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Cation and Concentration Dependence of Anionic Rearrangements Involving Hydride Shifts

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Abstract

The alkali metal salts of the polycyclic hydroxy-ketones 7 and 8 rearrange by intramolecular transfer of hydride between alkoxide and carbonyl carbons. Rates in DMSO solution, determined by dynamic ^{1}H NMR methods, show strong concentration dependence, increasing with dilution of the alkoxides. Rates are also strongly cation dependent, increasing in the order Li<Na<K. Intramolecular O...O distances in these rigid polycyclic structures are too large to permit their co-ordination to a common alkali metal cation, as occurs in the intermolecular Meerwein-Ponndorf-Verley-Oppenauer redox couple, and their behaviour is consistent with a mechanism involving dissociation of the salts prior to rearrangement. Analogies are drawn with other reactions involving formal collapse of alkoxide to carbonyl with expulsion of very strongly basic leaving groups. For the sodium and potassium salts, excess added [2.2.2] cryptand eliminates concentration dependence, and suppresses, but does not entirely eliminate cation dependence. Under these conditions, the salts of 8 are about 10 times more reactive than those of 7.

Reactions of hydride, as the simplest nucleophile, attract particular attention, and its addition to carbonyl carbon has, inevitably, been investigated by computational methods.[1] The prototype reaction, with formaldehyde, in the gas phase has also been examined experimentally,[2] but solution measurements are complicated by the high basicity of ionic hydride and its rapid reaction with most common solvents to yield dihydrogen and lyate anion. However, solution processes involving formal transfer of hydride between covalently bound sites are common. Especially relevant for investigation of pathways for the carbonyl addition are those involving transfer from alkoxide to carbonyl carbon (Figure 1) since both donating and accepting components map onto a generalized potential energy hypersurface for hydride+carbonyl interaction. Intramolecular reactions, i.e., base-catalysed rearrangement of hydroxy-ketones,[3] can allow a degree of control over stereochemistry and a detailed investigation of mechanism would be rewarding. Analysis of structure-reactivity relationships, for example, might yield angular preferences, and, importantly, indicate the distances at which such preferences become demanding.[4]

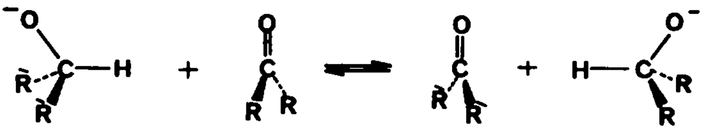
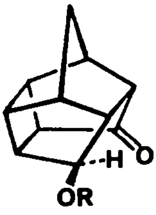


Figure 1 Hydride transfer from alkoxide to carbonyl carbon

With these considerations in mind, we have examined degenerate rearrangements and structures of the polycyclic hydroxy-ketones 1, 2, 3 ,[5] and 4.[6] Their sodium salts, generated in DMSO solution, react by rapid intramolecular transfer of hydride between the alkoxide and carbonyl carbons, and possible correlation between rates and structural features of the organic anions have been discussed in earlier papers.[7] These salts are expected to be strongly associated in solution and, while it was recognized that ion-pairing and other aggregation phenomena could affect the observed rates, we were unable to investigate them because use of dynamic ^{13}C N.M.R. methods restricted measurements to the most concentrated available solutions. In this paper, we consider specifically the role of cation in these anionic rearrangements.



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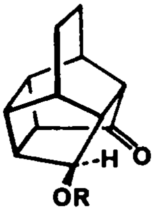

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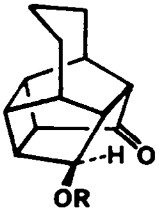

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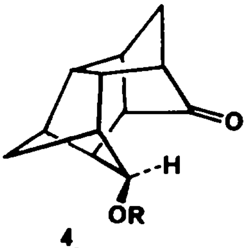

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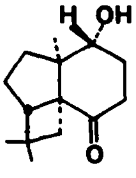
These are formally intramolecular variants of the familiar Meerwein-Ponndorf-Verley-Oppenauer (MPVO) redox couple, for which the currently accepted mechanism postulates initial co-ordination of oxygens of alkoxide and carbonyl partners to a common cation before transfer of hydride between carbon sites in a six-centre cyclic array,[8] with the cation thus behaving as a bifunctional catalyst. In intermolecular reaction, there is little difficulty in achieving this arrangement with no strong constraints on the oxygen-oxygen distances. In the X-ray crystal structures of the p-nitrobenzoates of 1, 2, 3, and 4, intramolecular O...O distances range from 4.88Å in 1 to 4.40Å in 4 and co-ordination of both oxygens to the same alkali metal cation (ionic radii of Li$^+$, Na$^+$ and K$^+$ are 0.60, 0.95, and 1.33Å respectively[9]) would require large distortions of these rigid polycyclic frameworks. The question arises as to the nature of the ionic species in the transfer, when structural features of the reactant exclude the six-centre cyclic transition states. Evidence that the mechanism can respond to the way in which the oxygen atoms are held by reactants has already been presented by Warnhoff *et al.*[10] 4-Hydroxycyclohexanone 5, was shown to undergo competitive inter- and intramolecular hydride transfers. While rates of the intermolecular reaction showed the characteristic cation dependence of the MPVO redox couple,[11] increasing for smaller more tightly co-ordinating cations (i.e., $Al^{+3}>Li^{+}>Na^{+}>K^{+}$), the order was reversed for the intramolecular process, matching earlier observations on the dihydropleiadienone 6.[12] Added cryptand or crown ether enhanced intramolecular reaction at expense of the intermolecular.



