Leaving Groups and Nucleofugality in Elimination and Other Organic Reactions

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"Parting is such sweet sorrow"—*Romeo and Juliet.*

In reactions in which bonds are broken, part of one reactant, the leaving group, becomes detached. This Account is concerned with leaving groups which depart with the bonding electron pair. Such groups are termed "nucleofuges".

Nucleofuges (Z) figure in two prominent types of reaction:
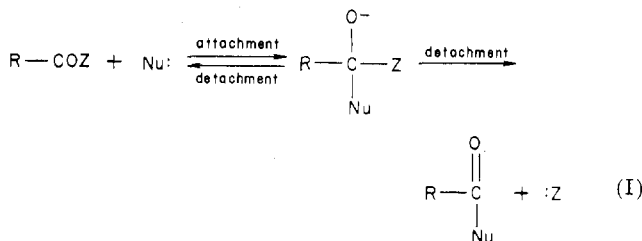
substitution

$$Nu: + R—Z \rightarrow Nu—R + :Z$$

elimination

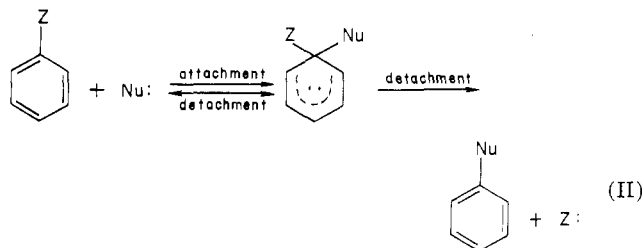$$B: + H—X—Y—Z \rightarrow BH + X{=}Y + :Z$$
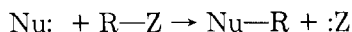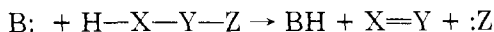
In these examples, the processes are *nucleophilic substitution* and *1,2-elimination*, respectively. These two simple types become more complex when reaction intermediates are involved. Thus, in oversimplified notation, eq I and II illustrate the processes.

carbonyl substitution

aromatic substitution

Against this background it is obvious that the leaving group can determine reactivity in nucleophilic substitution in aliphatic[1] and aromatic[2] systems and in elimination reactions[3] leading to alkenes, carbonyl compounds, and other multiply bonded systems.

Nucleofugality, the tendency of an atom or group to depart with the bonding electron pair, has, however, been little studied. There appear to be two reasons for this. Available data on most reactions cover only restricted ranges of leaving group (Table I), and many leaving groups in simple systems are the conjugate bases of strong acids. This has fostered the illusion[4] that nucleofugality depends in a simple way upon the $pK_a(H_2O)$ of the conjugate acid of the leaving group. The labels "good" and "poor" are often applied to leaving groups indiscriminately. We shall see that before these terms can be properly applied, the type of reaction and the involvement of the leaving group in it must be specified.

Determination of Nucleofugality. Ranges of leaving groups are summarized for a number of reactions in Table I. Limitation of the quantified range of leaving groups to halides, sulfonates, amines, and sulfides for displacements at carbon and for simple alkene-forming eliminations is striking. In contrast, eliminations forming carbonyl and phosphoryl ($>P{=}O$) groups are found in practice to involve wide ranges of leaving groups. Insofar as evaluation of nucleofugalities is concerned, all the information in Table I must be regarded as anecdotal. The rate of a reaction will reflect nucleofugality only if the leaving group is involved in its rate-determining step. Detailed knowledge of mechanism is thus required, and, especially for carbonyl substitutions, is not always readily available.

Even when the mechanism of the reaction is known, the nature of the step in which the leaving group departs may complicate determination of nucleofugality. In S_N1 reactions (Table ID) the type of leaving group is restricted and relative reactivities are dependent on the group R. For S_N2 reactions (Table IA) relative reactivities give no information about nucleofugality because of differential (and unquantified) interactions between the nucleophile and nucleofuge. For eliminations in the phenethyl series (Table IB), removal of the β proton and leaving group are concerted, and the contribution of the leaving group to reactivity cannot easily be assessed. A system with a wide range of leaving groups whose mechanism is capable of being unambiguously analyzed to give nucleofugalities is required to provide a body of information in this area. In particular, the leaving group should depart from a species whose structure varies only with the leaving

(1) R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Am. Chem. Soc.*, **90**, 5049 (1968).
(2) G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, **10**, 125 (1977).
(3) A. F. Cockerill and R. G. Harrison in "The Chemistry of Double-bonded Functional Groups", S. Patai, Ed., Wiley, New York, 1977.
(4) A. Streitwieser and C. H. Heathcock, "Introduction to Organic Chemistry", Macmillan, New York, 1976, p 141.

