

On Relative Leaving Abilities: Use of Isobasic Plots to Determine the Relative Nucleofugalities of Thiolates and their Oxy-analogues

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Summary The use of an isobasic plot shows that, when structures are analogous and pK_a values identical, RO^- departs from acetoacetate ester anions 5×10^3 times faster than RS^- and 79 times faster from fluorene-9-

carboxylic acid ester anions, a reversal of the apparent order of nucleofugality determined by measured rates of elimination of RS^- and RO^- .

ATTEMPTS have been made of late to assess quantitatively leaving ability (nucleofugality¹) from estimates or direct measurements of the rates of unimolecular processes involving extension of the bond restraining the nucleofuge in the transition-state, *e.g.* an (*E1cB*)_R¹⁻⁵ or S_N¹^{6,7} reaction. We have been studying nucleofugality in heterocumulene-forming (*E1cB*) ester hydrolyses, *e.g.* for acetoacetates² (**1a, b**) for which PhS⁻ departs 32 times as rapidly as PhO⁻, in contrast with the similar rates of expulsion of PhS⁻ and

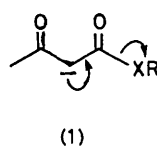
PhO⁻ from PhSO₂CHCH₂XPh (X = O, S).^{1,3} Direct comparison of these systems is complicated by differences in solvent used, the nature of the hybridisation changes occurring in the transition-state, *etc.* We now report on the *E1* fragmentation of fluorene-9-carboxylate ester anions (**2a, b**).

Activated *O*-aryl esters (**2a**) undergo basic hydrolysis by rate-determining elimination of aryloxy ion from the ester conjugate base.⁸ The structurally analogous *S*-aryl esters (**2b**) show similar saturation dependence of pseudo-first-order rate constant on hydroxide ion concentration. From such kinetics the alkaline plateau rate constants (*k'*) for the 4-NO₂, 4-Cl, 4-Me, and unsubstituted *S*-phenyl esters at 25 °C, 1.0 M ionic strength, were found to exhibit β_{L.G.} -0.99 (in line with an *E1cB* route⁹) and ΔS[‡] for the

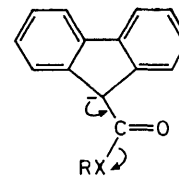
Table. Relative rates of elimination of RX⁻ (X = O and S) from various anions.

Substrate	R	p <i>K</i> _{ROH} - p <i>K</i> _{RSH} ¹	<i>k</i> _{el} (S/O) ^b
(1) ^a	4-NO ₂ C ₆ H ₄	2.42	1
(1) ^a	4-ClC ₆ H ₄	3.24	18
(1) ^a	Ph	3.38	32
(1) ^a	4-MeC ₆ H ₄	3.37	29
(1) ^a	Et ^h	5.50	5.4 × 10 ⁴
(2) ^c	4-NO ₂ C ₆ H ₄	2.42	29
(2) ^c	4-ClC ₆ H ₄	3.24	78.8
(2) ^c	Ph	3.38	178.1
(2) ^c	4-MeC ₆ H ₄	3.37	145.1
(2) ^c	Et ^h	5.50	1.28 × 10 ⁵
-OCH(Me)XR ^d	Et	5.50	153
PhCH-CH ₂ XR ^e	Ph	3.38	0.6
O=P(O) ₂ .XR ^f	4-NO ₂ C ₆ H ₄	2.42	3.4 × 10 ⁵
H ₂ N.COXR ^g	Ph	3.38	225

