# The Protonation of Indoles. Basicity Studies. The Dependence of Acidity Functions on Indicator Structure[1]

BY R. L. HINMAN AND J. LANG

Indicator ratios of indole and 24 of its derivatives have been measured in sulfuric acid using an ultra-violet absorption technique. A few examples have also been determined in perchloric acid. Despite the close structural similarity of the bases, the slopes (d log $I/dC_{acid}$) of the indicator ratio plots fell into three groups, corresponding to three structural types: those like indole itself which are unsubstituted in the hetero ring, those which are 1,3-disubstituted by alkyl groups, and all others which have any other variation of alkyl substitution in the hetero ring. The slopes of the indicator ratio plots of all three groups differ significantly from those of indicators of previously established indicator classes: $H_0$, $H_R$, and $H'_R$. From the acidity constants of the largest class of indoles values of a new acidity function, $H_1$, have been determined, which is a measure of the ability of the medium to donate a proton to an alkylindole. The effects of substituents on the acidity constants of the largest class of bases appear to be constant with position of substitution. From these substituent values a method is proposed for determining relative base strengths of indoles which do not obey the $H_1$ function.

The weakly basic character of indoles has long been known and is a fact of considerable theoretical interest. However, there have been no reports of adequate quantitative measurements of the basicity of indole itself nor of the variations in basicity that accompany ring substitution,[2] information we required in connection with other studies on the behavior of indoles in acidic media.[3] In attempting to determine basicities in the indole series, we have encountered a number of problems which have important consequences for the general question of measuring base strengths under the nonideal conditions of strongly acidic media.

To determine relative base strengths of very weak bases it is sufficient to compare the acid concentrations at which some common extent of protonation occurs. The titration curves constructed for this purpose give the relative base strengths directly in the nonideal media under study. However, if quantitative data are desired, it has been customary to use the method of Hammett which was intended to provide acidity constants on a scale which is an extension of the pH scale. In contrast to the titration curves, the acidity constants are measures of the extent of protonation in dilute aqueous solution. Questions as to the validity and utility of these numbers as obtained by the Hammett method have been raised and are discussed in this paper. However, since such acidity constant values are of a familiar type, which is readily handled, and since no satisfactory substitute has been put forth, the standard approach to obtaining these values was followed in the present work.

For very weak uncharged bases which undergo monoprotonation in concentrated acids according to $BH^+ \rightleftarrows B + H^+$, acidity constants can be expressed in terms of the acidity function $H_0$ in eq. 1, where $I$ is the indicator ratio $C_{BH^+}/C_B$ and $H_0 = -\log (a_{H^+}f_B/f_{BH^+})$.[4,5]

$$pK_a = H_0 + \log I \qquad (1)$$

The indoles appeared suitable for this type of treatment because in concentrated acids they undergo exclusively monoprotonation, as shown in eq. 2.[3c] Protonation is accompanied by a marked decrease in the intensity of the ultraviolet absorption maximum of the free base near 220 m$\mu$[3a,c] (Fig. 1), affording a method of determining the indicator ratio. However, when

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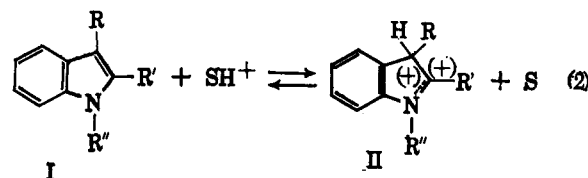
log $I$ was plotted against $H_0$, the slopes for the various indoles differed significantly from the value of unity required by eq. 1.[2] The indoles also deviated from $H'_R$, the acidity function which has been developed[6] for arylolefins to which the indoles bear some structural resemblance.

**Indicator Ratio Plots.**—Hammett demonstrated[7] that in regions of overlap of indicator ratio plots the difference in acidity constants of two bases is given by eq.

$$pK_1 - pK_2 = \log I_1 - \log I_2 - \frac{f_{B(1)}f_{BH^+(2)}}{f_{BH^+(1)}f_{B(2)}} \qquad (3)$$

3. The existence of parallel and overlapping indicator ratio plots has been taken to mean that the activity coefficient ratio $f_B/f_{BH^+}$ has the same value for the two bases at a given concentration of acid, making the last term in eq. 3 zero at that acid concentration, and permitting determination of the relative base strengths from the measured values of $I$. Although it was originally proposed[7] that the activity coefficient ratio would have the same value for *all* uncharged indicators at a given concentration of acid, making eq. 3 useful for comparing base strengths of all very weak bases, a number of important exceptions to this postulate

(1) A preliminary account of this work was presented before the Organic Division, 139th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 8, 1961.

(2) Acidity constants of indole and five of its methyl derivatives were reported recently (G. Berti, A. da Settimo, and D. Segnini, *Gazz. chim. ital.*, 91, 571 (1961)). Since these results were based on the $H_0$ acidity function, they differ in numerical value from those obtained in the present work, but the relative order is the same as that reported here.

(3) (a) R. L. Hinman and J. Lang, *Tetrahedron Letters*, 21, 12 (1960); (b) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, 26, 2339 (1961); (c) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, 84, 2534 (1962).

(4) L. A. Flexer, L. P. Hammett, and A. Dingwall, *ibid.*, 57, 2103 (1935).

(5) M. A. Paul and F. A. Long, *Chem. Rev.*, 57, 1 (1957).

(6) (a) N. C. Deno, P. 1. Groves, and G. Saines, *J. Am. Chem. Soc.*, 81, 5790 (1959). (b) N. C. Deno, P. 1. Groves, J. J. Jaruzelski, and M. N. Lugasch, *ibid.*, 82, 4719 (1960). (c) The use of $H'_R$ for $H_R - \log a_{H_2O}$ was introduced by A. J. Kresge and Y. Chiang, *Proc. Chem. Soc.*, 81 (1961).

(7) (a) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, 54, 2721 (1932); (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.
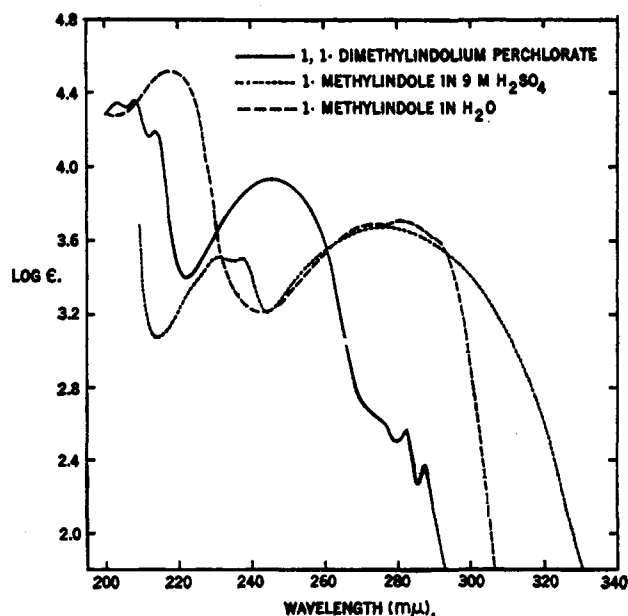
Fig. 1.—Ultraviolet spectra of the 3-protonated conjugate acid of N-methylindole and of a model of the N-protonated conjugate acid.

have been found.[5,6,8] The indoles constitute a particularly significant case against the generality of $H_0$ or $H'_R$, both because of the large number of examples examined, and because they undergo protonation on carbon but the conjugate acid bears the charge on both nitrogen and carbon.