Table I
Leaving Groups (Z) in Familiar Reactions

A. Nucleophilic Substitution at sp^{3}C[a]

$$N_3^- + Me-Z \xrightarrow{MeOH} MeN_3 + :Z$$

Z	k_{rel}
Me$_2$S	1
OP(O)(OMe)$_2^-$	6.2
Cl$^-$	20
Br$^-$	1250
I$^-$	2000

B. Alkene-Forming Elimination[b]

$$EtO^- + PhCH_2CH_2Z \rightarrow EtOH + PhCH=CH_2 + :Z$$

Z	k_{rel}	Z	k_{rel}
F$^-$	1	NMe$_3$	760
Cl$^-$	68	Br$^-$	4100
OTs$^-$	392	I$^-$	26600
		SMe$_2$	37900

C. Nucleophilic Substitution at sp^{2}C

Z	k_{rel}	Z	k_{rel}
SC$_6$H$_4$-p-NO$_2$	1[c]	Cl	11.6[d]
OPh$^-$	2.0[c]	OC$_6$H$_4$-p-NO$_2^-$	29.6[c]
I$^-$	2.2[d]	NO$_2^-$	5750[c]
Br$^-$	7.6[d]	F$^-$	6900[c]

D. Dissociation: S$_N$1[e]

$$R-Z \rightarrow \overset{+}{R} + \overline{Z}$$

Z	k_{rel}	Z	k_{rel}
OSO$_2$CF$_3^-$	2.5 × 10^{14}	Br$^-$	5 × 10^5
OSO$_2$C$_6$H$_4$-p-Br	7.5 × 10^9	Cl$^-$	1.3 × 10^4
OSO$_2$C$_6$H$_4$-p-Me	2.5 × 10^9	OCOC$_6$H$_4$-p-NO$_2$	1

E. Nucleophilic Substitution at S[f]

$$Ph_3CSZ + BuNH_2 \rightarrow Ph_3CSNHBu + :Z$$

Z	k_{rel}
Cl$^-$	400
Br$^-$	191
SCN$^-$	2.2
I$^-$	1

[a] Reference 1. [b] Reference 3. [c] G. Bartoli, M. Fiorentino, and P. E. Todesco, unpublished results reported in ref 2. [d] A. L. Beckwith, G. D. Lehay, and J. Miller, *J. Chem. Soc.*, 3552 (1952). [e] Data from T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row, New York, 1976, p 223. Values are approximate as they are not independent of R. [f] E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc. B*, 2187 (1971).

Scheme I

$$G\diagup\diagdown Z + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{+}{B}H + G\diagup\diagdown\overline{Z}$$

$$1 \qquad\qquad 2$$

$$E2 \diagdown \qquad k_2 \Big\downarrow$$

$$G\diagup\diagdown\diagdown + :Z$$
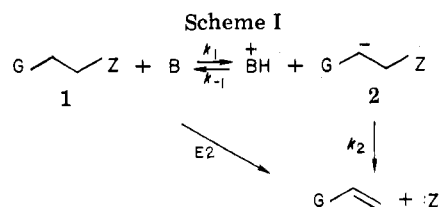
group. A few systems capable of yielding such information have been described. So far, activated (carbanionic) eliminations have given the most information over the widest range of leaving groups.

Activated Alkene-Forming Eliminations

The rather narrow range of leaving groups for al-

Table II
Activation of Alkene-Forming Eliminations[a]

