

ION PAIRING EFFECTS ON ALKALI METAL ALKOXIDE FRAGMENTATIONS
AND REARRANGEMENTS IN DIMETHYL SULPHOXIDE

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STEVEN MICHAEL PARTINGTON

Chemistry Department,
University of Manchester,
Manchester,
M13 9PL

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Abstract

This thesis describes an investigation into ion pairing effects on the rates of reaction of three alkoxides under anaerobic conditions in dimethyl sulphoxide (DMSO) solution. The alkoxides of 4,4-dimethyl-2-phenyl-1,5-hexadien-3-ol (1) perform the anionic oxy-Cope rearrangement in DMSO in the presence of an excess of methylsulphonyl carbanion (usually referred to as the diasyl anion), to give the enolate of 6-methyl-2-phenyl-5-heptenal, whose appearance is monitored by u.v. spectroscopy. The alkoxide of 3-methyl-1,2,3-triphenyl-2-butanol (7), and the alkoxide of 1,2,3-triphenyl-2-propanol (8) fragment in diasyl/DMSO to give the enolate of deoxybenzoin (in both cases), along with cumene (in the fragmentation of (7)), and toluene (in the fragmentation of (8)).

The rate of reaction of the alkoxides was measured at variable diasyl concentrations (diasyl lithium, sodium and potassium being used) at constant temperature and alcohol concentration, and at constant diasyl concentration (at constant temperature and alcohol concentration) with the cation concentration being varied by addition of alkali metal halides. The variation of the observed rate was compared with the prediction of a scheme proposed by Cram to explain the reactivity of alkoxides in fragmentation reactions. The findings of the thesis support the predictions of the scheme with regard to the variation of the observed rate in the presence of added metal halides. The variation of the observed rate in the presence of variable diasyl concentrations does not agree with the scheme's prediction, and it is believed that the variation of base as well as cation concentration that occurs on variation of the diasyl concentration is in some way the cause of this.

The fragmentation of (8) was performed in the presence of the cation complexing agents [2.1.1.] and [2.2.2.] cryptand, and the observed behaviour agrees almost exactly with the theoretical predictions.

Since obtaining his first degree at the University of Manchester in 1983 (BSc. (Hons.), first class), the author has been working in the Department of Chemistry under the supervision of Dr. C. I. F. Watt. The results of this research are embodied in this thesis.

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other institute of learning.

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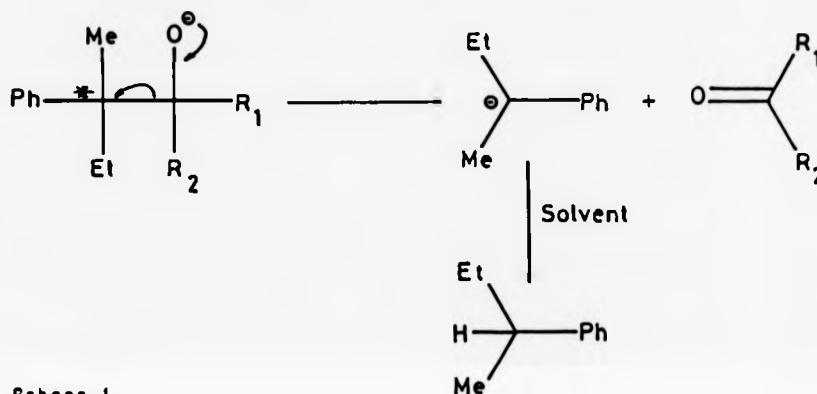
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CHAPTER ONE

Introduction and review

INTRODUCTION

In the late 1950's and early 1960's, Cram and his co-workers⁽¹⁾ used the alkoxide fragmentation reaction shown below to investigate the stereochemistry of the hydrocarbon formed after protonation of the proposed intermediate carbanion.



Scheme 1

The reaction was referred to as an S_N1 reaction, as it is formally electrophilic substitution of a C-C bond by a proton at the chiral centre (*). Its progress was followed by the formation of the chiral hydrocarbon product 2-phenylbutane, which was produced in each fragmentation. A variety of solvents were used (dioxan, ethanol, *t*-butanol, benzene, ethylene glycol, diethylene glycol, dimethyl sulphoxide (DMSO), N-methyl aniline), and different bases were used to generate the alkoxides (usually the anions derived from the solvent whenever possible). It was observed that the stereochemistry (inversion, retention, racemisation) of the product depended on the dielectric constant of the solvent and the ability of the solvent to donate a proton to the intermediate carbanion. Cram noticed that the reaction required the mildest conditions

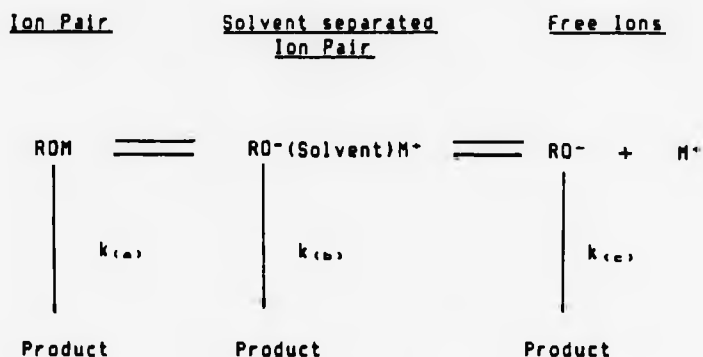
when using DMSO as the solvent, and that in each solvent the potassium alkoxide fragmented considerably faster than the sodium alkoxide which in turn fragmented faster than the lithium alkoxide. Illustrative data for the fragmentation of 2,3-diphenyl-3-methyl-2-pentanol ($R_1 = \text{Me}$, $R_2 = \text{Ph}$, from the diagram above) is shown below, the yields referring to the yield of 2-phenylbutane.

Table 1. Representative data from Cram's fragmentations

<u>Base</u>	<u>Temp</u>	<u>Solvent</u>	<u>Time</u>	<u>Yield</u>
LiOBu ^t	170°C	DMSO	24 hr	25 %
NaOBu ^t	75°C	DMSO	24 hr	28 %
KOBu ^t	25°C	DMSO	12 hr	68 %
KOBu ^t	102°C	t-BuOH	48 hr	64 %

Although the data is qualitative, it can be seen from the wide variety of conditions needed, that the effects observed on changing the cation in the same solvent, or changing the solvent are not small effects but involve orders of magnitude in the reaction rates.

It was suggested that these rate differences could be explained in terms of ion pairing effects, and Cram proposed a scheme which involved free ions, solvent separated ion pairs, and contact ion pairs, as well as carbanions as intermediates. This scheme was used to explain the stereochemical results obtained by Cram for the fragmentation in different solvents, and also to explain the observed rate differences.



Scheme 2

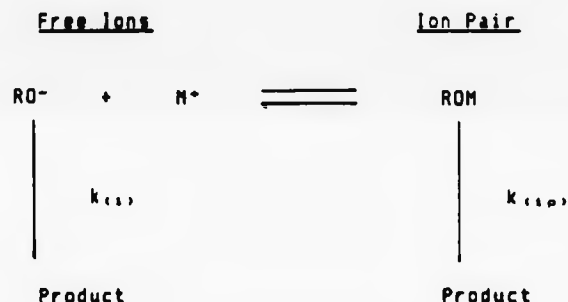
It was suggested that $k_{(c)} \sim k_{(b)} \gg k_{(a)}$, and that while the values of $k_{(a)}$ were believed to vary with the nature of the cation, the values of $k_{(b)}$ and $k_{(c)}$ were believed to be relatively insensitive to the nature of the cation. The proposal was made that the potassium alkoxides were more dissociated than the sodium alkoxides which in turn were more dissociated than the lithium alkoxides, and therefore the potassium alkoxides were expected to provide a greater proportion of free ions and solvent separated ion pairs than were the sodium or lithium alkoxides. If the free ions and solvent separated ion pairs reacted much faster than the contact ion pairs (as proposed), then this greater dissociation of the potassium alkoxides would explain the enhanced reactivity compared to the sodium and lithium alkoxides. Evidence to support the order of dissociation of alkali metal alkoxides in DMSO came from later conductometric studies by Exner and Steiner⁽²⁾ whose values for the ion pairing constants of the *t*-butoxides at 25°C are given below in table (2).



Table 2 : Ion pairing constants for t-butoxides in DMSO

	<u>LiOBu^t</u>	<u>NaOBu^t</u>	<u>KOBu^t</u>
K _{ip}	10 ⁶	10 ⁴	280

Since Cram proposed that $k_{ip} \sim k_{is}$, a simplified version of the scheme can be put forward, with the free ions and solvent separated ion pairs being combined into one term (referred to as "free ions" for ease of reference). This simplified scheme agrees with the suggestion of Acree⁽³⁾.



Scheme 3

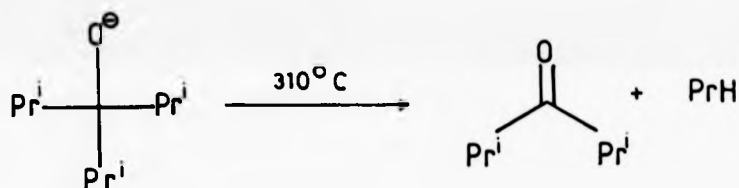
This scheme results in the rate equation given below, for first order disappearance of starting material, and first order appearance of product.

$$\text{Rate} = k_{is}[RO^-] = k_{ip}[ROM] + k_{is}[RO^-]$$

This leads to the expression for the observed rate constant given below, the derivation of which is given in Appendix 3.

$$k_{obs} = \frac{k_{is} + k_{ip}K_{ip}[M^+]}{1 + K_{ip}[M^+]}$$

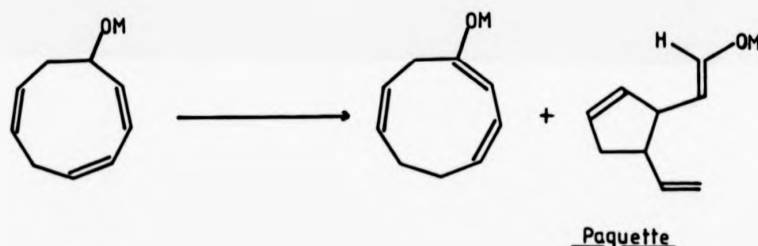
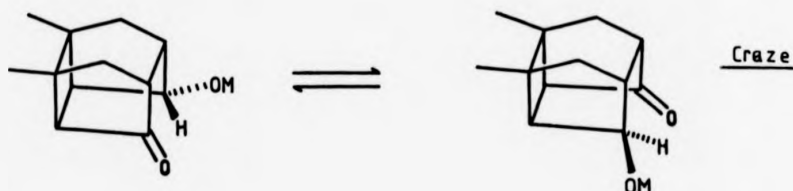
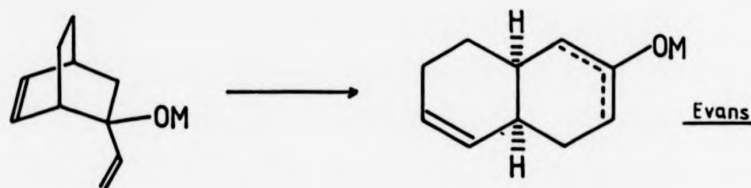
Contemporary with Cram's work on alkoxide cleavage reactions, Zook⁽⁴⁾ was investigating the same type of fragmentation reaction of alkali metal alkoxides. Zook's alkoxides were completely aliphatic, and generally required higher temperatures than the alkoxides used by Cram. Cram's leaving group was the benzylic carbanion of 2-phenylbutane which is resonance stabilised whereas the aliphatic carbanion leaving groups used by Zook possessed no resonance stabilisation. Zook also noticed that the potassium alkoxides fragmented faster than the sodium alkoxides which fragmented faster than the lithium alkoxides.



Zook (1959)

Following Cram's work, other reactions have been reported that show the same order of alkoxide reactivity ($\text{K}^+ \gg \text{Na}^+ \gg \text{Li}^+$). Evans⁽⁵⁾ reported the same order of alkoxide reactivity for the anionically accelerated oxy-Cope rearrangement, and reported a rate increase of 10^{17} for the reaction of the potassium alkoxide of the bicyclic dienol shown below, in the presence of 3 or more equivalents of 18-crown-6-ether compared to the reaction of the parent alcohol with no added base. Similar trends have also been reported by Craze and Matt⁽⁶⁾ working on hydride transfer in cage hydroxy-ketones, and by Paquette⁽⁷⁾

working on competition between [1,5]-hydride shifts and [3,3]-sigmatropic shifts in cyclononatrienol systems.

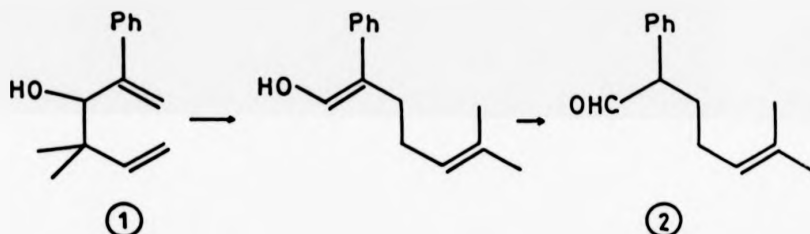


As yet, the available data is qualitative or at best semi-quantitative, and so accurate and reliable data with which to stringently test Cram's scheme and to determine its general applicability to alkoxide reactions has not become available.

The aim of this work has been to provide the data with which to test the scheme and to allow investigation of the effects of ion pairing on alkoxide reactivity. Two types of alkoxide reaction were chosen for use in this work. One reaction was an alkoxide fragmentation of the type used by Cram, for which he proposed his scheme, and the other reaction was an anionic oxy-Cope

rearrangement of the type used by Evans. The two types of reaction are similar in that they both involve formal collapse of a tetrahedral alkoxide with expulsion of a poor leaving group. In the case of the oxy-Cope rearrangement, the leaving group is trapped intramolecularly as part of a concerted reaction, whereas in the case of the S_N1 fragmentation reactions the leaving group breaks away from the other half of the molecule.

Previous work⁽¹⁾ describes the reasons for the selection of the dienol 4,4-dimethyl-2-phenyl-1,5-hexadien-3-ol (1) as the alcohol of choice for the investigation of the oxy-Cope rearrangement, and describes the synthesis of this alcohol.



Interpretation of the data from this work would be considerably simplified by complete deprotonation of the alcohols used, and so an extremely strong base was required. The reactions were to be followed by u.v. spectroscopy with the appearance of an enolate product being monitored at the wavelength of its maximum absorption. Because enolate solutions are sensitive to oxygen⁽²⁾, all of the work needed to be carried out under an inert gas, and argon was chosen for this purpose. Homogeneous solutions were required for the u.v. spectroscopy, which meant that both the alcohol and the base used needed to be soluble in the chosen solvent. The solvent of choice was dimethyl sulphoxide (DMSO) which allowed the anion of the solvent, methylsulphinyli methide

(usually referred to as the diasyl anion), to be used as the base. DMSO has a pK_a of 35.1⁽¹⁰⁾ in DMSO with alcohols having pK_a values of 27-31⁽¹¹⁾ in DMSO, and so it was expected that the alcohols used would be completely deprotonated in a solution of diasyl in DMSO. In addition to this, the diasyl concentration was such that it was always present as a large excess compared to the alcohol concentration, the excess varying between a factor of 30 and 1400, being typically about 300. It is expected that homo-hydrogen bonding of the alkoxide to alcohol that had not been deprotonated⁽¹²⁾ would not be encountered at alcohol concentrations between 10^{-4} and 6×10^{-3} mol/l. DMSO has a dielectric constant of 46.4 at 25°C⁽¹²⁾, is a good dissociating organic solvent, and has been used by many workers⁽¹³⁾ as the solvent in a variety of investigations involving strong base. In view of these factors, it was decided that for this initial work the DMSO/diasyl solvent/base system would be used rather than the possible alternatives which included cyclohexylamine/caesium cyclohexylamide which has been used by Streitwieser⁽¹⁴⁾, or 1,3-diaminopropane and its potassium salt (initially used by Brown⁽¹⁵⁾), and developed by Arnett⁽¹⁶⁾.

Initially it was hoped that an alcohol of extremely similar structure to those used by Crae could be used for the fragmentation reaction, with the reaction being monitored by the appearance of an enolate (from the ketone half of the fragmented alcohol). The requirements for a suitable substrate were that it would fragment at a reasonable rate with diasyl lithium, sodium or potassium at temperatures below 35°C, and that it would produce an enolate which could be observed in the u.v. To

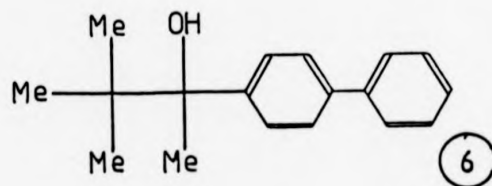
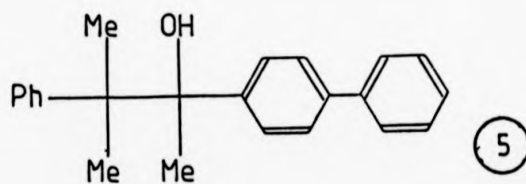
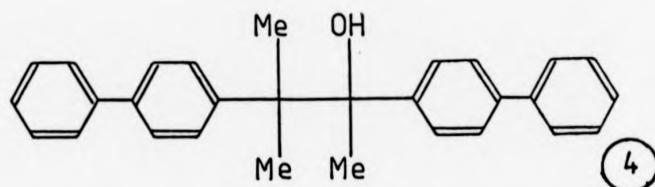
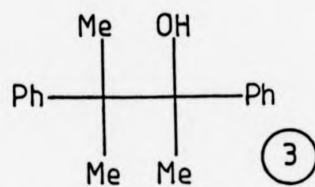
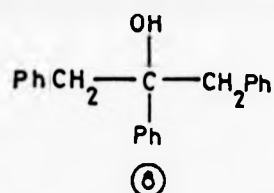
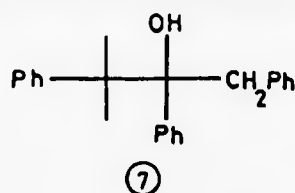


Figure (1)

obtain fragmentation at a reasonable rate, the part of the molecule which was to become the leaving carbanion usually possessed an aromatic group to stabilise the negative charge. For reasons described later, the alcohols shown in figure (1) were synthesised but proved to be unsuitable for monitoring of the fragmentation by this method.

The two alcohols (7) and (8) shown below were eventually chosen and proved to be suitable for monitoring of the reaction by u.v. spectroscopy. Alcohols of this type had been avoided earlier as it was expected that they would dehydrate relatively easily⁽¹⁷⁾ to give the appropriately substituted stilbenes, but at no time during use of these alcohols in fragmentation reactions were any products other than products of the fragmentation observed.



The Cope rearrangement⁽¹⁸⁾ and the oxy-Cope rearrangement⁽¹⁹⁾ have been previously reviewed, and so work on the alkoxide fragmentation, and anionic reactivities in DMSO and relevant non-aqueous systems is reviewed here. The reported crystal structures of benzylna and benzyllithium (the benzyl anion is the leaving group in the fragmentation of (8)), and the crystal structures of the lithium and potassium methoxides, and of the alkali metal *t*-butoxides are also reviewed.

pK_a's in non-aqueous solvents

Early work on measuring relative acidities of organic compounds and establishing crude pK_a scales in organic solvents was carried out in the 1930's by Conant and Wheland^{'17'} working in diethyl ether, and by M^cEwan^{'20'} working in benzene as solvent. Some of M^cEwan's values are given in table (3).

Table (3) : Selection of M^cEwan's pK_a's in benzene

<u>Acid</u>	<u>pK_a</u>
Ethanol	18
Acetophenone	19
Phenylacetylene	21
Diphenylamine	23
Triphenylethane	33
Cumene	37

Cram^{'21'} compiled a composite pK_a scale which used data from a variety of solvents, and effectively summarised the work on acidities in non-aqueous solvents up to the early 1960's, this scale being referred to as the MSAD (M^cEwan, Streitwieser, Applequist, Dessy, upon whose work the scale was based) scale. Work on an acidity scale in DMSO did not begin until after the development of the DMSO/diasyl solvent/base system, which was first reported by Corey and Chaykovsky^{'22'}. The use of the diasyl anion meant that solutions of very strong base could be prepared in DMSO, with those solutions being homogeneous. The diasyl anion has been used for virtually all work on acidities of weak acids in 100% DMSO.

Early pK_a measurements in 100% DMSO were reported by Steiner and Gilbert⁽²³⁾ using an overlapping series of indicators, and spectroscopically measuring the equilibrium constant for the reaction below, where HIn is the indicator, and AH is the acid in question.



The scale developed by Steiner was based on a value of 18.4 for the pK_a of 4-nitroaniline. This was the H_- value for this compound determined by Stewart and O'Donnell⁽²⁴⁾ in aqueous sulpholane based on an aqueous reference state. Steiner also reported data and pK_a values for mixtures of 0.11% water:99.89%, and 0.02% methanol:99.98% DMSO.

Direct measurements of acidities in DMSO using a glass electrode up to pK_a values of about 12 had been carried out by Kolthoff⁽²⁵⁾, and this technique was used by Ritchie and Uschold⁽²⁶⁾ to extend the range of directly measured pK_a values up to 28. Ritchie used diisyl caesium as the base in this work. Slow electrode response when working with compounds of very low acidity ($pK_a > 20$) made these readings at high pK_a values somewhat unreliable. Ritchie^(26b) reported that the agreement between the directly measured "absolute" (i.e. with reference to a standard in the solvent in which the measurements were made) pK_a values and those of Steiner was fortuitous. The reason for the good agreement was that the pK_a of the compound used to anchor Steiner's scale (4-nitroaniline) shows only a small change with change of solvent. If a different compound (with a larger change in pK_a on changing solvent) had been chosen to anchor Steiner's scale, then

the 2 scales would not have shown such agreement. Ritchie concluded that no single H_- acidity function could be constructed to be applicable to acids of different structures that would be valid in 100% DMSO.

Work on H_- values of a family of aniline indicators was carried out by Stewart and Dolean⁽²⁷⁾ using DMSO containing varying amounts of water. This scale was based on a value of 13.84 for the pK_a of 2,4-dinitrodiphenylamine, determined earlier by Stewart and O'Donnell⁽²⁸⁾. This work showed that the basicity of the hydroxide ion increased dramatically as the proportion of water in the DMSO decreased. However, the general usefulness of the H_- function was questioned, and Kreevoy⁽²⁹⁾ concluded that H_- functions cannot give accurate pK_a values when the structure of the acid varies appreciably from the structures of the indicators used to establish the scale.

In 1975, Bordwell⁽³⁰⁾ reported that a complete pK_a scale in DMSO had been established. The scale was based on direct measurements by potentiometric and conductometric methods, and by comparison of the results of these measurements with spectrophotometric results. An overlapping series of indicators was established, using an adaptation of the method of Steiner⁽³¹⁾, and the scale was extended from the region of direct measurements (approx $pK_a = 5$) upwards, to allow the pK_a of the solvent DMSO itself to be found, this value being 35.1. In earlier work, Bordwell⁽³⁰⁾ had arbitrarily anchored the pK_a scale on a value of 20.5 for fluorene. With the direct measurements becoming available, the pK_a values quoted in Bordwell's pre-1975 work were re-assessed and increased

by 2.1 pK_a units, thus giving the pK_a of fluorene in DMSO a value of 22.6. All of the work in the establishment of this scale used diisyl potassium as the base, and an extremely wide range of compounds have been assigned pK_a values in DMSO using this method, a few of which are shown in table (4).

Table (4) : Bordwell's pK_a 's for selected acids in DMSO

<u>Acid</u>	<u>pK_a</u>
Benzoic acid	8.7
Acetylacetone	13.3
Nitromethane	17.2
Cyclopentadiene	18.1
Dibenzyl sulphone	23.9
Acetophenone	24.7
Acetone	26.5
Phenylacetylene	28.8
Aniline	30.7
Triphenylmethane	30.7
Acetonitrile	31.2

Work by Arnett⁽³⁾ using calorimetric techniques to find the heats of deprotonation of a variety of compounds in DMSO using diisyl potassium as the base showed that there was a very good correlation between Bordwell's pK_a values and the heats of deprotonation. There was a reasonable correlation ($R = 0.97$) when using all compounds investigated (a total of 77), but deviations from the best fit line tended to fall into families of compounds

with similar structural features.

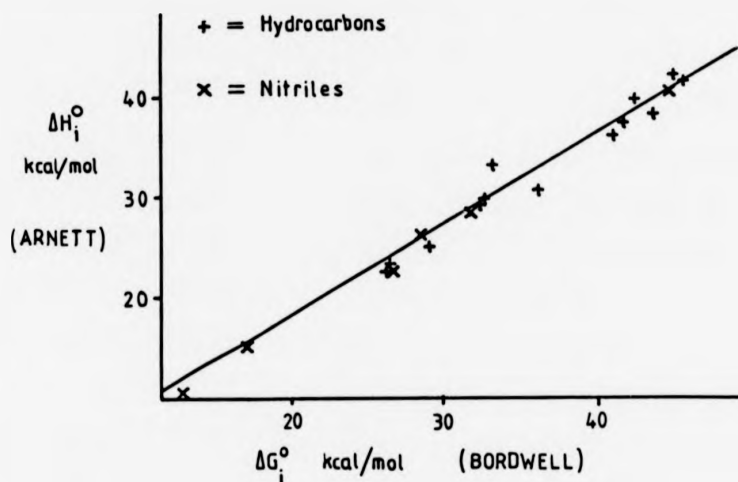


Figure (2) : Comparison of Arnett's heats of deprotonation with Bordwell's free energies of deprotonation (calculated from pK_a 's)

Arnett has extended this calorimetric technique to other solvent/base systems, and has compared potassium *t*-butoxide in DMSO with dimethyl potassium in DMSO and the potassium salt of 1,3-diaminopropane in 1,3-diaminopropane (KAPA in DAP). Brown⁽¹⁰⁾ has estimated from kinetic evidence that KAPA/DAP is about 10^6 times more basic than dimethyl K / DMSO. Experimental heats of deprotonation were found to be about 9 kcal/mol more exothermic in KAPA/DAP than in dimethyl K / DMSO, which in turn were about 4 kcal/mol more exothermic than in potassium *t*-butoxide/DMSO. The KAPA/DAP system was used to deprotonate DMSO, evolving between 8 to 10 kcal/mol, which corresponds to a pK_a difference of about 6 units. On attempted deprotonation of cyclohexylamine with KAPA/DAP, negligible deprotonation was observed. For *p*-phenyl toluene, partial deprotonation was observed

using KAPA/DAP, as had also been observed by Streitwieser⁽³²⁾ using caesium cyclohexylamide in cyclohexylamine (CsCHA/CHA), and so it was concluded that these two systems have similar basicities.

The CsCHA/CHA system has been extensively used by Streitwieser⁽³³⁾ in the study of the acidity of hydrocarbons. The scale is arbitrarily referenced to a value of 18.49 for the $pK(\text{CsCHA})$ of 9-phenylfluorene which had been determined in aqueous sulpholane using H₂ techniques. The solvent CHA has a low dielectric constant, and there is extensive ion pairing, with even caesium salts existing almost exclusively as ion pairs⁽³⁴⁾, and so Streitwieser refers to the pK_a values in this system as ion pair acidities. There is a correlation between the pK_a values of Bordwell and the ion pair acidities of Streitwieser, which fits the equation;

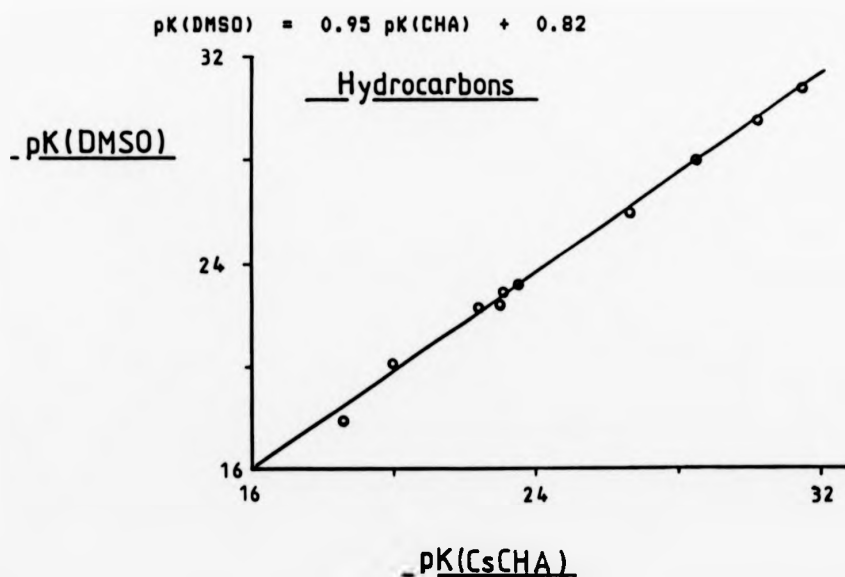


Figure (3) : Comparison of Bordwell's pK_a 's in DMSO for hydrocarbons with Streitwieser's pK_a 's in CHA

Streitwieser⁽³⁸⁾ has also established an acidity scale in tetrahydrofuran (THF) using cumyl caesium as the base, as the anion of THF is unstable and decomposes to give ethene and acetaldehyde enolate⁽³⁹⁾. As with Streitwieser's CHA scale, the THF scale is arbitrarily referenced to a pK_a of 18.49 for 9-phenylfluorene. This scale in THF also correlates well with Bordwell's scale in DMSO, fitting the equation;

$$pK(DMSO) = 0.94 pK(THF) + 1.42 \quad R = 0.996$$

The pK_a 's of simple alcohols had been reported by M^cEwen⁽²⁰⁾ to lie in the region of 16 to 19 in benzene, and by Ballinger⁽⁴⁰⁾ to be 15.5 for methanol and 15.9 for ethanol in water, and this appeared to be the generally accepted pK_a range for these compounds for many years. Whiting⁽⁵⁷⁾ reported using diisyl sodium as the base when titrating simple alcohols to stoichiometric endpoints using triphenylmethane as the indicator. When titrating alcohols in DMSO using diisyl potassium as the base, and triphenylmethane as the indicator, Steiner⁽³⁷⁾ reported observing endpoints after less than one equivalent of diisyl had been added. The endpoints were observed after addition of between 0.31 and 0.64 equivalents of diisyl potassium had been added. The reason for this was that in DMSO, the acidities of these alcohols are comparable to that of triphenylmethane, which is in marked contrast to the M^cEwen scale where there is a pK_a difference of 13 to 16 units between the acidities of alcohols and the acidity of triphenylmethane. In hydroxylic solvents, alkoxides are considerably stabilised by hydrogen bonding to the solvent, whereas

in a non-hydroxylic solvent such as DMSO (which is a good organic solvent for cation solvation, but a poor solvent for anion solvation) this hydrogen bonding is not present. This means that in DMSO, alcohols are many orders of magnitude less acidic than in hydroxylic solvents.

In solvents such as DMSO, "homohydrogen bonding" can occur when forming the alkoxides of alcohols using diethyl as the base. In this case, the alkoxide hydrogen bonds to the unconverted alcohol,



and so non-stoichiometric endpoints are observed when using potentiometric methods, or indicator methods when not taking this phenomenon into consideration. Using potentiometric measurements, Ritchie⁽³⁰⁾ measured the pK_a 's of alcohols in DMSO, but Bordwell⁽¹¹⁾ has reported that these values are 2.1 units too low because of the decision to anchor Ritchie's scale to the H_0 value of *p*-nitroaniline measured in aqueous sulpholane, and because of the slow electrode response at such low acidities. The pK_a values for the simple alcohols that can be calculated using Arnett's⁽¹³⁾ heats of deprotonation data are believed by Bordwell⁽¹¹⁾ to be affected by ion pairing, homohydrogen bonding, and the levelling effect of the solvent. Bordwell has determined the pK_a 's of simple alcohols using (2.2.2.) cryptand to eliminate ion pairing of the potassium alkoxides, and taking into account the effects of homohydrogen bonding and solvent levelling on the measured values. A comparison of the values of Ritchie⁽³⁰⁾, the values calculated from Arnett's data⁽¹³⁾, and the data of

Bordwell⁽¹¹⁾ is given in table (5).

Table (5) : pK_a's of simple alcohols in DMSO, from different sources

<u>Acid</u>	<u>pK_a values</u>		
	<u>Ritchie</u>	<u>Arnett</u>	<u>Bordwell</u>
MeOH	27.0	27.9	29.0
EtOH	27.4	28.2	29.8
i-PrOH	-	29.3	30.2
t-BuOH	29.2	29.4	32.2
H ₂ O	>29.0	27.5	31.4

This order of acidity found by Bordwell for simple alcohols is in the opposite direction to the gas phase order determined by Brauman⁽³⁹⁾ of $t\text{-BuOH} > i\text{-PrOH} > \text{EtOH} > \text{MeOH} \gg \text{H}_2\text{O}$. Brauman postulated that "the stabilisation property of alkyl groups for both positive and negative saturated ions in the gas phase arises from the polarisability of the alkyl group and its proximity to the charged centre". The difference in the DMSO solution phase acidity compared to the gas phase order shows "the importance of solvation and/or ion pairing to acidity ordering in solution"⁽¹³⁰⁾.

Work on ion pairing of alkali metal alkoxides in DMSO/dimethyl solutions was carried out in 1974 by Exner and Steiner⁽²⁾, using conductivity measurements. They reported that the ionic conductivities of anions were much greater than those of cations of comparable size, indicating that DMSO solvates cations

much more strongly than it solvates anions. They also measured the association constants for dimsyl lithium, sodium, potassium, and caesium, as shown in table (6).



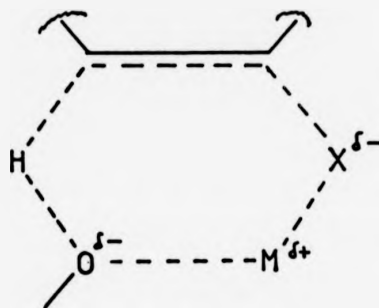
Table (6) : Ion-pairing constants for metal dimsyl solutions in DMSO, using the data of Exner and Steiner

Dimsyl Li	$K_{\text{dim}} = 370$
Dimsyl Na	$= 127$
Dimsyl K	$= 15$
Dimsyl Cs	$= 5$

It was observed that for the *t*-butoxides in DMSO, homohydrogen bonding was occurring when alcohol and alkoxide were present in the DMSO solution. The values of the ion pairing constants for the *t*-butoxides were determined, and it was reported that the ion pairing constants for the methoxides were larger, although no numerical values were quoted.

Work in 99% DMSO : 1% water was carried out by Baciocchi⁽⁴⁴⁾ on the reactivity of free and ion paired phenoxides in syn and anti elimination reactions of chlorides. For the syn elimination of trans-2,3-dihydro-2,3-dichlorobenzofuran, it was observed that the rate constant for the reaction of ion paired lithium phenoxide was only 30 times smaller than the rate constant for the reaction of the free phenoxide (using the nomenclature of the simplified version of Cram's scheme, $k_{\text{ip}} = 30.k_{\text{free}}$). For the anti elimination of 2-phenethyl chloride, it was observed that the rate of reaction of the ion pairs was so close to zero as to suggest negligible

reactivity of these ion pairs ($k_{11} \gg k_{12}$). The reason for the enhanced reactivity of the ion pairs in the syn elimination was believed to be the 6 membered transition state where an advantageous interaction between the leaving group and the cation is possible.



In reactions forming benzo-18-crown-6 ether (B-18-C-6) in 99% DMSO, Illuminati⁽¹²⁾ observed that addition of inert alkali metal salts (NaBr, KBr, RbBr, CsBr) to the reaction mixture enhanced the reaction rate, with only LiBr retarding the reaction rate. This result was in marked contrast to the model (non-crown forming) reactions that were carried out, where the reaction rate fell with increasing cation concentration (as is predicted by Cram's scheme⁽¹³⁾).

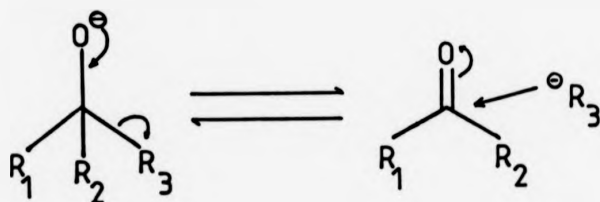


The results of their model reactions, and the crown forming reactions were explained in terms of the reacting phenoxides existing as an equilibrium mixture of free ions and ion pairs. For the model reactions, the rate of reaction of the ion pairs was negligible. The enhanced reactivity of the ion pairs in the crown forming reaction is attributed to the transition state binding the cation more strongly than either the starting material or the product. The rate enhancement was greatest for addition of potassium bromide, this corresponding with the fact that B-18-C-6 complexes the potassium cation strongest.

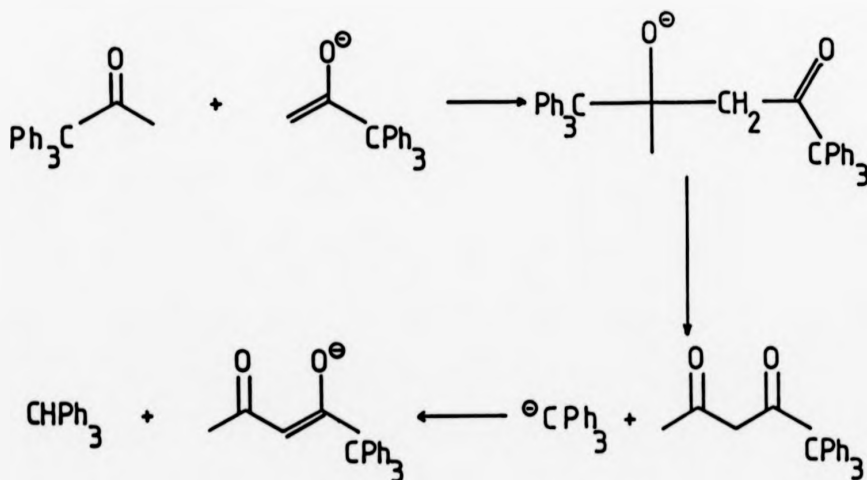
Further evidence of the rate depressing effect of added alkali halides on (non-crown forming) phenoxide reactions in 99% DMSO was provided by Mandolini⁴³. The rate of reaction of the ion pairs (lithium, sodium, potassium) was greatest for the potassium phenoxides, and slowest for the lithium phenoxides, because of the tighter binding of the lithium cation to the negatively charged oxygen (because of the larger charge density of the small lithium cation). There is a lower charge density on the potassium cation, and so it is not bound as tightly in the ion pair, and so shows greater reactivity than the lithium (or sodium) ion pair.

Fragmentation reaction

The type of alkoxide fragmentation reaction that has been used in this work to investigate ion pairing effects in DMSO is formally the collapse of a tetrahedral intermediate with the expulsion of a poor leaving group (a carbanion). As such, the fragmentation is the reverse reaction of addition of an organometallic compound to a ketone.



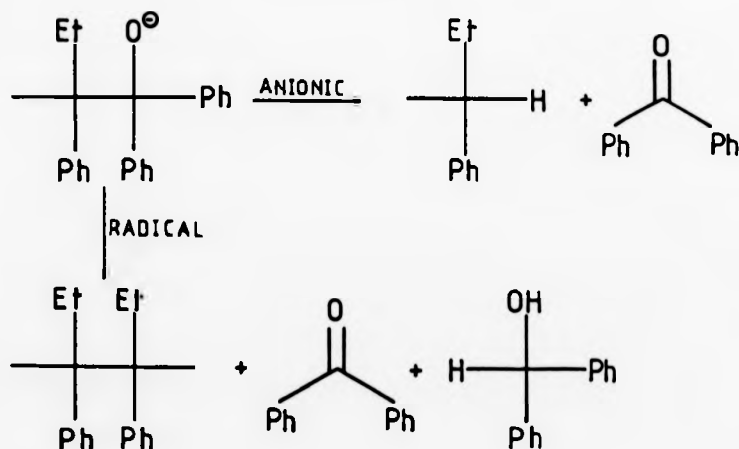
This type of fragmentation was originally observed by Ellison and Kenyon⁽⁴⁴⁾ in refluxing sodium hydroxide solution, with the highly resonance stabilised triphenylmethyl anion acting as the leaving group.



