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Advances in the Chemistry of Ambident Enolate and Phenoxide Ions

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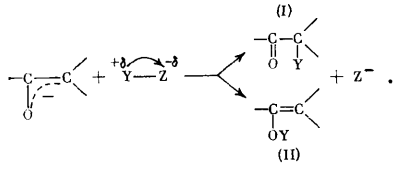
The reactivities of ambident enolate and phenoxide ions in alkylation reactions are examined. It is shown that the mode of *C*- and *O*-alkylation of an ambident anion is determined by the structures of the alkyl group and the group eliminated from the alkylating agent, the nature of the solvent, and the type of counter ion. The influence of each of these factors on the dual reactivity of the enolates of carbonyl and β-dicarbonyl compounds and esters as well as phenoxides and naphthoxides is analysed in detail.
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I. INTRODUCTION

Enolate ions are the most important type of ambident anions. Without exaggeration, one may claim that enolate ions are the key reagents in organic synthesis. When faced with the problem of forming a new carbon–carbon bond, the organic chemist usually turns to the large group of reactions (alkylation, acylation, aldol and ester condensations, and Dieckmann and Michael condensations) of alkali metal enolates. On the other hand, enolate ions, being typical representatives of the class of ambident anions, should manifest a dual reactivity in reactions with electrophiles, forming not only *C*-substitution products (I) but also *O*-substitution products (II).



Nevertheless up to the middle 1960s, not more than 3–4 examples of *O*-alkylation of alkali metal enolates of carbonyl and β-dicarbonyl compounds and esters were known. Systematic studies on the factors determining the mode of reaction of enolate ions were begun only in the last decade. This became possible, firstly, owing to the discovery of exact methods for the analysis of the composition of the reaction mixture (gas–liquid chromatography and ^{1}H NMR) and, secondly, following the introduction into practical organic synthesis of dipolar aprotic solvents. Bimolecular nucleophilic substitution reactions between anions and neutral molecules (the alkylation of enolate ions) are much faster in dipolar aprotic solvents than in a proton-donating medium. This difference is determined primarily by the weak solvation of the anions in dipolar aprotic solvents. For many enolate ions in solvents such as monoglyme, dimethylformamide (DMF), and dimethyl sulphoxide (DMSO), *O*-alkylation reactions were carried out for the first time. In the general case, the mode of reaction of the enolate ion is determined by the following main factors: (1) the nature of the counter ion; (2) the nature of the solvent; (3) the nature of the electrophile; (4) the structure of the ambident anion.

The influence of each of the above factors on the ratio of the products of the *C*- and *O*-alkylation of metal derivatives of carbonyl and β-dicarbonyl compounds and esters will be examined in succession. The reaction products have been analysed quantitatively during the last 10–15 years and attention will be concentrated on this research. Ambident phenoxide ions are in all respects very close analogues of enolate ions. In order to emphasise the close relation between these two classes of ambident anions, data on the *C*- and *O*-alkylation of phenoxide ions have been included.

II. DEPENDENCE OF THE MODE OF THE ALKYLATION REACTION ON THE NATURE OF THE CATION

An important factor influencing the ratio of the alkylation products of metal enolates and phenoxides is the nature of the cation. The influence of the nature of the alkali metal cation on the ratio of the *C*- and *O*-isomers has been investigated in greatest detail. In this case, the problem reduces in essence to the solution of the problem of the state of these salts in solution. Alkali metal enolates can exist in solution in the form of associated species comprising ion pairs with different degrees of aggregation, and, in a fairly basic and polar solvent, in the form of monomeric ion pairs of different types and as free ions. Naturally, the nature of the solvent has a decisive influence on the position of equilibrium between the different forms of ionic species. The degree of association of ion pairs depends also on the size, charge density, and hardness of the cation and anion. Sodium and potassium alkoxides form, for example, associated species of the type $(ROM)_3$ even in a basic and polar solvent such as DMSO.[1,2] The degree of association in a less polar medium and also for small cations with a high charge density (Li^+, Mg^{2+}, etc.) is even greater[2-5]. As regards the tendency towards self-association, alkali metal enolates occupy an intermediate position between alkoxides and alkali metal salts of carbanions, which are monomeric in solvents, coordinating effectively alkali metal cations[6]. The molecular weight of the sodium salt of n-butyl malonate (in 0.1 *N* solution in benzene) exceeds 11 000 which corresponds to the formation of a monodisperse

micelle comprising 40–50 monomeric ion pairs of this salt, i.e. almost a colloidal particle [7,8]. However, in a more polar and, what is more important, a more basic medium, the degree of association decreases sharply. Thus the sodium salt of butyrophenone in ether exists in the form of a three-dimensional association of ion pairs [9], while in dimethoxyethane (DME) [10] the degree of association is lower still. The addition of small amounts of dipolar aprotic solvents such as DMF [8,11], DMSO [12], and hexamethylphosphoramide (HMP) [13] to solutions of alkali metal enolates in media of low polarity breaks up the ionic association complexes until the formation of monomeric ion pairs. The same effect is achieved by the introduction of strong complex-forming agents: polyglymes and macrocyclic polyesters [14]. In dipolar aprotic solvents at concentrations below 0.2 M, alkali metal enolates (with the exception of lithium salts) are hardly associated. In the ion pair of an alkali metal enolate, the cation is coordinated to the hard oxygen centre of the enolate ion and the electrostatic interaction between the two oppositely charged ions is intensified with decrease of the radius and with increase of charge density in the sequence $Cs^+ < Rb^+ < K^+ < Na^+ < Li^+$ i.e. with increase of the hardness of the cation. Ion association has a marked influence on the reactivity of the anion. The electrostatic interaction between the ions in the ion pair in media of moderate polarity is very considerable; the free ion is as a rule the most reactive species and ion association therefore causes an appreciable decrease of nucelophilic reactivity. For ambident anions, association of the cations with one of the reaction centres causes a disproportionate diminution of the nucleophilic properties of both reaction centres. In an ion pair with an enolate ion, the alkali metal cation is associated with a hard oxygen centre, which leads to an increase of the fraction of the product of *C*-alkylation of the ion pair relative to the free anion.

The ratio of the *C*- and *O*-isomers increases particularly markedly on association of ions pairs into dimers, trimers, and larger aggregates. The agglomeration of ion pairs is undoubtedly the main cause responsible for the exclusive formation of the products of *C*-alkylation and *C*-acylation of alkali metal enolates of carbonyl and β-dicarbonyl compounds in benzene, dioxan, petroleum ether, and other non-polar and weakly basic solvents. In the general case the ratio of the *C*- and *O*-isomers in the alkylation of alkali metal enolates in an aprotic medium should decrease in the sequence $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+ > NR_4^+$, but the effect should be smoothed out on passing to more basic and polar solvents.

Curtin et al. [15] showed that, in the alkylation of sodium and potassium 2,6-dimethylphenoxides with allyl bromide in ether, the dienone/ether ratio diminishes from 1 to 0.5 when Na^+ is replaced by K^+. A detailed study of the influence of the nature of the cation in the alkylation of phenoxides has been carried out using β-naphthol salts as an example [16] (Table 1).

The yield of the *O*-isomer increases in the sequence $MgBr^+ \ll Na^+ < K^+ < N(CH_3)_4^+$; the exclusive formation of the *C*-alkylation product from magnesium β-naphthoxide is striking. An increase of the fraction of the *O*-alkylation product for tetraalkylammonium enolates was noted by Nesmeyanov and Sazonova in the methoxymethylation of alkali metal derivatives of ββ-diphenylpropiomesitylene. [17] In the alkylation of ammonia-saturated acetoacetic ester (AAE) with chloroacetone in ether, Hurd and Wilkinson detected only the *O*-isomer; when the same alkylating agent reacts with the sodium salt of AAE in alcohol, only the *C*-alkylation product is formed [18]. An appreciable increase of the ratio of the *C*- and *O*-isomers, from 3.4 to 7.7, was observed also in the alkylation of alkali metal salts of the benzophenone dianion with methyl iodide in liquid ammonia when the potassium counter ion was replaced by sodium [19]. The influence of the alkali metal cation has also been studied for the alkylation of the enolates of cyclic β-ketoesters with ethyl α-bromopropionate in a 2 : 5 DMF–benzene binary mixture [20]. The results show that, regardless of the size of the ring, the yield of the *O*-alkylation product increases for all the β-ketoesters in the series of cations $Li^+ < Na^+ < K^+$. The ratio of the *O*- and *C*-isomers increases most sharply on passing from the sodium enolate of 2-ethoxycarbonyl-1-indanone to the potassium enolate.

Table 1. The alkylation of β-naphthol salts with benzyl bromide.

Cation	Solvent	Total yield, %	Relative yield, %	
			O-isomer	*C*-isomer
K^+	Dioxan; 100°	46	58	42
Na^+	Dioxan; 100°	49	48	52
Li^+	Dioxan; 100°	47	47	53
$MgBr^+$	Dioxan; 100°	64	—	100
K^+	Alcohol–benzene (1 : 1)	47	84	16
NMe_4^+	Alcohol–benzene (1 : 1)	50	91	9

In dipolar aprotic solvents, where alkali metal enolates are partly dissociated, the influence of the alkali metal cation is extremely weak [21–24]. For example, the ratio of the *C*- and *O*-isomers of the products of the alkylation of alkali metal enolates of acetylacetone (AcAc) with ethyl toluene-*p*-sulphonate in HMP at 20°C is almost independent (with the exception of the lithium salt) of the nature of the counter ion [24]. The above ratio also does not change with decrease of the concentration of the enolate and when HMP is replaced by another solvent containing the phosphine oxide group (diaphos, mediphos). When ethyl toluene-*p*-sulphonate is replaced by ethyl bromide and particularly ethyl iodide, the yield of 2-ethoxypent-2-en-4-one decreases sharply, but remains constant for sodium, potassium, and tetrabutylammonium enolates. This means that the reactive species is the "free" AcAc anion. In a more differentiating solvent (DMF), the relative yield of the *O*-alkylation product increases in the series of cations $Li^+ < Na^+ < K^+ \sim Cs^+$, i.e. not only the ions but also the ion pairs of acetylacetonates participate in the reaction.

The fraction of the *O*-alkylation products of enolates increases particularly markedly on passing to quaternary ammonium enolates. The formation of the products of the *O*-alkylation of tetrabutylammonium enolates of AAE, AcAc, and benzoylmalonic ester has been noted even in a weakly basic medium such as chloroform and methylene chloride [25–27].

