The "Charge" Effect in Nucleophilic Displacement Reactions

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Abstract: A previous study on the reactivity of isopropyl methylphosphonofluoridate with various anions of hydroxybenzenes indicated that the incorporation of a cationic site into the benzene nucleus increased the reactivity of the anion relative to its basic strength. In this work, the reactivities of different cationically substituted nucleophiles have been determined. One class of nucleophiles, called "α" nucleophiles because they possess an unshared electron pair on the (α) atom adjacent to the attacking atom, showed no (anions of hydroxamic acids) or only a slight (anions of keto oximes) "charge" effect, i.e., their reactivities were equal to or only slightly greater than would be expected for a nucleophile of the same class of the same basic strength but possessing no cationic group in the molecule. A second class of nucleophiles, the anions of hydrated aldehydes, similar to the hydroxybenzenes in that the atom adjacent to the attacking atom contained no unshared electron pair, exhibited a "charge" effect qualitatively and quantitatively similar to that shown by the hydroxybenzenes. An explanation for the different responses to the "charge" effect shown by the "α" and "non-α" nucleophiles is offered. The "charge" effect studies are not only useful practically, but also may be used in separation of factors in nucleophilicity. These studies support the designation of a separate classification for "α" nucleophiles when discussing reactivity.

In recent studies[2] it has been observed that anions of hydroxybenzenes containing cationic groups are more reactive than other hydroxybenzenes of the same proton basicity in displacement of fluoride ion from isopropyl methylphosphonofluoridate (GB) in aqueous solution. It was also shown that the magnitude of the increase in reactivity was related to (a) the distance between the cationic and anionic sites, the difference increasing as the distance between the loci of the charges decreases, and (b) to the number of cationic groups in the nucleophile, each cationic site contributing independently in accordance with its distance from the anionic site. Thus, for example, it was shown that the monoanion of the protonated 3-aminomethylcatechol was approximately five times as reactive as the monoanion of a catechol of the same proton basicity but possessing no cationic group, whereas the monoanion of 4-aminomethylcatechol was less than twice as reactive as a noncationic monocatecholate anion of comparable basicity. Also, the monanion of the protonated 3-dimethylaminomethylcatechol was approximately six, the monoanion of the diprotonated, 3,6-bis(dimethylaminomethyl)catechol 38, and the monoanion of the 3,4,6-tris(dimethylaminomethyl)catechol 75 times as reactive as their noncationic-bearing, but same proton basicity, analogs.[2b]

The enhanced reactivity shown by a nucleophile containing a cationic site ("charge" effect) has been explained on the basis that pK_a of the conjugate acid is not a true measure of the basicity of the nucleophile toward neutral substrates; that the basicity of a cationic-bearing nucleophile is greater to a neutral substrate than would be predicted from the pK_a of the conjugate acid, since the Coulomb repulsion factors operative in ionization phenomena are absent in reaction with a neutral substrate.

While the effect of a cationic group on the reactivity of the hydroxybenzenes in displacement reactions of the phosphonyl ester, GB, has been established, the effect of cationic substitution in nucleophiles other than the hydroxybenzenes in this displacement reaction has not been assessed. In this paper, we report on the effect of cationic substituents on the reactivity of the anions of hydroxamic acids, keto oximes, and hydrated aldehydes in displacement of fluoride ion from GB in aqueous solution.[3]

Experimental Section

Materials. Picoline, isonicotine, nicotinehydroxamic acids, and the corresponding methiodides were synthesized according to the directions of Hackley, et al.[4] o-Diethylaminoethoxybenzohydroxamic acid was kindly supplied by Dr. R. E. Plapinger. Chloral, pyruvic aldehyde (as an aqueous solution), and 2-, 3-, and 4-pyridine carboxaldehydes were obtained from commercial sources. The 2- and the 4-pyridine carboxaldehydes were converted to their methiodides according to the procedure of Steinberg, Poziomek, and Hackley.[3c] The methiodide of 1,1-dimethyl-2-dimethylamino-propionaldehyde was prepared from the commercially available free base by reaction with methyl iodide in diethyl ether, mp 230°. Anal. Calcd for $C_8H_{18}INO$: C, 35.4; H, 6.6. Found: C, 35.5; H, 6.8. Compounds 1, 2, 3, and 11 in Table III were kindly supplied by Dr. G. M. Steinberg.[5] The other compounds were prepared according to published procedures.[6] All compounds were of high purity using elemental analyses, neutralization equivalents, and sharpness of melting point criteria except pyruvic aldehyde which was determined to be 49.6% by analysis.

Determination of pK_a Values. The compounds were made up to be approximately 0.01 M with the ionic strength adjusted to 0.1 with KCl. A 3-ml aliquot, adjusted to the desired temperature and maintained at that temperature to ±0.1°, was titrated potentiometrically with a microsyringe (total volume 0.5 ml) cali-

(1) (a) Edgewood Arsenal, Md. (b) University of Delaware, Newark, Del.

