Green Chemistry

Cutting-edge research for a greener sustainable future

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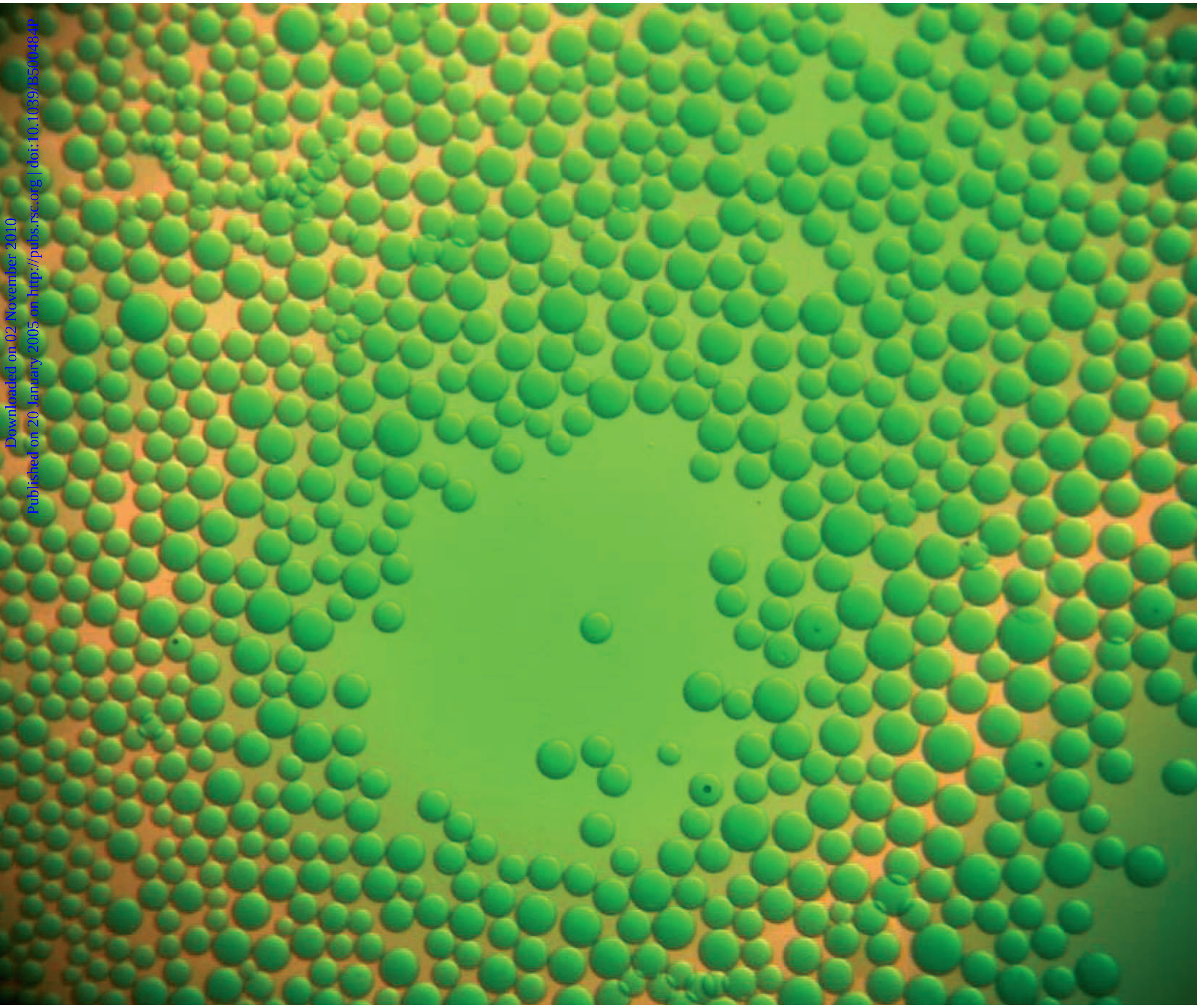

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Polyethylene glycol solutions in water—a review of solvent properties and metal coordination capabilities by Chen, Spear, Huddleston and Rogers

Cover

Dispersed droplets of an aqueous biphasic system (polyethylene glycol (PEG)–ammonium sulfate) illustrate the hydrophobic/hydrophilic separation of a dye without the use of VOCs. Described within are the unique solvent properties of aqueous solutions of PEG and aqueous biphasic systems which lead to their uses in synthetic chemistry, in chemical reaction engineering, and to facilitate the separation of reactants, catalysts, and products in aqueous biphasic reactive extraction for catalytic and enzymatic processes. (Photo by Scott Spear).

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Green Chemistry

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COMMUNICATION

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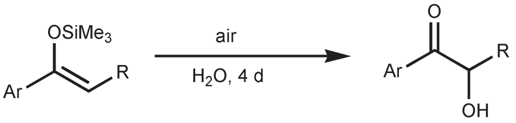
Water-promoted direct aerobic oxidation of enol silyl ether to α-hydroxyl ketones without catalyst

Hui-Jing Li, Jun-Ling Zhao, Yong-Jun Chen, Li Liu, Dong Wang* and Chao-Jun Li*

Various α-hydroxyl ketones were generated in good yields *via* water promotion of the oxidation of aromatic silyl enol ethers by air without the use of any catalyst.



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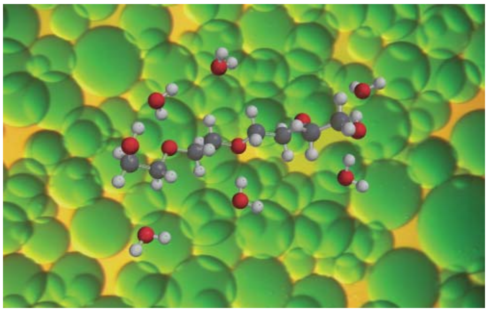
Polyethylene glycol and solutions of polyethylene glycol as green reaction media

Ji Chen,† Scott K. Spear, Jonathan G. Huddleston and Robin D. Rogers*

The solvent properties of aqueous solutions of polyethylene glycol are reviewed and applications of alternative solvent systems of this type, in chemical synthesis, catalysis and reactive extraction, are considered.



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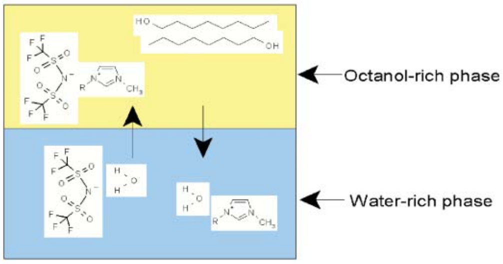
Octanol–water partition coefficients of imidazolium-based ionic liquids

Laurie Ropel, Lionel S. Belvèze, Sudhir N. V. K. Aki, Mark A. Stadtherr and Joan F. Brennecke*

Measurements of octanol–water partition coefficients of imidazolium ionic liquids indicate that these compounds do not pose a risk of bioconcentration or bioaccumulation.



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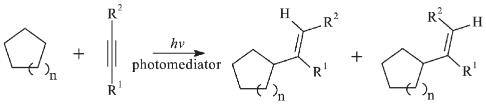
A comparative analysis of the functionalisation of unactivated cycloalkanes using alkynes and either sunlight or a photochemical reactor

Roisin A. Doohan and Niall W. A. Geraghty*

Carbon–carbon bond formation through the solar reaction of cycloalkanes with alkynes introduces functionality into the hydrocarbon while avoiding the metals, peroxides, and toxic by-products normally associated with this important synthetic process.



$R^1 = H, R^2 = CO_2CH_3; R^1 = R^2 = CO_2CH_3; n = 1,2$

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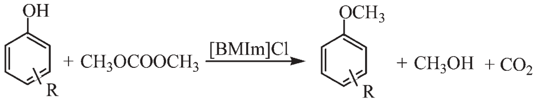

Catalytic O-methylation of phenols with dimethyl carbonate to aryl methyl ethers using [BMIm]Cl

Zhen Lu Shen,* Xuan Zhen Jiang, Wei Min Mo, Bao Xiang Hu and Nan Sun

Two important aspects of green chemistry, the replacement of toxic and salt-forming reagents and the use of recyclable catalysts, are tackled in this paper. Phenols are O-methylated in excellent yields by the green reagent dimethyl carbonate. Moreover, the ionic liquid [BMIm]Cl can be reused several times without loss of catalytic activity.

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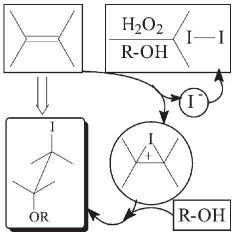

Hydrogen peroxide induced iodine transfer into alkenes

Marjan Jereb,* Marko Zupan and Stojan Stavber

Efficient, environmentally benign, acid- and metal-free, regio- and stereoselective iodofunctionalisation of alkenes with iodine, assisted by a 'green' 30% aqueous solution of hydrogen peroxide, following iodine atom economy is presented.

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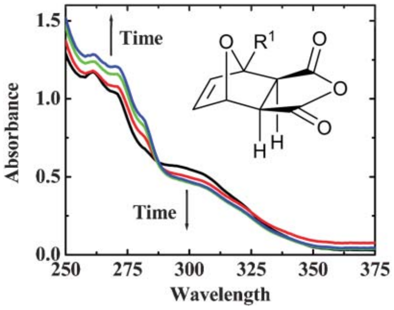

Diels–Alder reactions between maleic anhydride and furan derivatives in supercritical CO_2

Dáire J. Cott, Kirk J. Ziegler, Vincent P. Owens, Jeremy D. Glennon, Andrew E. Graham and Justin D. Holmes*

The development of chemical reactions that are environmentally friendly and which proceed with enhanced selectivity is a major goal for synthetic chemists. This paper illustrates the potential of utilising CO_2 as a synthetic medium for Diels–Alder cycloadditions involving furan derivatives.

AUTHOR INDEX

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Renewables and Green Chemistry

DOI: 10.1039/b500769k

Green Chemistry is rapidly gaining prominence in many countries with the emergence of awards, undergraduate degree programs, and major research funding initiatives, with spectacular achievements in the field on a regular basis. Much of the earlier research focused on the general areas of waste minimisation in chemical synthesis, especially in using alternative reaction media such as ionic liquids and supercritical carbon dioxide, solventless reactions, catalysis, oxidation reactions, alternative energy sources and energy usage, toxicity, and atom efficiency, and other issues associated with minimising waste.

Given the increase in greenhouse gas emissions due to the use of petroleum (and other fossil fuels) and the impending limits of this non-renewable resource as evidenced by petrol price increases, there is a need to develop renewable resources such as biomass as the feedstock for the chemical industry and as an energy source. This includes biomass that is traditionally discarded as waste (see below). The advantages of deriving our chemical, and energy needs, from renewable sources including biomass are obvious and crucial to our way of life. The switch to the use of biomass as a feedstock and an energy source is an important global initiative in getting the world onto a sustainable trajectory.[1]

Technology roadmaps for the comprehensive use of biomass will play an important role in identifying key areas of research and development. Systematic consideration of biomass properties and best available technologies is required together with addressing triple bottom line issues. Chemicals derived from biomass will be a 'supply chain' for the chemical industry for transformation into a plethora of compounds. Clearly these will need to be based on green chemistry, taking advantage of the aforementioned early focus in the field as discussed above, and ongoing developments.

The above so called waste should be considered a valuable resource for new technologies. In fact, all forms of biomass, including the residue from the chemical processing of biomass, are a potential renewable source. In this context, the Western Australian State Government has a policy of zero landfill waste by 2020.[2] While this is unlikely to be achieved it nevertheless gives a clear message and challenge from Government that scientists and engineering need to be engaged in solving the problem. It is a major challenge for consideration—'Landfill' opportunities for green chemistry!

The shift to renewable feedstocks based on biomass is a formidable challenge, and much needs to be done. Research centres dedicated to this are appearing on a regular basis.[3] Despite this the use of biomass in green chemistry initiatives has received little attention in *Green Chemistry*, with a limited number of articles dedicated to the field since the journal was founded in 1999. Articles on renewable feedstocks, and energy, are welcomed. They can be in the general areas of deriving chemicals from waste from aquaculture, fisheries, agricultural and plantation forestry, and the biomass from crops grown exclusively as a source of biomass, as in the palm oil industry in Malaysia,[4] extraction and conversion of high value added compounds, biofuels, gasification, biopolymers, carbon for mineral processing, and more.

Other challenges/areas in biomass utilisation include: (a) Bio-catalysis as a route to commodity chemicals, using microbes and enzymes. (b) Separation of cellulose, hemicellulose, and lignin, alternative energy sources and new separation technology. (c) Biodegradable polymers using carbohydrate feedstocks. (d) Liquid and gaseous fuels and lubricants, chiral feedstocks for drug syntheses, *etc*. (e) Mineral processing—alternative energy sources and reductants, bio-flotation, and smelting. (f) Gasification and pyrolysis as a route to liquid fuels, feedstock for the chemical industry, hydrogen for the 'hydrogen economy', and carbon material. In addition, economic and management issues, including developing low cost processes with a small footprint, for use in rural areas, transport of biomass, compactions, life cycle assessment, *etc*. need to be addressed, along with social issues including community awareness and impacts on the rural community and ecosystem functions.

Professor Colin Raston
Editorial Board Chair, Green Chemistry
University of Western Australia

References

1 P. Anastas, Meeting the challenges of sustainability, *Green Chem.*, 2003, **5**, G29.
2 The Western Australian State Sustainability Strategy, 2003, Government of Western Australia, Quality Press, ISBN 0 737 0212 X.
3 (*a*) http://www.bc.bangor.ac.uk/; (*b*) http://web.utk.edu/%7Etfpc/; (*c*) http://www.nesungrant.cornell.edu/; (*d*) http://www.wwrrec.cf.ac.uk/about/objectives.asp.
4 Malaysian Palm Oil Promotion Council, http://www.mpopc.org.my.

New Associate Editor - The Americas

DOI: 10.1039/b500233h

Chao-Jun Li was born in 1963 and received his BSc at Zhengzhou University (1983), his MS at the Chinese Academy of Sciences in Beijing (1998) and his PhD (with honor) at McGill University (1992) under the direction of T. H. Chan and D. N. Harpp. While at McGill he was awarded a Max Bell Graduate Open Fellowship and a Clifford Wong Graduate Fellowship. He spent 1992–94 as an NSERC Postdoctoral Fellow in Barry M. Trost's laboratory at Stanford University (US), and following that went to Tulane University (US) as an assistant professor. He was promoted to associate professor with tenure in 1998 and full professor in 2000. In 2003, he became a Canada Research Chair (Tier I) in Green Chemistry and a Professor of Chemistry at McGill University in Canada.

While at Tulane University, Li received an NSF Career Award (1997), an Outstanding Young Scientist Award (Overseas) from NSF of China (2000), a Presidential Green Chemistry Challenge Award from the US EPA (2001), a Faculty Research Award from the Faculty of Arts and Sciences at Tulane (2002), and an Annual Award from the Business Association of New Orleans (2002). He was an Eli Lilly Teaching Fellow in 1995 and a Japan Society for Promotion of Science (Senior) Fellow in 2002. He is an honorary research professor at the Chemistry Institute of the Chinese Academy of Science (1996–) and a guest professor at the University of Science and Technology in China (2001). He was a visiting professor (with Robert G. Bergman) at University of California at Berkeley (2002).

Li has served as an International Co-coordinator of Green Chemistry Conferences in China (2000–). He was a consulting editor of *The Encyclopedia of Sciences and Technologies* (2002) and *The Year Book of Sciences and Technologies* (2002) and was on the Editorial Advisory Boards of *Letters in Organic Chemistry* and *Mini Reviews in Organic Chemistry*.

His current research efforts are to develop a Green Chemistry for organic synthesis based upon innovative and fundamentally new organic reactions that will defy conventional reactivities and possess high "atom-efficiency". He has published over 160 original research papers and reviews and co-authored with T. H. Chan a book, *Organic Reactions in Aqueous Media* (John Wiley, 1997).

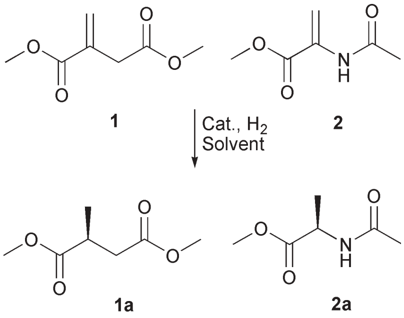
Highlights

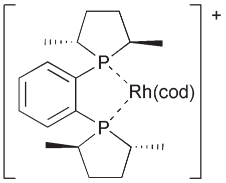
DOI: 10.1039/b418928k

Markus Hölscher reviews some of the recent literature in green chemistry

Asymmetric hydrogenation catalysts derived by noncovalent anchoring on aluminosilicates

The heterogenization of homogeneous catalysts is one of the intensely investigated scientific approaches for the generation of efficient catalysts. Although the field has seen many fascinating developments over the years problems like catalyst leaching and loss of activity often could not be solved to a satisfactory extent. Sheldon and coworkers from the Delft University of Technology took a promising step forward by anchoring a homogeneous catalyst on mesoporous aluminosilicate AlTUD-1, which was subsequently used as catalyst for the hydrogenation of dimethyl itaconate **1** and 2-acetamidoacrylate **2** (*Chem.—Eur. J.*, 2004, **10**, 5829–5835).

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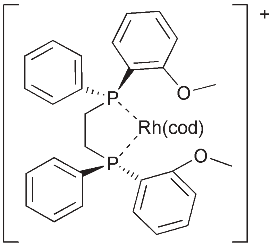
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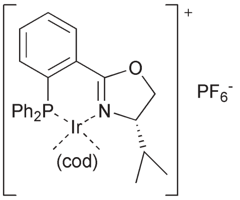
The strategy relies on the mesoporous aluminosilicate carrier as an anionic host, to which the cationic rhodium complexes **3** and **4** were bound noncovalently by ion exchange. The Al : Rh ratio was carefully chosen to be 10 : 1, increasing the chances of the complexes being re-immobilized, in case they were mobilized during the catalytic reaction. The authors found a strong dependence of the catalytic activity (TOFs between >1000 and 19) on the solvent chosen in hydrogenations of **1** with ee-values being largely unaffected by the solvent and ranging between 96 and 98%, when **3**-AlTUD-1 was the catalyst. Catalyst leaching was found to be as low as 0.1%. The hydrogenation of **2** with **3**-AlTUD-1 proceeded with TOFs >350, ee-values of 90% and a leaching of 0.05% in MTBE. When **4**-AlTUD-1 was chosen as the catalyst ee-values dropped drastically and leaching increased.

Carbon nanotube polymer nanocomposites prepared in the presence of supercritical CO_2

Besides the well known applications of supercritical CO_2 ($scCO_2$) in extraction processes and as an extremely helpful reaction medium in homogeneous catalysis, more and more fields emerge for the use of this unique solvent. Liu, Xu and coworkers from the Chinese Academy of Sciences, Beijing, developed an interesting approach for the preparation of hexadiyne derived polymers, which coat the inner and outer surfaces of carbon nanotubes (*Chem. Commun.*, 2004, 2190–2191). Solid state polymerization of diacetylenes (DAs) results in polymers, which exhibit potentially useful properties for use in electrical transport and nonlinear optical and thermochromic applications. Carbon nanotubes (CNTs) are also envisaged to be helpful in the construction of various nanoelectronic elements. The authors combined both materials by introducing DAs into CNTs. The monomers were first dissolved in ethanol, CNT was added subsequently and after a thorough mixing of the two components supported by the application of ultrasound, the solution was transferred to an autoclave in which it was heated to 35 °C after pressurization with CO_2 (12 MPa). After 10 h reaction time the solution was released from the autoclave and the sample was heated to 200 °C to polymerize the monomers. Detailed FTIR spectroscopic and XPS analytic investigations proved the polymer was coating the inner and outer surfaces of the CNT. UV-Vis and fluorescence spectra showed the optical properties of the polymer to be similar to those of the neat polymer, meaning that the CNT–DA-polymer composite might very well be suitable for application in optical materials.

Ionic liquid–CO_2 media for catalytic, enantioselective hydrogenation of imines

Chiral secondary amines are interesting building blocks, which are exploited industrially *e.g.* for the production of (*S*)-metolachlor. Chiral iridium complex **1** is one of the catalysts that performs enantioselective imine hydrogenations with high levels of asymmetric induction.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However, the immobilization of this catalyst in unconventional reaction media has been problematic, and this issue has now been addressed again by Leitner and coworkers from RWTH-Aachen (*J. Am. Chem. Soc.*, 2004, **126**, 16142–16147). The combination of ionic liquid (IL) and supercritical CO_2 ($scCO_2$) introduces a number of advantages such as higher efficiency for the hydrogenation reaction itself, facile product removal without cross contamination by catalyst or IL, and greatly enhanced long-term stability of the catalyst. The testing of different ILs and reaction conditions led to an optimized reaction protocol for the hydrogenation of *N*-(1-phenylethylidene)aniline to the corresponding (*R*)-phenyl-(1-phenylethyl)amine with conversions of >99% and ee-values of 78% with ethyl methyl imidazolium bis(trifluoromethylsulfonyl)imide ([EMIM][BTA]) as the IL. The long-term stability of the catalyst was tested using IL butyl methyl imidazolium hexafluorophosphate ([BMIM][PF_6]), showing that in 7 consecutive runs neither activity nor enantioselectivity changed markedly.

Magnetic carbon coated nanoparticles as catalyst carriers for the production of fine chemicals

The beneficial use of heterogeneous catalysts depends among other criteria crucially on the size of the catalyst particle (activity) and on facile product–catalyst separation without catalyst deactivation or product contamination (recyclability). Since liquid-phase reactions are important for many industrial applications it would be advantageous to have catalysts with small particle sizes, hence increasing catalyst activity. However, catalyst particle sizes in the submicrometer range are almost impossible to separate from the product by conventional means. Tsang *et al.* from the University of Reading recently advanced significantly in this field by developing carbon coated catalyst particles with a magnetic core, thus enabling facile catalyst separation from the reaction mixture by applying magnetic fields (*Angew. Chem.*, 2004, **116**, 5763–5767). In a typical synthesis a solution of nitroferricyanide (III) dihydrate, nickel nitrate and poly(vinyl alcohol) were mixed in water at room temperature. This solution was sprayed into the headspace of a jar filled with saturated ammonia solution under defined conditions. The droplets precipitated immediately and the collected solid was dried and heated to 1173 K under nitrogen. Immersion of the particles in boiling concentrated HCl furnished functionalization with OH groups. Wet impregnation with Pd containing solutions yielded the final catalyst. XRD analyses showed the particles to be approximately 11 nm in diameter, and TEM micrographs proved the existence of an FeNi core encapsulated by thin, quasi-spherical carbon structures with lattices similar to graphite. The relative sizes of alloy core and carbon coating were found to depend on the amounts of metal precursors and poly(vinyl alcohol) used which opens the possibility of tailoring the particles for applications. Preliminary results for the hydrogenation of nitrobenzene with Pd@C–FeNi particles showed the reaction to proceed at an initial rate of 1.529 (μmol nitrobenzene converted to aniline per second). Catalyst separation was simply achieved by applying an external magnetic field generating a particle free solution.

Water-promoted direct aerobic oxidation of enol silyl ether to α-hydroxyl ketones without catalyst

Hui-Jing Li,[a] Jun-Ling Zhao,[a] Yong-Jun Chen,[a] Li Liu,[a] Dong Wang*[a] and Chao-Jun Li*[b]

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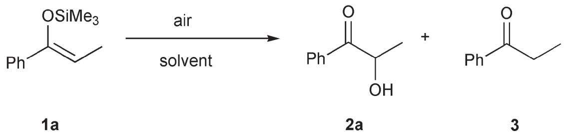
Clean oxidation of aromatic silyl enol ethers in water by air without the use of any catalyst generates α-hydroxyl ketones in good yields (69–86%).

The α-hydroxyl carbonyl moiety is a common structural unit in the molecules of many natural products and pharmaceuticals.[1] Various methods have been developed for the formation of such derivatives, with the oxidation of the α-position to a carbonyl group as the most direct one.[2] In this respect, Crombie and Godin demonstrated that α-hydroxylation of an α-aryl ketone could be achieved by passing air through an alkaline solution of the ketone.[3] However, the autoxidation reaction was limited to steroid-type compounds.[4] On the other hand, the oxidation of preformed enolates and enolate derivatives such as enol silyl ethers has been both versatile and synthetically useful. Among the methods that proceed *via* the oxidation of preformed enolates, the most convenient and reliable α-hydroxylation procedure is the oxidation of enol silyl ethers of ketones. Indeed, oxidation of enol silyl ethers has been carried out by using various methods including organic peracids,[5] singlet oxygen (generated *in situ* under photolytic conditions),[6] osmium tetraoxide,[7] hypervalent iodine systems,[8] lead (IV) salts,[9] chiral ketone/oxone systems,[10] and ozonolysis.[11] While all these methods can generate the desired products efficiently, they require either the pre-generation of the oxidant or the use of a stoichiometric amount of heavy metal-based oxidant. It has been recognized that developing clean oxidation is one of the most important challenges in green chemistry research.[12] The cleanest and most ideal reagent for oxidation reactions would be air.[13] Furthermore, water is the most abundant and one of the most desirable solvents for chemical syntheses.[14] Although there has been great progress in transition-metal catalyzed aerobic oxidation of organic compounds in water, in the pharmaceutical industry it is even more desirable to develop such oxidations without using any transition-metals in order to achieve the lowest metal level in pharmaceutical agents for FDA's safety control.[15] Taking the development of such oxidation reactions as a general goal, we wish to report our exploratory results of a highly efficient oxidation of aromatic silyl enol ethers to α-hydroxyl ketone by air without the use of any catalyst in water.

Initially, the solution of 1-phenyl-1-trimethylsiloxypropene **1a** was stirred in a given solvent at room temperature for 4 days under an atmosphere of air (Table 1). No oxidation product **2a** was detected when an organic solvent such as ethanol, acetone, tetrahydrofuran and benzene (entries 1 and 5–7) was used. The exposing of **1a** to air in solvent-free conditions did not provide the desired product **2a** either (entry 8). It is interesting to note that when a mixture of ethanol and water (1 : 1) was used, the corresponding oxidation product was obtained in 25% yield (the mole percent of product obtained related to its theoretical amount based on the moles of silyl enol ether used) together with 35% hydrolyzed product. When the amount of water in the solvent mixture of water–ethanol increased, the yields of **2a** increased from 25% to 74%, accompanied by a decrease in the amount of hydrolysis product **3** phenylpropanone, from 35% to 16% (entry 2 and 3). When the oxidation was carried out in neat water in the absence of any catalyst, **2a** was obtained in 86% yield and only 9% of **3** was produced (entry 4). Thus, water is an essential medium for accelerating the oxidation reaction of silyl enol ether under an air atmosphere. It is worth mentioning that under a nitrogen atmosphere the oxidation reaction did not proceed at all, with the starting material recovered completely after 4 days. On the other hand, the addition of $Ga(OTf)_3$ accelerated the rate of the reaction (entry 9). The use of other Lewis acids, such as $Cu(OTf)_2$ and $Yb(OTf)_3$, led to a significant increase in the amount of hydrolysis product in water (entries 10 and 11). (Note: the addition of the extra Lewis acids is less green too.)

Table 1 Oxidation of 1-phenyl-1-trimethylsiloxypropene under various conditions



Entry[a]	Solvent	Time/d	Yield (%)[d] 2a	Yield (%)[d] 3
1	C_2H_5OH	4	—	—
2	$C_2H_5OH–H_2O$ (1 : 1)	4	25	35
3	$C_2H_5OH–H_2O$ (1 : 9)	4	74	16
4	H_2O[b]	4	86	9
5	Acetone	4	—[e]	—
6	THF	4	—[e]	—
7	C_6H_6	4	—[e]	—
8	—[c]	4	—[e]	—
9	$H_2O–Ga(OTf)_3$[f]	2	81	8
10	$H_2O–Cu(OTf)_2$[f]	2	53	40
11	$H_2O–Yb(OTf)_3$[f]	2	62	35

[a] All reactions were carried out at room temperature. [b] De-ionized water. [c] Solvent-free. [d] Isolated yield. [e] Starting material was recovered. [f] Catalyst loading, 20 mol%.

Subsequently, various enol silyl ethers **1b–i** were converted to α-hydroxyl ketones by this method by using air as the oxidizing reagent in water for 4 d without using any catalyst (Scheme 1), to

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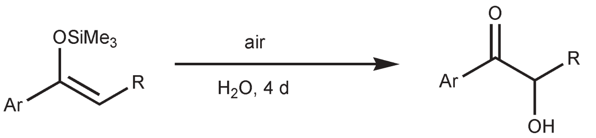


Scheme 1

give α-hydroxyl ketones **2b–h** in good yields of 69–86% (Table 2). The reaction was found to be strongly influenced by the steric effect. When the R group in the silyl enol ether was changed from a methyl group to a benzyl group, the product yield decreased from 86% to 69%. In addition, for aryl substituted enol silyl ethers, the presence of a bulky substituent on the phenyl ring also decreased the yield of the oxidation product (entries 5–7 *vs.* entry 1). The oxidation of the enol silyl ether of 1-naphthyl aldehyde (**1h**) gave only a trace amount of product **2h** due to the large steric hindrance (entry 8). On the other hand, the electronic effect of the substituent on the phenyl ring did not influence the yield significantly (compare entries 4 and 5). The use of aliphatic enol silyl ether (**4**) did not generate the oxidation product, with the starting material hydrolyzed completely in water (entry 10). However, enol silyl ether generated from α-tetralone (**1i**) is more stable in water; its oxidation reaction in water proceeded smoothly to give product **2i** in 72% yield (entry 9).

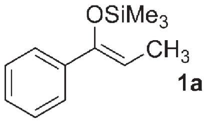
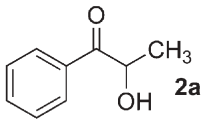
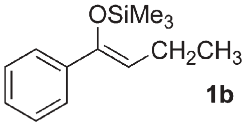
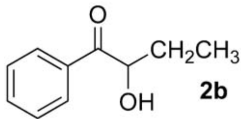
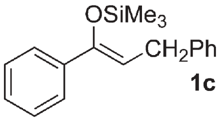
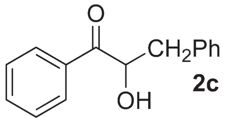
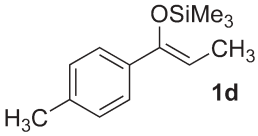
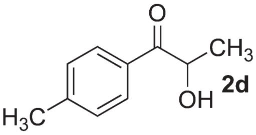
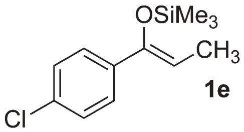
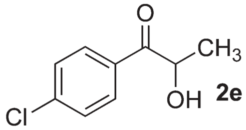
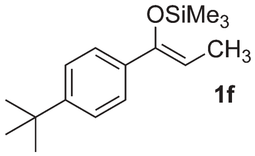
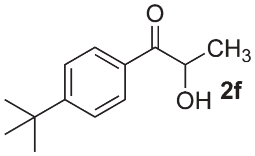
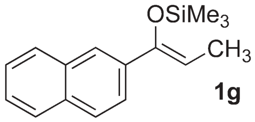
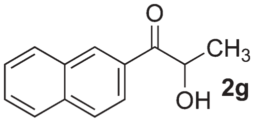
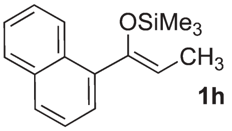
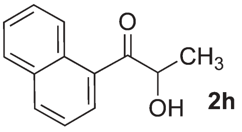
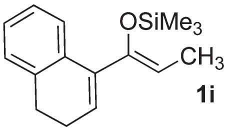
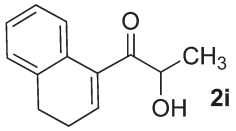
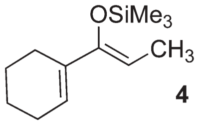
The exact mechanism of this novel uncatalyzed and water-promoted aerobic oxidation reaction of enol silyl ethers is not very clear and was studied briefly. When the mixture of enol silyl ether in water was kept in the dark, the oxidation reaction proceeded smoothly to give the corresponding α-hydroxyl ketone in a yield similar to the one generated from the reaction under visible light. Furthermore, when DMPO (a spin-trapping reagent[16] for the oxygen radical) was added in the oxidation reaction in water, no ESR signal was observed. A KI–starch solution test was found to be positive, which demonstrated the formation of peroxide during the oxidation reaction.[17] As a control experiment, a negative result was observed under the same conditions in the absence of enol silyl ether. Based on these experimental observations, a tentative mechanism for the product formation is proposed in Scheme 2. Such a mechanism is consistent with the one proposed for the oxidation reaction of enolate, activated by counterion complexation in a six-membered transition state.[18]

In conclusion, a method for oxidation of aromatic silyl enol ethers by air was developed in water without the use of any catalyst. This method generates α-hydroxyl ketones in good yields. Further work is in progress to increase the rate of the reaction as well as decrease the amount of by-products, which are important for both making the method more green and for practical applications.

Experimental

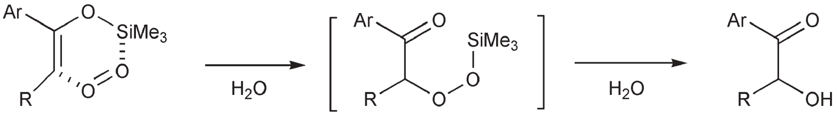
A representative experimental procedure is as follows. The enol silyl ether (0.1 mmol) in water (de-ionized water, 2 mL) was stirred at room temperature under an air atmosphere, monitored by TLC until the enol silyl ether disappeared. The mixture was extracted by ethyl acetate (2 × 10 mL) and the organic layer was dried over Na_2SO_4. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether (bp 30–60 °C)–ethyl acetate = 6 : 1) to give the corresponding α-hydroxyl ketone.

Table 2 Uncatalyzed aerobic oxidation of various enol silyl ethers in water

Entry	Enol silyl ether	Product	Yield (%)[a]
1	 **1a**	 **2a**	86
2	 **1b**	 **2b**	74
3	 **1c**	 **2c**	69
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	82
6	 **1f**	 **2f**	75
7	 **1g**	 **2g**	73
8	 **1h**	 **2h**	Trace
9	 **1i**	 **2i**	72
10	 **4**	—[b]	

[a] Isolated yield. [b] Hydrolysis product was obtained (90%).

Characterization of the compounds. Most products are known compounds except entry 6 in Table 2. The new compound **2f** has been fully characterized. **2f**: ^{1}H NMR δ = 1.35 (s, 9H), 1.50 (d, J = 7.2 Hz, 3H), 3.81 (d, J = 6.9 Hz, 1H), 5.16–5.21 (m, 1H), 7.55, 7.90 (AA′BB′, J = 6.9, 8.4 Hz, 4H); ^{13}C NMR δ = 22.5, 31.0,



Scheme 2

35.3, 69.2, 125.8, 128.7, 130.0, 156.5; 201.9. **2f**: ν_{max}: 3473, 2965, 1679, 1605, 1274, 1109 cm^{-1}. HRMS: calcd. For $C_{13}H_{18}O_2$: 206.1307, found: 206.1301.

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References

1 F. A. Davis and B.-C. Chen, *Chem. Rev.*, 1992, **92**, 919.
2 (*a*) A. B. Jones, *Oxidation adjacent to C=X bonds by hydroxylation methods*, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, 1990, vol. **7**, p. 151–189; (*b*) J. Christoffers, A. Baro and T. Werner, *Adv. Synth. Catal.*, 2004, **346**, 143.
3 L. Crombie and P. J. Godin, *J. Chem. Soc.*, 1961, 2861.
4 (*a*) L.-K. Sy and G. D. Brown, *Tetrahedron*, 2002, **58**, 897; (*b*) L.-K. Sy and G. D. Brown, *Tetrahedron*, 2002, **58**, 909.
5 (*a*) G. M. Rubottom, M. A. Vazquez and D. R. Pelegria, *Tetrahedron Lett.*, 1974, **15**, 4319; (*b*) L. A. Paquette, H. S. Lin and J. C. Gallucci, *Tetrahedron Lett.*, 1987, **28**, 1363.
6 (*a*) G. M. Rubottom and M. I. L. Nieves, *Tetrahedron Lett.*, 1972, **13**, 2423; (*b*) E. Friedrich and W. Lutz, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 413; (*c*) C. W. Jefford and C. G. Rimbaut, *J. Am. Chem. Soc.*, 1978, **100**, 6515.
7 J. P. McCormick, W. Tamasik and M. W. Johnson, *Tetrahedron Lett.*, 1981, **22**, 607.
8 R. M. Moriarty, O. Prakash and M. P. Duncan, *Synthesis*, 1985, 943.
9 G. M. Rubottom, J. M. Gruber and G. M. Mong, *J. Org. Chem.*, 1976, **41**, 1673.
10 Y. Zhu, Y. Tu, H. Yu and Y. Shi, *Tetrahedron Lett.*, 1998, **39**, 7819.
11 (*a*) R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 1974, **15**, 2027; (*b*) W. S. Zhou, B. Jiang and X.-F. Pan, *J. Chem. Soc., Chem. Commun.*, 1988, 791.
12 T. J. Collins, *Acc. Chem. Res.*, 2002, **35**, 782.
13 M. Beller, *Adv. Synth. Catal.*, 2004, **346**, 107.
14 (*a*) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley, New York, 1997; (*b*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic and Professional, London, 1998; (*c*) A. Lubineau and J. Auge, in *Modern Solvent in Organic Synthesis*, ed. P. Knochel, Springer, Berlin, 1999; (*d*) *Aqueous-Phase Organometallic Catalysis*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 2004.
15 C. J. Li, *Angew. Chem. Int. Ed.*, 2003, **42**, 4856.
16 G. M. Rosen, A. Beselman, P. Tsai, S. Pou, C. Mailer, K. Ichikawa, B. H. Robinson, R. Nielsen, H. J. Halpern and A. D. MacKerell, Jr., *J. Org. Chem.*, 2004, **69**, 1321.
17 *Vogel's Textbook of Practical Organic Chemistry*, Thames Polytechnic, London, 5th edn., 1989, p. 402.
18 E. J. Baily, D. H. R. Barton, J. Elks and J. F. Templeton, *J. Chem. Soc.*, **1962**, 1578.

Polyethylene glycol and solutions of polyethylene glycol as green reaction media

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In this review, we examine the concept that aqueous biphasic reactive extraction (ABRE) can successfully integrate the solvent properties of polyethylene glycol (PEG) and its phase-transfer characteristics into a single efficient system which can additionally be manipulated to facilitate the separation of reactants and/or catalysts from products. We also suggest that the properties of these systems may recommend them as being relatively environmentally benign in comparison to the current use of organic solvents in extraction and in reactive extraction. In developing this concept, we review a number of the physical and chemical properties of PEG and aqueous solutions of PEG in the context of recent applications to chemical reaction engineering. Thus, we cover the interesting physical properties of PEG solutions in water, their unique solvent properties, and finally the metal cation coordination ability of PEG solutions. These properties are important in the application of low molecular weight liquid PEG as a solvent in chemical reactions; in the use of PEG as an alternative phase-transfer catalyst (PTC); and in the application of ABRE in the development of alternative pulping processes, catalytic chemistry, and enzymatic catalysis.