G	k_{rel}	G	k_{rel}
	GCH$_2$CH$_2$Cl → GCH=CH$_2$ + Cl$^-$		
H	1[b]	PhCO	2.3 × 10^{10} [d]
Ph	2.1 × 10^2 [c]	PhSO$_2$	2.4 × 10^{10} [d]
CN	1.9 × 10^{10} [d]		
	GCH$_2$CH$_2$OPh → GCH=CH$_2$ + OPh$^-$ [e]		
Ph$_3$P$^+$	5.32 × 10^{11} [f]	CN	1.35 × 10^6
Me$_2$S$^+$	2.79 × 10^9	CO$_2$Et	8.65 × 10^5
Ac	4.50 × 10^8	(PhCH$_2$)$_2$NSO$_2$	2.9 × 10^5
CHO	3.76 × 10^8	PhSO	1.70 × 10^4
SO$_2$OEt	1.04 × 10^7	CONH$_2$	1.62 × 10^4
PhSO$_2$	5.00 × 10^6	NMe$_3^+$	4.40
MeSO$_2$	2.08 × 10^6	CO$_2^-$	1

$$GG'CHCH_2CMe_2NO_2 \rightarrow GG'C=CH_2 + CMe_2NO_2^-{}^g$$

G	k_{rel}
G = PhSO$_2$; G' = H	1
G = MeSO$_2$; G' = MeS	2 × 10^4
G = G' = MeSO$_2$	6 × 10^9

[a] Reactions in EtONa/EtOH at 25 °C. [b] Estimated from reaction with EtBr at 55 °C (E. D. Hughes, C. K. Ingold, S. Masterman, and B. J. McNulty, *J. Chem. Soc.*, 899 (1940)). [c] C. H. De Puy and C. A. Bishop, *J. Am. Chem. Soc.*, 82, 2535 (1960). [d] Reference 15. [e] Reference 6. [f] P. F. Cann and C. J. M. Stirling, unpublished work. [g] Reference 35.

kene-forming eliminations is seen in Table IB. Reactions of this type are greatly accelerated (Table II) when a carbanion-stabilizing group, G (Scheme I), is placed β to the leaving group, Z. Typically, it was found[5] that substitutents Z, such as OPh, SO$_2$Ph, and OEt, essentially unknown to depart as anions in simple eliminations or substitutions (Table I), were readily eliminated under basic conditions when situated β to a sulfonyl group (1; G = PhSO$_2$). The potential degree of activation of elimination reactions is very large. It can be estimated from the data in Table II that replacement of two β-hydrogen atoms in ethyl bromide by two methanesulfonyl groups raises reactivity in elimination by a factor of 10^{20}. These realizations prompted further exploration of the range of activation (Table II).[6,7] Importantly for present purposes, such activation tremendously widens the range of leaving groups susceptible to quantitative investigation.

Extension of the range of leaving groups in activated eliminations has had important application in the protection of amino groups[8,9] and of carboxyl groups,[10,11] but further discussion of these applications lies outside the scope of this Account.

Quantitative Comparison of Leaving Groups. Reactivities in 1,2-eliminations under activation by carbanion stabilizing groups with a selection of leaving groups are given in Table III.[12-15] The unactivated

(5) C. J. M. Stirling, *Chem. Ind. (London)*, 933 (1960).
(6) J. Crosby and C. J. M. Stirling, *J. Chem. Soc. B*, 671 (1970).
(7) P. J. Thomas and C. J. M. Stirling, to be published.
(8) A. T. Kader and C. J. M. Stirling, *Proc. Chem. Soc. London*, 363 (1962); *J. Chem. Soc.*, 258 (1964).
(9) A. Edberle, J.-L. Fauchere, C. I. Tesser, and R. Schwyzer, *Helv. Chim. Acta*, 58, 2106 (1975).
(10) A. W. Miller and C. J. M. Stirling, *J. Chem. Soc. C*, 2612 (1968).
(11) E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1718 (1976).
(12) D. R. Marshall, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1898 (1977).
(13) P. J. Thomas and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1130 (1978).
(14) S. P. Monaghan and C. J. M. Stirling, unpublished work.
(15) D. R. Marshall, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1914 (1977).

