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A Simple Interpretation of Nucleophilic Reactivity*

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Zusammenfassung: Es werden der Begriff der nucleophilen Reaktivität eingeführt und die bei A-priori-Errechnungen der Geschwindigkeitskonstanten von heterolytischen Reaktionen auftretenden Schwierigkeiten kurz erörtert. Anhand eines Extremfalles, bei dem die Übergangsstruktur der Struktur eines Anlagerungszwischenproduktes ähnelt (wie z.B. bei nucleophiler aromatischer Substitution), wird ein empirisches Verfahren entwickelt, wobei die Geschwindigkeitskonstante mit der Lösungsenergie und Elektronenaffinität des Nucleophilen sowie mit der Energie der zwischen nucleophilem und elektrophilem Zentrum gebildeten Bindung in Beziehung gesetzt wird.

Auf diese Weise kann die nucleophile Reaktionsordnung, und damit die Selektivität, für eine gegebene Übergangsstruktur interpretiert werden. Der Einfluß des Lösungsmittels auf die nucleophile Reaktionsordnung kann ebenfalls vorausgesagt werden. Es wird gezeigt, daß die für die nucleophile Reaktivität vorgeschlagene allgemeine Gleichung der von EDWARDS vorgeschlagenen ähnelt, die erfolgreich auf eine große Anzahl von nucleophilen Reaktionen angewandt wurde.

Die Anwendung solcher Reaktionsordnungen auf die Voraussage der Lage einer Bindungsspaltung in gewissen Fällen, und damit auf die Voraussage der Zusammensetzung der Reaktionsprodukte, wird diskutiert und kurz erläutert. Auf der gleichen Grundlage wird ferner die Selektivität von Ionen mit zwei Reaktionszentren diskutiert.

Es wird aufgezeigt, daß BRÖNSTEDS Katalysengesetz und HAMMETTS $\sigma\varrho$-Beziehungen Vereinfachungen der für die nucleophile Reaktivität vorgeschlagenen Gleichung darstellen und daß die Größe der Reaktionsparameter (BRÖNSTEDS α oder HAMMETTS ϱ) vorwiegend durch das Ausmaß an im Übergangszustand gebildeter Bindung bestimmt wird. Durch die Basenstärke des Nucleophilen bedingte Veränderungen der Zusammensetzung des Produktes können durch Annahme geeigneter Übergangsstrukturen für die verschiedenen alternativen Reaktionen erklärt werden.

Es ist das Ziel dieser Veröffentlichung, einen allgemeinen Weg zur Auslegung der nucleophilen Reaktivität aufzuzeigen und zu versuchen, eine möglichst einfache Erklärung für die zahlreichen Beobachtungen und Erfahrungsregeln zu finden, welche Reaktivität und nucleophile Struktur miteinander in Beziehung setzen.

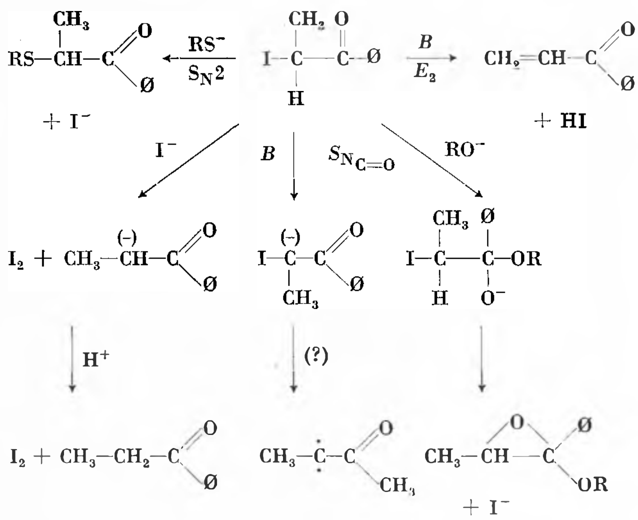
I. Introduction

The concept of nucleophilic reactivity[1] (or nucleophilicity) was introduced to represent the reactivity of an electron donor in an organic displacement reaction. In the past, the nucleophilic reactivity order for a given electrophilic centre was frequently identified with the order of basicity of the reagents towards protons, but it has been known for some time that many weakly basic ions, e.g. I^-, Br^-, $S_2O_3^{2-}$, are very reactive towards the saturated carbon atom.[2] Until recently, most of the accurate rate measurements available referred to alkylation reactions in which a common nucleophilic order is usually observed[3] (unless the reaction proceeds by way of preliminary ionisation, when considerable variations in the nucleophilic order are observed[4]). This has led to the idea that a common nucleophilic order holds for all reactions, independent of the nature of the electrophilic centre, as represented quantitatively for example by the empirical equation of SCOTT and SWAIN,[3]

$$\log k/k_0 = sn$$

in terms of a parameter n characteristic of the nucleophile only and s characteristic of the substrate.

This equation, which has been superseded by other empirical equations[5] introducing a parameter for the interaction of the nucleophile with the electrophilic centre, cannot be a general one since it does not explain the selectivity of the reagent when various alternative reactions are possible, as illustrated for example by the various nucleophilic displacements which are possible for α-halo-ketones.



* The basis of lectures and seminars given at the Universities of Chicago, Purdue, Maryland and Pennsylvania State, in October, 1961.

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[1] INGOLD, *Structure and Mechanism in Organic Chemistry*, Cornell, 1953, p. 200.

[2] MC.CLEARY and HAMMETT, *J. Amer. Chem. Soc. 63* (1941) 2254; BRÖNSTED, *ibid. 51* (1929). See also HINE, *Physical-Organic Chemistry*, New York 1956, p. 138.

[3] SWAIN and SCOTT, *J. Amer. Chem. Soc. 75* (1953) 146.

[4] OGSTON, HOLIDAY, PHILPOT and STOCKEN, *Trans. Faraday Soc. 44* (1948) 45.

[5] EDWARDS, *J. Amer. Chem. Soc. 76* (1954) 1540.

An examination of the above reactions reveals several general features, which are important in an interpretation of nucleophilic reactivity, and in interpreting the nature of the reaction products obtained in the various cases. Thus strong bases (e.g. RO^-) tend to react at the more electron-deficient centres (e.g. C=O and H), whereas large polarisable ions (which are, in general, weaker bases) tend to react at the centres of higher electron density. Of particular interest is the reaction of I^- at the iodine atom, which may be described as a nucleophilic displacement at the iodine atom, or as an oxidation of the iodide ion. It is not surprising therefore to find a close correlation in several types of reaction between the nucleophilic reactivity and the oxidation-reduction potential of the anion.[5]

It should also be pointed out that α- and β-eliminations always proceed simultaneously, although β-elimination usually predominates. For reasons which will be discussed below (p. 186), an increase in basic strength of the nucleophile (together with conjugation in the carbanion) is expected to promote α-elimination and carbene formation. It is surprising that the importance of α-elimination in organic reactions has been recognised only relatively recently.[6]

The interpretation of reactivity orders in terms of the structure of the nucleophile and the nature of the electrophilic centre is therefore extremely important in determining the choice of reagent, and in predicting the nature of the reaction products, and consequently arouses much current interest.

Fundamentally, the problem involves the calculation of the interaction energies between the nucleophile, the displaced group and the electrophilic centre for the configuration representing the transition state. The classical studies of Polanyi, Evans and their collaborators[7] have shown the importance of the various energy factors involved, and have provided a useful model for a displacement reaction. Briefly, the transition state is represented by a combination of the resonance structures,

$$\mathrm{N}^- \underset{r_1}{\quad} \mathrm{X} \ldots\ldots \underset{r_2}{} \mathrm{Y} \qquad \text{and} \qquad \mathrm{N} \ldots\ldots \underset{r_1}{} \mathrm{X} \underset{r_2}{\quad} \mathrm{Y}^-$$

The interaction energies between N and X and between X and Y are calculated for given sets of values of the internuclear distances, r_1 and r_2, from the Morse functions for the NX and XY bonds, the corresponding repulsion energies, R, the polarisation energies, P, of the ions and neutral molecules, and from the solvation energies of the ions, ΔH. The activation energy $\Delta E_{\rm I}$ is then given by

$$\Delta E_{\rm I} = a\Delta H_{\rm N} - P_{\rm N-XY} + R_{\rm N-XY} + b\,D_{\rm X-Y}$$

and

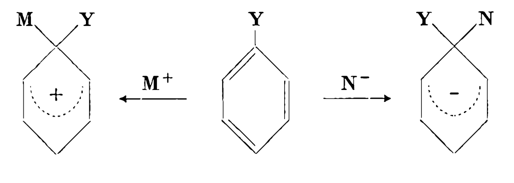
$$\Delta E_{\rm II} = \Delta H_0 + \Delta E_{\rm I} = a'\Delta H_{\rm X} - P_{\rm Y-NX} + R_{\rm Y-NX} + b'\,D_{\rm N-}$$

where D represents the dissociation energy of a particular bond, and ΔH_0 the heat of reaction. The minimum value of $\Delta E_{\rm I}$ satisfying these two equations gives the activation energy (if the exchange energy between I and II is neglected) and the internuclear distances, r_1 and r_2, in the transition state.

Owing to the unrealistic electronic description of the transition state, to the empirical model adopted for the desolvation of the ions N and X, and to the many uncertainties in the energy calculations, the results can be regarded as only semi-quantitative. Qualitatively however one may observe that an increase in nucleophilic reactivity may be produced by (i) a decrease in the solvation energy of N; (ii) a decrease in the repulsion energy between N and X; and (iii) an increase in the N—X bond energy. Since a change in the nucleophile produces a change in all these energy factors, the net influence on the reactivity will depend on the relative magnitude of these contributions which, in turn, depends on the structure of the transition state.

In the following discussion, the transition state of a particular reaction will be represented by the charge distribution and internuclear separation of the NXY system, as deduced from usual physical-organic investigations of each type of reaction.

As a starting point, substitution at an unsaturated centre will be considered, since the transition state structure may be identified approximately with the structure of the addition intermediate.[8] This assumption is generally made in theoretical calculations of chemical reactivity based on molecular orbital theory which have led to successful interpretations of nucleophilic and electrophilic aromatic substitution.[9]



II. Transition states of unsaturated systems

For complete bond formation between N and X the corresponding energy change may be calculated thermodynamically,

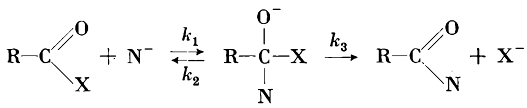
$$\Delta E = \Delta H_{\rm N} + E_{\rm N} - D_{\rm X-N} + E_2\,,$$

where $E_{\rm N}$ is the electron affinity of N and E_2 is a constant for a given substrate.

[6] Hine, *J. Amer. Chem. Soc. 72* (1950) 2438.
[7] Ogg and Polanyi, *Trans. Faraday Soc. 31* (1935) 604; Evans and Polanyi, *ibid. 34* (1938) 11; Baughan and Polanyi, *ibid. 37* (1941) 648.

[8] Hammond, *J. Amer. Chem. Soc. 77* (1955) 334.
[9] See for example R.D. Brown, *J. Chem. Soc. 1959*, 2224.

