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The Basicities of Substituted Pyridines and their 1-Oxides

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The basicities of a series of substituted pyridines and pyridine 1-oxides have been determined; it is shown that the data are well represented by the Hammett equation with ρ-values of 5.71 and 2.09, respectively. The applicability of the Hammett equation to the prediction of the effects of substituents on the reactivity of heterocyclic aromatic compounds is discussed.

It has recently been suggested that the effect of replacing a $>$CH group in benzene by a heteroatom, *e.g.*, $>$N,[2] or by a substituted heteroatom, *e.g.*, $>$N$^+$—O$^-$,[3] can be expressed in terms of the Hammett equation,[4] and substituent constants for these two groups have been proposed. The present paper deals with the question whether the above procedure can be reversed, *i.e.*, whether the Hammett equation can be used to predict the effect of substituents on the reactivity of the heteroatom, or of a side-chain attached to the heteroatom in a heterocyclic aromatic compound. Unfortunately, few experimental data on the reactivity of simple monosubstituted monocyclic heterocyclic compounds have been reported.

The basicities of several substituted pyridines are found in the literature.[5] We have further determined the basicities of several additional derivatives of pyridine by potentiometric titration, and have redetermined some of the literature values to ensure a consistent series for the application of the Hammett equation. The experimental data are listed in Table I,[6] and are plotted against substituent constants (σ) in Fig. 1.

In order to test the applicability of the Hammett equation to a reaction of a sidechain attached to the heteroatom, we have determined the basicities of a series of 3- and 4-substituted pyridine 1-oxides. These data were obtained by a standard spectrophotometric method[7]; the results are tabulated in Table II, and are plotted against substituent constants in Fig. 2. A further reason for undertaking this investigation was our desire to gain additional information concerning the tautomeric equilibria in 4-amino- and 4-hydroxypyridine 1-oxides[3,8]; and in the pyridine 3- and 4-carboxylic acids[5b,e]; none of these equilibria had been completely elucidated. These equilibria will be discussed in detail in the following paper.[9]

Discussion[10]

Figures 1 and 2 show that, to a reasonable approximation, the Hammett equation represents the

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[1] Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio.

[2] (a) H. H. Jaffé, *J. Chem. Phys.*, **20**, 1554 (1952); (b) *cf.* also R. C. Elderfield and M. Siegel, THIS JOURNAL, **73**, 5622 (1951); M. Simonetta and G. Favini, *Gazz. chim. ital.*, **84**, 566 (1954).

[3] H. H. Jaffé, THIS JOURNAL, **76**, 3527 (1954).

[4] (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[5] (a) A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948); (b) E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 410 (1949); (c) *ibid.*, 414 (1949); (d) H. H. G. Jellinek and M. G. Wayne, *ibid.*, **55**, 173 (1951); (e) H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, **58**, 548 (1954); (f) C. Golumbic and M. Orchin, THIS JOURNAL, **72**, 4145 (1950); (g) E. F. G. Herington, *Discs. Faraday Soc.*, **9**, 26 (1950); (h) R. F. Evans, E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953); (i) H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan*, **73**, 140 (1953).

[6] Throughout this paper basicities are expressed in terms of the pKa's of the conjugate acids.

[7] (a) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932); (b) L. P. Hammett and M. A. Paul, *ibid.*, **56**, 827 (1934); (c) Ref. 4a, p. 267.

[8] E. Shaw, THIS JOURNAL, **71**, 67 (1949).

[9] H. H. Jaffé, *ibid.*, **77**, 4445 (1955).

[10] At this point we shall assume that the assignments of pK's made in Tables I and II for the compounds possessing two functional (acidic or basic) groups are correct. The assignments will be justified in the following paper, *cf.* ref. 9.

