

Ion Pairing and Reactivity of Alkali Metal Alkoxides

K. J. Msayib and C. I. F. Watt

Chemistry Department, University of Manchester, Manchester M13 9PL

1 Introduction

Almost twenty years ago, two important volumes edited by Michael Szwarc¹ reviewed the chemistry of ions and ion pairs and emphasized their role in many organic reactions. At that time it was already clear that states of solvation or association could affect the reactivity of ionic reagents in spectacular ways. In the intervening years, organic chemists generally have become aware of these phenomena, and indeed, have used them to good effect in some important synthetic and industrial processes. Szwarc's editorial preface remains a valuable introduction for all who seek an understanding of this particular subject.

In this article, some properties and reactions of alkoxides of relatively simple alcohols are examined, with a view to re-emphasizing the importance of taking ion pairing into account in considerations of reactivity of these common reagents. We follow Szwarc in noting that the role of solvent and counterion can only be fully appreciated by comparison with behaviour of the anions in the gas phase where their properties are determined solely by their molecular structure, momentum, and vibronic state. Where possible, solution behaviour will be compared with that in the gas phase.

Computational studies on alkoxides indicate that there is a hyperconjugative interaction (Figure 1) between the lone pairs on oxygen and substituents of the alcohol carbon.² This is an α -(C-R) bond weakening effect; the calculations on methanol and methoxide give C-H bond dissociation energies of 397.9 and 310.6 kJ mol⁻¹, respectively. As will be seen later, this has important consequences for the reactivity of alkoxides as compared to alcohols. The effect is attenuated by the presence of alkali metal cations, and sodium and potassium methoxides have corresponding bond dissociation energies of 337.4 and 330.7 kJ mol⁻¹.



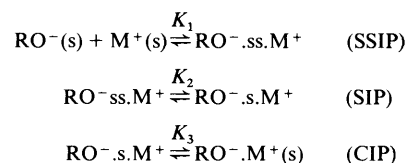
Figure 1 Hyperconjugation in alkoxides.

Despite the hyperconjugative interaction, charge is largely localized on the oxygen, and solvation at the anionic centre is expected to be similar to that of fluoride or hydroxide. These are the smallest and hardest of anions and interact strongly with

solvent electrostatically, and by hydrogen bonding in protic solvents. Interaction with counterion may also occur, and the nature of that ion and its solvation must be considered in any description of ion-pairing behaviour. In the alkali metal series, ionic radii increase and hardness decreases from Li⁺ to Cs⁺. On electrostatic considerations alone, Li⁺ is expected to interact most strongly with either solvent or with the alkoxide anion. In any particular solvent, degrees of association between anion and cation will reflect a competition between the alkoxide and one or more solvent molecules for coordination with the cation.

2 Association and Aggregation

Ion pairs, according to Bjerrum, exist when the electrostatic attraction between ions of opposite charge is large enough to overcome the random thermal motion of the ions. When the distances between ions are large compared with the size of the ions or solvent molecules, solvent can be treated as a dielectric continuum and the equilibrium constant for formation of such ion pairs (K_{ip}) is related to their charge, solvent dielectric constant, and temperature by the Bjerrum relationship.³ Spectral properties of the ions should be the same as those at infinite dilution. The assumptions of this relationship break down in high dielectric solvents, and alternative definitions of ion pairs based on the relationships of solvent molecules and ions have been developed. These are the familiar solvent-separated (SSIP), solvent-shared (SIP), and contact ion-pairs (CIP) as shown in Scheme 1. A relationship derived by Fuoss, also based on electrostatic considerations, allows calculation of an association constant (K_a) for formation of the last type. For ions of high charge and solvents of low dielectric constant, often the case for alkoxides in organic solvents, $K_a > K_{ip}$. In terms of Scheme 1, K_{ip} might be identified with K_1 , and then $K_a = K_{ip} \cdot K_2 \cdot K_3$. For alkoxide solutions, the theory usually does no better than provide a qualitative framework for discussion. Certainly, no current theory deals quantitatively with all ion-pair types, and non-electrostatic effects, most importantly hydrogen bonding, have to be superimposed on coulombic interactions. Measures of association are, however, available from experiment.



Scheme 1 Ion pairing in alkoxide solutions.

None of the various ion-paired entities migrate in an electrical field but rather reorientate themselves as an electrical dipole. Conductivity experiments, therefore, provide a measure of an overall association constant, K_{ass} , related to the constants in the scheme by equation 1.

$$K_{ass} = \frac{[\text{RO}^-\cdot\text{M}^+(s)] + [\text{RO}^-\cdot\text{s}\cdot\text{M}^+] + [\text{RO}^-\cdot\text{ss}\cdot\text{M}^+]}{[\text{RO}^-(s)][\text{M}^+(s)]} \quad (1)$$
$$K_{ass} = K_1(1 + K_2 + K_2 \cdot K_3)$$

Table 1 collects the best values of ion association constants (K_{ass}) determined by conductivity studies⁴ on solutions of alkali metal

Dr. K. J. Msayib

B.Sc. 1977 University of Basra
Ph.D. 1987 University College, Cardiff
Post-doctoral Research 1989 University of Manchester
Currently: seeking employment.

