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Reactivity of Nucleophilic Reagents toward Esters

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The reactivities of a group of compounds of widely varying structure toward the ester *p*-nitrophenyl acetate have been measured in aqueous solution. The anions of hydrogen peroxide, methyl hydroperoxide and hydrazoic acid react abnormally rapidly. This abnormal reactivity is not due to a concerted acid–base attack with hydrogen bonding, but may be correlated with the high polarizability of peroxide and azide. Hydroxylamine and hydrazine, which have normal polarizabilities, N-dimethylhydroxylamine, N-hydroxypiperidine, pyridine N-oxides and anions of hydroxamic acids, relatively acidic oximes and hypochlorous acid also react abnormally rapidly. Reactivity toward esters, and presumably the high reactivity of enzymes, appear to be dependent on more factors than are encompassed in a simple two-parameter equation or correlation with reactivity toward saturated carbon.

Enzymes are notable for their extraordinarily rapid rates of reaction and Swain and others have suggested that this reactivity is the result of a "push–pull," bifunctional character of the active site.[1] Although Swain and Brown's model of the α-pyridone-catalyzed mutarotation of glucose[1] is open to the objection that it is observed in nonpolar solvents, while an enzyme must compete with and be more efficient than water, it recently has been suggested that a number of unusually rapid chemical reactions in aqueous solution, including those of hydroxylamine and hydroperoxide anion, with activated acyl groups and related compounds, may proceed with concerted mechanisms of this kind.[2] The evidence for this conclusion is, however, often indirect and Green, *et al.*, have shown that N-hydroxyphthalimide reacts rapidly with isopropyl methylphosphonofluoridate and suggest that the high reactivity of hydroxamic acids and related compounds is associated with an influence of surrounding atoms on the attacking atom rather than a concerted acid–base attack of the hydroximic tautomer.[3] The present investigation was carried out to examine the reactivities of a group of compounds of varying structure with a single ester substrate in an attempt to obtain further information about the various factors which may affect reactivity toward activated acyl groups.

Experimental[4]

Materials.—Reagent grade inorganic salts were generally used without further purification; organic reagents were redistilled or recrystallized before use. Trimethylamine N-oxide hydrochloride,[5] m.p. 206–207°; *p*-nitrophenyl acetate,[6] m.p. 78–79°; N-hydroxypiperidine hydrochloride,[7] m.p. 141°; 4-aminopyridine N-oxide,[8] m.p. 232–237°; N-dimethylhydroxylamine hydrochloride,[9] m.p. 106°; isonitrosoacetone,[10] m.p. 67–69°; isonitrosoacetylacetone,[11] m.p. 74–76°; N-hydroxyphthalimide,[12] m.p. 232–233°; hypochlorous acid,[13] and aqueous methyl hydroperoxide[14] were prepared by published procedures. Hydrogen peroxide and methyl hydroperoxide were standardized by titration with permanganate and the latter compound was shown not to contain residual hydrogen peroxide by testing with titanium sulfate.[15] Hypochlorous acid was standardized by iodometric titration. Deuterium oxide, 99.8%, was obtained from the Atomic Energy Commission through the courtesy of the Department of Chemistry, Harvard University. Deuterium oxide and water were glass distilled before use. Reagents with readily exchangeable hydrogen atoms were dissolved in D_2O, evaporated to dryness, and redissolved in D_2O before use.

Methods.—Rate measurements at 400 or 330 mμ and calculation of rate constants were carried out as previously described.[16] Reactions with dilute solutions were generally carried out in 0.1 *M* phosphate buffer without further correction for ionic strength; for reactions with concentrated ionic reactants, constant ionic strength was maintained with NaCl or KCl. Approximately 10^{-4} *M* ethylenediaminetetraacetic acid was added to runs with unstable reactants to prevent trace metal-catalyzed decomposition; 0.02 *M* ethylenediaminetetraacetic acid itself was shown not to react with *p*-nitrophenyl acetate at an appreciable rate. Solutions of unstable reactants were made up immediately before use. Half-neutralized solutions of N-hydroxyphthalimide showed appreciable hydrolysis to phthalhydroxamic acid after several hours, as shown by disappearance of the red N-hydroxyphthalimide anion and appearance of ferric chloride reacting product. Unless otherwise noted, reaction products were not isolated or characterized.

Second-order rate constants were calculated from the slopes of plots of the observed pseudo first-order rate constants against the concentration of the reactive ionic species of the nucleophilic reagent. The intercepts at zero reagent concentration agreed satisfactorily with the rates of *p*-nitrophenol appearance in buffer alone under the same conditions, and the observed rates were first-order in respect to the nucleophilic reagent. For reactions in which the reactive ionic species is not the predominant form at neutral *p*H, such plots were generally made at several *p*H values, as indicated in Table I, and the second-order constants calculated from the concentration of the reactive species at each *p*H using the Henderson–Hasselbach equation. Rates of uncatalyzed base hydrolysis were determined at ionic strength 0.3 in triethylamine buffers and found to follow the equation $\log k = p\text{H} - 11.05 \pm 0.03$ from *p*H 10.4 to

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11.1, with k_2, based on *p*H and $K_W = 10^{-14}$, equal to 890 l. mole^{-1} min.$^{-1}$; this may be compared to previously reported values of 990 (in 28% alcohol at 30°),[17] 1300[18] (estimated) and 30,600 (in 5% dioxane solutions which caused an acceleration of the rate of hydrolysis of acetylimidazole).[19] The rate constants were not changed by increasing the buffer concentration from 0.05 to 0.10 *M*. The rate of the uncatalyzed reaction with water was taken as the intercept of a plot of the rate of hydrolysis against the concentration of acetate buffer at *p*H 5.2 after a small correction for the hydroxide ion-catalyzed hydrolysis at this *p*H; the value obtained is somewhat smaller than previously reported values which were obtained under slightly different conditions.[17-19]

The reaction with hypochlorite was complicated by a fast reaction of hypochlorite with *p*-nitrophenolate to give a more acidic, yellow compound, and a slow further reaction to give a colorless product. Under the experimental conditions employed the former reaction with *p*-nitrophenolate was found to be ten times faster than the reaction with *p*-nitrophenyl acetate and rate constants were therefore calculated from the rate of appearance of the yellow product; a measurement of the rate of *p*-nitrophenyl acetate disappearance at 278 mμ gave essentially the same rate constant. The second, slow reaction did not interfere at low hypochlorite concentrations if the final readings were taken immediately upon completion of the reaction. While the rate constants obtained are not precise, they are considered to be correct to within less than an order of magnitude. The corresponding reaction of *p*-nitrophenyl acetate with hypobromite gave a faintly yellow product which, (in contrast to the product of the reaction with hypochlorite) reacted further with hydroxylamine to give one equivalent of hydroxamic acid and an intensely yellow compound. This suggested that the initial reaction of hypobromite was not with the acetyl group; this reaction was not investigated further.

