[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, BIOCHEMICAL RESEARCH DIVISION, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

The Kinetics of the Reaction of Isopropyl Methylphosphonofluoridate (Sarin) with Substituted Benzohydroxamic Acids. II

BY RONALD SWIDLER,[1] ROBERT E. PLAPINGER AND GEORGE M. STEINBERG[2]

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The reaction between a series of *p*-substituted benzohydroxamic acids and sarin has been examined kinetically in near neutral aqueous solution and the results examined in terms of the Hammett relationship. The results obtained are consistent with a previously postulated reaction sequence involving an initial rate-determining attack on sarin by the hydroxamate anion followed by a Lossen rearrangement. The observed ρ-value of -0.76 is consistent with a gross mechanism involving the attack of an anion upon a neutral molecule but is inconsistent with a rate step involving the Lossen type of rearrangement (-2.5). Reaction between sarin and a wide variety of hydroxamic acids has been examined in terms of the Brönsted relationship. Good correlation was observed between rate and acidic dissociation, the relationship fitting the equation $\log k = 0.80(pK_A\text{-}14) + 5.55$. In reaction at constant pH in the presence of a large excess of hydroxamic acid, maximum rate is observed with an hydroxamic acid having $pK_A = p\text{H} + 0.60$.

In a previous communication[3] from these laboratories we have reported in detail the kinetics of the reaction between isopropyl methylphosphonofluoridate (sarin) and benzohydroxamic acid in near neutral aqueous media. These results established the initial phosphorylation of the benzohydroxamate ion (equation 1) as rate limiting.

$$(\mathrm{RCONHO})^- + \mathrm{PnX} \xrightarrow{k_1} \mathrm{RCONHOPh} + \mathrm{X}^- \quad (1)$$

$$\mathrm{RCONHOPn} + \mathrm{OH}^- \xrightarrow{k_{1a}} \underset{\mathrm{I}}{(\mathrm{RCONOPn})^-} \quad (1a)$$

$$\underset{\mathrm{I}}{(\mathrm{RCONOpn})^-} \xrightarrow{k_2} \mathrm{RNCO} + \mathrm{PnO}^- \quad (2)$$

$$\mathrm{RNCO} + (\mathrm{RCONHO})^- \xrightarrow{k_3} (\mathrm{RCONOCONHR})^- \quad (3)$$

where R = phenyl: Pn = $i\text{-PrO(CH}_3\text{)(P=O)}^-$

Both the ensuing Lossen rearrangement of I (equation 2) and the further reaction of the resultant isocyanate with another benzohydroxamate ion (equation 3) were demonstrated to be faster than the initial step. Since acid is produced in each of the steps, the contribution of each step to the rate profile could be determined by measuring the rate of production of acid ($\mathrm{d}Q_{\mathrm{acid}}/\mathrm{d}t$) at constant pH. Equation 4 was established as being correct for this system.

$$\mathrm{d}Q_{\mathrm{acid}}/\mathrm{d}t = k[\text{sarin}][\text{benzohydroxamate ion}] \quad (4)$$

As part of a program directed toward attaining a better understanding of the fundamental chemical behavior of organophosphorus compounds, and especially the inordinate reactivity of phosphono- and phosphorofluoridates toward the hydroxamate anion, we undertook a systematic study of the kinetics of the reaction of sarin with a series of readily accessible hydroxamic acids of widely varying structure.[4] From such a study we hoped to establish: (1) the value of comparing relative reactivities of a series of hydroxamic acids toward sarin by studying the rate of acid production, (2) the most probable mechanistic path for the reaction, (3) the Hammett ρ-value, and (4) the utility of a modified Brönsted equation in predicting which member of the family of hydroxamic acids would give the optimum rate of reaction with sarin.

Experimental

Reagents.—The synthesis of the *p*-substituted benzohydroxamic acids has been described.[5] Caprohydroxamic acid (m.p. 65°) was prepared from ethyl caproate following the procedure of Blatt for benzohydroxamic acid.[6] All acid samples were repeatedly crystallized and dried. All inorganic salts were of C.P. grade. Sarin[7] (99% purity) was obtained from the Chemical Research Division of these laboratories. It was stored in small vials in a desiccator. Purity was checked periodically by determining the quantity of free acid present in the sarin sample.