Dr. C. I. F. Watt

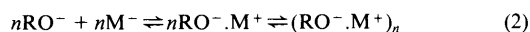
B.Sc. 1966 University of Edinburgh
Ph.D. 1971 Carnegie-Mellon University
Post-doctoral Research 1972 University of Stirling
Lecturer in Chemistry 1976 University of Manchester
Currently: Senior Lecturer in Chemistry at University of Manchester.

Table 1 Ion pairing constants of alkali metal alkoxides in alcohol solution

Cation	K_{ass} (25 °C) in			
	CH ₃ OH	C ₂ H ₅ OH	n-C ₃ H ₇ OH	i-C ₃ H ₇ OH
Li ⁺	12.1	212	1207	large
Na ⁺	7.5	102	672	19200
K ⁺	0	90	762	18000
Rb ⁺	3	93	858	17300
Cs ⁺	4.5	121	992	15200

alkoxides in their parent alcohols. The constants increase rapidly with alcohol molecular weight, and reflect not so much an increased affinity of the higher alkoxides for the cation but rather a decreased ability of the alcohol to solvate the cations, with dielectric constants decreasing from 32.6 for methanol to 18.3 for isopropyl alcohol. Constants decrease as cation size increases, although the relationship is not always smooth. In methanol for example, which is the most structured of the solvents, the ion pairing passes through a minimum when the cation is potassium. For solutions in propanols, the association constants are so large that 0.1 M alkoxide solutions are more than 90% ion pairs.

In the higher alcohols, the ions are not only paired but the ion pairs themselves form aggregates (equation 2).



Degrees of aggregation have been determined ebulliometrically for some of the same alkoxide/alcohol solutions.⁵ Trends in apparent extent of aggregation (n_{app}), defined as the ratio of the experimental value of the molecular weight (determined by the boiling point elevation of solutions of the alkoxide) to the theoretical molecular weight of the monomeric salt, make clear the relationship between n_{app} and solvent dielectric constant. For both water and methanol, values (see Table 2) are close to the limit (0.5) expected for complete dissociation for all the alkoxides at concentrations below 0.5 M, and are in accord with conductivity measurements. For the sodium and potassium alkoxides, n_{app} increases as dielectric constant of the alcohol decreases, indicating the formation of largely monomeric ion pairs in the higher alcohols. The lithium alkoxides behave more erratically, with an indication of formation of higher aggregates in the least polar solvents. In t-butyl alcohol, the apparent degree of association changes from 2.08 at low concentration (0.06 molal) to 3.98 at 0.59 molal.

The effects of added crowns on these associations have also been studied.⁶ For the t-butyl alcohol solutions, where ion pairing and aggregation are most pronounced, the effects are not clear cut. With potassium t-butoxide solutions, the best matched crowns (18-crown-5 or 15-crown-5)⁷ seem to yield both 1:1 and 2:1 crown ether:ion pair complexes, rather than separated alkoxide and complexed cation. With lithium t-butoxide, none of the readily available crowns (18-crown-6, 15-crown-5, or 12-crown-4) give any evidence of complex formation.

The differences in behaviour between hydrogen-bonding pro-

Table 2 Apparent degree of association of alkali metal alkoxides in ca.0.3 molal alcohol solutions

ROH	ϵ (25 °C)	n_{app}		
		Li ⁺	Na ⁺	K ⁺
H ₂ O	78.5	0.62	0.55	0.55
CH ₃ OH	32.6	0.62	0.57	0.55
C ₂ H ₅ OH	24.3	0.70	0.66	0.65
n-C ₃ H ₇ OH	20.1	0.94	0.83	0.82
i-C ₃ H ₇ OH	18.3	1.41	0.84	0.84
t-C ₄ H ₉ OH	12.1	3.76	0.84	0.69

tic solvents and aprotic dipolar media and the importance of hydrogen bonding in solvation of the alkoxides in protic solvents is dramatically illustrated by comparable studies on alkoxide solutions in dimethylsulfoxide which has a dielectric constant ($\epsilon = 37.7$) larger than methanol. Ion pairing constants for solutions of lithium, sodium, potassium, and caesium t-butoxides in dimethylsulfoxide, determined conductometrically by Exner and Steiner⁸ are 10^8 , 10^6 , 270, and 200 respectively, decreasing as cationic radius increases. Addition of the alcohol to the dimethylsulfoxide alkoxide solutions yields an increase of conductivity which peaks at the stoichiometric amount, showing that it can dissociate ion pairs; the heat of solution of t-butyl alcohol in 0.1M potassium t-butoxide in dimethylsulfoxide⁹ is $-16.7 \text{ kJ mol}^{-1}$. The data are nicely consistent with the formation of the hydrogen bonded homoconjugate anion (equation 3). Specific hydrogen bonding of this type must also contribute greatly to the solvation of alkoxides in protic solvents, but is less easily observed therein.