(2) (a) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, J. Am. Chem. Soc., 86, 3075 (1964); (b) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, R. A. Stephani, and E. Cook, ibid., 86, 4959 (1964).
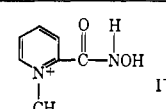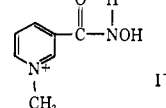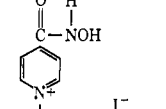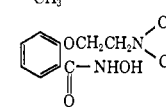
(3) For studies on the chemistry and mechanisms of the reaction between GB and hydroxamic acids, see (a) R. Swidler and G. M. Steinberg, ibid., 78, 3594 (1956); GB and keto oximes: (b) A. L. Green and B. Saville, J. Chem. Soc., 3887 (1956); GB and hydrated aldehydes: (c) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., J. Org. Chem., 26, 368 (1961).

(4) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, J. Am. Chem. Soc., 77, 3651 (1955).

(5) G. M. Steinberg and J. Bolger, J. Am. Pharm. Assoc., 46, 188 (1957).

(6) For pertinent references on the preparation of compounds, 4, 5, 6, 7, 8, 9, and 10 (Table III) see O. Touster, Org. Reactions, 7, 327 (1953).

Table I. pK_a and k_2 (Reaction with GB) for
Charged Hydroxamic Acids at 30°

Compd	pK_a	k_2, l. mole^{-1} min^{-1}
	5.25	2.11 ± 0.08[a]
	6.41	20.94 ± 0.37[b]
	5.95	8.09 ± 0.09[b]
	8.42	630 ± 10[c,d]

[a] Average of three determinations. [b] Average of four determinations. [c] Average of two determinations. [d] Experiments on this compound run at 25°.

Table II. "Charge" Effects in Hydroxamic Acids[a]

Compd	pK_a	Log k_c	Log k_2	Log k_2/k_c
	5.29	0.36	0.32	−0.04
	6.41	1.26	1.32	+0.06
	5.95	0.89	0.91	+0.02
	8.42	2.87	2.80	−0.07

[a] Calculated from the equation log k_2 = 0.80pK_a − 3.87 at 30° (see Table I).

brated in units of 0.005 ml, and estimable to 0.0005 ml with 0.1 N CO$_2$-free NaOH solution. (A Radiometer automatic titrator was used.)

Determination of Reaction Velocities and Rate Constants. The general procedure for determination of reaction velocities and methods for calculation of the bimolecular rate constants has been previously described.[2a,7]

In all cases the nucleophiles were in sufficient excess so that their concentrations remained, to all intents and purposes, constant, resulting in first-order kinetics.

For the hydroxamic acids and the hydrated aldehydes, the reaction velocities were determined by analyzing the GB concentrations with time, enzymatically, taking advantage of the anticholinesterase properties of GB.

The reaction velocities for the α-keto oximes were determined manometrically from the CO$_2$ produced upon reaction of the acidic products of GB oxime reaction with sodium bicarbonate. The half-time of the reaction was taken as the time required to produce 50% of the total CO$_2$ produced. The bimolecular rate constants were calculated from the first-order rate constants and the concentration of the anions according to the equation
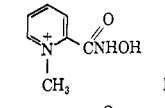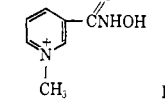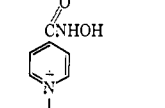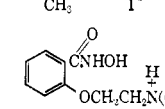
$$k_2 = k_{obsd}([H^+] + K_a)/K_a[C_0]$$

where k_2 is the bimolecular rate constant in l. mole^{-1} min^{-1}, k_{obsd} is the first-order rate constant in min^{-1}, K_a is the ionization constant of the hydroxamic acid, oxime, or hydrated aldehyde, and [C_0] is the initial concentration of the acid.

Results

Table I gives the pK_a values of four cationic-bearing hydroxamic acids and the bimolecular rate constants of their anions with GB. Table II contains the data by which one can compare the reactivities of the anions of the above hydroxamic acids with the anions of noncationic-bearing hydroxamic acids. The values listed under the heading "Log k_c" have been calculated from the equation[8,9] relating the log of the bimolecular rate

(7) T. Wagner-Jauregg and B. E. Hackley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1952).

(8) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959).

(9) R. W. Swidler, R. E. Plapinger, and G. M. Steinberg, *J. Am. Chem. Soc.*, **81**, 3271 (1959).

constant with the pK_a for the nucleophile, viz., log k_c = 0.80pK_a − 3.87; those under the heading "Log k_2" are the experimentally determined values. Log k_2/k_c, then, denotes the deviation of the experimental value from that predicted from the equation of the "normal" nucleophiles of the class under study.

The almost negligible (within experimental error) difference between the logarithms (<0.1, see ref 2a) of bimolecular rate constants of the cationic hydroxamic acids (k_2) and the hydroxamic acids containing no cationic groups (k_c), considering that the distance of separation between the cationic and anionic sites and the type of group producing the charge (i.e., pyridine, aliphatic amine) has been varied over rather wide limits, is strong evidence that there is no "charge" effect on the hydroxamic acid anion similar to that found for the hydroxybenzenes.