Table III
Comparison (k_{obsd}^{rel}) of Leaving Groups[a] and Reactivities in Elimination

$$G\diagdown\diagup Z \longrightarrow G\diagdown\diagdown + :Z$$

Z	G = $PhSO_2$[b]	G = CN[b]	G = PhCO[b]	G = 2-hexyl[c]
Cl^-	2230	6500	24.4	2×10^4
OTs^-	1.9×10^4	5.2×10^4		4×10^6
OAc^-	61	47	0.28	16
OPh^-	1	1	1	1
OMe^-	1.2×10^{-4}	1.8×10^{-3}	3.1×10^{-6}	
p-MeC_6H_4SMe	1.8×10^6			
SO_2Ph	3.0	182	33	63
SPh^-	0.06	0.11	3.4	0.13
S^{2-}	4.9×10^{-4}			
$SePh^-$	0.89	3.7		1.3
NMe_2Ph	1.5×10^5	1.3×10^5		
$NMeTs^-$	9.7×10^{-5}			
$NMeAc^-$	1.3×10^{-5}	2.7×10^{-4}	1.0×10^{-5}	
NMe_2^-	very slow			
NTs^{2-}	$\sim 10^{-11}$			
PPh_3		9.4×10^4		
$P(O)(OEt)_2^-$	3.4×10^{-5}	7.8×10^{-3}	3.7×10^{-5}	
$CMe_2NO_2^-$	1.2×10^{-8}		$\sim 10^{-9}$	
CN^-		very slow	very slow	

[a] There are minor variations in group structure but not type. [b] For reactions with EtONa/EtOH at 25 °C. [c] For reactions with t-BuOK/t-BuOH.[16]

system studied by Bartsch and Bunnett[16] is included for comparison. It must again be stressed that no direct information on nucleofugality is available from these raw data.

Before nucleofugalities can be extracted from these data, two conditions must be satisfied. It must be established that the leaving group departs in the rate-determining step, and the effect of the leaving group on deprotonation must be quantified. These conditions require detailed knowledge of mechanism.

Mechanisms of Elimination. Three must be considered (see Scheme I).

Concerted Process (E2). Removal of the β proton and departure of the leaving group occur in a single transition state. This mechanism[3,17] is characterized by substantial primary kinetic deuterium isotope effects, variable with Z and different from those for deprotonation of simple models. Rate constants are different (in all known examples larger) from those for deprotonation of appropriate model substrates. This mechanism is not capable of yielding information on nucleofugality because, as discussed above, departure of the leaving group is coupled with deprotonation.

Stepwise Processes. If the intermediate carbanion (2) is formed in only very small concentrations, the steady-state assumption gives eq 1. Two broad alternatives exist. If $k_2 \gg k_{-1}[BH^+]$, then $k_{obsd} = k_1$ and

$$k_{obsd} = k_1k_2/(k_{-1}[BH^+] + k_2) \tag{1}$$

ternatives exist. If $k_2 \gg k_{-1}[BH^+]$, then $k_{obsd} = k_1$ and the rate of elimination is determined by the rate at which the substrate is deprotonated. Reactions with this mechanism, (E1cb)$_I$,[15,18] show primary deuterium isotope effects. They give no information on leaving group ability.

If $k_2 \ll k_{-1}[BH^+]$, then

$$k_{obsd} = k_1k_2/k_{-1}[BH^+] \tag{2}$$

This expression is the product of the equilibrium

constant for deprotonation and the rate constant for expulsion of the leaving group. The mechanism, (E1cb)$_R$,[18] is characterized by a primary kinetic deuterium isotope effect of unity when deuterated and isotopically normal substrates are compared in protic solvents. The observed rate constant is much less than the deprotonation rate constant.

In contrast to E2 and (E1cb)$_I$, the (E1cb)$_R$ mechanism is capable of yielding information on leaving group ability in terms of the relative magnitudes of k_2 provided that relative values of k_1/k_{-1} can be obtained. These k_1/k_{-1} values vary with the leaving group because of the differential polar effects of the leaving group upon the preequilibrium deprotonation.

Polar Effects on the Deprotonation of Carbon Acids. To obtain values of k_2 from eq 2, one must evaluate deprotonation equilibrium constants k_1/k_{-1}. These are very small for deprotonation of monosulfones, nitriles, and ketones in media such as alcoholic solutions of alkoxides. It is known, however, that for 1,1-bis-sulfones[19] and -nitriles[20] rate constants for reprotonation of the derived carbanions by acids in water approach the diffusion-controlled limit when $\Delta pK_a > 8$. If it is assumed that reprotonation of the much more basic carbanions derived from monosulfones and mononitriles is diffusion controlled (and hence insensitive to structural effects, especially the polar effect of the leaving group), relative values of k_1/k_{-1} may be assessed from relative values of k_1 alone.