In acetate and phosphate buffers at *p*H 4.8–7.3 anomalously fast reactions were observed with acetoxime, but addition of an equimolar amount of acetone caused a 6–10 fold rate decrease, suggesting that the observed reaction resulted from hydrolysis to free hydroxylamine. In *t*-butylamine buffer at *p*H 10.2–10.5 the rate was proportional to the concentration of acetoxime anion and was not affected by addition of acetone.

Measurement of the rate of the reaction with potassium cyanate was complicated by the low reaction rate and cyanate decomposition. From runs in 1 *M* potassium cyanate at *p*H 8.6 in diethylaminopropionitrile buffer the second-order rate constant was estimated to be less than 0.006 l. mole^{-1} min.$^{-1}$.

Reaction rates of acetylimidazole with azide were determined from the rate of acetylimidazole disappearance at 260 mμ at four azide concentrations between 0.0025 and 0.01 *M* in 0.05 *M* phosphate buffers at *p*H 6.42 and 6.87; the observed second-order rate constants were 362 and 146 l. mole^{-1} min.$^{-1}$, respectively, giving 2.6×10^5 l. mole^{-1} min.$^{-1}$ for reaction with the acetylimidazolium cation (pK_a 3.6).

Infrared spectra were obtained with a Perkin–Elmer model 21 spectrophotometer using calcium fluoride cells with 0.05-mm. path length and Raman spectra were taken on a Cary recording spectrophotometer. Infrared spectra of isonitrosoacetone and isonitrosoacetylacetone in deuterium oxide showed strong peaks at 1695, 1673 and 1590(m) cm.$^{-1}$ and at 1712, 1678 and 1598(m) cm.$^{-1}$, respectively.

Alkylation of Hydroxylamine in Aqueous Solution.—A 2.0 *M* aqueous solution of neutralized hydroxylamine hydrochloride was allowed to react with one molar equivalent of methyl iodide at room temperature with good stirring. When the reaction had gone to completion, an aliquot was diluted to 0.1 *M* and on titration showed a pK_a' of 5.8 (pK_a of N-methylhydroxylammonium ion, 5.96[20]) with no indication of more acidic products (pK_a of methoxyammonium ion, 4.60[20]).

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Results and Discussion

The rates of reaction of a group of nucleophilic reagents which react with *p*-nitrophenyl acetate at a measurable rate in aqueous solution at 25° are given in Table I. The results are conveniently discussed in terms of factors which may affect nucleophilic reactivity toward esters.

Basicity.—In Fig. 1 the reaction rates, taken from Table I and the literature, are plotted logarithmically against the basicity in water of the attacking nucleophilic reagent. An arbitrary line of slope 0.8 is drawn through several typical amines. Bruice and Lapinski[17] have shown that the reactivities of a series of compounds toward *p*-nitrophenyl acetate in 28.5% ethanol at 30° fall on lines of slope 0.8, but with separate lines for substituted imidazoles, pyridines and certain oxygen anions. At least one compound from each of these series has been included in Fig. 1 to serve as points of reference for these series in aqueous solution at 25°. This work and the trend of the values in Fig. 1 show that, particularly within a given reaction series, basicity is of great importance in nucleophilic reactivity toward esters, as recently emphasized

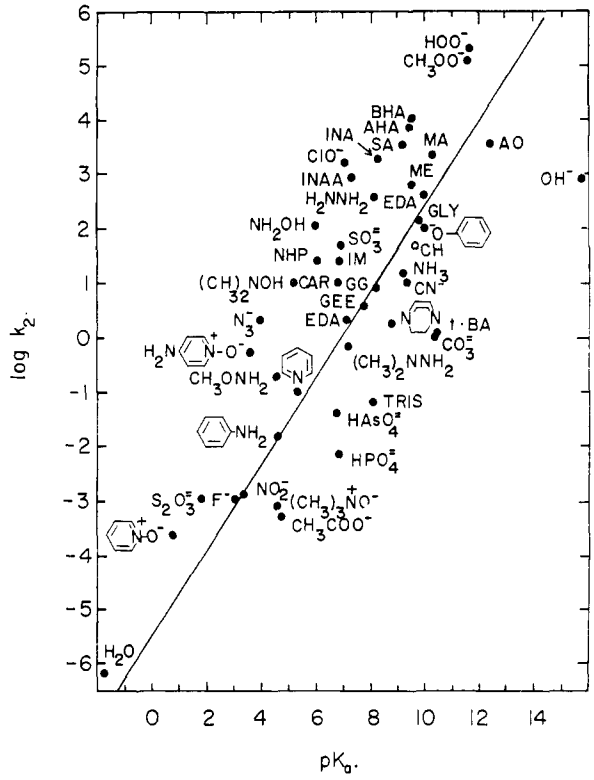

Fig. 1.—Rates of nucleophilic reactions with *p*-nitrophenyl acetate in aqueous solution at 25° plotted against the basicity of the attacking reagent. Abbreviations and references (see also Table I): GEE, glycine ethyl ester[16]; GLY, glycine[16]; GG, glycylglycine[25]; IM, imidazole[2]; AHA, acetohydroxamic acid[2,26]; BHA, *n*-butyrylhydroxamic acid[2]; CH, chloral hydrate anion at 30°[27]; hydroperoxide anion[2]; methoxyamine[16]; hydroxylamine.[2] No statistical corrections have been made.

