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SUPERNUCLEOPHILES—I

THE *ALPHA* EFFECT

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Abstract—A possible explanation of the alpha effect, i.e. enhanced reactivity of nucleophiles possessing a lone pair adjacent to the reactive center is offered, based on the theory of charge and frontier controlled reactions. The enhanced reactivity results from an orbital splitting that raises the energy of the highest filled orbital of the nucleophile and increases the frontier controlling effect. Accordingly, it should be observed only in reactions involving a large covalent bond formation component in the rate determing step.

Experimental data seem to confirm these conclusions.

THERE has been evidence[1] that certain nucleophiles *sometimes* react much faster than would be expected from their proton basicities. These nucleophiles include the anion of hydrogen peroxide, hydroxylamine, oxime anions, hydrazine, the hypohalite anions, and hydroxamic acids. All of these nucleophiles have in common the presence of an atom with unshared electron pairs adjacent to the nucleophilic center. Because of this structural feature, the increased reactivity of these nucleophiles has been called the *alpha* effect.[2] In Table 1, new experimental data are presented together with some relevant literature data. As can be seen, such an enhanced reactivity appears more markedly with certain substrates and may even disappear completely as with ethyl acetate.

We would like to propose an explanation of the phenomenon based upon the recently developed theory of charge and frontier orbital control.[3] From Polyelectronic perturbation treatment of the interaction between an electron donor (nucleophile) with an acceptor (electrophile), the free energy change can be represented in a given solvent by two terms:*

$$\Delta G^{\ddagger} = (\text{charge-charge interaction term}) + (\text{covalent interaction term}) \qquad (1)$$

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* Eq (1) in detail is

$$\Delta G^{\ddagger} = -q_r q_s \frac{e^2}{R\varepsilon} + 2 \sum_{\substack{m \\ \text{occupied} \\ \text{orbitals} \\ \text{of donor}}} \sum_{\substack{n \\ \text{unoccupied} \\ \text{orbitals of} \\ \text{acceptor}}} \frac{(C_r^m)^2 (C_s^n)^2 \beta^2}{E_m^* - E_n^*} \qquad \text{(i)}$$

where q_r is the charge on atom r in the nucleophile; q_s is the charge on atom s in the electrophile; R is the distance between r and s; ε is the dielectric constant: C_r^m is the coefficient of the atomic orbital r in the molecular orbital m of energy E_m^*, C_s^n is the coefficient of the atomic orbital s in the molecular orbital n of energy, E_n^*; and β is the resonance integral of the bond forming between the nucleophile and the electrophile.

The first term represents the electrostatic interation between the two reacting atoms while the second one represents the covalent bond formation in the transition state.

If the orbital energy difference, $E^*_m - E^*_n$, (Footnote 4) is very large then the rate of formation of the transition state is controlled by the first term and will be a charge controlled reaction.

On the other hand, if the energy difference between the highest occupied molecular orbital of the donor and the lowest unoccupied one of the acceptor (both frontier orbitals) is small, then the rate of reaction will be controlled by the charge transfer or covalency of the new bond. In such a case the second term† of (i) will predominate and the reaction will be frontier controlled.[3]

We now wish to suggest that the enhanced reactivity of these super-nucleophiles‡ results from an orbital splitting that raises the energy of the highest filled orbital, E^*_m, thus increasing the frontier controlling effect. In Fig. 1 the schematic orbital diagrams of HO^- and ClO^- are presented. In ClO^-, an interaction occurs between the $p\pi$ orbitals of the oxygen and the chlorine atoms producing such a splitting of levels. The net result is that the highest filled molecular orbital in ClO^- is much higher than in HO^-. On each side of the Figure, an acceptor orbital of some electrophile is shown. Process B with ClO^- requires less energy and is faster than process A with HO^- as the nucleophile.