Kinetic Data.—As previously described[3] the rate of reaction of sarin with each hydroxamic acid was measured by recording the rate of addition of standard alkali to a reaction mixture (0.1 *N* potassium nitrate) maintained at a fixed *p*H by a Beckman autotitrator at a constant temperature of 30.5 ± 0.2°. An auxiliary set of electrodes was placed in the reaction beaker so that the *p*H could be verified with a Beckman model G *p*H meter. In all runs *ca.* 10-fold molar excess of the hydroxamic acid over sarin was maintained to obtain first-order kinetics.

The reaction was allowed to proceed to 4–5 half-times, a half-time being defined as the time in minutes necessary for 50% completion of the reaction. Each datum was then corrected for the previously determined blank change in acidity due to carbon dioxide absorption and autohydrolysis of the hydroxamic acid. The first-order rate constant for the corrected acid production was calculated by a least squares computation of the slope of the straight line obtained by the Guggenheim procedure.[8] Reaction half-times were maintained where feasible within the range of 7–20 minutes by adjustment of hydroxamic acid concentration. As discussed in an earlier paper,[3] shorter half-times lead to instrumental errors and with longer half-times a correction would have to be made for the parallel reaction of sarin with solvent which has a half-time of 250–300 minutes at *p*H 7.6.

With two exceptions satisfactory pseudo first-order plots were obtained over the time interval of the measurement.[9] One might have suspected a possible change in rate profile when electron-withdrawing groups were substituted on the benzohydroxamic acid moiety (*e.g.*, *p*-nitro) due to contribu-

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[1] Stanford Research Institute, So. Pasadena, Calif.

[2] To whom requests for reprints should be sent.

[3] R. Swidler and G. M. Steinberg, THIS JOURNAL, **78**, 3594 (1956).

[4] The results of a parallel study have been reported: A. L. Green, G. L. Sainsbury, B. Saville and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

[5] B. E. Hackley, Jr., R. Plapinger, M. Stolberg and T. Wagner-Jauregg, THIS JOURNAL, **77**, 3651 (1955).

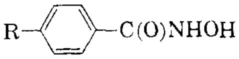
[6] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 67.

[7] Caution! Sarin is extremely toxic and should be handled in a fume hood of large capacity.

[8] E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

[9] In the case of mesitohydroxamic acid a satisfactory first-order relationship was not observed; however, in this case 5–6 moles of acid was produced instead of the usual 3. With caprohydroxamic acid the first-order plot remained perfectly linear for only 1–1.5 half-times, although the quantity of acid produced was the theoretical.

TABLE I



KINETICS OF THE REACTION OF *p*-SUBSTITUTED BENZOHYDROXAMIC ACIDS WITH SARIN IN AQUEOUS 0.1 *N* POTASSIUM NITRATE SOLUTION AT 30.5 ± 0.2° AND AT CONSTANT *p*H

R	*p*H	*p*K_A	$[HA]_{tot}$ × 10^4 M[a]	$[A^-]$ × 10^4 M[b]	[Sarin] × 10^4 M	k_{obs} × 10^4, sec.$^{-1}$[c]	*k*, l./mole sec.[d]
Methyl	7.58	8.93	6.00	0.27	0.52	7.17 (2)	26.5
	7.56		6.00	.26	.52	6.77 (2)	26.0
Methoxy	7.58	9.03	6.12	.22	.56	7.78 (2)	35.4
	7.78		3.06	.16	.56	5.63 (2)	35.2
	7.58		3.06	.11	.56	3.95 (2)	35.9
Fluoro	7.60	8.70	6.15	.45	.69	9.37 (3)	20.8
Nitro	7.57	8.01	6.12	1.63	.64	8.07 (2)	4.95
	7.38		6.12	1.18	.64	6.20 (2)	5.25
Cyano	7.60	8.16	6.12	1.32	.61	9.95 (2)	7.53
Hydrogen	7.60	8.80	6.39	0.38	.67	7.47 (2)	20.6

[a] Total concentration of the hydroxamic acid ($[HA]_{tot} = [HA] + [A^-]$). [b] Molar concentration of the hydroxamate ion. [c] Average k_{obs} from the number of identical runs given in parentheses. [d] $k = k_{obs}/[A^-]$ with average precision of 5–7%.

tion of the second step in the reaction sequence (equation 2). The results do not indicate such a change.

