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Dual Reactivity of Ambident Anions

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The present state of the problem of the dual reactivity of ambident anions, i.e. anions with two reactive centres, is reviewed. The factors influencing the reactions of such anions are discussed and certain relations are interpreted from the standpoint of the principle of hard and soft acids and bases.
The bibliography includes 120 references.

CONTENTS

I. Introduction 844
II. Relations between the structure and dual reactivity of ambident anions 844
III. Thermodynamically and kinetically controlled reactions 845
IV. Nucleophilic properties of the reactive centres of ambident anions 845
V. Behaviour of ambident anions in substitution reactions at a saturated carbon atom (alkylation) 847
VI. Behaviour of ambident anions in substitution reactions at an unsaturated carbon atom and at heteroatoms 855

I. INTRODUCTION

Ambident anions are those which have two reactive centres linked into a single conjugated (mesomeric) system†. Ambident anions are capable of forming two series of derivatives in reactions with electrophilic agents, i.e. according to Nesmeyanov and Kabachnik[3] they exhibit dual reactivity. Examples of anions of this kind are the enolates of β-dicarbonyl compounds, phenoxides, cyanide, thiocyanate, and nitrite ions, the anions of nitro-compounds, oximes, carboxylic acid amides, dialkyl phosphorothioites, and dialkyl phosphorothioates, the anions of heterocyclic aromatic compounds or their derivatives (pyrrole, indole, 2-hydroxypyridine, hydroxypyrimidine, etc.), and others.

The capacity of such anions to react in two ways has been known for a long time but the factors influencing the mode of reaction have been virtually unknown and only in the last fifteen–twenty years have studies illuminating this problem been carried out.

Although there exist two modern reviews on the dual reactivity of ambident anions, published in 1964[2] and 1965[4] respectively, this field is developing so rapidly that a new review of the literature is required, particularly since during the period which has elapsed new hypotheses, which can be applied to this problem, have appeared and become established in chemistry. On the other hand, a fairly large number of contradictory data have accumulated in the literature and require a detailed discussion.

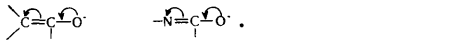
Therefore the author's aim is not to review the entire enormous literature on the dual reactivity of ambident anions, particularly since extensive literature data, apart from the reviews already mentioned[2,4], have been compiled also in a number of earlier publications[1,3,5,6], but merely to give a general account of the present state of the problem in the light of the work carried out in recent years.

† The term "ambident anion" was proposed by Kornblum[1]. Gompper[2] suggests that such compounds be called "ambifunctional", but this name is less widely used. The term "polydent anions" is employed to designate anions with three and more reactive centres.

II. RELATIONS BETWEEN THE STRUCTURE AND DUAL REACTIVITY OF AMBIDENT ANIONS

As already stated, both reactive centres of the ambident anion form a single mesomeric system and therefore the negative ionic charge is distributed between the two atoms which can be involved in the formation of a covalent bond on reaction with electrophilic agents. However, as a rule the main bulk of the charge is concentrated at one of the nucleophilic atoms and usually the atom which is more electronegative (according to Pauling's electronegativity scale of atoms); at the same time the less electronegative donor atom is more polarised[1,3,7]‡. Thus the bulk of the negative charge in enolate anions and the anions of nitro-compounds is concentrated at the oxygen atom, while the carbon atom is more polarised; a similar relation obtains between the oxygen and nitrogen atoms in the nitrite ion and the anion of 2-hydroxypyridine, and between the nitrogen and carbon atoms in the pyrrole and cyanide anions.

Despite the fact that one donor atom has a higher electron density than the other, the reactions with electrophilic agents by no means always take place at the point with the highest electron density; very often the covalent bond is formed with the less electronegative atom. Nesmeyanov and Kabachnik[3] call this phenomenon reactive centre transfer§. They note[3] that the capacity of ambident anions to react with reactive centre transfer is related not so much to the distribution of the negative charge in the anions as to the capacity of the conjugated system for the electromeric shift of electron density necessary for the reaction, for example:



‡ The high polarisability of the less electronegative atom is probably due either to the considerable double bond character of its linkage, as in the case of the α-carbon atom in enolates, or a significant polarisability of the atom as such (phosphorus, sulphur, etc. atoms).

§ The old concept that the reason for the dual reactivity of ambident anions is the existence of two anionic tautomers, each of which gives rise to its own series of derivatives, was disproved in the same investigation[3].

Thus the problem of the relation between the structure of the ambident anion and its capacity to react in different ways reduces largely to finding the relation between the structural parameters of the anion and the ease of the electromeric shift of electron density.

It is well known that certain ambident anions show a greater tendency to react in a particular way than others even though their structures are similar. Thus the anions of acetoacetic ester and acetylacetone exhibit a much greater tendency to react via the oxygen atom, than the anion of malonic ester; the anion of phenol also tends to react much more readily via the oxygen atom than the anion of β-naphthol (see, for example, Kornblum and Lurie[8]). In contrast to the anions of monobasic carboxylic acids, the phthalimide ion is alkylated virtually only at the nitrogen atom[3]. More such examples may be quoted. At the same time it must be emphasised that these data are purely qualitative, since so far very few studies have been made in which the dual reactivities of various ambident anions, including those with similar structures, were compared in sufficient detail under standard conditions using electrophiles of different types.

Unfortunately there are no reliable criteria which would relate the electron structure or some other parameters of ambident anions (or their conjugate acids) to their capacity to react with transfer of the reaction centre.

An attempt has been made[9] to relate the dual reactivity of the anions of β-dicarbonyl compounds to the distribution of π-electron density and certain other electronic parameters, obtained by the LCAO-MO method (in the Hückel approximation). However, as stated above, the capacity of the ambident anion to react in a particular way is not directly related to the distribution of electron density. At the same time one cannot exclude the possibility that this approach will prove fruitful in the case of electrophiles with significant positive charges, which usually react at the site with the greatest electron density (see Section V). Moreover, the tendency to react via the oxygen atom can probably be estimated using data for the variation of the electron density at this atom in a series of related anions[9]. However, we believe that in the general case the electron density at a carbon atom cannot be correlated with its reactivity (as was done by Gren and Vanag[9]) (see also Klopman[10]).

This does not of course imply that in principle the quantum-chemical approach is inapplicable to the estimation of the dual reactivity. The recent study by Klopman[10], where the possibility in principle of a quantum-mechanical calculation of the reactivity of ambident systems (by the method of polyelectron perturbation) was demonstrated, has attracted attention from this standpoint.

Thus the relation between the structure and dual reactivity of ambident anions constitutes one of the least investigated problems.

III. THERMODYNAMICALLY AND KINETICALLY CONTROLLED REACTIONS

In the discussion of the factors influencing the mode of the reactions of ambident anions, it is necessary to distinguish clearly thermodynamically and kinetically controlled reactions. In kinetically controlled reactions the composition of the products is determined by the relative nucleophilicity of each of the donor atoms in the ambident anion in relation to the given electrophilic agent. On the other hand, in thermodynamically controlled reactions the most stable compound is the final product regardless of the reaction mechanism. The energy (heat) of formation of the compound, which can be estimated from the bond and conjugation energies[2], is a measure of its stability.

The reaction is thermodynamically controlled when the interaction of the electrophilic agent with the ambident anion is reversible. When the relative amounts of the reaction products are not determined by the nucleophilicity of the donor atoms but by their basicity in relation to the atom at which the substitution takes place—for example in alkylation by the basicity in relation to a saturated carbon atom[11].

It has been noted[2] that in many cases conclusions concerning the products of thermodynamically controlled reactions can be drawn from the basicity of particular donor atoms in relation to the proton: an electrophilic agent will form a bond preferentially with the atom of the ambident anion which is most basic in relation to the proton (the basicity in relation to the proton usually decreases in the series C > N > O > S).

The available data confirmed this hypothesis. For example, the product of the alkylation of the enolates of β-dicarbonyl compounds at the more basic atom (the carbon atom) is thermodynamically more stable than the *O*-alkylation product[12]. Similarly the product of the *N*-alkylation of the nitrite ion (nitroalkane) is more stable than the *O*-alkylation product (the corresponding alkyl nitrite)[13].

The question arises: in which cases should one expect the reaction with electrophilic agents to be thermodynamically controlled? In other words, in which cases are the reaction products capable of decomposing into the starting materials? Gompper[2] noted that this occurs frequently when the experiments are carried out with stable cations or when relatively stable cations (for example triarylcarbonium ions, the carbonium ions formed in the Mannich reaction, and aryldiazonium ions) are formed as intermediates. Thermodynamic control is also observed in reactions with electrophilic agents containing multiple bonds (for example, aldehydes and ketones—the addition of ambident anions to the carbonyl group). Moreover the tendency to undergo thermodynamically controlled reactions should increase with the stability of the anion. Thermodynamically controlled reactions are dealt with in greater detail by Gompper[2].

