate micellar solutions.[20] The effectiveness of micellar-based aqueous systems appears to be varied, with some research groups indicating little effect and others reporting large rate enhancements and selectivities in the Diels−Alder cycloaddition.[17,21] In our work we observed that surfactants can have a significant effect on product selectivity and yield but the surfactant must be used at concentrations around or above their critical micellar concentration (cmc) to ensure that micellar aggregates were present.[22] Furthermore that optimization of the reaction pH is important and can have a significant effect on reaction outcome.[22,23]

Scheme 2. **Diels−Alder reaction in a micellar solution containing the leucine-derived surfactant 4**



Scheme 3. **Three-component hetero Diels−Alder reaction using lanthanide triflate**



Whilst the addition of these and other additives increases the complexity of the aqueous media utilized they can overcome problems through the micellar solubilisation of substrates and when chiral surfactants are used, induce enantioselectivities in the reaction products.[24] For example, the reaction between cyclopentadiene and nonyl acrylate **3** in water at acidic pH containing the leucine derived surfactant **4** led to a 15% ee in the *endo* adduct **5** (Scheme 2).[24,25]

Other additives that can be added to aqueous-based reactions include Lewis acids which have applications as catalysts in organic transformations, in particular Diels−Alder reactions.[26] In recent years, a number of water-tolerant Lewis acids have been described such as: the nitrates $Cu(NO_3)_2{\cdot}3H_2O$, and Zn^{2+}, Ni^{2+}, Co^{2+} analogues;[27] lanthanide triflates, $Ln(OTf)_3$,[28] and others including indium trichloride.[29] Yield and product selectivity enhancements have been observed in a range of systems. A representative example is the lanthanide triflate catalysis of a three-component hetero Diels−Alder reaction (Scheme 3).[30] Lanthanide triflates were used in a pH range of 5−7, and when no $Ln(OTf)_3$ was added the product **6** (**6a** + **6b**) was isolated in only 4% yield; however with added lanthanide catalyst the yield of **6** was increased to 64%.[30]

Another pericyclic reaction, the Claisen condensation was reported to be accelerated in aqueous solvents several years ago, and since then the influence of water has been demonstrated on a number of substrates.[31] The origin of the rate acceleration has been considered by several groups, and solvent-induced polarization and transition state hydrogen bonding effects have been suggested.[31] A further cyclisation reaction is the 1,3-dipolar cycloaddition reaction. In the early 1980s Lee reported the 1,3-dipolar cyclisation of dipolarophiles with nitrile oxides in aqueous−organic biphasic systems, where the nitrile oxide was generated in situ and

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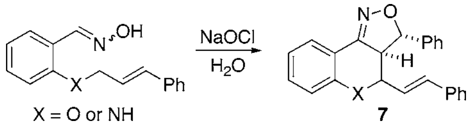
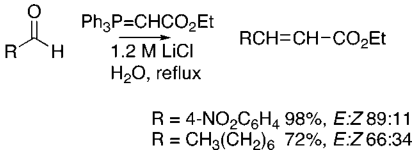
(14) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365−1372.
(15) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1931**, *490*, 243−257.
(16) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7817−7818.
(17) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901−1904.
(18) Grieco, P. A.; Yoshida, K.; He, Z. M. *Tetrahedron Lett.* **1984**, *25*, 5715−5718.
(19) Lubineau, A.; Queneau, Y. *Tetrahedron Lett.* **1985**, *26*, 2653−2654.
(20) Tascioglu, T. *Tetrahedron* **1996**, *52*, 11113−11152.
(21) Braun, R; Schuster, F.; Sauer, J. *Tetrahedron Lett.* **1986**, *27*, 1285−1288.
(22) Diego-Castro, M. J.; Hailes, H. C. *Tetrahedron Lett.* **1998**, *39*, 2211−2214.
(23) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646−650.
(24) Diego-Castro, M. J.; Hailes, H. C. *Chem. Commum.* **1998**, 1549−1550.
(25) Diego-Castro, M. J.; Hailes, H. C.; Lawrence, M. J. *J. Colloid Interface Sci.* **2001**, *234*, 122−126.
(26) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439−455.
(27) Otto, S; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 9517−9525.
(28) Marshman, R. W. *Aldrichimica Acta* **1995**, *28*, 77−84.
(29) Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739−2749.
(30) Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169−2172.
(31) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219−226.