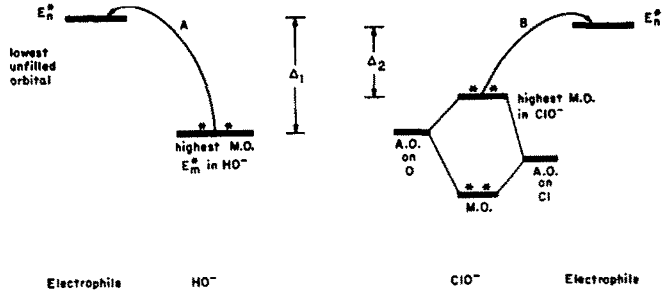

Fig 1. Orbital energy level diagram of the nucleophilic attack by HO^- and ClO^- on an electrophile with a frontier orbital of energy, E_n^*.

The intermediate so formed is now being stabilized by a partial three orbital "covalent type" bond and its disruption i.e. bond breaking, becomes increasingly difficult as no further assistance by the incoming group can occur.

The overall effect thus predicted by this theory is that nucleophiles possessing an overlapping pair of bioccupied orbitals will exhibit an enhanced nucleophilic reactivity but lead to a decreased rate of decomposition to products.

For a reagent to be able to display its supernucleophilicity, it has obviously to participate largely in the rate determining step. Three cases, therefore, may occur, depending on whether the rate determining step is:

1. The formation of a new bond followed by an easy decomposition of the transition state (good leaving group). The rate of the determining step is strongly increased and the system will exhibit a large alpha effect.

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† See footnote on p. 4549.

‡ The name is suggested to clearly distinguish the *alpha* effect from the α constant used in the Oxibase Scale.[6]

2. The breaking of a bond (or loss of solvation) following, or on top of, a charge controlled attack by the nucleophilic agent. The rate of the determining step is slightly decreased; no alpha effect.
3. The simultaneous but partial formation of a new bond and departure of the leaving group. The rate of the determining step is unaffected or slightly increased, depending on the relative ability of the nucleophile and the leaving group to donate (accept) electrons.

Whereas the two first cases correspond to "largely charge controlled" reactions (with a sizeable frontier component in case 1), the last possibility occurs more frequently as a "frontier controlled reaction". In the latter case, the rate will depend mostly on the ease of removal of electrons from the nucleophile but no dramatic alpha effect is to be expected unless bond formation is significantly larger than bond breaking in the transition state.

Some confirmation of these ideas can be sought within the framework of the Edwards equation or the Oxibase Scale.[4], † Thus α could be pictured as a measure of the tendency of the electrophile to accept electrons and to form a covalent bond i.e. related to the magnitude of the frontier control component of the rate. Likewise β could be related to the availability of the charge on the electrophile and thus its ability to coordinate an additional atom (bond formation). To a certain degree, therefor, the ratio‡ of α/β would be a measure of the tendency for the reaction to be frontier controlled and β to the extent with which bond formation has occurred, relative to bond breaking, in the transition state.

α/β	large	frontier control
α/β	small	charge control

Whereas the basicity towards a proton is a composite phenomena controlled largely by the charge-charge interaction term,§ the ease of oxidation of a nucleophile is clearly related to the energy of the highest occupied "frontier orbital", E^{*}_{m}.

If our interpretation of the relationship between supernucleophilicity and the oxybase scale is correct, we would expect that a supernucleophile such as NH_2NH_2 would be more easily oxidized[5] than NH_3 and the Oxibase Scale† E value would be larger since E^{*}_{m} has increased. The experimentally determined E values or a few

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† The Edwards equation now also called the Oxibase Scale is

$$\log(k/k_0) = \alpha E + \beta H$$

with

$$\begin{aligned}
&X^- + AY \xrightarrow{k} AX + Y^- \\
&H_2O + AY \xrightarrow{k} AOH + Y^- + H^+ \\
&\mathbf{E} \equiv \varepsilon^0 + 2{\cdot}60\,\mathrm{V} \\
&2X^- \rightleftharpoons X_2 + 2e^- \qquad \varepsilon^0 \\
&X^- + H^+ \rightleftharpoons HX \qquad \mathrm{pK} \\
&\mathbf{H} \equiv \mathrm{pK} + 1{\cdot}74
\end{aligned}$$

A plot can be prepared by dividing by **E**.

$$\mathbf{E}^{-1}\log(k/k_0) = \alpha + \beta\,(\mathbf{H}/\mathbf{E})$$

‡ The ratio of A/B in the Edwards Polarization equation (see Ref 2) has been used as a measure of hard and soft character.