Ionization Constants.—The ionization constants of the *p*-substituted acids were determined by the simple expedient of half-neutralizing a 0.01 *N* solution of the acid in 0.1 *N* potassium nitrate and assuming the *p*K_A to be equal to the *p*H of the resulting solution.[10] In several cases confirmation was obtained by conventional potentiometric titration. The latter values checked closely (within 0.1 *p*K unit) with those obtained by half-neutralization; however, since ionic strength was not controlled, only the half-neutralization values are reported.

Results and Discussion

Under the conditions of this study, the hydroxamic acids were present in large excess and hence their concentrations remained substantially constant during the course of the reaction, so that the reactions were observed to follow first-order kinetics. Thus

$$k_{obs} = k[\text{hydroxamate ion}] \text{ and,} \qquad (5)$$

$$dQ_{acid}/dt = k_{obs}\,[\text{sarin}] \qquad (5a)$$

Hammett Relationship.—In Table I there are recorded the ionization constants and kinetic data for a series of *p*-substituted benzohydroxamic acids. Figure 1 is a conventional Hammett plot[11] of *p*K_A *vs.* σ and Fig. 2 a similar plot of log *k* *vs.* σ. The σ-values are taken from ref. 11b. The Hammett σ-values, together with their standard deviations (*s*), correlation coefficients (*r*) and log k_0 values have been calculated according to the methods suggested by Jaffé[12] and are given in Table II.

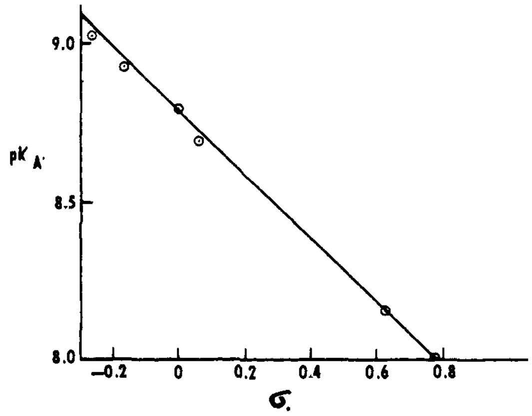


Fig. 1.—Hammett plot of *p*K_A *vs.* σ for *p*-substituted benzohydroxamic acids.

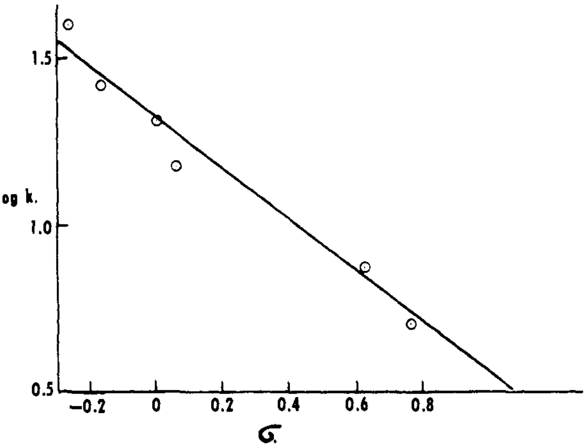


Fig. 2.—Hammett plot of log *k* (*k* is second-order rate constant in l./mole sec.) *vs.* σ for the reaction between sarin and a series of *p*-substituted benzohydroxamate anions.

TABLE II

p-SUBSTITUTED BENZOHYDROXAMIC ACIDS. HAMMETT ρ-VALUES FOR *p*K_A'S AND RATE CONSTANTS FOR REACTION WITH SARIN[a]

Solvent, 0.1 *N* KNO_3; temperature, 30°

	pK_A	Reaction rate constant, l./mole sec.
ρ	0.977	−0.762
s	.016	.035
r	.999	.996
n	6	6
−log k_0	8.773	−1.328

[a] For methods of calculation of *s*(standard deviation) and *r* (correlation coefficient), see ref. 12; *n* is the number of compounds involved in the calculation of ρ; −log k_0 is the intercept of the regression line with the ordinate, *i.e.*, at σ = 0.

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(10) For effect of concentration on observed *p*K_A, see ref. 3.

(11) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 186 ff.; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(12) Reference 11b, p. 253.