Henceforth in the discussion of factors influencing the dual reactivity of ambident ions, we shall consider only kinetically controlled reactions, although one must bear in mind that the possibility of thermodynamic control was not fully excluded in all the investigations considered.

IV. NUCLEOPHILIC PROPERTIES OF THE REACTIVE CENTRES OF AMBIDENT ANIONS

The problem of the dual reactivity of ambident anions in kinetically controlled reactions is the problem of the relative nucleophilicity of each of the donor atoms of the anion linked into a single mesomeric system.

The reactivity of the electron donor (nucleophilic agent) in substitution reactions (nucleophilicity) is determined by a number of factors[7,14-16]. The principal of these are the basicity and polarisability of the given nucleophilic atom and also the α-effect (the presence of an unshared electron pair at an adjacent atom)[7,17]. It follows that the contribution of each of these parameters to the overall reactivity of the nucleophilic agent depends to a considerable degree on the nature of electrophilic atoms at which the substitution takes place[7,14].

However, in the case of ambident anions it is impossible to determine the polarisability and basicity of each reaction centre independently of one another and consequently it is impossible to estimate in this way their nucleophilicity, since the two nucleophilic atoms are not independent but are linked into a single mesomeric system. Indeed in order to determine a parameter such as polarisability, it is necessary to know the molecular refraction of each of the donor atoms of the anion[7,17], whereas in fact it is only possible to determine the refraction of the anion as a whole. As regards the basicity (in relation to the proton), it is found that the protonation of the anion necessary to determine the basicity takes place with very significant redistribution of electron density in the conjugated system and consequently the equilibrium position does not reflect the "independent" basicity of each donor atom in the anions, particularly the atom with the lower electron density.

At the same time, although it is impossible to estimate quantitatively (or semiquantitatively) the reactivity of the donor centres of the ambident anion, it is possible to make a purely qualitative estimate of the relative nucleophilicities of both atoms of the anion in relation to a specific type of electrophilic agent. The principle of hard and soft acids and bases recently put forward by Pearson[13,18-21] is particularly suitable in this context. According to this principle, all Lewis bases (electron donors or nucleophilic agents) can be divided into two classes: hard and soft bases (some of these bases occupy an intermediate position). Similarly Lewis acids (electron acceptors or electrophilic agents) are also divided into two classes—hard and soft acids—some occupying an intermediate position.

Hard bases are Lewis bases with a high electronegativity, low polarisability, and resistant to oxidation, i.e. hard bases firmly retain their valence electrons.

Soft bases are Lewis bases with a low electronegativity, high polarisability, and readily oxidised, i.e. they retain their valence electrons less firmly.

Hard acids are Lewis acids with a high electronegativity, and a low polarisability; these properties correspond to a high positive charge and a small size of the acceptor atom and the absence from it of an unshared electron pair.

Soft acids are Lewis acids with a low electronegativity and a high polarisability; this property corresponds to a low positive charge (or absence of charge), a large size of the acceptor atom, and the presence of an unshared electron pair (p or d electrons) at this atom. It has been noted that not all the properties enumerated must necessarily be present together to assign an acid to a particular class[20].

The fundamental postulate of the concept of hard and soft acids and bases is as follows: hard bases are preferentially coordinated to hard acids and soft bases to soft acids.

According to Pearson, organic and inorganic molecules are regarded as acid–base complexes. For example, CH_3I is a complex of the acid CH_3^+ and the Lewis base I^-, CH_3COCl is a complex of the acid CH_3CO^+ and the base Cl^-, etc.[13,20] Consequently, it is possible to estimate the hardness (softness) of a given molecule in particular reactions, i.e. to estimate the hardness or softness of a particular reaction centre (atom) and of course it is necessary to take into account the mutual effects of all components of the complex.

Pearson enumerates the most widespread hard and soft acids and bases[19,20]. Examples of hard bases are: OH^-, H_2O, RO^-, ROH, R_2O, F^-, Cl^-, $CH_3CO_2^-$, SO_4^{2-}, NO_3^-, and RNH_2; soft bases: RS^-, RSH, R_2S, I^-, R_3P, C_2H_4, H^-, R_3C^-, and others.

Examples of hard acids are: the proton, cations of alkali and alkaline earth metals, aluminium, the carbonyl carbon atom (RCO^+), the phosphorus atom in the phosphoryl group (R_2PO^+), the sulphur atom in the sulphonyl group (RSO_2^+), and the hydrogen atom involved in the formation of a hydrogen bond; soft acids: cations of univalent copper, silver, univalent and divalent mercury, the sulphenyl sulphur atom (RS^+) and selenium and tellurium atoms in analogous groupings (RSe^+, $ReTe^+$), iodine, bromine, and oxygen atoms in those molecules where they behave as electrophilic centres (I^+, Br^+, HO^+, RO^+), BH_3, carbenes, and others. Among acids with intermediate properties mention should be made of the saturated carbon atom (R_3C^+) and the aromatic carbon atom ($C_6H_5^+$). For a more detailed list of soft and hard acids and bases, see Pearson[19,20] (and also Pearson and Songstad[13]).

It should be noted that the principle of hard and soft acids and bases is empirical and in fact constitutes a generalisation of experimental data. However, recently Klopman[10] gave a theoretical explanation of the principle of hard and soft acids and bases using the quantum-mechanical perturbation theory. He showed that[10] the softness (hardness) of a particular acid (acceptor atom) is determined by the energy of the lowest vacant orbital and the softness of a base (donor atom) by the energy of the highest occupied orbital, and, apart from the energies of orbitals themselves, account must be taken also of the solvation energy, i.e. the softness (hardness) is influenced by the solvent.

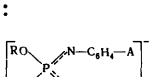
We shall now consider the applications of the concept of hard and soft acids and bases to ambident anions. As shown in Section II, one of the atoms of the ambident anion is usually more electronegative and the major part of the negative ionic charge is concentrated there, while the second atom is more polarisable.

Comparison of these data with the characteristic features of hard and soft bases (see above) leads to the conclusion that usually the less electronegative and more polarisable donor atom of the anion is a soft base while the more electronegative atom is a hard Lewis base[7,10,13,22]¶.

Thus in enolate anions the oxygen atom is hard and the carbon atom is soft[10,22]; in the thiocyanate anion the nitrogen atom is hard and the sulphur atom is soft[10]; in the nitrite ion the oxygen atom is hard and the nitrogen atom is soft[10]; etc.

The application of the principle of hard and soft acids and bases to ambident anions makes it possible to predict the preferential mode of reaction of these anions with various electrophilic agents: the soft donor atom of the ambident anions will be preferentially bound to a soft electrophilic agent, while the harder atom will be bound to a hard electrophilic agent. As will be shown below, this useful principle is confirmed by numerous experimental data.

¶ There are of course sometimes also ambident anions where both donor atoms have similar electronegativities and are included, according to Pearson's classification in a common series of bases (soft or hard). However, in this case too one of the atoms will be softer than the other. Such a situation will arise when, for example, both donor atoms are the same and differ only in substituents, as in the anions of *OO*-dialkyl-*NN'*-diarylphosphamidines (see Kabachnik and Gilyarov[23] and the references quoted by them):



An important conclusion, which may be derived from this principle, is as follows: the order of the relative nucleophilicities of the donor atoms of ambident anions can be decisively influenced by the nature of the electrophilic atoms at which substitution takes place. Therefore subsequently the principal features of the behaviour of ambident anions will be examined for each type of electrophilic centre separately. In the first place we shall examine substitution at a saturated carbon atom for which there are most data and then at other electrophilic centres (a carbonyl carbon atom, certain heteroatoms, etc.). This does not, of course, imply that the relative nucleophilicities of the donor atoms are the sole factors which influence the mode of reaction of ambident anions. As will be shown in subsequent sections, factors such as steric effects, solvent effects, the state of the salt in solution, and certain others frequently play a very considerable and sometimes a decisive role.

V. BEHAVIOUR OF AMBIDENT ANIONS IN SUBSTITUTION REACTIONS AT A SATURATED CARBON ATOM (ALKYLATION)

The factors which influence the mode of reactions of ambident anions have been investigated in greatest detail for the alkylation of these anions (substitution reactions at a saturated carbon atom). These data will be examined in the present section.

1. Electronic Effects in the Alkylating Agent

In 1955 two papers appeared almost simultaneously and proved to have a very significant influence on the understanding of the dual reactivity in ambident systems at the present time. In the first of these by Nesmeyanov and Kabachnik[3], apart from the general postulates concerning the causes of dual reactivity and the relation between the phenomenon with tautomerism, mentioned above, the fundamental relations determining the mode of reaction of ambident anions were generalised insofar as it was possible on the basis of the experimental data available at the time.