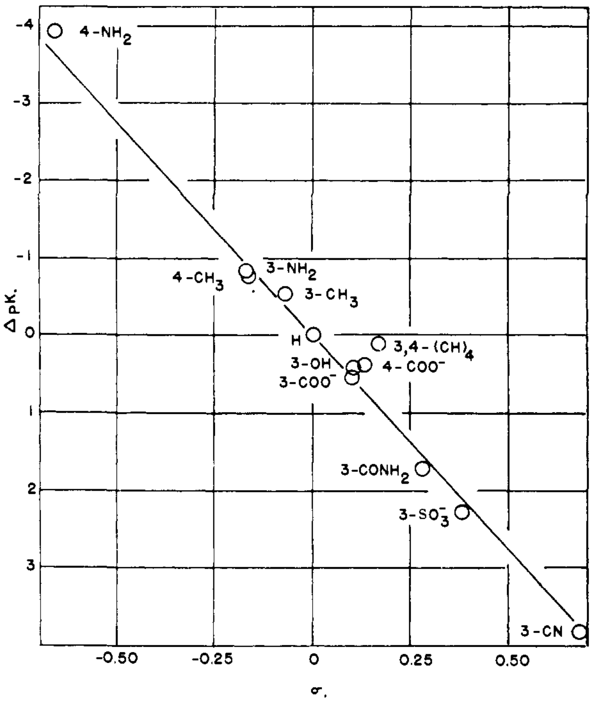


Fig. 1.—Plot of the relative pK's of the conjugate acids of substituted pyridines against substituent constants.

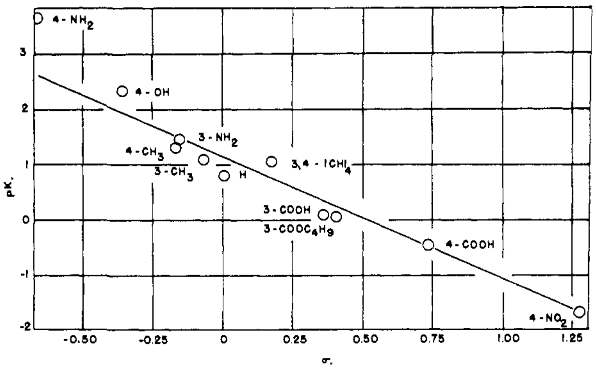
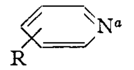


Fig. 2.—Plot of the pK's of the conjugate acids of substituted pyridine 1-oxides against substituent constants.

TABLE I

THE BASICITIES OF SUBSTITUTED PYRIDINES



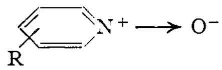
(Determined in water at 23–25°.)

R	σ[b]	pK	ΔpK[c]
4-NH$_2$[d]	−0.660	9.17[e]	−3.94[e]
4-CH$_3$	− .170	6.11	−0.82[f]
3-NH$_2$[g]	− .161	6.09	− .80[h]
3-CH$_3$	− .069	5.82	− .53[i]
H	0	5.29[j]	0
3-OH[k]	+0.102[l]	4.86	+0.43
3-COO$^-$[m]	.104	4.77	.52[n]
4-COO$^-$[o]	.132	4.90	.39[p]
3-NHCOCH$_3$	(.154)[q]	4.43	.86
3,4-(CH$_4$)[r]	.170	5.4[s]	.1[s]
3-CONH$_2$	.280	3.40[t]	1.72[t]
4-CONH$_2$	(.267)[q]	3.61[u]	1.51[u]
3-SO$_3^-$	.381	2.9[v]	2.3[v]
3-CN	.678	1.45	3.84

[a] *Cf.* footnotes 6 and 10. [b] Substituent constants, *cf.* ref. 4b. [c] The difference $\Delta pK = pK_{\text{pyridine}} - pK_{\text{substd.pyridine}}$ where both values refer to work of the same authors, and under the same experimental conditions, is given here and used in the plot in Fig. 1 and the calculations of the reaction constants in Table III in order to minimize difficulties arising out of the different values for pK_{pyridine} obtained in different studies. [d] $pK_1 = -6.77$, *cf.* ref. 5i. [e] From ref. 5a. [f] From ref. 5f we calculate $\Delta pK = -0.6$, from ref. 5g, −0.70. [g] $pK_1 = -1.3$[v]. [h] From ref. 5a we calculated $\Delta pK = -0.75$. [i] From ref. 5f we calculate $\Delta pK = -0.3$, from ref. 5 g, −0.56. [j] Ref. 5a gives 5.23 (potentiometric), ref. 5b, 5.12 (spectroscopic), ref. 5f, 5.5 (by distribution between solvents), ref. 5g, 5.16 (spectrophotometric). [k] $pK_2 = 8.68$, hence σ-(m-N$\leqslant$) = 0.547. [l] For H$_2$O; *cf.* Table 12, ref. 4b. [m] $pK_1 = 2.09$; ref. 5c gives $pK_1 = 3.55$, ref. 5h, $pK_1 = 2.09$; this discrepancy will be discussed in the following paper, *cf.* ref. 9. [n] From ref. 5c we calculate $\Delta pK = 0.28$, from ref. 5h, 0.41. [o] $pK_1 = 1.80$, ref. 5e gives $pK_1 = 1.70$, ref. 5h gives $pK_1 = 1.82$. [p] From ref. 5e we calculate $\Delta pK = 0.17$, from ref. 5 h, 0.38. [q] Calculated from this reaction series. [r] Isoquinoline. [s] From ref. 5f. [t] From ref. 5d. [u] From ref. 5e. [v] This determination was not completely satisfactory; the value is reliable only to ±0.15 unit.