By protonation of the indoles in various acid concentrations titration curves of the type shown in Fig.
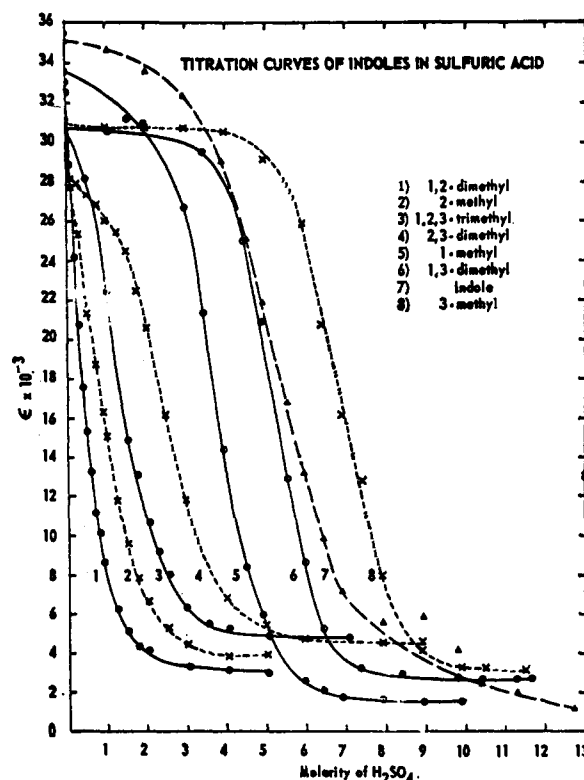


Fig. 2.—Titration curves of indole and its methyl derivatives obtained from ultraviolet absorption spectra in sulfuric acid.

2 were determined. From data of this type indicator ratio plots of twenty-five indoles were made by means of the usual method.[5] For most of the bases measure-

TABLE I

ACIDITY CONSTANTS OF INDOLES WHICH OBEY $H_1$

| No. | Indole | Molarity of acid where $\log I = 0$[a] | $pK_a$ | $\dfrac{d \log I}{d(C_{H_2SO_4})}$[b] | No. of observations | Std. error of slope | Range of acid concn. ($M$) over which slopes were measured |
|---|---|---|---|---|---|---|---|
| 1 | 1,2-Dimethyl | 0.09 | +0.30[c,g] | 0.77[d] | 4[d] | 0.01[d] | 0.90–1.50[d] |
| 2 | 2,5-Dimethyl | .10 | + .26[c] | .73 | 5 | .03 | 0.70–2.00 |
| 3 | 2-Methyl | .76 | − .28[c] | .73 | 4 | .01 | 1.25–2.00 |
| 4 | 2-Ethyl | .92 | − .41[e] | .64 | 5 | .06 | 1.01–2.28 |
| 5 | 1,2,3-Trimethyl | 1.22 | − .66[f] | .68 | 5 | .02 | 1.51–2.52 |
| 6 | 2,5-Dimethyl-3-n-propyl | 1.78 | −1.03[e] | .68 | 7 | .02 | 0.24–2.96 |
| 7 | 2-Methyl-3-n-propyl | 2.31 | −1.40[e] | .64 | 6 | .02 | 1.05–3.44 |
| 8 | 2,3-Dimethyl | 2.46 | −1.49[f] | .67 | 9 | .01 | 1.00–3.96 |
| 9 | 1-Ethyl | 3.66 | −2.30[e] | .74 | 14 | .02 | 2.53–4.83 |
| 10 | 1-Methyl | 3.70 | −2.32[f] | .68 | 9 | .02 | 2.96–4.93 |
| 11 | 1,2-Dimethyl-5-nitro | 4.60 | −2.94[e] | .68 | 11 | .02 | 3.44–5.93 |
| 12 | 2-Methyl-5-nitro | 5.54 | −3.58[f] | .68 | 22 | .01 | 4.46–6.89 |
| 13 | 3-t-Butyl | 5.91 | −3.84[e] | .68 | 5 | .03 | 4.82–6.99 |
| 14 | 3-Ethyl | 6.53 | −4.25[e] | .70 | 5 | .02 | 5.93–7.89 |
| 15 | 3-n-Propyl | 6.66 | −4.34[e] | .75 | 6 | .02 | 5.51–7.89 |
| 16 | 3-Methyl | 6.95 | −4.55[f] | .71 | 9 | .03 | 5.92–8.88 |
| 17 | Indole-3-acetic acid | 9.27 | −6.13[f] | .70 | 5 | .03 | 8.20–10.25 |
| 18 | Tryptamine | 9.51 | −6.31[f] | .77 | 9 | .02 | 8.47–10.87 |

Av.  0.70 ± 0.03

[a] Calcd. from slope and intercept of plot of $\log I$ vs. $C_{H_2SO_4}$.  [b] Calcd. by least squares.  [c] Average of values obtained by extrapolation to infinite dilution of plot of $(\log I − C_H{}^+)$ vs. $C_{acid}$ for hydrochloric, sulfuric, and perchloric acids; av. dev. = ±0.01.  [d] Value probably high because curvature of plot makes uncertain which points should be used for determining of slope (Table VII).  [e] Calcd. from value of $H_1$ at $\log I = 0$.  [f] By overlap method.  [g] Reported value +0.34, obtained by extrapolation method in hydrochloric acid.[2]

(8) See, for example: (a) R. W. Taft, Jr., J. Am. Chem. Soc., 82, 2966 (1960); (b) W. M. Shubert and R. H. Quacchia, ibid., 84, 3778 (1962), 85, 1278 (1963); (c) A. J. Kresge and Y. Chiang, ibid., 84, 4343 (1962); (d) a careful re-evaluation of the reliability of the substituted anilines originally used by Hammett has been made by M. J. Jorgenson and D. R. Hartter, ibid., 85, 878 (1963); (e) R. H. Boyd, ibid., 85, 1555 (1963).

ments were made at one wave length, but for a few of the alkylindoles two or three wave lengths were taken near the absorption maximum of the free base, while three or four quite different wave lengths were selected
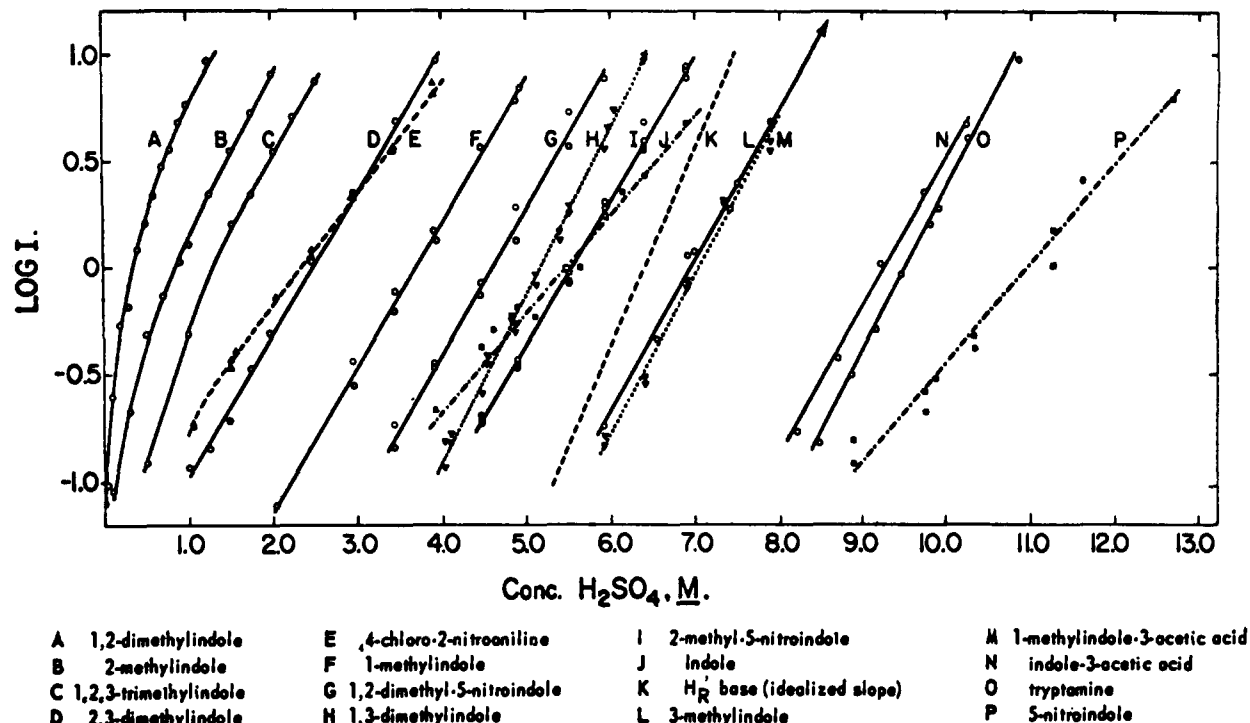
Fig. 3.—Indicator ratio plots of representative indoles in sulfuric acid ($I = C_{BH^+}/C_B$).

