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SUPERNUCLEOPHILES—II

ORBITAL INTERACTIONS AND NUCLEOPHILICITY

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Abstract—The role of adjacent lone pair centers upon the nucleophilic reactivity of various amines with *p*-nitrophenyl acetate has been studied. The kinetics of appropriately substituted hydroxy- and methoxyamines, as well as unsubstituted analogs are presented. The effect of orbital orientation was evaluated theoretically for 1-aminoethanol using CNDO/2. The results of the theoretical study imply a small through-bond and an even smaller through-space lone pair interaction. Kinetically, rate enhancements resulting from such interactions are not observed.

In a previous study[1] we have shown that the alpha effect, the enhanced reactivity of nucleophiles possessing lone pair centers adjacent to the nucleophilic center, may be rationalized on the basis of orbital splitting.

Nucleophilic addition or substitution may be viewed as a donor-acceptor interaction in which the nucleophile transfers its electrons from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electrophilic acceptor.[2]

The alpha effect may manifest itself whenever there is a lone pair center adjacent (alpha) to the nucleophilic center. The lone pair orbitals of such a species interact intramolecularly, resulting in the mutual splitting or repulsion of the lone pairs. As both orbitals are occupied, the HOMO is raised in energy and brought in closer proximity to the LUMO of the acceptor. Assuming that the criterion of a good leaving group and a soft acceptor site are invoked, the transfer of electrons should be facilitated (Fig. 1).

It has since been suggested by Hoffman[3] that localized sets of orbitals may interact directly (through space) or indirectly (through bond coupling). Such an interaction between non-adjacent lone pairs has reportedly been seen in photoelectron spectra experiments and could manifest itself as a "gamma" or "delta" effect in the nucleophilic reactivity of the appropriate reagents.

In order to investigate this eventuality, we undertook the study of the reactions of various hydroxy- and methoxyamines with the aryl ester, p-nitrophenyl acetate. Previous studies by Jencks[4-8] and other researchers[9,10] had revealed rate accelerations with this ester for the reactions of nucleophiles possessing either the hydroxy-moiety or the amino-moiety in alpha of the nucleophilic center.

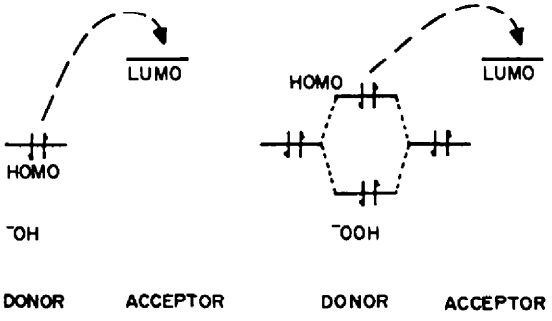

Fig. 1.

EXPERIMENTAL

Reagents. Fisher reagent grade inorganic salts were utilized without further purification. Commercial amines, with the exception of ethylamines, were fractionally distilled over KOH with the middle cut being taken for kinetic runs. The amines were used immediately upon purification for the preparation of the amine buffer solns and the kinetics were run within 48 hr of buffer preparation. *p*-Nitrophenyl acetate (Aldrich) was recrystallized twice, once from ethanol–benzene and then again from benzene (80–81°). All buffer solns and the ester soln were stored at zero degrees when not in use. *p*-Nitrophenyl acetate solns were prepared weekly, as the ester underwent slow hydrolysis during storage.

The following amines were used: t-butylamine, Eastman, observed boiling point, 44.0–44.5°; triethylamine, Matheson, Coleman and Bell, 83.5–84.5° morpholine, gift courtesy of the Chemistry Department of Case Western Reserve University, 39.0–40.0° (20 mm); ethylamine, 70% in water, Matheson, Coleman and Bell; 1-amino-2-hydroxyethane, 95%, Aldrich, 65.0–66.0° (21 mm); 1-amino-2-methoxyethane, Aldrich, 86.5–87.5°, 1-aminopropane, Matheson, Coleman and Bell, 45.0–46.5°; 1-amino-3-hydroxypropane, 99%, Aldrich, 62.0–65.0° (8.5 mm); 1-amino-3-methoxypropane, gift of the Chemistry Department of Case Western Reserve University, 42.5–44.0° (23 mm); 2-aminopropane, 99%, Aldrich, 31.0°; 1-hydroxy-2-aminopropane, Aldrich, 72.0–73.0° (11 mm); 1-methoxy-2-aminopropane, Aldrich, 94.5–94.7°.