As an example of this kind of transition state we may consider the displacement at a carbonyl centre. It is now widely accepted that such reactions proceed through an addition intermediate,[10] and when the energy of this intermediate is considerably greater than that of the ground state, as is normally the case, the energy and hence the structure of transition state and intermediate will be similar,[8]



The activation energy is then given by

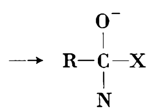
$$\Delta E = \Delta H_N + E_N - D_{C\text{-}N} + (E_\pi - E_O - \Delta H_O)\,, \quad (1)$$

where E_π is the energy of the carbonyl π-bond, E_O the electron affinity of oxygen, and ΔH_O the solvation energy of the intermediate oxy-anion. For the reaction of the OH^- or RO^- ion it may be assumed that $\Delta H_N + E_N \approx E_O + \Delta H_O$ so that

$$\Delta E = E_\pi - D_{C\text{-}N}\,. \quad (2)$$

Using the values given for the C—O and C=O bond energies and for the H_3C—OH dissociation energy given by COTTRELL,[11] a reasonable value of 6.5 k·cal/mole is obtained for the activation energy of the reaction of the hydroxide ion with an acylating agent. By also making allowance for the entropies of the solvated ions, which are known accurately in several cases,[12] the free energies for the acylation of a series of anions may be calculated (Table 1).

Table 1: Calculated free energies for the reaction R — COX + N^-



	$D_{C\text{-}N}$	$(\Delta H_N + TS_N)$	E_N[29]	ΣE	$\Delta F_{C\text{-}N}$
F^-	107	121	83.5	97.8	23.5
Cl^-	80	93.5	88.2	101.7	27.4
Br^-	67	88.7	81.6	103.3	29.1
I^-	53	81.3	74.6	102.9	28.7
HO^-	90	116.8*	54	–	6.5
HS^-	70	95.9*	60	–	11.2

* In view of the uncertainty of the solvation energies of HO^- and HS^-, the free energies of reaction for these ions were calculated from the pK_a values of water, H_2S and HF as follows

$$\Delta F_{CF} - \Delta F_{C\text{-}O} = (D_{C\text{-}F} - D_{C\text{-}OH}) - (D_{HF} - D_{HOH}) + RT(\ln K_{H_2O} - \ln K_{HF})\,.$$

[10] BENDER, *Chem. Rev. 60* (1960) 53.

[11] COTTRELL, *The Strengths of Chemical Bonds*, Butterworths, 1958, p. 270.

[12] POWELL and LATIMER, *J. Chem. Physics 19* (1951) 1139.

$$\Sigma E = \Delta H_N + TS_N + E_N - D_{C\text{-}N} + (E\pi - E_O - \Delta H_O).$$

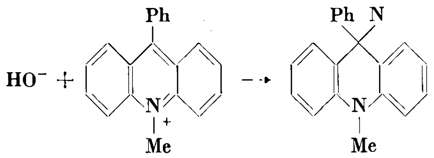
The relative values of ΔF for the halide ions may be compared with the equilibrium data for the reactions in aqueous solution,

$$N^- + CH_3I \rightleftarrows CH_3N + X^-$$

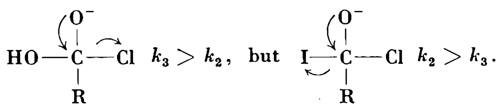
given by BATHGATE and MOELWYN-HUGHES.[13]

Ion	N^-	F^-	Cl^-	Br^-	I^-
$(-\Delta F)$ k·cal/mole		0.7	−1.0	−1.54	0

Although the agreement between these values and the computed values is poor, in both cases the order $F^- > Cl^- > Br^-$ (which is the reverse of the nucleophilic order observed for alkylation) is obtained. The values for HO^- and HS^- ions compare favourably with the values recently determined by BUNNETT, HAUSER and NAHABEDIAN[14] for the reaction



The reactivity order predicted by the data of Table 1 agrees qualitatively with the experimental data observed for the reactions of ethyl chloroformate[15] and *p*-nitrophenyl acetate[16] given in Table 2. It is observed however that the rate differences (e.g. between F^- and HO^- and between RS^- and HO^-) are considerably smaller than those predicted from the calculated values of Table 1. This difference suggests that the transition state is reached before the C—N bond formation is complete, so that the rate of reaction should be represented[10] by $k_1k_3/k_2 + k_3$. The value of k_2/k_3 depends on the relative ionisation tendency of the groups N and Y, e.g.



Rate constants are given in $l \cdot mole^{-1}\ sec^{-1}$ at (a) 0° and (b) 25°. The ions I^-, Br^-, CNS^- are less reactive than the solvent (water).

In the reactions considered in Table 2, $k_3 > k_2$; hence the rate of reaction is given by k_1 as has been hitherto assumed. This is supported in the case of the reaction

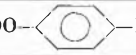
[13] BATHGATE and MOELWYN-HUGHES, *J. Chem. Soc. 1959*, 2642.

[14] BUNNETT, HAUSER and NAHABEDIAN, *Proc. Chem. Soc. 1961*, 305.

[15] GREEN and HUDSON, *Proc. Chem. Soc. 1959*, 149; *J. Chem. Soc. 1962*, 1055.

[16] JENCKS and CARRIUOLO, *J. Amer. Chem. Soc. 83* (1961) 1743.

Table 2: Rate constants for substitution of carbonyl compounds

Nucleophile	(a) EtOCOCl	(b) MeCOO––NO_2
Me_2CNO^-	500×10^3	3,700
OH^-	167	890
PhO^-	50	105
NO_2^-	31	0.0013
N_3^-	17.5	2.2
F^-	0.22	0.001
$HO \cdot CH_2 \cdot CH_2\text{–}S^-$	–	620

with hydroxide ions by the rate order[17] $CH_3COF > CH_3COCl$.

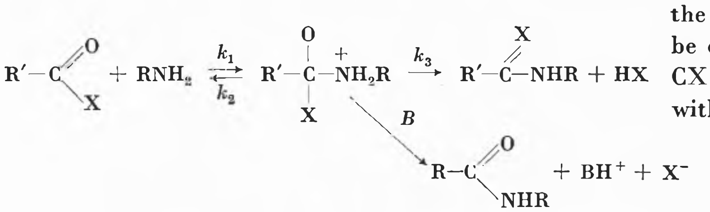
The importance of the leaving group, and hence of k_3/k_2 in determining the observed rate, is discussed by Wiberg[18] who points out that, in general, less basic ions do not displace more basic groups from acylating agents, as shown qualitatively in Table 3.

Table 3: The reactions of some anions with acid derivatives

	HO^-	HO_2^-	RCO_2^-	I^{-*}
Ethyl acetate	+	—	—	—
Phenyl benzoate	+	+	—	—
Acetic anhydride	+	+	+	—
Benzoyl chloride	+	+	+	+

* Benzoyl iodide can be prepared from the reaction of benzoyl chloride with potassium iodide.

Evidence for a pre-equilibrium (with $k_2 > k_3$) is also provided by the reactions of amines with esters, which are usually base-catalysed.[19] Although various detailed mechanisms have been suggested,[19] the first stage involves the formation of an addition intermediate which then decomposes in a rate-determining step,



The high value of the Brönsted coefficient ($\alpha \sim 0.7$) obtained[20] by varying the leaving group X (see p. 184) suggests that bond breaking is advanced in the rate-determining stage (but not in the catalysed process, where $\alpha \sim 0.2$) in support of this interpretation.

III. The generalised transition state

When the bond distance N—C is large, the interaction energy is given by (a) the de-solvation energy of N^- and (b) the polarisation energy between N^- and the electrophilic centre with charge q, which may be represented approximately in terms of the polarisability of N^- (p) as follows,

$$\Delta E_I = a \Delta H_N - p \frac{q^2}{2 r_1^4} . \tag{3}$$

Various workers[3, 5] have discussed the influence of the polarisability of the nucleophile on the reactivity and useful correlations have been obtained. A comparison of equations (1) and (3) shows that the form of the N—C interaction energy is quite different for small and large values of r_1 and may lead to a crossing of the corresponding energy curves for two nucleophiles, and hence inversion of the reactivities as the C—N distance changes. This is represented graphically in Fig. 1 for F^- and I^- ions.

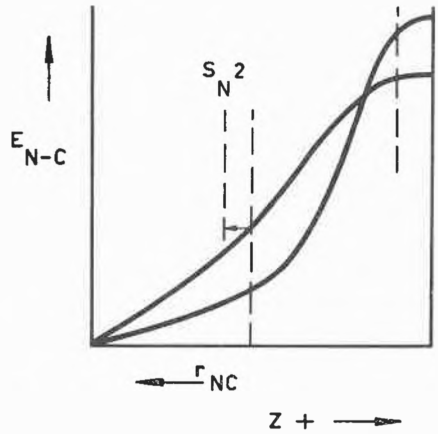


Fig. 1

In order to represent equation (3) by an equation of the same form as equation (1), the transition state may be considered to be formed by partial ionisation of the CX bond to give $C^{\delta+} \ldots\ldots X^{\delta-}$, followed by interaction with the nucleophile, viz.

$$N^- \quad \overset{\delta+}{C} \ldots\ldots \overset{\delta-}{X} \longrightarrow \overset{(1-z)-}{N} \underset{r_1}{\ldots\ldots} \overset{(\delta-z)+}{C} \underset{r_2}{\ldots\ldots} \overset{\delta-}{X} .$$

Theoretically, this poses the difficult problem of calculating σ-bond energies for a system in which the electronegativities of the atoms change with distance, which cannot be solved satisfactorily at present.

The polarisation energy may be regarded as arising from the transfer of charge ze from N^- to $C^{\delta+}$ requiring an energy βE_N and giving a bond energy νD_{C-N}, and gaining electrostatic energy λI_C where I_C is the ionisation potential of carbon. There is, of course, no simple relation between p and E_N in general, but the combined function $\beta E_N - \lambda I_C$ is probably a better measure of the polarisation for appreciable values of z, since p can only be applied when the polarising field is small (i.e. $z \to 0$).

[17] Swain and Scott, *J. Amer. Chem. Soc. 75* (1953) 246.
[18] Wiberg, *J. Amer. Chem. Soc. 77* (1955) 2519.
[19] Bunnett and Davis, *J. Amer. Chem. Soc. 82* (1960) 665; Jencks and Carriuolo, *ibid. 675.*
[20] Bruice and Mayahi, *J. Amer. Chem. Soc. 82* (1960) 3067.

We are not concerned here with the fundamental calculation of the C—N bond energy, which will depend on bond polarity in addition to the separation distance. However, since D_{C-N} for a polar bond is closely related to the electrostatic component, the total bond energy may conveniently be represented as a continuously decreasing function of D_{C-N} with increasing distance.

Thus, referring to the above transition state,

$$\Delta E_1 = (\alpha \Delta H_N + \beta E_N - \nu D_{C-N}) - \lambda I_C ,$$
$$\Delta E_2 = (\nu' D_{C-X} - \beta' E_X - \alpha' \Delta H_X) + \lambda' I_C .$$

Here, ΔE_2 represents the partial ionisation energy of the C—X bond, and gives the inertia of the reaction, ΔE_1 the driving force in terms of the electron transfer from N_1 to C.