1. Introduction

Regulatory pressure is increasingly focusing on the use, manufacture, and disposal of organic solvents, and thus the development of nonhazardous alternatives (one of several goals of green chemistry and engineering) is vitally important for the continued and sustainable development of the chemical enterprise.[1,2] There are many potential advantages to replacing volatile organic compounds (VOCs) with water or various types of aqueous solutions. The most obvious are low cost, reduced flammability, reduced toxicity, and reduced environmental risk as a result of discharges of the supporting phase. Water and aqueous-based solvent systems may represent an increasingly significant choice for the replacement of traditional solvents in synthetic chemistry. Other leading VOC solvent alternatives include supercritical fluids, ionic liquids, immobilized solvents, solventless conditions, and the use of fluorous solvents.[1]

A recent special edition of *Chemical Reviews* and a recent American Chemical Society Symposium volume highlighted some aspects of the use of water and aqueous solutions in green chemistry,[3,4] however, relatively few articles have focused on the use of aqueous PEG solutions and related materials in chemical reactions. This is despite the fact that, unlike several of the 'neoteric solvents' such as ionic liquids (ILs) where toxicity and environmental burden data are for the most part unknown, complete toxicity profiles are available for a range of polyethylene glycol (PEG) molecular weights and indeed, many are already approved for internal consumption by the US FDA.[5,6]

Table 1 lists a number of recent reviews of organic reactions conducted in water and aqueous solutions including the use of high temperature water, soluble polymer supports, micellar solutions, and PEG derivatives. In this context, PEG has been used as a solvent and phase-transfer catalyst (PTC) in organic synthesis.

A number of recent reviews have also covered PEG chemistry and its applications in biotechnology and medicine,[22,23] PEG and PEG-supported catalysis,[24] PEG-based aqueous biphasic systems (ABS) as alternative separation media,[25] aqueous two-phase systems (ATPS) in bioconversion,[26–28] and PEG and its derivatives as solvent and PTC in organic synthesis.[20,21] However, none of these articles has focused on PEG solutions as alternative reaction media. Here we present a comprehensive review and analysis of the role of aqueous solutions of PEG in the development of alternative reaction media, an area of green chemistry which seems to have been rather overlooked in comparison to other solvent systems such as, for example sc-CO_2 and ILs.[4,29,30]

Our interest in PEG solutions as green reaction media was spurred by several factors including; the present high interest in green separation chemistry,[31–38] our long-term study of PEG–metal ion coordination,[39–44] our studies of ABS solvent properties,[45–49] and our application of aqueous biphasic reactive extraction (ABRE) in the development of alternative processes for wood pulping and green catalytic oxidation systems.[50–57] In this review, we draw together five strands of the current literature: (1) the interesting physical properties of aqueous PEG solutions; (2) the unique solvent properties and cation coordination ability of PEG solutions; (3) the application of low molecular weight liquid PEG as a solvent in

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Table 1 Selected reviews of water and aqueous solutions used as green reaction media

Medium and main reaction type	Ref.
High temperature water as reaction medium	5,7
Organometallic reactions performed in water	8–11
Reactions mediated by soluble polymers as catalysts and supports including PEG	12,13
Micellar solutions as catalysis and reaction media	14–19
PEG and its derivatives as PTC and solvents for organic synthesis	20,21

chemical reactions; (4) PEG as an alternative PTC; and (5) the application of ABRE in the development of green pulping processes, catalytic chemistry, and enzymatic catalysis.

2. Aqueous PEG solution properties

Polyethylene glycol, PEG: HO–(CH_2CH_2O)$_n$–H, is available in a variety of molecular weights from 200 to tens of thousands. At room temperature, the water soluble and hygroscopic polymer is a colorless viscous liquid at molecular weight <600 and a waxy, white solid at molecular weights >800.[58] The numerical designation of PEGs generally indicates the number average molecular weight (*e.g.*, PEG-2000), although typically they are not monodisperse polymers. Liquid PEG is miscible with water in all proportions, and solid PEG is highly soluble in water, for example, PEG-2000 has a solubility of about 60% in water at 20 °C. Lower molecular weight liquid PEGs can be used as solvents in their own right with or without addition of water. These we define loosely here as low molecular weight PEG.

PEG has a number of benign characteristics that underlie, for example, its application in bioseparations.[59] PEG is on the FDA's GRAS list, (compounds Generally Recognized as Safe) and has been approved by the FDA for internal consumption.[60,61] PEG is weakly, if at all, immunogenic, a factor which has enabled the development of PEG–protein conjugates as drugs.[62–65] Aqueous solutions of PEG are biocompatible and are utilized in tissue culture media and for organ preservation.[59]

Unlike VOCs, low molecular weight liquid PEGs are nonvolatile. The vapor density for low molecular weight PEG is greater than 1 relative to air according to available MSDS data,[66] and this is consistent with the industry standard for selection of alternative solvents to VOCs.[1] PEG also has low flammability, and is biodegradable.

PEG has been found to be stable to acid, base, high temperature,[50,56,57,67] O_2, H_2O_2 high oxidation systems,[68] and $NaBH_4$ reduction systems,[69,70] although partial oxidation of the PEG terminal –CH_2OH group to –COOH may occur in such systems as H_2O_2–Na_2WO_4.[56] In addition, PEG may be recovered from aqueous solution by extraction with a suitable solvent or by direct distillation of water or solvent.[71]

2.1. Phase separation

Aqueous solutions of PEG display a miscibility gap characterized by lower and upper critical solution temperatures (LCST and UCST, respectively) in which the polymer and water segregate into polymer-rich and polymer-poor phases.[45] The physical basis of this behavior is dependent upon the amphipathic nature of the polymer chain with its hydrophobic methylene groups interspersed with ether groups which can compliment the hydrogen bonded structure of water.[72–76] Hydration/dehydration of these groups promotes the observed behavior.

Similar phase incompatibility may be found in a number of different polymers such as PEG–PPG co-polymers, polyvinylpyrrolidone, poly-*N*-isopropylacrylamide, and in the clouding of non-ionic surfactants.[25,59,77] Additionally, aqueous solutions of PEG phase separate in the presence of other, incompatible, but still water soluble polymers. The exact nature of phase separation here is incompletely understood, but appears to be an UCST phenomenon perhaps based on incompatible hydrogen bonded structures, or on an excluded volume mechanism.[25,59,78]

PEG-based biphasic systems are generally formed by the addition of PEG and other water soluble polymers such as Dextran, above critical concentrations, however, many other pairs of polymers show incompatibility (and not only in aqueous solution);[25] the phase separation of Ficoll and Dextran is an important example.[59,77,79] Alternatively, 1-butyl-3-methylimidazolium chloride may be combined with a kosmotropic salt such as K_3PO_4, above critical concentrations in aqueous solution resulting in two distinct aqueous phases.[80] This is simply an extension of the temperature induced phase separation of PEG as a result of the lowering of the cloud point brought about by the salting-out effects of the salts.[81] These effects follow the Hofmeister series.[45]

Thus, aqueous PEG solutions may display phase separation under controlled conditions. Such phase separated solutions are known as ABS (Aqueous Biphasic Systems) or alternatively, ATPS (Aqueous Two-Phase Systems), and have been exploited in bioseparation for nearly fifty years since their discovery by Albertsson.[59]

A typical phase diagram for the system, PEG-2000–$NaHSO_4$ in 50% H_2O_2–H_2O at room temperature is shown in Fig. 1. Mixture compositions lying to the left of the binodal

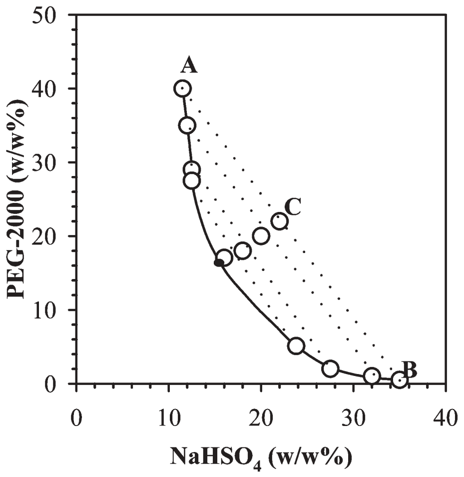


Fig. 1 The phase diagram for PEG-2000–$NaHSO_4$ in 50% H_2O_2 at room temperature used for catalytic oxidation of cyclic olefins.[56,57]

curve are monophasic, whereas mixture compositions to the right of the binodal curve are biphasic. Tie lines (*e.g.*, A–B in Fig. 1) connect mixture compositions to points on the binodal curve (the nodes A and B) representing the compositions of the two phases in equilibrium. All mixture compositions lying on the same tie line give identical compositions of the equilibrium phase. Only the relative volume of the phase changes, and this may be used as a means to manipulate recovery of products. The length of the tie line is called Tie Line Length (TLL).[59] Increasing PEG or salt concentration results in longer TLL and increasing phase divergence. The phase divergence has been shown to be proportional to the chemical potential difference between the phases. Thus, solute preference for one phase over another increases with increasing phase divergence.[45]

Differences in phase preference between species can be adjusted by controlling the ABS system composition. The fact that PEG, and other polymers, form biphasic systems, having tunable phase properties is an important advantage that allows the development of versatile reactive extraction systems; a property of PEG solutions which has yet to be fully exploited.[56,57]

2.2. Solution polarity

The poor solubility of organic reactants and their intermediates in water is the main limitation to the widespread application of water as a reaction solvent. Enhancement of the solubility of organic solutes in aqueous solutions, including the use of supercritical water, surfactants, co-solvents, and complexants,[7,82–84] is an important aspect of the application of aqueous solutions as alternative solvents. For example, supercritical water is characterized by a reduced dielectric constant and a weaker hydrogen bonded network, which greatly increases the solubility of organic compounds.[7,82] Eckert *et al.* have pointed out that this unusual combination of physical properties can provide environmentally benign separation and reaction processes.[82]

Similarly, surfactants with polar and non-polar regions orient themselves into micelles with a hydrophobic solvent-like interior and a polar water-exposed surface. Organic solutes become localized in the interior or within the surface of the micelle, and this is believed to be responsible for the success of organic and enzyme catalyzed reactions in micellar media.[14–16] A significant application of micellar catalysis lies in the field of homogeneous catalysis. In such systems, aqueous micellar solutions serve, not only as the reaction medium, but also to improve reaction selectivity and to facilitate catalyst recycling.[9,17–19] In metal-mediated carbonyl additions, the allylmetal intermediate complexes are formed as a result of the action of a wide variety of intermolecular forces, and as a result can effectively "activate" the metal center of some organometallic reagents and enhance allylation and other organometallic reactions in water.[11,85]

The water soluble polymer PEG can be considered a co-solvent in water which leads to an apparent decrease of the aqueous solution polarity.[77,84] The consequent increase in solubility of organic molecules has led to the application of PEG as a solvent and a PTC in organic synthesis.[20,21]

PEG, in aqueous solution, acting as a co-solvent, significantly changes many of the properties of water.[83] Solutions of PEG in water may be viewed as monophasic, consisting of two homogeneously mixed components, or as biphasic, having large hydrated polymer molecules separated by regions of free water.[77] Zaslavsky has made the argument that the latter viewpoint invites comparison of the resultant solution properties to the effects ascribed to vicinal water, *i.e.* water adjacent to solid interfaces, which has significantly different properties from pure water.[77] In comparison to bulk water, vicinal water shows a decrease in density and dielectric relaxation, and an increase in viscosity and ionic conductance.[77]

Perhaps of even more significance to a discussion of PEG solutions as reaction media, is the effect of PEG on the polarity of aqueous solutions. Solution polarity is frequently measured by reference to the solvatochromatic properties of certain polarity sensitive dyes, in particular to Reichardt's betaine, from which is derived the E_T scale of polarity.[25] Zaslavsky found that the $E_T(30)$ values of PEG-6000–Dextran-500 were very close to, but somewhat less than those of pure water and the values decreased with increasing polymer concentration.[86]

We have found in the PEG-2000–K_3PO_4 system, that values of $E_T(30)$ are considerably lower than water at the critical point, and decrease in the PEG-rich phase with increasing phase divergence.[46] However, for the lower salt-rich phase, the apparent polarity as measured by $E_T(30)$ increases with increasing TLL and distance from the critical point until it is virtually indistinguishable from that of water. Thus, there is an increasing difference in the polarity of the two phases as measured by this technique.

The polarity difference in PEG–Dextran and PEG–K_3PO_4 ABS with TLL is shown in Fig. 2. PEG–Dextran shows a small difference in polarity between the phases, whilst the greatest difference is found for PEG–K_3PO_4 ABS and this difference increases with TLL. In broad terms, the polarity of the PEG-rich phase could be described as being similar to a short chain alcohol when measured on the $E_T(30)$ scale.[46]

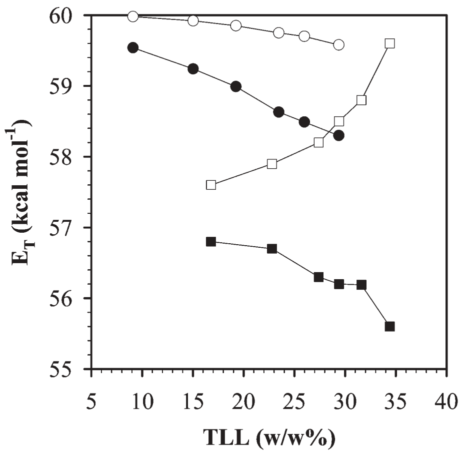


Fig. 2 Solvent polarity scale for PEG-6000–Dextran-500[86] and PEG-2000–K_3PO_4[46] ABS systems: (○) Dextran-rich bottom phase in PEG–Dextran ABS, (●) PEG-rich top phase in PEG–Dextran ABS, (□) K_3PO_4-rich bottom phase in PEG–K_3PO_4 ABS, (■) PEG-rich top phase in PEG–K_3PO_4 ABS.

The relative affinity of the solvent medium for a non-polar CH_2 group, ΔG_{CH_2}, has also been used to measure the solvent properties of different organic solvents, and various aqueous polymer solutions.[46] This scale is not related to the polarity of the medium, but to the free energy of cavity formation or the cohesive energy density. The polarity of the separated top and bottom phases of a PEG-2000–K_3PO_4 ABS have been thoroughly investigated.[48] The relationship between $-\Delta G_{CH_2}$ and the degree of phase separation of the co-existing phases of the ABS, expressed in terms of the difference in concentration of the total number of ethylene oxide monomers (ΔEO) or the TLL between the phases, was investigated in various PEG–salt ABS differing in salt type (K_3PO_4, K_2CO_3, $(NH_4)_2SO_4$, NaOH, Li_2SO_4, $MnSO_4$, $ZnSO_4$) and PEG molecular weight.[48] No matter the salt type, the concentration, or the molecular weight of PEG, $-\Delta G_{CH_2}$ was the same at the same degree of phase divergence (expressed as ΔEO, ΔPEG, or TLL). That is the free energy of transfer of a methylene group in all PEG–salt systems investigated was the same at the same degree of phase divergence. The difference in concentration of the polymers between the phases at a given temperature has been shown to be a measure of the chemical potential difference between the phases.[45]

Fig. 3 shows both the $E_T(30)$ and $-\Delta G_{CH_2}$ relative solvent hydrophobicity scales as applied to PEG-based ABS and some organic solvents and surfactant solutions.[46] $E_T(30)$ is given for the organic phase (PEG in the case of ABS), and $-\Delta G_{CH_2}$ represents the free energy of transfer from the aqueous to the organic phase. The $E_T(30)$ values of both PEG-6000–Dextran-500 and PEG-2000–K_3PO_4 aqueous polymer solutions are closer to that of pure water than most of the organic solvents shown in Fig. 3. However, it is possible to construct ABS, such as the PEG–K_3PO_4 system mentioned previously, having phase compositions such that $-\Delta G_{CH_2}$ may range from zero to about 0.85 kcal mol^{-1}. Not only does this mean that the hydrophobicity of the system is controllable, but in some cases the free energy of transfer may approach and exceed that of many organic solvents. It may thus be possible to achieve considerable solubility of some organic solutes in such systems, and this may allow certain organic reactions to be carried out in these relatively hydrophobic aqueous solutions.

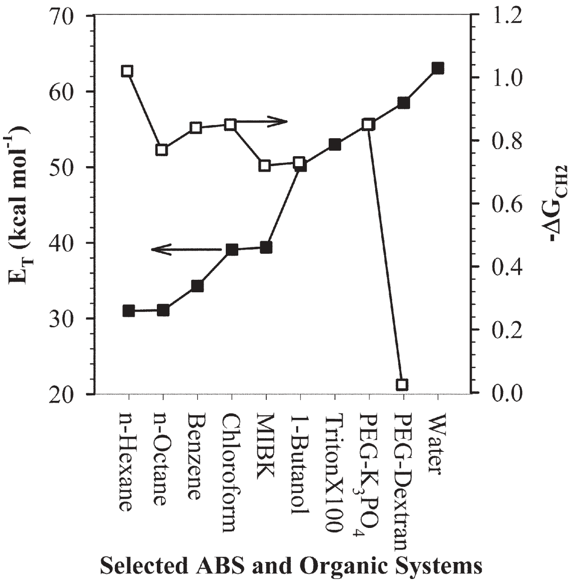


Fig. 3 Relative solvent polarity E_T (■) and $-\Delta G_{CH_2}$ (□) for selected PEG-based ABS solutions and for some organic solvents.

The molar transition energy, E_T, however, taken from the wavelength of absorption of the long wavelength absorbance band of Reichardt's betaine dye,[87] includes not only the effect of molecular dipole and induced dipole interactions, but also the ability of the solvent to interact with the betaine by hydrogen bond donation.[87] Also, the free energy of transfer of a methylene group is only a measure of the energy associated with cavity formation, ignoring the contribution of molecular interactions between solute and solvent to the overall free energy of transfer for all solutes beyond simple alkyl chains.

Huddleston *et al.* have characterized the phases of selected polymer–polymer and polymer–salt systems in terms of their polarity using the Kamlett and Taft π^* parameter (relative polarity/polarizability),[46] and extended these studies to include α (hydrogen bond acidity) and β (hydrogen bond basicity)[49] contributions to solute selectivity in these systems using a suite of solvatochromatic indicators. The parameters π^* and β were found to show little difference between the two phases in PEG-2000–$(NH_4)_2SO_4$ or K_3PO_4 ABS, but a big difference was found for the α value.[49] At 37% w/w TLL, the α value between the PEG-2000-rich top phase and K_3PO_4 salt-rich phase could be as low as 0.3. The hydrogen bond donation ability was greatly depleted in the PEG-rich top phase. The solvatochromatic study of π^*, β, and α lends support to later conclusions, derived from the application of linear free energy relationships (LSER),[48] that polarity and solvent basicity play little part in solute distribution in ABS.

Other studies using solvatochromatic probes and the solvation model of Kamlett and Taft, have found that low molecular weight PEG, such as pure PEG-300, has a polarity value ($\pi^* = 0.94$) greater than methanol (0.63), a hydrogen bond acceptor ability ($\beta = 0.60$) similar to methanol (0.62), and a hydrogen bond donor ability ($\alpha = 0.45$) less than methanol (0.93).[88] In the Hansen three component description of solubility behavior, the solubility parameters for tetraethylene glycol have been determined in terms of a dispersion component ($\delta_d^2 = 16.6$), polarity component ($\delta_p^2 = 5.7$) and a hydrogen bonding component ($\delta_h^2 = 16.8$) and these parameters were found to be similar to those of n-propanol.[89]

Linear solvent free-energy relationships (LSERs or LFERs) based on chemical equilibria and Gibbs energy relationships, have been applied to the investigation of the solvent properties of ABS.[46,48] The general solvation equation of Abraham is usually given as in eqn. 1:

$$\log SP = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + vV_x \qquad (1)$$

where c is a constant, R_2 is the solute excess molar refraction, π_2^H is the solute dipolarity/polarizability obtained from partition measurements, and α_2^H and β_2^H are the effective solute hydrogen bond acidity and basicity, respectively. V_x is the McGowan volume of the solute. The coefficients c, r, s, a, b, and v obtained by linear regression of the partitioning data of a suitable solute set, may be used to characterize the properties of the solvent. For a PEG-2000–$(NH_4)_2SO_4$ ABS these were found to be −0.05, 0.65, −0.21, 0.21, −1.31, and 1.71, respectively.[48]

LSERs are useful in the determination of the solute–solvent interactions that govern solute partitioning in ABS, and it is also possible to compare ABS to, for instance, aqueous micellar systems and traditional organic–aqueous biphasic systems.[90] Such comparisons may greatly aid the selection of suitable solvent systems in a search for replacements for VOC systems. The solvent properties which were found to be of prime importance in driving solute partitioning in ABS, were solvent hydrogen bond acidity (donation ability) and the free energy of cavity formation.

2.3. PEG–metal ion complexes

PTCs are usually used to transport an aqueous reagent into an organic phase in an activated state, so that the reaction can proceed as a consequence of bringing the aqueous reagent and organic reagent together.[67] PEG has the ability to serve as a PTC since the polyethylene oxide chains can form complexes with metal cations, similar to crown ethers.[21] To maintain electroneutrality, such PEG–metal cation complexes must bring an equivalent anion into the organic phase, thus making the anion available for reaction with the organic reactants. Many factors affect phase catalytic activity, such as PEG molecular weight, chain end effects, and the nature of the associated cations and anions.

Fig. 4 shows that the stability constants, log *K*, for PEG complexes with Na^+ in ethanol (using a Na^+ electrode with Ag^+/AgCl as the reference electrode) depend on both the PEG molecular weight and the end-group substituents.[91–93] The degree of complexation of solid alkali metal salts by PEG-400 is strongly dependent on both the salt anion and cation as shown in Fig. 5.[94,95] For the Na^+ and K^+ salt–PEG complexes, commonly used in phase-transfer reactions, there is a greater dependency on the nature of the anion than the cation. The anions OH^-, F^-, HSO_4^-, and HCO_3^- were found (by conductimetric and refractive index measurements) to be ion paired with the PEG cation complex, and assumed to be relatively naked anions, while Cl^-, Br^-, I^-, SCN^-, NO_3^-, NO_2^-, and HF_2^- were assumed to be disassociated anions with significant solvation shells.[95]

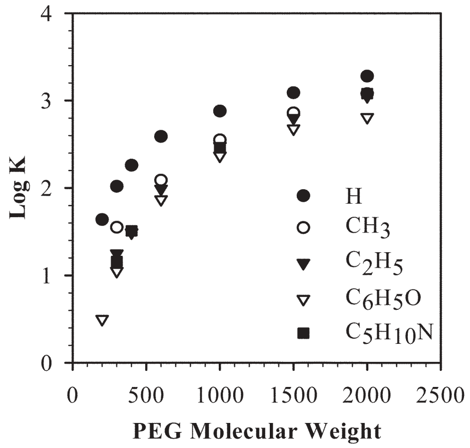


Fig. 4 The stability constants of PEG–Na^+ complexes with various PEG molecular weights and functional group substituents.[91–93] PEG terminal groups were symmetrically substituted (see legend) and the molecular weight was set as that of the unsubstituted PEG.

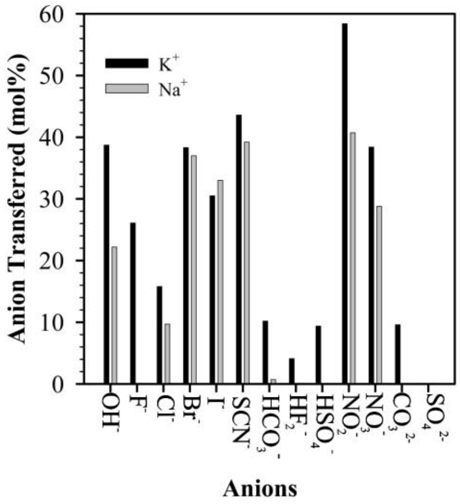


Fig. 5 The metal ion (K^+ and Na^+) transfer ratio (mol%) from solid alkali metal salts of different anions to PEG-400.[94,95]

The binding constants of Na^+ with PEG, with PEG monomethyl ethers (PEG-MME), with PEG dimethyl ethers (PEG-DME), and with crown ethers have been measured in anhydrous MeOH solutions.[96] The binding constants (*K*) of one PEG chain containing 3–312 EO units with the sodium cation show a linear relationship with the number of binding sites available.[96] It has also been proposed that for some alkoxylation reactions, several catalytic centers exist in a single PEG molecule.[97] Dramatically reduced costs of PEG compared to crown ethers are a considerable incentive for investigating the properties of these "crown-like" PTCs.

PEG–cation complex structures have been analyzed by a variety of methods (Table 2) such as single crystal X-ray structure analyses, mass spectrometry, NMR, IR and Raman spectroscopy, powder X-ray diffraction, and electrochemistry. X-Ray analyses have shown that low molecular weight PEG (expressed as $(EO)_n$) can usually form single crystal complexes with metal cations in acetonitrile, methanol, and their mixtures. For example, Sr^{2+} will typically organize 3–6 EO units into a pseudocyclic crown ether-like equatorial array. Thus $(EO)_3$ or $(EO)_4$ chains complex Sr^{2+} in a 2 : 1 fashion, whereas longer chains $(EO)_9$–$(EO)_{10}$ are able to helically wrap the Sr^{2+} ion.[44] Because Sr^{2+} can be completely wrapped by (EO) units, the complex is given a hydrophobic exterior, effectively dehydrating the metal cation, and allowing

Table 2 Structural analyses of PEG–metal cation complexes

Analysis method	Metal ions
X-Ray crystal structure	Hg,[39] Bi,[40] Pb,[41] Ln,[42] U,[43] Sr[44]
Mass spectrometry	Li, Na,[99,100] Cs[101]
NMR	Na, Ca, K, Sr,[102,103] Li[104]
IR and Raman spectroscopy	Li,[105,106] Na[107]
X-Ray powder diffraction	Li,[108,109] Na,[110] K,[111] Rb[112]
Electrochemistry	Li[113]

$Sr(EO)_n^{2+}$ complexes to be transferred to an organic phase. This is the basis for the synergistic extraction of Sr^{2+} from aqueous solution using a mixture of cobalt dicarbollide and PEG.[98]

Compared with crown ether complexation, the same PEG can coordinate different sizes of metal cations such as Sr^{2+} (1.12 Å)[44] and Li^+ (0.76 Å),[114] thus, PEG presents a more flexible structure for metal cation complexation. Extraction by PEG polymer complexation also represents a considerable cost saving over crown ether complexation.

Pb^{2+} and $(EO)_5$ can form $Pb(EO)_5$ chelate rings, and the six oxygen donors arrange themselves in a nearly hexagonal equatorial plane, so that the anion can approach the two axial sites.[41] Lanthanides have important applications in organic synthesis in protic solvents, and the crystal structures of dozens of LnX_3 (X = Cl^-, SCN^-, NO_3^-) complexes formed with a range of small PEGs ($(EO)_3$ to $(EO)_7$) have been investigated by Rogers *et al.*[42] These results showed that different EO chain lengths result in differences in the coordination sphere and can, in some cases, require additional inner-sphere ligands, such as an anion, water, or solvent molecules. These results have been the subject of extensive review.[42]

The complexation of metal ions with PEG has also been investigated by ^1H NMR spectroscopy. There is a strong ion–dipole binding affinity with metals, and the preferred coordination numbers for Na^+ and Ca^{2+} of 6 EO, and for Sr^{2+} of 7 EO, have emerged using the ion radius concept.[102,103] Mass spectrometry has shown that the lowest energy structure $Na^+(EO)_9$ results from the Na^+ ion being "solvated" by seven nearest neighbor atoms, and thus, the cation is completely encased by the $(EO)_9$.[99]

IR and Raman spectroscopic studies of a PEG–Na^+ complex in the context of the development of polymer electrolytes, $(EO)_nNaCF_3SO_3$, have shown that free ions, ion pairs, and aggregates exist due to the interaction of Na^+ with $(EO)_n$ and $CF_3SO_3^-$ at different concentrations.[107] The electrochemical characterization of the Li^+/Li redox electrode reaction in solid polymer electrolytes (SPEs) of PEG-10000–$LiClO_4$ shows higher conductivity than polyethylene oxide (PEO) electrolytes due to the increase in the number of carriers and the facilitation of the formation of the conduction pathways.[113] A powder X-ray diffraction study shows that Li^+–EO_3 forms isolated and helical EO chains with Li^+ inside the helix,[108] which is similar in conclusion to the results of X-ray crystallographic studies. In the case of Li^+–EO_6 complexation, double helical EO chains were shown to surround the Li^+ cations, so that the anions were left outside the helical structure unpaired with Li^+ ions.[109] The conclusions were supported spectroscopically by FT-IR and Raman studies that showed that Li^+ is completely surrounded by the two EO_6 chains forming a cylindrical structure without significant anion coordination in the EO_6:$LiAsF_6$ complex.[105]

PEGs certainly have the ability to form complexes with metal cations. This property may be of some importance in the application of PEGs as alternative PTCs and in ABRE processes. Crown ether metal ion complexation depends on the fixed size of the cavity in the center of the crown. However, fixed molecular weight PEGs show more flexible selectivity in the binding of different size metal cations due to changes in helical conformation. During the phase-transfer process, PEG may transfer metal cations from the aqueous phase to the organic phase by complexation and partition. The corresponding anion is also forced to transfer to maintain electroneutrality, thus the inorganic or organic solvated anion may be activated in the organic phase for participation in the chemical reaction.

3. Liquid PEG as reaction solvent

PEG and its aqueous solutions represent interesting solvent systems for solvent replacement, and may stand comparison to other currently favored systems such as ionic liquids, supercritical carbon dioxide, and micellar systems. Recently, Sheftel has reviewed the general toxicological action of PEG such as acute toxicity, the mean lethal doses of all molecular weights of PEG, short and long-term, reproductive toxicity, and the mutagenicity *in vitro* or *vivo*.[115] Additionally, relevant laws or regulations governing use in the European Union and from the US FDA were also included. One important difference between using PEG and other 'neoteric solvents' is that all of the toxicological properties, the short and long-term hazards, and the biodegradability, *etc.*, are established and known. For many of the other alternative solvent systems, lengthy investigations will be required to establish the necessary background safety and toxicological information.

PEG is a hydrophilic polymer, easily soluble in water and many organic solvents including: toluene, dichloromethane, alcohol, and acetone, but it is not soluble in aliphatic hydrocarbons such as hexane, cyclohexane, or diethyl ether.[58] The non-polar and hydrophobic hexane, slightly polar 2-octanone, and mildly polar heptanol, all showed some solubility in 70% PEG-300(aq), giving solutions of 0.01, 0.1, and 0.8 M, respectively.[88] Solubilities of 1.7 M and 0.5 M were found for 2,3-dimethyl-1,3-butadiene in PEG-300 and its 90% PEG aqueous solution, and 4.5 M and 1.2 M for 1-bromobutane in these two media, respectively.[88] This solubility enhancement has been applied to aqueous synthesis in both Diels–Alder and S_N1 reactions.[88,116,117]

Of particular interest, is the high solubility of some salts in PEG-400, such as 1.8 M CH_3COOK, 2.1 M KI, 1.1 M KNO_3, 0.25 M KCN, and 0.16 M $K_2Cr_2O_7$. This has enabled the use of this medium in some homogeneous oxidation and substitution reactions resulting in high yields.[118] The solubility of these salts in PEG is comparable with their solubility in dimethylsulfoxide (DMSO). PEG-1500 used in a phenoxide allylation reaction was claimed to effectively enhance the solubility of the reactant allyl chloride in PEG aqueous solution.[119]

Low molecular weight liquid PEGs can be regarded as protic solvents with aprotic sites of binding constituted by the EO units. A few inorganic salts and many organic substrates are soluble in low molecular weight liquid PEG, and thus, they have been proposed as solvents for organic reactions.[71,88,116,117] PEGs have been termed "host" solvents[71] due to their ability to form complexes with metal cations as illustrated in Figs. 4 and 5.

Three main types of reactions have been investigated: substitution, oxidation, and reduction. However, application of liquid PEG is not limited to these reactions, polymerization of methyl methacrylate and styrene has been reported in PEG-400, and a higher rate of polymerization of methyl methacrylate was found than that in toluene, but the rate was slower for styrene in PEG-400 than that in xylene. Moreover, the easy removal of the copper catalyst following the reaction is comparable with the performance of other solvent alternatives such as 1-butyl-3-methylimidazolium hexafluorophosphate and fluorinated biphasic systems.[120] Other types of liquid PEG have been used in substitution and reduction reactions such as high molecular weight PEGs including molecular weights of 900, 1000, 2000, and 3400 in conjunction with sc-CO_2 above the melting point of the PEG.[121–123] The similar small molecular weight liquid polypropylene glycols (PPG) 425 and 1000 have also found application in solvent substitution.[88,116,117,124,125]

3.1 Substitution reactions

Table 3 provides examples of substitution reactions performed using liquid PEG as the solvent. Potassium thioacetate in PEG-400 has been used as a nucleophilic reagent to substitute alkyl halides, tosylates, or mesylates, and the product yields were about 92–98%.[127] The hydrolysis rate constant for the synthesis of 2-chloro-2-methylpropane in PEG-300–H_2O has been compared to those found for acetic acid, methanol, ethanol, and acetone as co-solvent with H_2O, and rate constants were found to increase by 1–3 orders of magnitude at high mass% PEG(aq) over those found for the above organic co-solvents. The Diels–Alder reaction rates of 2,3-dimethyl-1,3-butadiene with nitrosobenzene in PEG-300 showed a 3.3 fold increase compared to the same reactions in dichloromethane, and a 2.5 fold increase over that found in ethanol. 2,3-Dimethyl-1,3-butadiene in reaction with acrolein showed a 14 fold increase in rate constant in 70 mass% PEG-300(aq) over that in methanol.[88,116] PPG-425 showed a similar enhancement of reaction rate, but this was lower than that of PEG-300.[88,116]

The reaction of sodium *p*-toluenesulfonate monohydrate with various alkyl halides in PEG-400 or its diethyl ether have been investigated, and it has been shown that sulfones can be

Table 3 Substitution reactions in PEG solvent media

Substrate (R*X*)	Substitution (Y)	PEG	Product	Ref.
R-CH_2Br	CH_3COO^-, I^-, $C_6H_5O^-$, CN^-	PEG-400	R–CH_2Y	126
R = C_6H_5, C_3H_7, C_9H_{19}, C_7H_{15}				118
R_1-CHX-R_2 R_1 = C_7H_{15}, C_9H_{19}, $C_{11}H_{23}$, $C_{10}H_{21}$, C_6H_5 R_2 = H, CH_3 X = $CH_2C_6H_4SO_2$, CH_2SO_2, Cl, Br, I	CH_3COS^-	PEG-400	R_1-CHY-R_2	127
$(CH_3)_3CCl$	H_2O	PEG-300	$(CH_3)_3COH$	88
$(CH_3)_2C$=CHCl		PPG-425	$(CH_3)_2C(OH)CH_3$, $(CH_3)_2CHCH_2OH$	117
$CH_2CH(CH_3)CH(CH_3)CH_2$	CH_2=CH-CHO C_6H_5-N=O	PEG-300 PPG-425	OCH-C_6H_7-$(CH_3)_2$ C_6H_5-NOC_4H_4-$(CH_3)_2$	88
R′X R′ = $C_6H_5CH_2Cl$, $BrCH_2Br$ R″-Br R″ = C_2H_5, n-C_4H_9, n-C_8H_{17}, CH_2=$CHCH_2$	RSO_2^-	PEG-400 PEG-400-C_2H_5	R-SO_2-R′ + S_2O_2R′	128
R_1-$(SO_3$-$R_2)_n$ R_1 = n-C_8H_{17}, n-C_6H_{13}-CH, $(CH_3)_3CCH_2$, $C_6H_5(CH_2)_2$ R_2 = CH_3, 4-$CH_3C_6H_4$, 2-$C_{10}H_{10}$, 2,4,6-$(CH_3)_3C_6H_5$	F^-	PEG-400	R_1-$(F)_n$	129
ArNH_2 Ar = C_6H_5, *p*-PhCOC_6H_4, 1-$C_{10}H_9$, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$, *o*-$CH_3OC_6H_4$, *m*-$CH_3OC_6H_4$, *p*-$C_6H_5C{\equiv}CC_6H_4$	Cl^-, Br^-, I^-, CN^-	PEG-200-CH_2Cl_2	ArY	130
R-C_6H_4Br	C_6H_5-$B(OH)_2$	PEG-400	R-C_6H_4-C_6H_5	131
$(C_6H_5)_2CNCH_2CO_2$PEG	R_2X	PEG-3400	$(C_6H_5)_2CNCHR_2CO_2$PEG	121
R-C_6H_4-Br R = Cl, OCH_3, CH_2O_2	CH_2=CHX X = C_6H_5, $CO_2C_2H_5$, n-$CH_3(CH_2)_3O$	PEG-2000 ($Pd(CH_3OAc)_2$ catalyst)	R-C_6H_4-CH=CHX	122

obtained in good to excellent yields, while the alkylation of sodium *p*-toluenesulfinate and *N*, *N*′-dimethylformamide in methanol gives only moderate yields.[128] The reaction of KF with the mesylates and tosylates of alcohols has been found to provide good yields of fluoro derivatives in PEG-400 compared to methanol and apolar crown ethers.[129] The diazotization and Sandmeyer reactions of arylamines in PEG-CH_2Cl_2 were found to be effective for the preparation of halogenoarenes and cyanoarenes even in 10 mM dilute substrate. This is still comparable with these reactions in various organic solvents (*e.g.*, xylene, DMSO, 18-crown-6, chloroform, and tetrahydrofuran (THF)), giving high yields only in high concentrations of substrate ($\geqslant$73 mM)).[130] The ordinary aqueous Sandmeyer reactions reported in *Organic Synthesis* gave only very poor yields.[130]

A Schiff base protected glycine modified by end functionalized PEG-3400 reacted readily with various electrophiles without the need for other organic solvents under microwave activation. PEG served as both polymer support and solvent in this reaction. The reaction was comparable with that in acetonitrile.[121] The microwave-assisted Suzuki cross-coupling of arylboronic acids with aryl halides using $PdCl_2$ as catalyst and KF as base in PEG-400 was found to offer ease of operation and the ability to recycle the catalyst. The recyclability of the $PdCl_2$ and PEG-400 solvent by ether extraction makes the reaction more economic and thus, increases its viability for commercial exploitation.[131]

Molten liquid PEG-2000 at 80 °C was used as reaction solvent for Heck coupling reactions and gave a fast reaction rate and high yield.[122] The reaction rate, yield, and regio- and stereoselectivities in this solvent system are comparable with the conventional organic solvents dimethyl formamide (DMF), DMSO, CH_3CN, and the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate. The recyclability of both PEG-2000 and $Pd(OAc)_2$ can be achieved by simple ether extraction of the product, and the higher yield can be sustained even after four subsequent experiments.

