

## Smart Solvents for Benign Separations

Solvent management is the key to chemical processes, which invariably involve both reactions and separations. Solvents bring reactants (and catalysts) together and facilitate purification processes. The goal always is for solvents that yield economical and environmentally benign processes.

A classic difficulty in chemical synthesis is the reaction of an organic substrate with an inorganic salt. Typically, a phase transfer catalyst (PTC) such as a quaternary ammonium salt is utilized.<sup>1</sup> After the reaction, the PTC must be separated from the product; this is not a trivial task. Another option is to use solvents that tend to dissolve both organic and inorganic species such as dimethyl sulfoxide (DMSO) and ionic liquids (ILs); both of which provide for a difficult separation.

DMSO has a high boiling point; therefore, distillation is costly and removing the last traces can be extremely difficult. Further if the product is thermally labile, its use is completely precluded. DMSO is also miscible with water and most organic solvents making liquid extraction an unlikely alternative. As a result, we seek to design solvents that remain highly polar—in order to dissolve both organic and inorganic substrates for reaction – but somehow change properties for product isolation – by means of a built-in “switch”. For example if we could “order” an involatile solvent to suddenly become volatile, it could be easily removed. This would occur if the solvent molecule underwent scission into two gas molecules.

Ideally, a solvent should have a number of properties for use as a reaction medium, including the following:

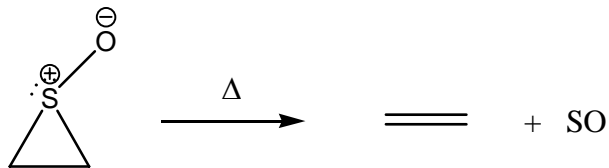
- Useable liquid range (preferably room temperature)
- Chemical stability for the reaction (i.e. the solvent does not react)
- Dissolve both organics and salts

For separation, the solvent should also possess:

- Decomposition at moderate conditions with reasonable rate
- Decomposition products have very low or very high vapor pressure
- Easy recombination to form solvent

Solvents that fulfill the above requirements do not yet exist. Therefore, the concept of a built-in switch, in which molecules possess a “handle” that can be used to switch properties, appears particularly attractive. Switchable molecules respond to some user input, such as heat, resulting in the change of some property, thus directly impacting the overall system. This project entails product design of such novel switchable molecules, using structure-property relationships, and aims at demonstrating their potential applications.

Thiirane oxide is a cyclic analog to DMSO and is anticipated to possess similar solvent properties. Unlike DMSO, thiirane oxide undergoes thermal decomposition at temperatures above 100 °C to form ethylene and sulfur monoxide<sup>2,3</sup> as shown in Figure 1. Herein lie the unique properties of thiirane oxide: first, it allows a switch in polarity from a DMSO analog to a small unsaturated hydrocarbon: second, the solvent can be eliminated under moderate conditions for easy product isolation. The aim of this work is to demonstrate the concept of “switchable” or “smart” solvents which combine high reaction performances with easy separation upon application of an external stimulus.



**Figure 1.** Decomposition of thiirane oxide to ethylene and sulfur monoxide.

Thiirane oxide is reported in the literature and can be easily synthesized from ethylene sulfide<sup>4</sup>. Although there is some mechanistic controversy, the decomposition of thiirane oxide is believed to occur via a cheletropic mechanism which extrudes one molecule of SO and one molecule of ethylene. By the principle of microscopic reversibility, the back-reaction, to reform thiirane oxide is possible. However, the rapid disproportionation of SO<sup>5</sup> potentially renders the solvent reformation reaction impractical. This would classify thiirane oxide as a cleavable or “sacrificial” solvent. This solvent constitutes proof-of-concept, but would have limited applications.

In order to establish thiirane oxide as a DMSO analog, solvent parameters were measured and compared to DMSO (Table 1). The  $E_T30$  value is based on the UV absorbance of Reichardt’s dye (2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl) phenolate dihydrate, C<sub>41</sub>H<sub>29</sub>NO 2H<sub>2</sub>O).

	DMSO	Thiirane Oxide
$\alpha$	0	0
$\beta$	0.76	0.74
$\pi^*$	1.00	1.02
$E_T30$	189 kJ/mol	191 kJ/mol
$\epsilon$	46.7	45

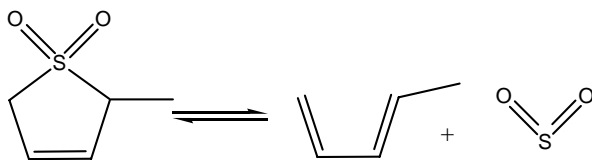
**Table 1.** DMSO and Thiirane oxide solvent parameters.

$\alpha$  for DMSO and thiirane oxide are both 0. Finally, we measured a value of 45 for the dielectric constant,  $\epsilon$ , of thiirane oxide, and a value of 46.7 for DMSO, which matches the literature value.