The counter ion has been found to have an unusual influence in the alkylation of alkali metal enolates of 2-ethoxycarbonylcyclopentanone in DMSO. [28] On alkylation with isopropyl iodide or butyl bromide, the sodium enolate unexpectedly gives rise to a greater amount of the *O*-isomer than does the potassium enolate. These data are in sharp conflict with those of other studies concerning the influence of the cation on the ratio of the *C*- and

O-isomers in an aprotic medium. If it is supposed that the main reactive species is in this case the ion pair of the alkali metal enolate, the different types of behaviour of the sodium and potassium enolates must be associated with the different degrees of solvation of the cation in ion pairs. The ion pair of sodium enolate may prove to be more reactive, since DMSO is coordinated more effectively to the sodium cation than to the potassium cation[29].

Strictly speaking, all the above data yield only a quantitative and extremely superficial picture of the influence of the alkali metal cation on the ratio of the *C*- and *O*-isomers in the reaction products. This ratio is determined by at least two processes involving the free enolate ion and ion pairs (and in some cases there is also a possibility of their agglomeration), and by the relative contribution of each process. In order to characterise quantitatively the influence of the cation, it is necessary to determine $(C/O)_p$—the ratio of the isomers in the alkylation of the ion pair of the alkali metal enolate. $(C/O)_{obs}$ and $(C/O)_p$ can, in principle, differ fairly markedly. Table 2 presents the ratios $(C/O)_{obs}$, $(C/O)_p$, and $(C/O)_{ion}$ for the alkylation of alkali metal salts of methyl 3-hydroxybenzofuran-2-carboxylate with methyl iodide in methanol[30]. The data presented in Table 2 clearly demonstrate significant differences between these quantities as a function of the nature of the cation; at the same time, it is easily seen that the general sequence in the variation of the quantities $(C/O)_p$ and $(C/O)_{obs}$ as function of the nature of the counter ion does not change. This factor is very significant, since it justifies the hypothesis that $(C/O)_{obs}$ can serve as a criterion in the estimation of the influence of the nature of the cation on the dual reactivity of alkali metal enolates. The data in Table 2 also reveal a considerable difference in the influence of the nature of the counter ion in aprotic and protic media. The ratio of the *C*- and *O*-isomers in the methylation of salts of the β-hydroxycoumarate ester in methanol decreases on passing from Li^+ to Na^+, but increases again for potassium and bispiperidinium salts.

Table 2.

Cation	$(C/O)_{obs}$	$(C/O)_p$	$(C/O)_{ion}$	Cation	$(C/O)_{obs}$	$(C/O)_p$	$(C/O)_{ion}$
Li^+	5.9	5.0	6.0	K^+	4.4	2.63	6.0
Na^+	3.5	2.1	6.0	Bipy*	5.0	4.1	6.0

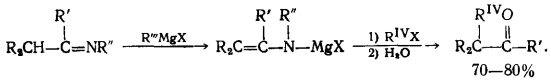
*Bipy = bispiperidinium cation.

The data obtained by Stetter and Dierichs[31] for the alkylation of the lithium, sodium, and potassium salts of dihydroresorcinol with butyl bromide in methanol serve as a very clear example of this difference. The ratio of the *C*- and *O*-isomers decreased in the sequence $K^+ > Na^+ > Li^+$, which is the opposite to that corresponding to the influence of the cation in an aprotic medium. The interpretation of data for the influence of the nature of the counter ion in protic solvents is very difficult. As will be shown below, proton-donating solvents solvate selectively and effectively the oxygen centre of the enolate ion, which promotes the reaction at the second centre of the ambident anion. Thus the selective solvation of the enolate ion via hydrogen bonding as well as the shielding of the oxygen centre in the ion pair owing to the electrostatic interaction with the alkali metal cation lead to an increase of the ratio of the *C*- and *O*-isomers in the alkylation products. In principle, a situation may arise in which the shielding of the oxygen atom of the enolate ion by solvent molecules owing to hydrogen bonding is stronger than the electrostatic interaction with the cation in the ion pair, which is particularly likely for large cations with a low charge density (Cs^+, NR_4^+, $AsPh_4^+$, etc.), i.e., in contrast to an aprotic medium, in a protic medium the case where $(C/O)_{ion} > (C/O)_p$ is quite real[30] (Table 2).

Many examples of the alkylation of covalent metal derivatives of carbonyl and β-dicarbonyl compounds are known. A change in the amount of ionic character of the bond has a very strong influence on the ratio of the *C*- and *O*-alkylation products. In addition, one must also take into account the structure of metallic derivatives of ketoenols. Whereas the enolate structure has been generally acknowledged for alkali metal, alkaline earth metal, and thallium derivatives[32], there is convincing evidence that the mercurated carbonyl and β-dicarbonyl compounds exist in the keto-form[33-37]. Derivatives of tin and germanium, where a metallotropic equilibrium between the *O*- and *C*-forms has been demonstrated, constitute an intermediate group[38-41]. It has been suggested, although without adequate arguments, that the magnesium derivatives of certain ketoenols also exist in the form of a mixture of two metallotropic forms[42-45].

In the solution of the problem of the structure of metal derivatives of carbonyl compounds, the application of Pearson's principle of hard and soft acids and bases (HSAB)[46] has been extremely fruitful. Alkali metal cations and the Mg^{2+}, Tl^+, and R_3Si^+ cations, which belong to the group of hard acids, should be coordinated to the hard oxygen centre of the enolate ion, while soft Lewis acids, for example the mercury cation, should be coordinated to the soft carbon centre. For an intermediate group (R_3Ge^+ and R_3Sn^+), there is a possibility of the existence of both forms with different equilibrium positions between them.

Magnesium enolates and magnesium salts of aldehyde and ketone derivatives are alkylated solely at the carbon atom. Stork and Dowd[47] found that the alkylation of the magnesium derivative of an imine is one of the best methods for the selective mono-*C*-alkylation of carbonyl compounds. Asymmetric ketones are alkylated at an unsubstituted carbon atom:

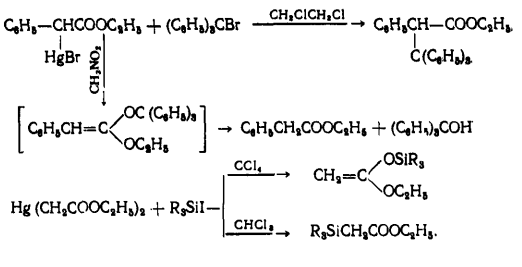


The alkylation of the magnesium salts of various ketoenols in HMP has been investigated in greatest detail. It has been shown[48] that, on treatment with a wide variety of alkylating agents, products of *C*- and di-*CC*-alkylation only are formed with high yields. The alkylation of thallium enolates by alkyl halides without a solvent[49] or in benzene[50] also gives rise to high yields of *C*-isomers. Taylor et al.[50] suggested that this reaction be used as a preparative method for the mono-*C*-alkylation of ketoenol systems. Their data permit the conclusion that the alkylation of thallium(I) enolates is the best method for the synthesis of *C*-isomers in a chromatographically pure form. However, it has been recently reported[51] that the alkylation of the thallium(I) salt of dihydroresorcinol gives rise to the *O*-alkylation products regardless of the nature of the solvent. Evidently, depending on the pK_a of the β-dicarbonyl compound, a change in the mode of reaction

in the alkylation of thallium(I) enolate is to be expected, in which the compound with the lower pK_a undergoes preferential *O*-alkylation. Hooz and Smith[52] reinvestigated the alkylation of the thallium enolates of AAE and AcAc by methyl, ethyl, and isopropyl iodides. Their data are in striking conflict with those of Taylor et al. Firstly, the selective mono-*C*-alkylation of the enolate was not observed in any instance and the reaction mixture always contained mono- and di-alkylation products. Secondly, *C*-ethylation and *C*-isopropylation is accompanied by the competing *O*-alkylation reaction. The latter factor is particularly surprising bearing in mind that magnesium enolates are alkylated at the carbon atom. Thus thallium(I) used as a counter ion in the alkylation reaction resembles the lithium cation more closely than an alkaline earth metal cation.

Silver enolates are known to exhibit an enhanced tendency towards the formation of *O*-alkyl derivatives. For example, when alkyl halides interacted with the silver derivatives of dihydroresorcinol[53], AcAc [54], AAE [55], and certain bicyclic triketones[56], *O*-alkylation products were isolated. At the same time the alkylation of the silver and mercury salts of the diazoacetic ester by benzyl and allyl bromides in ether leads to the formation of *C*-alkylation products with retention of the diazo-group[57]. The alkylation of tin derivatives of ketoenols has been studied in relation to an extremely limited number of examples and only *C*-alkylation products could be detected (with a low yield) in the reaction mixture[58-62].

Numerous studies have been made on the alkylation of α-mercurated derivatives of carbonyl compounds. It has been established that these compounds do not react with the majority of alkylating agents, positive results being obtained solely when mild alkylating agents were used: allyl, benzyl, and trityl halides. γ-Mercuribis-AAE gives rise to a low yield of a mixture of α-allyl- and $\alpha\alpha$-diallyl(benzyl)-AAE on alkylation with allyl and benzyl iodides[63]. A high yield of the products of the alkylation of mercury derivatives of oxo-compounds has been observed only when trityl halides were used as the alkylating agents[64-67]. An important condition for the occurrence of this reaction is nucleophilic cooperation by the leaving group of the alkylating agent. Thus ethyl α-bromo-mercuriphenylacetate does not react with trityl perchlorate, but is alkylated under the influence of bromotriphenylmethane, which involves the nucleophilic cooperation of bromine[66]; the mode of the alkylation reaction depends very strongly on the nature of the solvent:



The reaction is very sensitive to a change in the structure of the alkylating agent. Thus mercuribisacetylaldehyde interacts with chlorotriphenylmethane to form $\beta\beta\beta$-triphenylpropionaldehyde, while the analogous reaction with chlorotri-(*p*-nitrophenyl)methane gives rise to the enol ether as the only product[35]. The above examples illustrate the extremely high sensitivity of the mode of reaction to factors whose influence cannot be predicted beforehand.

III. THE INFLUENCE OF THE SOLVENT ON THE RATIO OF THE *C*- AND *O*-ALKYLATION PRODUCTS

The solvent has an extremely marked influence on the rate and mode of alkylation of phenoxides and enolates. In the early stages of the study of the problem of the dual reactivity of ambident systems, it was already noted that a change of solvent can alter completely the mode of reaction. Thus Claisen et al.[68] showed that the alkylation of sodium phenoxide by allyl bromide in alcohol or acetone leads to the formation of allyl phenyl ether, while in benzene and ether the product is *o*-allylphenol.