TABLE I

RATES OF REACTION OF NUCLEOPHILIC REAGENTS WITH *p*-NITROPHENYL ACETATE AT 25.0°

Compound	pK_a[a]	pH	Concn. range, *M*	Number of detns.	k_2,[b] l. mole^{-1} min.$^{-1}$
N,N-Dimethylhydroxylamine	5.2[c]	7.7[d]	0.025–0.05	4	10.7
N-Hydroxypiperidine		7.7[d]	.025–0.05	2	7.5
Trimethylamine N-oxide	4.6[e]	5.7	.1–1.0	3	0.00088
4-Aminopyridine N-oxide	3.7[f]	6.7[d]	.05–0.10	2	0.57
Pyridine-N-oxide	0.8[f]	5.1[g]	.2–1.0	3	0.00025
		1.3[h]	.2–1.0	3	0.00029
N-Hydroxyphthalimide (NHP)	6.1[i]	6.2[d]	.0004–0.004	6	28.9
Isonitrosoacetylacetone (INAA)	7.4[j]	6.7[d]	.01–0.04	4	910
		6.2[d]	.01–0.04	3	875
Isonitrosoacetone (INA)	8.3[j]	6.7[d]	.01–0.04	3	2000
		6.3[d]	.01–0.04	3	2600
Salicylaldoxime (SA)	9.2[j]	6.7[d]	.008–0.016	2	3200
5-Methyl-1,2,3-cyclohexanetrione 1,3-dioxime[k]	8.3	6.7[d]	.008	1	2070
1,2,3-Cyclohexanetrionetrioxime[k]	8.0	6.7[d]	.008	1	870
5-Methyl-1,2,3-cyclohexanetrionetrioxime[k]	8.0	6.7[d]	.008	1	880
Acetoxime (AO)	12.4[l]	10.2[m]	.025–0.1	3	3700
		10.5[m]	.025–0.1	3	3500
Potassium hypochlorite	7.1[n]	6.2[d]	.00063–0.005	4	1670
		6.7[d]	.0003–0.005	5	1520
Methyl hydroperoxide	11.5[o]	6.7[d]	.08–0.24	3	108,000
		6.2[d]	.08–0.24	3	125,000
Hydrazine	8.1[p]	6.8[q]	.0033–0.0133	3	310
		7.5[q]	.0033–0.0133	3	373
		8.2[q]	.0033–0.0067	2	403
N,N-Dimethylhydrazine	7.2[p]	7.6[q]	.0067–0.0266	3	0.73
Sodium azide	4.0[r]	5.0[h]	.1–0.5	3	2.2
Sodium sulfite	7.1[s]	6.8[q]	.02–0.10	3	46
Sodium thiosulfate	1.9[t]	5.6[d]	.2–1.0	3	0.0011
Mercaptoethanol (ME)	9.5[u]	6.8[d]	.01–0.06	3	620
		7.2[d]	.01 0.06	3	700
Sodium mercaptoacetate (MA)	10.3[u]	6.7[d]	.01–0.06	3	2400
		7.2[d]	.01–0.06	3	2600
Ammonium chloride	9.2[v]	6.0[d,h]	.02–1.0	3	16
Ethylenediamine (EDA)	7.0[u]	6.4[h]	.05–0.20	3	420[w]
	10.0[u]	7.4[h]	.05–0.20	3	
		8.2[h]	.05–0.20	3	2.0[w]
t-Butylamine (*t*-BA)	10.5[v]	10.4[h]	.05–1.0	5	1.1
Aniline	4.6[u]	6.5[d]	.06–0.24	3	0.015
Pyridine	5.4[x]	5.7[h]	.2–1.0	3	0.10
Triethylenediamine (1,4-diazobicycloöctane)	8.8[y]	8.6[q]	.05–0.20	3	1.94
Carnosine (CAR)	6.8[z]	6.8	.01–0.02	2	10.4
Histidylhistidine	5.6	6.9	.01–0.017	2	5.6[aa]
	6.8[z]				
Tris-(hydroxymethyl)-aminomethane (TRIS)	8.1[u]	8.2[h]	.2–0.5	3	0.070
Phenol	10.0[u]	6.7[d]	.1–0.4	3	105
Potassium cyanide	9.3[bb]	10.4[m]	.025–0.10	3	10.8
Potassium carbonate	10.4[u]	8.8[h]	.1–1.0	3	1.06[cc]
		9.2[h]	.1–1.0	3	1.00
Sodium arsenate	6.8[z]	6.7[h]	.05–0.5	3	0.041
Potassium phosphate	6.9[u]	5.9[h]	.05–0 5	3	.0074
Sodium nitrite	3.4[bb]	6.5[d]	.2–1.0	3	.0013
Potassium acetate	4.8[u]	5.2[h]	.1–1.0	3	.00051
Potassium cyanate[dd]	3.5	8.6	.2–1.0	3	< .006
Sodium fluoride	3.1[ee]	5.9[d]	.2–1.0	3	.0010
Water[ff]	−1.7	5.2	55	1	6×10^{-7}
Hydroxide ion[gg]	15.7	10.4–11.1		12	890

[a] Or pK'_a. For oximes, NHP, peroxides, thiols, ammonium chloride and phenol the pK_a refers to the acidic dissociation constant of the listed compound; in other cases it refers to the dissociation constant of the conjugate acid of the listed compound. The preferred site of protonation of N-dimethylhydrazine is unknown. [b] For the reacting ionic species, corresponding to the pK_a given in column 2. [c] Ref. 20. [d] 0.1 *M* phosphate buffer. [e] T. D. Stewart and S. Maeser, THIS JOURNAL, **46**, 2583 (1924). [f] H. H. Jaffé and G. O. Doak, *ibid.*, **77**, 4441 (1955). [g] 0.1 *M* acetate buffer. [h] Ionic strength maintained constant with NaCl or KCl at a value corresponding to the highest concentration of reagent used. [i] Ref. 3. [j] Ref. 21. [k] Not recrystallized; pK values from titration of 0.01 *M* solution in 0.1 *M* KCl. [l] R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.* (*London*), **A197**, 141 (1949). [m] 0.1 *M t*-butylamine buffer. [n] Ref. 13. [o] A. J. Everett and G. J.

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for H_2O *vs.* RO^- by Bender and Glasson,[28] and is of much greater importance than for SN2 displacements on saturated carbon.[23,29] However, azide and carbonate show similar reaction rates, in spite of a million-fold difference in basicity, and hydroxylamine is over 10^4 times as reactive as phosphate in spite of the greater basicity of the latter compound. From these and other examples it is clear that basicity alone does not determine reactivity. It is nevertheless convenient to consider the influence of other factors in terms of deviations from the relationship to basicity.

It is of interest that there does not appear to be a break in the curve, suggestive of a change in the rate-limiting step,[30] as the basicity of the attacking reagent becomes less than that of the leaving *p*-nitrophenolate ion (pK_a 7.0).

Polarizability.—Polarizability may be expected to be an important factor in nucleophilic reactivity which is not reflected in the basicity of the attacking reagent and Edwards has proposed a quantitative two-parameter correlation of nucleophilic reactivity with polarizability and basicity.[23b] Although polarizability in the direction of bond formation in the transition state rather than over-all polarizability presumably is the significant factor in reactivity, this correlation is reasonably successful for many displacement reactions of simple molecules.