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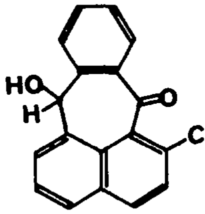

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We have examined these effects using hydroxy- ketones 7[13] and 8. Like 1, 2, 3, and 4, these hold the functionality in a rigid cage framework in which hydride transfer induces degenerate rearrangement as shown in Figure 2. Molecular modelling, and empirical force field calculation[14] of the structures gives intramolecular O...O distances of 4.263 and 4.629Å respectively, similar to those found in 1, 2, 3, and 4. However, with methyl groups at exchanging sites (4 and 4' in 7 and 3b and 3b' in 8), the high field region of their 'H N.M.R. spectra were expected to be amenable to a full line shape analysis, so that this more sensitive N.M.R. method could be used to examine reactivity in solutions over a wider range of concentrations than was possible with the ^{13}C method.

7: R_1=Me, R_2=H_b

8: R_1= H, R_2= Me

M = H, Li, Na, K

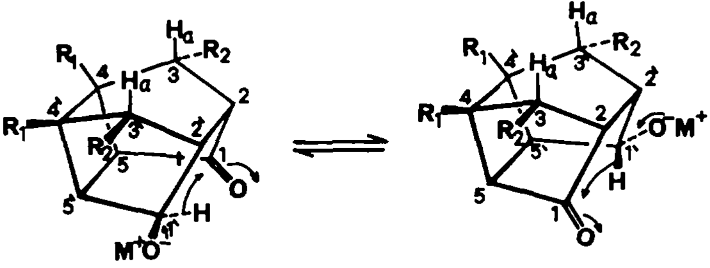
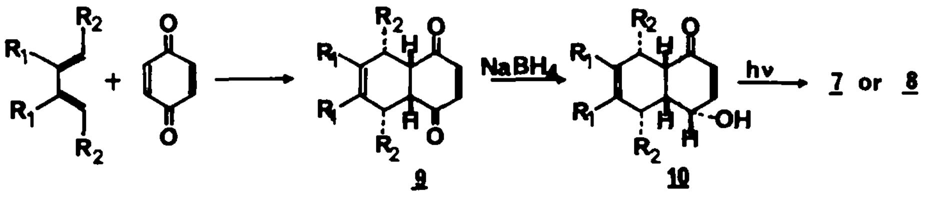


Figure 2 Degenerate rearrangement of 7 and 8 by intramolecular hydride transfer between alkoxide and carbonyl carbons.

Both 7 and 8 were prepared from the appropriate diene-benzoquinone Diels-Alder adduct following the sequence developed by Appel and co-workers[15] for the synthesis of 7 (Scheme 1). The analytical and spectroscopic properties of these compounds and the intermediates 9, 9a, 10, and 10a, were in full accord with the indicated structures, and with available literature data.



a: R_1=Me, R_2=H. b: R_1=H, R_2=Me.

Scheme 1 Preparations of 7 and 8

The 'H N.M.R. spectra of 7 and 8 are shown in Figure 3 and the assignments therein are fully supported by the results of decoupling and 2D-N.M.R.

experiments.[16] It is clear that signals from hydrogens attached directly to the cage frameworks are complicated by long-range coupling across W-type H-C-C-C-H arrangements in these molecules. The alcohol methines (H_1, which are not shown) do not participate in any such arrangement, and, with near 90° dihedral angles to hydrogens at adjacent bridgeheads, give rise to sharp singlets.

Signals from the potentially exchanging methyl groups in 7 appear as a well resolved pair of singlets ($\delta\nu$ = 37Hz at 300MHz) centred at δ1.09 p.p.m. This region of the spectrum also contains a signal (δ0.88 p.p.m.) assigned to H_{3b}, which is shown by molecular modelling to lie in the shielding cone of the C_1 carbonyl group. The signal from its potentially exchanging partner, $H_{3b'}$, appears at δ1.56 p.p.m., and both show large geminal coupling to H_{3a} or $H_{3a'}$, and a smaller vicinal coupling to H_2 or $H_{2'}$ at adjacent bridgeheads. For the purposes of the dynamic N.M.R. experiments, the bandshape in this region was modelled mathematically; since couplings would not be averaged by the expected exchange process, corresponding lines of the H_{3b} + $H_{3b'}$ signals were treated as arising from four two-site exchanging systems. After scaling and population adjustment to model a small amount of "slant" from second order effects, their contributions were summed with a fifth pair representing the methyl group signals.[17]

