Solvents as Phase-transfer Catalysts in Reactions initiated by Solid Bases

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For reactions initiated by solid bases (*e.g.* potassium hydroxide, sodium hydroxide, potassium carbonate), solvents (*e.g.* water, Bu^{t}OH, polyethylene glycol, MeCN, Me_2SO) may act as solid-liquid phase transfer catalysts (*e.g.* for C–H, N–H or O–H alkylation by alkyl halides, or epoxidation by sulfonium or sulfoxonium salts).

Deprotonation using hydroxide ions in liquid–liquid phase-transfer catalysis (LLPTC)[1] or using solid hydroxides in DMF[2] or in Me_2SO,[3] provide convenient and economical alternatives to condensation or substitution reactions initiated by stronger bases such as sodamide or butyl lithium.[4] In a more recent advance, reactions in the 'absence' of solvent are of great current interest because they provide cleaner manufacturing technology, and reactions without solvents are safer in rapid laboratory scale reactions heated in microwave ovens.[5]

While there have been several detailed mechanistic studies of reactions initiated by hydroxides in LLPTC,[1] less is known about the mechanism of solid–liquid phase-transfer catalysis (SLPTC).[6,7] It is usually assumed that reactions involve a heterogeneous reaction between the solid base and the substrate,[3,6,7] possibly followed by an interfacial reaction between deprotonated substrate and a PT catalyst.[6]

However, there is some extensive mechanistic evidence pertaining to reactions of solid bases. For the epoxidation of aldehydes by sulfonium or sulfoxonium salts in the presence of solid bases, the stabilised S-ylide **1** can be observed spectroscopically on the surface of the base,[7a] and the generalisation was made that there is a direct reaction between the sulfonium (or sulfoxonium) salt and the solid base even for less stable ylides [eqn. (1)].[7b]

$$\underset{\mathbf{2}}{Me_3SI} + KOH \xrightarrow{\text{Heterogeneous}} \underset{\mathbf{3}}{Me_2\overset{+}{S}\text{–}\overset{-}{C}H_2} + H_2O + KI \qquad (1)$$

In contrast, we have found from kinetic investigations of competing processes that an alternative heterogeneous component of the reaction is proton abstraction from solvent (*e.g.* Me_2SO, MeCN) by the solid base [eqn. (2)], followed by a homogeneous reaction between the conjugate base of the solvent and the sulfonium salt to give the S-ylide [eqn. (3)].

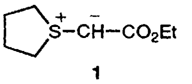
$$KOH(s) + MeCN \xrightarrow{\text{Heterogeneous}} K^+\,\overset{-}{C}H_2CN + H_2O \qquad (2)$$

$$\overset{-}{C}H_2CN + Me_3SI \xrightarrow{\text{Homogeneous}} Me_2\overset{+}{S}\text{–}\overset{-}{C}H_2 + MeCN \qquad (3)$$

Scheme 1 Acetonitrile acting as a solid–liquid phase-transfer catalyst

According to this mechanism [eqns. (2) and (3)] the solvent acts as a SLPTC agent, because it aids the reaction by transporting an organic-soluble base from the surface of the solid inorganic base to the liquid phase. Typical phase-transfer catalysts such as tetrabutyl ammonium salts[6,8] and aliquat[9] may also be effective in SLPTC, but many solid–liquid reactions involving solid bases are successful even if conventional PTC agents are absent.[2,3,7] In these latter cases solvent may act as SLPTC [eqns. (2) and (3)] and consideration of this mechanism should aid the optimisation of reaction conditions for these syntheses.

Our general conclusions are based on detailed kinetic studies of the reaction of furfural (**4**, 0.02 mol) with trimethyl sulfonium iodide (Me_3SI, **2**, 0.02 mol) and potassium hydroxide pellets (KOH/H_2O, 0.04 mol), magnetically stirred in MeCN (40 ml, containing 0.1 ml of added water) at 60 °C. Products were mainly the epoxide **5**,[7] along with small amounts of furfuryl alcohol, furoic acid (Cannizzaro reaction) and the acrylonitrile derivative **6**.[10] Rates depended on the condition of the KOH (whole or crushed pellets), on the amount of water added initially, and on the rate of stirring. Reproducible kinetic results (±10%) were obtained by independent researchers (SJL and AHL, working years apart) in well-stirred solutions (not sufficiently vigorous to crush the pellets).