Raston and co-workers have shown that PPG-425, HO–$(CH(CH_3)CH_2)_n$–H, can be a solvent for aldehyde synthesis from 4-hydroxybenzaldehyde, K_2CO_3, and the corresponding bromo- or dibromoalkane at 60 °C.[124] PPG-1000 was also successfully used in indium metal mediated synthesis of homoallylic amines.[125] Yields and reaction times were better than and comparable with aqueous reactions and those employing traditional organic solvents. In addition, the product was easily isolated.

PPG is a viscous liquid with a negligible vapor pressure, stable under these reaction conditions, and is easily recovered. However, in contrast to PEG used as a solvent, most commercially available PPG, such as Dow PPGs from molecular weight 250 to 4000, are viscous liquids. Low molecular weight PPG-250 and 425 are in fact water soluble, but PPG shows an inverse temperature–solubility relationship, along with a rapid decrease in water solubility as the molecular weight increases. PPG-2000 has only 0.012% w/w solubility in water at 25 °C, and this may invite exploitation as a relatively more hydrophobic phase in comparison to PEG. These physical properties may limit the wide use of PPGs as reaction media.

3.2. Oxidation reactions

Oxidation reactions conducted in PEG-200 and PEG-400 are given in Table 4. Among the few oxidants examined, $K_2Cr_2O_7$, which is relatively soluble in PEG-400, can oxidize benzyl bromide with good yields.[71] This is similar to the reaction of $Na_2Cr_2O_7$ in hexamethylphosphoramide (HMPA) and crown ether using the same substrate. Aerobic oxidations catalyzed by a polyoxometalate, $H_5PV_2Mo_{10}O_{40}$, in PEG-200 or 400 solvents showed wider application to alcohols, cyclic dienes, sulfides, and in the Wacker reaction.[68] Only 5% weight loss during benzyl alcohol oxidation after three recycles was observed in a solvent recycling process due to PEG degradation, resulting from a 1.7% weight loss for each cycle. No oxidation of the terminal hydroxyl of PEG occurred.

The dihydroxylation of olefins has been conducted using PEG-400 as solvent and OsO_4 as catalyst,[132] and high yields of diols were achieved in a short time (2–3 h). The PEG-400 and OsO_4 were easily reused by simple extraction of product diols using ether, and more than 90% yield was sustained even after 5 recycles. Additionally, the reaction was suitable for asymmetric dihydroxylation (Sharpless reaction) with high yield and good enantioselectivity.

Table 4 Oxidation reactions in PEG solvent media

Substrate	Oxidant	PEG	Product	Ref.
$C_6H_5CH_2Br$	$K_2Cr_2O_7$	PEG-400	C_6H_5CHO	71
R-CH_2OH R = R′-C_6H_4	Aerobic oxidation (catalyzed by $H_5PV_2Mo_{10}O_{40}$)	PEG-200 PEG-400	R-CHO	68
C_nH_{2n-4} (cyclic dienes)	Same as above	PEG-200	C_nH_{2n-6}	68
R-S-R (sulfide)	Same as above	PEG-200	R-SO_2-R (sulfoxides and sulfones)	68
$CH_3CH{=}CH_2$	Aerobic oxidation (catalyzed by $H_5PV_2Mo_{10}O_{40}$ and palladium)	PEG-200	CH_3COCH_3	68
$R_1CH{=}CHR_2$ $R_1 = C_nH_{2n+1}$, C_6H_5 R_2 = H, C_nH_{2n+1}, C_6H_5	*N*-Methylmorpholine (NMO) (catalyzed by OsO_4)	PEG-400	$R_1CH(OH)CH(OH)R_2$	132

Table 5 Reduction reactions in PEG solvent media

Substrate	Reductant	PEG	Product	Ref.
$CH_3COC_6H_{13}$	$NaBH_4$	PEG-400	$CH_3CHOHC_6H_{13}$	71
R_1-COO-R_2 R_1 = alkyl, aryl R_2 = CH_3, C_2H_5	$NaBH_4$	PEG-400	R_1-CH_2OH	134
R_1-CHX-R_2 R_1 = alkyl, aryl X = Cl, Br, I R_2 = H, CH_3, C_4H_9	$NaBH_4$	PEG-400	R_1-CH-R_2	135
R-COCl R = $C_{15}H_{31}$, C_9H_{19}, C_6H_5, *p*-BrC_6H_4	$NaBH_4$	PEG-400	R-COH	135
C_6H_5-CH=CH_2	H_2	PEG-900	C_6H_5-CH_2CH_3	123

3.3. Reduction reactions

Table 5 lists some important reduction reactions which have been demonstrated utilizing PEG as solvent. In PEG-400, carbonyl compounds could be reduced by $NaBH_4$ more efficiently than by slow reaction in THF.[71] It was also found that the reduction of alkyl and aryl esters to the corresponding alcohols by $NaBH_4$ in PEG-400 was enhanced, where these compounds had been considered inert toward reduction in other organic solvents.[134] The halide reduction by $NaBH_4$ in PEG-400 is comparable to that in a variety of polar protic solvents such as DMSO, sulfone, HMPA, and DMF, and the acyl chloride reduction can effectively occur in PEG-400 as a substitute for the inert solvent dioxane.[135] Lindlar's catalyst, Pd–$CaCO_3$ poisoned with PbO, is found to partially reduce triple bonds in alkynes to *cis*-olefins in PEG-400,[133] and PEG and the catalyst can be used 3–5 times without loss of activity or yield.

The waxy solid PEG-900 at 155 bar pressure in sc-CO_2 at 40 °C, showed liquid solvent characteristics, and was successfully used as the solvent for hydrogenation of styrene.[123] The $RhCl(PPh_3)_3$-catalyzed hydrogenation of styrene to ethyl benzene in PEG-900 at 155 bar, 55 °C in sc-CO_2 was conducted as a homogeneous catalysis reaction. Ethyl benzene was extracted into sc-CO_2, and the catalyst-containing PEG phase was reused without loss.[123]

4. PEG as phase-transfer catalyst (PTC)

PEGs and their many derivatives have been extensively investigated as PTCs, and are used in many commercial processes to replace expensive, and environmentally-harmful PTCs.[20,21,24,136,137] Of the commonly used PTCs, linear PEGs are much cheaper than analogous macrocyclic crown ethers and cryptands.[138] PEGs are also more stable at high temperatures, up to 150–200 °C, and show higher stability to acidic and basic conditions than quaternary onium salts.[67]

4.1. Free phase-transfer catalysts

4.1.1. Williamson ether synthesis. The novel Williamson reaction has been successfully conducted in a liquid–solid or liquid–liquid biphasic system using PEG as PTC with or without organic solvent as shown in Table 6. Williamson ether

Table 6 PEGs as free PTCs in Williamson ether syntheses in bases

R_1 of substrate (R_1OH)	Substrate (R_2X)	PEG and solvent	Product	Ref.
C_nH_{2n+1} n = 10, 12	$C_nH_{2n+1}X$ n = 4, 8 X = Br, Cl, I	PEG-350–2000 PEG-$(C_2H_5)_2$ No solvent	R_1-O-R_2	139–141
C_6H_5, 4-Cl-C_6H_4, 3,5-$(CH_3)_2$-C_6H_3, 4-OH-C_6H_4, C_6H_5-C_6H_4	$C_nH_{2n+1}X$ $C_nH_{2n}X$ $C_6H_5CH_3X$ n = 1, 2, 3, 4, 8 X = Cl, Br, I	PEG-400, 1500, 6000 No solvent	R_1-O-R_2	119 142–145
OC_4H_4-CH_2,[a] or	XRX	PEG-400, 600, 800–C_6H_6 or CH_2Cl_2	$(OC_4H_4CH_2O)_2R$	146
Ar = $CH_3C_6H_4$, Cl-C_6H_4, NO_2-C_6H_4, HO_2CCH_2-C_6H_4, OHC-C_6H_4, C_6H_5-C_6H_4	X = Br, Cl R = $(CH_2)_n$, $C_2H_5OC_2H_5$ n = 1, 4, 5		or Ar-ORO-Ar	147
PEG-300, PPG-425, 1000	RBr R = C_nH_{2n+1} n = 2, 4, 6	PEG-300 PPG-425, 1000 KOH/no solvent	PEG-OR or RO-PEG-OR	148

[a] Furfuryl alcohol.

synthesis is an important nucleophilic substitution reaction (S_N2) and involves the synthesis of an ether using an alkyl halide and an alkoxide in an alcoholic solvent. The yield of decan-1-ol during etherification using PEG-2000 as PTC is 84%, which is equal to that found by using 18-crown-6, and higher than the 72% yield found using Kryptofix222 (cryptand).[139] The crown ether and cryptand are very expensive, may constitute toxins or irritants, and are sensitive to humidity.[139] On the other hand, in PEG-300 or PEG-1000, the etherification is also sensitive to H_2O content. A 15% ratio of H_2O/KOH is the optimum H_2O content, and a 30% ratio of H_2O/KOH results in a great decrease in yield. Excess H_2O is presumed to limit the formation of the intermediate alcoholate, and thereby decrease the yield of ether.[148] Both 5% PEG and etherified PEG as PTC are able to enhance the alkyl alcohol etherification reaction with high yield.[139] Catalytic activity is attributed to the presence of sufficient oxygen atoms in the EO units. The hydroxyl group weight percent of 5% PEG-2000 is about 0.085% in this reaction, and the consumption of electrophilic halogenated reactant is very small.[148]

4.1.2. Substitution reactions. One of the most common areas for the application of PEGs as PTCs is in nucleophilic substitution reactions. As listed in Table 7, typical anionic nucleophilic reagents are hydroxides, halides, sulfides, cyanides, cyanamides, carboxylates, sulfonates, and others. The diaryl 1,4-phenylenedioxydiacetic acid and diaryl 1,4-phenylenedioxydiacetate synthesis using PEG-400 as PTC showed good to excellent yields under mild conditions, with short reaction times and simple operation.[149] *N*-Acylation reactions, normally considered difficult, could be conducted using PEG-400 as PTC with high yield.[152] Although 3–6 fold more PEG was needed to achieve the same yield as obtained using 18-crown-6 during *p*-dibromobenzene synthesis, the much lower

Table 7 PEGs as free PTCs in substitution reactions

Substrate	Nucleophilic reagents	PEG/solvent and base	Product	Ref.
Cl-CH_2CO_2H	OH-C_6H_4-OH	PEG-600/$CH_3C_6H_5$	HO_2CCH_2-O-C_6H_4-O-CH_2CO_2H	149
p-$ClOCCH_2$-O-C_6H_4-O-CH_2COCl	R-C_6H_4-OH	PEG-400/CH_2Cl_2	R-C_6H_4-$OCCH_2$-O-C_6H_4-O-CH_2CO-C_6H_4-R	149
m-$(ClCOCH_2O)_2$-C_6H_4	ArOH Ar = X-C_6H_5 X = Cl, NO_2, C_6H_5, CH_3	PEG-400/NaOH	$(ArO_2CCH_2O)_2$-C_6H_4	150 151
C_6H_4-N_2HC-R R = H, $C_6H_5OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$, 2,4,5-$Cl_3C_6H_2OCH_2$	$ArOCH_2COCl$ Ar = C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$	PEG-400/ CH_3CN, K_2CO_3	C_6H_4-N_2HC $(COCH_2OAr)R$	152
p-Y-C_6H_4-$N_2^+BF_4^-$ Y = Br, NO_2	CCl_3Br CH_3I	PEG-1000/ CH_3COOK, $CHCl_3$	*p*-Y-C_6H_4-Br *p*-Y-C_6H_4-I	153
p-Y-C_6H_4-$N_2^+BF_4^-$ Y = Br, NO_2		PEG-1000/ CH_3COOK/C_6H_6	*p*-Y-C_6H_4-C_6H_5	153
C_6H_4-$C_2H_2NHR_1$ R_1 = H, C_6H_5	R_2X R_2 = CH_3, C_6H_5, $C_{12}H_{25}$ X = Br, I	PEG-OCH_3/ $NaOH/C_6H_5CH_3$	C_6H_4-$C_2H_2NR_1R_2$	154
$C_6H_5CH_2Cl$	KSCN	PEG w/o sc-CO_2	$C_6H_5CH_2SCN$	142,155
p-CH_3-C_6H_4-SO_2Cl	MF M = Li, Na, K, Rb, Cs	PEG-115–40000/ CH_3COCH_3	*p*-CH_3-C_6H_4-SO_2F	156
p-X-C_6H_4-Y X = Br, Cl Y = Br, Cl, H	MOR M = alkali metal R = alkyl, aryl	PEG-150–20000000/ KOH	*p*-Y-C_6H_4-OR	97
2-OC_4H_4-CO_2H	C_6H_5-SO_2Cl	PEG-400	2-C_4H_4O-CO_2-SO_2-C_6H_5	157
R-CO-Cl R = Ar-C_4H_4O, 2-ClC_6H_4	NH_4SCN	PEG-400/CH_2Cl_2	RCOSCN	158 159
$POCl_3$	ArONa Ar = RC_6H_4, 2,4-$Cl_2C_6H_3$ R = CH_3, C_4H_8, Cl, C_6H_5	PEG/$CHCl_3$	$(ArO)_3PO$	160
$C_8H_{17}Cl$	NaCN	PEG/$C_{10}H_{22}$	$C_8H_{17}CN$	96
CH_2Br_2	R-C_6H_4-CO_2K	PEG-600/CH_3CN	R-C_6H_4-CO_2-CH_2-CO_2-C_6H_4-R	161
C_6H_5-CH_2Br	CH_3CO_2K	PEG/CH_3CN	C_6H_5-CH_2OCH_3	162

cost of PEG is an important compensating factor.[153] Ultrasound has been found to be effective in enhancing *N*-alkylation of a variety of amines by alkyl halides using PEG-350 methyl ether.[154]

PEG as PTC has been employed in a sc-CO_2 solvent to convert benzyl chloride with potassium cyanide to form phenylacetonitrile, although the yield is lower than a similar reaction employing tetraheptylammonium cyanide. Nevertheless, this is a promising beginning for the development of a low cost, green reaction process.[155] The effect of PEG molecular weight on catalytic effectiveness in the reaction of mono- and di-halobenzenes with alkoxide ions to form monoalkoxybenzenes has been examined.[97] The yield of product was found to increase with primary, secondary, and tertiary alkoxide ions, and high molecular weight PEG was more effective than low molecular weight PEG. The synthesis of *N*-phenyl-*N′*-2-chlorobenzoyl-thiourea from 2-chlorobenzoyl chloride and ammonium thiocyanate using PEG-400 as PTC is more effective than with most quaternary ammonium salts and crown ethers.[159]

4.1.3. Oxidation and reduction reactions. PEG as PTC has been used successfully in many conventional redox reactions. A variety of autoxidation and reduction reactions examined in this solvent are listed in Table 8. The cobalt-catalyzed carbonylation of benzyl halide using PEG-400 proved to be cheaper than using quaternary ammonium salts or crown ethers, and more stable than the use of quaternary ammonium salts, which suffer from irreversible degradation under the same conditions.[163] An acceptable yield can be achieved even without organic solvent for the oxidation of benzyl chloride under the above conditions.[163] A combination of ultrasound with PEG as PTC can effectively change base-catalyzed autoxidation of alkylnitrobenzenes from a dimeric product to a carboxylic acid.[164] PEG-400 and inexpensive $CoCl_2$ in $KCN–BF_3·Et_2O–FeCl_2$ have proved to be useful for the production of carboxylic acids of iodoarenes and iodoalkanes under mild conditions, compared to the use of a catalyst involving a platinum complex.[165]

PEG with $NaBH_4$ and PEG–$NaBH_4$ complexes have been used in the reduction reactions of ketones and aldehydes.[69,70,169] Free PEG can catalyze ketone reduction by $NaBH_4$,[169] while the PEG–$NaBH_4$ derivative can selectively reduce aldehydes in the presence of ketones without concurrent reduction of the ketone group.[69] Base-catalyzed autoxidation of picoline showed that PEG-6000 in benzene was more effective than the use of crown ethers or quaternary ammonium salts,[166] and the reaction can replace previously used expensive aprotic polar solvents such as DMF, Me_2SO, and HMPA. The conversion of vinyl dibromides to 1-bromoalkyne in PEG-400 has been shown to be superior to the same reaction using benzyltriethylammonium.[167] The conversion of aldehydes to homologous acids by a simple two-step procedure using PEG is also considered more practical than the widely used conversion of *p*-anisaldehyde to *p*-methoxyphenylacetic acid.[167] The conversion of alkylene to lactone by manganese carbonyl under PEG-400 has been shown to perform almost as well as the more expensive reaction employing benzyltriethylammonium chloride.[168]

PEG as PTC has also been investigated in the form of a liquid–gas phase reaction in the isomerization of allylbenzene by diffusion and adsorption.[170] The results showed remarkably higher activity for dehydrohalogenation of 2-bromoethyl benzene than the use of benzyltriethylammonium and 18-crown-6.[171]

4.2. PEG-supported PTC

In addition to its own phase-transfer activity, PEG has also been employed as a polymer support for other PTCs. PEG has been modified with some typical PTCs such as crown ethers, ammonium salts, cryptands, and polypodands to enhance

Table 8 Oxidation and reduction reactions using PEG as PTC

Substrate	Oxidant or reductant/catalyst	PEG/solvent and base	Product	Ref.
C_6H_5-CH_2OH	KOCl	PEG-6000/$CH_3COOC_2H_5$	C_6H_5-CHO	142
R-C_6H_4-CH_2X X = Cl, Br	Air/$Co_2(CO)_8$	PEG-400/2-CH_3-C_4H_9OH	R-C_6H_4-CO	163
p-NO_2-C_6H_4-CH_3	O_2	PEG-400/C_6H_5-CH_3/KOH	*p*-NO_2-C_6H_4-CO_2H	164
RI R = CH_3-$C_6H_4CH_3(CH_2)_n$	Air/$CoCl_2$	PEG-400/KCN/KOH	RCO_2H	165
C_6H_5-CH_2-C_6H_5	O_2	PEG-6000	C_6H_5-CO-C_6H_5	166
$RCH{=}CBr_2$ R = $CH_3C_6H_4$, C_6H_4, CH_3, $CH_3OC_6H_4$, $CH_3CH{=}CH$	Air/Pd(diphos)$_2$	PEG-400/NaOH	RCH_2COOH	167
C_6H_5-C≡CH	$Mn(CO)_3Br$	PEG-400/NaOH	C_6H_5-$C_5H_6O_2$	168
R_1COR_2 R_1 = C_6H_5, $C_6H_5CH_2$ R_2 = CH_3, C_6H_5	$NaBH_4$	PEG-400/C_6H_6	$R_1CH(OH)R_2$	169 69
RCOY Y = H, R′, OR″, RCH_2Br	PEG–Li(Na, K)BH_4	PEG-350	RC(OH)Y RCH_3	70

phase-transfer in two-phase reactions. 16-Crown-5, 19-crown-6, and 18-crown-6 ethers have been attached to PEG-3400 and PEG-6800 and demonstrated effective transfer of metal picrates into CH_2Cl_2 from H_2O, which were able to catalyze the reaction of CH_3COOK with benzyl bromide.[162] The quantitative recovery of these crown–PEG polymers from CH_2Cl_2 and acetonitrile can be achieved by ether precipitation.

The covalent attachment of quaternary ammonium salts to PEG-600 resulted in higher reaction rates for dehydrobromination of 2-bromoethylbenzene at 85 °C than those of PEG and quaternary salts alone.[172] In the dehydrohalogenation of 4-bromo-1-chloroethylbenzene to 4-bromostyrene, the catalytic activity of PEG-600–ammonium salt depended on both the PEG end hydroxyl substitution and ammonium salt structure.[172] The PEG-5000–quaternary ammonium salt complex was also easily recovered by precipitation using hexane, diethyl ether, and *tert*-butyl methyl ether, in which PEG is not soluble, and by filtration, without activity loss.[12,173,174]

PEG monoalkyl ether ($(EO)_n$, $n = 3, 4, 5$) has been attached to hexachlorophosphazene to form cyclophosphazenic polypodands, and these compounds were found to have higher phase-transfer catalytic activity for nucleophilic substitution and alkylation reactions,[175,176] especially when commercial Brij 30 (polyoxyethylene-4-lauryl ether) was used as the reactant. The reaction may be competitive with most commonly used PTCs because of the high catalytic activity and low price.[176] The use of PEG of molecular weights from 2000 to 20000 as soluble polymer supports for catalysts and reagents has been reviewed by Janda and co-workers.[12]

5. Aqueous biphasic reactive extraction (ABRE)

The term aqueous biphasic reactive extraction (ABRE) has been used to describe the use of ABS as biphasic reaction media in which controlled partitioning of reactants, catalysts, and products, by choice of phase systems and manipulation of TLL, can be used to enable higher reaction yields, greater product selectivity, and simultaneous separation of reactants, products, and catalysts.[50]

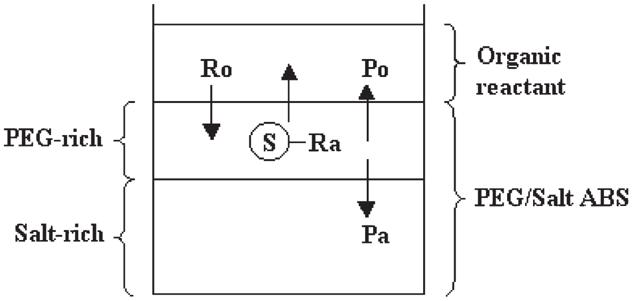
ABS have been used for separations primarily relating to biological solutes and particles for almost half a century.[31,59,79,177,178] Recent extension of this technology has been directed toward application as green separation media[25] including, separation of organic hydrocarbon species[32,33,45] and metal ions.[34–38] However, both PEG and ABS have been largely ignored as "green reaction media" until recent papers indicated their application as new solvents for delignification of cellulose,[50–55] cyclic olefin oxidation,[56,57] polyoxometalate catalyzed aerobic oxidation,[68] S_N1, Diels–Alder, and enzymatic reactions,[88,116,117] and olefin catalytic oxidation to diols.[132]

ABRE has three main characteristics: (1) phase separation benefiting separation of reactants and products, and providing a reaction driving force; (2) the PEG-rich top phase in PEG–salt ABS has organic solvent-like properties as a medium for reaction; (3) ABS components, PEG and metal salts, may be included in the form of PTCs[56,57] and metal-catalysts.[50] Two types of ABRE have been noted. One takes the form of a three-phase reaction,[56,57,179–181] and the other a two-phase reaction.[50–55] The three-phase reaction results from adding organic reactants with or without corresponding supporting organic solvent into an ABS, thus, the system forms three phases initially as shown in Scheme 1. The three phases are usually composed of the light organic phase, and the typical PEG–salt ABS made of the PEG-rich top phase and salt-rich bottom phase. The two-phase reaction results from the chemical or enzyme catalyzed reaction supported only by the normal ABS biphases as demonstrated in Scheme 2.

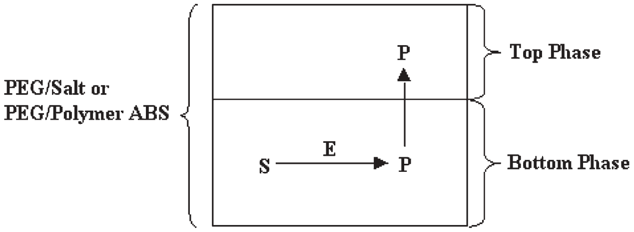
5.1. Three-phase reactions

In order to enhance reaction rate and yield, PEG–salt ABS were formed to increase the organic reactant solubility and PEG concentration in the PEG-rich top phase, which has been described as an ABRE process applied to catalytic oxidation,[56,57] substitution, and isomerization reactions.[179–181] The currently rather limited number of investigations of ABRE processes listed in Table 9, suggest that the role of ABS may be very important for increasing the reaction yield, however, the underlying mechanism is still largely unexplored. For the reactions shown in Scheme 1, ABS formation results in a PEG-rich top phase, which facilitates an increase in the solubility of some organic reactants.[56,57,119] Secondly, phase separation is useful for reactant and product separation, and thirdly, alteration of the reactant, product or catalyst distribution may be used to manipulate the reaction rate. In three-phase reactions, many solvophilic and solvophobic reactants may display some solubility in and partition, at least to some extent, to the PEG-rich top phase and the reaction may occur in this phase.[56,57,180]

In the synthesis of n-butyl phenyl ether by three-phase catalysis,[181] addition of NaOH resulted in a higher reaction rate than the addition of other kinds of salts such as NaCl,



Scheme 1 Three-phase ABRE: Ro = organic reactant; Ra = aqueous reactant; Po = organic product; Pa = aqueous product; S = PTC.



Scheme 2 Typical enzyme hydrolysis reaction in ABS: S = substrate; E = enzyme; P = product.

Table 9 Three-phase ABRE: ABS and organic solvent

ABS and PEG	Organic phase	Product	Ref.
C_4H_9ONa + PEG + NaOH (PEG-600, 3000)	C_6H_5-CH_2Cl (in C_6H_6 or $C_{12}H_{26}$)	C_6H_5-CH_2-OC_4H_9	179 181–183
$(Hex)_4NBr$ + PEG + KOH (PEG-200)	2-$C_8H_{17}Br$ (in $C_{12}H_{26}$)	C_8H_{16}	184
KOH + PEG (PEG-400–6000)	CH_3O-C_6H_4-CH_2-CH=CH_2 (in C_6H_5-CH_3)	CH_3O-C_6H_4-CH=CH-CH_3	180
H_2O_2 + PEG + $NaHSO_4$ (PEG-600–20000)	C_6H_{10} C_5H_8	HOOC-$(CH_2)_4$-COOH HOOC-$(CH_2)_3$-COOH	56 57

KBr and NaBr. PEG and OH^- easily form ABS due to the more negative Gibbs free energy of hydration (ΔG_{hyd}) of the hydroxide anion than that of Cl^- and Br^-. In the three-phase reaction, the mechanism shown in Scheme 1 is supposed to be that of organic reactant diffusion into the PEG-rich top aqueous phase[56,57] (or PEG as PTC carrying aqueous reactant into the organic phase[181]), with subsequent reaction resulting in product precipitation (or dissolution) in the bottom phase, or alternatively, organic product partition into the organic phase.[179] For the above reaction, in an ABS made up of PEG-3000, tetrahexylammonium bromide/KOH and dodecane as organic phase, the production rate of the three-phase system was seven times higher than a corresponding aqueous–organic two-phase system, however when toluene was added as the organic phase, no ABS was formed, because PEG-3000 is soluble in toluene. The yield in toluene was about 10% lower than that in dodecane under the same experimental conditions. The ether production rate and its selectivity are dependent on the initial concentration of n-butanol.[181]

Synergistic effects of PEG and $(Hex)_4NBr$ in the form of a third phase for dehydrohalogenation of 2-bromooctane, and butylphenyl ether have been studied.[184] The amount of quaternary ammonium salt can be reduced to one-nineteenth of the original amount and easily recycled without any loss in catalytic activity in the 2nd and 3rd recycle.[184]

The mechanism of base-catalyzed three-phase reactions with PEG has been studied using the isomerization of allylanisole as a model reaction.[180] The kinetically controlled reaction is successful only under three-phase conditions due to the phase separation of NaOH–PEG aqueous solutions. A potential advantage lies in the fact that PEG is more stable under the experimental conditions, under which quaternary ammonium salts undergo Hoffmann elimination and deactivation.

Recently, we have developed a new green catalytic oxidation of cyclic olefins (*e.g.*, cyclohexene, cyclopentene, and 1,2,3,6-tetrahydrophthalic anhydride (THPA)) to dicarboxylic acid (*e.g.*, adipic acid, glutaric acid, and 1,2,3,4-butanetetracarboxylic acid (BTCA)) in a PEG-2000–$NaHSO_4$ 50% H_2O_2 ABS and in the absence of organic solvent and specific PTC. Phase separation in PEG–$NaHSO_4$ was found to be essential to enhance reaction yield.[56,57] The ABS selection, and effect on adipic acid yield were carefully investigated, and in this ABRE process, the results showed that phase compositions, TLL, and PEG molecular weight can all affect the reaction yield. This model reaction demonstrated the potential "green" characteristics of the use of organic solvent-free, inexpensive, low toxicity PEG and $NaHSO_4$ ABS components, combined with an ecologically benign and clean oxidant (50% H_2O_2).

5.2. Biphasic reactions

5.2.1. Chemical reactions. ABS have been used as alternative delignification processes for hardwood and softwood paper pulping analogous to organosolv pulping. The reactions of delignification in alkaline medium during organosolv pulping are the α-ether cleavage of the free phenolic hydroxyl to quinone methide, and β-ether cleavage of associated phenolic hydroxyl groups combined with condensation reactions.[185] ABS have been proposed as similar in process concept to organosolv pulping,[51] but without the involvement of an organic solvent. ABRE has some obvious advantages compared with the organosolv process: (1) it utilizes a wholly aqueous medium; (2) some of the phase forming components, *e.g.*, Li_2SO_4, can serve as highly effective metal-catalysts for the delignification reaction;[52] (3) reaction enhancement can be achieved by cellulose and lignin partitioning to opposite phases;[53,54] (4) solubility of lignin in the polymer solutions is improved; and (5) the activation energy for the reaction is reduced by improving reagent access through swelling of the fibers.[50] The ABRE pulping process has been shown to compare favorably with the best organosolv practice.[55]

Hydrogel microspheres of methylacrylate bound Dextran polymer can be obtained from the polymerization of methylacrylate bound Dextran in PEG-10000–methacrylated Dextran (Dextran-40000 or 220000) ABS without using organic solvent.[186] A 90% yield can be obtained within short times at relatively low concentrations of radical initiators potassium peroxydisulfate (KPS) and tetramethylethylenediamine (TEMED). Comparison of microspheres from ABS with a macroscopic hydrogel product with a system confined to one aqueous phase, showed a higher reaction rate. With the macroscopic hydrogel process in one phase, the KPS concentration decreased gradually with time, whereas for the microspheres in ABS, the KPS concentration remained constant due to the partition equilibrium between KPS in the PEG-rich top phase and the Dextran-rich bottom phase.

5.2.2. Enzyme reactions. Aqueous two-phase systems have been widely studied for protein purification and immobilization, and also to remove product during biotranformations catalyzed by free cells or enzymes.[26,28,187] Several important enzyme catalyzed biomass hydrolyses and biosyntheses, including processes applicable to cellulose, antibiotics, starch, cyclodextrin, and fermentation processes, have been examined. These ABRE systems for enzymatic hydrolysis can lead to enhanced reaction rates, as well as cost and energy savings, all achieved without the involvement of any organic solvent in the process.

The enzyme hydrolysis and biomass bioconversions in ABS listed in Table 10, represent important applications of ABRE in bioengineering.[26,28] Compared with one-phase reactions, several important characteristics are illustrated in Scheme 2. (1) The ABS must selectively distribute enzyme and substrate to one phase (the bottom phase was assumed in Scheme 2), while the desired product should be partitioned to the other phase (the top phase was assumed in Scheme 2). This can be achieved through differences in molecular weight or molecular structure. The un-hydrolyzed biomass, such as cellulose or starch, is macromolecular, while products, such as glucose or cellobiose, are much smaller. Transformation of substrate to product by an enzyme confined in the bottom phase can effectively enhance reaction by distribution of product to the top phase. Even if the low molecular weight product is evenly partitioned between the phases, the reaction can still be conducted by continuous removal of product from one phase. (2) Product inhibition can effectively be avoided by separation of enzyme and product into two different phases. (3) In some cases, product hydrolysis can be effectively prevented due to partition in the high concentration PEG phase.[199]

In the bioconversion of cellulose to ethanol, the enzymes for hydrolysis, and enzyme recycling constitute the major portion of the process costs.[189] Biphasic systems can be used in cellulose pretreatment, hydrolysis, and fermentation. Both the cellulose substrate and cellulolytic enzyme may be partitioned to the bottom phase, while the hydrolysis product, glucose and some soluble reducing sugars, will be partitioned to the top phase.[189–192] Use of ultra filtration technology[193] and an attrition bioreactor[194] in combination with ABRE, have been found to enhance the reaction rate and improve the yield.[193,194]

Various crude starches have been hydrolyzed by the synergistic action of α-amylase and glucoamylase in PEG–Dextran and PEG–starch ABS.[188] The main advantage in the use of starch is that the starch serves as one of the phase forming polymers, which markedly decreases the cost of the reaction.[188] The enzyme hydrolysis of corn starch in ABS using α-amylase immobilized on ultra fine silica particles by covalent cross linking with glutaraldehyde has been studied,[195] and the enzyme showed high activities. The immobilized enzyme was partitioned to the PEG-rich top phase in PEG–Dextran ABS, and the products were recovered from the bottom phase. Bovine Hb and papain immobilized on ultrafine silica particles by covalent crosslinking with glutaraldehyde have been studied in PEG-6000–Dextran-60000.[195] The immobilized papain was totally partitioned to the top PEG-rich phase, and the soluble peptide product was found in the bottom phase.

Conversion of native waxy maize starch to glucose by α-amylase and glucoamylase has also been conducted in a PEG-20000–crude Dextran ABS in combination with membrane ultra filtration.[196] A continuous stream of glucose could be produced, and PEG, Dextran, and the starch-degrading

Table 10 Enzyme hydrolysis in ABS

Substrate	Enzyme	PEG and ABS	Product	Ref.
Cellulose $(C_6H_{10}O_5)_n$	Endo-β-glucanase Exo-β-glucanase β-Glucosidase	PEG-40000, 200000 Dextran (MW = 1, 4, 11, 50, 200 × 10^4)	Glucose $(C_6H_{12}O_6)$	189–194
Starch or native starch	α-Amylase; Glucoamylase Amyloglucosidase	PEG-6000, 20000 Dextran (MW = 5–7 × 10^4) PEO-PPO-2500 $MgSO_4$, $(NH_4)_2SO_4$	Maltose, glucose	195–198
p-Nitrophenyl α-mannoside *p*-Nitrophenyl β-galactoside	α-Mannosidase	PEG-8000 Dextran-500000	Oligosaccharides	199
Bovine hemoglobin	Papain	PEG-6000 Dextran (MW = 5–7 × 10^4) Ultra fine silica particles (Snowtex 30)	Soluble peptides	195
N-Acetyl-L-methionine	Acylase	PEG-600 K_3PO_4	Acetic acid and L-methionine	200,201
Penicillin G Potassium salt Benzylpenicillin (BP)	Penicillin acylase	PEG-6000, 20000 K_3PO_4	6-Aminopenicillanic acid (6-APA)	202–204
7-amino-deacetoxicephalosporanic acid (7-ADCA) Phenylglycine methyl ester (PGME)	Penicillin G acylase	PEG-400 $MgSO_4$	Cephalexin	205,202
$C_{21}H_{30}O_5$ (Hydrocortisone)	Bacterium	PEG Reppal-PES	Prednisolone	187

enzymes could be recycled. It was possible to cut the starch bioconversion time almost in half by employing a PEO-PPO-2500–$MgSO_4$ ABS compared to a single phase process.[197,198] (PEO-PPO-2500 is a random copolymer of ethylene oxide and propylene oxide with an average molecular weight of 2500.)

PEG-8000–Dextran-500000 ABS have also been applied to the synthesis of oligosaccharides by reverse action of Jack bean α-mannosidase.[205] The reaction and whole yields were similar in two-phase systems and one-phase aqueous buffer systems, but the yield of product per unit of enzyme increased ten fold when using the ABS. This is likely to become a rapidly developing area of the application of ABRE systems since the availability of carbohydrate enzymes in high purity and modest cost has increased with the advent of the wide application of genetic manipulation (GM) techniques.[206]

Cephalexin has been synthesized in ABS by using penicillin G acylase (PGA) as a catalyst and 7-amino-deacetoxicephalosporanic acid (7-ADCA) and phenylglycine methyl ester (PGME) as substrates. A 60% yield of cephalexin was achieved in ABS compared to 21% in an entirely aqueous single phase reaction.[202] The deacylation of penicillin G has been studied using penicillin acylase in a PEG–K_3PO_4 ABS. In this system, the cells partitioned to the bottom phase and the products to the top phase.[203] Cephalexin synthesis from 7-ADCA and PGME catalyzed by PGA, which is covalently immobilized inside a glyoxyl-agarose porous support, can be conducted in PEG-600–$(NH_4)_2SO_4$ ABS. The yield of 90% in the biphasic reaction was higher than that of 55% found in the monophasic reaction.[199]

Chirally selective enzymatic acylase hydrolysis of *N*-acetyl-L-methionine into acetic acid and L-methionine was carried out in PEG–K_3PO_4 ABS in liquid–liquid centrifugal partition chromatography (CPC), and the products and reactants were obtained separately in the same process.[200,201]

Enzyme-biocatalysts are often considered to be inherently green, clean, and nontoxic as opposed to traditional catalysts, which are often toxic metal compounds. Enzymatic syntheses are capable of providing high stereo- and regio-selectivities without using chemical protection-deprotection.[207] ABS may have an important contribution to make in this area. ABS allow manipulation of product and reactant distributions allowing the possibility of separation and yield enhancements. ABS also provide a benign non-denaturing environment for enzymes in contrast to classical solvent media.

6. Conclusions

In recent years PEG aqueous solutions have been widely used in many different kinds of reaction systems. Their low-toxicity, low volatility, and biodegradability represent important environmentally benign characteristics, which are particularly attractive when combined with their relatively low cost as a bulk commodity chemical. In addition, aqueous PEG solutions may often substitute for expensive and often toxic PTCs. The developed state of knowledge with regard to the toxicological properties of PEG is of considerable current advantage compared to the paucity of knowledge for many other potential alternative solvent systems.

The wide range of reactions conducted in pure liquid PEG demonstrates its resilience to degradation and the low occurrence of unwanted side reactions. The role of PEG as a cheap substitute PTC supports the idea that it can assist in promoting the molecular proximity of reactants and catalysts. ABRE combines many of the above advantages along with a measure of process integration and intensification in which chemical synthetic steps are combined with extractive steps. Aqueous solutions of polymers, and in particular PEG, can profoundly affect water structure, reducing cohesivity and some aspects of hydrogen bonding and thereby increasing the solubility of relatively less polar species.

The critical phase formation phenomena associated with PEG aqueous solutions are uniquely important in ABRE, since this brings together phases having different properties and which may be described as having different degrees of hydrophobicity. These phases are uniquely tunable and thus, taken together, ABRE systems can cover a large range of relative difference in chemical potential difference between the phases. In order to achieve this, ABRE systems need to be thought of as a continuum of self-similar systems ranging from Dextran–Ficoll and similar systems, through to PEG–Dextran, and ultimately, PEG–salt ABS. In all of these systems, the polymer molar concentration difference between the phases is proportional to the chemical potential difference engendered across the interface. Metal salts and metal-catalysts may be expected to benefit from solubility in the lower salt-rich phase and yet continued solubility in the more hydrophobic phase may provide for intimate contact with less polar species.

Phase separation can also provide a driving force for chemical reaction through the law of mass action by separation of reactants and products at the moment of formation. Phase separation in ABRE processes may also significantly aid in catalyst and product recovery by providing means of distribution to different phases. In turn, this can aid in the efficient use of reactants and the recycling of catalysts.

Solute distribution is controllable to a much greater extent than with conventional extraction systems. With careful design, this can result in enhanced reaction rates and improved yields in specific reactions. It is also possible to achieve the result that expensive and inefficient recycling and recovery steps can be minimized.