Now, although the transition state structure will change with a change in N^- in order to minimise the total energy of the system, it is reasonable to assume that changes in the N—C interaction energy are normally greater than the corresponding changes in the C—X interaction energy. In view of the impossibility of calculating the ΔH, E and D functions theoretically, the following simplification is made. Suppose that ΔE_2 and ze have fixed values for a given bond C—X as N changes. Then,

$$\Delta E = \alpha \Delta H_N + \beta E_N - \nu D_{C-N} + C . \qquad (4)$$

As shown by the following considerations, this overestimates the differences in ΔE, but should not lead to a change in sign. Consider a change from nucleophile N_1 to N_2 with an increased electronegativity, i. e. $(\alpha \Delta H_{N_2} + \beta E_{N_2}) > (\alpha \Delta H_{N_1} + \beta E_{N_1})$. Suppose that the transition state structure is such that the gain in bond energy νD_{C-N} is less than this increase in electron affinity, which is probably the case for reactions at saturated centres. Under these conditions, the charge transfer to the centre $C^{\delta+}$ is less for $N_2(z'e)$ than for N_1 (ze) (see Fig. 1). Thus the energy maximum of the system will be reached only after a further extension of the C–X bond, requiring an energy δE_2. The increased charge on $C^{\delta+}$ produces a further increase in the polarisation energy, such that

$$(\delta E_2 - \delta E_1) < (E_1)_z - (E_1)_{z'} \text{ and } z' \longrightarrow z .$$

This leads to the general conclusion that the interaction energy E_1 decreases and the C—X separation increases with a decrease in the nucleophilic reactivity of N, which provides an energetic interpretation of the gradual change in transition state structure (frequently referred to as a change from the S_N2 to S_N1 mechanism[21] with a change in the reagent.

[21] Winstein, Grunwald and Jones, *J. Amer. Chem. Soc. 73* (1951) 2700; Swain and Langsdorf, *ibid. 73* (1951) 2813. Brown and Hudson, *J. Chem. Soc. 1953*, 3352; Bird, Hughes and Ingold, *ibid. 1954*, 634; Gold, Hilton and Jefferson, *ibid. 1954*, 2756. Hawthorne and Cram, *J. Amer. Chem. Soc. 76* (1954) 3451; Swain and Moseley, *ibid. 77* (1955) 3727.

In order to simplify equation (4) further, we shall assume that $\alpha \sim \beta$, so that

$$\Delta E = \alpha(\Delta H_N + E_N - \theta D_{C-N}) + C .$$

This will not be so, since the laws for $\alpha \Delta H_N = f(z)$ and $\beta E_N = g(z)$ will in general be different. One would expect, for instance, that the de-solvation will be relatively more important than polarisation for large N—C distances, so that one of these terms will be overestimated. The discrepancy is to some extent reduced, since E_N and ΔH_N are frequently related.

Now D_{C-N} is a highly variable function of C—N distance and consequently of α, such that

$$\theta \rightarrow 1 \text{ as } \alpha \rightarrow 1 \text{ and } \theta \rightarrow 0 \text{ as } \alpha \rightarrow 0$$

and $\quad \theta < 1$ when $1 > \alpha > 0$.

The simplest function of this kind is $\theta = \alpha^n$. This leads to the following equation,

$$\Delta E = \alpha(\Delta H_N + E_N - \alpha^n D_{C-N}) + \text{constant}. \qquad (5)$$

This equation is similar in form to the empirical equation proposed by Edwards[5] with one parameter $(\Delta H_N + E_N)$ characteristic of the nucleophile and one a function also of the electrophilic centre. The two equations may be compared if we assume that, for polar bonds, D_{C-N} increases with D_{H-N}, i. e. the bond energy of the conjugate acid of the nucleophile. Examination of bond-energy data[11] shows that the two energies increase almost linearly, i. e. $D_{C-N} = \Phi D_{H-N} +$ constant. Equation (5) then reduces to

$$\Delta E = (\alpha - \Phi \alpha^{n+1}) (\Delta H_N + E_N) + \\ + \Phi \alpha^{n+1} (\Delta H_N + E_N - D_{C-H}) + C' .$$

Since $\Delta H_N + E_N$ is closely related to the redox potential of the anion E_r, it follows that

$$\log k/k_0 \simeq x E_r + y \, pK_a . \qquad (6)$$

The important difference is that, whereas x and y are empirical constants, the ratio $\Phi \alpha^{n+1}/\alpha - \Phi \alpha^{n+1}$ gives, according to the present interpretation, a measure of the extent of bond formation in the transition state. A similar conclusion has recently been drawn* by Pearson and Edwards[22] by analysing the data, which is represented satisfactorily by equation (6).

* The author is indebted to Professor R.G. Pearson of Northwestern University for a copy of this paper in advance of publication, and acknowledges interesting discussions on this subject with Professor M.L. Bender.

[22] Edwards and Pearson, *J. Amer. Chem. Soc. 84* (1962) 16.

Reactivities calculated by equation (5) are compared with the nucleophilic constants given by SWAIN[3] and EDWARDS[5] in Table 4, using the arbitrary value of $n = 0.5$. (It should be mentioned that the form of the equation is not highly dependent on the value of n chosen.) The relationship between ΔE (calculated) and the nucleophilic parameter n shows that the nucleophilic reactivity towards alkylating agents can be represented fairly well by a combination of the energy factors, ΔH_N, E_N and D_{C-N}.

Table 4: Nucleophilic order towards a saturated carbon atom

	$[\Delta H_N + TS_N + E_N]$	D_{C-N}	Calc.* n	Swain n	Electrode Potential[5]	$h\nu$**
F^-	204.8	107	(2.0)	2.0	–	–
Cl^-	181.7	80	3.19	3.04	−1.36	137.5
Br^-	170.3	67	3.74	3.89	−1.09	122.8
I^-	155.9	53	4.72	5.04	−0.53	104.2
HO^-	170.8	90	4.38	4.20	−0.95	129
HS^-	155.9	70	5.06	5.12	−0.49	103

* Calculated from $n = a\,(\Delta H_N + TS_N + E_N - a^n D_{C-N})$, where $a = 0.125/RT$ and $n = 0.5$.
** From charge transfer spectra.[23]

General conclusions

From the general form of equation (5), and from a consideration of the changes in the energy terms with the reaction conditions, the following generalisations may be made.

(a) The nucleophilic order will change from that given by $\Delta H_N + E_N$ to that given by $\Delta H_N + E_N - D_{C-N}$ as the charge on the electrophilic centre increases, as already demonstrated by the change from an acyl to an alkyl carbon atom. This conclusion that polarisable ions (e.g. I^- and RS^-) tend to react at polarisable centres (e.g. $\geq C-$ and $-S-$), whereas non-polarisable ions (e.g. F^- and HO^-) tend to react at charged non-polarisable centres (e.g. $=C=O$, $>SO_2$ and $\geq P=O$) is similar to a general rule advanced by BUNNETT[24]. This will be considered further when additional experimental evidence is discussed in the following section.

(b) As shown in Fig. 2, which illustrates the change in the relative reactivity of, for example, the iodide and fluoride ions with increasing charge transfer to the electrophilic centre, the selectivity changes in a regular way with the transition state structure. Thus k_{N_1}/k_{N_2} decreases with a decrease in the bond-forming energy in the transition state produced by substituting electron releasing groups at the electrophilic centre, as shown by the data in Table 5 for the reaction of substituted benzyl bromides with thiophenoxide and methoxide ions.[25] It is observed that the ratio k_{PhS}/k_{MeO} decreases with decrease in the Hammett σ-value for the substituent in the alkyl halide. A similar change in the ratio k_I/k_{HO} has been pointed out by BUNNETT.[26]

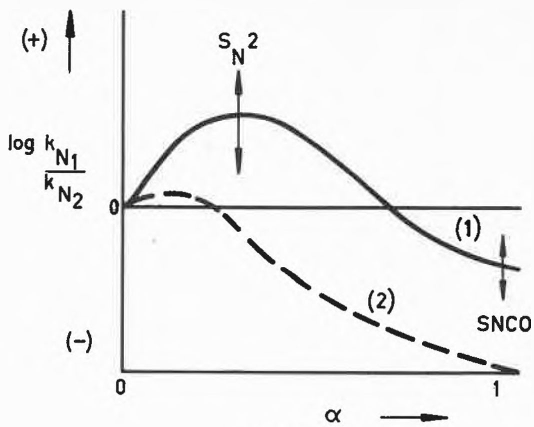


Fig. 2

Table 5: The relative reactivity of thiophenylate and methylate ions towards p-substituted benzyl bromides[25] in methanol at 20°

R	k_{PhS^-}	$10^2 k_{CH_3O^-}$	$\log k_{PhS^-}/k_{MeO^-}$	σR
CH_3O	4.92	0.96	2.70	−0.27
H	1.08	0.055	3.30	0
Br	2.57	0.079	3.52	0.23
NO_2	7.49	0.141	3.72	0.78

k is given in $l \cdot mole^{-1}\, min^{-1}$ units.

Similarly in nucleophilic aromatic substitution a regular change in structure produces a regular change in selectivity.[27] In this case, however, an increase in positive charge at the reactive carbon atom, which is expected to increase the bond-forming energy, decreases the selectivity, as shown by the data collected by BUNNETT[26] and given in Table 6.

Table 6: Reactions of nucleophilic reagents with 1-halo-2,4-dinitrobenzenes

Halogen	k_{PhS^-}/k_{MeO^-}	$k_{piperidine}/k_{MeO^-}$
F	59	0.85
Cl	1950	0.98
Br	4840	1.43
I	16800	1.48

In this case, although the transition state structure changes with change in the halogen atom, it tends to approach (in the case of the fluoride particularly) that of the addition intermediate.[27] The selectivity values are therefore given by the right-hand side of Fig. 2.

[23] FRIEDMAN, *J. Chem. Physics 21* (1953) 319.
[24] BUNNETT, *J. Amer. Chem. Soc. 79* (1957) 5969.
[25] HUDSON and KLOPMAN, *Helv. Chim. Acta 44* (1961) 1914.
[26] BUNNETT and BASSETT, *J. Amer. Chem. Soc. 81* (1959) 2104.
[27] BUNNETT and ZAHLER, *Chem. Rev. 49* (1951) 273.

Further examples of these variations in selectivity with structure have been given by BUNNETT,* and the subject will be discussed again in a subsequent section dealing with the relationship between nucleophilic reactivity and basicity (p. 183).

(c) A change in solvent produces greater changes in the solvation energy of the nucleophile, ΔH_N, when this is large, e.g. for F^- and HO^-, than when the ion is less strongly solvated. Hence the nucleophilic order changes with a change in solvent in a direction shown in Fig. 2 by the change from (1) to (2). The more strongly solvated ions become relatively more nucleophilic in the less polar solvents, although, as pointed out by WINSTEIN,[28] anomalous orders may be obtained because of ion association in such solvents, and the rate constants are further modified by general salt effects.

The change in nucleophilic order with solvent in alkylation has been demonstrated clearly by PARKER[30] (Table 7), who showed that (1) the reactivity in aprotic solvents is considerably greater than in water and alcohol, and (2) that the ratio of the reactivities in an aprotic and in a protonic solvent is greater for F^- and similar small ions than for the larger ions.

Table 7: The influence of solvent on nucleophilic reactivity towards methyl iodide[30]

	Swain n	$\frac{k_{Me_2N\cdot CHO}}{k_{EtOH}}$	$\frac{k_{Me_2CO}}{k_{H_2O}}$
NaPi	4.77	20	–
KCNS	4.9	550	–
LiI	5.04	–	2.5×10^4
LiBr	3.89	5.5×10^4	2.1×10^5
NaN_3	4.00	4.5×10^4	–
NaCN	5.10	$> 5 \times 10^4$	–
LiCl	3.04	1.3×10^6	1.5×10^6
KF	2.00	$> 10^6$	–

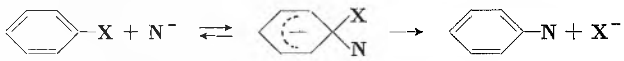
This is particularly important in preparative work, in guiding the choice of solvent. For example, fluorination can readily be carried out[31] by nucleophilic displacement in the appropriate solvent, e.g.

$$R{-}OSO_2\text{Ø} + F^- \longrightarrow RF + \text{Ø}SO_3^-.$$

It is now widely realised that a relatively small change in solvent can completely change the course of a reaction,[32] and an understanding of the rôle of solvent in displacement reactions* could be of considerable use in synthetic chemistry.