TABLE II

THE BASICITIES OF SUBSTITUTED PYRIDINE 1-OXIDES,[a]



(Determined in water at 23–25°.)

R	σ[b]	λ, mμ[c]	pK
4-NH$_2$[d]	−0.660	...	3.65[e]
4-OH[f]	− .357	...	2.36[e]
4-CH$_3$	− .170	256	1.29
3-NH$_2$	− .161	234	1.47[g]
3-CH$_3$	− .069	252	1.08
H	0	252	0.79
3,4-(CH)$_4$[h]	0.170	234, 250	1.01
3-COOH[i]	.355	257	0.09
3-COOC$_4$H$_9$	.398[j]	257	0.03
4-COOH[k]	.728	273	−0.48
4-NO$_2$	1.270	245, 313	−1.7[l]

[a] *Cf.* footnotes 6 and 10. [b] Substituent constants from ref. 4b. [c] The wave length used for the determination. [d] $pK_1 = -6.27$, *cf.* ref. 5i. [e] By potentiometric titration. [f] $pK_2 = 5.80$, *cf.* ref. 3. [g] $pK_1 = -2.1$, $\lambda = 216$ mμ. [h] Isoquinoline 2-oxide. [i] $pK_2 = 2.73$, *cf.* ref. 3. [j] The value for m-COOC$_2$H$_5$. [k] $pK_2 = 2.86$, *cf.* ref. 3. [l] *Cf.* footnote v, Table I.

effects of substituents on the reactivity of the heteroatom and of the side-chain attached to the heteroatom. The relevant reaction constants (ρ) and the usual measures of the precision[4b] with which the data are represented by the Hammett equation are given in Table III. Examination of Figs. 1 and 2, and of Table III, however, indicates that elimination of the points for the 4-hydroxy-, 4-amino- and 3,4-(CH)$_4$-groups leaves the data appreciably better represented by the Hammett equation. This fact is not surprising since it has been found previously[4b] that the p-hydroxy- and p-dimethylamino groups, in reactions of strongly electron attracting side-chains, should be assigned substituent constants smaller (more negative) than the normal values. The same conclusion is probably valid for the p-amino group; further the $\geqslant N^+$—H- and $\geqslant N^+$—OH-groups are among the most electron attracting "side-chains" which can be visualized (*cf.* the substituent constants for these groups listed in

TABLE III

REACTION CONSTANTS FOR THE REACTIVITY OF SUBSTITUTED PYRIDINES AND PYRIDINE 1-OXIDES[m]