| A | 1,2-dimethylindole | E | 4-chloro-2-nitroaniline | I | 2-methyl-5-nitroindole | M | 1-methylindole-3-acetic acid |
|---|---|---|---|---|---|---|---|
| B | 2-methylindole | F | 1-methylindole | J | Indole | N | indole-3-acetic acid |
| C | 1,2,3-trimethylindole | G | 1,2-dimethyl-5-nitroindole | K | $H_R'$ base (idealized slope) | O | tryptamine |
| D | 2,3-dimethylindole | H | 1,3-dimethylindole | L | 3-methylindole | P | 5-nitroindole |

for the nitroindoles (Table VI). The data used for calculation of the indicator ratio plots of Fig. 3 correspond to the steep portions of the curves in Fig. 2 with values of log $I$ limited[8b] to ± 1.0 (Table VII).

Despite the close structural similarity of the twenty-five indoles, the slopes of the plots of log $I$ vs. $C_{H_2SO_4}$ fell into three groups (Fig. 3 and Tables I and II).

spans a range of 2–3 $M$ in acid concentration, with the group as a whole covering the range from 0.1 to 12 $M$. By comparison, a slope of 0.52 was obtained for 4-chloro-2-nitroaniline, a typical Hammett indicator, measured under the same conditions from 1 to 5 $M$ acid. (Values of d log $I/dH_0$ average about 1.3 for this group of indoles). All of these indoles have one or

## TABLE II
### ACIDITY CONSTANTS OF DEVIANT INDOLES

| No. | Indole | Molarity of acid where log $I = 0$[a] | $pK_a$[b] | $\dfrac{d \log I^c}{d(C_{H_2SO_4})}$ | No. of observations | Std. error of slope | Range of acid concn. ($M$) over which slopes were measured |
|---|---|---|---|---|---|---|---|
| 1 | Indole | 5.49 | −3.5 | 0.46 | 12 | 0.03 | 3.92–6.89 |
| 2 | 5-Methyl | 5.07 | −3.3 | .41 | 13 | .02 | 3.43–7.34 |
| 3 | 5-Nitro | 10.99 | −7.4 | .47 | 11[d] | .03 | 8.91–12.50 |
| 4 | 6-Nitro | 10.29 | −6.9 | .41 | 10 | .02 | 7.89–10.91 |
| 5 | 1,3-Diethyl | 4.94 | −2.2 | .82 | 4 | .05 | 4.88–6.40 |
| 6 | 1,3-Dimethyl | 5.16 | −3.3 | .78 | 27 | .01 | 4.03–6.40 |
| 7 | 1-Methylindole-3-acetic acid | 7.04 | −4.6 | .74 | 10 | .03 | 5.93–7.89 |
| 8 | 4-Chloro-2-nitroaniline | 2.33 | −0.99[e] | .52 | 17 | .01 | 1.5–4.9 |

[a] Calcd. from slope and intercept of least squares treatment of log $I$ vs. $C_{H_2SO_4}$. [b] Based on $H_1$ scale. [c] From least squares treatment. [d] Measured at 290 mμ. Reported value −1.03 (ref. 5).

Similar correspondence of slope and structure was found in the few cases examined in perchloric acid (Table III). The different slopes observed are reminiscent of the differences reported for phloroglucinol and its alkyl ethers,[8b,c] but the much larger number of bases studied in the indole series show that each slope is representative of a *class* of indicator bases within which the plots are closely parallel.

For the largest group, comprising the eighteen indoles of Table I, d log $I/d(C_{H_2SO_4}) = 0.70 \pm 0.03$, ranging from 0.64 to 0.77.[9] The plot for each member

(9) By analogy with results reported for indicator bases of the $H_0$ type[8d] and the $H_R$ and $H'_R$ types[6] it might be expected that successive plots, though linear, would have increasingly steep slopes with increasing acid concentration. However, this is clearly inconsistent with the requirement that indicator ratio plots be parallel to permit the use of eq. 3 for the cal-

more alkyl groups in the hetero ring, ranging from methyl and ethyl at the 1- and 2-positions to $t$-butyl, carboxymethyl, and β-aminoethyl at the 3-position.

The members of the other two groups of indoles are listed in Table II. Those like indole itself which are unsubstituted in the hetero ring (no. 1–4) show d log $I/d(C_{H_2SO_4}) = 0.44 \pm 0.03$, ranging from 0.41 to 0.47, while indoles which are 1,3-disubstituted (no. 5–7) have steeper slopes than the other two groups: d

culation of the necessary acidity constants. The main group of indoles conforms reasonably well to the requirement of parallelism throughout the series, whereas the other types of indicators may in fact be composed of groups of bases, similar to the three groups of indoles reported here. It should be noted, however, that there is no *a priori* reason to expect linear plots. Data have usually as in the present work been forced to fit this requirement for simplicity of treatment. The constancy of d log $I/dC_{H_2SO_4}$ is a consequence of this method.

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Table III

Acidity Constants in HClO₄

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| No. | Indole | Molarity of acid where $\log I = 0$[a] | $pK_a$ | $\dfrac{d \log I}{d(C_{HClO_4})}$ | No. of observations | Std. error of slope | Range of acid concn. ($M$) over which slopes were measured |
|---|---|---|---|---|---|---|---|
| 1 | 1,2-Dimethyl | 0.27 | 0.30[c] | [b] | | | |
| 2 | 2-Methyl | 0.64 | −0.28[c] | [b] | | | |
| 3 | 2,3-Dimethyl | 2.04 | −1.44[d,e] | 0.73 | 12 | 0.01 | 1.36–3.04 |
| 4 | 1-Methyl | 3.20 | −2.30[d] | .77 | 13 | .01 | 2.15–4.30 |
| 5 | 2-Methyl-5-nitro | 4.99 | −3.70[d] | .80 | 77 | .01 | 3.81–6.04 |
| 6 | Indole[g] | 4.87 | −3.61[f] | .62 | 12 | .02 | 3.53–6.04 |
| 7 | Indole[h] | 4.88 | −3.62[f] | .66 | 7 | .06 | 3.53–4.65 |
| 8 | 1,3-Dimethyl | 4.57 | −3.37[f] | .96 | 10 | .03 | 3.53–5.36 |

[a] Calcd. from slope and intercept as computed from least squares plot of $\log I$ vs. $C_{HClO_4}$. [b] Plot was curved. [c] Calcd. from extrapolation to infinite dilution of $\log I - [H^+]$ vs. acid concn.; average of values obtained from HCl, H₂SO₄, and HClO₄ solutions with av. dev. = ±0.01. [d] By overlap method. [e] Value of −1.38 was obtained by extrapolation method. [f] Calcd. from $H_1$ where $\log I = 0$. [g] Using all values of $\log I$ between −1.0 and +1.0. [h] Using only those values of $\log I$ at which Beer's law is obeyed.