On the other hand, ABRE processes represent complex systems with a large number of variable reaction parameters, requiring optimization and analysis, such as temperature, pH, the addition of particular reactants, or the formation of products or soluble intermediates. All these factors will need to be carefully considered in the design of ABRE processes.

In the course of our recent studies on ABRE processes, we have identified two-types of ABRE process. The first is a three-phase system which includes insoluble liquid organic reactants. The second type is a biphasic process in which the reactants are completely soluble. In the former case, as for example in the oxidation of cyclic olefins in a PEG–$NaHSO_4$–H_2O_2–H_2O ABS, the solubility of the cyclic olefins in the PEG-rich phase is of prime importance. Successful design of the ABS, including selection of PEG molecular size and salt type, depends on an understanding of ABS phase behavior and phase polarity. Such reactions may be applicable in many organic synthetic processes.

Pure biphasic processes may be widely applicable where most components are more soluble. However, even here the existence of a third phase may be noted in some cases, for example a phase of residual solid wood pulp in alternative delignification processes for hardwood and softwood paper pulping in PEG–salt ABS. Such ABRE pulping processes were shown to compare favorably with Kraft type processes and with current organosolv practice. Another example may be given in the form of enzyme hydrolysis reactions, for example the degradation of cellulose in PEG/polymer ABS has shown these ABRE systems can lead to enhanced reaction rates, and cost and energy savings.

It may be anticipated, given the greater availability, higher purity, and reduced cost of enzymes resulting from the impact of rDNA technology, combined with the exquisite specificity of these enzymes and our increasing ability to engineer their properties, that the use of enzymatic synthesis in synthetic chemistry will greatly expand in the years to come. In this context, ABRE processes provide a compatibility with macromolecular stability unmatched by any other extractive solvent systems. Thus, the application of ABRE in the development of controlled enzymatic synthesis, for example of complex carbohydrates, is very promising.

It is to be hoped that this review will further stimulate interest in the extension of ABS applications to yet more novel catalytic processes and reactive extractions. The application of ABRE in synthetic organic chemistry represents both an opportunity and a challenge, and the wide availability of PEG at low cost may give such processes a promising future in green chemistry and green engineering.

Abbreviations

ABRE	Aqueous biphasic reactive extraction
ABS	Aqueous biphasic systems
7-ADCA	7-Amino-deacetoxicephalosporanic acid
ATPS	Aqueous two-phase systems
BTCA	1,2,3,4-Butanetetracarboxylic acid
CPC	Centrifugal partition chromatography
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
GM	Genetic manipulation
GRAS	Generally recognized as safe
HMPA	Hexamethylphosphoramide
IL	Ionic liquid
KPS	Potassium peroxydisulfate
LCST	Lower critical solution temperature
PEG	Polyethylene glycol
PGA	Penicillin G acylase
PGME	Phenylglycine methyl ester
PPG	Polypropylene glycol
PTC	Phase-transfer catalyst
sc-CO_2	Supercritical carbon dioxide
TEMED	Tetramethylethylenediamine
THF	Tetrahydrofuran
THPA	1,2,3,6-Tetrahydrophthalic anhydride
TLL	Tie line length
UCST	Upper critical solution temperature
VOC	Volatile organic compound

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References

1 P. T. Anastas, in *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002, p. 1.
2 J. Sherman, B. Chin, P. D. Huibers, R. Garcia-Valls and T. A. Hatton, *Health Perspect.*, 1998, **106**, Suppl 1, 253.
3 L. R. Pratt, *Chem. Rev.*, 2002, **102**, 2625.
4 *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002.
5 N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725.
6 U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751.
7 P. E. Savage, *Chem. Rev.*, 1999, **99**, 603.
8 C. J. Li, *Chem. Rev.*, 1993, **93**, 2023.
9 U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751.
10 T. H. Chan, L. H. Li, Y. Yang and W. S. Lu, in *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002, p. 166.
11 C. J. Li, J. X. Haberman, C. C. K. Keh, X. H. Yi, Y. Meng, X. G. Hua, S. Venkatraman, W. C. Zhang, T. Nguyen, D. Wang, T. S. Huang and J. H. Zhang, in *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002, p. 178.
12 T. J. Dickerson, N. N. Reed and K. D. Janda, *Chem. Rev.*, 2002, **102**, 3325.
13 D. E. Bergbreiter, *Chem. Rev.*, 2002, **102**, 3345.
14 S. Tascioglu, *Tetrahedron*, 1996, **52**, 11113.
15 N. W. Fadnavis and A. Deshpande, *Curr. Org. Chem.*, 2002, **6**, 393.
16 S. N. Shtykov, *J. Anal. Chem.*, 2000, **55**, 608.
17 J. H. M. Heijnen, V. G. De Bruijn, L. J. P. Van den Broeke and J. T. F. Keurentjes, in *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002, p. 191.
18 G. Oehme, I. Grassert, E. Paetzold, R. Meisel, K. Drexler and H. Fuhrmann, *Coord. Chem. Rev.*, 1999, **185–186**, 585.
19 G. Oehme, in *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 2002, vol. **2**, p. 835.
20 G. E. Totten and N. A. Clinton, *J. Macromol. Sci. Rev. Macromol. Chem. Phys.*, 1988, **C28**, 293.
21 G. E. Totten, N. A. Clinton and P. L. Matlock, *J. Macromol. Sci. Rev. Macromol. Chem. Phys.*, 1998, **C38**, 77.
22 *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*, ed. J. M. Harris, Plenum Press, New York, 1992.
23 *Poly(ethylene glycol) Chemistry and Biological Applications*, ed. J. M. Harris and S. Zalipsky, ACS Symposium Series 680, American Chemical Society, Washington, DC, 1997.
24 C. M. Starks, C. L. Liotta and M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman & Hall, New York, 1994, p. 158.
25 J. G. Huddleston, H. D. Willauer, S. T. Griffin and R. D. Rogers, *Ind. Eng. Chem. Res.*, 1999, **38**, 2523.
26 F. Tjerneld and H. O. Johansson, *Int. Rev. Cytol.*, 2000, **192**, 137.
27 R. Hatti-Kaul, *Mol. Biotechnol.*, 2001, **19**, 269.

28 *Methods in Biotechnology, Vol. 11, Aqueous Two-Phase systems, Methods and Protocols*, ed. R. Hatti-Kaul, Human Press, NJ, 2000, p. 411.
29 *Ionic Liquids, Industrial Applications to Green Chemistry*, ed. R. D. Rogers and K. R. Seddon, ACS Symposium Series 818, American Chemical Society, Washington, DC, 2002.
30 *Ionic Liquids as Green Solvents: Progress and Prospects*, ed. R. D. Rogers and K. R. Seddon, ACS Symposium Series 856, American Chemical Society, Washington, DC, 2003.
31 R. D. Rogers and M. A. Eiteman, *Aqueous Biphasic Separations: Biomolecules to Metal Ions*, Plenum Press, New York, 1995.
32 J. G. Huddleston, H. D. Willauer, K. R. Boaz and R. D. Rogers, *J. Chromatogr. B*, 1998, **711**, 237.
33 R. D. Rogers, H. D. Willauer, S. T. Griffin and J. G. Huddleston, *J. Chromatogr., B: Biomed. Appl.*, 1998, **711**, 255.
34 R. D. Rogers, A. H. Bond, C. B. Bauer, J. H. Zhang and S. T. Griffin, *J. Chromatogr., B: Biomed. Appl.*, 1996, **680**, 221.
35 R. D. Rogers, A. H. Bond, J. H. Zhang and C. B. Bauer, *Appl. Radiat. Isot.*, 1996, **47**, 497.
36 R. D. Rogers, A. H. Bond, C. B. Bauer, J. H. Zhang, S. D. Rein, R. R. Chomko and D. M. Roden, *Solvent Extr. Ion Exch.*, 1995, **13**, 689.
37 R. D. Rogers, A. H. Bond and C. B. Bauer, *Sep. Sci. Technol.*, 1993, **28**, 139.
38 R. D. Rogers, A. H. Bond and C. B. Bauer, *Sep. Sci. Technol.*, 1995, **30**, 1203.
39 R. D. Rogers, A. H. Bond and J. L. Wolff, *J. Coord. Chem.*, 1993, **29**, 187.
40 R. D. Rogers, A. H. Bond, S. Aguinaga and A. Reyes, *J. Am. Chem. Soc.*, 1992, **114**, 2967.
41 R. D. Rogers, A. H. Bond and D. M. Roden, *Inorg. Chem.*, 1996, **35**, 6964.
42 R. D. Rogers, J. H. Zhang and C. B. Bauer, *J. Alloys Compd.*, 1997, **249**, 41.
43 R. D. Rogers, M. M. Benning, R. D. Etzenhouser and A. N. Rollins, *J. Coord. Chem.*, 1992, **26**, 299.
44 R. D. Rogers, M. L. Jezl and C. B. Bauer, *Inorg. Chem.*, 1994, **33**, 5682.
45 H. D. Willauer, J. G. Huddleston and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2002, **41**, 1892.
46 J. G. Huddleston, H. D. Willauer and R. D. Rogers, *J. Chromatogr., B: Biomed. Appl.*, 2000, **743**, 137.
47 H. D. Willauer, J. G. Huddleston, S. T. Griffin and R. D. Rogers, *Sep. Sci. Technol.*, 1999, **34**, 1069.
48 H. D. Willauer, J. G. Huddleston and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2002, **41**, 2591.
49 J. G. Huddleston, H. D. Willauer and R. D. Rogers, *Phys. Chem. Chem. Phys.*, 2002, **4**, 4065.
50 Z. Guo, M. Li, H. D. Willauer, J. G. Huddleston, G. C. April and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2002, **41**, 2535.
51 M. Li, H. D. Willauer, J. G. Huddleston and R. D. Rogers, *Sep. Sci. Technol.*, 2001, **36**, 835.
52 Z. Guo, J. G. Huddleston, R. D. Rogers and G. C. April, *Ind. Eng. Chem. Res.*, 2003, **42**, 248.
53 H. D. Willauer, J. G. Huddleston, M. Li and R. D. Rogers, *J. Chromatogr., B: Biomed. Appl.*, 2000, **743**, 127.
54 Z. Guo, G. C. April, M. Li, H. D. Willauer, J. G. Huddleston and R. D. Rogers, *Chem. Eng. Commun.*, 2003, **190**, 1155.
55 Z. Guo, Ph.D thesis, *Assessment of Aqueous Biphasic Systems (ABS) as an Alternative Delignification Process*, The University of Alabama, Tuscaloosa, 2002.
56 J. Chen, S. K. Spear, J. G. Huddleston, J. H. Holbrey, R. P. Swatloski and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2004, **43**, 5358.
57 J. Chen, S. K. Spear, J. G. Huddleston, J. H. Holbrey and R. D. Rogers, *J. Chromatogr., B: Biomed. Appl.*, 2004, **807**, 145.
58 F. E. Bailey, Jr. and J. V. Koleske, *Poly(Ethylene Oxide)*, Academic Press, New York, 1976.
59 P. Å. Albertsson, *Partition of Cell Particles and Macromolecules*, Wiley, New York, 3rd edn., 1986.
60 J. M. Harris, in *Polyethylene Glycol Chemistry, Biotechnical and Biomedical Applications*, ed. J. M. Harris, Plenum Press, New York and London, 1992, p. 7.
61 D. A. Herold, K. Keil and D. E. Bruns, *Biochem. Pharmacol.*, 1989, **38**, 73.
62 M. G. Peglation, *Cancer Treat. Rev.*, 2002, **28**, 13.
63 D. Bhadra, S. Bhadra, P. Jain and N. K. Jain, *Pharmazie*, 2002, **57**, 5.
64 G. E. Francis, D. Fisher, C. Delgado, F. Marlik, A. Gardiner and D. Neale, *Int. J. Hematol.*, 1998, **68**, 1.
65 F. M. Veronese, P. Caliceti, O. Schiavon and M. Sergi, *Adv. Drug Delivery Rev.*, 2002, **54**, 587.
66 Carbowax PEG-200 MSDS of Canadian Center for Occupational Health and Safety (CCOHS), Record Number 2426725, Oct. 2002, http://www.safety.vanderbilt.edu/pdf/hcs_msds/carbowaxPEG200.pdf.
67 S. D. Naik and L. K. Doraiswamy, *AIChE J.*, 1998, **44**, 612.
68 A. Haimov and R. Neumann, *Chem. Commun.*, 2002, 876.
69 J. R. Blanton, *Synth. Commun.*, 1997, **27**, 2093.
70 J. R. Blanton, *React. Funct. Polym.*, 1997, **33**, 61.
71 E. Santaniello, A. Manzocchi and P. Sozzani, *Tetrahedron Lett.*, 1979, **20**, 4581.
72 R. Kjellander and E. Florin, *J. Chem. Soc., Faraday Trans. 1*, 1981, **77**, 2053.
73 R. Kjellander, *J. Chem. Soc., Faraday Trans. 2*, 1982, **77**, 2025.
74 M. Carlsson, D. Hallen and P. Linse, *J. Chem. Soc., Faraday Trans.*, 1995, **91**, 2081.
75 G. Karlström, *J. Phys. Chem.*, 1985, **89**, 4962.
76 H. O. Johansson, G. Karlstrom, F. Tjerneld and C. A. Haynes, *J. Chromatogr., B: Biomed. Appl.*, 1998, **711**, 3.
77 B. Y. Zaslavsky, *Aqueous Two-Phase Partitioning: Physical Chemistry and Bioanalytical Applications*, Marcel Dekker, New York, 1995.
78 Y. Guan, T. E. Treffry and T. H. Lilley, *J. Chromatogr., A*, 1994, **668**, 31.
79 H. Walter and G. Johansson, *Aqueous Two-Phase Systems, Vol. 228, Methods in Enzymology Series*, Academic Press, New York, 1994.
80 K. E. Gutowski, G. A. Broker, H. D. Willauer, J. G. Huddleston, R. P. Swatloski, J. D. Holbrey and R. D. Rogers, *J. Am. Chem. Soc.*, 2003, **125**, 6632.
81 J. G. Huddleston, T. K. Looney, G. A. Broker, S. T. Griffin, S. K. Spear and R. D. Rogers, *Ind. Eng. Chem. Res.*, 2003, **42**, 6088.
82 C. A. Eckert, B. L. Knutson and P. G. Debenedetti, *Nature*, 1996, **383**, 313.
83 S. H. Yalkowsky, *Solubility and Solubilization in Aqueous Media*, Oxford University Press, New York, 1999.
84 S. H. Yalkowsky and S. Banerjee, *Aqueous Solubility: Methods of Estimation for Organic Compounds*, Marcel Dekker, New York, 1992.
85 C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149.
86 B. Y. Zaslavsky, A. A. Borvskaya, N. D. Gulaeva and L. M. Miheeva, *Biotechnol. Bioeng.*, 1992, **40**, 1.
87 C. Reichardt, *Chem. Rev.*, 1994, **94**, 2319.
88 N. F. Leininger, R. Clontz, J. L. Gainer and D. J. Kirwan, in *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, ed. M. A. Abraham and L. Moens, ACS Symposium Series 819, American Chemical Society, Washington, DC, 2002; p. 208.
89 N. P. Cheremisinoff, *Industrial Solvent Handbook*, Marcel Dekker, New York, 2nd edn., 2003.
90 M. H. Abraham, A. M. Zissimos, J. G. Huddleston, H. D. Willauer, R. D. Rogers and W. E. Acree, *Ind. Eng. Chem. Res.*, 2003, **42**, 413.
91 L. Toke and G. T. Sazbo, *Acta Chim. Acad. Sci. Hung.*, 1977, **93**, 421.
92 L. Toke, G. T. Sazbo and K. Somogyi-Werner, *Acta Chim. Acad. Sci. Hung.*, 1979, **101**, 47.
93 G. T. Sazbo, K. Aranyosi and L. Toke, *Acta Chim. Acad. Sci. Hung.*, 1982, **110**, 215.
94 R. Neumann and Y. Sasson, *J. Mol. Catal.*, 1985, **31**, 81.
95 R. Neumann, S. Dermeik and Y. Sasson, *Isr. J. Chem.*, 1985, **26**, 239.
96 G. W. Gokel, D. M. Goli and R. A. Schultz, *J. Org. Chem.*, 1983, **48**, 2837.
97 R. Neumann and Y. Sasson, *Tetrahedron*, 1983, **39**, 3437.
98 P. Selucky, J. Plesek, J. Rais, M. Kyrs and L. Kadlecova, *J. Radioanal. Nucl. Chem.*, 1991, **149**, 131.

99 G. Von Helden, T. Wyttenbach and M. T. Bowers, *Science*, 1995, **267**, 1483.
100 G. Von Helden, T. Wyttenbach and M. T. Bowers, *Int. J. Mass Spectrom. Ion Processes*, 1995, **146–147**, 349.
101 T. Wyttenbach, G. Von Helden and M. T. Bowers, *Int. J. Mass Spectrom. Ion Processes*, 1997, **165–166**, 377.
102 S. Yanagida, K. Takahashi and M. Okahara, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1294.
103 S. Yanagida, K. Takahashi and M. Okahara, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3111.
104 L. J. M. Sawers, D. P. Tunstall and P. G. Bruce, *Solid State Ionics*, 1998, **107**, 13.
105 C. P. Rhodes and R. Frech, *Macromolecules*, 2001, **34**, 1365.
106 L. Ducasse, M. Dussauze, J. Grondin, J. C. Lassegues, C. Naudin and L. Servant, *Phys. Chem. Chem. Phys.*, 2003, **5**, 567.
107 C. P. Rhodes and R. Frech, *Solid State Ionics*, 1999, **121**, 91.
108 G. S. MacGlashan, Y. G. Andreev and P. G. Bruce, *Nature*, 1999, **398**, 782.
109 P. Lightfoot, M. A. Mehta and P. G. Bruce, *Science*, 1993, **262**, 883.
110 P. Lightfoot, M. A. Mehta and P. G. Bruce, *J. Mater. Chem.*, 1992, **2**, 379.
111 B. G. Bogdanov, M. Michailov and C. V. Uzov, *J. Polym. Mater.*, 1991, **8**, 193.
112 J. B. Thomson, P. Lightfoot and P. G. Bruce, *Solid State Ionics*, 1996, **85**, 203.
113 D. K. Cha and S. M. Park, *J. Electroanal. Chem.*, 1998, **459**, 135.
114 G. A. Broker, J. Chen, J. G. Huddleston, S. T. Griffin, J. Baldwin, J. D. Holbrey, S. K. Spear and R. D. Rogers, *Structural Chemistry of Tetraethylene Glycol Complex of LiCl*, in preparation.
115 V. O. Sheftel, *Indirect Food Additives and Polymers: Migration and Toxicology*, Lewis Publishers, Inc., Boca Raton, FL, 2000, p. 1114.
116 N. F. Leininger, R. Clontz, J. L. Gainer and D. J. Kirwan, *Chem. Eng. Commun.*, 2003, **190**, 431.
117 N. F. Leininger, J. L. Gainer and D. J. Kirwan, *AIChE J.*, 2004, **50**, 511.
118 E. Santaniello, A. Manzocchi and P. Sozzani, *Tetrahedron Lett.*, 1979, **20**, 4581.
119 M. L. Wang and K. R. Chang, *Can. J. Chem. Eng.*, 1991, **69**, 340.
120 S. Perrier, H. Gemici and S. Li, *Chem. Commun.*, 2004, 604.
121 B. Sauvagnat, F. Lamaty, R. Lazaro and J. Martinez, *Tetrahedron Lett.*, 2000, **41**, 6371.
122 S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.*, **2002**, 4399.
123 D. J. Heldebrant and P. G. Jessop, *J. Am. Chem. Soc.*, 2003, **125**, 5600.
124 B. A. Roberts, G. W. V. Cave, C. L. Raston and J. L. Scott, *Green Chem.*, 2001, **3**, 280.
125 P. C. Andrews, A. C. Peatt and C. L. Raston, *Green Chem.*, 2004, **6**, 119.
126 E. Santaniello, in *Crown Ethers and Phase Transfer Catalysis in Polymer Science*, ed. L. J. Mathias and C. E. Carraher, Jr., Plenum Press, New York, 1984, p. 397.
127 P. Ferravoschi, A. Fiecchi, P. Grisenti, E. Santaniello and S. Trave, *Synth. Commun.*, 1987, **17**, 1569.
128 K. Sukata, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 613.
129 D. Badone, G. Jommi, R. Pagligrin and P. Tavecchia, *Synthesis*, 1987, 920.
130 N. Suzuki, T. Azuma, Y. Kaneko, Y. Izawa, H. Tomioka and T. Nomoto, *J. Chem. Soc., Perkin Trans. 1*, 1987, 645.
131 V. V. Namboodiri and R. S. Varma, *Green Chem.*, 2001, **3**, 146.
132 S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Chem. Commun.*, 2003, 1716.
133 S. Chandrasekhar, Ch. Narsihmulu, G. Chandrashekar and T. Shyamsunder, *Tetrahedron Lett.*, 2004, **45**, 2421.
134 E. Santaniello, P. Ferraboschi and P. Sozzani, *J. Org. Chem.*, 1981, **46**, 4584.
135 E. Santaniello, A. Fiecchi, A. Manzocchi and P. Ferraboschi, *J. Org. Chem.*, 1983, **48**, 3074.
136 *Phase-Transfer Catalysis: Mechanisms and Syntheses*, ed. M. E. Halpern, ACS Symposium Series 659, American Chemical Society, Washington, DC, 1997.
137 J. M. Harris, N. H. Hundley, T. G. Shannon and E. C. Struck, in *Crown Ethers and Phase Transfer Catalysis in Polymer Science*, ed. L. J. Mathias and C. E. Carraher, Jr., Plenum Press, New York, 1984, p. 371.
138 C. B. Dartt and M. E. Davis, *Ind. Eng. Chem. Res.*, 1994, **33**, 2887.
139 B. Abribat, Y. Le Bigot and A. Gaset, *Synth. Commun.*, 1994, **24**, 2091.
140 B. Abribat, Y. Le Bigot and A. Gaset, *Tetrahedron*, 1996, **52**, 8245.
141 B. Abribat and Y. Le Bigot, *Tetrahedron*, 1997, **53**, 2119.
142 D. Balasubramanian, P. Sukumar and R. Chandani, *Tetrahedron Lett.*, 1979, **20**, 3543.
143 E. Angeletti, P. Tundo and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1137.
144 M. L. Wang and K. R. Chang, *J. Mol. Catal.*, 1991, **67**, 147.
145 S. Slaoui, R. Le Goaller, J. L. Pierre and J. L. Luche, *Tetrahedron Lett.*, 1982, **23**, 1681.
146 J. Sun and C. G. Yan, *Synth. Commun.*, 2002, **32**, 1735.
147 M. M. Salunkhe, B. P. Kavitake, S. V. Patil and P. P. Wadgaonkar, *J. Chem. Res. (S)*, 1995, 503.
148 B. Abribat, Y. Le Bigot and A. Gaset, *Synth. Commun.*, 1994, **24**, 1773.
149 T. B. Wei, J. C. Chen, X. C. Wang, Y. M. Zhang and L. L. Wang, *Synth. Commun.*, 1996, **26**, 1447.
150 X. C. Wang, Z. Li, L. M. Gao, T. B. Wei and J. C. Chen, *Synth. Commun.*, 2000, **30**, 2083.
151 X. C. Wang, T. B. Wei, J. C. Chen and J. R. Li, *Synth. Commun.*, 1996, **26**, 2765.
152 L. L. Wang, S. J. Lu, S. B. Li, Y. M. Zhang and T. B. Wei, *Synth. Commun.*, 1998, **28**, 1005.
153 R. A. Bartsch and I. W. Wang, *Tetrahedron Lett.*, 1979, **20**, 2503.
154 R. S. Davidson, A. M. Patel, A. Safdar and D. Thornthwaite, *Tetrahedron Lett.*, 1983, **24**, 5907.
155 K. Chandler, C. W. Culp, D. R. Lamb, C. L. Liotta and C. A. Eckert, *Ind. Eng. Chem. Res.*, 1998, **37**, 3252.
156 E. N. Krylov and T. A. Buslaeva, *Russ. J. Gen. Chem.*, 1997, **67**, 106.
157 T. B. Wei and Y. M. Zhang, *Synth. Commun.*, 1999, **29**, 2943.
158 T. B. Wei, J. C. Chen and Y. M. Zhang, *Synth. Commun.*, 1995, **25**, 1885.
159 Y. M. Zhang, T. B. Wei and L. L. Wang, *Synth. Commun.*, 1997, **27**, 751.
160 V. K. Krishnakumar, *Synth. Commun.*, 1984, **14**, 189.
161 B. P. Kavitake, M. M. Salunkhe and P. P. Wadgaonkar, *Synth. Commun.*, 1997, **27**, 1703.
162 J. M. Harris, N. H. Hundley, T. G. Shannon and E. C. Struck, *J. Org. Chem.*, 1982, **47**, 4789.
163 C. Zucchi, G. Pályi, V. Galamb, E. Sámpár-Szerencsés, L. Markó, P. Li and H. Alper, *Organometallics*, 1996, **15**, 3222.
164 R. Neumann and Y. Sasson, *Chem. Commun.*, 1985, 616.
165 J. T. Lee and H. Alper, *Organometallics*, 1990, **9**, 3064.
166 R. Neumann and Y. Sasson, *J. Org. Chem.*, 1984, **49**, 1282.
167 P. Li and H. Alpert, *J. Org. Chem.*, 1986, **51**, 4354.
168 J. X. Wang and H. Alpert, *J. Org. Chem.*, 1986, **51**, 273.
169 B. G. Zupancic and M. Kokalj, *Synth. Commun.*, 1982, **12**, 881.
170 R. Neumann and Y. Sasson, *J. Mol. Catal.*, 1985, **33**, 201.
171 Y. Kimura and S. L. Regen, *J. Org. Chem.*, 1983, **48**, 195.
172 S. Grinberg and E. Shaubi, *Tetrahedron*, 1991, **47**, 2895.
173 R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and G. Tocco, *Org. Lett.*, 2000, **2**, 1737.
174 D. Albanese, M. Benaglia, D. Landini, A. Maia, V. Lupi and M. Penso, *Ind. Eng. Chem. Res.*, 2002, **41**, 4928.
175 M. P. Bullitta, E. Maccioni, L. Corda and G. Podda, *J. Heterocycl. Chem.*, 1993, **30**, 93.
176 A. Gobbi, D. Landini, A. Maia, G. Delogu and G. Podda, *J. Org. Chem.*, 1994, **59**, 5059.
177 J. G. Huddleston, A. Veide, K. Kohler, J. Flanagan, S. O. Enfors and A. Lyddiatt, *Trends Biotechnol.*, 1991, **9**, 381.
178 J. G. Huddleston and A. Lyddiatt, *Appl. Biochem. Biotechnol.*, 1990, **26**, 249.
179 H. C. Hsiao, S. M. Kao and H. S. Weng, *Ind. Eng. Chem. Res.*, 2000, **39**, 2772.
180 R. Neumann and Y. Sasson, *J. Org. Chem.*, 1984, **49**, 3448.
181 H. C. Hsiao and H. S. Weng, *J. Chem. Technol. Biotechnol.*, 2001, **76**, 959.
182 G. Jin, T. Ido and S. Goto, *Catal. Today*, 2001, **64**, 279.

183 T. Ido, T. Yoshikawa, G. Jin and S. Goto, *Kagaku Kogaku Ronbunshu*, 2002, **28**, 88.
184 G. Jin, T. Ido and S. Goto, *J. Chem. Eng. Jpn.*, 1999, **32**, 417.
185 T. J. McDonough, *Tappi J.*, 1993, **76**, 186.
186 R. J. H. Stenekes and W. E. Hennink, *Polymer*, 2000, **41**, 5563.
187 R. Hatti-Kaul and B. Mattiasson, *Appl. Microbiol. Biotechnol.*, 1986, **24**, 259.
188 A. Karakatsanis and M. Liakopoulou-Kyriakides, *Starch/Stärke*, 1998, **50**, 349.
189 F. Tjerneld, I. Persson, P. Å. Albertsson and B. Hahn-Hägerdal, *Biotechnol. Bioeng.*, 1985, **27**, 1036.
190 F. Tjerneld, I. Persson, P. Å. Albertsson and B. Hahn-Hägerdal, *Biotechnol. Bioeng.*, 1985, **27**, 1044.
191 I. Persson, H. Stålbrand, F. Tjerneld and B. Hahn-Hägerdal, *Appl. Biochem. Biotechnol.*, 1992, **27**, 27.
192 C. F. Mandenius, B. Nilsson, I. Persson and F. Tjerneld, *Biotechnol. Bioeng.*, 1988, **31**, 203.
193 F. Tjerneld, I. Persson, P. Å. Albertsson and B. Hahn-Hägerdal, *Biotechnol. Bioeng. Symp.*, 1986, **15**, 419.
194 F. Tjerneld, I. Persson and J. M. Lee, *Biotechnol. Bioeng.*, 1991, **37**, 876.
195 A. Kondo, T. Urabe and K. J. Higashitani, *J. Ferment. Bioeng.*, 1994, **77**, 700.
196 M. Larsson, V. Arasaratnam and B. Mattiasson, *Biotechnol. Bioeng.*, 1989, **33**, 758.
197 M. Li, J. W. Kim and T. L. Peeples, *Biochem. Eng. J.*, 2002, **11**, 25.
198 M. Li, J. W. Kim and T. L. Peeples, *J. Biotechnol.*, 2002, **93**, 15.
199 O. H. Hernandez-Justiz, R. F. Fernandez-Lafuente, M. Terreni and J. M. Guisan, *Biotechnol. Bioeng.*, 1998, **59**, 73.
200 J. L. Den Hollander, B. I. Stribos, M. J. Van Buel, K. Ch. A. M. Luyben and L. A. M. Van der Wielen, *J. Chromatogr., B: Biomed. Appl.*, 1998, **711**, 223.
201 J. L. Den Hollander, Y. W. Wong, K. Ch. A. M. Luyben and L. A. M. Van der Wielen, *Chem. Eng. Sci.*, 1999, **54**, 3207.
202 D. Z. Wei, J. H. Zhu and X. J. Cao, *Biochem. Eng. J.*, 2002, **11**, 95.
203 L. C. Liao, C. S. Ho and W. T. Wu, *Process Biochem.*, 1999, **34**, 417.
204 E. Andersson, B. Mattiasson and B. Hahn-Hägerdal, *Enzyme Microb. Technol.*, 1984, **6**, 301.
205 T. J. Bartlett, R. A. Rastall, N. H. Rees, M. W. Adlard and C. Bucke, *J. Chem. Technol. Biotechnol.*, 1992, **55**, 73.
206 T. K. Mong, H. K. Lee, S. G. Duron and C. H. Wong, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 797.
207 A. Pandey, S. Sarfaraz and L. Iyengar, in *Green Chemistry: Environment Friendly Alternatives*, ed. R. Sanghi and M.M. Srivastava, Narosa Publishing House, New Delhi, India, 2003, p. 294.

Octanol–water partition coefficients of imidazolium-based ionic liquids

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Ionic liquids (ILs) are low melting organic salts that are being vigorously investigated as possible replacements for volatile organic solvents. While they cannot contribute to air pollution due to their negligible vapor pressure, they do have significant solubility in water. As a result, this is the most likely medium through which ILs will enter the environment. Therefore, it is important to understand how ILs will influence aquatic ecosystems. A simple thermodynamic measurement that has been extremely useful in estimating effects of chemical pollutants on aquatic environments is the octanol–water partition coefficient (K_{OW}). It is an extremely important quantity because it describes the hydrophobicity or hydrophilicity of a compound and has been correlated with bioaccumulation and toxicity in fish, as well as sorption to soils and sediments. Here we present measurements of the K_{OW} of twelve imidazolium-based ILs at room temperature, using the slow-stirring method. For the butylmethylimidazolium cation, K_{OW} values range from 0.003 to 11.1, depending on the choice of anion. In addition, we find that the K_{OW} values increase with increasing alkyl chain length on the cation and that replacing the acidic hydrogen on the carbon between the two nitrogens in the imidazolium ring with a methyl group has negligible effect on the K_{OW}. However, all of the K_{OW} values measured, even for the most "hydrophobic" imidazolium-based ILs, are less than 15 so these ILs will not accumulate or concentrate in the environment.

Introduction

Low melting organic salts or ionic liquids (ILs) have been vigorously investigated in the past decade.[1–5] Much work has focused on their ability to serve as solvents for reactions and their potential as phase-transfer catalysts. In addition, they are known for their good heat transfer properties and high conductivities. Their stability, large liquidus range and good solvation properties for both polar and nonpolar compounds[6] make them interesting as solvents for chemical reactions and separations. Their physical properties are tunable by wise selection of cation, anion and substituents. The more common ILs are based on imidazolium, pyridinium or quaternary ammonium salts. Some recent reviews providing an overview of the potential of these salts for synthesis, catalysis, and separations are available.[1–4]

Since ionic liquids are nonvolatile, they cannot contribute to atmospheric pollution. However, they all show some solubility in water and their effect on aquatic organisms is just starting to be investigated.[7–10] A key parameter in the assessment of environmental risk and in the prediction of the fate of chemicals in the environment is the octanol–water partition coefficient (K_{OW}). It is an extremely important quantity because it describes the hydrophobicity or hydrophilicity of a compound. K_{OW} is the basis of correlations to calculate bioaccumulation[11–15] and toxicity in fish,[16] as well as sorption to soils and sediments.[17,18]

By definition, when equilibrium is reached, the activity of a compound, a_i, in the water-rich phase and the octanol-rich phase must be the same ($a_i^{w} = a_i^{o}$). Since $a_i = \gamma_i x_i$ then:

$$\frac{x_i^{o}}{x_i^{w}} = \frac{\gamma_i^{w}}{\gamma_i^{o}} \tag{1}$$

where x_i is the mole fraction and γ_i is the activity coefficient in the water-rich (^{w}) and octanol-rich (^{o}) phases, respectively. At constant pressure and temperature, for sufficiently dilute solutions of the test compound, mole fractions and concentrations are proportional. Moreover, if the test compound is sufficiently dilute in both phases that it can be considered at "infinite dilution," then the activity coefficients should not change with small variations in the concentrations. In this case, namely extremely dilute concentrations (C_i) of the test compound in both phases, the partition coefficient should be a constant, independent of composition. This is also called the Nernst distribution law:

$$K_{ow} = \frac{C_i^{o}}{C_i^{w}} \tag{2}$$

One must note that octanol and water are not completely immiscible. At 25 °C, the solubility of water in octanol is quite large, approximately 0.275 mole fraction,[19] but the solubility of octanol in water is just 7.5×10^{-5} mole fraction.[20] These solubilities depend on the temperature of the solution and can affect the partitioning of the solute between the two solvents. Moreover, octanol and water form an emulsion that can be a significant source of error in the measurement of K_{OW}.

Using the definition of mole fraction and the hypothesis that the solute is infinitely dilute, it is possible to express the partition coefficient in terms of activity coefficients. In the

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water-rich phase, the number of moles of solute and octanol are negligible compared to the density of water (55.5 mol L^{-1}) so $C_i^{\mathrm{w}} = 55.5x_i^{\mathrm{w}}$, where C_i^{w} is the concentration of the solute in the water-rich phase and x_i^{w} is the mole fraction of the solute in the water-rich phase. Likewise, in the octanol-rich phase, the number of moles of the solute is negligible. However, the amount of water in the octanol-rich phase is large and the molar density of the solution is approximated as the sum of the density of pure octanol (2.3 mol L^{-1}) and the molar solubility of water (6.07 mol L^{-1}) in the octanol, meaning that $C_i^{\mathrm{o}} = 8.37x_i^{\mathrm{o}}$, where C_i^{o} is the concentration of the solute in the octanol-rich phase and x_i^{o} is the mole fraction of the solute in the octanol-rich phase.

Using the definition of the octanol–water partition coefficient, K_{OW},

$$K_{\mathrm{ow}} = \frac{C_i^{\mathrm{o}}}{C_i^{\mathrm{w}}} = \frac{8.37x_i^{\mathrm{o}}}{55.5x_i^{\mathrm{w}}} \tag{3}$$

and using eqn. (1), the relationship between the octanol–water partition coefficient for very dilute solutions and the infinite dilution (signified by ∞) activity coefficients is:

$$K_{\mathrm{ow}} = \frac{C_i^{\mathrm{o}}}{C_i^{\mathrm{w}}} = 0.1508\frac{\gamma_i^{\infty,\mathrm{w}}}{\gamma_i^{\infty,\mathrm{o}}} \tag{4}$$

K_{OW} is defined for the same species of the solute in the two liquid phases. This can be difficult to determine for species such as acids or salts, where the degree of dissociation may be greater in the aqueous phase than in the octanol-rich phase. As shown in Fig. 1, we anticipate that ILs ($[M_{v+}X_{v-}]$) will have a greater tendency to dissociate in the water-rich phase. The true octanol–water partition coefficient is the ratio of the concentration of the undissociated species in the two phases:

$$K_{\mathrm{ow}} = \frac{[M_{\upsilon+}X_{\upsilon-}]^{\mathrm{octanol}}}{[M_{\upsilon+}X_{\upsilon-}]^{\mathrm{water}}} \tag{5}$$

However, due to the difficulty of this measurement, the octanol–water partition coefficient commonly reported is the concentration of both undissociated and dissociated (if any) salt in the octanol phase divided by the total concentration (both dissociated and undissociated) in the water phase. This is the case for the values reported here since we use UV-vis spectroscopy, which detects the imidazolium ring on the cation (whether dissociated or undissociated), for determination of concentrations in both phases. Therefore, the K_{OW} values reported here are:

$$K_{\mathrm{ow}} = \frac{[M_{\upsilon+}X_{\upsilon-}]^{\mathrm{octanol}} + [M^{Z+}]^{\mathrm{octanol}}}{[M_{\upsilon+}X_{\upsilon-}]^{\mathrm{water}} + [M^{Z+}]^{\mathrm{water}}} \tag{6}$$

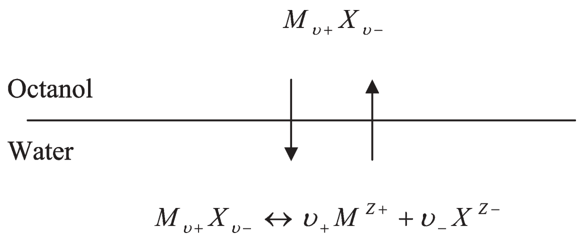

Fig. 1 Partitioning of an organic salt between octanol and water.

Many direct and indirect methods are available to experimentally measure K_{OW},[21] and the more current ones are detailed below in the Experimental section. There are numerous publications of experimentally determined K_{OW} values. We draw attention to one compilation of values for organic compounds by Leo *et al.*,[22] who used the "shake-flask" method and developed a fragment or group distribution method to evaluate the K_{OW} values.