Scheme 4. **One-pot 1,3-dipolar cycloaddition in water to generate isoxazolines**



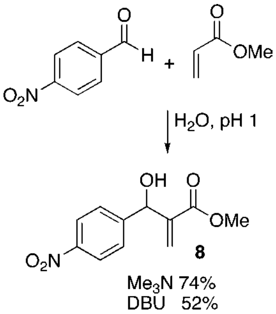
Scheme 5. **Wittig reaction using a stabilized ylid in water**



some triethylamine was required in several of the reaction systems.[32] A more recent kinetic study followed the reaction between benzonitrile *N*-oxide and several dipolarophiles in aqueous media and concluded that with electron-rich dipolarophiles the cycloaddition was accelerated in water.[33] Whilst more frequently homogeneous or biphasic mixed solvent systems have been used for this reaction, the use of water alone is less common. In a recent study we investigated the cycloaddition reaction in a one pot reaction in water only, to synthesise benzopyran and quinoline-based isoxazolines (Scheme 4).[34] Oximes were treated with aqueous sodium hypochlorite solution which in situ generated the nitrile oxide and then underwent the cycloaddition reaction. Although the starting material (Scheme 4, X = O or NH) appeared to have a very low solubility in water and the reaction was slower in water than water−THF mixtures, the solid product **7** was isolated at the end of the reaction in high purity in over 90% yield simply by filtration. Such a facile isolation procedure can be one of the key advantages of performing reactions in water. The methodology was then extended to the synthesis of a novel dimeric adduct, a cyclophane which was formed very cleanly and in high yield in water again in a one-pot reaction.[34]

The Wittig reaction is used extensively in synthetic chemistry and is classically carried out in anhydrous organic solvents in the presence of base. However, recently it has been reported that when using stabilized phosphorous ylids, that the reaction can readily be performed in water; indeed the reactions were faster than when carried out in organic solvents.[35] Most reactions were complete in 5−60 min in refluxing water, and the presence of LiCl (1.2 M) as a salting out agent was also found to be beneficial. When aromatic aldehydes were used, the trans/cis (*E*/*Z*) selectivities were similar to those achieved in toluene, although lower selectivities and yields were achieved with aliphatic aldehydes (Scheme 5). In our own work we have performed analogous Wittigs using the same stabilized ylid where they readily proceeded in quantitative yield at room temperature in water in 16 h.[36]

Scheme 6. **Baylis−Hillman reaction in aqueous acidic media**



Another useful carbon−carbon bond forming reaction is the Baylis−Hillman reaction. The reaction is typically catalysed by tertiary amine bases and has been reported to be accelerated in water or binary aqueous solvent mixtures.[37,38] The rate acceleration in water has been attributed to hydrogen bonding with a smaller contribution from hydrophobic effects.[39] Lewis acids and lanthanide triflates have been used for the reaction in organic solvents; however in our work we investigated the use of aqueous acidic conditions where interestingly the reaction readily proceeded in up to 74% yield, depending on the substrate and tertiary amine used.[40] As shown in Scheme 6 the reaction was carried out at pH 1, and with triethylamine as the tertiary amine, **8** was formed in 74% yield and, with DBU, 52% yield. This work again highlights the advantages of using aqueous media for organic transformations where adjustment of the pH of the solution can be important.

There are an increasing number of oxidation reactions that are now being developed in water using H_2O_2 and O_2 as water compatible oxidants. Examples include the high yielding oxidation of primary alcohols to aldehydes and secondary alcohols to ketones using O_2 and a water-soluble palladium(II) bathophenanthroline complex.[41] The catalyst was stable and recyclable, and an O_2/N_2 mixture was utilized together with a pressure of 10−30 bar.[41] Also palladium nanoparticles (ARP-Pd) have been used with 1 atm of O_2 in refluxing water.[42] Hydrogen peroxide has been used with a tungstate complex and quaternary ammonium-hydrogensulfate as an acidic phase transfer catalyst in aqueous biphasic systems for the oxidation of alcohols, alkenes, and sulfides.[43] Hydrogen peroxide in a biphasic reaction system has also been utilised for the oxidation of alcohols with a polyoxometalate ($Na_{12}[WZn_3(H_2O)_2(ZnW_9O_{34})_2]$) prepared in situ.[44,45] Importantly, the catalyst could be reused with little loss of catalytic activity.