The ρ-value of -0.76 for the reaction rate is wholly inconsistent with a rate step involving the Lossen type of rearrangement (ρ-value *ca.* -2.5[13]), but is of the proper sign and order of magnitude for a step involving the attack of an anion upon a neutral molecule (*e.g.*, ρ-values for reaction of phenate ion with a series of neutral electrophilic reagents varies between -0.77 and -0.99[11b]). The excellence of fit of the Hammett plot for *p*-substituted benzohydroxamic acids over a rather wide range of σ-values suggests a mechanistic unity through the series. This, together with the excellence of the first-order plots obtained in the kinetic runs,[9] established the validity of the presently described method of comparing the relative reactivities of a series of hydroxamic acids with sarin by studying the rate of acid production at constant *p*H.

Brönsted Relationship.—In Table III there are presented kinetic and pK_A data for a number of aliphatic hydroxamic acids and several *o*-substituted benzohydroxamic acids. As indicated in Fig. 3, which contains data taken from Tables I and III, the hydroxamic acids not only fit a linear free energy relationship of the Hammett type but an even more general linear free energy relationship of the Brönsted type[14] (equations 6 and 6a)

$$k = G_B K_B{}^{\beta} = G_B\,(K_w/K_A)^{\beta} \qquad (6)$$

$$\log_{10} k = \log_{10} G_B + \beta(pK_A - 14) \qquad (6a)$$

(where k is the second-order rate constant as defined in eq. 4, G_B and β are constants which are fixed for a given reaction under defined reaction conditions (*i.e.*, temp., solvent); K_B and K_A are, respectively, the basic and acidic dissociation constants of the hydroxamate anion and its conjugate acid and K_w is the ionization constant of water. The excellent fit of the *o*-substituted compounds emphasizes the absence of proximity effects during the reaction[15]; see, however, footnote 9. The straight line in Fig. 3 is a plot of equation 6a, the values of the constants $\log G_B = 5.55$ (std. dev. = 0.105) and $\beta = 0.80$ (std. dev. = 0.02) were determined by a least squares calculation.

For practical purposes, such as chemotherapeutic activity, water purification, decontamination, etc., it may be important to obtain maximum rate of decomposition of the sarin. It is clear from Fig. 3 that maximum rate will be obtained by employing the most weakly acidic hydroxamic acid available and performing the reaction at a *p*H at which there is substantially complete dissociation, *i.e.*, $pH \geq pK_A + 2$.

However, if the choice of *p*H is limited so that dissociation of the weakly acidic congeners is incomplete, the compound of highest pK_A will not necessarily produce most rapid reaction. For purposes of comparison we may arbitrarily set conditions so that *p*H and $[HA_{Tot}]$ (the analytical concentration of hydroxamic acid, *i.e.*, $[HA_{Tot}] = [HA] + [A^-]$) are fixed and the hydroxamic

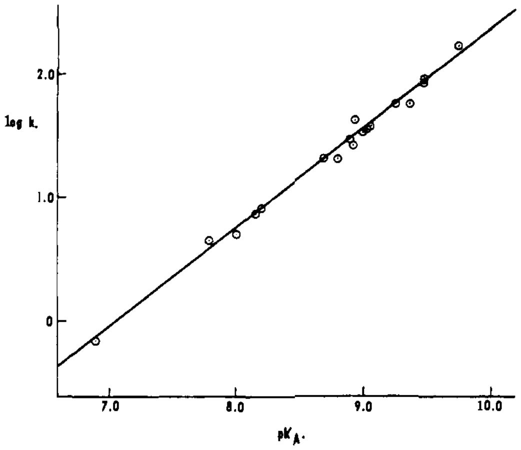

Fig. 3.—Relationship between log k (k is second-order rate constant in l./mole sec.) and pK_A for the reaction between sarin and the anions of a variety of hydroxamic acids.

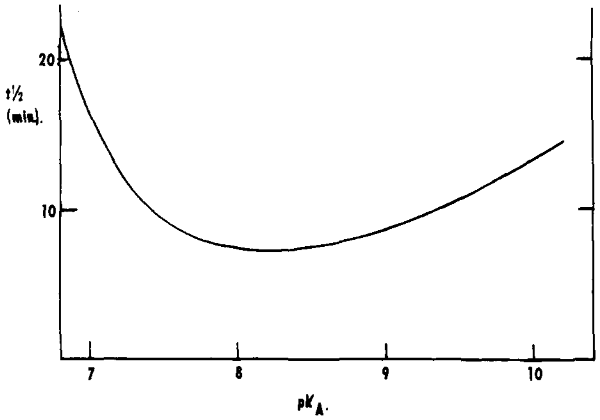

Fig. 4.—Relationship between reaction half-time ($t_{1/2}$) and pK_A; $[HA_{Tot}] = 10^{-3}\,M$, *p*H 7.6, 30°.

