# Piperylene sulfone: a labile and recyclable DMSO substitute

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**The properties and uses of piperylene sulfone as a new, recyclable dipolar, aprotic solvent for conducting organic reactions are presented.**

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. These include ionic liquids,[1] supercritical fluids,[2] gas-expanded liquids,[3] and perfluorinated solvents.[4] The choice of the right solvent is critical not only for a successful chemical transformation but also for the subsequent separation and purification processes.[5] 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.[6] The latter approach is limited because the phase transfer catalysts are difficult to separate and recycle.[2c,3e] 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.[7]

We now report a separable and recyclable dipolar, aprotic solvent, piperylene sulfone (PS),[8] 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 re-use. It is therefore an example of a switchable solvent.[3,9] We also report the rates of anionic nucleophilic substitution reactions in both piperylene sulfone and DMSO.

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).[10]

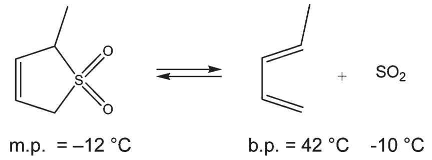

**Fig. 1** Piperylene sulfone reversible reaction to *trans*-1,3-pentadiene and sulfur dioxide.

Piperylene sulfone is a close mimic of DMSO in terms of its solvent properties. Properties of solvents are usually characterized by the Kamlet–Taft parameters ($\pi^*$, $\alpha$ and $\beta$)[11] the $E_T(30)$ parameter developed by Reichardt *et al.*,[12] and the dielectric constant ($\varepsilon$).[13] Each of these parameters has now been measured for piperylene sulfone and compared to the corresponding values for DMSO. These values, along with other pertinent physical constants (bp, mp, dipole moment) are summarized in Table 1. The only significant difference between the two solvents is the β-value; which indicates that DMSO is better than piperylene sulfone at accepting hydrogen bonds.

To demonstrate that piperylene sulfone can serve as a solvent for chemical processes, the new solvent was tested as a medium for anionic nucleophilic substitution reactions. The second-order rate constants for the reaction of benzyl chloride with a variety of anionic nucleophiles were studied in both piperylene sulfone and DMSO at 40 °C (Table 2).[14] It was discovered early in this research that traces of water added to the piperylene sulfone enhanced the rate of reaction. Indeed, no reaction was observed with potassium cyanide in dry piperylene sulfone (see Table 2). Only in the presence of trace amounts of water (0.1 wt%) did the reaction take place. As a consequence, studies were conducted in dry DMSO, DMSO containing 3 wt% water, dry piperylene sulfone, and piperylene sulfone containing from 0.1 to 10 wt% water.[15] Since most of the nucleophilic salts were only partially soluble in all the solvent systems studied the reactions were

**Table 1** Comparison of solvent properties for DMSO and PS at 25 °C

| Properties | DMSO | PS |
|---|---|---|
| Boiling point/°C | 51 (7 Torr) | 85 (7 Torr) |
| Melting point/°C | 16–19 | −12 |
| Dipole moment (D) | 4.27 | 5.32 |
| $\alpha$ | 0 | 0 |
| $\beta$ | 0.76 | 0.46 |
| $\pi^*$ | 1.00 | 0.87 |
| $E_T(30)$/kJ mol$^{-1}$ | 189.0 | 189.0 |
| $\varepsilon$ | 46.7 | 42.6 |

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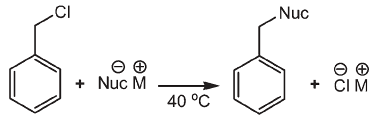
**Table 2** Second-order rate constants for the nucleophilic displacement in DMSO, DMSO with 3% water, PS and PS with 1% water at 40 °C



| Second-order rate constant, $k \times 10^4$/l mol$^{-1}$ s$^{-1}$ | | | | |
|---|---|---|---|---|
| NuM | DMSO | DMSO (3% $H_2O$) | PS | PS[a] (1% $H_2O$) |
| PTA[b] | >1800 | >1800 | >1800 | >1800 |
| SPTC[c] | >1800 | >1800 | >1800 | >1800 |
| KSCN | 1.4 ± 0.1 | 1.7 ± 0.1 | 2.1 ± 0.1 | 2.3 ± 0.2 |
| KOAc | 3.4 ± 0.1 | 11.0 ± 0.1 | 0.013 ± 0.004 | 0.19 ± 0.1 |
| KCN | 5.8 ± 0.1 | 17 ± 0.1 | —[d] | 0.15 ± 0.01 |
| $CsN_3$ | 69 ± 0.8 | 16.7 ± 5 | 2.4 ± 0.9 | 5.8 ± 0.9 |
| CsOAc | 22.7 ± 0.6 | 16.4 ± 0.9 | 0.35 ± 0.04 | 0.35 ± 0.06 |