In the assessment of the influence of solvents on the dual reactivity of the salts of ambident anions, one must distinguish two types of interaction of the solute with the solvent: the specific solvation of the cation and the interaction of the solvent with the ambident anion proper. Alkali metal enolates are to some extent associated to ion pairs and more complex aggregates of ion pairs in the majority of organic solvents. The degree of association of alkaline earth metal enolates and phenoxides is undoubtedly even greater. The derivatives of other metals must be evidently regarded as covalent compounds with different amounts of ionic character. As noted above, the position of equilibrium between different forms of ionic species depends to a large extent on the nature of the solvent. In weakly polar and weakly basic solvents (hydrocarbons, ether, dioxan, etc.), the ion pairs of alkali metal enolates are highly associated, which is the reason for the formation of *C*-alkylation products in these media. The introduction of dipolar aprotic solvents and linear polyethers (glymes) into the medium where alkali metal enolates exist as associated species causes the disruption of the latter to ion pairs. The disruption of ionic association complexes is accompanied by an appreciable acceleration of the alkylation of alkali metal enolates. Zaugg and coworkers[7,69] showed that the addition of even small amounts (< 5%) of certain dipolar aprotic solvents to a benzene solution of the sodium enolate derived from the n-butylmalonic ester causes a sharp acceleration of *C*-alkylation under the influence of butyl bromide. The acceleration of the reaction is caused by the specific solvation of the cation by molecules of the dipolar aprotic solvent; in the presence of the polar component, the reaction rate constant varies in parallel with the basicity of this solvent. The continuous increase of the rate of reaction with increase of the DMF and DMSO concentrations in binary mixtures with benzene[69] is evidently due to the gradual disruption of the associated species following the introduction of the polar component[8]. The ratios of the rates of reaction in benzene, tetrahydrofuran (THF), DME, DMF, and DMSO are 1 : 14 : 80 : 970 : 1420 respectively[69]. In dipolar aprotic solvents, alkali metal enolates apparently exist as ion pairs and free ions. A study of the alkylation of alkali metal enolates in an aprotic medium revealed a general feature: an increase of the basicity of the aprotic solvent promotes *O*-alkylation; the ratio of *C*- and *O*-alkylation products is not correlated with the dielectric constant of the aprotic solvent and is determined mainly by the capacity of the solvent for the specific solvation of the cation, which depends in its turn on the basicity of the solvent. The quantity $\Delta\delta_\infty$—the change in the chemical shift of the chloroform proton at an infinitely low concentration of chloroform in the given solvent— may serve as a measure of the basicity of the aprotic solvent[70]; the quantity ΔH_{solv}—the enthalpy of solvation of the sodium cation—may serve as a more reliable characteristic of the basicity of the solvent[71] (Table 3)

The fraction of the product of the *O*-alkylation of the sodium salt of 2,6-dimethylphenol increases in the sequence benzene < toluene < $O(C_3H_7)_2$ < $O(C_2H_5)_2$.[15] The influence of the solvent is more clear-cut in the reaction of sodium β-naphthoxide with benzyl bromide and methyl iodide[79] (Table 4).

Table 3. The values of $\Delta\delta_\infty$ and ΔH_{solv} for certain aprotic solvents[70,71].

Solvent	$\Delta\delta_\infty$, p.p.m.	ΔH_{solv}, kcal mole^{-1}	Solvent	$\Delta\delta_\infty$, p.p.m.	ΔH_{solv}, kcal mole^{-1}
HMP	—2.03	—0.58	Acetonitrile	—0.63	0 06
N-Methylpyrrolidinone	—2.03	—	DME	—0.84	—0.45
Tetramethylurea	—1.37	—	Tetraglyme	—	—4.82
DMSO	—1.34	—0.34	Sulpholane	—0.68	—
DMF	—1.30	—0.23	THF	—0.80	—0.08
Acetone	—0.94	0.00	Dioxan	—0.64	—0.06

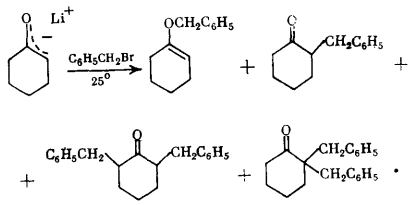
The increase of the yield of the *O*-isomer on passing to dipolar aprotic solvents has also been observed in the alkylation of the sodium salt of dimethyloctalone by benzyloxymethyl chloride[74].

Table 4. The *C*- and *O*-alkylation of sodium β-naphthoxide.

Solvent	Yield of isomers*, %			
	O-isomer	*C*-isomer	*O*-isomer	*C*-isomer
	Benzyl bromide		Methyl iodide	
DMF	97	—	91	4
DMSO	95	—	90	3
DME	70	22	86	10
THF	60	36	80	13

*The absolute yields are quoted.

A similar effect has been observed[75] in the methylation and ethylation of the potassium enolates derived from acetophenone, cyclohexanone, cyclopentanone, and other ketones by dimethyl and diethyl sulphates. A very small amount of the enol ether (~3%) is formed even in the benzylation of the lithium enolate derived from cyclohexanone in HMP, while in ether and DME a complex mixture of products of *C*- and *CC*-alkylation is formed[76].



Ether	—	45%	5%	5%
Dimethoxyethane	—	51%	4%	9%
Hexamethylphosphoramide	3%	27%	5%	20%

The ratio of the *C*- and *O*-products obtained from alkali metal enolates derived from β-dicarbonyl compounds also diminishes when weakly polar aprotic solvents are replaced by dipolar aprotic solvents. It has been shown[77] that the yield of the *O*-isomer in the alkylation of the potassium salt of AAE by butyl chloride at 100°C increases on passing from acetone to dipolar aprotic solvents (Table 5).

Table 5. The alkylation of the potassium salt of AAE with butyl chloride.

Solvent	Yield of *O*-isomer, %	Solvent	Yield of *O*-isomer, %
N-Methylpyrrolidinone	51	DMSO	47
NN-Dimethylacetamide	49	Acetonitrile	19
DMF	46	Acetone	10

The influence of the solvent on the ratio of the products of the *C*- and *O*-alkylation of the tetrabutylammonium salt of AcAc by isopropyl iodide is less pronounced (Table 6)[78]. The low ratios of the *C*- and *O*-products in weakly polar and weakly basic media are probably associated with the large interionic distance in the ion pair of the tetrabutylammonium salt (the Stokes radius of the NBu_4^+ cation is independent of the nature of the solvent and amounts to 3.85 Å).[79]

Table 6. The *C*- and *O*-alkylation of the tetrabutylammonium enolate of acetylacetone with isopropyl iodide.

Solvent	Yield of isomer, %		Ratio of *C*- and *O*-isomers	Solvent	Yield of isomer, %		Ratio of *C*- and *O*-isomers
	C-isomer	*O*-isomer			*C*-isomer	*O*-isomer	
DMSO	42	58	0.72	Chloroform	51	49	1.04
Acetone	42	58	0.72	Dioxan	63	37	1.91
Acetonitrile	48	52	0.92	Toluene*	69	5	13.8

*26% of the enolate was recovered unchanged.

The influence of the nature of the solvent on the mode of alkylation of alkali metal enolates has been investigated in greatest detail for the AAE and AcAc enolates[80]; the experimental data are presented in Tables 7 and 8. These show in the first place that the influence of aprotic solvents is determined mainly by the values of $\Delta\delta_\infty$ and ΔH_{solv} for the sodium cation in the given medium and not by the dielectric constant. The ratio of the *C*- and *O*-ethylation products is correlated quite satisfactorily with the above parameters of the solvent basicity. The comparatively low yield of β-ethoxyethyl crotonate in tetraglyme and the higher yield of the *O*-isomer in acetonitrile then in monoglyme show that the basicity of the solvent is not the only factor determining the ratio of the isomers. The polarity of the medium also plays a definite role. The solvent basicity is of decisive importance in the disruption of ionic association complexes into monomeric ion pairs, while the medium polarity influences mainly the position of the equilibrium between ions and ion pairs. Aprotic solvents can be approximately divided into four groups in terms of their influence on the process: 1. highly basic dipolar aprotic solvents (HMP, diaphos, mediphos), in which the reacting species is the enolate ion and the isomer ratio is determined by its mesomerism. 2. Dialkylamides, DMSO, and pyridine, in which the reactive species

are not only ions but also K–AAE and Na–AcAc ion pairs. 3. Moderately polar and weakly basic solvents (acetonitrile, acetone, and sulpholane). The coordinating capacity of these solvents in relation to alkali medium cations is low, so that the contribution of ion pairs and possibly also of higher association complexes increases sharply, which leads to an increase of the ratio of the *C*- and *O*-products by a factor greater than 2. 4. Weakly polar solvents (ether, dioxan, THF, methylene chloride) in which *C*-alkylation takes place exclusively. The reacting species is apparently an association complex comprising several ion pairs. In DME and tetraglyme, which effectively solvate alkali metal cations but are at the same time insufficiently polar, a certain amount of the *O*-isomer is formed. It has been found that the addition of even small amounts of complex-forming agents such as glymes and particularly of macrocyclic crown polyethers alters significantly the ratio of the *C*- and *O*-alkylation products[81,82]. Thus the fraction of the *O*-alkylation product obtained in the alkylation of the potassium salt of AAE with ethyl toluene-*p*-sulphonate in benzene, ether, and dioxan increases approximately by a factor of 100 after the introduction of an equimolar amount of dicyclohexyl-18-crown-6 ether[81].

Table 7. The ethylation of the potassium enolate of acetoacetic ester with diethyl sulphate (c_0 = 0.33 M, t = 20°C).

Solvent	Yield, %				ε	$\Delta\delta_{\infty}$, p.p.m. (Ref.70)
	total yield	*O*-isomer*	*C*-isomer*	dialkylation products*		
HMP	93	83	15	2	30	—2.03
Diaphos	91	83	16	1	31.6	—
N-Methylpyrrolidinone	90	80	18	2	32	—
Tetramethylurea	95	78	20	2	23	—1.37
DMF	93	71	26	3	36.7	—1.30
DMSO	92	70	27	3	49	—1.34
Pyridine	—	63	35	2	12.3	—
Propylene carbonate	78	51	46	3	65	—
N-Methylformamide	75	40	58	2	170	—
Acetone	67	38	51	11	20.5	—0.94
Acetonitrile	—	32	61	7	37.5	—0.63
Tetraglyme	95	26	68	6	7.7	—
Monoglyme	88	18	74	8	7.3	—0.84
Sulpholane	80	15	76	9	44	—0.68
Ethanol	84	8	87	5	24.3	—
THF	78	<1	94	6	7.6	—0.80
Ethyl ether	—	<1	95	5	4.3	—
Dioxan	85	<1	96	4	2.2	
Methylene chloride	—	<1	97	3	8.9	—
t-Butyl alcohol	—	<1	94	6	10	—

*The relative yields are quoted.