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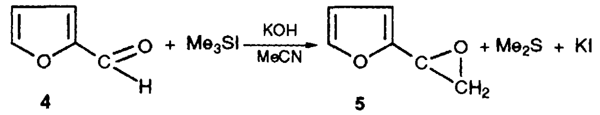
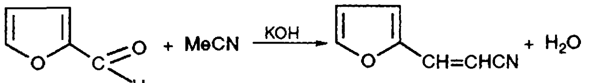
The acrylonitrile coproduct **6** provides for the reaction mechanism important clues, which are not available from studies of alkylations:[6] (*a*) a direct link between epoxidaton [eqn. (4)] and the competing acrylonitrile formation [eqn. (5)]



4 **5** (4)



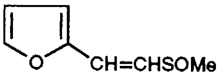
6 (5)

can be established. Bases strong enough to initiate epoxidation in the presence of Me_3SI also initiate acrylonitrile formation in the absence of Me_3SI. Conversely, with weaker bases including some hydroxides, when epoxidation does not occur, formation of **6** does not occur either (Table 1). The common step in successful reactions is presumably deprotonation of the acetonitrile to its conjugate base [eqn (2)][4a,10] (*b*) Reaction between the conjugate base and Me_3SI, [eqn. (3)] is required to explain the following observations: (*i*) in the absence of Me_3SI, the acrylonitrile product **6** is formed about five times faster than the epoxide, but **6** is only a minor product of the reaction (<5%) when the MeCN solvent is saturated with Me_3SI (solubility 18 mass% at 60–65 °C); (*ii*) the rate of formation of **6** in the absence of Me_3SI is unaffected by the addition of other iodides (KI or Bu_4NI), so a general electrostatic effect of salt is unlikely to be the cause of inhibition of formation of **6** by Me_3SI. (*c*) The homogeneous nature of the reaction shown in eqn. (3) is demonstrated by the observation that a fivefold dilution of the reaction mixture

Table 1 Comparison of various bases for epoxidation [eqn. (4)] and acrylonitrile formation [eqn (5)]

Base	Epoxidation reaction	Acrylonitrile reaction
KOH/H_2O[a]	Yes[b,c]	Yes[b]
NaOH[a]	Yes[b]	Yes[b]
K_2CO_3[d]	No reaction[c]	No reaction[b]
$Ca(OH)_2$[e]	No reaction[b]	No reaction[b]
$Ba(OH)_2$[f]	No[c,g]	No[b,h]

[a] Pellets. [b] This work. [c] Ref. 7*b*. [d] BDH (99%). [e] BDH (96%). [f] BDH (98%). [g] The Cannizzaro reaction probably occurred—see footnote *h*. [h] Although no acrylonitrile product was formed, the Cannizzaro reaction occurred.



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leads to a fivefold decrease in rate, and an increase in the yield of **6** from <10% after 50% reaction to 40% at the end of the reaction. In further support: (*i*) an interfacial reaction would be accelerated by tetrabutylammonium ions,[6] in contrast to the above result for Bu_4NI; (*ii*) if the MeCN is replaced by solvents such as diisopropyl ether in which Me_3SI is insoluble, the yield of epoxide **5** is negligible, and the Cannizzaro reaction then dominates.

Acidities in Me_2SO are helpful guides to relative acidities in other aprotic media.[10] Water has a pK_a of 31.2 in Me_2SO, and the pK_a of Me_3S^+ is 18.2,[11] so there is a strong driving force for eqn. (1). Other relevant pK_as are: MeCN (31.3), Bu^tOH (32.2), and Me_2SO (35).[11] The pK_a values indicate that these solvents should be deprotonated by KOH in an analogous way to acetonitrile [eqn. (2)], and we have obtained the adduct **7** by reaction between KOH and furfural in Me_2SO.

As expected from the above data, Me_2SO and Bu^tOH are suitable solvents for the epoxidation of furfural [yield 70%, eqn. (4)]. Other similar reactions have been carried out using Bu^tOH.[12] For alkylations involving weakly acidic C–H, N–H, or O–H bonds using KOH in Me_2SO, it is reasonable to propose that the active base is $MeSOCH_2^-$ and that the reaction occurs by solvent acting as solid–liquid phase-transfer catalyst.

The new mechanism, illustrated in Scheme 1 for MeCN as catalyst, offers new opportunities for the optimisation of syntheses. For example, it implies that instead of typical quaternary salts as catalysts, weakly acidic phase-transfer catalysts such as polyethylene glycols should be investigated further. Also the new mechanism may explain some of the non-thermal effects observed under microwave heating.[5]

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