Values of k_1 have been derived from rates of detritiation of model substrates under the conditions of the elimination reactions. The primary kinetic tritium isotope effect is evaluated via measurement of the rate of deuterium incorporation from the solvent and evaluation of the solvent deuterium isotope effect under the same conditions.[21] The Taft plot for detritiation of sulfones is given in Figure 1. It is rectilinear over

(16) R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.*, **91**, 1376 (1969).
(17) F. G. Bordwell, *Acc. Chem. Res.*, **5**, 374 (1972).
(18) F. G. Bordwell, M. M. Westling, and K. C. Yee, *J. Am. Chem. Soc.*, **92**, 5950 (1970).
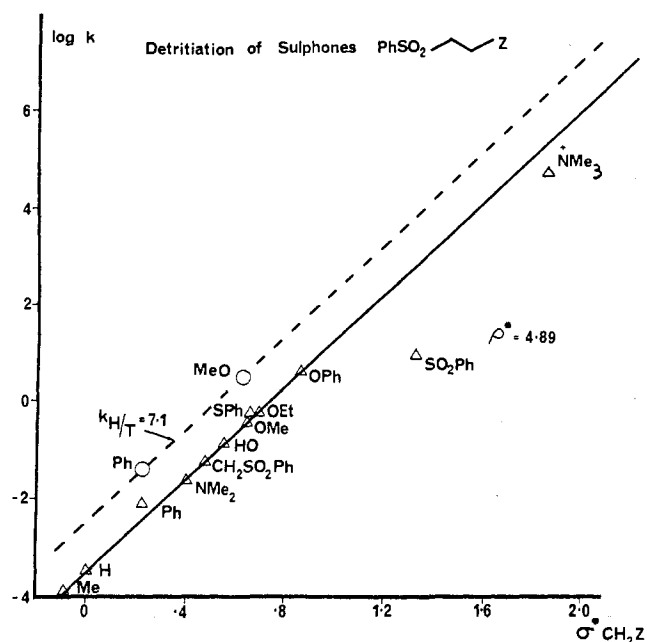(19) J. Hine, J. C. Phillips, and J. I. Maxwell, *J. Org. Chem.*, **35**, 3943 (1970).
(20) F. Hibbert, F. A. Long, and E. A. Walters, *J. Am. Chem. Soc.*, **93**, 2829 (1971).
(21) P. J. Thomas and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1909 (1977).

Figure 1. Detritiation (—) and deprotonation (- - -) of sulfones, $PhSO_2CH_2CH_2Z$, vs. $\sigma^*_{CH_2Z}$. Experimental values of Z = Ph and Z = OMe obtained from rates of deuterium incorporation from EtOD with allowance for the solvent deuterium isotope effect (see text).

a reactivity range of $10^{9.5}$, a $\sigma^*_{CH_2Z}$ range of 2.0, and for Z groups in which the first atom is variously carbon, nitrogen, sulfur, oxygen, and for both neutral and positively charged Z groups. Similar plots have been constructed for nitriles,[21] ketones,[21] and nitro compounds.[22] Armed with these plots, one can obtain k_1 values and hence relative values of k_1/k_{-1} for substrates with appropriate activating and leaving groups. Values of k_{obsd} for the elimination reactions are then divided by relative values of k_1/k_{-1}, giving relative values of k_2. This procedure is, of course, appropriate only for the substrates for which the mechanistic criteria for the $(E1cb)_R$ reaction are satisfied, values of $\sigma^*_{CH_2Z}$ can be obtained, and the assumption of diffusion-controlled reprotonation of the intermediate carbanion is valid. The fact that for G = PhSO₂, CN, or PhCO primary kinetic tritium isotope effects *are* found for deprotonations shows that this is not a perfect assumption, but for G = PhSO₂ or CN it is undoubtedly not far from the truth. It is certain that values of k_{-1} will be little altered by variation of Z. Rejection of the possibility that internal return from the carbanion to substrate occurs has been discussed elsewhere.[13]

Nucleofugalities

The values of k_{obsd}/k_1 ($\equiv k_2/k_{-1}$) give relative values of k_2. The value of $\log (k_{obsd}/k_1) + 11$ is defined as the leaving group rank[12] to emphasize its quantitative nature in the context of this Account. Values are given in Table IV for three types of activating group. Several features of the results deserve comment:

(i) Neutral leaving groups (from 'onium salts) are highly ranked, even when the very large contribution of k_1 to k_{obsd} is taken into account.