A similar reaction, with the same leaving group, was observed by

Zook and Greene(45) in the aldol condensation of 1,1,1-triphenyl-2-propanone, which gave triphenylmethane and the enolate of 1,1,1-triphenyl-2,4-pentadione as the products, as shown above.

As noted earlier, this type of fragmentation was chosen by Cram⁽¹⁴⁾ for his studies of electrophilic substitution at saturated carbon. A wide variety of substrate alcohols were synthesised, with the leaving group being the benzylic carbanion of 2-phenylbutane in almost every case. Using the nomenclature of the penultimate diagram, for Cram's fragmentations the group R_3 was kept constant, and it was noted that the rate of reaction was fastest for alcohols which had the bulkiest R_1 and R_2 groups. It was also noted that tertiary alcohols fragmented under milder conditions than did secondary alcohols. When both R_1 and R_2 were aromatic, then radical cleavage as well as anionic cleavage was observed, this being most apparent when using the lithium alkoxides.



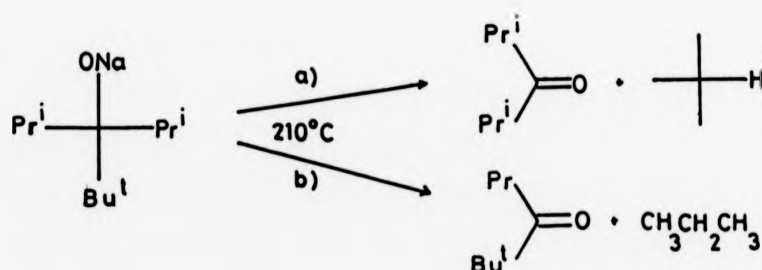
This was deduced by the formation of the hydrocarbon

3,4-diethyl-3,4-diphenylhexane (when R_1 and R_2 are phenyl), this being a mixture of the racemic and meso forms, by the formation of benzhydrol, and by the recovery of racemic starting material (from optically active starting material). Competition between anionic and radical cleavage when both R_1 and R_2 are phenyl is linked to the stability of the benzophenone ketyl⁽²¹⁾.

Cram found that the stereochemical course of the S_N1 reaction (retention, inversion or racemisation) was independent of (i) the stereochemistry of the leaving group, (ii) the concentration of the metal cation, (iii) the acidity of the electrophile (over a range of 14 pK_a units), (iv) the concentration of the electrophile. The stereochemical course of the reaction was dependent on the dielectric constant of the solvent, and its ability as a proton donor. Solvents with a low dielectric constant gave predominantly retention of configuration at the carbanionic centre, which was explained as being a result of the alkoxide existing almost entirely as contact ion pairs in these solvents, which leads to the formation of an asymmetric ion pair solvated at the front face by the proton donor and by the leaving group. This leads to protonation at the front face of the carbanion, and so gives retention of configuration. Solvents with a high dielectric constant which are good proton donors (eg. ethylene glycol) give predominantly inversion of configuration. This is explained as being a result of the ion pairing equilibrium lying in favour of the solvent separated ion pairs and the free ions. This results in the formation of a carbanion which is solvated at the front face by the leaving group, and at the back face by the (proton donating) solvent, and so the product is protonated from the back

face to give inversion. If the solvent has a high dielectric constant, but is a poor proton donor (eg. DMSO), then the carbanion exists long enough to become symmetrically solvated, thus giving a racemic product.

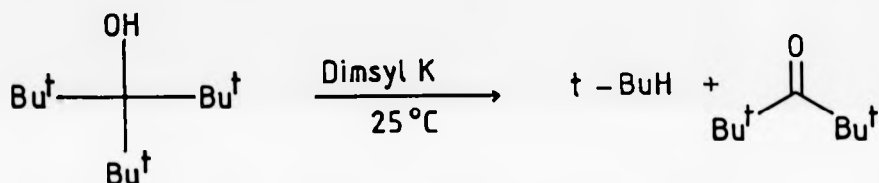
Contemporary with Craa's work on this reaction, Look⁽⁴⁾ noticed that on attempting to prepare a sodium alkoxide from di-*t*-butyl-neopentylethanol, extensive fragmentation occurred giving ketones and gaseous hydrocarbons as the products. This led to an investigation into the fragmentation of hindered tertiary aliphatic alkoxides, using the parent alcohols as solvent, with the reactions being carried out at relatively high temperatures (160° to 392°C). The proton source for these reactions was either excess alcohol, or the enolisable ketone product. As well as noticing that the rate of reaction of the alkoxides was in the order $K^+ \gg Na^+ \gg Li^+$, Look also reported that the most highly branched alcohols fragmented under the mildest conditions. Exact comparisons were difficult to make, as the range of temperatures during the fragmentations varied from run to run, the ranges being between 10°C and 98°C.



$$a) : b) = 3 : 2$$

From this work it was clear that the *t*-butyl anion was eliminated in preference to the *i*-propyl anion (the product ratio was 3:2 in favour of cleavage to the *t*-butyl anion, despite the statistical advantage of 2:1 for the *i*-propyl group) in the fragmentation of the sodium alkoxide of di-*i*-propyl-*t*-butylmethanol.

In 1978, Arnett⁽⁴⁴⁾ reported the instantaneous fragmentation of an aliphatic tertiary alcohol, tri-*t*-butylmethanol, at room temperature in diisyl potassium/DMSO. This was in contrast to the elevated temperatures required by Zook for the fragmentation of other slightly less sterically congested tertiary alkoxides.

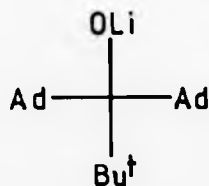


Arnett 1978

Arnett was investigating the heats of deprotonation of a series of alcohols in DMSO/diisyl potassium, and had observed a steady decrease in the heats of deprotonation as bulky groups were successively substituted on the α -carbon. For tri-*t*-butylmethanol, however, an extremely exothermic reaction was observed which gave a heat of deprotonation which was much greater than expected from the previously noted trend. Isolation of the quenched products showed no alcohol to be present in solution, only di-*t*-butyl ketone, with a gaseous product formed that was identified as isobutane. Arnett believed this reaction to proceed by an anionic cleavage mechanism rather than by a radical mechanism because of the total absence of

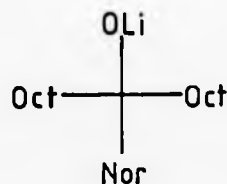
any radical coupling products and because of the initiation of the reaction by the strong base, diisyl potassium. The heat of reaction (-23.2 kcal/mol) corresponded closely with the strain difference between tri-t-butylmethane and 1,1-di-t-butylethane calculated by Schleyer⁴⁷ of -25kcal/mol, and Arnett concluded that this difference in strain energies was probably the driving force for the reaction.

A similar fragmentation of completely aliphatic tertiary alkoxides under mild conditions was reported by Lomas and Dubois⁴⁸. Despite using the less reactive lithium alkoxides (less reactive than the sodium or potassium alkoxides), fragmentation occurred in HMPA at 25° C. Use of diisyl lithium/DMSO gave fragmentation of only the most highly hindered alkoxides, whereas use of HMPA caused alkoxides that were stable in diisyl lithium/DMSO to fragment.



Fragments in diisyl Li/DMSO
and in HMPA

Ad = 1-adamantyl
Nor = 1-norbornyl



Fragments in HMPA, not
in diisyl Li/DMSO

Oct = 1-bicyclo[2.2.2]octyl

Using Allinger's MM2 force field⁴⁹, they calculated the difference in strain energies between the starting material and the products. They assumed that the reaction free energy was reflected by the difference in strain energies, and from this they

calculated the rate ratios expected for formation of the different anions from the alkoxides. Comparison of this with the experimental product distribution allowed an order of stability of the carbanions to be elucidated.

Table (7) : Order of stability of some aliphatic carbanions, using the data of Lomas and Dubois

<u>Carbanion</u>	<u>Relative stability</u>
1-Norbornyl	Most stable
<u>t</u> -butyl	
1-Adamantyl	
1-bicyclo[2.2.2]octyl	Least stable

These differences correspond to a pK_a range of less than 2 units. The methyl anion has been calculated to be pyramidal by ab initio calculations⁽¹⁰⁾, and if this is a general requirement for carbanions rather than a peculiarity of the methyl anion, then the order could be explained on steric grounds. The 1-norbornyl group is already deformed in the right direction for pyramidalisation, and the t-butyl group is sufficiently flexible to accommodate this, whereas the 1-adamantyl and 1-bicyclo[2.2.2]octyl groups are relatively rigid structures.

Lomas⁽¹²⁾ has also investigated the thermolysis of the alcohols used in the anionic fragmentation in HMPA. In contrast to the 25°C used for the anionic reactions, the thermolyses of these alcohols required temperatures between 155°C and 400°C. The reactions proceed by C-C bond fission to give radicals, with the usual products being a hydrocarbon corresponding to one of the R

groups of the tertiary alcohol, a ketone (from loss of the R group), and the secondary alcohol which corresponds to the ketone formed.

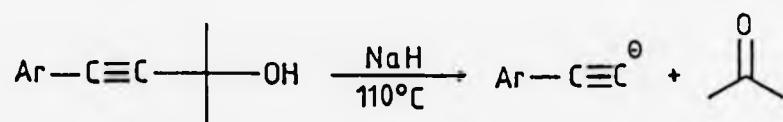
A reversible Grignard addition to ketones using crotylmagnesium chloride was reported by Benkeser⁽⁵⁷⁾, with the Grignard reagent being able to add to the ketone in the form of an α -methallyl group or a crotyl group. Benkeser concluded that the thermodynamically more stable crotyl products could be formed directly, or by a reversal process from the kinetic α -methallyl products. This also applied to the crotyllithium reagent.

The alkoxide fragmentation reaction has been used synthetically by Havens and Hergenrother⁽⁵⁸⁾ whose leaving group was the substituted acetylenic carbanion, and by Snowden⁽⁵²⁾ whose leaving group was the allylic carbanion.

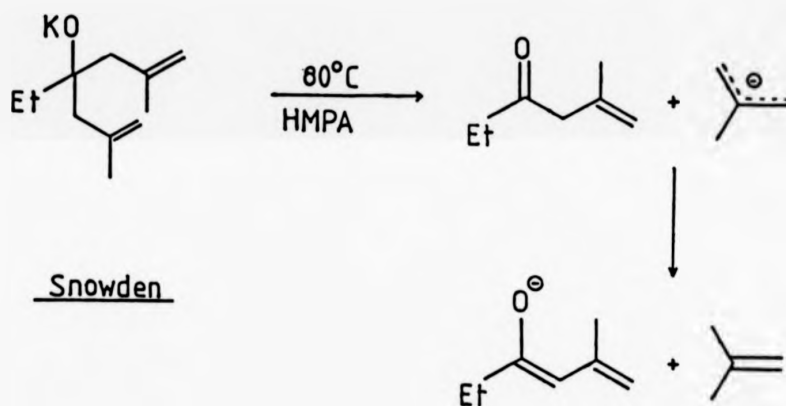
Fragmentation of cyclopropoxides to give propanones has been observed by De Puy⁽⁵⁹⁾, Jencks⁽⁶⁰⁾ and by Stirling⁽⁶¹⁾.

The fragmentation reaction has been observed in the gas phase, as well as in solution. Using a pulsed ion cyclotron resonance (ICR) spectrometer, and methoxide as the deprotonating agent, Arnett⁽⁶²⁾ observed fragmentation of tri-*t*-butylmethanol under conditions which showed only deprotonation for ethanol, *i*-propanol, *i*-butanol, neo-pentanol, and di-*t*-butylmethanol.

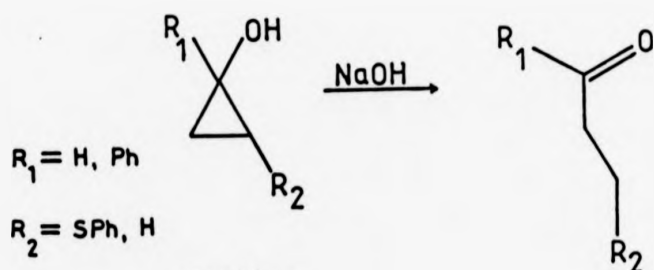
Using a CO₂ laser, fragmentation of 2-substituted 2-propoxides in the gas phase has been observed by Brauman⁽⁶³⁾. The conclusion was drawn that the reaction proceeded by a stepwise heterolytic pathway, and that the products reflected the stabilities of the intermediates rather than the stabilities of the final products, these conclusions being supported by their observed deuterium isotope effects.



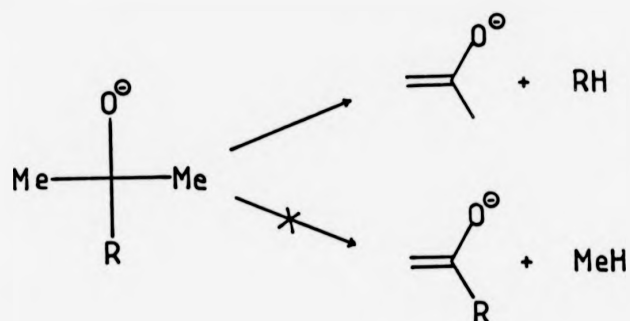
Havens



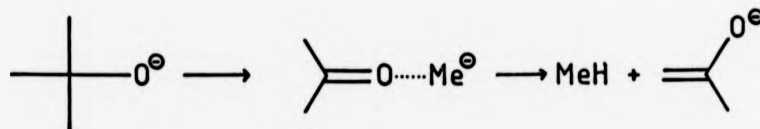
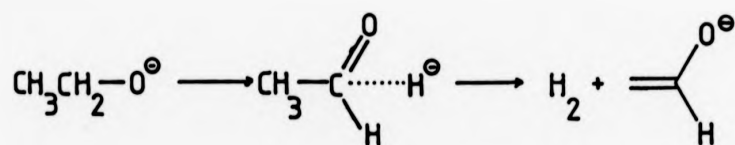
Snowden



Stirling



Hayes⁽²²⁾ has observed the gas phase fragmentation of ethoxide and *t*-butoxide using a 70 eV mass spectrometer, to give initially the ion-molecule complexes, which then dissociate to give the enolates along with hydrogen and methane respectively. Hayes concluded that both ab initio calculations (4-31G level) and kinetic isotope effects were consistent with the stepwise mechanism for elimination of hydrogen (from ethoxide) and methane (from *t*-butoxide), with the key intermediates being the "solvated" (by the ketone or aldehyde formed) hydride or methyl anions respectively.

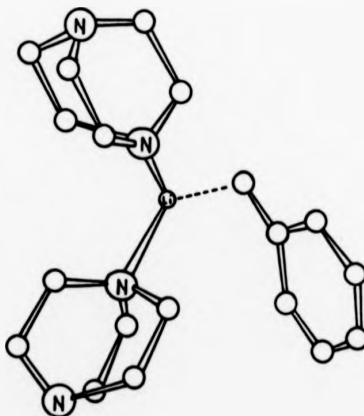


X-Ray Crystal Structures

The leaving group in the fragmentation of (8) is the benzyl carbanion, with the cation being lithium, sodium, or potassium. Crystal structures are available for benzyllithium (complexed with triethylenediamine (TEDA))⁽⁴⁰⁾, and with diethyl ether⁽⁴²⁾, and for benzylna⁺ (complexed with tetraethylethylenediamine (TMEDA))⁽⁴¹⁾, but no crystal structures are available for the cumyl anion which is the leaving group in the fragmentation of (7).

Benzyllithium / TEDA

The crystal structure of this compound was found to consist of "infinite polymeric chains oriented along the *a* axis parallel to the *c* direction". The empirical formula is one lithium



atom to one amine molecule, with the basic repeating unit consisting of a lithium atom, a benzyl group, and two half triethylenediamine cages. The average bond length in the aromatic rings was 1.40 Å, and the delocalised nature of the carbanion was shown by the bond length

of the benzyl carbon to the *ipso* carbon, of 1.39 Å. In this compound, the lithium is three coordinate. This is the first report of a three coordinate lithium in a carbanion, lithium being usually four coordinate. The structure of the repeating unit is shown above, the diagram being taken from reference (60).

Gan^(12*) reported that in toluene solution with one equivalent of TMEDA, benzyllithium formed aggregates, with the equilibrium shown below being important at concentrations above 0.1 mol/l.



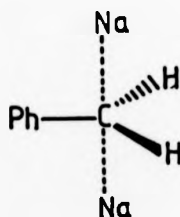
Benzyllithium / Diethyl ether

The crystal structure of this compound was determined to be polymeric, with the geometry about each benzyl carbon being approximately trigonal-bipyramidal. Each lithium atom interacts with two benzyl carbons and one ether molecule in order to propagate the polymeric chain. This differs from the benzyllithium/TEDA complex where the amine ligand has two nitrogens and can propagate the polymeric chain by interaction with one nitrogen from each of two TEDA molecules. Power^(12*) concluded that in concentrated solutions (1-2 molar), the crystal structures of organolithium compounds closely resemble the composition of the solutions.

Benzylsodium / TMEDA

The crystal structure of this compound was determined by Schleyer^(11*), and shows that this is a tetramer which prefers an eight membered ring rather than a tetrahedral arrangement, the first

organoalkali metal tetramer found which exhibits this preference. Each benzyl carbon is pentacoordinate, possessing trigonal-bipyramidal geometry. The complex has approximate D_{2h} symmetry. The four sodium atoms define a square, each edge of which is intersected by a benzyl carbon, and the resulting eight membered ring puckers into a crown conformation. The average geometry of the benzyl groups shows almost exactly the same variation in C-C-C angles and C-C bond lengths as reported by Power(3) for benzyllithium. The distance between the sodium atom and the benzyl carbon is 2.64 Å, and the distance between the sodium atom and the ipso carbon is 2.76 Å, believed by Schleyer to indicate bridging of these positions by sodium to some extent. A diagram showing the trigonal-bipyramidal geometry about the benzylic carbon is shown below.

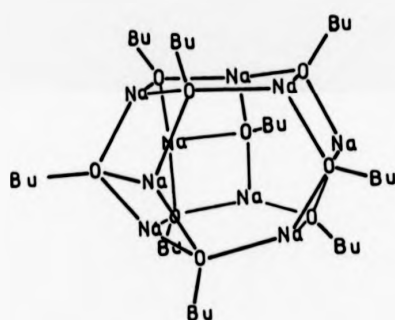


No crystal structures were available for any of the alkoxides used in this work, and so the crystal structures of other alkoxides are mentioned here.

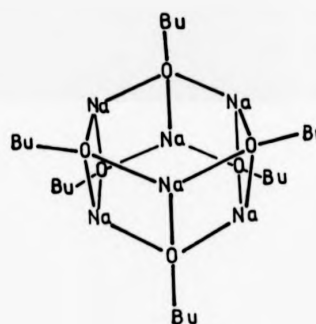
Sodium t-butoxide

The crystal structure of this molecule was determined by Greiser and Weiss⁽⁴³⁾, who reported that it existed as a mixture of

hexamers and nonamers. They originally reported that the space group was Cc, although this was later amended⁽⁶⁶⁾ to space group R3c. The cell consists of six hexameric units and six nonameric units, the centre of each unit lying on a triad axis. There is considerable rotational disorder associated with the *t*-butoxy groups. The hexamer has oxygen and sodium atoms alternately at the corners of a hexagonal prism, and the nonamer has its O-Na skeleton formed by two hexagons with three additional O-Na pairs between them. The nonamer and hexamer structures are shown below, the diagram being taken from reference (63).



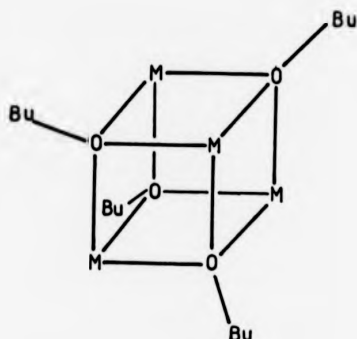
Nonamer



Hexamer

Potassium, rubidium and caesium *t*-butoxides

The structures of these alkoxides have been reported by Weiss⁽⁶⁶⁾ to consist of tetrameric units. The oxygen of the alkoxide and the cation are situated alternately at the corners of a slightly distorted cube, as shown below.



Lithium methoxide

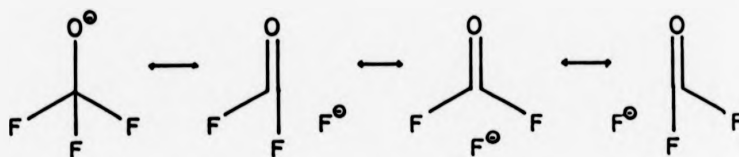
The crystal structure of this compound was determined by Wheatley⁽⁴⁰⁾, who reported that it existed as a polymer, with each lithium atom being surrounded by a tetrahedral array of oxygen atoms. Wheatley also investigated the crystal structures of the sodium and potassium methoxides, but found that firm conclusions could not be drawn from his experimental data.

The crystal structure of potassium methoxide has been reported by Weiss⁽⁴⁷⁾ to be tetragonal. It has a double layer structure with KOMe units arranged perpendicular to the plane with their methyl groups alternately on either side of the layer.

Tris(dimethylamino)sulphonium trifluoromethoxide⁽¹²⁴⁾

The alkoxide exhibits distorted tetrahedral geometry, with O-C-F bond angles of 116.5° and 115.8°, and F-C-F bond angles of 101.7° and 102.2°. The C-F bond lengths are much longer (1.397 Å and 1.390 Å) than in CF₃-OR (R = F, Cl, CF₃), where the bond lengths are 1.319 to 1.327 Å. The C-O bond length is much shorter (1.227 Å) than in CF₃-OR compounds, where the bond lengths are 1.365 to 1.395 Å. This lengthening of the C-F bonds, and shortening of the C-O bond

is attributed to negative hyperconjugation. Calculations estimate that this contributes about 20% to the bonding in the trifluoromethoxide.



CHAPTER TWO

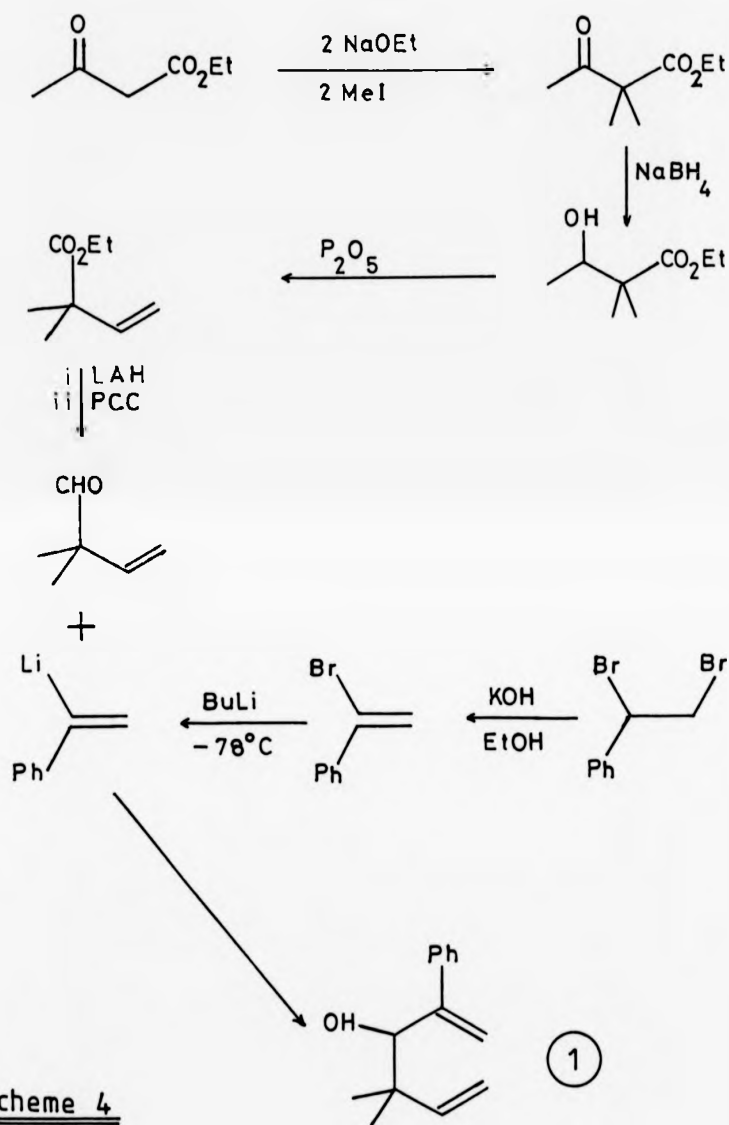
Discussion of synthetic work

6-Methyl-2-phenyl-5-heptenal (2)

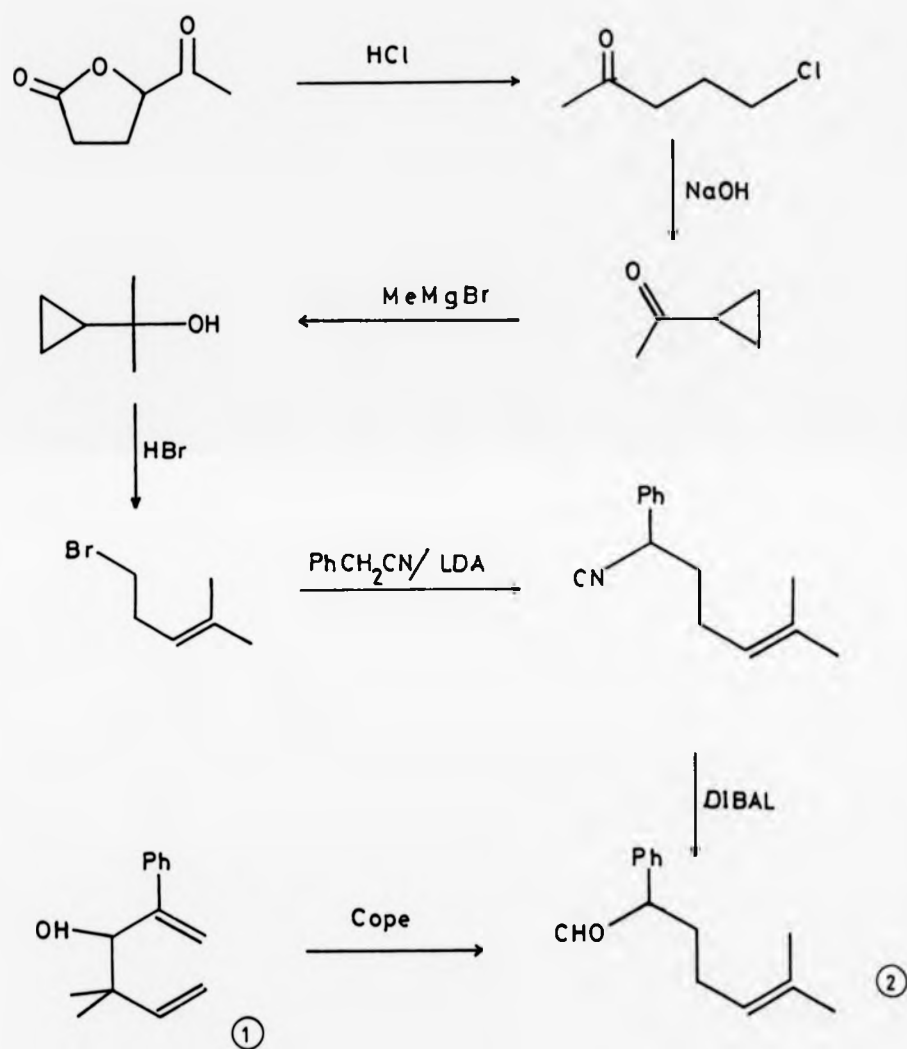
The synthesis of 4,4-dimethyl-2-phenyl-1,5-hexadien-3-ol (1) has been previously described (see Scheme 4), and the product of its oxy-Cope rearrangement had been identified by its spectral properties alone⁽⁶⁾. This aldehyde (2) has now been prepared independently to allow comparison with the product of the oxy-Cope rearrangement, thus constituting a classical structure proof by rational synthesis.

This synthesis is shown in Scheme (5), starting from acetyl butyrolactone, and used literature methods to convert it to 5-chloro-2-pentanone⁽⁴⁰⁾, and to convert this to methylcyclopropyl ketone⁽⁴¹⁾. These steps proceeded smoothly. An attempt to prepare 5-iodo-2-methyl-2-pentene directly from methylcyclopropyl ketone using the method of Biernacki⁽⁴²⁾ was made. This involved treatment of the ketone with methylmagnesium iodide, with this mixture then being added to concentrated sulphuric acid. Upon attempted distillation, the result was an intractable black tar. The conversion of methylcyclopropyl ketone to the halo-alkene was then carried out in two steps which used literature methods and proceeded smoothly. The preparation of 2-cyclopropyl-2-propanol was carried out by addition of methylmagnesium bromide to the ketone, with the alcohol being isolated. The required halo-alkene (5-bromo-2-methyl-2-pentene) was then prepared by addition of 48% hydrobromic acid at 15°C, as described by Julia⁽⁴³⁾.

An attempt to follow the same procedure as Farbre⁽⁴⁴⁾ in the reaction of the anion of phenylacetonitrile with 5-bromo-2-methyl-2-pentene using sodium amide as the base in



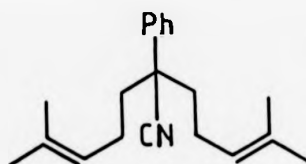
Scheme 4



Scheme 5

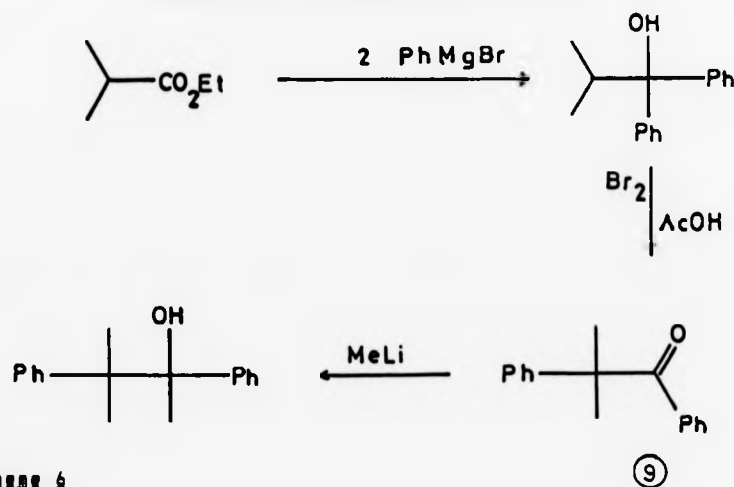
hexane solvent gave very poor results, and so the base used to deprotonate phenylacetonitrile was changed to lithium di-isopropylamide in THF solvent. This procedure gave the required nitrile in 31% yield.

One reason for the relatively low yield was the fact that the product nitrile could be deprotonated, and then react with more bromide. This resulted in the formation of the doubly alkylated species below, which was identified by its mass spectrum.



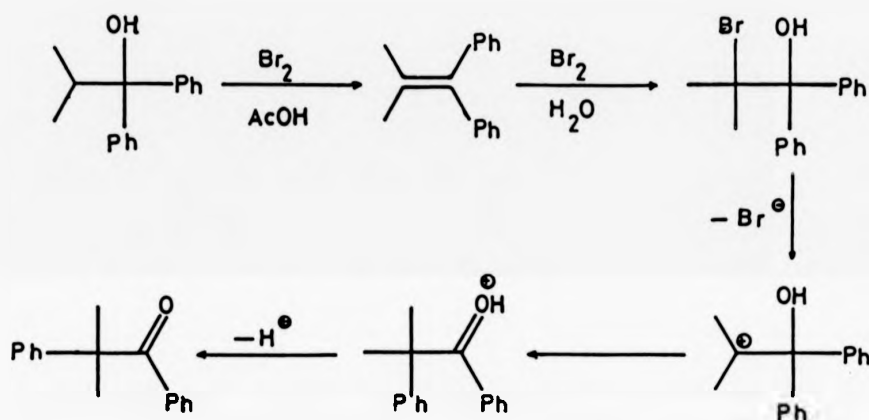
The final step involved conversion of the nitrile into the required aldehyde, using an adaptation of the procedure of Trofimenko⁽⁷²⁾. This reaction proceeded relatively smoothly, in 66% yield, using di-isobutyl aluminium hydride (DIBAL).

2,3-Diphenyl-3-methyl-2-butanol (3)



Scheme 6

This alcohol (3), which was expected to undergo S_N1 cleavage when treated with strong base such as dimsyl, was synthesised as described by Shilton⁽⁷³⁾, as shown in Scheme (6). The preparation of 1,2-diphenyl-2-methyl-1-propanone (9), involves the oxidative rearrangement of 1,1-diphenyl-2-methyl-1-propanol with bromine in 80% acetic acid/water, which is believed by Shilton⁽⁷³⁾ to proceed by the following mechanism.



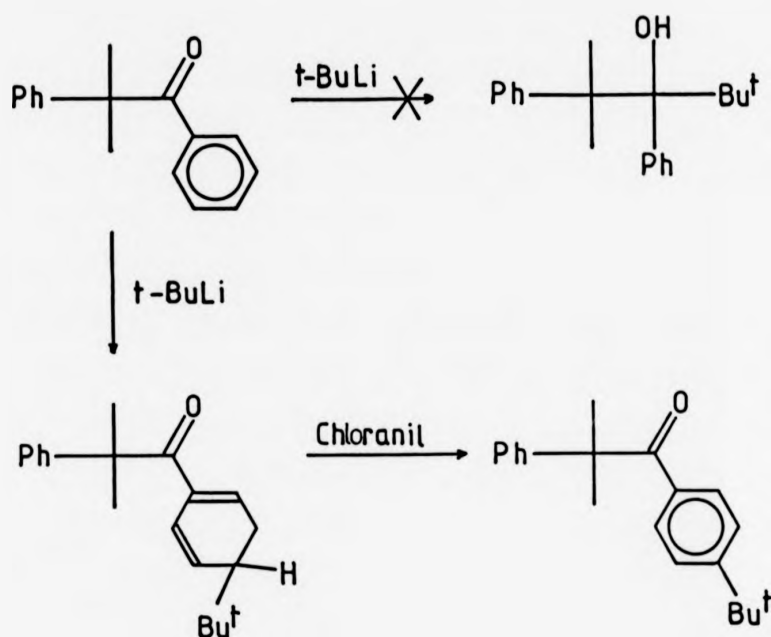
Initially the solution was not refluxed for long enough, and the alkene 1,1-diphenyl-2-methyl-1-propene was recovered as the major reaction product. Addition of this alkene to the reagent, with longer reflux time resulted in formation of the required ketone.

This overall rearrangement (alcohol to ketone) did not proceed smoothly. The reaction was monitored by g.l.c., and to remove the peaks due to the starting material, and then the alkene, it was necessary to add more than the stoichiometric amount of bromine. It became clear that brominated products were being formed, bromination probably occurring on one (or both) of the aromatic

rings. On distillation, two yellow liquid fractions were obtained, leaving a dark red-brown residue which contained (by g.l.c. analysis) no product ketone (9), but several compounds with long g.l.c. retention times, these being believed to be the brominated compounds. These brominated compounds were believed to be the main cause of the yield being only 56%, and were not characterised. The reaction of ketone (9) with methylolithium to yield the required alcohol (3) proceeded smoothly.

In order to provide another alcohol similar to (3), but which could not directly dehydrate, the synthesis of the tertiary alcohol 3,4-diphenyl-2,2,4-trimethyl-3-pentanol was attempted, by treating ketone (9) with *t*-butyllithium. Upon treatment of (9) with *t*-butyllithium, using the same procedure as for the reaction with methylolithium, it was clear that the reaction was not progressing smoothly. Analysis by g.l.c. showed that several products were formed, the major component being about 40% of the total mixture. After silica column chromatography, this major product was obtained as 85% of a mixture.

The i.r. spectrum of this fraction showed no O-H absorption, but did show a carbonyl at 1670 cm^{-1} , typical of an α,β -unsaturated ketone. The n.m.r. spectrum showed an intact *t*-butyl group, and also 3 protons at alkene-type chemical shifts. However, there were more aromatic protons present, compared to the alkene protons, than were expected for the working hypothesis compound, "*t*-butyl ketone 1". The n.m.r. spectrum could be interpreted, however, as a 3:1 mixture of "*t*-butyl ketone 1" and "*t*-butyl ketone 2".

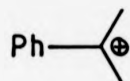


"t-butyl ketone 1"

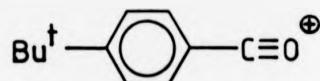
"t-butyl ketone 2"

Close examination of the g.l.c. trace of this fraction, using a slow temperature program, revealed a peak just behind the main peak, almost coincident with it, which was about 1/3 of the height of the major peak. If the working hypothesis were correct, then the minor component would be "t-butyl ketone 2", and the main peak would be converted into this second peak upon rearomatization of the cyclohexadienyl ring. This was attempted by refluxing the fraction with chloranil, a widely used reagent for rearomatization reactions⁽⁷⁾, in toluene. After purification by preparative t.l.c., the product was obtained 93% pure. The n.m.r. of this was totally consistent with that expected for "t-butyl ketone 2" with only 2 aliphatic signals (both singlets) in

addition to the aromatic signals. The i.r. spectrum showed a carbonyl at 1680 cm^{-1} , and the g.l.c./M.S. showed a (correct) molecular weight of 280 (two lower than the molecular weight obtained by g.l.c./M.S. analysis of "t-butyl ketone 1"), and major fragments at $m/e = 161$ and 119.



$$m/e = 119$$



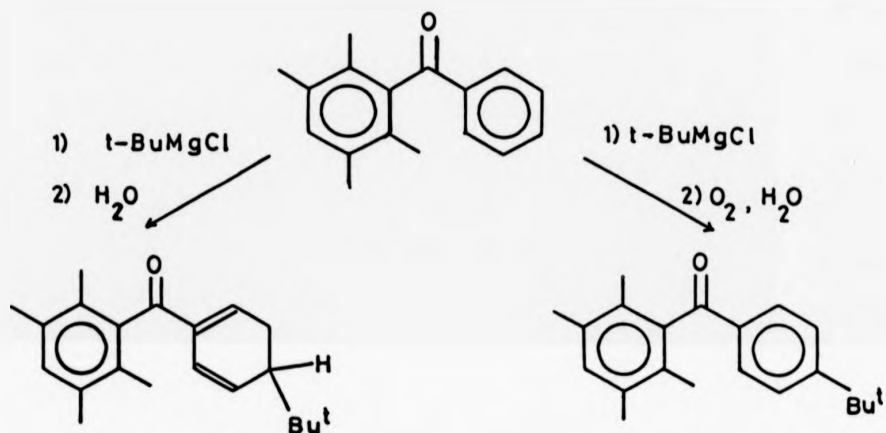
$$m/e = 161$$

The g.l.c./M.S. of "t-butyl ketone 1" showed major fragments at $M/E = 163$ and 119. This is in agreement with the structure proposed for "t-butyl ketone 1".

It is believed that because of the extremely large degree of steric hindrance at the carbonyl site, the carbonyl carbon being attached to a phenyl and a cumyl group, the bulky t-butyllithium attacked preferentially at the para position of the aromatic ring that is bonded to the carbonyl carbon. The t-butyllithium attacks in an analogous manner to 1,6 addition to a conjugated dienone, with the diene part of the molecule being present in this case as part of the aromatic ring. The t-butyllithium presumably attacks at the para position on the phenyl ring, rather than the similarly activated ortho positions, because of the lower degree of steric hindrance to attack at this position.

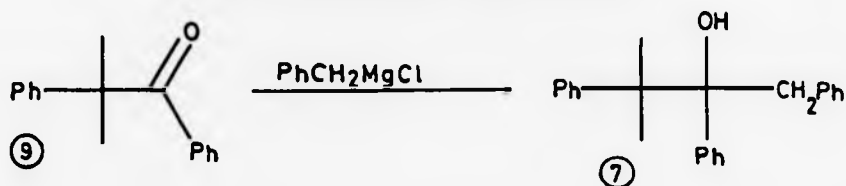
This type of conjugate addition to aromatic ketones is not common, but has been previously observed with Grignard reagents, with 1,4^{17a} and 1,6¹⁷⁷ addition occurring. This type of reaction

has been reviewed by Fuson (70). Fuson (77) reported that addition of *t*-butylmagnesium chloride to duryl phenyl ketone resulted in the formation of the product (below) containing a cyclohexadienyl ring when air was rigorously excluded from the reaction vessel. If air was not rigorously excluded, then the observed product was the fully aromatic ketone.