$\log I/d(C_{H_2SO_4}) = 0.78 \pm 0.03$, ranging from 0.74 to 0.82. Although the differences between these values and those of the main group of indoles appear to be outside the limit of experimental error (see particularly the data for indole and 1,3-dimethylindole in Table II), it is difficult to be certain that the deviations in slope represent class differences due to variations in indicator structure alone.[10] This is especially true for the 1,3-disubstituted cases for which the deviations in slope are particularly small and for which thoroughly reliable data are available only for 1,3-dimethylindole. However, the fact that even more pronounced differences have been observed in perchloric acid (Table III) prompts us to treat the 1,3-disubstituted indoles as a separate class.

For indole and its group the differences in slope from that of the large class of bases in both sulfuric and perchloric acids are much greater, although even here the decision to consider these as a separate class must be exercised with caution since these bases are hardest to work with, the data having considerable scatter, particularly in the region above 8 $M$ sulfuric acid (Fig. 2) and 5 $M$ perchloric acid. The need for caution is emphasized by the lack of obvious reasons for the deviations,[11a] and the fact that pyrrole and its methyl derivatives all have about the same slope.[11b] Attempts to eliminate the more obvious side reactions such as autoxidation and dimerization[3b] by working with degassed solutions or at concentrations of indole 1/20 of those used for the data of Fig. 2 and Table II neither changed the slope significantly nor eliminated the erratic results. Beer's law was followed at all concen-

(10) The problem of deciding when slopes of indicator ratio plots are truly parallel has been treated only superficially in the literature. For example, deviations in indicator ratio plots no larger than those reported here have been treated as real effects of indicator structure,[8b,c] and what appears to the eye as nonparallel plots of deviation greater than those described here have been referred to as having "good parallelism."[8d] (See also ref. 28.) The many uncertainties such as medium effects and side reactions in the measurement of protonation of reactive bases require that extreme caution be exercised in making judgments based on deviations in slopes of indicator ratio plots. A recommended practice would be to report the slope of ($\log I_1 - \log I_2$), measured at the same acid concentration, vs. the concentration of acid.

(11) (a) The failure to find any correlation between structure and widely and apparently randomly varying values of $d \log I/d(C_{acid})$ in families of closely related bases has been encountered recently in a number of instances, most notably among the alkyl ethers (E. M. Arnett and C. Y. Wu, J. Am. Chem. Soc., 84, 1680 (1962)) and a variety of substituted benzamides (A. R. Katritzky, A. J. Waring, and K. Yates, Tetrahedron, 19, 465 (1963)). The possibility of varying extents of hydrolysis in the latter cases was not discussed, however. (b) Y. Chiang and E. B. Whipple, J. Am. Chem. Soc., 85, 2763 (1963).

trations of acid used for determining the indicator ratios of indole (see Table III).

The deviations of these slopes from each other and particularly from those of the indicators used to define the previously established acidity functions $H_0$ and $H'_R$ might be a result of two factors other than differences in indicator structure. The first of these is the effect of medium on the values of $\epsilon_B$ and $\epsilon_{BH^+}$. This source of error was first pointed out by Hammett in his original conception of acidity function theory.[7] Recently, Noyce has presented a clear picture of the effect of medium on indicator ratio plots,[12] and has emphasized the importance of vertical shifts of spectra with medium as well as the lateral shifts described in earlier work. The effects of medium on the spectra of the indole bases appear to be small. Lateral shifts are precluded by the existence of isosbestic points in all three groups of bases. Vertical changes in $\epsilon_{BH^+}$ are generally no more than 5% over a range of acid concentration several molar beyond that of complete protonation (Fig. 2). The situation with respect to $\epsilon_B$ is not as clear. With 3-methyl- and 1,3-dimethylindole there is little change in $\epsilon_B$ (Fig. 2). With other bases varying degrees of drift exist, and since points in very dilute acid were not determined it is not known whether the curves would become flat in these areas. By taking $\epsilon_B$ at the acid concentration where the steep portion of the titration curve begins, the value of $d \log I/d(C_{H_2SO_4})$ is increased, but usually by an amount within the limits of precision for the slope. For example, the slope of 1,2,3-trimethylindole derived with the value of $\epsilon_B$ from pure water is 0.70. Using $\epsilon_B$ as the value in 0.5 $M$ acid gives a slope of 0.72. In view of the small differences and the fact that no simple method for systematic choice of values of $\epsilon_B$ is available, we have arbitrarily taken $\epsilon_B$ as the value in water. Values of $\epsilon_{BH^+}$ have been taken arbitrarily as those at 100% protonation (15 $M$ acid for indole), i.e., the point at which the titration curve becomes flat (see Experimental). This method has to recommend it the general agreement of the values of $d \log I/d(C_{H_2SO_4})$ throughout each series,[9] which supports the conclusion that medium effects are not significant.

The titration curves of indole (Fig. 2) and of other members of its class are the only ones to show large vertical changes after complete protonation has been

(12) D. S. Noyce and M. J. Jorgenson, ibid., 84, 4312 (1962).

achieved. However, because of the erratic nature of the measurements (note scatter of points in Fig. 2), it is not certain that this change is due to an effect of the medium. Even allowing for a large medium effect taking $\epsilon_B$ at 2.96 $M$ acid and $\epsilon_{BH}^+$ at 9.77 $M$ acid (effectively 8 and 91% protonation, respectively), changes the slope from 0.42 to 0.58, leaving it still far outside the range for the other groups of indoles. Although in this case the effect of medium cannot be unequivocally excluded, it is clear that it cannot be the principal factor responsible for the slope differences between indole and its derivatives. Even use of an expression which permitted continuous variation of $\epsilon_B$ and $\epsilon_{BH}^+$ with changing acid composition revealed only minor changes in slopes.

The second factor is peculiar to the particular class of bases under study. Since values of d log $I$/d-$(C_{H_2SO_4})$ for most of the indoles fall between those of $H'_R$ bases and of $H_0$ bases, it was considered possible that in regions of partial protonation, where the n.m.r. spectra are not resolved sufficiently to permit identification of the various components of the mixture, a significant fraction of N-protonation might be taking place along with C-protonation.[13] If the equilibria for C-protonation followed $H'_R$ and those for N-protonation obeyed $H_0$, the slopes of the indole indicator ratio plots would fall between the slopes of the other two classes of indicators, although a different acidity function would still be necessary to account for the slope of indole itself.

The possibility of such an occurrence was eliminated in two ways. The gap between the indole concentrations used in the ultraviolet absorption measurements ($10^{-5}$–$10^{-4}$ $M$) and those (0.3–0.8 $M$) of the n.m.r. measurements—on which the proof of 3-protonation in the completely protonated indole depends[3c]—was bridged by taking ultraviolet spectra of thin layers of acidic solutions of a number of indoles at the same concentrations as those used in the n.m.r. measurements. Although the absorption intensities could not be compared with those of the more dilute solutions because the path length was unknown, the positions of $\lambda_{max}$ and the ratios of peak heights were remarkably close to those of the more dilute solutions. For a 5% solution ($\sim$0.3 $M$) of 1,2,3-trimethylindole in 12 $M$ sulfuric acid, for example, $\lambda_{max}$ = 232, 239, and 276 m$\mu$, the same values as those of a 9.65 × $10^{-5}$ $M$ solution in 12 $M$ acid. Values of O.D.$^{239}$/O.D.$^{276}$ and O.-D.$^{239}$/O.D.$^{245(min)}$ were 0.83 and 2.48 for the concentrated solutions compared to 0.87 and 2.47 for dilute solutions.