Reductions can also be performed in water, notably with water-compatible sodium or lithium borohydrides, for ex-

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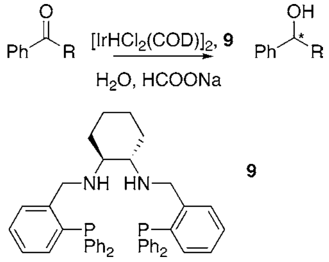
(32) Lee, G. A. *Synthesis* **1982**, 508−509.
(33) Van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801−8805.
(34) Bala, K.; Hailes, H. C. *Synthesis* **2005**, 3423−3427.
(35) Wu, J.; Zhang, D.; Wei, S. *Synth. Commun.* **2005**, *35*, 1213−1222.
(36) Faulkner, S.; Hailes, H. C. Unpublished results.
(37) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413−5418.
(38) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723−4725.
(39) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510−514.
(40) Caumul, P.; Hailes, H. C. *Tetrahedron Lett.* **2005**, *46*, 8125−8127.
(41) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636−1639.
(42) Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194−197.
(43) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1997−1986.
(44) Sloboda-Rozner, D.; Alsters, P. L.; Neumann, R. *J. Am. Chem. Soc.* **2003**, *125*, 5280−5281.
(45) Nardello, V.; Aubry, J.-M.; De Vos, D. E.; Neumann, R.; Adam, W.; Zhang, R.; ten Elshof, Witte, P. T.; Alsters. P. L. *J. Mol. Catal. A: Chem.* **2006**, *251*, 185−193.

Scheme 7. **Use of an iridium hydride complex and ligand 9 in an asymmetric transfer hydrogenation**

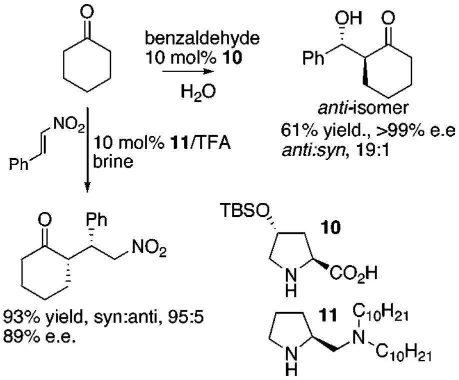


ample, for the reduction of aldehydes or ketones. Sodium borohydride has also been used with amphiphilic dendrimers derived from PAMAM and D-gluconolactone for the reduction of prochiral ketones, in water or using heterogeneous (THF) reaction conditions, and good enantioselectivities were observed.[46] Other systems for the reduction of ketones in water include the following: amino acid based cationic surfactants to introduce enantioselectivities with aryl ketones;[47] iridium hydrides used in transfer hydrogenations, such as $[Cp^*Ir^{III}(bpy)H]^+$ ($Cp^* = \eta^5\text{-}C_5Me_5$, bpy = 2,2′-bipyridine)[48] and $[IrHCl_2(COD)]_2$ with the chiral diaminodiphosphine PNNP ligand **9** (Scheme 7) to generate secondary alcohols in high ee's and almost quantitative yield.[49] Also amine boranes bearing hydrophobic substituents for the selective reduction of ketones in water.[50]

Reductive aminations in water are particularly challenging because of the competing reduction of the carbonyl moiety. Despite this there are several reports, for example, reductive aminations using α-picoline-borane in water in the presence of small amounts of ethanoic acid.[51] The highest yields were achieved using anilines as the amine source.[51] The reductive amination of α-keto acids in water has also been described in high yield using the iridium hydride complex $[Cp^*Ir^{III}(bpy)H]^+$.[52]

There is currently significant interest in the use of organocatalysis in synthesis,[53] and recently there have been several reports describing asymmetric organocatalytic processes in water. These include the use of proline-based catalysts in a direct aldol reaction leading to very high stereo- and enantioselectivities (>99% ee) in the product using **10** (Scheme 8)[54] and the Michael addition of ketones and aldehydes with β-nitrostyrene and **11** in brine.[55] With the growing interest in performing organocatalytic reactions in water, it is likely that there will be an increasing number of organic conversions that can be carried out with high selectivities under these conditions.