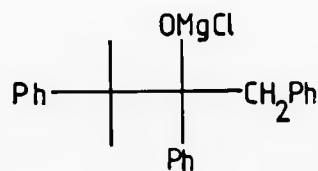
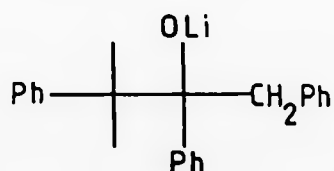
It was observed that on leaving "*t*-butyl ketone 1" in a stoppered flask for several months, no "*t*-butyl ketone 1" remained as it had been oxidised, presumably by the atmosphere, to "*t*-butyl ketone 2".

3-methyl-1,2,3-triphenyl-2-butanol (7)



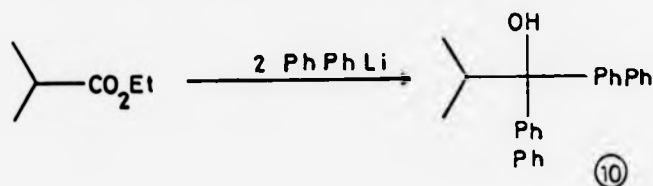
The synthesis of 3-methyl-1,2,3-triphenyl-2-butanol,

required the preparation of benzylmagnesium chloride⁽⁶³⁾. The Grignard reaction was carried out in diethyl ether, with refluxing for one hour after addition of the ketone (9), prepared as described for the synthesis of (3). The major impurity in the product alcohol (7) appears to be (by comparison of g.l.c. retention times with authentic deoxybenzoin, and from the i.r. spectrum of the impure alcohol) deoxybenzoin. This is the product of the S_N1 cleavage reaction which is to be studied in DMSO. The chloromagnesium alkoxide is formed during the synthesis of (7), and the lithium alkoxide is formed when (7) is treated with diisyl lithium, and so the fragmentation occurs in refluxing ether (when it is not required) as well as in DMSO in the presence of diisyl (when it is required).



2,3-di(biphenyl)-3-methyl-2-butanol (4)

The alcohol 1,1-di(biphenyl)-2-methyl-1-propanol (10) was synthesised using a variation of Shilton's procedure⁽⁷³⁾ for the preparation of 1,1-diphenyl-2-methyl-1-propanol, which used addition of phenylmagnesium iodide to ethyl isobutanoate. The Grignard reagent of 4-bromobiphenyl proved to be difficult to make, and the aryllithium of this bromide was made instead, using butyllithium to effect the lithium/bromine exchange. Attempts to



nake biphenyllithium in diethyl ether at -78°C gave no apparent product when reacted with ethyl isobutanoate, and when using THF as solvent at ice bath temperature, the major product was 4-butylbiphenyl. Using THF as solvent at -78°C gave the best results, and this was adopted as the procedure to use whenever biphenyllithium was required.

It was expected that the rearrangement of alcohol (10) to the ketone 1,2-di(biphenyl)-2-methyl-1-propanone (11) would proceed under milder conditions than the reflux used by Shilton⁽⁷³⁾ for the phenyl analogue of the reaction. This is because of the greater resonance stability of the carbonium ion intermediate, as biphenyl groups have now replaced the phenyl groups. However, because of the low solubility of (10) in 80% acetic acid, reflux temperatures were needed to dissolve the alcohol. This resulted in the reaction being less clean than expected.

Reaction of ketone (11) with methyl lithium (prepared as described by Bryce-Smith and Turner⁽⁸⁰⁾) proceeded smoothly to give alcohol (4).



In passing, it is worthwhile noting that when (4) which had

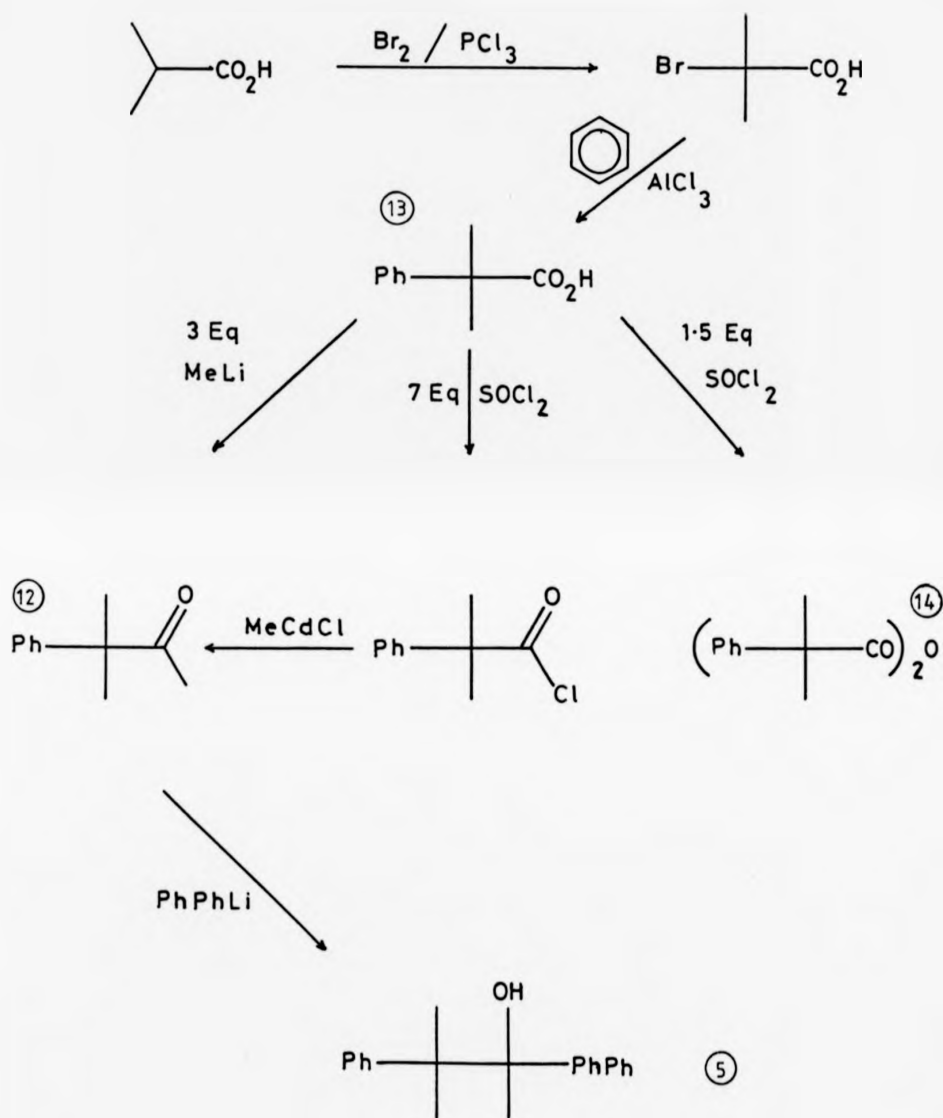
not been recrystallised was added to DMSO in the absence of added base, the S_N1 fragmentation (expected in the presence of dimethyl) occurred. After recrystallisation from toluene, however, no fragmentation occurred in DMSO without added base. The fragmentation of the crude alcohol is attributed to lithium isopropoxide (the reaction is quenched with isopropanol) which must have been precipitated along with alcohol (4) during the separation of (4).

2-biphenyl-3-methyl-3-phenyl-2-butanol (5)

The synthesis of 3-methyl-3-phenyl-2-butanone (12) was to have been carried out using the synthetic route described by Campaigne and Maulding⁽¹⁰⁾ shown in Scheme (7).

This route worked for the first two steps, to obtain 2-methyl-2-phenyl-propanoic acid (13). Conversion of this acid to the acid chloride was attempted using the prescribed 1.55 equivalents of thionyl chloride in toluene (Campaigne and Maulding used benzene as solvent). This resulted in a very small yield (15%) of the anhydride (14).

Reflux of acid (13) in benzene with 3.5 equivalents of thionyl chloride for thirty minutes resulted (after distillation of the thionyl chloride and benzene) in a mixture of acid chloride (34%), unconverted acid (20%), and acid anhydride (46%). Reflux of this mixture with a further 3.5 equivalents of neat thionyl chloride resulted in a 9:1 mixture of acid chloride to anhydride, which separated well on bulb to bulb distillation under reduced pressure. This acid chloride was then added to a solution of methylcadmium chloride, and after work-up the mixture was analysed by g.l.c. . This showed at least eight "major" components, and several other

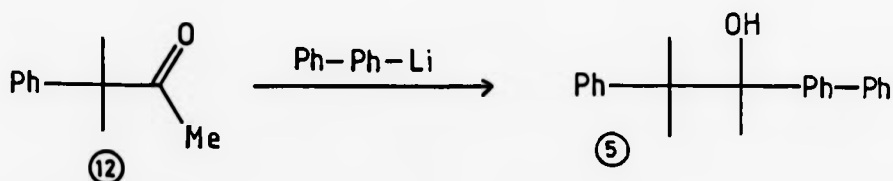


Scheme 7

minor components in the mixture. No one component represented more than 10% of the total mixture, and so this reaction was abandoned.

The ketone (12) was successfully prepared by the action of methyllithium on acid (13). A similar reaction had been reported by Bare and House⁽¹²⁾, using lithium hydride to form the carboxylate salt, and then one equivalent of methyllithium to form the ketone. They warned against the addition of the acid to the methyllithium solution, reporting that this usually resulted in formation of an alcohol by reaction of the methyllithium with any ketone present (which would be liberated in the presence of any water).

Use of the Bare method gave disappointing yields of ketone (12), and so the reaction was carried out by adding a solution of acid (13) dropwise into a well stirred solution of 3 equivalents of methyllithium. This reaction proceeded in excellent yield, with little or no trace of side-reaction products. The reaction to form 2-biphenyl-3-methyl-3-phenyl-2-butanol (5) proceeded reasonably, using ketone (12) and biphenyllithium (prepared as described earlier).



CHAPTER THREE

General considerations in the anionic reactions

A great deal of time and effort was expended in finding suitable substrates and conditions for the alkoxide reactions. The requirements for the substrates were: (i) that the reaction was first order, (ii) that it produced an enolate whose appearance could be monitored by u.v. spectroscopy, and (iii) that it proceeded at a reasonable rate (half lives between 0.25 seconds and about 4 hours) at temperatures below 30°C. It had been decided that the main base/solvent system to be used was dimsyl/DMSO, and so the product enolates needed to absorb well away from the absorption of the dimsyl solutions. In addition to this, another base/solvent system was investigated to determine its usefulness as a medium for the alkoxide reactions, this being t-butoxide/t-butanol.

t-Butoxide/t-Butanol

It had been hoped that it would be possible to follow the anionic oxy-Cope rearrangement of (1) using u.v. spectroscopy, in the t-butoxide/t-butanol base/solvent system.

In order to obtain the maximum absorption wavelength of the enolate of the aldehyde 6-methyl-2-phenyl-5-heptenal (2), aldehyde (2) was added to solutions of sodium t-butoxide in t-butanol, and potassium t-butoxide in t-butanol. The u.v. spectra that were observed showed the maximum absorption wavelengths to be 305 nm (for Na⁺) and 307 nm (for K⁺), with extinction coefficients of approximately 10^4 in each case. The absorptions appeared rapidly, then decayed slowly (over 2-3 hours), possibly due to slow diffusion of oxygen and/or atmospheric moisture into the u.v. cells, causing quenching of the enolates. The u.v. cells that were used were normal u.v. cells that had B14

sockets attached to them, and the sockets were sealed with rubber septum caps. Before use, the cells were flushed with argon using inlet and outlet needles. The parent aldehyde showed no u.v. absorption in *t*-butanol in the region of the absorption which appeared after addition of *t*-butoxide, neither does it show any absorption above 300 nm in DMSO. The position of the enolate absorption in DMSO is 352 nm (for the sodium enolate), and a solvent shift of 47 nm on moving from DMSO to *t*-butanol seemed very large. Substantial solvent shifts have been reported by Arnett¹⁴ for alkali metal enolates, for example the lithium enolate of dibenzoylmethane has a maximum absorption at 361 nm in DMSO, and a maximum absorption at 312 nm in carbon tetrachloride.

When a solution of the aldehyde in DMSO (4ml) (no absorption >300 nm) was treated with potassium *t*-butoxide (0.4 ml of 0.52 molar solution), a new absorption appeared at 343 nm. This represents a solvent shift of 36 nm from 100% *t*-butanol to 90% DMSO/10% *t*-butanol for the potassium enolate of (2). The same process was carried out for 1-phenyl-2-propanone, which forms a very similar enolate, to demonstrate that the solvent shifts were not just a property of the enolate of aldehyde (2). The enolate of 1-phenyl-2-propanone was also shown to have similar solvent shifts.

Table (8) : U.V. data for enolates in different solvent/base systems

	<u>1-phenyl-2-propanone</u>	<u>Aldehyde (2)</u>
<i>t</i> -BuOH/KOBu ^t	309 nm	307 nm
DMSO/KOBu ^t	339 nm	343 nm
DMSO/Diisyl Na	-	352 nm

The u.v. data given in table (8) indicates that the difference in

the observed absorption maxima in t-butanol and DMSO is the result of a large solvent effect, rather than non-formation of the enolate in t-butoxide/t-butanol. This type of effect has been observed by Bunce⁽¹⁰⁾, on the u.v. spectrum of triphenylmethyl lithium, with the absorption maximum changing from 446 nm in diethyl ether to 500 nm in THF or diaethoxyethane (DME). This was interpreted as being due to greater dissociation of the ion pair from being a contact ion pair in ether to being a solvent separated ion pair in THF or DME. This explanation would fit with the observed behaviour of the enolate of (2), with the absorption being at longer wavelength in the more dissociating solvent (DMSO), and at shorter wavelength in the less dissociating solvent (t-butanol), corresponding to the presence of contact ion pairs in t-butanol, and solvent separated ion pairs or free ions in DMSO.

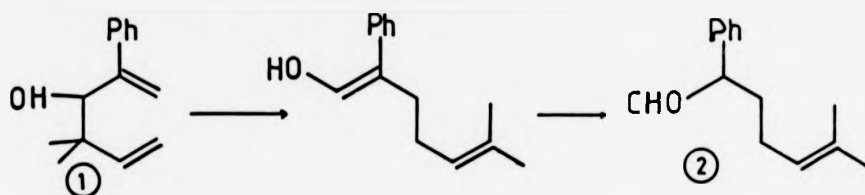
Having established the position of the absorption maximum of the enolate, attempts were made to follow the anionic oxy-Cope rearrangement by u.v. spectroscopy. Using sodium t-butoxide/t-butanol, however, no reaction was observed at 27°C over a period of 3 days, the alcohol (1) being unchanged (monitoring the reaction by capillary g.l.c.), and no reaction was observed after heating this solution at 50°C for 2 hours. Addition of an excess of 18-crown-6 ether to the solution, and heating to 50°C for one hour also gave no reaction. Use of potassium t-butoxide also gave no reaction under the above conditions.

From these results it appeared that the anionic oxy-Cope rearrangement of (1) does not proceed at a detectable rate when using the t-butoxide/t-butanol solvent/base system, and use of this system for this purpose was discontinued.

An attempt was made to observe the enolate of acetophenone in potassium *t*-butoxide/*t*-butanol, to see whether the S_N1 cleavage of the tertiary alcohol 2,3-diphenyl-3-methyl-2-butanol (3) could be followed by u.v. spectroscopy in this solvent/base system. No new u.v. absorption was observed on adding potassium *t*-butoxide solution to a solution of acetophenone in *t*-butanol, and so it was concluded that *t*-butoxide is not sufficiently basic in *t*-butanol to quantitatively deprotonate acetophenone. In DMSO, it would be expected that the *t*-butoxide anion would quantitatively deprotonate acetophenone (pK_a 's in DMSO are *t*-butanol = 32.2⁽¹¹⁾, acetophenone = 24.1⁽¹⁰⁾), but in hydroxylic solvents alkoxide anions are much less basic because of hydrogen bonding to the solvent. In water, the pK_a of acetophenone is 18.24⁽¹²⁾, and the quoted pK_a of *t*-butanol in water is approximately 19 using McEwan's⁽²⁰⁾ value in benzene referring it to Unnack's⁽¹⁷⁾ value for methanol in water (as used by Lowry and Richardson⁽¹⁸⁾). As can be seen from these values, acetophenone and *t*-butanol have similar acidities in water (and would be expected to have similar acidities in *t*-butanol), and so it is not unreasonable that *t*-butoxide has been observed not to quantitatively deprotonate acetophenone in *t*-butanol. Therefore the use of this solvent/base system for this purpose was discontinued.

Suitability of the alcohols as substrates

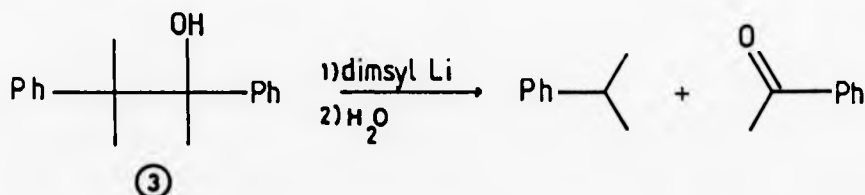
It had previously been decided that the oxy-Cope rearrangement of 4,4-dimethyl-2-phenyl-1,5-hexadien-3-ol (1) was to be investigated in DMSO using the dimsyl anion as the base. The synthesis and thermal oxy-Cope rearrangement of this alcohol have been previously described⁽¹⁹⁾, as has the thermal rearrangement of



the trimethylsilyl ether of (1), and the preliminary work on the anionic rearrangement in DMSO. The rearrangement of this alcohol was investigated using dimsyl lithium, dimsyl sodium, and dimsyl potassium, with or without added alkali metal halides.

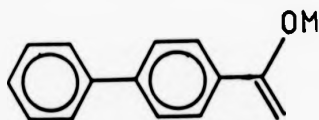
To provide another alkoxide reaction, in addition to the anionic oxy-Cope rearrangement, with which to test Cram's scheme, it was decided that a fragmentation of the type used by Cram for his stereochemical investigations would be used.

The alcohol 2,3-diphenyl-3-methyl-2-butanol (3) was synthesised, and its cleavage in dimsyl lithium/DMSO monitored by g.l.c at 20°C.



The products of this cleavage reaction were identified by g.l.c./M.S. analysis and by g.l.c. co-injection, as acetophenone and cumene. The intention was to follow the cleavage using u.v. spectroscopy to monitor the appearance of the acetophenone enolate, but this proved to be impractical since the acetophenone enolate absorption maximum (328 nm, extinction coefficient $\sim 10^4$) occurs on the side of the dimsyl absorption. Therefore,

any slight change in the dimsyl absorption during the kinetic runs would result in changes in absorption at the maximum absorption wavelength of the enolate, where the reaction would be monitored. This would lead to an apparent deviation from first order kinetics, and so would give an erroneous rate constant for the reaction. This reaction, therefore, could only be used when employing extremely dilute dimsyl solutions which had only very small absorptions at this wavelength. This meant that a different alcohol was required, which would give an enolate absorption well away from the dimsyl absorption. The replacement of the phenyl groups in (3) with biphenyl groups to give 2,3-di(biphenyl)-3-methyl-2-butanol (4) was expected to increase the rate of fragmentation, to give an enolate with an absorption maximum well away from the dimsyl absorption, and to increase the extinction coefficient of the enolate.



Enolate of (15)

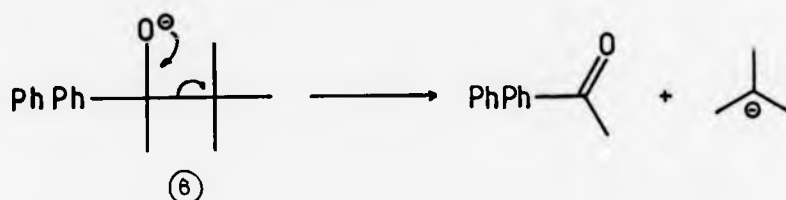
All of these expectations were correct. On treatment of (4) with dimsyl lithium, a new absorption was observed at 373 nm (extinction coefficient approximately 2000), and this was also observed when 1-biphenylethanone (15) was treated with dimsyl lithium. The apparent position of the enolate absorption depends on the dimsyl absorption, and the true enolate absorption was found by subtraction of the dimsyl absorption (which had been run earlier, with no other solutions present) from the absorption of the enolate/dimsyl solution.

Trial fragmentations, monitored by g.l.c., using dimsyl lithium showed complete disappearance of starting material to give two new products. On mixing of the dimsyl and alcohol solutions, initially a pink colour was observed for about 0.1 seconds before the solution turned the yellow colour of the enolate of (15). The cause of this pink colour is not known. The identity of the products was confirmed by g.l.c./M.S. comparison with authentic material (a sample of 2-biphenylpropane (16) was synthesised as described in the experimental section, and (15) was purchased from Aldrich Chemical Company), and by g.l.c. co-injection.

Attempts to follow the first order reaction by u.v. spectroscopy using a Hi-Tech SFA-11 stopped flow apparatus proved unsuccessful, as even at just above the freezing point of DMSO, using relatively concentrated dimsyl lithium (0.1 molar), only very small absorption changes were observed, indicative of the exponential tail of a very rapid reaction (compared to the other alkoxide reactions described in this work, with a half life of less than 0.2 seconds). This meant that the fragmentation of this alcohol could not be monitored using the available equipment.

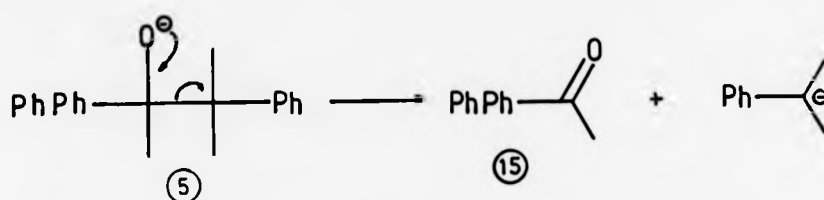
In view of this, 2-biphenyl-3,3-dimethyl-2-butanol (6) was prepared, as it was hoped that this alcohol would fragment to give the same enolate as resulted from fragmentation of (4), at a much slower rate since the leaving group was expected to be the *t*-butyl anion which is not resonance stabilised, unlike the other carbanions reported in this thesis. Fragmentations yielding aliphatic carbanions have been observed by Dubois and Lomas⁽⁴⁸⁾, Arnett⁽⁴⁹⁾ and Zook⁽⁵⁰⁾, as noted in the review.

Expected reaction



The attempted fragmentation of this alcohol was carried out initially using diisyl lithium as the base. After 70 minutes at 20°C, and a further 55 minutes at 45°C in solution with 0.03 molar diisyl lithium, no new products were observed by g.l.c. Reasoning from the anionic oxy-Cope rearrangement of (1) which shows a rate enhancement of 11300 for the potassium alkoxide compared to the lithium alkoxide (at the same metal ion concentration and temperature), a solution of (6) was treated with a 0.1 molar solution of diisyl potassium and left for 24 hours at 20.0°C. No new peaks were observed by g.l.c., and after heating the solution to 40°C for 30 minutes, there were still no new peaks observed. Raising the temperature above this level would result in decomposition of the diisyl potassium⁽¹⁰⁾ thus making it impractical to attempt to observe the fragmentation at higher temperatures. Therefore fragmentation of (6) does not proceed at a measurable rate under these conditions, and therefore this makes this alcohol unsuitable for kinetic study.

In order to work with an alcohol which would undergo the fragmentation at a reasonable and measurable rate, and would give a u.v. absorption from the enolate formed, that would be well clear of the diisyl absorption, 2-biphenyl-3-methyl-3-phenyl-2-butanol (5) was prepared.

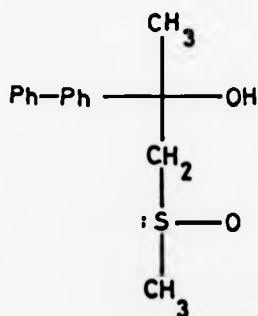


This alkoxide was expected to fragment with the cumyl anion as the leaving group, and so should fragment at a reasonable rate (as does alcohol (3) which possesses the same leaving group), and after fragmentation will give the enolate of (15) with its absorption maximum at 373 nm. On trial kinetic runs, however, it was found that as well as the first order increase of the enolate absorption from the product enolate, there was a steady linear increase in absorption, which continued long after the end of the first order reaction. This behaviour was observed when using both diisyl lithium and diisyl sodium.

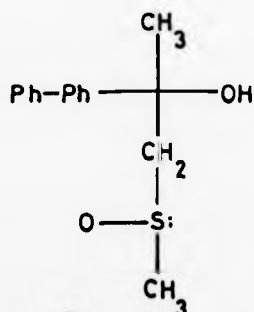
A preparative scale fragmentation was carried out using diisyl lithium and alcohol (5) at 35°C for 45 minutes, followed by quenching with dilute hydrochloric acid, and extraction with chloroform. The products of this reaction were cumene (identified by g.l.c. co-injection), 1-biphenylethanone (15) (identified by n.m.r. and i.r. spectra), and another product or set of products which were polar and had long g.l.c. retention times. The same preparative scale reaction was carried out using ketone (15) and diisyl lithium (heated at 35°C for 6 hours). After quenching and extraction, the products were recovered ketone and two new products (in equal ratios) which gave matching spectra (i.r. and M.S.), identical t.l.c. R_f values, and identical g.l.c. retention times, as the products of the preparative scale fragmentation. These compounds proved impossible to separate by preparative t.l.c., with the u.v.

active band being split into two, to give two "fractions", the upper half of the band giving one compound as the major component, and the lower half of the band giving the other compound as the major component.

Corey⁽¹⁰⁾ reported nucleophilic attack by diethyl sodium on cyclohexanone, and by diethyl lithium on cycloheptanone, to give β -hydroxy sulfoxides. The working hypothesis, therefore, was that diethyl lithium had nucleophilically attacked ketone (15) (after it had been formed by S_N1 cleavage of alcohol (5) , and in competition with deprotonation to give the enolate) to give a β -hydroxy sulfoxide. Asymmetrically substituted sulfoxides are chiral at sulphur⁽¹¹⁾, and as the β -hydroxy sulfoxide has another chiral centre in the molecule, separated from the asymmetrically substituted sulfoxide by a methylene group, it will exist as diastereoisomers (17a) and (17b). The spectroscopic data supported the hypothesis that the two products were diastereoisomeric β -hydroxy sulfoxides.



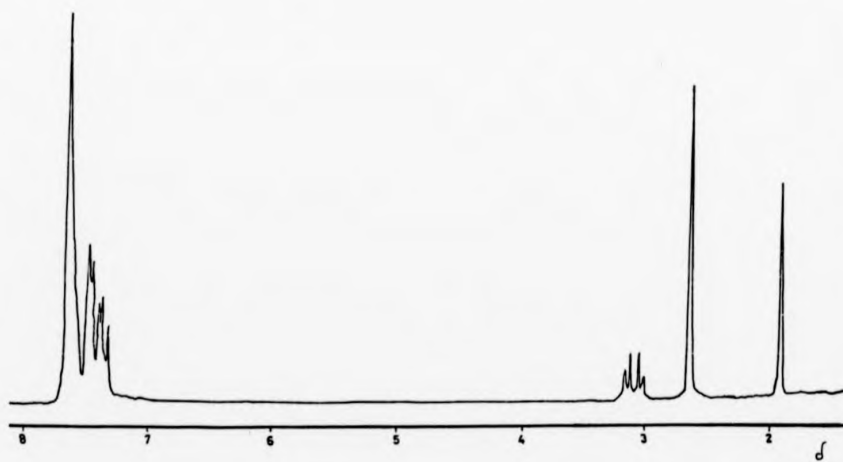
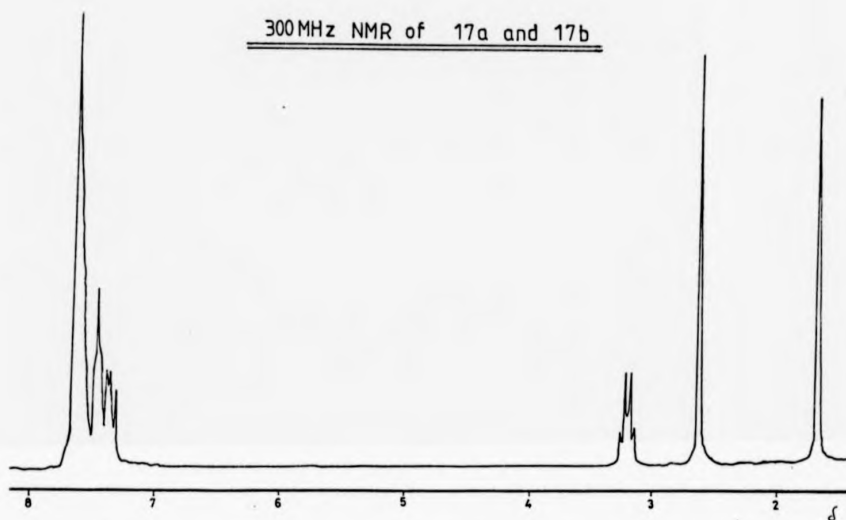
(17a)



(17b)

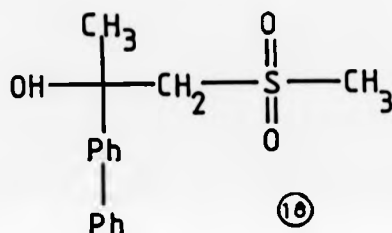
The n.m.r. spectra of the 2 "fractions" were used to identify which signal originated from which compound, and so the

300MHz NMR of 17a and 17b



n.m.r. spectra of each of the two compounds could be elucidated. The mixture of the 2 compounds believed to be diastereoisomeric β -hydroxy sulfoxides was treated with 3-chloroperbenzoic acid.

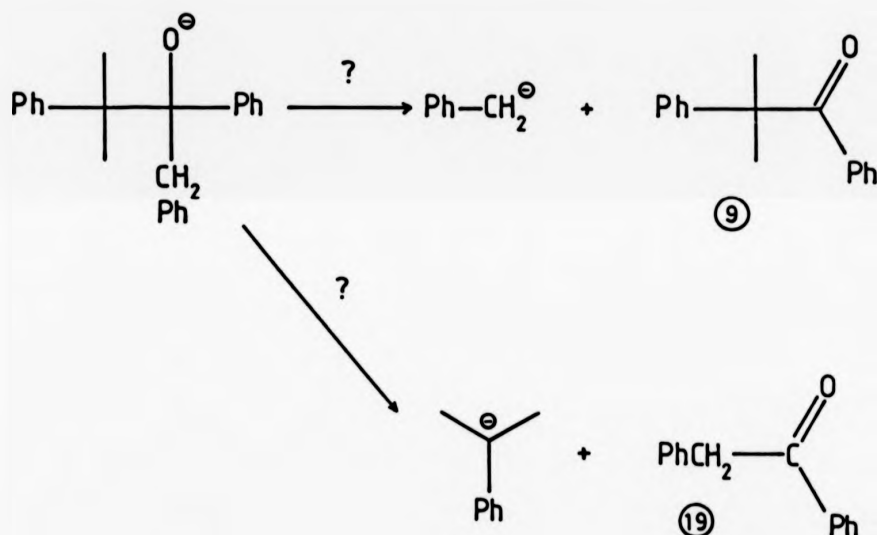
If the hypothesis were correct, this would oxidise the sulfoxide to a sulphone, and remove the chirality at sulphur. As expected, the n.m.r. of the product showed that the two sets of signals from the diastereoisomeric sulfoxides had been converted to a single set of signals which were explained by the expected product of this reaction, the β -hydroxy sulphone (18).



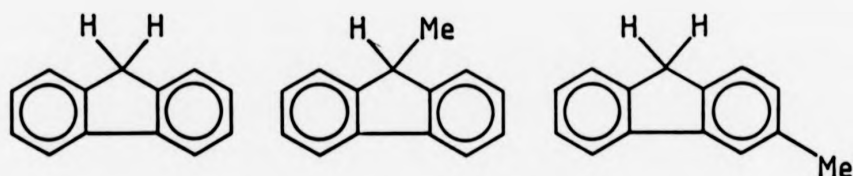
It is likely that β -hydroxy sulfoxides would be observed for the fragmentation of (3) (which gives acetophenone as a product), and for the fragmentation of (4) (which gives the same ketone as a product as does the fragmentation of (5)). In these cases, however, there were other reasons for not using the alcohols as substrates for kinetic study (given earlier), and these reasons were found before the presence of β -hydroxy sulfoxides was looked for. In the case of the anionic oxy-Cope rearrangement, no products were observed other than aldehyde (2), the Cope product (i.e. no 1,3 rearrangement was observed, no β -hydroxy olefin cleavage (a known side reaction of the thermal oxy-Cope rearrangement)¹⁰ was observed, and no formation of β -hydroxy sulfoxides was observed).

In order to work with an alcohol which would fragment to

give an enolate with an absorption well away from the diacyl absorption, with a large extinction coefficient (less alcohol needed), and that (hopefully) would not be nucleophilically attacked by diacyl lithium, 3-methyl-1,2,3-triphenyl-2-butanol (7) was synthesised. This could fragment to give cumene and the enolate of (19), which is 1,2-diphenylethanone (deoxybenzoin), or it could fragment to give toluene and the non-enolisable ketone 1,2-diphenyl-2-methyl-1-propanone (9).



Work by Bordwell⁽²²⁾ on the acidities of substituted fluorenes in DMSO indicates that substitution of a hydrogen by a methyl group at the anionic centre increases the acidity of the hydrocarbon, whereas substitution of a hydrogen on the aromatic ring, away from the anionic centre, leads to a drop in acidity. From this, it might be expected that the cleavage of (7) would proceed to give the anion of the more acidic hydrocarbon, which is cumene.



pK_a (DMSO) 22.6

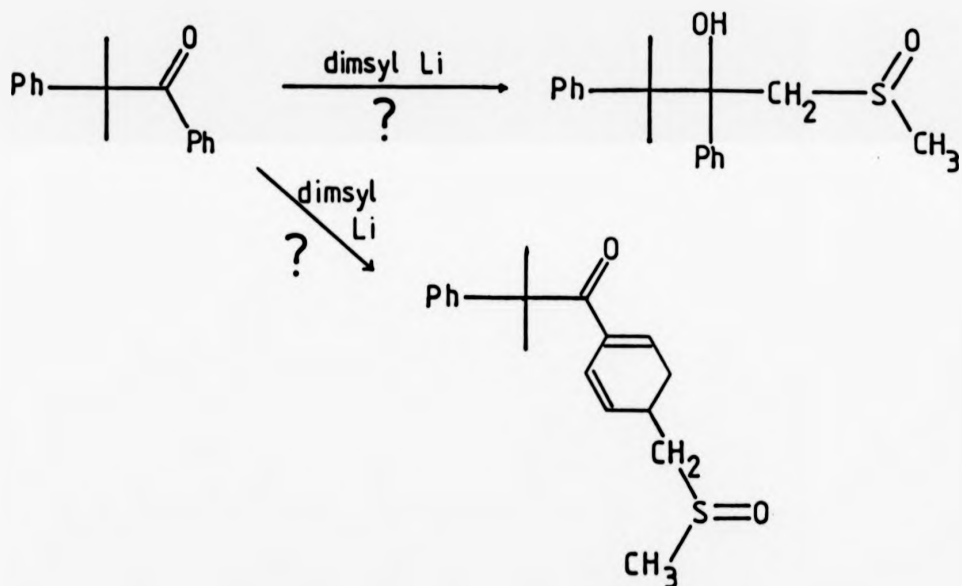
223

23.1

There would be a greater relief of non-bonded interactions on elimination of the cumyl anion (as a result of the two methyl groups) than on elimination of the benzyl anion, this also favouring the elimination of the cumyl anion. Force field calculations using Allinger's MM2 force field⁴⁷ indicate that cleavage to cumene and deoxybenzoin is favoured in terms of steric energy by 2.08 kcal/mol compared to cleavage to toluene and ketone (9).

A small scale fragmentation was carried out using diisyl lithium and alcohol (7), which showed complete disappearance of the starting material, and the appearance of 2 new products. Cumene was identified by its g.l.c. retention time (and recognised by its characteristic smell), and the other product was shown to have an identical g.l.c. retention time as deoxybenzoin. The identity of the products was demonstrated by g.l.c. co-injection with authentic cumene and deoxybenzoin. To demonstrate that the possible alternative cleavage of (7) to give the benzyl anion and ketone (9) was not occurring, (9) was treated with diisyl lithium for 15 minutes at 20°C, and g.l.c. analysis of the quenched and

extracted products showed no (9) to be present. However, the g.l.c. analysis did show peaks which had long retention times, and were very polar on t.l.c. plates. These were not isolated, but it is believed that these products are sulphur-containing, arising from nucleophilic attack by dimsyl lithium on (9). The products may be the diastereoisomeric β -hydroxy sulfoxides resulting from nucleophilic attack at the carbonyl carbon or may arise from nucleophilic attack by dimsyl lithium on the aromatic ring attached to the ketone carbonyl, as this hindered ketone undergoes such a reaction with *t*-butyllithium, as described earlier.



Treatment of alcohol (7) with dimsyl lithium resulted in a u.v. absorption at 390 nm, with an extinction co-efficient of approximately 10^4 . The exact value of the extinction co-efficient depends on the concentration of cation present, being lower when the concentration of the cation is higher, and vice

versa. Therefore, the extinction coefficient is highest when ion-pairing is at its lowest (when the concentration of cation is low), and when there is the highest concentration of free enolate.

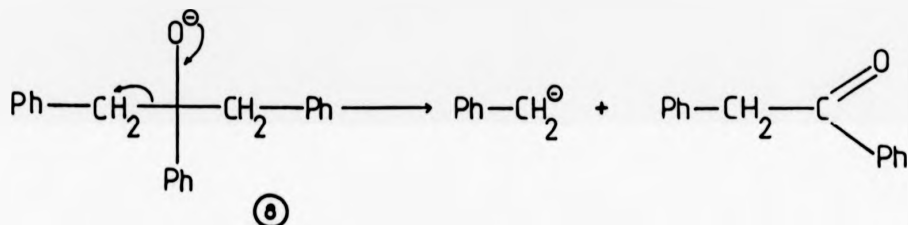
Treatment of (7) with diisyl sodium gave a u.v. absorption at 394 nm, and treatment of deoxybenzoin with the same batch of diisyl sodium also gave a u.v. maximum at 394 nm. Therefore, the fragmentation of (7) proceeds to give cumene and the enolate of deoxybenzoin, rather than toluene and ketone (9). Upon treatment of a solution of (7) with diisyl sodium in one of the specially designed u.v. cells at 20°C for two weeks, the only products that were observed on quenching (with aqueous acetic acid) and extraction (with diethyl ether) were the fragmentation products, cumene and deoxybenzoin. No evidence for β -hydroxy sulphoxides was found.

The rate of cleavage of (7) with diisyl lithium (half lives in the region of 5 to 15 seconds at 18.6°C) required use of the stopped flow apparatus. The rate enhancement observed on switching to diisyl sodium made it impossible to monitor the cleavage of this alcohol for a set of runs with variable diisyl sodium concentration, as the half lives of the reactions were too short. Investigation of the variation of the rate of cleavage with varying lithium concentration was carried out: (i) by varying the diisyl concentration, and (ii) keeping the diisyl concentration constant and varying the total lithium concentration by use of a solution of lithium iodide in DMSO. The effect of varying the sodium iodide concentration while keeping the diisyl sodium concentration constant was also investigated.

Because alcohol (7) performed the cleavage reaction in the

required manner, but did so at such a rate as to make monitoring of variable dimethyl sodium runs and any runs using dimethyl potassium impossible with the available equipment, it was necessary to obtain an alcohol which performed the fragmentation in a slower manner.