IV. Reaction at aromatic and olefinic centres

Apart from alkylation and acylation, there is little systematic data on the variation of the nucleophilic rate order with the structure of the organic compound. In nucleophilic aromatic substitution BUNNETT and DAVIS[33] have pointed out considerable differences in the nucleophilic order (Table 8) compared with that characteristic of reaction at a saturated carbon atom. In aqueous solution the PhS- ion is considerably more reactive than MeO^- towards 2-4 dinitrochlorobenzene[33] whereas, according to BEVAN and HIRST,[34] these ions have similar reactivities towards *p*-nitrofluorobenzene in ethanol. Also in alcoholic solvents, iodide and bromide ions have low reactivities compared to the alkoxide and phenoxide ions[27] suggesting, by analogy with the case of acylation discussed in a previous section, a Wheland type of transition state,[35]



It follows therefore that, particularly in the case of the aromatic fluorides, the bond-forming energy is considerably more important than in the transition state for reaction at a saturated carbon atom. As mentioned previously however, the transition state structure is sensitive to substituents, and the extent of bond formation in the various structures probably covers a range from a typical S_N2 displacement to a typical acylation.

Similarly, substitution reactions of fluoro-olefins show the nucleophilic order characteristic of addition. Thus

Table 8: Nucleophilic reactivities towards aromatic halides

p-nitrofluorobenzene[34] (methanol 25°)					
	MeO^-	PhS^-	PhO^-	$PhNH_2$	Cl^-
k_2	1.8×10^{-4}	1.7×10^{-4}	$\sim 10^{-6}$	1.6×10^{-8}	1.7×10^{-14}
2-4 dinitrochlorobenzene (dioxane-water)[33] **					
	PhS^-	CH_3O^-	PhO^-	HO^-	$C_5H_{10}N$
k_2	1300	2.2	0.72	0.07	4.48
	OEt^-	OMe^-	OPh^-	I^-	Br^-
k_2[27]	4.95 (a)	1.50 (b)	0.90 (a)	0.01 (c)	0.003 (c)

k_2 is given in $l \cdot mole^{-1} min^{-1}$ units. (a) in ethanol at 25°, (b) in methanol at 25°, (c) in ethylene glycol at 175°

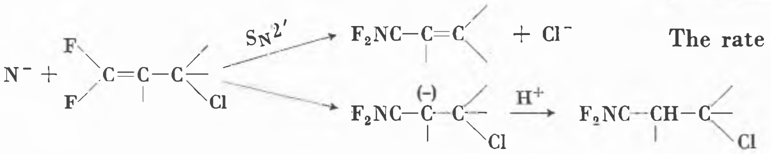
* The author wishes to acknowledge that other explanations are possible, although he does not favour the interpretation given by BUNNETT[26] which attributes the selectivity changes to changes in the polarisibility of the displaced group or other nearby substituents.

[28] WINSTEIN, SAVEDOFF SMITH, STEVENS and GALL, *Tetrahedron Letters 1960*, No. 1, p. 24.
[29] PRITCHARD, *Chem. Rev. 52* (1953) 529.
[30] PARKER, *J. Chem. Soc. 1961*, 1328.
[31] PATTISON and MILLINGTON, *Canad. J. Chem. 34* (1956) 757. BERGMANN and SHAHAK, *Chem. & Ind. 1958*, 157.

* In the recent discussion of nucleophilic reactivity by PEARSON and EDWARDS,[22] solvent effects are deliberately omitted. It is the view of the author that solvation is one of the most important factors controlling nucleophilicity, and hence the two factors cannot be separated.
** See also BUNNETT and DAVIS, *J. Amer. Chem. Soc. 80* (1958) 4337.

[32] KORNBLUM, BERRIGAN and NOBLE, *J. Amer. Chem. Soc. 82* (1960) 1257; KORNBLUM and LURIE, *ibid. 81* (1959) 2705.
[33] BUNNETT and DAVIS, *J. Amer. Chem. Soc. 76* (1954) 3011.
[34] BEVAN and HIRST, *J. Chem. Soc. 1956*, 254.
[35] WHELAND, *J. Amer. Chem. Soc. 64* (1942) 900.

MILLER *et al.* [36] have established qualitatively the order $F^- \gg Cl^- > Br^-, I^-$ for S_N2' displacements and nucleophilic addition, which proceed more rapidly than the alternative S_N2 displacement, viz.



These reactions were however carried out in acetone or dimethylformamide in which solvents the nucleophilic order towards a saturated carbon atom is $F^- \sim Cl^- \sim Br^- \sim I^-$. The selectivity is greater in the case of the fluoroolefins, owing to the decrease in electron density at the reaction centre (cf. p. 178), and the importance of this rate order in the preparation of fluorocarbons has been strongly emphasized by MILLER,[36] who has developed several novel synthetic routes.

As in the corresponding reactions of aromatic halides, thioanions are reactive towards vinyl halides, which are normally very inert towards nucleophilic reagents. Whereas bases, e.g. MeO^-, give the corresponding acetylene,[37] thiolate ions give the corresponding substituted product.[38] The latter reaction is however complex and proceeds in some cases by preliminary elimination followed by nucleophilic addition,

$$ROH + CH{\equiv}CH{-}X \xleftarrow{RO^-} X{-}CH_2{=}CH_2{-}X \xrightarrow{RS^-} RS{-}CH_2{=}CH_2{-}S{-}R$$

Further examples of the change from substitution to elimination with a change in the nucleophile will be given in a later section.

V. Phosphorylation

The considerable interest in organophosphorus chemistry at the present time, in particular the relationship between chemical constitution, reactivity and biological action has led to many accurate measurements of the rate of displacement of groups substituted at the phosphoryl centre.[39,40] The rate orders obtained by DOSTROVSKY and HALMANN[40] for the displacement reactions of di-isopropyl phosphorochloridate (Table 9),

$$(Pr^iO)_2POCl + N^- \rightarrow (Pr^iO)_2PON + Cl^-$$

show the strong influence of the bond-forming energy term in the transition state, produced by the high electron deficiency of the phosphorus atom.

Table 9: The reactivity of anions in ethanol towards di-isopropyl phosphorochloridate,[40] at 0°

	F^-	EtO^-	PhO^-	PhS^-
k_2 ($l \cdot m^{-1}\,sec^{-1}$)	0.03	0.01	0.003	< 0.0003

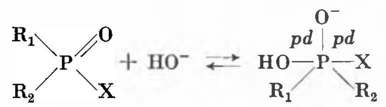
The rate sequence $F^- > MeO^-$ is not predicted by the Edwards equation (6), nor by equation (5) using the value for the P—F bond energy in PF_3. In view of the absence of satisfactory bond energy data for phosphoryl compounds, the latter equation cannot be applied. The high F^- reactivity is however almost certainly due to the high electrostatic interaction energy with the P^+ centre.

In general, the nucleophilic reactivity tends to follow the pK_a of the corresponding conjugate acid as shown by the extensive data of MILLER[41] for the reaction between oxygen and sulphur anions and diphenyl phosphorochloridothioate. Some representative values are given in Table 10.

Table 10: The rate of reaction of $(PhO)_2PSCl$ with anions in ethanol at 58°

	$Bu^{\gamma}O^-$	$C_5H_{11}S^-$	PhO^-	PhS^-	$MeCOO^-$
10^2k ($l \cdot m^{-1}\,sec^{-1}$)	121	36	27	4.5	0.34
pK_a	~19	10.8	9.94	6.65	4.76

This order also suggests that the transition state structure is similar to that of the corresponding pentacovalent intermediate, although it must be noted that in this case,[42] in contrast to acylation, no ^{18}O exchange of the phosphoryl oxygen atom has been observed in the hydrolysis of several phosphoryl compounds. This may possibily be due to the weaker *pd* bond energies of the axial bonds which form the reaction coordinate,[43] viz.



The high reactivity of certain weakly basic oxy-anions, e.g. NO_2^- and ClO^-, may also be attributed in part to the high P—O bond energy (~ 100 *k* cal/mole), although other structural factors probably enhance the reactivity.[44,45] This effect has recently been discussed in detail

36 FRIED and MILLER, *J. Amer. Chem. Soc. 81* (1959) 2078.
37 MILLER and NOYES, *J. Amer. Chem. Soc. 74* (1952) 629.
38 TRUCE and BOUDAKIAN, *J. Amer. Chem. Soc. 78* (1956) 2748.
39 LARSSON, *Svensk. Kem. Tidskr. 70* (1958) 10. HEATH, *J. Chem. Soc. 1956*, 3796; HUDSON and KEAY, *ibid. 1956*, 2463; *1960*, 1859.
40 DOSTROVSKY and HALMANN, *J. Chem. Soc. 1953*, 503.

41 MILLER, *J. Amer. Chem. Soc. 84* (1962) 403.
42 HALMANN, *J. Chem. Soc. 1959*, 305; DOSTROVSKY and HALMANN, *ibid. 1956*, 1004; BUNTON, SILVER, OLDHAM and VERNON, *ibid. 1958*, 3574; WESTHEIMER, *Chem. Soc. Special Publications 8* (1957) 1.
43 GILLESPIE, *J. Chem. Soc. 1952*, 1002; CRAIG, MACCOLL, NYHOLM, ORGEL and SUTTON, *ibid. 1954*, 332.
44 GREEN, SAVILLE, SAINSBURY and STANSFIELD, *J. Chem. Soc. 1958*, 1583.
45 EPSTEIN, ROSENBLATT and DEMEK, *J. Amer. Chem. Soc. 78* (1956) 341.

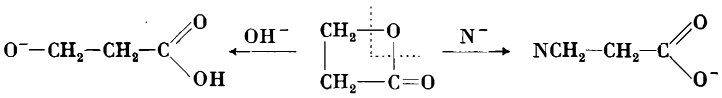
by Pearson and Edwards,[22] who have drawn attention to the fact that this enhanced reactivity is always exhibited by ions containing a lone pair of electrons on the atom adjacent to the nucleophilic atom. They then explained the reactivity by conjugation of this lone pair with the orbitals of the partial bonds in the transition state. This subject and possible explanations will be discussed further in a subsequent section, when the validity of the Brönsted law is discussed.

The systems discussed in the previous sections show that the increasing influence of the bond-forming energy in the transition state as the electron density, and consequently electron repulsion at the reaction centre decreases, modifies the nucleophilic reactivity in a regular way. In the following section, reference will be made to reactions at other centres, e.g. hydrogen and sulphur, in a discussion of the use of nucleophilic orders in the prediction of the course of reactions and the nature of the reaction products where several alternative paths are possible.

Nucleophilic reactivity orders for other inorganic molecules have been discussed recently by Pearson and Edwards,[22] and will therefore not be considered further here.