The data (Table III) were used to determine the effect of "charge" on the nucleophilicity of the anions of keto oximes.

A plot of the data in Table III is shown in Figure 1, the circles representing values of noncationic-bearing oximes, whereas the x's are for compounds containing a positive charge. The equation of the line drawn through the circular points ("base" line) is

$$\log k_c = 0.642p K_a - 3.25$$

Table IV lists the relevant data for assessing the "charge" effect. As in the previous instance, the values listed under the heading "Log k_c" have been calculated from the equation of the "base" line relating the bimolecular rate constant of the anion of keto oximes with GB and the pK_a of the keto oximes, viz., log k_c = 0.642pK_a − 3.25. Again, log k_2/k_c is the deviation of the experimental value from that predicted from the equation of the "normal" keto oximes. These data suggest that there is an effect of charge on the reactivity of the anions of keto oximes although, perhaps, not as pronounced as in the case of the hydroxybenzenes. A similar conclusion can be drawn from

Table III. Data for Keto Oximes at 30°

$$\underset{R-\overset{O}{\overset{\|}{C}}-\overset{R'}{\overset{|}{C}}=NOH}{}$$

Compd	R	R'	pK_a	k_2, l. mole^{-1} min^{-1}
1	CH_3	$\overset{+}{CH_2N(C_2H_5)_2}$ $\overset{|}{CH_3}$	6.95	15.9
2	CH_3	$\overset{H}{\overset{|}{CH_2N(CH_3)_2}}$	7.05	29.0
3	CH_3	$CH_2\overset{+}{N}\bigcirc$	7.15	35.9
4	CH_3	$COOC_2H_5$	7.20	19.0
5	CH_3	$\overset{O}{\overset{\|}{CCH_3}}$	7.50	37.7
6	$\overset{H}{\overset{|}{C}}=NOH$	H	7.65	49.8
7	$HON\underset{}{\overset{O}{\diagdown}}\underset{}{\diagup}NOH^b$		7.95	$(69.6)^a$
8	CH_3	H	8.35	127
9	$\bigcirc$	H	8.40	127
10	$\underset{S}{\diagdown\diagup}$	H	8.45	149.4
11	CH_3	$\overset{+}{CH_2CH_2N(C_2H_5)_2}$ $\overset{|}{CH_3}$	8.60	248.6
12	$\overset{CH_3}{\underset{CH_3}{}}>C=CH$	H	8.90	275.0

^{a} (69.6) value corrected for first oxime dissociation. ^{b} Complete structure.

Table IV. "Charge" Effects in Keto Oximes

Compd	Compd structure	pK_a	Log $k_c{}^a$	Log k_2	Log k_2/k_c
1	$\overset{O}{\overset{\|}{}}\ \overset{+}{CH_2N(C_2H_5)_2}$ $\overset{|}{CH_3}$ $CH_3C-C=NOH$	6.95	1.21	1.20	−0.01
2	$\overset{O}{\overset{\|}{}}\ \overset{+}{CH_2N(CH_3)_2}$ $\overset{|}{H}$ $CH_3C-C=NOH$	7.05	1.27	1.46	0.19
3	$\overset{O}{\overset{\|}{}}\ CH_2\overset{+}{N}\bigcirc$ $\overset{|}{H}$ $CH_3C-C=NOH$	7.15	1.34	1.55	0.21
11	$\overset{O}{\overset{\|}{}}\ \overset{+}{CH_2CH_2N(C_2H_5)_2}$ $\overset{|}{CH_3}$ $CH_3C-C=NOH$	8.60	2.27	2.40	0.13

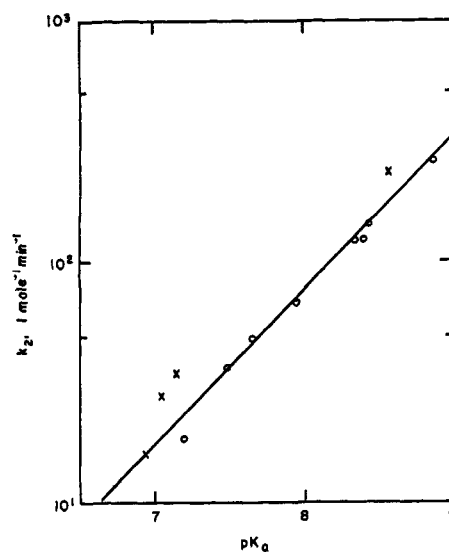^{a} Calculated from the equation log k_c = 0.642pKa − 3.25, temperature 30°.

Figure 1. Plot of log k_2 vs. pK_a for reaction of 12 keto oximes with GB at 30°: x, charged keto oximes; O, uncharged keto oximes.

an analysis of the data of Green, et al.,[10] on the rate constants of oximes with GB.