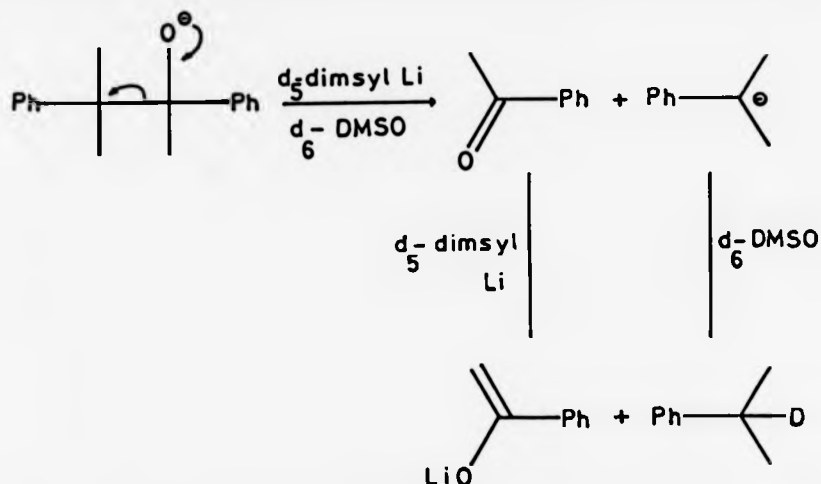
The alcohol that was chosen was 1,2,3-triphenyl-2-propanol (8), which was prepared in one step by addition of 1,3-diphenyl-2-propanone to a solution of phenylmagnesium bromide. This symmetrical tertiary alcohol does not have a choice of stabilised carbanions (as (7) does), and so the leaving group in the anionic fragmentation of this alcohol is the benzyl anion.



It was hoped that replacement of a cumyl group with a benzyl group at the oxygen-bearing carbon would slow the reaction for the same reasons that were used to explain the preference of (7) to fragment via the cumyl anion. This proved to be the case, and investigation of the fragmentation using dimethyl potassium and dimethyl sodium (both with and without the appropriate metal iodides) was carried out. The fragmentation using dimethyl lithium proved to be too slow for a set of runs to be carried out at reasonable temperatures (below 30°C), although for comparison with the rates observed for the sodium and potassium alkoxide fragmentations, individual runs were performed using dimethyl lithium. The fact that the

reaction proceeded slowly allowed use of [2.2.2.] cryptand (for complexing sodium and potassium) and use of [2.1.1.] cryptand (for complexing lithium).

Fate of the carbanion leaving group in the fragmentation reaction

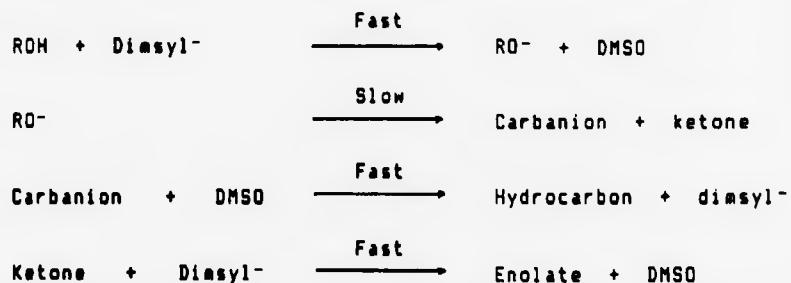


In the fragmentation reactions, the intermediate carbanion could be protonated by the ketone formed by the fragmentation, or by the solvent (DMSO). To determine whether the "new" proton originates from the DMSO, a cleavage reaction was carried out in d_6 -DMSO using d_5 -dimsyl lithium and 2,3-diphenyl-3-methyl-2-butanol at 20°C. The cumene formed by the reaction was analysed by g.l.c./M.S. and compared to the g.l.c./M.S. of "normal" cumene. The cumene formed by the reaction showed a 94% incorporation of deuterium compared to the "normal" cumene. As a control experiment, cumene was dissolved in d_6 -DMSO (for 24 hours), then analysed by g.l.c./M.S. which showed no deuterium incorporation. Cumene was also dissolved in a 0.1 molar solution of d_5 -dimsyl lithium (in d_6 -DMSO) for 12 hours, and analysed by g.l.c./M.S. which showed no deuterium incorporation. Therefore the methine proton of the cumene formed in the S_N1 cleavage of (3) originates from the solvent, DMSO. This is in agreement with the findings of Craze⁽⁷⁾ who reported that when using a solvent which could be deprotonated by the product carbanion, then

protonation by the solvent occurred. When using a solvent which the carbanion could not deprotonate, then protonation of the carbanion occurred by removal of an enolisable proton from the product ketone.

For the fragmentation reactions, if the rate determining step were deprotonation of the product ketone or deprotonation of the starting alcohol, then the rates observed would not be a true measure of the fragmentation reaction rate.

Scheme (8)



There is strong evidence in favour of the fragmentation step being the rate determining step of the reaction, as it is expected that proton transfer from the starting alcohols and from the product ketones will be extremely rapid compared to the fragmentation step. Arnett⁽¹⁴⁾ has reported that a wide variety of alcohols and ketones (including acetophenone and deoxybenzoin) release their heats of deprotonation in diasyl potassium/DMSO immediately, indicating near instantaneous deprotonation. Ritchie⁽¹⁰⁰⁾ has concluded that there is diffusion control of proton transfer between carbanions and oxygen acids in DMSO. There are also large differences between the estimated pK_a values of the starting alcohols compared to DMSO, and the pK_a values of the product ketones compared to DMSO.

In addition to this, the stopped flow apparatus was used

in an attempt to observe the deprotonation of deoxybenzoin. Taking points every 0.01 seconds, the absorption of the deoxybenzoin enolate was present from the mixing of the reagents onwards, with no change in absorption. Therefore the deprotonation was complete in less than 0.01 seconds, and was probably complete long before this time. This is considerably faster than any of the fragmentations for which kinetic data is reported, and so deprotonation of the product ketone is not the rate limiting step in these reactions.

This possible complication does not arise in the case of the anionic oxy-Cope rearrangement, as the reaction is intramolecular, with the molecule retaining its negative charge after deprotonation of the alcohol. Therefore no proton transfer is needed to produce the product enolate.

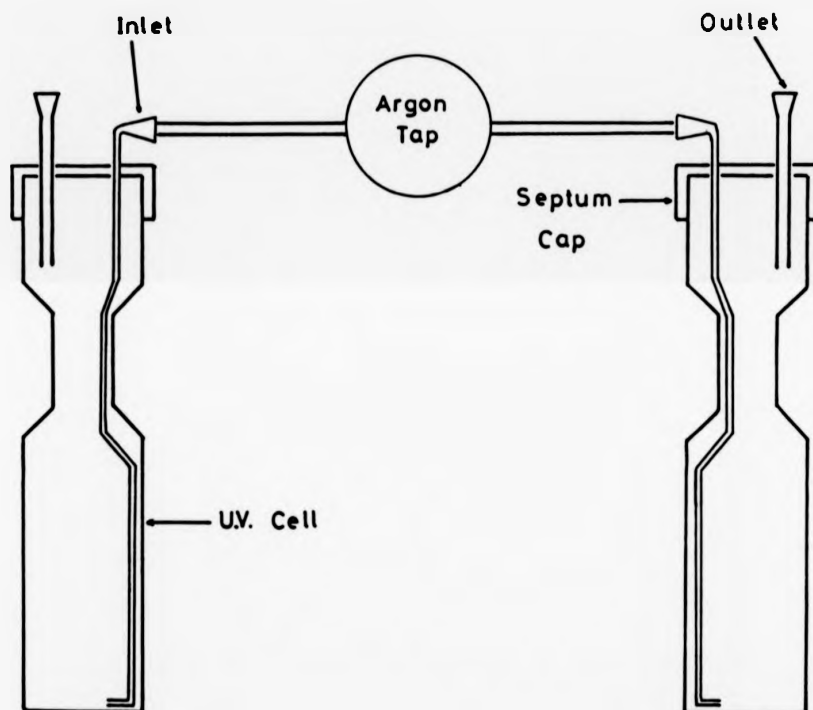
Development of Experimental Method

Considerable time and effort was put into developing the experimental technique used for the u.v. kinetics to the stage where it was possible to produce reproducible data. The main problems were caused by the extreme sensitivity of the dimethyl sulfoxide solutions that were used, to water (quenching occurs to give hydroxide and DMSO, as water has a pK_a of 31.4 in DMSO⁽¹¹⁾, compared to the pK_a of DMSO which is 35.1⁽¹²⁾), and to oxygen which oxidises the dimethyl sulfoxide ion ultimately to sulphonates⁽¹³⁾. The experimental techniques for u.v. kinetics which were described previously for the preliminary anionic work⁽⁸⁾ were not used for the work described in this thesis.

Double Cell Technique

In an attempt to obtain reproducible results under

conditions which were as close to identical as could be achieved with the equipment available, kinetic runs were made in pairs. Using the apparatus below, the two cells were flushed with argon for 10 minutes. The argon that was used had been passed through a pentane/liquid nitrogen trap (-131°C)^(*), which proved superior at water removal (as measured by Karl Fischer titration of DMSO which had argon bubbled through it) than a sodium/potassium alloy trap, or a calcium hydride trap.



The u.v. cells were situated in a thermostatted cell block inside the spectrometer, which had an adapted lid (heightened by 5 cm) to allow the u.v. cells and the argon line adapter to fit inside the spectrometer without the chance of breaking the delicate u.v. cells. After flushing with argon, the cells were then stoppered

before addition of 2.4 ml of alcohol solution (2.3×10^{-4} molar in DMSO) to each cell. One syringe was filled with 5ml of the alcohol solution, and this syringe was then used to add 2.4 ml to each cell. Originally a "Rocket" 5 ml syringe was used, which was not gas-tight, and later a Hamilton 1005 LT gas-tight 5 ml syringe was used. The alcohol solution was then allowed to equilibrate to temperature in the cell block for 20 minutes, with the exit needles stoppered. Then the stoppers were removed with a positive argon flow (causing bubbling in the cells), and a solution of diisyl lithium in DMSO was added to each cell, using the bubbling argon to mix the contents of the cells. The same 1 ml syringe was used to add the diisyl to the cells, with the same volume of diisyl being added to each cell. When 0.4 ml of diisyl was to be added to each cell, the syringe was filled with 0.9 ml of diisyl, and then this was used to add 0.4 ml to each cell, without having to refill the syringe when adding diisyl to the second cell. Originally an Optima 1 ml syringe was used for this purpose, which was not gas-tight, and later a Unimetrics gas-tight TP4001 syringe was used.

After approximately ten seconds of mixing by the argon flow, the cells were stoppered, the spectrometer lid closed, and the absorption at 365 nm monitored with respect to time, using a Tekman TE220 chart recorder. The cell programmer of the spectrometer moved the two cells into the beam in turn, thus allowing both cells to be monitored. The reactions were monitored out to 5 half-lives, and the first order rate constant for appearance of enolate product was calculated by use of a non-linear regression analysis computer program⁽¹⁾. The concentration of diisyl lithium was determined by titrating the stock solution against formanilide⁽²⁾ using triphenylmethane as an indicator⁽³⁾.

A typical set of data using this technique is given below in table (9).

Table (9) : Typical rate data using double cell technique

<u>[Diasyl Li]</u>	<u>k (cell 1) ($s^{-1} \times 10^3$)</u>	<u>k (cell 4) ($s^{-1} \times 10^3$)</u>
0.0297	1.80	2.34
0.0297	1.74	1.87
0.0297	1.73	2.46
0.0205	3.08	2.51
0.0185	2.68	2.76
0.0494	0.620	FAILED

As can be seen from the above data, sometimes there was good reproducibility on double runs (the runs with [diasyl] = 0.0185 mol/l agree to within 2%), but quite often the discrepancy between the 2 rate constants under supposedly identical conditions was large (the runs for the 3rd set for [diasyl] = 0.0297 mol/l differ by 30%). Also, as demonstrated here by cell 4 for [diasyl] = 0.0494 mol/l, a run could fail due to the inlet needle moving into the beam, caused by the motion of the cell programmer. This prevented any meaningful readings being taken for that cell whenever it occurred. Other problems were believed to include poor mixing of the alcohol solution and the diasyl solution during the ten seconds that argon was bubbling into the cell to mix them. However, longer bubbling of argon through the cells could lead to quenching of the diasyl by water present in the argon, as had previously occurred when using longer bubbling times. Also, although the alcohol solution was allowed time to equilibrate to temperature, the apparatus allowed no method of allowing the diasyl to equilibrate to

temperature prior to addition. This meant that the solution in the cell after mixing was not at the temperature of the cell block, and until the cell contents had equilibrated to temperature, the data was actually being collected at variable temperature.

In view of these drawbacks, and the poor reproducibility of the technique, it was abandoned in favour of the use of the apparatus shown below, which was adapted from the design of Bunce⁽⁷⁴⁾.

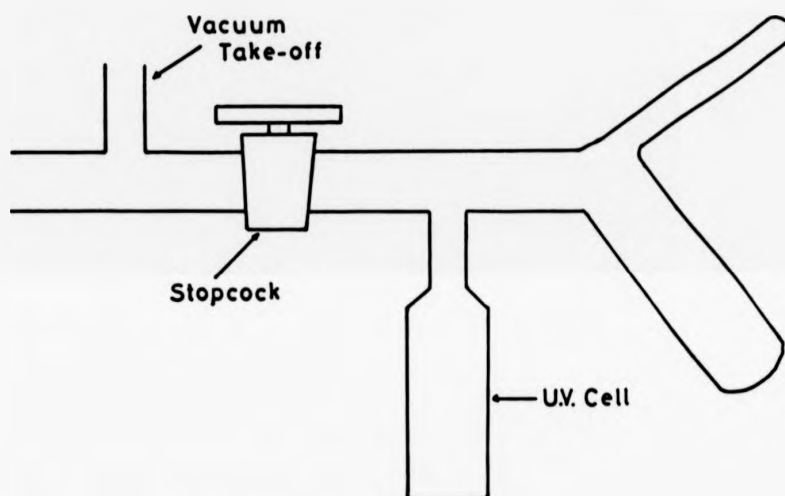


Figure (6)

This apparatus allows the alcohol solution, the diacyl solution, and the apparatus itself to be equilibrated to temperature. No argon flow (introducing water into the solutions) is needed as the whole apparatus is put under argon before addition of the solutions, and mixing is achieved by pouring the mixture from one arm of the apparatus to the other arm several times before pouring the mixture into the u.v. cell. Also there are no needles

which could move into the beam and ruin the run.

Using this apparatus, the data was usually reproducible to about $\pm 5-6\%$. Rather than attempt to exactly reproduce individual runs, it was decided that the sets of runs would be repeated to give duplicate data sets for each set of conditions. This technique was used for the slower runs with half lives of greater than one minute. A detailed description of the use of this apparatus is given in the experimental section. Using this apparatus, each individual run showed a first order appearance of enolate with each run being monitored out to 5 half-lives. The infinity values calculated by the non-linear regression program and the experimental infinity values agreed extremely closely. Using this apparatus, infinity values have been observed to be stable over 15 half-lives. The cation concentrations were determined by atomic absorption spectroscopy for each individual run.

One problem with this technique is that when working at temperatures close to room temperature, the temperature of the liquid inside a uv cell which is inside the thermostatted cell block is up to 1.2°C higher than the temperature of the water bath. This is a result of the the heat generated by the spectrometer. For runs with long half-lives, these will equilibrate to the temperature of the cell block quickly compared to the length of time of the run, but the faster runs will be conducted effectively at a variable temperature. This problem seems to be unavoidable, and is probably a considerable source of uncertainty in the kinetic runs at lower (close to room temperature) temperatures.

Preparation and stability of dimsyl solutions

Initially, solutions of dimsyl lithium were prepared using lithium amide and DMSO, with heating to 35°C for up to 4 hours. Frequently this resulted in pale yellow solutions of dimsyl lithium, with some undissolved solid being present at the bottom of the flask. Because the reactions were to be monitored by u.v. spectroscopy, it was necessary that the dimsyl solutions did not absorb in the region of the spectrum where the product enolate absorbed, and this was not the case when the dimsyl solutions were yellow. When the reaction was attempted with lithium hydride, very little reaction was observed even after warming for several hours at 35°C, with the bulk of the hydride being undissolved. Total base titration of the solution with standard HCl and phenolphthalein indicator, showed very little base to be present. Use of butyllithium to deprotonate DMSO was initially avoided as commercial solutions of butyllithium are frequently coloured (yellow), and it was felt that this would result in yellow dimsyl lithium. The reaction between butyllithium and DMSO is extremely rapid, with a white solid being formed at the interface between the DMSO and the hexane layer (butyllithium being present as a solution in hexane), which dissolved in the DMSO on stirring. Use of yellow commercial *n*-butyllithium (Koch-Lite) resulted in yellow dimsyl lithium, but use of butyllithium (which was clear and colourless) that was prepared by the author, gave clear and colourless solutions of dimsyl lithium. This was the method of preparation that was used for all of the preparations of dimsyl lithium reported, except for the dimsyl lithium runs with [2.1.1.] cryptand for 1,2,3-triphenyl-2-propanol. Later in the work it was found that use of Aldrich butyllithium solutions stored in "Sure-Seal" bottles also

gave clear and colourless dimsyl lithium solutions, and this was used for the cryptand runs.

Initially dimsyl sodium was prepared as described by Bordwell⁽¹⁰⁾, using a suspension of sodium hydride in mineral oil, washing this six times with purified 40/60 petrol (washed twice with concentrated sulphuric acid, and distilled from calcium hydride), removing the petrol under vacuum, adding DMSO, and stirring at 35°C for up to 4 hours. This method usually resulted in yellow dimsyl sodium being produced, and was also time-consuming. A better method of preparation for dimsyl sodium involved the use of a suspension of sodium amide (purum, from Fluka A.G.) in toluene. The suspension was washed with purified 40/60 petrol (as when using sodium hydride), the petrol removed under vacuum, and on addition of DMSO to the white powder, a clear colourless solution of dimsyl sodium resulted. The ammonia produced was removed under vacuum. The reaction of sodium amide with DMSO was quite rapid, with no more solid dissolving after about two minutes. There was always a very small residue of solid present at the bottom of the flask (probably sodium hydroxide), and the dimsyl was then transferred to another flask on the argon line by gas-tight syringe, leaving the residue behind. This method of preparation was used for all of the kinetic runs involving dimsyl sodium.

Initially dimsyl potassium was prepared in the same way as the initial preparations of dimsyl sodium, using a suspension of the hydride in mineral oil. It proved extremely difficult to remove all of the mineral oil by washing with petrol (>10 washes). Use of this method always resulted in bright yellow dimsyl potassium solutions. McDonald⁽¹⁰²⁾ has reported variations in different batches of potassium hydride. Following the success of the use of a sodium

amide suspension in toluene, a suspension of potassium amide⁽²⁴⁾ in toluene was prepared. When extreme care was taken to ensure that the potassium amide did not come into contact with oxygen, use of this suspension resulted in clear colourless solutions of diisyl potassium. This method of preparation was used for all kinetic runs involving the use of diisyl potassium. If the potassium amide did come into contact with oxygen, then a yellow solution of diisyl potassium resulted.

When the diisyl solutions were kept out of contact with any traces of oxygen or moisture, it was possible to keep them in a usable condition for 2 days (for the diisyl sodium and diisyl potassium solutions), and for up to a week for the diisyl lithium solutions. Once any diisyl solution had begun to turn yellow (from contact with oxygen), the colour became more intense with time, even though there was no further contact with oxygen.

Catalysis of the oxy-Cope rearrangement by hydroxide in DMSO

When attempts were made to use diisyl lithium concentrations below about 0.01 molar for the oxy-Cope rearrangement, using the method of bubbling argon through the solutions for mixing (in the u.v. cells fitted with B14 sockets and septum caps), then instead of the rate increasing further compared to the more concentrated solutions (as expected from the scheme), the rate decreased dramatically (usually by a factor of 10 to 20). Addition of a small amount of such a solution to triphenylmethane under argon failed to give the deep red colour, characteristic of the triphenylmethyl anion, indicating that the diisyl solution had been quenched to give hydroxide and DMSO.

Checking of the the water content⁽²⁵⁾ by Karl Fischer

titration of a solution of alcohol (1) in DMSO in the uv. cell after bubbling argon through it for 20 minutes, showed that there was sufficient water present to quench all of the dimethyl lithium. A 0.01 molar solution of water in DMSO represents approximately 200 ppm. There was a much lower water content in the solution before bubbling argon through it. Quenching of dimethyl lithium would give a solution of lithium hydroxide in DMSO containing a small amount of water. It has been shown that the hydroxide ion is a very strong base in DMSO containing a small amount of water⁽²⁷⁾, and has a H_- value within 2-3 units of the pK_a 's of typical secondary alcohols in DMSO. Typical values for the pK_a 's of secondary alcohols in DMSO are 27-29⁽¹¹⁾.

Stewart⁽²⁷⁾ has shown the hydroxide ion to have an H_- value of 26 in a solution of 99.5 mole% DMSO, 0.5 mole% water. This applies to a solution of 0.011 molar tetramethylammonium hydroxide in 99.5% DMSO, as measured by its effect on arylamine ionisation. Stewart's quoted H_- values are H_- at half ionisation, thus making $H_- = pK_a$, from the equation:

$$H_- = pK(HA) + \log \frac{[A^-]}{[HA]}$$

Where HA is the arylamine being deprotonated.

In the case of the quenched anionic oxy-Cope reactions, it is believed that lithium hydroxide behaves as a strong base, and in this case this would lead to an equilibrium being set up between alcohol (1) and its lithium alkoxide.



The alkoxide then reacts via the anionic oxy-Cope

rearrangement, and so the slow rate of reaction can be attributed to the presence of only an equilibrium concentration of the alkoxide, compared to the "normal" case when the diisyl is not all quenched, and the alcohol is quantitatively deprotonated.

The preliminary report^(*) on the anionic oxy-Cope rearrangement using diisyl sodium as the base, and the same "argon bubbling" technique, reported rates of reaction between 10^{-3} s^{-1} and 10^{-2} s^{-1} at a water bath temperature of 17.5°C , at sodium ion concentrations of about 0.1 molar. The DMSO used for this preliminary work was distilled from calcium hydride under vacuum. From the later work on the anionic oxy-Cope rearrangement, it appears that the preliminary work gave rates which were an order of magnitude too slow, this being due to quenching of the diisyl. This would also explain the non-reproducibility of the early anionic work. One reason for the quenching of the diisyl solutions in the preliminary work was the method of distillation of the DMSO, as it is now known that distillation from sodium amide gives DMSO with a lower water content than distillation from calcium hydride. For all of the anionic work reported in this thesis, the DMSO was distilled from sodium amide under vacuum, as described in the experimental section.

Since the "argon bubbling" technique was replaced by use of the specially designed UV cells (see "Development of experimental method"), the quenching of diisyl solutions has not been observed.

CHAPTER FOUR

Collected kinetic data

The data obtained from the kinetic runs on the variation of the rate of reaction of the alcohols (1), (7), and (8) with variable cation concentration are to be compared with the predictions of the simplified version of Craa's scheme. However, before any significance was placed on the results obtained from these kinetic runs, it was necessary to carry out a number of control experiments in addition to those previously performed(8). Experiments establishing the following were successfully carried out:

- 1) The appearance of the enolate absorption followed first order kinetics for each of the 3 reactions that were used, with a standard deviation from the best fit of less than 1% in each case, and usually better than 0.5%. A typical data set is shown in appendix (1).
- 2) The calculated and experimental infinity values agreed extremely closely for each of the 3 reactions used.
- 3) The infinity values for all reactions were stable up to at least 15 half-lives, with data being collected out to 5 half-lives.
- 4) The absorptions of the metal diethyl solutions were stable over the duration of the kinetic runs.
- 5) The absorptions of the 3 alcohols in DMSO were stable over the period of the experiments.
- 6) The reaction rate of the oxy-Cope rearrangement of (1) showed no

dependence on the alcohol concentration, and the rates of reaction of alcohols (7) and (8) showed a similar lack of dependence on the initial alcohol concentration.

7) For the kinetic runs with added solutions (alkali metal halides, [2.1.1.] cryptand, [2.2.2.] cryptand, or 12-crown-4 ether), the absorption of the metal diethyl solutions with these added solutions was stable over the period of the experiments.

8) For the fragmentation of 1,2,3-triphenyl-2-propanol (8), the product ketone (deoxybenzoin) was identified by g.l.c. co-injection with authentic material, by g.l.c./M.S. comparison with authentic material, and by comparison of the enolate of authentic deoxybenzoin in diethyl sodium solution with that of the reaction product in diethyl sodium solution (the u.v. spectra being identical).

9) For the fragmentation of 3-methyl-1,2,3-triphenyl-2-butanol (7), the product deoxybenzoin was identified as for (8), and the product cumene was identified by g.l.c. co-injection with authentic material, and by g.l.c./M.S. comparison with authentic material.

10) For 4,4-dimethyl-2-phenyl-1,5-hexadien-3-ol (1), the product aldehyde had previously been identified by its spectral properties^(a). This aldehyde has now been independently synthesised (as described earlier), and the reaction product further identified by g.l.c. co-injection, and by comparison of the enolate of the authentic aldehyde in diethyl sodium solution with the reaction product enolate absorption in diethyl sodium solution (identical u.v. spectra).

RESULTS OF ANIONIC WORK

All concentrations are in moles per litre, all rate constants are in seconds⁻¹, the quoted temperatures refer to the cell block temperature, and the quoted activities have been calculated using the data of Bonner⁽¹⁰³⁾.

Oxy-Cope rearrangement of (I) : Variable [dimethyl Li]

Set 1 : [ROH] = 2.55×10^{-4} mol/l : 26°C

Table (10)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10³</u>	<u>k_{obs} x 10³</u>
0.1298	17.4	0.131
0.0826	13.7	0.275
0.0385	8.94	1.27
0.0214	6.37	2.23
0.0163	5.42	4.07
0.0133	4.80	6.66

Set 2 : [ROH] = 2.55×10^{-4} mol/l

Table (11)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10³</u>	<u>k_{obs} x 10³</u>
0.1286	17.3	0.285
0.0819	13.6	0.477
0.0548	10.9	0.879
0.0395	9.07	1.50
0.0270	7.30	2.68
0.0234	6.72	4.28
0.0159	5.34	7.16

Qxy-Cope rearrangement of (1)

Constant [diastyl Li], variable [LiCl] : 30.8°C

Set 1 : [ROH] = 2.55×10^{-4} mol/l

Table (12)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] $\times 10^2$</u>	<u>Act. (Li⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^3$</u>
0.0062	0.30	0.296	9.71
0.0105	0.72	0.615	5.32
0.0144	1.09	0.812	4.57
0.0178	1.41	0.951	3.49
0.0270	2.23	1.22	2.73
0.0273	2.26	1.23	2.52
0.0336	2.79	1.36	2.03
0.0341	2.83	1.37	2.05
0.0539	4.41	1.66	1.44
0.0740	5.87	1.95	1.21
0.2317	14.7	-	0.55

Set 2 : [ROH] = 2.55×10^{-4} mol/l

Table (13)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] $\times 10^2$</u>	<u>Act. (Li⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^3$</u>
0.0099	0.40	0.40	4.09
0.0148	0.88	0.76	2.54
0.0178	1.17	0.91	3.29
0.0190	1.28	0.95	1.71
0.0221	1.57	1.07	2.05
0.0340	2.62	1.39	1.38
0.0506	3.97	1.68	0.95
0.0530	4.16	1.72	1.12
0.0877	6.66	2.14	0.65
0.1470	10.3	2.61	0.57
0.2283	14.5	-	0.26

Oxy-Cope rearrangement of (1)

Constant (dimethyl Li), variable [Li] : 30.8°C

Set 1 : [ROH] = 1.80×10^{-2} mol/l

Table (14)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] $\times 10^2$</u>	<u>Act. (Li⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^3$</u>
0.0102	0.41	0.41	7.53
0.0138	0.77	0.75	5.63
0.0149	0.88	0.86	4.47
0.0187	1.26	1.19	3.15
0.0227	1.66	1.51	2.76
0.0333	2.72	2.28	1.92
0.1217	1.16	8.46	0.66

Set 2 : [ROH] = 1.80×10^{-2} mol/l

Table (15)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] $\times 10^2$</u>	<u>Act. (Li⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^3$</u>
0.0109	0.42	0.42	10.5
0.0133	0.66	0.66	6.99
0.0182	1.15	1.10	5.02
0.0206	1.39	1.30	4.01
0.0267	2.00	1.79	2.84
0.0387	3.20	2.68	2.11
0.0977	9.10	6.55	0.95

Oxy-Cope rearrangement of (1) ; Variable [2.1.1.1] cryptand

[Diary] Li] = 3.32×10^{-2} mol/l ; [ROM] = 3.70×10^{-4} mol/l ; Set 1

Set 1 ; 20.7°C

Table (16)

<u>Equivalents of [2.1.1.1]</u>	<u>$k_{\text{obs}} \times 10^3$</u>
0.00	0.47
0.15	0.79
0.24	1.86
0.29	1.78
0.36	2.71
0.43	5.56
0.45	7.68
0.50	Approx. 50

[Diary] Li] = 5.44×10^{-2} mol/l ; [ROM] = 3.7×10^{-4} mol/l

Set 2 ; 20.7°C

Table (17)

<u>Equivalents of [2.1.1.1]</u>	<u>$k_{\text{obs}} \times 10^3$</u>
0.00	0.18
0.15	0.36
0.29	0.63
0.37	2.09
0.43	5.53
0.47	4.96
0.51	Too fast to measure

Oxy-Cope rearrangement of (1) : Variable [dimyl Na]

Set 1 : [ROH] = 1.80×10^{-4} mol/l : 18.6°C

Table (18)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^2$</u>	<u>k_{obs} $\times 10^2$</u>
0.0365	1.347	24.1
0.0490	1.610	16.8
0.0509	1.647	11.1
0.0590	1.797	8.97
0.0781	2.117	4.90
0.0889	2.281	4.21
0.1431	2.985	1.46
0.1872	3.464	1.01

Set 2 : [ROH] = 1.80×10^{-4} mol/l

Table (19)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^2$</u>	<u>k_{obs} $\times 10^2$</u>
0.0370	1.358	21.1
0.0474	1.578	10.4
0.0623	1.856	5.69
0.1115	2.595	2.04

Oxy-Cope rearrangement of (1) : 18.6°C : Set 1

Constant [Diary] Na], variable [Na] : [ROH] = 2.0×10^{-4} mol/l

Table (20)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^2$</u>	<u>Act. (Na⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^2$</u>
0.0287	1.16	1.16	7.63
0.0317	1.46	1.45	6.69
0.0380	2.09	1.99	5.03
0.0427	2.56	2.35	3.56
0.0522	3.51	3.00	2.94
0.0677	5.06	3.94	2.18
0.1004	8.33	5.90	1.65
0.1548	13.8	8.83	1.34

Set 2 : [ROH] = 4.5×10^{-4} mol/l

Table (21)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^2$</u>	<u>Act. (Na⁺)_{free} $\times 10^2$</u>	<u>k_{obs} $\times 10^2$</u>
0.0281	1.15	1.15	8.18
0.0307	1.41	1.41	6.29
0.0372	2.05	1.97	4.24
0.0552	3.86	3.19	3.29
0.0675	5.09	3.95	2.43
0.1042	8.76	6.19	1.70
0.1443	12.8	8.40	1.24

Oxy-Cope rearrangement of (1) : 18.6°C : Set 1

Constant [Diene] K], variable [K1] : [RQH] = 2.0×10^{-4} mol/l

Table (22)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>Act. (K⁺)_{free} x 10²</u>	<u>k_{obs} x 10</u>
0.0483	3.25	3.25	10.5
0.0540	3.82	3.75	10.1
0.0751	5.93	5.08	7.60
0.0924	7.66	6.00	5.46
0.1312	11.5	7.85	4.45
0.1563	14.1	9.01	3.35
0.1688	15.3	9.41	2.95
0.2153	20.0	-	2.30
0.2569	24.1	-	1.96

Set 2 : [RQH] = 2.0×10^{-4} mol/l

Table (23)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>Act. (K⁺)_{free} x 10²</u>	<u>k_{obs} x 10</u>
0.0246	1.91	1.91	25.0
0.0352	2.97	2.85	22.0
0.0664	6.09	4.85	14.2
0.0850	7.94	5.97	11.9
0.1034	9.78	6.37	10.2
0.1286	12.3	7.46	6.79
0.1773	17.1	9.40	5.07
0.2022	19.6	-	4.83
0.2162	21.0	-	3.44
0.3116	30.5	-	2.16

Oxy-Cope rearrangement of (1) : 30.8°C

Constant [Diethyl Li] with variable 12-crown-4 ether

[Li⁺] = 0.0484 mol/l , [ROH] = 3.7 x 10⁻⁴ mol/l

Table (24)

<u>Eg. of 12-C-4</u>	<u>k_{obs} x 10⁴</u>	<u>Rate Increase Factor</u>
0.0	9.01	1.0
1.0	8.54	0.95
3.0	10.6	1.16

Oxy-Cope rearrangement of (1) : [M⁺] = 0.062 mol/l

[ROH] = 2.0 x 10⁻⁴ mol/l : 18.6°C : Comparison

Table (25)

	<u>Li⁺</u>	<u>Na⁺</u>	<u>K⁺</u>
<u>k_{obs}</u>	1.20 x 10 ⁻⁴	3.71 x 10 ⁻²	1.36
<u>k_{rel}</u>	1	308	11330

Fragmentation of 3-methyl-1,2,3-triphenyl-2-butanol (7)

Variable [Diary] Li] : 18.7°C

Set 1 : [RDM] = 2.5×10^{-4} mol/l

Table (26)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10³</u>	<u>k_{1,2,3} x 10²</u>
0.0089	3.73	12.8
0.0111	4.29	14.8
0.0179	5.73	10.4
0.0184	5.83	9.10
0.0191	5.96	6.79
0.0220	6.48	8.06
0.0274	7.36	4.80
0.0289	7.59	5.42

Set 2 : [RDM] = 2.5×10^{-4} mol/l

Table (27)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10³</u>	<u>k_{1,2,3} x 10²</u>
0.0088	3.72	12.0
0.0184	5.83	6.78
0.0214	6.38	5.98
0.0315	7.97	4.37
0.0348	8.45	3.07
0.0364	8.66	4.25
0.0488	10.2	2.09

Fragmentation of (7) : 18.6°C : Set 1

Constant [Diisyl Li], variable [Li]: [ROH] = 1.1×10^{-4} mol/l

Table (28)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10²</u>	<u>Act. (Li⁺)_{free} x 10²</u>	<u>K₁ x 10²</u>
0.0121	0.45	0.45	6.65
0.0148	0.72	0.72	5.76
0.0189	1.14	1.10	4.10
0.0197	1.22	1.16	3.26
0.0254	1.79	1.63	2.41
0.0270	1.94	1.71	2.16
0.0453	3.78	2.97	1.08

Set 2 : [ROH] = 1.1×10^{-4} mol/l

Table (29)

<u>[Total Li⁺]</u>	<u>[Free Li⁺] x 10²</u>	<u>Act. (Li⁺)_{free} x 10²</u>	<u>K₁ x 10²</u>
0.0250	0.70	0.70	4.02
0.0264	0.84	0.84	2.84
0.0305	1.25	1.22	2.44
0.0317	1.37	1.33	2.62
0.0334	1.54	1.47	1.68
0.0461	2.80	2.40	1.06
0.0475	2.95	2.50	0.99
0.0700	5.19	4.02	0.59
0.0921	7.41	5.38	0.40

Fragmentation of (7) : 18.6°C : Set 1

Constant [Dissvl Na], variable [Na], [ROH] = 1.1×10^{-4} mol/l

Table (30)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] x 10²</u>	<u>Act. (Na⁺)_{free} x 10²</u>	<u>k_{obs} x 10</u>
0.0186	0.88	0.88	9.08
0.0211	1.12	1.12	6.04
0.0278	1.80	1.70	6.26
0.0312	2.14	1.97	4.26
0.0474	3.76	3.02	3.39
0.0518	4.20	3.28	2.43
0.0604	5.06	3.80	1.89
0.1046	9.48	6.52	1.21
0.1323	12.3	8.18	0.96

Set 2 : [ROH] = 1.1×10^{-4} mol/l

Table (31)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] x 10²</u>	<u>Act. (Na⁺)_{free} x 10²</u>	<u>k_{obs} x 10</u>
0.0265	1.10	1.10	7.97
0.0281	1.27	1.26	6.84
0.0322	1.67	1.63	5.65
0.0371	2.16	2.04	4.27
0.0544	3.89	3.18	3.12
0.0609	4.54	3.59	2.58
0.0687	5.33	4.06	2.09
0.1313	11.6	7.82	1.41

Fragmentation of (7) : 18.6°C : [M⁺] = 0.062 mol/l

[ROH] = 1.1 x 10⁻⁴ mol/l : Comparison

Table (32)

	<u>Li⁺</u>	<u>Na⁺</u>
<u>k₁₂₃₄₅</u>	1.38 x 10 ⁻²	5.41 x 10 ⁻¹
<u>k₁₂₃₄₅</u>	1	39

Fragmentation of 1,2,3-triphenyl-2-propanol (8)

Variable [Diary] Na] : 30.8°C

Set 1 : [ROH] = 7.1×10^{-2} mol/l

Table (33)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^3$</u>	<u>$k_{(obs)} \times 10^3$</u>
0.0041	2.99	5.83
0.0049	3.41	6.07
0.0094	5.52	3.10
0.0108	6.08	3.77
0.0143	7.37	2.21
0.0146	7.48	2.16
0.0271	11.2	1.34
0.0409	14.4	0.89
0.0558	17.4	0.51
0.0730	20.5	0.47

Set 2 : [ROH] = 7.1×10^{-2} mol/l

Table (34)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] $\times 10^3$</u>	<u>$k_{(obs)} \times 10^3$</u>
0.0078	4.85	3.81
0.0141	7.32	2.11
0.0146	7.48	2.45
0.0181	8.62	1.75
0.0283	11.5	1.19
0.0333	12.7	1.00
0.0473	15.8	0.73
0.0729	20.3	0.47

Fractionation of (B) : 30.8°C : Set 1

Constant [Dissyl Na], variable [Na] : [ROH] = 7.1×10^{-2} mol/l

Table (35)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] x 10²</u>	<u>Act. (Na⁺)_{free} x 10²</u>	<u>K_{app} x 10⁴</u>
0.0191	0.89	0.89	17.3
0.0248	1.47	1.43	12.5
0.0343	2.42	2.17	8.51
0.0349	2.48	2.22	7.61
0.0500	4.00	3.16	5.24
0.0653	5.52	4.09	3.80
0.2120	20.2	-	0.78

Set 2 : [ROH] = 7.1×10^{-2} mol/l

Table (36)

<u>[Total Na⁺]</u>	<u>[Free Na⁺] x 10²</u>	<u>Act. (Na⁺)_{free} x 10²</u>	<u>K_{app} x 10⁴</u>
0.0191	0.90	0.90	16.7
0.0251	1.49	1.45	12.3
0.0293	1.92	1.80	8.66
0.0422	3.20	2.68	6.75
0.0471	3.69	2.97	5.12
0.0966	8.64	6.00	1.87
0.2150	20.4	-	0.67
0.2320	22.1	-	0.61

Fragmentation of (8) at 21.2°C: Variable [Dimethyl K]

[ROH] = 9.3×10^{-2} mol/l: Set 1

Table (37)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>k_{obs} x 10³</u>
0.0076	0.69	9.30
0.0116	1.01	8.88
0.0155	1.30	6.85
0.0171	1.41	5.93
0.0208	1.67	5.17
0.0251	1.95	4.74
0.0283	2.14	4.13
0.0362	2.60	3.62
0.0464	3.15	2.99
0.0497	3.32	2.79
0.0569	3.67	2.45

Set 2: [ROH] = 9.3×10^{-2} mol/l

Table (38)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>k_{obs} x 10³</u>
0.0142	1.20	5.24
0.0194	1.57	4.55
0.0251	1.94	4.07
0.0300	2.24	3.52
0.0356	2.57	3.23
0.0415	2.89	2.94
0.0507	3.37	2.47
0.0637	3.99	2.19
0.0761	4.53	1.87
0.0881	5.03	1.73
0.1000	5.49	1.54

Fragmentation of (8): 21.2°C; Variable [Dimethyl K]

Set 3 : [ROH] = 7.1×10^{-2} mol/l

Table (39)

<u>[Total K⁻]</u>	<u>[Free K⁻] $\times 10^2$</u>	<u>k_{obs} $\times 10^3$</u>
0.0080	0.72	6.61
0.0091	0.81	6.36
0.0117	1.02	5.62
0.0146	1.23	5.15
0.0185	1.51	4.63
0.0244	1.90	4.26
0.0276	2.10	3.73
0.0281	2.13	3.45
0.0341	2.49	3.27
0.0407	2.85	2.84
0.0505	3.36	2.50
0.0579	3.72	2.19

Fragmentation of (8) : 26.0°C : Set 1

Constant [Diaryl K], variable [K1] : [ROH] = 7.1×10^{-2} mol/l

Table (40)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>Act. (K⁺)_{free} x 10²</u>	<u>k_(free) x 10³</u>
0.0261	2.00	2.00	8.33
0.0309	2.49	2.44	6.82
0.0319	2.59	2.52	6.62
0.0375	3.14	2.92	6.02
0.0565	5.04	4.04	4.35
0.0711	6.48	4.80	3.60
0.0987	9.22	6.14	2.56
0.1210	11.5	7.15	2.06
0.2160	20.8	-	1.31
0.2331	22.4	-	1.06

Set 2 : [ROH] = 7.1×10^{-2} mol/l

Table (41)

<u>[Total K⁺]</u>	<u>[Free K⁺] x 10²</u>	<u>Act. (K⁺)_{free} x 10²</u>	<u>k_(free) x 10³</u>
0.0281	2.13	2.13	8.12
0.0347	2.79	2.71	6.84
0.0470	4.02	3.53	5.30
0.0572	5.03	4.01	4.39
0.0864	7.93	5.61	3.26
0.1080	10.1	6.61	2.58
0.1503	14.2	8.39	1.90
0.1991	19.0	-	1.30
0.3262	31.2	-	0.80
0.4423	42.2	-	0.55

Fractionation of (8) : 18.6°C ; Variable [2.2.2.] cryotand

[Diisyl K] = 0.0147 mol/l ; [ROH] = 6.5×10^{-2} mol/l

Table (42)

<u>Equivalents of [2.2.2.]</u>	<u>$k_{(2.2.2.)} \times 10^3$</u>
0.00	3.88
0.27	4.89
0.54	6.70
0.68	8.19
0.81	8.57
1.00	8.60
1.16	8.39
1.35	8.66

[Diisyl Na] = 0.0150 mol/l ; [ROH] = 6.5×10^{-2} mol/l

Table (43)

<u>Equivalents of [2.2.2.]</u>	<u>$k_{(2.2.2.)} \times 10^3$</u>
0.00	0.37
0.39	0.89
0.65	2.30
0.78	7.60
1.00	9.89
1.17	9.93
1.30	1.00

Fragmentation of (8) : 18.6°C : Variable [2.1.1.] cryptand

[Dimethyl Li] = 0.0154 mol/l : [ROH] = 6.5×10^{-2} mol/l

Table (44)

<u>Equivalents of [2.1.1.]</u>	<u>$k_{\text{obs}} \times 10^3$</u>
0.00	3.02×10^{-3}
0.46	1.97×10^{-2}
0.62	7.82×10^{-2}
0.76	1.08
1.00	4.89
1.25	5.57
1.54	7.42
2.00	8.16

Fragmentation of (8) : 30.8°C : [M⁺] = 0.0154 mol/l

[ROH] = 7.1×10^{-2} mol/l

Table (45)

	<u>Li⁺</u>	<u>Na⁺</u>	<u>K⁺</u>
<u>k_{obs}</u>	2.67×10^{-3}	1.73×10^{-3}	1.68×10^{-3}
<u>k_{obs}</u>	1	65	630

Fragmentation of (8) : Variable temperature

$[ROH] = 6.5 \times 10^{-3} \text{ mol/l}$; $[Diisyl K] = 1.1 \times 10^{-2} \text{ mol/l}$

$[2.2.2.] = 1.46 \times 10^{-2} \text{ mol/l}$; Excess cryptand

Table (46)

<u>Temperature (°C)</u>	<u>$k_{\text{obs}} \times 10^2$</u>
18.8	0.64
24.3	1.36
29.6	2.47
33.1	6.56
37.1	11.7
43.1	26.0

Comparison of alcohols (7) and (8) at 18.6°C

$[Diisyl Na] = 0.0218 \text{ mol/l}$; $[ROH] = 7.1 \times 10^{-3} \text{ mol/l}$

Table 47

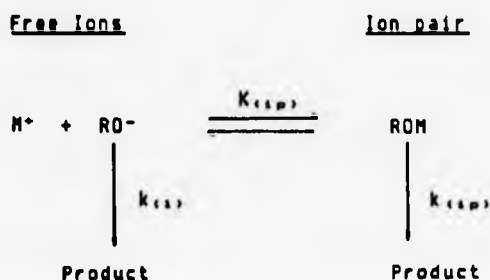
	<u>Alcohol (7)</u>	<u>Alcohol (8)</u>
<u>k_{obs}</u>	$1.55 \times 10^{-4} \text{ s}^{-1}$	0.891 s^{-1}
<u>k_{crs}</u>	5750	1

CHAPTER FIVE

Discussion of experimental data

Discussion of results

Application of the simplified version of Cram's scheme, results in the equation below the scheme, which is derived in appendix (3). This is the equation which results when making no assumptions.



$$\text{Rate} = k_{1222} \cdot [ROM] = k_{11} \cdot [RO^-] + k_{12} \cdot [ROM]$$

$$k_{1222} = \frac{k_{11} + k_{12} \cdot K_{12} \cdot [M^+]}{1 + K_{12} \cdot [M^+]} \quad \text{Equation 1}$$

$[M^+]$ represents the activity of the free metal ion.

