

## Smart Solvents

Much of the work in our laboratory has for many years focused on applications of tunable solvents. Tunable solvents are solvents where a small change in some variable causes a large change in properties. Supercritical fluids are tunable solvents, where for example a small change in pressure gives a big change in density which results in an enormous change in solubilities. Nearcritical water and gas-expanded liquids are also tunable solvents. However, another emerging class of novel solvents are switchable or “smart” solvents which respond to some impetus (light, heat, pH, etc.) to have a step change in properties. A smart solvent that can be switched reversibly from a liquid with one set of properties to another that has very different properties, upon command.

Solvents are vital to many industrial reaction processes. They affect reaction rates, chemical equilibria, and the efficiency of heat and mass transfer. The literature is filled with reports of the development of novel solvents such as supercritical fluids, gas-expanded liquids, ionic liquids, and perfluorinated solvents. The choice of the right solvent is critical not only for a successful chemical transformation but also for the subsequent separation and purification processes. The reactions of organic substrates with inorganic salts are particularly challenging because they traditionally need either a dipolar, aprotic solvent or a biphasic mixture of solvents combined with a phase-transfer catalyst. The latter approach is limited because the phase transfer catalysts are difficult to separate and recycle. The former option, dipolar, aprotic solvents, is expensive (in terms of money and energy) because such solvents are very difficult to remove by distillation. Dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA), for example, have boiling points of 189, 153 and 235°C, respectively. In addition, it is rarely practical to recycle and reuse such solvents.

Indeed, the pharmaceutical industry has emphasized the need for a dipolar, aprotic replacement for DMSO. We have developed a separable and recyclable dipolar, aprotic solvent, piperylene sulfone (PS), which combines the excellent reaction medium properties of dipolar, aprotic solvents with the “volatility” of low boiling solvents necessary for facile isolation and purification of products. While piperylene sulfone is not volatile itself, it is readily converted (or “switched”) into volatile species. These volatile species can be collected elsewhere and recombined back into piperylene sulfone for reuse. It is therefore an example of a switchable solvent.

Piperylene sulfone is a liquid at room temperature with a melting point of -12°C. It is easily synthesized by a reaction of trans-1,3-pentadiene (trans-piperylene) and sulfur dioxide. At temperatures greater than 100°C it cleanly and efficiently decomposes back to gaseous trans-1,3-pentadiene (bp 42 °C) and sulfur dioxide (bp -10 °C) (Fig. 1). Piperylene sulfone is a close mimic of DMSO in terms of its solvent properties. Properties of solvents are

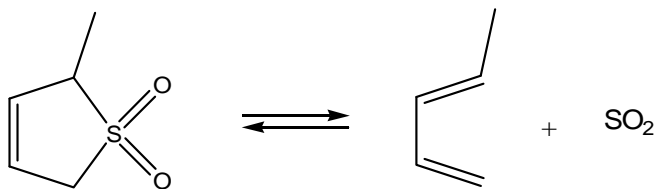


Figure 1. Reversible decomposition of PS

usually characterized by the Kamlet–Taft parameters ( $\pi^*$ ,  $\alpha$  and  $\beta$ ), the ET(30) parameter, and the dielectric constant ( $\epsilon$ ), and for the most part quite those of PS are similar to those of DMSO. Further, to demonstrate that piperylene sulfone can serve as a solvent for chemical processes, PS was tested as a medium for anionic nucleophilic substitution reactions and in general gave similar rates when a trace of water was added. The effect of the water could be attributed to the difference in hydrogen bond accepting ability, as indicated by the slightly different  $\beta$ -values of the two solvents. We conjecture that DMSO solvates the cation more strongly than the PS facilitating greater ion-pair separation between the cation and the anion thus enhancing the nucleophilicity of the anion