In particular it was pointed out that the mode of reaction is very significantly influenced by the electrophilic properties of the alkylating agent. Thus in salts of ketoenols or carboxylic acid amides where the bond between the oxygen atom of the anion and the metal cation is highly ionised and the alkylating agent is a cation or a strongly electrophilic molecule, a reaction involving the oxygen atom frequently takes place; on the other hand, when the electrophilic properties of the reactant are weak, the reaction takes place at the carbon atom of the enolate anion or correspondingly at the nitrogen atom of the amide anion.

Thus the electronic structure of the alkylating agent has a very significant influence on the mode of reaction of ambident anions.

In another paper, by Kornblum et al.,[1] it was shown that, when silver nitrite reacts with alkyl halides, the tendency towards alkylation at the atom with the maximum electron density, i.e. at the oxygen atom of the ambident nitrite ion, increases sharply on passing from primary to secondary and then to tertiary halides. This behaviour is related to the finding that the reaction of silver nitrite with alkyl halides takes place via an intermediate S_N2–S_N1 mechanism and, with increasing S_N1 character (the carbonium character) of the transition state, there is an increase in the tendency towards *O*-alkylation of the nitrite ions; on the other hand, the carbonium character of the transition state increases in the above series of alkyl halides.

Indeed, the silver ion coordinated to the halogen atom of the alkyl halide polarises the carbon–halogen bond, induces at the carbon atom a partial positive charge, and thereby increases the S_N1 character of the transition state, the ease of polarisation of the carbon–halogen bond increasing on passing from primary to secondary and further to tertiary alkyl halides and consequently the carbonium character of the transition state also increases in this series†.

Kornblum et al.[1] quoted a number of other data confirming his idea of the decisive effect of the nature of the transition state on the mode of alkylation of the nitrite ion; in particular, it was shown for the reaction of substituted benzyl bromides with $AgNO_2$ that the proportions of *O*- and *N*-alkylation of the nitrite ion are not associated with steric effects.

Generalising their own and the literature data, Kornblum et al.[1] put forward an extremely important rule, the essential feature of which may be formulated as follows: when an ambident anion reacts with electrophilic agents, an increase in the S_N1 character of the transition state increases the tendency towards the reaction at the most electronegative atom, i.e. the atom with the highest electron density. Conversely, an increase in the S_N2 character of the transition state leads to an increase of the tendency towards the formation of a bond with the less electronegative atom (that is, the more polarisable atom with a lower electron density).

In the light of this rule, the difference in the behaviour of silver and alkali metal salts of ambident anions becomes understandable. Silver ions are a very effective means of increasing the carbonium character of the transition state, polarising the carbon–halogen bond by electrophilic interaction with the halogen atom, while alkali metal atoms do not have this property.

Hence, when silver salts are employed, there should be an increase in the tendency towards reactions at the atom with the maximum electron density (compared with alkali metal salts). Conversely, when silver salts are replaced by alkali metal salts, there is an increase in the tendency towards the formation of a covalent bond with the atom of the ambident anion where the electron density is lower.

Kornblum et al. quote a number of examples confirming this conclusion. Thus in the reaction of nitrite ions with alkyl halides, the replacement of silver nitrite by sodium nitrite (or other alkali metal nitrites) leads to a sharp increase in the fraction of *N*-alkylation products and a corresponding decrease of the fraction of *O*-alkylation products[1,24]. Similarly in the alkylation of the anion of 2-hydroxypyridine by ethyl iodide the silver salt gives mainly the *O*-derivative, while the potassium salt gives only *N*-ethylpyridone[25,26]. Alkylation of the silver salts of carboxylic acid amides by alkyl halides favours *O*-alkylation in a similar manner, while the alkali metal salts give the *N*-derivatives (for the literature, see Kornblum et al.[1]). Alkali metal cyanides react with alkyl halides to form mainly nitriles, while silver cyanide forms isonitriles[27,28], etc.

† This is associated with the fact that the more stable the carbonium ion which the alkyl halide can form the greater is the degree of polarisation of the carbon–halogen bond under the influence of the silver ion.

It should not of course be thought that the use of silver salts will always lead solely to alkylation products at the site of maximum electron density. The capacity to react in a particular way is in the first place the function of the structure of the alkyl halide. In the case of alkyl halides which are incapable of undergoing a significant polarisation of the carbon–halogen bond under the influence of silver ions, the reaction at the less electronegative centre may prevail. For example, in the interaction of the esters of α-iodocarboxylic acids with silver nitrite the yield of *N*-alkylation products reaches 80–85%.[29] In the methylation of the silver salt of 2-hydroxypyridine by methyl iodide (in dimethylformamide) the yield of the *N*-alkylation product is 74% and that of the *O*-alkylation products only 12%.[30]

Moreover, the ratio of the products will also depend on the nature of the anion: in the case of anions which are particularly apt to undergo reactions at the more polarisable centre, even in the presence of silver ions, the reaction involves virtually exclusively this centre, as happens, for example, in the alkylation of the silver salts of 2-hydroxypyrimidine and 2-hydroxy-5-nitropyrimidine by primary alkyl halides (the *N*-alkylation products are mainly formed)[31].

Apart from silver ions, the carbonium ion character in the transition state can of course be effectively increased also by other metal ions, for example those of mercury and copper, which are capable of polarising the carbon–halogen bond and inducing a positive charge at the carbon atom. Similarly other well known factors promoting the occurrence of the S_N1 process will increase the tendency towards reactions at the centre with the maximum electron density.

Kornblum et al.[1] quote certain examples of this kind. Thus the sodium salt of acetoacetic ester is alkylated by primary alkyl halides only at the carbon atom (in solvents of relatively low polarity) while chloromethyl ether, which usually reacts with nucleophilic agents by an S_N1 mechanism, forms only the *O*-derivative[32]. Certain other examples of the greater tendency of α-chloroethers towards reactions at the oxygen atom, compared with alkyl halides, are quoted by Nesmeyanov and Kabachnik[3].

It should be borne in mind that the nature of the transition state is by no means always as clear as in the case of silver salts. Even when electrophiles with a high tendency towards reaction by an S_N1 mechanism are employed, the nature of the process is quite obscure, since the reaction mechanism is influenced, apart from the structure of the alkylated agent, also by other factors, the nature of the solvent being decisive in most cases‡.

One should also be on one's guard against a misunderstanding of Kornblum's rule. From the standpoint of present-day knowledge, this rule should not be interpreted as implying that, when a reaction takes place via an S_N2 mechanism, the product resulting from the attack on the least electronegative atom is always formed. Kornblum's rule implies only that, for a given specific ambident anion, the transition from the S_N2 mechanism to an intermediate mechanism S_N2–S_N1 (and further to S_N1) will be accompanied by an increase of the fraction of the products of the alkylation of the centre with the maximum electron density and that, other conditions being equal, this increase will be greater the more pronounced is the carbonium ion character of the transition state. Conversely, for a given anion the transition from an S_N1 mechanism to an S_N2 mechanism will lead to a decrease of the fraction of this product. On the other hand, the relative amounts of the products in an S_N2 process will depend on other factors (see below) including the structure of the anion itself and its capacity for a transfer of reaction centre. Kornblum's rule can be readily interpreted in terms of Pearson's principle of hard and soft acids and bases (see Section IV). Indeed the increase of carbonium ion character of the transition state under the influence of the solvent or an electrophilic catalyst (for example, silver ions) implies that the C–X bond is polarised in the alkylating agent R_3C–X, in consequence of which a partial positive charge appears (or increases) at the carbon atom and hence its polarisability diminishes. This implies that the carbon atom at which the substitution takes place becomes harder. On the other hand, an increase in the hardness of an electrophilic centre will increase, in accordance with the principle of hard and soft acids and bases, the tendency towards reactions at the harder atom of the ambident anion, i.e. the atom with the maximum electron density (usually the more electronegative atom).

The interpretation with the aid of the principle of hard and soft acids and bases extends the scope of Kornblum's rule. In the first place it should be noted that the appearance of a significant positive charge at the carbon atom of the electrophile and the decrease of the polarisability of this atom (increase of its hardness) may be related not only to the effect of particular reagents (electrophilic catalysts or the solvent) but also to the effect of highly electronegative polar groups or atoms in the electrophile itself. Examples of this kind will be quoted below in connection with the problem of the effect of the substituting group on the mode of reaction.

Moreover, factors which increase the hardness of the saturated carbon atom will of course operate also in relation to other electrophilic centres.

Consequently Kornblum's rule can be formulated as follows in a general form: an increase in the positive charge at an electrophilic centre (for example a carbon atom) and also a decrease in its polarisability will increase the tendency towards the reaction at the atom in the ambident anion with the greatest electron density§. The converse postulate holds for the donor atom with the lowest electron density.

It must be emphasised that the effect of the electrophilic properties of the substrate on the mode of reaction of ambident anions (see above), noted by Nesmeyanov and Kabachnik[3], agrees well with the above postulate, since an increase in the electrophilic properties of the substrate is identical with an increase in the hardness of the acceptor atom.