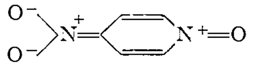
Reaction	Solvent	T, °C.	ρ	s[a]	r[b]	n[c]	Ref.
pK $RC_5H_4NH^+$	H_2O	~25	5.714[d]	0.296	0.989	12	[e]
			(5.685[f]	.147	.995	10[g]	[e])
pK $RC_5H_4NOH^+$	H_2O	~25	2.571[h]	.381	.967	11	[e]
			(2.088[i]	.121	.994	8[j]	[e])
$RC_5H_4N + 2\text{-Cl-3-}NO_2C_5H_3N \rightarrow$	99.8%	50	−2.777	.045	.991	3	11
$2\text{-}RC_5H_4N^+\text{-3-}NO_2C_5H_3N$	C_2H_5OH	60	−2.555	.033	.994	3	11
		70	−2.614	.050	.988	3	11
$RC_5H_4N + 2\text{-Cl-5-}NO_2C_5H_3N \rightarrow$	C_2H_5OH	50	−2.807	.091	.966	3	11
$2\text{-}RC_5H_4N^+\text{-5-}NO_2C_5H_3N$		60	−2.820	.031	.996	3	11
$RC_5H_4N + 2\text{-}NO_2\text{-4-}ClC_5H_3N \rightarrow$	C_2H_5OH	20	−2.655	.024	.997	3	11
$4\text{-}RC_5H_4N^+\text{-2-}NO_2C_5H_3N$		30	−2.494	.013	.999	3	11
$RC_5H_4N + 2,4\text{-}(NO_2)_2C_6H_3Cl \rightarrow$	C_2H_5OH	50	−2.835	.040	.993	3	11
$2,4\text{-}(NO_2)_2C_6H_3N^+C_5H_4R$							
$RC_5H_4N + CH_3I \rightarrow RC_5H_4N^+CH_3I^-$	$C_6H_5NO_2$	30	−1.266	.105	.663	8	12
Shift of 2689 cm.$^{-1}$ band of CH_3OD[k]	RC_5H_4N	25	−0.0191	.0005	.990	4	13
Heat of mixing of RC_5H_4N with CH_3Cl[l]	..		−0.738	.029	.976	4	13
$RC_5H_4N + C_2H_5I \rightarrow RC_5H_4N^+C_2H_5I^-$[n]	$C_6H_5NO_2$	60	−1.284	.087	.736	8	12
$RC_5H_4N + (CH_3)_2CHI \rightarrow$							
$RC_5H_4N^+CH(CH_3)_2I^-$[n]	$C_6H_5NO_2$	80	−1.073	.065	.772	8	12
$RC_5H_4N + Ag^+ \rightarrow RC_5H_4N^+Ag$[n]	H_2O	25	−2.067	.335	.901	11	[o]

[a] The standard deviation from the regression line. [b] The correlation coefficient. [c] The number of compounds entering the determination of ρ. [d] s_ρ (the standard error of ρ) = 0.271; $-\log k^0 = -0.104$, based on ΔpK values, *cf.* Table I. [e] This investigation. [f] $s_\rho = 0.187$; $-\log k^0 = -0.017$. [g] Omitting values for 4-NH_2 and 3,4-$(CH)_4$. [h] $s_\rho = 0.240$; $-\log k^0 = 1.223$. [i] $s_\rho = 0.068$; $-\log k^0 = 0.935$. [j] Omitting values for 4-NH_2, 4-OH and 3,4-$(CH)_4$. [k] In order to make ρ and s_ρ dimensionless, $\Delta\nu/\nu^0$ was correlated with σ, where $\Delta\nu$ is the band shift, and $\nu^0 = 2476$ cm.$^{-1}$ is the wave number of the band in pyridine (R = H) as solvent; *cf.* ref. 4b. [l] In order to make ρ and s_ρ dimensionless, $\Delta H/\Delta H^0$ was correlated with σ, where ΔH and ΔH^0 are the heats of mixing using substituted and unsubstituted pyridine, respectively. [m] ADDED IN PROOF.—Since this paper was accepted for publication, H. C. Brown and X. R. Mihm, THIS JOURNAL, **77**, 1723 (1955), have reported the pK's of several alkyl-substituted pyridines. For the picolines, their ΔpK values are in excellent agreement with ours. Addition of the remainder of their data to the correlation leads to: $\rho = 5.623 \pm 0.231$, $r = 0.987$, $s = 0.268$, $n = 17$. [n] ADDED IN PROOF. [o] R. K. Murmann and F. Basolo, THIS JOURNAL, **77**, 3484 (1955).

the following paper).[9] It has also been noted previously that the group 3,4-$(CH)_4$ has an especially high polarizability,[4b] and consequently it is not surprising to find that this group requires a σ-value smaller than normal opposite the highly electron attracting reaction centers encountered in this work. An indication of the magnitude of these effects is obtained by using reaction constants calculated with omission of the three groups in question (*cf.* Table III) to derive substituent constants for these groups. The following values are obtained in this manner: from the basicities of the pyridines: 4-NH_2, $\sigma = -0.681$; 3,4-$(CH)_4$, $\sigma = 0.022$; from the pyridine 1-oxides: 4-NH_2, $\sigma = -1.28$; 4-OH, $\sigma = -0.67$; 3,4-$(CH)_4$, $\sigma = -0.03$. The effect in 4-aminopyridine is unexplainably small. It is interesting to note that isoquinoline 2-oxide is actually a stronger base than pyridine 1-oxide, so that the 3,4-$(CH)_4$-group has a base strengthening effect in this case, instead of its normal base weakening or acid strengthening effect.