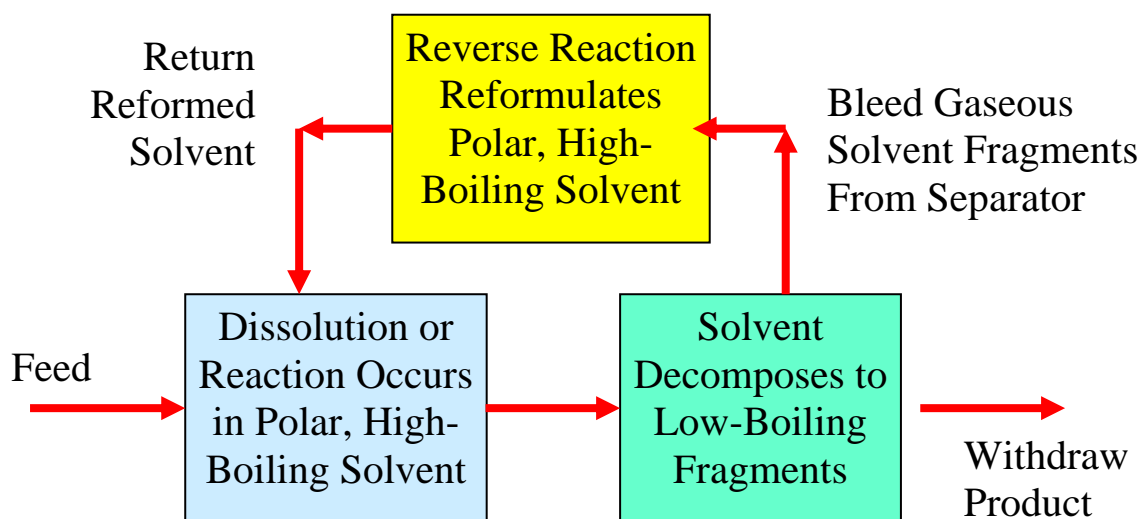


Figure 2. Example of an extraction or reaction with product purification and solvent recycle and reuse using PS.

A complete process (Fig. 2), taking advantage of PS's switchability, would include a feed (reactants), the reaction to products (where PS is serving as an inert solvent), a decomposition stage (where PS is converted into gaseous trans-1,3-pentadiene and SO<sub>2</sub> and products are removed), and a reformation stage (where the gases are reconverted back into PS). Other processes where PS has been used as a recyclable solvent are oxidation reactions and asymmetric transfer hydrogenation reactions.

Chemical production processes often involve multiple reaction and separation steps, and the type of solvent that is optimum for a particular step may be different from the one needed in the next step. The solvent is therefore usually removed after each step and a new solvent added in preparation for the next, significantly adding to the economic cost and environmental impact of the process. This cumbersome procedure would be unnecessary if a solvent's properties could be adjusted for the following step while still in the reaction vessel, enabling the same solvent to be used for several consecutive reaction

or separation steps. Moderate changes in temperature and pressure are incapable of triggering significant changes in the properties of conventional solvents.

We have devised such a system, in which a non-ionic liquid (an alcohol and an amine base) converts to an ionic liquid (a salt in liquid form) upon exposure to an atmosphere of carbon dioxide, and then reverts back to its non-ionic form when exposed to nitrogen or argon gas. Such switchable solvents should facilitate organic syntheses and separations by eliminating the need to remove and replace solvents after each reaction step. Our reversible ionic liquids can change the nature and properties of a solvent under very mild conditions.

We found that exposure of a 1:1 mixture of the two non-ionic liquids, namely DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) and 1-hexanol, to gaseous CO<sub>2</sub> at one atmosphere and at room temperature causes conversion of the liquid mixture to an ionic liquid (Fig. 1a, b). This is readily converted back into a nonionic liquid by bubbling N<sub>2</sub> or argon through the liquid at room temperature or, for a more rapid reaction, at 50°C. As shown in Figure 3 to the right, a, Protonation of DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) (a) in the presence of an alcohol and carbon dioxide is reversed when CO<sub>2</sub> is removed. (b) Polarity switching in the reaction shown in a, in which CO<sub>2</sub> causes a nonpolar liquid (shown in blue) mixture of hexanol and DBU to change over one hour into a polar, ionic liquid (shown in red); nitrogen gas reverses the process by stripping out CO<sub>2</sub> from the reaction. (c) The different polarity of each liquid under the two conditions is illustrated by the miscibility of decane with the hexanol/DBU mixture under nitrogen, before exposure to CO<sub>2</sub>: however, decane separates out once the mixture becomes polar in the presence of CO<sub>2</sub>. Again, N<sub>2</sub> reverses the process.