Secondly, point-by-point comparisons of the spectra of partially protonated indoles from 215–230 m$\mu$ can be accounted for satisfactorily in terms of two species only: the free base and its conjugate acid.[14] The spectrum (Fig. 1) of a synthetic model (III) of the N-protonated species[15] is such that the presence of more

than a few per cent of the latter would preclude the constancy of the calculations, and produce recognizable anomalies in the spectrum in the 275 m$\mu$ region as well. For these reasons we conclude that N-



III
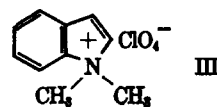
protonation does not take place to a significant extent in the indicator ratio measurements, that the indicator ratio plots of Fig. 3 are truly representative of the equilibrium expressed by eq. 2, and that deviations of these plots from those of the $H_0$ and $H'_R$ indicators are a consequence of differences in indicator structure.

In this connection it is of interest to consider whether the acidity function dependencies of the indoles and their relationship to $H_0$ and $H'_R$ can be accounted for in even a qualitative way by solvation effects. Although the indoles undergo protonation on carbon, as do the arylolefins which they formally resemble, the charge in the conjugate acid, solvation of which would be expected to be more important than that of the free base,[8] is distributed mainly between the nitrogen and the $\alpha$-carbon, as indicated in II. Evidence of the large share of the positive charge borne by the $\alpha$-carbon is provided by the average increase in acidity constant of 2.9 log units accompanying introduction of a methyl group at the $\alpha$-position (Table I) and by the very low field position of $\alpha$-ring protons (9.40 p.p.m.) in the n.m.r. spectra of the indole conjugate acids.[3c,16] (The chemical shift of ring protons in the $\beta$-position is $\sim$4.6 p.p.m.[16]) Interaction of the indole conjugate acids with solvent would therefore be expected to occur principally at the 1- and 2-positions. Recently proposed explanations[8a] of the relationship of indicator solvation and acidity function dependency lead one to the prediction that the indicator ratio plots of the indoles would fall between $H_0$ and $H'_R$ and that methyl substitution of the 1- or 2-positions would be accompanied by further shifts toward $H'_R$. In very general terms the observations can be accounted for in this way but important exceptions exist. The majority of the twenty-five indoles studied have values of d log $I$/d($C_{H_2SO_4}$) between those of the $H_0$ ane $H'_R$ bases, but for indoles 1–4 in Table II the slopes are less than those of the $H_0$ bases. Again, taking indole as the parent, the changes in slope which accompany substitution at the 1-, 2-, or 3-positions to form the bases of Table I are in the direction to be expected of decreased solvation of the conjugate acids. However, there is no apparent structural reason for a change of slope to accompany substitution at the 3-position. From a simple consideration of solvation in terms of hydrogen bonding,[8a] 3-methyl- and 1-methylindole would be expected to have different slopes for their indicator ratio plots, with the former differing little if any from indole. Other discrepancies of this type are apparent from Tables I and II. Though it could be proposed that introduction of a substituent anywhere on the hetero ring requires a re-ordering of the

(13) The possibility of N-protonation was suggested by the observation of acid-catalyzed exchange of N-H and by isolation of N-protonated salts of some indoles.[3c] The relatively slow exchange rate of the 2-proton indicates that the contribution from 2-protonation can be neglected.[3c] Moreover, results with the methylpyrroles suggest that 2- and 3-protonation would obey similar acidity functions.[11b]

(14) Above 230 m$\mu$ systematic increases in $C_{BH}^+$ were found as calculated from $(C_{total}\epsilon_B - O.D.)/(\epsilon_B - \epsilon_{BH}^+)$. In this range the spectra of the protonated indole and the free base are nearly coincident (Fig. 1) so that the errors are large.

(15) R. L. Hinman and J. Lang, J. Org. Chem., 29, 1449 (1964).

(16) Chemical shifts in ref. 3c are not reported in p.p.m. The values given here are taken from spectra of the conjugate acids of indole and 1,2,3-trimethylindole in sulfuric acid with tetramethylammonium chloride as the reference. These values are corrected to the TMS scale by adding 198.7 c.p.s.[11b]

TABLE IV

$H_1$ VALUES FOR SULFURIC AND PERCHLORIC ACIDS

| Molarity of acid | $H_1$ ($H_2SO_4$) | Based on cmpd. no. | $H_1$ ($HClO_4$) | Based on cmpd. no. |
|---|---|---|---|---|
| 0.10 | +0.91 | 3 | +0.85 | 3 |
| .25 | + .54 | 3 | + .37 | 3 |
| .50 | + .08 | 3 | − .07 | 3 |
| .75 | − .23 | 3 | − .38 | 3 |
| 1.00 | − .49 | 3 | − .60 | 3 |
| 1.50 | − .84 | 3, 5, 8 | − .99 | 3, 8 |
| 2.00 | −1.18 | 3, 5, 8 | −1.41 | 8 |
| 2.50 | −1.54 | 3, 5, 8 | −1.77 | 8, 10 |
| 3.00 | −1.85 | 8, 10 | −2.16 | 8, 10 |
| 3.50 | −2.19 | 8, 10, 11 | −2.54 | 10 |
| 4.00 | −2.53 | 10, 11 | −2.92 | 10, 12 |
| 4.50 | −2.88 | 10, 11, 12 | −3.32 | 12 |
| 5.00 | −3.22 | 10, 11, 12 | −3.71 | 12 |
| 5.50 | −3.56 | 11, 12 | −4.11 | 12 |
| 6.00 | −3.89 | 11, 12, 16 | −4.51 | 12 |
| 6.50 | −4.23 | 12, 16 | | |
| 7.00 | −4.57 | 16 | | |
| 7.50 | −4.91 | 16, 17 | | |
| 8.00 | −5.25 | 16, 17 | | |
| 8.50 | −5.57 | 17, 18 | | |
| 9.00 | −5.93 | 17, 18 | | |
| 9.50 | −6.30 | 17, 18 | | |
| 10.00 | −6.66 | 17, 18 | | |
| 10.50 | −7.03 | 17, 18 | | |
| 11.00 | −7.45 | 18 | | |
| 11.50 | −7.79 | 18 | | |
| 12.00 | −8.11 | 18 | | |

solvation shell, compared to that of indole, it is clear that the observed variations within the indole series are not explained by a simple treatment of solvation. In the pyrrole series substitution by methyl at the 1-, 2-, or 3-positions has little effect on the slope of the indicator ratio plot,[11b] although from the hydrogen-bonding treatment a change might be anticipated in the first case. It has been suggested that the variation of $f_B$ with acid composition may be significant and dependent on structure[8d,e]; this may be more important than has generally been recognized.

**The Acidity Function $H_1$.**—From the indicator ratio plots of Fig. 3 the relative base strengths of the indoles for which parallel plots are observed can be obtained by use of eq. 3. Since the thermodynamic $pK_a$'s of the strongest bases, 1,2-dimethyl- and 2-methylindole, could be determined independently by the usual extrapolation procedure,[2,5] by the classical treatment of acidity functions the $pK_a$'s of all the bases are known and related to dilute aqueous solution as the standard state.[17] For the indoles this treatment would apply only to the largest group (referred to as the $H_1$ type), the acidity constants of which are listed in Table I.