Preparation of cis - 1 - *amino* - 2 - *hydroxyacenaphthene. cis* - 1 - Amino - 2 - hydroxyacenaphthene (m.p. 106–111°) was synthesized from acenaphthenequinone.[11] Acenaphthenequinone (m.p. 259–262) was prepared using similar oxidative procedures to that reported.[12]

pKa measurements. All pKa's of amines were determined from their half neutralization points by titration with 1.0 N HCl using an automatic titration assembly by Radiometer of Copenhagen.

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The titration assembly included a TITRATOR 11, and SBR 2c TITRIGRAPH, a pH meter 28, and a syringe burette type SBU 1a.

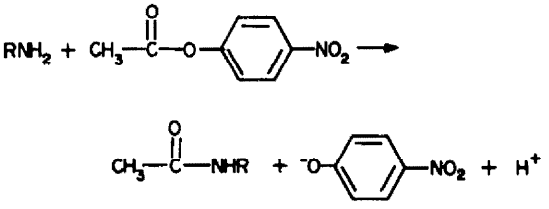
Rate measurements. Rates of aminolysis of *p*-nitrophenyl acetate were measured under conditions of constant ionic strength, constant temp and varying pH and amine concentrations. The pH was maintained during each reaction by a buffer consisting of an excess of the approximately half-neutralized amine reagent.

All solns were made up using distilled water which had been boiled to remove CO_2 and which had been deoxygenated by passing a stream of N_2 through it. All solns except the *p*-nitrophenyl acetate soln were prepared using KCl to maintain a constant ionic strength of 0.5 N.

Rate measurements were obtained by monitoring the appearance of *p*-nitrophenolate anion at 400 nm using a CARY 15 recording spectrophotometer. The sample compartment was equipped with a thermostated cell jacket attached to a Precision Scientific Porta Temp water circulator and temp. regulator. The sample temp. was kept at 25.0 ± 0.1°. The reaction was usually followed to 60–90% completion.

Product evaluation. The products of the reactions of hydroxyamines with *p*-nitrophenyl acetate were evaluated in order to ascertain whether the O-acyl or N-acyl derivatives predominated. The method of Hestrin[13] (hydroxyamic acid–ferric chloride) was used to test the mixture. The results of this analysis showed total absence of esters indicating that the reaction of amino-alcohols with *p*-nitrophenyl acetate resulted in the exclusive formation of the N-acyl derivative.

Evaluation of the rate constant. The total rate law for the reaction of amines with *p*-nitrophenyl acetate



was expressed as follows:

$$\text{Rate} = k_2[\text{Amine}][\text{Ester}] + k_3^{\text{Amine}}[\text{Amine}]^2[\text{Ester}] + k_3^{OH^-}[\text{Amine}][OH^-][\text{Ester}] + k_{H_2O}[H_2O][\text{Ester}] + k_{OH^-}[OH^-][\text{Ester}] \quad (1)$$

in which k_2 represents the second order rate constant for the aminolysis of the ester, k_3^{Amine} and $k_3^{OH^-}$ represent the third-order catalytic constants for the general base catalysis of the reaction by an additional molecule of amine or by hydroxide ion, k_{H_2O} is the second-order rate constant for hydrolysis of the amine, and k_{OH^-} is the second-order rate constant for the saponification of the ester by hydroxide ion.

By making the substitution:

$$k_2^{\text{apparent}} = k_2 + k_3^{\text{Amine}}[\text{Amine}] + k_3^{OH^-}[OH^-]. \quad (2)$$

Equation (1) becomes

$$\text{Rate} = k_2^{\text{app}}[\text{Amine}][\text{Ester}] + k_{H_2O}[H_2O][\text{Ester}] + k_{OH^-}[OH^-][\text{Ester}]. \quad (3)$$

Using pseudo-first-order conditions, we measured "apparent" rates under various conditions of pH and amine concentration. The various rate constants are then determined by multivariate regression analysis, using an *ad hoc* computer program.