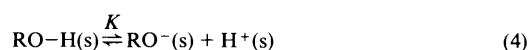


Methoxides are even more strongly associated than t-butoxides in dimethylsulfoxide, reflecting both reduced steric effects and increased localization of charge. As with the alcohol solutions, higher aggregates may form. Cryoscopic measurements¹⁰ show that 0.5M potassium t-butoxide is largely dimeric while lithium t-butoxide is tetrameric even at very low concentrations.

Differences between protic and aprotic media are also evident in rates of proton transfers. Rate constants for transfers between oxygen and nitrogen bases in DMSO¹¹ are well below expected diffusion-controlled limits. Brønsted correlations yield low values of β and primary kinetic isotope effects are small. Clearly, unlike the case in alcoholic medium, the actual proton-transfer step is not rate limiting, and it has been suggested that desolvation is involved in the rate-limiting step.

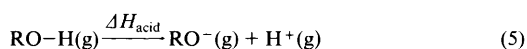
3 Acidities

Since the measurement of solution acidities and the construction of acidity scales has been discussed extensively elsewhere,¹² this aspect of alcohol behaviour will be touched on only briefly. The solution acidities of alcohols are strongly solvent dependent. Acidity constants defined in equation 4 include contributions from solvation of the neutral alcohol, proton, and the anion.



In any particular solvent, solvation of the proton is constant, and in most cases, solvation of the neutral acid is much smaller than of the anion. Alcohols are about $10^{1.5}$ times more acidic in water than in dimethylsulfoxide, reflecting the importance of hydrogen bonding in the solvation of the localized negative charge of the anion. The order of acidities also differs in these solvents. In water, the order is MeOH ($\text{p}K_{\text{a}} = 15.5$) > EtOH ($\text{p}K_{\text{a}} \sim 15.9$) \sim H₂O ($\text{p}K_{\text{a}} = 15.75$), with the propanols and butanols being too weakly acidic to measure. In dimethylsulfoxide, the order is MeOH ($\text{p}K_{\text{a}} = 29$) > isopropyl alcohol ($\text{p}K_{\text{a}} = 30.25$) > H₂O ($\text{p}K_{\text{a}} = 31.2$) > t-butyl alcohol ($\text{p}K_{\text{a}} = 32.2$). In neither case is the effect of structural variation in accord with the expected electronic effects of alkyl substitution. These anomalies only disappear when comparisons are made using gas phase data, indicating that their origin lies in solvation and aggregation effects. Indeed, comparison of gas and solution acidities has been used to quantify the extent of differential solvation.

Gas phase acid-base properties, shown quantitatively by heats of deprotonation (equation 5), are now measured by a variety of experiments, all of which use mass spectrometric methods to detect and quantify negative ions.



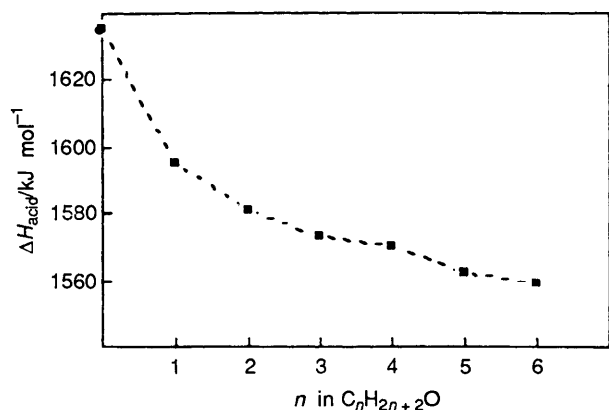
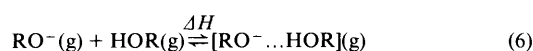


Figure 2 Dependence of gas-phase ΔH_{acid} on chain length for straight-chain alcohols.

The thermochemical data have most recently been collected by Lias *et al.*¹³ Figure 2 presents selected data for the series of saturated straight-chain alcohols from methanol to hexanol ($\Delta H_{\text{acid}} = 1595$ and 1559 kJ mol^{-1} respectively), and includes water ($\Delta H_{\text{acid}} = 1635$ kJ mol^{-1}), which in the gas phase is a weaker acid than any of the alcohols. In the alcohol series, heats of deprotonation decrease with molecular weight, a trend rationalized in terms of the ability of even tightly bound electrons to respond to charge by an induced dipole mechanism. These polarizability effects over-ride a small inductive effect associated with alkyl substitution which is expected to act in the acid weakening sense. Although the experimental uncertainties are about ± 10 kJ mol^{-1} , the smaller fractional increases in molecular weight (and numbers of electrons) between the higher alcohols seem to match nicely the changes of acidity between these members of the series.