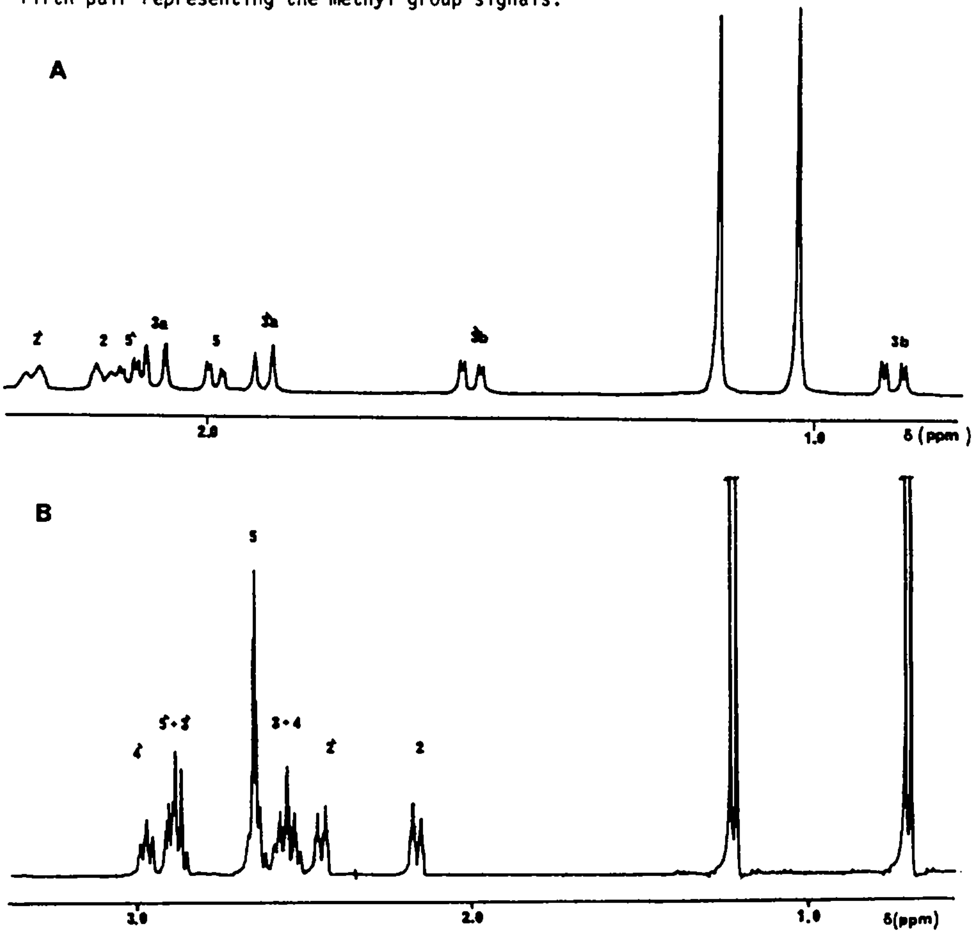


Figure 3 ^1H NMR spectra of 7-H (spectrum A) and 8-H (spectrum B) in d_6-DMSO solution. The numbers indicating assignments correspond to those in Figure 2.

In the case of 8, the high field region contains only two well resolved signals ($\delta\nu$ = 155Hz at 300MHz) from the potentially exchanging methyls. Each signal shows coupling to H_{3a} or $H_{3a'}$, and this simple bandshape was modelled by treating the corresponding lines as arising from two uncoupled two-site exchanging systems and summing their contributions.

Solutions of various concentrations of the sodium salts were made up by addition of stoichiometric amounts of d_6-dimsyl sodium to d_6-DMSO solutions of the hydroxy-ketones. As a check on the anion preparations, diphenylmethane was added to the solutions as an indicator.[10] Bordwell's measurements[19] give pKa's for 2-propanol, diphenylmethane, and DMSO of 30.2, 32.1, and 35.1 respectively. Control experiments, titrating 2-adamantanol, a secondary alcohol with molecular weight comparable to 7 and 8, with separately standardised dimsyl sodium gave a sharp colourless to yellow change at the expected endpoint. Similar behaviour was found with the hydroxy-ketones themselves.

Rates of rearrangement were obtained by least squares fitting of calculated and experimental spectra over the regions containing the signals from the exchanging methyl groups. These turned out to be strongly concentration dependent, and, to obtain spectra near the methyl signal coalescence points at temperatures above the freezing point of DMSO, spectrometers with operating frequencies ranging from 80 to 400MHz were used. Ionization induces some changes in chemical shifts; most notably, the alcohol methine moves downfield by nearly 0.5 p.p.m. in both hydroxy-ketones on salt formation. Smaller changes also occur in the high field signals, so that static parameters for the spectra do not correspond exactly to those of the parent hydroxy-ketones. With the sodium salts, rates were such that it was always possible to obtain these from measurements on the spectra. Typical spectra are shown in Figure 4, which also illustrates concentration dependence. The hydroxy-ketones could be recovered unchanged from these solutions and we associate the rates with the depicted rearrangement.