DISCUSSION OF RESULTS

The reaction conditions and second-order rate constants found for the various amines are presented in Table 1. The rates of reaction were all found to vary linearly with concentration of free amine, indicative of a first-order relationship to amine concentration. Thus, catalysis by an additional molecule of free amine assisting in the transition state was ruled out ($k_3^{\text{Amine}} \sim 0$). However, evaluation of the rates under conditions of constant free amine concentration and varying pH indicated that catalysis by hydroxide ion does play a significant role in most of the reactions. The catalytic constants ($k_3^{OH^-}$) for the various amines are presented in the last column of Table 1. A brønsted plot constructed with the second order rate constants showed considerable scatter of points. However, closer inspection of the data reveals that, as is often the case, better relationships between pKa and $\log k_2$ exist within structurally similar amines (Fig. 2). Thus amino groups attached to secondary carbons generate a Brønsted correlation line which lies below that of amines attached to primary carbons. Both lines however, have essentially similar slopes ($\alpha = \sim 0.88$). It is found, in general, that

Table 1. Summary of rate constants and conditions for the reactions of nucleophiles with *p*-nitrophenyl acetate in water at 25°C. Ionic strength maintained at 0.5

Compound	pKa	pH	Amine, M	k_2 (M^{-1} min^{-1})	$k_3^{OH^-}$ (M^{-2} min^{-1})
1. Ethylamine	10.8	10.8	0.001–0.003	579.0	3.79×10^5
2. 1-Amino-2-hydroxyethane	10.4	10.4	0.0025–0.01	126.0	1.39×10^5
3. 1-Amino-2-methoxyethane	9.7	9.7	0.0034–0.009	137.0	5.77×10^4
4. -n-Propylamine	10.9	10.9	0.002–0.009	651.0	1.44×10^6
5. 1-Amino-3-hydroxypropane	10.5	10.5	0.004–0.01	261.0	8.95×10^5
6. 1-Amino-3-methoxypropane	10.3	10.3	0.004–0.007	367.0	2.90×10^6
7. iso-Proplamine	10.9	10.9	0.008–0.03	76.0	1.00×10^5
8. 1-Hydroxy-2-aminopropane	9.9	9.9	0.015–0.044	13.9	3.49×10^3
9. 1-Methoxy-2-aminopropane	9.7	9.7	0.008–0.04	12.6	3.53×10^3
10. t-Butylamine	10.8	10.8	0.01–0.11	3.73	—
11. Morpholine	8.9	8.9	0.007–0.098	37.5	—
12. *cis*-1-Amino-2-Hydroxyacenaphthene	8.4	8.4	0.002–0.004	0.607	1.39×10^6
13. Diethylamine	11.3	11.3	0.009–0.037	16.7	6.56×10^4
14. Piperazine[a]	10.10	6.7	0.1	430.0	—
15. Piperidine[a]	11.42	8.3	0.05–0.3	2900.0	—
16. Hydroxide	15.7	10.8	—	500.0	—

[a]Ref. 4.

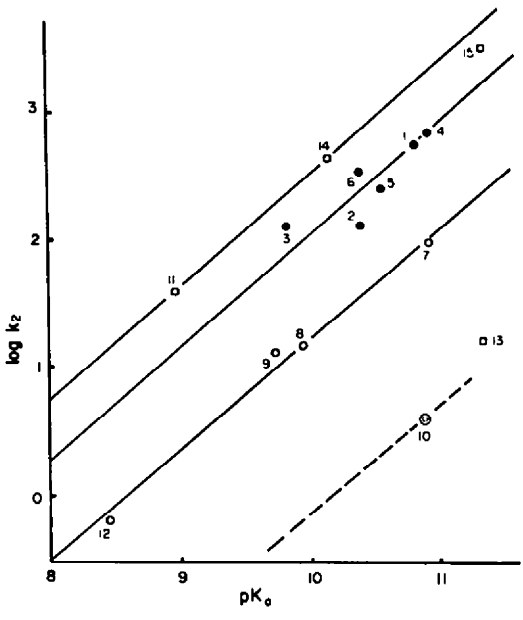


Fig. 2.

increased alkyl substitution upon the nitrogen bearing carbon leads to decreased reactivity without concommitant decrease in basicity;

e.a. Reactivity: Ethylamine > iso-Propylamine > t-Butylamine.