§ In such systems largely controlled by the charge-charge term, the *alpha* effect is very small ($\Delta_1 \ll \Delta_2$). The reactivity may even by decreased (see data on ethyl acetate and the proton in Table 1) if the adjacent atom is very electronegative thus reducing the charge density on the nucleophilic center.

Unpublished quantum mechanical calculations on HO^- and HOO^- show this to be the case (R. E. Davis and J. B. Louis). Thus we can easily explain why HOO^- is less basic than HO^- but more nucleophilic.

TABLE 1. DATA ON THE ALPHA EFFECT[p]

Nucleophile	Substrate	Relative Rate[a]	Ref
Class A[b]			
HO^-	benzonitrile	1	c
HOO^-	benzonitrile	66000	c
HO^-	*p*-nitrophenylacetate	1	d
HOO^-	*p*-nitrophenylacetate	306	d
HO^-	sarin	1	e
HOO^-	sarin	51	e
HO^-	benzyl bromide	1	o
HOO^-	benzyl bromide	35	o
NH_3	methyliodide	1	f
NH_2NH_2	methyliodide	12·4	f
HO^-	bromoacetate	1	g
NH_2O^-	bromoacetate	3·6	g
NH_3	bromoacetate	2·9	g
NH_2NH_2	bromoacetate	23·2	g
$(CH_3)_2C{=}N{-}O^-$	bromoacetate	5·1	g
HO^-	ethyl tosylate	1	g
ClO^-	ethyl tosylate	8·3	h
NH_2NH_2	ethyl tosylate	3·0	g
Class B[i]			
HO^-	ethyl acetate	1	j
HOO^-	ethyl acetate	$<10^{-4}$	j
		Relative K	
HO^-	H_3O^+ (basicity)	1	l
$(CH_3)_2C{=}N{-}O^-$	H_3O^+	$10^{-3\cdot4}$	m
HOO^-	H_3O^+	$10^{-4\cdot1}$	n
NH_3	H_3O^+	$10^{-6\cdot3}$	n
NH_2NH_2	H_3O^+	$10^{-7\cdot7}$	m
ClO^-	H_3O^+	$10^{-8\cdot4}$	m
NH_2O—	H_3O^+	$10^{-9\cdot7}$	n

[a] Relative second order rate constant on the substrate.

[b] Class in which the *alpha* effect is present.

[c] Ref 1*c*. 50% aqueous acetone at 50°.

[d] Ref 1*b*. Water at 25°.

[e] L. Larsson, *Svensk Kenusk Tidshrift* **70**, 405 (1958). Water at 25°.

[f] R. G. Pearson, H. Sobel and J. Songstad, *J. Am. Chem. Soc.* **90**, 319 (1968). Methanol at 25°.

[g] This study in water at 25°.

[h] R. E. Davis, R. Nehring, W. J. Blume and C. R. Chuange, *J. Am. Chem. Soc.* **91**, 91 (1969).

[i] Class in which no *alpha* effect is observed.

[j] Reported in Ref 1*c*; HOO^- data of R. A. Joyner, *Z. Anorg. Chem.* **77**, 103 (1912).

[l] Equilibrium constants relative to one molecule of HO^- in solution.

[m] Ref 1*b*.

[n] J. O. Edwards, *J. Am. Chem. Soc.* **76**, 1540 (1954).

[o] R. G. Pearson and D. N. Edgington, *Ibid.* **84**, 4608 (1962).