TABLE III

KINETICS OF THE REACTION OF SARIN WITH A VARIETY OF HYDROXAMIC ACIDS IN AQUEOUS 0.1 *N* POTASSIUM NITRATE SOLUTION AT 30.5 ± 0.2° AND *p*H 7.6[a]

Acid	pK_A	$k_{obs} \times 10^4$, sec.$^{-1}$	k, l./mole sec.[d]
o-Nitrobenzohydroxamic[b]	8.20	14.5	7.4
o-Aminobenzohydroxamic[b]	9.00	13.2	35.3
o-Hydroxybenzohydroxamic[b]	7.8[e]	17.8	4.6
o-Dimethylaminobenzohydroxamic[b]	9.05	12.8	37.5
Oxalodihydroxamic	6.90	5.9	0.707
vic-cis-Cyclohexanodihydroxamic[b]	9.75	11.7	168
Valerohydroxamic	9.37	9.6	57.5
Caprohydroxamic	9.48	11.0	84.3
ω-Hydroxydecanohydroxamic[c]	9.26	12.2	57.1
ω-Carbamidononanohydroxamic[c]	9.49	11.1	87.7
Gluconohydroxamic[c]	8.94	18.8	43.1
Crotonohydroxamic	8.90	(19.7)[f]	29.2

[a] In all runs the total concentration of the hydroxamic acid ($[HA] + [A^-]$) was $10^{-3}\,M$, while that of sarin was $10^{-4}\,M$. [b] Ref. 15. [c] These data made available by Dr. G. Endres. [d] $k = K_{obs}/[A^-]$. [e] The pK_A value is uncertain due to slight decomposition of the compound in alkali. [f] Hydroxamic acid concentration, $1.365 \times 10^{-3}\,M$; data made available by Dr. D. Rosenblatt.

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(13) R. F. Tietz and W. E. McEwen, THIS JOURNAL, **77**, 4007 (1955).

(14) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 209 ff.

(15) This matter has been discussed in greater detail in a publication by M. A. Stolberg, W. A. Mosher and T. Wagner-Jauregg, THIS JOURNAL, **79**, 2618 (1957).

acid is in sufficient excess over sarin so that its concentration remains substantially constant during the course of reaction. Under these conditions, the reaction rate, k_{obs}, can be calculated from equation 7 which is derived from equations 5 and 6.[16]

$$k_{\mathrm{obs}} = \frac{G_{\mathrm{B}}[\mathrm{HA_{Tot}}]\ K_{\mathrm{A}}}{[\mathrm{H}^+] + K_{\mathrm{A}}} \left(\frac{K_{\mathrm{w}}}{K_{\mathrm{A}}}\right)^{\beta} \mathrm{sec.}^{-1} \qquad (7)$$

Substituting numerical values for G_{B} and β established above, we obtain

$$k_{\mathrm{obs}} = \frac{3.5 \times 10^{-9}\ [\mathrm{HA_{Tot}}]\ K_{\mathrm{A}}^{0.20}}{[\mathrm{H}^+] + K_{\mathrm{A}}}\ \mathrm{sec.}^{-1} \qquad (7a)$$

As an example, we have plotted in Fig. 4 the quantitative relationship between reaction half-time ($t_{1/2} = 0.693/k_{\mathrm{obs}}$) and hydroxamic acid pK_{A} at $[\mathrm{HA_{Tot}}] = 10^{-3}$ *M*, and at *p*H 7.6, under the stipulated conditions.

The general relationship between pK_{A} and *p*H for *maximum reaction rate at fixed p*H, equation 8, can be derived from equation 7 by integration of the expression $\mathrm{d}k_{\mathrm{obs}}/\mathrm{d}K_{\mathrm{A}} = 0$. For the reaction

$$pK_{\mathrm{A}} - p\mathrm{H} = \log \frac{\beta}{1 - \beta} \qquad (8)$$

under consideration in the present study, where the value of $\beta = 0.80$, maximum rate will be obtained with the hydroxamic acid of $pK_{\mathrm{A}} = p\mathrm{H} + 0.60$.

