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STRUCTURE AND REACTIVITY OF ALKALI METAL ENOLATES

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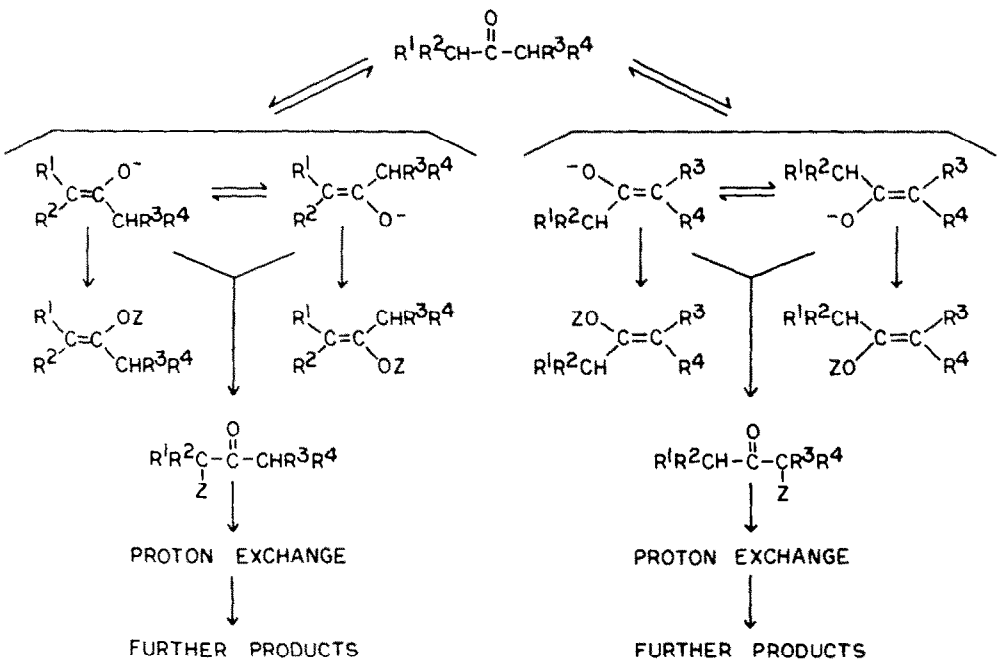
CONTENTS

1. INTRODUCTION

A very large number of common and synthetically useful reactions involve alkali metal enolates as intermediates. A full understanding of the mechanism of these reactions is complicated not only because enolization may lead to several structurally and stereochemically isomeric enolate ions but also because the subsequent reaction of each enolate ion may lead to a multiplicity of products. The complexity of such systems is illustrated in the annexed scheme. It is clear that, for a particular set of



reactants, the actual course of reaction may be the result of kinetic or thermodynamic control at any of several places in this scheme. In this review, we intend to confine our attention to the reaction of the enolate ion itself. The systems discussed yield products which are not determined by the initial proton transfer leading to the enolate ions, although subsequent proton transfers involving products may occasionally complicate the picture. As our main objective will be to focus attention on the relation between various ionic or ion paired species and reactivity, we further restrict the scope to include only alkylation and certain acylation reactions. Thus some very important reactions such as the aldol condensation, Michael addition, Claisen condensation, etc. lie outside the scope of this review. It is our hope, however, that the fundamental concepts which are considered here will ultimately have an impact in these related areas. Similarly, ambident anions derived from other classes of compounds are not considered. These include the anions of nitro compounds, nitriles, ketonitriles, esters, oximes, ketosulfoxides, ketosulfones, amides, pyridones, indoles and various dianions (including those of β-dicarbonyl compounds). All of these are formally analogous to the enolate ion and in many instances their reactivities appear to be governed by the same factors.[1-3]

We will consider explicitly the alkylation of the enolate ions of simple ketones and β-dicarbonyl compounds (including β-keto esters). In addition, we will review the analogous chemistry of phenoxide ions since some work in this area adds materially to our understanding of enolate ions. We will *not* include the alkylation of α,β-unsaturated carbonyl compounds. This area, which has been reviewed by Conia,[4] involves an additional problem of product orientation and makes it inappropriate for our consideration at this time.

The central problem in the understanding of the reactions of alkali metal enolate ions is the relation between the structures of these salts in various solvents and their reactivities towards various electrophiles. Since the occurrence of free ions, ion pairs, and aggregates is intimately related to various properties of the solvent, we have adopted the following rough classification of the common solvents.

Class A

Non-polar or very weakly polar solvents with virtually no ability to solvate cations or anions.

Examples. Alkanes, benzene, methylene chloride, chloroform.

Class B

Weakly polar solvents which can, however, solvate cations.

Examples. Ether, tetrahydrofuran (THF), dimethoxyethane (DME), di-, tri- and tetra-glymes, aliphatic tertiary amines, pyridine.

Class C

Polar aprotic solvents with good cation solvating power but with no ability to directly solvate anions.

Examples. Hexamethylphosphoric triamide (HMPT), dimethylsulfoxide (DMSO), dimethylformamide (DMF), acetone, acetonitrile.

Class D

Polar protic solvents which can solvate both anions (hydrogen bonding) and cations.

Examples. Water, ammonia, methanol, ethanol.

Although one may debate the classification of certain borderline cases, this division nevertheless provides a convenient vehicle for our subsequent discussions.

Our subsequent discussion is divided into two parts. The first reviews the information concerning the structures of alkali metal enolate ions in solution and in the crystalline state, which is provided by X-ray, spectroscopic and physicochemical methods. The second part covers kinetic and product orientation studies. In this part, we have attempted to analyze the data in terms of the possible species present in solution. The material discussed also forms the basis for the rational selection of conditions for maximizing desired products. It will be clear that there still exist many important gaps in our knowledge. We have drawn particular attention to certain of these in the hope of stimulating further research in the field.

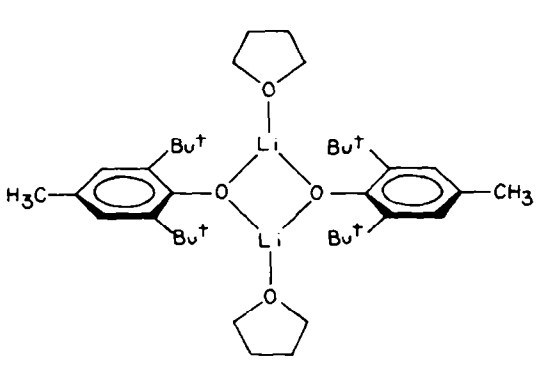
Earlier reviews which include the area under consideration here, as well as other aspects of the alkylation and acylation of carbonyl compounds, have been published by Shevelev,[1] Gompper,[2] House[5,6] and d'Angelo.[7]

2. STRUCTURAL EVIDENCE FROM X-RAY, SPECTROSCOPIC AND PHYSICOCHEMICAL METHODS

In this section, we attempt to bring together results of studies which use a variety of methods to investigate the degree of aggregation, the formation of simple ion pairs and the existence of free ions in various solvent systems. We also include findings which may throw some light on the detailed structures of the ion pairs and their aggregates. The three classes of salts under consideration are phenoxides, simple enolates and the enolates of β-dicarbonyl compounds, and they will be discussed in that order.

2.1 *Phenoxides*

The most direct information concerning the aggregated nature of phenoxide salts is provided by studies of colligative properties in class A and B solvents. The cryoscopically determined apparent molecular weight of lithium 2,6-di-t-butylphenoxide in dioxane corresponds to a dimer.[8] The mono-THF solvate of lithium 2,6-di-t-butyl-4-methylphenoxide in benzene solution was similarly found to be a dimer. That these systems are dimeric rather than tetrameric, as found for lithioisobutyrophenone in similar solvents (see below) may be a consequence of the sterically crowded environment of the oxygen atoms (possibly, less hindered phenoxides may exist as tetramers, but the requisite data is not yet available). The structure 1 was advanced for the THF



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solvate in benzene and the significant shielding of both the α- and β protons of the bound THF (relative to free THF in benzene) was cited as supporting evidence.

Reichle[9] reports that the degree of aggregation of 0.08 M potassium phenoxide in THF at 37° is 3.2. This determination was made by osmometry, which is a notoriously difficult technique for dealing with air and moisture sensitive compounds. The same salt (0.2 M) in diglyme at 160° was found by ebullioscopy to have an aggregation number of 1.5.

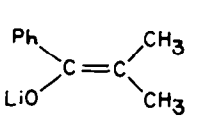
It is probable that alkali metal phenoxides are monomeric in class C and D solvents since several conductivity studies have shown extensive dissociation to the free ions in these solvents.[10-13] It is conceivable, however, that the ionic species include triple ions, at least at high concentration.

Studies of proton chemical shifts, particularly for the p-position,[14,15] and UV spectral data for phenoxide salts in a wide variety of solvents indicate that the electron distribution in the anion is significantly affected by the solvent. These findings have not been rationalized in terms of structural postulates but have been taken as reflecting the relative "tightness" of contact ion pairs. It is noteworthy that Hudrlik and Dabrowski[15] have found that in class B solvents there is a reasonable correlation between the chemical shift of the para proton of potassium phenoxide and its nucleophilic reactivity, but that class C solvents cause marked deviation from this relationship. This may well be a consequence of aggregation in the former class of solvents.

There is virtually no information concerning the solvation of alkali metal phenoxide ion pairs.[16,17] X-ray crystallographic structures of such compounds suggest coordination numbers of 4 for lithium[18] and 6–9 for the other alkali metal cations.[18-20] The solvation of phenoxide ions by hydrogen bonding (class D) solvents is evident from studies of proton chemical shifts[21] and electronic spectra.[21-23]

2.2 *Enolates of simple aldehydes and ketones*

There seems little doubt that, irrespective of the degree of association or aggregation of alkali metal enolates, the cation is never intimately associated with the carbon terminus of the ambident anion. For example, Zook *et al.*[24] found that the typical CO stretching frequency (1720 cm^{-1}) moves to a much lower value (1575 cm^{-1}) on conversion to its sodio derivative. Similarly, House[25] reported that both lithio- and sodiophenylacetone exhibit pairs of strong absorptions in the region 1550–1585 cm^{-1}, in contrast to the analogous mercury derivatives which possess a normal CO absorption at 1670 cm^{-1}. The mercury derivatives were shown unequivocally to have a carbon–mercury bond by the observation, in their proton NMR spectra, of spin–spin coupling between the α-proton(s) and ^{199}Hg. Examination of the proton spectra of lithioisobutyrophenone (2) in various solvents (including tetraglyme at 200°) shows the two Me groups are non-equivalent, thus proving that the C(1)–C(2) bond has considerable double bond character.[26] Furthermore, House and Trost[27] have shown that the E and Z isomers of 3-lithio-2-heptanone retain their stereochemical integrity even when heated for 45 min at 73° in dimethoxyethane. Heiszwolf and Kloosterziel[28] have used the vicinal coupling constants of potassiocroton-aldehyde (3) in liquid ammonia and those of the analogous pentadienyl anion as indices of the bond orders in these systems and have concluded



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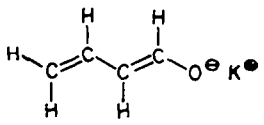

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that the negative charge on the former anion is localized to a large degree on oxygen.

The above evidence eliminates structures possessing carbon–metal bonds, but does not exclude the presence of free ions. In other words, the barrier to rotation about the potential carbon–carbon double bond may well be high even in the free anions.

It is known from conductivity studies that several sodium enolates are undissociated in diethyl ether.[24,29] On the other hand, a small degree of dissociation was observed in sodio-n-butyrophenone in dimethoxyethane, and it was suggested that, in view of the apparent trimeric nature of the salt in this solvent, the conducting anion might be $[Na_2(enol)_3]^-$. The existence of multiple ions in other systems is well established.[30] The addition of approximately 10 equivalents of DMSO produced a 10-fold increase in conductivity and it is possible that substantial concentrations of free, monomeric anions exist in pure DMSO and other class C solvents.

The degree of aggregation of lithioisobutyrophenone in class B solvents has been investigated through studies of ^{13}C spin-lattice relaxation times. This approach offers some advantages over the usual measurements of colligative properties in that it is applicable over a large temperature range and, in certain instances, it can be used to determine the molecular sizes of individual components in a mixture. The results of these studies show that 0.5 M lithioisobutyrophenone is essentially a tetramer in dioxolane, dioxane, THF, and tetrahydropyran. In dimethoxyethane, however, there exist two species which exchange rapidly on the NMR time scale at room temperature, but which give rise to discrete signals at −50°. The ^{13}C relaxation time for the p-carbon atom of the major (approx. 80%) component corresponds to a dimeric species, whereas the minor component is more highly aggregated and is probably a tetramer.[31]

An important finding concerning lithioisobutyrophenone in class B solvents is that it forms "ate" complexes with lithium chloride and bromide, which have the formula $Li_4X(Enol)_3$, (X = Cl or Br).[26,31] Even in dimethoxyethane, the addition of lithium chloride yields this tetrameric complex. A kinetic study in dioxolane, using dynamic NMR, showed that the exchange of the organic anion between the tetrameric enolate and its "ate" complex involves a rate determining dissociation of the latter. This is a useful result since it allows the prediction that reactions of lithioisobutyrophenone, which proceed by prior dissociation of the tetramer, should be retarded by the addition of relatively low concentrations of lithium chloride.

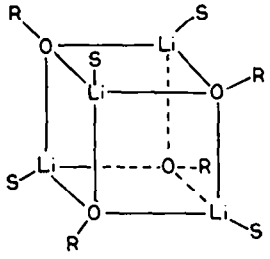
There appear to be two tetrameric structures for lithioisobutyrophenone in dioxolane, THF and dioxane. These are characterized by the differences between the proton chemical shifts for the pairs of non-equivalent Me groups. The two species in dioxolane coexist in the temperature range −40° to +40°C and exchange rapidly on the NMR time scale. Their ^{13}C spectra are virtually identical, indicating that the electron distribution in the anion is the same in each species. The thermodynamic

parameters for the equilibrium between the two species are consistent with increased solvation of the species which predominates at low temperatures. Thus far, attempts to determine the extent of primary solvation in these two structures have been unsuccessful.[31]

The above studies have led to the formulation of the solvated tetramer as **4** and the solvated dimer as **5**.[31] Similar structures have also been suggested by House *et al.*[32] as possible candidates for metal enolate aggregates. The principal factor which contributes to the stability of **4** is that it provides the maximum number of close interactions between oppositely charged ions and maintains a coordination number of 4 (or perhaps 5 in the low temperature species) for the lithium ions. The formation of the dimer **5** in dimethoxyethane is no doubt attributable to the chelation effect.

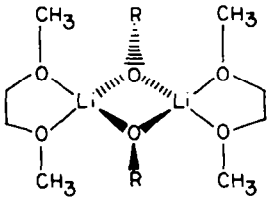
Similar experiments have not been carried out with the higher alkali metal salts. There is, however, evidence based on ebullioscopic molecular weight determinations which indicates that, in ether and in the concentration range 0.13–0.63 M, sodio-n-butyrophenone is a trimer.[33] In dimethoxyethane, this salt has an apparent aggregation number in the range 2.5–2.7.[34] The existence of trimers for sodium enolates in class B solvents may reflect a requirement for 6-coordination by the cation, which models suggest may be sterically more favorable in a cyclic trimer than in the electrostatically more stabilized cubic tetramer.