VI. Applications of nucleophilic orders

(a) *The position of bond fission.* The recognition of different nucleophilic orders for a particular type of electrophilic centre, and an appreciation of the factors determining and influencing such orders, may be extremely useful in predicting the reaction centre in molecules containing several electrophilic atoms. Thus it is well known that many ions react at the saturated carbon atom of β-lactones,[46] the rate constants following the Swain nucleophilic constant closely, as follows,



The hydroxide ion however gives the same products by alkyloxygen and by acyl-oxygen fission, but in this case the latter has been established by ^{18}O analysis.[47] The rate of reaction is considerably greater than that predicted by the Swain equation. If, as discussed in a previous section, the Swain order is characteristic of a bimolecular S_N2 reaction at a saturated carbon atom, the abnormally high reactivity of a basic ion may be attributed to reaction at a more electron-deficient atom. Similar considerations explain the reaction of alkoxide ions at the carbonyl centre of α-halo ketones[48] and similar centres. On this basis, Hudson and Harper[49] concluded that the alkaline hydrolysis of esters of pentacovalent phosphorus proceeds exclusively with P—O fission, a conclusion recently verified by ^{18}O analysis.[50]

This, and similar generalisations have numerous potential applications in synthetic chemistry, e.g. as illustrated by the elegant method of anionic debenzylation of pyrophosphates and phosphate esters developed by Clark and Todd[51] for use in nucleotide synthesis.

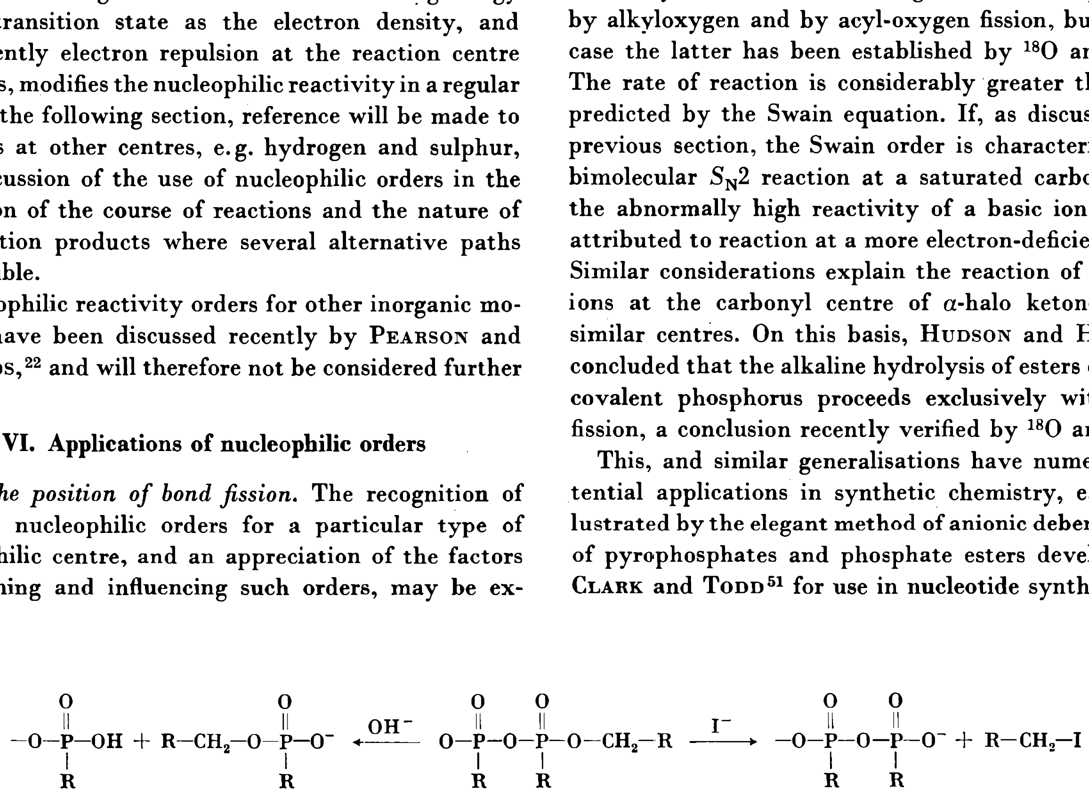


Table 11: Reactions of 2-4 dinitrophenyl p-toluenesulphonate with nucleophilic reagents

Reagent	Conditions	Yields (%) of Products S–O fission	C–O fission
$C_6H_5S^-$	60% dioxan, 27°, 2 hrs.	0	92
$CH_3COCHCO_2C_2H_5^-$	Tetrahydrofuran, 27°, 10 min.	0	93
$C_6H_5NH_2$	60% dioxan, 27°, 3.5 hrs.	8	88
Piperidine	67% acetone, 33% methanol, 0°, 2 hrs.	23	72
$C_6H_5O^-$	60% dioxan, 27°, 2 hrs.	67	32
CH_3O^-	67% acetone, 33% methanol, 0°, 5 min.	87	12

Sulphonate esters, which are widely used in preparative chemistry, behave similarly. Thus Bunnett and Bassett[26] have shown that the position of bond fission varies with the nature of the nucleophile (Table 11) as predicted by the general rule developed on p. 178.

[46] Bartlett and Small, *J. Amer. Chem. Soc. 72* (1950) 4867.
[47] Olsen and Hyde, *J. Amer. Chem. Soc. 63* (1941) 2459.
[48] Stevens, Malik and Pratt, *J. Amer. Chem. Soc. 72* (1950) 4758.
[49] Harper and Hudson, *J. Chem. Soc. 1958*, 1356.
[50] Barnard, Bunton, Llewellyn and Welch, *J. Chem. Soc. 1961*, 2670.
[51] Clark and Todd, *J. Chem. Soc. 1950*, 2030.

Similarly, Bordwell and co-workers[52] have shown that neopentyl *p*-toluenesulphonate undergoes C—O fission with mercaptide ions, iodide ions and with morpholine, and S—O fission with methoxide ions.

Finally, the relative rates of substitution and β-elimination of alkylating agents may be rationalised in a similar manner. Thus Hine[53] has shown that thiophenylate ions give 100% substitution of ethylene dihalides, whereas hydroxide ions give ~ 100% elimination,

$$\mathrm{PhS{-}CH_2{-}CH_2{-}SPh} \xleftarrow{\mathrm{PhS^-}} \mathrm{Br{-}CH{-}CH{-}Br} \xrightarrow{\mathrm{HO^-}} \mathrm{CH_2{=}CH{-}Br}$$

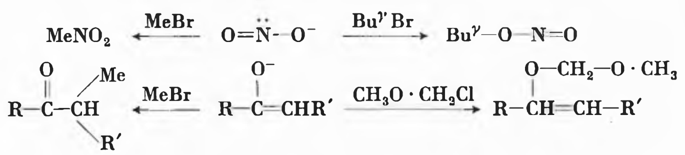
This and similar observations can be explained if the β-proton is assumed to be more electrophilic than the saturated carbon atom, since the force field of a proton is more intense than that of a carbonium ion. This is by no means self-evident, and as will be shown in a later section, the field of the proton in the transition state (and hence the extent of elimination) is very sensitive to substitution, particularly at the β-carbon atom.

The above considerations lead to the following reaction mechanism for the alkaline hydrolysis of β-disulphonates[54] which give an almost quantitative yield of the aldehyde.

$$\mathrm{RSO_2{-}O{-}CH_2{-}CH_2{-}O{-}SO_2R} \xrightarrow[\mathrm{E_2}]{\mathrm{HO^-}} \mathrm{CH_2{=}CH_2{-}O{-}SO_2{-}R} \xrightarrow[\text{S-O fission}]{\mathrm{HO^-}} \mathrm{CH_3{-}CHO} + \mathrm{MeSO_3^-}$$

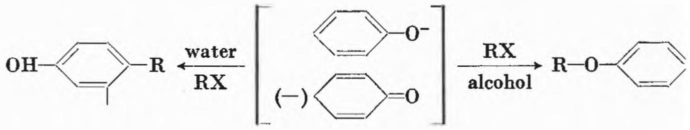
The general principles discussed in this section are particularly useful in interpreting the reactions of polyfunctional compounds containing several hetero-atoms, e.g. the specific removal of protecting groups, and in the reactions of organo-metalloid compounds, and many other examples can be found in the literature.

(b) *Ambident ions.* The relative reactivity of different nucleophilic atoms in a given molecule towards an electrophilic centre may also be interpreted on the same basis. According to Kornblum and his co-workers,[55] the most electronegative atom of the nucleophile tends to react at the more electron-deficient centre, following the increased importance of the bond-forming energy. The alternative reactions may be illustrated by the following examples.



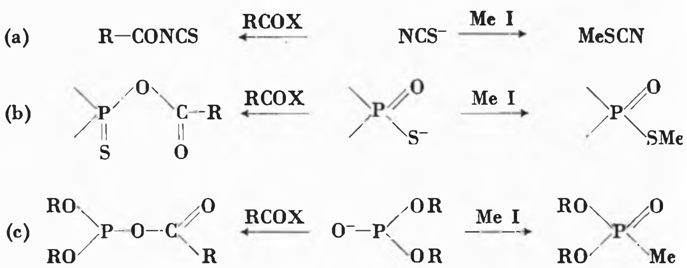
It is noted that in an S_N2 displacement of a primary halide the atom with the lowest electron density (hence lowest solvation energy) is the more reactive, whereas the highly charged oxygen atom is the more reactive towards incipient carbonium ions (owing to the high C^+O^- interaction energy).

Recent studies[56] have shown however that the detailed explanation of these and similar results is highly complex and various specific effects have to be taken into account. These complications will not be discussed further here, although it is pointed out that the change in the reaction with changes in the solvent follow the general rule discussed on p. 179 (note c). Thus an increase in solvation energy, produced for example by a change from ethanol to water,[32] promotes the reaction at the least solvated centre, e. g.



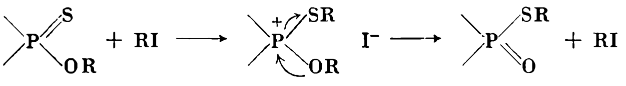
In solvents of low polarity however additional specific effects caused by ionic association modify the product composition.[57]

The principles of ambident reactivity may also be used to explain the reactivity of such ions at saturated and unsaturated centres. Thus again the more electronegative ion tends to react at the most electrophilic centre, as shown by the following examples.

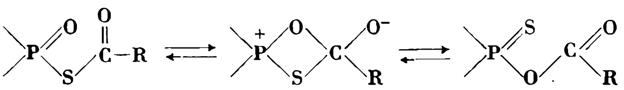


Although this concept provides a rational interpretation, it should be pointed out that few of these reactions have been studied mechanistically. It is quite possible that the products finally isolated are determined by thermodynamic factors, and that the rate-determining stage involves the alternative atom. Thus it is well known, with reference to reaction (b), that thiono-esters are readily converted to thiolates in the presence of alkyl halides,[58] viz.

[52] Bordwell, Pitt and Knell, *J. Amer. Chem. Soc. 73* (1951) 5004.
[53] Hine and Langford, *J. Amer. Chem. Soc. 78* (1956) 5002.
[54] Foster and Hammett, *J. Amer. Chem. Soc. 68* (1946), 1736. Rosen, Ph. D. Thesis, London 1958.
[55] Kornblum, Smiley, Blackwood and Iffland, *J. Amer. Chem. Soc.* 77 (1955) 6269.
[56] Kornblum and Weaver, *J. Amer. Chem. Soc. 80* (1958) 4333; Kornblum, Pink and Yobka, *ibid. 83* (1961) 2779.
[57] Kornblum and Lurie, *J. Amer. Chem. Soc. 81* (1959) 2705; Curtin, Crawford and Wilhelm, *ibid. 80* (1958) 1391.
[58] Fukuto and Metcalf, *J. Amer. Chem. Soc. 76* (1954) 5103.



Moreover, re-arrangements of carboxylate derivatives via fourmembered cyclic intermediates[59] are frequently observed and the following re-arrangement is possible.



The above interpretation should therefore be regarded as mainly speculative, although it does provide a useful working hypothesis for further investigations of these and similar reactions.