Cram⁽¹²⁾ proposed that the contribution from reaction of the ion pairs was negligible ($k_{12} \ll k_{11}$), and other workers have also come to this conclusion^(12,3). Making this assumption, then the rate equation reduces to the equation below.

$$k_{1222} = \frac{k_{11}}{1 + K_{12} \cdot [M^+]} \quad \text{Equation 2}$$

A more useful form of this equation is given below in equation 3.

$$\frac{k_{(1)}}{k_{(2)}} - 1 = K_{(1,2)}[M^+] \quad \text{Equation 3}$$

If $K_{(1,2)}[M^+]$ is large compared to unity, then the equation reduces to ;

$$k_{(2)} = \frac{k_{(1)}}{K_{(1,2)}[M^+]} \quad \text{Equation 4}$$

For the relatively highly associated sodium and lithium alkoxides, equation (4) should apply, but for the potassium alkoxides (using Exner and Steiner's⁽²⁾ value of 280 for $K_{(1,2)}$ for $KOBu^+$ in DMSO as an estimate), $K_{(1,2)}[K^+]$ is not expected to be large compared to unity and equation (3) probably cannot be used. When equation (4) is applicable, then a plot of $\ln(k_{(2)})$ against $\ln[M^+]$ should give a straight line of gradient equal to -1, with an intercept of $(k_{(1)}/K_{(1,2)})$. Treatment of the data for the oxy-Cope rearrangement at constant diasyl concentrations with variable metal halide concentrations (LiCl, LiI, NaI) in this manner gave quite good straight lines (correlation coefficient, $R > 0.994$), but the observed gradient in each case was close to -0.78 as shown in figure (7), rather than -1.00. This probably indicates that the use of concentrations (which would have greatly simplified the interpretation of the data) rather than activities cannot be justified.

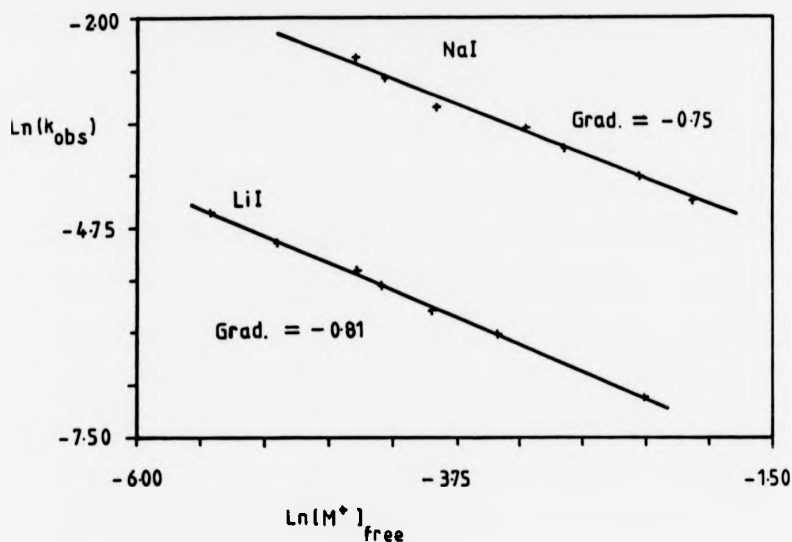


Figure (7) : Oxy-Cope rearrangement of (1) at 30.8°C : $\ln(k_{obs})$ vs $\ln[M^+]_{free}$ for variable LiI and NaI : Data from tables (14) and (15) for Li^+ and tables (18) and (19) for Na^+

Mandolini^(42,43) has used an adapted form of the Debye-Huckel equation to calculate activities of alkali metal halides in 99% DMSO: 1% water, as shown below.

$$\text{Log}(\gamma_{\pm}) = -1.12 I^{1/2} + 1.65 I \quad I = \text{ionic strength}$$

γ_{\pm} is the activity coefficient.

He reports that this equation accounts well for the non-ideal behaviour of alkali metal halides in this medium up to ionic strengths of 0.1 molar. Data is available⁽¹⁰³⁾ for the experimentally determined activity coefficients of some alkali metal halides in 100% DMSO (which is the solvent used in all the work reported in this thesis). The data in table (48) shows the discrepancies between the calculated activity coefficients and the experimental activity coefficients.

Table (48) Calculated and experimental activity coefficients
for alkali metal halides in DMSO

<u>Conc (mol/l)</u>	<u>LiCl</u>	<u>NaI</u>	<u>KI</u>	<u>Calculated</u>
0.0025	0.910	0.984	0.969	0.887
0.01	0.777	0.942	0.906	0.803
0.05	0.556	0.827	0.784	0.679
0.10	0.473	0.805	0.732	0.647

The equation used by Mandolini gives the same value for the activity coefficient at a given concentration regardless of the nature of the alkali metal cation or the nature of the halide anion, whereas the experimental data of Bonner⁽¹⁰³⁾ (using cryoscopic methods) shows that (for the chlorides) the lithium salt behaves in a manner closer to ideality than does the sodium salt, which in turn behaves more ideally than the potassium salt. The same order is seen for the sodium and potassium iodides (sodium behaving more ideally), with there being no data available for lithium iodide. Also, the iodides behave more ideally than do the corresponding chlorides. For the iodides, the calculated activities are lower than the experimental activities at all concentrations for which experimental data is available. For the chlorides, the calculated values are lower than the experimental values at very low concentrations, and higher than the experimental values at higher concentrations. Therefore the equation used by Mandolini for 99% DMSO : 1% water is not applicable to 100% DMSO.

Experimental activity coefficients have been determined for lithium chloride, sodium iodide and potassium iodide (of the halides

used in the work reported in this thesis), but not for lithium iodide, although realistic estimations of the activity coefficients at various concentrations for this salt can be made if the trend observed for the chlorides, and for the sodium and potassium iodides is extrapolated to lithium iodide. In addition to the alkali metal halides, the corresponding metal diacyl salts are also present in solution. No data is available concerning activity coefficients for metal diacyl solutions, and so this is a major source of uncertainty in the handling of the data. For the variable metal halide runs, the assumption has been made that the activity coefficient of the diacyl present is one, and the activities of the various metal halides have been found using Bonner's⁽¹⁰³⁾ data. The runs for which the concentration of free cation is above 0.1 molar have been omitted, as there is no experimental data on the activity coefficients of the halide solutions above this concentration. The concentrations of free cation have been calculated using the data of Exner and Steiner⁽²⁾ for the diacyl solutions, the data of Calas-Perraud⁽¹⁰⁴⁾ for the sodium and potassium iodides, and the data of Casapieri⁽¹⁰⁵⁾ for lithium chloride. The quoted gradients for the graphs (below) are the weighted means (at least two data sets were taken in each case), and the quoted (+/-) values are the standard deviations, calculated from the formulae in appendix (4), as described by Young⁽¹⁰⁶⁾.

To allow for activities, the concentration term (for the alkali metal halides) has been replaced by the activity of the free cation which is given by :

$$\text{Activity of Free } M^+ = [M^+]_{\text{free}} \cdot \gamma_{\pm}$$

Where γ_{\pm} is the activity coefficient.

Variable Diasyl Concentration Runs

For each of the alcohols studied, the initial investigations of the dependence of the reaction rate upon the cation concentration were carried out by varying the diasyl concentration at constant temperature and alcohol concentration. For (1), kinetic runs with variable diasyl lithium and variable diasyl sodium concentrations were performed. For (7), runs with variable diasyl lithium concentrations were performed, and for (8), runs with variable diasyl sodium and potassium concentrations were performed. The data in each case has been treated using equation (4) which gives a graph of $\ln(k_{\text{obs}})$ against $\ln[M^+]_{\text{obs}}$, except for the variable diasyl potassium runs where it is stated in the text that equation (3) has been used.

1) Oxy-Cope rearrangement of (1)

For the variable diasyl runs, estimations of the activity coefficients were not made, since there is no available data, and so the data reported below uses concentrations. As can be seen from figure (8), the plots of $\ln(k_{\text{obs}})$ against $\ln[M^+]_{\text{obs}}$ give straight lines ($R = 0.996$ for Li^+ , $R = 0.995$ for Na^+) with gradients of -2.86 (± 0.08) for Li^+ at a temperature of 26.0°C , and -3.49 (± 0.12) for Na^+ , at a temperature of 18.6°C . The gradients of these lines show the reaction to be much more sensitive to changing the diasyl concentration than would be predicted by the scheme. Plotting $\ln(k_{\text{obs}})$ against $\ln[\text{Total } M^+]$ gives gradients of -1.62 (± 0.05) for Li^+ and -2.01 (± 0.07) for Na^+ .

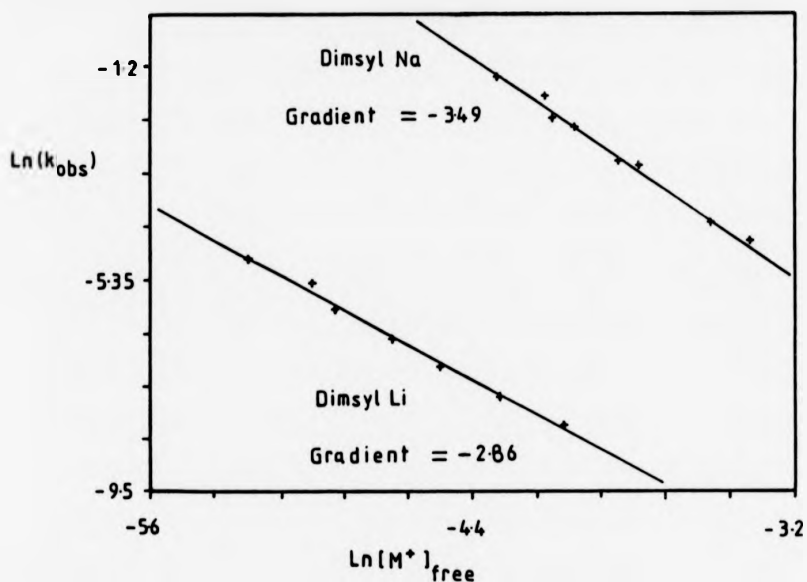


Figure (8) : Oxy-Cope rearrangement of (1) : $\ln(k_{obs})$ vs $\ln[M^+]_{free}$ for variable [Diasyl Li] at 26.0°C and variable [Diasyl Na] at 18.6°C : Data from tables (10), (11) for Li^+ , and from tables (18) and (19) for Na^+

Even if the diasyl solutions were 100% ionised (which they are not, $K_{app} = 370$ for diasyl lithium, and 127 for diasyl sodium⁽²⁾), the reaction rate is still more sensitive than predicted by the scheme. Clearly, the fact that changing the cation concentration by varying the diasyl concentration also varies the base concentration must be having an effect in this case.

2) Fragmentation of (7)

For this fragmentation, the only variable diasyl runs that were carried out were variable diasyl lithium runs, carried out at 18.7°C, as the reaction was too fast for variable diasyl sodium runs to be performed. As can be seen from figure (9), the data from these runs is rather scattered (for the best fit straight

line, $R = 0.96$), and therefore the exact value of the gradient of the graph of $\ln(k_{obs})$ against $\ln[Li^+]_{free}$ ($-1.55 (\pm 0.17)$) is somewhat unreliable.

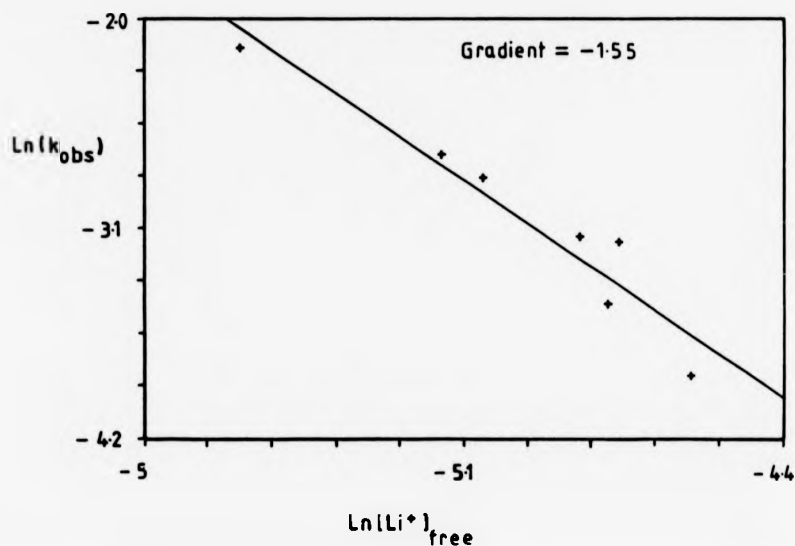


Figure (9) : Fragmentation of (7) : $\ln(k_{obs})$ vs $\ln[Li^+]_{free}$ at 18.7°C , with variable [Diasyl Li] : Data from tables (28) and (29)

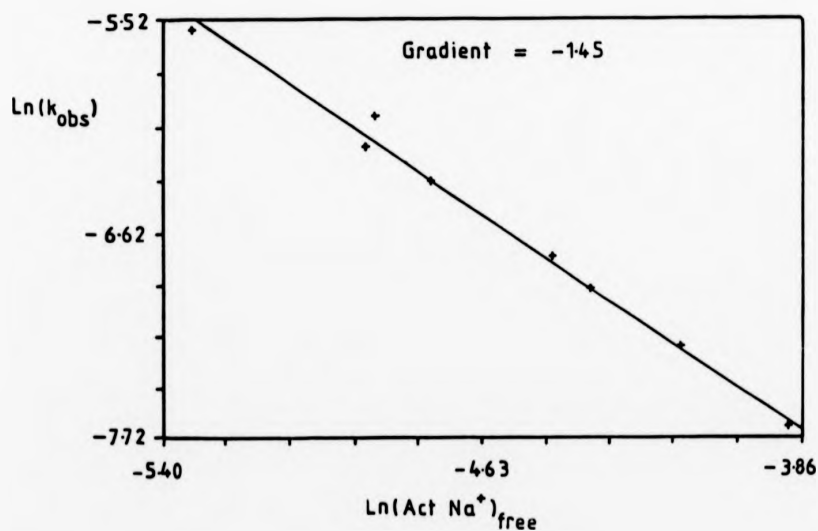


Figure (10) : Fragmentation of (8) : $\ln(k_{obs})$ vs $\ln[Na^+]$ at 30.8°C with variable [Diasyl Na] : Data from tables (33) and (34)

3) Fragmentation of (8)

For this fragmentation, runs were performed using variable diisyl sodium and potassium concentrations. For the variable diisyl sodium runs, the usual equation (4) was used, and the graph of $\ln(k_{\text{obs}})$ against $\ln[M^+]_{\text{free}}$ gives a straight line ($R = 0.992$) gradient of -1.45 (± 0.05), at 30.8°C , as shown above in figure (10).

For the variable diisyl potassium runs, equation (3) should apply rather than equation (4). If equation (4) is used, then a degree of curvature in the plot is seen. However, using data from the variable temperature fragmentation of (8) in the presence of excess [2.2.2] cryptand using diisyl potassium (see later in this chapter), the limiting rate (k_{lim}) at this temperature can be calculated. This allows a graph of $(k_{\text{lim}}/k_{\text{obs}}) - 1$ against $[K^+]$ to be plotted, using equation (3).

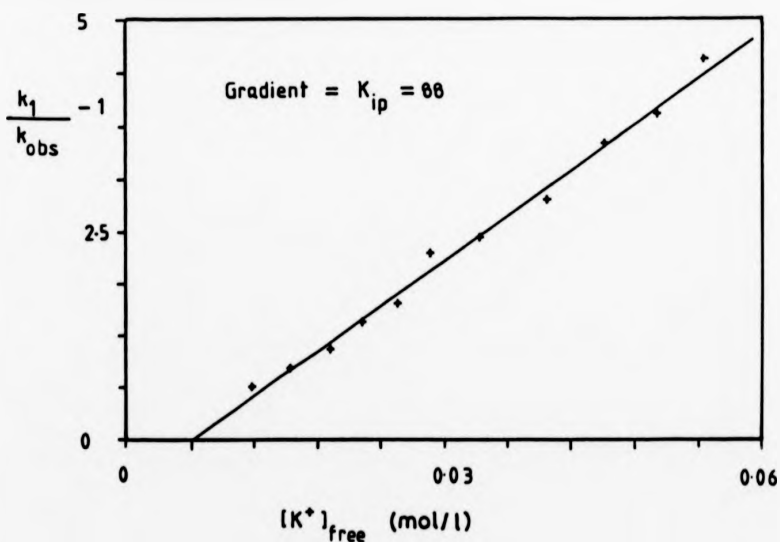


Figure (11) : Fragmentation of (8) : Plot of $((k_{\text{lim}}/k_{\text{obs}}) - 1)$ vs $[K^+]_{\text{free}}$ at 21.2°C : Variable [Diisyl K] : Data from tables (37), (38) and (39)

The gradient of this graph should be the value of the ion pairing constant K_{ip} , for the potassium alkoxide of (8). The good linearity of the graphs ($R = 0.995$), and the good correlation from three data sets indicates that this approach is applicable. The value of K_{ip} , obtained from this is 88 (± 2), at 21.2°C, as shown above in figure (11).

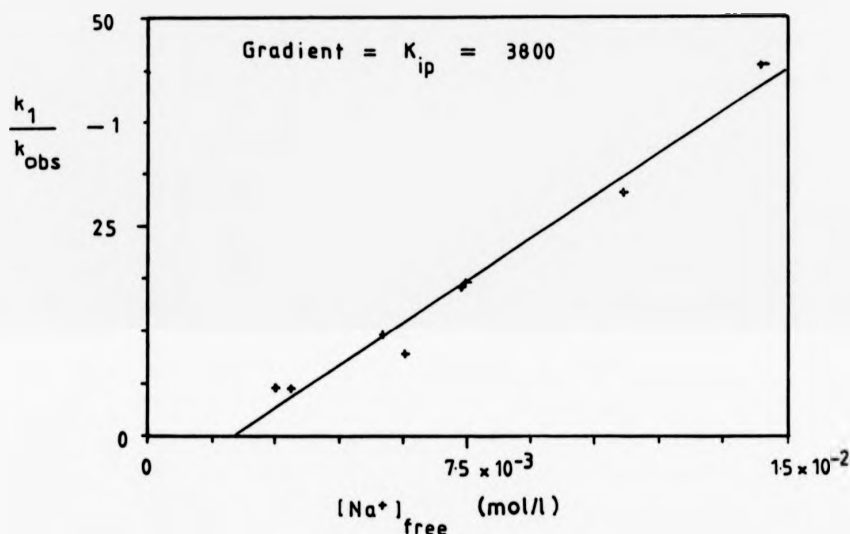


Figure (12) : Fragmentation of (8) : Plot of $((k_{11}/k_{obs}) - 1)$ vs $[Na^+]_{free}$ at 30.8°C : Variable [diethyl Na] : Data from tables (33) and (34)

The same approach can be used to calculate the ion pairing constant for the sodium alkoxide of (8), although the nature of the graph means that the gradient obtained depends heavily on the slower points (with a large value of $((k_{11}/k_{obs}) - 1)$). A straight line is obtained ($R = 0.991$), which gave the value of K_{ip} as $3.8 (\pm 0.2) \times 10^3$ at 30.8°C, as shown in figure (12).

Variable metal halide concentration runs

Because variation of the dimethyl concentration varies the base concentration as well as the cation concentration, kinetic runs were then performed for all alcohols using alkali metal halides to vary the cation concentration whilst keeping the dimethyl concentration constant, at constant alcohol concentration and constant temperature. This means that the effect of changing the cation concentration alone can be looked at. All of the data has been treated using equation (4), except where stated, when equation (3) was used.

1) Oxy-Cope rearrangement of (1)

(1) Lithium Chloride

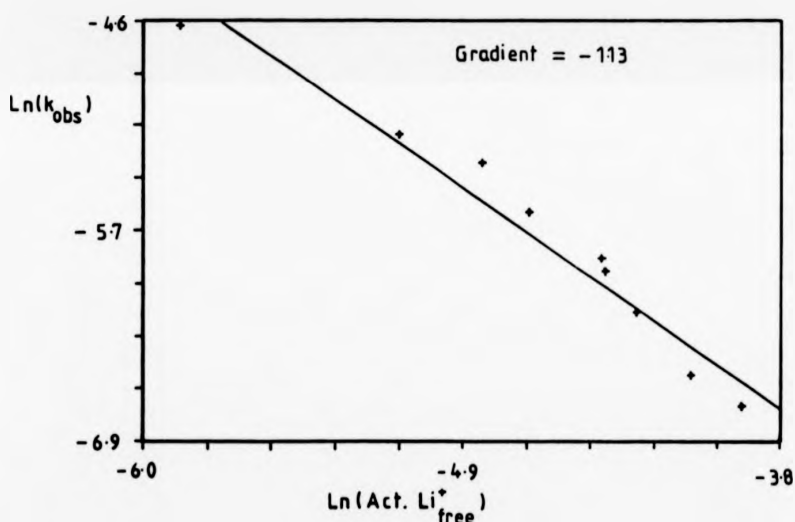


Figure (13) : Oxy-Cope rearrangement of (1) : $\ln(k_{\text{obs}})$ vs $\ln(\text{Act. Li}^+_{\text{free}})$ at 30.0°C : Variable $[\text{LiCl}]$: Data from tables (12) and (13)

For these runs, the graph of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. Li}^+_{\text{free}})$ gives a straight line ($R = 0.978$) with a gradient of -1.13 (± 0.07), at 30.0°C , as shown above in figure (13).

(ii) Lithium Iodide

For the lithium iodide runs, the graph of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. Li}^+)_{\text{free}}$ gives an excellent straight line ($R = 0.997$) with a gradient of -0.86 (± 0.02) at 30°C , as shown below in figure (14). Using the same plot as in figures (13) and (14), but with concentrations instead of activities, the gradients of the LiI and LiCl graphs are very similar (-0.81 (± 0.01) for LiI and -0.76 (± 0.02) for LiCl).

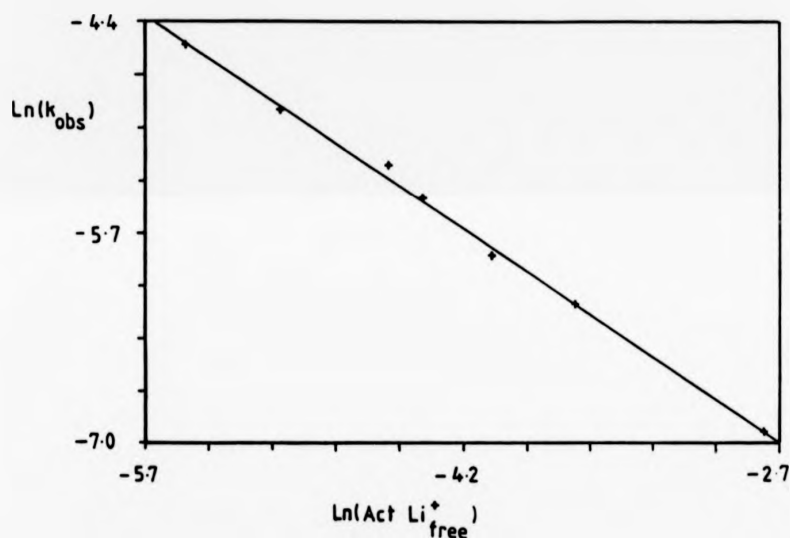


Figure (14) : Oxy-Cope rearrangement of (1) : $\ln(k_{\text{obs}})$ vs $\ln(\text{Act. Li}^+)_{\text{free}}$ at 30.8°C : Variable [LiI] : Data from tables (14) and (15)

The difference in the two sets of halide runs lies in the different activities of the halides. The activity coefficients for lithium iodide have been estimated, assuming that the trend of the lithium salt behaving closer to ideality than the sodium salt, which behaves more ideally than the potassium salt (which is true for the

chlorides) is applicable to the iodides. The gradients of the graphs when using activities should be -1.00 , and the difference between the two results is quite large.

(iii) Sodium Iodide

For these runs, the graph of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. Na}^+)_{\text{free}}$ gives a straight line ($R = 0.993$) with a gradient of -0.94 (± 0.03) at 18.6°C , which is closer to the predicted value of -1.00 than either of the added lithium halide data sets for this reaction, as shown in figure (15).

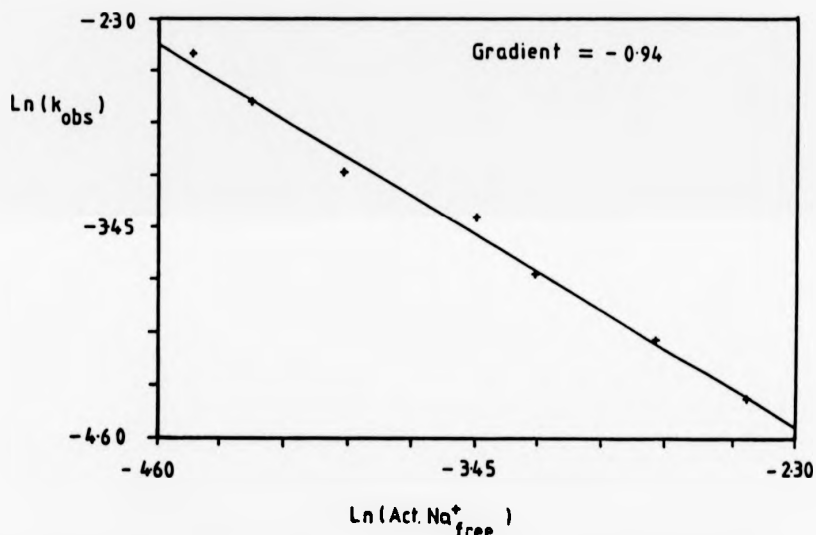


Figure (15) : Oxy-Cope rearrangement of (1) : $\ln(k_{\text{obs}})$ vs $\ln(\text{Act. Na}^+)_{\text{free}}$ at 18.6°C : Variable $[\text{NaI}]$: Data from tables (20) and (21)

(iv) Potassium Iodide

For the potassium iodide runs, equation (4) should not be used for reasons described earlier, and also there is no estimate of the limiting rate of the reaction, as the reaction was too fast to perform a set of variable temperature runs in the presence of excess cryptand (as was carried out for (8)). This means that a plot to

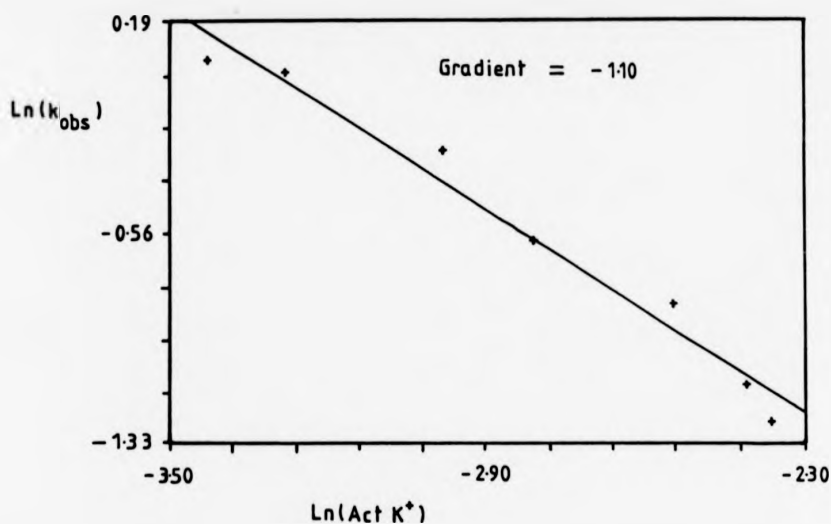


Figure (16) : Oxy-Cope rearrangement of (1) : $\text{Ln}(k_{\text{obs}})$ vs $\text{Ln}(\text{Act. K}^+)$, r_{res} at 18.6°C ; Variable $[\text{KI}]$; Data from tables (22) and (23)

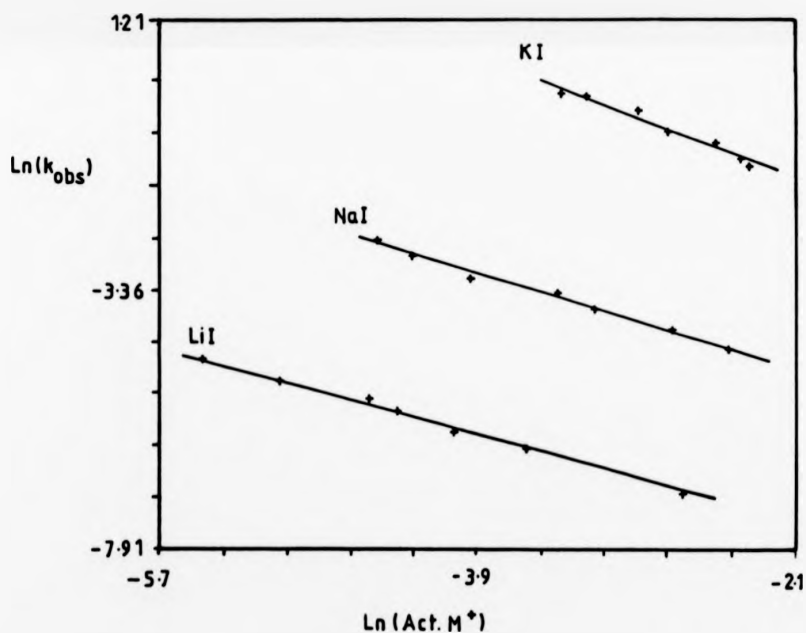


Figure (17) : Oxy-Cope rearrangement of (1) : $\text{Ln}(k_{\text{obs}})$ vs $\text{Ln}(\text{Act. M}^+)$, r_{res} at 18.6°C for K^+ and Na^+ , 30.8°C for Li^+ ; Variable $[\text{MI}]$; Data from tables (14) and (15) for Li^+ , tables (20) and (21) for Na^+ , and tables (22) and (23) for K^+

find the ion pairing constant (using equation (3)) cannot be carried out (as was performed for (8)). If a graph using the usual equation of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. M}^+)_{\text{obs}}$ is drawn, then considerable dispersion from linearity ($R = 0.97$) is seen, as is shown in figure (16). The curvature is much more exaggerated if points with $[\text{K}^+] > 0.1$ mol/l are included. In figure (17), a comparison of the graphs of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. M}^+)_{\text{obs}}$ for the three metal iodides is shown.

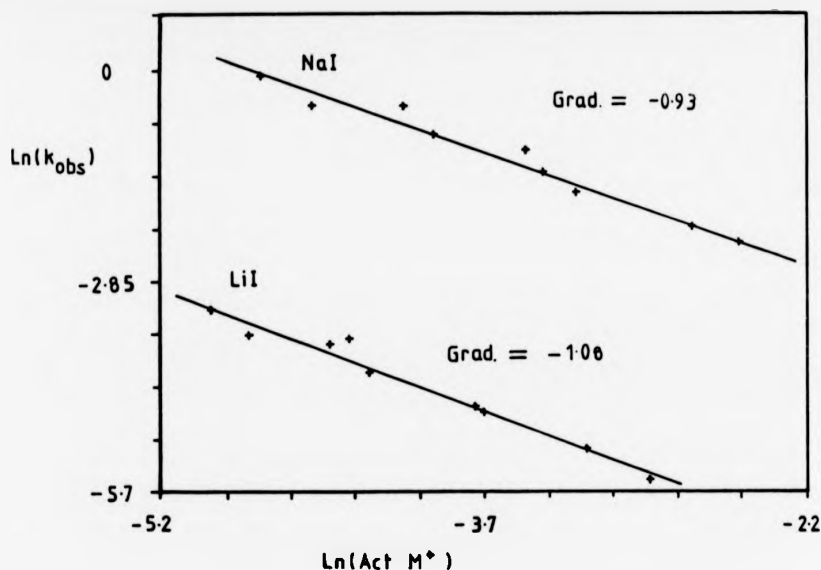
2) Fragmentation of (7)

(i) Lithium Iodide

For the lithium iodide runs, the graph of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. Li}^+)_{\text{obs}}$ gave a straight line ($R = 0.988$) with a gradient of -1.08 (± 0.06) at 18.6°C , which is reasonably close to the predicted value, and larger than the value of -0.86 for the added lithium iodide runs for the oxy-Cope rearrangement of (1).

(ii) Sodium Iodide

For the added sodium iodide runs, the graph of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. Na}^+)_{\text{obs}}$ gave a straight line ($R = 0.992$) with a gradient of -0.93 (± 0.04), at 18.6°C . This is in good agreement with the value of 0.94 for the added sodium iodide runs for the oxy-Cope rearrangement, and is in reasonable agreement with the predicted value of -1.00 . A comparison of the two iodides is shown in figure (18).



Figure(18) : Fragmentation of (7) : $\text{Ln}(k_{\text{obs}})$ vs $\text{Ln}(\text{Act. M}^+)$, $T = 18.6^\circ\text{C}$; Variable [MI] : Data from tables (28) and (29) for Li^+ , and from tables (30) and (31) for Na^+

3) Fragmentation of (8)

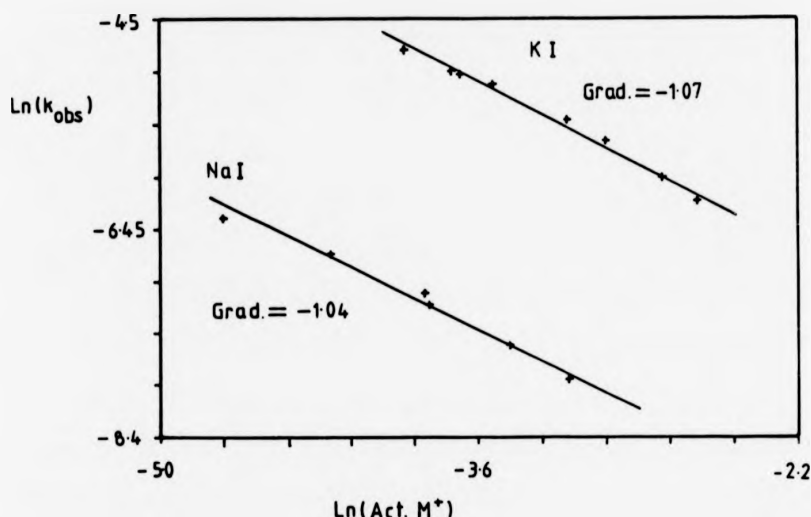
(i) Sodium Iodide

The graph of $\text{Ln}(k_{\text{obs}})$ against $\text{Ln}(\text{Act. Na}^+)$, $T = 30.8^\circ\text{C}$, gives a straight line ($R = 0.990$) with a gradient of -1.04 (± 0.06), at 30.8°C , which is in good agreement with the predicted value, and in fair agreement with the values obtained for the variable sodium iodide runs using alcohol (1) (gradient = -0.94), and using alcohol (7) (gradient = -0.93).