Hitherto we have considered the influence of the solvent on the ratio of the *C*- and *O*-isomers in the alkylation of enolates and phenoxides taking into account only the specific solvation of the cation. Another and more interesting possibility in the influence of the solvent on the dual reactivity of ambident anions is associated with the specific solvation of the ambident anion itself. The two reaction centres of enolate and phenoxide ions differ sharply in their electronegativity and the distribution of electron density. The hard oxygen atom serves simultaneously as the centre of the highest electron density. The hardness and electronegativity differences are responsible for the more extensive solvation of the oxygen centre of the enolate ion. Selective solvation of the oxygen atom causes a disproportionate diminution of the nucleophilic properties of the two centres of the ambident anion, which entails an increase of the fraction of the *C*-alkylation products. Thus, like the counter ions in ion pairs formed from enolate and phenoxide ions, solvation effects lead to the shielding of the atom with the higher electron density. "Shielding" plays a major role primarily in a protic medium as a result of the formation of a strong hydrogen bond with the oxygen centre of the ambident anion. Kornblum called this phenomenon "selective solvation"[72,83].

Table 8. The ethylation of the sodium salt of acetylacetone with ethyl toluene-*p*-sulphonate (c_0 = 0.3 M; t = 20°C).

Solvent	Yield, %				ε	$\Delta\delta_{\infty}$, p.p.m.	ΔH_{solv} (Ref.71)
	absolute yield	*C*-isomer	*O*-isomer	dialkylation product*			
Diaphos	93	10	90	<1	31.6	—	—
Mediphos	90	10	90	<1	24.6	—	—
HMP	90	10	90	<1	30	—2.03	—0.58
N-Methylacetamide	75	20	80	<1	179	—	—
N-Methylpyrrolidinone	75	22	78	<1	32	—2.05	—
α-Pyrrolidinone	36	22	78	<1	—	—	—
Tetramethylurea	92	19	77	4	23	—1.37	—
DMSO	77	25	75	<1	49	—1.34	—0 34
DMF	74	26	74	<1	36.7	—1.30	—0.23
Propylene carbonate***	58	47	51	2	65	—	—
Acetone***	37	64	36	<1	20.5	—0.94	0.00
Acetonitrile***	45	65	35	<1	37.5	—0.63	+0.06
Dimethoxyethane	32	77	13	10	7.3	—0.84	—0.45
Sulpholan	28	77	11	12	44	—0.68	—

*The relative yields are quoted.
**The yields of dialkylation products (mixture of the *CC*-isomers with a small amount of the *CO*-isomers) [?not shown (Ed. of Translation)].
***The reaction proceeds heterogeneously at 50°C.

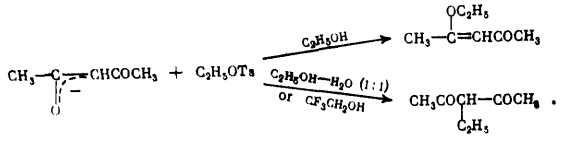
Table 9. The influence of specific solvation on the mode of reaction of the ambident anion.

Solvent	Yield, %			
	C-isomer	*O*-isomer	*C*-isomer	*O*-isomer
	Sodium phenoxide + allyl chloride		Sodium β-naphthoxide + benzyl bromide	
Ethanol	—	100	28	52
Methanol	—	100	34	57
Water	41	49	84	10
2,2,3,3-Tetrafluoropropanol	37	58	—	—
2,2-Trifluoroethanol	42	37	85	7
Phenol	78	22	—	—

In the classical studies by Claisen at the beginning of the XXth century, it was shown that phenoxides are alkylated in alcoholic media exclusively at the oxygen atom. When solvents capable of forming stronger hydrogen bonds were used, it was possible to alter the mode of reaction. Thus the addition of water lowers the yield of the *O*-isomer in the reaction of sodium phenoxide with allyl bromide in an alcoholic medium[84]. This effect becomes enhanced when the reaction is carried out in water or phenol. A sharp increase of the ratio of the *C*- and *O*-isomers is observed when fluorinated alcohols are used as solvents[72,83] (Table 9). The increase of the fraction of the *C*-alkylation product takes place in parallel with the increase of the tendency of the solvent towards the formation of strong hydrogen bonds with the oxygen atom of the phenoxide ion. Experimental evidence for the

selective solvation of the heteroatom of the ambident anion in protic media was obtained in a study[85] where a strong hypsochromic shift of the absorption maximum was observed in the ultraviolet spectrum of the anion of 1-nitroindene on passing from dipolar aprotic solvents to water and trifluoroethanol, which is the strongest donor species in the formation of a hydrogen bond.

An analogous effect was noted in the NMR and ultraviolet spectra of alkali metal phenoxides in solvents of different classes[86]. It is striking that the absorption bands of the 1-nitroindene anion in trifluoroethanol and of the *aci*-form of a nitro-compound in water are very similar. This shows that the reactivity of solvated anions of this kind approaches that of the protonated form, as a result of which the activation energy for the substitution reaction involving the other, unshielded centre is also much higher than in any aprotic medium. Indeed, the rate of alkylation of sodium phenoxide in water and trifluoroethanol is extremely low[83]. Selective solvation of the oxygen centre of the anion has been observed also for the enolate ions of β-dicarbonyl compounds. The low yield of the product of the *O*-alkylation of the potassium salt of AAE by diethyl sulphate in ethanol and particularly in *N*-methylacetamide and *N*-methylformamide (Table 7)[80], despite the exceptionally high value of ϵ and the high solvating capacity of these solvents in relation to alkali metal cations, is undoubtedly due to the selective solvation of the oxygen atom in the AAE anion via hydrogen bonding. A stronger hydrogen bond donor is necessary if selective solvation of the AcAc anion is to be possible. Such an effect is manifested in water and in trifluoroethanol[87]. The ratio of the *C*- and *O*-isomers is almost fully inverted in trifluoroethanol relative to alkylation in ethanol, where the *O*-isomer is virtually the only reaction product. The addition of water to the alcohol also alters the mode of reaction, and in 50% alcohol the only product of the alkylation reaction is 3-ethylacetylacetone. Thus, by altering slightly the reaction conditions, it is possible to change completely the mode of alkylation:



In another study[88], it was shown that the rate constant for the *O*-alkylation of the potassium salt of AAE by ethyl toluene-*p*-sulphonate increases by a factor of 400 on passing from ethanol to HMP, while the rate of *C*-alkylation increases only by a factor of 25. The decrease of the ratio of the *C*- and *O*-isomers by a factor of 16 when alcohol is replaced by HMP as the reaction medium reflects the influence of selective solvation on the mode of alkylation of the ambident AAE anion.

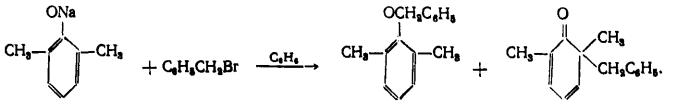
It is of interest to compare data for the selective solvation of various phenoxide and enolate ions. In conformity with the HSAB principle, protic solvents solvate, like hard Lewis acids, the harder oxygen centre of the ambident anion. The harder the oxygen centre of the anion, the harder the acid and the stronger the donor component of the hydrogen bond needed to shield the centre. The AAE anion is solvated selectively by ethanol. In relation to the AcAc ion, ethanol is an insufficiently hard Lewis acid; in this case methanol, trifluoroethanol, and water are effective. When the phenoxide ion is alkylated, the formation of the *C*-isomer is observed only in water, trifluoroethanol, and phenol (Table 9).

IV. DEPENDENCE OF THE REACTION PATHWAY ON THE STRUCTURE OF THE ELECTROPHILE

The most important factor determining the mode of alkylation of enolates and phenoxides is the nature of the electrophile. Here account must be taken simultaneously of the electronic and steric effects of the alkyl group and of the nature of the leaving group of the alkylating agent. Different ambident anions manifest different sensitivities in relation to the nature of the electrophile; phenoxides and naphthoxides are least sensitive. The alkylation of these salts by alkyl toluene-*p*-sulphonates, dialkyl sulphates, and alkyl halides usually leads to the formation of the corresponding ethers.

1. The Structure of the Alkyl Group

Claisen and Eisleb[89] showed that the products of the *C*-alkylation of alkali metal phenoxides can be obtained only when allyl and benzyl halides are used as alkylating agents. However, using the results of the gas–liquid chromatographic (GLC) analysis of reaction mixture, Kornblum and coworkers showed that, when sodium β-naphthoxide is acted upon by methyl iodide in ethanol, 12% of the *C*-isomer is formed and, following the replacement of methyl iodide by propyl bromide, only traces of the *C*-isomer are detected[72]. The use of allyl and benzyl halides as alkylating agents leads to a significant increase of the yield of *o*-substituted phenols. Thus Gomberg and Buchler[90] observed for the first time the formation of 50% of *o*-benzylphenol in the alkylation of sodium phenoxide by benzyl chloride in water. Somewhat later Claisen at al. isolated *o*-benzylphenol as the sole product of the reaction of sodium phenoxide with benzyl bromide in toluene or ether (in 80–90% yield)[91]. The composition of the mixture of benzylation products depends on the nature of the substituent in the benzene ring of benzyl bromide. It has been shown that, in the alkylation of sodium β-naphthoxide in acetone by benzyl bromide and *p*-nitrobenzyl bromide, only benzyl ethers are formed, while alkylation with *p*-methoxybenzyl bromide gives rise to a mixture of 47% of the *O*-isomer and 24% of 1-(*p*-methoxybenzyl)-2-naphthol.[92] The formation of *o*-allylphenol when allyl bromide in ether is used as the alkylating agent was observed by Claisen et al.[91] The yield of the *C*-isomer increases in alkylation by γ-substituted allyl bromides. The alkylation of sodium phenoxide by γ-phenylallyl bromide in benzene leads to the formation of *o*-(γ-phenylallyl)phenol only[93]. A significant increase of the yield of the *C*-isomer (a mixture of *o*- and *p*-alkylphenols) is observed in the alkylation of 2,6-disubstituted phenoxides, although the formation of the *o*-isomer requires in this case the breakdown of the aromaticity of the system. The formation of a considerable amount of dienone was observed in a study of the alkylation of the sodium salt of 2,6-dimethylphenol by benzyl bromide in benzene[94]:



A high yield of the dienone was obtained in the reaction of sodium 2,6-di-(t-butyl)-4-methylphenoxide with methyl iodide[95]. However, the alkylation of alkali metal phenoxides and naphthoxides leads to the formation of *O*-alkylation products except in the case of sterically hindered phenols.

The opposite behaviour is observed in the alkylation with alkyl halides of alkali metal and other metal enolates derived from ketones, esters, and β-dicarbonyl compounds. In this case, *C*-alkylation products are formed preferentially. The influence of the nature of the alkylating agent on the ratio of the *O*- and *C*-isomers has been studied in detail[12] in the alkylation of the sodium enolates of certain alkyl aryl ketones in ethyl ether and glymes (Table 10):

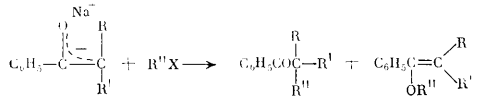


Table 10. The ratio of the products of the *O*- and *C*-alkylation of the sodium enolates of alkyl aryl ketones.