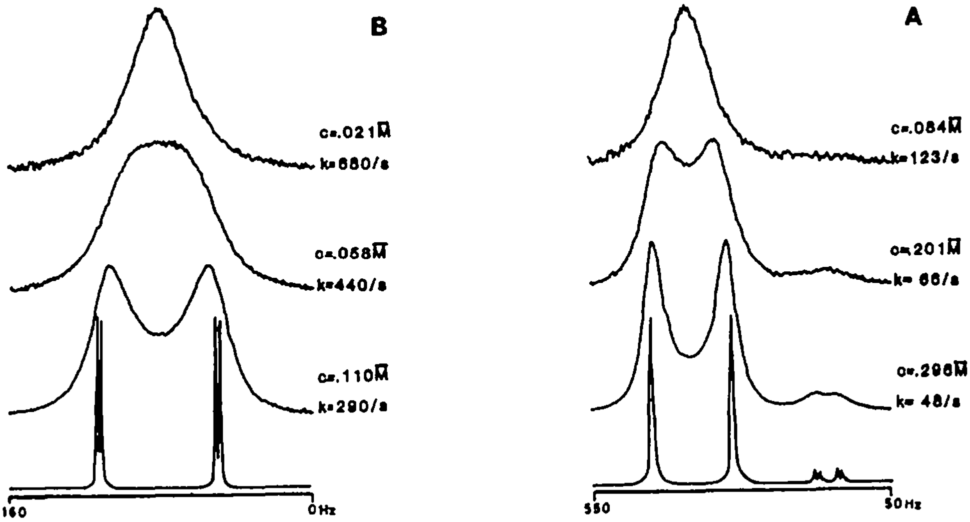


Figure 4: High field region of the ^{1}H NMR spectra of 7-Na at 84°C (spectrum A) andof 8-Na at 36° (spectrum B).

Solutions of the lithium and potassium salts were prepared in the same way, using the appropriate metal dimsyl. With the lithium salts, diphenylmethane again served usefully as an indicator, giving sharp development of yellow colour at equivalence point. With the potassium salts, however, the yellow colour of diphenylmethide could be observed well before addition of the full equivalent of base. Although the colour was not stable until the full equivalent was added, it could persist for between 10 and 40 seconds depending on the exact mixing conditions. Similar behaviour was observed when the sodium and potassium salts were generated in presence of excess of the cation complexing agent, [2.2.2] cryptand.[20] This behaviour may be linked to the formation of tightly hydrogen-bonded homoconjugate anions[21] at half equivalence point.

The lithium salts were least reactive, and, indeed, the spectra of the lithium salt of 7 showed barely detectable line broadening within the accessible temperature range. In these cases, rates were calculated from the line broadening using the slow exchange approximation,[22] rather than by a full line shape analysis. In contrast, rates of the potassium salts, and of the sodium salts with added cryptand, were fast, so that the methyl signals were well through coalescence at the lowest accessible temperatures, even at 400MHz. In these cases, static parameters for the line shape analysis were obtained by extrapolation of the chemical shift behaviour at low base additions to those at the full equivalent. We cannot claim great accuracy for this procedure [23] but the shift differences obtained for the methyl signals were very close to those observed directly in the lithium and sodium salts in the absence of cryptand.

The collected rate data are presented in Tables 1 and 2. The best data are those for 7-Na at 84° and 95°, 7-K at 28°, 8-Li at 82°and 8-Na at 36°. These all have 95% confidence limits [24] (based on the fit of experimental and calculated spectra) of less than +/-5% of the tabulated value. Because of the approximations and extrapolations involved in obtaining the fastest and slowest rates, their corresponding confidence limits are much larger. We believe that 95% confidence limits of +/-30% of the quoted values does not over-estimate the accuracy of our data in these cases.[23] Nevertheless, since the spread in the rates is several orders of magnitude, it is possible to discern trends and relationships.

Table 1: Rates of rearrangement of 7 (Li, Na, and K) in d_6-DMSO solution

Cation + salt Concentration	k_{obs} (T) ($x.sec^{-1}$. (°C))	x
M = Li .161M	8.0 (90)	10^0
.080M	8.8 (90)	
.042M	11.1 (90)	
.029M	12.9 (90)	
M = Na .401M	3.3 (84), 6.1 (95)	10^1
.297M	4.8 (84), 8.1 (95)	
.201M	3.6 (75), 6.6 (84), 10.3 (95)	
.084M	3.1 (65), 7.1 (75), 12.3 (84), 19.4 (95)	
.046M	6.5 (65), 19.6 (84)	
M = Na .100M	6.8 (22)	10^2
+ .060M	6.5 (22)	
cryptand .020M	6.6 (22)	
M = K .044M	2.2 (22), 5.2(28)	10^2
.022M	3.6 (22), 7.8(28)	
.011M	4.1 (22), 10.7(28)	
.006M	7.0 (22),	
M = K .160M	8.6 (21)	10^2
+ .070M	10.7 (21)	
cryptand .025M	7.0 (21)	

Table 2: Rates of rearrangement of 8 (Li, Na, and K) in d_6-DMSO solution.

Cation + salt Concentration	k_{obs} (T) ($x.sec^{-1}$. (°C))	x
M = Li .166M	2.9 (82), 5.0 (93)	10^1
.083M	3.7 (82), 6.4 (93)	
.062M	4.4 (82), 7.4 (93)	
.041M	3.5 (65), 5.0 (74), 6.8 (82), 12.9 (88)	
.030M	4.4 (65), 7.3 (74), 9.9 (82)	
M = Na .200M	1.9 (32), 2.6 (36), 3.5 (41), 4.3 (46)	10^2
.110M	1.6 (25), 2.2 (32), 2.9 (36), 3.7 (41), 7.2 (46)	
.058M	4.4 (36), 5.7 (41)	
.021M	5.6 (32), 6.3 (36)	
.010M	8.4 (24)	
M = Na .138M	4.1 (24)	10^3
+ .094M	4.3 (24)	
cryptand .068M	5.0 (24)	
M = K .06 M	11.1 (25)	10^3
.025M	10.4 (25)	
M = K .200M	9.4 (24)	10^3
+ .100M	9.1 (24)	
cryptand .025M	11.6 (24)	