For sets of isomers, gas-phase heats of deprotonation do not depend on whether the hydroxyl is attached to primary, secondary, or tertiary carbon. In the $\text{C}_4\text{H}_9\text{OH}$ isomers for example, the values are 1570 (n-butyl alcohol), 1568 (isobutyl alcohol), 1566 (s-butyl alcohol), and 1567 (t-butyl alcohol) kJ mol^{-1} , overlapping well within experimental uncertainty. For wider comparison, toluene has $\Delta H_{\text{acid}} = 1600$ kJ mol^{-1} and is deprotonated by hydroxide in the gas phase. Dimethylsulfoxide, CH_3SOCH_3 , has $\Delta H_{\text{acid}} = 1564$ kJ mol^{-1} , and has about the same gas-phase acidity as the butanols. Space does not allow a discussion of substituent effects,¹⁴ but the stabilizing effects of delocalization of charge in the oxy-anions are worth noting. Aldehydes or ketones, which yield enolates, have heats of deprotonation some 30 to 40 kJ mol^{-1} less than those of alcohols with the same numbers of heavy atoms. For carboxylic acids, where charge is delocalized onto a second oxygen, the value is between 105 and 115 kJ mol^{-1} lower.

Experiments in which effects of complexing the alkoxides with one or more neutral molecules in the gas phase provide an important link between solution and gas-phase measurements. With alcohols, hydrogen-bonded anions of the form $[\text{ROH} \cdots \text{OR}]$ are formed exothermically, equation 6, with enthalpies lying between -80 and -100 kJ mol^{-1} . For the complexes of methoxide with water, methanol, ethanol, propanol, and t-butyl alcohol, the enthalpies are -100 , -91 , -85 , -83 , and -79 kJ mol^{-1} respectively, showing that the complexes have decreasing stability with increasing molecular weight. The rates of proton transfer between alkoxides and alcohols have also been measured, and are appreciably lower than collision rates.¹⁵



These homoconjugate ions may be regarded as monosolvated alkoxides. Larger clusters are formed, and the anion stabiliza-

tion continues as the clusters grow in size, although the initial complex formation has much the largest effect. Similar experiments have examined gas-phase equilibria for clustering of anions and cations with dimethylsulfoxide¹⁶ to provide the link between gas and solution properties in aprotic dipolar solvents. Interactions here are electrostatic, and since the dipole in dimethylsulfoxide is largely on the $>\text{S}^+-\text{O}^-$ group, cations which can approach the accessible oxygen, are more stabilized than iso-electronic anions which are hindered by the methyl groups from approaching the $>\text{S}^+$ end of the dipole. Interestingly, in comparing the complexation of chloride by water or dimethylsulfoxide, it is dimethylsulfoxide which binds more strongly as the first solvent molecule. Unfortunately, data are not available for fluoride or for methoxide since these deprotonate dimethylsulfoxide. For larger clusters, however, water provides the better solvation. In both water and dimethylsulfoxide, smaller anions are better solvated than large, but the decrease with size is less pronounced with dimethylsulfoxide.

4 Reactivities of Alkoxides in Solution

The reactivities of solutions of anionic reagents in organic solvents generally show dependences on concentration and on the nature of cation. Alkoxides are no exception and we now examine some recent examples of effects on rates and on product distributions. Reactivity variations have been taken to reflect differences in ion pairing and differential reactivity of ion paired and 'free' anions, but the interpretation of the concentration dependence is not always clear cut since ionic strength changes can also contribute to rate changes. With this proviso, the framework for attempted quantitative treatments is usually that of Acree, formulated shortly after the turn of the century.¹⁷ Scheme 2 presents the formalism, and defines the constants k_i and k_p as characterizing the reactions of free and paired ions respectively.

$$v = k_{\text{obs}} \cdot c \quad (7)$$

$$k_{\text{obs}} = ak_i + (1-a)k_p \quad (8)$$

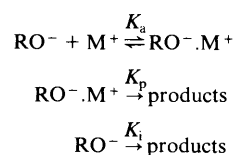
$$K_a = (1-a)/(a^2 \cdot c \cdot \gamma_{\pm}^2) \quad (9)$$

For a reaction rate given by equation 7 where c is total alkoxide concentration, the first-order rate constant is related to k_i and k_p by equation 8 where a is the degree of dissociation of the ion pairs. The law of mass action relates a to association constant, K_a , total concentration of alkoxide, c , and the mean activity coefficient of the dissociated ions, γ_{\pm} , by equation 9.

This simple scheme recognizes only two kinetically active forms of alkoxide, and strictly identifies them with the conducting and non-conducting states with no distinction made between tight and loose ion pairs of various types. There is no reason, however, to expect that the kinetically distinguishable populations¹⁸ should exactly match those determined by conductometric methods, since some ion pairs, possibly solvent separated species, may have reactivities approaching those of free ions in particular reactions.

The kinetic effects of ion pairing are apparent even in the simplest of alkoxide reactions. In the classical Williamson ether synthesis, alkoxides displace halide from appropriate alkyl halides.

Sodium ethoxide, for example, reacts cleanly with benzyl chloride to yield the ethyl benzyl ether. When rates of disappearance of benzyl chloride are measured under pseudo-first-order



Scheme 2 General scheme for reaction of alkoxides in solution.

conditions with large excesses of sodium ethoxide, $[\text{EtONa}]$, second-order rate constants, k_2 , are obtained by dividing the pseudo-first-order rate constants by the ethoxide concentration. These 'constants' are not independent¹⁹ of total ethoxide concentration.