(ii) Potassium Iodide

For these runs, it is expected that equation (3) should be used rather than equation (4), although if equation (3) is used, and the usual graph is plotted, only a very small degree of curvature is observed (the best fit straight line has $R = 0.995$), in marked contrast to the added potassium iodide runs when using alcohol (1). The gradient of the graph of $\text{Ln}(k_{\text{obs}})$ against $\text{Ln}(\text{Act. M}^+)$, $T = 30.8^\circ\text{C}$, is

-1.07 (+/- 0.03), at 26.0°C, and a comparison of the sodium and potassium iodides is given below in figure (19).



Figure(19) : Fragmentation of (8) : $\text{Ln}(k_{\text{obs}})$ vs $\text{Ln}(\text{Act. M}^+)$, at 30.8°C for Na^+ , and 26.0°C for K^+ ; Variable [MI] ; Data from tables (35) and (36) for Na^+ , and from tables (40) and (41) for K^+

If the same approach is carried out for these variable potassium iodide runs as was carried out for the variable dimethyl runs for alcohol (8), a value for the ion pairing constant of the potassium alkoxide of (8) at this temperature can be estimated from a plot of $(k_{\text{ip}}/k_{\text{obs}}) - 1$ against $\text{Act}(\text{M}^+)$. The gradient of the straight line ($R = 0.994$) should be K_{ip} , this being 124 (+/-4), as shown in figure (20).

It should be noted that the value of K_{ip} found from this data differs from that found from the variable dimethyl data which was 88 (+/- 2) because of the difference in temperatures, and because activities were used for the potassium iodide runs, whereas no activities were known for the variable dimethyl potassium runs (and so concentrations were used).

The values obtained for the ion pairing constant of the

potassium alkoxide of (8) of 88 at 21.2°C (when using concentrations), and 124 at 26.0°C (when using activities) are of a similar order of magnitude as the value of the ion pairing constant of potassium *t*-butoxide in DMSO at 25.0°C of 270, which was determined by Exner and Steiner⁽²⁾. The value of the ion pairing constant of the potassium alkoxide of (8) is expected to be smaller than that of KOBu^c. Alcohol (8) has two benzyl groups and a phenyl group attached to the central carbon, whereas *t*-butanol has only three methyl groups, and this extra steric bulk is expected to hinder ion pair formation.

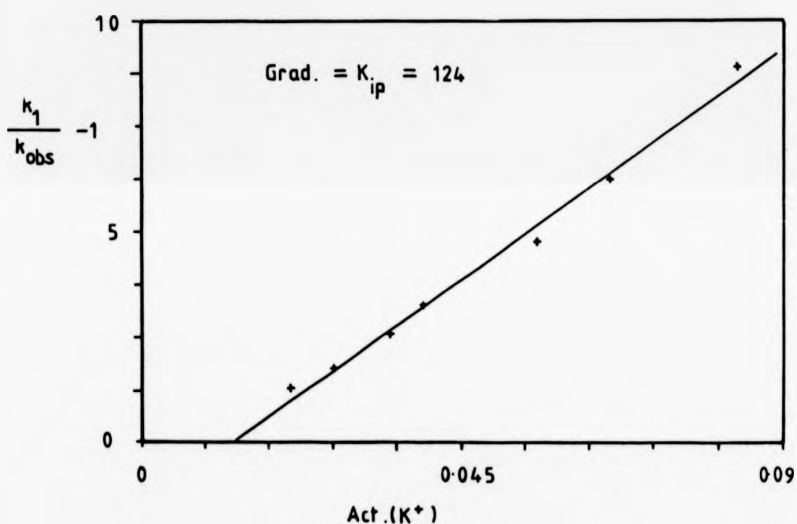
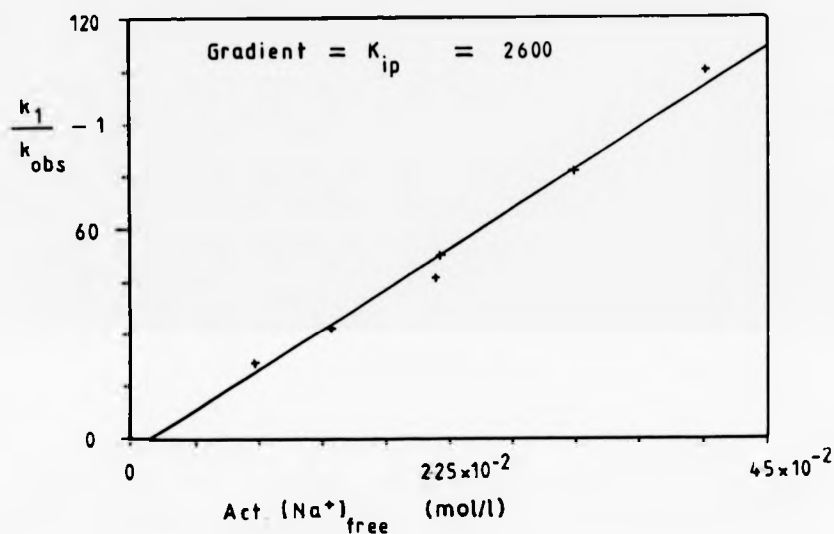


Figure (20) : Fragmentation of (8) : $((k_{11}/k_{obs}) - 1)$ vs Act.(K⁺) at 26.0°C : Variable [K⁺] : Data from tables (40) and (41)

The value of the ion pairing constant of the sodium alkoxide of (8) at 30.8°C can be calculated using the same approach, although for these runs the gradient obtained is heavily dependent on the slower points. A straight line is obtained ($R = 0.994$) which gave the value of K_{ip} as $2.6 \times (+/- 0.2) \times$

10^3 . This is of the same order of magnitude as was obtained (at the same temperature) for the sodium alkoxide of (8) using the variable diethyl sodium data, although the actual value differs somewhat from that obtained earlier (3.8×10^3). Both of these values of K_{ip} are considerably lower than the value obtained by Exner and Steiner⁽²⁾ for the sodium alkoxide of *t*-butanol in DMSO at 25°C, which was 10^4 .



Figure(21) : Fragmentation of (8) : $((k_{11}/k_{obs}) - 1)$ vs Act.(Na⁺) at 30.8°C : Variable [NaI] : Data from tables (35) and (36)

The major reason for the cause of this difference is expected to be steric hindrance to ion pairing, as described above. The steric hindrance to ion pairing has a larger effect on the K_{ip} value of the sodium alkoxide of (8) than on the potassium alkoxide of (8), compared to the alkoxides of *t*-butanol, which is the simplest tertiary alcohol. The compression of the differences between the potassium and sodium alkoxides (in comparison with *t*-butanol) has been observed, not only in the values of the ion

pairing constants, but also in the rate differences of the different metal alkoxides, as described later.

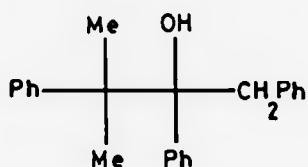
If the data from all of the added halide runs from each of the alcohols (except the added KI runs for the oxy-Cope rearrangement, which shows considerable curvature), are compared, then the average gradient is -1.01 , with a standard deviation of 0.09 . This would indicate that the prediction of the scheme is valid. In each case, the rate decreases with increasing cation concentration (with the other variables kept constant), as predicted by the scheme. The value for the gradient of the graphs of $\ln(k_{\text{obs}})$ against $\ln(\text{Act. M}^+)_{\text{obs}}$ is predicted to be -1.00 , and this is in agreement with the average experimental value for the reactions and halides studied, although it should be noted that assumptions needed to be made concerning the activities of the diethyl solutions.

Using dimethylformamide (DMF) as solvent, Mandolini⁽¹⁰⁷⁾ reported that the rate depressing effect of adding sodium or lithium perchlorate to a solution of a phenoxide in an intramolecular ether-forming reaction was greater than expected, and interpreted this as being due to formation of highly unreactive ion triplets at high cation concentrations. However, Mandolini also reported that no evidence for the formation of ion triplets could be found when working on analogous reactions in DMSO. This is in keeping with the findings from this work, where there is no systematic deviation from the predicted dependence of the rate on the cation concentration for the added halide runs, and so there is no evidence for ion triplet formation.

Comparison of alcohol reactivity

A comparison was made of the rates of reaction of the two alcohols which performed the fragmentation reaction under identical conditions ($[\text{dimethyl Na}] = 0.0217 \text{ mol/l}$, temperature = 18.6°C), as shown below, (the actual rates being 0.891 s^{-1} for (7), and $1.55 \times 10^{-4} \text{ s}^{-1}$ for (8)).

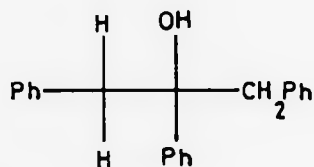
Alcohol (7)



K₁ = 0.891

5750

Alcohol (8)



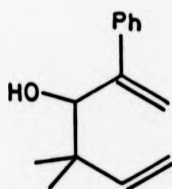
1

This rate difference can be explained by three factors. The leaving carbanion for (7) is the cumyl anion, whereas for (8) the leaving carbanion is the benzyl anion. Cumene is more acidic than toluene in cyclohexylamine (estimated pK_a 's are $40.7^{(33)}$ and $41.2^{(32)}$ respectively), and from the established correlation between pK_a values in CHA and DMSO⁽³⁴⁾, it will be more acidic in DMSO also. Therefore, fragmentation of (7) gives a more stable carbanion than does fragmentation of (8). There is a greater degree of steric compression in (7) than (8), because of the presence of the two methyl groups attached to the central carbon, where there are hydrogens in (8). Use of Allinger's MM2 force field⁽⁴⁷⁾ gives a value of 5.54 kcal/mol for the steric energy of the minimum energy conformer of (8), and a value of 15.6 kcal/mol for the steric energy

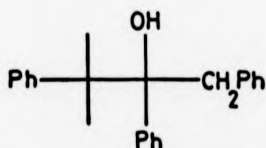
of the minimum energy conformer of (7), a difference of over 10 kcal/mol. It is expected that this will result in the free energy of activation for fragmentation of (7) being considerably lower than for the fragmentation of (8). If all of the 10 kcal/mol difference in steric energies were reflected in the relative free energies of activation, then this would give a rate factor of approximately 10^4 for the fragmentation of (7) compared to (8). Also, it is expected that the steric hindrance to ion pair formation will be greater for (7) than for (8), and so alkoxides of (7) are expected to be more dissociated than the corresponding alkoxides of (8). This would mean that there would be a greater proportion of free ions present in the solutions of the alkoxides of (7) than for (8), and so this would cause a greater observed reaction rate. The argument of steric hindrance to ion pairing has been used by Arnett¹⁴ as a partial reason for the instantaneous fragmentation of tri-*t*-butylethanol in diisyl potassium at 25°C.

Variation of rate with cation

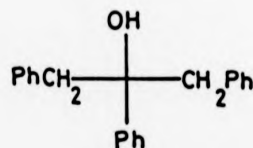
Alcohol (1)



Alcohol (7)



Alcohol (8)



Li⁺ : Na⁺ : K⁺
1 : 309 : 11300

Li⁺ : Na⁺
1 : 39

Li⁺ : Na⁺ : K⁺
1 : 64 : 630

The relative rates of reaction of the various alkali metal alkoxides for each individual alcohol have been measured, with the cation concentration and temperature being kept constant for each alcohol, with the results being shown below. The steric hindrance to ion pairing argument can be used to explain the relative rate ratios of $\text{Li}^+ : \text{Na}^+ : \text{K}^+$ for the three alcohols.

As the lithium alkoxides are the most highly associated, they receive the greatest effect from the steric hindrance to ion pairing. In effect, the steric hindrance to ion pairing causes a levelling effect on the rate differences of the alkoxides of a given alcohol on going from Li^+ to Na^+ to K^+ . The greater the hindrance, the more levelling is seen, and the smaller is the rate increase factor on changing the cation from Li^+ to Na^+ to K^+ . The most hindered of the three alcohols is (7), as it is a tertiary alcohol with phenyl, cumyl and benzyl groups attached to the carbon bearing the alkoxide oxygen. This shows the smallest rate increase factor on going from Li^+ to Na^+ of 39, no runs with K^+ being measurable. The second most hindered of the three alcohols is (8), as it is a tertiary alcohol with two benzyl groups and one phenyl group attached to the central carbon. This shows the intermediate rate factor increase of 64 on going from Li^+ to Na^+ , and a rate enhancement of a factor of 10 on going from Na^+ to K^+ . The least hindered alcohol is (1), which is a secondary alcohol, and this shows the largest rate enhancements of 308 on going from Li^+ to Na^+ , and of 37 on going from Na^+ to K^+ . This concurs with what is expected from the steric hindrance to ion pairing argument.

A reason for the acceleration of the oxy-Cope rearrangement by ionisation of the hydroxyl group, and indeed a

reason for the acceleration of all reactions involving the cleavage of a bond adjacent to a carbon to alkoxide oxygen bond was provided from calculations performed by Goddard⁽¹⁰⁾. Using ab initio generalised valence bond and configuration interaction theoretical methods, the bond strengths of the carbon to hydrogen bonds of methanol, sodium methoxide, potassium methoxide, and the free methoxide were calculated. The results of these calculations are shown below in table (49).

Table (49) : C-H bond energies for alkali metal methoxides
calculated by Goddard

<u>Substrate</u>	<u>Bond Energy at 0 K (D₀)</u>	<u>Change in D₀</u>
H-CH ₂ OH	90.7 kcal/mol	0.0
H-CH ₂ ONa	80.6 kcal/mol	-10.1
H-CH ₂ OK	79.6 kcal/mol	-11.7
H-CH ₂ O ⁻	74.2 kcal/mol	-16.5

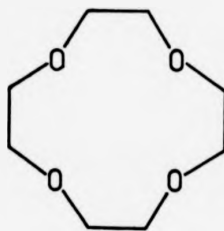
These calculations predict a substantial weakening of the bond adjacent to the carbon to oxygen bond, on formation of the sodium alkoxide. This bond becomes weaker on formation of the potassium alkoxide, and weaker still (by 16.5 kcal/mol compared to methanol in this case) on formation of the free alkoxide. Goddard reported that this bond weakening effect was expected to be quite general, and that the results of the calculations could be applied to many chemical systems. In reactions where the bond adjacent to the carbon to oxygen bond breaks (such as the oxy-Cope rearrangement and the alkoxide fragmentation reaction used in this work), the

calculations predict, therefore, that formation of the alkoxide will result in a lower bond energy for the bond to be broken. If this bond breakage is involved in the rate determining step of the reaction, then formation of the alkoxide will result in enhanced rates. Formation of the free alkoxide results in the smallest value of the bond strength, and so it is expected from this that the free alkoxide will react fastest, which is in accordance with the experimental findings.

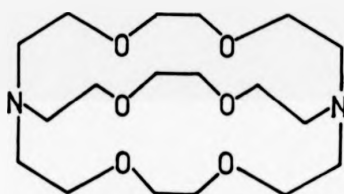
Crowns and Cryptands

The families of multidentate ligands known as crown ethers and cryptands are extremely efficient complexing agents for metal cations, and this field has been extensively investigated¹¹⁰. The specificity of many of these ligands for particular cations has been explained in terms of the size of the appropriate cation providing the best fit into the cavity of the ligand¹¹⁰. The crown ether that has been used in this work is 12-crown-4 ether (12-C-4) for complexing Li⁺, and the cryptands that have been used are [2.1.1.] cryptand for complexing Li⁺, and [2.2.2.] cryptand for complexing Na⁺ and K⁺. The cryptands compete with the solvent (and in this work they also compete with the alkoxide anion) for the metal cation, and the values of the association constant K_a at 25°C in DMSO solvent¹¹¹ are given below, with perchlorate as the counterion (which does not compete with DMSO for the cation).



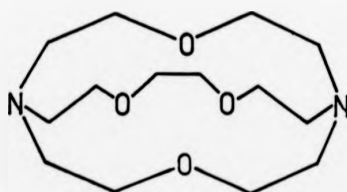


12-C-4 Ether



[2.2.2.]

Cryptand



[2.1.1.]

Cryptand

Table 50 : Association constants for metal cryptates in DMSO

<u>Cation</u>	<u>Cryptand</u>	<u>K_c</u>
Li ⁺	[2.1.1.1]	6.3×10^6
Na ⁺	[2.2.2.1]	2.2×10^6
K ⁺	[2.2.2.1]	1.0×10^7

It was expected, therefore, that if the K_c value for the cryptate in DMSO was considerably greater than the ion pairing constant for the alkoxide in DMSO, then the cryptand would complex an equivalent quantity of cation, and so remove it from the ion-pairing equilibria. This is expected to be the case for the less associated sodium and potassium alkoxides, although for the lithium alkoxide it is expected that the K_{ip} value for ion pairing and the K_c value for the cryptate will be of a similar order of magnitude. In the case where the K_c value is much larger than the K_{ip} value, when the concentration of the cryptand in the solution is less than the concentration of cation then the rate should increase with increasing cryptand concentration (as predicted by Craze's scheme, as the concentration of free alkoxide would increase with increasing cryptand concentration). When the concentration of cryptand is equal to the concentration of cation, then all of the cation should be complexed by the cryptand, and all of the alkoxide should be present as free alkoxide (with no ion pairs present). Increasing the cryptand concentration above the cation concentration should have no further effect, as all of the alkoxide is present as free alkoxide, reacting with the limiting rate k_{111} . Qualitatively, therefore, it is expected that a graph of observed rate constant against concentration of cryptand

would look like figure (21), with the value of the rate constant levelling off after the concentrations of cation and cryptand become equal.

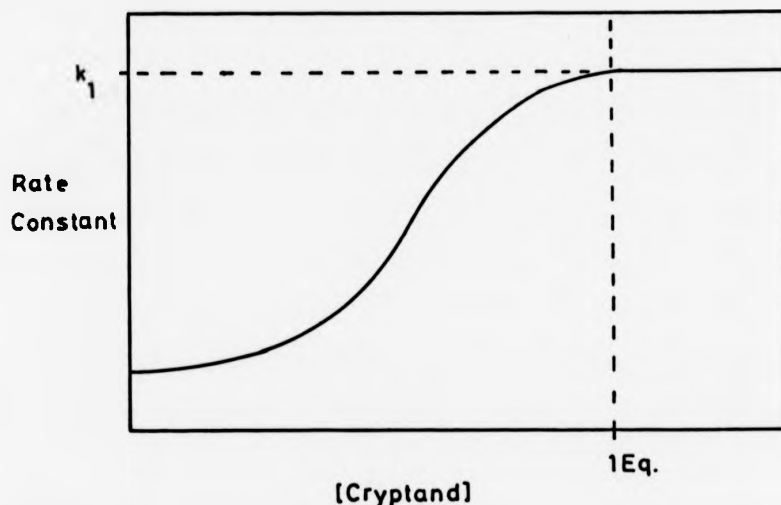


Figure.(22) : Expected graph when plotting rate constant against concentration of cryptand at constant $[M^+]$ in the general case

A detailed derivation of the relationships between $[M^+]_{free}$, K_c , and $K_{1:1}$, is given in appendix 5, and can be used (see later) to calculate theoretical data for comparison with the experimental data.

This type of behaviour, with a limiting rate increase being observed, has been reported by Evans⁽¹⁶⁾ and Paquette⁽¹⁷⁾, both using 18-crown-6 ether (18-C-6) as the complexing agent for the potassium alkoxides of alcohols undergoing the oxy-Cope rearrangement (Evans), and 1,5-hydrogen migration (Paquette), in THF. Because 18-C-6 is not as efficient at complexing potassium as [2.2.2.] cryptand (K_c in DMSO at 25°C is 1.62×10^5 for 18-C-6⁽¹⁸⁾ and 10^7 for [2.2.2.] cryptand⁽¹⁹⁾), the rate limiting increases were observed by Evans after addition of 3 equivalents of

18-C-6, and by Paquette after addition of 5 equivalents of 18-C-6.

With a view to investigating this expected rate increase on complexation of the cation, the oxy-Cope rearrangement of (1) was carried out in the presence of 12-C-4. The generally accepted literature view⁽¹²²⁾ on the complexation of Li^+ was that 12-C-4 was the best crown ether for complexing lithium. However, the value for the association constant of the Li^+ complex with 12-C-4 in DMSO was given as approximately one ($\text{Log}_{10} (K_a) \sim 0$) by Smetana and Popov⁽¹²³⁾.

It was recently reported⁽¹¹²⁾ that the association constant for the Li^+ complex with 12-C-4 in methanol was less than unity. A similar lack of complexation of Li^+ was reported by Jackman⁽¹²⁴⁾, who observed that addition of 12-C-4 to a solution of lithioisobutyrophenone in either dioxolane and dimethoxyethane gave a negligible change in the ^{13}C n.m.r. spectrum of the enolate. Addition of the lithium-specific [2.1.1] cryptand resulted in appreciable changes in the ^{13}C n.m.r. spectrum of the enolate. These results were interpreted as showing little complexation of the lithium cation by 12-C-4 under these conditions.

When using 12-C-4 with diisyl lithium for the anionic oxy-Cope rearrangement, the experimental result is in agreement with there being little complexation of the lithium cation by 12-C-4 in DMSO. There is a 5% decrease in rate on addition of 1 equivalent of 12-C-4, and a 10% increase in rate on addition of 3 equivalents of 12-C-4. The experimental error is usually $\pm 6\%$, although it may be as high as $\pm 10\%$ on some occasions. The 5% decrease in the rate on addition of 1 equivalent of 12-C-4 is definitely within the experimental error, and the 10% increase on addition of 3 equivalents may be within the experimental error,

although this small rate increase may be due to a small amount of complexation of the Li^+ by the crown ether.

In view of the failure of 12-C-4 to complex Li^+ effectively in DMSO for this reaction, it was not used for the fragmentation reactions. For the anionic oxy-Cope rearrangement, [2.1.1.] cryptand was used in conjunction with diisyl lithium, and this was the only complexing agent for which data was collected for this reaction. For the fragmentation of (8), in addition to the use of [2.1.1.] cryptand with diisyl lithium, [2.2.2.] cryptand was used with diisyl sodium and diisyl potassium.

For the anionic oxy-Cope rearrangement at 19.5°C using diisyl lithium with varying amounts of [2.1.1.] cryptand, data could only be collected up to about 0.5 equivalents of cryptand, since the rate of reaction became too fast to monitor at greater cryptand concentrations using the u.v. cells.

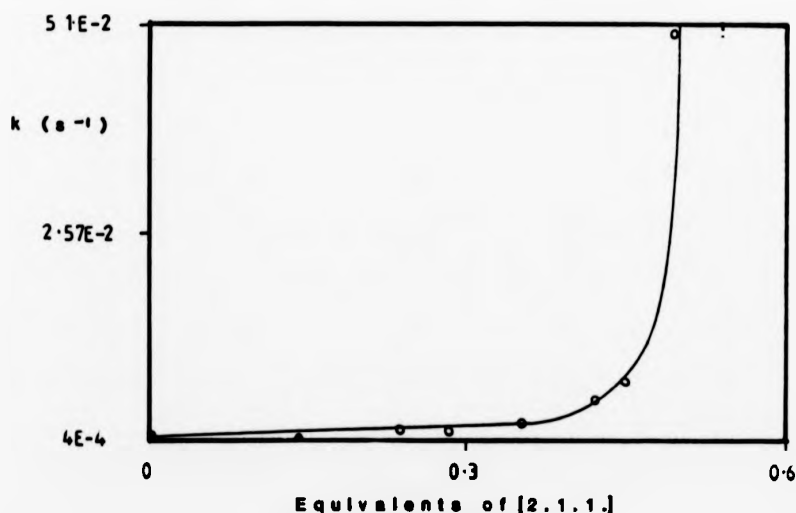


Figure.(23) : Oxy-Cope rearrangement of (1) : k_{obs} vs [2.1.1.] cryptand at 18.6°C : [Diisyl Li] = 0.033 mol/l : Data from tables (16) and (17)

Because the same apparatus needed to be used in order to keep the concentrations of alcohol and dimethyl constant for each run (with only the cryptand concentration varying), it was not possible to switch from the u.v. cells to the stopped flow apparatus for faster runs. For this reaction, the rate of rearrangement of the potassium alkoxide at 0.02 mol/l was just measurable at 18.6°C (half life of about 0.25 seconds). The limiting rate would be expected to be rather faster than this, and so it would not be possible to observe a limiting rate increase for the oxy-Cope rearrangement, as it would be too fast to measure. The graph of the observed rate against the concentration of [2.1.1] cryptand is shown above in figure (22).

Because the fragmentation of 1,2,3-triphenyl-2-propanol (8) was much slower than the oxy-Cope rearrangement under the same conditions, there seemed a greater likelihood of observing a limiting rate for the fragmentation of this alcohol. When the reaction was carried out at 18.6°C, a rate limiting increase was seen for the potassium alkoxide of (8) with excess [2.2.2.] cryptand. A very similar rate limiting increase was observed for the sodium alkoxide of (8) with [2.2.2.] cryptand. The limiting rate should correspond to the rate of reaction of the free ions, k_1 from the scheme. For the lithium alkoxide of (8) with [2.1.1.] cryptand, a limiting rate increase was not observed on addition of up to 2 equivalents, although the rate at which the observed rate was increasing when more than one equivalent of cryptand was present was rapidly decreasing. This is shown clearly in the plot of $\ln(k_{obs})$ against concentration of cryptand (figure.(25)), where the lithium plot virtually levels off above one equivalent of added cryptand. That a limiting rate increase was not

observed for the lithium alkoxide of (8) is not too surprising as the ion pairing constant for the lithium alkoxide is expected to be of a similar order of magnitude as the K_c value of the cryptand, and so the alkoxide can compete effectively with the cryptand for the lithium ions. The fastest rate observed for the lithium alkoxide of (8) was very close to the observed limiting rates for the sodium and potassium alkoxides, and so it is expected that the rate observed with 2 equivalents of [2.1.1.] cryptand is close to the limiting rate for the lithium alkoxide.

A cubic equation in free cation concentration, in the presence of added cryptand, can be derived (see appendix 5). The value of $[M^*]_{\infty}$ can then be calculated for varying cryptand concentrations, and these values are put into equation 2. This allows the calculation of the theoretical curves (for the plot of $\ln(k_{\infty})$ against cryptand concentration) for dimethyl lithium in the presence of [2.1.1.] cryptand, and dimethyl potassium and sodium in the presence of [2.2.2.] cryptand. These theoretical curves are shown in figure (24), and compared with the experimental curves in figure (25). To calculate the theoretical curves, the values of certain constants needed to be inserted into the cubic equation. The value of the limiting rate (k_1) was taken from the dimethyl sodium runs as $1 \times 10^{-2} \text{ s}^{-1}$ for each case, the values of K_c (cryptate formation equilibrium constants) were those given by Cox⁽¹¹⁾, and the concentrations of the cations were the experimentally determined values. The values for the ion pairing constants of the alkoxides were as follows. The value of $K_{1,p}$, used for the potassium alkoxide was 88, as determined from the variable dimethyl potassium runs (see figure 11). The value of $K_{1,p}$, used for the sodium alkoxide was 2600, as determined from the variable sodium

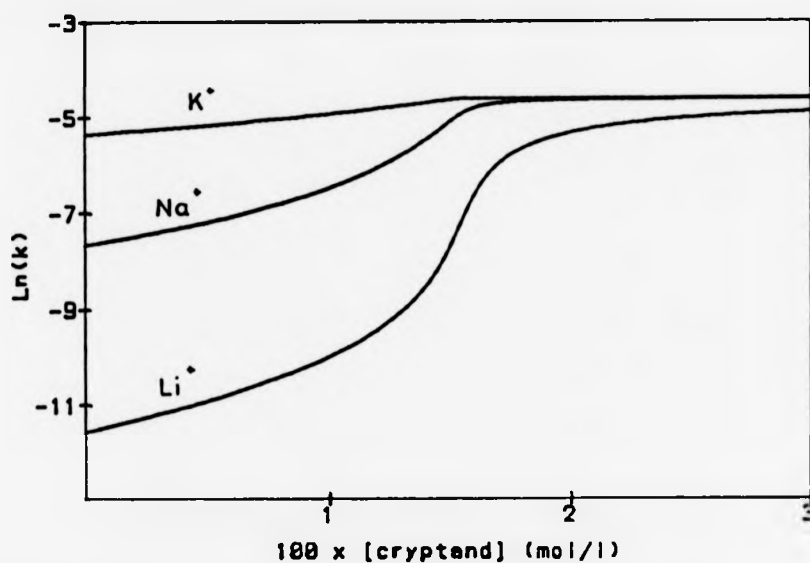


Figure 24: Computer generated plots of $\text{Ln}(k)$ against concentration of added cryptand.

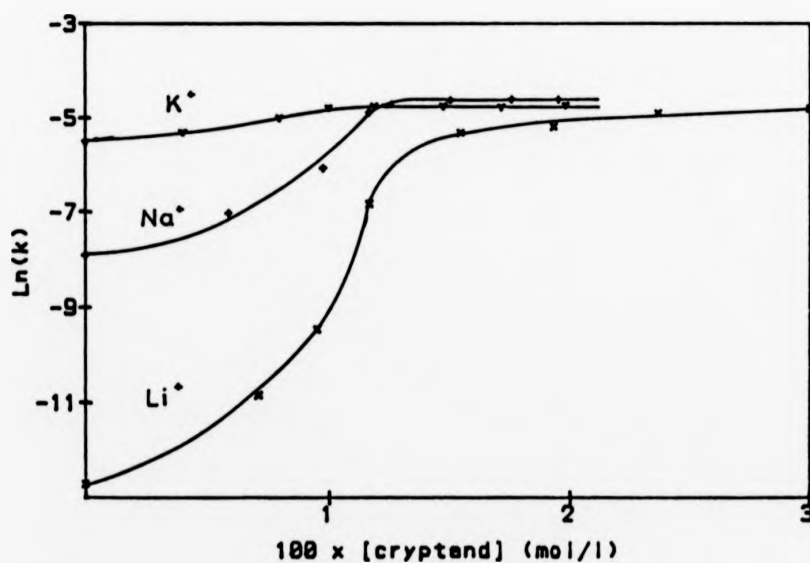


Figure 25 Experimental plots of $\text{Ln}(k)$ against concentration of added cryptand

iodide runs (see figure 21). The value of $K_{1,p}$ for the lithium alkoxide was estimated as 2×10^5 , as this gave the best fit to the data.

As can be seen from figures (24) and (25), the experimental and theoretical curves correspond very closely, and are virtually superimposable for the diisyl sodium and potassium curves. For the diisyl lithium curves, the only point for which there is disagreement between the experimental and calculated data is for the run with no cryptand present. It should be noted that although data was collected out to five half-lives for the other points, for this particular run (as a result of the extremely long half-life of 64 hours) data was only collected for the first half-life. This makes this point the least reliable experimental point on figure (25).

Estimation of $k_{1,p}$ for each cation

The runs with added cryptand allow estimation of the upper limits for the value of the rate constant for reaction of the ion pairs ($k_{1,p}$) for each cation at 18.6°C. From the scheme, $k_{1,p}$ must be the slowest reaction rate possible at that temperature for the given cation, and so any rate observed must still be faster than $k_{1,p}$.

(i) For the diisyl potassium runs with [2.2.2] cryptand, the slowest rate constant observed was $3.88 \times 10^{-3} \text{ s}^{-1}$ at 18.6°C. For the variable potassium iodide runs (at 26.0°C), the factor between the calculated rate for $[K^+] = 0.0147 \text{ mol/l}$ and the slowest observed rate ($[K^+] = 0.442 \text{ mol/l}$) is 28, the rate constants being 1.53×10^{-3} and $5.46 \times 10^{-4} \text{ s}^{-1}$. Assuming that this factor remains unchanged on going from 26.0°C to 18.6°C, then the upper limit for

the rate of reaction of the potassium ion pair is $1.4 \times 10^{-4} \text{ s}^{-1}$.

(ii) For the diethyl sodium runs with (2.2.2.) cryptand, the slowest rate constant was $3.67 \times 10^{-4} \text{ s}^{-1}$ at 18.6°C , with $[\text{Na}^+]$ being 0.015 mol/l . For the variable sodium iodide runs (at 30.8°C), the factor between the rate of reaction with $[\text{Na}^+] = 0.015 \text{ mol/l}$ and the slowest run (with $[\text{Na}^+] = 0.232 \text{ mol/l}$) was 35.5, the actual rate constants being 2.16×10^{-3} and $6.08 \times 10^{-6} \text{ s}^{-1}$. Assuming that this factor is unchanged on going from 30.8°C to 18.6°C , the upper limit for $k_{1,2}$ for Na^+ at 18.6°C for this reaction is $1.03 \times 10^{-6} \text{ s}^{-1}$. This is a factor of 10^3 smaller than the limiting rate ($k(1)$) observed at this temperature.

(iii) For the diethyl lithium runs with (2.1.1.) cryptand, the slowest rate constant observed was $3.02 \times 10^{-4} \text{ s}^{-1}$. As no variable lithium halide runs were performed (because of the extremely slow rate of reaction, even at 30°C), a comparison cannot be made using actual data. However, if there is a similar rate factor for the difference between the rate when $[\text{M}^+] = 0.015 \text{ mol/l}$ and the slowest rate for lithium as there is for sodium and potassium, of about 30, then an estimate can be made. This would give the upper limit for the rate of reaction of the lithium ion pair as 10^{-6} s^{-1} .

This variation of the value of $k_{1,2}$ with the different cations reflects the nature of the ion pairs, with the small lithium cation having the greatest charge density of the 3 cations, and so binding more tightly to the localised negative charge of the alkoxide oxygen than do the other cations. The trend is followed by the other cations, with the potassium cation (with the lowest charge density of the 3 cations) being bound to the smallest extent in the

ion pair, and so this ion pair reacts faster than the sodium or lithium ion pairs.

For equation (2) to apply, the top line of equation (1) must approximate to k_{11} , (i.e. $k_{11} \gg k_{11p} \cdot K_{11p} \cdot [M^+]_{\text{free}}$). The values obtained for reaction of alcohol (8) allow evaluation of the validity of this assumption. In each case, the value for k_{11} will be taken to be 10^{-2} s^{-1} . The values obtained for the expression are upper limits in each case, as the value for k_{11p} is an upper limit, and concentrations of free cation are used rather than the (not known) activities.

(i) For diisyl lithium, the value of K_{11p} was not evaluated, but the value of 2×10^3 that was estimated earlier will be used. This gives a value of $(10^{-2} \times 2 \times 10^3 \times 3 \times 10^{-3}) = 6 \times 10^{-4} \text{ s}^{-1}$. This is negligible compared to the value of 10^{-2} s^{-1} for k_{11} .

(ii) For diisyl sodium, the expression gives a value of $(2.6 \times 10^3 \times 7 \times 10^{-3} \times 10^{-3}) = 1.8 \times 10^{-4} \text{ s}^{-1}$, which is 56 times smaller than the value of k_{11} , and it should be noted that this is an upper limit on the value of the expression. It is expected, therefore, that the expression will have only an extremely small effect on the value of the top line in equation (1).

(iii) The value of the expression for diisyl potassium is $(1.4 \times 10^{-4} \times 88 \times 0.012) = 1.5 \times 10^{-4} \text{ s}^{-1}$, which is 67 times smaller than the value of k_{11} , and so the expression will only have an extremely small effect on the value of the top line in equation (1).

From these estimations of the upper limit for the value of

the expression on the top line of equation (1), which is omitted to obtain equation (2), it can be seen that this assumption is justified.

Temperature dependence of fragmentation rate of (8)

As the rate of reaction is dependent on the nature and the concentration of the cation, attempts to obtain activation parameters at arbitrary metal counterion concentrations would be meaningless. Only when the ion pairing effects due to the cation are eliminated can the activation parameters be relevant. The fragmentation of alcohol (8) was carried out at variable temperature in the presence of excess [2.2.2] cryptand, using diisyl potassium, and the activation parameters for the fragmentation of the free alkoxide were determined.

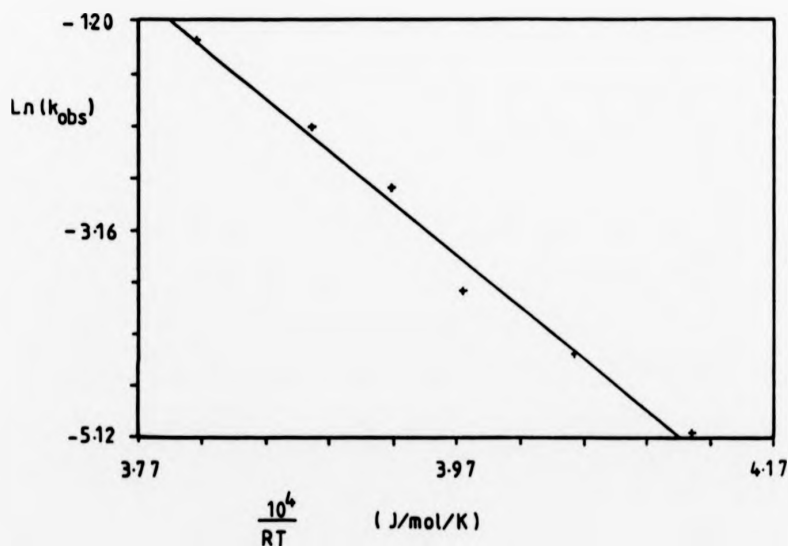


Figure. (25) : Fragmentation of (8) : $\ln(k_{obs})$ vs $(10^4/RT)$ in the presence of excess [2.2.2.] cryptand : [Diisyl K] = 1.1×10^{-2} mol/l

Table (51) : Activation parameters for fragmentation of (8)

Free energy of activation	=	20.3	+/-	3.5	kcal/mol
Enthalpy of activation	=	28.3	+/-	2	kcal/mol
Entropy of activation	=	27	+/-	6	cal/mol/K
Ln(A)	=	44.6			
Correlation coefficient	=	0.993			

For this reaction, there is a large positive entropy of activation (27 ± 6 cal/mol/K). This is to be expected, as the reaction forms two product molecules (carbanion and ketone) from one starting material molecule (alkoxide). The starting alkoxide has a negative charge localised on the oxygen, this requiring ordering of the solvent, and as the reaction proceeds this charge becomes more diffuse, requiring less solvent ordering and so giving a positive entropy of activation. There is less localisation of the negative charge in the initial products (delocalised carbanion and ketone) or in the final products (enolate anion and hydrocarbon) than in the starting material, which also contributes to the positive entropy of activation. This value compares with the values obtained by Lomas⁽¹²⁷⁾ for thermal fragmentation (to radicals) of sterically congested tertiary alcohols, of 16-22 cal/mol/K.

The enthalpy of activation (28.3 kcal/mol) is considerably lower than that reported by Lomas, who observed values in the range 40-62 kcal/mol (with the most highly hindered alcohols having the lowest enthalpies of activation), indicating that reaction via the anionic fragmentation is strongly favoured in energetic terms (under strongly basic conditions) compared to homolytic fission of a

carbon-carbon bond. This was also observed by Lomas and Dubois⁴⁰, who reported that fragmentation of tertiary alcohols that required elevated temperatures (generally > 200°C) for thermal fragmentation reacted at 25°C under anionic conditions (HMPA and butyllithium), although no activation parameters were quoted for the anionic fragmentations.

CHAPTER SIX

Experimental section

Experimental Section

Proton n.m.r spectra were carried out on either a Perkin-Elmer 90 MHz R32 NMR spectrometer or a Varian SC 300 MHz spectrometer, using deuterio-chloroform as solvent and TMS as internal reference standard. Infra red spectra were carried out on a Pye Unicam SP3-200 spectrophotometer, using 0.1 mm solution cells with carbon tetrachloride as solvent. Mass spectra were recorded on a Kratos MS 25 machine operating at 70 eV. The g.l.c./M.S. spectra were run on a Perkin-Elmer Sigma 3 g.l.c. machine in conjunction with the Kratos MS 25. For all chemical ionisation spectra, ammonia was the C.I. reagent used. Ultra violet spectra were carried out on a Pye Unicam SPB-300 UV/VIS spectrophotometer, using DMSO or ethanol as solvent. The cell block in the spectrometer was kept at constant temperature using a Haake E3 thermostat bath. For g.l.c., a Carlo Erba Strumentazione machine with a 20 m OV-1 glass capillary column using hydrogen carrier gas and a flame ionisation detector was used in all cases. Merck G alumina was used for alumina columns, Merck Kieselgel 60 H silica for silica columns, and Merck Kieselgel 60 PF254 silica for preparative t.l.c.. For t.l.c., Merck pre-coated silica backed plates with a 0.2 mm layer of Kieselgel 60 F254 were used. All micro-analyses were carried out by the University of Manchester Micro-Analysis Laboratory under the direction of Mr. M. Hart. For atomic absorption spectroscopy, a Perkin Elmer 603 atomic absorption spectrophotometer was used in all cases. Empirical force field calculations were carried out using the MM2 program mounted on the CDC7600 at UMRC.