We are aware of two previous efforts to measure or compute octanol–water partition coefficients for some ionic liquids.[23,24] Domanska *et al.*[23] measured binary liquid–liquid equilibrium (LLE) for several alkylmethylimidazolium chlorides ([C$_n$mim][Cl], for n = 4, 8, 10 and 12) with both water and octanol. They used the solubility data of [C$_n$mim][Cl] in each solvent to estimate K_{OW} values (K_{OW} ≈ solubility of IL in pure octanol/solubility of IL in pure water). However, the concentration of the IL was rather high in each phase and the authors could not take into account the mutual saturation of the solvents (*i.e.*, they measured the solubility in each of the pure solvents). Chou *et al.*[24] measured the K_{OW} of [emim][PF$_6$] and [bmim][PF$_6$] by using a shake-flask method but did not centrifuge their samples to eliminate the emulsion created by the shaking process. Although the ILs were present at low concentrations, the value of K_{OW} for [bmim][PF$_6$] and the trend they observed with increasing alkyl chain length are inconsistent with those obtained in this study.

For the present study, we used the slow-stirring method to measure the octanol–water partition coefficients of dilute samples of several imidazolium-based ionic liquids. We examine the effect of anion on K_{OW} for a series of 1-butyl-3-methylimidazolium ([bmim]) salts and the effect of cation on K_{OW} for a series of bis(trifluoromethylsulfonyl)imide ([Tf$_2$N]) salts.

Experimental

K_{OW} measurement methods

Methods available for measuring octanol–water partition coefficients include the shake-flask method, estimation by high performance liquid chromatography (HPLC), the generator column method, and the slow-stirring method. In the shake-flask method, octanol and water are mutually saturated, then shaken with the test chemical in a container, such as a centrifuge tube, for about five minutes. The octanol and water phases are separated by centrifugation, and the concentrations of the test chemical are measured in each phase.[25] This method can result in erroneous K_{OW} values even after centrifugation since microdroplets of octanol may remain in the water phase. The presence of the octanol in the water phase causes inaccurately high measurements of hydrophobic chemicals in the water phase.[26] K_{OW} estimation by HPLC is performed by comparing the retention time of a test chemical with the retention times of several reference chemicals. The column packing is hydrophobic (*e.g.*, hydrocarbons chemically bonded to silica) while the mobile phase is hydrophilic (*e.g.*, an aqueous solution) so water-soluble chemicals are eluted first and oil-soluble chemicals last. A correlation established between the reference chemicals' retention times and previously measured K_{OW}s is used to calculate the K_{OW} values.[27]

Estimation by liquid chromatography is only recommended for test chemicals with K_{OW} values greater than one.[26,27] In the generator column method, water presaturated with octanol is slowly passed through a column, which is packed with a solid support that has been coated with octanol containing a small amount of the test chemical. The aqueous solution leaving the column is assumed to be in equilibrium with the octanol phase on the packing so analysis of the aqueous phase concentration yields the K_{OW}.[28] Care must be taken to ensure that measurements taken using the generator column method do not include errors caused by interaction between the test chemical and the column packing. In the slow-stirring method,[29] a small amount of the test chemical is mixed with either octanol saturated with water or water saturated with octanol. Then, the presaturated octanol and water, one of which contains the test chemical, are stirred slowly in a flask to minimize the stagnant diffusion layer between the phases while preventing emulsification. Once the concentrations in each phase have stabilized, the test chemical concentrations are measured in each phase to determine the K_{OW}.

Experimental method

In this study, the slow-stirring method[29] was used because it is a direct method for measuring K_{OW}s with accurate results over a wide range of values without the need for complex equipment.[30] The apparatus consisted of a 40 mL, 27.75 mm diameter, 98 mm tall, clear, glass vial containing a 1 cm Teflon coated magnetic stir bar. The glass vial's lid was an open-top screw cap sealed with a septum made of 90 mil silicone covering 10 mil Teflon. 12 gauge Teflon tubing with a Kel-F® hub by Hamilton Company protruded through the septum into the vial so that the hub sat above the septum and the tubing's end hung approximately 85 mm below the septum. A white rubber septum was fitted inside the tubing's hub to seal the tubing. A diagram of the experimental apparatus is shown in Fig. 2.

Approximately 15 mL of distilled, deionized water that had been presaturated with 1-octanol was added to a vial containing a magnetic stir bar. The vial's lid was set loosely on the vial so that one end of the Teflon tubing was located below the water's surface. Approximately 15 mL of octanol–IL "stock" solution, consisting of 1-octanol, which was presaturated with water and contained a known amount of IL, was carefully added to the vial so that the solution did not emulsify. Once the octanol "stock" solution was added, the lids were tightened on the vials to prevent octanol evaporation.

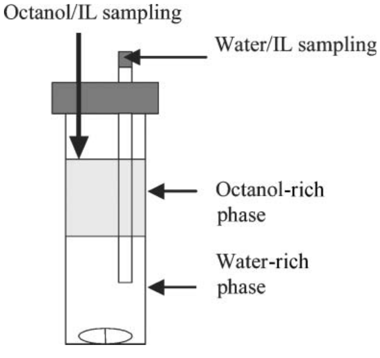

Fig. 2 Apparatus used for the slow-stirring method.

The vials were stirred slowly to prevent emulsification and were maintained at room temperature (24 ± 2 °C). Samples were taken from the octanol-rich phase by penetrating the silicone septum with a syringe. Samples were withdrawn from the water-rich phase using a syringe with a four-inch stainless steel needle inserted through the tubing directly into the aqueous phase to prevent octanol contamination. Samples of each phase were taken from all vials during at least three sampling events occurring over a 10 to 43 day period. Sampling ceased when the concentrations in both phases stabilized. Concentrations of IL in each phase were measured using UV-vis spectroscopy (Cary 1, Varian), which has a sensitivity of ±0.01 absorbance units. Samples taken from the vials were diluted if necessary so that the measured absorbance was less than 1. Pure deionized water or octanol saturated with water was used in the reference cell. When samples from the octanol-rich phase were diluted with pure octanol, the reference cell contained octanol saturated with water diluted at the same ratio.

To best represent the concentrations of IL that may be found in ecological systems if IL was released to the environment, the K_{OW}s were measured at very dilute concentrations. The starting concentration of IL in the octanol phase was less than 2×10^{-2} mol L^{-1}, just enough to ensure that the IL could be measured accurately in both phases. The final concentrations of IL in the octanol phase were between 6.43×10^{-6} mol L^{-1} and 1.47×10^{-4} mol L^{-1} and in the water phase were between 1.47×10^{-4} and 1.18×10^{-2} mol L^{-1}.

Twelve imidazolium-based ILs were studied, namely 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), 1-butyl-3-methylimidazolium nitrate ([bmim][NO_3]), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), 1-butyl-3-methylimidazolium chloride ([bmim][Cl]), 1-butyl-3-methylimidazolium bromide ([bmim][Br]), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([emim][$(CF_3SO_2)_2N$] or [emim][Tf_2N]), 2,3-dimethyl-1-ethylimidazolium bis(trifluoromethylsulfonyl)imide ([emmim][Tf_2N]), 2,3-dimethyl-1-propylimidazolium bis(trifluoromethylsulfonyl)imide ([pmmim][Tf_2N]), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf_2N]), 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([hmim][Tf_2N]), 2,3-dimethyl-1-hexylimidazolium bis(trifluoromethylsulfonyl)imide ([hmmim][Tf_2N]), and 3-methyl-1-octylimidazolium bis(trifluoromethylsulfonyl)-imide ([omim][Tf_2N]).

For [bmim][BF_4], [bmim][NO_3], [bmim][PF_6], and [bmim][Br], five vials made from the same "stock" solution of a particular concentration of IL dissolved in water-saturated octanol were made to verify experimental precision. In addition, we measured K_{OW} values for several of the ILs using a second stock solution and in all cases the values were within the standard deviation of the different samples from the first stock solution. For [bmim][Cl] we prepared five stock solutions of varying dilute concentrations with one vial tested per stock solution and the values obtained were consistent within ±10.3%. Thus, for these five ILs ([bmim][BF_4], [bmim][NO_3], [bmim][PF_6], [bmim][Br] and [bmim][Cl]), where concentrations in the water phase were less than 0.014 mol L^{-1}, we found that the K_{OW} values were essentially independent of concentration (as they should be in the dilute limit). Thus, the uncertainty is adequately represented by the standard deviation of either replicates from the same stock solution or replicates from separate stock solutions. Unfortunately, for the Tf_2N ILs we found that the K_{OW}s were slightly concentration dependent, even at total concentrations less than 10^{-3} mol L^{-1}. Thus, for ILs with the Tf_2N anion, K_{OW}s of five stock solutions at various dilute concentrations were measured to determine the variability more accurately. Specifically, [bmim][Tf_2N], [hmim][Tf_2N], [hmmim][Tf_2N], and [omim][Tf_2N] K_{OW}s were measured using five stock solutions with one vial per stock solution. For a different sample of [bmim][Tf_2N], as well as [emim][Tf_2N], [emmim][Tf_2N] and [pmmim][Tf_2N] (all samples obtained from Covalent Associates, as described below) we initially measured the K_{OW} values with five replicates from the same stock solution. Later we repeated measurements for [bmim][Tf_2N], [emmim][Tf_2N] and [pmmim][Tf_2N] with multiple samples from one or more different stock solutions in order to better understand the concentration dependence of the K_{OW} values and the resulting uncertainties in the values we report below.

Materials

The list of chemicals used in the synthesis of ionic liquids in this study, including CAS number, source and grade, and purification method (if any) is as follows: 1-methylimidazole (616-47-7, Aldrich 99%, redistilled over KOH), 1,2-dimethylimidazole (1739-84-0, Aldrich 98%, redistilled over KOH), 1-bromobutane (109-65-9, Aldrich 99%, washed with concentrated sulfuric acid and distilled over P_2O_5), 1-chlorobutane (109-69-3, Aldrich 99.5%, redistilled), 1-bromohexane (111-25-1, Aldrich 98%, washed with concentrated sulfuric acid and distilled over P_2O_5), 1-bromooctane (111-83-1, Aldrich 99.5%, washed with concentrated sulfuric acid and distilled over P_2O_5), ammonium tetrafluoroborate (13826-83-0, Aldrich 97+%, used without purification), silver nitrate (7761-88-8, Aldrich 99+%, used without purification), and lithium bis(trifluoromethylsulfonyl)imide (90076-65-6, 3M 98%, used without purification, or Aldrich 97%, used without purification). Solvents used to measure K_{OW}s were distilled, deionized water from a Millipore purification unit and Sigma-Aldrich, 99+%, HPLC grade 1-octanol.

[bmim][PF_6]. 1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) was purchased from Sachem, Inc. and was purified by washing with water to remove any residual acid and by mixing with activated carbon to remove colored compounds. The [bmim][PF_6] from Sachem is reported to contain less than 3 ppm chloride. Measurements by our laboratory confirmed that the sample contained less than 10 ppm chloride.

[emim][Tf_2N], [emmim][Tf_2N], and [pmmim][Tf_2N]. 1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([emim][Tf_2N]), 2,3-dimethyl-1-ethylimidazolium bis(trifluoromethylsulfonyl)imide ([emmim][Tf_2N]) and 2,3-dimethyl-1-propylimidazolium bis(trifluoromethylsulfonyl)imide ([pmmim][Tf_2N]) were obtained from Covalent Associates, Inc. and were all electrochemical grade (>99% purity). These samples were used as received. The [emim][Tf_2N] and [emmim][Tf_2N] contained approximately 50 ppm chloride. The [pmmim][Tf_2N] contained approximately 38 ppm chloride.

[bmim][Tf_2N]. 1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf_2N]) was either obtained from Covalent Associates, Inc. or synthesized in our laboratory. The sample from Covalent Associates was electrochemical grade (>99% purity) and was used as received. The sample synthesized in our laboratory was made using previously published methods.[31] 1-Butyl-3-methylimidazolium bromide ([bmim][Br], see synthesis below) was reacted with lithium bis(trifluoromethylsulfonyl)imide ($LiTf_2N$) from Aldrich in water. It formed two layers. The IL layer was washed with water to remove any excess $LiTf_2N$ or [bmim][Br]. The bromide content of this sample was less than 10 ppm.

Seven other of the ionic liquids were synthesized in our laboratory, as well, using previously published methods.[31,32]

[bmim][Cl], [bmim][Br], [hmim][Br], and [omim][Br]. 1-Methylimidazole was reacted with an excess of an alkyl halide (1-chlorobutane, 1-bromobutane, 1-bromohexane, or 1-bromooctane) in a round-bottom flask under a nitrogen atmosphere to produce the 1-alkyl-3-methylimidazolium halide ([bmim][Cl], [bmim][Br], [hmim][Br], or [omim][Br]).

[hmmim][Br]. 2,3-Dimethyl-1-hexylimidazolium bromide was synthesized in the same manner as [hmim][Br] with the exception that 1,2-dimethylimidazole was used instead of 1-methylimidazole.

[bmim][BF_4]. The 1-butyl-3-methylimidazolium bromide was reacted with an excess of ammonium tetrafluoroborate in a dichloromethane solution, and the ionic liquid [bmim][BF_4] was formed. The product ammonium halide and any residual ammonium tetrafluoroborate were removed from the ionic liquid by washing with water. It was cleaned with activated carbon to remove any colored compounds and dried under vacuum for 48 h to remove organic solvents (*e.g.* dichloromethane) and water. The bromide and ammonium contents of this IL were less than 8 ppm and 18 ppm, respectively.

[bmim][NO_3]. The 1-butyl-3-methylimidazolium bromide ([bmim][Br]) was reacted with an excess of silver nitrate ($AgNO_3$) in water. Silver bromide (AgBr) precipitates out of the solution so the solution ([bmim][NO_3] + $AgNO_3$) was filtered to remove AgBr and dried under vacuum to remove water. It was then titrated with a dilute solution of [bmim][Br] in dichloromethane (DCM) until no formation of AgBr was observed. The solution was filtered and dried under vacuum to remove all the solvents. The [bmim][NO_3] contained less than 500 ppm bromide and less than 19 ppm silver.

[hmim][Tf_2N]. 1-Hexyl-3-methylimidazolium bromide ([hmim][Br]) was reacted with lithium bis(trifluoromethylsulfonyl)imide ($LiTf_2N$) from 3M in water. It formed two layers. The IL layer was washed with water to remove any excess of

LiTf$_2$N or [hmim][Br]. The [hmim][Tf$_2$N] contained less than 20 ppm bromide.

[hmmim][Tf$_2$N]. 2,3-Dimethyl-1-hexylimidazolium bis(trifluoromethylsulfonyl) imide was synthesized in the same manner as [hmim][Tf$_2$N] with the exception that [hmmim][Br] was used instead of [hmim][Br]. The bromide content was less than 18 ppm.

[omim][Tf$_2$N]. 3-Methyl-1-octylimidazolium bis(trifluoromethylsulfonyl)imide was synthesized in the same manner as [hmim][Tf$_2$N] with the exception that [omim][Br] was used instead of [hmim][Br]. The bromide content was less than 14 ppm.

All synthesized ionic liquids were analyzed by proton NMR spectroscopy to ascertain the lack of any major impurities. Halide (Cl^- and Br^-) and ammonium ion content were measured using an Oakton Ion 510 Series pH/mV/Ion/°C meter with Cole-Parmer Ion Specific Probes (27502-13 for Cl^-, 27502-05 for Br^-, and 27502-03 for NH_4^+). Silver content was measured using inductively coupled plasma-optical emission spectroscopy (ICP-OES).

The water contents of all these ILs were not of consequence since they were all mixed with water during the experiment and their concentration was determined by UV-vis spectroscopy (Cary 1, Varian).

Results

Extinction coefficients

Extinction coefficients, ε, of the ILs in octanol and water were necessary for determining the concentrations of IL in each phase, and the resulting K_{OW} values. Thus, extinction coefficients for each of the ILs were measured, and are shown in Table 1. Also shown in Table 1 is the extinction coefficient of benzaldehyde, which is a compound that we chose to verify our experimental technique for measuring K_{OW} values. The reported extinction coefficients are the average values obtained using at least three "stock" solutions containing IL–octanol, IL–octanol saturated with water, or IL–water. Since the solubility of octanol in water is below the detection limit of our apparatus, the ILs' extinction coefficients in pure water were used to determine IL concentrations in the water phase. For the octanol-rich phase, the calibration was made with either pure octanol, or octanol saturated with water. The latter was necessary when the extinction coefficient in pure octanol and pure water were very different, so that the presence of the water dissolved in the octanol-rich phase significantly changed the value of ε. This was the case for [bmim][PF$_6$], [bmim][NO$_3$], [bmim][Br], [hmmim][Tf$_2$N], and [omim][Tf$_2$N]. The reported uncertainties in the extinction coefficients are the standard deviations for all of the "stock" solutions (at least three) used for a particular IL–solvent system.

All of the extinction coefficients were measured at the wavelength of maximum absorption (λ_{max}) except [bmim][Br] in water. The wavelength of maximum absorption for this system was below the cut-off wavelength of the cuvettes used so the measurements for this system were done at a fixed wavelength of 210 nm.

K_{OW} values

The values of the K_{OW}s measured are shown in Table 2. As indicated in the Experimental section, concentrations were measured in the two phases until the K_{OW} values no longer changed with time. The uncertainties reported are either

Table 2 Octanol–water partition coefficients (K_{OW}s) measured

Compound	K_{OW}	Concentration range in water phase/mol L^{-1}
Benzaldehyde—literature value[22]	30.2	
Benzaldehyde	36.5, 29.6	
[bmim][BF$_4$]	0.0030 ± 0.0002	
[bmim][NO$_3$]	0.0038 ± 0.0001	
[bmim][PF$_6$]	0.0220 ± 0.0008	
[bmim][Cl]	0.0040 ± 0.0003	
[bmim][Br]	0.0033 ± 0.0005	
[emim][Tf$_2$N]	0.09–0.11	2.8×10^{-4}–2.8×10^{-3}
[emmim][Tf$_2$N]	0.07–0.12	3.2×10^{-4}–2.9×10^{-3}
[pmmim][Tf$_2$N]	0.12–0.24	1.4×10^{-3}–2.8×10^{-3}
[bmim][Tf$_2$N]	0.11–0.62	1.5×10^{-4}–2.2×10^{-3}
[hmim][Tf$_2$N]	1.42–1.66	3.2×10^{-4}–3.8×10^{-4}
[hmmim][Tf$_2$N]	1.35–1.79	3.6×10^{-4}–4.9×10^{-4}
[omim][Tf$_2$N]	6.3–11.1	9.9×10^{-5}–2.1×10^{-4}

Table 1 Extinction coefficients of benzaldehyde and imidazolium-based ionic liquids in water and octanol

Compound	λ_{max} in water/nm	ε in water/L mol^{-1} cm^{-1}	λ_{max} in octanol/nm	ε in octanol/L mol^{-1} cm^{-1}	λ_{max} in octanol saturated with water/nm	ε in octanol saturated with water/L mol^{-1} cm^{-1}
Benzaldehyde	250	13710 ± 510	245	12980 ± 280		
[bmim][BF$_4$]	211	4270 ± 140	212	4510 ± 140		
[bmim][NO$_3$]	204	13140 ± 420	209	11420 ± 370	208	12100 ± 390
[bmim][PF$_6$]	212	4510 ± 100	212	2890 ± 100	212	4300 ±100
[bmim][Cl]	211	4880 ± 210	213	4510 ± 220		
[bmim][Br]	210[a]	6850 ± 320	209	5440 ± 100	207	5150 ±100
[emim][Tf$_2$N]	211	4380 ± 28	213	4354 ± 83		
[emmim][Tf$_2$N]	211	5788 ± 63	213	5941 ± 156		
[pmmim][Tf$_2$N]	211	5780 ± 177	213	5768 ± 152		
[bmim][Tf$_2$N]	211	4407 ± 20	212	4582 ± 114		
[hmim][Tf$_2$N]	211	4434 ± 102	213	4509 ± 96		
[hmmim][Tf$_2$N]	211	5480 ± 109			213	5683 ± 20
[omim][Tf$_2$N]	211	4279 ± 79	212	4575 ± 104	212	4373 ± 23

[a] Not wavelength of maximum absorbance, see text.

standard deviations of multiple vials prepared from the same stock solution or multiple vials prepared from different stock solutions, as detailed in the Experimental section. These uncertainties are greater than the uncertainty determined by propagation of error in the various measurements including what we would expect from the variation in room temperature over the course of the experiments. The K_{OW} values for the [Tf_2N] ILs are given as ranges since even in the dilute region, the K_{OW} values for these compounds varied with concentration.

Discussion

As shown in Table 2, two different researchers in our group (both results are shown) were able to satisfactorily reproduce the literature value of benzaldehyde. Thus, we conclude that our apparatus and experimental technique are adequate for K_{OW} measurements.

Our results indicate that the imidazolium-based ILs measured here are extremely hydrophilic. In particular, the K_{OW}s of all of the imidazolium-based ILs with any anion other than the bis(trifluoromethylsulfonyl)imide anion ([Tf_2N]) are much lower than many commonly used industrial solvents, as seen in the comparisons shown in Table 3, where we include one of the most hydrophilic and one of the most hydrophobic ionic liquids. ILs containing [Tf_2N] have slightly larger K_{OW} values, similar to polar solvents such as methanol and acetone, but they are still much lower than nonpolar solvents, such as benzene or hexane.

Measurements of [Tf_2N] ILs with varying alkyl chain lengths on the cation (compare [emim][Tf_2N], [bmim][Tf_2N], [hmim][Tf_2N] and [omim][Tf_2N]) show that K_{OW} increases as alkyl chain length on the cation increases, as shown in Fig. 3. Increasing affinity for more hydrophobic compounds with increasing cation alkyl chain length is consistent with previous studies,[33,34] where it was found that the solubility of imidazolium-based ionic liquids in alcohols increased as alkyl chain length on the cation increased. This was attributed to greater van der Waals interactions between the IL alkyl chain and longer chain alcohols. Thus, K_{OW} increases with increasing number of carbons on the cation alkyl chain, as one would expect.

In addition, replacing the hydrogen atom attached to the carbon between the nitrogens in the imidazolium ring with a methyl group had very little effect on the K_{OW}. This can be seen by comparing the measured K_{OW} of [emim][Tf_2N] with [emmim][Tf_2N] or by comparing [hmim][Tf_2N] with [hmmim][Tf_2N]. As shown by Crosthwaite *et al.*,[33] adding a methyl group to the imidazolium ring eliminates a hydrogen bonding site, thus reducing water solubility. Therefore, we might expect the K_{OW} of the alkyldimethylimidazolium salts to be a bit higher than the equivalent alkylmethylimidazolium salts. However, the data show that the values are virtually indistinguishable.

Table 3 Comparison of K_{OW} values of ILs with those of common organic compounds

Compound	K_{OW}
[bmim][Cl]	0.004
Methanol[22]	0.17
Acetone[22]	0.575
Caffeine[40]	0.85
[omim][Tf_2N]	6.3–11.1
Benzene[22]	135
Cyclohexane[41]	2 754
N-hexane[41]	10 000

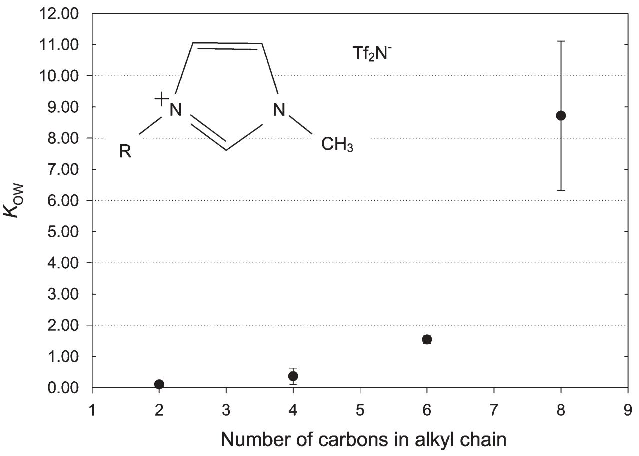

Fig. 3 Relationship between the K_{OW} and the number of carbons in the alkyl chain on the cation of n-alkylmethylimidazolium bis(trifluoromethylsulfonyl)imides.

By examining the K_{OW} values of all the salts with the [bmim] cation, one can determine the effect of the anion. [bmim][Br], [bmim][BF_4], [bmim][NO_3] and [bmim][Cl] are all completely miscible with water at room temperature. Conversely, [bmim][PF_6] and [bmim][Tf_2N] are only partially miscible with water at room temperature, with [bmim][Tf_2N] showing the lowest mutual solubility.[33] The K_{OW} values follow this trend of anion hydrophilicity. The K_{OW} of [bmim][Tf_2N] is more than an order of magnitude higher than that of [bmim][PF_6], which is itself almost five times greater than the K_{OW} values of [bmim][Br], [bmim][Cl], [bmim][BF_4] and [bmim][NO_3]. It should be pointed out that our initial measurements of [bmim][Cl] did not follow this trend. Careful analysis of that initial sample (later discarded) indicated that there was some small amount (perhaps about 1 mole percent) of residual methylimidazole in the sample. Methylimidazole and the imidazolium cation absorb UV radiation at approximately the same place in the UV spectrum. Since the K_{OW} value for methylimidazole is relatively high, around 3.31,[22] even a small amount of methylimidazole impurity can skew the K_{OW} results substantially. As a result, we were quite cognizant of the importance of eliminating impurities in the samples used for these measurements.

As mentioned several times above, we found that the K_{OW}s of the [Tf_2N] ILs were dependent upon concentration, even in the relatively dilute region investigated here. This is shown clearly in Fig. 4, where we plot the K_{OW} values we obtained for [bmim][Tf_2N] at various concentrations in the water-rich phase. At higher concentrations, the apparent K_{OW} increases, essentially in a linear fashion. Plotted on this graph are values we obtained with both the sample from Covalent Associates and the sample made in our laboratory. We were initially concerned that an impurity (we observed the formation of some solids in the Covalent [bmim][Tf_2N] sample in some unrelated experiments) in the Covalent sample was causing anomalous results and, thus, synthesized our own sample. However, careful investigation showed that the results from the two samples were entirely consistent, as shown in Fig. 4. The main problem is that, even at these dilute concentrations (10^{-4}–10^{-3} mol L^{-1} in the water-rich phase) we are not at infinite dilution. We are limited in our ability to perform the experiments at even lower concentrations by the detection limits of the UV-vis spectrometer. Thus, we report all the K_{OW} values for the ILs as rough ranges, with the knowledge that the actual, infinite dilution, K_{OW} values are probably somewhat smaller than those reported here. If data is available over a wide enough range of composition (*i.e.* like [bmim][Tf_2N]), one could extrapolate the K_{OW} values as a function of concentration to infinite dilution to get infinite dilution K_{OW} values. Since this is not the case for most of the compounds studied here, we did not pursue this avenue. Note that we observed absolutely no concentration dependences in the K_{OW} values of the ILs with any of the other anions.

K_{OW} values measured by our laboratory differ significantly from results presented by Chou *et al.*[24] and Domanska *et al.*[23] Chou *et al.* reported K_{OW} values for [bmim][PF_6] and [emim][PF_6] of 0.005 and 0.012, respectively, at their lowest concentrations. The value for [bmim][PF_6] is significantly lower than our value of 0.022. Although Chou *et al.* used somewhat higher concentrations than used in this study (3×10^{-2} mol L^{-1}, compared with our maximum aqueous concentration of 7.7×10^{-3} mol L^{-1}), we do not think this explains the discrepancy since we found the K_{OW} values of [bmim][PF_6] to be essentially independent of concentration in the range we investigated. There are several other possible reasons for the discrepancy. First, Chou *et al.* used the shake-flask method without centrifugation. Since octanol and water form an emulsion, it is entirely possible that their phases were not properly separated. The fact that they report a larger K_{OW} value at their lowest concentrations for a more hydrophilic compound ([emim][PF_6]), which is entirely unexpected, gives further support to the possibility of experimental difficulties with their technique. A second possibility is that the differences are due to different rates of [bmim][PF_6] degradation in water. Hardacre and coworkers[35] have shown that PF_6 and BF_4 anions can hydrolyze at rates that are significant even at room temperature. Thus, our results for [bmim][PF_6] and [bmim][BF_4] may have additional uncertainty due to the influence of hydrolysis products. Domanska *et al.*[23] estimated K_{OW} values for [$C_n$mim][Cl] ILs at 298.15 K by dividing the solubility of the IL in octanol by the solubility of the IL in water. Domanska *et al.* concluded that K_{OW}s generally increase as the alkyl chain length on the imidazolium cation increases, which is consistent with our findings. Similar to our observations, Domanska *et al.* found that [bmim][Cl] is more soluble in water than octanol, but their K_{OW} value (0.48) is several orders of magnitude higher than the one reported here (0.004). The difference is likely due to the fact that Domanska *et al.* were simply reporting the ratio of solubility of the IL in pure octanol and pure water, rather than an actual infinite dilution partitioning of the IL between the aqueous phase and the octanol-rich phase. The slow stirring method we followed to actually measure the K_{OW} is generally considered a better representation of ecological conditions, where the oil and the water are equilibrated with each other and the IL is present in very dilute amounts.

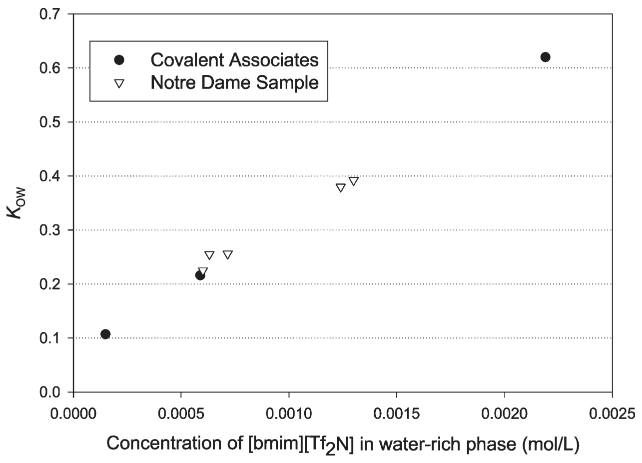

Fig. 4 Variation of [bmim][Tf_2N] K_{OW} with concentration.

Using the octanol–water partition coefficient data obtained here, it is possible to use various correlations that are available to estimate bioaccumulation and/or bioconcentration of ILs. Bioconcentration is the process by which the concentration of a chemical increases in an aquatic organism due to its contact with water. Generally, the absorption of the chemical occurs through the skin and the respiratory organs of the organism. In addition, the organism may ingest the chemical *via* the food chain, in a process called biomagnification. Bioaccumulation is the sum of these two effects. Both the bioaccumulation factor (BAF) and the bioconcentration factor (BCF) depend on the partitioning of the chemical between the biota and the water:

$$\text{BAF or BCF} = \frac{C_b}{C_w} \tag{7}$$

where C_b is the concentration of the chemical in the biota and C_w is the concentration of the chemical in the water. Since octanol is a reasonable model of the lipids in fish and other organisms, many correlations have been developed to estimate BCF from K_{OW}.[13,36–38] Using some of these correlations, we have computed the BCF for one of the more hydrophobic ILs we investigated, [hmim][Tf_2N], using the "high-end" values we obtained. The estimated values of the BCF of [hmim][Tf_2N] are shown in Table 4. Compounds with BCF values greater than 1000 have high bioaccumulation potential. BCF values

Table 4 Bioconcentration factor of [hmim][Tf_2N], based on the experimentally measured K_{OW} and several correlations available in the literature

Correlation used	Reference	log BCF for [hmim] [Tf_2N]	BCF for [hmim] [Tf_2N]
$\log BCF = 0.85 \log K_{OW} - 0.70$	36	−0.51	0.31
$\log BCF = 1.00 \log K_{OW} - 1.32$	13	−1.1	0.08
$\log BCF = 0.91 \log K_{OW} - 1.975 \log(6.8 \times 10^{-7} K_{OW} + 1) - 0.786$	38	−0.6	0.25
For $\log K_{OW} < 1$, $\log BCF = 0.5$	37	0.5	3.16

between 1000 and 250 indicate moderate potential, and BCF values less than 250 indicate low potential.[39] We found that the BCF of [hmim][Tf_2N] is between 0.08 and 3.16, much less than 250. Therefore, the ILs investigated in this study will not bioaccumulate to any extent in aquatic organisms.

Conclusions

The octanol–water partition coefficients of dialkylimidazolium ionic liquids range between 0.003 and 11.1 at room temperature. The values are lowest for the ILs that are totally miscible with water, namely 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), 1-butyl-3-methylimidazolium nitrate ([bmim][NO_3]), 1-butyl-3-methylimidazolium chloride ([bmim][Cl]), and 1-butyl-3-methylimidazolium bromide ([bmim][Br]). The ILs with the bis(trifluoromethylsulfonyl)-imide anion, which are commonly described as "hydrophobic," have higher K_{OW} values. Moreover, we found that the K_{OW} values of the ILs with the bis(trifluoromethylsulfonyl)-imide anion depended on concentration, even at the dilute concentrations studied. Thus, their values are given as ranges. Nonetheless, it is easy to see that the K_{OW} values increase with increasing alkyl chain length on the cation but replacing the acidic hydrogen on the C2 carbon in the imidazolium ring with a methyl group has essentially no effect on the K_{OW}. The K_{OW} is an extremely important quantity because it describes the hydrophobicity or hydrophilicity of a compound and has been correlated with bioaccumulation and toxicity in fish, as well as sorption to soils and sediments. Since all of the K_{OW} values are very small, we can conclude that these ILs will not accumulate or concentrate in the environment.

Acknowledgements

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References

1 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
2 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, 2003, 364.
3 P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.*, 2000, **39**, 3773.
4 J. F. Brennecke and E. J. Maginn, *AIChE J.*, 2001, **47**, 2384.
5 *Ionic Liquids as Green Solvents: Progress and Prospects.*, ed. R. D. Rogers and K. R. Seddon, ACS Symposium Series 856, American Chemical Society, Washington, DC, 2003, 599.
6 L. A. Blanchard and J. F. Brennecke, *Ind. Eng. Chem. Res.*, 2001, **40**, 287; Addition/Correction, 2001, **40**(11), 2550.
7 J. Ranke, K. Molter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2004, **58**, 3, 396.
8 F. Stock, J. Hoffmann, J. Ranke, R. Stormann, B. Ondruschka and B. Jastorff, *Green Chem.*, 2004, **6**, 286.
9 R. J. Bernot, M. A. Brueseke, M. A. Evans-White and G. A. Lamberti, *Environ. Toxicol. Chem.*, 2005, in press.
10 B. Jastorff, R. Stormann, J. Ranke, K. Molter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuchter, B. Ondruschka and J. Filser, *Green Chem.*, 2003, **5**, 136.
11 B. G. Oliver and A. J. Niimi, *Environ. Sci. Technol.*, 1983, **17**, 287.
12 C. T. Chiou, *Environ. Sci. Technol.*, 1985, **19**, 57.
13 D. Mackay, *Environ. Sci. Technol.*, 1982, **16**, 274.
14 M. C. Barber, L. A. Suarez and R. R. Lassiter, *Can. J. Fish. Aquat. Sci.*, 1991, **48**, 318.
15 R. V. Thomann, *Environ. Sci. Technol.*, 1989, **23**, 699.
16 H. Konemann, *Toxicology*, 1981, **19**, 209.
17 A. Delle Site, *J. Phys. Chem. Ref. Data*, 2001, **30**, 187.
18 S. W. Karickhoff, *Chemosphere*, 1981, **10**, 833.
19 A. Apelblat, *Ber. Bunsen-Ges. Phys. Chem.*, 1983, **87**, 2.
20 Y. Marcus, *J. Solution Chem.*, 1990, **19**, 507.
21 J. Sangster, *Octanol–Water Partition Coefficients: Fundamentals and Physical Chemistry*, John Wiley and Sons, Chichester, New York, Weinheim, Brisbane, Singapore, Toronto, 1997, 170.
22 A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71**, 525.
23 U. Domanska, E. Bogel-Lukasik and R. Bogel-Lukasik, *Chem.—Eur. J.*, 2003, **9**, 3033.
24 C.-H. Chou, F.-S. Perng, D. S. H. Wong and W. C. Su, in *Proceedings of the 15th Symposium on Thermophysical Properties*, Boulder, CO, USA, 2003, http://symp15.nist.gov.
25 US Environmental Protection Agency, *Product Properties Test Guidelines: Partition Coefficient (n-Octanol/Water), Shake Flask Method*, OPPTS 830.7550, EPA 712-C-96-039, US Environmental Protection Agency, Washington, DC, 1996.
26 Organisation for Economic Cooperation and Development, *Guidelines for Testing of Chemicals: Partitional Coefficient (n-Octanol/Water), Flask Shaking Method, 107*, Organisation for Economic Cooperation and Development, Paris, France, 1981.
27 US Environmental Protection Agency, *Product Properties Test Guidelines: Partition Coefficent (n-Octanol/Water), Estimation By Liquid Chromatography*, OPPTS 830.7570, EPA 712-C-96-040, US Environmental Protection Agency, Washington, DC, 1996.
28 US Environmental Protection Agency, *Product Properties Test Guidelines: Partition Coefficient (n-Octanol/Water), Generator Column Method*, OPPTS 830.7560, EPA 712-C-96-039, US Environmental Protection Agency, Washington, DC, 1996.
29 D. N. Brooke, A. J. Dobbs and N. Williams, *Ecotoxicol. Environ. Saf.*, 1986, **11**, 251.
30 J. Debruijn, F. Busser, W. Seinen and J. Hermens, *Environ. Toxicol. Chem.*, 1989, **8**, 499.
31 P. Bonhote, A. P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Gratzel, *Inorg. Chem.*, 1996, **35**, 1168.
32 L. Cammarata, S. G. Kazarian, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2001, **3**, 5192.
33 J. M. Crosthwaite, S. N. V. K. Aki, E. J. Maginn and J. F. Brennecke, *J. Phys. Chem. B*, 2004, **108**, 5113.
34 C. T. Wu, K. N. Marsh, A. V. Deev and J. A. Boxall, *J. Chem. Eng. Data*, 2003, **48**, 486.
35 C. Villagran, M. Deetlefs, W. Pitner and C. Hardacre, *Anal. Chem.*, 2004, **76**, 2118.
36 G. D. Veith, D. L. Defoe and B. V. Bergstedt, *J. Fish. Res. Board Can.*, 1979, **36**, 1040.
37 W. M. Meylan, P. H. Howard, R. S. Boethling, D. Aronson, H. Printup and S. Gouchie, *Environ. Toxicol. Chem.*, 1999, **18**, 664.
38 J. Devillers, S. Bintein and D. Domine, *Chemosphere*, 1996, **33**, 1047.
39 D. T. Allen and D. R. Shonnard, *Green Engineering: Environmentally Conscious Design of Chemical Processes*, Prentice Hall PTR, Upper Saddle River, NJ, 2002, 552.
40 M. S. Mirrlees, S. J. Moulton, C. T. Murphy and P. J. Taylor, *J. Med. Chem.*, 1976, **19**, 615.
41 P. Ruelle, *Chemosphere*, 1993, **40**, 457.