Indeed, although the order of the electrophilic reactivities depends on the nature of the nucleophilic agent, one usually has in mind the electrophilicity in relation to highly basic nucleophiles with little tendency towards polarisation, i.e. hard Lewis bases. Consequently in this sense an increase in electrophilicity implies a higher reactivity in relation to the harder donor atom of the ambident anion.

Since its publication (1955), Kornblum's rule became generally recognised. However, recently a number of papers have been published in which the rule is criticised.

‡ Usually the reaction mechanism is strongly affected also by electrophilic catalysts: for example Ag^+ and Hg^{2+} ions or compounds such as $AlCl_3$, SbF_5, AsF_6, and certain others.

§ That is, the contribution of electrostatic forces to the overall reactivity increases.

Thus Cardillo et al.[33] found that, in the alkylation of the sodium derivative of indole in tetrahydrofuran (THF), the yield of *C*-alkylation products increases and that of *N*-alkylation products falls on transition from primary to secondary and further to tertiary alkyl bromides. Hence the authors conclude that, contrary to Kornblum's rule, an increase in the S_N1 character of the process favours attack at the least electronegative atom (carbon atom).

However, we believe that the observed relations, are not associated with a change in mechanism (the reaction is carried out in a relatively non-polar aprotic solvent which does not favour S_N1 processes) but merely with steric effects, since models show that in indoles alkylation at the nitrogen atom is sterically more difficult than at a carbon atom (in the 3-position of the pyrrole ring).

Cardillo et al.[33] and Le Noble and Puerta[34] consider that another contradiction with Kornblum's rule is the fact that allyl and benzyl halides, which the authors believe should impart to the transition state an appreciable S_N1 character, show a considerable tendency to alkylate the centre with the minimum electron density, greatly exceeding in this property the corresponding saturated alkyl halide.

This type of behaviour is general, since it is observed in the alkylation of various ambident systems: the enolates of acetoacetic ester[34] and acetophenone derivatives[35], the β-naphthoxide anion[36,37], salts of 2-hydroxypyridine[30], 2-hydroxypyrimidine[31], pyrrole[38], indole[33], etc. In all these examples the fraction of *O*- or correspondingly *N*-alkylation in the presence of benzyl and allyl derivatives is much less than when the corresponding n-propyl and ethyl halides are employed and is approximately at the level for methyl halides.

However, the widely held view that allyl and benzyl halide derivatives react preferentially by a unimolecular nucleophilic substitution mechanism (S_N1) is erroneous. Indeed, despite the fact that these halides are capable of forming relatively stable carbonium ions even in media favouring S_N1 processes (water, alcohols), the reaction with nucleophilic agents takes place only via an S_N2 mechanism[39]. Alkylation of the ambident phenoxide anions by halides of this kind in water is also an S_N2 process[40,41]. Moreover, allyl and benzyl halides are greatly superior in their reactivity in typical S_N2 reactions to the corresponding saturated halides[42].

Thus the contradiction with Kornblum's rule is only apparent, particularly since in the studies quoted above the alkylation was investigated in the majority of cases in aprotic dipolar solvents for which S_N1 processes are relatively a typical[43].

It is noteworthy that the reactivities of nucleophiles towards a particular electrophile in S_N2 reactions may be expressed by the equation[44,45]

$$\lg (k_N/k_0) = \alpha E_n + \beta H,$$

where k_N is the rate constant for the given nucleophilic agent, k_0 the rate constant for a standard nucleophilic agent (usually the solvent), E_n and H are constants characterising the nucleophiles, and α and β are constants characterising the electrophiles; α is the polarisability of the atom at which the substitution takes place[46] and β is a measure of the positive charge at this atom[47].

In substitution at a saturated carbon atom the β constant is so low that the term βH may be neglected[48] (see also Palm[49]) and the reactivity of the electrophilic agent in S_N2 reactions can be measured simply by the polarisability of its acceptor atom (in the absence of significant steric effects).

Consequently the higher reactivity of allyl and benzyl halides in S_N2 reactions compared with the corresponding saturated halogeno-derivatives is related to the higher polarisability of the allyl (benzyl) carbon atom. This implies in turn that the allyl (benzyl) carbon atom is a softer Lewis acid than the acceptor carbon atom of the corresponding saturated halide, which we believe to account for the very high tendency of allyl and benzyl derivatives to react at the more polarised, i.e. the softer centre in the ambident anion.

If this view is correct, then in general an increase in the reactivity of the alkylating agent in bimolecular nucleophilic substitution reactions will increase the tendency towards reactions involving the more polarised atom in the ambident anion¶.

Indeed, the available data confirm that the tendency to react at the more polarised (less electronegative) atom decreases in the series (see, for example, Refs. 30, 34, 35, 50) $CH_3X > C_2H_5X > n\text{-}C_3H_7X >$ iso-C_3H_7X (for the same groups X and identical conditions), which corresponds to the variation of reactivity in S_N2 processes.

In many cases this relation can of course be explained by steric effects, particularly for branched-chain halides. In addition, particularly strong steric effects, which prevent the attack on one of the centres of the ambident anion, may reverse this series. Such examples will be quoted in the next subsection.

It has now become clear that the nature of the substituted group X in the alkylating agent RX has a significant influence on the mode of reaction of ambident anions. Thus in the alkylation of the anion of the acetoacetic ester in solvents of a wide variety of polarities the fraction of *O*-alkylation products increases when X† is varied in the series $RI < RBr < RCl < (RO)_2SO_2$, i.e. the tendency towards reaction at the atom with the maximum electron density increases with increase of the electronegativity of X[34,51-54].

A similar relation was observed also in the alkylation of certain other anions. For example, in the ethylation of the anions of the series of monocarbonyl compounds the fraction of *O*-alkylation products increases sharply on transition from C_2H_5Br to $p\text{-}CH_3C_6H_4SO_2OC_2H_5$.[35] In the alkylation of the pyrrole anion the fraction of the *N*-alkylation product increases on passing from allyl bromide to allyl toluenesulphonate[38]. In the reaction of salts of *p*-toluenesulphinic acid with CH_3I the *S*-methylation product (sulphone) is mainly formed, and, when dimethyl sulphate, methyl toluenesulphonate or alkoxyphosphonium salts are employed as alkylating agents, the *O*-methylation product is formed (ester of sulphinic acid)[55].

The question arises how the effect of the substituted group on the mode of reaction of ambident anions may be explained‡. One of the explanations was given by Beletskaya, Reutov, and coworkers[53]: when the electronegativity of the X group increases, there is a simultaneous increase of the partial positive charge at the carbon atom at which the substitution takes place and a decrease in its polarisability[47], which indicates an increase in the electrophilicity of the alkylating agents. In other words, there is an increase in the hardness of the acceptor carbon atom

¶ The same idea was put forward by le Noble and Puerta[34] albeit without any explanation.

† When R and the reaction conditions remain constant.

‡ This effect is not related to a change in mechanism, since in the studies quoted the reactions were carried out under the conditions of an S_N2 process.

and consequently an increase in the tendency towards reaction at the harder centre of the ambident anion.

Another explanation of this phenomenon in terms of the principle of hard and soft acids and bases was given by Pearson and Songstad[13,22]. By considering the transition state of S_N2 processes, these workers concluded that the grouping of several soft or several hard bases around the carbon atom at which substitution takes place stabilises the transition state and hence increases the rate of reaction (the so called symbiotic effect). Hence it follows that, when the substituting group X is eliminated as an anion which is a hard Lewis base (X = Cl or OSO_2OR), the electrophilic agent reacts at a higher rate at the harder centre of the ambident anion. Conversely, when X^- is a soft base (X = Br or I), then the reaction at the softer centre predominates. It must be emphasised that not all ambident anions are equally sensitive to changes in the substituted group. Thus in the anions of 2-hydroxypyridine[30] and particularly 2-hydroxypyrimidine and its derivatives[31] the change in the group eliminated has little effect on the mode of reaction.

An apparent contradiction with the above relations in the alkylation of certain ambident anions by *p*-nitrobenzyl derivatives (*p*-$NO_2C_6H_4CH_2X$) should be pointed out. Thus in the reaction of these derivatives with the lithium salt of 2-nitropropane the fraction of the *O*-alkylation product decreases in the following sequence as X is varied: I > Br > *p*-$CH_3C_6H_4SO_2O$ > Cl, with a corresponding increase in the fraction of *C*-alkylation[56,57]. However, subsequently it was found that in this case *C*-alkylation is a radical-anion chain process and not a nucleophilic substitution reaction[58-61]:

$$p\text{-}NO_2C_6H_4CH_2X + (CH_3)_2C{=}NO_2^- \rightarrow [p\text{-}NO_2C_6H_4CH_2X]^{\cdot-} + (CH_3)_2C^{\cdot}{-}NO_2$$
(A) (B)

$$B \rightarrow p\text{-}NO_2C_6H_4\dot{C}H_2 + X^-,$$
(C)

$$A + C \rightarrow [(CH_3)_2C(NO_2){-}CH_2C_6H_4{-}NO_2\text{-}p]^{\cdot-},$$
(D)

$$D + p\text{-}NO_2C_6H_4CH_2X \rightarrow (CH_3)_2C(NO_2){-}CH_2C_6H_4{-}NO_2\text{-}p + B \quad \text{etc.}$$

On the other hand, nucleophilic substitution leads solely to *O*-alkylation.