Clearly, the rates of rearrangement are both cation and concentration dependent. Extrapolation to comparable temperature and alkoxide concentration gives an approximate ordering of $1:10^2:10^4$ for the Li, Na, and K salts of both 7 and 8, in agreement with Warnhoff's observations.[10] Such strong cation dependence was probably first noted by Cram[25] in the fragmentation of t-alkoxides used as a source of transient carbanions. More recently, the same pattern has been found in the anionic oxy-Cope rearrangement,[26] and, indeed, in other anionically accelerated pericyclic reactions.[27] These reactions (Figure 5) involve, formally at least, collapse of a tetrahedral intermediate to carbonyl with expulsion of a highly basic anion. In the first case the leaving group is the benzylic carbanion, protonated by solvent. In the others, the leaving groups are allyl anion or hydride, trapped intramolecularly, probably with a substantial degree of concert between the bond breaking and making process.

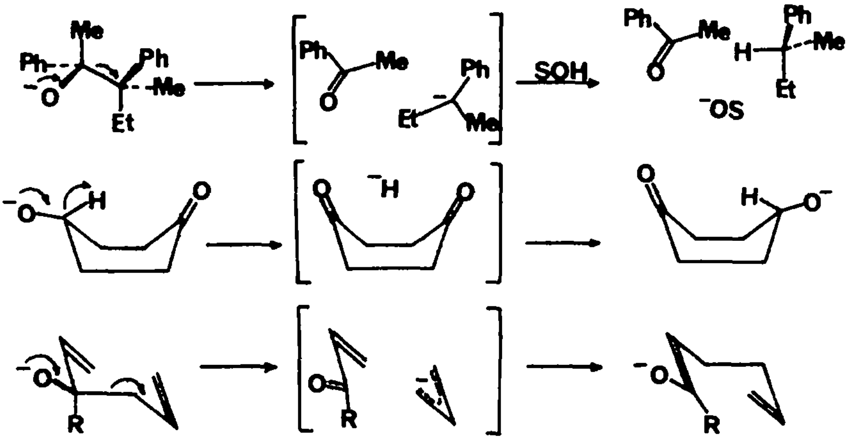


Figure 5 Anionic rearrangements and cleavages which show strong dependence on cation and solvent. Species in brackets may be intermediates or transition states.

$$M^+ + {}^-OR \overset{K_{ip}}{\rightleftharpoons} \overset{+}{M}\overset{-}{O}R$$

$$^-OR \xrightarrow{k_1} P$$

$$\overset{+-}{M\,O}R \xrightarrow{k_2} P$$

Scheme 2

To account for his observations, Cram suggested a kinetic scheme in which alkoxide (RO^-) contact and solvent-separated ion-pairs, and solvated ions were treated as kinetically distinguishable species, all capable of giving product. While the simplified scheme (scheme 2) shown does not differentiate ion-pair types, it retains the main features of Cram's proposal. Dissociated ions are much more reactive than paired species and react at rates characteristic of the organic anion, i.e., k_1 should be insensitive to the nature of the cation, and $k_1 \gg k_2$. Provided the ion-pairing constant, K_{ip}, is large, the rate law takes the form:

$$v = \left[k_2 + k_1/(K_{ip}.c)^{.5}\right]c \qquad (1)$$

where c is the total alkoxide concentration. The large cation effects, it was suggested, arise almost entirely from differences in K_{ip} for the lithium, sodium and potassium alkoxides.

Exner and Steiner[28] have measured conductance of DMSO solutions of alkali metal methoxide and t-butoxide and found large differences in the equivalent conductivities of the various alkali metal salts, which they interpreted in terms of differing degrees of ion-pairing and aggregation. Ion-pairing constants for the lithium, sodium and potassium t-butoxides were estimated as 10^8, 10^6, and 270 respectively, and, as Exner and Steiner pointed out, these are of the order required to account for reactivity differences in many base induced reactions. More recently, Arnett and Small[29] have presented evidence from calorimetric measurements, of the strong interaction between alkoxide anions and alkali metal cations in DMSO. Similar phenomena in phenolate and enolate solutions have been investigated.[30]

The increases in rate on dilution of the alkoxide solutions are also in qualitative agreement with a scheme requiring a dissociation prior to hydride transfer. In fact, the equation:

$$k_{obs} = A.\ c^{n} \qquad (2)$$

reproduces the data within its experimental uncertainty, and non-linear regression to the better data sets gives values of n between -.5 and -.9, and of A ranging from 18.4 to 115 (Table 3). Unfortunately, with the small numbers of data points in each set, these numbers are not well determined.

The most economical reaction sequence consistent with the data (Scheme 3) is an adaption of Cram's. We suggest that the solutions contain aggregated anions, and make the simplifying assumption that the hydride transfer which exchanges the methyls occurs only in a dissociated species, RO^- or R^*O^-, which might be a separately solvated ion or part of a solvent separated ion-pair. There is some recent justification for neglect of hydride transfer in more tightly associated species. The effect of metal co-ordination on H-C bond energies in methoxide anion, has been investigated using ab initio GVB and CI theoretical methods,[31] which showed that co-ordination to Na^+ or K^+ strengthens this bond by 6.4 and 4.8 kcal.mol.$^{-1}$ respectively. If cations have similar effects on more complex alkoxides, and all the bond energy differences showed in the hydride transfer, these anions, which are relatively weakly solvated by DMSO,[32] could be up to ~10^3 more reactive than metal cation co-ordinated species.