Scheme 8. **Asymmetric aldol and Michael addition organocatalytic reactions in water**



Organometallic and asymmetric organometallic-catalysed reactions in water also have extensive applications although it is beyond the scope of this review to describe these in detail. Traditionally, most organometallic reactions have been performed under anhydrous conditions and using an inert atmosphere; however reports on the use of water in homogeneous organometallic-catalysed reactions have been increasing. Transformations in water in addition to those mentioned above include, for example, cyclopropanations, carbonylations, and alkylations which are described in several reviews.[8,56−58] A range of catalysts have been utilised using ruthenium-, rhodium-, palladium-, and gold-based compounds. Of particular interest is the use of the water-soluble Pd(TPPTS) catalyst (TPPTS is $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$) in carbonylation processes, including carbonylation with CO of benzyl chloride in aqueous biphasic media, to give phenyl acetic acid.[59,60] This strategy has advantages over alternative routes to phenylacetic acid which use sodium cyanide in a two-step process.

One major concern of the use of water has always been the solubility of the reacting substrates in water. This issue and the advantages of using water alone as a solvent have recently been highlighted with the description of organic reactions "on water".[61,62] Here, Sharpless et al. discuss the assumption that substrate solubility is required for efficient reactions to occur. They challenge this with examples, noting that some reactions proceed efficiently, with rate accelerations, in water when the organic substrates are "insoluble", referring to the reactions as "on water". They describe several reactions including cycloadditions, an ene reaction, Claisen rearrangement, and nucleophilic ring opening of an epoxide.[61,62] In all cases optimal reaction conditions included the use of water only, for example, the reaction between the

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(46) Schmitzer, A. R.; Franceschi, S.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Thion, L.; Erard, M.; Vidal, C. *J. Am. Chem. Soc.* **2001**, *123*, 5956−5961.

(47) Roy, S.; Das, D.; Dasgupta, A.; Mitra, R. N.; Das, P. K. *Langmuir* **2005**, *21*, 10398−10404.

(48) Abura, T.; Ogo, S.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 4149−4154.

(49) Xing, Y.; Chen, J.-S.; Dong, Z.-R.; Li, Y-Y.; Gao, J.-X. *Tetrahedron Lett.* **2006**, *47*, 4501−4503.

(50) Uyeda, C.; Biscoe, M.; LePlae, P.; Breslow, R. *Tetrahedron Lett.* **2006**, *47*, 127−130.

(51) Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, *60*, 7899−7906.

(52) Ogo, S.; Uehara, K.; Abura, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 3020−3021.

(53) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138−5175.

(54) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958−961.

(55) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 4966−4967.

(56) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221−237.

(57) Kobayashi, S.; Manabe, K. *Chem.—Eur. J.* **2002**, *8*, 4094−4101.

(58) Castillon, S.; Claver, C.; Diaz, Y. *Chem. Soc. Rev.* **2005**, *34*, 702−713.

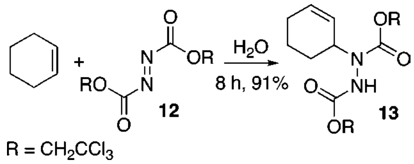
(59) Kohlpaintner, C. W.; Beller, M. *J. Mol. Catal. A: Chem.* **1997**, *116*, 259−267.

(60) Papadogianakis, G.; Maat, L.; Sheldon, R. A. *J. Mol. Catal. A: Chem.* **1997**, *116*, 179−190.

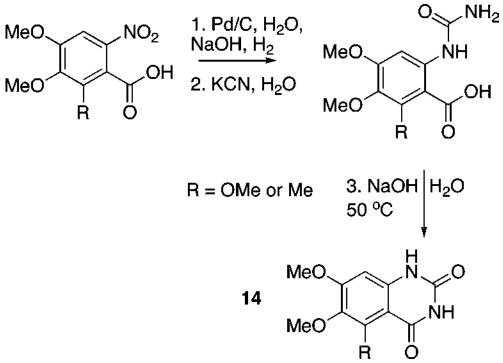
(61) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279.

(62) Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005**, *435*, 746−747.