Experimental preparative

1,1-diphenyl-2-methyl-1-propanol

This was synthesised using the method of Shilton⁽²³⁾. Into a 250 ml round bottomed 3-necked flask was added magnesium turnings (5.3g, 0.22 moles), this being covered by diethyl ether (25 ml) which had been distilled from lithium aluminium hydride ("dry ether"). Then, a 15 ml portion of a solution of bromobenzene (35g, 0.22 moles) in dry ether (100 ml) was added slowly with stirring. Once the reaction had started, the remainder of the bromobenzene solution was added dropwise, to keep the solution gently boiling. The resulting solution was stirred until all of the magnesium had dissolved, to give a dark brown solution of phenylmagnesium bromide. To this solution was added dropwise a solution of ethyl isobutanoate (12 g, 0.103 moles) in dry ether (50 ml), the flask being cooled in an ice bath. After one hour, addition was complete and the solution was then refluxed for a further hour. This solution was then cooled in ice, poured slowly onto crushed ice, this slurry then being poured into an ammoniacal solution of ethylenediaminetetraacetic acid (EDTA, 100 ml of saturated solution). The ether layer was separated, dried over sodium sulphate, evaporated under reduced pressure, and then distilled under reduced pressure. The product, 1,1-diphenyl-2-methyl-1-propanol (16.54g), distilled at 116°C to 120°C at 0.15 mmHg. The product was a clear colourless viscous liquid, obtained in 71% yield.

(Found : C, 84.5; H, 8.0; $C_{16}H_{18}O$ requires C, 85.0; H, 8.0%); η_{inh} (CCl₄), 3615 (m), 3060 (m), 3030

(m), 2975 (s), 1600 (w), 1485 (s), 1442 (s), 1155 (s), 1005 (s); δ , (CDCl₃), 6.85-7.4, m, 10H; 2.77, apparent quintet, J = 7 Hz, 1H; 1.78, s, 1H; 0.85, d, J = 7 Hz, 6H; m/e, (E.I.): 209 (15%), 183 (100%), 105 (90%), 77 (40%); (C.I.), 209 (100%), 183 (38%), 105 (25%).

1,2-diphenyl-2-methyl-1-propanone

This was synthesised using the method of Shilton⁽⁷³⁾. To a mixture of water (20 ml) and glacial acetic acid (80 ml) was added 1,1-diphenyl-2-methyl-1-propanol (10 g) with stirring. To this solution was added bromine (3.5 ml), dropwise down the condenser. After the addition was complete, the solution became a dark green-brown colour, which became a dark brown after refluxing for 30 minutes. Analysis of the mixture by g.l.c. showed that a substantial amount of starting material was still present, and so a further addition of bromine (1.5 ml) was made, and the solution refluxed for a further 30 minutes. Water (200 ml) was added, the organic phase extracted with 40/60 petrol (4 x 50 ml), washed with water, then with dilute aqueous sodium hydroxide solution, separated, dried over sodium sulphate, evaporated under reduced pressure, and distilled under reduced pressure. From this distillation, 3 fractions were obtained at a pressure of 0.75 mmHg. The first fraction distilled at 115-120°C, the second at 120-126°C, leaving a dark red-brown residue which (by g.l.c. analysis) contained no product. The combined fractions 1 and 2 contained the required product ketone as the major component (83%) of a mixture (7.15g). This gives a yield of 56%. This material was not purified further.

ν_{max} (CCl₄), 3055 (w), 3020 (w), 2965 (m), 1710 (m), 1670 (s), 1585 (m), 1445 (m), 1245 (m), 975 (m) ; δ_{H} (CDCl₃), 6.95-7.45, m, 10H ; 1.55, s, 6H ; m/s, (E.I.), 224 (M⁺) (1%), 119 (79%), 105 (100%), 91 (65%), 77 (67%), 41 (33%)

2,3-diphenyl-3-methyl-2-butanol

This was synthesised using the method of Shilton⁽⁷⁴⁾. A solution of 1,2-diphenyl-2-methyl-1-propanone (3.4g, 1.52×10^{-2} moles) in dry diethyl ether (10 ml) was stirred under a flow of nitrogen for 15 minutes. To this solution was added methyllithium solution (14 ml of a 1.2 molar solution in ether, 1.6×10^{-2} moles) dropwise by syringe, whilst keeping the solution under a flow of nitrogen. After addition was complete, the solution was refluxed for 5 minutes, then isopropanol (10 ml) was added with stirring, followed by water (25 ml). The organic layer was separated, and the aqueous layer washed with ether. The combined organic layers were then dried over sodium sulphate, filtered, and evaporated under reduced pressure. Monitoring of the reaction by g.l.c. showed that all of the starting material had been consumed, and that only one new peak (product) appeared. Assuming that the starting material was 3.4g of 83% pure material, then the yield of 3.00g corresponds to 100%. The crude product was a pale viscous yellow liquid which was purified by bulb-to-bulb distillation under reduced pressure (150°C, 0.15 mmHg), silica column chromatography (eluting with a hexane/ether gradient), and preparative TLC. This gave a white crystalline solid (m.p. = 68-69.5°C ; Lit. value = 70°C⁽⁷⁴⁾) which on recrystallisation from aqueous ethanol gave crystals, m.p. 69-70°C.

(Found : C, 84.6; H, 8.5; $C_{18}H_{16}O$ requires C, 85.0; H, 8.4%); ν_{max} (CCl_4), 3600 (m), 3060 (w), 2990 (s), 1600 (w), 1385 (m), 1070 (m), 1035 (m); δ_H ($CDCl_3$), 7.2-7.42, m, 10H; 1.73, s, 1H; 1.48, s, 3H; 1.36, s, 3H; 1.14, s, 3H; m/e, (E.I.), 222 (M - water) (16%), 121 (100%), 105 (73%), 91 (44%), 77 (42%), 43 (64%); C.I. : 240 (M+) (7%), 223 (100%), 121 (43%), 119 (40%), 105 (52%), 91 (28%).

2,3-diphenyl-3-methyl-1-butene

To phosphorus pentoxide (0.5g) in a Buchi distillation bulb was added 2,3-diphenyl-3-methyl-1-butanol (0.2g), and this mixture was then heated to 100°C at 0.15 mmHg. A clear colourless liquid distilled over (0.13g, 70%), this being the product alkene.

ν_{max} (CCl_4), 3060 (m), 3030 (m), 2980 (s), 1610 (m), 1440 (m), 1250 (m), 1230 (m), 910 (m); δ_H ($CDCl_3$), 6.6-7.4, m, 10H; 5.31, d, J=2Hz, 1H; 5.07, d, J=2Hz, 1H; 1.41, s, 6H.

2-methyl-2-phenyl-1-(5'-t-butyl)-cyclohexa-2',4'-dienyl-1-propanone

To a solution of 1,2-diphenyl-2-methyl-1-propanone (2 ml of a mixture containing 83% of the ketone) in dry diethyl ether (8 ml), which had been stirred under a flow of nitrogen for 20 minutes, was added *t*-butyllithium solution (4 ml of a 2.3 molar solution in hexane) dropwise by syringe. The solution went a dark red-brown colour. After 20 minutes, a further addition of *t*-butyllithium was made (2 ml). The solution was warmed gently for 10 minutes, then

quenched with isopropanol (10 ml), then water (20 ml).

The organic phase was extracted with 40/60 petrol (2 x 25 ml), dried over sodium sulphate, and evaporated under reduced pressure. Analysis of the reaction mixture by g.l.c. showed that several products were formed, one of these constituting 40% of the mixture. This mixture was then subjected to silica column chromatography, eluting with a hexane/ether gradient. One fraction gave the major product as 85% of a mixture.

γ_{max} (CCl₄), 3030 (w), 2985 (s), 2885 (w), 1670 (s), 1595 (w), 1455 (m), 1360 (m), 1240 (m); δ_H (CDCl₃), 7.2-7.41, m, 5H; 6.28, dd, J=8Hz, 1Hz, 1H; 6.17, t, J=4Hz, 1H; 5.78, dd, J=8Hz, 1Hz, 1H; 1.84-2.2, m, 3H; 1.50, s, 3H; 1.47, s, 3H; 0.78, s, 9H; m/e, (E.I.): 282 (M⁺) (10%), 226 (32%), 163 (100%), 148 (42%), 135 (40%), 119 (95%), 105 (82%), 91 (96%), 77 (75%), 57 (99%); (C.I.): 300 (M+18) (2%), 283 (M+1) (100%), 225 (40%), 163 (57%), 119 (35%), 105 (28%), 91 (15%)

2-methyl-2-phenyl-1-(4'-t-butyl)-phenyl-1-propanone

2-methyl-2-phenyl-1-(5'-t-butyl)-cyclohexa-2',4'-dienyl-1-propanone (30 mg) was dissolved in toluene (5 ml), and chloranil (60 mg, approx 2 equivalents) was added. The mixture was then refluxed for 24 hours. Monitoring of the reaction by g.l.c. showed that all of the starting material had reacted. The toluene was removed under reduced pressure, and the product then purified by preparative t.l.c. to give the product ketone as 93% of a mixture. Recrystallisation from 40/60 petrol gave the product as a white crystalline solid, melting point 110-111°C.

(Found: C, 85.4; H, 8.7; $C_{20}H_{24}O$ requires C, 85.7; H, 8.6%); ν_{max} (CCl_4), 3030 (w), 2980 (s), 1680 (s), 1605 (m), 1460 (m), 1255 (m), 970 (m); δ_H ($CDCl_3$), 2-7.6, m, 9H; 1.61, s, 6H; 1.28, s, 9H; m/e, (E.I.): 280 (1%), 161 (100%), 119 (35%), 118 (40%), 91 (55%), 77 (25%); (C.I.): 298 (1%), 281 (100%), 161 (92%), 119 (20%), 91 (12%)

5-Chloro-2-pentanone and Methylcyclopropyl ketone

These were prepared using the method of Cannon¹⁴, without modification.

2-Cyclopropyl-2-propanol

To a 250 ml 3-necked flask fitted with a dropping funnel, a mechanical stirrer and a reflux condenser, was added magnesium turnings (5.0 g). To this was added slowly a solution of methyl iodide (30 g) in dry diethyl ether (80ml), with stirring. After the magnesium had dissolved, a solution of methylcyclopropyl ketone (17g) in dry ether (40 ml) was added slowly. This was stirred for 30 minutes before addition of a saturated solution of ethylenediaminetetraacetic acid (100 ml). The organic layer was separated, the aqueous layer washed with ether (3 x 50ml), and the organic phases combined and dried over sodium sulphate. The ether was removed by distillation, and then the product was distilled, coming over at 120-122°C (760mmHg). This gave the product as a clear colourless liquid (15.2 g, 75%).

ν_{max} (CCl_4), 3500-3300 (s), 3100 (w), 2980 (s), 1465 (w), 1375 (m), 1150 (m); δ_{H} (CDCl_3), 2.25, 1H, s, (removed by D_2O); 1.15, 6H, s; 0.9, 2H, m; 0.3, 3H, m.

5-Bromo-2-methyl-2-pentene

This was prepared using the method of Julia⁽⁷⁰⁾. To 2-cyclopropyl-2-propanol (6.7 g) in a 100 ml flask cooled in ice was added a solution of 48% hydrobromic acid over a period of 2 minutes, and the mixture stirred vigorously. To this was then added 40/60 petrol (30 ml), and the organic phase separated. The aqueous phase was washed with 40/60 petrol (3 x 10 ml), and the organic phases combined. The organic phase was then washed with saturated sodium bicarbonate solution (20 ml), and saturated sodium chloride solution (20 ml), before being dried over sodium sulphate and filtered. The petrol was then removed by distillation at atmospheric pressure, and the product distilled under reduced pressure, coming over at 85-86°C at 84mmHg. This gave a colourless liquid (5.7 g, 43%).

ν_{max} (CCl_4), 2960 (s), 2930 (s), 1430 (w), 1370 (w), 1265 (w); m/e, (E.I.), 164 (9%), 162 (9%), 83 (63%), 69 (62%), 55 (56%), 41 (100%); δ_{H} (CDCl_3), 5.19, 1H, t (J=7Hz); 3.55, 2H, t (J=8Hz); 2.57, 2H, q (J=7Hz); 1.75, 3H, s; 1.65, 3H, s.

4-Methyl-2-phenyl-5-heptenenitrile

The condensation procedure used was an adaptation of the method of Farbr⁽⁷¹⁾.

For this reaction, lithium di-isopropylamide was prepared

using the method of Ponticello¹¹¹⁰. To tetrahydrofuran (20 ml) in a flask cooled with an ice bath was added di-isopropylamine (1.3g) that had been distilled from calcium hydride. Prior to use, the flask had been flushed with nitrogen for 30 minutes. To the solution was added n-butyllithium (8.2 ml of a 1.6 molar solution in hexane) slowly by syringe. The solution was then stirred for 10 minutes.

To the LDA solution was added a solution of phenylacetonitrile (1.43 g) in THF (10 ml) dropwise by syringe, and the mixture stirred for 10 minutes before cooling to -78°C. A solution of 5-bromo-2-methyl-2-pentene (2.0 g) in THF (20 ml) was added by syringe, and the mixture stirred for a further 2 minutes. The solution was then allowed to warm to room temperature, and was left to stand for 20 minutes before addition of water (40 ml). The organic layer was separated, the aqueous layer extracted with ether (2 x 10 ml), and the organic layers combined and dried over sodium sulphate. The ether was removed by evaporation under reduced pressure, and the product purified by silica column chromatography using a hexane/ether gradient. This gave the product as a colourless liquid, 0.7 g (31 %).

ν_{max} (CCl₄), 3020 (w), 2960-2860 (s), 2350 (w), 1495 (m), 1450 (s), 1370 (m); δ_H (CDCl₃): 7.39, 5H, s; 5.12, 1H, t (J=7Hz), 3.8, 1H, t (J=8Hz); 2.3-1.8, 4H, m; 1.78, 3H, s; 1.63, 3H, s; m/e, (E.I.), 199 (55%), 184 (16%), 171 (23%), 117 (53%), 69 (52%), 55 (90%), 41 (100%); (C.I.), 217 (M+18, 100%), 200 (42%), 199 (53%), 171 (20%)

6-Methyl-2-phenyl-5-heptenal

This reaction used an adaptation of the method described by Trofimenko¹⁷². To a solution of 6-methyl-2-phenyl-5-heptenonitrile (0.7 g) in hexane (20 ml) was added a solution of di-isobutylaluminium hydride (3.5 ml of a 1.0 molar solution in hexane), in a 50 ml flask that had been flushed with nitrogen for 20 minutes prior to use. The mixture was stirred for 2 hours at room temperature before careful addition of methanol (5 ml). The mixture was then transferred to a beaker and decomposed with ice-cold dilute sulphuric acid until all solid had dissolved. The layers were separated, the aqueous layer washed with ether (4 x 20 ml), the organic layers combined and dried over sodium sulphate. The ether was removed by evaporation under reduced pressure to give the product (0.46g, 66%). The product was purified by silica column chromatography using a hexane/ether gradient, and further purified by bulb to bulb distillation under reduced pressure (100°C, 0.1 mmHg), to give the pure aldehyde (0.2 g).

ν_{max} (CCl₄), 3050 (w), 2950 (m), 2810 (w), 2720 (w), 1725 (s), 1495 (w), 1450 (m); δ_{H} (CDCl₃), 9.8, 1H, d (J=2Hz), 7.17-7.47, 5H, m; 5.12, 1H, t (J=7Hz); 3.52, 1H, dt (J=2Hz, 7Hz); 1.74-2.27, 4H, m; 1.70, 3H, s; 1.52, 3H, s; m/e, (E.I.): 120 (65%), 104 (32%), 91 (41%), 69 (44%), 41 (100%), (C.I.): 220 (M+18, 100%), 203 (20%), 185 (38%), 120 (27%).

1,1-Di(phenyl)-2-methyl-1-propenal

To a three necked 50 ml flask equipped with a stopper, a septum cap, and a connection to a nitrogen line, was added 4-bromo

biphenyl (1.00g, 4.3×10^{-3} moles), and tetrahydrofuran (20 ml of distilled THF). The solution was stirred under a flow of nitrogen for five minutes, and then cooled to -78°C . The solution was then kept under positive nitrogen pressure during the addition of *n*-butyllithium solution (2.8 ml of 1.6 molar solution in hexane, 4.4×10^{-3} moles), over a period of two minutes with continuous stirring. The mixture was then stirred for a further five minutes at -78°C , before dropwise addition (via syringe) of a solution of ethyl isobutanoate (0.25 ml ester in 0.5 ml THF, 2.1×10^{-3} moles). The mixture was then stirred at -78°C for thirty minutes, then the dry ice/acetone bath was removed, and the solution allowed to warm to room temperature. To the mixture was then added saturated sodium sulphate solution (20 ml), and the organic phase was then separated, dried over magnesium sulphate, filtered, and evaporated under reduced pressure. This gave the product as a white solid (0.55g, 1.5×10^{-3} moles, 71%). The product was purified using silica column chromatography, and then recrystallised from absolute ethanol, to give a white crystalline solid, melting point 163.5 to 165°C .

(Found: C, 88.5; H, 7.2; $\text{C}_{20}\text{H}_{20}\text{O}$ requires C, 88.9; H, 6.9%); ν_{max} (CCl_4), 3500 (w), 3010 (m), 2975 (m), 2940 (m), 1605 (m), 1588 (s), 1390 (w), 1165 (m), 1030 (m), 840 (s); δ_{H} (CDCl_3), 7.2-7.75, m, 18H; 2.97, septet, $J=7\text{Hz}$, 1H; 2.12, s, 1H; 0.95, d, $J=7\text{Hz}$, 6H; m/e , (E.I.): No M^+ , 360 ($\text{M}-\text{H}_2\text{O}$) (57%), 335 (100%), 181 (91%), 152 (65%); (C.I.): 378 (M^+) (26%), 361 (61%), 335 (100%), 181 (26%).

1,2-Di(biphenyl)-2-methyl-1-propanone

This was synthesised using an adaptation of the method described by Shilton and Grant⁽⁷³⁾.

To 1,1-di(biphenyl)-2-methyl-1-propanol (2.5g, 6.6×10^{-3} moles) in a 250 ml flask was added a mixture of 80% acetic acid:20% water (150 ml), and the mixture refluxed until the solid dissolved. To this was added bromine (8.5 ml of a 0.78 molar solution in 80% acetic acid, 6.6×10^{-3} moles) slowly down the condenser. After a further two minutes reflux, water (100 ml) was added, the mixture cooled, and extracted with diethyl ether (4 x 50 ml). The organic layer was then washed with water (50 ml), sodium hydroxide solution (2 x 70 ml of 1 molar solution), separated, dried over magnesium sulphate, filtered, and evaporated under reduced pressure. This gave a viscous yellow oil (2.1g) which contained the product as the major component (75% of the mixture). This gives a yield of 64 %. The product ketone was recrystallised from absolute ethanol, to give a white crystalline solid, melting point 115-6°C.

(Found : C, 89.8; H, 6.6; $C_{26}H_{24}O$ requires C, 89.4; H, 6.4%); ν_{max} (CCl₄), 3010 (w), 2980 (w), 1675 (s), 1600 (s), 1485 (m), 1250 (m), 985 (m); δ_H (CDCl₃), 7.26-7.73, m, 18H; 1.65, s, 6H; m/e , (E.I.): No M^+ , 195 (84%), 181 (100%), 152 (31%); (C.I.): 377 (M+1) (100%), 282 (20%), 195 (54%), 181 (32%).

2,3-Di(biphenyl)-3-methyl-2-butanol

This was synthesised using an adaptation of the method described by Shilton and Scott⁽⁷⁴⁾.

A solution of 1,2-di(biphenyl)-2-methyl-1-propanone (0.8g, 2.12×10^{-3} moles) in dry diethyl ether (10 ml) was stirred under nitrogen for five minutes. To this was added methyllithium solution (1.7 ml of a 1.4 molar solution, 2.38×10^{-3} moles) dropwise with stirring. The solution was refluxed for five minutes after addition of the methyllithium, and then isopropanol (10 ml) was added, followed by water (25 ml). A white precipitate appeared in the organic layer, and after separation of the layers, this precipitate was filtered off and dried in a vacuum desiccator. The aqueous layer was washed with diethyl ether (20 ml), and the organic layers combined. The organic phase was then dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give a white solid which was then combined with the precipitate that had been filtered off earlier, to give the product (0.75g, 90%). The product was purified by two recrystallisations from toluene, to give a white crystalline solid, melting point 249 to 249.5°C.

(Found: C, 89.1; H, 7.2; $C_{26}H_{20}O$ requires C, 88.8; H, 7.1%); λ_{max} (EtOH), 258 nm, ϵ_{max} (EtOH) \sim 11000; ν_{max} (CCl_4), 3600 (w), 3560 (w), 3080 (w), 3010 (m), 2960 (m), 1490 (s), 1090 (m), 1010 (m); δ_H ($CDCl_3$), 7.3-7.8, m, 18H; 1.85, s, 1H; 1.58, s, 3H; 1.47, s, 3H; 1.42, s, 3H; m/e, (E.I.): No M^+ , 374 ($M-H_2O$) (1%), 335 (3%), 197 (9%), 181 (31%), 152 (18%), 43 (100%); (C.I.): 394 (M^+) (0.5%), 375 (37%), 197 (100%), 195 (87%), 181 (16%).

2,3-Di(biphenyl)-3-methyl-1-butene

To 2,3-di(biphenyl)-3-methyl-2-butanol (42 mg) was added

dichloromethane (5 ml), and phosphorus pentoxide (0.1g), and the mixture refluxed for twenty minutes. The liquid was then decanted from the residue, the residue washed with dichloromethane (2 x 5ml), the combined dichloromethane washings filtered through Celite, and then evaporated under reduced pressure to give the product (34mg, 85%).

ν_{max} (CCl_4), 3030 (m), 2970 (s), 1600 (w), 1485 (s), 1010 (m), 700 (s); δ_{H} (CDCl_3), 7.4-7.85, m, 16H; 6.9-7.1, m, 2H; 5.56, d, J=2 Hz, 1H; 5.36, d, J= 2 Hz, 1H; 1.63, s, 6H.

2-Biphenyl-2-propanol

To magnesium turnings (0.15 g, 6.25×10^{-3} moles) in a 3 necked 50 ml flask equipped with a condenser a stopper and a separating funnel, was added dry diethyl ether (15ml), and the mixture stirred for five minutes under nitrogen. To this was added dropwise a solution of iodoethane (6.0×10^{-3} moles) in dry ether (4 ml), and the mixture stirred for thirty minutes, after which time almost all of the magnesium had dissolved. To the Grignard solution was added a solution of 1-biphenylethanone (4-acetyl biphenyl) (1.00g, 5.1×10^{-3} moles) in dry ether (15ml) dropwise, and the resulting mixture was then refluxed for twenty minutes. An ammoniacal solution of ethylenediaminetetraacetic acid (20 ml) was added, the layers separated, the aqueous layer washed with ether (3 x 10 ml), the combined organic layers dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give a yellow solid (0.82g, 76%). This was purified by recrystallisation from 100/120 petrol to give a white solid, melting

point 93-94°C.

ν_{max} (CCl_4), 3390 (m), 3450 (m), 3050 (w), 2980 (s), 1608 (m), 1490 (m), 1370 (m), 1330 (m), 1120 (s), 960 (m); δ_{H} (CDCl_3), 7.2-7.7, m, 9H; 2.31, s, 1H; 2.59, s, 6H.

2-Biphenylpropane

This was synthesised using an adaptation of the method of Papa⁽¹⁷⁾.

To 2-biphenyl-2-propanol (0.5 g, 2.36×10^{-3} moles) was added ethanol (5 ml), sodium hydroxide solution (15 ml of a 1 molar solution), toluene (10 ml), and the solution heated to 90°C. To this was added Raney's alloy (1.5g) down the condenser over a period of 45 minutes, with stirring. The mixture was then refluxed for twenty hours, cooled and extracted with toluene (3 x 15 ml). The organic layer was dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give the product as a yellow liquid (0.254 g, 55%).

λ_{max} (THF), 252 nm, ϵ_{max} (THF), 12000, λ_{max} (DMSO), 271 nm, ϵ_{max} (DMSO), 12000; ν_{max} (CCl_4), 3060 (w), 2960 (s), 2935 (s), 2880 (m), 1605 (m), 1485 (m), 1460 (m), 1115 (w); δ_{H} (CDCl_3), 7.1-7.65, m, 9H; 2.9, septet, $J=7\text{Hz}$, 1H; 1.25, d, $J=7\text{Hz}$, 6H; m/e, (E.I.): 196 (M^+) (77%), 181 (100%), 166 (51%), 165 (67%), 152 (44%), 77 (32%); (C.I.): 196 (91%), 181 (100%), 165 (15%), 152 (10%)

3,3-Dimethyl-2-butanone (Pinacolone)

This was synthesised using the procedure of Hill and Flosdorf⁽¹¹⁾, without modification.

2-Biphenyl-3,3-dimethyl-2-butanol

To 4-bromobiphenyl (1.00 g, 4.3×10^{-3} moles) was added tetrahydrofuran (20 ml of distilled THF) in a 50 ml flask, the flask flushed with nitrogen, and then cooled to -78°C . To the solution was added by syringe, *n*-butyllithium solution (3 ml of 1.5 molar solution in hexane) dropwise, to give a green solution. This was stirred at -78°C for five minutes, then pinacolone (0.5 ml, 4×10^{-3} moles) was added dropwise, causing the solution to become colourless. The solution was stirred at -78°C for a further thirty minutes, and then warmed to room temperature. Saturated sodium sulphate solution (30 ml) was added, the organic layer separated, the aqueous layer washed with ether (3 x 15 ml), and the combined organic layers dried over magnesium sulphate. The organic phase was then filtered and evaporated under reduced pressure to give a colourless oil which slowly solidified, (0.9g). Analysis of the product by g.l.c. showed the crude mixture to have a major product which constituted 70% of the mixture, giving a yield of 62%. The product was obtained in a pure state by preparative t.l.c.

(Found : C, 85.3; H, 8.8; $\text{C}_{16}\text{H}_{22}\text{O}$ requires C, 85.0; H, 8.7%); ν_{max} (CCl_4), 3610 (m), 3060 (w), 2990 (s), 1605 (w), 1495 (s), 1385 (m), 1105 (m) ; δ_{H} (CDCl_3),

7.31-7.75, m, 9H; 1.69, s, 3H; 1.45, s, 1H; 1.05, s, 9H; m/e, (E.I.): 236 (30%), 197 (92%), 181 (100%), 152 (71%); (C.I.): 237 (100%), 197 (91%), 181 (18%), 152 (9%).

2-Bromo-2-methyl-propanoic acid

This was synthesised using the method described by Marvel⁽¹¹⁾.

To a 250 ml flask equipped with a condenser was added 2-methyl-propanoic acid (isobutyric acid, 38g, 0.43 moles), phosphorus trichloride (1 ml), and bromine (24 ml, 0.46 moles). The mixture was then heated for twenty hours at 80°C, a further addition of bromine (2 ml) made, and the mixture then heated at 100°C for ninety minutes. The mixture was then distilled at water pump pressure, with the product distilling at 110 to 112°C, to give a white crystalline solid (57 g, 79%).

δ_H (CDCl₃), 2.13, s, 1H; 1.9, s, 6H

2-Methyl-2-phenyl-propanoic acid

This was synthesised as described by Campaigne and Maulding⁽¹²⁾.

To aluminium chloride (100g, 0.75 moles) was added dry benzene (200 ml). A solution of 2-bromo-2-methyl-propanoic acid (57g, 0.34 moles) in benzene (50 ml) was added slowly down the condenser, and the mixture then refluxed for six hours before being left to stand overnight. The mixture was then cautiously poured into a mixture of ice and 20% sulphuric acid (1 litre). The organic layer

was separated, and washed with sulphuric (2 x 50 ml of 10% acid), water (50 ml), before being extracted with sodium hydroxide (5 x 80 ml of 1 molar solution). The alkaline layer was treated with decolourising charcoal, and filtered into a 20% solution of ice cold sulphuric acid (400 ml). A white precipitate appeared, which was filtered and dried to give a white crystalline solid (38g, 67%) of melting point 79.5-80.5°C (Lit: 78-80°C).

ν_{max} (CCl₄), 3200-2700 (s), 3060 (w), 2975 (m), 1705 (s), 1285 (m), 1155 (m); δ_H (CDCl₃), 11.70, s, 1H; 7.15-7.5, m, 5H; 1.60, s, 6H; m/e, (E.I.), 164 (24%), 119 (100%), 91 (90%), 77 (28%), 41 (54%)

2-Methyl-2-phenyl-propanoyl chloride

To a solution of 2-methyl-2-phenyl-propanoic acid (13 g, 7.9×10^{-2} moles) in dry benzene (150 ml) was added thionyl chloride (20ml, 0.274 moles), and the mixture refluxed for thirty minutes. The benzene and excess thionyl chloride were then removed by distillation to give a mixture of acid chloride, acid anhydride, and unconverted acid. To this mixture was added a further amount of thionyl chloride (20 ml), and the mixture refluxed for thirty minutes. The mixture was then distilled from bulb to bulb under reduced pressure (100°C/0.4mmHg) to give the acid chloride (11.2g, 77 %) as a viscous liquid.

δ_H (CDCl₃), 7.22-7.40, s, 5H; 1.67, s, 6H

3-Methyl-3-phenyl-2-butanone

This was synthesised using an adaptation of the method of Bare and House⁽²⁾.

A 50 ml flask was flushed with nitrogen for 15 minutes, prior to the addition of a solution of methyllithium (12 ml of 0.82 molar in pentane, 9.8×10^{-3} moles). This was then cooled to ice bath temperature, and a solution of 2-methyl-2-phenyl-propanoic acid (0.5g, 3.0×10^{-3} moles) in dry ether (10 ml) was added dropwise with vigorous stirring, which was continued for a further hour. The mixture was pipetted into a well stirred solution of 1 molar hydrochloric acid (25 ml), neutralised by addition of sodium hydroxide solution, and separated. The aqueous layer was extracted with ether (2 x 10 ml), the organic layers combined, dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give the product ketone (0.41g, 82%) as a colourless liquid.

ν_{max} (CCl₄), 3090 (w), 3060 (w), 3030 (w), 2980 (s), 2935 (m), 2880 (w), 1710 (s), 1600 (w), 1485 (m), 1440 (m), 1350 (m), 1235 (m), 1120 (m); δ_H (CDCl₃), 7.15-7.35, s, 5H; 1.84, s, 3H; 1.44, s, 6H; m/e, (E.I.): 162 (M⁺) (2%), 147 (4%), 119 (100%), 91 (81%), 77 (15%); (C.I.): 180 (M+18) (100%), 163 (M+1) (58%), 119 (85%), 91 (32%).

2-Biphenyl-3-methyl-3-phenyl-2-butanol

To a solution of 4-bromobiphenyl (2.25g, 9.8×10^{-3} moles) in distilled THF (20 ml), in a 50 ml flask that had been flushed with nitrogen for five minutes, was added n-butyllithium (6.7 ml

of a 1.5 molar solution in hexane, 0.01 moles) dropwise at -78°C . The resulting solution was then stirred at -78°C for ten minutes before dropwise addition of a solution of 3-methyl-3-phenyl-2-butanone (1.5g, 9.3×10^{-3} moles) in distilled THF (5 ml). The mixture was stirred at -78°C for thirty minutes, before warming to room temperature, addition of saturated sodium sulphate solution (30 ml), and separation of the layers. The aqueous layer was washed with ether (2 x 15 ml), the organic layers combined, dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give a pale yellow solid (2.8g, which by G.C. analysis was 85% of the correct component, to give 82% yield).

The product was purified by recrystallisation from absolute ethanol, treatment with activated charcoal, filtering, and recrystallisation twice from 100/120 petrol. This gave a white crystalline solid, melting point 131.5 to 133°C .

(Found : C, 87.8; H, 7.8; $\text{C}_{23}\text{H}_{24}\text{O}$ requires C, 87.4; H, 7.6%); ν_{max} (CCl_4), 3575 (w), 3050 (w), 2975 (s), 1595 (w), 1490 (s), 1370 (m), 1165 (m), 1075 (m); δ_{H} (CDCl_3), 7.1-7.65, m, 14H; 1.85, s, 1H; 1.49, s, 3H; 1.40, s, 3H; 1.37, s, 3H; m/e, (E.I.): No M^+ , 298 (6%), 196 (44%), 181 (100%), 152 (59%), 118 (61%); (C.I.): 316 (M^+) (0.5%), 299 (8%), 214 (8%), 197 (100%), 181 (15%), 119 (40%).

2-Biphenyl-2-hydroxypropyl methyl sulphoxide

To a solution of dilithyl lithium in dimethyl sulphoxide (25 ml of a 0.15 molar solution, 3.75×10^{-3} moles), prepared as described above, under an argon atmosphere, was added a

solution of 1-biphenylethanone (0.25g, 1.3×10^{-3} moles) in DMSO (2 ml). The solution turned dark brown (from colourless), and was stirred at 35°C for six hours. The mixture was then poured into dilute hydrochloric acid (20 ml of 1 molar solution, 0.02 moles), tested for pH to ensure that the solution was acidic, and extracted with ether (3 x 25 ml). The ether layer was then dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give a mixture which was analysed by g.l.c. to show three major components, one of which was recovered starting ketone. Separation of the two other major components from the ketone was achieved by silica column chromatography eluting with a dichloromethane/diethyl ether gradient. The two components proved impossible to separate by column chromatography (or by preparative t.l.c.). This gave the two diastereoisomers of the product beta-hydroxy-sulphoxide (76 mg, 22%).

ν_{max} (CCl₄), 3395 (m), 2995 (s), 1480 (m), 1403 (m), 1070 (s), 1005 (s); δ_{H} (CDCl₃), a) 7.3-7.8, m, 9H; 3.25, AB pair (J= 12 Hz), 2H; 2.65, s, 3H; 1.71, s, 3H; b) 7.3-7.8, m, 9H; 3.15, AB pair (J=12 Hz), 2H; 2.67, s, 3H; 1.95, s, 3H; m/e, (E.I.): 274 (M⁺) (3%), 256 (4%), 240 (32%), 211 (63%), 193 (90%), 182 (95%), 178 (100%), 165 (55%), 153 (75%), 152 (99%); (C.I.): 275 (M⁺) (4%), 257 (45%), 242 (32%), 241 (82%), 214 (29%), 198 (58%), 197 (100%), 196 (65%), 195 (95%), 181 (34%), 153 (12%)

2-Biphenyl-2-hydroxypropyl methyl sulphone

To a solution of 2-biphenyl-2-hydroxypropyl methyl sulphoxide (76 mg, 2.8×10^{-4} moles, a mixture of diastereoisomers)

in dichloromethane (5 ml) was added 3-chloroperbenzoic acid (125 mg, 7.2×10^{-3} moles), and the mixture stirred for twenty minutes. To the solution was added saturated sodium sulphite solution (5 ml), and then saturated sodium bicarbonate solution (5 ml). The organic layer was separated, dried over magnesium sulphate, filtered, and evaporated under reduced pressure to give the product (76 mg, 94%).

ν_{max} (CCl_4), 3485 (m), 3030 (w), 2980 (w), 2930 (w), 1490 (m), 1405 (m), 1305 (s), 1280 (s), 1120 (s), 1085 (m); δ_{H} (CDCl_3), 7.3-7.8, m, 9H; 4.29, s, 1H; 3.53, AB pair ($J=14$ Hz), 2H; 2.51, s, 3H; 1.75, s, 3H; m/e, (E.I.): 290 (2%), 272 (12%), 196 (81%), 181 (98%), 153 (80%), 152 (100%), 94 (51%), 79 (95%); (C.I.): 308 (M+18, 10%), 291 (10%), 290 (38%), 273 (26%), 197 (98%), 181 (70%), 153 (45%), 152 (55%), 112 (57%), 32 (100%), 30 (100%).

3-Methyl-1,2,3-triphenyl-2-butanol

The solution of benzylmagnesium chloride in ether was prepared as described by Prout et al.⁽¹³⁾.

To a 100 ml three necked flask fitted with a condenser, a separating funnel, a magnetic stirrer, and a stopper, that had been flushed with nitrogen for ten minutes, was added magnesium turnings (0.135 g, 5.6×10^{-3} moles) and dry diethyl ether (10 ml). To this was added a solution of distilled benzyl chloride (0.6 ml, 5.2×10^{-3} moles) in dry ether (10 ml), followed by a crystal of iodine and two further pieces of freshly cleaned magnesium, which initiated the reaction. The mixture was refluxed for one hour, before addition of a solution of 1,2-diphenyl-2-methyl-1-propanone (0.8g, 3.6×10^{-3} moles, synthesised as described previously) in distilled toluene

(6 ml). The mixture was then refluxed for one hour, before pouring onto crushed ice (10g), followed by addition of an ammoniacal solution of ethylenediaminetetraacetic acid (20 ml of a saturated solution), and separation of the layers. The aqueous layer was extracted twice with ether (10 ml), the organic layers combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure. This gave a viscous yellow liquid (0.91g) which contained the product as the major component of a mixture (approximately 55% of the mixture, a yield of 44%). The product was purified by silica column chromatography, eluting with a hexane/ether gradient, and by crystallisation from 100/120 petrol to give a white crystalline solid, melting point 86 to 87°C.

(Found : C, 87.7; H, 7.8; $C_{23}H_{24}O$ requires C, 87.4; H, 7.8%); ν_{max} (CCl₄), 3560 (m), 3040 (m), 2960 (s), 1600 (w), 1440 (s), 1375 (m), 1355 (w), 1102 (m); δ_H (CDCl₃), 6.9-7.65, m, 15H; 3.44, d, J=14 Hz, 1H; 3.05, d, J=14 Hz, 1H; 1.55, s, 1H; 1.48, s, 3H; 1.43, s, 3H; m/e, (E.I.): No M⁺, 298 (1%), 197 (100%), 147 (30%), 119 (71%), 105 (99%), 91 (83%), 77 (76%); (C.I.): 334 (M+18) (15%), 315 (M+1) (2%), 197 (57%), 167 (22%), 119 (100%), 105 (61%), 91 (22%).

1,2,3-Triphenyl-2-propanol

A 100 ml 3-necked flask fitted with a reflux condenser and 2 septum caps was flame dried and allowed to cool under a flow of nitrogen. To this was added magnesium (0.24 g) and dry ether (10ml), and the mixture was stirred magnetically. A solution of bromobenzene (1.53 g) in dry ether (15 ml) was then added slowly,

and the mixture stirred until all of the magnesium had dissolved. To this was added a solution of 1,3-diphenyl-2-propanone (2.0 g) in dry ether (20 ml), and the mixture was then refluxed for one hour, after which it was allowed to cool to room temperature. Ice (5 g) was added, and a saturated solution of EDTA (50 ml) was also added. The organic layer was separated, the aqueous layer washed with ether (3 x 15 ml), the organic layers combined and dried over sodium sulphate. The organic layer was then filtered, and the ether removed under reduced pressure to give the product as a white solid (1.62g, 60%). The product was purified by silica column chromatography using a pentane/ether gradient, and then was recrystallised to give the pure alcohol, melting point 85-86°C.

(Found : C, 87.4; H, 7.0; $C_{21}H_{20}O$ requires C, 87.5; H, 6.9%); ν_{max} (CCl_4), 3560 (m), 3100-3020 (m), 2960 (s), 2930 (s), 1600 (w), 1495 (m), 1450 (m), 1100 (m); δ_H ($CDCl_3$), 7.4-6.9, 15H, m; 3.25, 2H, d, $J=13$ Hz; 3.02 2H, d, $J=13$ Hz; 1.68, 1H, s, (removed by D2O); m/e, (E.I.): 270 (5%), 198 (44%), 197 (100%), 105 (92%), 91 (86%), 77 (80%); (C.I.): 306 (6%), 289 (2%), 288 (12%), 271 (53%), 197 (75%), 105 (100%), 91 (92%).

Potassium amide

This was prepared using an adaptation of the method of Hauser and Dunnivant⁽⁷⁷⁾.