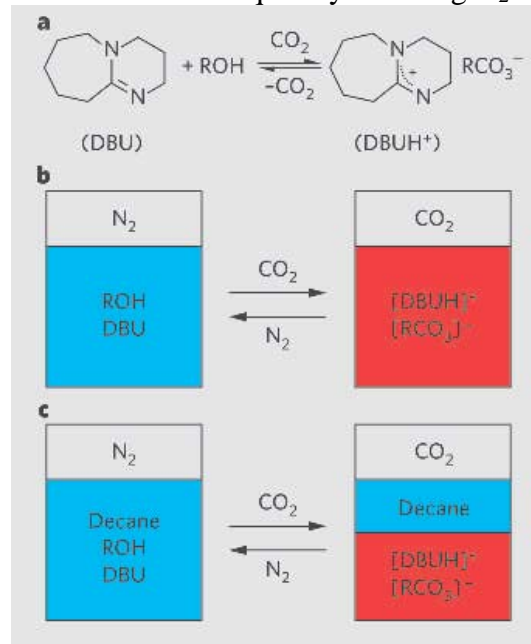


Figure 3. Mechanism of reversible ionic liquid formation

These changes are demonstrated by chemical shifts in key protons, as revealed by <sup>1</sup>H-NMR spectroscopy, and by solvatochromic measurement of the polarity of the solvent before and after exposure to CO<sub>2</sub>. Our non-ionic liquid is as nonpolar as chloroform, according to measurements using Nile Red as solvatochromic dye (see supplementary information), whereas the liquid under CO<sub>2</sub> is as polar as dimethylformamide or propanoic acid. The polarity changes in this switchable solvent system are demonstrated by testing the solubility of decane, a nonpolar compound, in each liquid: it is miscible with the liquid under N<sub>2</sub> but not with that under CO<sub>2</sub> (Fig. 1c). Thus N<sub>2</sub> and CO<sub>2</sub> at 1 bar can be used as triggers of miscibility and immiscibility, respectively.

Many other reversible ionic liquids have been demonstrated. Guanidine and an alcohol also react with CO<sub>2</sub> at ambient temperature and pressure to form a reversible ionic liquid (Figure 4), and this too can be readily reversed by either an inert gas sparge or by modest heating. The reversible ionic liquids based on guanidine offer many opportunities for tuning, as there are five different substituent groups which can be used to tune properties.

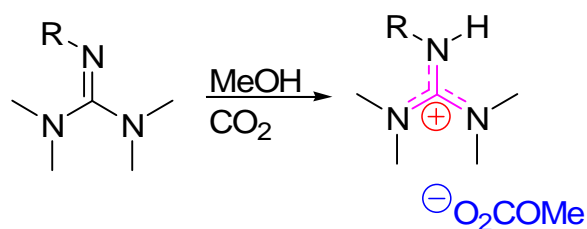


Figure 4. Guanidine-based reversible ionic liquids.

Finally we have also developed a series of single-component reversible ionic liquids (Figure 5). These too react with CO<sub>2</sub> at ambient temperature and pressure to form a reversible ionic liquid and can also be readily reversed by either an inert gas sparge or by modest heating. There is an important processing advantage in avoiding the feed and recycle of two chemicals. The inclusion of the Si moiety offers two advantages: it renders the ionic liquid less viscous and also improves the electron distribution for the reversibility function.

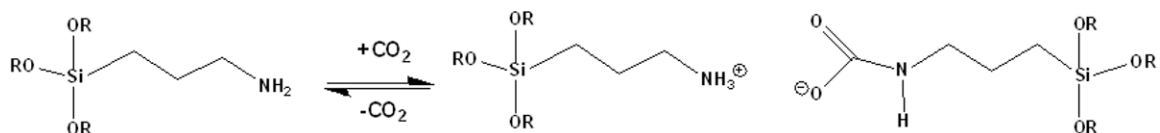


Figure 5. Example of a single-component reversible ionic liquid