Data on seven aldehydes, three of which contain cationic groups, and ninhydrin are shown in Table V. That the effect of a cationic substituent in a hydrated aldehyde on the nucleophilicity of its anion is marked can be seen by comparison of the reactivities of the anions of chloral and 2-formyl-1-methylpyridinium iodide, and pyruvic aldehyde and 4-formyl-1-methyl-pyridinium iodide. The pK_a values of the first two compounds are almost identical, viz., 9.94 and 9.95, yet their reactivities differ by almost an order of magnitude [k_2(chloral) = 32 l. mole^{-1} min^{-1}; k_2(2-formyl-1-methylpyridinium iodide) = 215 l. mole^{-1} min^{-1}]. Similarly, the bimolecular rate constant for the reaction between GB and the anion of pyruvic aldehyde (pK_a of conjugate acid = 11.0) is 102 l. mole^{-1} min^{-1}; the bimolecular rate constant for the reaction between GB and the anion of 4-formyl-1-methylpyridinium iodide, whose conjugate acid pK_a is less than that of pyruvic aldehyde, viz., 10.72, and hence may be expected to be less than 102 l. mole^{-1} min^{-1}, is 302 l. mole^{-1} min^{-1}.
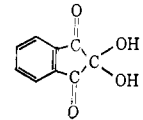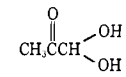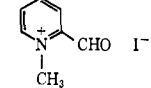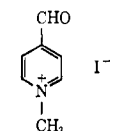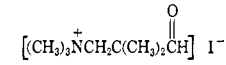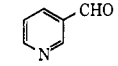
Moreover, the effect of charge appears to be quantitatively similar in the hydrated aldehydes and the hydroxybenzenes. It was shown in the latter series that log k_2/k_c (where k_2 is the bimolecular rate constant of the anion of "charged" hydroxybenzene with GB and k_c is the bimolecular rate constant of an anion of hydroxybenzene of the same proton basicity but possessing no cationic group) could be estimated from the relationship

$$\log k_2/k_c = c/d^2$$

where c, a proportionality constant, equals 12.7 and d is the distance between the cationic and anionic sites in Angstrom units. The distance between the cationic and anionic sites in the anion of 2-formyl-1-methyl-pyridinium iodide is estimated from Dreiding models to be 2.64 or 3.64 Å depending upon whether the anionic site is assumed to reside on the oxygen atom

(10) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stanfield, J. Chem. Soc., 1583 (1958).

Table V. Summary of Data for Reaction of Hydrated Aldehydes and Ninhydrin with GB at 25°

Compd	pK_a	k_2, l. mole^{-1} min^{-1}
(ninhydrin hydrate structure)	8.82	13.3 ± 0.1[a]
H Cl$_3$CCOH OH	9.95	32.0 ± 0.4[a]
O CH$_3$CCH(OH)OH	11.0	102 ± 5[b]
1-methylpyridinium-2-CHO I$^-$	9.94	214 ± 2.5[a,d]
1-methylpyridinium-4-CHO I$^-$	10.72	302 ± 6[a,d]
$[(CH_3)_3\overset{+}{N}CH_2C(CH_3)_2\overset{O}{\overset{\|}{C}}H]$ I$^-$	13.6	8450 ± 350[a]
pyridine-3-CHO	13.0	960 ± 112[a]
pyridine-4-CHO	12.05	459 ± 37[c]

[a] Two determinations. [b] Three determinations. [c] Five determinations. [d] Data obtained with the cooperation of Dr. George M. Steinberg.

closest to or farthest from the nitrogen atom. If the latter value is chosen, then, from data on the hydroxybenzenes, it would be predicted that the reactivity of 2-formyl-1-methylpyridinium iodide with GB would be 12.7/3.642^2 or 0.96 log unit higher than that of chloral (hydrated aldehyde of the same pK_a but possessing no cationic group). The actual difference is 0.83 log unit.

Also, the bimolecular rate constant of the reaction between GB and the anion of a hydrated aldehyde (containing no cationic substituent) whose conjugate acid has a pK_a equal to 10.72 may be expected to be[11] approximately 87 l. mole^{-1} min^{-1}. Hence the enhancement in rate shown by the 4-formylpyridinium methiodide over that which might be expected from its pK_a is 0.54 log unit (log 302 − log 87). The distance between the anionic and cationic sites in the 4-formylpyridinium methiodide from Dreiding models is 4.88 A. Using this value for d, and $c = 12.7$, one would predict from the data on hydroxybenzenes a logarithmic increase in rate of 0.53 log unit, in very good agreement with the value of 0.54 obtained above.