A 100 ml gas-line flask (which had a stopcock side-arm), was connected to a dry-ice condenser, and the apparatus was flame dried under argon. To the flask was then added freshly cut potassium metal (2 g) which had been washed with 40/60 petrol, and

ferric nitrate (0.1 g). Onto this was condensed ammonia (40 ml), and the solution turned a bronze colour, and then a deep blue colour. After stirring under argon for 2 hours, a further addition of ferric nitrate (0.1 g) was made, and stirring continued for 45 minutes after which time the solution turned grey. The ammonia was then allowed to evaporate, and redistilled toluene (30 ml) was added. The suspension of potassium amide in toluene was then transferred to an argon line where it was stored under argon.

Purification of DMSO

The purification procedure used was as described by Bordwell⁽¹⁰⁾. To DMSO (800 ml) in a one litre flask with a magnetic stirrer was added sodium amide (approx 5 g), and a Vigreux column, condenser, and 1l collection flask connected to it. The apparatus was flame dried under vacuum, and the DMSO then distilled at 0.1 mmHg keeping the pot temperature below 60°C. After distillation, the DMSO was transferred by cannula under argon into a 1l flask (which had been flushed with argon for 20 minutes), fitted with a 3 way PTFE stopcock.

In later work, the DMSO was distilled directly into the storage flask which had been fitted with a "Rotaflo" stopcock that was then kept closed after the distillation. This removed the necessity for a transfer of the purified DMSO, and so reduced the possibility of moisture absorption.

Metal Dimethyl Solutions

(i) Dimethyl Lithium

Purified DMSO (13 ml) was added to a 25 ml flask which was

attached to an argon line, and was fitted with a magnetic stirrer. This was then degassed using an oil pump, the vacuum being released by argon. To this was added n-butyllithium (3 ml of a 1.6 molar solution in hexane) using a gas tight syringe. A white solid appeared in the hexane layer, which dissolved in the DMSO on stirring. After 5 minutes no more gas was evolved, and the hexane was removed by oil pump vacuum, the vacuum being released with argon. This gave a clear colourless solution of dimsyl lithium, best results being obtained when using a butyl lithium solution that had been prepared in these laboratories and stored on the argon line, rather than using commercially available n-butyllithium solution.

(ii) Dimsyl Sodium and Dimsyl Potassium

A 50ml gas-line flask that was fitted with a magnetic stirrer, was flushed with argon, and to this was added a suspension of the metal amide in toluene. The flask was rapidly replaced on the argon line, evacuated using an oil pump, and the vacuum then released with argon. The amide was then washed four times with 40/60 petrol (5 ml) that had been shaken with concentrated sulphuric acid and then distilled from calcium hydride. In the case of potassium, it was especially necessary to prevent possible contact with oxygen at any stage, as this resulted in the amide turning yellow which in turn gave yellow dimsyl potassium. The flask was then evacuated with stirring to give the amide as a fine white powder. To this was added DMSO (25ml), and the mixture stirred for five minutes. The solution was then evacuated to remove the ammonia formed, and when no further gas was evolved the vacuum was released with argon, to give a clear colourless solution of the appropriate metal dimsyl

solution.

n-Butyllithium

This was prepared using the method of Bryce-Smith and Turner⁽¹⁰⁾. A 100 ml three-necked flask fitted with a magnetic stirrer, a condenser, an addition funnel, and a stopcock fitted with a septum cap, was flushed with nitrogen for 20 minutes. To this was added pentane (25 ml) which had been washed three times with concentrated sulphuric acid, and distilled from calcium hydride. Into the flask was then extruded lithium wire (1.7 g, 0.24 moles) from a lithium press, and the apparatus flushed with nitrogen for a further five minutes. The mixture was then refluxed gently on an oil bath, and a solution of 1-chlorobutane (10 ml, 8.8 g, 0.096 moles) in pentane (25ml) added from the addition funnel over a period of three hours. After addition was complete, the solution was refluxed for a further hour. The resulting solution was slightly cloudy, but colourless, and a purple solid collected at the bottom of the flask. The solution was then filtered under nitrogen through a porosity 4 frit into a gas-line flask, to give a clear and colourless solution of butyl lithium (approx 1.9 molar). This solution was then attached to an argon line, and kept under positive argon pressure.

Experimental Kinetics

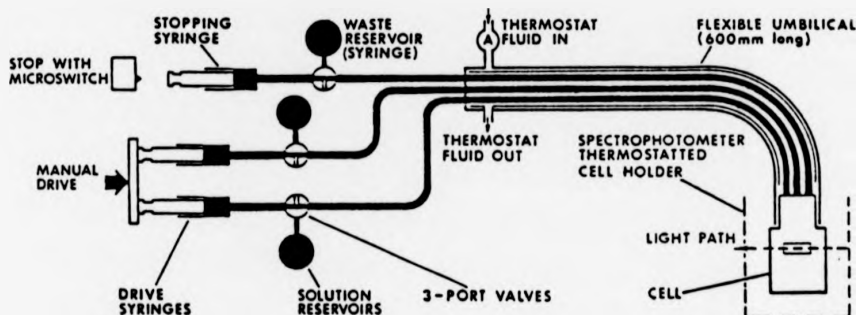
The method that was used for all of the slower runs (the runs with half-lives of greater than one minute) involved use of the specially designed u.v. apparatus which is shown in figure (6). This apparatus was evacuated (0.5 mmHg) using an oil pump, the vacuum then being released with argon to put the whole apparatus under

argon. Using a gas-tight 5 ml syringe, dimethyl solution (2.4ml) was added through the septum cap into the larger of the two "arms" of the apparatus, and using a 1 ml gas-tight syringe, alcohol solution (0.4 ml of 2.5×10^{-3} molar in DMSO) was added into the smaller arm. The apparatus was then clamped with the two arms and the u.v. cell below the water level of a thermostatted bath, which thermostatted the cell block of the u.v. spectrometer. The bath was kept at constant temperature for any set of runs, the actual temperature depending on the cation and the alcohol in question. The apparatus was kept in the bath for ten minutes, then removed, swiftly dried with a tissue, and the reactants mixed by pouring the contents of one arm into the other, and then pouring the mixture from arm to arm several times. The mixed solution was then poured into the UV cell which is part of the apparatus, the apparatus placed in the thermostatted cell block of the spectrometer, the lid closed, the spectrometer zeroed, and the chart recorder set running.

For the runs with "added solutions" (metal halides or cryptands in DMSO), the dimethyl arm of the apparatus had dimethyl solution (2.0 ml) injected into it, and 0.5 ml of a mixture of DMSO and the added solution. The composition of the mixture varied from no added solution (i.e. 0.5 ml of DMSO) to being all added solution. This was carried out in order to vary the concentration of the added solution whilst keeping the dimethyl concentration constant. The usual procedure was then followed.

For the early runs using this technique, the data was processed by reading off the chart recorder paper, and manually entering the data into a BBC micro-computer, which used a non-linear regression analysis program to calculate the first order rate constant for the reaction. Later, the spectrometer was connected to

a scaler which scaled the the spectrometer's output voltage so that it could be fed directly into the BBC micro-computer's games paddle which contains an analogue to digital converter. For faster runs, (with half lives shorter than one minute), a Hi-Tech SFA-11 stopped flow apparatus was used (as shown below).



Before use, the apparatus was stored in a vacuum oven at 40°C and oil pump pressure, and after being set up as in the diagram, was flushed with argon for 30 minutes. The plastic solution reservoir syringes supplied with the apparatus were replaced by Weber 10ml glass syringe barrels, fitted with rubber septum caps. At all times, the contents of the reservoir syringes were kept under positive argon by means of a double headed outlet on the argon line which was fitted with two needles, each of which were pushed through the septum cap of one of the reservoir syringes. The drive syringes were also flushed with argon.

To one of the reservoir syringes was added dimethyl solution (10 ml), and to the other reservoir syringe was added alcohol solution in DMSO (10 ml), this being done with the 3-port valves being closed to the rest of the apparatus. The valves were then opened to the respective drive syringes, and the reagent solutions

were then used to fill and empty the drive syringes several times, until no more gas bubbles could be eliminated from the drive syringes. The drive syringes were then filled to capacity (approx. 1 ml), the 3-port valves turned so that the drive syringes were open to the u.v. cell, but closed to the reservoirs, and then emptied. This procedure was then repeated, which filled the apparatus with reagent solution. After this, the drive syringes were again filled, and when emptied, the data sampling system (an ADC, and a BBC micro-computer) was started. The change in absorption at the wavelength of interest was then monitored with respect to time, in the usual manner.

When duplicate runs agreed to within 5% of each other, the solution collected in the waste syringe (which had been the contents of the u.v. cell) was removed, and 1.0 ml of this was then diluted with a known volume of distilled water, and used for atomic emission spectroscopy to obtain the cation concentration for those runs. To set up for runs using a different diasyl concentration, after the apparatus had already been used, the apparatus was flushed through with alcohol solution (2 x 1 ml) and the new diasyl solution (2 x 1 ml), these "double shots" being injected simultaneously, by means of the drive plate. The solution which collected in the waste syringe was then discarded, and the waste syringe replaced by a clean dry waste syringe. The usual procedure was then followed.

For runs with "added solutions" (metal halides, cryptands), the added solution was mixed with the diasyl solution using a 5ml gas-tight syringe, in the reservoir syringe. For new concentrations, the reservoir syringe was replaced with a clean, dry reservoir syringe (that had been flushed with argon) for each new concentration.

Added Halide Runs

To a 25 ml gas-line flask was added the appropriate halide (approx. 2 g), and the flask attached to an argon line. The flask was then evacuated under oil pump vacuum, and the contents of the flask heated to 500°C for 5 to 10 minutes to remove any water present. The flask and its contents were then allowed to cool under vacuum to room temperature, before release of the vacuum by argon. A septum cap was attached to the stopcock attachment of the flask, and DMSO (15 ml) added. A sonic bath was then placed so that the flask was immersed in the water of the bath, and the sonic bath was then switched on for one hour. The solutions obtained in this way always contained a solid residue of undissolved halide, but as the metal ion concentration was determined independently (by atomic emission spectroscopy), and only the liquid was used for the kinetics (the halide solution being removed by syringe from above the undissolved halide) it was not necessary to obtain completely homogeneous solutions.

Added Cryptand Runs

The cryptands ([2.1.1.] and [2.2.2.]) were obtained from Merck, and were purified by bulb to bulb distillation under reduced pressure ([2.2.2.] at 200°C and 0.3 mmHg, and [2.1.1.] at 170°C at 0.3 mmHg) before making up the solutions in DMSO. An appropriate amount of cryptand (~ 100mg) was weighed into a gas line flask, attached to the gas line, and the flask evacuated (0.5 mmHg). The vacuum was then released with argon, and DMSO (2 ml) added. The mixture was then stirred until all of the cryptand dissolved, after which the solution was used as an "added solution".

APPENDICES

Appendix 1

The experimental data was collected using a timer program "TUES2", the details of which are given below.

The first order rate constants were calculated from the data using a non-linear regression analysis computer program, "NONLIN"⁽⁹⁵⁾, the details of which are given below. This fits the data to an equation of the form :

$$Y(I) = Q(1) + (Q(2)-Q(1)) \cdot \exp(-(Q(3) \cdot X(I)))$$

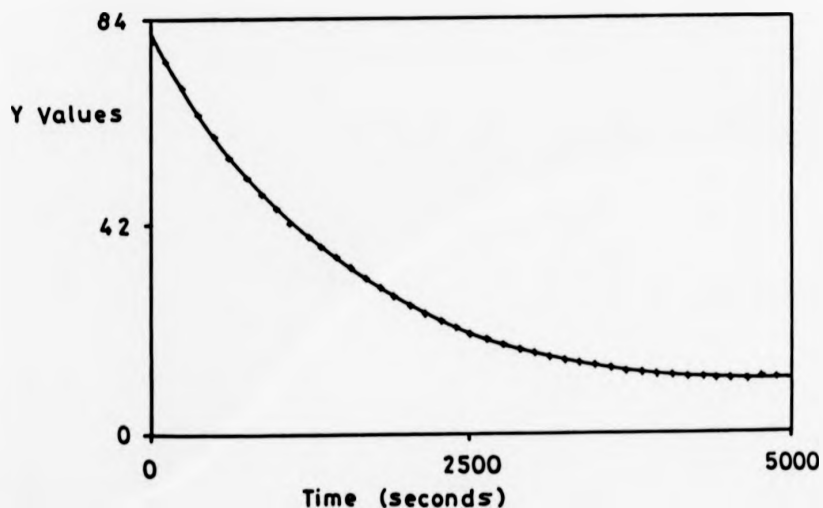
Where $Q(1)$ = infinity value

$Q(2)$ = initial value

$Q(3)$ = rate constant

$Y(I)$ and $X(I)$ are the experimental Y and X values for point number 1.

The values of $Q(1)$, $Q(2)$, and $Q(3)$ were all allowed to vary, thus obtaining the best fit from the data for each parameter. In all cases, the experimental and calculated values for the infinity and zero values agreed very closely. The graph obtained from a typical data set, and the tabulation of the calculated and experimental points are given below.



Fragmentation of (B) : Dimsyl Sodium : Run 7

Parameter values in the equation:-

$$Y(I)=Q(1)+(Q(2)-Q(1))*\exp(-(Q(3)*X(I)))$$

Parameter	Value	Std.Dev.
Q(1) Infinity Value	8.039445646	5.606725953E-2
Q(2) Initial value	80.9239032	6.792882396E-2
Q(3) Decay Constant	7.25903265E-4	1.922866534E-6

These parameters have been adjusted by non-linear regression to data

Pt no	X(I) (time)	W(I) (weight)	Y(I) (exptl)	F(I) (calcd)	Y(I)-F(I) (residual)
1	0	1	8.0490E1	8.0924E1	-4.3390E-1
2	120	1	7.4920E1	7.4844E1	7.6283E-2
3	240	1	6.9450E1	6.9271E1	1.7925E-1
4	360	1	6.4320E1	6.4163E1	1.5730E-1
5	480	1	5.9560E1	5.9481E1	7.9229E-2
6	600	1	5.5340E1	5.5189E1	1.5058E-1
7	720	1	5.1260E1	5.1256E1	3.9378E-3
8	840	1	4.7790E1	4.7651E1	1.3917E-1
9	960	1	4.4440E1	4.4346E1	9.3637E-2
10	1080	1	4.1250E1	4.1318E1	-6.7558E-2
11	1200	1	3.8410E1	3.8541E1	-1.3142E-1
12	1320	1	3.6020E1	3.5997E1	2.3121E-2
13	1440	1	3.3670E1	3.3665E1	5.3935E-3
14	1560	1	3.1500E1	3.1527E1	-2.6898E-2
15	1680	1	2.9500E1	2.9568E1	-6.7521E-2
16	1800	1	2.7690E1	2.7772E1	-8.1601E-2
17	1920	1	2.5980E1	2.6125E1	-1.4550E-1
18	2040	1	2.4610E1	2.4617E1	-6.7202E-3
19	2160	1	2.3300E1	2.3234E1	6.6194E-2

20	2280	1	2.1980E1	2.1966E1	1.3741E-2
21	2400	1	2.0730E1	2.0804E1	-7.4452E-2
22	2520	1	1.9610E1	1.9740E1	-1.2957E-1
23	2640	1	1.8780E1	1.8764E1	1.6484E-2
24	2760	1	1.7780E1	1.7869E1	-8.8890E-2
25	2880	1	1.7000E1	1.7049E1	-4.8896E-2
26	3000	1	1.6210E1	1.6297E1	-8.7307E-2
27	3120	1	1.5600E1	1.5608E1	-8.4174E-3
28	3240	1	1.4990E1	1.4977E1	1.3003E-2
29	3360	1	1.4430E1	1.4398E1	3.1749E-2
30	3480	1	1.3891E1	1.3868E1	2.3215E-2
31	3600	1	1.3330E1	1.3382E1	-5.1571E-2
32	3720	1	1.2990E1	1.2936E1	5.4081E-2
33	3840	1	1.2580E1	1.2527E1	5.2556E-2
34	3960	1	1.2190E1	1.2153E1	3.6955E-2
35	4080	1	1.1920E1	1.1810E1	1.1012E-1
36	4200	1	1.1480E1	1.1495E1	-1.5341E-2
37	4320	1	1.1260E1	1.1207E1	5.2957E-2
38	4440	1	1.0960E1	1.0943E1	1.7205E-2
39	4560	1	1.0770E1	1.0701E1	6.9409E-2

Sum of squares of residuals = 0.440488491

Root mean square of residuals = 0.106275946

Variance of the fit = 1.258538546E-2

"NONLIN"

```

10DIM X(50),Y(50),W(50),Q(5),Z(5),A(5,5),B(5,50),IPVX(5,3),F(50),SIGMA(5)
20MODE7:CLS
30IF AX=0 OR BX=0 THEN GOTO 580
40PROCcard
50PROCpvr
60PRINT"Non-linear regression analysis""Enter values for tolerances for th
e fit""
70INPUT"Convergence tolerance = "CTOL"Divergence tolerance = "DTOL
80CLS:PRINT"Fitting in progress:-""Iter param      value      correction"
90H=1.0:FOR MCX=1 TO 20
100FORIMX=1 TO NX
110PROCFgeval(1,X(IMX)):F(IMX)=TY
120NEXTIMX
130FOR IMX=1 TO MX:Z(IMX)=0.0
140FOR JMX=1 TO MX:A(IMX,JMX)=0.0
150 NEXT JMX:NEXTIMX
160FORIMX=1 TO NX
170FORJMX=1 TO MX
180FOR LMZ=1 TO JMX
190A(JMX,LMZ)=A(JMX,LMZ)+W(IMX)*B(JMX,IMX)*B(LMZ,IMX)
200NEXTLMZ:NEXTJMX:NEXTIMX
210FORIMX=2 TO MX:LMZ=IMX-1
220FORJMX=1TOLMX:A(JMX,IMX)=A(IMX,JMX)
230NEXTJMX:NEXTIMX
240FORIMX=1TONX:DIF=Y(IMX)-F(IMX)
250FORJMX=1 TO MX
260Z(JMX)=Z(JMX)+W(IMX)*DIF*B(JMX,IMX)
270NEXT JMX:NEXT IMX
280PROCMatinv
290IF D=0.0 THEN GOTO 560
300TEST=0.0:PRINT" TAB(2);MCX;
310FOR IMX=1 TO MX:DELA=0.0
320FOR JMX=1 TO MX:DELA=DELA+A(IMX,JMX)*Z(JMX)
330NEXTJMX:TEST=TEST+ABS(DELA/Q(IMX))
340Q(IMX)=Q(IMX)+H*DELA
350BX=10:PRINT TAB(6);IMX;:BX=&0001040C
360PRINT TAB(15);Q(IMX);
370PRINT TAB(28);DELA:NEXT IMX
380BX=10:IF TEST<CTOL THEN GOTO 410
390IF TEST>DTOL THEN GOTO 570
400NEXTMCX:PRINT"Limit of 20 iterations":GOTO 420
410PRINT"Convergence achieved"
420PRINT"Press <space> for tabulated""best values and standard deviations"
430REPEAT:UNTIL GET=32:CLS
440C=OPENUP("HEADER"):INPUTC,TI#:CLOSE#C
450S=0.0:PRINT"TI#;FOR IMX=1 TO NX
460PROCFgeval(2,X(IMX)):F(IMX)=TY
470S=S+W(IMX)*(Y(IMX)-F(IMX))^2
480NEXTIMX:S=S/(NX-MX-1)
490PRINT"Number of data points=";NX""Variance of the fit =" ;S
500PRINT"Parameter      value      std. dev."
510FORJMX=1 TOMX:SIGMA(JMX)=SQR(ABS(S*A(JMX,JMX)))
520PRINT" Q(" ;JMX) " ;:BX=&0001040F
530PRINT TAB(15);Q(JMX);
540PRINT TAB(28);SIGMA(JMX):BX=10
550NEXTJMX:PROCpvr:FX=1:GOTO 590
560PRINT"Tough luck! The matrix is singular.""Try more data points, or a new
set""of initial guesses." :GOTO 590
570PRINT"Tough luck! The system is diverging.""Try more data points, or a ne
w set""of initial guesses." :GOTO 590
580PRINT"The routine requires parameter values""and at least five data point
s"
590PRINT""Press <space> to return to menu"
600REPEAT:UNTIL GET=32:CHAIN"CHOICE"

```

```

610DEFPROCmatinv
620D=1.0;STOL=1.0E-20;FOR JMX=1 TO MX
630IPVX(JMX,3)=0;NEXTJMX
640FORIMX=1 TO MX;AMAX=0.0
650FORJMX=1 TO MX;IF IPVX(JMX,3)=1 THEN GOTO 700
660FORKMX=1 TO MX;IF IPVX(KMX,3)=1 THEN GOTO 690
670IF AMAX>ABS(A(JMX,KMX)) THEN GOTO 690
680IROX=JMX;ICOX=KMX;AMAX=ABS(A(JMX,KMX))
690NEXTKMX
700NEXTJMX
710IF AMAX<STOL THEN GOTO 970
720IPVX(ICOX,3)=1;IPVX(IMX,1)=IROX
730IPVX(IMX,2)=ICOX;IF IROX=ICOX THEN GOTO 770
740FORLMX=1 TO MX;SWAP=A(IROX,LMX)
750A(IROX,LMX)=A(ICOX,LMX)
760A(ICOX,LMX)=SWAP;NEXT LMX
770PIVOT=A(ICOX,ICOX)
780D=D*PIVOT;A(ICOX,ICOX)=1.0
790FOR LMZ=1 TO MX
800A(ICOX,LMZ)=A(ICOX,LMZ)/PIVOT
810NEXT LMZ;FOR LM1X=1 TO MX
820IF LM1X=ICOX THEN GOTO 870
830T=A(LM1X,ICOX);A(LM1X,ICOX)=0.0
840FOR LM2X=1 TO MX
850A(LM1X,LM2X)=A(LM1X,LM2X)-A(ICOX,LM2X)*T
860NEXT LM2X
870NEXT LM1X
880NEXT IMX;NSPX=0
890FOR IMX=1 TO MX;LMX=MX-IMX+1
900IF IPVX(LMX,1)=IPVX(LMX,2) THEN GOTO 930
910JROX=IPVX(LMX,1);JCOX=IPVX(LMX,2)
920NSPX=NSPX+1;FOR KMX=1 TO MX
930SWAP=A(KMX,JROX);A(KMX,JROX)=A(KMX,JCOX)
940A(KMX,JCOX)=SWAP;NEXT KMX
950NEXT IMX
960D=D*((-1)^NSPX);ENDPROC
970D=0.0;ENDPROC
980DEFPROCfbval(FBX,TX)
990AIP=EXP(Q(3)+(-TX));BXP=Q(2)-Q(1)
1000TY=Q(1)+BXP*AIP;IF FBX=2 THEN ENDPROC
1010G(1,IMX)=1-AIP;G(2,IMX)=AIP;G(3,IMX)=AIP*TX*(-BXP)
1020ENDPROC
1030DEFPROCpvrd
1040C=OPENUP("PARVALS");INPUT#C,MX,S
1050FOR IMX=1 TO MX
1060INPUT#C,IMX,Q(IMX),SIGMA(IMX)
1070NEXT IMX;CLOSE#C;ENDPROC
1080DEFPROCpvwr
1090C=OPENOUT("PARVALS");PRINT#C,MX,S
1100FOR IMX=1 TO MX
1110PRINT#C,IMX,Q(IMX),SIGMA(IMX)
1120NEXT IMX;CLOSE#C;ENDPROC
1130DEFPROCcmrd
1140C=OPENUP("COMTAB");INPUT#C,NX
1150FOR IMX=1 TO NX
1160INPUT#C,IMX,X(IMX),W(IMX),Y(IMX),F(IMX),DIF
1170NEXT IMX
1180INPUT#C,DIF2;CLOSE#C;ENDPROC

```


TUES 2

```

10 DIM PROG 300,constant 5,BUFFL 256, BUFFH 256, POINT 1,COMDAT 6,messa 40,me
ssb 40
20MODE7
30*FX225,240
40PROCsetpars
50MODE0
60$ASCI=&FFE3;OSWRCH=&FFEE;OSWORD=&FFF1;OSBYTE=&FFF4;EVENTV=&0220
70$mess="Run in progress. PLEASE DONT TOUCH"
80$messb="Finished. Hit RED1 to continue"
90PROCasmb1
100PROCSAMPLE
110CLS:MODE7:PRINT"WRITING FILE"
120 PROCWRITE
130 CHAIN"POOG5"
140END
150DEFPROCasmb1
160FOR PASS=0 TO 2 STEP 2
170P%=PROG
180OPT PASS
190\SETUP\Sets up initial values, addresses, and enables events
200 LDA#25:STA COMDAT
210 LDA#69:STA COMDAT+1
220 LDA#0:STA COMDAT+2:STA COMDAT+3
230 STA COMDAT+4:STA COMDAT+5
240\The array COMDAT stores the graphics commands
250\COMDAT and COMDAT+1 are equivalent to the PLOT69 command
260 LDA#EVENT MOD 256:STA EVENTV
270 LDA#EVENT DIV 256:STA EVENTV+1
280\The address of the EVENT routine are stored in the vectors EVENTV and EVEN
TV+1
290 LDA #16:LDX #1:JSR OSBYTE
300\Equivalent to *FX16,1 selects channel 1 only of the AD convertor
310 LDA #14:LDX #5:JSR OSBYTE
320\Equivalent to *FX14,5 enables the timer crossing zero event
330 LDA#0:STA POINT
340\POINT stores the point count which is set to zero initially here
350 JSR SMESS
360\Print the start message
370 JSR AVRED
380\Read the ADC for the first time
390.TLOOP\The timer loop
400 LDX POINT:INX
410\Get the value of the count and add 1
420 BNE TLOAD:JSR FMESB:RTS
430\If new value zero print end message and return to basic
440\If the new value is not zero branch to label TLOAD
450.TLOAD\load and start timer
460 STX POINT
470\First store the new value of the point count
480 LDA#4
490 LDX#constant MOD 256
500 LDY#constant DIV 256
510 JSR OSWORD:RTS
520\The value of the time delay is stored in Constant This OSWORD loads and st
arts the timer
530.EVENT\The set of routines called when timer runs out
540 PHA:TXA:PHA:TYA:PHA:PHP
550\First store the registers in stack
560 JSR TLOOP\Restart the timer
570 JSR AVRED\Take a ADC reading
580 JSR GRAPH\Plot the ADC value
590 PLP:PLA:TYA:PLA:TXA:PLA
600\Restore the registers from stack before return
610 RTS
620.AVRED\Read ADC and store data in BUFFL and BUFFH
630.LDA#&80:LDX #1:JSR OSBYTE
640\Equivalent to *FX128,1 reads ADC 1

```

```

650TXA:PHA:LDX POINT
660\save lab of read in stack,load X with point value
670PLA:STA BUFFL,X:STA COMDAT+4
680\store lab in point X of array BUFFL and in COMDAT+4 for graphics
690TYA:STA BUFFH,X:STA COMDAT+5
700\store msb in point X of array BUFFH and in COMDAT+5 for graphics
710RTS
720.GRAPH\Plot the point for ADC
730LDX#6
740.SCALY\Scales the raw ADC value to fit the graph by dividing by 2^6
750LSR COMDAT+5
760ROR COMDAT+4
770DEX:BNE SCALY:LDX#0:LDY#6
780\COMDAT+5 COMDAT+4 contain the value to be plotted on the Y-axis
790.COMMD\The plot command sequence
800LDA COMDAT,X:JSR OSWRCH
810INX:DEY:BNE COMMD
820\equivalent to VDU25 69 X Y
830LDA#5:CLC:ADC COMDAT+2
840STA COMDAT+2:LDA COMDAT+3
850ADC#0:STA COMDAT+3:RTS
860\Add 5 to the X-value store in COMDAT+2 and COMDAT+3
870.SMESS\beeps and write start message
880 JSR BEEP:LDX#0
890 .REPA LDA messa,X:JSR OSASCI
900 INX:CMP#&0D:BNE REPA:RTS
910.FMESS\beeps and write the end message
920 JSR BEEP:LDX#0
930 .REPB LDA messb,X:JSR OSASCI
940 INX:CMP#&0D:BNE REPB:RTS
950.BEEP:LDA#7:JSR OSASCI:RTS
960J
970\constant=-TINT:?(constant+4)=&FF
980NEXT PASS
990ENDPROC
1000DEFPROCsetpars
1010PRINT"" This routine captures 256 data points""from the Analogue-Digital
converter""channel 1 at specified time intervals""which should be longer th
an 0.1 seconds.""
1020INPUT""Enter a value for the time interval""(in centiseconds please)""
TINT
1030CLS:ENDPROC
1040DEFPROCsample
1050MOVE1,1:DRAW 1,1023:DRAW1279,1023:DRAW1279,1:DRAW1,1
1060GX=&00010409
1070PRINT"Interval ="TINT/100" sec."
1080VDU28,40,1,79,0
1090PRINT"Hit REDO to trigger run"
1100REPEAT:UNTIL BET=240
1110CALL PROG
1120REPEAT:UNTIL BET=241
1130ENDPROC
1140 DEF PROCWRITE
1150 *DRIVE1
1160 GX=256:W=1:DUM=0.0
1170 C=OPENOUT("RAWDATA")
1180 PRINT#C,GX
1190 FOR IMX=0 TO 255
1200 X=(TINT*IMX)/100
1210 ADDR=256+?(BUFFH+IMX)+?(BUFFL+IMX)
1220 Y=(100.0-(ADDR/655.2))
1230 PRINT#C,IMX+1,X,W,Y,DUM,DUM
1240 NEXT IMX
1250 PRINT#C,DUM
1260 CLOSE#C
1270 *DRIVE0
1280 ENDPROC

```

Appendix 2

The overall process occurring during a Karl Fischer titration can be summarised as follows⁽¹⁹⁾.



The organic base RN is usually pyridine.

The above equation shows that the stoichiometry of iodine needed to water consumed is 1 : 1, and this forms the basis of the Karl Fischer titration. In the case of the KF 652 Coulometer, the iodine needed is generated electrochemically within the titration vessel itself. The quantitative relationship between the electrical charge passed and the amount of iodine liberated allows accurate measurement of the water content of the sample being titrated. An alternating current is applied to a pair of indicator electrodes. The alternating voltage thus generated decreases drastically if traces of iodine are present, and during the titration all the iodine produced electrochemically is immediately removed by reaction with the water that is present. When all of the water has been titrated, the first trace of free iodine causes the voltage to drop dramatically, this voltage drop being used to detect the end point. As the coulometric Karl Fischer titration is an absolute method, it should not require any calibration of the reagent, unlike the "normal" Karl Fischer titration method where the reagent is not completely stable and requires periodic recalibration⁽²⁰⁾.

The reagent used was a mixture of 30ml chloroform, 1ml diethanolamine, 50 ml methanol, and 40 ml "improved" Karl Fischer reagent⁽²¹⁾. The improved reagent consists of iodine, pyridine,

and sulphur dioxide in molar ratios 1 : 10 : 3 ,in ethylene glycol monomethyl ether as solvent.

APPENDIX 3

a) Using Cram's scheme, The ion-pairing equilibrium concerning the alkoxide is as shown below:



$$K_{(i,p)} = \frac{[ROM]}{[M^+][RO^-]}$$

Now rate of appearance of product = $k_{(i)}[RO^-] + k_{(i,p)}[ROM]$, and using the ion-pairing equation, we have :

$$[RO^-] = \frac{[ROM]}{[M^+].K_{(i,p)}} \text{ to give : Rate} = \frac{k_{(i,p)}[ROM] + k_{(i)}[ROM]}{K_{(i,p)}[M^+]}$$

$$[ROM] = [ROM] + [RO^-] \text{ and Rate} = k_{(obs)}[ROM]$$

$$\text{Therefore ; Rate} = k_{(obs)}[ROM] = k_{(obs)}([ROM] + [RO^-])$$

$$k_{(obs)} = [ROM].(k_{(i,p)} + \frac{k_{(i)}}{K_{(i,p)}[M^+]}) \cdot \left(\frac{1}{[ROM] + [ROM]/[K_{(i,p)}[M^+]]} \right)$$

$$k_{(obs)} = (k_{(i,p)} + \frac{k_{(i)}}{K_{(i,p)}[M^+]}) \cdot \left(\frac{K_{(i,p)}[M^+]}{1 + K_{(i,p)}[M^+]} \right)$$

$$k_{(obs)} = \frac{k_{(i)} + k_{(i,p)}K_{(i,p)}[M^+]}{1 + K_{(i,p)}[M^+]} \quad \text{EQUATION 1}$$

Assuming that the contribution from reaction of the ion pairs is negligible ($k_{(i,p)} \ll k_{(obs)}$), then this equation reduces to ;

$$k_{(obs)} = \frac{k_{(1)}}{1 + K_{(1p)} \cdot [M^+]} \quad \text{EQUATION 2}$$

If $K_{(1p)} \cdot [M^+]$ is large compared to unity, then the equation reduces to ;

$$k_{(obs)} = \frac{k_{(1)}}{K_{(1p)} \cdot [M^+]} \quad \text{EQUATION 3}$$

For the relatively highly associated sodium and lithium alkoxides, equation 3 is expected to apply, but for the potassium alkoxides, equation 2 should be used as $K_{(1p)} \cdot [K^+]$ is not expected to be large compared to unity.

b) For metal dimsyl solutions we have the equilibrium :



$$\text{Where } K_{\text{dim}} = \frac{[\text{dmsylM}]}{[\text{dmsyl}^-][\text{M}^+]}$$

The value of K_{dim} at 25°C is known for $\text{M} = \text{Li, Na, K, Cs}$

As there should only be the dimsyl ion as the counterion for the metal cation, and as the total charge must balance, then $[\text{M}^+] = [\text{dmsyl}^-]$ where these are the concentrations of the free ions. Putting this into the ion pairing equation, we have :

$$[\text{M}^+]^2 = \frac{[\text{dmsylM}]}{K_{\text{dim}}}$$

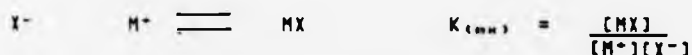
What is actually measured is the total concentration of metal cation present in the solution :

$$\text{Total Measured } [\text{M}^+] = [\text{dmsylM}] + [\text{M}^+]_{\text{free}}$$

This then leads to the quadratic equation below that can be solved to give the concentration of free M^+ for each different solution.

$$K_{\text{dim}}[\text{M}^+]^2 + [\text{M}^+] - [\text{Total measured } \text{M}^+] = 0$$

c) In the case of the added MX solutions, there are 2 equilibria concerned with the concentration of free M^+ :



The concentration of dmsyl is kept constant for the variable halide runs, and so the concentration of free M^+ from the dmsyl can be treated as being constant, and can be calculated using the quadratic equation from Appendix 3b. This will be denoted as $[M^+]_{dmsyl}$.

For the added MX solution, the cation concentration due to this is given by the measured total cation concentration minus the total cation concentration from the dmsyl. This will be denoted as $[Total \text{ added } M^+]$.

$$[Total \text{ added } M^+] = [MX]_{(ion \text{ pair})} + [M^+]_{(free, \text{ due to } MX)}$$

Now the $[M^+]_{(free, \text{ due to } MX)}$ must be equal to $[X^-]_{(free)}$, which makes the MX ion-pairing equation as below :

$$([M^+]_{(free, \text{ due to } MX)})^2 = \frac{[MX]}{K_{(mx)}}$$

This then leads to the quadratic equation to give the concentration of free M^+ due to the added MX :

$$K_{(mx)}[M^+]^2 + [M^+] - [Total \text{ added } M^+] = 0$$

The $[M^+]_{(free \text{ due to } MX)}$ from this equation can then be added to the constant term $[M^+]_{dmsyl}$ to give the total

free M^+ concentration for each individual run.

$$(\text{Total free } M^+) = [M^+]_{\text{free due to } MX} + [M^+]_{\text{assembly}}$$

Appendix (4)

The gradient of each individual run is calculated using a linear least squares computer program⁽¹²⁾, which also calculates the standard deviation of the fit. The value of the gradient which is quoted in the discussion of results section is the weighted mean of the two data sets. This is calculated using the method described by Young⁽¹⁰⁾.

$$X = \frac{\text{Sum of } (X_i / \text{Sigma}_i)}{\text{Sum of } (1 / \text{Sigma}_i)}$$

The quoted +/- values are the standard deviations calculated using the method described by Young⁽⁴⁾.

$$(\text{Sigma})^{-2} = \text{Sum of } (1 / (\text{Sigma}_i)^2)$$

Appendix 3

When cryptand is present, along with the dimsyl and the alkoxide, the following equilibria are set up:



A cubic equation for $[\text{M}^+]$ can be obtained, as derived below.

$$\text{Total cryptand concentration} = [\text{crypt}]_0 = [\text{crypt}] + [\text{cryptM}^+]$$

$$\text{Total cation concentration} = [\text{Tot.M}^+] = [\text{dimsylM}] + [\text{cryptM}^+] + [\text{M}^+]$$

($[\text{ROM}]$ is less than 1/200 of the value of $[\text{Tot.M}^+]$, and so this term is neglected.)

$$\text{Free dimsyl concentration} = [\text{dimsyl}^-] = [\text{M}^+] + [\text{cryptM}^+]$$

$$[\text{cryptM}^+] = K_c \cdot [\text{M}^+] \cdot [\text{crypt}] \quad \text{and} \quad [\text{crypt}] = [\text{crypt}]_0 - [\text{cryptM}^+]$$

$$\frac{[\text{cryptM}^+]}{[\text{crypt}]_0 - [\text{cryptM}^+]} = K_c \cdot [\text{M}^+] \quad ; \quad \frac{[\text{crypt}]_0}{[\text{cryptM}^+]} - 1 = \frac{1}{K_c \cdot [\text{M}^+]}$$

$$\frac{[\text{crypt}]_0}{[\text{cryptM}^+]} = \frac{1 + K_c \cdot [\text{M}^+]}{K_c \cdot [\text{M}^+]} \quad ; \quad [\text{cryptM}^+] = \frac{K_c \cdot [\text{M}^+] \cdot [\text{crypt}]_0}{1 + K_c \cdot [\text{M}^+]}$$

$$[\text{Tot. M}^+] = [\text{M}^+] + \frac{K_c [\text{M}^+] [\text{crypt}]_0}{1 + K_c [\text{M}^+]} + [\text{dmsylM}]$$

$$[\text{dmsylM}] = ([\text{M}^+] + [\text{cryptM}^+]) \cdot [\text{M}^+] \cdot K_d$$

$$[\text{dmsylM}] = K_d [\text{M}^+]^2 + \frac{K_c K_d [\text{M}^+]^2 [\text{crypt}]_0}{1 + K_c [\text{M}^+]}$$

$$\begin{aligned} [\text{Tot. M}^+] &= [\text{M}^+] + \frac{K_c [\text{M}^+] [\text{crypt}]_0}{1 + K_c [\text{M}^+]} \\ &\quad + K_d [\text{M}^+]^2 + \frac{K_c K_d [\text{M}^+]^2 [\text{crypt}]_0}{1 + K_c [\text{M}^+]} \end{aligned}$$

This leads to a cubic equation of the form ;

$$[\text{M}^+]^3 + P [\text{M}^+]^2 + Q [\text{M}^+] + R = 0$$

$$P = \frac{(K_c + K_d + K_c K_d [\text{crypt}]_0)}{K_c K_d}$$

$$Q = \frac{(1 + K_c [\text{crypt}]_0 - K_c [\text{Tot. M}^+])}{K_c K_d}$$

$$R = - \frac{[\text{Tot. M}^+]}{K_c K_d}$$

This cubic equation can be solved by standard mathematical methods⁽¹²⁷⁾. For the values of the constants that apply for the

fragmentation of (B) with cryptands, the solution of the cubic equation yields three real and unequal roots. Two of these roots are negative, and so these do not have any physical significance. The other root is used as the value of $[M^*]$, which can be calculated for any value of initial cryptand concentration. This is used to calculate the value of k_{obs} for any initial cryptand concentration, using equation 2 from appendix 3a.

$$k_{obs} = \frac{k_{11}}{1 + K_{11P} \cdot [M^*]}$$

The natural logarithm (Ln) of the k_{obs} value for each cryptand concentration can be taken, and then the theoretical curves can be plotted for comparison with the experimental curves shown in figure 24.

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