(ii) There is *no* general correlation of leaving group

Table IV
Leaving Group Ranks[a,b]

$$G\diagdown Z \xrightarrow[25\,°c]{EtO^-/EtOH} G\diagup + :Z$$

Z	G = PhSO₂	G = CN	G = PhCO
PhSe⁻	10.4	10.0	c
p-Tolyl-SMe	9.8		c
PhNMe₂	9.2	10.7	c
P(O)(OEt)₂⁻		8.0	7.7
PhO⁻	8.9	8.2	c
PhS⁻	8.7	7.9	c
PhSO₂⁻	8.7	9.6	c
PhSO⁻	7.1		c
MeO⁻	6.1	6.3	6.8
N(Me)Ts⁻	5.4		
N(Me)Ac⁻	5.0	6.6	6.3[d]
C(Me)₂NO₂⁻	2.6		
CN⁻		<0.5	<0.5
CMe(SO₂Et)₂⁻	-3.6[e]		
CMe(CO₂Et)₂⁻	-3.7[e]		

[a] $(\log k_{obsd} - \log k_1) + 11$. [b] References 12, 13, and 35. [c] $(E_1cB)_I$ or E2; hence the rank not calculable. [d] G = Ac; Z = N(CH₂Ph)Ac. [e] Estimated from reactions with G = (MeSO₂)₂.

rank with $pK_a^{ZH}(H_2O)$. The groups Me₃N, PhO⁻, ⁻N(Me)Ts, and CN⁻ all have a $pK_a^{ZH}(H_2O)$ value of about 10. Their ranks span at least 10 (log) units. Small variations of structure within a series of leaving groups of the same type, e.g., aryloxy, do, however, show a correlation with pK_a.[13]

(iii) Negatively charged nitrogen and especially carbon leaving groups have very low ranks.

(iv) A double negative charge on the leaving group reduces reactivity substantially (Table III). Removal of the methyl group from N(Me)Ts, and replacement of -SPh by -S⁻ show this effect.[14]

(v) Ranks do not correlate[12,13] with nucleophilicity of Z: toward carbon as measured by reactivity toward methyl iodide[23] or even electrophilic alkenes.[24]

(vi) Variations of rank with activating group are not large. Low sensitivity to structural effects[25] and polar effects (low values of β_{LG}) in eliminations of phenoxide from phenoxy sulfones[13] suggest that expulsion of the leaving group occurs with rather little double bond formation. It is perhaps not surprising, therefore, that differences between activating groups such as PhSO₂ and CN, which might be expected as a result of their differential interactions with the developing double bond, do not make themselves felt.

(vii) It might be expected that rank orders should vary with solvent due to the differing solvation of different Z groups. This is found not to be the case in the comparison of phenoxide and thiophenoxide as leaving groups.[13] The finding is again consistent with the very small degree of bond extension to the leaving group in the transition state for its expulsion.

(viii) Ring strain encourages departure of a range of abnormal leaving groups,[26] and nucleofugality can be very substantially altered by straining the bond to the leaving group. Methoxide is a middle rank nucleofuge, but incorporation of the C–O bond in an oxiran ring

(22) P. F. Cann and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 817 (1974).

(23) R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968).

(24) P. De Maria and A. Fini, *J. Chem. Soc., Perkin Trans. 2*, 1773 (1973).

(25) R. P. Redman, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1135 (1978), and references cited therein.

(26) C. J. M. Stirling, *Chem. Rev.*, **48**, 517 (1978).

raises reactivity more than a millionfold.[27]

Theoretical Aspects

For a reaction in solution, it is reasonable to suppose that cleavage of a bond to a leaving group must involve[28] the C–Z bond strength [D(C–Z)], the ability of Z to accept the electron pair of the C–Z bond as reflected in the electron affinity of Z, and the solvation energy of the leaving group.