That solvent and cation influence the charge distribution in enolates is indicated by their effect on the chemical shift of the α-proton(s) (Table 1). It is expected that a cation proximal to the O atom will withdraw



s = solvent

4



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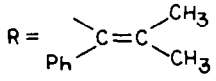
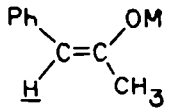
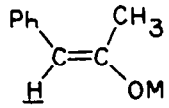
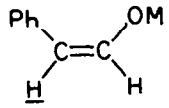
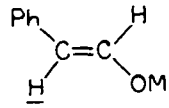
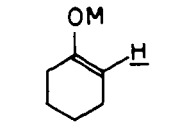


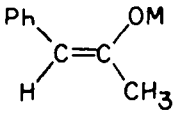
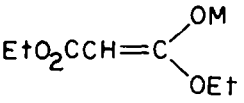
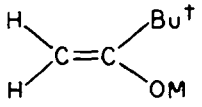
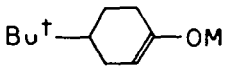
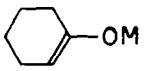
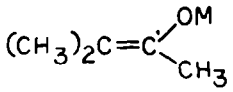
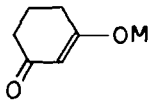
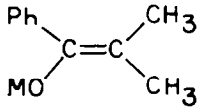
Table 1. Chemical shifts (δ, ppm) of α-protons in alkali metal enolates at 25°C

Enolate	M	Solvent	δ	Ref.
	Li	DME	4.83	25
	Li	THF	4.93	25
	Li	Et_2O	5.02	25
	Na	THF	4.88	25
	K	$NH_3(\ell)$[a]	4.67	94
	Li	DME	5.25	25
	Li	Et_2O	5.57	25
	K	$NH_3(\ell)$[a]	4.39	94
	K	$NH_3(\ell)$[a]	4.91	94
	Li	$THF-d_8$	4.16	56
	Li	glyme	4.24	56
	Li	3:2 THF-HMPT	~4.16	56
	K	glyme	~3.9	56
	K	3:2 glyme-HMPT	~3.72	56

a: At −20°C.

negative charge from the α-position to the oxygen, thereby decreasing the shielding of the α-proton. In general, increased size of the cation and increasing cation solvating power of the solvent are seen to produce this trend. Proton chemical shifts, however, may be significantly affected by long range shielding contributions arising from nearby solvent molecules or from changes in conformation of the enolate ion (e.g. a change in orientation of a phenyl substituent). ^{13}C chemical shifts provide a much better

Table 2. ^{13}C chemical shifts of the α-carbon and carbonyl carbon in alkali metal enolates[a]

Enolate	M^+	Solvent	$\delta(C_\alpha)$, ppm	$\delta(C{=}O)$, ppm	Ref.
	Na	DME + 1.0 to 2.0 eq. dicyclohexyl-18-crown-6	90.7	170.3	57
	K	DME	91.8	170.7	57
	Li	DME + 4.1 eq. HMPT	93.1	167.4	57
	Na	DME	93.4	169.3	57
	Li	Et_2O + 5.1 eq. HMPT	94.1	166.4	57
	Li	THF + 3.9 eq. HMPT	94.4	166.0	57
	Li	DME	95.3	164.7	57
	Li	THF + 0.9 eq. 18-crown-6	96.4	163.7	57
	Li	THF + 1.1 eq. 12-crown-4	96.5	163.9	57
	Li	THF	97.1	162.5	57
	Li	Et_2O	97.8	160.6	57
	Na	DMF	62.1	171.4	57
	Li	DME	73.5	176.8	57
	Li	DME	91.5	158.4	57
	Li	DME	91.7	158.6	57
	Li	DME	92.3	150.6	57
	Na	DMF	102.3	193.5	57
	Li	1,3-Dioxolane (40°)	96.2	155.3	31
	Li	1,3-Dioxolane (-46°)	96.4	155.8	31
	Li	1,3-Dioxolane + 0.1 M LiCl (40°)	96.3	155.2	31
	Li	Dioxane (40°)	96.1	155.1	31
	Li	THF-d_8 (40°)	95.6	155.6	31
	Li	Tetrahydropyran (40°)	95.8	155.0	31
	Li	DME (40°)	93.3	156.0	31
	Li	DME[b] (-50°)	91.2	156.2	31
	Li	DME[c] (-50°)	95.8	154.6	31
	Li	DME + 0.21 M LiCl (40°)	95.8	155.0	31

a: All temperatures at 25°C except where otherwise noted.
b: Major (85%) component.
c: Minor (15%) component.

probe for electron distribution at the α-position. INDO calculations show that decreasing the localization of the negative charge on oxygen results in a decrease in charge density at the oxygen-bearing C atom as well as the expected, substantial increase at the α-position. Pertinent chemical shift data are presented in Table 2. Similar, but even larger variations have been reported by Fellmann and Dubois[35] for the sodium and bromomagnesium salts of the enolate of 2,2-dimethyl-3-pentanone. The data in Table 2 indicate that, in those class B solvents in which tetramers prevail, the chemical shifts exhibit only minor changes, presumably associated with changes in solvent basicity. Formation of the dimer in dimethoxyethane, however, evidently effects a substantial change in charge distribution, resulting in increased charge density on the α-carbon. This is a result which is also predicted by INDO calculations. Increasing the atomic number of the alkali metal cation has the same effect. A large change (Fellmann and Dubois, see above) is brought about by the addition of 18-crown-6 ethers to the sodium salt, but it is not known if this yields the free ion or a very loose contact ion pair. The effect of adding small quantities of HMPT shows that this compound is effective in solvating lithium, a result which is amply confirmed by the reactivity studies presented in Part 3. The only anomolous result is the failure of 12-crown-4 to significantly effect the chemical shifts of lithiophenylacetone in THF. This crown ether is known to complex strongly with the lithium cation and, as will be described later, it has quite a dramatic effect on the reactivity of lithioisobutyrophenone in class B solvents.

Data in Table 2 indicate that the electron distribution in the enolate in the tetrameric species is virtually unaffected by conversion of the tetramer to the "ate" complex, $Li_4Cl(Enol)_3$. A final point of interest is that the addition of LiCl to lithioisobutyrophenone in DME causes changes in chemical shifts which are consistent with the conversion of dimer to tetramer.

2.3 *Enolates of β-dicarbonyl compounds*

In addition to the problems associated with ion pair formation and aggregation which we have considered above, two other problems arise in the case of the alkali metal enolates of β-dicarbonyl compounds. The first of these is associated with the ability of the enolate to act as a chelating ligand. This will clearly influence the tendency for the salts to form ion pairs. Thus, we will find that when chelation is sterically favored, as it is in some systems, it results in enhanced ion pair formation. Furthermore, chelation will presumably influence the degree of aggregation of these ion pairs as well as the actual structures of the aggregates.

The second problem concerns the stereochemistry or preferred conformation of the enolate ion. In the general case, four configurations are possible and these are depicted in Fig. 1. Although these four arrangements are frequently found to exchange slowly on the NMR time scale, they should properly be regarded as conformations because they will generally interconvert rapidly compared with the rates of their reactions with electrophiles. Furthermore, since only the ZZ conformation can form a chelate with the counterion, we expect there will be an interesting interplay between stereochemistry and ion pair formation.

Chelation of alkali metal cations by bidentate ligands is well established. Truter, Nyholm *et al.*[36-38] have demonstrated the existence of a wide range of complexes of the type $(M^+L^-)(HL)$ in which L is a bidentate ligand involving oxygen and nitrogen or, more frequently, two O atoms. Direct evidence is provided by several detailed X-ray crystallographic studies which are of interest in that they delineate some of the possible geometries of "coordinated" alkali metal cations. Schröder and Weber[39] have reported that the structure of 2,4-pentandionato-lithium (lithium acetylacetonate; Li(acac)) consists of endless chains in which $Li(acac)_2^-$ ions are connected by lithium cations. The basic structural unit is depicted in Fig. 2. The $Li(acac)_2^-$ ion involves an essentially square planar configuration of four O atoms about the central Li cation. The bridging Li cations are in an approximately tetrahedral environment provided by two pairs of O atoms of neighboring $Li(acac)_2^-$ ions. The Li–O distances correspond to ionic bonding, being 1.93 and 1.95 Å for the square planar and tetrahedral bonds respectively. The Li–O bond distance in lithium hydrogen maleate dihydrate, for instance, is 1.99 Å.[40]

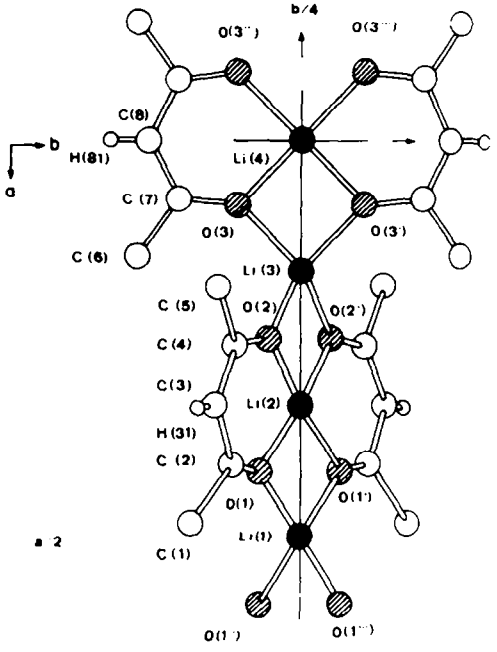


Fig. 2. Basic structural unit of 2,4 - pentandionato - lithium (lithium acetylacetonate).[39]

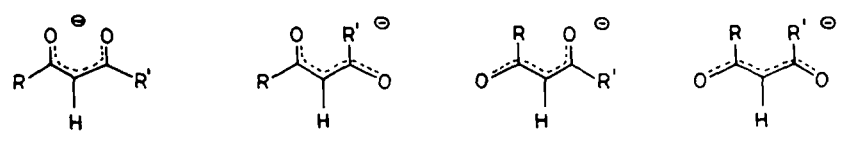


Fig. 1. Possible configurations of the anion of $RC^1OC^2H_2C^3OR'$.

An X-ray structure of 1 - phenylbutane - 1,3 - dionato(ethylene glycol)sodium is reproduced in Fig. 3.[41] In this system, each sodium ion is chelated by only one $acac^-$. The ion, however, has a pentacoordinate, square pyramidal environment, the remaining three ligands being one oxygen each of two ethylene glycol molecules and one oxygen of a neighboring $acac^-$ ion. The Na–O distances are in the range 2.29–2.36 Å which corresponds to ionic bonding. The presence of an $Na(acac)_3^{2-}$ ion has been demonstrated by X-ray crystallography to occur in dirubidium tris(hexafluoroacetylacetonato)sodate,[42] and its structure is shown in Fig. 4. The sodium ion is hexacoordinate with a trigonal prismatic arrangement of the six ligands. The sodium ion is hexacoordinate with a trigonal prismatic arrangement of the six ligands. The six Na–O distances are in the range 2.20–2.47 Å.

The potassium ion appears to be able to accomodate 7–9 nitrogen and oxygen ligands. Thus, in potassium *o*-nitrophenoxide hemihydrate the metal ion has seven short oxygen distances with the organic anions acting as bidentate ligands.[43,44] 8-Coordinate potassium is found in potassium picrate[45,46] and certain crown ether complexes.[47,48] In the monohydrate of the potassium salt of 4-hydroxy-3,5-dinitrofurazan, the cation has eight short K–O distances (2.86–3.11 Å) and one K–N distance of 3.11 Å.[48]

We turn now to a consideration of the physicochemical evidence for the nature of the salts of the enolates of β-dicarbonyl compounds in solution.

Zaugg *et al.*[49,50] have shown that sodio diethyl n-butyl-malonate in class A solvents (benzene and cyclohexane) exists as an inverse micelle comprised of some 40–50 monomer units. Sedimentation studies showed that the salt is monodispersed and that the critical micelle concentration is extremely low (3 mM in cyclohexane). In contrast, the salt appears to be essentially monomeric in dimethoxyethane, the critical micelle concentration being greater than 0.28 M. This study is an important one and it raises the question as to the nature of the salts of simple enolates and phenoxides in class A solvents.

Lithium hexafluoroacetylacetonate (0.1 M) in dioxane has been shown by cryoscopy to be monomeric.[51] Its N,N,N',N'-tetramethylethylenediamine adduct dissociates to its monomeric components in the same solvent. This adduct does not dissociate in benzene and shows some evidence of aggregation above a concentration of 0.07 M. Dioxane is a typical class B solvent and the above results suggest that lithium and, by implication, the other alkali metal β-diketonates are not aggregated in these solvents. Nevertheless, there is evidence that lithium salts can form triple ions in the presence of either excess Li^+ or $(acac)^-$. It has been shown[52] that lithium perchlorate greatly increases the solubility of lithium acetylacetonate in acetonitrile, a class C solvent,

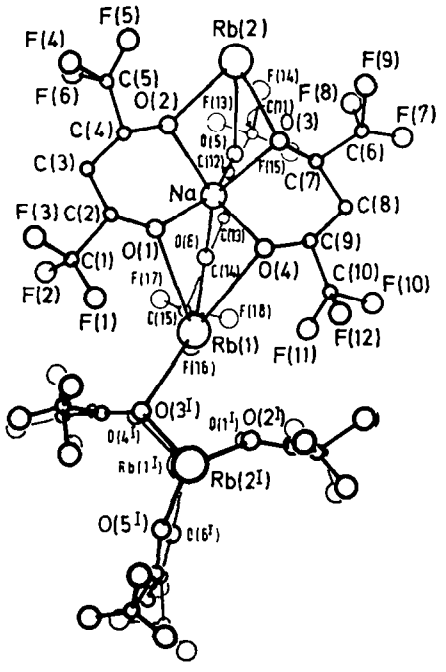


Fig. 4. Basic structural unit of dirubidium tris(hexafluoroacetylacetonato) sodate.[42]

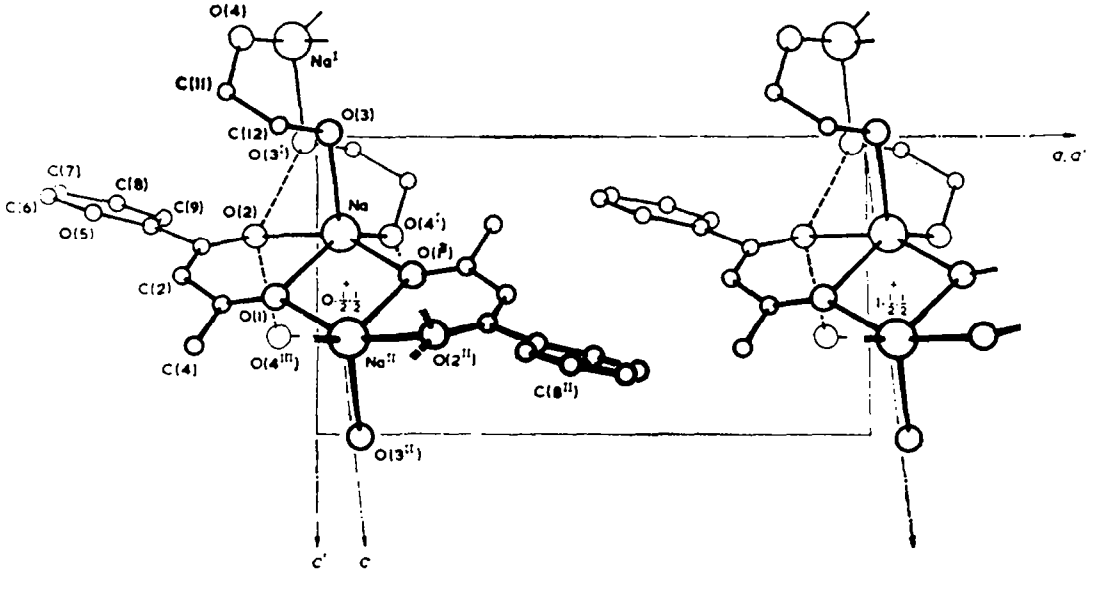


Fig. 3. Basic structural unit of 1 - phenylbutane - 1,3 - dionato(ethylene glycol) sodium.[41]

and a quantitative analysis of the data fits the following scheme.

$$Li(acac) + Li^+ \rightleftharpoons [Li_2(acac)]^+; \quad K = 1.1 \times 10^3\ M^{-1}$$

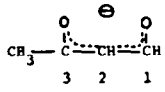
$$[Li_2(acac)]^+ + ClO_4^- \rightleftharpoons [Li_2(acac)]^+ClO_4^-; \quad K = 15\ M^{-1}.$$

A similar, but much weaker effect was found with Na(acac). Lithiodimedone forms the triple ion but dibenzoylmethane does not. It would appear that these triple ions are characteristic of the EE, or W configuration (Fig. 1), and are not formed by anions such as that of benzoylmethane which, for steric reasons, is probably constrained in the U conformation.