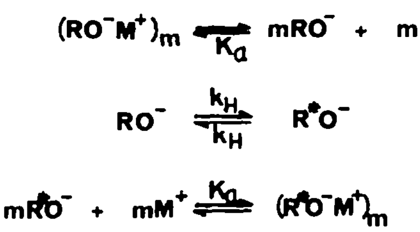


Table 3 Parameters in equation (2) and comparison with equation (3)

Data Set	Equation (2)		Equation (3)	
	A	n	m	$k_H K_a^{-1/2m}$
7-Na at 84°	18	-.77	2.2	17.8
7-Na at 95°	32	-.71	1.7	32.4
7-K at 22°	101	-.52	1.0	101.0
8-Li at 82°	39	-.91	5.6	34.2
8-Na at 36°	115	-.46	0.9	112.0

The association governed by K_a combines both ion-pairing and aggregation, and provided the constant is large, equation 3 relates the pseudo-first order rate constants, k_{obs}, from the N.M.R. experiments to the constants in Scheme 3 and to the total metal alkoxide concentration, c.

$$k_{obs} = \left[k_H.(2.m.K_a)^{-1/2m}.2^{\frac{1}{2}}\right].c^{(1/2m - 1)} \qquad (3)$$

Comparison with equation 2 and its fit to the experimental data yields some crude estimates of the aggregation numbers, m, and for $k_H.\ K_a^{-1/2m}$ which are shown in Table 3. The sodium salts of 7 appear to be mainly dimeric, while its potassium salts are monomeric. In 8, the lithium salts appear to be very highly aggregated, but the sodium salts are only monomeric. Without independent measurement of the equilibrium constant, K_a, it is not possible to obtain values for k_H.

The effect of excess cation complexing agent, [2.2.2]cryptand, on the rates is also revealing. The [2.2.2]cryptates of the Na and K cations form rapidly,[33] and their stability constants in DMSO have been measured as $10^{5.4}$ and 10^7 respectively,[34] suggesting that the cryptand will compete effectively against alkoxide anion for the cations.

In the event, added cryptand enhanced observed rates of exchange. When there were more than 1.2 equivalents present, rates were not detectably dependent on the ratio of cryptand to alkoxide and data included in Tables 2 and 3 is for ratio cryptand : alkoxide = 2.2. For the sodium and potassium salts of both 7 and 8, the dependence on alkoxide concentration was then barely detectable, suggesting either, that the mechanism of rearrangement no longer involves a dissociative step, or the reactivities of associated and dissociated species are now closely comparable. Interestingly, the cation dependence is much reduced, but not entirely eliminated by the cryptand. For both hydroxy-ketones, the K:Na alkoxide rate ratio drops to ca 2. X-ray crystal structures of sodium[35] and potassium[36] cryptates show that they can be regarded as large nearly spherical cations with radius of about 5Å. Judging by M^+...O distances in cryptates, the radii of potassium cryptates are typically 0.2Å larger than those of sodium. Presumably, the hydride transfer now occurs in a metal ion cryptate-alkoxide ion-pair,[37] and there is a residual effect on reactivity despite encapsulation of the cation.[38]

This interpretation of the effect of cryptand is necessarily tentative. These are concentrated solutions and there will be medium effects which we cannot quantify. The results serve to emphasize the difficulty in extracting a reliable measure of reactivity to be used in correlations with structural features of the organic anions.[39] Nevertheless, the cryptand clearly reduces interaction between cation and anion and the tabulated data indicate that 8-Na or 8-K is ca 10 times more reactive than the corresponding salts of 7 under these conditions. Detailed discussion of molecular geometry of 7 and 8 will be reserved until X-ray crystal structures determinations are complete, but we note here that this rate factor can be rationalised in terms of relief of different ground state strains. Most obviously, there is a close non-bonded interaction between alcoholic oxygen and the C$_3$-methyl in 8 which is absent in 7 and which would be relieved as the alkoxide carbon assumes more carbonyl character.

Experimental section

I.r. spectra were recorded on a Pye-Unicam SP3-200 spectrometer. ^{1}H N.M.R. spectra were recorded at 80 MHz on a Bruker WP 80, or at 220 MHz on Perkin-Elmer R 34 or at 300 MHz on a Varian SC 300, or at 400 MHz on a Bruker WH 400. ^{13}C N.M.R. spectra were recorded at 20.1 MHz on the Bruker WP 80 spectrometer. Analytical g.l.c. were run on a Carlo-Erba Strumentazione fitted with a 25 m. OV-1 crossbond SCOT column with hydrogen at 2 ml.min.$^{-1}$ as the carrier. Mass spectra were determined on a AEI MS 9 instrument, routinely with electron impact ionization at 70 e.v. Silica gel GF$_{254}$ was used for analytical t.l.c., and PF$_{254}$ for preparative t.l.c.