In alkene-forming elimination, all the evidence points to a low degree of bond extension in the transition state so that the differential solvation factor between leaving groups, which at large degrees of extension might have been important, is small. This is found experimentally.[13]

The circumstance of small C–Z bond extension makes this a particularly suitable case for the use of simple perturbation treatment[29] as applied to carbanions.[30]
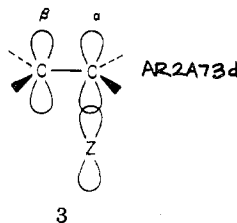
In the carbanion 3, departure of the leaving group proceeds by transfer of electrons from the 2p orbital on C_β to the antibonding σ^* orbital of the C–Z bond, weakening it to the extent of the cleavage occurring in the transition state. Neglecting repulsion terms, perturbation theory gives expression 3, where β is the

$$\Delta E_p \simeq \frac{-2C_n{}^2 C_{\sigma^*}{}^2 \beta^2}{E^* - E^0} \tag{3}$$

resonance integral appropriate to a bond extension, C_n is the coefficient of the 2p orbital on C_α, i.e., approximately unity (low degree of electron transfer), C_{σ^*} is the coefficient on carbon in the orbital σ^* of energy E^*, and E^0 is the energy of the C_α 2p orbital. As $C_n \simeq 1.0$ and β is constant, then

$$\Delta E_p \simeq \frac{\text{constant} \times c_{\sigma^*}{}^2}{E^* - E^0}$$

When E^* is large, as for C–C, C–N, and C–O bonds, $E^* - E^0$ is nearly constant and $\Delta E_p \simeq k C_{\sigma^*}{}^2$. When E^* is lower lying, as for C–S and C–Se bonds, then $E^* - E^0 \rightarrow \infty$ and E_p is not proportional to $C_{\sigma^*}{}^2$. The coefficient C_{σ^*} increases with the electronegativity of Z, and E^* increases in the majority of systems with the C–Z bond energy. Both energy changes are in the same direction,

3

and hence transition-state stabilization, identical with rank in this situation, is determined by a high degree of polarity in the C–Z bond with a contribution from D(C–Z) (eq 4).

$$\text{rank} = f(D_{\text{C–C}} - D_{\text{C–Z}}) - f[\sigma^*_Z(\text{Taft})] \tag{4}$$

This treatment accounts for the features i, ii, iii (because the C vs. N electronegativity difference is very small), iv (for the same reason), v, and vi *provided that the C–Z bond is strong.*

Ranking of several "familiar" leaving groups such as F, Cl, Br, I, OAc, and OTs is not possible in these systems; the reactions show primary deuterium isotope effects indicating the (E1cb)$_1$ or (for Br and I) the E2 mechanism.[15] It is remarkable that for fluoride as leaving group the departure is very rapid notwithstanding the very high C–F bond strength; the importance of bond polarity is evident.

Transfer of charge to the leaving group is probably also assisted by its delocalization in the leaving group, and the rank order $^-CMe_2NO_2 > {}^-CMe(SO_2Me)_2 > {}^-CMe(CO_2Et)_2$ is consistent with this idea.

When the C–Z bond is weaker (as with second- and third-row elements, especially sulfur and selenium), E^* decreases and the significance of C–Z polarization in determining rank decreases. The sulfur and selenium leaving groups are all highly ranked.

Similar arguments have been presented earlier in connection with leaving groups in phosphorylation reactions.[31]

Ranks are specific for cleavage of a C–Z bond in elimination from (stabilized) carbanions. There is no suggestion that this is a universal scale of nucleofugality. There are *some* possible generalizations as comparison with the scarce information on leaving group abilities in other systems shows.

Comparisons with Nucleofugality in Four Other Systems

Imine-forming eliminations allow[32] internal comparisons between leaving groups. Rate constants for expulsion of amines are about 2×10^5 larger than for alkoxide ions of about the same p$K_a{}^{ZH}$. Table IV shows for cyano-activated alkene-forming elimination the substantially higher rank of amine vs. phenoxide leaving groups of approximately the same p$K_a{}^{ZH}$. The authors properly emphasize the noncorrelation of leaving group ability with p$K_a{}^{ZH}$.

In **carbonyl-forming elimination**, recent work[33] shows that the rate constants for expulsion of the leaving group from 4 and 5 are about the same. This

| 4 | 5 | 6 |
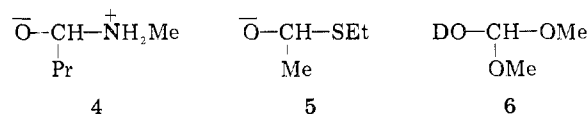
is in contrast with the substantial difference in rank observed for alkene-forming elimination (Table IV).