The evidence for the formation of $Li(acac)_2^-$ comes from an elegant NMR study by Raban *et al.*[53] They have shown that the lithium ion quantitatively promotes the adoption of the ZZ configuration by the acac anion, due no doubt to the chelation effect. At −57° the EZ and ZZ conformers interchange slowly on the NMR time scale, the former giving two Me signals of equal intensity and the latter only one. Thus it proved possible to titrate a solution of Na(acac) (0.69 M, 34% ZZ, 66% EZ) or Na(acac) plus 18-crown-6 (100% EZ) in methanol-d_4. Total conversion to the ZZ conformer was effected by the addition of 0.5 equivalents of lithium perchlorate, indicating the formation of the triple ion. At the concentrations employed it is likely that the triple ion is partially paired as $Na^+[Li(acac)_2]^-$. Double salts involving protonated 1,8-bis(dimethylamino)naphthalene, $(TMNDH)^+$ and alkali metal hexafluoroacetylacetonates, M(hfac) have been prepared.[54] $(TMNDH)^+[Li(hfac)_2]^-$ and the corresponding sodium derivative have been shown to be 1:1 electrolytes in nitromethane. Conductance measurements for another compound, formulated as $K^+(TMNDH)^+[K(hfac)_3]^{2-}$, indicated that it is a 2:1 electrolyte. Both types of anions bear a close analogy to some of the solid state structures described above. The $Li(acac)_2^-$ ion, which is square planar in the crystalline state (Fig. 2) may be tetrahedral in solution since INDO calculations[55] show the analogous malondialdehyde anion as being 12 kcal mole^{-1} more stable in the tetrahedral configuration.

Ion pair dissociation constants have been determined for alkali metal salts of a number of β-dicarbonyl compounds in class C and D solvents and data for some β-ketoester systems are presented in Table 3. As expected, dissociation increases with the size of the cation. HMPT and ethanol support dissociation to about the same degree and DMSO is somewhat less effective. The tendency towards dissociation is strongly influenced by the ability of the free anion to adopt the EE conformation. This provides the greatest separation of the two O atoms, which carry the bulk of the negative charge. Thus, the salts of cyclic β-ketoesters which cannot assume the EE conformation are much more strongly associated. Similarly, it has been shown that lithio-dibenzoylmethide and -dipivaloylmethide, both of which would have heavily hindered EE configurations, are totally non-conducting in DMSO,[64] in contrast to lithium acetylacetonate which exhibits significant conductivity at the same concentration.[65]

The stereochemistry of the anions of β-dicarbonyl compounds, and its relation to ion pairing phenomena has been extensively studied by NMR spectroscopy. Bacon *et al.*[66] examined the proton spectra of sodiomalondialdehyde in both D_2O and DMSO. The spectrum consists simply of a doublet and triplet with a coupling constant of 9.8–10.1 Hz. Since this value is typical of a *trans* coupling in these systems, it was concluded that, under the conditions of observation (room temp.), the EE conformer is is overwhelmingly populated. Very careful and much more extensive studies of β-ketoaldehydes have been made by Esakov, Petrov and Ershov *et al.*, while Raban and his colleagues have investigated the acetylacetone systems. Relevant data from these and other studies are assembled in Table 4. The Russian workers showed that the rates of isomerization about the 1,2 and 2,3 bonds in the enolate ion **6**, for example, differ widely. ($\Delta G^{\ddagger}_{1,2} = 16 \pm 1.6$; $\Delta G^{\ddagger}_{2,3} = 13 \pm 1.3$ kcal mole^{-1}).



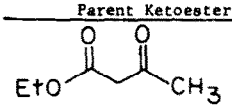
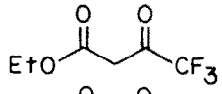
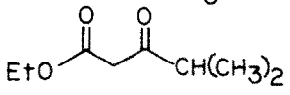
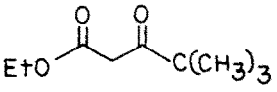
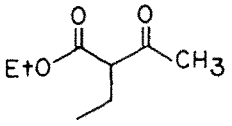
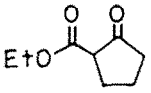
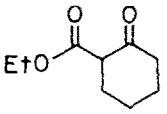
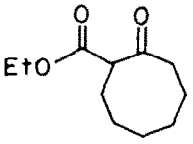
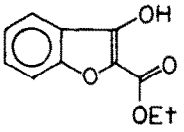
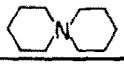
6

Both processes should probably be viewed as rotations about partial double bonds[71] although the 1,2 process, which is only observable when the amount of ZZ conformer is sufficient for detection, must also involve the making and breaking of the chelate ring. In practical terms, the NMR studies of the conformational equilibria require observations of spectra at low temperatures (< −50°). In the case of the aldehydes, the stereochemistry of the 1,2-bond is unequivocally established by the magnitude of J_{12}. The Russian workers were also able to assign the configuration of the 2,3-bond by measuring the homonuclear Overhauser enhancement of the olefinic protons associated with the irradiation of the 3-Me protons. Interestingly, this technique showed that, at room temperature, both the E(2,3) and Z(2,3) conformations of **6**, which are exchanging rapidly on the NMR time scale, are present since irradiation of the Me protons enhanced the absorptions of both olefinic protons.

In interpreting the data in Table 4, it has generally been assumed that, in the absence of compelling steric interactions, the Z,Z isomers only exist as ion pairs, chelation being necessary to offset the coulombic repulsions between the two O atoms. This conclusion is substantiated by the following observations. First, Na(acac) in methanol[53] and pyridine,[68] and the sodium enolates of β-ketoaldehydes in DMF[67] can be converted entirely to the E,E and/or E(1,2), Z(2,3) conformers by the addition of one equivalent of 18-crown-6. Secondly, the proportion of Z,Z-conformation can often be increased by the addition of a common alkali metal salt. Finally, the proportion of Z,Z conformer is sometimes decreased by dilution. In other systems, such as the salts of dibenzoyl- and dipivaloylmethane, adoption of the Z,Z configuration is a consequence of unfavorable steric interactions in the other conformers. As mentioned above, Arnett and dePalma[64] have shown that the potassium, cesium, and tetramethylammonium salts of dipivaloylmethane in DMSO are strongly dissociated, indicating that, in this system at least, the electrostatically unfavorable free Z,Z ion can exist.

The following conclusions can be drawn from the data in Table 4. For the three solvents studied, the ability to effect ion pair dissociation is in the order DMF < CH_3OH < H_2O. The tendency towards dissociation is

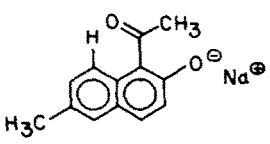
Table 3. Proton dissociation constants of β-ketoesters, derived from conductivity measurements

Structure of Parent Ketoester	M^+	Solvent	Temp	$10^3 K_{diss}$	Conc. Range ($X10^3$M)	Ref.
	Na	EtOH	25°	1.8-686	0.977-250	58
	Na	HMPT	20°	2.9-3.3	5.19-83.0	59,60
	K	HMPT	20°	7.1-8.4	5.14-82.3	59,60
	Cs	HMPT	20°	14.8-15.7	5.00-80.0	59,60
	Cs	HMPT	20°	2.2-3.4	5.00-80.0	60,61
	Cs	HMPT	20°	6.1-5.5	4.92-78.7	60,61
	Cs	HMPT	20°	0.08-0.11	4.19-77.0	60,61
	Na	DMSO	25°	1.0-12.6	0.237-47.4	62
	Na	HMPT	25°	2.3-23	0.255-51.0	62
	Na	DMSO	25°	0.29-0.15	0.250-50.0	62
	Na	DMSO	25°	0.18-0.077	0.250-51.1	62
	Na	DMSO	25°	0.14-0.040	0.251-50.3	62
	Li	MeOH	50°	3.4-5.6	0.801-280.9	63
	Na	MeOH	50°	19.5-27.4	0.469-93.80	63
	K	MeOH	50°	24.3-57.6	0.996-114.6	63
		MeOH	50°	15.4-147	0.206-115.7	63

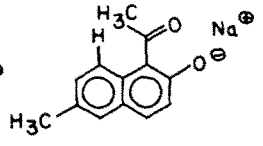
also in the expected order Li < Na < K. In the case of ketoaldehydes, $RCOCH_2CHO$, the nature of the substituent R evidently has little influence on the proportion of Z,Z conformer and hence on ion pair dissociation. Possibly there is a small effect when R = t-Bu due to the inability of this system to adopt the most stable E,E configuration. In other ketoaldehyde salts, there appears to be a fine balance between steric effects favoring the E(1,2), Z(2,3) configuration and electrostatic effects which favor the E,E configuration.

Several β-ketoesters are included in Table 4. Assignments in these systems are based on NOE studies.[70] In general, acetylacetone and ethyl acetoacetate salts exhibit a very similar tendency to form ion pairs, which is greater than that of ketoaldehyde salts. This is a result of the virtual absence, in the latter, of unfavorable steric interactions in the E,E conformer.

Phenolic aldehydes and ketones in which the hydroxyl function is *ortho* to the CO group yield anions which are formally very similar to those of β-dicarbonyl compounds. There is evidence from chemical shift data that both the Li and Na salts of salicylaldehyde are at least partially associated as ion pairs in DMSO.[72] An interesting example, viz. 1 - acetyl - 2 - hydroxy - 6 - methylnaphthalene sodium salt (**7**), has been studied by Bisanz and Bukowska.[73] The proton chemical shifts for **7** in D_2O and for the parent phenol in DMSO are very similar. In contrast, the *peri* H atom of **7** in DMSO is deshielded by 0.8 ppm. The preferred conformation in this latter system is clearly **7a** in which the CO group is expected to deshield the *peri* proton.[74] Evidently, the conformation **7b**, which is electrostatically less favor-



7a



7b

Table 4. ^{1}H NMR studies of the conformational equilibria of alkali metal salts of β-dicarbonyl compounds

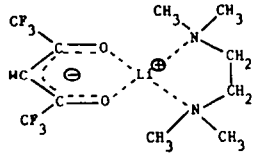
(RCOCHR"COR')						Relative percentages of conformers			Coupling Constants (Hz)			
R	R'	R"	Cation	Solvent	Temp (°C)	% ZZ	% EZ	% EE	ZZ	ZE	EE	Ref.
Me	H	H	Li	DMF	30	100	0	0	3.9	--	--	67
Me	H	H	Na	DMF	-60	55	(45)		3.8	10.4	9.9	67
Me	H	H	K	DMF	-60	0	(100)		--	10.4	9.8	67
Me	H	H	Li	MeOH	-60	36	13	51	4.2	10.4	10.7	67
Me	H	H	Na	MeOH	-60	0	80	20	--	10.5	10.7	67
Me	H	H	K	MeOH	-60	0	82	18	--	10.5	10.7	67
Et	H	H	Li	DMF	30	100	0	0	4.0	--	--	67
Et	H	H	Na	DMF	-30	60	40	0	3.9	10.5	--	67
Pr^i	H	H	Na	DMF	-30	60	40	0	3.8	10.4	--	67
Pr^i	H	H	K	DMF	-30	0	100	0	--	10.3	--	67
Bu^t	H	H	Li	DMF	30	100	0	0	4.0	--	--	67
Bu^t	H	H	Na	DMF	-30	65	35	0	4.0	10.0	--	67
Bu^t	H	H	K	DMF	-30	0	100	0	--	9.8	--	67
Bu^t	H	H	Li	MeOH	-60	52	48	0	4.4	10.2	--	67
Bu^t	H	H	Na	MeOH	-60	0	100	0	--	10.2	--	67
Bu^t	H	H	K	MeOH	-60	0	100	0	--	10.3	--	67
Ph	H	H	Li	DMF	30	100	0	0	3.9	--	--	67
Ph	H	H	Na	DMF	-30	60	40	0	3.8	9.7	--	67
Ph	H	H	K	DMF	-30	0	100	0	--	9.8	--	67
Ph	H	H	K	MeOH	-60	0	74	26	--	10.3	9.8	67
P-Anisyl	H	H	Li	MeOH	-60	30	56	14	4.2	10.0	10.2	67
P-Anisyl	H	H	Na	MeOH	-60	0	81	19	--	10.1	10.6	67
EtO	H	H	Na	DMF	-30	60	40	0	4.3	10.3	--	67
Me	Me	H	Na	Pyridine-d_5 [a]	-65 to -46	(100)		0		b		68
Me	Me	H	Li	MeOH-d_4	< -50	97-100	0	0-3		b		53
Me	Me	H	Na	MeOH-d_4	< -50	35	65	0		b		69
Me	Me	H	Me_4N	MeOH-d_4	-57	3-4	96-7	0		b		53
Bu^t	Bu^t	H	Li	DMSO	25	~100	0	0		b,c		64
Ph	Ph	H	Li	DMSO	25	~100	0	0		b,c		64
Me	OEt	H	Li	DMF	-50	100	0	0		b,d		70
Me	OEt	H	Na	DMF	-50	100	0	0		b,d		70
Me	OEt	H	K	DMF	-50	100	0	0		b,d		70
Me	OEt	H	Me_4N	DMF	-60	8	(92)			b,d		70
Me	OEt	H	Li	MeOH	-30	95	(5)			b,d		70
Me	OEt	H	Na	MeOH	-30	46	(54)			b,d		70
Me	OEt	H	K	MeOH	-30	30	(70)			b,d		70
Me	OEt	H	Me_4N	MeOH	-30	0	(100)			b,d		70
Me	OEt	Me	Na	DMF	-30	66	(34)			b,d		70
Me	OEt	Me	K	DMF	-30	0	(100)			b,d		70
Me	OEt	Me	Na	MeOH	-30	0	(100)			b,d		70
Me	OEt	Me	K	MeOH	-30	0	(100)			b,d		70

a. In the presence of 18-crown-6 polyether.
b. Determined by chemical shift.
c. Augmented by conductivity measurements.
d. Augmented by nuclear Overhauser effect (nOe).

able, in water is stabilized by a H-bonded bridge with the solvent. It is noteworthy that this phenomenon is not observed for the acetylacetonate ion in methanol[53,69] or the malondialdehyde ion in water.[66]

The electronic spectra of enolate ions provide some insight into their structures. Zaugg and Schaefer[16] have examined the UV spectra of alkali metal salts of β-dicarbonyl compounds and have been able to make certain inferences regarding ion pair formation. In particular, they conclude that the E,E (and presumably the E,Z) conformers are more highly dissociated than the Z,Z conformer. They also conclude that the Z,Z anions are less strongly involved in H-bonding in hydroxylic solvents than are the anions with the other two configurations.

Vibrational spectroscopy is potentially a valuable means of detecting cation-anion interactions. Although a number of studies have been reported,[51,64,75–86] there is still considerable uncertainty regarding assignments to O–Li stretching modes in the lithium enolates of β-dicarbonyl compounds. Possible reasons for this state of affairs are the complexity of solid state spectra, interference from solvent absorption in solution spectra, and the too infrequent use of Raman spectroscopy. Funck and Jungerman[75] have studied the IR spectra of the lithium enolates of several β-diketones and β-ketoesters and have used the shifts between ^{7}Li and ^{6}Li to identify metal-sensitive vibrations. They draw attention to the difficulty in analyzing the spectrum of crystalline Li(acac), which possesses three different LiO_4 tetrahedra and one square planar LiO_4. Shobatake and Nakamoto[51] have used the isotope shift to assign Li–O stretching frequencies in the complex **8** (in benzene) to absorptions at 544 and 527 cm^{-1}. Arnett and dePalma have identified cation (and anion) sensitive bands in the spectra of the alkali metal enolates of dipivaloyl- and dibenzoyl-methane in THF. The assignment of these bands to discrete vibrational modes was not attempted; nor are the states of aggregation of these salts in THF known.



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2.4 *Summary*

The picture which emerges from the preceding discussions is that, in all but very dilute solutions, enolate and phenoxide ions are to some extent ion-paired, although substantial concentrations of free ions are found in class C and D solvents. In this connection it is clear that conductivity measurements provide vital information. A tendency for these salts to aggregate is observed in class B and, strongly, in class A solvents. Colligative properties and ^{13}C spin-lattice relaxation times provide useful evidence of aggregation, but too few studies of this type have been performed. The analyses of NMR spectra in terms of stereochemistry, ion pairing and electron distribution have added materially to our understanding of the nature of these salts in solution, particularly in the case of the salts of β-dicarbonyl compounds.

We will see in Part 3 that the conclusions drawn from physicochemical studies form a reasonable basis for discussing the kinetics and structure-reactivity relationships for the reactions of alkali metal enolates.

3. REACTIVITIES OF ENOLATE IONS

Since our main objective in this review is to discuss the relation between the reactivities of enolate ions and their structures in solution, we will begin this section with a consideration of the effect of solvent on reactivity because the solvent plays a dominant role in defining the structures of the reactive species. We will then turn to consideration of other factors, such as the nature of the cation, structure of the electrophile and structure of the enols from which the salts are derived. We will also briefly consider two special types of reactions of enolate ions, *viz.* cycloalkylation and alkylations leading to the formation of a new chiral center.