Scheme 9. **Reaction between azidocarboxylate 12 and in water to give 13**



Scheme 10. **Synthesis at pilot plant scale of 5-substituted-6,7-dimethoxy-1-*H*-quinazoline-2,4-diones 14**



azido carboxylate **12** and cyclohexene (Scheme 9). In organic solvents or neat, a reaction time of at least 24 h was required to generate **13** in 60−70% yield.[61] However, using "on water" conditions the reaction was complete in 8 h. They reported that reaction mixing was more uniform in water than under neat conditions and that in water a molten organic phase was formed during the reaction, giving the product as a white solid, isolable by simple filtration.

For some reactions they reported optimal yields and reaction conditions under no-solvent conditions similar to those when water was used; however the use of water was considered to be desirable for safety reasons and the mixing of reagents. Several reasons were discussed for the enhanced rates under aqueous conditions compared to when organic solvents were used, including whether substrates had a very low solubility in water, surface tension energetics, and the previously studied hydrophobic and hydrogen bonding effects in water.[61,62] Although a full understanding of the reasons has yet to be established, there is no doubt that the use of water as a reaction medium could have an outstanding impact on chemical synthesis, including at a process scale.

Attempts have been made to develop some chemical processes in water. One recent example of a full chemical process with all steps carried out in water is the synthesis of two 5-substituted-6,7-dimethoxy-1-*H*-quinazoline-2,4-diones **14** which have been prepared on a pilot plant scale (Scheme 10).[63] 2-Nitrobenzoic acids were the starting materials of choice, and it was hoped that throughout the synthesis, through adjustment of the pH of the aqueous solution, organic solvents could be avoided. The initial hydrogenation step was carried out in water, ideal since it is a nonflammable solvent, under basic conditions. Direct replacement of the hydrogen with nitrogen and, after filtration, treatment of the filtrate with KCN led to formation of urea. The pH of the aqueous solution was then adjusted to >13 which after heating generated the cyclic product **14**. Finally, lowering of the pH of the solution to 8 led to the precipitation of **14**.

Many of the reactions described above have been carried out in water only as a solvent, which clearly has significant advantages in some cases; however biphasic reaction systems are frequently used, and some of these have also been detailed above. Aqueous biphasic systems can be advantageous particularly at scale because if for example the catalyst resides in the aqueous layer with the product in an organic layer, catalyst recycling via phase separation is possible.

One further advantage of using water as a reaction media is the potential combination of water-based chemistries with biocatalysts, which have many advantages over chemical strategies due to their mild reaction conditions, high chemo-, regio-, and stereoselectivities, and environmental compatability.[1] With more chemical conversions being carried out in water, this opens up the potential to implement biocatalytic steps together with synthetic conversions. Furthermore, strategies are being used to evolve and improve the properties of biocatalysts for use at scale and to evolve enzymes for incorporation into chemical synthetic routes for the more efficient production of compounds.[64] An elegant example is the combination of biocatalytic and chemical steps in a one-pot dynamic kinetic resolution using amino acid oxidases to deracemise α-amino acids.[65] An alternative approach is to carry out the engineering of de novo synthetic pathways of biocatalysts in water for further synthetic manipulations. For example, the one-pot synthesis of amino-diols using two enzyme systems, a de novo transketolase and β-alanine/pyruvate transaminase.[66] The development of new or improved biocatalysts and their use in water, potentially coupled with chemical steps, holds significant potential.

In recent years there has also been growing interest in the use of high-temperature water (HTW) and supercritical water (SCW) as reaction media. HTW can be broadly defined to be near-critical liquid water (200 °C $< T <$ 374 °C), and SCW is formed at $T >$ 374 °C, $P >$ 221 bar.[67,68] As the temperature of water increases from 25 °C to 300 °C it becomes less dense, and the dielectric constant decreases, as does the level of hydrogen bonding. As a result HTW behaves like many organic solvents, and organic compounds exhibit high solubilities, with full miscibility in SCW. SCW is also miscible with gases such as carbon dioxide.[67,68] In addition, water is a weak electrolyte at room temperature but dissociates to a greater extent on increasing the temperature, resulting in higher concentrations of H_3O^+ and OH^- at neutral conditions, which can catalyze chemical reactions. The ability to perform acid- or base-catalysed reactions without the addition of strong acids or bases could lead to a more environmentally benign process, avoiding solution neutralization, and thus facilitating downstream processing. Several acid- and base-catalysed reactions have been reported

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(63) Connolly, T. J.; McGarry, P.; Sukhtankar *Green Chem.* **2005**, *7*, 586−589.