Although of doubtful quantitative significance because of the high probability of error in extrapolation of the

(11) The least-squares equation of the line using the data for chloral, pyruvic aldehyde, 3- and 4-formylpyridine, and ninhydrin is: log k_2 = 0.465pK_a − 2.95. The bimolecular rate constant for the reaction between a noncationically substituted hydrated aldehyde of pK_a = 10.22 would be expected to be ca. 87 l. mole^{-1} min^{-1}.

data to pH 13.6, it is nevertheless of qualitative value that the anion of a hydrated aldehyde containing no cationic group whose conjugate acid has a pK_a of 13.6 may be expected to have a k_2 value of ca. 1800 l. mole^{-1} min^{-1}. The value found for the cation-bearing anion of the aldehyde, 2,2-dimethyl-3-trimethylammoniopropanol iodide (pK_a of the conjugate acid = 13.6), was considerably higher, viz., 8450 l. mole^{-1} min^{-1}.

Table VI lists the distances of separation between the cationic and anionic sites in anions of hydroxamic acids, keto oximes, and hydrated aldehydes, the expected deviations from "normal" that these nucleophiles would show if their behavior were similar to that of the hydroxybenzenes, and the deviation calculated as the logarithm of ratio of the experimentally determined bimolecular rate constants with GB to the bimolecular rate constants of a nucleophile in the same class and of the same proton basicity.

The values of d shown in Table VI for the keto oximes require explanation. The distance of separation of the charges in the keto oximes and hydroxamic acids is difficult to estimate due to free rotation of groups; Dreiding models indicate that the distance of separation of charge in the keto oximes designated as compounds 2 and 3 in Table III can vary from 2.8 to 4.4 A. However, with the larger value there is no steric crowding of the oximino group by the alkyl groups on the amine. That there should be no steric obstruction is suggested by the almost identical deviations from the "base" line shown by compounds 2 and 3 in Figure 1, even though the groups attached to the nitrogen are different. The model having a distance of separation of ca. 4 A was one in which substitution of ethyl groups for a hydrogen and a methyl (conversion of compound 2 to compound 1 in Table III) produced a structure in which the oxygen of the oximino group was slightly sterically hindered. Steric hindrance in compound 1 is suggested by kinetic data (see Figure 1 and ref 2a). Similar considerations led to a value of ca. 5 A for the distance of charge separation in compound 11.

In all cases the locus of positive charge was assumed to reside on the pyridinium or amino nitrogens; the site of high electron density was assumed to be on the oximino oxygens in the case of the anions of the hydroxamic acids[12] and keto oximes and on the alcoholic oxygen in the case of the hydrated aldehydes.

Discussion

From the data in Tables II, IV, V, and VI, one concludes that a cationic substituent greatly enhances the reactivity of anions of hydrated aldehydes (relative to their proton basicities), enhances only slightly the reactivity of the keto oximate anion, and has negligible effect upon the reactivity of anions of the hydroxamic acids. Furthermore, the response of the hydrated

(12) The choice of the locus of high electron density is obviously arbitrary; in the anions of the hydroxamic acids and keto oximes, the sites of high electron density can be assumed to reside on either of two oxygens or the oximino nitrogen. O. Exner and B. Kakac [Collection Czech. Chem. Commun., 28, 1965 (1963)] conclude from ultraviolet absorption studies on hydroxamic acids and their anions that the site of electron density in the anion is on the carbonyl oxygen; G. M. Steinberg and R. W. Swidler, J. Org. Chem., 30, 2362 (1965), and R. E. Plapinger, ibid., 24, 802 (1959), argue that the anion exists in at least two and possibly three forms.

Table VI. Predicted and Actual Deviations from "Normal" for Anions of Hydroxamic Acids, Keto Oximes, and Hydrated Aldehydes

Compd	d, Å	c/d^2 (predicted)[a]	Log k_2/k_c (actual)[b]	Compd	d, Å	c/d^2 (predicted)[a]	Log k_2/k_c (actual)[b]
Hydroxamic acids				**Hydrated Aldehydes**			

Hydroxamic acids:

Structure 1 (pyridinium, N-CH$_3$, C(=O)-N(O$^-$)(H)):
4.4^e / 2.2^f, 0.65 / 2.62, -0.04

Structure 2:
6.0^e / 3.5^f, 0.35 / 1.00, 0.06

Structure 3:
6.0^e / 4.4^f, 0.35 / 0.65, 0.02

Structure 4 (benzene ring with C(=O)–NH and O–CH$_2$CH$_2$$\overset{+}{N}$H(C$_2H_5$)$_2$):
8.6^e / 0.0^f, 0.17 / $\cdots$, 0.07 / $\cdots$

Keto Oximes

Structure: $CH_3CC{=}NOH$ with O and $CH_2\overset{+}{N}{<}^{(C_2H_5)_2}_{CH_3}$:
4.0^c, $Ca.\,0.79$, -0.01

Structure: $CH_3C{-}C{=}NOH$ with O and $CH_3\overset{+}{N}(CH_3)_2$, H:
4.0^c, $Ca.\,0.79$, 0.19

Structure: $CH_3{-}\overset{O}{C}{-}C{=}NOH$ with $CH_2{-}\overset{+}{N}$H(ring):
4.0^c, $Ca.\,0.79$, 0.21