R	R′	Solvent	Alkylating agents					
			MeI	AllBr	EtBr	n-PrBr	Iso-PeBr	EtOTs
H	C_6H_5	DMF	0.0	0.0	0.0	—	0.0	—
CH_3	CH_3	Ether	0.0	—	—	0.0	—	0.63
CH_3	CH_3	DME	—	—	0.19	0.25	0.36	—
CH_3	CH_3	Diglyme	0.0	0.05	0.16	0.27	—	1.2
C_2H_5	CH_3	Diglyme	—	0.2	0.61	—	—	2.4
C_2H_5	C_2H_5	Diglyme	—	—	0.76	—	—	3.0
C_6H_5	C_6H_5	Diglyme	0.09	—	18	100	—	—
C_6H_5	C_6H_5	t-Butyl alcohol	0.04	—	1.4	2.5	—	—
C_6H_5	mesityl	t-Butyl alcohol	—	—	100	—	—	—

The data presented in Table 10 show that the ratio of the *O*- and *C*-isomers increases with increase of the length of the alkyl group in the alkylating agent and is very sensitive to the influence of the steric effect in the alkylating agent and the substrate. The fraction of the *O*-alkylation product increases with increase of the bulk of the substituent at the α-carbon atom of alkyl phenyl ketone, which is particularly notable for diphenylacetophenone and mesitylphenylacetophenone, which undergo mainly the *O*-alkylation reaction. *C*-Alkylation is more sensitive to the steric effect, since in this case the carbon atom in the product has the tetrahedral sp^3 configuration, in contrast to the planar sp^2 configuration arising in the *O*-alkylation of the enolate. Thus steric hindrance favours the *O*-alkylation of alkali metal enolates. The ratio of the *O*- and *C*-isomers increases on moving along Table 10 from left to right and from above downwards, which reflects the influence of the steric effect in the alkylating agent and the substrate on the mode of the alkylation reaction. The sharp increase of the products of the *O*- and *C*-propylation of the sodium enolate of diphenylacetophenone on passing from diglyme to t-butyl alcohol is caused, according to the authors, by the selective solvation of the enolate ion via hydrogen bonding. The influence of the structure of the substituent of the alkylating agent on the mode of the competing *C*- and *O*-alkylation reactions has also been studied for alkali metal salts of β-dicarbonyl compounds. The relative yield of the *O*-isomer in the alkylation of the sodium salt of 1-cyanocyclohexanone increases on passing from methyl iodide to ethyl, n-propyl, and isopropyl iodides (18, 35, 41, and 79% respectively), but falls sharply when allyl and benzyl bromides are used, for which the yields of the *O*-isomers are only 4 and 12%.[96] Bearing in mind that the reaction mixtures were analysed by the preparative separation of the components, presumably some of the data do not reflect the true ratio of the *C*- and *O*-isomers. The yield of the *C*-alkylation products is particularly high for allyl and benzyl halides, which we already noted previously for alkali metal phenoxides and isobutyrophenone enolates. A similar sequence has also been observed in the alkylation of the sodium salt of ethyl β-hydroxycoumarate in alcohol[97], where the ratio of the *C*- and *O*-isomers decreased in the sequence allyl ≫ benzyl > CH_3 > C_2H_5 > n-C_3H_7. When sodium enolate was allowed to react with dimethyl sulphate, only the *O*-alkylation product was isolated. A sharp increase of the yield of the *O*-isomer on passing from methyl iodide to ethyl iodide was also noted in a study of the *C*- and *O*-alkylation of the sodium salts of dihydroresorcinol in alcohols[31]; a further increase of the length of the carbon–carbon chain in the alkyl substituent has only a slight influence on the ratio of the products of *C*- and *O*-alkylation.

An important stage in the study of the dual reactivity of ambident enolate ions was reached with the report[98] that, under the classical conditions of the *C*-alkylation of the sodium salt of AAE by alkyl halides in alcohol (the Conrad method), 6–8% of the *O*-alkylation product is obtained when s-butyl iodide is used. This report stimulated systematic study of the dual reactivity of the enolates of β-dicarbonyl compounds using the most modern methods for the analysis of the reaction mixture. Before the appearance of this report, *O*-alkylation of alkali metal enolates of β-ketoesters and β-diketones was regarded as an unusual and to some extent an exceptional phenomenon. Only isolated examples were known in which *O*-alkylation was the main or at least the competing reaction pathway. In particular, it was known that, in the interaction of the sodium salt of AAE with chloromethyl ether in ethyl ether, ethyl β-alkoxycrotonate is formed[99], the enol ether being the main product of the methylation of AAE and AcAc with diazomethane.[100] Kabachnik and coworkers showed with the aid of GLC analysis[101] that a small amount of the *O*-alkyl derivative is formed even in the alkylation of the sodium salt of AAE by alkyl bromides in alcohol and also in the reaction of the dry sodium salt of AcAc with an alkyl iodide in the absence of solvent. The increase of the content of *O*-alkylation products on passing to reagents with s-alkyl substituents is noteworthy, this being associated with the steric hindrance to the competing *C*-alkylation reaction. The influence of the nature of the alkyl group on the ratio of the *C*- and *O*-isomers was investigated also in the alkylation of the tetrabutylammonium salts of AAE,[25] AcAc,[27] and benzoylmalonic ester[28] by alkyl iodides in chloroform (Table 11). A sharp increase of the yield of the *O*-isomer was also observed on passing to isopropyl iodide. The fraction of the *O*-alkylation product increases significantly when methyl iodide is replaced by ethyl iodide.

A thorough investigation of the influence of the structure of the alkyl group and of the leaving group of the alkylating agent on the mode of the *C*- and *O*-alkylation of the potassium salt of AAE in DMSO and HMP was carried out by Le Noble and Morris[23] (Table 12).

The relative yield of the *O*-isomer for any alkylating agent is significantly higher in HMP than in DMSO. The products of *CO*-dialkylation were detected in the above study with the aid of GLC. As noted previously, steric hindrance is very strongly reflected in the mode of the alkylation reaction. This effect is particularly notable relative to data for alkylation with propyl and isopropyl chlorides and s-butyl chloride, where the ratio of the

C- and *O*-isomers varies by a factor >4; neopentyl chloride alkylates the AAE enolate ion only at the oxygen atom. A similar sharp difference is observed on passing from benzyl chloride to diphenylmethyl chloride, whereupon the ratio of the *C*- and *O*-isomers decreases from 6.7 to 1.6. The data presented in Table 12 also indicate the necessity for taking into account the electronic effects in the alkyl group of the alkylating agent. The steric hindrance due to the allyl and propyl groups is approximately the same, but the ratios of the products of the *C*- and *O*-alkylation of potassium enolate under the influence of allyl and s-propyl chlorides nevertheless differ very markedly. It is quite evident that the difference is due to electronic effects. The high polarisability of the allyl group promotes substitution at the carbon atom of the enolate ion—the most polarised centre in the given ambident system.

Table 11. The alkylation of the tetrabutylammonium enolates of β-dicarbonyl compounds in chloroform.

RI	Yield*, %							
	C-isomer	*O*-isomer	*CC*-isomer	*C*-isomer	*O*-isomer	*CC*-isomer	*C*-isomer	*O*-isomer
	acetoacetic ester			acetylacetone			benzoyl-malonic ester	
CH_3I	80	—	10	98.5	—	—	100	—
C_2H_5I	83.5	—	9	72	12	16	54	46
$n\text{-}C_4H_9I$	90	—	5	87	13	—	47	53
$iso\text{-}C_3H_7I$	70	23.5	—	50.5	49.5	—	14	86

*The absolute yields of reaction products are quoted.

Extensive experimental data concerning the influence of the nature of the alkyl group on the mode of reaction of phenoxide and enolate ions are inconsistent with Kornblum's rule [102], which predicts the mode of alkylation of the ambident anion. The ratio of the *C*- and *O*-alkylation products should be determined by the competing interaction of the alkylating agent with two nucleophilic centres, as postulated in the classical theory of nucleophilic substitution. The significant difference is that in ambident nucleophiles both centres are linked via the mesomeric effect. According to Kornblum's rule, the fact that the transition state in the reaction between an ambident anion and the alkylating agent is identical with or similar to the S_N2 type promotes the formation of products corresponding to substitution at the most polarised reaction centre of the ambident anion; when a mechanism of the S_N1 type operates, attack is directed to the most electronegative centre, which behaves simultaneously as the centre of the highest electron density and the lowest polarisability. The formation of a mixture of products implies that the reaction proceeds in the intermediate S_N1–S_N2 region. The oxygen atom in enolate and phenoxide ions is the centre of maximum electron density and the carbon atom is the most polarised centre. According to Kornblum's rule, a higher ratio of the *C*- and *O*-isomers of the alkylation products was to be expected for allyl and benzyl halides than for other alkyl halides. The transition state in the reaction involving allyl, benzyl, and diphenylmethyl halides occurs as a rule in the boundary region with a much greater contribution of the S_N1 mechanism than for methyl, ethyl, and other alkyl halides with an n-alkyl group. [103] In all the examples quoted above, the ratio of the *C*- and *O*-isomers for benzyl and allyl halides is in fact much higher than for n-alkyl halides. Alkylation of alkali metal enolates by n-alkyl chlorides [23,104] is a bimolecular nucleophilic substitution process. However, the main products of this reaction are enol ethers, which is completely contrary to Kornblum's rule in its initial form. Finally, it is known that silylation of alkali metal enolates of carbonyl and β-dicarbonyl compounds [105,106] and certain esters [107] leads to the formation of silyl-substituted enols, despite the fact that this reaction proceeds via an S_N2 mechanism.

Table 12. The *C*- and *O*-alkylation of the potassium salts of acetoacetic ester.