(17) It should be noted that the classical method[7] of tying the whole group of bases and the acidity function to dilute aqueous solution as the standard state implies that a plot of log $I$ vs. $C_{acid}$ for any of the indicator bases would be parallel to that of the most basic indicator all the way into the standard state. Yet the limits of existing spectrophotometric techniques obviously preclude experimental verification of such parallelism. The recognition of very marked dependence of acidity function on indicator structure means that there is no assurance of parallelism of indicator ratio plots beyond the range of experimental observation. And if the indicator plots are not parallel into the standard state, the acidity constants are not thermodynamic $pK$'s and cannot be compared to those obtained either from another acidity function or by direct measurement in the standard state. Until this question can be resolved there will be serious doubt about the meaning of "acidity constants" derived by the acidity function method. For the present, however, we shall continue to use dilute aqueous solution as a convenient zero point.
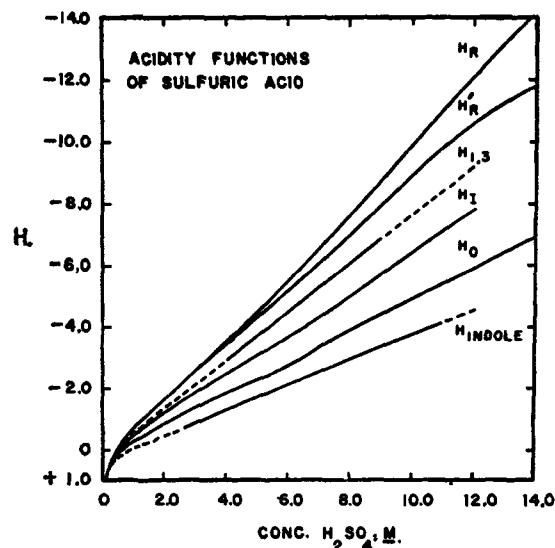


Fig. 4.—Comparison of various indicator acidity functions determined in sulfuric acid.

From the acidity constants of the nine members of the series with the smallest standard errors in d log $I$/d($C_{H_2SO_4}$) plus the two weakest bases, values of a new acidity function $H_1$ have been determined for sulfuric acid from 0.1 to 12 $M$ by means of the relation $H_1 = pK_{BH^+} - \log I$. Values of $H_1$ are listed in Table IV. The relationship of $H_1$ to $H_0$, $H_R$, and $H'_R$ is shown in Fig. 4. The plot of $H_1$ vs. $H_0$ is linear from 0.1 to 12 $M$ sulfuric acid with $dH_1/dH_0 = 1.27$, whereas $dH'_R/dH_0 = 1.83$ from about 1 to 11 $M$ sulfuric acid.

To the extent that the deviations from $H_1$ are valid reflections of differences in indicator structure, each of these deviations defines a different acidity function. The whole acidity function curve defined by the deviant class of indoles cannot be determined for lack of bases strong enough to permit determination of their $pK_a$'s in dilute acids. However, an approximation to the acidity function curve for indole and its group can be drawn from the knowledge that d log $I$/d($C_{H_2SO_4}$) = $dH$/d($C_{H_2SO_4}$) and that by classical acidity function theory all acidity functions will become equal to each other and to pH in dilute aqueous solution. Assuming that the deviant function like $H_1$ does not intersect $H_0$ or $H'_R$ more than once, the curve shown in Fig. 4 can be drawn. Although this treatment serves to dramatize the variety of acidity functions, it must be emphasized that the assumptions are of uncertain validity (cf. footnote 17).

Many deviations from $H_0$ are now known,[8,11,18,19] showing clearly that rather than two acidity functions corresponding to two broad classes of bases—those that protonate on carbon and those that protonate on nitrogen or oxygen[20]—there is more likely a continuum of functions for protonation equilibria similar to that described by Bunnett[21] in the area of kinetics. It should be noted that $H_0$ does not represent one edge of the continuum, as the acidity function defined by

(18) Pyrrole and a number of its methyl derivatives define an acidity function close to that of $H_1$.[11b]

(19) (a) F. A. Long and J. Schulze, J. Am. Chem. Soc., **86**, 327 (1964). (b) E. M. Sorett and G. W. Mack, ibid. **86**, 2671 (1964).

(20) See, for example, J. F. Bunnett, ibid., **83**, 4968 (1961).

(21) J. F. Bunnett, ibid., **83**, 4956 (1962).

indole has a still smaller slope.[22] In short, it is clear that the idea of a generally applicable indicator-based acidity function, as originally envisioned, is an unattainable ideal.

The considerable variation of acidity function with indicator structure is also pertinent to the significance of $H_-$ and $H_+$ functions. The examples which have been reported have values which are the same as or deviate only slightly from those of $H_0$.[5,23] When the structures of the indicators differ from those of the $H_0$ bases, the effect of charge is likely to be overshadowed by the effect of the indicator structure itself, rendering the terms $H_-$ and $H_+$ meaningless as representations of acidity functions dependent on charge alone. Similar cautions apply to the development of acidity functions in nonaqueous media. The critical role played by indicator structure makes generalized functions in these media[24] as unattainable as those in water. Moreover, with a new class of bases in a nonaqueous solvent,[25] observed deviations from $H_0$ values for aqueous media may be due to the structure of the indicators as well as to the solvent.

Even if one accepts as thermodynamic acidity constants the values obtained by the acidity function method,[17] the existence of many indicator-based acidity functions means that caution must be exercised in determining acidity constants of a new class of bases, or even of new members of a class for which the acidity function dependence has been established. Marked deviations of d log $I/d(C_{acid})$ among compounds closely related in structure have been noted above.[11,19] Recently the basicities of a number of alkylindoles were determined by assuming that indoles are indicators of the $H_0$ type.[2] The fact that indole follows an acidity function different from that of its alkyl derivatives could not be detected by the method used in the earlier work. Other examples of $pK_a$ measurements in which the applicability of $H_0$ has been assumed include those for acetophenones,[26] flavones,[27] and imidazoles.[28] Thorough examination of the literature would no doubt reveal many more such cases. However, the apparent gravity of this situation may be in part offset by the possibility of obtaining operationally meaningful differences in basicity when the insistence on thermodynamic acidity constants referred to dilute aqueous solution is removed. This point is developed in the following discussion.

**Acidity Constants of Indoles.**—In Table I are listed the acidity constants of the large group of indoles on which the $H_1$ function is based. The agreement between these values and those determined in perchloric acid (Table III) is noteworthy. Acidity constants of the other group of indoles derived by assuming that $H_1$ applies to them also (see discussion below) are listed in Table II.

The effects of methyl substitution at the various positions of the $H_1$ indoles are summarized in Table V: a methyl at the 1-position increases the base strength by an average of 0.7 unit; at the 2-position the increase is 2.9 units, while at the 3-position a *decrease* of about 1.1 $pK$ unit is observed. Thus 2-methylindole is estimated to be $10^4$ times as basic as 3-methylindole. The greatly enhanced basicity of the 2-methylindoles makes it possible to analyze for them by potentiometric titration in nonaqueous media; 2-methylindoles can be determined in the presence of 3-methylindoles by this method.[3a,29]

The effect of a substituent group at a given position is fairly constant (deviations of about ±0.15 $pK$ unit are observed) regardless of other substitution. From the additive relationships new $pK_a$'s can be predicted. From the $pK_a$ of 2-methyl-5-nitroindole a value of $-2.9$ was predicted for 1,2-dimethyl-5-nitroindole. The observed value was $-2.94$ (no. 11 and 12, Table I).

The effects of methyl substitution on $pK_a$ can be understood in terms of the equilibrium of eq. 2. Since a methyl would be more effective in stabilizing a positive charge than an unshared pair of electrons or a double bond, a 1-methyl group would stabilize the conjugate acid more than the free base. Similarly, a 2-methyl group would stabilize the large fraction of positive charge on that ring carbon, which, when methyl-substituted, resembles a tertiary carbonium ion. Substitution of the 3-position by methyl stabilizes the parent base relative to the conjugate acid. Moreover, the presence of a group at the 3-position reduces by one the number of hydrogens available for hyperconjugative stabilization of the positive charge at the 2-position of the conjugate acid. Substitutions on the 3-methyl group must also influence the position of the equilibrium by effects on the parent base, since additional groups attached to the 3-methyl are well shielded from the charge-bearing centers of the conjugate acid. Steric effects probably play a role here also. Models of 3-$t$-butylindole and its conjugate acid show that protonation would be accompanied by considerable relief of strain by moving the substituent at the 3-position out of contact with the 4-position.

