Enhanced Reactivity of Nucleophiles: Orbital Symmetry and the So-called "α-Effect"

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Summary Two explanations of the "α-effect" are advanced: (a) electron repulsion due to p_π–p_π overlap and (b) intramolecular catalysis when (a) cannot operate.

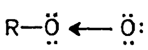
THERE has been much speculation in recent years on the origin of the enhanced reactivity of nucleophiles with lone pairs of electrons on the atom adjacent to the nucleophilic centre [*e.g.* (Ib)], sometimes known as the "α-effect".[1] Here we examine the consequences of the mutual interaction of such electron pairs from a simple M.O. point of view.

Initially, let us consider the reaction of a simple nucleophile, *e.g.* an alkoxide or phenoxide ion with no adjacent lone pairs [*e.g.*(Ia)]. Here the introduction of a substituent, *e.g.* an electron-attracting group, (i) decreases the charge on the nucleophilic atom, leading to a decrease in basicity of the nucleophile, and (ii) decreases the energies of the p-orbitals which are perturbed on the approach of an electrophile, and then enter into covalent bonding. Thus both factors lead to a decrease in reactivity (or affinity).

If we now compare for example an alkoxide ion (Ia) and hydroperoxide ion (Ib), the inductive effect of the adjacent oxygen atom decreases the charge on the nucleophilic atom thus reducing the interaction with an incoming electrophile. This explains the observed decrease in pK_a of the conjugate acid.†

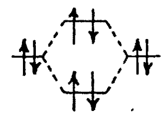
$R{-}CH_2{-}O^-$

(Ia)



$R{-}\ddot{O} \leftarrow \ddot{O}{:}^-$

(Ib)



(II)

Overlap of the doubly occupied p_π orbitals on adjacent atoms however leads to orbital splitting (II), with an increase in energy of the highest occupied level. This produces changes in physical properties of the ion, *e.g.* ionisation potential, redox potential, and polarisability. A similar explanation of the enhanced reactivity of "α-nucleophiles" with particular reference to ClO⁻, HOO⁻, N_3^-, has been given recently by Ingold,[2d] who considers the orbital splitting to give rise to inhomogeneous polarisability. We suggest that reaction of such a nucleophile is accompanied by a decrease in p_π—p_π repulsion,[2] since one of these orbitals forms a σ-bond, and p_π-σ orbitals interactions are in general less than p_π–p_π interactions. This produces an increase in reactivity.

The energy change may be estimated from the corresponding orbital energies[3] of (II), using an extended Hückel procedure,‡

$$E_+ = (\alpha + \beta)/1 + S \qquad E_- = (\alpha - \beta)/1 - S$$

For 4 electrons, $\Delta E_r = -4(\beta S + \alpha S^2)/1 - S^2$

The corresponding π-bond energy (for 2 electrons) is,

$$E_\pi = 2(\beta - \alpha S)/1 + S$$

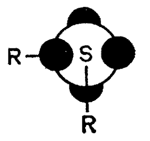
Hence, $$\Delta E_r \simeq -2E_\pi S$$

These considerations thus lead to the following rule: *A positive "α-effect" is produced by a decrease in the overlap integral of orbitals containing lone pairs of electrons in the course of a chemical reaction.*

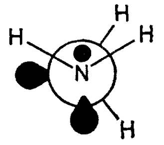
The magnitude of the effect is thus determined by the conformation of the nucleophilic species, and "α-nucleophiles" may be divided into two types:

(i) Those such as ROO⁻, ClO⁻, RSS⁻, where p_π–p_π overlap is considerable in the ground state, leading to high repulsion energy ΔE_r. Enhanced reactivities should be observed in the reactions of these nucleophiles with all types of electrophiles, whether saturated or unsaturated.[5]

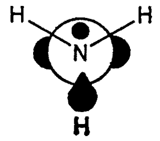
(ii) The conformation of other nucleophiles, *e.g.* NH_2–NH_2, NH_2–OH, RSSR, is such to minimise the p_π–p_π (or sp^3–sp^3) repulsion in the ground state, as shown by the Newman projections (IIIa—c).



III(a) R–S–S–R
$\theta = 90°$



III(b) NH_2–NH_2
$\theta \simeq 90°$



III(c) NH_2–OH
$\theta = 180°$ (or 0°)

The ground-state conformation and rotational barriers of molecules of this kind, including peroxides,[6a] (also F_2O_2[6b]) disulphides,[6c] hydrazine[6d] (also N_2F_4,[6e]) diphosphine,[6f] and hydroxylamine[6g] have been examined in great detail in recent years, and can be explained[7] by a simple rule similar to that suggested above.

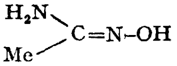
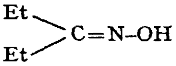
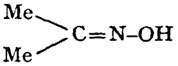
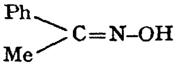
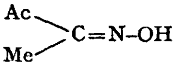
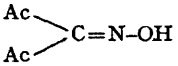
Accordingly, such molecules do not exhibit an "α-effect" due to electron repulsion, and consequently the rate enhancements which have been found in certain reactions must be attributed to other causes. Thus Jencks[5b,8] has attributed the abnormal reactivity of hydroxylamine to intramolecular (either base or acid) catalysis, and we have suggested a similar mechanism to explain the acylation of neutral amidoximes.[9]

Moreover, oximate anions in which a lone pair of electrons on oxygen is conjugated, should not exhibit an "α-effect" due to electron repulsion, since the lone pair on nitrogen is in an sp^2 orbital, and we find no rate enhancement in the reactions of ketoximate anions with p-nitrophenyl acetate.

† CH_3OO^- is $10^{4\cdot5}$ less basic than $CH_3{\cdot}CH_2O^-$.

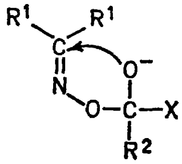
‡ Assuming a value of $E_\pi = 2$ ev and the value[4] of $S = 0{\cdot}07$ for the O–O bond, $\Delta E_r = 0{\cdot}28$ ev corresponding to a rate difference of $10^{4\cdot6}$. This is similar to the maximum value observed[5a] for the "α-effect" of HOO⁻.

Rate enhancements in reactions of oximate anions with p-*nitro-phenyl acetate in water at* 25°

Oxime	pK_a	Rate enhancement[a]
 $\mathrm{H_2N(Me)C{=}N{-}OH}$	12·9	1·2
 $\mathrm{Et_2C{=}N{-}OH}$	12·60	1·0
 $\mathrm{Me_2C{=}N{-}OH}$	12·42	1·0
 $\mathrm{Ph(Me)C{=}N{-}OH}$	11·48	2·7
 $\mathrm{Ac(Me)C{=}N{-}OH}$	9·38	100
 $\mathrm{Ac_2C{=}N{-}OH}$	7·38	933

[a] Defined as the ratio (bimolecular rate constant for oximate anion/bimolecular rate constant for a phenoxide or alkoxide anion of the same basicity).

The rate increases that we observe in the reactions of certain relatively acidic oximes (Table) should therefore be attributed to intramolecular catalysis[10] of the kind indicated in (IV) for a typical acylation reaction.



(IV)

The complex case of hydroxamic acids will be dealt with in a separate communication.

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