The ratio of the *C*- and *O*-alkylation products reflects merely the competition between two different reactions. When nucleophilic substitution is faster than the radical-anion process, then *O*-alkylation predominates (X = I); on the other hand, when nucleophilic substitution is slow (for example, when X = Cl), the radical reaction predominates and consequently *C*-alkylation takes place preferentially. The anion of 2-ethoxycarbonyl-3-coumaranone reacts by a similar mechanism with *p*-nitrobenzyl derivatives[62,63].

In connection with the problem of the effect of the substituted group, the alkylation of ambident anions by trialkyloxonium salts should be examined. The trialkyloxonium cation R_3O^+ is strongly electrophilic, i.e. it should be fairly hard and should exhibit an appreciable tendency towards reactions involving the centre with the highest electron density. The available literature data largely confirm this conclusion.

For example, the anions of acetoacetic ester and of acetylacetone are usually alkylated by primary alkyl halides at a carbon atom in media of low polarity[6,50], while in the reaction where the triethyloxonium salt (in ether) is employed *C*-alkylation is accompanied by appreciable *O*-alkylation[64]. The triethyloxonium salt reacts similarly with the diethyl phosphorothioate anion (a mixture of *S*- and *O*-derivatives is formed; with alkyl halides, only *S*-alkylation takes place[65]), the anion of 2-hydroxypyridine (both *O*- and *N*-alkylation take place)[66], and certain other ambident systems. The anions of nitroalkanes give only *O*-alkylation products[67-69].

However, in the alkylation of the anion of acetoacetic ester in hexamethylphosphoramide (HMP) the triethyloxonium salt gives an unexpectedly lower amount of the *O*-alkylated product than the less electrophilic diethyl sulphate[52,53]. The authors suggest that in this case the alkylating agent is not the triethyloxonium cation itself but its complex with HMP, which reduces significantly its electrophilicity.

It is noteworthy that in the general case the interaction of an ambident anion with an alkylating agent of opposite sign need not by any means necessarily lead to products of attack on the centre with the maximum electron density. According to Kornblum[1], for reaction at the most electronegative atom to occur, it is more important that the bond between the alkyl residue and the group to be eliminated should break readily, which is not always so with 'onium salts. Moreover, examples are known where 'onium salts show a lower tendency towards reactions involving the centre with the maximum electron density than other alkylating agents.

Thus, in the alkylation of the anion of acetoacetic ester with a benzyldimethylphenylammonium salt, the *C*-alkylation product is formed in high yields[70]. The anions of mononitroalkanes usually give only *O*-alkylation products, but in the reaction with diphenyliodonium salts they are phenylated at a carbon atom[71,72]. Other examples are also known.

Carbonium ions are harder Lewis acids than oxonium salts and consequently in kinetically controlled reactions they should alkylate preferentially the centre of maximum electron density. However, the available data, although extremely limited, show that this is not always the case.

Thus for the most reactive carbonium ion selectivity may be lost owing to the extremely high reactivity; a decrease in the energy of the carbonium ion may lead to an increase of selectivity. Relations of this kind are observed in reactions of phenoxide ions with carbonium ions[8]: on passing from $(CH_3)_3C^+$ via $(C_6H_5)_2\dot{C}H$ to $(C_6H_5)_3C^+$, the fraction of *O*-alkylation increases. While the trimethylcarbonium ion gives about 25% of the *O*-alkylated isomer and about 75% of the *C*-alkylated isomer, the percentages of the two isomers produced by the triphenylcarbonium ion are about 95% and about 5% respectively.

Diazomethane, which is rather an unusual alkylating agent, in many cases methylates preferentially the centre with the maximum electron density in reactions with the conjugate acids of ambident anions (see, for example Refs. 55, 73, and 74).

Kornblum[1] explained this phenomenon by the following sequence of reactions:

$$R{-}CCH_2COOC_2H_5 \xrightarrow{CH_2N_2} R{-}C(O^-){=}CHCOOC_2H_5 + \dot{C}H_3N_2 \rightarrow R{-}C(OCH_3){=}CHCOOC_2H_5 + N_2.$$

i.e. in the first stage of the process diazomethane behaves as a base, which results in the formation of an ambident anion and a methyldiazonium ion. The latter, which exhibits an appreciable tendency towards *O*-alkylation reactions, methylates the centre with the maximum electron density.

The amount of data on the application of other diazoalkanes is much less. It is known that in the alkylation of

α-pyridones diazoethane gives a much higher yield of the O-alkylation product than diazomethane[75].

In conclusion of this section, we may note that according to Pearson a saturated carbon atom is an intermediate (boundary) Lewis acid (see Section IV) and therefore, as can be seen from the data quoted above, even relatively slight changes in the structure of the alkylating agent and also in the reaction conditions (see below) lead to appreciable alteration in the mode of alkylation of ambident anions.

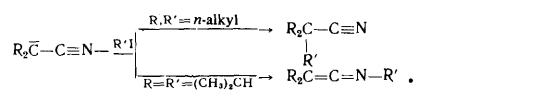
2. Steric Effects

In those cases where one of the reaction centres of the ambident anion is sterically more accessible than the other, steric factors have a very appreciable influence on the mode of reaction, frequently surpassing in this respect the electronic effect, particularly when the steric requirements of the alkylating agent are also stringent.

Thus, in the alkylation of potassium phenoxide by alkyl iodides (in a mixture of t-butyl alcohol and the dimethyl ether of tetraethylene glycol), only the O-alkylation product is formed, while in the case of 2,6-di-(t-butyl)phenoxide both O- and C-alkylated derivatives are formed under these conditions, the fraction of the C-alkylation products (mainly in the *p*-position) increasing sharply on passing from methyl iodide to ethyl and further to isopropyl iodide (in the latter case C-alkylation takes place exclusively)[76].

Thus a decrease in the steric accessibility of the oxygen atom compared with a carbon atom (particularly in the *para*-position) has a very significant effect on the mode of reaction. This effect increases with steric hindrance in the alkyl halide and leads to results opposite to those which would have been expected from purely electronic effects in the alkyl halide (see p. 6).

Alkylation of α-cyanocarbanions usually leads only to C-alkylated isomers:



However, when R and R′ are isopropyl groups, appreciable amounts of the N-alkylation product are formed[77].

In the enolates of carbonyl compounds the oxygen atom is sterically more accessible than the carbon atom[78]. For this reason, the fraction of O-alkylation increases significantly both with the size of the substituent at the carbon reaction centre of the anion and with increasing steric hindrance in the alkyl halide.

Thus alkylation of the anions of acetoacetic ester and acetylacetone by primary alkyl halides in alcohols or non-polar solvents usually takes place exclusively at the carbon atom, while in the presence of secondary alkyl halides under the same conditions, appreciable amounts of enolic ethers are produced[50].

In the alkylation of the anion of acetoacetic ester in polar aprotic solvents the fraction of O-alkylation also increases significantly with the branching of the hydrocarbon group in the alkyl halide[34,78]; for example, with neopentyl chloride only the O-alkylated isomer is formed[78].

In the alkylation of the enolates of α-substituted acetophenones the amount of the O-alkylated product increases sharply with the size of the α-substituents[35], which indicates a significant effect of steric hindrance in the enolate on the mode of reaction. The alkylation of the anions of 2-hydroxypyrimidine and its derivatives is hardly affected by the nature of the solvent, the cation, and the group substituted. The structure of the alkyl halide has the main influence: on passing from methyl to isopropyl halide, the fraction of O-alkylation increases, which the authors attributed solely to steric effects, since models show that alkylation at the nitrogen atom imposes more stringent steric requirements than attack on the oxygen atom[31]. A similar conclusion was reached also for the anion of 2-hydroxypyridine[30].

Steric effects have also been used to account for the increase of the fraction of O-alkylation of the anion of benzophenone oxime and its derivatives on passing from methyl bromide to benzyl bromide[79].

3. Effects of the Solvent

The solvent usually has a very significant influence on the mode of reaction of ambident anions. Earlier (see p. 5) the effect of the solvent on the behaviour of alkylating agents was already noted. Here we shall consider the interaction of the solvent with the ambident anion–counterion system and the influence of such interaction on the mode of alkylation.

In a study of the behaviour of ambident anions in aprotic solvents the following general feature was observed: an increase in the polarity of the aprotic solvent favours alkylation at the centre with the maximum electron density. For example, in the alkylation of the anions of 2,6-dimethylphenol the fraction of O-alkylated products decreases in the following sequence as the solvent is varied: ethyl ether > isopropyl ether > toluene > benzene[80]. The fraction of the N-alkylation products of the anion of pyrrole decreases in the sequence tetrahydrofuran > dioxan > isopropyl ether > ethyl ether > benzene, toluene, n-heptane, methylcyclohexane[81].