The high reactivity of the hydroperoxide ion toward nitriles,[30] phosphoryl halides[31,2h] and esters[2] has led to suggestions that hydrogen bonding stabilizes the transition states for these reactions.[2d,2h,31] The almost equally high reactivity of the methyl hydroperoxide anion (Fig. 1) indicates that hydrogen bonding does not account for the abnormally high reactivity of peroxide anions toward esters; the apparent low nucleophilic reactivity of *t*-butyl hydroperoxide[32] may represent a steric effect.[32a] Hydrogen peroxide is known to have an abnormally high molar refraction and polarizability which even led Brühl to suggest that there was some double bond character to the bond between the two oxygen atoms.[33] Although the reason for this abnormal polarizability is still obscure, it provides a reasonable explanation for the observed high reactivity. The highly reactive azide ion has a molar refraction of 12.27.[34] Although exact comparison is difficult, this value is considerably greater than twice the bond refraction of 4.12 for the N=N bond[35] and suggests that this high reactivity may also be associated with an unusually high polarizability. Finally, the abnormally high reactivity of sulfur, which is evident in thiols, sulfite and thiosulfate, may be associated with its relatively high polarizability, and the low reactivity of hydroxide ion may be attributed to its low polarizability.

On the other hand, hydroxylamine and hydrazine, which are several orders of magnitude more reactive than would be expected from their basicity, have molar refractions which are normal, in that they agree well with the sum of atomic refractions calculated from molecules which do not display abnormal reactivity.[36] Similarly, fluoride is the only halide ion to show a measurable rate of reaction with *p*-nitrophenyl acetate (Tables I and III). While the lack of reaction of other halides may be due to their low basicity, the normal reactivity of fluoride, which has a very low polarizability,[23b] is remarkable. Basicity and polarizability alone clearly do not account for the observed order of reactivities.

General Acid Catalysis, Hydrogen Bonding and Proton Transfer.—It was previously suggested that the remarkably high reactivity of the hydroxylamine oxygen atom toward esters might result from hydrogen bonding from the nitrogen atom of hydroxylamine, in either the neutral or dipolar form, to oxygen of the substrate or to intramolecular proton transfer from the hydroxylamine oxygen to nitrogen in the activated complex.[2] The observed rate constant for the reaction of hydroxylamine with *p*-nitrophenyl acetate, shown in Fig. 1, includes reactions at both the nitrogen and oxygen atoms of hydroxylamine[2] and both, but particularly that for oxygen, are abnormally fast. Hydrogen bonding to a carbonyl group is known to occur in peracids,[37] hydroxamic acids[2] and diethyl α-phen-

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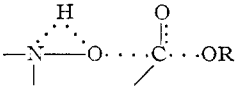
(37) J. R. Rittenhouse, W. Lobunez, D. Swern and J. G. Miller, THIS JOURNAL, **80**, 4850 (1958).

ylhydrazoöxalacetate,[38] which have structures similar to the probable transition states for these reactions. Reaction of hydroxylamine in the zwitterionic form has been proposed previously, but for reasons which were later shown to be incorrect.[39]

N,N-dimethylhydroxylamine also reacts abnormally rapidly with *p*-nitrophenyl acetate (Fig. 1). This shows that the reaction is not sensitive to the steric hindrance resulting from the substitution of two methyl groups on the atom adjoining the attacking oxygen and rules out aid to the reaction by hydrogen bonding from the *uncharged* form of hydroxylamine. Addition of a third methyl group, to form trimethylamine-N-oxide, reduces the reactivity to a barely detectable level (Fig. 1). This may be due to steric hindrance or to elimination of the possibility of hydrogen bonding from the dipolar form.

For quantitative comparison with other reactions, it is necessary to know the extent to which hydroxylamine exists in aqueous solution in the neutral form, NH_2OH, and in the dipolar form $\overset{+}{N}H_3O^-$. In an attempt to obtain information on this point, infrared and Raman spectra were taken of hydroxylamine and methoxyamine and of their conjugate acids in aqueous and deuterium oxide solutions. Infrared spectra of hydroxylammonium and methoxyammonium chlorides show strong shoulders on the lower frequency side of the H_2O and D_2O peaks, presumably due to the $-NH_3^+$ and $-ND_3^+$ groups and their interactions with the solvent, while only small shoulders, of equal intensity for both compounds, were observed with hydroxylamine and methoxyamine. Raman spectra gave similar results and also showed N–H peaks at 3270 and 3245 cm.$^{-1}$ for hydroxylamine and methoxyamine, respectively, which were absent in their conjugate acids (*cf.* ref. 40). These results suggest that hydroxylamine exists predominantly as NH_2OH in aqueous solution, as is also the case for the hydroxylamine crystal.[41] The observed basicity of hydroxylamine appears to represent, therefore, the basicity of the nitrogen atom. If the observed reaction on oxygen is due to a small fraction present in the dipolar form, then the reactivity of the oxygen anion is higher and its basicity higher than shown for the uncharged molecule in Fig. 1. If the uncharged molecule reacts, attack of the hydroxyl group may be aided by intramolecular proton transfer to the nitrogen atom



(if a stable tetrahedral intermediate exists,[42] the O–C bond would be fully formed in the transition state). The distinction between these possibilities rests on a precise localization of the proton with time: such localization may not be possible if the hydrogen atom is covalently bonded to both donor atoms, as has been suggested in other cases of intramolecular hydrogen bonding.[43]

The reaction of hydroxylamine with *p*-nitrophenyl acetate shows only a small deuterium isotope effect, with a k_{H_2O}/k_{D_2O} ratio of 1.3 (Table II); the ratio of O to N acylation was found to be unchanged in deuterium oxide. For the reaction with phenyl acetate, which gives almost exclusively O-acylation, both the uncatalyzed and the catalyzed reactions must be considered.[16] The uncatalyzed reaction shows a k_{H_2O}/k_{D_2O} ratio of 1.5 and the catalyzed reaction, which represents principally general base catalysis under the conditions of the experiment, shows a k_{H_2O}/k_{D_2O} ratio of 2.2 (Table II). The deuterium isotope effect in the catalyzed reaction is consistent with proton transfer in the rate-limiting step, but the relatively smaller effects found in the uncatalyzed reactions are not appreciably greater than might be expected from nonspecific solvent effects.[44] The absence of a large isotope effect does not, however, rule out proton transfer in the rate-limiting step of the uncatalyzed reaction, since some examples of general base-catalyzed ester aminolysis, which almost certainly involve a proton transfer in the rate-limiting step, do not show significant deuterium isotope effects.[16]

TABLE II

REACTIONS OF HYDROXYLAMINE WITH *p*-NITROPHENYL ACETATE AND PHENYL ACETATE IN DEUTERIUM OXIDE

	H_2O	D_2O		k_{D_2O}/k_{H_2O}
p-Nitrophenyl acetate	110[a]	83	l. mole^{-1} min.$^{-1}$	1.3
Phenyl acetate,				
uncatalyzed	0.70[b]	0.48	l. mole^{-1} min.$^{-1}$	1.5
catalyzed[c]	4.80[b]	2.18	l.^{2} mole^{-2} min.$^{-1}$	2.2

[a] Ref. 2. [b] Ref. 16. [c] The catalyzed reaction includes both general base- and general acid-catalyzed terms; with the NH_2OH/NH_3OH^+ buffer ratio of 2.33 used in these experiments, however, 90% of the catalyzed reaction represents general base catalysis. The rate constants given are based on the *total* hydroxylamine concentration and were obtained from a series of 6 determinations in 0.093–0.93 *M* hydroxylamine, as described in ref. 16.

