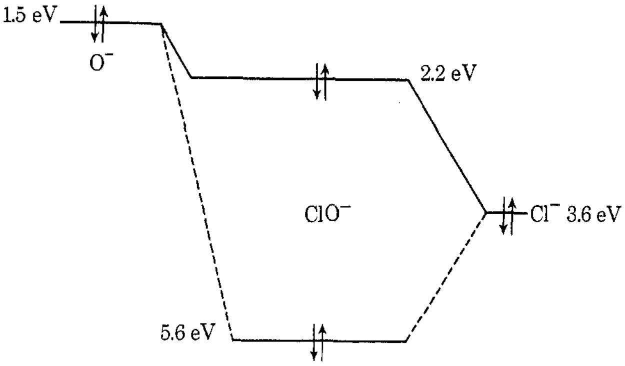
Aromatic Transition States and the α Effect

Summary: An explanation for the α effect (enhanced reactivity of nucleophiles possessing an unshared electron pair adjacent to the nucleophilic center) is offered; an aromatic transition state is proposed and analyzed in terms of Zimmerman's Möbius–Hückel approach.

Sir: It is often observed that certain nucleophiles show an enhanced reactivity relative to analogous species with similar p*K* values. These rapidly reacting nucleophiles are characterized by a lone pair of electrons adjacent to the nucleophilic site. This structural feature has caused the increased reactivity to be termed the "α effect."[1] Since only a few systematic studies have been carried out,[2–5] it is difficult to determine the scope of this phenomenon. α effects, however, do appear to be operable in attack of oxy anions (*e.g.*, ClO^-) and hydrazines on Malachite Green[3,4] and on phenylacetates[2,6] and addition of peroxide to benzonitrile.[7] Although it has been claimed[8] that an α effect exists for a simple S_N2 displacements, recent evidence contradicts this assertion.[3] Other reactions for which the α effect may exist include Michael addition of peroxides,[9,10] aromatic nucleophilic displacement,[4,11] and bisulfite addition to carbonyl groups and to oximes.[12]

Although many explanations have been advanced to account for the enhanced reactivity of these nucleophiles, none appears to be entirely satisfactory. These explanations include polarizability of the transition state,[7] enhanced product stability,[4,13] intramolecular general base catalysis,[4,14] and lone pair–lone pair repulsion with associated energy level splitting.[15,16] The first three mechanisms have been discussed by Dixon and Bruice[4] who have concluded that other factors must be involved. A major flaw in the explanation based upon lone pair–lone pair repulsion is the assumption that energy-level splitting necessarily raises the energy of the highest occupied molecular orbital. Highly accurate all-electron quantum chemical calculations and associated thermodynamic analysis show that, in the case of ClO^-, the ionization potential is 2.2 ± 0.4 eV,[17] whereas the value for O^- is 1.478 ± 0.002 eV[18] and for Cl^- is 3.613 ± 0.003 eV[19] (Chart I).

CHART I



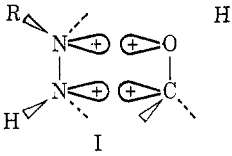
It is clear that simple application of orbital splitting cannot account for the α effect of ClO^- but it is not apparent whether this is a unique situation.[20] In any case, it is obvious that other explanations must be considered.

Any general theory of the α effect must include an explanation of two facts: (1) the rate effect cannot be accounted for solely by a consideration of product stabilities[4] (*i.e.*, an interaction must exist in the transition state which is absent in both reactants and products); (2) the α effect has only been definitely observed for attack of nucleophiles on substrates with π bonding. All previous theories are unable to explain one or both of these phenomena.

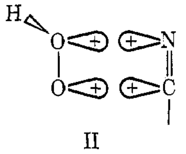
We wish to offer an explanation based on the occurrence of an orbital interaction in the transition state which is absent in both reactants and products. This model accounts for the fact that the α effect is only observed for substrates containing π orbitals and explains rate enhancements greater than predicted on the basis of product stabilities.

Zimmerman[21] has devised a method of analyzing orbital interactions in transition states. He has shown that cyclic transition states may be classified into two types. Hückel transition states are characterized by an even number (including zero) of sign inversions between adjacent orbitals in a ring. These transition states exhibit marked stability with [4n + 2] electrons. In contrast, Möbius transition states with an odd number of nodes between orbitals show analogous stability for 4n electrons. Photochemical reactions, of course, show opposite tendencies. Although this approach is not subject to rigorous quantitation, its success has been well documented.[21]

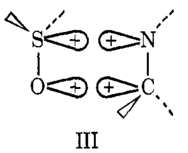
Using this approach we may analyze the transition states for α effect nucleophiles and non α effect nucleophiles. For example, in addition to a carbonyl group by hydrazine, a 6-electron aromatic transition state may be invoked (I). An analogous transition state may be envisioned for peroxide addition to benzonitrile (II) and bisulfite addition to oximes (III). It will be



I



II



III

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[1] (a) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962). (b) For a recent review of the α effect, see N. J. Fina and J. O. Edwards, *Int. J. Chem. Kin.*, **5**, 1 (1973).

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[3] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).