Acknowledgments.—We would like to express our appreciation to Mr. Omer O. Owens and Dr. Brennie E. Hackley, Jr., for their assistance, and Dr. Gerard Endres and Dr. David Rosenblatt for having provided us with unpublished data.

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(16) For derivation and discussion of these relationships, see J. Epstein, D. E. Rosenblatt and M. Demek, THIS JOURNAL, **78**, 341 (1956), and G. M. Steinberg, R. Swidler and S. Seltzer, *Science*, **125**, 336 (1957). Similar relationships have been developed independently by A. L. Green, G. L. Sainsbury and M. Stansfield, private communication.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

An Acidity Function for the Solvent System Consisting of 20 Vol. % Ethanol and 80 Vol. % Sulfuric Acid–Water Mixtures[1]

BY SI-JUNG YEH AND H. H. JAFFÉ

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A series of 32 mono- and disubstituted derivatives of azobenzene was used to establish an H_0 scale in the solvent system 20% ethanol–80% sulfuric acid–water mixture. *o*- and *p*-nitroaniline were used to connect this scale to potentiometrically measured *p*H's. The scale extends from dilute solution to 19 *N* acid. The scale is of particular interest since the indicators used are structurally closely related, and the B/BH^+ *vs.* acid concentration curves for the various indicators are almost exactly parallel in the overlap regions. The scale is compared with the H_0 scale in aqueous sulfuric acid.

The H_0 function originally introduced by Hammet and co-workers[2] is a tremendously useful acidity scale for the measurement of base strengths of weak, uncharged bases in aqueous acids, because it provides a quantitative measure of the ability of the aqueous solution under consideration to transfer a proton to the uncharged base. The H_0 functions for aqueous solutions of various strong acids have been established by the use of series of different indicators such as the derivatives of aromatic amines.[3] A basic requirement for the validity of an acidity function is that the plot of log $(\mathrm{B}/\mathrm{BH}^+)$ *vs.* acid concentration be parallel for all indicators used in the regions of overlapping acid concentrations in which measurement of log $(\mathrm{B}/\mathrm{BH}^+)$ is experimentally possible.[3] This condition has rarely been met in the past. It has been suggested that the use of structurally closely related indicators would greatly aid in achieving this ideal.[2,3]

Many weak organic bases are insufficiently soluble in dilute aqueous acid for convenient measurements of the *pK* by a spectrophotometric method, but addition of a small amount of an organic solvent, *e.g.*, ethanol, permits such measurements. Although the concept of the H_0 function can be extended to mixed solvent systems, the addition of a solvent with low dielectric constant to the aqueous acid also raises a problem as to the validity of the H_0 function in such mixed solvent systems.

The H_0 function for solutions of hydrochloric acid in ethanol has been studied by Braude[4] up to 1 *M* acid concentration using a single indicator, *p*-nitroaniline. Braude and Stern[5] have extended this study to a mixed solvent system containing varying proportions of ethanol at fixed hydrochloric acid concentrations of 0.1 *M* and 1 *M*, and have reported that, with increasing ethanol concentration, H_0 goes through a minimum at equimolar proportion of the two solvent. Grunwald and co-workers[6] have measured the *pK*'s of various uncharged bases in ethanol and water mixtures by a potentiometric method, and found that the *pK*'s in the mixed solvents are significantly different from the values in pure water; *e.g.*, the *pK* of aniline goes from 4.64 in pure water to 4.16 in 35 wt. % ethanol, passes through a minimum of 3.75 at 80 wt. % ethanol and increases to 5.70 in pure ethanol. These data demonstrate that the *pK* values are dependent on the solvent system and that for the measurement of the *pK* of a weak un-

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(1) This work was supported by a Bonita Geho Memorial Grant for Cancer Research from the American Cancer Society. This support is gratefully acknowledged.

(2) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932).

(3) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

(4) E. A. Braude, *J. Chem. Soc.*, 1971 (1948).

(5) E. A. Braude and E. S. Stern, *ibid.*, 1976 (1948); E. A. Braude and E. S. Stern, *Nature*, **161**, 169 (1948).

(6) E. Grunwald and B. J. Berkowitz, THIS JOURNAL, **73**, 4939 (1951); E. Gutbezahl and B. Grunwald, *ibid.*, **75**, 559 (1953); **75**, 565 (1953).