(64) Hibbert, E. G.; Baganz, F.; Hailes, H. C.; Ward, J. M.; Lye, G. J.; Woodley, J. M.; Dalby, P. A. *Biomolecular Engineering* **2005**, *22*, 11−19.

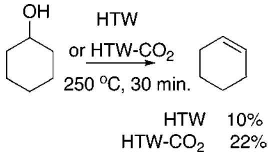
(65) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114−119.

(66) Ingram, C. U.; Bommer, M.; Smith, M. E. B.; Dalby, P. A.; Ward, J. M.; Hailes, H. C.; Lye, G. *Biotechnol. Bioeng.*, in press.

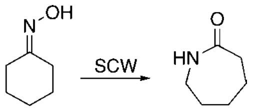
(67) Hunter, S. E.; Savage, P. E. *Chem. Eng. Sci.* **2004**, *59*, 4903−4909.

(68) Savage, P. E. *Chem. Rev.* **1999**, *99*, 603−621.

Scheme 11. **Dehydration of cyclohexanol in HTW or HTW−CO_2**



Scheme 12. **Conversion of cyclohexanone oxime to ϵ-caprolactam in SCW**



in HTW in the absence of an added catalyst, for example: the dehydration of 1,4-butanediol to give THF;[69] aldol[70] and Claisen−Schmidt condensations;[71] the acylation of activated aromatics with ethanoic acid but no added acid catalyst to give hydroxyacetophenones;[72] alkylation of phenols with *tert*-butanol;[73] and dehydration of cyclohexanol[73] (Scheme 11). Interestingly, the addition of CO_2 to the HTW reaction medium increased the yield of cyclohexene (Scheme 11) at 250 °C by more than a factor of 2.[73] The rate enhancement can be attributed to the reaction between CO_2 and water to give carbonic acid, which upon dissociation in HTW will increase the hydronium ion concentration. The hydration of cyclohexene has also been described in HTW where the addition of CO_2 was also found to increase the yield of cyclohexanol generated.[67]

SCW reaction conditions have also been used for numerous reactions which have been reviewed, including carbon−carbon bond forming reactions such as Diels−Alder cycloadditions,[74] and Heck arylations,[75] aminations,[76] and hydrogenations.[77,68] For example, ϵ-caprolactam has been generated in 83% yield in SCW from cyclohexanone oxime via an acid-catalysed Beckman rearrangement (Scheme 12).[78] The yield was increased further to 100% under dilute acidic conditions with the addition of HCl or H_2SO_4.[78]

Recently, the aerobic oxidation of methyl aromatics has also been described in SCW in the continuous mode using manganese(II) bromide as a catalyst in good yield.[79] For instance, the oxidation of *p*-xylene to the corresponding diacid was achieved in 90% yield (with the loss of one methyl group in 3−6% yield probably due to thermal decarboxylation). The reaction conditions were adjusted to achieve a single SCW phase reaction containing oxygen and the organic substrate. Clearly the use of HTW and SCW with their potential to catalyse acid- and base-catalysed transformations and their interesting solubility properties together with the possible development of more environmentally benign processes is likely to have an increasing number of applications in organic synthesis.

In summary, the application of water as a solvent in organic transformations has been growing in recent years across a wide range of chemical transformations. With its special properties in terms of rate accelerations, and influence on product selectivities, or ease of product isolation, and the range of conditions such as inclusion of additives, pH range, use of biphasic systems, and high-temperature conditions that can be utilized, water will continue to play an important role as a solvent in chemical processes.