3.1 *Solvent effects*

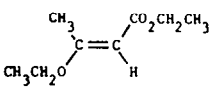
3.1.1 *Class C solvents.* We begin our discussion with class C solvents because, at least in some circumstances, the reactive form of the enolate in such solvents is unequivocally known. For several systems it has been demonstrated that alkylation proceeds through the intermediacy of the free enolate ion. A typical example is provided by the work of Reutov *et al.* in which the alkylation of the Na, K and Cs enolates of ethyl acetoacetate by ethyl toluenesulfonate in HMPT was studied.[59]

These reactions are first order in alkylating reagent but *less* than first order with respect to the enolate salt. This phenomenon is clearly a consequence of an equilibrium between free ions and some type of anion pair since the rate of alkylation is depressed by the common ion effect of added, inert alkali metal salts (e.g. $M^+ClO_4^-$, $M^+BPh_4^-$). The kinetics of such systems can be analyzed in terms of the Acree equation[87] (1)

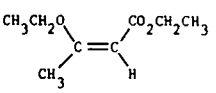
$$k_{obs} = k_i\alpha + k_{ip}(1-\alpha) \qquad (1)$$

in which k_i and k_{ip} are the rate constants for the reactions of free and paired ions, respectively, and α is the degree of dissociation of the ion pairs. The quantity α must be determined from conductivity measurements in the concentration range of interest. In the examples under consideration, the plots of $k_{obs}/(1-\alpha)$ vs $\alpha/(1-\alpha)$ were found to be linear and to pass through the origin, thus proving that alkylation of the free ions is the only significant pathway.

In agreement with the above conclusion, the C/O ratio (i.e. k_c/k_o, the ratio of the rates of carbon to oxygen alkylation) was found to be independent of the concentration of the enolate salt and the nature of the cation. Furthermore, only the "*trans*" enol ether **9a** is formed. This geometric isomer is derived from the EE (or EZ) conformation which, as we saw in Section 2.3, is characteristic of the free anion. Only in the presence of high concentrations of the common cation is there evidence for the ion pair pathway; thus, the addition of 10 equivs. of $NaClO_4$ to 0.0424 M sodium enolate in HMPT causes a change in the C/O ratio from 0.13 to 0.18.



9a



9b

HMPT is one of the best class C solvents. The cation solvating powers of DMSO and DMF are expected to be less. Arnett and dePalma[88] have applied the Acree equation to the reactions of methyl iodide with the alkali metal and Bu_4N^+ salts of dibenzoyl- and dipivaloylmethane in DMSO and have concluded that, with the exception of the lithium salt, the reactions proceed through the free enolate ion. On the other hand, the degree of dissociation is evidently smaller in DMF; so small in fact that the Acree equation can no longer be applied with confidence and alternative methods must be used to determine k_i and k_{ip}. Reutov *et al.*[89] have examined the reactions of Na, K and Cs enolates of ethyl acetoacetate with ethyl *p*-toluenesulfonate in this solvent and found that the C/O ratio as well as the observed rates varied with initial concentration of enolate. Furthermore, addition of 18-crown-6 ethers, which complex with these cations, effected a rate increase with a concomitant decrease in the C/O ratio. Since, in the presence of the crown ether, the K and Cs enolates give the same rate and C/O ratio, the values so obtained correspond to the limiting values for the free anion, i.e. to k_i and $[C/O]_i$. The rate constant, k_{ip}, for the reaction of the ion pair was then obtained using the method of Szwarc *et al.*[90] as follows.

$$K_{diss} = \alpha^2 C_o/(1-\alpha)$$

where K_{diss} is the dissociation constant and C_o the initial concentration of enolate salt. If $\alpha \ll 1$

$$\alpha = (K_{diss}/C_o)^{1/2}$$

and

$$k_{obs} = k_{ip} + (k_i - k_{ip})K_{diss}^{1/2} C_o^{-1/2}. \quad (2)$$

Since k_{obs} was found to be substantially less than k_i (determined from the crown ether experiments), the approximation $\alpha \ll 1$ is valid and k_{ip} is then found as the intercept of the plot of k_{obs} vs $1/\sqrt{C_o}$. Some pertinent data are given in Table 5. It is interesting that the reactivity of the potassium ion pair is only approximately 100 times less than that of the free ion. An important result is that $(C/O)_i < (C/O)_{ip}$.

The fact that a linear relation between k_{obs} and $1/\sqrt{C_o}$ was observed in the previous example indicates that the ion pairs are monomeric. It does not, however, permit a distinction between solvent separated and contact ion pairs. It has been shown[91] that the lithium enolate of ethyl acetoacetate in either HMPT or DMF gives substantial quantities of the "*cis*" enol ether **9b** which is expected if it is the chelated contact ion pair. However, the Na, K and Cs salts in DMF yield predominately the "*trans*" ether **9a** which indicates that the ion pairs involving the large cations in DMF have solvent separated structures.

Reutov *et al.*[92,93] have surveyed the rates of C- and O-alkylation of the free ethyl acetoacetate ion in a variety of class C solvents using the addition of dibenzo[18]crown-6 to the potassium salt to generate the free ion. Their results are summarized in Table 6. The rates do not vary greatly and appear to correlate better with the magnitude of the permanent dipole moment of the solvent than with its dielectric constant.

Although several studies of the kinetics of alkylation of phenols in class C solvents have been reported, they have not led to an unequivocal identification of the reactive ionic species. Table 7 gives the relative rates of reaction of sodium, potassium, and Bu_4N^+ phenoxides with n-butyl chloride.[10,95] At the concentrations of the phenoxides used, the potassium salt in DMF is ap-

Table 5. Rate constants ($\times 10^5$ l mol^{-1} sec^{-1}) for the reactive O- and C-centers in the alkylation of alkali metal salts of ethyl acetoacetate by ethyl tosylate in DMF AT 25°[89]

Cation	k_1	k_1^C	k_1^O	k_{1p}	k_{1p}^C	k_{1p}^O	C/O_1	C/O_{1p}
Na				11.7	4.5	7.2		0.625
	460	80	380				0.210	
K				5.0	2.8	2.2		1.27

Table 6. Rate constants (l mol^{-1} sec^{-1}) for O- and C-alkylation of the anion of ethyl acetoacetate by ethyl tosylate in various class C solvents at 25°C

Solvent	D (Dielectric Constant)	μ (Dipole Moment)	$10^3 k_1^O$	$10^3 k_1^C$	C/O
Acetonitrile	37.5	3.4	1.47	0.43	0.29
Dimethylsulfoxide	47	3.9	3.05	0.75	0.24
N,N-Dimethylformamide	37	3.9	3.8	0.8	0.22
Tetramethylenesulfone[a]	44	4.8	6.8	1.5	0.22
N,N-Dimethylacetamide	38	3.7	6.4	1.1	0.17
Tetramethylurea	23	3.5	14.8	2.2	0.15
N-Methylpyrrolidone	32	4.1	19.3	2.7	0.14
Hexamethylphosphoric triamide	30	4.3-5.5	24.3	3.2	0.13

a. At 30°.

Table 7. Relative rates of reaction of sodium, potassium and tetrabutylammonium phenoxides[a] with n-butyl chloride[b] in various solvents at 25°C[10,95]

Solvent	Cation	Relative Rate
THF	K	1.0
1:9 Acetonitrile/Dioxane	K	1.1
1:1 Acetonitrile/Dioxane	K	36
Acetonitrile	K	140
Acetonitrile	Bu_4N^c	960
DMF	Na	1000
1:9 Acetonitrile/Dioxane	Bu_4N^c	1200
1:1 Acetonitrile/Dioxane	Bu_4N^c	1700
DMSO	Na	1900
THF	Bu_4N^c	2100
Tetraglyme	K	2400
DMSO	K	3900
DMF	K	5200
DMF	Bu_4N^c	7400

a: [Phenoxide] = 0.0229 to 0.0250 M.
b: [Bu^nCl] = 0.100 M.
c: 0.0250 eq. $Bu_4N^+Cl^-$ added to the potassium salt, giving ~90% $K^+ \rightarrow Bu_4N^+$ exchange.

proximately 50% dissociated so that it is likely, although not proven, that these systems all involve reactions of the free anions and that the observed differences in rates simply reflect the degree of dissociation of the salts. Clearly, a more detailed kinetic analysis based on the Acree equation or on crown ether experiments are necessary to rule out the possible participation of ion pairs in these reactions.

Information concerning the nature of simple enolates in class C solvents is even more sparse. Zook and Miller[96] have determined the C/O ratios for the alkylation of the alkali metal enolates of alkyl phenyl ketones by alkyl halides in DMSO and some of their data are presented in Table 8. It is seen that these ratios are essentially cation independent, indicating that these reactions proceed via the free anions.

3.1.2 *Class D solvents.* An additional complication arises in studies of protic solvent systems, namely the possible kinetic interference from the acid-base equilibria of the type

$$\text{Enol}^- + \text{ROH} \rightleftharpoons \text{Enol} + \text{RO}^-.$$

Whether this equilibrium will affect the rate of consumption of base by the alkylating agent will depend not only on the equilibrium constant but also on the relative rates of reaction of the two anions with the alkylating agent. Rhoads and Decora[97] have pointed out that a simple test for interference from this source can be made by varying the concentration of the β-dicarbonyl compound while maintaining the concentration of M^+OR^- and alkylating reagent constant. Any variation in the observed second order rate constant then indicates reaction with the solvent anion, RO^-. In the examples which will now be discussed, the pK_a of the β-dicarbonyl compound is far too low, relative to that of the solvent, for interference of this type to occur.

Brändström[98] has shown that the rates of reaction of the enolate ion of ethyl acetoacetate in both methanol and t-butanol are cation dependent and that the reaction of methyl iodide with the sodium enolate in ethanol exhibits a common ion (Na^+) rate depression on the addition of sodium iodide. A detailed analysis,[58] based on the Acree equation showed that, in ethanol, the reaction involves both the free enolate and its ion pair (Table 9). Indeed, for the sodium and potassium salts the

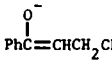
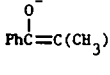
Table 9. Rate constants ($\times 10^3$ l mol^{-1} sec^{-1}) for the methylation by methyl iodide of the alkali metal enolates of ethyl acetoacetate in ethanol at 25°C[58]

Cation	k_1	k_{1p}
Li	(2.0)[a]	0.22
Na	2.0	1.4
K	2.0	1.7

a: Assumed.

two pathways have very similar rates. Analogous experiments with ethyl β-hydroxycoumarilate, **10** in methanol gave similar results (Table 10).[99] This study included the bispiperidinium (**11**) salt for which the rates of reaction of the ion pair to yield the C- and O-methyl derivatives actually exceeded both the corresponding

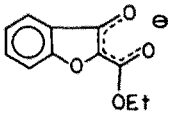
Table 8. C/O[a] ratios for the reactions of two enolate ions with alkyl halides in DMSO at 30°C[96]

Enolate Ion	M^+	C/O Ratios		
		n-Amyl Chloride	i-Butyl Chloride	n-Amyl Iodide
	Li	0.77	1.9	5.0
	Na	0.83	1.9	4.3
	Cs	0.77	---	---
	Li	0.45	1.4	---
	Na	0.48	1.5	---

a: Refers to k^C/k^O.

Table 10. Rate constants ($\times 10^4$ l mol^{-1} sec^{-1}) and C/O ratios for the reactions of alkali metal salts of ethyl β-hydroxycoumarilate with methyl iodide in methanol at 50°C[99]

	C-alkylation		O-alkylation			
Cation	k_1	k_{ip}	k_1	k_{ip}	k_{ip}^C/k_{ip}^O	k_1^C/k_1^O
Li	6.0	0.50	0.97	0.10	5.0	6.2
Na	5.5	2.7	0.97	1.3	2.1	5.7
K	5.8	3.3	0.97	1.3	2.6	6.0
Bispiperidinium (11)	5.5	13	0.88	3.2	4.1	6.2



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rates of reactions of the free enolate ion. The data in Table 11 reveals modest sensitivities of the rates and C/O ratios for the lithium enolate to the structure of the alcoholic solvent.

Simultaneous involvement of the phenoxide ion and its ion pairs with Li^+, Na^+ and K^+ has also been established. Indeed, this system was one of a number which constituted the classic studies by Acree. Schroder and Acree[87] used the rate data of Segaller[100] and the conductivity data of Robertson and Acree[11] to derive k_i and k_{ip} for the reactions with methyl, ethyl and n-propyl iodides (Table 12). The partitioning of the reaction between the two pathways is similar to that observed for ethyl acetoacetate under comparable conditions.

Table 11. Rate constants ($\times 10^5$ l mol^{-1} sec^{-1}) and C/O ratios for the reactions in various alcohols of the lithium salt[a] of ethyl β-hydroxycoumarilate with methyl iodide at 50°C[99]

Solvent	k^C	k^O	k^C/k^O
MeOH	17	2.8	6.0
EtOH	13	2.2	5.8
n-PrOH	7.3	1.7	4.4
n-BuOH	4.5	~1.5	~3.0

a: [Lithium enolate] ≃ 0.1 M.

Table 12. Rate constants ($\times 10^5$ l mol^{-1} sec^{-1}) for the reactions of alkali metal salts of phenol with alkyl iodides in ethanol at 25°C[87,100,11]

	Methyl Iodide		Ethyl Iodide	
Cation	k_1	k_{ip}	k_1	k_{ip}
Li	47.8	6.55	8.90	1.52
Na	47.0	7.95	9.18	1.64
K	47.2	6.17	8.63	1.68

Enolate salts of simple aldehydes and ketones in class D solvents have not been studied. These systems are, of course, severely complicated by the fact that the pK_a's of the ketones usually are much higher than those of the solvents. Furthermore, in many cases (e.g. $R^1R^2CHCOCHR^3R^4$) equilibration of the two possible enolates will occur.

The comparable magnitudes of the rate constants k_i and k_{ip} in class D solvents is attributed to a reduction of the reactivity of the "free" anion by hydrogen bonding with the solvent. According to Parker *et al.*,[101] phenoxide ions are powerful H-bond acceptors and the same is almost certainly true of the enols of mono- and dicarbonyl compounds.

3.1.3 *Class B solvents.* These solvents can solvate cations to varying extents, but, in general, their low dielectric constants will tend to favor some degree of aggregation. Arnett, Ko and Chao[102] have measured "observed" heats of solvation of the sodium cation by a wide variety of class B solvents. It is believed that these quantities, some of which are assembled in Table 13, provide a "rough qualitative guide" to the cation solvating power of class B solvents.

The observed rate constant for the reaction of the

Table 13. Heats of solvation (kcal/mol) of sodium cation[a] by various class B solvents at 25°C[102]

Solvent	ΔH_{obs}
Trimethoxymethane	-0.02 ± 0.01
1,3,5-Trioxane	-0.04 ± 0.06
1,4-Dioxane	-0.06 ± 0.003
THF	-0.08 ± 0.007
1,3-Dioxolane	-0.08 ± 0.003
1,2-Dimethoxypropane	-0.21 ± 0.012
1,2,3-Trimethoxypropane	-0.26 ± 0.01
DME (glyme)	-0.45 ± 0.02
Diglyme	-0.83 ± 0.03
Triglyme	-2.58 ± 0.05
Tetraglyme	-4.82 ± 0.06
Dicyclohexyl-18-crown-6 ether	-5.99 ± 0.36
Pentaglyme	-6.09 ± 0.08

a: Solutions of $Na^+BPh_4^-$ in acetone were used.

potassium enolate of ethyl acetoacetate with ethyl tosylate in dioxane is less than 10^{-7} l mol^{-1} sec^{-1} [103] compared with 1.8×10^{-2} for the free ion in HMPT.[59] This appears to be a consequence of aggregation because the addition of 18-crown-6 greatly accelerates the reaction and, furthermore, the tetraphenylarsonium salt, which presumably forms monomeric contact ion pairs in dioxane reacts with a rate constant of 7.2×10^{-3} l mole^{-1} sec^{-1}. The addition of crown ethers does not eliminate the cation dependence of the observed rates, C/O ratios, and O-*cis*/O-*trans* ratios (Table 14), which demonstrates that contact ion pairs still occur in the presence of the crown ethers. The observed decrease in the O-*cis*/O-*trans* ratio with increasing cation radius may, however, indicate that these contact ion pairs eventually become so weak as to resemble solvent-separated ion pairs. The nature of the aggregates which exist in dioxane in the absence of crown ethers is unknown.