The tendency towards reactions at the centre with the maximum electron density increases even more when dipolar aprotic solvents are employed—dimethylformamide (DMF), dimethylacetamide (DMAA), dimethyl sulphoxide (DMSO), hexamethylphosphoramide (HMP), and others.

Such behaviour is observed in the alkylation of a wide variety of ambident anions: the enolates of β-dicarbonyl compounds (see, for example Kurts et al.[54]), β-naphthoxides[36], salts of pyrrole[38], indole[33], 2-hydroxypyridine[30], and others. The effect of aprotic solvents was investigated in greatest detail during recent years[36,54,78,81]. It is noteworthy that dipolar aprotic solvents also differ significantly among one another in terms of their influence on the mode of alkylation of ambident anions. Thus in the alkylation of the anions of acetoacetic ester and acetylacetone the greatest yield of the O-alkylated isomers is observed in hexamethylphosphoramide and the tetramethyldiamide of methylphosphonic acid. These are followed by aprotic solvents of the amide type: DMF, DMAA, tetramethylurea, etc., and also dimethyl sulphoxide in which the fraction of the O-alkylated isomer is lower; the amount of O-alkylated derivatives is reduced still further in acetone, acetonitrile, and tetramethylene sulphone. These are followed by solvents of the ether type which are of relatively low polarity and also certain halogeno-derivatives in which the amount of O-alkylated products is as a rule close to zero[54] (see also Refs. 34, 51–53, 78, 82).

This does not of course imply that the use of dipolar aprotic solvents always leads to preferential alkylation of the centre with the maximum electron density. The final result depends both on the properties of the anion itself, and on the relative importance for the given anion of particular factors which influence the mode of reaction.

For example, silver nitrite in a relatively non-polar solvent (ethyl ether) is appreciably alkylated at the oxygen atom[1], while the use of alkali metal nitrites in a dipolar aprotic solvent (DMF) significantly increases the fraction of *N*-alkylation[1,24], i.e. in the case of nitrite ions, the alkylating agent (or more correctly its form produced by modification under the influence of silver ions) has a greater effect than the solvent. On the other hand, the solvent has virtually no influence on the mode of reaction of the anions of 2-hydroxypyrimidine on some of its derivatives[31].

The question arises of the reasons for the influence of aprotic solvents on the mode of reaction of ambident anions. Aprotic solvents, including dipolar solvents, as a rule solvate anions only very slightly[43] and therefore the change in the mode of reaction is probably not associated to any appreciable extent with the interaction between the aprotic solvent and the anion.

Kornblum[36] attributed the effect of aprotic solvents to their dielectric properties. However, subsequently, it was found that the effect of such solvents is not determined by their dielectric constants[54,78] but by their capacity to solvate cations[35,38,54,78,81].

This type of relation can be explained as follows. Like other electrolytes[83,84], the salts formed by ambident anions and their counterions are associated to some extent in the majority of organic solvents to ion pairs (or more highly aggregated species). In view of the electrostatic orientation of ions, it is likely that the cation will be preferentially coordinated to the atom in the ambident anion with the maximum electron density§ (hard nucleophilic atom)[2], i.e. in the association of the ambident anion and the counterion the centre with the highest electron density is screened, which hinders the reaction at this site; in consequence, the relative reactivity of the second nucleophilic centre increases (an approach to this problem, in many ways similar to that described, was employed by Nesmeyanov and Kabachnik[3]). The increase in the degree of solvation of the cation by the solvent, for example on passing from solvents of low polarity to dipolar aprotic solvents, leads to a weakening of the coordination of the cation to the ambident anion and hence facilitates the reaction at the atom with the maximum electron density.

The increase in the degree of solvation of cations by the solvent can probably lead both to a weakening of the bond between the cation and anion within the ion pair and to an increase of the degree of dissociation of the ion pair. Both these effects will facilitate attack on the harder atom of the ambident anion. However, at present the available experimental data are insufficient to estimate in a specific case which of these effects is responsible for the change in the mode of reaction.

It is noteworthy that the determination of the capacity of the solvent to solvate cations is not a simple problem although such estimates have been made for a series of the most widely used solvents[43]. In this connection the correlation[78] between the relative amounts of both *O*- and *C*-alkylated isomers in the alkylation of the anion of acetoacetic ester and the basicity of the solvent (the increase of the fraction of the *O*-alkylated isomer with the basicity of the solvent) merits attention. However, at present there are too few data to arrive at a conclusion concerning the applicability of such correlations to a wide range of systems.

Protic solvents—alcohols, unsubstituted amides, and others—behave as hydrogen bond donors and, in contrast to aprotic solvents, usually readily solvate anions[43].

Kornblum found for phenoxides[40,41] and β-naphthoxides[36] that, despite the fact that protic solvents effectively solvate cations[43], alkylation in them greatly promotes reactions involving the most polarised (soft) centre of the ambident anion and prevents attack on the centre with the maximum electron density.

The effectiveness of protic solvents as media promoting reactions at the softer nucleophilic atom of the ambident anion very greatly increases when solvents capable of forming stable hydrogen bonds are employed. For example, phenol salts in aprotic solvents (dimethylformamide, tetrahydrofuran, ethyl ether, and even toluene) are alkylated exclusively at the oxygen atoms; the use of protic solvents such as methyl, ethyl, and t-butyl alcohols also does not alter the mode of reaction. However, in solvents such as water, fluorinated alcohols, and phenol, which form significantly stronger hydrogen bonds than simple aliphatic alcohols[85,86], *C*-alkylation of phenoxide anions takes place to a considerable degree (the yield of *C*-alkylated isomers approaches 80% in some cases)[40,41]. It has been noted that in this case both *C*- and *O*-alkylation takes place via an S_N2 mechanism.

According to Kornblum[40,41], the effect of protic solvents can be accounted for as follows: owing to hydrogen bonding, these solvents selectively and effectively solvate the centre with the maximum electron density (for example, the oxygen atom)¶, as a result of which the accessibility of this centre is greatly reduced and substitution at the other centre (a carbon atom) may successfully compete with that at the oxygen atom. Hence it becomes clear why the solvent capable of forming the strongest hydrogen bonds (water, phenol, fluorinated alcohols) are especially effective: an increase in the strength of the hydrogen bond will increase the energy required to desolvate the atom with the maximum electron density and hence will increase the activation energy for reaction at this atom.

Kornblum[41] suggested the name "selective solvation" for the capacity of protic solvents to solvate selectively the centre with the maximum electron density and thereby prevent the reaction at this centre. This type of effect of protic solvent on the mode of reaction is observed also for other ambident anions. For example, in the alkylation of the anion of acetoacetic ester the yield of the *O*-alkylated isomer falls sharply on passing from dipolar aprotic solvents to alcohols (ethyl and t-butyl alcohols) and to a substituted amide (*N*-methylacetamide) and in alcohols the yield of the *O*-alkylated isomer falls almost to zero[54].

In the alkylation of the enolates of monocarbonyl compounds[35] and 2-hydroxypyridine salts[30] transition from polar aprotic solvents to alcohols also leads to a significant decrease of the amount of the *O*-alkylated isomer. It is noteworthy that even relatively small amounts of added protic solvents influence the mode of reaction[34,52,53,87]. Thus in the ethylation of the enolate of acetoacetic ester in hexamethylphosphoramide the addition of equimolar amounts of protic solvents (water, t-butyl alcohol) significantly increases the fraction of *C*-alkylation[52,53,87].

§ At least in the case of alkali and alkaline earth metal cations and also ammonium ions, i.e. hard Lewis acids (see Section IV). For metal cations which are soft Lewis acids (for example Hg^{2+}), there is a possibility of coordination at the most polarised atom in the ambident system.

¶ We may recall that the hydrogen atom behaves as a hard Lewis acid in the formation of a hydrogen bond (see Section IV).

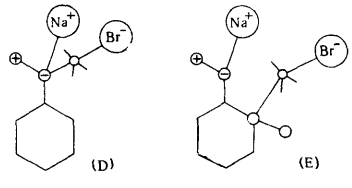
At the present time the explanation of the effect of protic solvents on the mode of reaction given by Kornblum is generally accepted, (see, for example, Refs. 30, 35, 52, 54, 87)†.

Factors such as the heterogeneity or homogeneity of the medium in which the reaction is carried out are closely related to the influence of solvents.