VII. The effect on the reactivity of substitution in the nucleophile

As a further simplification of the general equation (5), the effect of substitution in the nucleophile on the rate of reaction will be considered. According to the simplified model used in section III, bonding is produced by the transfer of charge ze from the nucleophile to the reaction centre, so that for a given nucleophilic atom, $\lambda D_{\text{C-N}}$ may be assumed to be constant, the localisation energy being incorporated in E_{N}.

Thus, if the following two substitutions are compared,

$$\overset{(-)}{\text{N}} \overset{ze}{\cdots\!\!\rightarrow} \overset{\delta+}{\text{C}} \ldots\ldots \overset{\delta-}{\text{X}} \quad \text{and} \quad \emptyset\!-\!\overset{(-)}{\text{N}} \overset{ze}{\cdots\!\!\rightarrow} \overset{\delta+}{\text{C}} \ldots\ldots \overset{\delta-}{\text{X}}$$

$$\lambda D_{\text{C-N}} \simeq \lambda D_{\text{C-N}\emptyset}$$

so that $\Delta E = a(\Delta H_{\text{N}} + E_{\text{N}}) + C_1$.

Under these conditions, therefore, the nucleophilic order is a function of the nucleophile only, and a common nucleophilic order is predicted for all substitutions.

Similarly, a comparison of the equilibria

$$\text{H}^+ + \text{N}^- \rightleftharpoons \text{HN} \quad \text{and} \quad \text{H}^+ + \text{N}^- - \emptyset \rightleftharpoons \text{HN}\,\emptyset$$

gives $\Delta H = \Delta H_{\text{N}} + E_{\text{N}} + C_2$ when $D_{\text{H-N}} \sim D_{\text{H-N}\emptyset}$

and combination of the two equations leads to

$$\Delta E = a\Delta H + \text{constant}$$

or if entropy differences are neglected,

$$\log k = apK_a + \text{constant}. \qquad (7)$$

This equation, first proposed by Brönsted in the form of the general catalysis law,[60] leads directly to the more general Hammett relation,[61]

$$\log k = \log k_0 + \varrho\sigma \qquad (8)$$

and similar free energy relationships.

[59] Al-Kazimi, Tarbell and Plant, *J. Amer. Chem. Soc. 77* (1955) 2479.
[60] Brönsted and Pedersen, *Z. physik. Chem. 108* (1924) 185.
[61] Hammett, *Physical Organic Chemistry*, McGraw Hill, 1940, p. 186.

These equations may be derived in several ways depending on the model of the reaction which is taken. In particular the Brönsted relation is usually interpreted by considering potential energy profiles and by assuming a regular variation, with substitution in N, of one of the energy factors used to compute the profiles.[62] More recently, attempts have been made to interpret the Hammett parameters in terms of localisation energies.[63] All these treatments are however mainly empirical, leading to the same generalisation that the change in reactivity with the substituent, represented by the reaction constant, a or ϱ, will decrease with electron density at the electrophilic centre.[64]

Surprisingly, very few systematic studies, apart from general base catalysis,[65] of the relationship beween the reaction constant obtained by variation of the nucleophile, and the structure of the electrophile have been made. The many applications of the Hammett equation[61] have been largely confined to changes in substitution at the reaction centre. It should be noted that the Brönsted equation is more useful in representing changes in reactivity produced by changes in the nucleophile than the Hammett equation, which is restricted to aromatic systems.

Representative values of the coefficient a for the various types of reaction may be calculated from a simple electrostatic treatment, based on an original calculation by Ri and Eyring[66] of the isomer distribution in electrophilic substitution, and used by Price[67] to interpret the Hammett equation.

The interaction energy between the nucleophile and electrophilic centre at the separation distance characteristic of the transition state is assumed to be entirely electrostatic, and the reaction imagined to proceed as follows.

$$\underset{\text{I}}{\text{N}^- + \overset{\delta+}{\text{C}} \underset{r_2}{\ldots\ldots} \overset{\delta-}{\text{X}}} \xrightarrow{E_1} \underset{\text{II}}{\overset{(-)}{\text{N}} \underset{r_1}{\ldots\ldots} \overset{\delta+}{\text{C}} \underset{r_2}{\ldots\ldots} \overset{\delta-}{\text{X}}} \xrightarrow{\Delta E = 0} \underset{\text{III}}{\overset{(1-z)-}{\text{N}} \underset{r_1}{\ldots\ldots} \overset{(\delta-z)+}{\text{C}} \underset{r_2}{\ldots\ldots} \overset{\delta-}{\text{X}}}$$

In reality $E_{\text{III}} < E_{\text{II}}$ owing to the polarisation $\overset{(-)}{\text{N}} \frown\!\!\rightarrow \overset{\delta+}{\text{C}}$ leading to covalent bond formation. It is reasonable to assume however that the greater the field at C^+, the greater the interaction energy with N^-, and to use the electrostatic energy as a measure of this. In this connection, it is noted that recent studies[68] have shown that for a polar molecule, e.g. LiH, the force constant and bond length may be calculated fairly accurately by assuming the wavefunctions for the electrons of the

[62] Bell, *Proc. Roy. Soc. A 154* (1936) 414. Horiuti and Polanyi, *Acta Physiochim. U.R.S.S. 2* (1935) 505.
[63] Sixma, *Rec. Trav. Chim. Pays-Bas 72* (1953) 673; Jaffe, *J. Chem. Physics 20* (1952) 279, 778, 1554, *21* (1953) 415.
[64] Jaffe, *Chem. Rev. 53* (1953) 191.
[65] Bell, *The Proton in Chemistry*, Methuen, 1959, p. 155.
[66] Ri and Eyring, *J. Chem. Physics 8* (1940) 433.
[67] Price, *Chem. Rev. 29* (1941) 60.
[68] Platt, *J. Chem. Physics 18* (1950) 932. Gaspar *et al.*, *Acta Physica Hung. 7* (1957) 151, *10* (1959) 149; *Ann. Physik 2* (1958) 208.

anion to be essentially unaltered by the positive ion embedded in the charge cloud of the anion.

If z' is the charge on the nucleophile,

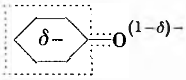
$$\Delta E = z' \cdot \delta / r_1 + E_2.$$

Similarly for combination with a proton $\Delta H = z'/r_1 +$ constant, so that

$$\Delta E = \left(\frac{r_0}{r_1} \cdot \delta\right) \Delta H + \text{constant},$$

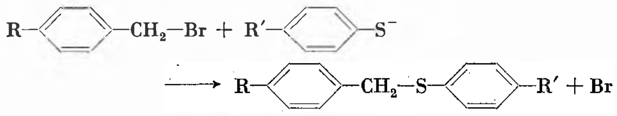
or $$\log k = \left(\frac{r_0}{r_1} \cdot \delta\right) pK_a + \text{constant}. \qquad (9)$$

It follows therefore that $\alpha \equiv \frac{r_0}{r_1} \cdot \delta$, where δ is the effective charge on the electrophilic centre in the transition state which results in polarisation of the nucleophile and bond formation.

It should be noted that the removal of charge in the ground state of an ion from the nucleophilic atom to the conjugating group, e.g.  is related to the conjugation energy, which changes the electron affinity of the nucleophile.[69] Thus the treatments calculating the electrostatic N—C interaction energy, and the energy required to remove a charge ze from the nucleophile, measure the same effect.

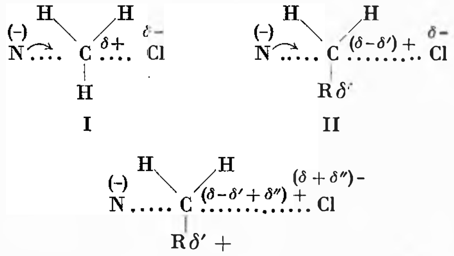
In order to investigate the relationships given in equations 7 and 9 we have performed several systematic investigations of the variation of α (or ϱ) with structure.

(a) The changes in reactivity produced by changing R′ for a given value of R in the following reaction have been measured in methanol solvent.[70]



In this case, the Brönsted relation is not accurately obeyed, the sensitivity increasing with the pK_a of the thiophenol. It is this kind of deviation which has led Brown,[71] Taft[72] and others to define substituent constants (e. g. σ^*) in terms of a reference reaction. Since the deviations observed in the present case are of the same form for each bromide, linear relations of the Hammett kind were obtained by plotting the log k values for the various substituents R against the value with the same nucleophile, for the unsubstituted bromide. The slope of each line, ϱ_N, is found to be proportional to the substituent constant of R, σ_R. Since σ_R represents the change in charge density at the electrophilic centre produced by R, this relation provides a quantitative demonstration of equation 9.

This principle is widely used in the interpretation of the mechanism of substitution and was first advanced by Hughes and Ingold[73] in a qualitative form in the famous concept of duality of mechanism. It is of some interest to interpret the original postulate in terms of the above view. If the electronic distribution in the transition state for the reaction of a methyl halide is represented by structure I below,

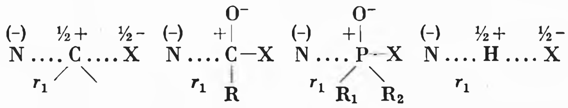


I II

III

substitution of an electron-releasing group, e.g. CH_3 reduces $\delta+$ to $(\delta - \delta')+$, thus reducing the interaction with the nucleophile (II). The transition state is reached by a further extension of the C—X bond giving an increased charge δ'' (smaller than δ') on the carbon atom which now carries the charge $(\delta - \delta' + \delta'')$. The net effect is that although the charge on the central carbon atom $(\delta - \delta' + \delta'')$ of the substituted compound, and hence the selectivity, is less than that on the methyl carbon atom (δ), the charge on the group as a whole $(\delta + \delta'')$ is greater than that on the methyl group, i. e. the ionisation tendency is increased. This gives an alternative interpretation of the gradual change in mechanism[21] ($S_N2 \rightarrow S_N1$).

(b) By assuming characteristic transition state structures for substitution at various centres as follows,



alkylation *acylation* *phosphorylation* *general base catalysis*

and assuming the electronegativities of N and X to be similar, values of α, calculated according to equation (9), may be compared with experimentally determined values[74] in Table 12, for reactions in a common solvent. (In this treatment, changes in nucleophilic reactivity produced by changes in solvent would have to be treated by introducing a factor for the changes in the electronegativities of N and X.)

The available data, collected in Table 13, show that the value of α increases regularly with the electron deficiency at the electrophilic centre, and the agreement

[69] Coulson and Daudel, *Dictionary of Values of Molecular Constants*, 1959; see also ref. 25.
[70] Klopman and Hudson, *J. Chem. Soc. 1962*, 1062.
[71] Brown and Okamoto, *J. Amer. Chem. Soc. 79* (1957) 1913.
[72] Taft, *J. Physic. Chem. 64* (1960) 1812.
[73] Hughes, Ingold and Patel, *J. Chem. Soc. 1933*, 526; Hughes and Ingold, *ibid.* 1571; see ref. 1, p. 310.
[74] Hudson and Loveday, *J. Chem. Soc. 1962*, 1068.

Table 12

Reaction	r_1(Å)	α(calc.)	α(obs.)
(1) Alkylation (S_N2)	1.83	0.26	0.22
(2) General base catalysis	1.36	0.37	0.47*
(3) Acylation	1.42	0.70	0.78
(4) Phosphorylation	1.76	0.55	0.5 to 0.7**

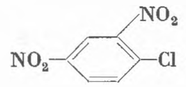
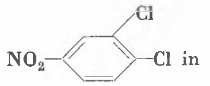
* Value given for the general base catalysed hydrolysis of an ester.[75] Values of α for the rate-determining ionisation of pseudo-acids[65] are not considered owing to the high electronegativity of the leaving groups. These reactions are considered separately in the next column.