8,9-Dimethylbicyclo[4.4.0]deca-3,8-diene-2,5-dione (9a) and 7,10-Dimethylbicyclo[4.4.0]deca-3,8-diene-2,5-dione (9b): These were prepared according to published methods by Diels-Alder addition of p-benzoquinone and the appropriate substituted butadiene.[40]

8,9-Dimethyl-5-hydroxybicyclo[4.4.0]deca-3,8-diene-2-one (10a): This compound was prepared by reduction of the dione, 7, following the method of Appel et al.[15] Sodium borohydride was added in portions to a cooled (0°) , stirred, solution of the dione (1.97 g) in a mixture of methanol (100 ml) and water (2 ml). The reaction was monitored by t.l.c. on silica plates eluting with ether. When all the dione was consumed, acetic acid (0.5 ml) was added to the mixture before evaporating the solution to small volume (ca. 20 ml) on rotary film evaporator. The residual solution was diluted with water (100 ml) and extracted with ether. The combined extracts were dried (MgSO$_4$) and evaporated to an oil which was chromatographed on silica, eluting with 1:1, v:v 40-60 petrol:ether, to give the product (1.2 g). Recrystallization from petrol:ether gave plates, m.p. 109-110°, ν_{max}(CCl$_4$) 3620, 1690, 1450, 1380, 1203, and 1080 cm.$^{-1}$, δ_H(CDCl$_3$) 1.56 (3H, s), 1.62 (3H, s), 1.98 (2H, m), 2.05 (1H, bs), 2.34 (1H, bs) 2.69 to 2.61 (3H, m), 4.91 (1H, bs), 5.99 (1H, dd, J 10 and 2.5 Hz), 6.73 (1H, dt, J 10 and 2.5 Hz) p.p.m., m/e 131 (100%), 146 (97), 91 (82), 159 (70), 93 (66), 77 (57), and 174 (47).

7,10-Dimethyl-5-hydroxybicyclo[4.4.0]deca-3,8-diene-2-one (10b): This compound was prepared by sodium borohydride reduction of the dione (8), as described above. Reduction of the dione (0.85 g) yielded, after chromatography, the hydroxyketone (0.47 g) as a colourless oil which would not crystallize, ν_{max}(CCl$_4$) 3620, 3550, 3020, 1675, 1460, and 1380 cm^{-1}, $_H$(CDCl$_3$) 1.13 (3H, d, J 10 Hz), 1.16 (3H, d J 10 Hz), 2.58 (3H, m) 2.83 (1H, dd, J 10 and 6 Hz), 2.90 (1H, bs, exchanges with D$_2$O), 4.70 (1H, bs), 5.61 (2H, s), 6.00 (1H, d, J 12 Hz), 6.88 (1H, dd, J 12 and 5 Hz) p.p.m., m/e 93 (100%), 109 (88), 84 (87), 91 (66), 67 (55), 131 (53).

8,9-Dimethyl-5-hydroxytetracyclo[4.4.0.0^{3,9}.0^{4,8}]decan-2-one (7): This compound was prepared by photocyclization of the unsaturated hydroxyketone (10a) following the method of Appel et al. A benzene solution of the hydroxyketone (0.73 g in 100 ml) was placed in the well of a photochemical reactor. Dry nitrogen was bubbled through the solution for 15 minutes before irradiation through quartz with a medium pressure mercury lamp. The conversion was monitored by g.l.c. When conversion was complete (ca. 2hrs), the solvent was removed on the rotary evaporator and the residue was chromatographed on silica, eluting with ether:light petroleum, 1:1, v:v, to give the product (0.66 g) as a crystalline solid. Recrystallization from ethylacetate gave crystals, m.p. 122-123° (lit 122-122.5 °), $\nu_{max}(CCl_4)$ 3400, 1740, 1120, 1088, 985, and 960 cm^{-1}, $\delta_H(C_2D_6SO)$ 0.88 (1H, dd, J 13.1 and 3.2Hz), 1.02 (3H, s), 1.15(3H, s), 1.56 (1H, dd, J 12.5 and 3.2Hz), 1.90 (1H, d, J 12.5Hz), 1.99 (1H, dd, J 9.4 and 2.5Hz), 2.09 (1H, d,J 13.1Hz), 2.13 (1H, dd, J 9.4 and 3.1Hz), 2.17 (1H, dt, 10.0 and 2.5Hz), 2.29 (1H, dt, J 10.0 and 3.0Hz), 3.83(1H, s), 4.82 (1H, s). $\delta_C(CDCl_3)$ 19.46(q), 32.78(t), 33.87(t), 39.90(s), 43.16(d), 44.48(s) 46.16(d), 47.70(d), 48.25(d), 74.63(d), and 218.19(s) p.p.m., m/e 146 (100%), 131 (76), 96 (73), 159 (32), and 91 (30). (Found C, 74.9; H, 8.6%; $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

