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# IONIC LIQUIDS IN ORGANIC SYNTHESIS

Room-temperature ionic liquids provide unique environment for organic reactions



**NOVEL MEDIA** Ionic liquids exhibit many favorable features compared with conventional molecular solvents. MERCK PHOTO

[MICHAEL FREEMANTLE, C&EN LONDON](#)

The unique chemical and physical characteristics of ionic liquids are increasingly enticing chemists to explore their use as media for organic synthesis.

"Over the past five years or so, there has been a dramatic increase in the number of publications in the field of ionic liquids," observes Sanjay V. Malhotra, assistant professor of chemistry at [New Jersey Institute of Technology \(NJIT\)](#). "A fairly large percentage of these publications are from organic chemists who have recognized the potential of the liquids as viable media for organic reactions."

Ionic liquids offer numerous advantages over conventional organic solvents for carrying out organic reactions, Malhotra notes. "In many cases, product recovery is easier, catalysts can be recycled, and the ionic liquids can be reused," he says. "In addition, their thermodynamic and kinetic behavior is different. Rates of reaction are often enhanced and selectivity is frequently better."

The use of ionic liquids in organic synthesis could find applications in fields as diverse as pharmaceuticals, fine chemicals, biotechnology, medical sciences, nanotechnology, bioremediation, and environmental and nuclear sciences, Malhotra suggests.

Ionic liquids are low-melting-point salts that have attracted considerable attention recently as greener alternatives to classical environmentally damaging solvents, according to Annie-Claude Gaumont, chemistry professor at the University of Caen, France.

"The interest is mainly due to their peculiar properties such as absence of flammability, lack of measurable vapor pressure, and good ability to dissolve organic, organometallic, and even some inorganic compounds," she says.

Gaumont points out that the most common classes of ionic liquids are alkylammonium salts, alkyipyridinium salts, and N,N'-dialkylimidazolium salts. "Numerous organic, organometallic, and biocatalyzed reactions have been performed in these media," she says.

**THE RANGE** of ionic liquids continues to grow. [Merck](#), in Darmstadt, Germany, now has a

portfolio of several hundred commercially available ionic liquids including salts containing imidazolium, pyridinium, phosphonium, ammonium, or guanidinium cations.

Many commonly used ionic liquids contain the hexafluorophosphate ( $\text{PF}_6^-$ ) anion, which is unstable in water. "To address the hydrolytic instability of ionic liquids with these anions, Merck has developed a range of new hydrophobic anions as replacements for the  $\text{PF}_6^-$  anion," explains Urs Welz-Biermann, project manager for ionic liquids at Merck.

The new anions are tris(perfluoroalkyl)trifluorophosphates--also known as FAP anions--such as  $[(\text{C}_2\text{F}_5)_3\text{PF}_3]^-$ . They form room-temperature ionic liquids with 1-hexyl-3-methylimidazolium, 1-butyl-1-methylpyrrolidinium, and related cations.

"FAP ionic liquids possess high hydrolytic stability," Welz-Biermann says. "Even after boiling in water for five hours, no hydrogen fluoride is formed."

FAP ionic liquids were developed for battery applications but can be used for organic synthesis. They have been used, for example, as solvents for the oxidation of benzyl alcohol to benzaldehyde and benzoic acid using a platinum catalyst, as well as for the oxidation of cinnamyl alcohol to cinnamaldehyde and cinnamic acid using a palladium catalyst.

Frank Endres, professor of extractive metallurgy and electrochemistry at the Technical University of Clausthal, Germany, has shown that FAP ionic liquids can be used as media for the electrosynthesis of conducting polymers. In a recent paper, he and his coworkers reported that air- and water-stable FAP room-temperature ionic liquids are suitable as solvents for the electropolymerization of benzene to form poly(*p*-phenylene) [*Electrochem. Commun.*, **6**, 422 (2004)].

"Poly(*p*-phenylene) is an important conducting polymer as it is well suited for the manufacture of blue polymer light-emitting diodes," Endres notes. "Until now, it has been a challenge to make the polymer electrochemically, as water- and oxygen-free conditions are required. Therefore, only solvents like 18 M sulfuric acid or liquid sulfur dioxide were feasible for its electrosynthesis. We have shown that 1-hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate is well suited for the electropolymerization of benzene under mild conditions."