** Values for $(EtO)_2P(O)—O—P(O)—(OEt)_2$ and EtO(Me)P(O)CN are given in Table 13. The values for the fluorides are not considered in view of the high electronegativity of fluorine.

Table 13: Values of the Brönsted coefficient α for reactions of nucleophiles with alkylating, acylating and phosphorylating agents

Compound	Nucleophiles	α	Reference
$MeOSO_3^-$	$R·C_6H_4O^-$	0.16	(a)
$Cl·CH_2·COO^-$	$R·COO^-$	0.20	(b)
$Br·(CH_2)_3·OH$	$R·C_6H_4O^-$	0.22	(c)
$CH_2·CH_2$ (–O– bridged)	$R·C_6H_4O^-$	0.32	(d)
$2.4(NO_2)_2·C_6H_3·Cl$	$R·C_6H_4O^-$	(0.50)*	(e)
EtO·COCl	$R·C_6H_4O^-$	0.78	(c)
$p·NO_2·C_6H_4·O·COCH_3$	$R·C_6H_4O^-$; $R·C_5H_4N$	0.80	(f)
$(CH_3CO)_2·O$	$R·C_5H_4N$	0.92	(g)
$Et_2N(OEt)P(O)CN$	R_2CNO^-	0.50	(h)
$(EtO)_2P(O)OP(O)(OEt)_2$	R_2CNO^-	0.70	(h)
$Pr^iO·(Me)·POF$	$R·CO\ NHO^-$	0.82	(h)
$Pr^iO·(Me)·POF$	$R·C_6H_3(OH)O^-$	0.90	(i)

* Recent results by Knowles, Norman and Prosser[76] for

 and  in 20 % water- 80 % dioxan mixtures suggest a higher value ($\alpha \rightarrow 1.0$). It should be pointed out however that in both cases the rates obtained in partly aqueous media are compared with pK_a values in water. The value in the Table should therefore be regarded as an approximate one.

(a) Green and Kenyon, *J. Chem. Soc. 1950*, 1595; (b) Smith, *J. Chem. Soc. 1943*, 521; (c) Hudson and Loveday, *J. Chem. Soc. 1962*, 1068; (d) Goldsworthy, *J. Chem. Soc. 1926*, 1254; (e) Miller, Leaky, Liveris and Parker, *Australian J. Chem. 1956*, 382; (f) Bruce and Lapinski, *J. Amer. Chem. Soc. 80* (1958) 2265; (g) Gold and Jefferson, *J. Chem. Soc. 1953*, 1409; (h) Green, Saville, Sainsbury and Stansfield, *J. Chem. Soc. 1958*, 1583; (i) Epstein *et al.*, *J. Amer. Chem. Soc. 78* (1956) 341.

between the calculated and experimental values of α (Table 12) is very good bearing in mind the simplicity of the treatment.

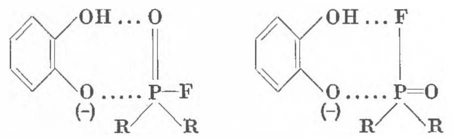
[75] Jencks and Carriuolo, *J. Amer. Chem. Soc. 83* (1961) 1743.
[76] Knowles, Norman and Prosser, *Proc. Chem. Soc. 1961*, 341.

The value of α also varies with the nature of the leaving group, although the data of Smith[77] for the reactions of α halogeno acetate ions show that a change from the chloride to the bromide has little effect. This is probably due to the small change in electronegativity (x_y), and relatively large variations in α have been observed[44] in the reactions of certain phosphoryl compounds (see Table 14), when larger changes in the electronegativity of the displaced group are made.

Table 14: Change in the value of α with the leaving group in phosphorylation reactions

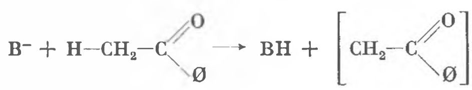
	$Et_2N(OEt)POCN$	$[(EtO)_2PO]_2O$	$Pr^iO(Me)POF$
x_y	2.5	3.5	4.0
α	0.5	0.7	0.8

The value of α is further increased when the charge transfer from the nucleophile is assisted by hydrogen bonding to the phosphoryl group, as in the reaction of fluoridates with catechol,[45]



This change in α is brought about in these cases by a decrease in the electron density at the reaction centre in the ground state, thus increasing the polarisation of the nucleophile and hence the charge transfer in the transition state.

A different effect is observed when the leaving group is highly conjugated in the transition state, but not in the ground state. Here a change in the leaving group has little effect on the electronic distribution in the ground state. This situation has been examined very carefully by Bell and his collaborators[65] in the rate-determining ionisation of pseudo-acids, e.g.



It is found (Table 15) that the coefficient α decreases regularly with the pK_a of the conjugate acid of the displaced group (i.e. with the electronegativity of the displaced group which appears at first sight to be at variance with the change discussed above (see Table 14).

In this case, the change is due to the regular variation in the transition state structure with changes in conjugation in the displaced groups and may be interpreted as follows.

[77] Smith, *J. Chem. Soc. 1943*, 521.

Table 15: The change in the Brönsted exponent α with structure of the ketone in the base-catalysed bromination of ketones[65]

Ketone	α	pK_a
$CH_3 \cdot CO \cdot CH_3$	0.88	20.0
$CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$	0.89	18.7
$CH_3 \cdot COCH_2 \cdot Cl$	0.82	16.5
$CH_3 \cdot CO \cdot CH_2 \cdot Br$	0.82	16.1
$CH_3 \cdot CO \cdot CH \cdot Cl_2$	0.82	14.9
$CH_2 \cdot CO \cdot CHCO_2 \cdot C_2H_5$ └$(CH_2)_3$┘	0.64	13.1
$CH_3 \cdot CO \cdot CH_2 \cdot CO_2C_2H_5$	0.59	10.5
$CH_2 \cdot CO \cdot CH \cdot CO_2 \cdot C_2H_5$ └$(CH_2)_4$┘	0.58	10.0
$CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot C_6H_5$	0.52	9.7
$CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$	0.48	9.3
$CH_3 \cdot CO \cdot CHBr \cdot CO \cdot CH_3$	0.42	8.3

Two reactions will be compared, producing a non-conjugated group (I) and a highly conjugated group respectively, (II) as follows,

$$\underset{\text{I}}{\overset{(-)\quad \delta+ \quad \delta-}{N \ldots H \ldots X{-}\emptyset_1}} \qquad \underset{\text{II}}{\overset{(-)\quad \delta+ \quad (\delta-)}{N \ldots H \ldots X{=}\emptyset_2}} \qquad \underset{\text{IA}}{\overset{(-)\ +\quad \delta-}{N\,H \ldots X{-}\emptyset_1}}$$

$$E_1 \quad E_2 \qquad\qquad E_1 \quad E_2$$

In the first case, $E_2 > E_1$, and hence the configuration of the transition state has not been reached. Thus an increase in the bondforming energy represented by a closer approach of N to H is necessary in order to reach the energy barrier. This structure is represented by IA where $\overset{-}{N}\overset{+}{H}$ represents almost complete bond formation in terms of the electrostatic model discussed above. In the second case, $E_2 < E_1$, i.e. the transition state has already been reached. Since the perturbation of the nucleophile by the field of the incipient proton is greater in IA than in II, the value of α is greater for the ketone giving the less conjugated anion. It is interesting to note that the value of α for a nitroparaffin[78] is greater than that predicted from the corresponding pK_a and the series given in Table 15. This may be due to the inductive effect of the NO_2 group in the ground state.

Bender[79] has also given data for the reaction between pyridines and *p*-substituted phenyl acetates showing that the value of α increases with conjugation in the displaced ion although the changes here are relatively small, probably because the transition state structure is close to that of the intermediate.

VIII. β-Elimination and substitution

The change in the value of α with the nature of the reaction centre may be used to interpret, and in some cases to predict, the product composition. In kinetic studies of competing substitution and β-elimination reactions of alkyl halides in methanol solution,[80] the following values have been found for the coefficients α_S and α_E.

Table 16

	n-BuBr	$Ph \cdot CH_2 \cdot CH_2 \cdot Br$	$p\text{-}NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CH_2Br$
α_S	(0.39)*	0.38	–
α_E	(0.35)*	0.56	0.83

The value of α_E is slightly less than the value of α_S in the case of *n*-butyl bromide*, although according to the calculated values in Table 12, α_E should be somewhat greater than α_S. The differences are however small, and the main conclusion can be drawn that in the absence of strong additional conjugation effects, $\alpha_S \sim \alpha_E$, and the yield of olefin is not very sensitive to changes in the nucleophile, as shown by the data in Table 17. This is also shown by data obtained by Segaller[81] for the % elimination of t-amyl iodide. This reaction presumably proceeds via an incipient carbonium ion.

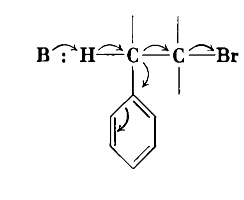
Table 17: Yield of olefin (%) in the reactions of alkylating agents with various basic reagents

Nucleophile	OEt^-	OPh^-	$p\text{-}NO_2 \cdot C_6H_4O^-$
n-butyl bromide[80]	6.4		
t-amyl iodide*[81]	50	40	33
β-phenyl ethyl bromide[80]	~98	47	17
n-propyl trimethyl ammonium salts[82]	81	15	~0**

* Relative values.
** *m*-nitrophenylate.

The selectivity is considerably greater in the corresponding reactions of *n*-propyl trimethyl ammonium salts, as shown by the data of Ingold and Hanhart[82] in Table 17.

Substitution at the β-carbon atom of electron-attracting groups usually increases α_E considerably by the withdrawal of electrons from the nucleophile to the alternative electronegative centre, viz.



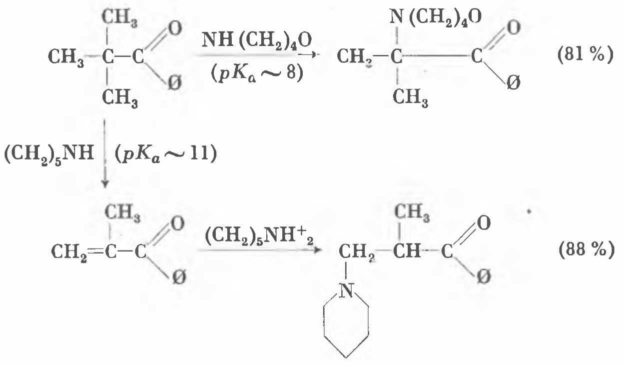
Under these conditions, the yield of olefin increases rapidly with the basicity of the nucleophile, as shown by the data for β-phenyl ethyl bromide in Table 1.7

* These are approximate values.

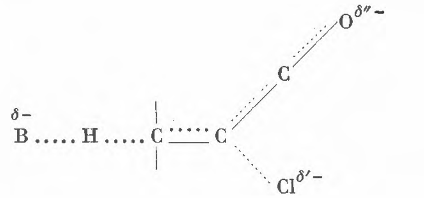
[78] Bell and Spencer, *Proc. Roy. Soc. A 251* (1959) 41.
[79] Bender, ref. 10, p. 33.
[80] Hudson and Klopman, unpublished results.
[81] Segaller, *J. Chem. Soc. 1913*, 1431.
[82] Ingold and Hanhart, *J. Chem. Soc. 1927*, 997.