A study of the C/O ratios and approximate rates for the reaction of sodioacetylacetone with alkyl iodides in THF containing varying amounts of tetraglyme has been interpreted as indicating the existence of various types of monomeric ion pairs.[104] Thus it is suggested that small quantities of the glyme give an intimate ion pair with the cation exteriorly solvated by tetraglyme rather than THF (as in the pure solvent). It is probable, however, that the species in pure THF is an aggregate. It has been shown[105] that the sodium enolate of ethyl acetoacetate reacts with ethyl tosylate in THF to give a low yield of enol ethers (C/O = 9) consisting mainly (> 90%) of the *cis* isomer. Such behavior is characteristic of a chelated ZZ conformation. Cation complexation with 18-crown-6 changes this product distribution so that 15% of the *cis* isomer is formed; however, with [2.2.2] cryptate, high yields of exclusively the *trans* enol ether are obtained. This latter result is very similar to that described above for dioxane and is again characteristic of solvent-separated or very weakly interacting solvent-separated ion pairs.

Bram *et al.*[106] have made a detailed study of the alkylation of the enolates of ethyl acetoacetate in DME and have been able to draw some interesting conclusions regarding the species involved. The data for the effect of concentration and added common ion salt, given in Table 15, is interpreted in terms of aggregation of the potassium enolate as set out in the following scheme.

Table 14. Rate constants ($\times 10^5$ mol^{-1} sec^{-1}) for the reactions of ion pairs of ethyl acetoacetate salts with ethyl tosylate in the presence of dicyclohexyl-18-crown-6[a] in dioxane at 25°C[103]

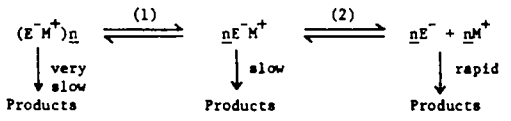
Cation	Radius (Å)	k_{obs}	k_{ip}^{c}	k_{ip}^{o}	k_{ip}^{c}/k_{ip}^{o}	O-cis/O-trans
Na	0.97	6.3	4.4	1.9	2.3	0.60
K	1.33	27	16.0	11.0	1.4	0.43
Rb	1.48	44	23.0	21.0	1.1	0.43
Cs	1.69	93	45.5	47.5	0.95	0.12
Ph_4As	4.30	720	160	560	0.29	0.00
Free Anion	∞	2600[b]	--	--	--	--

a: Sufficient crown ether was added such that on further addition the observed rate constant did not change.
b: Obtained by extrapolation to $r_i = \infty$ in the plot of log k_{obs} vs. $1/r_i$, where r_i = radius of the cation.

Table 15. Effects of concentration and added $KBPh_4$ on the alkylation of the potassium enolate of ethyl acetoacetate in 1,2-dimethoxyethane at 40°C[106]

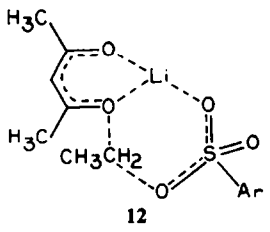
Alkylating Reagent	[Enolate], M	[$KBPh_4$], M	10^4 k_{obs} ($\ell \cdot mol^{-1} \cdot sec^{-1}$)	k^c/k^o	O-cis / O-trans
	0.05	--	42.5	--	--
CH_3CH_2I	0.10	--	32.3	--	--
	0.10	0.025	35.0	--	--
	0.05	--	2.30	41	~1
CH_3CH_2Br	0.10	--	1.50	39	~1
	0.10	0.025	1.68	53	a
	0.05	--	1.14	4.7	0.9
CH_3CH_2OTs	0.10	--	0.853	5.4	1.0
	0.10	0.025	0.950	6.0	1.3

a: "mostly cis".



While the effect of increasing concentration can be interpreted in terms of displacement to the left of either or both the equilibria (1) and (2), the common ion salt effect rules out free ions and the equilibrium (2) as the only kinetically significant factors. The *increase* in rate produced by the common ion salt is attributed to a secondary (ionic strength) salt effect which displaces equilibrium (1) to the right (i.e. deaggregation[107]). The effect of the addition of a common cation salt on the equilibrium (2) should be to decrease the concentration of free enolate ion. This in turn should decrease the O-*cis*/O-*trans* and C/O ratios as observed and should increase the overall rate of reaction. This is *not* observed. As discussed in Section 2.3, $LiClO_4$ forms a 1:1 complex with Li(acac) and so it is possible that, in the present case, the addition of the potassium ion changes the structure of the aggregate. Clearly, this system merits further investigation.

The studies by the French workers[106] produced another interesting result. It is expected that the "tightness" of ion pairing (either as monomers or aggregates) will be greatest for Li^+, the smallest alkali metal cation, and will decrease monotonically with increasing ionic radius of the cation. This trend is certainly exhibited by the rates of alkylation given in Table 16. Furthermore, the O-*cis*/O-*trans* ratios also follow the predicted order, it being expected that the tightest ion pairing will involve the chelated ZZ conformation. Generally (see below) the tightness of ion pairing is also reflected in the C/O ratio because strong involvement of the O atoms in chelation directs alkylation towards the C atom. This last prediction is fulfilled by the C/O ratios found for alkylation by ethyl bromide and iodide (Table 16). In the alkylation by ethyl tosylate, however, the C/O ratio for the lithium salt is clearly anomolous lying as it does between the values for the potassium and cesium salts. Bram *et al.* suggest that in this system, the Li^+ may provide electrophilic assistance for the ionization of the tosylate ion. The appropriate 6-membered transition state **12** would then favor O-alkylation but, since the chelate ion pair (or its aggregate) is involved, the resulting enol ether would have the "*cis*" configuration. Electrophilic assistance in the alkylation of enolate salts had previously been considered by Brändström[107] and by Kurts and Beletskaya,[108] but the results just presented may provide the first direct evidence for its occurrence. Since the natures of the aggregates are not known, however, the possibility exists that the anomolous result for the lithium salt reflects a change in structure of the aggregate rather than electrophilic catalysis. Further work in this area is badly needed.



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Several studies of the influence of class B solvents on the reactivities of sodium and potassium phenoxide with several electrophiles have been reported[9,95,109] and some representative data are presented in Table 17.

That the structure of the aggregate influences the course of alkylation is borne out by a study of the reactions of lithioisobutyrophenone in class B solvents. In Section 2.2, evidence concerning the structures of aggregates of this salt was presented. In dioxolane, for instance, the tetramer **4** exists and the following evidence suggests that this is the kinetically significant species in alkylation reactions.[55] It is known that the rate controlling step in the exchange of the enolate between the tetramer and its "ate" complex $Li_4Cl(Enolate)_3$ is dis-

Table 17. Relative rates of reactions of alkali metal phenoxides with n-butyl bromide at 25°C[95,109]

	Relative rates	
Solvent	K^+	Na^+
Dioxane	0.06	--
THF	1.0	1.0
1,2-Dimethoxyethane	8.1	7.7
Diglyme	75	100
Tetraglyme	938	860

Table 16. Rate constants ($\times 10^4$ l mol^{-1} sec^{-1}) and product ratios for the ethylation of salts of ethyl acetoacetate in 1,2-dimethoxyethane at 40°C[106]

	CH_3CH_2OTs			CH_3CH_2Br		CH_3CH_2I	
Cation	k_{obs}	C/O	O-cis/O-trans	k_{obs}	C/O	k_{obs}	C/O
Li	0.0050	2.2	> 20	0.011	73	0.266	> 100
Na	0.38	6.0	6	0.67	60	16	> 100
K	1.1	4.7	0.9	2.3	41	42.5	> 100
Cs	--	1.7	0.3	--	10.3	--	43
NBu_4	180	0.26	a	510	2.9	5420	8.4

a: Traces of O-cis.

sociation of the latter.[26] Therefore, the addition of lithium chloride to the enolate will reduce the concentrations of less aggregated species as well as depressing their rates of formation from the tetrameric species. Added lithium chloride, however, causes a slight *increase* in the rates of alkylation in dioxolane by both dimethyl sulfate (Table 18) and methyl iodide.[55]

Table 18. Data for the methylation of lithioisobutyrophenone (0.16 M) by dimethyl sulfate in two class B solvents[55]

	1,3-Dioxolane			1,2-Dimethoxyethane		
Additive	Temp. (°C)	Half-life (min)	C/O[a]	Temp. (°C)	Half-life (min)	C/O[a]
--	40	10	0.79	40	1	1.6
--	50	8	0.72	--	--	--
LiCl[b]	50	5	1.0	--	--	--
15-Crown-5[c]	43	< 1	0.39	--	--	--
12-Crown-4[c]	46	< 1	0.25	42	< 1	0.39
HMPT[d]	32	<< 1	0.15	46	<< 1	0.19

a: Product ratio.
b: 1.2 equivalents.
c: 1 equivalent.
d: 4 equivalents.

In Section 2, it was shown that two tetrameric species of lithioisobutyrophenone exist in dioxolane. These are characterized by the chemical shift differences between the two Me groups, and their relative concentrations vary with temperature. These two species undergo alkylation with dimethyl sulfate at similar rates but with different C/O ratios. Thus the observed chemical shift differences ($\Delta\delta$) between the pair of nonequivalent Me groups correlates well with the C/O ratio obtained over the temperature range in which the two species coexist (Fig. 5). Had the two species reacted at very different rates no change in the C/O ratio would have been observed since the products would have always been derived from the more reactive species.

As expected, the rate of alkylation of lithioisobutyrophenone by dimethyl sulfate in DME is greater (approx. 10 times) than in dioxolane. Surprisingly, however, the C/O ratio is also greater in the former solvent. Generally, the opposite result is observed, i.e. the better cation solvating solvent leads to more O-alkylation. This result suggests that steric arrangements of aggregates, as well as electron distribution in the ambident anion, may be important in controlling the orientation in reactions in which aggregates are the reacting species. The addition of crown ethers or HMPT (4 equiv. per Li^+) to solutions in either dioxolane or DME produces the expected increases in overall reactivity and in the extent of O-alkylation. These results are summarized in Table 18. In contrast to the above observations, Zook *et al.*[24] have shown that the corresponding sodium enolate gives the expected decrease in the C/O ratio when the solvent for alkylation by n-propyl bromide is changed from diethyl ether (> 50) to DME (4.0) or diglyme (3.7).

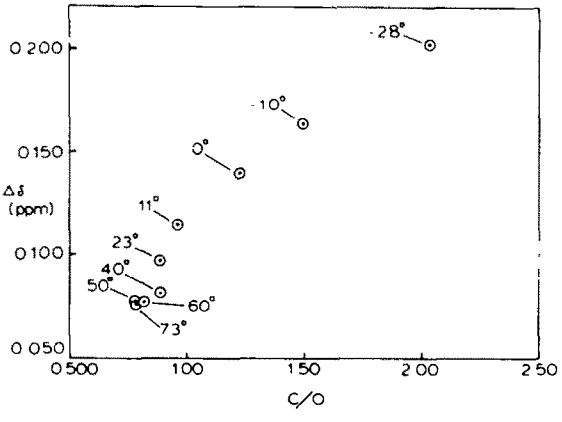


Fig. 5. Plot of $\Delta\delta$ (difference between ^1H chemical shifts of the two methyl groups of lithioisobutyrophenone in 1,3-dioxolane at the indicated temperature, °C) vs the C/O ratio for alkylation of lithioisobutyrophenone by dimethyl sulfate in 1,3-dioxolane at that temperature.[26,55]

3.1.4 *Class A solvents.* The investigations by Zaugg *et al.* have shown that diethyl sodio-(1-methylbutyl)malonate forms micelles in benzene and cyclohexane (Section 2.3). Under these conditions, alkylation by ethyl bromide proceeds smoothly although the reaction involves complex kinetics.[49] The alkylation is catalyzed by the addition of small quantities of good cation solvating solvents such as DMF and HMPT, the implication being that these solvents break down the micelles to smaller aggregates, possibly even to monomeric contact ion pairs. The addition of quaternary ammonium ions also accelerates these reactions so that phase transfer catalysts may be used to effect alkylations in class A solvents.[110–113]

Phenoxides have been alkylated in class A solvents. Thus Claisen *et al.*[114] showed that, whereas in ethanol or acetone sodium phenoxide and allyl chloride yield the O-allyl ether, in benzene *o*-allylphenol is obtained. Kornblum and Lurie,[115] however, have shown that the reaction leading to the C-alkylated product occurs heterogeneously. As the reaction proceeds, the phenoxide salt goes into solution in which state it undergoes exclusive O-alkylation. They make the point that O-alkyl attack on the crystalline salt cannot occur.

House *et al.*[5] found that the lithium salts of 4-t-butylcyclohexanone and α-tetralone give large C/O ratios when alkylated with trialkyloxonium salts in methylene chloride. Normally these reagents are expected

to favor O-alkylation (Section 3.3) and it is possible that in methylene chloride the enolate salts are extensively aggregated, perhaps even to the extent of forming micelles.

3.2.5 *Summary.* Reactions of all three types of ambident anions in class C solvents are well understood. For the large cations, at least, the principal and often exclusive reaction path involves the free anion. These conditions will afford the highest yields of O-alkylated product for a given alkylating reagent and cation. Some solvents, such as acetone and acetonitrile, may be borderline between classes B and C and further experiments are required to delineate their behavior.

In class D solvents, the reactivity of the free enolate ion, which is hydrogen bonded to the solvent, is comparable with that of the ion pair, both giving similar C/O ratios which are substantially greater than for the free ions in class C solvents.

Conditions for exclusive C-alkylation are best found in class B solvents or in heterogeneous reactions in class A solvents. In the former, the salts, particularly those involving lithium, tend to be strongly aggregated so that with suitable alkylating agents (Section 3.4) high yields of C-alkylated products result. Class B solvents also have the advantage of reducing the degree of dialkylated products which can arise if the rates of alkylation and proton transfer are comparable (see Section 3.6).

It should be stressed that the nature of the aggregates formed in class B solvents can influence reactivity, particularly the C/O ratio. The structures of these aggregates and their relation to the structure of the constituent enolate ion is very imperfectly understood. This area thus constitutes an important direction for further investigation. The role of electrophilic assistance by the cation requires confirmation and further clarification. The occurrence of such ordered transition states might, if properly understood, lead to the development of stereospecific as well as regiospecific alkylations.

3.2 *Cation effects*

With the realization that the overall reactivity in general, and the rate of O-alkylation in particular, is a function of the strength of the interaction between the cation and anion, the role of the cation becomes relatively easy to understand. For simple contact ion pairs, the reactivity is expected to be a function of the ionic radius, r_i, of the cation. This type of relation is well illustrated by the results of the study of the alkylation of the enolates of ethyl acetoacetate in dioxane containing sufficient quantities of dicyclohexyl-18-crown-6 to complex the cations.[103] Under these conditions monomeric contact ion pairs predominate and good linear relations between log k_{obs} and $1/r_i$ (Fig. 6) and log C/O and $1/r_i$ (Fig. 7) are observed. Good linear relations of this type are not expected under conditions which favor aggregation. Bram *et al.*[105] have, in fact, observed marked deviations from linearity for both C- and O-alkylation of the salts of ethyl acetoacetate in dimethoxyethane.

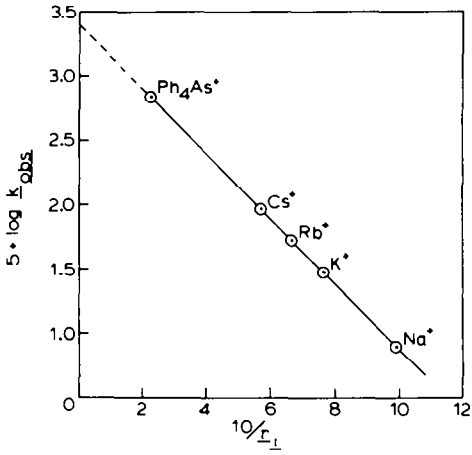


Fig. 6. Correlation between the observed rate constant for the ethylation (in dioxane at 25°C by ethyl tosylate) of ion pairs[a] of ethyl acetoacetate salts with the reciprocal crystallographic radius of the cation.[103]

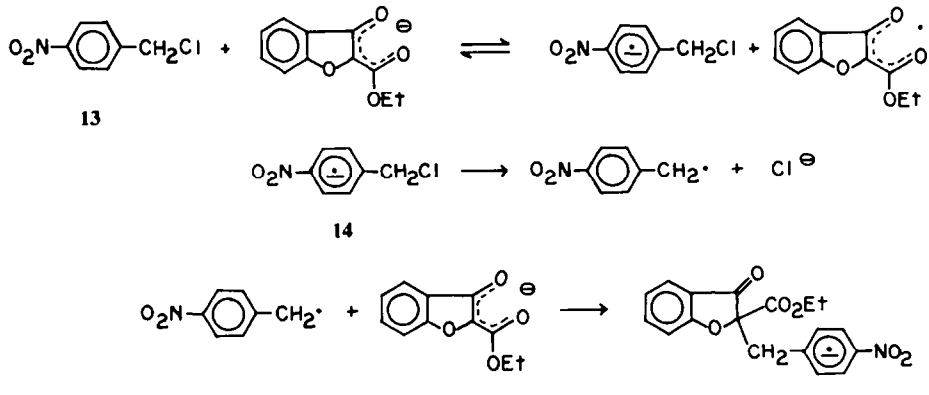
[a]In the presence of dicyclohexyl-18-crown-6.