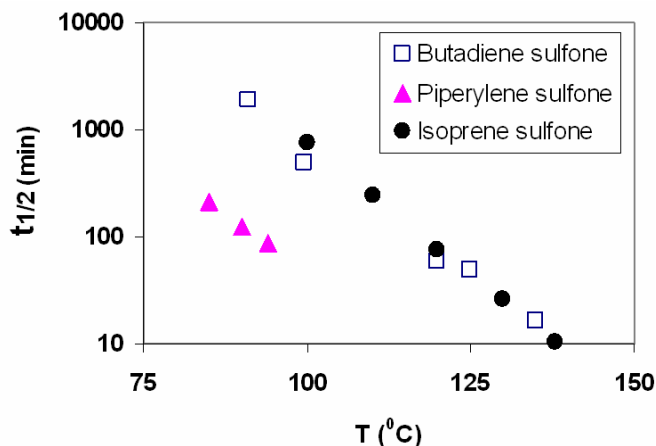
Another measure of a solvent’s strength is its Kamlet-Taft parameters<sup>6</sup>  $\alpha$ ,  $\beta$ , and  $\pi^*$ . The  $\pi^*$  value is a measure of dipolarity/polarizability and is based on the shift in UV absorbance of *N,N* dimethyl-*p*-nitroaniline. DMSO is defined to have a value of 1.00. We measured a value of 1.02 for thiirane oxide. The H-bond accepting ability  $\beta$  is based on the UV shift in absorbance of *p*-nitroaniline. We measured values of 0.76 for DMSO and 0.74 for thiirane oxide. The H-bond donating ability

Another retro-cheletropic reactions which in fact can be reversible is given by sulfone decomposition. We are studying piperylene sulfone, see Figure 2 below, as a second generation switchable solvent. The sulfone of piperylene was selected for several reasons – a larger liquid

range, a better reaction equilibrium, and faster decomposition rates. Piperylene sulfone is a liquid at room temperature (mp =  $\sim -12$  °C), in contrast to the higher-melting sulfones made from butadiene (mp = 64-65 °C), isoprene (mp = 63-64 °C), and dimethylbutadiene (mp = 134-136 °C).<sup>7</sup> Further, piperylene sulfone has a reasonable decomposition rate at moderate temperatures.<sup>8</sup> Figure 3 shows that the piperylene sulfone decomposition occurs both more rapidly and at a lower temperature than other sulfones.



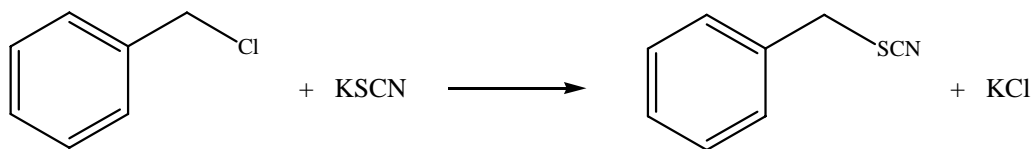
**Figure 2.** Reversible synthesis of piperylene sulfone from piperylene and SO<sub>2</sub>.



**Figure 3.** Thermal decomposition of sulfones<sup>27</sup>

Upon decomposition, piperylene sulfone releases two products: 1,3-pentadiene and sulfur dioxide via a similar pericyclic mechanism as thiirane oxide. 1,3-pentadiene may polymerize, but much less readily than ethylene. In fact, the polymerization has been successfully depressed for this application. Further, the sulfur dioxide is a stable gas that can be recycled along with the 1,3-pentadiene to re-form the solvent. This reversible process is not only feasible, it is economically and ecologically advantageous.

The key to the use of thiirane oxide or any switchable solvent is the separation by decomposition. We have demonstrated the post-reaction decomposition and removal of the reaction products, using nucleophilic substitution as a proof-of-principle to test the switchable solvents on a “real world” type reaction, Figure 4. The benzyl chloride reaction with inorganic salts, such as potassium cyanide, potassium thiocyanate, and sodium azide to form benzyl derivatives is being studied.



**Figure 4.** Nucleophilic substitution of benzyl chloride with thiocyanate ion.

A potential process for such a reversible solvent is shown below in Figure 5. The reaction is run in the highly polar liquid solvent. When the reaction is complete, heating causes dissociation of the solvent into gaseous species and the product stream is purified. The solvent fragments are then separated and reformed to new solvent. Note that the process is virtually completely self-contained with only reactants coming in and only products exiting – the hallmark of “green chemistry.”