Alkylation of hydroxylamine is known to occur preferentially on the nitrogen atom in alcohol solution, so that trimethylamine-N-oxide is formed before oxygen alkylation occurs.[45] To rule out the possibility of significant O-alkylation in aqueous solution, hydroxylamine was allowed to react with one mole of methyl iodide in water at room temperature. Titration of the products showed no detectable methoxyamine formation, confirming the lack of abnormal nucleophilic reactivity of the hydroxylamine oxygen toward saturated carbon.

Hydrazine also reacts abnormally rapidly with *p*-nitrophenyl acetate while N,N-dimethylhydrazine does not (Fig. 1). In contrast to the situation with hydroxylamine, this is consistent with aid to the reaction from hydrogen bonding from the *uncharged* form of hydrazine. Hydrazine also reacts

(38) B. H. Arison, A. E. Erickson, N. R. Trenner and E. F. Schoenewaldt, *Chemistry & Industry*, 1627 (1958).

(39) (a) F. Haber, *Ber.*, **29**, 2444 (1896); (b) P. Baumgarten and H. Erbe, *ibid.*, **71**, 2603 (1938).

(40) H. J. Bernstein and W. H. Martin, *Trans. Roy. Soc. Can.*, III, **31**, 95 (1937).

(41) R. E. Nightingale and E. L. Wagner, *J. Chem. Phys.*, **22**, 203 (1954).

(42) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

(43) (a) E. W. Gill and E. D. Morgan, *Nature*, **183**, 248 (1959); (b) L. Paoloni, *J. Chem. Phys.*, **30**, 1045 (1959). See also S. Yeh and H. H. Jaffé, THIS JOURNAL, **81**, 3279 (1959).

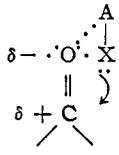
(44) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

(45) W. R. Dunstan and E. Goulding, *ibid.*, **75**, 792 (1899).

rapidly with cyanic acid and carbon dioxide[46] and Bunnett has suggested that hydrogen bonding may aid the reaction of hydrazine in nucleophilic aromatic substitution.[47]

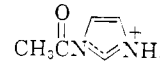
The anions of hypochlorous acid, of a group of relatively acidic oximes, including isonitrosoacetone, isonitrosoacetylacetone and pyridine-2-aldoxime methiodide, and of hydroxamic acids, including N-hydroxyphthalimide, react with *p*-nitrophenyl acetate at rates several orders of magnitude faster than most other oxygen nucleophiles of comparable basicity (Fig. 1). Isonitrosoacetylacetone anion reacts at the same rate as hydroxide ion, although it is 10^8 times less basic. Acetoxime anion, which is a considerably stronger base, does not exhibit such a striking rate enhancement, but still reacts rapidly compared to hydroxide ion. Pyridine-N-oxide and 4-aminopyridine-N-oxide react considerably more slowly, but are much weaker bases, and compared to other compounds of comparable basicity these compounds also show an enhanced reactivity. A high reactivity of oxime and hydroxamic acid anions and of hypochlorite has also been observed for reactions of phosphoryl halides.[2c,2i,3,21] Infrared spectra of isonitrosoacetone and isonitrosoacetylacetone in deuterium oxide showed normal carbonyl peaks, arguing against aid to the reaction by hydrogen bonding from a neighboring hydrated carbonyl group or the enolic form of the carbonyl group (*cf.* ref. 48). Such hydrogen bonding is further ruled out by the high reactivities of pyridine-2-aldoxime methiodide, N-hydroxyphthalimide and hypochlorite.

Although carbonyl activation through hydrogen bonding to a Brönsted acid is not possible, the possibility remains that the abnormal reactivity of these compounds results from an interaction of the carbonyl oxygen atom with a group which acts as a Lewis acid in the attacking reagent



For hypochlorite, such a rate-enhancing interaction would involve bonding of oxygen lone pair electrons to the d-orbitals of the halide, for which there is some precedent in the bonding of both lone pair electrons of acetone to molecular bromine[49] and the apparent coördination of the weakly basic chloride ion to hypochlorous acid[50]; such an interpretation seems preferable to an interaction with the carbonyl group due to a partial positive charge of the chlorine atom in a two-atom ion carrying an over-all negative charge.[2c] For the other compounds listed above and for azide the oxygen lone pair electrons may interact with the unsaturated group on the attacking reagent. There is some precedent for such interaction in the effect of mutual interaction on the infrared absorption spectra of carbonyl groups,[51] in the abnormally rapid displacement reactions of phenacyl halides, in which there appears to be some overlap of the attacking nucleophilic reagent with the carbonyl group,[52] and in the π-bonding of metals with available electrons for back-conjugation to ligands with available orbitals. Nevertheless, it should be emphasized that definitive proof for such bifunctional general acid catalysis is not available; the alternative is that the attacking atom in this group of compounds has a peculiar reactivity toward carbonyl carbon and phosphorus, but not toward saturated carbon. Although no satisfactory explanation for such a difference in reactivity is readily apparent, the large number of factors which may affect nucleophilic reactivity implies that rate differences should be attributed to a single cause with considerable caution.

Electrostatic Effects.—For charged substrates, nucleophilic reactions will be affected by the sign and distance from the reaction center of charges in the attacking molecule. In Fig. 2 are shown the rates of a series of reactions with the positively charged acetylimidazolium ion



The most striking difference from the *p*-nitrophenyl acetate series is the relatively increased reactivity of compounds, such as carboxylic acids, phosphate, arsenate, phenol and mercaptoethanol, which react in the anionic form. The same compounds attack the negatively charged acetyl phosphate ion slowly or not at all.[53,54] Aksnes and Prue and others[55] have treated the effect of electrostatic interactions on ester hydrolysis quantitatively.