^a Data from ref. 2 and R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, 1970, **92**, 5956. ^b Nucleofugality ratio, *i.e.* ratio of rates of elimination of RS⁻ to RO⁻ from substrate. ^c This work. ^d From ref. 7. ^e From ref. 3; *k*_{el}(S/O) is here the antilogarithm of the difference in rank between PhS⁻ and PhO⁻. ^f X = O data (39 °C) taken from A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, 1967, **89**, 415. X = S data (35 °C) taken from S. Milstein and T. H. Fife, *ibid.*, p. 5820. No correction has been made for the temperature difference. ^g Calculated from *k*_{HO} = 2.3 × 10⁵ dm³ mol⁻¹ s⁻¹ for NH₂COSPh, *k*_{HO} = 220 dm³ mol⁻¹ s⁻¹ for NH₂COOPh (p*K*_{ester} = 15.1) as given in H. Al-Rawi and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 2671, assuming that a common linear relationship (with slope = 0.26) links p*K*_{ester} with p*K*_{L.G.} for NH₂COXR for both *S*- and *O*-esters. Such a relationship has been reported for *O*- and *S*-acetoacetates³ and yields 14.4 as the p*K* of NH₂COSPh. Hence, *k*_{el} (= *k*_{HO}⁻ · *K*_w/*K*_a) = 6.3 × 10⁵ s⁻¹ for this ester (*cf.* *k*_{el} = 2.8 × 10³ s⁻¹ as estimated in H. Al-Rawi and A. Williams for -NHCOOPh). ^h Calculated from the appropriate linear free energy relationships (ref. 2) between log₁₀*k'* and p*K*_{RXH}. ¹ Data for thiol p*K*_a's were from P. DeMaria, A. Fini, and F. M. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1969, except for EtSH which was from J. P. Danel and C. J. Noel, *J. Am. Chem. Soc.*, 1960, **82**, 2511. Values for the ROH p*K*_a's were from W. P. Jencks and J. Regenstein in 'Handbook of Biochemistry', 2nd edn., ed. H. A. Sober, Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, Section J-187.



(1)



(2)

a; X = O

b; X = S

S-phenyl ester was -1.1 ± 1.5 cal deg⁻¹ mol⁻¹ at 25 °C, again typical of an *E1* process for such a system.⁹ The basic hydrolysis of these thioesters is thus similar to that of the activated (*E1cB*) oxygen-analogues allowing direct nucleofugality comparisons for ArO⁻ and ArS⁻ via the *k'* terms for the fluorenyl-anionic site (see the Table). From the Table, it can be seen that the relative eases of departure of RS⁻ and RO⁻, for a given RO⁻/RS⁻ structural pair, vary considerably with substrate, *e.g.* the rate ratio for 4-NO₂C₆H₄X⁻ ranges from 1 for acetoacetates to 3.4 × 10⁵ for phosphate dianions in agreement with previous anticipations.¹⁻³ One would certainly expect differences between structurally dissimilar *residua* (*i.e.* those portions of the molecule from which nucleofuges depart, MeCOCH₂CO-, *etc.*) However, comparison of (1) and (2), for which