Structure: $CH_3{-}C{-}C{=}NOH$ with O and $CH_2CH_2\overset{+}{N}(C_2H_5)_2$, CH$_3$:
5.0, $Ca.\,0.51$, 0.13

Hydrated Aldehydes:

Structure (pyridinium, N-CH$_3$, CH(OH)$_2$):
3.64^e / 2.64^f, 0.96 / 1.82, 0.85

Structure (HO–C(OH)–H on pyridinium ring, N-CH$_3$):
4.88, 0.532, 0.54

Structure ($\overset{+}{N}(CH_3)_3$, CH$_2$, CH$_3$CCH$_3$, HOCOH, H):
5.0^d, 0.51, 0.68

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[a] Calculated from the fraction c/d^2, where $c = 12.7$, $d =$ distance of separation of charges in Angstrom units. [b] $k_2 =$ experimental bimolecular rate constant of the reaction between GB and the anion of compound listed; k_c is the bimolecular rate constant calculated from the following equations: hydroxamic acids: log $k_c = 0.80pK_a - 3.87$; keto oximes: log $k_c = 0.642pK_a - 3.25$; hydrated aldehydes: log $k_c = 0.456pK_a - 2.95$, where pK_a is the negative logarithm of the acid dissociation constant of the compound listed. The equations relating log k_c with pK_a are from ref 3 (hydroxamic acids), Figure 1 of this paper (keto oximes), and Table V of this paper (data on the reactivity of the anions of chloral, pyruvic aldehyde, 3- and 4-formylpyridine, and ninhydrin with GB). [c] This distance can vary from approximately 2.8 to 4.4 Å, depending upon the configuration adopted, a "stretched out" configuration giving a value of 4.4. [d] "Stretched out" configuration. [e,f] The positive charge is assumed to reside on the nitrogen; the negative, on the oxygen. The value of superscript f is the smallest distance of separation; that of e, the largest.

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aldehydes to the "charge" effect is quantitatively similar to that of the hydroxybenzenes.

The reactivity of the anions of compounds with GB increases in the order: hydrated aldehydes $\sim$ phenols $<$ oximes $<$ hydroxamic acids whereas the effect of introduction of a charged substituent decreases in the same order. One is tempted to relate the "charge" effect with reactivity, the "charge" effect becoming less important as the intrinsic reactivity of the nucleophile increases. However, the anions of hydroxybenzenes of the catechol and pyrogallol type respond to the "charge" effect equally as well as the anions of phenol or of the hydrated aldehydes do, and yet have re-

activities of the same order as those of the anions of the oximes and hydroxamic acid.[13] Correlation of "charge" effect with the reactivity is not justified. Nor does there appear to be any correlation between the magnitude of the effect caused by introduction of a cationic substituent and the value of the slope (a measure of the degree of bond formation in the transition state) in the equation relating the logarithm of the bimolecular rate constant with the pK_a of the

(13) Compare, for example, the equation of the line relating the bimolecular rate constants of the anions of pyrocatechols with GB, viz., log $k_2 = 0.76pK_a - 3.70$, with that of the anions of hydroxamic acid and GB, viz., log $k_2 = 0.80pK_a - 3.87$.

conjugate acid of the reacting nucleophile for different classes of nucleophiles. The slopes for the anions of phenols,[2a] catechols, and pyrogallols[2b] (which show marked "charge" effects) are 0.59, 0.80, and 0.76; those of keto oximes and hydroxamic acids are 0.64 and 0.80.

It is, however, perhaps of some significance that of the classes of nucleophiles studied, those which appear to respond only slightly (keto oximate anion) or not at all (anions of hydroxamic acids) to the "charge" effect are "α" nucleophiles,[14] that is, the atom adjacent to the nucleophilic one contains an unshared pair of electrons, whereas those which show marked "charge" effects (anions of hydrated aldehydes, hydroxybenzenes) are "non-α" nucleophiles.[15]

Because the anions of the keto oximates are partially affected by a cationic substituent, they may be classified as "α" nucleophiles possessing some "non-α" character. In fact, if one assumes that the keto oximate anion possesses 68% "α" character and 32% "non-α" character (the rationale for the assignment of 68 and 32% is given below) and that the "charge" effect acts only on "non-α" nucleophiles, then it can be shown that the predicted log k_2/k_c for compounds **2** and **3** (distance of separation of charged groups is approximately 4 A) is 0.25 and for compound **11** (distance of separation is approximately 5 A), 0.16, in good agreement with the values of log k_2/k_c, viz., 0.19, 0.21, and 0.13, found for the three compounds (Table VI).

The values of 68 and 32% were arrived at by treating the free energy of activation as a sum of independent contributions[16] attributable to the "α" and "non-α" characters of the nucleophile. Thus, one may write

$$\log k_2 = \log k_\alpha + \alpha_n \log k_{\alpha n} \qquad (1)$$

where k_2 is the bimolecular rate constant for the nucleophile in question with a given substrate at a given temperature; k_α and $k_{\alpha n}$ are the bimolecular rate constants due to "α" and "non-α" contributions for a given basicity of the nucleophile; and α and α_n are constants ranging from 0 to 1 with $\alpha + \alpha_n = 1$.