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A comparative analysis of the functionalisation of unactivated cycloalkanes using alkynes and either sunlight or a photochemical reactor

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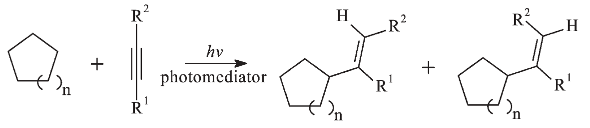
Using a standard mercury vapour lamp or sunlight, the synthetically difficult task of introducing functionality into unactivated cycloalkanes through C–C bond formation is accomplished in the presence of a soluble or supported photomediator and an alkyne bearing an electron-withdrawing group. The reaction involves the regiospecific addition of a photochemically generated cycloalkyl radical to the β-carbon of the alkyne. The use of solar radiation and a potentially recyclable polymer-bound photomediator for this fundamentally important synthetic process is particularly attractive from the clean/green chemistry perspective.

Introduction

Carbon–carbon bond formation is a fundamental synthetic process that generally involves a carbon atom which is activated by the presence of an adjacent functional group. The absence of functional groups on saturated hydrocarbons such as cycloalkanes, and ethers such as THF and dioxolanes, renders these compounds challenging with respect to their chemical transformation.[1,2] The other problems encountered in activating these systems include achieving regioselectivity and preventing over-reaction of the initially functionalised alkane or ether. These functionalisations have been previously carried out using the reaction of electrophilic benzotriazole reagents with 1,3-dioxolane,[3] the Gif oxidation procedure devised by Barton[4] and reactions which involve either the direct or indirect generation of alkyl and ether radicals. The indirect generation of cycloalkyl radicals, and ultimately the functionalisation of cycloalkanes, has been achieved in numerous ways through the use of metal catalysts[5] as well as appropriate radical precursors. These methods include the reaction of alkyl halides with tributyltin hydride[6] or tris(trimethyl)silane,[7] the oxyalkylation of cyclohexane and cyclooctane,[8] the ethylation and vinylation of cyclohexane using polyoxotungstates as catalytic photoinitiators,[9] the photolysis of alkylcobalt compounds,[10] and the chain-transfer reaction of acetylenic triflones using AIBN.[11] The functionalisation of unactivated systems by the direct generation of alkyl radicals has been achieved through the use of peroxides and a variety of other radical initiators. In this context the photochemical generation of radicals is particularly attractive as it avoids the use of metal catalysts and toxic reagents. In the case of cycloalkanes the peroxide initiated reactions include alkylation using di-*tert*-butyl peroxide,[12] chlorination using a *tert*-butoxy radical,[1] and oxidation using *tert*-butyl hydroperoxide.[13] Most of these processes have been extended to include cyclic ethers, examples being the alkylation[3] of 1,3-dioxolane, and the alkenylation, allylation and vinylation of THF by reaction with acetylenic triflones.[14–17] The production of SO_2 and the need to synthesise the reagents required, renders the reactions involving triflones, and those involving chloroethylsulfonyl oxime ethers[18] which have been used to obtain acylated derivatives of cycloalkanes and ethers, problematic.

The photochemical generation of radicals such as cyclopentyl, cyclohexyl and adamantyl has been achieved by both mercury[19,20] and ketone photomediation. Functionalisations carried out in this way include acylation of cycloalkanes and sulfination of cycloalkanes to afford sulfinic acid derivatives,[21] alkylation of ketene dithioacetal *S,S*-dioxides,[22] acetylation of adamantane,[23] the synthesis of β-cycloalkylnitriles from α,β-unsaturated nitriles,[24] and the photochemical decomposition of ethyl azidoformate in cyclohexane producing cyclohexylurethane.[25] Indeed the chain transfer reaction of acetylenic triflones with ethers and cycloalkanes has also been shown to proceed efficiently using irradiation in place of AIBN.[11] It is the solar chemistry version of the photochemical production of alkyl radicals from alkanes using ketones, which is of relevance to the work described in this paper. This method of hydrogen abstraction occurs as a result of the absorption of a photon by a carbonyl group, usually a ketone, which subsequently exhibits alkoxy radical character in its n,π* triplet state. The excited ketone, for example benzophenone, is then able to abstract a hydrogen atom from a cycloalkane producing a cycloalkyl radical which can undergo a number of reactions including recombination, disproportionation or further hydrogen abstraction. We have shown previously that the cycloalkyl radical generated in this way can undergo Michael-type addition to an electron-deficient alkyne[26] (Scheme 1), behavior which is consistent with its nucleophilic character.[27] This paper focuses on the possibility of carrying out such a functionalisation under solar conditions and reports



$R^1 = H, R^2 = CO_2CH_3; R^1 = R^2 = CO_2CH_3; n = 1,2$

Scheme 1

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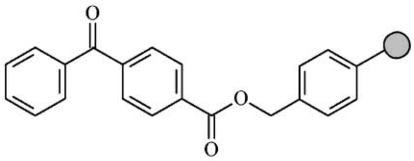
results which allow the solar photochemistry approach to be compared to the use of a conventional photochemical reactor.

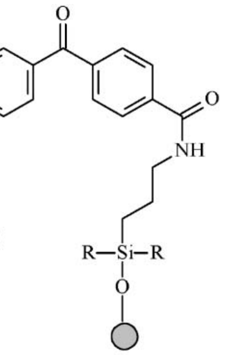
Reports of the photoreactions of alkynes with cycloalkanes first appeared in 1969 when Buchi and Feairheller,[28] and independently Grovenstein *et al.*,[29] described the irradiation of cyclohexane solutions of ethyl propiolate and dimethyl acetylenedicarboxylate (DMAD). These direct photoreactions gave products resulting from the insertion of ethyl propiolate and DMAD into the C–H bond of cyclohexane in yields of 5% and 10%, and reaction times of 24 h and 14 days, respectively. The cyclohexyl group was shown to add selectively to the β-carbon of ethyl propiolate. In 1993 Metzger and Blumenstein[30] investigated the formation of *Z* and *E* alkenes in a thermally initiated radical chain reaction of alkynes with cycloalkanes and again found that the cyclohexyl group added regiospecifically to the unsubstituted end of the alkyne triple bond. As we have shown, the use of a photomediator has a dramatic effect on the C–C bond forming reaction between alkynes and cycloalkanes in terms of reaction times and yields. Initial studies found benzophenone to be one of the most efficient photomediators. In hexane it has an absorption band at 346 nm (log ε = 2.1), with a shoulder at 361 nm (log ε = 2.0),[31] and thus can be excited electronically using sunlight. The ease with which cycloalkyl radicals can be produced in this way and the fact that they subsequently undergo C–C bond forming reactions with alkynes under these conditions, coupled with the possibility of carrying out the reaction using solar irradiation, makes the process synthetically important and environmentally attractive. The programme of work carried out at the Plataforma Solar de Almeria (PSA) which is described here, provides experimental data, which allow the use of a standard photochemical reactor and solar radiation to be compared. The possibility of using a supported, and thus potentially recyclable, photomediator was also considered.

Results and discussion

Experiments involving cyclopentane and cyclohexane, and both methyl propiolate (MP) and DMAD were carried out under solar irradiation and using a Rayonet photochemical reactor (350 nm). These reactions involved benzophenone as a soluble photomediator (Table 1) or the supported photomediators **5** and **6** (Table 2).

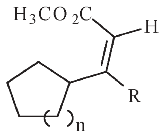


5

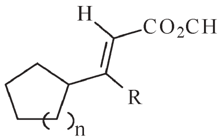


6

The reactions of cyclopentane and cyclohexane with MP in the presence of benzophenone, resulted in the formation of mixtures of the (*Z*)- and (*E*)-propenoates, **1a** and **1b** (Fig. 1 and Fig. 2), and **2a** and **2b**, respectively, with the (*E*)-isomer predominating (Scheme 1). No evidence of secondary photochemical isomerisation was observed, and thus it can be concluded that the *Z* : *E* ratio reflects the stereoselectivity of the addition of the cycloalkyl radical to the alkyne. The only other low molecular weight products observed were the corresponding cycloalkanones and cycloalkanols, which are formed in trace amounts (GC-MS). The benzophenone mediated solar and Rayonet reactions of MP are initially very rapid but slow considerably towards the end. A further trend in these reactions is that the reactivity of cyclopentane is greater than that of cyclohexane.[32,33]



1a, R = H; n = 1
2a, R = H; n = 2
3a, R = CO_2CH_3; n = 1
4a, R = CO_2CH_3; n = 2



1b, R = H; n = 1
2b, R = H; n = 2
3b, R = CO_2CH_3; n = 1
4b, R = CO_2CH_3; n = 2

The reactions of cyclopentane and cyclohexane with the disubstituted alkyne, DMAD, resulted in the formation of the (*Z*)- and (*E*)-3-cycloalkyl-2-pentenedioates, **3a** and **3b** (Fig. 3

Table 1 A comparison of reactions carried out using benzophenone and a photochemical reactor or solar radiation

	Rayonet reactor (350 nm)			Solar irradiation		
Reaction[a]	Time/h[b]	*Z* : *E* Ratio[c]	Yield (%)[c]	Time/h[b]	*Z* : *E* Ratio[c]	Yield (%)[c]
C_5H_{10} HC≡C–CO_2CH_3	2.5	1 : 1.7	95	3.7	1 : 1.8	77
C_6H_{12} HC≡C–CO_2CH_3	4.5	1 : 1.5	59	6.5	1 : 1.8	48
C_5H_{10} H_3CO_2C–C≡C–CO_2CH_3	2.5	12 : 1	74	4.0	28 : 1	78
C_6H_{12} H_3CO_2C–C≡C–CO_2CH_3	3.75	13 : 1	64	4.5	10.5 : 1	55

[a] Reaction conditions: benzophenone (0.43 mmol, 0.011 M), cycloalkane (40 ml), alkyne (3 mmol), dodecane as internal standard. [b] Time for complete consumption of the alkyne. [c] GC.

Table 2 A comparison of reactions carried out using supported photomediators in a photochemical reactor or using solar irradiation

	Rayonet reactor (350 nm)			Solar irradiation		
Reaction	Time/h[a]	$Z:E$ Ratio[b]	Yield (conversion) (%)[b]	Time/h[a]	$Z:E$ Ratio[b]	Yield (conversion) (%)[b]
C_5H_{10} $HC{\equiv}C\text{–}CO_2CH_3$	7.5 18	1 : 1.7 1 : 1.5	57(100)[c] 62(100)[d]	55 12	1 : 1.6 1 : 1.7	20(71)[e] 29(61)[d]
C_6H_{12} $HC{\equiv}C\text{–}CO_2CH_3$	40	1 : 1.4	31(72)[c]	13.5	1 : 1.6	3(24)[c]
C_5H_{10} $H_3CO_2C\text{–}C{\equiv}C\text{–}CO_2CH_3$	55	2.5 : 1	42(100)[c]	52	2.5 : 1	34(83)[e]
C_6H_{12} $H_3CO_2C\text{–}C{\equiv}C\text{–}CO_2CH_3$	15	2.2 : 1	49(100)[c]	6.5	1.5 : 1	7(4)[c]

[a] Total reaction time. [b] GC. [c] Reaction conditions: **5** (2 g), cycloalkane (40 ml), alkyne (3 mmol), dodecane as internal standard. [d] Reaction conditions: as before, **6** (2 g). [e] Reaction conditions: as before, **5** (2 × 1 g).

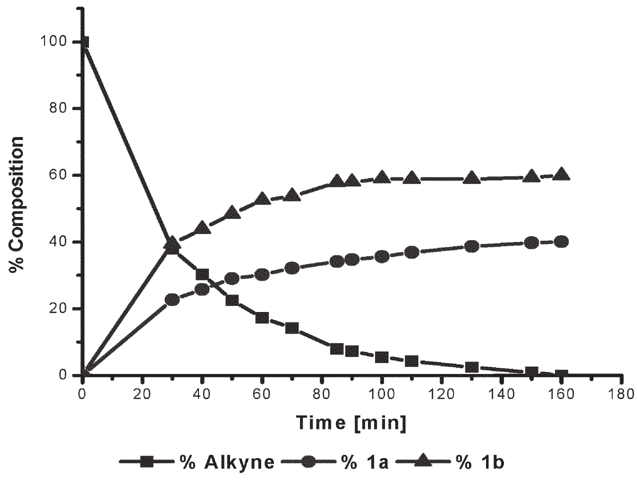


Fig. 1 Rayonet reaction of MP, cyclopentane and benzophenone.

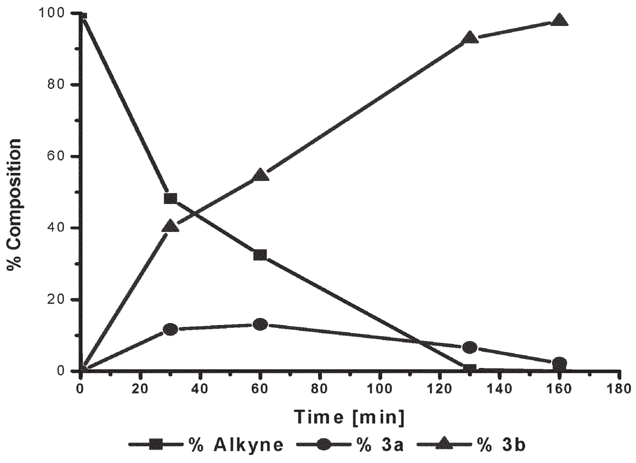


Fig. 3 Rayonet reaction of DMAD, cyclopentane and benzophenone.

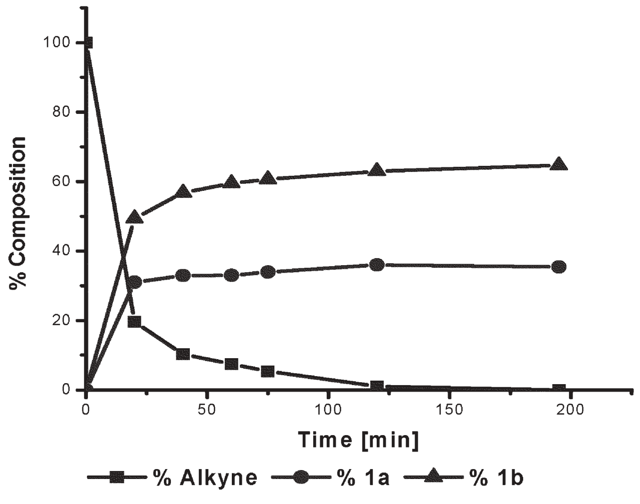


Fig. 2 Solar reaction of MP, cyclopentane and benzophenone.

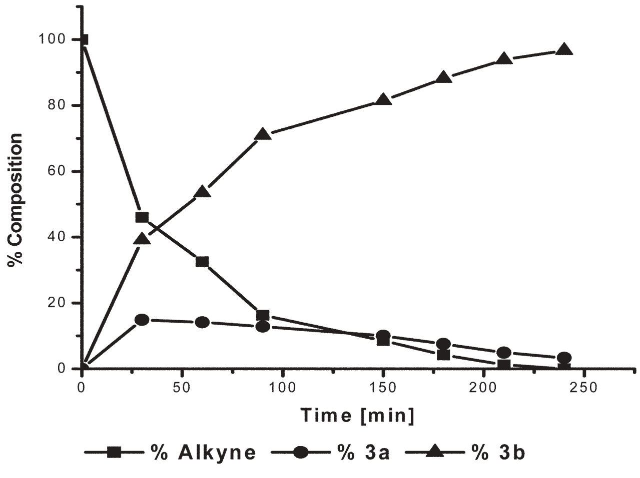


Fig. 4 Solar reaction of DMAD, cyclopentane and benzophenone.

and Fig. 4), and **4a** and **4b**, respectively. However, in contrast to the MP reactions, both the solar and Rayonet reactions are relatively stereoselective as a result of a secondary *cis*/*trans* photoisomerisation process. DMAD was found to be slightly less reactive than MP, and the greater reactivity of the cyclopentane ring system was again apparent.

Further analysis of the data obtained (Table 1), indicates that although the solar reactions using a soluble photomediator require longer reaction times than those carried out in the photochemical reactor, they give comparable GC yields in most cases, and indeed in one case, the reaction of cyclopentane and DMAD, the yield obtained is slightly higher. Surprisingly, the *Z* : *E* ratio of the products obtained from cyclohexane and DMAD is lower when solar radiation is used, despite the longer reaction time. The reaction of cyclopentane and MP under solar irradiation conditions (Fig. 2) is initially faster than the corresponding reaction in a Rayonet reactor (Fig. 1) whereas the opposite occurs in the reaction of DMAD and cyclopentane.

The use of the supported photomediators **5** and **6** leads to significantly increased reaction times, and in general the supported photomediators perform poorly in comparison to the soluble benzophenone, particularly under solar irradiation (Table 2). A uniform suspension of the supported mediator was achieved using a magnetic stirrer and the settling times of the solid when stirring was stopped suggested that mechanical breakdown of the support was not a problem. The formation of the alkenes using MP in the Rayonet reactor and using solar radiation leads, as before, to the predominant formation of the (*E*)-isomers, **1b** and **2b**. The (*Z*)-isomers, **3a** and **4a** are again the major products formed when DMAD is used. However in the latter case, despite the long reaction times, the *Z* : *E* ratio is much smaller than that observed for the corresponding reactions involving soluble benzophenone. The time course data for the solar reactions of cyclopentane with MP (Fig. 5) and DMAD (Fig. 6) show that the supported photomediator **5** becomes rapidly deactivated. On addition of a further portion of the resin bound mediator the reaction recommences, but soon ceases again. The concept that the photomediator is becoming inactive is supported by the fact that the photosensitized isomerisation of the primary photoinsertion products, normally observed with DMAD, does not occur, despite the long reaction times, as evidenced by the *Z* : *E* ratios (Table 2).

One possible reason for this deactivation is the formation of a polymeric coating on the surface of the particles of supported photomediator. Alternatively, deactivation may occur as a result of photochemical reactions involving the polystyrene resin. A significant loss of reactivity is also observed in solar reactions involving cyclohexane and the Merrifield resin bound benzophenone **5** (Fig. 7), which with MP resulted in 24% conversion, and a yield of only 3%, after 13.5 h.

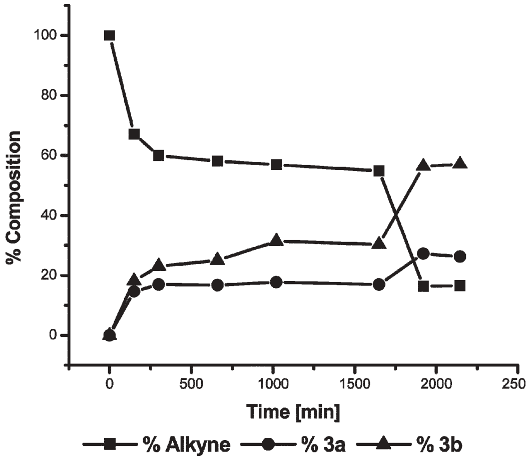


Fig. 6 Solar reaction of DMAD and cyclopentane in the presence of **5**.

The aminopropylsilica bound benzophenone **6** is a more effective photomediator for these reactions. The solar irradiation of a cyclopentane solution of MP containing **6** (Fig. 8) gives a yield of 29% (61% conversion of the alkyne) after 12 h and 62% (100% conversion) after 18 h irradiation in a Rayonet reactor. The supported benzophenone **6** appears to be more robust as although the reactions are slow they do not stop altogether. A 3 to 7 fold increase in the amount of cycloalkanols and cycloalkanones occurs when supported photomediators are used under solar conditions or in the Rayonet reactor. These products are formed by reaction of cycloalkyl radicals with molecular oxygen and their formation would be expected if other reactions of the cycloalkyl radical, such as those with the alkyne, were inefficient. This suggests that accessibility of the alkyne to the cycloalkyl radical, rather than problems in generating the radical, may be responsible for the poor performance of the supported photomediators. In the wider context of the overall mechanism, the GC monitoring (using dodecane as internal standard) of the reactions involving benzophenone clearly shows that its concentration does not change during the course of the reaction. It would

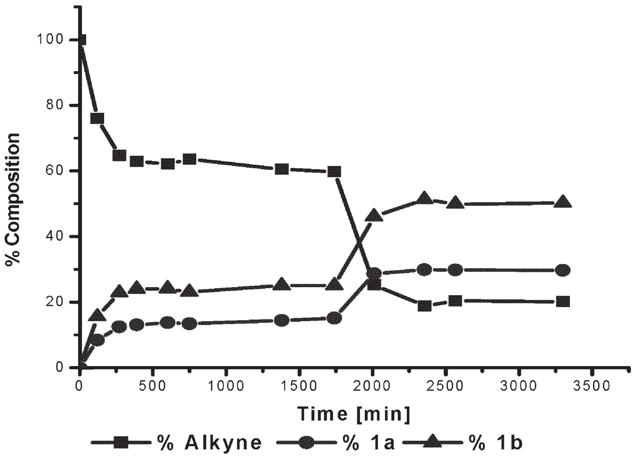


Fig. 5 Solar reaction of MP and cyclopentane in the presence of **5**.

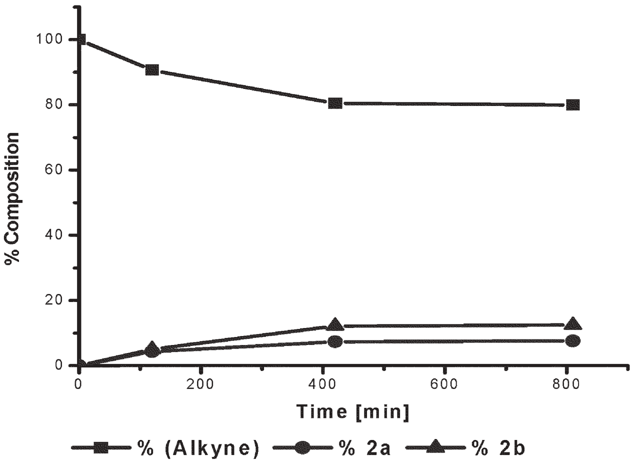


Fig. 7 Solar reaction of MP, cyclohexane and **5**.

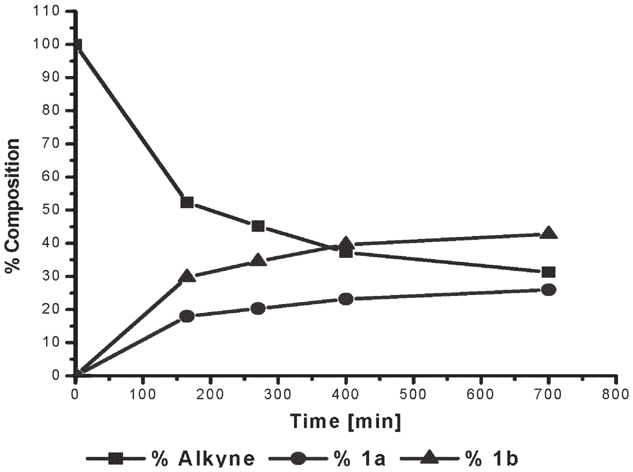


Fig. 8 Solar reaction of MP, cyclopentane and **6**.

thus appear that the reaction is based on an inefficient chain process, involving the alkyne and cycloalkyl radicals, which is terminated relatively quickly by hydrogen transfer from a benzhydroxyl radical.

Conclusions

The fundamentally important process of functionalising saturated cycloalkanes through C–C bond formation has been achieved through the use of a photomediator and solar radiation. This method has the additional environmental advantage that it does not involve the use of metals such as tin,[6] or the production of by-products such as SO_2,[11,18] which are features of other methods. The reaction is regiospecific with cycloalkane insertion occurring at the unsubstituted end of the alkyne. Although the reaction of monosubstituted alkynes is only moderately stereoselective, the involvement of a photomediator controlled secondary photoisomerisation leads to high $Z : E$ ratios with disubstituted alkynes such as DMAD. In keeping with the results obtained with other systems, cyclopentane was found to be more reactive than cyclohexane. The use of solar radiation with benzophenone, a soluble photomediator, gave results that were broadly comparable to those obtained with a conventional photochemical reactor. A Merrifield resin supported form of benzophenone, **5**, was less efficient under both standard UV and solar irradiation, the reduction being most marked in the latter case in which the photomediator appeared to become rapidly deactivated. More promising results were obtained with the supported photomediator **6**, a 3-aminopropyl functionalised silica gel. Overall the C–H activation process described in this paper, involving solar radiation and a potentially recyclable photomediator, is very attractive in the context of clean/green chemistry.

Experimental

The cycloalkanes and alkynes were distilled before use. The photochemical reactions were carried out in cylindrical Pyrex tubes. A Rayonet Photochemical Reactor, RPR-100, encompassing sixteen 350 nm mercury lamps was used. IR spectra were measured on a Perkin Elmer Spectrum 1 FT-IR. ^1H NMR and ^{13}C NMR were measured on a Jeol JNM-LA400 spectrometer at probe temperatures using $CDCl_3$ as solvent and TMS as the internal standard. All GC analyses at NUI, Galway, were carried out on an RTX-5 (Restek) column, while at PSA a HP-5 (Agilent) column was used. GC-MS analyses were carried out on a Micromass GCT spectrometer together with an Agilent 6890 capillary gas chromatograph equipped with a HP-5 column.

General procedure for photochemical reactions using benzophenone as photomediator

A solution of benzophenone (0.08 g, 0.43 mmol) and dodecane (0.37 g, 2 mmol) in cycloalkane (40 ml) was degassed with N_2 for 20 min in a cylindrical Pyrex tube. The alkyne (3 mmol) was added and the stirred solution was irradiated using 350 nm lamps until all the alkyne had been consumed (GC). The crude product mixture contained the *cis* and *trans* alkene products, and also trace amounts of the corresponding cycloalkanols and cycloalkanones (GC-MS). Subsequent to the removal of excess solvent the mixture was adsorbed onto silica (50 g) and eluted with bp 40–60 °C petroleum ether–ether (95 : 5). All products were obtained as clear, sweet smelling oils. The solar reactions carried out at PSA involved placing the cylindrical Pyrex tubes on a flat sheet of aluminium foil which was angled towards the sun. Exposure to solar radiation continued until all of the alkyne had been consumed (GC). A series of experiments involving different cycloalkanes and alkynes were carried out in a Rayonet reactor and under solar irradiation using the same general reaction conditions (Table 1).

General procedure for photochemical reactions using a supported photomediator

The cycloalkane (40 ml) and supported photomediator were degassed for 20 min using N_2. Dodecane (0.37 g, 2 mmol) and the alkyne (3 mmol) were added and the mixture was stirred vigorously and irradiated using 350 nm lamps. GC analysis of the crude product mixture indicated the presence of the expected products. The supported photomediator was washed with dichloromethane (100 ml), ether (100 ml), ethanol (100 ml) and methanol (100 ml). Removal of the solvent gave the products together with trace amounts of the cycloalkanols and cycloalkanones. The support was then dried and weighed resulting in 99% recovery.

The corresponding solar reactions at PSA were carried out as indicated above. In some cases further quantities of the supported photomediator were added and its effect monitored. A series of experiments involving different cycloalkanes and alkynes were carried out in a Rayonet reactor and under solar irradiation using the same general reaction conditions (Table 2).

Synthesis of supported photomediators

5. The synthesis of the benzoylated polystyrene-divinylbenzene resin was accomplished using 2% cross-linked chloromethylated styrene/divinylbenzene (200–400 mesh, 2.0–2.5 mmol Cl^- g^{-1}) and the method of Blossey and Neckers.[34]

The resulting resin was obtained as a yellow solid and contained approximately 0.4 mmol photomediator per gram of support (gravimetric analysis). It was oven dried under vacuum (40 °C), stored in a desiccator, and ground prior to use.

6. The synthesis of silica bound benzophenone was accomplished using 3-aminopropyl-functionalised silica gel (1 mequiv. $NH_2\ g^{-1}$, 9% functionalised) and the method of Ayadim and Soumillion.[35] The resulting supported photomediator was obtained as a light-yellow powder and contained approximately 0.59 mmol photomediator per gram of support (gravimetric analysis). It was dried under vacuum (40 °C) and stored in a desiccator prior to use.

Analytical data

1a, Methyl (*Z*)-3-cyclopentyl-2-propenoate.[26] IR (cm^{-1}): 1721 (C=O), 1644 (C=C), 1176 and 1151 (C–O), 819 (CH=CH). ^1H NMR: δ 1.26 (ms, 2H), 1.61–1.69 (ms, 4H), 1.90 (ms, 2H), 3.67 (m, 1H, C*H*–CH=CH), 3.70 (s, 3H, OCH_3), 5.67 (d, 1H, CH–CH=C*H*, J_{cis} = 11.2 Hz), 6.12 (t, 1H, CH–C*H*=CH, $J_{vic} = J_{cis}$ = 11.2 Hz). ^{13}C NMR: δ 166.9, 155.6, 117.4, 50.8, 39.0, 33.3, 25.5. *m*/*z* (%) 154 (18), 122 (20), 111 (11), 95 (18), 94 (100), 87 (30), 79 (48), 67 (51).

1b, Methyl (*E*)-3-cyclopentyl-2-propenoate.[26,36] IR (cm^{-1}): 1721 (C=O), 1654 (C=C), 1171 and 1148 (C–O), 983 (CH=CH). ^1H NMR: δ 1.36 (ms, 2H), 1.60–1.69 (ms, 4H), 1.82 (ms, 2H), 2.58 (m, 1H, C*H*–CH=CH), 3.70 (s, 3H, OCH_3), 5.81 (d, 1H, CH–CH=C*H*, J_{trans} = 15.6 Hz), 6.96 (dd, 1H, CH–C*H*=CH, J_{vic} = 7.8 Hz and J_{trans} = 15.6 Hz). ^{13}C NMR: δ 167.2, 153.6, 118.7, 51.1, 42.6, 32.2, 25.0. *m*/*z* (%) 154 (100), 122 (31), 111 (27), 95 (28), 94 (75), 87 (27), 79 (29), 67 (14).

2a, Methyl (*Z*)-3-cyclohexyl-2-propenoate.[30] IR (cm^{-1}): 1725 (C=O), 1652 (C=C), 1181 and 1175 (C–O), 820 (CH=CH). ^1H NMR: δ 0.99–1.30 (ms, 5H), 1.54–1.72 (ms, 5H), 3.24 (m, 1H, C*H*–CH=CH), 3.63 (s, 3H, OCH_3), 5.58 (d, 1H, CH–CH=C*H*, J_{cis} = 11.3 Hz), 5.96 (t, 1H, CH–C*H*=CH, $J_{vic} = J_{cis}$ = 11.3 Hz). ^{13}C NMR: δ 166.7, 155.9, 117.1, 50.9, 37.3, 32.2, 25.8, 25.4.

2b, Methyl (*E*)-3-cyclohexyl-2-propenoate.[30] IR (cm^{-1}): 1721 (C=O), 1650 (C=C), 1195 and 1169 (C–O), 983 (CH=CH). ^1H NMR: δ 1.12–1.34 (ms, 5H), 1.65–1.77 (ms, 5H), 2.13 (m, 1H, C*H*–CH=CH), 3.72 (s, 3H, OCH_3), 5.78 (d, 1H, CH–CH=C*H*, J_{trans} = 15.7 Hz), 6.91 (dd, 1H, CH–C*H*=CH, J_{vic} = 6.9 Hz and J_{trans} = 15.7 Hz). ^{13}C NMR: δ 167.4, 154.4, 118.3, 51.2, 40.3, 32.2, 25.7, 25.5.

3a, Dimethyl (*Z*)-2-cyclopentyl-2-butenedioate.[26] IR (cm^{-1}): 1722 (C=O), 1642 (C=C), 1163 (C–O). ^1H NMR: δ 1.50–1.71 (ms, 6H), 1.71–1.87 (ms, 2H), 2.76 (m, 1H, C*H*–CH=CH), 3.71 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.80 (s, 1H, C=CH). ^{13}C NMR: δ 169.0, 165.1, 154.6, 116.4, 51.8, 51.4, 44.0, 30.5, 24.4.

4a, Dimethyl (*Z*)-2-cyclohexyl-2-butenedioate.[26] IR (cm^{-1}): 1723 (C=O), 1644 (C=C), 1165 (C–O). ^1H NMR: δ 1.14–1.31 (ms, 5H), 1.67–1.90 (ms, 5H), 2.30 (m, 1H, C*H*–CH=CH), 3.71 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.77 (s, 1H, C=CH). ^{13}C NMR: δ 169.3, 165.6, 156.3, 116.1, 52.0, 51.6, 42.2, 30.8, 25.8, 25.5.

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References

1 P. A. MacFaul, I. W. C. E. Arends, K. U. Ingold and D. D. M. Wagner, *J. Chem. Soc., Perkin Trans. 2*, 1997, 135.
2 A. F. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879.
3 A. R. Katritzky, H. H. Odens and M. V. Voronkov, *J. Org. Chem.*, 2000, **65**, 1886.
4 D. H. R. Barton, M. J. Gastiger and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1983, 41.
5 G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1699.
6 D. P. Curran, *Synthesis*, 1988, 417.
7 P. Dowd and W. Zhang, *Chem. Rev.*, 1993, **93**, 2091.
8 T. Hara, T. Iwahama, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2001, **66**, 6425.
9 B. S. Jaynes and C. L. Hill, *J. Am. Chem. Soc.*, 1993, **115**, 12212.
10 G. Pattenden, *Chem. Soc. Rev.*, 1988, **17**, 361.
11 J. Gong and P. L. Fuchs, *J. Am. Chem. Soc.*, 1996, **118**, 4486.
12 I. Tabushi and K. Fukunishi, *J. Org. Chem.*, 1974, **39**, 3748.
13 F. Launay, A. Roucoux and H. Patin, *Tetrahedron Lett.*, 1998, **39**, 1353.
14 J. Xiang and P. L. Fuchs, *J. Am. Chem. Soc.*, 1996, 11986.
15 J. Xiang, W. Jiang, J. Gong and P. L. Fuchs, *J. Am. Chem. Soc.*, 1997, **119**, 4123.
16 J. Xiang, W. Jiang and P. L. Fuchs, *Tetrahedron Lett.*, 1997, **38**, 6635.
17 J. Xiang, J. Evarts, A. Rivkin, D. P. Curran and P. L. Fuchs, *Tetrahedron Lett.*, 1998, **39**, 4163.
18 S. Kim, N. Kim, W. Chung and C. H. Cho, *Synlett*, 2001, 937.
19 S. H. Brown and R. H. Crabtree, *Tetrahedron Lett.*, 1987, **28**, 5599.
20 S. H. Brown and R. H. Crabtree, *J. Am. Chem. Soc.*, 1989, **111**, 2935.
21 R. R. Ferguson and R. H. Crabtree, *J. Org. Chem.*, 1991, **56**, 5503.
22 A. M. Gonzalez-Cameno, M. Mella, M. Fagnoni and A. Albini, *J. Org. Chem.*, 2000, **65**, 297.
23 I. Tabushi, S. Kojo and K. Fukunishi, *J. Org. Chem.*, 1978, **43**, 2370.
24 A. M. Cardarelli, M. Fagnoni, M. Mella and A. Albini, *J. Org. Chem.*, 2001, **66**, 7320.
25 W. Lwowski and T. W. Mattingly, *J. Am. Chem. Soc.*, 1965, **87**, 1947.
26 N. W. A. Geraghty and J. J. Hannan, *Tetrahedron Lett.*, 2001, **42**, 3211.
27 B. Giese and S. Lachhein, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 768.
28 G. Buchi and S. H. Feairheller, *J. Org. Chem.*, 1969, **34**, 609.
29 E. Grovenstein, T. C. Campbell and T. Shibata, *J. Org. Chem.*, 1969, **34**, 2418.
30 J. O. Metzger and M. Blumenstein, *Chem. Ber.*, 1993, **126**, 2493.
31 *CRC Handbook of Chemistry and Physics*, ed. D. R. Lide, CRC Press, Boca Raton, FL, 78th edn., 1997.
32 J. G. Traynham and Y. S. Lee, *J. Am. Chem. Soc.*, 1974, **96**, 3590.
33 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994, p.769.
34 E. C. Blossey and D. C. Neckers, *Tetrahedron Lett.*, 1974, **15**, 323.
35 M. Ayadim and J. P. Soumillion, *Tetrahedron Lett.*, 1996, **37**, 381.
36 R. D. Hubbard and B. L. Miller, *J. Org. Chem.*, 1998, **63**, 4143.

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Catalytic O-methylation of phenols with dimethyl carbonate to aryl methyl ethers using [BMIm]Cl†

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A facile synthesis of aryl methyl ethers from phenols and dimethyl carbonate has been achieved in the presence of 1-*n*-butyl-3-methylimidazolium chloride ([BMIm]Cl). The reaction is carried out at 120 °C under atmospheric pressure. Aryl methyl ethers are obtained with excellent yields (>99%) at 100% selectivity for O-methylation. Moreover, [BMIm]Cl can be easily reused without loss of activity.

Introduction

Aryl methyl ethers, which are valuable intermediates for the preparation of dyes, agrochemicals, fragrances and pesticides, are conventionally synthesized by O-methylation of the corresponding phenols with dimethyl sulfate or methyl halides. However, these methods require not only corrosive and toxic reagents but a stoichiometric amount of strong base to neutralize acidic by-products, which results in large quantities of inorganic salts that require disposal. The O-methylation of phenols with methanol in the presence of a strong acid catalyst[1] or a heterogeneous catalyst in vapor-phase at high temperature has been extensively studied.[2–6] In most of these reactions, the conversions of phenols are not satisfactory and the selectivities to aryl methyl ethers are complicated by C-methylation. Thus, dimethyl carbonate (DMC), a green chemical, has emerged as a safe, cheap, efficient and environmentally acceptable alternative to methyl halides, dimethyl sulfate and methanol.[7–9]

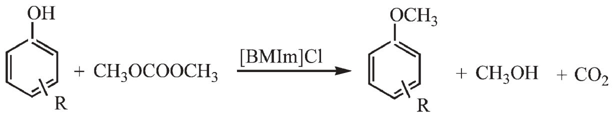
Tundo and coworkers performed the reactions of phenols with DMC under gas–liquid phase-transfer catalysis (GL-PTC) conditions in a continuous-flow process at a temperature of 160 to 180 °C.[10,11] Although aryl methyl ethers are produced with high selectivities, this procedure is not suitable for high boiling point phenols. Over alkali ion-exchanged zeolite and alumina–silica, high yields of aryl methyl ethers are obtained in the vapor-phase reaction of phenol with DMC.[12,13] But by-products of C-methylation are always observed. Over $CrPO_4$, $AlPO_4$, $CrPO_4$–$AlPO_4$ and $AlPO_4$–Al_2O_3, a mixture of O- and C-methylated products is obtained in the reaction of phenol with DMC. The vapor-phase methylation of catechol with DMC over alumina and modified alumina has been studied.[14–16] Calcined Mg–Al hydrotalcite has also been reported as a catalyst in the reaction of catechol with DMC.[17,18] In an autoclave, phenols are O-methylated by DMC in the presence of pentaalkylguanidines[19] or caesium carbonate.[20] Under atmospheric pressure, an efficient batch synthesis of aryl methyl ethers has been developed in the presence of K_2CO_3–crown ether,[21] K_2CO_3–Bu_4NBr[22] or DBU.[23] However, there is an obvious disadvantage due to the difficulty of catalyst–product separation and the reutilization of homogeneous catalysts. Ouk *et al.* reported that O-methylation of phenols with DMC can be carried out in the presence of Bu_4NBr at 130 °C[24] or K_2CO_3 at 160 °C[25] in a semi-continuous process. However, the complete conversion of substrates cannot be achieved.