Whereas a 3-ethyl group is base-strengthening compared to a 3-methyl, 2-ethyl is slightly base-weakening compared to 2-methyl. The latter effect is attributed to the relative stabilizations of the conjugate acids by methyl and ethyl, for which hyperconjugation can be invoked.

The 5-methyl group in the indole ring system causes an average increase of about 0.4 $pK$ unit (compare no. 2–3 and 6–7, Table I), remarkably close to the 0.5 unit difference between the $pK_a$'s of aniline and $p$-toluidine.[30] The 5-nitro group causes a decrease of 3.3 $pK$ units (no. 1–11 and 3–12, Table I); the difference between aniline and $p$-nitroaniline is 3.6 units.[30]

Since indoles behave in many reactions like a special class of vinylamines[3b]—both classes undergo protona-

(22) Certain amides also have smaller slopes than required by adherence to $H_0$ (J. T. Edward and I. C. Wang, Can. J. Chem., **40**, 966 (1962)) and ref. 11a.

(23) For $H_+$ see J. C. D. Brand, W. C. Horning, and M. B. Thornley, J. Chem. Soc., 1374 (1952); T. G. Bonner and J. C. Lockhart, ibid., 364 (1947). For $H_-$ see R. H. Boyd, J. Am. Chem. Soc., **83**, 4288 (1961), and J. T. Edward and I. C. Wang, Can. J. Chem., **40**, 399 (1962).

(24) (a) R. Stewart and J. P. O'Donnell, J. Am. Chem. Soc., **84**, 493 (1962); (b) E. M. Arnett and C. F. Doughty, ibid., **86**, 409 (1964).

(25) S. Yeh and H. H. Jaffé, ibid., **81**, 3274 (1959).

(26) R. Stewart and K. Yates, ibid., **80**, 6355 (1958).

(27) C. T. Davis and T. A. Geissman, ibid., **76**, 3507 (1954).

(28) G. G. Gallo, C. R. Pasqualucci, P. Radaelli, and G. C. Lancini, J. Org. Chem., **29**, 862 (1964).

(29) That 2-methylindole is much more basic than skatole was first recognized by Oddo, who found that the former will dissolve readily in concentrated hydrochloric acid, whereas skatole will not (B. Otto, Gazz. chim. ital., **63**, 898 (1933)). We have found that fairly concentrated solutions (10–20% by weight) of any of the indoles studied can be prepared in concentrated sulfuric acid.

(30) H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, Inc., New York, N. Y., 1955, Chapter 14.

TABLE V

PREDICTED pK VALUES OF DEVIANT INDOLES USING SUBSTITUENT EFFECTS

Substituent effects ($H_1$ scale in sulfuric acid)

| | | |
|---|---|---|
| Δ1-CH₃ +0.7 ± 0.11 | | Δ3-Pr -1.2 ± 0.09 |
| Δ2-CH₃ +2.9 ± .16 | | Δ5-NO₂ -3.3 ± .03 |
| Δ3-CH₃ -1.1 ± .16 | | Δ5-Me +0.5 ± .09 |

| Calculation based on | Calcd. pK of indole | Calculation based on | Calcd. pK of 1,3-diCH₃-indole | Calculation based on | Calcd. pK of 5-NO₂-indole |
|---|---|---|---|---|---|
| 1-CH₃ | -3.0 | 1-CH₃ | -3.4 | 1,2-DiCH₃-5-NO₂ | -6.5 |
| 2-CH₃ | -3.2 | 3-CH₃ | -3.8 | 2-CH₃-5-NO₂ | -6.5 |
| 3-CH₃ | -3.4 | 1,2,3-TriCH₃ | -3.2 | Indole | -6.5 |
| 1,2-DiCH₃ | -3.3 | Indole | -3.6 | Av -6.5 ± 0.00 | |
| 2,3-DiCH₃ | -3.3 | Av. -3.5 ± 0.2 | | | |
| 1,2,3-TriCH₃ | -3.2 | | | | |
| 2-CH₃-3-C₃H₇ | -3.1 | | | | |
| 2,5-DiCH₃-3-C₃H₇ | -3.2 | | | | |
| 2-CH₃-5-NO₂ | -3.2 | | | | |
| 1,2-DiCH₃-5-NO₂ | -3.2 | | | | |
| Av. -3.2 ± 0.1 | | | | | |

tion at the β-carbon, and dimerize in acidic media— it is of interest that the same general effects of substitution on basicity are found in simple representatives of the vinylamines, such as the $\Delta^2$-pyrrolines and $\Delta^2$-tetrahydropyridines. 1,2-Dimethyl-$\Delta^2$-pyrroline and 1,3,4-trimethyl-$\Delta^2$-pyrroline have $pK_a$'s of +11.9[31] and +9.6,[32] respectively, while the $pK_a$ values for 1,4,4-trimethyl-, 1,2-dimethyl-, and 1-methyl-3,5-diethyl-$\Delta^2$-tetrahydropyridine are +10.5,[33] +11.4,[31] and +9.5,[32] respectively.

Although useful correlations of pK values and structure can .be worked out among bases for which the indicator ratio plots are parallel (including those cases for which only relative pK's are known, e.g., within each class of deviant indoles), a much more complex problem is presented by those indicator bases which have overlapping but nonparallel plots. An extreme case is presented by the plots of indole and 1,3-dimethylindole in Fig. 3. Although the titration curves of Fig. 2 show that 1,3-dimethylindole is the stronger base in the range of 4–6 M acid, when the value of log I is used as a measure of basicity, in 4 M acid indole is the stronger base, in 4.72 M acid the bases are of equal strength, and in 6 M acid 1,3-dimethyl-indole is the stronger base. When the nonparallel plots do not intersect in the region studied, the qualitative differences in base strength will be as apparent as they will from titration curves, but quantitative differences in base strength will still depend on the acid concentration at which the comparison is made. Since deviations of indicator ratio plots from parallelism must be due largely to differences in solvation, the values of log $I_1$ — log $I_2$ for nonparallel indicator ratio plots are as much a measure of base strength differences at one acid concentration (i.e., in a medium of fixed composition) as are $pK_a$ differences in water. In neither case are the differences simply related to differences in intrinsic base strengths, for each base and conjugate acid pair is solvated in unknown and different ways. In water this problem is manifested in the well-known but complex variations in base strengths observed among 1, 2, and 3° amines.[34]

The problem is aggravated in strongly acidic media

by the sensitivity of indicator ratio plots to solvation effects. Although this sensitivity has been valuable in probing for solvation differences between bases,[8] for determination of relative base strengths the importance of comparing the less solvent-sensitive titration curves (Fig. 2) as well as indicator ratio plots cannot be overemphasized. This is illustrated particularly well by the indole bases. Since the methyl-indoles which obey $H_1$ show additive effects of methyl substitution on basicity, one can predict basicities of deviant indoles on the $H_1$ scale, as shown in Table V. Although it might be inferred from the widely different acidity function behavior of the three classes of indoles that meaningful predictions could not be made, *the results correspond closely to those obtained by simply taking the pK of a deviant indole as the $H_1$ value at half-protonation.*

Thus, if one ignores the variations in $dH/d(C_{acid})$ and merely considers the half-protonation points on a single acidity scale, the basicities of all the methyl-indoles fall into a reasonable and self-consistent order *which is in agreement with the observed order of the titration curves themselves.* Although the acidity constants obtained in this way for deviant indoles are not thermodynamic values, the method avoids the need to build up whole acidity functions or to attempt long-range extrapolations to dilute aqueous solution as in Fig. 4. It seems reasonable, therefore, once an acidity function scale has been established for a class of bases, to determine base strengths of bases of related structure by simply using half-protonation points on this scale.