The magnitudes of the reaction constants in Table III deserve some comment. The values of ρ for the dissociation of the 1-hydroxypyridinium ions ($\rho = 2.09$) and of phenols ($\rho = 2.11$)[4b] are not significantly different. This fact is not surprising since it might have been anticipated that electronic effects are transmitted equally well through the isoelectronic groups $\rangle C—O—$ and $\rangle N^+—O—$. The value $\rho = 5.7$ for the dissociation of the pyridinium ions is of the same order of magnitude as values for heterolytic reactions involving nuclear substitution ($|\rho| = 3.9–5.9$).[4b] This result also might have been anticipated, since the bond broken in the dissociation of pyridinium ion is a bond to a ring atom.

Figure 2 is plotted on the basis of the assumption that the application of the Hammett equation to the pyridine 1-oxides requires the use of σ^*-values,[4b] and these values were used in the calculations of the reaction constants listed in Table III. This assumption is justified by the fact that the $\rangle N^+—O^-$ group, although strongly electron attracting, can also act as an electron source due to the importance of resonance structures such as I.[3]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Thus, it can be concluded that the Hammett equation very adequately represents the basicities of substituted pyridines and their 1-oxides. There is no reason to believe that it should not equally apply to other reactions of these and similar compounds. Partial confirmation of this view is found in the rates of the reaction of pyridine and β- and γ-picoline with 2-chloro-3-nitro-, 2-chloro-5-nitro- and 3-nitro-4-chloropyridine, and with 2,4-dinitrochlorobenzene.[11] All of these reaction series, although each only has three members, obey the Hammett equation well, with ρ-values between −2.1 and −2.8 (*cf.* Table III). The reactions of pyridine

[11] E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 3392 (1953); R. R. Bishop, E. A. S. Cavell and N. B. Chapman, *ibid.*, 437 (1952).

and some of its alkyl derivatives with methyl iodide have also been measured.[12] Unfortunately, the range of rate constants is so small that the data do not permit any definite conclusions. The rates of all the 3- and 4-alkylpyridines are almost identical but differ appreciably from the value for pyridine itself. The reaction constant is given in Table III, with the usual measures of the precision with which the data are represented. Finally, the electron donor ability in hydrogen bond formation of several substituted pyridines has recently been determined by measurement of the infrared frequency of the OD band of methanol-*d* in various pyridines as solvent, and by measurement of the heat of mixing of the same compounds with chloroform.[13] Both sets of data are well represented by the Hammett equation; the relevant reaction constants are listed in Table III.

Experimental

Materials.—3-Hydroxy- and 3-cyanopyridine, *n*-butyl nicotinate and sodium 3-pyridine sulfonate were kindly furnished to us by the Nepera Chemical Company. γ-Picoline was kindly furnished by the Carbide and Carbon Chemicals Company. Isonicotinic acid was obtained from Dr. R. L. McKee, Department of Chemistry, University of North Carolina. γ-Picoline was distilled and the center fraction used; the other compounds were not further purified. The melting points of 3-hydroxy- and 3-cyanopyridine and the boiling point of γ-picoline were in agreement with literature values. The identity of *n*-butyl nicotinate was checked by analysis (calcd. sapon. no. 179.3; found 173.3).

Pyridine Oxides.—The 1-oxides of pyridine, β-picoline, *n*-butyl nicotinate and the 2-oxide of isoquinoline were prepared by direct oxidation of the corresponding bases with hydrogen peroxide.[14] 4-Picoline 1-oxide was kindly furnished us by the Reilly Tar and Chemical Company. Pyridine 1-oxide was nitrated to 4-nitropyridine 1-oxide and reduced catalytically to the amino compound with palladium-on-charcoal.[14] The compound was isolated as the hydrochloride (*Anal.* Calcd.: N, 19.1. Found: N, 18.6). 4-Hydroxypyridine 1-oxide was prepared from the 4-nitro compound according to Ochai's directions.[14] (*Anal.*: N, 12.61. Found: N, 12.57.)