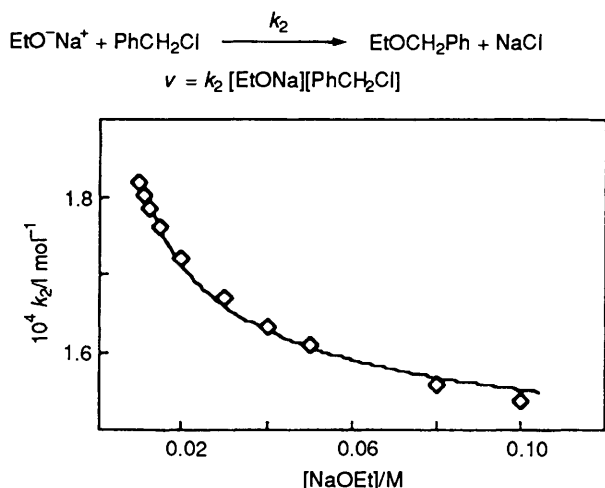


Figure 3 Dependence of second-order rate constants for reaction of benzyl chloride with sodium ethoxide in ethanol with total ethoxide concentration at 60°C.

Instead, as shown in Figure 3, rate constants increase by nearly 40% for the tenfold dilution from 0.1 M to 0.01 M sodium ethoxide. The data are accommodated within the general Acree treatment, Scheme 2, and treatment of the rate data can provide values for k_i and k_p . In this displacement at saturated carbon, the dissociated ions are more reactive than the ion pairs with $k_i/k_p = 3.2$ at 60°C. The data may also be treated to extract a value of K_a and, in this particular experiment, the rate measurements suggest that alkoxide is more associated than its electrical properties would indicate. Allowance must also be made for ion pairs which do not contribute to conductivity, but have the same reactivity as 'free ions'.

Measurements of this type on a series of ring-substituted benzyl halides have yielded values of k_i and k_p which establish separate Hammett type correlations.²⁰ These point to different mechanistic pathways for the substitutions with $\rho = +2.2$ for the free ions and $\rho = -0.6$ for the paired species.

For other simple reactions in which ethoxide behaves as nucleophile, different dependences upon concentration are found.

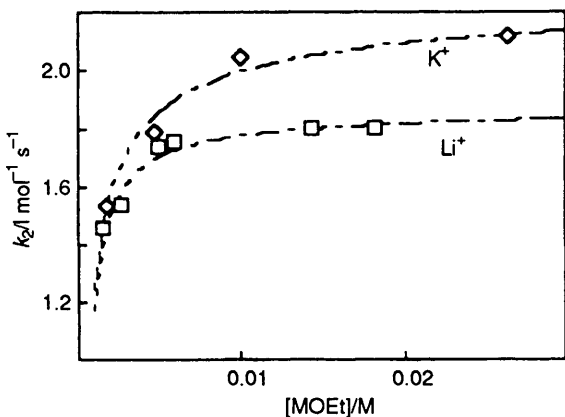
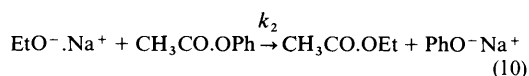
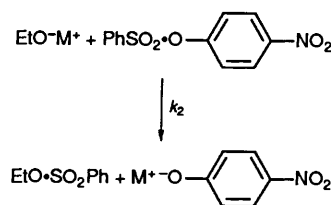


Figure 4 Dependence of second-order rate constants for reaction of ethoxides with phenyl acetate at 25°C.

In the reaction of ethoxide with phenyl acetate, equation 10, a nucleophilic displacement at acyl carbon by a $B_{AC}2$ mechanism, there is an increase in apparent second-order rate constant as alkoxide concentrations increase,²¹ as shown in Figure 4. The effect is least pronounced for lithium ethoxide. Potassium and caesium ethoxides show larger effects with almost 40% rate enhancement over the concentration range studied. Both cations catalyse the reaction and thus must bind more strongly to transition state than to alkoxides. The greater effect of potassium probably reflects its weaker binding to ethoxide rather than any special affinity with the transition state. In terms of competing reactions of paired and free alkoxides, the ion pairs are more reactive than the free ions, with $k_i/k_p = 0.47$ for the lithium ethoxide and $k_i/k_p = 0.34$ for the potassium ethoxide.



For nucleophilic displacements by ethoxide at sulfur and phosphorus, cases have been found where particular alkali metal cations inhibit reaction, while others show catalytic activity. In reaction of *p*-nitrophenyl benzenesulfonate with alkali metal ethoxides,²² equation 11, rates are dependent on both cation and total ethoxide concentration, as shown in Figure 5.