The size of the cation also parallels the degree of dissociation into free ions (Table 3), a fact which is useful in designing conditions for exclusive O-alkylation in class C solvents.

Thus, in general, the use of large cations in all solvents will favor O-alkylation. The principal exceptions will be those cases involving lithium cations and tosyl or sulfate leaving groups for which, in class B solvents, it is possible that electrophilic assistance directs alkylation towards the O-terminus of the ambident anion.

3.3 *The alkylating reagent*

The alkylation reaction may involve any of three mechanisms, *viz.* electron transfer, S_n1 or S_n2. The elec-



13 + 15 → 14 + Product

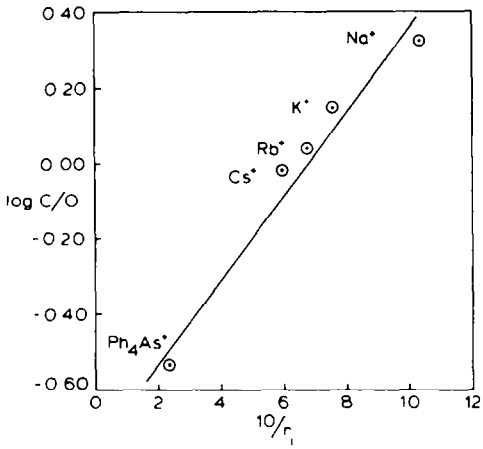
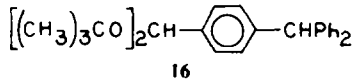


Fig. 7. Plot of $\log(k_{ip}^{C}/k_{ip}^{O})$ vs $10/r_i$ (r_i = radius of cation) for the reaction of ion pairs[a] of ethyl acetoacetate salts with ethyl tosylate in dioxane at 25°.[103]

[a] In the presence of dicyclohexyl-18-crown-6.

tron transfer process only operates in systems in which the alkylating agent can lead to a well-stabilized radical anion. This mechanism has been demonstrated for reactions of *p*-nitrobenzyl chloride,[116,117] and involves the chain process in which **13**, **14** and **15** are shown. The chain mechanism is characterized by a much higher C/O ratio than found for the S_n2 process. Thus, the above reaction in DMF gives C/O = 45 in contrast to 0.8 found for the analogous reactions of benzyl and *m*-nitrobenzyl chlorides. The reactions of the three corresponding iodides have identical C/O ratios (approx. 4) so with *p*-nitrobenzyl iodide the radical mechanism evidently cannot compete with the S_n2 process. The addition of traces of cupric salts inhibits the chain process and the reactions then exhibit C/O ratios characteristic of the ionic mechanism. These and similar substitution reactions which proceed *via* radical anion intermediates have been reviewed by Kornblum.[16c]

The involvement of the S_n1 mechanism in the alkylation of enolate ions is rare. t-Alkyl derivatives, which must necessarily react by this pathway, usually undergo the E_1 elimination with ease and yields of substitution products are very low. For example, the reaction of t-butyl chloride with sodio diethyl malonate in ethanol gave 6% C-alkylated product, no detectable enol ether and large amounts of isobutylene.[118] Triphenylmethyl halides react with sodiodipivalomethane in DMF and DMF/benzene mixtures to give predominantly C-alkylation. This reaction, however, involves aromatic substitution, the major product being **16**. The small amount



16

of O-alkylation which occurs results in the formation of the trityl ether. The overall reaction is unaffected by cupric chloride and therefore does not involve the electron transfer mechanism.[119] Tritylation of sodium phenoxide[120] and 2-naphthoxide[121] yield mainly C-alkyl products although the structures of the products were not rigorously established. Tris(*p*-nitrophenyl)methyl chloride reacts to give exclusively O-alkylation.

The overwhelming majority of alkylation reactions of enolate and phenoxide ions proceed by the S_n2 mechanism. Hard evidence for the bimolecular pathway has been obtained from those studies in which a first-order dependence on the enolate ion or ion pair has been demonstrated (Section 2.1.1). Hart and Eleuterio[122] have also shown that C-alkylation of the phenoxide ion by optically active α-phenylethyl chloride takes place with inversion of configuration.

Before analyzing the role of the alkylating reagent in the S_n2 reactions of enolate and phenoxide ions, it is important to realize that certain powerful alkylating agents may react rapidly with solvent in which case the active reagent will be the solvent conjugate. For example, it is known that reagents such as methyl fluorosulfonate, methyl trifluoromethylsulfonate and trimethyloxonium fluoroborate will transfer the Me cation to class C solvents such as HMPT, DMSO and DMF.[123] Arnett[88] has found that the alkylation of β-diketonates in DMSO by dimethyl sulfate does indeed involve $(CH_3)_2SO^+CH_3$.

The most important unifying concept for rationalizing C/O ratios in terms of the structure of the alkylating reagent is the symbiotic effect embodied in Pearson's theory of hard and soft acids and bases (HSAB theory).[124] In essence, the symbiotic effect is the tendency for similar groups (for example, all "hard" groups) to be attached to the same central atom. In the context of the S_n2 reaction, this hypothesis requires that replacement of a "hard" leaving group will occur more readily with a "hard" than a "soft" nucleophile. Since the O-terminus of the ambident enolate ion is "harder" than its C-terminus, low C/O ratios will be favored by alkylating agents, the leaving groups of which correspond to "hard" bases. For example, it is predicted that O-alkylation by alkyl halides will be favored in the order RI < RBr < RCl. Superimposed upon the intrinsic reactivity (HSAB effect) associated with the "hardness" or "softness" of the electrophile will be a variety of effects associated with steric hindrance, electrophilic assistance, and the encumbrance of the O-terminus by the cation or by hydrogen bonding. In order to isolate the HSAB effect, we will first consider the relation between C/O ratios and leaving groups in reactions in which the nucleophile is the free anion.

Table 19 summarizes data for reactions of a variety of

Table 19. Product ratio $(C/O)_{RX}/(C/O)_{ROTs}$ for sodium acetylacetonate and potassium ethyl acetoacetate alkylation reactions[126]

X	Me	Et	i-Pr	sec-Bu
	Sodium Acetylacetonate			
OTs	1	1	1	1
Cl	--	5.5	1.7	1.1
Br	230	12.5	2.6	1.3
I	~1000	45	6.1	3.6
	Potassium Ethyl Acetoacetate			
OTs	1	1	1	1
Cl	--	5.3	1.2	1.0
Br	50	13	2.4	1.7
I	160	53	8	5

alkylating reagents with the salts of acetylacetone and ethyl acetoacetate in HMPT, systems which are known (see Section 3.1.1) to react through the free anion. It is clear that the influence of the leaving group is indeed explicable in terms of the symbiotic effect so that the greatest degree of O-alkylation occurs with the relatively "hard" tosyl group. A more extensive collection of data supporting this thesis is presented in Table 20. The yields of dialkylated products are seen to increase with the softness of the groups attached to the reaction center of the nucleophile. Thus, allyl iodide reacts with sodioacetylacetonate and ethyl potassioacetoacetate to give exclusively C-alkylated products, the bulk of which are the diallyl derivatives.

Whereas the symbiotic effect explains the influence of the leaving group on C/O ratios, it appears to be but one of several factors governing the role of other substituents on the C atom undergoing substitution. In some situations the symbiotic effect appears dominant as illustrated in the representative examples given in Table 21. The effects of alkyl substituents, which have been the subject of several investigations,[126,128,129] appear to involve an interplay between steric and electronic (HSAB) effects. That attack by the oxygen terminus of the free

Table 20. The effect of the leaving group on product distributions for the methylation and ethylation of ethyl acetoacetate in HMPT

		Relative Yield (%)				
Alkylating Reagent	Cation	O	C	C,C	C/O[a]	Ref.
		Methylation				
CH_3I	K	5	31	64	19	125[b]
CH_3Br	K	14	42	44	6.1	125[b]
$(CH_3O)_2SO$	Na	61	37	2	0.64	125[b]
CH_3OTs	K	89	7	4	0.12	125[b]
		Ethylation				
CH_3CH_2I	K	13	71	16	6.7	126[c]
CH_3CH_2Br	K	39	38	23	1.6	126[c]
CH_3CH_2Cl	K	60	32	8	0.67	126[c]
$(CH_3CH_2)_3O^+BF_4^-$	K	71	18	11	0.41	127[c]
$(CH_3CH_2O)_2SO_2$	Cs	81	19	< 1	0.23	127[c]
$(CH_3CH_2O)_2SO_2$	K	83	15	2	0.20	127[c]
CH_3CH_2OTs	K	88	11	1	0.14	126[c]

a: C/O = (C + C,C)/O.
b: at 50°C.
c: at 20°C.

Table 21. Effect of alkylating reagent substituents on the products obtained from the reactions of alkyl chlorides with the potassium enolate of ethyl acetoacetate in HMPT

	Relative Yield (%)				
Alkyl Chloride	O	C	C,C	C/O	Ref.
CH_3OCH_2Cl[a]	100	0	0	0.0	126
$(CH_3)_2CHCl$[b]	81	19	0	0.23	128
$CH_3CH_2CH_2Cl$[b]	61	23	16[c]	0.64	128
Ph_2CHCl[b]	39	61	0	1.6	128
$CH_2{=}CH{-}CH_2Cl$[d]	17	45	38	4.9	126
$PhCH_2Cl$[b]	13	51	36	6.7	128

a: at 45°C.
b: at 100°C.
c: 8% C,C; 8% O,C.
d: at 20°C.

enolate ion is less sterically demanding than attack by the carbon terminus is established by the observation[128] that neopentyl chloride alkylates exclusively on oxygen. The surprisingly high degree of O-alkylation by the very soft electrophile, benzhydryl chloride (Table 21) is also doubtless due to steric effects. The data for several series of alkyl derivatives in Table 22 reveal that the

Table 22. The effect of structure of the alkylating reagent on the C/O ratios for the alkylation of sodioacetylacetone and the potassium enolate of ethyl acetoacetate in HMPT. The results are expressed as $(C/O)_{CH_3X}/(C/O)_{RX}$; large numbers correspond to increased O-alkylation[126]

X	Me	Et	i-Pr	sec-Bu
		Sodium Acetylacetonate		
I	1	7	35	57
Br	1	5	16	30
OTs	1	0.28	0.19	0.18
		Potassium Ethyl Acetoacetate		
I	1	3	13	26
Br	1	3.8	13	21
OTs	1	1	0.66	0.78

effect of alkyl substitution depends on the nature of the leaving group, in the sense that O-alkylation is favored in the order $CH_3- > CH_3CH_2- > (CH_3)_2CH-$ for the tosyl leaving group but in reverse order for halogen leaving groups. Pearson[124] has assigned $CH_3- > CH_3CH_2- > (CH_3)_2CH- > (CH_3)_3C-$ as the order of decreasing hardness. On the other hand, the opposite order is frequently found for electron donation to an electron deficient center such as a carbonium ion. In addition, steric effects, to which S_n2 reactions are rather sensitive, will increase with the number of alkyl groups at the reaction center. Reutov and his colleagues[126] have suggested that HSAB effects are unimportant for alkyl groups in S_n2 reactions and the observed results simply reflect the opposing influences of steric and electron donating effects, with the latter prevailing in the case of the tosyl leaving group.

The above conclusions apply to the reactions of the free anions of β-dicarbonyl compounds. Presumably, the analogous reactions of phenoxides and simple enolates would exhibit similar characteristics. No systematic studies of these substrates in HMPT are, however, available. The trends observed for the free anions are also found in class D, B and A solvents, although now the overall tendency for C-alkylation is greatly increased because the oxygen terminus is encumbered by hydrogen bonding, ion pairing or aggregation. These effects are readily seen in the survey of solvent effects reported by Reutov *et al.*[130] and reproduced in Table 23. In some cases reversal of orientation is most striking. Nevertheless, in any given solvent, the "hard" alkylating agents give the highest amount of O-alkylation. This conclusion is well supported by the results which Bram *et al.*[131,132] have obtained for reactions in dimethoxyethane (Table 24). Here one can also see the effects of relative "tightness" of ion pairs (or aggregates). Monocarbonyl enolate systems appear to behave in the same

Table 23. Solvent effects on the product distribution resulting from the ethylation of potassium ethyl acetoacetate[a] at 20°C[130]

	O	C	C,C
	Alkylating Agent $(EtO)_2SO_2$		
HMPT	83	15	2
DMF	71	26	3
DMSO	70	27	3
Pyridine	38	51	11
N-Methylacetamide	36	63	1
Acetonitrile[b]	32	61	7
DME	18	74	8
Ethanol	8	87	5
t-Butanol	0	94	6
THF	0	94	6
Diglyme	0	90	10
	Alkylating Agent EtBr		
HMPT	35	49	16
DMF	19	66	15
DMSO	19	66	15
Acetonitrile[b]	15	73	12
Acetone	21	67	12
DME[b]	0	96	4

a: [Enolate] = 0.33M. b: Heterogeneous reaction.

way. Table 25 presents some data for lithio- and sodioisobutyrophenone and it is clear that the C/O ratio is controlled by the "hardness" of the leaving group although again aggregation biases these systems towards C-alkylation.

It is clear from the data in Table 24 that Li^+ directs alkylation by ethyl tosylate towards the O-terminus and as suggested above (Section 3.1.3) this may be the result of electrophilic assistance through the 6-membered transition state, **12**. It has also been postulated[107,108] that alkyl halides favor C-alkylation because, in this case, electrophilic assistance through a 6-membered transition state would direct the attack of the alkyl group towards the C-terminus. However, there is no evidence to support this hypothesis. It is significant that the trimethylsulfonium cation, which cannot be involved in electrophilic assistance, gives exclusive C-alkylation of lithioisobutyrophenone in dioxolane,[55] a result which must therefore be attributed solely to the "softness" of the alkylating agent.

The overall rates of reaction (C + O alkylation) vary considerably with the structure of the leaving group. Conia[133,134] has determined the relative rates of alkylation of 2-methylcyclohexanone by a variety of alkylating agents using sodium t-amyloxide in toluene. His results, which are summarized in Table 26, serve as a guide to the experimentalist.

3.4 *Acylation*

We will not discuss this topic in depth since this would

Table 24. The effect of the leaving group on the C/O product ratio for the ethylation of salts of ethyl acetoacetate in DME[131,132]

Ethylating Reagent	Cation Li	Na	K	Cs	NBu_4
CH_3CH_2I	> 100	> 100	> 100	4.3	8.4
CH_3CH_2Br	70-75	60	41	10.3	2.9
$(CH_3CH_2O)_2SO$	3.8	14	--	--	0.30
$CH_3CH_2OSO_2CF_3$	3.6	3.8	--	--	0.30
$CH_3CH_2OSO_2F$	3.0	3.5	--	--	0.32
$CH_3CH_2OSO_2CH_3$	2.4	8.6	--	--	0.28
CH_3CH_2OTs	2.2-1.7	6-8.5	4.7	1.7	0.26
$(CH_3CH_2O)_2SO_2$	2.1	4.8	--	--	0.26

Table 25. The effect of the nature of the leaving group on the C/O product ratio for the alkylation of alkali metal enolates of isobutyrophenone in class B solvents.

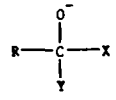
Solvent	Cation	CH_3I	$(CH_3)_3S^+$	CH_3OTs	$(CH_3O)_2SO_2$	CH_3CH_2Br	$CH_3CH_2CH_2Br$	$CH{=}CHCH_2Br$	CH_3CH_2OTs
Et_2O[a]	Na	> 100	--	--	--	--	> 100	--	1.6
DME[a]	Na	--	--	--	--	5.3	4.0	--	--
DME[b]	Li	> 100	--	--	1.6	--	--	--	--
Diglyme[a]	Na	> 100	--	--	--	6.2	3.7	20	0.83
1,3-Dioxolane[b]	Li	> 100	> 100	1.0	0.79	--	--	--	--
1,3-Dioxolane[b]	Li[c]	32	--	--	0.25	--	--	--	--
1,3-Dioxolane[b]	Li[d]	10	--	--	0.15	--	--	--	--

a: Ref. #24, 30°.
b: Ref. #55, 40°.
c: Plus 1 equivalent of 12-crown-4.
d: Plus 4 equivalents of HMPT.

necessate consideration of the voluminous literature of the Claisen condensation, Dieckmann cyclization, etc. There are, however, several studies of the acylation of enolate ions by acid chlorides and anhydrides which are pertinent to our current discussions.