[a] Only the rate constants for piperylene sulfone containing 1 wt% water are presented since the rates of reaction changed by only a factor of two for the entire water range studied. [b] Potassium thioacetate. [c] Sodium pyrrolidinedithiocarbamate. [d] No reaction.

heterogeneous and stirring was required. In general, the reactions are quantitative and the rates are slower in the piperylene sulfone solvent systems compared with the DMSO counterparts. This latter observation could be attributed to the difference in hydrogen bond accepting ability, as indicated by the β-values of the two solvents. It is conjectured 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.[16]

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 $SO_2$ and products are removed), and a reformation stage (where the gases are reconverted back into PS).[17]

In conclusion, piperylene sulfone has been shown to be a good medium for reactions of anionic nucleophiles with organic electrophiles. It is a dipolar, aprotic solvent which mimics the properties of DMSO. However, unlike DMSO, because of a facile and reversible reaction between *trans*-piperylene and sulfur dioxide, product isolation and solvent recycle are easily accomplished. Finally we recognize that PS cannot be substituted for DMSO in all reaction classes. We are currently investigating the breath of reactions which can be conducted in PS.

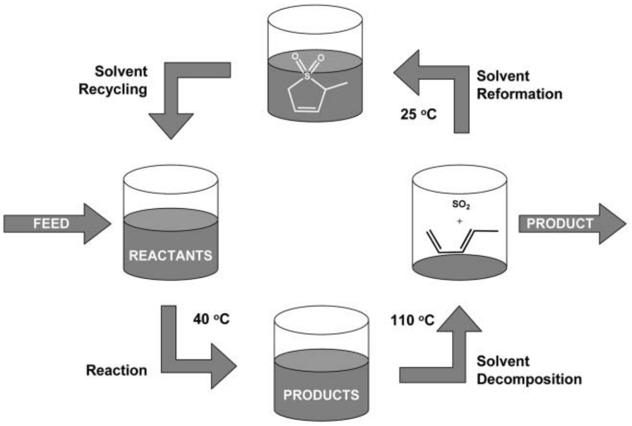


**Fig. 2** The process can be divided in four stages. Only one arrow comes in, the feed (reactants), and one arrow comes out, the products.

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10 In a thermogravimetric analysis (TGA) of piperylene sulfone the sample was heated at a rate of 5 °C min$^{-1}$ up to 120 °C and held constant at 120 °C for 30 min. No residual mass was left after 2500 s. The TGA also showed that, while piperylene sulfone is relatively stable up to 80 °C, its decomposition rate increases dramatically at 100 °C.

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14 *Standard procedure for the kinetics of reaction of benzyl chloride with anionic nucleophiles*: A reaction vessel was charged with 0.3 mmol of the anionic nucleophile salt and 1 mL of solvent. The mixture was stirred at 40 °C for 30 min and then benzyl chloride (0.15 mmol) was added. Samples were taken at regular intervals of 10 min over 1 h period and quenched by dissolution in toluene. The concentrations of reactants and products were quantified by GC/FID analysis. The errors on the rate constant values were calculated as the standard deviation from the average value of multiple repetitions.

15 It is conjectured that, as in the case of solid–liquid phase transfer catalysis, small quantities of water enhance the rate of reactions in heterogeneous systems by facilitating a more rapid dissolution of the salts in the solvent phase (ref. 6, pp. 113–119).

16 Ref. 6, p. 85.

17 *Reaction–decomposition–recovery–reformation procedure*: KSCN (1.5 mmol) and PS (5 mL) were placed in a vessel (40 °C) connected to another vessel containing liquid $SO_2$ (−30 °C). After 30 min of stirring benzyl chloride (0.75 mmol) was added to the first vessel. When all BnCl had reacted, the temperature of the first vessel was raised to 110 °C to begin the decomposition process. PS decomposes into *trans*-piperylene and $SO_2$ which condense into the second vessel; this mixture was stirred for 48 h. The residue of the first vessel was washed with water and then extracted with diethyl ether. Filtration over a short pad of silica gel and subsequent evaporation of the solvent, afforded pure benzyl thiocyanate in 96% yield (this preparative process was also repeated with the nucleophilic salts potassium thioacetate and sodium pyrrolidinedithiocarbamate to afford 97 and 99% isolated yields of products, respectively). The excess $SO_2$ was degassed from the second vessel and aqueous/organic back extraction work-up afforded pure PS in 87% yield. This percentage recovery is due to minor losses because of the small scale of the laboratory procedure – simple surface adhesion or adsorption accounts for most of these losses. Were the process scaled up it is anticipated that the percent recovery would be nearly quantitative.