There are of course reaction solvent systems other than water that offer an alternative to traditional hydrocarbon or chlorinated hydrocarbons. It is beyond the scope of this review to describe these in detail although key references are given below. Examples include the following: D-limonene which has been used to clean polyesters urethanes and vinyls instead of dichloromethane;[80] lactate esters, also used for cleaning purposes which are nontoxic and biodegradable;[80] and polyethylene glycol (PEG) which is nontoxic and nonvolatile as well as being miscible with water.[81] The use of PEG has been reviewed as a green reaction media where its phase-transfer properties and applications of PEG solutions in water have been highlighted. Also recent applications, as a scaffold and solvent for homogeneous Pd-catalysed carbon−carbon couplings such as Suzuki and Heck,[82] as a solvent for the Michael addition of amines to conjugated amines,[83] for catalytic hydrogenations with PtO_2,[84] and as a recyclable medium in asymmetric aldol reactions,[85] have been reported. Other reaction media have been described such as supercritical carbon dioxide, $scCO_2$,[86−88] and ionic liquids[86,89] which show considerable promise for a wide variety of processes.

Conclusions and Outlook

This short review has focused on the potential of water at ambient temperature and highlighted the use of HTW and SCW reaction conditions as alternatives to conventional organic media for use in synthetic conversions. Water holds much potential for use in organic processes due to its low

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(69) Richter, T.; Vogel, H. *Chem. Eng. Technol.* **2001**, *24*, 340−343.

(70) Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. *J. Phys. Chem. B* **2004**, *108*, 18108−18118.

(71) Nolem, S. A.; Liotta, C. L.; Eckert, C. A.; Gläser, R. *Green Chem.* **2003**, *5*, 663−669.

(72) Brown, J. S.; Gläser, R.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2000**, 1295−1296.

(73) Hunter, S. E.; Savage, P. E. *Ind. Eng. Chem. Res.* **2003**, *42*, 290−294.

(74) Korzenski, M. B.; Kolis, J. W. *Tetrahedron Lett.* **1997**, *38*, 5611−5614.

(75) Zhang, R.; Sato, O.; Zhao, F. Y.; Sato, M.; Ikushima, Y. *Chem.*−*Eur. J.* **2004**, *10*, 1501−1506.

(76) Tajima, K.; Uchida, M.; Minami, K.; Osada, M.; Sue, K.; Nonaka, T.; Hattori, H.; Arai, K. *Environ. Sci. Technol.* **2005**, *39*, 9721−9724.

(77) Crittendon, R. C.; Parsons, E. J. *Organometallics* **1994**, *13*, 2587−2591.

(78) Ikushima, Y.; Sato, O.; Sato, M.; Hatakeda, K.; Arai, M. *Chem. Eng. Sci.* **2003**, *58*, 935−941.

(79) Garcia-Verdugo, E.; Venardou, E.; Thomas, W. B.; Whiston, K.; Partenheimer, W.; Hamley, P. A.; Poliakoff, M. *Adv. Synth. Catal.* **2004**, *346*, 307−316.

(80) www.carbohydrateeconomy.org/library/admin/uploadedfiles/Biochemical-_Substitutions _in_the_polymer_Indus.html.

(81) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64−82.

(82) Corma, A.; Garcia, H.; Leyva, A. *J. Catal.* **2006**, *240*, 87−99.

(83) Kumar, R.; Chaudhary, P.; Nimesh, S.; Chandra, R. *Green Chem.* **2006**, *8*, 356−358.

(84) Chandrasekhar, S.; Prakash, S. J.; Rao, C. L. *J. Org. Chem.* **2006**, *71*, 2196−2199.

(85) Chandrasekhar, S.; Reddy, N. R.; Sultana, S. S.; Narsihmulu, C.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338−345.

(86) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195−218.

(87) Knox, D. E. *Pure Appl. Chem.* **2005**, *77*, 513−530.

(88) Licence, P.; Ke, J.; Sokolova, M.; Ross, S. K.; Poliakoff, M. *Green Chem.* **2003**, *5*, 99−104.

(89) Welton, T. Cood. *Chem. Rev.* **2004**, *248*, 2459−2477.

cost and availability and the advantages it can have on organic transformations. Whilst the move towards water and other solvents may be challenging and require a different approach to tackling some synthetic conversions, there has been significant growth in the number of reactions reported in water, and this is likely to continue. Coupled with the potential of biocatalysis and how this can enhance the efficiency of chemical synthesis through the use of designer enzymes and the promise demonstrated in the use of alternative systems, there are a range of alternative reaction solvents to utilize rather than hydrocarbon-based systems.

Received for review August 1, 2006.

OP060157X