The group reported in the same paper that another ionic liquid, 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, is also suitable as a solvent for the process.

"Both ionic liquids are Lewis neutral, colorless, odorless, nonhazardous, and not at all aggressive," Endres observes.

Room-temperature ionic liquids with low-nucleophilicity counterions, such as  $\text{PF}_6^-$  and tetrafluoroborate ( $\text{BF}_4^-$ ), constitute unique environments for investigating ionic reactions involving electron-deficient intermediates, in particular carbocations and onium ions, explains [Kenneth K. Laali](#), chemistry professor at Kent State University, in Ohio.

**"IN MANY CASES,** Lewis acids that show limited or no solubility in conventional organic solvents can be dissolved or immobilized in ionic liquids," he notes. "Moreover, these 'designer solvents' appear to be ideal media for employing various classes of onium salts as reagents for synthesis because of their increased solubility in ionic liquids compared with regular organic solvents."

Laali's group is currently exploring the use of ionic liquids as media for fundamentally important electrophilic reactions, many of which are industrially important. The reactions include nitrations, alkylations, acylations, and fluorinations.

Earlier this year, Laali showed that room-temperature ionic liquids can be used as solvents for the acid-catalyzed transfer of an acyl group from a sterically crowded aromatic ketone--acetylmesitylene, for example--to an activated aromatic substrate such as anisole. He carried out the work with Viorel D. Sarca, a visiting scientist from Baldwin Wallace College, Berea, Ohio [*Green Chem.*, **6**, 245 (2004)].

"Both acid-catalyzed transfer-acetylation, which is the reverse of the Friedel-Crafts acylation process, and deacetylation of aromatics have been known for some time," Laali explains. "They typically require the use of large quantities of strong protic or Lewis acids and elevated temperatures. The process described in our paper is a relatively mild, high-yielding alternative

using triflic [trifluoromethanesulfonic] acid as a catalyst and various room-temperature imidazolium-based ionic liquids as solvents in place of regular solvents such as nitromethane and 1,2-dichloroethane. We also showed that the ionic liquids can be recycled."

In the U.K., chemistry professor [Tom Welton](#) at Imperial College London, is attempting to quantify ionic liquid effects to discover how ionic liquids increase or decrease nucleophilicities. "Ionic liquids are more than just a bulk medium," he says. "They are made up of real ions that can have real effects. This is particularly true for their acid-base or hydrogen-bonding properties. It is the specific interactions between the ions present and the solute species that give rise to differences between ionic liquids. Therefore, to choose the best ionic liquid for an organic reaction, it is important to understand what these interactions are."

In a recent paper, Welton and coworkers reported the effect of ionic liquids on a class of charge-neutral nucleophiles [*J. Am. Chem. Soc.*, **126**, 11549 (2004)]. The group compared the reactivities of *n*-butylamine and related amines with methyl *p*-nitrobenzenesulfonate in several ionic liquids with the reactivities in the molecular solvents dichloromethane and acetonitrile. "We showed that the amines are more nucleophilic in the ionic liquids than in the molecular solvents," Welton says.

The group concludes that where the formation of an activated complex from charge-neutral starting materials involves the development of charges, the rates of reaction are accelerated by the use of an ionic liquid. The reaction is further accelerated by the formation of hydrogen bonds between a nucleophile and the ionic liquid's anion. On the other hand, formation of hydrogen bonds between a nucleophile and the ionic liquid's cation reduces its reactivity and "should be avoided," according to the authors.

At the University of Pisa, Italy, chemistry professor Cinzia Chiappe and researcher Daniela Pieraccini have been investigating how organic reactivity is influenced by the polarity of ionic liquids. "We have begun a systematic investigation of the effects of ionic liquids on rate constants of reactions that involve ionic intermediates, including electrophilic additions to double and triple bonds, electrophilic substitutions, and aliphatic nucleophilic substitutions," Chiappe notes.