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[17] P. A. G. O'Hare and A. C. Wahl, *J. Chem. Phys.*, **54**, 3770 (1971).

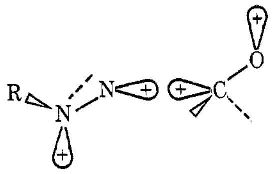
[18] R. S. Berry, J. C. Mackie, R. L. Taylor, and R. Lynch, *J. Chem. Phys.*, **43**, 3067 (1965).

[19] R. S. Berry and C. W. Reimann, *J. Chem. Phys.*, **38**, 1540 (1963).

[20] Although these energies are obtained from calculations on isolated molecules and thus may not be applicable to solutions, it should be realized that the original proposal of orbital splitting suffers from the same defect.[15,16]

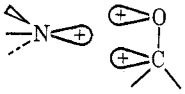
[21] H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971).

noted that we are proposing cyclic transition states for formally noncyclic reactions. The extra stability of these transition states over the corresponding acyclic transition states (*e.g.*, IV) is, of course, due to the aromatic character of this 6-electron cyclic array. Although a cyclic transition state clearly is entropically disfavored, we may estimate the magnitude of the entropy change on ring formation by a comparison of the model compounds butane and cyclobutane. For these compounds at 300°K, the entropy difference of these molecules is only 10.73 eu or 3.2 kcal/mol.[22] It is reasonable to suppose that the extra stability of an aromatic transition state more than compensates for this entropic loss.[23]



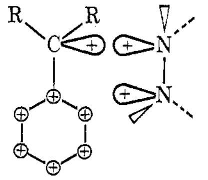
IV

Non-α-effect nucleophiles, on the other hand, cannot react through aromatic transition states similar to I–III and must react through acyclic transition states such as IV. Any interaction of a single orbital from the nucleophile with both orbitals of the π bond would produce a transition state such as V which is antiaromatic as it has only 4 electrons.

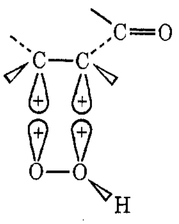


V

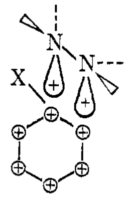
The occurrence of an α effect on the addition of nucleophiles to Malachite Green may be explained similarly. Treating Malachite Green as a substituted benzyl cation, an orbital arrangement such as VI may be drawn which has 10-π electrons and is therefore aromatic. Michael addition of peroxides and aromatic nucleophilic substitutions may be treated by drawing structures analogous to I and VI, respectively, such as VII and VIII.



VI



VII



VIII

Other reactions for which α effects have been observed are subject to related analysis. Although this treatment is apparently successful in explaining the enhanced nucleophilicities of certain species, a definitive experimental proof remains to be produced.

Acknowledgment.—Both J. F. L. and R. M. P. wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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RECEIVED MAY 22, 1973

[22] D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

[23] The nearly ubiquitous success of the Woodward–Hoffman rules indicates that the extra stability of these transition states is quite large.[24] For the pyrolysis of *cis*-3,4-dimethylcyclobutene, the extra stability is ≥15 kcal/mol.[25] Similar conclusions have been reached by Hsu, *et al*,[26] who performed *ab initio* SCF and CI calculations on the potential surfaces of cyclobutene, butadiene, and the corresponding electrocyclic transition states.

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The Reaction of Aryl Nitrones with Thionyl Chloride or Phosgene

Summary: Aryl nitrones react with thionyl chloride or phosgene to yield the corresponding *o*-chloroaniline hydrochlorides.

Sir: In the course of our investigations of aryl nitrones the immediate formation of a copious yellow precipitate was observed upon addition of a molar equivalent of thionyl chloride or phosgene to α,N-diphenylnitrone (Ia) dissolved in a minimum amount of benzene at room temperature. The precipitate was purified by sublimation [150° (760 Torr)] yielding a white crystalline substance, the mass spectrum of which exhibited a base peak at m/e 215. Elemental analysis indicated a composition of $C_{13}H_{11}Cl_2N$. The ir spectrum, measured as both Nujol and Fluorolube mulls, exhibited strong absorptions at 3.55 and 3.85 μ and medium absorptions at 4.28 and 5.03 μ, all of which have been shown to be characteristic of protonated nitrogen compounds.[1]

The reaction product was thus indicated to be the hydrochloride of benzylidene-*o*-chloroaniline (IIa), a fact confirmed by comparison with an authentic sample prepared according to a method described in the literature.[2] Similar analysis of the residue left after sublimation of the reaction mixture indicated the presence of a small amount of benzylidene-*p*-chloroaniline hydrochloride (IIa′).

This represents a new and interesting reaction route for nitrones. Previous investigations of the reaction of nitrones with acid chlorides (*e.g.*, $POCl_3$, PCl_3) have shown only rearrangement of the nitrone to the corresponding amide.[3]

The closest analogy to the presently reported system is that of aromatic amine oxides with acid chlorides; Meisenheimer reported[4] that quinoline *N*-oxide reacted with acid chlorides to yield 2- and 4-chloroquinoline.

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[4] J. Meisenheimer, *Ber.*, **59**, 1848 (1926).