Alkylating agent	Absolute yield, %		Relative yield, %							
			O-isomer		*C*-isomer		*CC*-isomer		*CO*-isomer	
	HMP	DMSO	HMP	DMSO	HMP	DMSO	HMP	DMSO	HMP	DMSO
n-Propyl chloride	89	73	61	47	23	25	8	28	8	—
Isopropyl chloride	78	52	81	62	19	38	—	—	—	—
n-Propyl bromide	—	66	—	31	—	40	—	23	—	—
n-Propyl iodide	—	74	—	14	—	50	—	36	—	—
Allyl chloride	88	80	17	0	45	100	38	—	—	—
Benzyl chloride	93	60	13	5	51	45	36	50	—	—
Methyl β-chloro-crotonate	—	60	—	10	—	90	—	—	—	—
s-Butyl chloride	75	—	86	—	14	—	—	—	—	—
Neopentyl chloride	13	—	100	—	—	—	—	—	—	—
Diphenylmethyl chloride	93	—	39	—	61	—	—	—	—	—
2,6-Dimethylbenzyl chloride	93	—	19	—	81	—	—	—	—	—
4-Methoxybenzyl chloride	88	—	11	—	57	—	32	—	—	—
4-Methylbenzyl chloride	97	—	13	—	54	—	33	—	—	—
4-Chlorobenzyl chloride	95	—	11	—	48	—	41	—	—	—
4-Trifluoromethyl-benzyl chloride	97	—	9	—	50	—	41	—	—	—

In a short review devoted to the theoretical principles of the problem of the dual reactivity of ambident anions, Gompper [108] treats Kornblum's rule somewhat differently. As a consequence of Coulombic attraction, a polar electrophile attacks primarily the atom of the ambident system which has the highest electron density. If the electrophile has a slight positive charge on the carbon atom linked directly to the leaving group, there is an enhancement of the role of the London intermolecular interaction dispersion forces, which stabilise the transition state involving the most polarised centre of the ambident anion. It is easily seen that this general formulation is in no way related to the classification according to which there exist two types of mechanisms of substitution at a saturated carbon atom; these mechanisms determine, according to Kornblum's view, the mode of reaction.

In conformity with Gompper's view, many reactions of enolates and phenoxides proceeding via the S_N2 mechanism lead to the formation of *O*-alkylation and *O*-acylation products. Gompper's view is close to Pearson's HSAB concept [46,109,110]. In conformity with the main postulate of this principle, an increase of the hardness of the alkyl group should promote *O*-alkylation. The sharp increase of the fraction of the *O*-isomer in the alkylation of alkali metal enolates [99] and enols [100] by chloromethyl ether and diazomethane must be attributed to the introduction into the alkyl group of hard methoxy- and diazo-groups. On the other hand, the tendency of allyl and benzyl halides to form products corresponding to substitution at the carbon atom of the enolate ion can be explained by the presence of the soft allyl or benzyl

group. Thus, knowing the relative hardness of the alkyl group linked to the same leaving group of the alkylating agent, it is possible, in principle, to predict the direction of attack on the ambident anion.

According to a current view, the alkyl group attached to an sp^3-hybridised carbon atom exhibits a small $-I$ effect. Certain thermodynamic and kinetic data [111-115] as well as dipole moment data [116] are consistent with this hypothesis. In a paper devoted to the application of the HSAB principle in organic chemistry, Pearson [109] quoted the following series based on the hardness of alkyl groups: t-C_4H_9 > iso-C_3H_7 > C_2H_5 > CH_3. However, there are few experimental data showing that the alkyl group attached to a saturated carbon atom has electron-accepting properties; furthermore, they are mainly concerned with the gas phase and it is not clear what situation obtains in the liquid phase. According to earlier and more common idea, based on kinetic data for S_N2 reactions in solution, the alkyl group at an sp^3-hybridised carbon atom exhibits a small $+I$ effect.

Table 13. The alkylation of the potassium enolate of acetoacetic ester with various alkylating agents in HMP (c_0 = 0.25 M).

R	X	Yield of isomer, %					t, °C
		total yield,	*O*-isomer	*C*-isomer	dialkylation products*	ratio of *O*- and *C*-isomers	
CH_3	OTs	96	89	7	4	8.1	20
	Br	87	14	42	44	0.16	20
	I	93	5	31	64	0.05	20
C_2H_5	OTs	90	88	11	2	7.5	20
	Cl	65	60	32	8	1.5	20
	Br	92	39	38	23	0.64	20
	I	95	13	71	16	0.15	20
n-C_4H_9	OTs	84	90	10	<1	9	20
	Cl	75	68	27	5	2.1	20
	Br	88	40	47	13	0.67	20
iso-C_3H_7	OTs	78	84	16	—	5.3	20
	Cl	70	81	19	—	4.3	20
	Br	90	69	31	—	2.2	20
	I	77	40	60	—	0.66	20
s-C_4H_9	OTs	78	86	14	—	6.2	40
	Cl	75	86	14	—	6.2	40
	Br	70	78	22	—	3.6	20
	I	60	56	44	—	1.3	20
Allyl	OTs	88	22	43	35	0.28	20
	Cl	88	17	45	38	0.21	20
	Br	92	—	48	52	0	20
	I	90	—	50	50	0	20
Neopentyl	OTs	40	100	—	—	—	80
CH_3OCH_2	Cl	75	100	—	—		45

*When RI and RBr are used, only $\alpha\alpha$-dialkyl-AAE derivatives are formed. When the alkylating agents are RCl and ROTs, a mixture of *CC*- and *CO*-dialkylation products is formed.

The ratio of the *C*- and *O*-isomers in the alkylation of enolate ions is determined by both electronic and steric factors, the latter always increasing the fraction of the *O*-isomer. Since it is not possible to estimate separately the contribution of each effect for the same leaving group, it remains obscure whether the increase of the ratio of the *C*- and *O*-isomers in the series s-C_4H_9 < iso-C_3H_7 < C_2H_5 < CH_3 [23,27,101] is caused by the simultaneous operation of both factors, which is consistent with the concept of the electron-accepting nature of the alkyl group attached to a saturated carbon atom, or whether the hardness of

Table 14. The alkylation of sodium acetylacetonate with various alkylating agents in HMP (c_0 = 0.5 M).

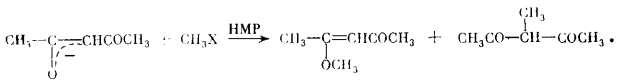
R	X	Yield of isomer, %					t, °C
		total yield, %	*O*-isomer	*C*-isomer	dialkylation products	ratio of *O*- and *C*-isomers	
CH_3	OTs	77	97	3	—	32	20
	Br	59	12	88	<1	0.14	20
	I	54	3	96	1	0.03	20
C_2H_5	OTs	90	90	10	—	9	20
	Cl	—	62	33	5	1.73	20
	I	84	17	60	23	0.20	20
	Br	73	42	41	17	0.72	20
n-C_3H_7	OTs	85	92	8	—	11	20
	Br	85	48	38	14	0.9	20
n-C_4H_9	OTs	81	96	4	—	24	20
	Cl	65	87	12	1	7.1	20
	Br	—	62	23	15	1.6	20
	I	—	24	39	37	0.32	20
n-C_6H_{11}	OTs	66	99	1	—	99	60
	Cl	65	95	4	1	19	50
	Br	84	68	12	20	2.1	65
	I	87	46	16	38	0.85	60
iso-C_3H_7	OTs	80	86	14	—	6.1	50
	Cl	—	79	21	—	3.5	50
	Br	79	70	30	—	2.3	50
	I	82	52	48	—	1.1	50
s-C_4H_9	OTs	53	85	15	—	5.7	50
	Cl	—	83	17	—	4.9	50
	Br	43	81	19	—	4.3	50
	I	62	62	38	—	1.6	50
Allyl	OTs	79	37	9	54	0.60	20
	Br	—	7	18	75	0.08	20
	I	85	—	22	78	—	20
Neopentyl	OTs	65	100	—	—	—	70
CH_3OCH_2	Cl	32	100	—	—	—	55
	I	—	82	18	—	4.5	20

*When RI, RBr, and Allyl OTs are used, only the *CC*-dialkylation product is formed. With RCl as the alkylating agent, there is a small admixture (~1%) of the *CO*-dialkylation products.

alkyl groups varies in a sequence which is the inverse of that proposed by Pearson and the electronic and steric effects therefore act in opposition and the ratio of the *C*- and *O*-isomers is determined by the dominant contribution of the steric effect when the leaving group consists of iodide, bromide, or chloride ions. In order to determine the relative hardness of alkyl groups, a study was made of the influence of the alkyl substituent at a saturated carbon atom of the alkylating agent on the ratio of the products of the *C*- and *O*-alkylation of alkali metal enolates of AAE and AcAc by alkyl toluene-*p*-sulphonates in HMP [117,118] (Tables 13 and 14). In this case, the sequence based on the influence of the alkyl group on the ratio of the *C*- and *O*-isomers, namely s-C_4H_9 ≥ iso-C_3H_7 > C_2H_5 > CH_3, is exactly the opposite of the sequence observed for halides. This implies that the two effects are opposed and that the polar effect plays a dominant role for alkyl toluene-*p*-sulphonates. The increase of the ratio of the *C*- and *O*-isomers in the sequence s-C_4H_9 > iso-C_3H_7 > C_2H_5 > CH_3 shows that the alkyl substituent at the reaction centre of the alkylating agent is electron-donating. Thus the hardness of alkyl groups in the alkylation of enolate ions varies contrary to the Pearson's hardness sequence derived from thermodynamic data. The qualitative identity of the sequence characterising the influence of alkyl groups in the alkylation of alkali metal enolates by alkyl halides and Pearson's hardness sequence implies that the steric effects of alkyl groups play the dominant role for these softer alkylating agents.

2. Effect of the Leaving Group

The nature of the leaving group of the alkylating agent is one of the factors controlling the mode of alkylation of alkali metal enolates. The fraction of the product of the *O*-alkylation of enolate ions increases in the sequence $I^- < Br^- < Cl^- < F^- < SO_4^{2-} < OTs^- < CF_3SO_3^-$. The data presented in Tables 13 and 14 show that the ratio of the *O*- and *C*-isomers in the methylation of the potassium salt of AAE and the sodium salt of AcAc decreases by a factor of 10^2–10^3 when methyl toluene-*p*-sulphonate is replaced by methyl iodide as the alkylating agent [117,118]:



X=OTs	97%	3%
X=I	3%	97%

The effect of the leaving group is distinct although less pronounced also in the ethylation of the two enolate ions. However, for the even softer iso-C_3H_7 and s-C_4H_9 groups, the nature of the leaving group has only a very weak influence on the mode of reaction. Thus the replacement of toluene-*p*-sulphonate by chloride or bromide in s-C_4H_9X is hardly reflected in the composition of the mixture of the alkylation products and for s-C_4H_9I the ratio of the *O*- and *C*-isomers is actually greater than unity. Thus the effect of the leaving group depends in its turn on the hardness of the alkyl group of the alkylating agent.