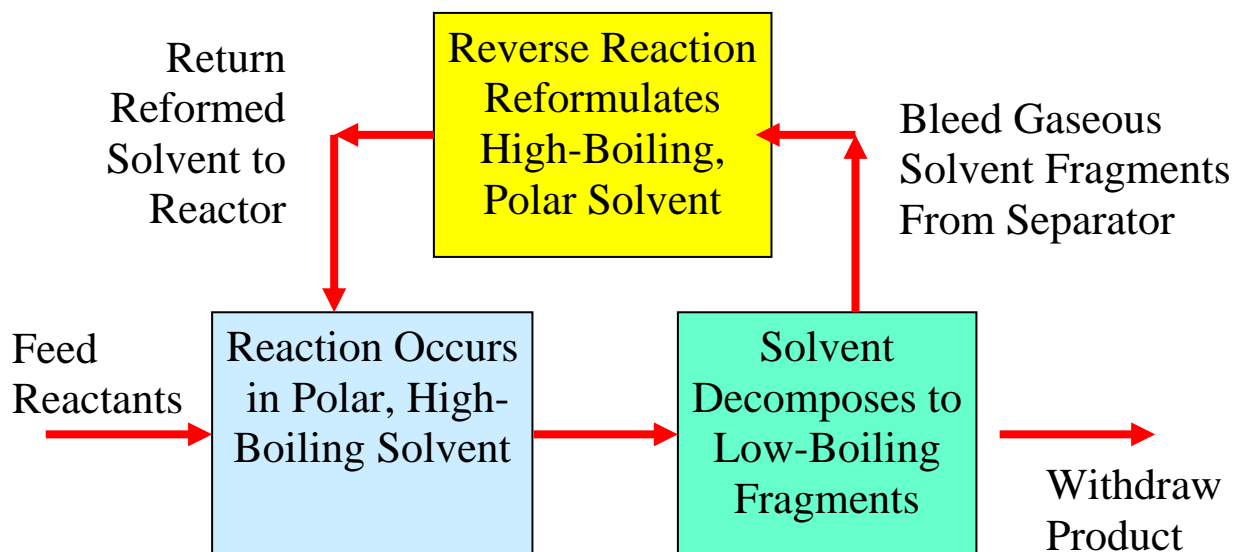
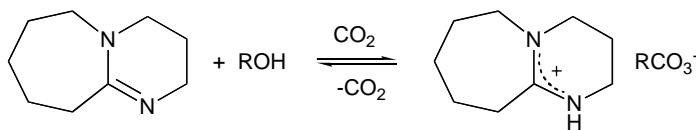


Figure 5. Process Diagram for Synthesis with a Recyclable Smart Solvent

A third type of smart solvent is a reversible ionic liquid. Ionic liquids (ILs), salts that are liquid at (or near) room temperature, have gained tremendous attention over the last several years. Besides being “super” solvents, ionic liquids have non-detectable vapor pressure making them even more attractive. Unfortunately, one of their major drawbacks for using ILs as a reaction media lies in the separation. It often requires great efforts to isolate the products from ionic liquid media due to difficulties associated with 1) distillation – negligible vapor pressure; 2) precipitation and crystallization – solid salt formation and 3) liquid extraction – water sensitivity of ILs..

The concept of “switchable” or “smart” ionic liquids is a powerful alternative to ease the separation step and remediate the current drawbacks. In conjunction with Dr. Philip Jessop at Queen’s University in Ontario, Canada, we have developed a solvent that switches from a molecular liquid (non-ionic) into an IL upon simple exposure to CO<sub>2</sub> gas, and then turns back to the molecular liquid upon N<sub>2</sub> or Ar gas bubbling. Figure 6 illustrates this conversion where exposing a 1:1 mixture of DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) and an alcohol to carbon dioxide will *reversibly* form an ionic liquid.



**Figure 6.** Reaction of DBU, alcohol, and CO<sub>2</sub> to form ionic liquid.

This polar-to-nonpolar switchable ionic liquid was recently reported for the reversible reaction of a 1:1 mixture of DBU and 1-hexanol with CO<sub>2</sub><sup>9</sup>. Spectroscopic determination yielded an E<sub>T</sub>30 value of 184 kJ / mol for the

DBU liquid under N<sub>2</sub> pressure and a value of 222 kJ / mol under CO<sub>2</sub> pressure for the IL. In other words, the polarity of the solvent is switched from nonpolar, comparable to chloroform, to

a polar solvent, comparable to dimethylformamide or propanoic acid. Characterization of the DBU ionic liquid by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and conductivity measurements have confirmed the  $[\text{DBUH}]^+[\text{RCO}_3]^-$  salt.

Separation techniques that allow efficient product isolation from ionic liquid media are still lacking. For instance, liquid extractions yield ionic liquid-contaminated products, which often require additional purification steps. Our concept eliminates the need for strenuous separation techniques altogether by “switching off” the polarity—or solvation power—of the ionic liquid allowing trivial separation. Theoretically, one could run a one step of a reaction in the less polar molecular liquid, and then convert to the ionic liquid for a subsequent step or easier separation. In all fairness, while our pioneering work using DBU opened new avenues, much more needs to be accomplished to transfer this technology from conceptual to laboratory scale, and ultimately, to industrial processes.

Often syntheses – especially of chiral molecules – require dozens of chemical steps in sequence, such as to protect, then react, then deprotect, etc. For example, Vitamin B<sub>12</sub> is made in 45 steps. Often there is a different solvent for each step, as some require polar solvents and some nonpolar. This means that at each step we put in a new solvent, and then afterwards, remove it, with all the expense and pollution involved. We propose solvents that can be changed (reversibly) from polar to nonpolar, eliminating these frequent solvent removal steps.

The types of solvents envisioned here, especially if recyclable, would have tremendous potential to transform processing, eliminating enormous cost and waste involved in multiple solvent steps.

## REFERENCES

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