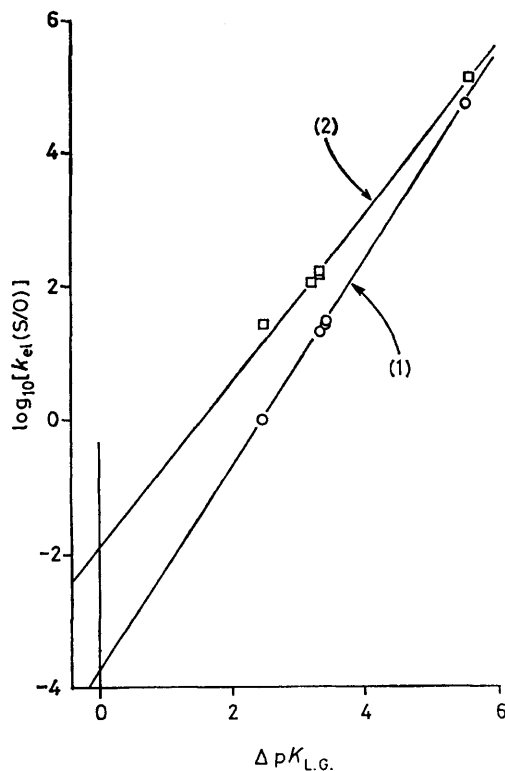


FIGURE. Plot of relative nucleofugalities of RS⁻ and RO⁻ (as log₁₀) vs. Δp*K*_{L.G.} (= p*K*_{ROH} - p*K*_{RSH}) for acetoacetate ester anions and fluorene-9-carboxylate ester anions. For the fluorene esters the line is for an equation, log₁₀[*k*_{el}(S/O)] = 1.25 Δp*K*_{L.G.} - 1.90 (*r* = 0.987), and for the acetoacetate esters, log₁₀[*k*_{el}(S/O)] = 1.53 Δp*K*_{L.G.} - 3.70 (*r* = 0.999): points are experimental, lines were derived by linear least squares correlation analysis.

transition-states are reasonably similar, shows surprisingly marked changes in S:O nucleofugal selectivity, especially for the more reactive RX^- pairs. For a given pair of substrates [*e.g.* (1) and (2)] relative nucleofugalities (S:O) depend on the molecular nature of R in RX^- . For $4\text{-NO}_2\text{C}_6\text{H}_4\text{X}^-$ the nucleofugal selectivity [$k_{\text{el}}(\text{S/O})$] is 29-times greater for (2) than for (1); for PhX^- the difference is 5.6-fold and for EtX^- it is only 2.4-fold. The arbitrary choice of, say, PhX^- , for nucleofugal comparison is unreasonable.

To help overcome this difficulty we have used the data for (1) and (2) (Table) to produce an isobasic plot (Figure). In this are plotted $\log_{10}(\text{nucleofugal selectivity, S/O})$ values *vs.* $\Delta\text{p}K_{\text{L.G.}}$ ($=\text{p}K_{\text{ROH}} - \text{p}K_{\text{RSH}}$) for a given structure of R, to give a reasonable correlation (see Figure and legend). At $\Delta\text{p}K_{\text{L.G.}} = 0$, we have consequently defined a thiol: phenol pair for which not only are the structures identical, saving the identity of the heteroatom, but also the basicities. At this particular point, any differences in the rates of elimination of RO^- and RS^- must be ascribed to some distinction between RO^- and RS^- not reflected in their $\text{p}K_{\text{a}}$ values and/or to the *residua*. In the fragmentations of (1) and (2) the bond restraining the nucleofuge is effectively fully cleaved, leading to similar departing anion sites for $\text{X} = \text{O}$ and $\text{X} = \text{S}$ in the transition-states for both (1) and (2). These sites will exhibit, in this special case of an advanced transition-state, approximately the same comparative solvation properties (for $\text{RS}^{\delta-}$ and $\text{RO}^{\delta-}$) as their

free solution counterparts (RS^- and RO^-). In this case the isobasic plot has allowed for intrinsic solvation differences between isostructural RS^-/RO^- pairs, undoubtedly a major contributor to $\Delta\text{p}K_{\text{L.G.}}$. For $\Delta\text{p}K_{\text{L.G.}} = 0$, RO^- is a *better* nucleofuge than RS^- by 5×10^3 for acetoacetates and by 79 for fluorene esters; this difference may stem from the different degrees of charge delocalisation in anions (2) (aromatic) and (1) and/or the different electron-withdrawing powers of the *residua*. The superior nucleofugality, at $\Delta\text{p}K_{\text{L.G.}} = 0$, of RO^- over RS^- reflects an intrinsic difference(s) between O and S nucleofuges, dependent on the nature of the heteroatom.¹⁰ It should be stressed that this isobasic plot analysis of nucleofugalities *reverses* the apparent order of nucleofugality as determined by direct measurement at the PhX^- level for both systems (1) and (2).

This apparent reversal indicates that there are two separable features which determine the experimental difference in rates of elimination of thiolates: phenolates of given structure from systems (1) and (2). The major contributor is the difference in the $\text{p}K_{\text{a}}$'s (mostly a solvation effect) of isostructural pairs of thiols: phenols. Working in opposition to this is an additional intrinsic difference in the natures of RO^- and RS^- as leaving groups.¹⁰

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