3-Picoline 1-Oxide Hydrochloride.—This compound has been described previously,[15] but it is not clear from the abstract that this compound was characterized. β-Picoline was oxidized with hydrogen peroxide in glacial acetic acid in the usual manner,[14] and the oxide distilled. It boiled at 91–105° (0.15 mm.) and did not crystallize on long standing. It was converted to the hydrochloride, which was recrystallized from alcohol. The yield (based on β-picoline) was 41%.

Anal. Calcd.: neut. equiv., 145.6. Found: neut. equiv., 146.9.

***n*-Butyl nicotinate 1-oxide** has not been prepared previously. It was obtained as an oil, b.p. 135–139° (0.16 mm.), which solidified on standing in the desiccator; yield 73%.

Anal. Calcd. for $C_{10}H_{13}O_3N$: sapon. no., 195.21. Found: sapon. no., 192.66.

3-Acetylaminopyridine 1-Oxide.—3-Acetylaminopyridine[16] was oxidized in glacial acetic acid with hydrogen peroxide by the general procedure of Ochiai.[14] The acetic acid was evaporated *in vacuo;* the residual oil crystallized upon treatment with ether. The crude compound was extracted with hot chloroform; the crystals which separated on cooling were combined with the chloroform insoluble residue, and the combined material was recrystallized twice with acetone. The yield was 26%; m.p. 215.5–216.5°.

From the chloroform mother liquor and the ether used in testing the original oil some starting material could be recovered, which indicated that the original oxidation had not been complete.

3-Aminopyridine 1-Oxide Hydrochloride.—3-Acetylaminopyridine was heated for four hours with 10% sodium hydroxide. The solution was neutralized to *p*H 6.3 with hydrochloric acid and then evaporated to dryness *in vacuo.* The residue was extracted with absolute alcohol; the solution was treated with charcoal, and, after filtration, a few drops of concentrated hydrochloric acid were added. A small amount of the sodium chloride precipitated and was removed by filtration. The desired compound crystallized upon the addition of ether. Recrystallization, by solution in alcohol followed by the addition of ether, failed to affect the neutral equivalent.

Anal. Calcd. for C_5H_6ON: neut. equiv., 146.58; N, 19.11. Found: neut. equiv., 153.3; N, 18.96.

***pK* Determinations.**—The *pK*'s of the substituted pyridines and of 4-amino- and 4-hydroxypyridine 1-oxide were determined by potentiometric titration in 0.04 *M* aqueous solution. The *pK*'s of the remaining compounds and the second *pK* of 3-aminopyridine, were determined by the method of Hammett and Deyrup[7a] in approximately 5×10^{-5} *M* solution in aqueous sulfuric acid. The spectra of the compounds are reported elsewhere.[17] The H_0 values of Hammett and Deyrup were used, corrected as indicated by Hammett and Paul.[7b] *p*H determinations (with a glass electrode) of some of the most dilute solutions of sulfuric acid indicated that the H_0 scale used actually merged into the *p*H scale. Hence, values obtained by the spectrophotometric method were comparable with the potentiometric values[18] except for a small uncertainty arising from the difference in concentration used in the two methods; however, it is doubtful that the uncertainties so introduced are larger than those inherent in the use of the acidity function. *pK*'s were reproducible to less than ±0.05 unit.

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[12] H. C. Brown and A. Cahn, THIS JOURNAL, **77**, 1715 (1955).

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[14] E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

[15] E. Ochiai, M. Ikehara, T. Kato and N. Ikekawa, *J. Pharm. Soc., Japan*, **71**, 1385 (1951); *C. A.*, **46**, 7101 (1952).

[16] R. Camps, *Arch. Pharm.*, **240**, 345 (1902).

[17] H. H. Jaffé, THIS JOURNAL, **77**, 4451 (1955).

[18] *Cf.* J. M. Vandenbelt, C. Henrich and S. G. Vanden Berg, *Anal. Chem.*, **26**, 726 (1954).