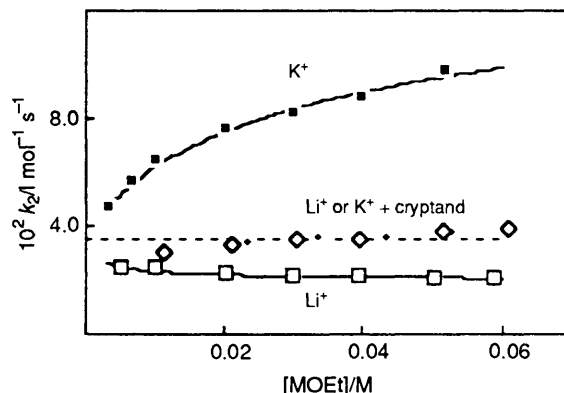


Figure 5 Dependence of second-order rate constants for reaction of alkali metal ethoxides with *p*-nitrophenyl benzenesulfonate at 25°C.

The concentration dependence for KOEt shows a strong upward curvature while that for LiOEt shows a smaller downward curvature. Both types of behaviour can be treated as described above, in terms of differential reactivity of ion pairs and 'free' ethoxide anions. In the case of LiOEt, $k_i/k_p = 1.61$, but for KOEt, the ion pairs are more reactive with $k_i/k_p = 0.21$. The description is entirely consistent with the finding that excess of the appropriate added cryptands, [2.2.2] for potassium and [2.1.1] for lithium ethoxide, almost completely suppresses concentration and cation dependences. Furthermore, added potassium salts enhance reaction, while added lithium salts decrease the rate.

Kinetic measurements alone yield information on the composition of the transition stage but not its structure. Leaving-group substituent effects in this reaction have been correlated with σ^+ constants²³ yielding similar ρ -values for KOEt(3.0), LiOEt(3.1), and EtO^- (3.4), implying that metal cations do not significantly alter the extent of S.O bond cleavage in the transition state. Catalysis by cation must follow from greater stabilization of transition state relative to ground state on binding to the cation.

Association constants given in Table 1 clearly indicate the greater ground-state stabilization by co-ordination of the localized alkoxide charge to lithium rather than potassium. In the displacement transition state, charge is expected to be more diffuse, being shared by two S—O sites, and schemes may be proposed which rationalize the better transition-state binding to potassium.

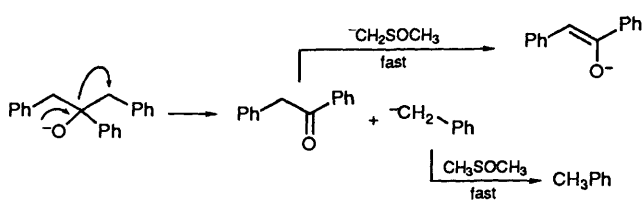
The reactivities of ions and ion pairs in these intermolecular reactions in hydroxylic solvent are relatively close. The fact that the 'free' alkoxide anions are well solvated by hydrogen bonding will tend to level their reactivities in the same way as acidities are levelled in basic media. In solvents where such levelling is absent, much larger variations in reactivity are to be expected and this is most beautifully shown in some intramolecular reactions of alkoxides in which charge is less localized in the transition state than in the alkoxide.

5 Intramolecular Reactions

5.1 Fragmentations

In Lewis acid–base formalism, simple alkoxides are complexes of ketones or aldehydes with very strongly basic hydride or alkyl anions, and indeed many practical syntheses of alcohols involve just such additions. Simple t-alkoxides are thermally quite stable, but fragmentation does occur in solution on prolonged exposure to high temperatures. Products are often consistent with a cleavage of a bond to one of the hydrocarbon groups yielding a carbanion and ketone followed by proton transfers. When steric compression of ring strain is relieved as in the case of tri-(1-adamantyl)methanol²⁴ or 1-phenyl-cyclopropanol²⁵ then reactions proceed under more moderate conditions. The importance of ion-pairing effects was first mooted by Cram²⁶ who studied fragmentations in which a benzylic anion was the formal leaving group in collapse of the alkoxide. In alcoholic solvents, reactions required $T > 90^\circ\text{C}$ and many hours for appreciable conversions. In dimethylsulfoxide, time and temperature were dramatically reduced, and a dependence on counterion was found with rates of fragmentation increasing by about three orders of magnitude on changing from lithium to potassium salts. Such strong dependence is in accord with the association constants found by Exner, provided the ion pairs are almost completely unreactive. More recent experiments have provided a quantitative support for the hypothesis.

Fragmentation of alkali metal salts of 1,2,3-triphenylpropan-2-ol²⁷ in dimethylsulfoxide solution yields toluene and the enolate of deoxy-benzoin. The reaction is easily followed by monitoring the UV-absorption of the enolate, and the effect of variation of cation, concentration, and substituent have all been determined. The kinetic effects of substituents in the terminal phenyl groups point to high development of negative charge at the departing benzyl group, supporting a reaction scheme involving anionic cleavage. Use of isotopically labelled substrates and solvent shows that the benzyl anion does not abstract a proton directly from the ketone; rather the departing benzyl anion deprotonates a dimethylsulfoxide molecule, and the dimethyl anion deprotonates the ketone. Secondary kinetic isotope effects for the benzylic hydrogens are large indicating rate-limiting formation of the benzyl anion, and Scheme 3 accommodates the data.