In a recent study, the two chemists examined the effect of imidazolium ionic liquids on the kinetic behavior of the electrophilic addition of trihalide species-- $\text{Br}_3^-$  and  $\text{ICl}_2^-$ --to alkenes and alkynes. They showed that the addition of  $\text{ICl}_2^-$  is more affected by the ionic liquid structure than the analogous reaction of  $\text{Br}_3^-$ , although both reactions are faster in ionic liquids than in molecular solvents. The results demonstrate the potential of imidazolium cations as hydrogen-bond donors in electrophilic addition reactions and confirm that the capability of the cations to form hydrogen bonds can be exploited to suppress unwanted substitution reactions, Chiappe and Pieraccini conclude.

Ionic liquids can also play a significant role in asymmetric synthesis, Caen's Gaumont says. Three different strategies can be envisioned, she says. First, an ionic liquid can be used as an environmentally friendly solvent to replace a less desirable organic solvent for an asymmetric reaction. Second, the ionic liquid can be employed to stabilize and/or recover a chiral catalyst. Finally, the ionic liquid can act as a chiral promoter [*Tetrahedron: Asymmetry*, **14**, 3081 (2003)].

"Chiral ionic liquids remain limited so far, although they could provide a simple entry into the area of chiral solvents with potential applications in resolution, chromatography, and synthesis," she says.

Last year, Gaumont and coworkers reported the synthesis of multigram quantities of enantiomerically pure chiral ionic liquids based on a thiazolinium cation [*Chem. Commun.*, **2003**, 2914]. "We designed a new family of chiral ionic liquids based on amino alcohols derived from the chiral pool," Gaumont notes. The chiral pool is a term used to include carbohydrates, amino acids, lipids, terpenes, and alkaloids obtained from plant and animal sources, and also synthetic enantiomers that are produced on a large scale.

"Our chiral ionic liquids are simply prepared by the thioacylation of 2-amino alcohols with a dithioester," she explains. "By judicious choice of the anion and the cation, salts with low melting points are obtained. This property makes them potential candidates for new chiral solvents."

The group is currently investigating the use of the chiral ionic liquid salts for the resolution of racemates and for asymmetric catalysis.

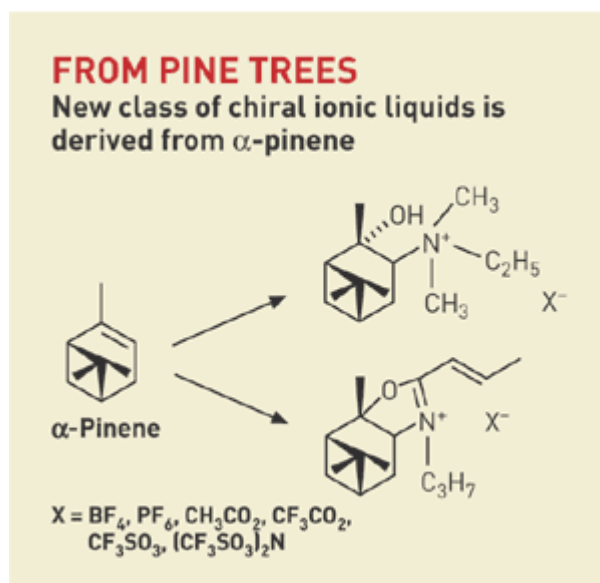
"Surprisingly, very few examples of chiral ionic liquids have been reported in the literature so far," Malhotra remarks. His group has been working on the synthesis of chiral ionic liquids prepared from  $\alpha$ -pinene and their use in asymmetric organic synthesis.

" $\alpha$ -Pinene is a readily available chiral auxiliary obtained from the pine tree," he explains. "A large number of reagents derived from this molecule are known to provide high enantioselectivity in various organic transformations. We have designed a series of chiral ionic liquids based on two  $\alpha$ -pinene chiral cations and a host of anions. We have also shown their effectiveness in providing asymmetric induction in carbon-carbon bond formation through two commonly used and industrially important reactions in organic synthesis." The two reactions are the addition of diethylzinc to aldehydes and the 1,4 conjugate addition of diethylzinc to  $\alpha$ , $\beta$ -unsaturated ketones.

"This is the first synthesis of such chiral ionic liquids from pinene and the first application of chiral ionic liquids in asymmetric organic synthesis," Malhotra says.