For reactions with GB, it can be assumed that values of k_α and $k_{\alpha n}$ can be obtained from data on the reactivity of the anions of hydroxamic acids (pure "α") and phenols (pure "non-α"). If the nucleophile in question is the keto oximate anion, the log k_2 can be calculated from the equation

$$\log k_2 = 0.642 p K_a - 3.25$$

Thus for a keto oximate anion whose conjugate acid has a $pK_a = 7.5$,[17] log $k_2 = 1.57$; log $k_\alpha = 2.13$ (calcu-

lated from the equation relating the bimolecular rate constants of the reaction between GB and hydroxamic acid anions, viz., log $k_\alpha = 0.80 p K_a - 3.87$, where $pK_a = 7.5$); and log $k_{\alpha n} = 0.390$ (calculated from the equation relating the bimolecular rate constants of the reaction between GB and phenolate anions at 25°, viz., log $k_{\alpha n} = 0.598 p K_a - 4.172$, and correcting to 30° using an Arrhenius activation energy value of 12.0 kcal/mole[18]).

Substituting the values for log k_2, log k_α, and log $k_{\alpha n}$ into eq 1 gives α_n equal to 0.32. Thus, by this line of reasoning the keto oximate anion possesses 68% "α" character and 32% "non-α" character.

Although other factors are doubtless of importance in nucleophilic reactivity, the success in quantitatively predicting the effect of charge in the keto oximes lends support to the treatment given herein and to the conclusion that the "charge" effect is applicable only to "non-α" nucleophiles. Also, the "charge" effect is useful in distinguishing between two effects, both related to proton basicity, in displacement of fluoride ion from GB. The lack of response of the "α" nucleophiles to the "charge" effect is considered evidence for (as Edwards and Pearson suggest[14]) an independent source in nucleophilicity.

Although one can state that there is a difference in the effectiveness of a cationic group on the reactivity of "α" and "non-α" nucleophiles, the reason for the difference is not immediately apparent. One can speculate that since the reactivity of an anion of a charged hydroxamic acid to a neutral substrate is reflected in the pK_a of its conjugate acid, whereas the reactivities of "non-α" nucleophiles are not, that the processes affecting ionization in the conjugate acids of the two nucleophiles are different. It has recently been suggested, for example, that the so-called "inductive" effect in the base-weakening effects of the trimethylammonio group on aniline may be a field effect.[19] The fact that m-aminophenyltrimethylammonium chloride is a weaker base than the para isomer is cited as evidence[20] that the trimethylammonio group does not exert a π-inductive effect. Likewise, in the phenol series, m-trimethylammoniumphenol is a stronger acid than the corresponding para isomer, suggesting that in the phenols also, the trimethylammonio group does not exert its effect via π induction. In contrast, the methiodide of isonicotinehydroxamic acid is a stronger acid than the methiodide of nicotinehydroxamic acid (Table I). It is therefore reasonable to postulate that the trimethylammonio group exerts a field effect in the phenols and a "π-inductive" effect in the hydroxamic acids.

Thus the trimethylammonio group will act as an electron sink in the hydroxamic acids; that is, there will be no electrostatic contribution by repulsion of the dissociating proton in the ionization of "α" acids. The cationic group, therefore, is no different in its action from any other electron-withdrawing group,

(14) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(15) Conceivably, the hydroxybenzenes may be considered to be partial "α" nucleophiles inasmuch as the α atom is conjugated with the β atom and hence partially "owns" an unpaired set of electrons. However, the hydroxybenzenes are classed as "non-α" nucleophiles because of the similarities in the nucleophilicities of their anions and the anions of alcohol and the hydrated aldehydes, whose classification as "non-α" nucleophiles is unequivocal. For example, Bruice, *et al.*, *Biochemistry*, **1**, 7 (1962), found in displacement of p-nitrophenol from p-nitrophenylacetate that phenols and aliphatic alcohols fall on the same line in a Brønsted plot; in displacement of fluoride ion from GB, anions of phenols and hydrated aldehydes of similar basicity have equal reactivities (*cf.* phenol $pK_a = 9.78$, $k_2 = 34$ l. mole^{-1} min^{-1}; with chloral, $pK_a = 9.95$, $k_2 = 32$ l. mole^{-1} min^{-1} (Table V)).

(16) For other examples of such treatment see R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965.

(17) An anion, whose conjugate acid has a $pK_a = 7.5$, has been selected since these calculations will be used to determine "charge"

effects in the keto oximes on compounds having pK_a values between 7 and 8.5 (Table IV).

(18) The Arrhenius activation energies for the reaction between GB and the anions of m-nitrophenol, p-nitrophenol, and m-hydroxybenzaldehyde are 11.3, 12.0, and 12.6, respectively (J. Epstein, Ph.D. Thesis, University of Delaware, 1966).