Gelin *et al.*[135] have studied the effect of solvent and cation on the reactions of a variety of acid chlorides with the enolate ion of ethyl acetoacetate. Table 27 shows the effect of the structure of the acid chloride on the C/O ratio for sodio ethyl acetoacetate in DME, under conditions for which the reaction is believed to be under kinetic control. It is clear that reactivity in acylation reactions is governed by steric factors, the symbiotic effect, and electron donating effect in much the same way as discussed for alkylation in the preceding section. In these reactions the enol ester formed is exclusively the "*cis*" isomer derived from the ZZ configuration. For reactions carried out in HMPT, however, mixture of *cis* and *trans* esters are obtained. The composition of these mixtures depends on the initial concentration of the enolate. Evidently, the reactivities of the ion pairs and free ions towards acid chlorides are much more nearly equal than observed for alkylation. This result is, of course, expected since acid chlorides are much more potent electrophiles than most alkylating reagents.

The effect of the leaving group is expected to be dominated by the symbiotic effect since the rate controlling step will doubtless be the formation of the usual tetrahedral intermediate.



House *et al.*[25] have shown that the reactions of 1-sodiophenylacetone in ether with acetic anhydride, acetyl chloride and acetyl bromide give C/O ratios of 0.1, 2 and 3.8, respectively. These authors attribute their results to the involvement of electrophilic catalysis. Since this mechanism involves an assisted S_n2 reaction at an s_p^2 hybridized C atom, a process for which there is no precedent, we feel that their results are better explained by the operation of the symbiotic effect in the usual $B_{AC}2$ mechanism for reactions of carbonyl compounds. This statement in no way denies the possibility of electrophilic assistance for reactions at s_p^3 centers.

Table 26. The effect of the alkylating reagent on the relative rates of alkylation[a] of 2-methylcyclohexanone in toluene[133,134]

Alkylating Reagent	Relative Rates	Alkylating Reagent	Relative Rates
n-BuBr	1	n-PrBr	1
n-PrBr	1.6	EtBr	1.5
EtBr	2.4	MeBr	30
EtI	6	CH_2=CH-CH_2Br	250
EtOTs	12	$PhCH_2Br$	600
$PhCH_2Cl$	17		
EtOBz[b]	25		
$(i\text{-PrO})_2SO_2$	82		
$(EtO)_2SO_2$	117	EtBr	1
MeI	223	EtI	2.5
CH_2=CH-CH_2Br	380	EtOTs	5
MeOBz[b]	970	EtOBz[b]	10
$PhCH_2Br$	1000	$(EtO)_2SO_2$	48
$(MeO)_2SO_2$	13,000		

a: Using 1 equivalent of sodium t-amyloxide as base.
b: -OBz refers to the benzenesulfonate group.

Table 27. Effect of the structure of the acid chloride on the orientation of acylation of the sodium enolate of ethyl acetoacetate in DME at −10°C[135]

R(R-COCl)	C/O[a] ratio
Ph-	99
CH_3-CH=C(CH_3)-	2.4
CH_3-CH=CH-	2.0
$PhCH_2$-	1.9
$PhCH_2CH_2$-	1.1
$(CH_3)_2$C=CH-	0.72
n-Pr	0.54
i-Bu	0.54
Et-	0.49
Me-	0.39
Cyclohexyl-	0.33
i-Pr-	0.22
s-Bu-	0.20
t-Bu-	0.042

a: The O-trans product is not obtained.

3.5 *Effect of the structure of the enolate ion*

Very few studies of the effects of substituents on the reactivities of enolate ions have been reported. Systematic investigations of various solvent systems which would delineate the relation of the position and nature of substituents to the formation of ion pairs and aggregates are badly needed.

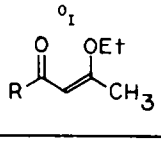
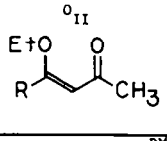
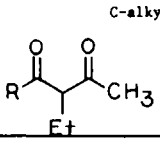
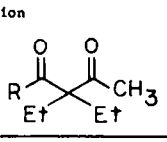
We will first consider the effects of substituents in β-dicarbonyl compounds on the rates and C/O ratios for alkylation of free anions. Table 28 contains data for reactions of enolates of β-dicarbonyl compounds having the general structure $RCOCH_2COCH_3$. It is seen that the effect of R on the C/O ratio is rather minimal for ethylation by diethyl sulfate in HMPT. Similar results are observed for γ-substituted β-ketoesters, data for which are presented in Table 29. Data for the CF_3 group is included in this table and it is seen that this group greatly decreases the nucleophilicity of the anion (it also decreases its basicity by 5 orders of magnitude!) presumably by inductive stabilization. The C/O ratio suggests that the inductive effect results in greater electron withdrawal from the α-C atom than from the more electronegative O atoms.

For most of the β-diketonates listed in Table 28, there is an additional problem of orientation in that there are two nonequivalent oxygen termini. Therefore, two structurally isomeric enol ethers may be formed. The principle factor controlling this type of orientation appears to be steric in origin. A notable exception is the case where R = OEt for which electronic factors direct attack exclusively to the keto rather than the ester oxygen.

In the less dissociating solvent, DMSO (Table 3) part of the reaction presumably occurs through ion pairs. In this situation, the t-Bu group directs attack towards carbon because it destabilizes the EE and E(3, 2)Z(1, 2) conformations which are favored by the free ion.

The effect of ring size on the reactivities of cyclic β-ketoesters has been examined by Rhoades *et al.*[62,138,139] The rate of O-alkylation in DMSO decreases somewhat with increasing ring size (Table 30) probably because of changes in the degree of ion pair dissociation. C-alkylation, however, increases more rapidly which must be due, in part, to changes in intrinsic reactivity. Rate data for C-alkylation in ethanol (Table 31) exhibits what is evidently a complex dependence on conformation.

Table 28. Orientation of O and C alkylation of β-dicarbonyl compounds of formula $RCOCH_2COCH_3$ as a function of the terminal group R. In each case the potassium enolate is alkylated by diethyl sulfate in DMSO or HMPT at 25°C

							
			DMSO		C/O	O_I/O_{II}	Ref.
$-CH_3$		(82)	18	--	0.22	--	136
-Et	50	25	25	--	0.33	0.50	136
$-Pr^n$	46	27	27	--	0.37	0.59	136
$-Pr^i$	58	18	24	--	0.32	0.31	136
$-Bu^t$	65	0	35	--	0.54	0.00	136
$-CH_2Ph$	53	27	20	--	0.25	0.51	136
$-CH_2OEt$	55	27	20	--	0.25	0.45	136
-OEt		(69)[a]	24	7	0.45[b]	--	127,137
$-CH_2CH_2OEt$	47	26	27	--	0.37	0.55	136
$-CH_2CH_2CO_2Et$	41	34	26	--	0.35	0.83	136
			HMPT				
$-CH_3$		(88)	12	--	0.14	--	136
-Et	54	30	16	--	0.19	0.56	136
$-Pr^n$	54	29	17	--	0.20	0.54	136
$-Pr^i$	--	--	--	--	--	--	136
$-Bu^t$	83	0	17	--	0.20	0.00	136
$-CH_2Ph$	55	33	12	--	0.14	0.60	136
$-CH_2OEt$	59	26	15	--	0.18	0.44	136
-OEt		(83)[a]	15	2	0.20[b]	--	127,137
$-CH_2CH_2OEt$	50	33	17	--	0.20	0.66	136
$-CH_2CH_2CO_2Et$	50	33	17	--	0.20	0.66	136

a: O-isomers not investigated.
b: Includes C,C-dialkylation.

Table 29. The effect of the terminal substituent in enolates[a] of β-dicarbonyl compounds of formula $RCOCH_2COCH_3$ on the alkylation rate constant ($\times 10^4$ l mol^{-1} sec^{-1}). In each case the alkylation is run in HMPT at 20°C using ethyl tosylate[60,61]

R	Cation	k	C/O[b]
CH_3	K	77.0	--
Pr^i	K	55.0	0.14
Bu^t	K	23.0	0.16
CH_3	Cs	108	0.13
Pr^i	Cs	68.0	0.14
Bu^t	Cs	25.0	0.14
CF_3	Cs	0.54	0.00

a: [enolate] = 0.02M.
b: Rate constant ratio.

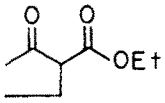
There has been no systematic study of the influence of an α-alkyl substituent on the rates of alkylation of enolate ions. Some scattered data relating to this problem are presented in Table 32, but they are too few to reveal any characteristic trend. It is clear, however, that the effect of the introduction of an α-substituent is a complex function of solvent, alkylating reagent and the type of enolate ion.

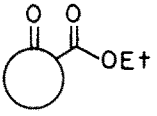
3.6 *Dialkylation*

When alkylation of enolate ions is employed for synthesis of α-alkyl aldehydes and ketones, it is usually important to choose conditions which minimize the formation of dialkyl derivatives or which avoid loss of regiospecificity in cases where two structurally isomeric enolate ions can exist. Both processes can occur if the proton transfer equilibrium between the unreacted enolate ion and C-alkylated product is established at a rate comparable with that of the alkylation reaction, a circumstance which frequently prevails when very "soft" alkylating agents are employed. For example, the reaction of sodioacetylacetonate in HMPT with one equivalent of allyl iodide proceeds exclusively by C-alkylation but the product consists of 78% of diallyl- and 22% monoallyl-acetylacetone.[126]

Bram *et al.*[105] have found that ethyl bromide afforded no ethyl diethylacetoacetate with the Li, Na and K enolates of ethylacetoacetate in DME and the Cs and tetrabutylammonium salts yielded only about 5% of this product. In the same reaction, the potassium enolate in HMPT and in DMSO gave 16–23%[126,128] and 6%,[128] respectively, of the dialkyl product. It appears that conditions favoring strong ion pairing or aggregation suppress proton transfer relative to alkylation and that mono-C-alkylation is best achieved using lithium or sodium enolates, "hard" alkylating reagents and class B solvents. The efficacy of class B solvents in this connection has already been mentioned in the literature.[142,143] These conclusions focus attention on Class B

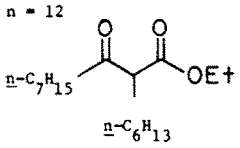
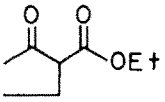
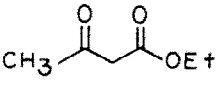
Table 30. Influence of the structure of β-ketoester sodium salts on the alkylation rate constants and C/O ratios ($\times 10^4$ l mol^{-1} sec^{-1}) at 30°C

Structure[a]	Solvent	Alk. Agent	k	C/O[b]	Ref.
n = 6	DMSO	i-PrI	12.0	1.44	62,138
n = 5			17.0	1.74	62,138
n = 8			33.0	7.72	62,138
			207.5	8.69	62

a: n refers to the number of carbons in the cyclic β-ketoester 

b: C/O refers to the rate constant ratio.

Table 31. Effect of the structure of β-ketoester sodium salts on the alkylation rate constants ($\times 10^4$ l mol^{-1} sec^{-1}) in ethanol at 30°C[97]

Structure[a]	Alk. reagent	k
n = 12	MeI	190
		176
n = 11		140
n = 15		130
		96.3
n = 7		92.8
n = 8		91.3
n = 9		80.7
n = 10		74.6
n = 5		27.6
		24.2
n = 6		18.6

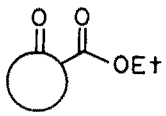
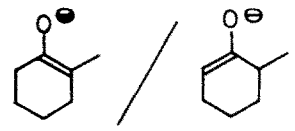
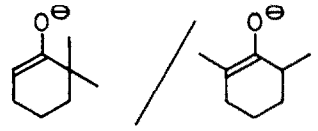
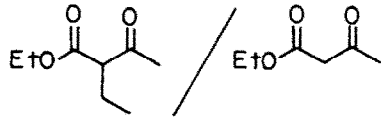
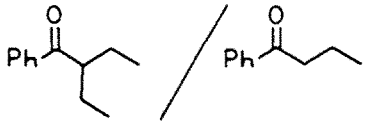
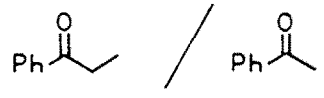
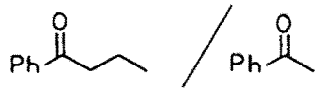
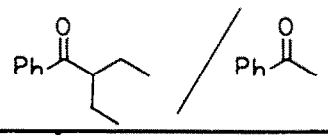
a: n refers to the number of carbons in the cyclic β-ketoester 

Table 32. Effect of an α-alkyl group on the relative rates of C-alkylation for various mono- and dicarbonyl compounds

Compared Compounds	Cation	Solvent	Alk. Agent	Rate Ratio	Ref.
	Li	DME	EtI	1.76	140
	Li	DME	EtI	1.61	141
	K	DME	n-BuBr	0.35	141
	Na	DMF	EtOTs	0.702	59,89
	Na	EtOH	MeI	4.0	97
	Na	DMSO	n-AmCl	0.255	96
	Na	Et_2O	EtBr	1.6	142
	Na	Et_2O	$PhCH_2Cl$	1.0	142
	Na	Et_2O	EtBr	1.0	142
	Na	Et_2O	EtI	0.285	142

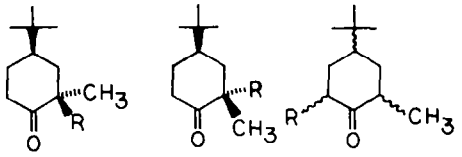
solvents and emphasize the need for a better understanding of the structures of the reactive species in such solvents.

3.7 *Stereochemistry of C-alkylation*

We will restrict our discussion to those systems in which the newly formed chiral center is not subject to epimerization under the reaction conditions, i.e. those cases in which the stereochemistry of the products is the result of kinetic control. Such systems include alkylations at tertiary carbon atoms (including the important case of alkylation at fused ring junctions) and of secondary carbon atoms in cases where it has been shown that proton transfer is much slower than alkylation.

A system in which the stereochemistry of alkylation has been extensively studied is 4-t-butylcyclohexanone in which the ring is known to be "locked" in the chair conformation. Conia and Briet[144,145] have examined the effect of the structure of the alkylating agent on the stereochemistry of the products derived from the sodium enolates of 2 - alkyl - 4 - t - butylcyclohexanone (Tables 33 and 34) and although there is some uncertainty regarding the assignments of configuration,[146] certain conclusions can be drawn. First, the stereochemistry is independent of the structure of the alkylating agent (Table 33). Secondly, for a given alkylating agent, the stereochemistry is independent of the nature of the 2-alkyl substituent (Table 34). In fact, the reaction shows very little stereoselectivity, there being only a slight preference for axial (if the stereochemical assignment is correct) entry of the substituent. Even less stereoselectivity is found for 4-t-butylcyclohexanone itself. House

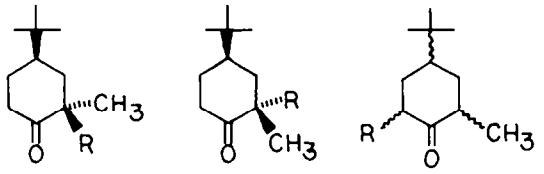
Table 33. Variation of the *cis/trans* ratio[a] with the structure of the alkylating reagent in the alkylation of the sodium enolate[b] of 2-methyl-4-t-butylcyclohexanone in benzene at 80°C



Alkylating Agent R	Leaving group	% cis product	% trans product	% 6-alkylation	cis/trans	Ref.
$CH_2{=}C(CH_3)CH_2$-	Cl	37	48	15	0.77	144,145[c]
$CH_2{=}CHCH_2$-	Br	38	50	12	0.76	144,145[c]
$(CH_3)_2CH$-	Br	36	52	12	0.69	144,145[c]
	I	~36	~52	12	0.69	146[d]
$PhCH_2$-	Br	33	57	10	0.58	144,145[c]

a: Relative percentages from the product mixture are shown.
b: Sodium t-amyloxide was used as the base.
c: The percentages shown have been reversed from the original references. See ref. #146, footnote #14.
d: DME is the solvent used, the cation used is Li^+.