This could best be explained by postulating that the steric hindrance by the large alkyl groups tend to decrease the ability of the corresponding amines to approach the electrophilic centers, and that this steric inhibition is more pronounced for the reaction with the ester than with a proton.

Further evidence supporting the importance of steric hindrance is provided by considering the effect of increased alkyl substitutions upon the nitrogen atom itself. Classically, one would expect the inductive effect produced by the electron donation of the additional alkyl group to increase the charge upon the nitrogen. This should increase both the basicity and the reactivity of amines substituted by more alkyl groups. Indeed, diethylamine is more basic than ethylamine, but less so than triethylamine. On the other hand, the tertiary triethylamine is much less active than diethylamine, itself much less reactive than ethylamine.

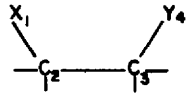
This again can be explained by the above steric considerations in which increased substitution decreased more the reactivity of amines with the esters than with the proton.

The cyclic secondary amines present an interesting, but as yet unresolved behavior. Linear Brønsted plots are observed for structurally similar species. The series piperidine, piperazine and morpholine fall on a straight line approximately parallel to those of linear amines (Fig. 2). However, the line is above any of the other ones indicating that, at equal pKa, they react faster than their acyclic counterparts. For example, piperidine reacts with the ester at a rate approximately 700 times that of its acyclic analog, diethylamine even though their pKa's are comparable. Whether this difference is to be attributed to steric or electronic (hybridization) factors is as yet unresolved.

The interpretation of the effect of a hydroxy or methoxy substitution in γ or δ to the amino group presents another stimulating challenge. The decrease in basicity and reactivity produced by these substituents can easily be explained by their electron withdrawing inductive effect that stabilizes the nitrogen lone pair and makes it less available for sharing with a proton (or the ester). On this basis however, the effect of a hydroxy group should be more pronounced than that of a methoxy group since it is more electronegative. Yet each of the methoxy amines that were studied had a lower pKa and about equal reactivity as the corresponding hydroxy amines.

Our results do not show any sizeable enhancement in the nucleophilic reactivity of the amino alcohols when compared to the corresponding unsubstituted amines. Although this can be interpreted as indicative of the absence of any gamma effect resulting from long range splitting effects, we are reluctant to do so for the following theoretical considerations.

Let us consider the interaction of lone pairs using the compound below as a model.



In this model, atoms X and Y are the lone pair centers. In order to evaluate their interaction, let us assume that there is no initial interaction of the lone pairs through space.

The molecular orbital correlation diagram is constructed from the molecular orbitals of the sigma bond between carbons two and three, and the symmetry-adapted combinations of the lone pairs. In this diagram, all symmetry is determined from the mirror plane which bisects the 2-3 sigma bond. Only orbitals of like symmetry may interact, therefore, the sigma bond interacts only with the $(n_1 + n_2)$ combination and the sigma starred orbital interacts with the $(n_1 - n_2)$ combination. Each interaction yields two new perturbed orbitals, with the non-bonding S orbital being raised in energy and the non-bonding A orbital being lowered in energy and falling below S.

If we now allow the lone pair orbitals to interact through space we find that the lobes of the lone pair orbitals match in SS and SA and are stabilized by interaction. In AS and AA the lobes of the orbitals do not match and the interaction is one of destabilization (Fig. 3). The result is that the SA orbital is lowered in energy while the AS orbital is destabilized.

If either the through-bond effect is considerably more important than the through space effect or *vice versa*,† then the lone pair orbitals are split and the HOMO is raised in energy. By application of the Generalized Perturbation treatment[14] one then finds that the transfer of

†It is noticeable however, that the symmetry of the HOMO will be different in the two cases. As a result, the mechanism of action may vary in order to accommodate the symmetry of the receptor's LUMO.

