A General Treatment of Enhanced Nucleophilic Reactivity

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Summary A semi-theoretical expression for the "α-effect" is derived and applied to the reactions of oximate, hydroxamate, and peroxide ions with benzyl halides and *p*-nitrophenyl acetate, and of a series of heterocyclic molecules with 2,4-dinitrophenyl acetate.

IT has been suggested recently that electron-pair repulsion is an important factor responsible for the high reactivity of some nucleophiles.[1] It is not clear, however, why this factor does not also lead to a high affinity for protons. In fact adjacent lone pairs exert a large influence on the rate of proton removal from pyridine and other nitrogen heterocycles.[2]

We derive here a general relationship for the so-called "α-effect", based on the polyelectron perturbation treatment of reactivity described elsewhere.[3]

The general equation can be written in a simplified form as follows,

$$\Delta E_p = k_1 q_r q_s + k_2/(\alpha_j - \alpha_k)$$

where q_r and q_s are the formal charges on nucleophile and electrophile respectively, and α_j and α_k are the corresponding orbital energies (see Figure 1).

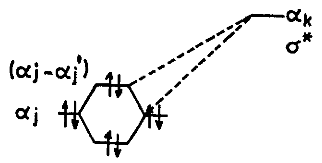

FIGURE 1

The difference in the perturbation energies ($\Delta\Delta E$) of two similar nucleophiles, one of which has a lone pair of electrons adjacent to the nucleophilic atom, *e.g.* RO_2^- and RO^-, reacting with a given electrophile is given in equation (1).

$$(-\Delta\Delta E) \approx k_1 q_r + k_2/\alpha_j - \{k_1 q_r' + k_2(\alpha_j - \alpha_j')\};\ \alpha_j \gg \alpha_k$$
$$\approx k_1 \Delta q_r - k_2 \alpha_j'/(\alpha_j)^2 \qquad (1)$$

Similarly for the interaction of the nucleophiles with a proton equation (2) holds.

$$(-\Delta\Delta H) \approx k_1^{\mathrm{H}} \Delta q_r - k_2^{\mathrm{H}} \alpha_j'/(\alpha_j)^2 \qquad (2)$$

Assuming that $(-\Delta\Delta E) \approx RT\Delta \log k$ and $(-\Delta\Delta H) \approx RT\Delta \log K_\alpha$, combination of equations (1) and (2) gives (3).

$$\frac{\Delta \log k}{\Delta \log K} = \frac{k_1 \Delta q_r - k_2 E_\pi}{k_1^{\mathrm{H}} \Delta q_r - k_2^{\mathrm{H}} E_\pi} \text{ where } E_\pi = \alpha_j'/(\alpha_j)^2 \qquad (3)$$

In the case of two nucleophiles, neither of which is an α-nucleophile, *i.e.* $\alpha_j' = 0$, equation (4) is obtained.

$$\Delta \log k_0/\Delta \log K = k_1/k_1^{\mathrm{H}} \equiv \beta \text{ (Brönsted)} \qquad (4)$$

The observed "α-effect" is given by

$$\Delta\Delta \log k = \Delta \log k^0 - \Delta \log k.$$

Combination of equations (2), (3), and (4) leads to equation (5)

$$\Delta\Delta \log k = \beta \cdot k_2^{\mathrm{H}}(m - 1)\alpha_j'/\alpha_j^2 \text{ where } m \equiv k_1^{\mathrm{H}} k_2/k_2^{\mathrm{H}} k_1 \qquad (5)$$

It follows from this treatment that an "α-effect" due to electron–electron repulsion can be observed only when $m > 1$, *i.e.* when $k_1^{\mathrm{H}}/k_2^{\mathrm{H}} > k_1/k_2$. This means that the Coulombic term for the interaction with a proton is *relatively* more important than that for a typical transition state of a substitution. The following general conclusions can be drawn from equation (5): (i) the "α-effect" (given by ΔΔ log *k*) increases with the magnitude of the Brönsted coefficient β; (ii) large "α-effect" depends on orbital symmetry (α_j' is a function of the lone-pair–lone-pair orbital overlap);[1c] (iv) the magnitude of the "α-effect" decreases with the magnitude of α_j, *i.e.* the ionisation potential of the nucleophile.

TABLE

Comparison of the "α-effect" for benzyl bromide RBr *and* p-*nitrophenyl acetate* (*PNPA*)

Nucleophile	$\Delta\Delta$ log *k* RBr	$\Delta\Delta$ log *k* PNPA	Ratio
$CH_3{\cdot}COCHNO^-$ [a]	0·60	2·00	3·3
$R{\cdot}CO{\cdot}N(Me)O^-$ [b]	1·10	2·10	1·9
HO_2^- [c]	1·70	3·50	2·1

Reaction of *p*-nitrobenzyl bromide; [b] ref. 1(c); [c] ref. 5, reactions in water at 25°.

Values of the "α-effect" for the reactions of benzyl bromide and *p*-nitrophenyl acetate (PNPA) with several nucleophiles are given in the Table. Although the hydroxamic acid data in the table refer to different hydroxamic acids, the relative values of the "α-effect" for the alkylating and acylating agent are comparable to the relative values of the corresponding Brönsted coefficients (β *ca.* 0·30 for benzyl bromide† and 0·80 for PNPA), in agreement with conclusion (i).

In a further series of experiments we measured the rate of reaction of several heterocycles with dinitrophenyl acetate. As shown in Figure 2, positive deviations from the Brönsted relationship are found only for pyridazine[1c] and isothiazole. The magnitude of the "α-effect" is considerably less than that observed for the reactions with oxyanions given in the Table. This agrees with conclusion (iv) since α_j for these anions is considerably less than α_j for the aromatic amines.

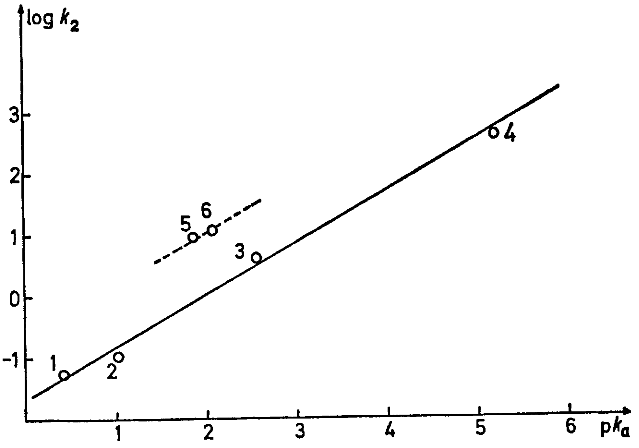

FIGURE 2. *Rate of reaction in water of dinitrophenyl acetate with the following nucleophiles* 1. *pyrazine*, 2. *pyrimidine*, 3. *thiazole*, 4. *pyridine*, 5. *isothiazole*, 6. *pyridazine* k *in* $l\ m^{-1}\ min^{-1}$ *at* 52 °C.

A more detailed examination of this general treatment is in progress.

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† The value for *p*-nitrobenzyl bromide is 0·31.

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