A team at the National University of Singapore, led by chemistry professor Loh Teck Peng, has been using ionic liquids and a chiral catalyst for asymmetric transformations. "We have shown that the direct aldol reaction catalyzed by l-proline can be carried out using recycled and reused ionic liquids containing the chiral catalyst without decrease in yields and enantioselectivities," Loh says. The aldol reaction is the acid- or base-catalyzed condensation of a carbonyl compound with the enolate or enol of another to generate a  $\beta$ -hydroxycarbonyl compound (an aldol). Direct catalytic asymmetric aldol reactions employ a small molecule, such as an amino acid, as a chiral catalyst.

Loh's group also has used ionic liquids as solvents for the condensation of three compounds: an amine, an aldehyde, and a compound containing an acidic hydrogen atom attached to a carbon or nitrogen atom. The reaction, known as the Mannich reaction, is catalyzed by acids or bases.



"**WE EXPLOITED** the highly polar nature of ionic liquids to catalyze the three-component asymmetric Mannich reaction using chiral aliphatic amines," Loh explains. "We also found that the reaction using aliphatic aldehydes, which does not work in water or organic solvents, proceeds smoothly in ionic liquids."

Chemistry professor [George W. Kabalka](#) and coworkers at the University of Tennessee, Knoxville, have also been investigating the use of ionic liquids for Mannich reactions. "We studied the Petasis reaction, which is a modern variation of the Mannich reaction involving an amine, a carbonyl compound, and an organoborane," Kabalka says. "The three-component process can be applied to a range of



boronic acids, amines, and carbonyl compounds."

The group recently used Petasis chemistry to generate highly functionalized amines by the reaction of potassium alkynyltrifluoroborates with amines and salicylaldehydes in the presence of benzoic acid and showed that ionic liquids such as butylmethylimidazolium tetrafluoroborate are suitable solvents for the reaction [*Tetrahedron Lett.*, **45**, 729 (2004)].

"The reaction, which does not occur in traditional organic solvents, provides high yields of functionalized propargylamines in ionic liquids," Kabalka says.

Kabalka's team also recently reported that styrene derivatives produce high yields of dimerized products regioselectively in the presence of diazonium salts and a palladium catalyst when allowed to react in ionic liquids [*Tetrahedron Lett.*, **45**, 2775 (2004)].

In Brazil, chemistry professor Jairton Dupont at the Federal University of Rio Grande do Sul has been investigating applications of transition-metal nanoparticles as catalysts in ionic liquids. "Ionic liquids can be regarded as liquid supports for transition-metal catalysts rather than as solvents," he says. They can be used to develop recyclable catalytic systems and enable extra stabilization of the catalysts.

The group has synthesized iridium(0), rhodium(0), platinum(0), and ruthenium(0) nanoparticles with diameters in the 2–3-nm range and a narrow size distribution in imidazolium ionic liquids by the reduction of metal salts with molecular hydrogen or by the controlled decomposition of organometallic compounds in the zero oxidation state.

"We have also prepared palladium(0) nanoparticles 'embedded' in ionic liquids and used them to catalyze the hydrogenation of 1,3-butadiene to 1-butene with excellent selectivity," Dupont says. "These ionic-liquid-supported Pd(0) nanoparticles are also effective recyclable catalysts for carbon-carbon coupling reactions such as the Heck reaction."

Recently, the group reported that Ru(0) nanoparticles dispersed in imidazolium ionic liquids are efficient catalysts for the selective partial hydrogenation of benzene to cyclohexene under mild conditions [*Chem. Eur. J.*, **10**, 3734 (2004)].

Meanwhile, chemistry professor Hermenegildo Garcia at the Technical University of Valencia, Spain, has also been studying the use of transition-metal complexes in imidazolium ionic liquids as reusable catalytic systems. "Our work on ionic liquids has mainly focused on the transformation of successful transition-metal-complex catalysts that work in conventional organic solvents into recoverable and reusable catalytic systems," Garcia says.

The work includes the use of salicylidene-ethylenediamines (also known as salens). The compounds form stable complexes with a variety of transition metals. The Spanish chemists have shown, for example, that carbon dioxide can be inserted into epoxides using chromium or aluminum salen complexes in imidazolium ionic liquids as reusable catalyst systems.