Scheme 3 Fragmentation of 1,2,3-triphenyl-2-propoxide.

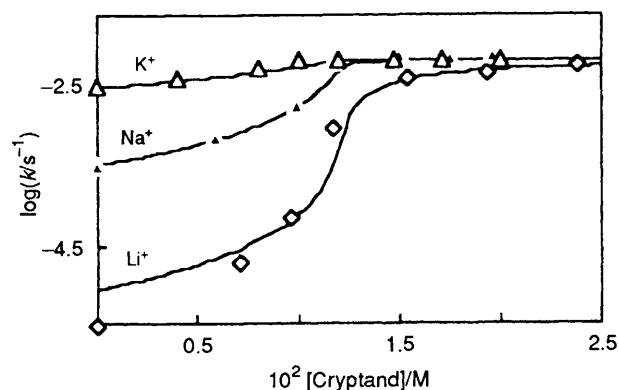


Figure 6 Dependence of rates of fragmentation of 0.012 M solutions of salts of 1,2,3-triphenylpropanol on addition of [2.2.2]cryptand (Na and K salts) or [2.1.1]cryptand (Li salts).

As with the fragmentations examined by Cram, the rates increase in the ratios 1:120:1300 ratio for alkoxides solutions as the 0.01 M lithium, sodium, and potassium salts. Figure 6 shows the effects of added cryptands ([2.2.2] for the potassium and sodium salts, and [2.1.1] for lithium) on the rates when the total cation concentration is held constant. Cryptands chosen associate rapidly with the appropriate cation in dimethylsulfoxide and yield cryptates with stability constants.²⁸ $K_{\text{stab}} > 10^5$, which are expected to be larger than the ion-pairing constants for this sterically hindered alcohol. For both the potassium and sodium salts, rates reach a limiting value when cryptand equivalent to total metal ion present is added. This may be identified with the reactivity of the free anion. For the lithium salts, the limiting value is only approached asymptotically. The solid lines in Figure 6 represent calculated behaviour taking into account the ion pairing and complexing equilibria, and assuming that $k_i/k_{\text{ip}} > 10^2$, even for the potassium salts. The fit to data is good except for the lithium salts at low cryptand concentrations. This is probably due to aggregation of these alkoxides which is not included in this treatment.

The observations above show that the half-life for the fragmentation of 1,2,3-triphenylpropoxide in dimethylsulfoxide is less than a second at 25°C . Interestingly, the 1,2,3-triphenyl-2-propanol used in these experiments is prepared in the conventional way by addition of benzylmagnesium chloride or benzyl-lithium to deoxybenzoin in ethereal solution to form initially the alkoxide. The apparent paradox serves to illustrate the importance of ion pairing in stabilizing the product of addition of carbanions derived from even relatively weakly acidic hydrocarbons such as toluene.

5.2 Rearrangements

A surprisingly large number of anionic rearrangements involve formal collapse of alkoxide to carbonyl with expulsion of a strongly basic leaving group which is intercepted intramolecularly by a second electrophilic site. In many cases, consideration of reaction stereoselectivities and energetics provides convincing evidence of concert between the bond-breaking and bond-making processes. Nevertheless, these show cation and concentration dependences similar to those in the fragmentations described above.

In the anionic oxy-Cope rearrangement, for example, the group is an allyl anion. In the reaction of 3-methyl-1,5-hexadiene-3-oxide, secondary deuterium kinetic isotope effects at the bond-breaking site (C-4) are large while those at the bond-making *termini* (C-1 and C-6), are small or inverse, indicating a highly dissociative transition state,²⁹ as shown in Figure 7. In tetrahydrofuran solution, potassium salts are 40 times more reactive than sodium salts, and the reaction of the lithium salt was not detectable under the same conditions. With the potassium salts, rates were enhanced by addition of 18-crown-6, and

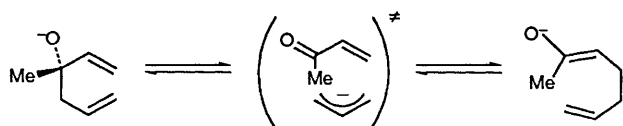


Figure 7 Anionic oxy-Cope rearrangement of 3-methyl-1,5-hexadiene-3-oxide.

in dimethylsulfoxide, reaction was about 1000 times faster than in THF, and increased with dilution of the solution. A quantitative treatment of cation and concentration dependence has not been undertaken in this case, but the behaviour is again indicative of a dissociation of the alkali metal alkoxide to a more reactive anion before the bonding changes occur.

Other strongly basic leaving groups may be involved. Hydroxy-ketones with appropriately placed ketone and alcohol groups suffer base-catalysed isomerizations involving transfer of hydride from alkoxide to carbonyl carbon. The reactions of rigid cage structures exemplified in Figure 8 have been examined in dilute aqueous base and in dimethylsulfoxide solution using stoichiometrically generated alkoxides. In water, reactions are specific base catalysed, and show no detectable cation dependence.³⁰ In dimethylsulfoxide solution, rates depend strongly on the nature of the cation, increasing in order $\text{Li}^+ < \text{Na}^+ < \text{K}^+$ in ratio 1:10²:10⁴, which is in line with the expected order of the dissociation constants for the alkoxides. Addition of more than one equivalent of the appropriate cryptand suppresses the concentration and cation dependence. As with the examples above, the pattern points to reaction *via* 'free' ions with $k_i/k_p > 100$, even for potassium alkoxides.