Recently, catalytic reactions using ionic liquids have attracted considerable interest because they possess the unique advantages of high thermal stability, negligible vapour pressure, immiscibility with a number of organic solvents, recyclability and interesting intrinsic physicochemical characteristics.[26–28]

Now herein, we report an efficient and environmentally friendly process for highly selective O-methylation of phenols with DMC (Scheme 1). The reaction is carried out in the presence of an ionic liquid 1-*n*-butyl-3-methylimidazolium chloride ([BMIm]Cl) at 120 °C. Selectivity of 100% for O-methylation is obtained and phenols are quantitatively converted to the corresponding aryl methyl ethers. Thus, it is easy to obtain high purity products without a complicated purification process. Moreover, [BMIm]Cl can be easily reused without significant loss of activity.

Experimental

In this study, several ionic liquids including 1-*n*-butyl-3-methylimidazolium chloride, 1-*n*-butyl-3-methylimidazolium bromide ([BMIm]Br), 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([BMIm]BF_4), 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([BMIm]PF_6) and 1-ethyl-3-methylimidazolium bromide ([EMIm]Br) were synthesized according to the procedures described in the literature.[29–31] 1-Methylimidazole was dried over potassium hydroxide and distilled under reduced pressure. DMC was fractionally



Scheme 1

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† Electronic supplementary information (ESI) available: GC-MS data for aryl methyl ethers. See http://www.rsc.org/suppdata/gc/b4/b411201f/

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distilled and stored with molecular sieve (4A). Other reagents were of analytic grade and used as received.

The reaction was carried out in a 100 mL three-necked flask equipped with a thermometer, a nitrogen inlet and a fractionating column, which was connected with a liquid dividing head. In a typical experiment, 0.1 mol phenol, 0.18 mol DMC and 0.05 mol ionic liquid were loaded into the reactor under a nitrogen atmosphere. Then the mixture was heated to 120 °C under stirring. The reaction was monitored by gas chromatography (HP-1102) equipped with a 30 m capillary column (OV-101). Once the reaction was completed, phenol conversion and aryl methyl ether yield were measured in the reaction mixture by GC using chlorobenzene as internal standard. After residual DMC was distilled from the reaction mixture, the products were obtained by distillation under reduced pressure and identified by GC-MS (HP 6890/5973).

Results and discussion

When the mixture of DMC and [BMIm]Cl were heated to 120 °C in the absence of phenolic substrate, no products were detected. This indicated that DMC could not react with [BMIm]Cl. Similarly, DMC could not react with the other ionic liquids. In order to investigate the catalytic activities of different kinds of ionic liquids, the reaction of phenol with DMC was selected as a model reaction. The reaction was carried out at 120 °C for 1.5 h, and the results are given in Table 1.

Without a catalyst, O-methylation of phenol with DMC afforded no product, while in the presence of an ionic liquid anisole could be obtained with a quantifiable yield. It was noteworthy that no C-methylated by-products were observed and the selectivity to anisole was always 100% in spite of varying ionic liquids (entries 1–5). However, ionic liquids with different anions showed quite different catalytic activities (entries 1–4). [BMIm]Cl was the most efficient catalyst and gave the highest yield of anisole (99.8%). [BMIm]Br had a lower catalytic activity and anisole was obtained in a 62.5% yield. Unexpectedly, the yields of anisole were only 21.6 and 12.2% when [BMIm]BF$_4$ and [BMIm]PF$_6$ were used as catalysts. The results suggested that the anion had a strong impact on the catalytic activity of the ionic liquid in this reaction. Similar yields of anisole were obtained when [BMIm]Br and [EMIm]Br were employed in the reaction of phenol with DMC, which indicated that chain length of the substituted group of imidazole was not an important factor in the catalytic activity of the ionic liquid. Compared with the ionic liquids, Bu$_4$NCl (tetrabutylammonium chloride) showed quite different catalytic activity. The selectivity to anisole was only 86.3%, and the main by-product was methyl phenyl carbonate. This suggested that the imidazolium moiety of the ionic liquids has a significant function in catalytic O-methylation of phenol with DMC.

Table 1 Reaction of phenol with DMC in the presence of different catalysts[a]

Entry	Catalyst	Conversion (%)	Selectivity (%)	Yield (%)
1	[BMIm]Cl	99.8	100	99.8
2	[BMIm]Br	62.5	100	62.5
3	[BMIm]BF$_4$	21.6	100	21.6
4	[BMIm]PF$_6$	12.2	100	12.2
5	[EMIm]Br	60.7	100	60.7
6	Bu$_4$NCl	22.9	86.3	19.8
7	none	0	—	0

[a] Reaction conditions: phenol = 0.1 mol, DMC = 0.18 mol, ionic liquid = 0.05 mol, temperature = 120 °C, time = 1.5 h.

On the basis of the results in Table 1, we focused our studies on the application of [BMIm]Cl to O-methylation of different phenols with DMC. The results are summarized in Table 2. In all cases, aryl methyl ethers were obtained with excellent yields at 100% selectivity for O-methylation.

The different reactivities of phenols were dependent on the substituents of the benzene ring. The 3-methylanisole yield of 99.7% and 4-methylanisole yield of 99.9% were obtained in a short reaction time, about 1.5 h, when *m*-cresol and *p*-cresol were used as substrates (entries 2 and 3). Longer reaction time (2.5 h) was required for the complete conversion of 3-*t*-butyl-4-hydroxyanisole, indicating that the steric hindrance was an important factor in determining the reactivities of phenols (entry 9). The presence of an electron-withdrawing group on the benzene ring decreased the reactivity of the substrate. For instance, a reaction time of 4.5 h was needed in the O-methylation of *p*-nitrophenol with DMC (entry 8).

A 1,4-dimethoxybenzene yield of 99.7% was obtained after 6.0 h in the reaction of hydroquinone with DMC. This indicated that hydroxy groups of polyphenols could also be totally O-methylated with DMC in this procedure (entry 10). Furthermore, this O-methylation method was suitable for naphthols, and satisfactory results could be achieved (entries 13 and 14). In summary, [BMIm]Cl showed a high catalytic activity for O-methylating types of hydroxy group on benzene rings.

In view of 'green chemistry', reuse of the catalyst is necessary. In the reaction of phenol and DMC, [BMIm]Cl

Table 2 O-methylation of phenols with DMC in the presence of [BMIm]Cl[a]

Entry	Substrate	Time/h	Selectivity (%)	Yield (%)
1	Phenol	1.5	100	99.8
2	*m*-Cresol	1.5	100	99.7
3	*p*-Cresol	1.6	100	99.9
4	*o*-Cresol	2.0	100	99.7
5	*o*-Methoxyphenol	1.8	100	99.8
6	2,3-Dimethylphenol	2.3	100	99.5
7	*p*-Chlorophenol	2.0	100	99.6
8	*p*-Nitrophenol	4.5	100	99.4
9	3-*t*-Butyl-4-hydroxyanisole	2.5	100	99.6
10	Hydroquinone[b]	6.0	100	99.7
11	4′-Hydroxyacetophenone	3.5	100	99.5[c]
12	4-Hydroxybenzophenone	4.5	100	99.4[c]
13	2-Naphthol	2.8	100	99.8
14	3-Naphthol	3.0	100	99.6

[a] Reaction conditions: phenol = 0.1 mol, DMC = 0.18 mol, ionic liquid = 0.05 mol, temperature = 120 °C. [b] The product was 1,4-dimethoxybenzene, DMC = 0.35 mol. [c] The yields of 4′-methoxyacetophenone and 4-methoxybenzophenone were determined by HPLC.

Table 3 Recycling of [BMIm]Cl in the reaction of phenol with DMC

Cycle	1	2	3	4	5
Selectivity (%)	100	100	100	100	100
Yield (%)	99.8	99.4	99.7	99.5	99.4

could be recovered after distillation of anisole under reduced pressure from the reaction medium. Before the reuse of [BMIm]Cl, it was purified under vacuum (*ca.* 5 mmHg) at 100 °C for 50 min, then checked by FT-IR and ^{1}H NMR. The spectra were the same as those of [BMIm]Cl before the reaction. The reaction of phenol with DMC was repeated in the same batch of [BMIm]Cl over five runs. As shown in Table 3, a high yield of anisole (99.4%) was maintained when [BMIm]Cl was reused five times.

Conclusion

The selective O-methylation of phenols with DMC is studied in the presence of [BMIm]Cl. Phenols can be converted into their corresponding aryl methyl ethers in high selectivities and yields, and no C-methylation products are obtained. The reaction has notable advantages and remarkable environmentally benign features: (1) it uses the cheap and non-toxic DMC; (2) sterically hindered phenols can be efficiently O-methylated; (3) aryl methyl ethers are quantitatively obtained, and waste of substrates can be avoided; (4) [BMIm]Cl can be easily recycled and reused without decreasing catalytic activity; (5) no hazardous wastes are produced, and the coproduct methanol can act as a material for a non-phosgene process for preparing DMC by oxy-carbonylation.

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References

1 K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.*, 1960, **25**, 832.
2 S. Balsama, P. Beltrame, P. L. Beltrame, P. Carniti, L. Forni and G. Zuretti, *Appl. Catal.*, 1984, **13**, 161.
3 S. C. Lee, S. W. Lee, K. S. Kim, T. J. Lee, D. H. Kim and J. C. Kim, *Catal. Today*, 1998, **44**, 253.
4 F. Cavani, T. Moni and D. Paoli, *Stud. Surf. Sci. Catal.*, 2000, **130**, 2633.
5 V. Vishwanathan, S. Ndou, L. Sikhwivhilu, N. Plint, K. V. Raghavan and N. J. Coville, *Chem. Commun.*, 2001, 893.
6 R. Bal and S. Sivasanker, *Appl. Catal., A.*, 2003, **246**, 373.
7 Y. Ono, *Appl. Catal., A.*, 1997, **155**, 133.
8 P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207.
9 Z. L. Shen and X. Z. Jiang, *J. Mol. Catal. A: Chem.*, 2004, **213**, 193.
10 P. Tundo, G. Moraglio and F. Trotta, *Ind. Eng. Chem. Res.*, 1989, **21**, 881.
11 A. Bomben, M. Selva, P. Tundo and L. Valli, *Ind. Eng. Chem. Res.*, 1999, **38**, 2075.
12 Z. H. Fu and Y. Ono, *Catal. Lett.*, 1993, **21**, 43.
13 T. Beutel, *J. Chem. Soc., Faraday Trans.*, 1998, **94**, 985.
14 Y. Fu, T. Baba and Y. Ono, *Appl. Catal., A.*, 1998, **166**, 419.
15 Y. Fu, T. Baba and Y. Ono, *Appl. Catal., A.*, 1998, **166**, 425.
16 Y. Fu, T. Baba and Y. Ono, *Appl. Catal., A.*, 1999, **176**, 201.
17 M. B. Talawar, T. M. Jyothi, P. D. Sawant, T. Raja and B. S. Rao, *Green Chem.*, 2000, **2**, 266.
18 T. M. Jyothi, T. Raja, M. B. Talawar and B. S. Rao, *Appl. Catal., A.*, 2001, **211**, 41.
19 G. Barcelo, D. Grenouillat, J. P. Senet and G. Sennyey, *Tetrahedron*, 1990, **46**, 1839.
20 Y. Lee and I. Shimizu, *Synlett*, 1998, 1063.
21 M. Lissel, S. Schmidt and B. Neumann, *Synthesis*, 1986, 382.
22 S. Ouk, S. Thiebaud, E. Borredon, P. Legars and L. Lecomtb, *Tetrahedron Lett.*, 2002, **43**, 2661.
23 W. C. Shieh, S. Dell and O. Repic, *Org. Lett.*, 2001, **3**, 4279.
24 S. Ouk, S. Thiebaud, E. Borredon and P. L. Gars, *Appl. Catal., A.*, 2003, **241**, 227.
25 S. Ouk, S. Thiebaud, E. Borredon and P. L. Gars, *Green Chem.*, 2002, **4**, 431.
26 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
27 T. Sima, S. Guo, F. Shi and Y. Deng, *Tetrahedron Lett.*, 2002, **43**, 8145.
28 J. Sun, S. Fujita, B. M. Bhanage and M. Arai, *Catal. Commun.*, 2004, **5**, 83.
29 J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker and R. D. Rogers, *Green Chem.*, 2001, **3**, 156.
30 P. Bonhote, A. P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Gratzel, *Inorg. Chem.*, 1996, **35**, 1168.
31 P. A. Z. Suarez, J. E. L. Dullius, S. Einlft, R. F. De Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217.

Hydrogen peroxide induced iodine transfer into alkenes

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Reactions of alkenes with elemental iodine activated by 30% aqueous hydrogen peroxide in the presence of methanol or water as the external nucleophile source result in the formation of vicinal iodo-alkoxy or iodo-hydroxy substituted alkanes. Beside the fact that only 0.5 equiv. or a slight excess of hydrogen peroxide and 0.5 equiv. of iodine are sufficient amounts of reactants, this transformation is conducted in the absence of acid, thus contributing significantly to the green chemistry concept.

Introduction

Iodinated organic molecules have been recognised for many years as important and versatile synthones in organic synthesis, and their usefulness has grown following the introduction of coupling reactions.[1] Investigations concerning their synthesis are often carried out with elemental iodine as the source of the iodonium donating agent, but due to its low electrophilicity a certain increase of its reactivity is usually necessary. This could be achieved by a solvent[2] or an acid,[3] while another method employs oxidation systems such as metallic salts[4–8] or oxides,[9,10] bis(tetra-n-butylammonium) peroxydisulfate,[11] hypervalent(III) iodine compounds,[12–16] the O_2–$H_5PV_2Mo_{10}O_{40}$ system,[17] a urea-hydrogen peroxide adduct[18] and F-TEDA-BF_4,[19] which is also convenient in ionic liquids intended as eco-friendly systems.[20] The interesting academic finding that iodine could also be activated by doubling its amount in the reaction mixture is wasteful, since a substantial amount of iodine is lost.[21]

Recently, the heterogeneous catalyst[22] Envirocat EPZ-10[R] and anionic surfactants were promoted for iodine activation.[23] Lately, hydrogen peroxide and sodium iodide in the presence of a strong acid were utilized for transformation of alkenes into iodohydrins, but a considerable excess of hydrogen peroxide was necessary,[24] an NaI–H_2O_2 system in combination with an organotelluride catalyst was also used for iodofunctionalisation.[25] Nevertheless, the majority of these systems suffer from health, safety, environmental and economic disadvantages. In a 'green' context,[26] iodination accompanied by iodine atom economy,[27] despite decades of effort, still remains an open challenge. We decided to connect both domains by developing a new method for iodofunctionalisation of organic molecules using hydrogen peroxide and iodine. Hydrogen peroxide is an excellent example of a environmentally benign chemical oxidant, recently highlighted by Noyori,[28] but searching for an appropriate catalytic system could present difficulties. Therefore, hydrogen peroxide activation studies have earned broad attention.[29] In continuation of our research concerning iodination without the loss of iodine (for example) on account of HI formation, we turned our attention to the search for an environmentally convenient oxidizer. Besides iodine, our efforts were focused on excluding any additives, especially toxic metallic salts and acids, since they could present obstacles in the reactions of acid sensitive molecules. We now report a new method for preparation of vicinal iodo substituted alkanes from alkenes using elemental iodine activated by hydrogen peroxide, which proved to be an excellent couple, without the use of an acid and any additional catalyst.

Results and discussion

Initially we treated a methanolic solution of styrene with 0.5 equiv. of iodine at room temperature and after an isolation procedure we detected not more than 20% of iodo-methoxy substituted product in the crude reaction mixture, the rest being a tar material. Similarly unpromising results were obtained using various solvents (dichloromethane, tetrachloromethane, ethyl acetate, diethy ether and acetonitrile) and test reactions on α-methyl styrene, indene and methylenecyclopentane, while 1,1-diphenylethene did not react under these conditions. At this point we decided to activate iodine with H_2O_2. In a typical experiment 0.5 mmol of hydrogen peroxide as a 30% aqueous solution was added to a methanolic solution of 1 mmol of 1,1-diphenylethene **1a** and 0.5 mmol of iodine and the reaction mixture stirred at 20 °C. After 18 h complete disappearance of the starting alkene was indicated and 2-iodo-1-methoxy-1,1-diphenylethane **2a**′ was isolated in almost quantitative yield. Encouraged by this result, we decided to elucidate the role of the reaction conditions on this transformation and the data obtained are presented in Table 1. We established that hydrogen peroxide plays an exceedingly important role in this reaction, since the conversion of 1,1-diphenylethene depends significantly on the amount of hydrogen peroxide. In the presence of an external nucleophile, complete disappearance of the starting material was achieved with only 0.5 equiv. or a slight excess of H_2O_2 and only 0.5 equiv. of elemental iodine (Table 1, entries 3, 9, 10, 13 and 14), while the sole products formed were the Markovnikov type iodo-containing adducts **2** and water, the only waste-product. The stoichiometry of this transformation completely follows the iodine atom economy law and could be schematically expressed by eqn. (1):

$$2(Ph)_2C{=}CH_2 + I_2 + H_2O_2 + 2NuH \rightarrow 2(Ph)_2NuC{-}CH_2I + 2H_2O \quad (1)$$

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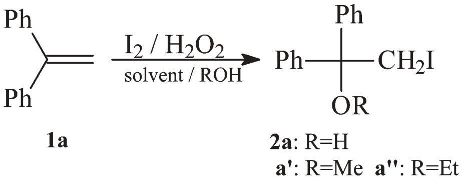
Table 1 The effect of reaction variables on the conversion of 1,1-diphenylethene **1a** to **2**[a]

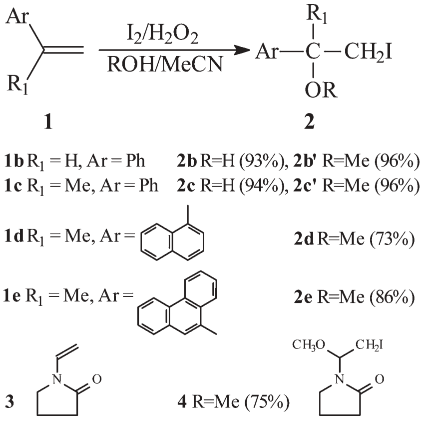


	Solvent	ROH/mmol	H_2O_2/mmol	Conv. of 1 (Yield of 2)[b]
1	MeOH	—	0.2	38
2		—	0.4	80
3		—	0.5	100 (96)
4		—	1	80
5		—	2	69
6		—	5	69
7	MeCN	H_2O (10)	0.5	100 (96)
8		MeOH (25)	1	85
9		MeOH (20)	0.5	100 (96)
10		MeOH (3)	0.5	100
11	MeCN	—	0.66	66[c]
12	EtOH	—	0.66	50
13	MeCN	EtOH (30)	0.55	100 (96)
14	CH_2Cl_2	MeOH (20)	0.5	100 (96)
15		MeOH (10)	0.5	98 (93)
16		MeOH (3)	0.5	54

[a] *Reaction conditions*: 1 mmol of **1**, 10 mL of solvent, 0.5 mmol of I_2, 0.5 mmol of H_2O_2 as 30% aq. solution, T = 20 °C, time 18 h. [b] Conv. of **1** det. from ^1H NMR spectra of the crude reaction mixture, yield of **2** after flash chromatography [c] **2a** was formed.

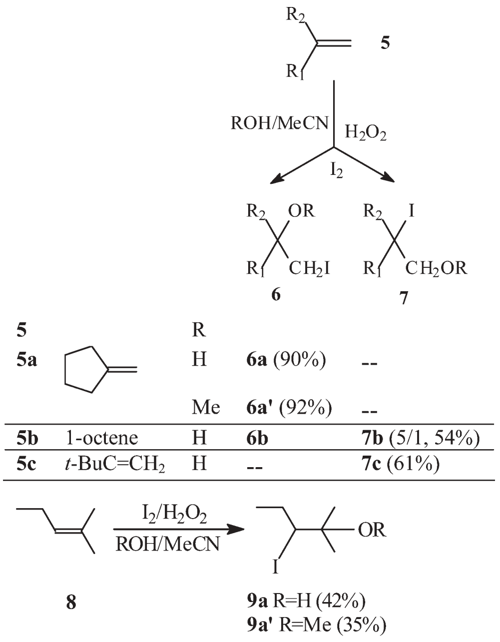
Methanol served as the reaction medium as well as the nucleophile source, and therefore we investigated the influence of the amount of nucleophile on the course of the reaction. A ten to thirty fold molar excess of water (Table 1, entry 7), methanol (entries 9, 14, 15) or ethanol (entry 13) as the sources of the external nucleophile added to **1** was found to be optimal for selective transformation to the corresponding product **2**. Further diminution of the amount of methanol close to the relative equimolar scale diminished the selectivity of the reaction since water became a competitive nucleophile and vicinal iodo hydrine **2a** was formed, as well as vicinal iodo methoxy ether **2a′** (entries 10 and 16), while the transformation of **1a** in neat acetonitrile led to vicinal iodo hydrine **2a** (entry 11). By using dichloromethane as the solvent, excellent conversion of **1a** to **2a′** was achieved when 10 or 20 mmol of methanol were added (entries 14 and 15).

Stimulated by these affirmative preliminary results, we decided to examine the H_2O_2–I_2 reaction system on a broader range of sensitive molecules like styrene and its derivatives. We recognised that the iodine transfer reaction induced by hydrogen peroxide is also useful in the case of styrene **1b** and α-methyl styrene **1c**. As shown in Scheme 1, both target alkenes could be effectively transformed to vicinal iodohydrins **2b** and **2c** or vicinal iodo-methoxy derivatives **2b′** or **2c′**, Markovnikov type regioselectivity was established. 2-Naphthyl **1d** and 9-phenanthryl substituted alkenes **1e** were also compatible with the H_2O_2–I_2 reaction system, thus yielding 2-iodo-1-methoxy-1-(1-naphthyl)ethane **2d** in good yield, and 2-iodo-1-methoxy-1-(9-phenanthryl)ethane **2e**. Finally, to our surprise, the reaction of 1-vinyl-2-pyrrolidinone **3** in MeOH was complete within two hours, yielding adduct **4** in high yield. The regioselectivity of iodofunctionalisation of alkenes **1–3** observed indicates the formation of a more stable carbocation intermediate.



Scheme 1 Regioselective iodofunctionalisation of polymerisation sensitive alkenes **1** and **3**. *Reaction conditions*: iodo-hydroxylation; 1 mmol of **1b** or **1c**, 0.5 mmol of I_2, 0.5 mmol of 30% of aqueous H_2O_2, 10 ml MeCN and 20 mmol of H_2O, reaction time 18 h at 20 °C. Iodo-methoxylation: 1 mmol of **1b**, **1c**, **1d** or **3**, 0.5 mmol of I_2, 0.5 mmol of 30% of aq. H_2O_2, 10 ml of MeOH, at 20 °C, reaction times as follows: 18 h in case of **1b** and **1c**, 24 h for **1d**, 2 h for **3**. In the case of **1e** 0.6 mmol of 30% aq. H_2O_2 was used and solv. mixt. MeOH–CH_2Cl_2 8 : 1, reaction time 24 h at 20 °C.

It is well established that the cyclic iodonium ion is an intermediate in iodination of organic molecules, but regioselectivity is greatly influenced by the substrate structure. It is known that electrophilic functionalisation of methylenecyclopentane **5a** and 1-octene **5b** could give both types of adducts,[30,6,23] but in the case of the exocyclic double bond in **5a** Markovnikov-type iodofunctionalisation was observed (Scheme 2). The reaction of the terminal double bond in **5b** led to two types of regioisomers **6b** and **7b** in a relative ratio of 5 : 1. The prevalence of product **6b** indicates the importance of carbocation stability, but this is not the only factor in this regard, since the origin of **7b** could be ascribed to steric circumstances. We found regioselectivity to be importantly influenced by substrate structure. Transformation of the more crowded 3,3-dimethyl-1-butene **5c** led exclusively to 1-hydroxy-2-iodo-3,3-dimethylbutane **7c**, termed an anti-Markovnikov type of adduct. Progressively intensified steric demands were reflected in a completely reversed mode of regioselectivity. Product **7c** supports the assumption that the cyclic iodonium ion is the reaction intermediate, the bulky *t*-butyl group preventing nucleophile attack on the C-2 atom and the C-1 atom thus remaining the only possible approach. Comparision of regioselectivity in the case of styrene **1b** with 3,3-dimethyl-1-butene **5c** clearly demonstrates predominant intermediate stabilisation over steric interaction in the case of **1b**, whereas in the case of **5c** steric hindrance is prevalent over the hyperconjugation effect. Ultimately, we found that transformation of 2-methyl-2-pentene **8**, possessing a more crowded nonterminal double bond, led exclusively to 2-hydroxy-3-iodo-2-methylpentane **9a** or to 3-iodo-2-methoxy-2-methylpentane **9a′**. Transformation of alkene **8**, despite its possession of a more substituted double bond than **5c**, indicates the involvement of a more stable carbocation, thus

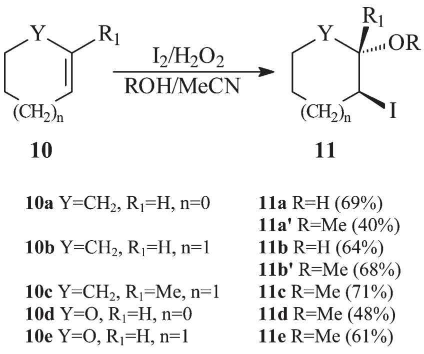


Scheme 2 The role of alkene structure on the regioselectivity of the addition. *Reaction conditions*: iodo-hydroxylation; 1 mmol of **5** or **8**, 0.5 mmol of I_2, 0.5 mmol of 30% of aqueous H_2O_2, 10 ml of MeCN, 15 mmol of H_2O, T = 20 °C, reaction time 20 h. Iodo-methoxylation; 1 mmol of **8**, 0.5 mmol of 30% of aqueous H_2O_2, 10 ml of MeOH, 20 h at 20 °C.

indicating that appropriate steric requirements could alter the regioselectivity type completely. We may conclude that alkene structure has a remarkable effect on the course of reaction.

Our study was continued by checking the stereochemical course of iodofunctionalisation using the H_2O_2–I_2 reaction system on a set of cyclic alkenes (Scheme 3). We found that cyclopentene **10a** and cyclohexene **10b** reacted in the *anti* mode, yielding *trans*-2-iodo-1-hydroxy substituted cycloalkanes **11a** and **11b** or *trans*-2-methoxy-1-iodocycloalkane derivatives **11a′** and **11b′**, respectively. Carbocation stability proved to be the dominant factor governing the iodofunctionalisation of 1-methylcyclohexene **10c**; the mode of addition is *anti*, thus yielding *trans*-2-iodo-1-methoxy-1-methylcyclohexane **11c**. The additional substituent (Me) at the double bond in molecule **10c** contributes essentially to the regioselectivity of the product formation, but has no influence on the manner of addition. We also targeted highly reactive and challenging alkenes **10d** and **10e**, since they possess an enol ether moiety and we established that both carbohydrate-related substrates reacted analogously, producing *trans*-2-methoxy-3-iodocycloalkane derivatives **11d** and **11e**. The ring size (5-mem/6-mem) and heteroatom were proved to have an insignificant influence on the stereochemical course of the reaction, the addition type being *anti*.

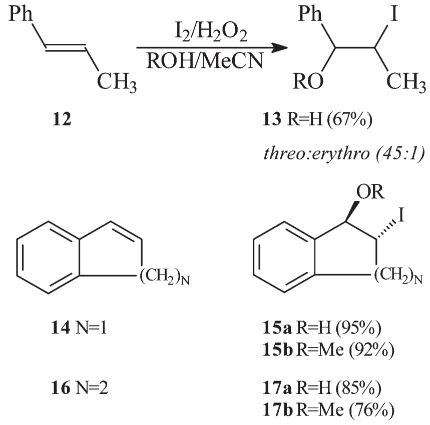
Finally, we tested the stereochemical course of reaction of the H_2O_2/I_2 system on *trans*-β-methylstyrene **12** compared to its cyclic, more rigid analogues, indene **14** and 1,2-dihydronaphthalene **16**, in order to evaluate the role of alkene geometry and ring size in the presence of an aromatic ring (Scheme 4). Alkene **12** is an interesting model substrate, known for its ability to form a partly bridged carbocation, thus having a possible strong impact on the reaction stereochemistry. By



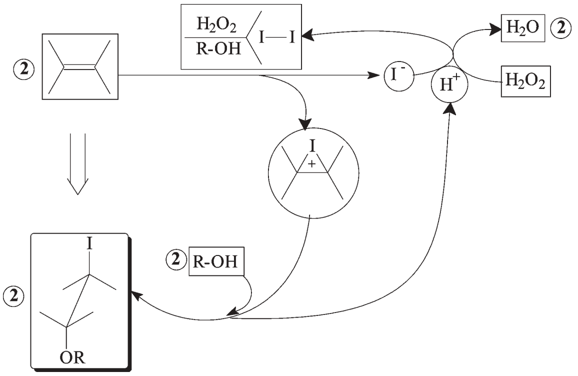
Scheme 3 The role of ring size and heteroatom on the steroselectivity of the iodofunctionalisation. *Reaction conditions*: iodo-hydroxylation; 1 mmol of **10**, 0.5 mmol of I_2, 0.6 mmol of 30% aqueous H_2O_2, 10 ml of MeCN, 20 mmol of H_2O, 20 h at 20 °C. Iodo-methoxylation; 1 mmol of **10**, 0.5 mmol of I_2, 0.6 mmol of 30% of aqueous H_2O_2, 20 h at 20 °C.

employing *trans*-β-methylstyrene **12**, it is also possible to distinguish between an opened and a cyclic iodonium intermediate; the latter would result in a product of uniform geometry. Reaction of **12** in a MeCN–H_2O mixture yielded 2-iodo-1-phenylpropan-1-ol **13**, the relative ratio of *threo* : *erythro* isomers being 45 : 1. These observations regarding the regio- and stereochemistry of the process indicate that cyclic iodonium reactive intermediates are preferentially involved in the course of the reaction, where addition typically has *anti* character. We found that indene **14** and 1,2-dihydronaphthalene **16** were stereoselectively transformed, regardless of whether the nucleophile was methanol or water, to *trans* iodo-substituted product **15a**, **15b**, **17a** or **17b** respectively. The results demonstrate that open *versus* cyclic alkene geometry has a trivial influence on the regio- and stereoselectivity, like ring size and the vicinity of the aromatic ring.

In Scheme 5 the electron and proton flows between alkene, I_2 and H_2O_2 are presented. In the first step, the triad I_2, H_2O_2 and ROH (the important role of the presence of H_2O_2 is evident from the introductory experiments) transform the alkene into a cyclic iodonium ion and iodide. The cyclic



Scheme 4 The role of alkene geometry and ring size on regio- and stereochemistry of the transformation. *Reaction conditions*: iodo-hydroxylation; 1 mmol of **12**, **14** or **16**, 0.5 mmol of I_2, 0.5 mmol of 30% of aq. H_2O_2, 10 ml of MeCN, 15 mmol of H_2O, 20 h at 20 °C. Iodo-methoxylation; 1 mmol of **14** or **16**, 0.5 mmol of I_2, 0.5 mmol of 30% of aq. H_2O_2, 10 ml of MeOH, 20 h at 20 °C.



Scheme 5 Proposed reaction pathways in iodofunctionalisation of alkenes.

intermediate is almost exclusively attacked by ROH at the less sterically hindered C-atom yielding an *anti* vicinal hydroxy or alkoxy iodo-substituted alkane, followed by a subsequent proton loss. This liberated proton has a catalytical role in the second iodide ion oxidation process, thus forming I^+, which could react with the I^- ion to form I_2. The fate of the newly generated I^+ could also be olefin attack, producing a second cyclic iodonium ion. The presence of H^+ is essential to keep the oxidative properties of H_2O_2, *i.e.* to act as an electron acceptor.

In conclusion we would like to stress that the demonstrated applicability of 30% hydrogen peroxide as an excellent promotor of selective iodine atom transfer into alkenes, using elemental iodine, contributes to this useful and effective transformation the very important attributes of a 'green' chemical reaction. In view of this very important fact, further exploitation of this reaction system for the halogenation of as wide a range of organic molecules as possible is in progress.

Experimental

Starting alkenes were purchased from Aldrich, Sigma and Merck, while **1d** and **1e** were prepared according to a known procedure.[31] Solvents (ACS grade) were purchased from Sigma and Merck and used as received. A commercially available 30% aqueous solution of hydrogen peroxide was used as received. Reaction mixtures were analyzed by TLC, and pure products were obtained after flash chromatography over SiO_2. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Chemical shifts of both ^1H NMR and ^{13}C NMR spectra are reported in ppm with TMS as the internal standard. ^1H NMR spectra were recorded on a Varian Inova 300 spectrometer at 300 MHz and ^{13}C NMR on the same instrument at 75 MHz. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. A standard KBr pellet procedure were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained on an Autospec Q instrument under impact (EI) conditions at 70 eV. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyzer.

General procedure

To a solution of 1 mmol of alkene **1**, **3**, **5a**, **8**, **10**, **14** and **16** in MeOH (10 ml) or to a solution of 1 mmol of alkene **1a**, **1b**, **1c**, **5**, **8**, **10a**, **10b**, **12**, **14** and **16** in a mixture of MeCN (10 ml) and water (amount indicated in Schemes 1–4), 127 mg (0.5 mmol) of elemental iodine and 57 mg or 69 mg of a 30% water solution of hydrogen peroxide (0.5 mmol or 0.6 mmol of pure H_2O_2) were added and the reaction solution stirred at room temperature for the time indicated (Schemes 1–4). The solvent was removed under reduced pressure and the crude reaction mixture was dissolved in 25 ml of CH_2Cl_2, washed with aqueous sodium thiosulfate pentahydrate (10%, 10 ml) and water (10 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated, the crude reaction mixtures were analysed by ^1H NMR, MS and TLC, while pure products were obtained after flash chromatography over SiO_2.The physico-chemical and spectroscopic characteristics of already known products **2a**,[16] **2a′**,[16] **2aa′**,[9] **2b**,[16] **2b′**,[16] **2c**,[16] **2c′**,[16] **6a**,[32] **6b**,[23], **7b**,[23] **11a**,[5] **11a′**,[10] **11b**,[5] **11b′**,[16] **11c**,[16] **11d**,[33] **11e**,[33] **13**,[34] **15a**,[14] **15b**,[22] **17a**,[35] and **17b**[22] were in agreement with published data. New compounds were validated as stated below:

1-Iodo-2-methoxy-2-(1-naphthyl)propane (2d)

Yield 73% of oily product, TLC CH_2Cl_2–petrolether (bp 40–60 °C) (1 : 1)/SiO_2; ^1H NMR δ 1.91 (3H, s), 3.06 (3H, s), 3.63 (1H, d, J = 10.5 Hz), 4.08 (1H, d, J = 9.8 Hz), 7.37–7.55 (4H, m), 7.79–7.88 (2H, m), 8.85 (1H, m); ^{13}C NMR: δ 18.9 (CH_2I), 25.9 (CH_3), 51.5 (OCH_3), 79.3 (C-2), 124.7, 125.6, 126.0, 126.3, 126.5, 129.1 and 129.7 (Ar–CH), 131.5, 134.6 and 135.8 (Ar–C); IR (neat) ν 3047, 2983, 2932, 2824, 1599, 1506, 1453, 1418, 1393, 1372, 1343, 1248, 1170, 1103, 1069, 1028, 878, 802, 777, 739, 660, 623 cm^{-1}; MS, *m*/*z* (%): 326 (M^+, 23%), 185 (6), 84 (100). Anal. calcd for $C_{14}H_{15}IO$: C 51.55, H 4.64. Found: C 51.59, H 4.86%.

1-Iodo-2-methoxy-2-(9-phenanthryl)propane (2e)

Yield 86% of white crystals, mp 100.3–103.3 °C; TLC CH_2Cl_2–petrolether (bp 40–60 °C) (1 : 1)/SiO_2; ^1H NMR δ 1.99 (3H, s), 3.11 (3H, s), 3.69 (1H, d, J = 10.5 Hz), 4.16 (1H, d, J = 10.6 Hz), 7.56–7.86 (6H, m), 8.64 (1H, d, J = 8.2 Hz), 8.74 (1H, dd, J = 9.5 Hz, J = 2.0 Hz), 8.96 (1H, dd, J = 7.7 Hz, J = 2.0 Hz); ^{13}C NMR: δ 18.6 (CH_2I), 26.0 (CH_3), 51.6 (OCH_3), 79.2 (C-2), 122.4, 123.2, 126.4, 126.8, 127.4, 128.1 and 128.9 (Ar–CH), 130.2, 130.6, 130.8, 131.2 and 134.0 (Ar–C); IR (neat) ν 3057, 2983, 2931, 2825, 1598, 1530, 1491, 1449, 1419, 1366, 1256, 1173, 1117, 1076, 891, 748 cm^{-1}; MS, *m*/*z* (%): 376 (M^+, 18%), 249 (9), 235 (100), 217 (33), 203 (33), 191 (32), 177 (19). Anal. calcd for $C_{18}H_{17}IO$: C 57.46, H 4.55. Found: C 57.34, H 4.71%.

1-(2-Iodo-1-methoxyethyl)pyrrolidin-2-one (4)

Yield 75% of oily product, TLC CH_2Cl_2–acetone (10 : 1)/SiO_2; ^1H NMR δ 2.02–2.15 (2H, m), 2.49 (2H, m), 3.15 (1H, dd, J = 7.9 Hz, J = 10.5 Hz), 3.31 (3H, s, OCH_3), 3.32–3.39 (3H, m), 5.35 (1H, dd, J = 6.0 Hz, J = 7.9 Hz, NCH); ^{13}C NMR: δ 2.6 (CH_2I), 18.2 (CH_2), 31.3 (CH_2), 40.4 (CH_2), 56.4 (OCH_3), 82.1 (CH–N), 176.3 (CO); IR (neat) ν 2934, 2889, 2830, 1693, 1456, 1414, 1271, 1099, 1075, 941, 619 cm^{-1}; MS, *m*/*z* (%): 270 (MH^+, 12%), 238 (98), 185 (48), 142, (42), 128, (100), 111 (22). Anal. calcd for $C_7H_{12}INO$: C 31.25, H 4.50, N 5.21. Found: C 31.35, H 4.63, N 5.11%.

1-Iodomethyl-1-methoxycyclopentane (6a′)

Yield 92% of oily compound, TLC CH_2Cl_2–n-pentane (2 : 3)/SiO_2; ^1H NMR δ 1.51–1.99 (8H, m), 3.16 (3H, s), 3.35 (2H, s); ^{13}C NMR δ 13.8 (CH_2–I), 24.6 (C-3,4), 36.1 (C-2,5), 49.8 (OCH_3), 84.8 (C–q); IR (neat) 2959, 2871, 2822, 2361, 2340, 1080 cm^{-1}; MS *m/z* (%): 240 (M^+, 2%), 113 (29), 99 (100), 85 (13). Anal. Calcd for $C_7H_{13}IO$: C 35.02, H 5.46. Found: C 35.29, H 5.69%.