Solvation and Abnormal Basicity.—A plot of reactivity against basicity can exhibit deviations due to abnormal basicity as readily as to abnormal reactivity. This is most clearly demonstrated in the amine series, in which primary amines show abnormally high basicity in aqueous solution, probably because of specific solvation of their conjugate acids by hydrogen bonding to the solvent.[24,56] The relatively low reactivity of ammonia and high reactivity of imidazole (Fig. 1) may be largely explained on this basis; the reactivity of a larger series of amines with phenyl acetate follows a similar pattern.[16] The polarizability of the amino nitrogen atom increases in the order $NH_3 \sim 1° < 2° < 3°$ in the amine series[57] and this may provide a further influence in the same direction. Swain, *et al.*, have suggested that rela-

(46) M. B. Jensen, *Acta Chem. Scand.*, **13**, 289 (1959).

(47) J. F. Bunnett and G. T. Davis, THIS JOURNAL, **80**, 4337 (1958).

(48) J. W. Churchill, M. Lapkin, F. Martinez and J. A. Zaslowsky, *ibid.*, **81**, 2110 (1959).

(49) O. Hassel and K. O. Strømme, *Acta Chem. Scand.*, **13**, 275 (1959).

(50) M. Anbar, S. Guttmann and R. Rein, THIS JOURNAL, **81**, 1816 (1959).

(51) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., Methuen, London, 1958, p. 379; C. G. Cannon, *Mikrochem. Acta*, 555 (1955).

(52) P. D. Bartlett and E. N. Trachtenberg, THIS JOURNAL, **80**, 5808 (1958).

(53) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).

(54) G. DiSabato and W. P. Jencks, unpublished experiments.

(55) G. Aksnes and J. E. Prue, *J. Chem. Soc.*, 103 (1959), and references therein.

(56) A. F. Trotman-Dickenson, *ibid.*, 1293 (1949); R. G. Pearson and D. C. Vogelsong, THIS JOURNAL, **80**, 1038, 1048 (1958).

(57) J. R. Partington, "An Advanced Treatise on Physical Chemistry," Vol. IV, Longmans, Green and Co., London, 1953, p. 48.

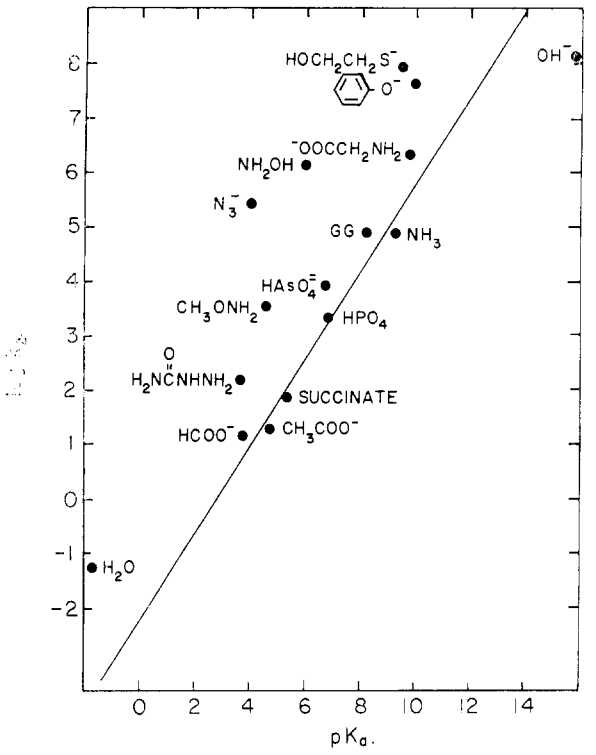
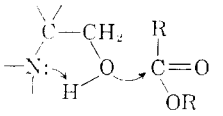


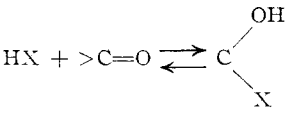
Fig. 2.—Rates of nucleophilic reactions with the acetylimidazolium cation in aqueous solution at 25° plotted against the basicity of the attacking reagent. Rate constants from ref. 53 except for azide, and $k_2 = k_{obs}K_{Ac\text{-}ImH^+}/K_{HA}$. The rate for OH^- is based on the assumption that the neutral hydrolysis of acetylimidazole represents an attack of OH^- on $AcImH^+$.

tively poor solvation of an ion may favor attack on carbon relative to binding to a proton.[58]

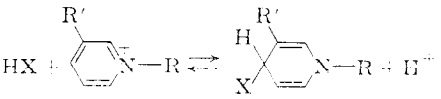
Steric Effects.—The interference of bulky groups near the reaction center is well illustrated by the low reactivity of *t*-butylamine (Fig. 1) and triethylamine; the latter compound did not react with *p*-nitrophenyl acetate at a measurable rate and was a convenient buffer for the measurement of the uncatalyzed hydrolysis rate. Triethylenediamine (1,4-diazobicycloöctane), a compound with a similar structure but with the ethylene groups pulled back by attachment to another nitrogen atom, reacts readily, although not as fast as primary amines. The measurable reactivity of tris-(hydroxymethyl)-aminomethane, which is more hindered at the nitrogen atom than *t*-butylamine, is surprising. The product of this reaction was converted quantitatively to hydroxamic acid by alkaline hydroxylamine under conditions in which esters, but not amides, form hydroxamic acids.[59] indicating that an oxygen rather than a nitrogen atom is the nucleophilic reactant with *p*-nitrophenyl acetate in this reaction.[59a] Since this hydroxyl group is 10^5 times as reactive as the hydroxyl group of water, this reaction may proceed with intramolecular general base catalysis in a manner similar to that proposed for the reaction of hydroxylamine and for the activation of the serine hydroxyl group in the active site of chymotrypsin[53]



Relative Bond Strengths to Protons and Carbon.—In many instances nucleophilic reactivity, as reflected in the stability of bonding to carbon in the activated complex,[60] may be correlated with unusually strong bonding to carbon, relative to protons, in equilibrium reactions. Such relatively strong binding to carbon is shown by hydroxylamine, hydrazine, semicarbazide,[61] mercaptans,[62] bisulfite[22] and hydrogen peroxide,[63] but not water, phosphate or "normal" amines,[61] since the former compounds will add to unhydrated carbonyl compounds in dilute aqueous solution to form addition compounds



Similarly, hydroxylamine, methoxyamine, sulfite and mercaptans, as well as potential carbanions, will add to the pyridinium ring of diphosphopyridine nucleotide in aqueous solution.[64] It is unlikely that a single type of hydrogen bonding could account for the stability of the addition compounds in these two different reaction series. This correlation is not completely general, however, since cyanide, which adds readily to the carbonyl group and to diphosphopyridine nucleotides, does not react rapidly and no addition compound formation from pyruvate could be detected in 1.3 *M* azide at *p*H 6.9 or 5.4, measured at 320 mμ.