"Imidazolium ionic liquids are good solvents for CO<sub>2</sub> and offer a suitable medium to develop homogeneous, recoverable catalytic systems under CO<sub>2</sub> supercritical conditions," Garcia explains. "There is interest in developing industrial processes to fix CO<sub>2</sub> to help meet the Kyoto protocol and alleviate greenhouse warming. CO<sub>2</sub> can also be a C<sub>1</sub> feedstock for supplying industry with formaldehyde and methanol as an alternative to methane."

In related work, the group showed that catalysts consisting of vanadyl salen complexes covalently anchored to an imidazolium ion are totally miscible with imidazolium ionic liquids, whereas they are insoluble in conventional organic solvents [*Tetrahedron Lett.*, **44**, 6813 (2003)]. "The catalyst shows high activity for the cyanosilylation of aldehydes, remains immobilized in the ionic liquid phase, and can be reused in consecutive runs, avoiding the leaching of vanadium," the authors note.

Another team of Spanish researchers, at the [University of Murcia](#), is using ionic liquids to

**ASYMMETRIC** Malhotra (seated) and his group have synthesized chiral ionic liquids for enantioselective transformations.

COURTESY OF SANJAY MALHOTRA



**ORGANOMETALLIC** Kabalka (from left), postdoc Bollu Venkataiah, and Ph.D. student Gang Dong study reactions involving organoboron compounds using ionic liquids as solvents.

COURTESY OF GEORGE W. KABALKA

immobilize enzymes and supercritical CO<sub>2</sub> to transport reactants and products into and out of the liquids. The team, headed by professor of biochemistry Pedro Lozano, is carrying out the work in collaboration with a group at the University of Rennes, France, led by chemistry professor Michel Vaultier.

"We are working on the design of green enzymatic processes in ionic liquid and supercritical CO<sub>2</sub> biphasic systems," Lozano says. "The excellent physical and chemical properties of ionic liquids, especially their high thermal stability and very low vapor pressure, make the liquids an environmentally attractive alternative to classical organic solvents for the development of green chemistry."

The Lozano and Vaultier teams synthesized five ionic liquids with quaternary ammonium cations containing functional side chains and tested their suitability in supercritical CO<sub>2</sub> biphasic systems for ester synthesis using *Candida antarctica* lipase B (CALB) as the catalyst [*Biotechnol. Prog.*, **20**, 661 (2004)]. "We showed that the ionic liquids are suitable reaction media for the synthesis under low-water conditions and that they act as excellent agents for stabilizing CALB," Lozano notes.

**THE TEAMS** also constructed a continuous biphasic reactor for the CALB-ionic liquid-supercritical CO<sub>2</sub> system and tested it with two ionic liquids for the synthesis of six short-chain alkyl esters. "We operated the bioreactor for aliphatic ester synthesis with excellent activity, selectivity, enantioselectivity, and operational stability," Lozano says.

At NJIT, Malhotra and Ph.D. student Chengdong Zhang have been investigating enzymatic synthesis of peptides from natural amino acids in ionic liquids. They synthesized various dipeptides in hydrophilic and hydrophobic ionic liquids using protease immobilized on a diatomaceous-earth matrix. "We found that by immobilizing the enzyme, its stability increased and the enzyme maintained higher catalytic activity in ionic liquids compared with the free enzyme," Zhang says. "We also showed that the enzyme maintains higher activity in hydrophobic ionic liquids."

The synthesis of peptides in ionic liquids is just one example of many recent explorations in the newly found but largely unexplored continent of ionic liquids, Malhotra observes.

"The rapid growth of interest in ionic liquids is mainly limited to people in academia and national laboratories," he cautions. "There is a lot of skepticism among industrial chemists, probably because our understanding of these materials is limited. Before we see industrial chemists enthusiastically involved in exploring the field, a lot of work has to be done. We need information on the toxicity and safety of these materials and their effect on the environment, as well as an assessment of their life cycles. Also, we need cost analyses compared with existing technologies. In addition, it is important to develop a good database of all the information available on ionic liquids. Unless we have all this information, the growth will be limited to a few sectors only."

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