[p] A referee very rightly pointed out that in most class A reactions, both OH^- and NH_3 fall below the Bronstedt line and the comparisons made above tend to mask this effect. It is our opinion however, that the observed decrease in reactivity of high p*Ka* reagents stems from the same phenomenon as that invoked for explaining the α effect. In those cases, it is the low E_m value of the reagents that prevents them to react at the rate one would have expected from a Bronstedt plot.

nucleophiles are presented[5] in Table 2. As expected, it is found that the value for NH_2NH_2 is larger than that of NH_3; ClO^-, much less basic than HO^- by $10^{+8.4}$, has an E value larger by 0·8 volt.

For an electrophile to show unusually faster rates with a supernucleophile, it is not only that the absolute value of the ratio of α/β must be large (frontier control) but also that β (extent of bond formation) be sizeable. Thus we can explain the following data:

there is no supernucleophilic effect on

$$\left.\begin{array}{l} H^+ \ (\alpha = 0, \beta = 1{\cdot}0) \\ \text{or on ethyl acetate}\dagger \ (\alpha = 0, \beta = 0{\cdot}8) \end{array}\right\} \text{type 2 transition state}$$

while supernucleophilic effects are observed, in order of approximate decreasing importance with

$$\left.\text{p nitrophenylacetate}\ddagger \ (\alpha = 0{\cdot}7, \beta = 0{\cdot}46)\right\} \text{ type 1 transition state}$$

$$\left.\begin{array}{ll} & \text{ethyl tosylate}^4 \ (\alpha = 1{\cdot}48, \beta = 0{\cdot}03) \\ & \text{benzyl bromide} \ (\alpha = 2{\cdot}50, \beta = 0{\cdot}002) \\ & \text{methyl iodide}^4 \ (\alpha = 2{\cdot}96, \beta = -0{\cdot}003) \\ \text{and} & \text{bromoacetate}^4 \ (\alpha = 2{\cdot}10, \beta = -0{\cdot}011) \end{array}\right\} \text{type 3 transition state}$$

Unfortunately not enough data are available on the reaction of normal nucleophiles on sarin to obtain a good estimate of α. Using the data of Larsson (see Table 1, *e*) on HO^-, CO_3^{-2} and ϕO^-, α is near 3 and β is fairly positive.

Superelectrophiles. In similar terms one can imagine electrophiles in which two empty atomic orbitals on two adjacent atoms would split one another (e.g. diboranes) pushing one empty acceptor molecular orbital down in energy, closer to the filled molecular orbital of some nucleophile. In such cases superelectrophilic effects should be observed. Further work is in progress to extend these ideas.

TABLE 2. OXIBASE SCALE E AND H VALUES OF SEVERAL NUCLEOPHILES IN H_2O AT 25°

Nucleophile	E volts[a]	H[a]	Ref
H_2O	0	0	[b, c]
HO^-	1·65	17·5	[c]
NH_3	1·84	11·2	[c]
NH_2NH_2	2·02	9·67	[d]
NH_2O^-	2·14	7·77	[e]
ClO^-	2·43	9·14	[f]

[a] See Ref 6.

[b] Defined.

[c] See Ref *6d*.

[d] Value obtained by K. Tsuda using ethyl tosylate, this study.

[e] This study by J. Louis using bromoacetate.

[f] R. E. Davis, R. Nehring, W. J. Blume and C. R. Chuang, *J. Am. Chem. Soc.* **91**, 91 (1969). Value obtained with ethyl tosylate. The E of Cl is only 1·24 volts (see Ref *c*).

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† Unpublished estimate by R.E.D. on the parameters of ethyl acetate. The β represents a lower bound.

‡ Oxibase Scale parameters computed from the kinetic data (Ref 1*b*) using data on CO_3^{-2}, HO^-, CH_3COO^-, C_5H_5N, CN^-, SO_3^{-2}, ϕNH_2, NO_2, and $S_2O_3^{-2}$ as nucleophiles relative to water.

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[5] W. M. Latimer, *The Oxidation States of the Elements and Their Potentials in Aqueous Solutions* (2nd Edition) pp. 39, 43, 50, 104, Data on O and N compounds Prentics-Hall, Englewood Cliffs, N.J. (1952)