Resonance.—The reactivity of a nucleophilic reagent whose basicity is largely dependent on resonance stabilization may be abnormal if resonance does not have the same effect on the transition state for nucleophilic attack as on acid–base equilibria. Bell has discussed the converse situation, for general acid catalysis, in detail[65] and Swain

(58) C. G. Swain, R. B. Mosely and D. E. Bown, THIS JOURNAL, **77**, 3731 (1955).

(59) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

(59a) C. Zioudrou and T. C. Bruice, as well as the present authors, have made similar observations for the reaction of N-acetylimidazole with tris-(hydroxymethyl)-aminomethane (personal communication).

(60) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956). Nucleophilic reactivity is discussed here generally in terms of a rate limiting attack of the nucleophilic reagent on the ester; if the breakdown of a tetrahedral intermediate (ref. 42) is the rate-limiting step, similar considerations will apply in most instances since the structure of the transition state is only slightly different and factors tending to stabilize the activated complex for nucleophilic attack will also increase the concentration of tetrahedral intermediate.

(61) W. P. Jencks, THIS JOURNAL, **81**, 475 (1959).

(62) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 245.

(63) (a) C. N. Satterfield and L. C. Case, *Ind. Eng. Chem.*, **46**, 998 (1954); (b) R. Criegee in Houben-Weyl, "Methoden der Org. Chem.," Vol. 8, Thieme, Stuttgart, 1952, p. 45; (c) P. L. Kooijman and W. L. Ghijsen, *Rec. trav. chim.*, **66**, 205 (1947).

(64) J. van Eys and N. O. Kaplan, *J. Biol. Chem.*, **228**, 305 (1957).

(65) R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).

and Scott have suggested that compounds with a localized negative charge will be more reactive toward carbonyl groups than toward saturated carbon, because of the greater distribution of charge in the transition state in the former case.[29] Although effects of this kind may be of importance in some instances, inspection of Fig. 1 reveals no consistent pattern: carbonate and carboxylate, which are stabilized by resonance, and hydroxide, chloral hydrate anion and phosphate,[66] which are not, show low reactivity, while α-carbonyl oxime anions and pyridine-N-oxides, which are resonance stabilized, and hydroxylamine, hydrazine and peroxide, which are not, all show abnormally high reactivity; deviations from the relationship to nucleophilic reactivity toward saturated carbon, while different, also appear to be random in respect to charge localization.

Other Correlations.—Swain and Scott[29] have shown that the rates of a large number of nucleophilic displacements on saturated carbon are correlated by the equation

$$\log k/k^0 = sn$$

where s is a measure of substrate discrimination and n is a measure of nucleophilic reactivity of the attacking reagent. The rates of *p*-nitrophenyl acetate decomposition in the presence of a group of weakly basic compounds, including such highly active reagents toward saturated carbon as iodide thiocyanate and thiourea, are given in Table III.

TABLE III

RATES OF *p*-NITROPHENYL ACETATE DECOMPOSITION IN THE PRESENCE OF UNREACTIVE COMPOUNDS IN 0.1 *M* PHOSPHATE BUFFER

Substance	*p*H	$k_{obs} \times 10^4$, min.$^{-1}$	Substance	*p*H	$k_{obs} \times 10^4$, min.$^{-1}$
Buffer alone	6.15	3.1	1 *M* KI	5.80	1.6
1 *M* $NaClO_4$	5.78	1.5	1 *M* KSCN	5.80	1.4
1 *M* KCl	5.73	2.7	1 *M* KNO_3	5.79	2.6
1 *M* NaCl	5.55	1.8	0.9 *M* K_2SO_4	5.85	3.7
1 *M* KBr	5.75	1.9	1 *M* thiourea	6.00	2.0

In each case the increase in the rate of reaction due to the addition of reagent was no greater than might be expected from non-specific salt or medium effects. It is clear from Table III and Fig. 1 that there is no simple relationship between nucleophilic reactivity toward saturated carbon and toward esters. A similar lack of correlation exists for phosphoryl halides,[67] ethyl chloroformate[68] and *p*-toluenesulfonate esters[69]; but it is of considerable interest that the reactions of benzoyl chloride appear to follow the Swain and Scott equation,[29] suggesting that the reactions of this compound may have more of the character of simple displacement reactions. A similar trend is evident with hydroxylamine: with relatively weak acylating agents acylation occurs almost exclusively on oxygen, while with benzoyl chloride and other highly reactive acylating agents, reaction occurs at the nitrogen atom,[2] as is the case for alkylation. High selectivity in acylation is thus exhibited by the least reactive acylating agents. The relative reactivity of nucleophilic reagents toward carbonyl carbon is similar to the relative order of affinity of ligands toward "group a" metals, while with saturated carbon, reactivity parallels affinity toward "group b" metals.[70]

Edwards has proposed more general correlation equations in which basicity and a second factor, E_n, which is related to reducing power[71] or polarizability and to nucleophilic reactivity toward saturated carbon, may be given variable weights.[23] If such a relationship held for reactions of esters, those compounds which show large positive deviations in Fig. 1 should have large E_n values relative to their basicity. Although this is the case in several instances, the relationship is not general: azide is over 100 times as reactive as aniline, in spite of its lower basicity and E_n value; thiosulfate and fluoride are equally reactive with only a tenfold difference in basicity in spite of being at opposite ends of the E_n scale (E_n = 2.52 and −0.15, respectively); phenolate is more reactive than ammonia and cyanide while it is only slightly more basic and is considerably lower on the E_n scale than these compounds.[72] Furthermore, many of the compounds which show large positive deviations are strong oxidizing rather than reducing agents. Considering the large number of factors which can affect reactivity, it would indeed be surprising if a simple two-parameter equation were completely successful.

In many of the highly reactive compounds, the reacting atom is directly linked to an electronegative element[8] with a free electron pair. While this is a striking characteristic of the abnormally reactive compounds, its significance is not clear and the nitrite ion reacts normally.