7,10-Dimethyl-5-hydroxytetracyclo$[4.4.0.0^{3,9}.0^{4,8}]$decan-2-one (8): This compound was prepared by irradiation of the unsaturated hydroxyketone (10b) as described above. Irradiation of the hydroxyketone (0.62 g) yielded, after chromatography, the cyclization product (0.56 g) as a crystalline solid. Recrystallization from ethyl acetate gave crystals, m.p. 83-84°, $\nu_{max}(CCl_4)$ 3620, 1739, 1140, 1090, 1059, and 910 cm^{-1}, $_H(C_2D_6SO)$ 0.70 (3H, d,J 7.5Hz), 1.22 (3H, d, J 7.5Hz), 2.16 (1H, dm, J 9.5Hz), 2.44 (1H, dm, J 9.5Hz), 2.52 (1H, tm, J 6.0Hz), 2.64 (1H, qm, J 7.5Hz), 2.88 (1H, qm, J 7.5Hz), 2.90 (1H, m, J 6.4 and 7.2Hz), 2.97 (1H, tm, J 6.8Hz), 4.03(1H,s), 4.98 (1H, s). $\delta_C(CDCl_3)$ 14.63(q), 17.41(q), 29.70(d), 34.16(d), 38.04(d), 42.21(d), 43.68(d), 47.63(d), 52.38(d), 77.04(d), and 220.16(s) p.p.m., m/e 82(100%), 31(79), 93(64), 41(62), and 110(56). (Found: C, 75.0; H, 8.5%; $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

Preparation of d_5-dimsyl solutions: d_6-DMSO was purchased from CEA and was used without further drying or purification from freshly opened vials. The agreement of two methods of base estimation described below in the dimsyl preparations showed that this material was suitable. Attempts to dry or further purify it did not improve the results. All manipulations were carried out under argon which had been bubbled through Na/K alloy on a gas line. Solutions were transferred by syringe or cannula. The potassium and sodium dimsyl solutions were prepared by published methods by reaction of sodium or potassium hydride and d_6-DMSO. Lithium dimsyl was prepared by reaction of lithium amide and d_6-DMSO, the reaction of lithium hydride being too slow to be practical. All preparations gave clear yellow or colourless solutions provided they were not heated above 45° during the preparative reactions.

Total base concentrations were determined by quenching an aliquot of the solution in distilled water and titrating against standard hydrochloric acid to the phenolphthalein endpoint. Each dimsyl solution was also titrated against known amounts of 2-adamantanol to the diphenylmethane endpoint. Base concentrations determined by both methods generally gave agreement and the preparations were discarded if the discrepancy was more than 5%. Typically, the dimsyl concentrations were between 0.2 and 1.0M, but the viscosity of the concentrated solutions caused some difficulty in microsyringe manipulation.

N.M.R. sample preparation: The hydroxy-ketones were stored at room temperature under high vacuum overnight before use. A typical sample preparation is described here. The [2.2.2] cryptand (0.712 g.) was weighed into a 5mm N.M.R. tube which was then heated at 50° under high vacuum until no further weight loss was detected (24 hrs.). The tube containing the cryptand (now 0.629 g., 0.167 mmol) was fitted with syringe cap and cannula and purged with argon from the gas line. The hydroxy-ketone (0.145 g., 0.076 mmol) was weighed into a flask fitted with a stirrer and mounted on the line. After purging with argon, d_6-DMSO (0.350 ml.), diphenylmethane (0.0001 ml), and anisole (0.001 ml) were added by microsyringe. The mixture was stirred to effect complete solution, before transferring to the N.M.R. tube by cannula under positive argon pressure. The cryptand dissolved readily with a little warming, and the N.M.R. spectrum was recorded. Known volumes of standard (0.63M) d_6-dimsyl sodium were then added through the cap by microsyringe. After shaking to mix, the N.M.R. spectra were recorded. Addition was continued until the stoichiometric quantity was added (0.120 ml.) by which time the yellow indicator colour was completely stable. The solution was then diluted with known volumes of d_6-DMSO (0.300 and 0.250 ml.) and the spectra determined. After the N.M.R. measurements were complete, the total volume line in the tube was marked, and the contents poured into aqueous acetic acid for recovery and analysis by GC/MS. The tube was cleaned and dried before filling to the mark with a microsyringe to measure the final volume of the sample. From the known quantities of solvent added, the concentrations of the final and intermediate alkoxide solutions were determined.

For samples without cryptand, the initial step was omitted. The hydroxy-ketones are quite volatile and sublime if heated under vacuum.

In some preparations, small excesses of base (up to 10%) were required to produce stable endpoints and we believe this reflects occasional inefficiences in the maintenance of inert atmosphere. Controls showed that the indicator and dimsyls react very rapidly with atmospheric O_2. On opening an N.M.R. tube to dry CO_2-free atmosphere, the yellow indicator colour is discharged from the top surface down in a matter of seconds.

Recovered material from the N.M.R. experiments was examined by GC/MS. Under the conditions of the N.M.R. experiments, no new organic compounds were formed, and deuterium was not incorporated by the hydroxy-ketones.

N.M.R. measurements: For measurements on the 300 and 400 spectrometers, chemical shifts were referenced to internal d_6-DMSO at 2.62ppm. relative to TMS and the solvent also provided internal deuterium field frequency lock. Acquisition times were between 3 and 3.5 seconds, with a pulse width of 5 μs. Spectral width was chosen to give a digital resolution of less than 0.5 Hz. Typically 40 to 50 transients gave spectra with acceptable noise levels. Probe temperatures were determined by insertion of a thermocouple in an N.M.R. tube, and were stable to 0.3°.

The necessary values for T2 for the line fitting calculations were estimated by the changes in the line width of the OCH_3 signal of the anisole in the sample. Except were noted in the text, field strengths and temperatures were chosen such that line broadening from exchange was large. Reasonable changes in T2 estimates (± 25%) affected the calculated rates by less than their 95% confidence limits.

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