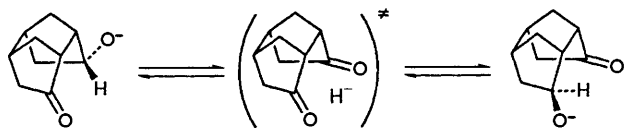


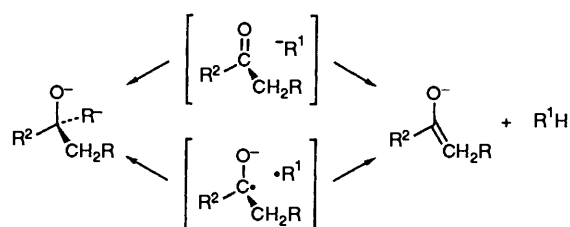
Figure 8 Rearrangements of polycyclic hydroxyketones.

It has been pointed out that these rearrangements are intramolecular variants³¹ of the Meerwein-Ponndorf-Verley redox reactions in which the hydride transfer occurs in a cyclic array with both alkoxide and carbonyl oxygens co-ordinated to the same cation. The cation, traditionally Al^{3+} , thus enhances polarization of the carbonyl group, and this effect must more than offset deactivation of the alkoxide donor. With the intramolecular processes such as those shown above, particularly in rigid cage structures, oxygen-oxygen distances are too large to allow such accommodation. Any electrophilic catalysis would arise from a second cation, and might be detectable as a rate increase at very high cation concentrations. Such an effect has not yet been detected.

5.3 Gas-Phase Reactions

These solution-phase cleavages and rearrangements of alkoxides have their gas-phase analogues. Indeed, in the absence of a stabilizing interactions with cation or solvent, even simple alkoxides suffer fragmentations, undergoing unimolecular decompositions³² to yield enolate by formal elimination of the hydrocarbon residues at the alcohol group.

For *t*-butoxide itself, competitive intramolecular deuterium kinetic isotope effects in infrared multi-photon-induced and collision-induced³³ fragmentations point to a stepwise process, with initial homolytic or heterolytic carbon-carbon bond cleavage. In a second step, rapid hydrogen atom or proton transfer occurs as shown in Scheme 4. The isotope effects do not identify the nature of the initial cleavage, but the relative order of leaving abilities of groups from anions such as *i*-propoxide, 2-trifluoromethyl-2-propoxide, and 2-phenyl-2-propoxide is consistent

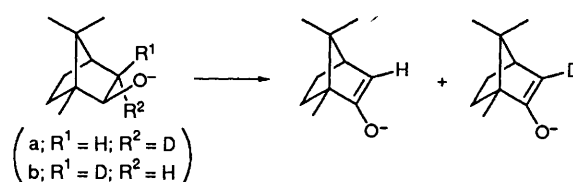


Scheme 4 Gas-phase fragmentations of *t*-alkoxides.

with heterolytic processes. With trialkylmethanols, where the electron affinity of the nucleofuge is very small, unusual orders of leaving ability are observed and may indicate a change of mechanism to a radical cleavage in these cases.

The gas-phase chemistry of 1,2,3-triphenylprop-2-oxide has also been examined, and direct comparisons may be made with its solution behaviour.³⁴ The mass spectrum of the ion is extremely clean, showing only a fragment at $m/e = 195$ corresponding to the enolate of deoxybenzoin. The reaction in dimethylsulfoxide and in the gas phase thus yield the same products. In the gas phase, however, the proton transfer which yields the products from the initial carbanion-alkoxide complex can only occur within the complex. Product ratios from fragmentations of selectively deuteriated material allow determination of kinetic isotope effects which are consistent with reversible formation of the complex from the alkoxide, followed by rate-limiting proton transfer.

On collisional activation, alkoxides of primary and secondary alcohols also fragment, and labelling studies, kinetic isotope effects, and computational studies suggest that reaction is initiated by formation of a hydride-aldehyde complex. When there is a β -hydrogen, as in the case of ethoxide,³⁵ there is net 1,2-loss of dihydrogen yielding the enolate of acetaldehyde in a two-step sequence. The interpretation of kinetic isotope effects is strongly dependent on the transition state models chosen, but a concerted H_2 loss seems to be excluded by the finding that the rigid alkoxide anions of the stereospecifically labelled *iso*-borneols, Scheme 5, lose H_2 and HD in the same ratio.³⁶ For alkoxides without a β -hydrogen,³⁷ such as methanol itself or benzyloxide, less efficient 1,1- or 1,3-eliminations may occur.



Scheme 5 Gas-phase decomposition of deuteriated *iso*-borneols.

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