While concerted general acid–base catalysis, possibly with three or more reacting catalytic groups,[73] is an attractive possibility as a partial explanation of the very high reactivity displayed by enzymes, other factors, such as polarizability, changes in solvation and basicity, steric and association effects and electrostatic interactions, may also influence reactivity and further study of such factors may prove to be of value in helping to elucidate the difficult problems of enzymic catalysis. It is probably significant in this connection that groups which have been implicated as part of the active sites of enzymes include sulfhydryl, imidazole and serine hydroxyl; all of these have abnormally high nucleophilic reactivity relative to their basicity.[53]

Acknowledgments.—We are grateful to Doctor John T. Edsall and Dr. Bruce Martin of the Department of Biology, Harvard University, for their

(66) R. G. Gillis, J. F. Horwood and G. L. White, THIS JOURNAL, **80**, 2999 (1958).

(67) (a) I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 508 (1953); (b) R. F. Hudson and D. C. Harper, *ibid.*, 1356 (1958).

(68) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 149 (1959).

(69) J. F. Bunnett and J. Y. Bassett, Jr., THIS JOURNAL, **81**, 2104 (1959).

(70) S. Ahrland, J. Chatt and N. R. Davies, *Quart. Revs.*, **12**, 265 (1958).

(71) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).

(72) See also the discussion of Bruice and Lapinski on this subject (ref. 17).

(73) P. D. Bartlett, in "Perspectives in Organic Chemistry," ed. A. Todd, Interscience Publishers, Inc., New York, N. Y., 1956, p. 25.

coöperation in obtaining Raman spectra, to Dr. John O. Edwards for stimulating discussion, and to the National Science Foundation and the National Cancer Institute of the National Institutes of Health (Grant C-3975) for financial support.

WALTHAM 54, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Benzylation and Related Alkylations of α-Dimethylaminophenylacetonitrile by Means of Alkali Amides. Dehydrocyanation of Products to Form Enamines[1]

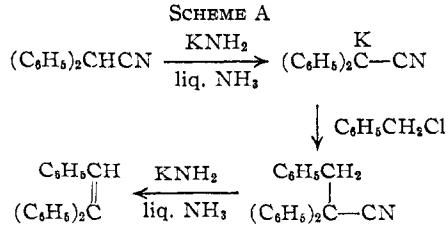
BY CHARLES R. HAUSER, HAROLD M. TAYLOR AND T. GLEN LEDFORD[2]

RECEIVED AUGUST 11, 1959

α-Dimethylaminophenylacetonitrile was benzhydrylated, benzhydrylated and α-phenylethylated with the appropriate halide by means of sodium amide or potassium amide in liquid ammonia. The resulting alkylation products were dehydrocyanated thermally or by means of potassium amide in liquid ammonia to form the corresponding enamines. Several types of reactions involving the latter products were effected.

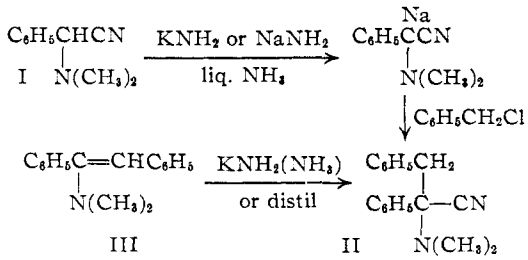
It has recently[3] been shown that diphenylacetonitrile can be benzylated, benzhydrylated and α-phenylethylated with the appropriate halides by means of potassium amide in liquid ammonia, and that the resulting alkylation products undergo dehydrocyanation on further treatment with this reagent. For example, the benzylation was realized in 96% yield, and the subsequent dehydrocyanation in 94% yield (Scheme A).

SCHEME A



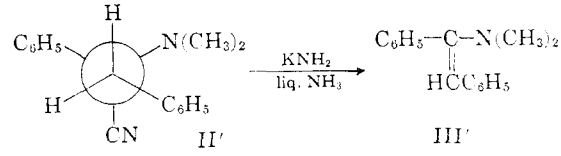
It has now been found that α-dimethylaminophenylacetonitrile (I) can be alkylated similarly with these halides, and that the alkylation products can be dehydrocyanated by further treatment with the alkali amide in liquid ammonia or even by heat alone. Thus, the benzylation of I gave alkylation product II in 91% yield, and the dehydrocyanation of this alkylation product formed enamine III in yields of 84–92% (Scheme B).

SCHEME B



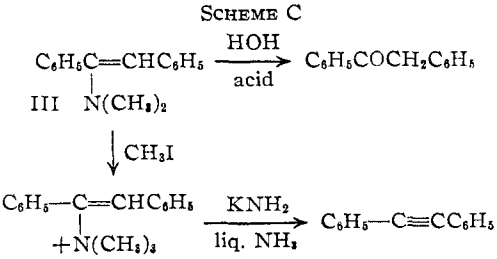
In contrast to the benzylation product of diphenylacetonitrile (see Scheme A), benzylation product II underwent dehydrocyanation[4] under the usual recrystallization conditions and during an attempted distillation *in vacuo*. However, the aminonitrile II was recrystallized satisfactorily from ether at low temperature.

The dehydrocyanation of benzylation product II by means of potassium amide in liquid ammonia produced an 84% yield of enamine III as a solid melting at 29–30°, but a liquid enamine was obtained in 92% yield when the dehydrocyanation was effected by an attempted distillation of II (see Scheme B). Apparently the former conditions formed largely a single geometrical isomer of the enamine whereas the latter conditions produced either the other isomer or a mixture of the two possible geometrical isomers of III.[5] It is suggested that the reaction with potassium amide involved the *trans* β-elimination of hydrogen cyanide from conformation II′ to give the geometrical isomer III′.



The enamine structure III was established by an acid-catalyzed hydrolysis of the dimethylamino group to form desoxybenzoin and by methylation followed by β-elimination of the resulting unstable methiodide (Scheme C).

SCHEME C



The type of acid-catalyzed hydrolysis indicated in Scheme C had previously been observed with

(1) Supported in part by a grant from Merck, Sharpe and Dohme, Rahway, N. J.

(2) Deceased, Eastman Kodak Co. Fellow, 1955–1956.

(3) C. R. Hauser and W. R. Brasen, THIS JOURNAL, **78**, 494 (1956).

(4) This greater ease of dehydrocyanation of II might be due to the participation of the free pair of electrons on the amino group in the elimination of the cyanide group (along with a β-hydrogen) or to another molecule of II functioning as an amino base facilitating the removal of the β-proton.

(5) Because of the free pair of electrons on the nitrogen, a relatively low energy barrier between the two geometrical isomers might be expected. The isolation of such a pair has been reported by J. J. Conn and A. Taurins, *Can. J. Chem.*, **31**, 1211 (1953).