In 1959, Kornblum and Lurie[8] found that the alkylation of phenol and *p*-t-octylphenol salts under truly heterogeneous conditions, i.e. on the surface of the crystals of the salts, leads exclusively to *C*-alkylation products, while the same reaction in solution yields only *O*-alkylation products. Their explanation of these results is as follows[8]. The alkylation of the oxygen atom should involve a linear transition state (D) in which the negative charge of oxygen is transmitted to the halogen atom of the alkylating agent. There are two factors which make such a transition state energetically unfavourable. In the non-polar solvents employed for the heterogeneous reaction the halide ion eliminated is solvated to only a very slight extent. However, a still more important factor is that the transfer of electron density from the oxygen atom will lead to electrostatic repulsion between the positively charged metal ions and to a sharp increase of the energy of the system, since in the crystal lattice the metal ions cannot move apart.

In a homogeneous medium the formation of the ether (the *O*-alkylation product) does not give rise to difficulties of this kind even if the entire salt is present in the form of ion pairs or larger aggregates, since in solution metal ions can readily move apart.

In contrast to the formation of ethers, *C*-alkylation takes place via a non-linear transition state (E) where the halide ions is "solvated" owing to the formation of an ion pair with the metal ion; moreover, the formation of this ion pair will prevent electrostatic repulsion between the metal ions when the oxygen atom loses its negative charge. Consequently, under heterogeneous conditions *C*-alkylation takes place preferentially:



(D) (E)

It is at present impossible to state whether this factor ("heterogeneity") does indeed have such an appreciable influence also in the case of other ambident anions or whether it applies only to phenol and similar systems, since there have been no studies of dual reactivity showing clearly that the "heterogeneous" reaction investigated takes place only on the surface of the crystal and not in solution.

4. Effect of the Cation and the State of the Salts in Solution

The nature of the counterion (cation) frequently has an appreciable effect on the mode of reaction of ambident anions. Above (see pp. 4–5) the specific effect of the silver cation and similar ions (electrophilic catalysts) has already been reported. Here we shall examine the effect of other cations.

In a study of the alkylation of ambident anions in aprotic solvents a single general relation was observed: the tendency of the ambident anions to react at the centre with the maximum electron density increases in the following sequence of cations: $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+ < NR_4^+$. Moreover, it has been shown in a number of cases that the Li^+ ion promotes the reaction at the centre with the maximum electron density more than the Mg^{2+} ion (β-naphthoxides[37], pyrrole salts[38]).

This type of relation has been observed in a wide variety of ambident systems: enolates of β-dicarbonyl[34,51–53,87] and monocarbonyl compounds[89], salts of naphthols[36,37], phenols[80], pyrrole[38,81], 2-hydroxypyridine[30], and others. The effect of the cations obtains both in relatively non-polar aprotic solvents and in dipolar aprotic solvents. Thus the tendency towards reactions involving the centre with the maximum electron density diminishes with decreasing radius of the cation and, for equal radii (Li^+ and Mg^{2+}), with increase of the charge, i.e. with increase of the hardness of the cation (see Section IV).

As already stated (see p. 9), salts formed by ambident anions and their counterions in solution are to some extent associated into ion pairs and the alkali metal or alkaline earth metal cation is preferentially coordinated to the hard nucleophilic atom of the ambident anion, which hinders the reaction at this atom. With increase of the hardness of the cation (decrease of the radius and increase of the charge), the degree of association of the cation with the centre having the maximum electron density will become more pronounced (a more "closely linked" ion pair will be formed) and thereby the reaction at this centre will be hindered. In consequence, the relative reactivity of the second, softer nucleophilic centre will increase.

The strengthening of the bond between the cation and anion leads to both an increase of the energy required to descreen the hard reaction centre and to a decrease of the degree of dissociation of the ion pairs. Both these factors will hinder the reaction at the atom with the maximum electron density. At the present time it is impossible to say in a specific case which of these factors is responsible for the change in the mode of reaction as the cation is varied.

It is important to note that, in contrast to Kornblum's hypothesis[36], the effect of the change of the cation can be followed also in dipolar aprotic solvents (dimethylformamide, dimethyl sulphoxide, and others), for example in the case of the anions of acetoacetic ester[34,51–53,87] and pyrrole[81], i.e. even in these solvents there is some association of the ambident anions with their counterions to form ion pairs‡. Only in solvents such as hexamethylphosphoramide, which very strongly solvates cations, have cases been found where a change of the cation does not affect the mode of reaction (the acetylacetonate anion[54] and also the anion of acetoacetic ester at elevated temperatures[78]). Probably in such cases the reactive species is the anion not combined in an ion pair[54,78] and the mode of reaction is determined solely by the mesomerism of the anion itself[54].

The postulate of the strengthening of the bond between the cation and the centre in the ambident anion having the

† Recently the hypothesis of the selective solvation by protic solvents of the hard centre in ambident anions was proved by spectroscopic methods for salts of phenols and certain nitro-compounds as examples[88].

‡ It has been shown by ultraviolet spectroscopy that the salts of phenol and acyclic β-dicarbonyl compounds are in most cases associated in dimethylformamide even at concentrations in the range 10^{-4}–10^{-5} M.[90]

maximum electron density as the radius of the cation is reduced was confirmed by spectroscopic methods for alkali metal salts of phenols and β-dicarbonyl compounds in 1,2-dimethoxyethane and dimethylformamide solutions [90]. It was also shown [90] that in these aprotic solvents association of the alkali metal cations with the anions of phenols and enols does not involve the formation of covalent bonds even for the most "closely linked" ion pairs and the interaction is purely ionic.

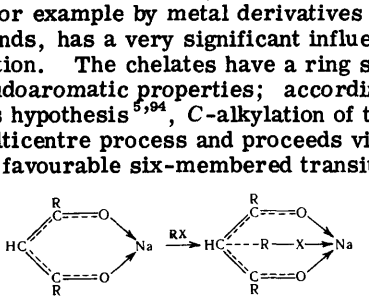
The effect of the cation in protic solvents has been investigated to a very limited degree. However, the available data show that, despite the high solvation capacity of polar protic solvents in relation to cations and anions [43], in many cases a cationic effect is observed [37,80,91], although examples may be quoted when the effect of the cation is insignificant [79]. Nevertheless there is no doubt that more detailed studies will lead to the discovery of ambident systems where the effect of the cation will be significant even in such media, particularly since in many cases association into ion pairs of ambident anions and their counterions has been observed even in a solvent such as water (see, for example, Zaugg and Schaefer [90]).

Thus the data presented show that association with cations reduces the tendency of the ambident anion towards reaction at the centre with the maximum electron density, at least in aprotic solvents. An example of direct experimental proof of this hypothesis is provided by the study by Smith and Milligan [92] of the effect of ion pair association on the mode and rate of alkylation of the fluorinone oxime anion.

However, in protic solvents in those cases where the centre with the maximum electron density in the ambident anion is more firmly solvated via hydrogen bonding than via association with the cation there is also a possibility of the opposite relation: a greater tendency towards reactions at this centre in ion pairs than in the unassociated anion [36,93].

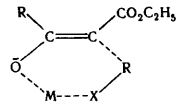
It must be emphasised that the state in solution of salts formed by ambident anions with their counterions (degree of association into ion pairs as a function of the solvent and the cation, the nature of the ion pairs formed—with the two ions in direct contact or separated by solvent species, the size of the ionic aggregates, etc.) has so far been clearly inadequately investigated, which hinders a quantitative estimation of the dual reactivities of both the associated species and the "free" anions.

According to Brändström [5,94], the formation of chelate compounds, for example by metal derivatives of β-dicarbonyl compounds, has a very significant influence on the mode of reaction. The chelates have a ring structure and have pseudoaromatic properties; according to Brändström's hypothesis [5,94], C-alkylation of these systems is a multicentre process and proceeds via the energetically favourable six-membered transition state:



On the other hand, if the reaction does not proceed by a cyclic transition state, O-alkylation takes place. This happens, for example, in the readily ionisable halogenoderivatives (RX), where the coordination with a metal ion or the effect of the solvent lead to the formation of a carbonium cation, which reacts at the site with the maximum electron density—at the oxygen atom.

It has recently been suggested that [95] the formation of a six-membered transition state (owing to coordination between the metal ion and the "nucleophilic" part of the alkylated agent), promoting C-alkylation, is possible also in the case of non-chelate structures, as can be seen from the scheme below:



This type of transition state should be promoted by solvents which cause least dissociation of the enolate and ionisation of the alkylated agent (protic and aprotic media of low polarity).

5. Effect of Certain Other Factors

Comparatively few data are available on the effect of factors other than those described above on the mode of reaction of ambident anions. In a number of examples it has been shown that, as the concentration of the "ambident" salts in aprotic solvents is reduced, the yield of the product of the alkylation of the centre with the maximum electron density increases [35,38,80,81,87]. Whereas in dipolar aprotic solvents [87] this phenomenon can be accounted for by an increase of the degree of dissociation of the ion pair, in aprotic media of low polarity (ethyl ether, tetrahydrofuran, and others [38,80,81]) the existence of unassociated anions is extremely doubtful; possibly in these media dilution leads to the dissociation of highly aggregated species into smaller aggregates, which increases the accessibility of the hard centre.