(19) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).

(20) J. D. Roberts, R. A. Clement, and J. J. Drysdale, *ibid.*, **73**, 2181 (1951).

e.g., NO₂, CN, etc. In the case of the acids of the nucleophiles of the phenol type, on the other hand, a substantial contribution to the ionization constant is made by electrostatic interaction of the cationic site and the proton, a repulsion of the latter assisting in its removal by the water molecules. Hence the basicity of the "α" nucleophile possessing a cationic charge to a neutral species will be reflected in its basicity to a proton (pK_a) and the reactivity of a "charged α" nucleophile is predictable from its pK_a.

Finally, it appears desirable to point out the implications of these conclusions on the general factors affecting nucleophilicity[14,21,22] and especially on the high reactivity shown by "α" nucleophiles.[14] In the anions of phenols and hydrated aldehydes, it is thought that the site of high electron density is highly localized in the nucleophile's oxygen,[23] whereas in the "α"

nucleophiles, it is felt that the electrons are highly mobile and distributed over several of the electronegative atoms.[24] The lack of mobility of the highly localized electrons is responsible for the relatively low slope (β) values[21] in the correlation equations of rate and pK_a of the "non-α" nucleophiles in their reactions with organophosphorus esters. (Higher slopes are obtained with such nucleophiles if other factors, such as H bonding, contribute to the formation of the transition state, *e.g.*, in catechol.) In contrast, the highly mobile electrons in the "α" nucleophile are much more available for transition-state bond formation and show generally higher slopes. It is interesting, too, in this connection that β for the anions of keto oximes, which it is postulated contain *some* "non-α" character, lies between that of the anions of phenols and those of hydroxamic acids.

(21) R. F. Hudson, *Chimia* (Aarau), **16**, 173 (1962).
(22) J. F. Bunnett, *Ann. Rev. Phys. Chem.*, **14**, 271 (1963).
(23) In apparent contradiction to the postulation that the electron density is localized on the phenolic oxygen, it is well known that phenols react with many electrophiles at ring positions rather than at the phenolate oxygen. indicating that there is a high electron density at the ring

positions. It is our feeling, however, that the high ring electron density results from the approach of the electron-deficient reactant; that in the presence of a localized substrate the distribution of electrons in the phenolate anions will be localized on the phenolic oxygen.
(24) See ref 12.

Secondary Deuterium Isotope Effects on a Cyclic Allylic Rearrangement[1]

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Abstract: Secondary α- and γ-deuterium isotope effects on the cyclic intramolecular rearrangement of allyl thionbenzoate to allyl thiolbenzoate have been measured. The α effect (1.06) is significantly smaller than that observed for (1.10–1.12) carbonium ion, carbanion, or radical pathways. With the γ effect (0.97), this result indicates that these effects are useful mechanistic criteria for allylic rearrangements. These results also indicate that the transition state structurally resembles reactant more than product, suggesting that this type of study will be useful in characterizing the position of a transition state along a reactant–product coordinate in such reactions.

Intramolecular allylic rearrangement reactions have occupied a position of considerable importance in the development of organic reaction mechanism theory.[2] Many of these reactions have been important in the study of carbonium ion processes[3] and others have been resistant enough to ordinary mechanistic probes to earn the sobriquet "no mechanism" reactions.[4]

It has long been recognized that a continuum of merging carbonium ion pair and cyclic mechanisms may connect these two classes of allylic rearrangements.[5] Since examples of carbanion and homolytic intramolecular allylic rearrangements are now known,[2,6] this

mechanistic continuum may be generalized to include, at the noncyclic limit, reactions of all three charge types, carbonium ion, radical, and carbanion, each merging with a cyclic reaction scheme at the other end of the continuum.

No satisfactory method for characterizing the mechanism of an intramolecular allylic rearrangement in terms of such a general cyclic to noncyclic continuum is presently available. A mechanistic criterion suited to this purpose should be insensitive to medium effects to permit its use in a wide variety of environments including the gaseous state. Methods for qualitatively placing a particular reaction along a carbonium ion cyclic continuum have been developed[7] and depend primarily on estimation of the polarity of the kinetically important transition state by means of kinetic solvent or substituent effects; reactions which are sensitive to polar effects are considered to involve carbonium ion pair mechanisms, and those which are insensitive are assigned cyclic mechanisms. The interpretation of

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) For a recent review, see P. B. D. de la Mare, "Molecular Rearrangements," P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 2.
(3) H. L. Goering, *Record Chem. Progr.*, **21**, 109 (1960), and later papers in this series.
(4) For a recent review, see S. J. Rhoads, ref 2, Chapter 10.
(5) S. Winstein, *Nature*, **173**, 898 (1954).
(6) G. S. Hammond and C. D. DeBoer, *J. Am. Chem. Soc.*, **86**, 899 (1964).
(7) S. G. Smith, *ibid.*, **83**, 4285 (1961).