The influence of the leaving group on the ratio of the *C*- and *O*-alkylation products has also been investigated in the alkylation of the benzophenone dianion [19]. The fraction of the *O*-isomer increases sharply on passing from methyl iodide to methyl toluene-*p*-sulphonate, for which *O*-alkylation becomes the sole reaction pathway. Although the benzophenone dianion is an extremely unusual ambident system, the overall dependence of the ratio of the *C*- and *O*-isomers on the nature of the leaving group remains the same as for the usual ambident enolate ions: $OTs^- < SO_4^{2-} < Br^- < I^-$. In the alkylation of the lithium salt of buryrophenone by pentyl halides in DMSO, the ratio of the *C*- and *O*-isomers diminishes from 5.0 for $C_5H_{11}I$ to 2.0 for $C_5H_{11}Br$ and to 0.77 for $C_5H_{11}Cl$. [119] In the study by von Auwers [96] quoted previously, it was also shown that, when the sodium salt of 1-cyanocyclohexanone is alkylated by alkyl halides in alcohol, bromides give rise to a higher yield of *O*-alkylation products than iodides. In the alkylation of the enolates of β-dicarbonyl compounds, the same effect of the leaving group is observed as for the enolates of monocarbonyl compounds. Kornblum et al. [120], who investigated the influence of the leaving group in the benzylation of the sodium salt of ethyl β-hydroxycoumarate in DMF, noted that the relative yields of the *O*-alkylation product are 18, 29, and 50% for the iodide, bromide, and chloride respectively. The same sequence has been observed in the alkylation of the potassium salt of AAE by alkyl halides in DMF [77] and in DMSO [22] and also in the alkylation of the sodium salt of a derivative of octalone by benzyloxymethyl halides in dioxan [121]. In all these instances, the fraction of the *O*-alkylation product increases as the leaving group becomes a harder Lewis base. Stetter and Dierichs [31] studied the influence of the leaving group on the ratio of the products of the *C*- and *O*-alkylation of the sodium enolate of dihydroresorcinol in alcohol [31] (Table 15). The ratio of the *C*- and *O*-isomers diminishes by a factor of at least 100 on passing from the iodide to the toluene-*p*-sulphonate. In another study, it was established on the basis of infrared spectroscopic and NMR data that the alkylation of the potassium enolate of AcAc by methyl iodide in acetone entails the formation of the *C*-alkylation product alone, while the use of dimethyl sulphate under analogous conditions leads to the formation also of a certain amount of the *O*-isomer [122]. The employment of triethyloxonium fluoroborate as the alkylating agent has a particularly promoting effect on the formation of a considerable amount of the *O*-alkylation product. Thus the alkylation of lithium enolate derived from 4-t-butylcyclohexanone by triethyloxonium fluoroborate in methylene chloride results in the formation of 23% of the ethyl ether of the enol [123], while the potassium enolates of cyclohexanone and acetophenone give rise to 69% of the enol ether under analogous conditions in DME. [124] Kabachnik and coworkers [125] showed that, when the sodium salt of AAE is treated with triethyloxonium fluoroborate in ether, ethyl β-ethoxycrotonate is also formed in a low (~15%) yield, while the sodium salt of AcAc gives rise to 28.5% of the *O*-isomer under the same conditions.

Table 15. The alkylation of the sodium salt of dihydroresorcinol.

RX	n-C_4H_9I	n-C_4H_9Br	n-C_4H_9OTs
Yield of *C*-isomer, %	43.5	30	0
Yield of *O*-isomer, %	56.5	70	100

The effect of the leaving group in the alkylation reactions of ambident anions can be explained within the framework of the HSAB principle by the so called symbiotic effect of the stabilisation of the transition state. It is suggested that a group of either several soft bases or several hard ligands at a saturated carbon atom of the alkylating agent should stabilise the transition state and should increase the rate of the process. In other words, the rate of reaction should increase if the entering and leaving groups are simultaneously either soft or hard bases. Pearson and Songstad adduce convincing evidence for the occurrence of the symbiotic effect in bimolecular nucleophilic substitution at a saturated carbon atom [126]. In relation to ambident enolate ions, this implies that the rate of the *C*-alkylation reaction increases if the leaving group in the alkylating agent is a soft base (iodide, bromide). The opposite effect—an increase of the rate of *O*-alkylation—is achieved when the leaving group is a hard base (toluene-*p*-sulphonate, perchlorate, fluoroborate, etc.). In certain cases such a change in the relative rates of the two processes leads to a complete change in the mode of reaction.

The ratio of the rate constants for the *C*- and *O*-alkylation of enolate anions under the influence of alkyl iodides and alkyl toluene-*p*-sulphonates characterises the degree of hardness of the two nucleophilic centres. In the *C*-ethylation of the enolate ion of α-ethylacetoacetic ester in DMF, [127] $k_{I^-}/k_{OTs^-} = 420$. In general, this is the expected result for the soft centre of the enolate ion. It was found that the rate of the competing *O*-alkylation reaction under the influence of ethyl iodide is also higher than in the reaction with ethyl toluene-*p*-sulphonate

(k_{I^-}/k_{OTs^-} = 13). Such a change in the rate of reaction on passing from a hard to a soft alkylating agent indicates a considerable softness of the AAE ambident anion. The same behaviour was observed a little later [128]. However, according to the latter data [128], the rate of reaction under the influence of ethyl fluorosulphonate and ethyl trifluoromethanesulphonate ("ethyl triflate") ($CF_3SO_3C_2H_5$) is much higher than for ethyl iodide, i.e. the rate of reaction does not vary in parallel with increasing softness of the leaving group. This anomaly is probably associated with the change in the nature of the interaction between the reacting species from a purely ion–dipole interaction for ethyl toluene-*p*-sulphonate, ethyl bromide, and ethyl iodide to a nearly ion–ion interaction in the case of ethyl fluorosulphonate and ethyl trifluoromethanesulphonate. The ratio of the *C*- and *O*-ethylation products decreases as usual under these conditions on passing from the iodide to the toluene-*p*-sulphonate and further to the trifluoromethanesulphonate ($CF_3SO_3^-$). Thus the fraction of the products of the *O*-alkylation of the enolate ions of carbonyl and β-dicarbonyl compounds increases as the leaving group becomes a harder base.

In other instances, for example in the alkylation of the alkali metal enolates of esters, which are apparently softer Lewis bases, *C*-alkylation products are formed exclusively even on treatment with toluene-*p*-sulphonates, fluorosulphonates, and trialkyloxonium salts. The opposite case is observed in the alkylation of the phenoxides and enolates derived from certain β-diketones (dihydroresorcinol, trifluoroacetylacetone, hexafluoroacetylacetone, etc.) when the *O*-isomer becomes the main reaction product (and sometimes the only product) even when an alkyl iodide is used. Consequently, on the basis of the symbiotic effect alone, one cannot predict in the general case the mode of alkylation of the enolate ion; it is only clear that the ratio of the *C*- and *O*-isomers will decrease as the leaving group becomes a harder base.

V. THE INFLUENCE OF THE NATURE OF THE AMBIDENT ANION

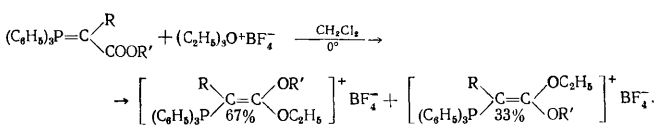
Analysis of data for the influence of the nature of the electrophile, the metal cation, and the solvent on the dual reactivity of the phenoxides and enolates derived from various carbonyl and β-dicarbonyl compounds and esters shows that there is a certain tendency in the influence of these factors. However, different systems exhibit unequal sensitivities. Certain ambident anions show an enhanced tendency towards *O*-alkylation and *O*-acylation, while for other enolate ions it has not so far been possible to detect the formation of the *O*-isomer. Hence the nature of the ambident system itself determines to an even greater extent than the electrophile the mode of reaction of the ambident enolate anion. Thus the enolates of alkyl phenyl ketones form a much larger amount of the *O*-isomer than the enolates of dialkyl ketones. According to the data of Zook et al. [12], the alkylation of the enolates of acetophenone and butyrophenone in monoglyme and diglyme by alkyl halides leads to the formation of considerable amounts of the *O*-alkylation products (Table 10). Under the same conditions, dialkyl ketones and alicyclic ketones undergo only *C*-alkylation.

The considerable influence on the mode of reaction by the nature of the ambident anion itself is manifested most clearly when data on the alkylation and acylation of the enolate ions of ketones and esters are compared. Whereas the mode of reaction can be altered selectively for the enolates of carbonyl and β-dicarbonyl compounds by choosing an appropriate medium or counter ion or by varying the "hardness" of the leaving group of the alkylating agent, the enolate ions of esters form solely *C*-alkylation and *C*-acylation products for reasons which are little understood. Lithium enolate derived from ethyl acetate and t-butyl acetate is alkylated at the carbon atom when acted upon by the diphenylcyclopropenylium cation [129], alkyl halides, methyl fluorosulphonate, and triethyloxonium fluoroborate [130]. Mainly as a result of studies by Rathke and coworkers and by Cregge and coworkers, excellent general methods have been developed for the *C*-alkylation and *C*-acylation of the lithium salts of esters and dilithium salts of carboxylic acids [131–136]. The lithium salts, obtained by treating the ester with lithium di-isopropylamide or lithium isopropylcyclohexylamide in THF at −78°C, can even be isolated in a pure form in many instances. Lithium enolates in benzene and toluene solutions are stable for several hours at least and, on treatment with an alkyl or acyl halide, give excellent yields of ester homologues or β-ketoesters [137]. A characteristic feature of these processes is the complete absence of dialkylation and diacylation products. The alkylation and acylation of lithium salts of esters is apparently the best preparative method for the synthesis of esters and β-ketoesters in a chromatographically pure form. The formation of mono-*C*-alkylation and acylation products, unaccompanied by the competing reaction involving the oxygen atom of the lithium enolate, has been observed in all cases.

Only three instances of the *O*-alkylation of ester enolates have apparently been described hitherto, among which the formation of a keten acetal was reliably demonstrated in only one case. *O*-Alkylation of an ester was observed for the first time in the intramolecular alkylation of the sodium enolate derived from the β-bromoethyl esters of cyanoacetic, malonic, acetoacetic, and *p*-nitrophenylacetic acids [138]. According to the author, of the four possible reaction pathways, only intramolecular *O*-alkylation actually occurs, leading to the formation of a keten ethylene acetal as the sole reaction product. The structure of the reaction products was demonstrated by infrared spectroscopy. Since the reaction products are derivatives of keten ethylene acetal, their structure could be demonstrated unambiguously by ^{1}H NMR data, but these were not quoted [138]. If keten ethylene acetals are indeed formed in the given reaction, as suggested by the author, the intramolecular *O*-alkylation of the ester is determined exclusively by the influence of the entropy factor, since in any other case one would expect the formation of a *C*-alkylation product, bearing in mind that the bromide ion is a soft base.