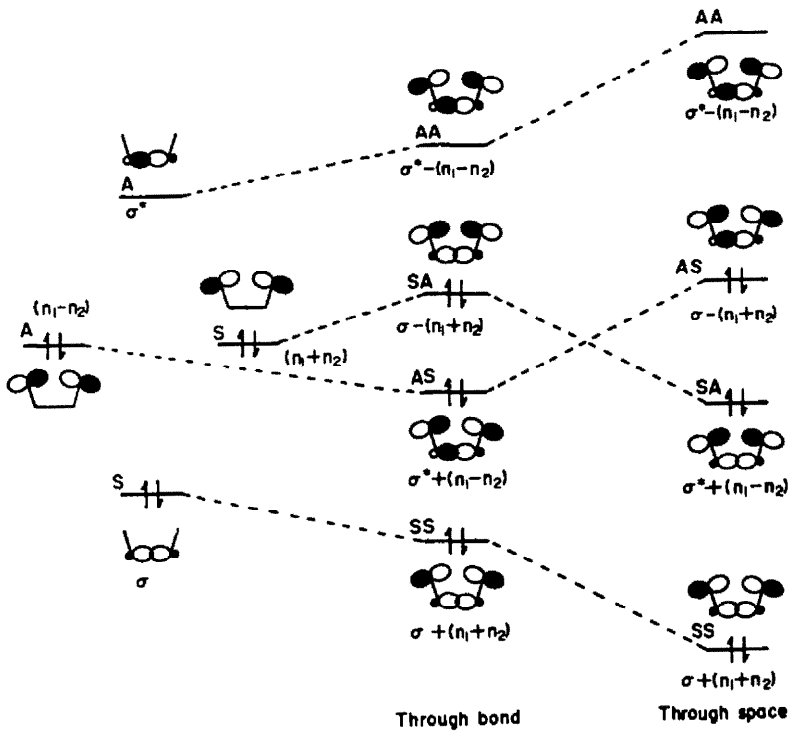


Fig. 3.

charge to the LUMO of an acceptor is facilitated and enhanced nucleophilic reactivity may be observed. On the other hand, if the through-space effect is of approximately the same magnitude as the through-bond effect, then the splitting by one effect is countered by that of the other and no splitting should occur. No rate enhancement should be seen.

In order to further quantitate these effects, CNDO/2 computations were performed upon various conformations of hydroxyethylamine. The completely staggered and eclipsed forms were calculated in order to mimick the through-bond and the through-space effects. From this calculation, it was found that the staggered conformation was slightly more stable than the eclipsed one. As predicted, the HOMO was found to shift down in proceeding from a predominantly through-bond effect in the eclipsed one and the SHOMO was found to be destabilized (Fig. 4). However, no change in symmetries was observed, the through-space effect was never large enough to compensate the through-bond effect.

On the basis of these calculations and the kinetic evidence, we believe that any through-space interaction that may exist in our amines is probably negated by through-bond interactions, even in the molecular system in which the lone pair centers are constrained such that their lone pair orbitals may overlap (*cis*-1-amino-2-hydroxyacenaphthene).

The question that remains to be elucidated is whether such a situation will always prevent any kinetic "gamma" effect to be observed. We believe that this is not necessarily so; larger through space interaction can be generated by third row atoms, less likely also to be tied in unwanted hydrogen bonds. Further studies should therefore include compounds such as aminomercaptans, possibly constrained in rigid conformations, where significant through space interactions between the lone pairs could exist and create a supernucleophilic situation.

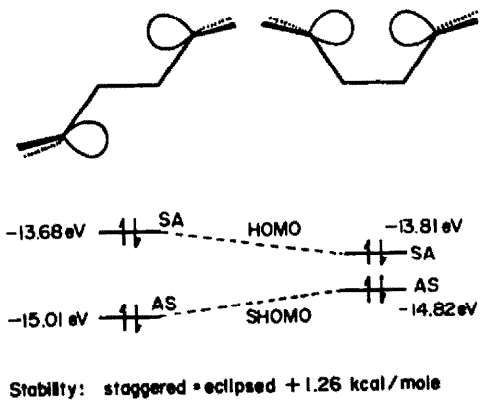


Fig.4.

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