Table 34.[a] The effect of the substituent in sodium enolates[b] of 2-substituted 4-t-butylcyclohexanones on the stereochemistry[c] of methylation by methyl iodide in benzene at 80°C[144,145]



2-substituent (R)	% cis product	% trans product	% 6-alkylation	cis/trans
$-CH_2-\overset{CH_2}{\overset{\|\|}{C}}-CH_3$	57	34	9	1.7
$-CH_2-CH{=}CH_2$	52	28	20	1.9
$-CH_2Ph$	58	25	17	2.3
$-CH_2CH(CH_3)_2$	52	19	29	2.7

a: The precentages shown have been reversed from the original references. See ref. #146, footnote #14.
b: Sodium t-amyloxide was used as the base.
c: Relative percentages from the product mixture are shown.

et al.[149,150] have shown that ethylation of lithio - 4 - t - butylcyclohexanone in DME with triethyloxonium tetrafluoroborate and with ethyl iodide give *cis/trans* ratios of 0.96 and 0.85, respectively. In discussing the possible stereoselectivities of these reactions, it is useful to consider the probable conformations of the reacting enolate ions, which are shown in the scheme below as structures **17**, **18** and **19**. For stereoelectronic reasons, the electrophile RX must approach in directions (labelled **a** and **e** in **17**) perpendicular to the plane of the enolate ion. As these two processes proceed along the reaction coordinate towards the C-alkylated products, the cyclohexane ring can gradually assume either a twist-boat conformation (**18**) leading to the equatorially substituted *cis* product (**20**), or a chair conformation (**19**) which gives the axially substituted *trans* isomer (**21**). Allinger *et al.*[147] have estimated that the twist-boat conformation is substantially less favorable than the chair form, and on this basis it has been concluded[134,148] that the favored pathway will be that involving the chair-like conformation which leads to the axial introduction of the substituent. Since, in practice, the above reactions show such low stereospecificity, it would seem that the transition states, even for the less powerful electrophiles, must resemble the reactants rather than the products. This has also been shown for the exocyclic carbonyl compound methyl-(4-t-butylcyclohexyl) ketone in DME at 25°. In this case the introduction of the methyl group is favored onto the opposite side (*trans*) from the t-butyl group, and the *cis/trans* ratio is 0.18.[166]

Further strong support for a reactant-like transition state in enolate alkylation is provided by House *et al.* in a chlorine isotope effect study with methyl chloride.[166]

The stereochemical results for the alkylation of several cyclic β-ketoesters are summarized in Table 35. All three entries have very similar stereochemistries in that the

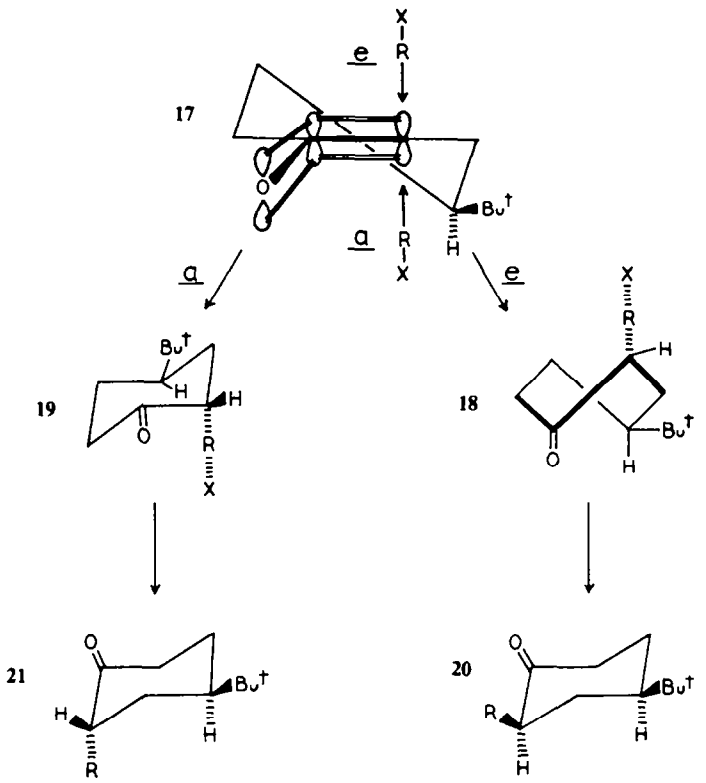
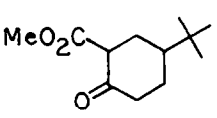
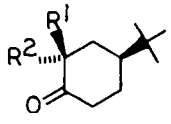
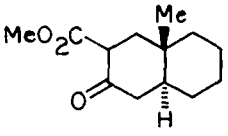
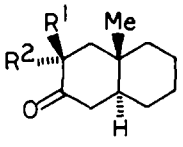
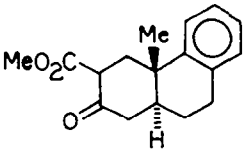
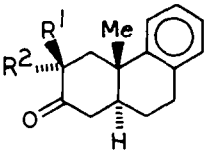


Table 35. Data indicating stereochemistry of alkylation of several cyclic β-ketoesters by methyl iodide in benzene at ambient temperatures

Parent β-ketoester	Cation	Products	R^1	R^2	%	Ref.
	Li		-Me	$-CO_2Me$	17	151
			$-CO_2Me$	-Me	83	
	Li		-Me	$-CO_2Me$	17[a]	151
			$-CO_2Me$	-Me	83	
	K		-Me	$-CO_2Me$	100	152
			$-CO_2Me$	-Me	0	

a: at 0°C.

cyclohexanone ring is constrained to the chair-like conformation. It is thus tempting to ascribe the striking change in the stereochemistry of the product for the last entry to the change in counter ion which doubtless is important in the class A solvent used for the reaction. A systematic study of this problem seems highly desirable in order to confirm the reported experimental findings and to delineate the precise role of cation and solvent in the apparent stereoselective control of alkylation of these β-ketoesters.

Reductive alkylation of α,β-unsaturated ketones with lithium in liquid ammonia leads to the regiospecific formation of an enolate ion. This process has been used for introducing alkyl groups into a number of steroidal and related systems. For example, various 17α-alkyl progesterone derivatives such as **22** have been synthesized in this way, the reaction apparently being stereospecific.[153]

Studies on angular alkylations of fused ring compounds by Johnson *et al.*[154] have produced valuable information concerning the effects of steric and elec-

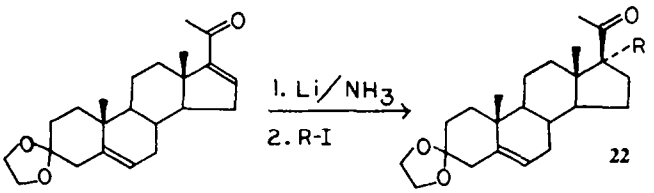
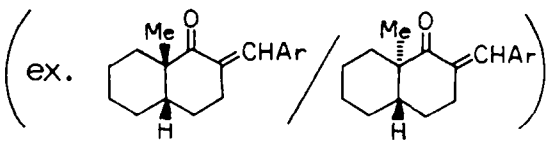
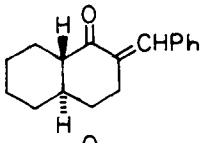
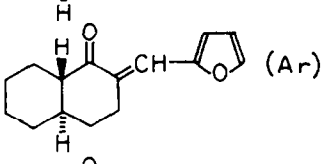
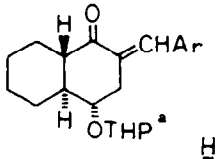
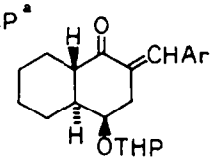
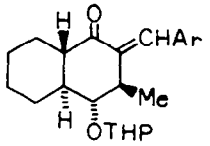
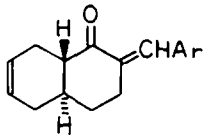
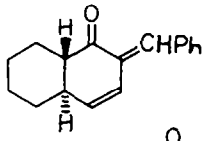
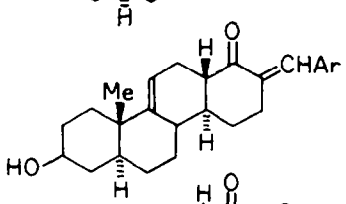
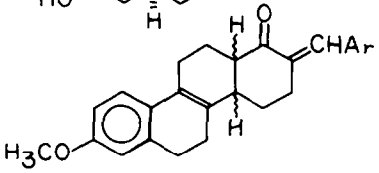
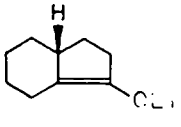


Table 36. Effect of the parent ketone structure on the *cis*-fused/*trans*-fused product ratio for the angular methylation of the potassium enolate by methyl iodide in t-butanol at 0°C[154]

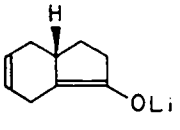
Structure	Parent ketone	cis-fused/trans-fused ratio
		
23		1.9
24		3.5
25		9.0
26		1.5
27		8.1
28		0.79
29		> 100
30		0.45
31		> 100

a: Refers to the tetrahydropyranyl protecting group.

tronic factors on the orientation of alkylation. Some results of these studies can be seen in Table 36. An apparent electronic effect is seen in comparing compounds **23** and **24**, where the only difference is the nature of the arylidene substituent used to block the less substituted α-position. It has also been reported that the use of the alkoxymethylene and alkylthiomethylene blocking groups seem to have an intrinsic property which gives low *cis/trans* ratios in angular alkylations.[155] The effect of the ring substituents on the *cis/trans* ratio can be seen from compounds **24** through **27**. Here, the choice of an α or β substituent at the 4-position is critical in determining the resultant stereochemistry. It is interesting that selected steric interactions with ring protons can be removed by introducing double bonds into the system. This can be seen by comparing compounds **23**, **28** and **29**; and also **30** and **31**, in which drastic changes in the *cis/trans* ratios are seen as the position of the double bond in the ring is varied. House and Blankley[156] have observed a much slighter effect on introduction of a double bond into a perhydroindan derivative. In this case, the lithium enolate **32** gives 98% *cis*, 2% *trans*; and the corresponding lithium enolate **33** gives 96% *cis*, 4% *trans* when alkylated in DME by methyl bromoacetate at 25°C. The stereochemistry of bridgehead alkylation of lithium enolates of 1-decalone derivatives has been probed by House and Umen.[167]



32



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In conclusion, there are numerous examples in the literature in which workers have reported surprise in finding that an alkylation of an enolate ion has led to products of unexpected stereochemistry. It is clear that predictions of the stereochemical course of alkylation of enolate ions is not really possible at present and that much systematic work in this area is needed.

3.8 *Cycloalkylation*

Baldwin[157-159] has formulated rules governing ease of ring closure in a variety of systems and the appropriate components of these rules must be superimposed on the various factors discussed above in order to understand and predict C/O ratios in cycloalkylation. In formulating these rules, Baldwin distinguishes between two types of C-alkylation, namely *endo* and *exo* depending whether the carbonyl product formed is an endocyclic or exocyclic ketone, respectively. The rules are rationalized[159] in terms of an "approach vector" between the reacting centers. In the present context, C-alkylation requires that the electrophilic center can assume the proper direction of approach *above* the α-C atom of the planar enolate ion so that the colinear transition state of the S_n2 replacement can be developed. Reaction at the oxygen center is presumably much less restrictive in that the lone pairs on oxygen are also available and therefore allow the development of the transition state in the plane of the mesomeric enolate ion. These two modes of attack are depicted in **34**, and the underlying principles are well

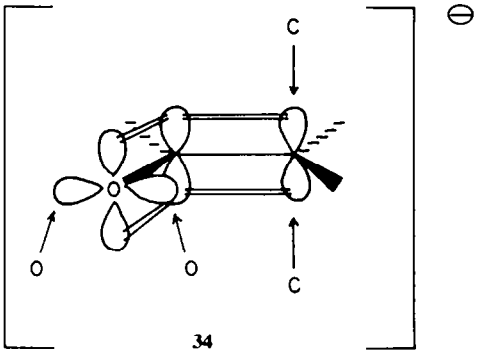

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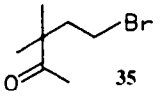
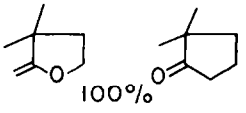
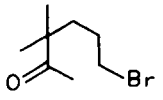
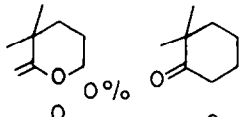
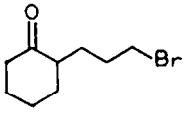
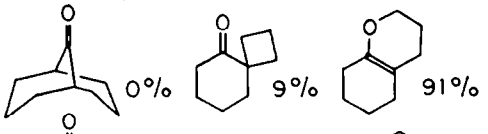
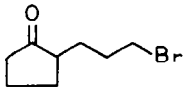
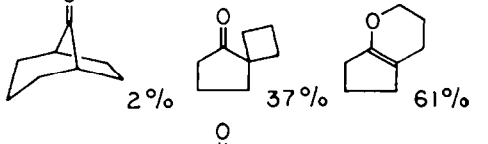
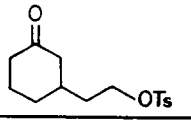
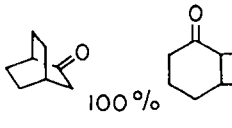
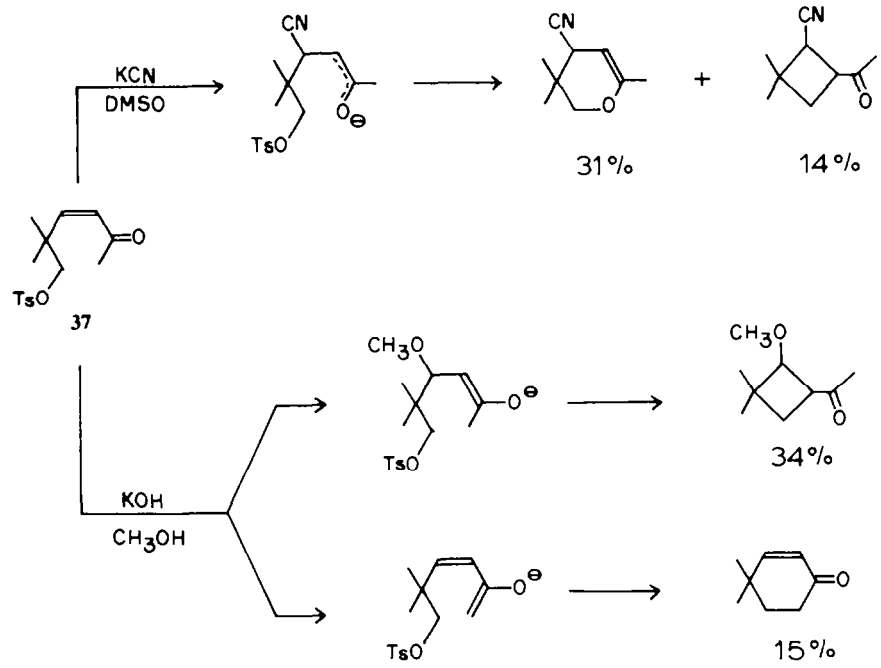
Table 37. Intramolecular alkylations of enolates

Substrate	Cation	Solvent	Temp. (°C)	Products and Relative Yields	Ref.
 **35**	K	Bu^tOH	25	 100% 0%	160
	Li	Et_2O	25		160
	K	Bu^tOH	25	 **36** 0% 100%	160
	Li	Et_2O	25		160
	K	Benzene	80	 0% 9% 91%	162
	K	Benzene	80	 2% 37% 61%	163
	Na	DME	25	 100% 0%	162



illustrated by the first two entries in Table 37. In these two examples the reactions were in class B and D solvents and the leaving group, Br^-, is a soft one. These conditions strongly bias the reaction towards C-alkylation, thus the result for **35** is particularly striking. It would be interesting to know if the exclusive formation of **36** would still be observed if the leaving group was tosylate and the reaction was performed in class C solvents. In this connection the results of Marschall, Tantau and Weyerstahl[161] are possibly significant. They showed that **37** on treatment with methanolic KOH afforded the products of both *endo* and *exo* C-alkylation whereas with KCN in the class C solvent DMSO the O-alkyl and *exo* C-alkylated products were produced.

Exo cyclizations are not subject to such stringent geometric restraints as their *endo* counterparts and such reactions are expected to show a similar dependence on the size of the forming ring as in reactions such as cycloamination,[164] cyclic Williamson syntheses, etc.

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