In another study, the mechanism of the transesterification reaction is accounted for by postulating that the sodium enolate of methyl *O*-(tetrahydropyranyl)mandelate is alkylated at the oxygen atom of the enolate ion under the influence of benzyl and allyl halides with formation of a keten acetal, which is then converted into benzyl or allyl mandelate. The authors do not present any evidence for the formation of a keten acetal as an intermediate. Benzyl and allyl halides are traditional agents for the selective *C*-alkylation of the enolate ions derived from ketones and β-dicarbonyl compounds. The *O*-alkylation of the enolate ion of an ester under the influence of these reagents therefore appears to be an improbable reaction pathway even theoretically. Naturally, the transesterification mechanism may not in fact include a stage where a keten acetal is formed as an intermediate. The only

reliably established example of the *O*-alkylation of an ester is the reaction between triethyloxonium fluoroborate and alkoxycarbonylmethylenetriphenylphosphorane, described by Bestman et al.[140]:



In this case, a mixture of the *cis*- and *trans*-isomers of a keten acetal is formed in a nearly quantitative yield (Table 16). The structure of the reaction products was demonstrated reliably by ^{1}H NMR and infrared spectroscopic data.

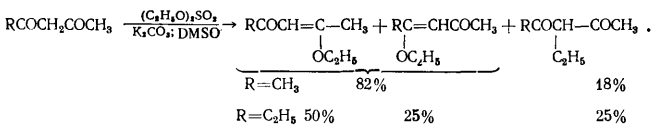
Table 16. The *O*-alkylation of alkoxycarbonylmethylenetriphenylphosphorane with triethyloxonium fluoroborate.

R	R′	Yield, %	R	R′	Yield, %	R	R′	Yield, %
H	CH_3	67	$C_6H_5CH_2$	C_2H_5	97	$CH_2COOC_2H_5$	C_2H_5	98
H	C_2H_5	68	C_6H_5	C_2H_5	99	$COOC_2H_5$	C_2H_5	95

Appreciable differences are observed between the capacities for *C*- and *O*-alkylation in the reactions of the enolates of cyclic and acyclic carbonyl compounds. For example, the ratio of the *C*- and *O*-isomers increases by a factor of 10 on passing from 2-ethoxycarbonylcyclohexanone to the α-ethylacetoacetic ester in the alkylation of sodium enolate by isopropyl iodide in DMSO.[141] A similar effect was observed also when data for the alkylation of the sodium salt of AAE and the sodium enolates of cyclic β-ketoesters by β-dimethylaminoethyl chloride were compared[142,143].

In a series of cyclic β-ketoesters, the ratio of the *C*- and *O*-isomers formed depends on the ring size. According to the results of Rhoads and Hasbrouck[144], the ratio of the products of the *C*- and *O*-alkylation of sodium enolates derived from 2-ethoxycarbonylcyclanones with 5–10-membered rings by isopropyl iodide in DMSO varies as follows: 1.74 (n = 3); 1.34 (n = 4); 15 (n = 5); 7.72 (n = 6); 32 (n = 8). Such marked differences between the ratios of the *C*- and *O*-isomers obtained for these compounds and the enhanced tendency of the five- and six-membered systems to undergo *O*-alkylation can be caused by a wide variety of factors: the different pK_a values of the β-ketoesters, conformational effects, and the different degrees of dissociation of the sodium enolates in DMSO. If the reacting species is not only the enolate ion of the 2-ethoxycarbonylcyclanone but also ion pairs, whose relative contributions for each β-ketoester may be different, the ratios of the *C*- and *O*-isomers quoted in the above study do not correspond to the dual reactivity of the free enolate ion. Finally, even a change in the formal charge in the ambident system alters markedly its capacity for reaction via two pathways. In contrast to the monoanions, the dianions of β-dicarbonyl compounds, formed when a β-diketone or a β-ketoester is treated with two equivalents of sodium amide in liquid ammonia[145] or after successive treatment with sodium hydride and butyllithium in DHF,[146] form only γ-*C*-alkylation products regardless of the nature of the alkylating agent. The alkylation of the dianions of β-dicarbonyl compounds has been investigated in detail by Hauser and coworkers (see the review of Harris and Harris[147]).

It is difficult to find a characteristic of an ambident nucleophile which might serve as a basis for correlation with the reactivity and the ratio of the *C*- and *O*-isomers, at least within the framework of ambident anions of a single class. Presumably, in the absence of steric hindrance, the pK_a of the ketone of the β-dicarbonyl compound can serve as a quantity of this kind. Indeed, according to Gelin and Rouet[148], the relative yield of the *C*-isomer is somewhat higher in the alkylation of the potassium enolate of acetylpropionylmethane than in the alkylation of the potassium enolate of acetylacetone:



This is consistent with the hypothesis that the ratio of the *C*- and *O*-isomers varies in parallel with the pK_a of the carbonyl compound. The data available at present show, however, that such a regularity does not occur in most instances. Thus, according to Heiszwolf and Kloosterziel[124], in the alkylation of the potassium salts of acetophenone, cyclohexanone, AAE, and AcAc by dimethyl sulphate in DMSO, the ratios of the *C*- and *O*-alkylation products are approximately the same for all the compounds enumerated, although the acidities of ketones and β-dicarbonyl compounds in DMSO differ by at least 3–7 pK_a units. The ratio of the *C*- and *O*-isomers in the ethylation of the potassium enolate of diacetylacetone also differs insignificantly from the analogous quantity for the weaker acid AcAc.[148]

When data for the alkylation of enolate ions and their closest analogues—ketimines, which also contain a hard nucleophilic centre, are compared, a considerable similarity between the effects of the leaving group is observed. The fraction of the *N*-alkylation product is particularly large when the leaving group of the alkylating agent is a hard base (sulphate, toluene-*p*-sulphonate).[149] In full agreement with the influence of the symbiotic effect, *C*-alkylation predominates for a soft leaving group and a small counter ion[149–151]:

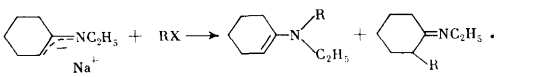
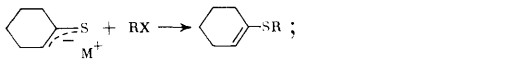


Table 17 lists the relative yields of the products of the *N*-alkylation (enamines) and *C*-alkylation of the sodium salts of certain substituted imines[149]. The ratio of the products of *N*- and *C*-ethylation is seen to be completely inverted for the anion of the acetophenone anil when ethyl iodide is replaced by triethyloxonium fluoroborate as the alkylating agent. The same effect has been observed also for other imines. Enamine is the main reaction product in the alkylation of the sodium salt of diethyl ketone *N*-ethylimine by a hard alkylating agent—dimethyl sulphate, but in the reaction involving a soft alkylating agent only the *C*-isomer was detected in the products, without an admixture of the enamine.

A completely different situation is observed in the alkylation of the sulphur analogues of carbonyl compounds and esters. As already stated, the mode of alkylation of alkali metal enolates of cyclohexanone depends mainly on the nature of the leaving group: alkyl halides form *C*-alkylation products, the *O*-isomer predominating in the reaction products on alkylation with diethyl sulphate

and ethyl toluene-*p*-sulphonate in DMSO.[75] On the other hand, alkali metal salts of tricyclohexanone are alkylated and acylated exclusively at the sulphur atom regardless of the nature of the leaving group[152]:



R = CH_3, C_2H_5, iso-C_3H_7, or $C_6H_5CH_2$; X = Hal or OTs.

The formation of *S*-alkyl derivatives has also been observed in the alkylation of salts of β-thioketoesters[153-155] under conditions such that the enolates of the acetoacetic and benzoylacetic esters are alkylated only at the carbon atom:

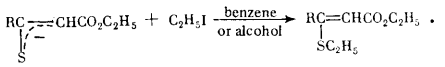
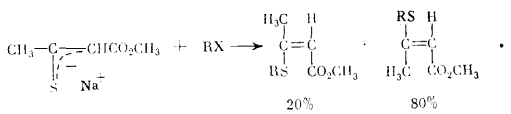


Table 17. The *C*- and *N*-alkylation of the sodium salts of *N*-substituted imines.

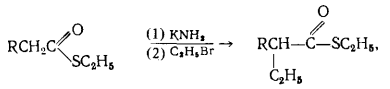
Solvent	Imine	Alkylating agent	Reaction products, %			
			unchanged imine	enamine	*C*-alkylated product	poly-alkylated products
Diethylcellosolve	Acetophenone anil	$(C_2H_5)_3O^+BF_4^-$	8	88	4	—
		$(C_2H_5O)_2SO_2$	9	49	42	—
		C_2H_5I	5	5	90	—
HMP	Cyclohexanone *N*-ethylimine	$(C_2H_5)_3O^+BF_4^-$	29	53	18	—
		$(CH_3O)_2SO_2$	11	75	10	4
		C_2H_5I	15	17	56	12
HMP	Diethyl ketone *N*-ethylimine	$(C_2H_5)_3O^+BF_4^-$	26	29	42	3
		$(CH_3O)_2SO_2$	17	57	26	—
		C_2H_5I	20	—	71	9

The salts of the β-thioketothioester $CH_3CSCH_2COSC_2H_5$ react similarly[153]. The alkylation of the sodium salt of thio-AAE by alkyl bromide or iodide in alcohol results in a mixture of the *Z*- and *E*-forms of β-alkylthiocrotonates in proportions of ~1 : 4 [154]:

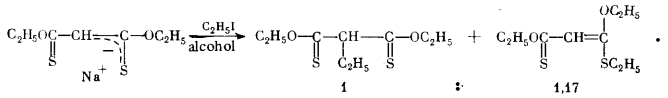


20% 80%

An enormous difference between the reactivities of enolates and enethiolates is also manifested in the alkylation of alkali metal salts of esters and their sulphur analogues. Thus, whereas the enolates of thiolo-esters form *C*-alkylation products like ordinary esters, for example[156]:

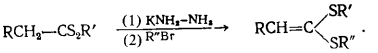


the enolates of thiono-esters[157,158] and dithioesters behave quite differently. The sodium salt of the thiono-ester of malonic acid reacts with ethyl iodide to form a mixture of the products of the *C*- and *S*-ethylation in approximately equal amounts:



1 : 1.17

The enethiolates of dithioesters are alkylated exclusively at the sulphur atom with formation of keten thioacetals in both polar and non-polar media[159,160]:



The reaction is insensitive both to the influence of the counter ion and to the effect of the leaving group. The different mode of reaction of enethiolates compared with enolates is undoubtedly due to the high polarisability or, in terms of the HSAB principle, the softness of the sulphur atom as the nucleophilic centre. However, the enormous difference in the behaviour of these two classes of ambident anions cannot be accounted for from the standpoint of a purely phenomenological approach, to which the application of the HSAB principle is in essence restricted when it is used to account for the reactivity of ambident anions. This remark applies fully also to the difference between the reactivities of the enolate ions of carbonyl compounds and esters. Evidently, in this case too the problem cannot be solved within the framework of the above concept. All these general theoretical problems require the development of a different approach to the problem of the dual reactivity of ambident systems.

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