It has been found for the anions of monocarbonyl compounds that, in contrast to aprotic media, in protic solvents the fraction of O-alkylation diminishes with dilution [35], which the authors attribute to enhanced effectiveness of the hydrogen bond§.

Even fewer data are available on the effect of temperature. In the alkylation of pyrrole salts in dioxan and toluene the fraction of the N-isomer increases with temperature [38]. In the case of the enolates of acetoacetic ester an increase of temperature entails an increase of the fraction of O-alkylation when the reaction is carried out in dimethyl sulphoxide [51].

The observed behaviour can be accounted for by an increase of the degree of dissociation of ion pairs (or larger aggregates) with increasing temperature, particularly since for the acetoacetic ester anions in hexamethylphosphoramide, where the reacting species is believed to be the "free" anion, a temperature effect is not observed [78]. However, this view does not explain the decrease of the fraction of O-alkylation of the enolate of acetoacetic ester with increasing temperature in N-methylpyrrolidinone [51].

A change in hydrostatic pressure does not usually affect the mode of alkylation, particularly when the reaction is performed in aprotic solvents [96,97]. However, in the alkylation of phenoxide and β-naphthoxide ions in protic media, an increase of pressure (to several thousand atmospheres) causes some increase in the fraction of C-alkylation [96-99], which is explained by an enhancement of the "selective" solvation of the oxygen atom (via hydrogen bonding) as the pressure rises [97-99].

§ Apparently in this case "selective" solvation has a greater influence on the mode of reaction than association with the cation.

VI. BEHAVIOUR OF AMBIDENT ANIONS IN SUBSTITUTION REACTIONS AT AN UNSATURATED CARBON ATOM AND AT HETEROATOMS

In contrast to substitution at a saturated carbon atom, the behaviour of ambident anions in substitution reactions at an unsaturated carbon atom has been much less investigated; there are even fewer data on substitution at heteroatoms. It is reasonable to suppose that many of the factors which influence the mode of alkylation will operate also in the case of other electrophilic agents. However, here one should take into account in the first place the nature of the electrophilic agent itself and its tendency to react at a particular centre of the ambident anion. The examples quoted below show that the principle of hard and soft acids and bases (see Section IV) is very useful for the estimation of such properties of electrophilic agents.

Substitution at an unsaturated carbon atom has been investigated mainly in acylation reactions (substitution at a carbonyl carbon atom). Since the carbonyl carbon atom is a hard Lewis acid, [13] (see also Section IV), it is to be expected that in acylation the reaction will take place to a considerable degree at the harder atom of the ambident anion (at the centre with the maximum electron density), and the tendency to react at this centre should be much greater than in alkylation (a saturated carbon atom is an intermediate Lewis acid).

The available data fully confirm this hypothesis, at least when carboxylic acid anhydrides and halides are employed as the acylating agents. Thus in the acylation of the enolates of monocarbonyl compounds, *O*-acylated isomers are formed preferentially, whereas under the same conditions alkylation gives either *C*-alkylated products or a mixture of the *C*-alkylated and *O*-alkylated isomers [89,100-102]. The enolates of β-dicarbonyl compounds are capable of giving both *C*- and *O*-acyl derivatives but in acylation they tend to undergo reaction at the oxygen atom more than in alkylation (see, for example, Refs. 3, 5, 94, and 103). Acylation of the phenoxide anion by acid halides probably takes place only at the oxygen atom under these conditions [2].

The salts of phosphorothioic acids are alkylated at the sulphur atom [104-106]; on the other hand, the acylation of these salts by acyl halides takes place preferentially at the oxygen atom [105,107]:

$$(RO)_2P(S)O^- \begin{cases} \xrightarrow{R'X} (RO)_2P(O)SR' \\ \xrightarrow{CH_3COCl} (RO)_2P(S)OCOCH_3 \end{cases}$$

Thiocyanate ions are acylated by acetyl chloride at the nitrogen atom, while alkylation takes place at the softer sulphur atom [13].

The mode of acylation of ambident anions is probably influenced by the same factors as in alkylation. Thus in the acylation of the anions of β-diketones an increase of the carbonium character of the transition state leads to an increase of the fraction of the *O*-acylated isomer [108]. The use of silver salts instead of alkali metal salts (with acyl chlorides as acylating agents) increases the tendency towards the acylation of the more electronegative atom [37,109].

An increase in electrophilicity (and consequently in the hardness) of the acylating agent increases the tendency towards reactions at the harder centre of the ambident anion. For example, in the acylation of the anions of 2-ethoxycarbonylcyclanones the fraction of *O*-acylation increases in the series [110]

$$ClCOOEt < ClCH_2COCl < CH_3COCl < CH_3COClO_4$$

Steric effects can also have a significant influence. Thus despite the fact that the salts of phenol are acylated only at the oxygen atom, the 2,6-di-t-butylphenoxide anion, the oxygen atom of which is strongly screened by bulky groups, is acylated by benzoyl chloride to give a *C*-acyl derivative [111].

As in alkylation, an increase of the polarity of the aprotic solvent favours the reaction at the centre with the maximum electron density (see, for example, Ferris et al. [110]). A change of the cation probably has the same effect as in alkylation [37,110].

The formation of chelates has a significant influence on the mode of acylation, as in alkylation reactions. It has been shown for the chelates of β-diketones that *C*-acylation is promoted when the reaction proceeds via a six-membered transition state (owing to the coordination of the "nucleophilic" part of the acylating agent to the metal ion and of the "electrophilic" part to the carbon reaction centre) [108,112].

The behaviour of ambident anions in substitution reactions at an olefinic carbon atom is illustrated using an example the substitution of the β-carbon atom in compounds of the type RCOCH = CHX, where X is the group eliminated (the β-ketovinylation reaction). The ketovinylation of the anions of β-dicarbonyl compounds and nitrocompounds and cyanide, thiocyanate, and nitrite ions takes place at the most polarised (softest) centre of the ambident anion [113]. At the same time the phenoxide anion is ketovinylated only at the oxygen atom even in water [113,114]. Thus the behaviour of ambident anions in the β-ketovinylation reaction is apparently in many respects similar to the behaviour of these anions in alkylation.

The information about the behaviour of ambident anions in substitution reactions at heteroatoms is extremely limited. However, the general tendency of electrophilic agents of this type to react at a particular centre of the ambident anion may be predicted by estimating the properties of the electrophilic agent as a Lewis acid (hard or soft).

Thus the phosphorus atom in the phosphoryl group is a hard Lewis acid (see Section IV), which is reflected in the behaviour of this electrophilic agent in relation to ambident anions. For example, the phosphorylation of phosphorothioate salts takes place, as in acylation, at the harder atom (the oxygen atom) [115]:

$$(RO)_2P(S)O^- + R_2P(O)X \rightarrow (RO)_2P(S)O\underset{\underset{O}{\|}}{P}R_2 + X^-$$

Similarly the phosphorylation of the thiocyanate ion takes place at the harder centre (the nitrogen atom) [16].

The silylation of enolates by chlorotrimethylsilane takes place only at the oxygen atom [116] (while alkylation takes place only at the carbon atom [101]), which is consistent with the classification of the silicon atom as a hard Lewis acid [20].

The sulphur atom in the sulphenyl group is a soft Lewis acid (see Section IV), which is confirmed by the marked tendency of this electrophilic agent to react at the softer (more polarised) atom of the ambident system. Thus in the reaction of the anions of mononitroalkanes with sulphenyl chlorides, only the corresponding *C*-substituted derivatives (α-nitrosulphides) are formed [117,118]; on the other hand, the alkylation of these anions as a rule leads only to *O*-substituted products [119].

The capacity of perchloryl fluoride ($FClO_3$) to fluorinate the anions of ketoenols, phenols, and nitroalkanes, at the carbon atom[120] suggests that the fluorine atom in this compound may be classified as a soft Lewis acid[7].

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The data, in their entirety, show that certain general relations controlling the dual reactivity of ambident anions can now be traced and knowledge of them can help the investigator in many cases to control the process in a particular way.

At the same time many problems still await solution. The author attempted to indicate these unsolved problems throughout the review. One of the most important problems of this kind is the relation between structure and dual reactivity of the anion. It is difficult to solve because the "true" reactivity of the ambident system is frequently subject to very marked changes under the influence of various factors (association with the cation, selective solvation, and others). Hence another problem arises—that of estimating the relative sensitivities of various anions to particular effects.

However, purely experimental data for the reactions of the various anions with a wide variety of electrophilic agents under comparable conditions are at present quite inadequate for the solution of these problems. Moreover, in connection with the introduction of precise methods of analysis and improved research techniques, many old data require revision.

In conclusion, we may note that one cannot exclude the possibility that in future, following a more detailed study of the reactivity of ambident anions and their structure, new concepts may appear, providing a deeper and more complete explanation of certain characteristics of the behaviour of ambident systems.

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