The rate of breakdown of the tetrahedral intermediate (6)[34] is aout 10^3 larger than that of elimination of methoxide from PhSO$_2$CHCH$_2$OMe.[12,21]

Carbon leaving groups are outstandingly poor in alkene-forming eliminations[12,35] but are common in carbonyl-forming eliminations such as reversion of cyanohydrin formation[36] and depolymerization of diacetone alcohol.[36]

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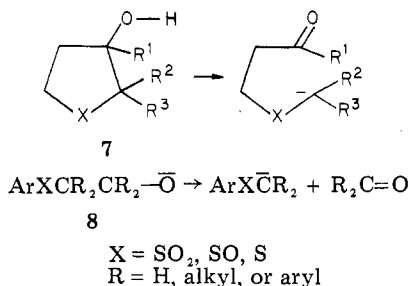(33) D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 451 (1977).

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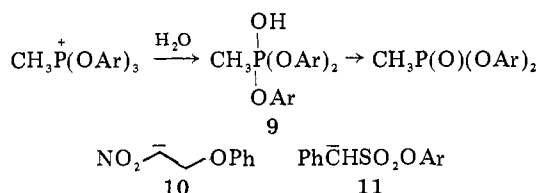(36) K. R. Brower, M. Muhsin, and H. E. Brower, *J. Am. Chem. Soc.*, **98**, 779 (1976).

For carbonyl-forming elimination, inherent reactivity is greater, the range of leaving groups is comparable, and selectivity is less than for alkene-forming elimination.

Comparison of different types of carbon leaving group is difficult for alkene-forming elimination because reactivity is low even with very high activation.[35] On this account, comparison of carbon leaving groups in carbonyl-forming eliminations is in progress[37] using systems **7** and **8**, and both this work and earlier work[38]

7

$$ArXCR_2CR_2{-}\overline{O} \rightarrow ArX\overline{C}R_2 + R_2C{=}O$$

8

$$X = SO_2, SO, S$$
$$R = H, \text{alkyl, or aryl}$$

shows variable sensitivity to substituents on and adjacent to the developing carbonyl group.

In **phosphoryl-forming elimination**, elimination of ⁻OAr from the pentacoordinate intermediate **9** occurs

$$CH_3\overset{+}{P}(OAr)_3 \xrightarrow{H_2O} CH_3\overset{OH}{\underset{OAr}{P}}(OAr)_2 \rightarrow CH_3P(O)(OAr)_2$$

9

$$NO_2{-}\!\!\sim\!\!{-}OPh \qquad Ph\overline{C}HSO_2OAr$$
$$\textbf{10} \qquad\qquad\qquad \textbf{11}$$

extremely rapidly;[39] the rate constant for loss of ⁻OPh from **9** (Ar = OPh) is about 8000 times greater than that from the anion **10**[40] and reflects the energetically favorable formation of the phosphoryl group.[41]

Sulfene-forming elimination[42] involving expulsion of aryloxide is much more sensitive to leaving group structure than is alkene-forming elimination. Change from phenoxy to *p*-nitrophenoxy as leaving group increases the rate of leaving group expulsion from **11** by a factor of 170 000. The same change for ion **2** (G = PhSO₂) accelerates 16-fold.[6,13] This suggests that bond cleavage is much more advanced for the former reaction. Those factors relevant to nucleofugality, important at large C–Z bond extensions, notably $D(C{-}Z)$, may be emphasized. If so, it can be predicted that the leaving group rank of PhS⁻ which is comparable to but smaller than that of phenoxide in alkene-forming reactions should be very much increased in sulfene-forming elimination. This reaction, like alkene- and carbonyl-forming eliminations, probably has a wide range of potential leaving groups but the inherent reactivity of this system is rather low.

Conclusions

Elimination but not substitution reactions offer the opportunity to define nucleofugality properly. Although work so far carried out on alkene-forming elimination suggests that leaving group ranks do not vary very much from system to system, it is clear that the results for this type of reaction will not be directly extensible to others such as carbonyl-forming elimination. Nucleofugality is dependent on the nature of the transition state, and the gross differences, such as those seen to exist between alkene-forming (early) and sulfene-forming (late) transition states, emphasize this point. Comparisons between accurate leaving group abilities offer the prospect of better understanding of the nature of heterolytic bond cleavage and of the properties of the transition states of important fundamental reactions. This area of physical organic chemistry is in a protracted infancy.

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