When $\alpha = 1.0$, the reaction becomes specific base-catalysed leading to an intermediate carbanion. Such intermediates have been recognised recently,[83] although the kinetic method, which has been applied extensively to studies of other rate-determining proton transfers,[65] does not seem to have been applied to β-elimination.*

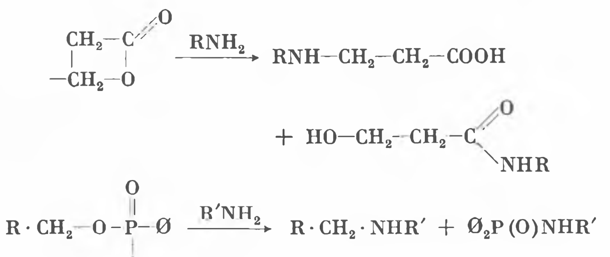
The relatively large value of α_E in a molecule where conjugation promotes further charge transfer from the nucleophile may also explain the recent observations of CROMWELL and HESS,[84] that piperidine gives predominant elimination and morpholine predominant substitution in an α-bromo ketone.



The above products would be obtained for a value of $\alpha_E - \alpha_S \sim 0.5$ using the pK_a values for the amines in water. The value of α_S would be less than the value given in Table 13, since the substitution occurs at a tertiary carbon atom, and the value of α_E may be increased by the conjugation represented as follows.



Similarly, the product compositions of reactions of bases with other reagents with competing electrophilic centres should vary regularly with the nucleophile, e.g.



* See however WEINSTOCK, PEARSON and BORDWELL, *J. Amer. Chem. Soc. 78* (1956) 3473.

[83] HINE, WIESBOECK and RAMSAY, *J. Amer. Chem. Soc. 83* (1961) 1222. LEITCH and BERNSTEIN, *Canad. J. Res. 28 B* (1950) 35.

[84] CROMWELL and HESS, *J. Amer. Chem. Soc. 83* (1961) 1237.

IX. The influence of the nucleophile on α

In discussing the reactions listed in Table 13, it was assumed that the value of α is the same for the various series of nucleophiles used. Recent studies have shown that this is the case for the reactions of p-nitrophenyl acetate[85] with phenols, anilines, pyridines and oximes, oxamates and phenols. In these cases, bond formation is almost complete in the transition state and it is therefor reasonable that the magnitude of the charge transfer is insensitive to changes in the nucleophile.

When the bond in the transition state is weak however, α may vary significantly with the type of nucleophile. The reaction between various substituted pyridines and ethyl methanesulphonate, a molecule which hydrolyses by a mechanism bordering on an S_N1 ionisation with weak interaction between the nucleophile and the carbon atom,[86] has been followed in water.[87] The relation between $\log k$ and pK_a gives a series of parallel lines depending on the number of α-substituents (Fig. 3). The separation of the lines is attributed to steric interaction between the α-methyl groups and the ethyl group, although it may be partly due to steric restriction of solvation[88] of the incipient quaternary ammonium ion.

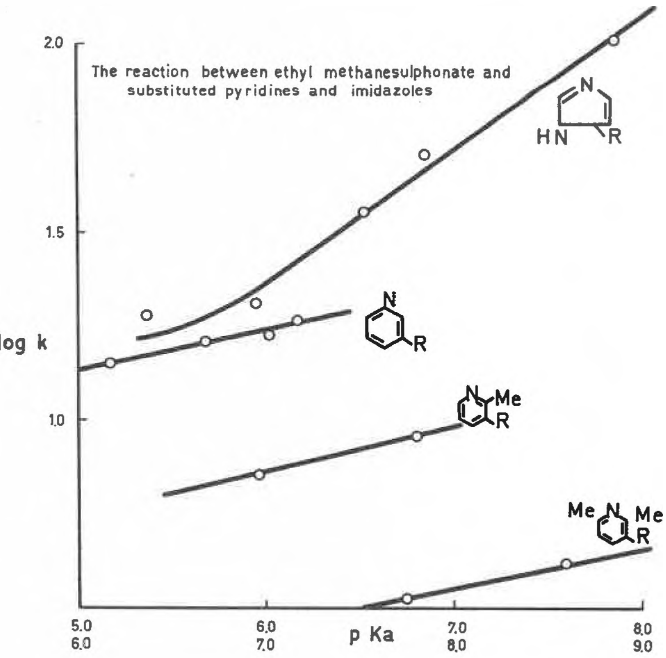


Fig. 3

The slope of the lines (0.16) is very low, in agreement with the weak bonding in the transition state. With

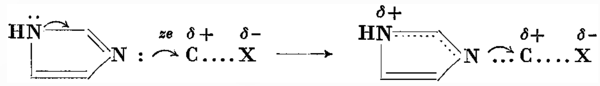
[85] BRUICE and LAPINSKI, *J. Amer. Chem. Soc. 80* (1958) 2265.

[86] GRUNWALD, WINSTEIN and JONES, *J. Amer. Chem. Soc. 73* (1951) 2700. ROBERTSON, *Canad. J. Chem. 31* (1953) 589, *33* (1955) 1536, *35* (1957) 1319.

[87] WITHEY, Ph.D. Thesis, London 1960.

[88] EVANS and HAMANN, *Trans. Faraday Soc. 47* (1951) 42.

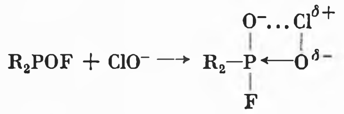
substituted imidazoles, however, only one line is obtained, owing to the reduced steric hindrance for the increased C—N—C angle. In this case, the slope is considerably greater than for the pyridines ($\alpha \sim 0.3$), which may be due to increased electron release from the nucleophile assisted by conjugation, viz.



This is in agreement with the general conclusion drawn on p. 177 that the extent of bond formation tends to increase with the decrease in the effective electronegativity of the nucleophile.

X. Reactivity of oxy-anions

Reference has already been made to the fact that many oxy-anions are considerably more active than predicted by the pK_a's of their corresponding conjugate acids. Within recent years, accurate data have been obtained for acylation[85] and phosphorylation,[44] (Table 18) and similar data are available for rate-determining proton transfers.[65] Various explanations of the "abnormally" high reactivities have been given, including bifunctional catalysis[89] of the following kind.



This is not very probable in view of the high electron density around the Cl-atom, and it is difficult to see how such a catalysis could operate in rate-determining proton transfers.[65]

Table 18: The reactivity of nucleophiles towards isopropyl methylphosphorofluoridate (B) and tetraethyl pyrophosphate (A)[44]

Nucleophile	$k_{(A)}$	$k_{(B)}$	pK_a	k_A/k_B
H_2O	0.0017	0.0001	0	17
NH_2OH	26	2.6	6	10
ClO^-	267	600	7.4	0.45
Ac_2 C : NO^-	35	73	7.4	0.48
Ac CH : NO^-	59	240	8.3	0.24
B_3 NHO^-	160	1,020	8.8	0.16
Ac CMe : NO^-	16	380	9.3	0.043
HO_2^-	2,180	94,000	11.8	0.023
HO^-	21	2,000	14	0.011

Recently, Pearson and Edwards[22] have suggested that the lone-pair electrons (or π-electrons) on the atom adjacent to the nucleophilic atom may conjugate with the reacting bonds, by a process which may be represented schematically as follows,

$$\ddot{A}\text{—}O^- + X\text{—}Y \longrightarrow \overset{(+)}{A}\text{⋯}O\text{⋯⋯}\overset{(-)}{X}\text{⋯⋯}\overset{(-)}{Y} \qquad (a)$$

by analogy with the process,

$$\ddot{A}\text{—}CH_2\text{—}Y \longrightarrow \ddot{A}\text{⌒}CH_2^+\text{⋯⋯}\overset{(-)}{X} \qquad (b)$$

Here the lone-pair electrons can enter the vacant orbital left by the electrons in the leaving group X. It is not clear, on the other hand, which orbitals are supposed to contain the lone-pair electrons in the transition state of (a). In view of the high electronegativity of the oxygen atom, the energy of the antibonding orbital of the O—X bond is probably too high to assist in the stabilisation of the transition state.

A more plausible, but less specific, explanation is that the approximations and proportionalities between the various energy factors which lead to the Brönsted equation do not hold when the structure of the nucleophile is changed, even though the nucleophilic atom is unchanged.[70] This suggestion may be represented by the following treatment. Suppose that the conjugation energy in the ion Ø—O⁻ is E_C, then the electron distribution is related to E_C. Thus the greater E_C, the smaller the formal charge on the oxygen atom (and hence the smaller the solvation energy of the ion). Using the same treatment as on page 176, we may write

$$RT \ln k = -\alpha E_r - \varkappa\beta E_r + C,$$

where $\varkappa E_r$ is the difference in solvation energy produced by the conjugation.

Since $\beta = 0$ when $\alpha = 0$ and $\beta = 1$ when $\alpha = 1$, we may write

$$RT \ln k = -\alpha E_r + \varkappa\alpha^m E_r + C_1.$$

For the combination of the nucleophile with a proton,

$$RT \ln K_a = \varkappa E_r - E_r + C_2.$$

Combination of these equations gives

$$\ln k = \alpha pK_a + \frac{\varkappa}{RT}(\alpha^m - \alpha)\, E_r + \text{constant}.$$

If we assume that for a given series of nucleophiles (e.g. a series of substituted phenols or amines), $m = 1$, the rate follows the Brönsted equation. If however $m \neq 1$ when different kinds of nucleophiles are compared (e.g. phenolate and carboxylate ions), the rates do not obey the Brönsted equation. Although this kind of interpretation is a very general one, the author believes that it is more reasonable than interpretations involving highly specific effects. Further investigation of this interesting problem is necessary before a satisfactory interpretation can be given.

In concluding this brief review of the rate data on some nucleophilic reactions, the author points out the surprising lack of systematic data on some of the simplest reactions. This is mainly due to the fact that physical-organic chemistry has been concerned primarily with

[89] Epstein, Bauer, Saxe and Demek, *J. Amer. Chem. Soc.* 78 (1956) 4068.

the structure and reactivity of the organic partner of the reaction, and has been less concerned with the nature of the interaction between the reactants, partly because of the intractability of this problem. For this reason, the interpretations given here are largely speculative and will have to be modified in the light of subsequent investigations. An attempt has been made, however, to present a simple and coherent interpretation of the reactivity of nucleophiles to provide a general basis for the discussion of a wide range of displacement reactions.

General summary

In view of the wide application of the interpretations and principles discussed in this review, it might be useful to summarise the main points which have emerged as follows.

(1) Electronegative ions (or molecules) tend to react at the more positive centres. The nucleophilic order is therefore related to the transition state structure.

(2) A polar solvent reduces the nucleophilic reactivity of a highly solvated ion (usually a highly electronegative ion) more than that of a weakly solvated ion. The nucleophilic order may therefore change with the solvent.

(3) For a series of nucleophiles with the same basic structure, the Brönsted catalysis law ($\log k = a pK_a +$ constant) usually holds. The magnitude of a increases with a decrease in electron density at the reaction centre. Hence there is a relationship between the selectivity given by a, and the nucleophilic order given by (1).

(4) The coefficient a decreases with conjugation in the displaced group.

(5) The coefficient a decreases with an increase in the solvating power of the solvent.

(6) The coefficient a tends to increase with the nucleophilic reactivity of the atom. The increase will be the greater the weaker the bond formed in the transition state.

(7) In the case of oxy-anions with different basic structures, the increase in reactivity above that predicted by the pK_a of the conjugate acid tends to increase with conjugation energy in the ion (i.e. with decrease in pK_a).