1-Hydroxy-2-iodo-3,3-dimethylbutane (7c)

Yield 61% of white crystals, mp 35.5–36.9 °C, TLC CH_2Cl_2/SiO_2; ^1H NMR δ 1.13 (9H, s), 2.05 (1H, dd, J = 9.0 Hz, J = 4.6 Hz, OH), 3.68 (1H, ddd, J = 12.5 Hz, J = 9.2 Hz J = 4.2 Hz), 3.79 (1H, ddd, J = 12.5 Hz, J = 9.2 Hz J = 4.2 Hz), 4.26 (1H, dd, J = 9.0 Hz, J = 3.4 Hz, CH); ^{13}C NMR: δ 29.0 (3 × CH_3), 34.7 (C-3), 61.7 (C-2), 65.9 (C-1); IR (neat) *v* 3336, 2963, 2868, 1364, 1257, 1133, 1070, 1044, 996, 943, 905 cm^{-1}. Anal. calcd for $C_6H_{13}IO$: C 31.60, H 5.75. Found: C 32.05, H 5.97%.

2-Hydroxy-3-iodo-2-methylpentane (9a)

Yield 42% of liquid, volatile product, TLC CH_2Cl_2/SiO_2; ^1H NMR δ 1.10 (3H, t, J = 7.1 Hz), 1.37 (3H, s), 1.42 (3H, s), 1.70–1.81 (2H, m), 2.00 (1H, br s, OH), 4.14 (1H, dd, J = 8.6 Hz, J = 5.2 Hz); ^{13}C NMR: δ 15.9 (C-5), 26.5 (CH_3), 27.1 (CH_3), 29.1 (CH_2), 60.8 (C-3), 72.5 (C-2); IR (neat) *v* 3419, 2970, 2933, 2875, 1458, 1377, 1327, 1280, 1156, 1117, 920, 898, 870, 800, 768 cm^{-1}; MS (EI, 70 eV) *m/z* 228 (M^+,<1), 213 (4), 170 (3), 128 (6), 101 (51), 86 (11), 71 (15) 59 (100); HRMS calcd. for $C_6H_{13}IO$: 228.0011, found 228.0018.

3-Iodo-2-methoxy-2-methylpentane (9a′)

Yield 35% of liquid, volatile product, TLC CH_2Cl_2–petrolether (bp 40–60 °C) (1 : 1)/SiO_2; ^1H NMR δ 1.08 (3H, t, J = 7.1 Hz), 1.35 (6H, s), 1.62–1.84 (3H, s), 3.23 (3H, s), 4.06 (1H, dd, J = 10.9 Hz, J = 2.7 Hz); ^{13}C NMR: δ 15.5 (C-5), 21.9 (CH_3), 24.9 (CH_3), 28.4 (C-4), 49.5 (C-3), 51.4 (OCH_3), 64.6 (C-2); IR (neat) *v* 2972, 2934, 2827, 1460, 1375, 1239, 1192, 1121, 1070, 799 cm^{-1}; MS (EI, 70 eV) *m/z* 242 (M^+, 1%), 227 (1), 211 (1), 199 (<1), 169 (1), 145 (<1), 137 (<1), 128 (2), 115 (22), 73 (100); HRMS calcd. for $C_7H_{15}IO$: 242.0168, found 242.0169.

Acknowledgements

The authors are grateful to Dr J. Plavec and A. Gačeša for ^1H and ^{13}C NMR spectra, T. Stipanovič and Prof. B. Stanovnik for elemental combustion analysis and to the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support.

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References

1 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524; N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; F. Diederich and P. J. Stang, *Metal-Catalysed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, Germany, 1998.
2 For some recent examples, see: J. D. White, G. Wang and L. Quaranta, *Org. Lett.*, 2003, **5**, 4109–4112; S. Ma, X. Hao and X. Huang, *Chem. Commun.*, 2003, 1082–1083; H. Rudler, B. Denise, A. Parlier and J.-C. Daran, *Chem. Commun.*, 2002, 940–941; W. S. Lee, K. C. Jang, J. H. Kim and K. H. Park, *Chem. Commun.*, 1999, 251–252.
3 I. R. L. Barker and W. A. Waters, *J. Chem. Soc.*, 1952, 150–153; S. Ahmad and S. Razaq, *Tetrahedron*, 1976, **32**, 503–506; A. Zweig, K. R. Huffman and G. W. Nachtigall, *J. Org. Chem.*, 1977, **42**, 4049–4052.
4 R. C. Cambie, R. C. Hayward, J. L. Roberts and P. S. Rutledge, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1858–1864.
5 C. A. Horiuchi, A. Ikeda, M. Kanamori, H. Hosokawa, T. Sugiyama and T. T. Takahashi, *J. Chem. Res. (S)*, 1997, 60–61.
6 N. Iranpoor and M. Shekarriz, *Tetrahedron*, 2000, **56**, 5209–5211.
7 M. I. Rodríguez-Franco, I. Dorronsoro, A. I. Hernández-Higueras and G. Antequera, *Tetrahedron Lett.*, 2001, **42**, 863–865.
8 S. Hajra and A. Karmakar, *Tetrahedron Lett.*, 2004, **45**, 3185–3188.
9 C. P. Forbes, A. Goosen and H. A. H. Laue, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2346–2350.
10 J. Barluenga, M. A. Rodríguez and P. J. Campos, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2807–2809.
11 J. P. Whang, S. G. Yang and Y. H. Kim, *Chem. Commun.*, 1997, 1355–1356.
12 C. G. Francisco, C. C. González, N. R. Paz and E. Suárez, *Org. Lett.*, 2003, **5**, 4171–4173.
13 J. Barluenga, F. González-Bobes and J. M. González, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2556–2558.
14 A. R. De Corso, B. Panunzi and M. Tingoli, *Tetrahedron Lett.*, 2001, **42**, 7245–7247.
15 H. Togo and M. Katohgi, *Synlett*, 2001, 565–581.
16 M. S. Yusubov, R. J. Yusubova, V. D. Filimonov and K.-W. Chi, *Synth. Commun.*, 2004, 443–450.
17 O. V. Branytska and R. Neumann, *J. Org. Chem.*, 2003, **68**, 9510–9512.
18 P. Lulinski, A. Kryska, M. Sosnowski and L. Skulski, *Synthesis*, 2004, 441–445.
19 M. Zupan, J. Iskra and S. Stavber, *Tetrahedron Lett.*, 1997, **38**, 6305–6306; S. Stavber, M. Jereb and M. Zupan, *Chem. Commun.*, 2002, 488–489; M. Jereb, S. Stavber and M. Zupan, *Synthesis*, 2003, 853–858; M. Jereb, S. Stavber and M. Zupan, *Tetrahedron*, 2003, **59**, 5935–5940.
20 C. Chiappe and D. Pieraccini, *Arkivoc*, 2002, 249–255.
21 A. M. Sanseverino and M. C. S. de Mattos, *Synthesis*, 1998, 1584–1586.
22 V. A. Mahajan, P. D. Shinde, A. S. Gajare, M. Karthikeyan and R. D. Wakharkar, *Green Chem.*, 2002, **4**, 325–327.
23 S. Cerritelli, M. Chiarini, G. Cerichelli, M. Capone and M. Marsili, *Eur. J. Org. Chem.*, 2004, 623–630.
24 J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros and J. M. González, *Chem. Eur. J.*, 2004, **10**, 1677–1682.
25 D. E. Higgs, M. I. Nelen and M. R. Detty, *Org. Lett.*, 2001, **3**, 349–352.
26 M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, 2002.
27 B. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.
28 R. Noyori, M. Aoki and K. Sato, *Chem. Commun.*, 2003, 1977–1986.
29 *Organic Peroxides*, ed. W. Ando, John Wiley & Sons Ltd., Chichester, 1992; *Peroxide Chemistry: Mechanistic and Preparative Aspects of Oxygen Transfer*, ed. W. Adam, Wiley-VCH, Weinheim, 2000; B. S. Lane and K. Burgess, *Chem. Rev.*, 2003, **103**, 2457–2474; G. Maayan, R. H. Fish and R. Neumann, *Org. Lett.*, 2003, **5**, 3547–3550; K.-H. Tong, K.-Y. Wong and T. H. Chan, *Org. Lett.*, 2003, **5**, 3423–3425.
30 T. Negoro and Y. Ikeda, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2547–2551.
31 *Vogels Textbook of Practical Organic Chemistry*, 3rd edn., Longman Group Limited, London, 1959.
32 T. Tabuchi, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, 1986, **27**, 3891–3894.
33 K. Maeda, H. Shinokubo and K. Oshima, *J. Org. Chem.*, 1997, **62**, 6429–6431.
34 G. H. Schmid and J. W. Gordon, *J. Org. Chem.*, 1983, **48**, 4010–4013.
35 M. Sukeda, S. Ichikawa, A. Matsuda and S. Shuto, *J. Org. Chem.*, 2003, **68**, 3465–3475.

Diels–Alder reactions between maleic anhydride and furan derivatives in supercritical CO_2

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A comparative analysis of the reactions between maleic anhydride and furan derivatives is presented in near and supercritical carbon dioxide and traditional organic solvents. Reaction kinetics were monitored by UV-vis absorbance spectroscopy in conjunction with an optimization technique which greatly simplified the experimental approach. In all of the reactions studied, supercritical carbon dioxide proved to facilitate a rate enhancement over conventional organic solvents. The reaction between maleic anhydride and furfuryl alcohol at 69 bar and 35 °C was found to proceed 10 times faster in CO_2 compared to reactions carried out in diethyl ether. All kinetic results were obtained from reactions undertaken in true homogeneous one phase fluid systems. The results achieved further indicate the potential of using carbon dioxide as a medium to carry out such chemical transformations through more environmentally acceptable processes.

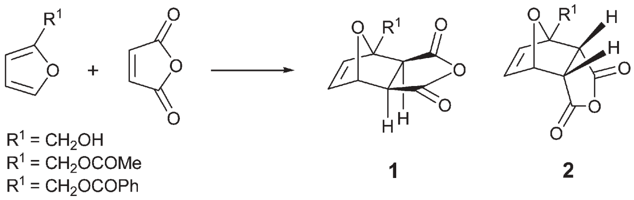
Introduction

The development of chemical reactions that are atom efficient, environmentally friendly and which proceed with enhanced selectivity is a major goal for the synthetic chemist. A number of diverse approaches to achieve these goals have been developed, and include new strategies for solid phase synthesis,[1] the use of supported catalysis,[2] ionic liquids[3] and the replacement of conventional solvents by supercritical fluid (SCF) media.[4] Primarily influenced through environmental considerations, supercritical carbon dioxide (sc-CO_2) has been shown to be an effective medium for a range of chemical transformations that have included cycloaddition reactions,[5] metal mediated reductions,[6] metal coordination chemistries,[7] hydrogenation[8] and alkylation.[9,10]

Few reactions can compete with the Diels–Alder cycloaddition with respect to the degree of structural complexity that can be achieved in a single step. Consequently, SCFs and in particular sc-CO_2, have attracted considerable interest as media for Diels–Alder reactions.[11] These studies have examined a number of facile Diels–Alder reactions of reactive components that give stable cycloadducts.[12,13] Several groups have reported on the effects of pressure, solvent density and fluid viscosity on the reaction rate and product distribution of cycloaddition reactions undertaken in sc-CO_2.[14–16] In particular, Paulaitis and Alexander showed that varying degrees of pressure (80–430 bar) and temperature (35–60 °C) can be utilised to control the rate of cycloaddition between maleic anhydride and isoprene. In their work a prominent increase in the reaction rate near the critical point, due to dramatic changes in activation volumes, was identified.[17] A far greater challenge, however, is presented by Diels–Alder reactions involving furans, given that these compounds are less reactive as the diene component in cycloaddition reactions due to the aromatic nature of the furan nucleus and because the highly strained products formed undergo facile cycloreversion.[18]

The synthetic application of Diels–Alder chemistry to furan derivatives has been extensively studied and successfully exploited in conventional organic solvents.[19] For example, the reaction between maleic anhydride and furfuryl alcohol gives rise to a substituted 7-oxa-norborn-2-ene structure that can be manipulated with impressive selectivity leading to a variety of interesting target molecules. Structurally related materials have been successfully utilized as intermediates in the synthesis of prostaglandins,[20] antibiotics,[21] agrochemicals[22] and a host of biologically active compounds.[23] However, ring strain in 7-oxa-norborn-2-ene systems and the aromatic character of the furan molecules combine to limit product yields in traditional organic solvents.[24] The thermal lability of these products precludes heating as a viable route to accelerate the rates of reaction as the cycloadduct readily reverts back to the starting materials[25] which undergo polymerization on heating.[26,27] While these limitations are problematic from a synthetic point of view, the retro reaction also significantly complicates kinetic measurements[28] leading to inaccurate assessment of reaction rates.

The work reported in this paper describes the reaction between maleic anhydride and various furan derivatives in near and sc-CO_2 (Scheme 1) and demonstrates how product



Scheme 1 Cycloaddition reactions of maleic anhydride with furan derivatives to form 7-oxa-norborn-2-ene products.

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yields and rate coefficients change as a function of fluid density. Owing to its relative simplicity, *in situ* UV-vis absorption spectroscopy was utilized in conjunction with optimization methods to determine the reaction kinetics of the systems under study.[26]

Experimental

Materials

Furfuryl alcohol (FA), furfuryl acetate (FAC), and furfuryl benzoate (FB) (Aldrich, Ireland) were redistilled under reduced pressure, dried over sodium sulfate and filtered before use. FA has a tendency to undergo a limited degree of polymerization under acidic conditions to form di-furfuryl ethers.[29] Purified samples of the alcohol were analysed by UV-vis absorption spectroscopy on a Hewlett Packard 8453 diode array spectrophotometer to ensure that no alcoholic polymers were present prior to experimentation.[30] Maleic anhydride (MA) (Aldrich, mp 54–56 °C, 99%) was purified using vacuum sublimation to remove maleic acid present in the commercial reagent. Elemental analysis was undertaken on all reactants using a CE440 elemental analyzer. Carbon dioxide (99.9%) was purchased from Irish Oxygen (Cork) and used as received. Deuterated acetone (Aldrich, 99.9 atom%) was used in all ^{1}H NMR experiments (300 MHz Bruker Spectrophotometer) to confirm the structures of all cycloadduct products synthesized in our reactions. For comparative purposes, reactions were carried out in acetonitrile (Aldrich, HPLC grade, 99%) and anhydrous diethyl ether (Aldrich, 99.8%) both being used as received.

In situ UV-vis absorbance measurements

All experiments were undertaken in a high pressure variable volume stainless steel cell. The cell was fitted with two UV-grade sapphire windows giving an optical pathlength of 2.6 cm. The cell was also fitted with a front view window to allow visual inspection of the reaction. Reaction temperature was controlled using an Isopad heating tape (Type ITWSS-M), which was thermostatted to ±0.2 °C using a platinum resistance thermometer and temperature controller. Pressure was controlled to ±1 bar using an Isco syringe pump (Lincoln, NE, 260 ml). An external magnetic stirrer drove a PTFE coated magnetic stirrer bar. All reactions were monitored within the reaction vessel using a Hewlett Packard 8453 UV-vis spectrophotometer. This approach allowed all reactions to be monitored without altering the composition of the system in preference to a sampling technique which can potentially alter the system's phase behaviour.[31]

Solubility measurements

The solubilities of each reactant individually, and reaction mixtures, at various temperatures and pressures above and below their critical point were measured in CO_2. A series of experiments were carried out whereby a pre-determined amount of an individual reactant was dissolved in CO_2 and its absorption spectrum was recorded allowing determination of molal extinction coefficients for each component. Fig. 1 shows the molal extinction coefficients (kg mol^{-1} cm^{-1}) of maleic anhydride, furfuryl alcohol and the cycloadduct derived from maleic anhydride and furfuryl alcohol, (1-hydroxymethyl-4,10-dioxa-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione) as a function of wavelength in sc-CO_2 at a temperature of 35 °C and pressure of 207 bar. The extinction coefficients of all compounds did not change significantly as a function of temperature or pressure. In multi-component systems, intermolecular interactions between reactants can significantly alter their solubilities in a SCF.[32] Consequently, the solubilities of mixtures of maleic anhydride and the furan derivatives were determined by UV-vis absorption spectroscopy to confirm that the reactions were indeed occurring in a single phase region.

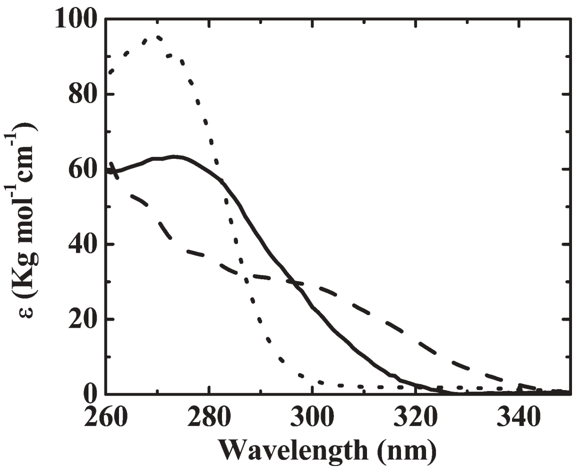

Fig. 1 Molal extinction coefficients of maleic anhydride (– – –), furfuryl alcohol (···) and the cycloadduct product (—) determined in sc-CO_2 at 35 °C and 207 bar.

Reaction procedure

In a typical reaction, 1–10 mg of maleic anhydride and the appropriate furan derivative were placed in the high-pressure cell with CO_2. The reaction cell was pressurized and thermostated to maintain the desired pressure and temperature respectively. The cell was allowed to equilibrate for 5 minutes whilst the reaction mixture was stirred. Absorption spectra of the reaction were taken every 90 seconds over a period of 2–3 hours to allow kinetic parameters to be determined. After 24 hours the cell was slowly depressurized and the contents remaining were dissolved in deuterated acetone (1 ml) for ^{1}H NMR analysis to confirm product distribution and the degree of conversion achieved.

Kinetic studies

A simplified method to extract kinetic data from the UV-vis absorbance spectra recorded was developed. The total absorbance of all species in CO_2 at a given wavelength (λ) can be described by a summation of Beer's law:

$$Abs_{\mathrm{Total}}(\lambda) = l(\varepsilon_{\mathrm{MA}}(\lambda)m_{\mathrm{MA}} + \varepsilon_{\mathrm{FA}}(\lambda)m_{\mathrm{FA}} + \varepsilon_{\mathrm{PROD}}(\lambda)m_{\mathrm{PROD}}) \quad (1)$$

where ε_x is the molal extinction coefficient of species x (kg mol^{-1} cm^{-1}) at wavelength λ (nm); l is the cell path length (cm) and m_x is the molal concentration of x (mol kg^{-1}). An optimization model was developed to determine the concentrations of reactants MA, FA and the cycloadduct (PROD) produced at any time point during the course of the reaction. This was achieved by minimizing the differences between the measured (EXP) and calculated (CALC) absorbance, as shown in eqn. (2):

$$\mathrm{Min}\phi = \sum_{\lambda}^{\lambda=250,\,251,\ldots600\ \mathrm{nm}} (Abs_{\mathrm{EXP}}(\lambda) - Abs_{\mathrm{CALC}}(\lambda))^2 \qquad (2)$$

The model solution was constrained by the mass balance equations (3) and (4):

$$m^0_{\mathrm{MA}} - m^t_{\mathrm{MA}} - m^t_{\mathrm{PROD}} = 0 \qquad (3)$$

$$m^0_{\mathrm{FA}} - m^t_{\mathrm{FA}} - m^t_{\mathrm{PROD}} = 0 \qquad (4)$$

Where m^0_x is the initial concentration of reactants and $m^{\mathrm{t}}_{\mathrm{x}}$ the molal concentration of species x at time t during the reaction. The optimization model was implemented with the generalized reduced gradient (GRG) algorithm described by Smith and Lasdon.[33]

^{1}H NMR analysis

Diels–Alder reaction of furans with dienophiles usually results in the formation of the thermodynamically more stable *exo* product (**1**, Scheme 1). The kinetic *endo* product (**2**), once formed, undergoes a facile retro reaction to reform the starting materials and is rarely observed in synthetic procedures. During our studies, variable amounts of the *endo* product were routinely observed as a minor product in crude reaction mixtures. Owing to the similarity of the UV-vis spectra, and hence the extinction coefficients of the two diastereoisomeric forms, it was not possible to differentiate between them using UV-vis spectroscopy. The ratio of *endo* to *exo* products produced from the cycloaddition reactions was therefore determined by ^{1}H NMR analysis of the crude reaction mixtures by integration of the characteristic bridgehead proton signals. For the *exo* product, no coupling is observed between the bridgehead proton and the vicinal *trans* (anhydride) proton since the dihedral angle is close to 90 degrees.[34] The signal therefore appears as a doublet at 5.1 ppm. For the *endo* product, however, coupling is observed between the bridgehead proton and the vicinal *cis* (anhydride) proton and so the signal appears as a doublet of doublets at a chemical shift of 5.5 ppm. The overall conversion of reactants to products was determined by integration of characteristic product signals against the maleic anhydride proton singlet at 7.1 ppm.

Results and discussion

Solubility of reactants in sc-CO$_2$

The importance of phase behaviour cannot be understated, because the outcome reaction can in some cases be determined by whether the reaction mixture is single or multiphase.[35] Kinetic studies were undertaken on single phase homogeneous mixtures, as determined from solubility studies, to eliminate inaccuracies due to the presence of a multiphase system.[36,37] Figs. 2(a) and 2(b) show the solubility of maleic anhydride (MA) and furfuryl alcohol (FA) in sc-CO$_2$ at 35 °C and 207 bar as determined by UV-vis absorption spectroscopy. Both compounds being polar have limited solubility in CO$_2$, however, at concentrations below 2.0 × 10^{-3} mol kg^{-1} each compound is totally soluble in sc-CO$_2$. It should be noted, however, that the solubility of a single solute in a SCF is not necessarily the same as in a multi-component system.[32,38] Phase behaviour of the two component systems, (maleic anhydride and the respective furan derivative) was therefore undertaken by UV-vis spectroscopy and visual observation. Maleic anhydride and the respective furan derivative were found to exist as a single homogeneous phase in sc-CO$_2$ when the additive concentration was below 2.0 × 10^{-3} mol kg^{-1}. Therefore, all reactions reported in this manuscript were undertaken at total reactant concentrations less than 2 × 10^{-3} mol kg^{-1}.

Kinetics of maleic anhydride and furfuryl derivatives in sc-CO$_2$

Fig. 3 shows the time dependent UV-vis absorbance changes for a typical reaction between maleic anhydride and furfuryl alcohol in sc-CO$_2$ at 35 °C and 207 bar. An increase in the absorbance with time is clearly seen in the region between 250–290 nm due to the formation of the product (PROD). At higher wavelengths, 300–350 nm, the absorbance decreases with time due to the disappearance of the reactants (MA

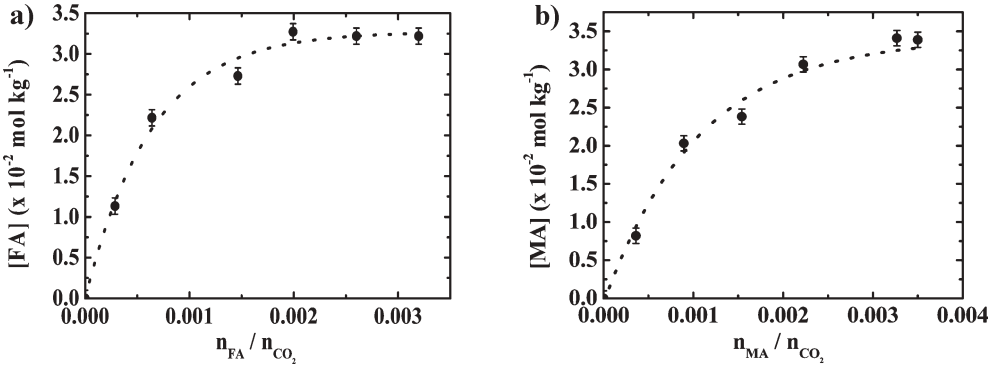

Fig. 2 Solubility of (a) furfuryl alcohol and (b) maleic anhydride in sc-CO$_2$ at 35 °C and 207 bar. Concentrations were determined from UV-vis absorbance measurements (see text) *vs.* the ratio of number of moles (n_x) of each compound to the number of moles of CO$_2$($n_{\mathrm{CO_2}}$).

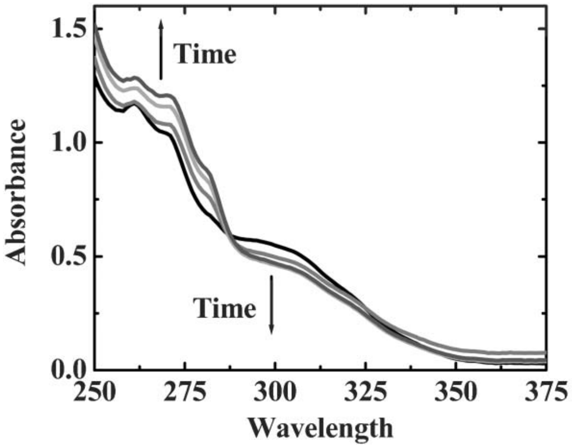

Fig. 3 Time dependent UV-vis absorbance changes recorded for a reaction between maleic anhydride and furfuryl alcohol in sc-CO_2 at 35 °C and 207 bar over a 2 hour time period.

and FA). Although there have been numerous studies of Diels–Alder reactions in sc-CO_2, no kinetic studies of the reactions between furans and maleic anhydride have been performed. Dewar and Pierini, and Lee and Herndon previously reported that the Diels–Alder reaction between maleic anhydride and furan in acetonitrile obeys second order kinetics,[28,39] and indeed our Diels–Alder cycloaddition reactions in sc-CO_2 also exhibit second order kinetics with the bimolecular rate coefficient given by eqn. (5):

$$\frac{1}{[\mathrm{MA}]_0-[\mathrm{FA}]_0}\ln\frac{[\mathrm{FA}]_0[\mathrm{MA}]_t}{[\mathrm{MA}]_0[\mathrm{FA}]_t}=k_1t \qquad (5)$$

Table 1 outlines the variation in rate coefficient (k_1) with increasing pressure for reactions carried out at 35 °C. A clear enhancement of the rate coefficient is observed for reactions carried out in sc-CO_2 compared with traditional organic solvents such as ether and acetonitrile. It is particularly noteworthy that the rate coefficient in near critical CO_2 at 69 bar is observed to be ten times greater than the same reaction undertaken in either ether or acetonitrile at the same temperature. This enhancement may be explained by the proximity of the critical point (T_c = 31.1 °C and P_c = 73.6 bar), where a local density augmentation effect[40] can occur through the clustering of solvent molecules around dilute solute species[11] enhancing solubility and increasing reaction rates.[41]

The Arrhenius plot shown in Fig. 4 demonstrates the temperature dependence of the rate coefficient for the reaction between furfuryl alcohol and maleic anhydride carried out in sc-CO_2 at 207 bar. An activation energy (E_A) of 68 kJ mol^{-1} is observed under these conditions. We believe there is an increased influence from the reverse reaction, primarily established from the thermal instability of the cycloadducts at temperatures of 45 °C and above. In light of this, and the inherent instability of the cycloadduct at elevated temperatures,[26] we investigated the effect that the reverse reaction has on the measured kinetics of the forward reaction (Scheme 1). The rate coefficient (k_{-1}) of the reverse reaction proved insignificant at temperatures between 20–35 °C for the cycloaddition of maleic anhydride with all of the furan derivatives studied. However, at a temperature of 45 °C the cycloadducts readily reverted to the starting materials. Fig. 5 shows a first order rate plot of the reverse reaction between maleic anhydride and furfuryl alcohol at a temperature of 45 °C and 207 bar. A rate coefficient (k_{-1}) for the reverse reaction of 0.58 × 10^{-4} s^{-1} was observed which constitutes a large influence over the forward reaction at this temperature.

Table 1 Variation in the rate coefficient (k_1, × 10^{-4} kg mol^{-1} s^{-1}) for the reaction between maleic anhydride and furfuryl alcohol with increasing pressure, at a constant temperature of 35 °C

CO_2 pressure/bar	k_{CO_2}	k_{Ether}	$k_{Acetonitrile}$
69	49.6	5.9	4.1
207	45.4	6.1	7.6
483	50.1	12.5	15.4

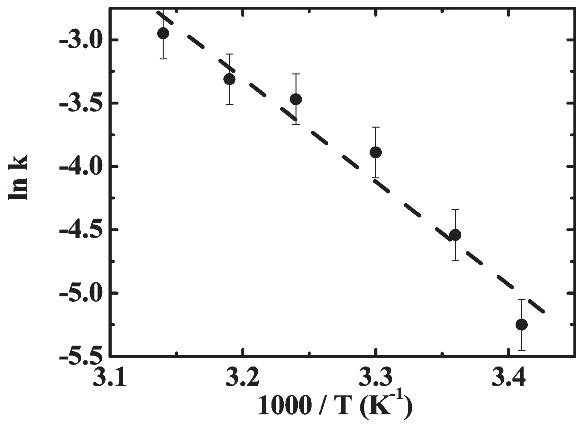

Fig. 4 Arrhenius plot determined for the reaction between maleic anhydride and furfuryl alcohol in sc-CO_2 at a constant pressure of 207 bar.

Product yields in CO_2

A significant increase in product yield was obtained in sc-CO_2 compared to reactions undertaken in diethyl ether and acetonitrile. The average product yield was 12% for reactions undertaken in diethyl ether after 2 hours at 35 °C. Table 2 shows that in CO_2 product yields up to 54% could be obtained at temperatures below 35 °C over the same time duration. Also

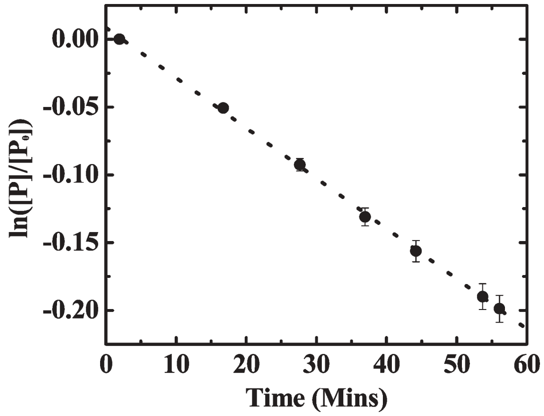

Fig. 5 First order rate plot of reverse reaction between maleic anhydride and furfuryl alcohol at 45 °C and 207 bar.

Table 2 Variation in the *endo* to *exo* product ratio for the reaction between maleic anhydride and furfuryl alcohol as a function of pressure, at a constant temperature of 35 °C

CO_2 pressure/bar	Yield (%)	Product ratio Exo	Endo	Solvent density/g cm^{-3}	Solvent viscosity/cP
69	50	0.76	0.24	0.21	0.019
207	42	0.6	0.4	0.87	0.085
345	44	0.62	0.38	0.95	0.105
483	54	0.65	0.35	1.00	0.122

shown in Table 2 is the variation in product yield as a function of fluid pressure. Large variations in product yield were not observed between the pressure range of 69–483 bar. Not surprisingly, the greatest product yield observed was obtained at the highest pressure studied, 483 bar, where solvent density and viscosity were also at a maximum relative to the other pressures under study.[42] A significant yield of over 50% was also observed at 69 bar and 35 °C, conditions that are close to the critical point of CO_2.

Substitution effects

Encouraged by the observed enhancement of the rate coefficient using sc-CO_2, we investigated how changing the substituent pattern on the parent furan structure affected the observed rate coefficients. An example of the variation in the rate coefficients is shown in Table 3 for reactions carried out in sc-CO_2 (207 bar and 35 °C) compared to those performed in diethyl ether at 35 °C. As the size of the substituent group increased the rate coefficient in both the organic solvent and sc-CO_2 decreased, most probably due to steric hindrance. However, in all cases the rate coefficients and product yields determined were greater in sc-CO_2 than in diethyl ether or acetonitrile. In particular, no product was formed in the reaction between maleic anhydride and furfuryl benzoate after 2 hours in diethyl ether, however, low conversions were achieved in sc-CO_2. Johnston and coworkers[43] previously reported that bulky substituents possess a greater affinity towards sc-CO_2, through an increased cohesive energy density between the solute and CO_2. It could be postulated that by increasing the size of the substituent, greater cohesive energy density exists between the benzoate substituent and sc-CO_2 as opposed to the substituent and diethyl ether.

Conclusions

In situ UV-vis absorbance methods have been employed to measure the kinetics of the Diels–Alder reactions of maleic anhydride with a number of furan derivatives in near and sc-CO_2 over a range of temperatures (20–45 °C) and pressures (69–483 bar). Rate coefficients and product yields for reactions in sc-CO_2 were compared to those obtained in traditional organic solvents such as ether and acetonitrile. Reactions carried out in sc-CO_2 proceeded up to ten times faster than reactions undertaken in ether or acetonitrile. Sc-CO_2 also facilitated the synthesis of the cycloadduct derived from furfuryl benzoate and maleic anhydride hitherto unobtainable in diethyl ether. These studies further illustrate the extraordinary potential of supercritical fluids, and in particular sc-CO_2, as synthetic media to access compounds unobtainable using conventional synthetic methodology

Table 3 Variation in the measured rate coefficients (k_1, $\times 10^{-4}$ kg mol^{-1} s^{-1}) for the reaction between maleic anhydride and various furan derivatives at 35 °C in sc-CO_2 (207 bar) and ether.

	k_{CO_2}	k_{Ether}	Ratio
Furfuryl alcohol	45.4	6.143	7.4 : 1
Furfuryl acetate	8.682	4.051	2.1 : 1
Furfuryl benzoate	1.248	0	—

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References

1 K. Akaji, K. Teruya and S. Aimoto, *J. Org. Chem.*, 2003, **68**, 4755.
2 B. F. G. Johnson, S. A. Raynor, D. B. Brown, D. S. Shephard, T. Mashmeyer, J. M. Thomas, S. Hermans, R. Raja and G. Sankar, *J. Mol. Catal. A: Chem.*, 2002, **182**, 89.
3 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley, New York, 1st edn., 2002.
4 M. Härröd, S. van den Hark, M. B. Macher and P. Møller, *Hydrogenation at supercritical single-phase conditions*, in *High Pressure Process Technology: Fundamentals and Applications*, ed. A. Bertucco and G. Vetter, Elsevier, London, 2001, pp. 496–508.
5 E. J. Beckman, *Ind. Eng. Chem. Res.*, 2003, **42**, 1598.
6 N. Shezad, R. S. Oakes, A. A. Clifford and C. M. Rayner, *Tetrahedron Lett.*, 1999, **40**, 2221.
7 J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495.
8 M. Chatterjee, Y. Ikushima and F. Y. Zhao, *New J. Chem.*, 2003, **27**, 510.
9 G. Deak, T. Pernecker and J. P. Kennedy, *J. Macromol. Sci., Pure Appl. Chem.*, 1995, **A32**, 979.
10 I. Komoto and S. Kobayashi, *Org. Lett.*, 2002, **4**, 1115.
11 R. A. Oakes, A. A. Clifford and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 2001, 917.
12 N. S. Isaacs and N. Keating, *Chem. Commun.*, 1992, 876.
13 A. A. Clifford, K. Pople, W. J. Gaskill, K. D. Bartle and C. M. Rayner, *J. Chem. Soc., Faraday Trans.*, 1998, **94**, 1451.
14 R. D. Weinstein, A. R. Renslo, R. L. Danheiser, J. G. Harris and J. W. Tester, *J. Phys. Chem.*, 1996, **100**, 12337.
15 S. Kim and K. P. Johnston, *Chem. Eng. Commun.*, 1988, **63**, 49.
16 Y. Ikushima, S. Ito, T. Asano, T. Yokoyama, N. Saito, K. Hatakeda and T. Goto, *J. Chem. Eng. Jpn.*, 1990, **23**, 96.
17 M. E. Paulaitis and G. C. Alexander, *Pure Appl. Chem.*, 1987, **59**, 61.
18 A. Albert, *Heterocyclic Chemistry*, Athlone Press, London, 2nd edn., 1968.
19 C. O. Kappe, S. S. Murphree and A. Padwa, *Tetrahedron*, 1997, **53**, 14179.
20 O. P. Vig, O. P. Chugh and V. K. Handa, *J. Indian Chem. Soc.*, 1975, **52**, 199.
21 A. Yasuda, M. Takahashi and H. Takaya, *Tetrahedron Lett.*, 1981, **22**, 2413.

22 N. Nottori, T. Kato, Y. Asano, M. Ueda, O. Kirino, S. Ooba, A. Fujinami and T. Ozaki, *Fungicidal Norbornanes and oxabicycloheptanes*, 1974, **890**, 72109.
23 P. Vogel, J. Cossy, J. Plumet and O. Arjona, *Tetrahedron*, 1999, **55**, 13521.
24 J. A. Moore, *J. Org. Chem.*, 1982, **48**, 1105.
25 R. B. Woodward, *J. Am. Chem. Soc.*, 1940, **62**, 1478.
26 A. Pelter and B. Singaram, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1383.
27 B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795.
28 M. J. S. Dewar and A. B. Pierini, *J. Am. Chem. Soc.*, 1984, **106**, 203.
29 M. Choura, M. N. Belgacem and A. Gandini, *Macromolecules*, 1996, **29**, 3839.
30 C. R. Mendonca, P. S. Batista, M. F. de Souza and S. C. Zilio, *Chem. Phys. Lett.*, 2001, **343**, 499.
31 A. R. Renslo, R. D. Weinstein, J. W. Tester and R. L. Danheiser, *J. Org. Chem.*, 1997, **62**, 4530.
32 F. P. Lucien and N. R. Foster, *J. Supercrit. Fluids*, 2000, **17**, 111.
33 S. Smith and L. S. Lasdon, *ORSA J. Comput.*, 1992, **4**, 1.
34 R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrometric Identification of Organic Compounds*, Wiley, New York, 5th edn., 1991.
35 J. Ke, B. X. Han, M. W. George, H. K. Yan and M. Poliakoff, *J. Am. Chem. Soc.*, 2001, **123**, 3661.
36 E. M. Glebov, L. G. Krishtopa, V. Stepanov and L. N. Krasnoperov, *J. Phys. Chem. A*, 2001, **105**, 9427.
37 E. M. Glebov, L. G. Krishtopa, V. Stepanov and L. N. Krasnoperov, *J. Phys. Chem. A*, 2003, **107**, 9249.
38 F. P. Lucien and N. R. Foster, *Ind. Eng. Chem. Res.*, 1996, **35**, 4686.
39 M. W. Lee and W. C. Herndon, *J. Org. Chem.*, 1977, **43**, 518.
40 J. E. Chateauneuf and J. F. Brennecke, *Chem. Rev.*, 1999, **99**, 433.
41 G. P. Jessop and W. Leitner, *Chemical Synthesis using Supercritical Fluids*, Wiley, New York, 1999.
42 R. Span and W. Wagner, *J. Phys. Chem. Ref. Data*, 1996, **26**, 1509.
43 W. Ryoo, S. E. Webber and K. P. Johnston, *Ind. Eng. Chem. Res.*, 2003, **42**, 6348.

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