The argument can be carried further since the question of which acidity function is appropriate remains open. Since the use of different acidity functions corresponds in effect to the use of different scale factors in the $pK_a$'s, the qualitative ordering and additivity of substituent effects are independent of the particular scale chosen. We have used $H_1$ for traditional reasons.

Viewed in the perspective of the original context in which acidity functions were devised, namely to provide a better description than acid concentration for the ease of protonation of an indicator, the original (and present) treatment using one acidity function scale still has utility. From this point of view slope deviations of indicator ratio plots are minor perturba tions. In fact, indicator ratio plots may have more

(31) R. Adams and J. E. Mahan. J. Am. Chem. Soc., **64**, 2588 (1942).
(32) N. J. Leonard and A. G. Cook, ibid., **81**, 5627 (1959).
(33) E. M. Kosower and T. S. Sorensen, J. Org. Chem., **27**, 3764 (1962).
(34) R. G. Pearson and D. C. Vogelsong, J. Am. Chem. Soc., **80**, 1038 (1958).

## TABLE VI
### ULTRAVIOLET ABSORPTION SPECTRA OF INDOLES AND THEIR CONJUGATE ACIDS

| Indole | | $\lambda_{max}$ and $\epsilon_{max}$[a] | | | | | | | | $\lambda$ and $\epsilon$ used for pK measurements[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Indole | B | 216 | 34800 | 266 sh | 5720 | 276 | 5780 | 287 | 4750 | 215 | 35100 |
| | | | | 270 | 5920 | 278 | 5790 | | | | |
| | BH$^+$ (12)[f] | 233 | 3920 | 238 | 3810 | 279–81 | 4810 | | | | 1320 |
| 1-Methyl | B | 219 | 34300 | 275 | 5920 | 282 | 6030 | 293 | 4530 | 219 | 33600 |
| | | | | | | 287 sh | 5540 | | | | |
| | BH$^+$ (9)[c] | 233 | 3240 | 238 | 3180 | 280–3 | 4700 | | | | 1550 |
| 1-Ethyl | B | 219 | 34300 | 274 sh | 5530 | 281 | 5730 | 292 sh | 4530 | 219 | 34600 |
| | BH$^+$ (9)[c] | 233 | 3430 | 238 | 3320 | 277 | 4870 | | | | 2050 |
| 2-Methyl | B | 220 | 33800 | 272 | 7160 | 277 | 7050 | 289 | 5370 | 221 | 30000 |
| | | | | | | 281 sh | 6900 | | | | |
| | BH$^+$ (4)[f] | 229–30 | 5180 | 236 | 4600 | 272–5 | 5600 | | | | 3850 |
| 2-Ethyl | B | 220 | 33800 | 272 | 7250 | 277 | 7200 | 288 | 5680 | 220 | 30800 |
| | | | | | | 280 | 7120 | | | | |
| | BH$^+$ (3)[c] | 224 sh | 4670 | 235 sh | 4700 | 272–4 | 5870 | | | | 3100 |
| | | 229 | 5280 | | | | | | | | |
| 3-Methyl | B | 222 | 32000 | 275 sh | 5400 | 281 | 5810 | 290 | 4920 | 223 | 31000 |
| | BH$^+$ (12)[f] | 236 | 4010 | 240 | 3800 | 285–7 | 4780 | | | | 1980 |
| 3-Ethyl | B | 222 | 34800 | 273–5 sh | 5340 | 280 | 5780 | 289 | 4960 | 220 | 31400 |
| | BH$^+$ (9)[c] | 233 | 4600 | 238 | 4260 | 283–4 | 4690 | | | | 1710 |
| 3-$n$-Propyl | B | 222–3 | 39600 | 274–5 sh | 5970 | 281 | 6460 | 289 | 5630 | 220 | 31200 |
| | BH$^+$ (9)[c] | 233 | 4770 | 238 | 4380 | 283–4 | 4930 | | | | 2050 |
| 3-$t$-Butyl | B | 222 | 36000 | 272 sh | 5060 | 280–1 | 5570 | 289 | 4790 | 220 | 33400 |
| | BH$^+$ (9)[c] | 235 | 5590 | 240 | 5330 | 288–90 | 4810 | | | | 2140 |
| Indole-3-acetic acid | B | 222 | 32200 | 273–4 sh | 5680 | 279 | 6000 | 294 | 5120 | 219 | 32100 |
| | BH$^+$ (12)[f] | 234 | 4420 | 239 | 4230 | 280–1 | 4770 | | | | 1800 |
| Tryptamine | B[g,h] | 218 | 34100 | 272 sh | 5180 | 277 | 5420 | 286 | 4500 | 218 | 34800 |
| | BH$^+$ (12)[g] | 234 | 4380 | 239 | 4130 | 287–8 | 4820 | | | | 1220 |
| 5-Methyl | B | 219 | 30200 | 269 | 5660 | 277 sh | 5240 | 295 | 3190 | 220 | 27200 |
| | | | | | | 284 | 4900 | | | | |
| | BH$^+$ (12)[c] | 239 | 4030 | 246 | 4920 | 271–4 | 5200 | | | | 1900 |
| 1,2-Dimethyl | B | 223 | 35500 | 276 | 7200 | 282 | 7650 | 291 | 6420 | 221 | 35500 |
| | BH$^+$ (5)[c] | 230 | 4550 | 237 | 4250 | 272–5 | 5600 | | | | 3080 |
| 1,3-Dimethyl | B | 225 | 31400 | 278 sh | 4740 | | | 288 | 5200 | 226 | 30700 |
| | BH$^+$ (10)[c] | 232 | 3790 | 237 | 3640 | 273–4 | 4840 | | | | 2750 |
| 1,3-Diethyl | B | 227 | 32400 | | | 280 sh | 4790 | 290 | 5330 | 226 | 31000 |
| | BH$^+$ (9)[f] | 234 | 4370 | 239 | 4270 | 280 | 4880 | | | | 2710 |
| 1-Methylindole-3-acetic acid | B | 224 | 33700 | 276 | 5250 | | | 286–7 | 5750 | 224 | 31900 |
| | | | | | | | | 297 sh | 4720 | | |
| | BH$^+$ (9)[c] | 231–2 | 4270 | 237 | 4140 | 280 | 4610 | | | | 2730 |
| 2,3-Dimethyl | B | 227 | 33300 | 276 sh | 6570 | 282 | 7070 | 290 | 6170 | 222 | 28500 |
| | BH$^+$ (6)[d,e] | 231 | 6870 | 237 sh | 5740 | 276–8 | 5830 | | | | 4560 |
| 2-Methyl-3-$n$-propyl | B | 225 | 38200 | 274 sh | 7120 | 282 | 7650 | 289 | 6890 | 224 | 28700 |
| | BH$^+$ (9)[c] | 230 | 6030 | 237 sh | 5240 | 279–80 | 5360 | | | | 4360 |
| 2,5-Dimethyl | B | 221 | 29700 | 272 | 7210 | 282 | 6770 | 293 | 4850 | 217 | 28200 |
| | | | | 276 sh | 7030 | | | | | | |
| | BH$^+$ (5)[c] | 234 | 5100 | 241 sh | 4510 | 284 | 6270 | | | | 2500 |
| 2,5-Dimethyl-3-$n$-propyl | B | 228 | 29400 | 279 sh | 6720 | 286 | 7130 | 297 | 5960 | 225 | 25000 |
| | BH$^+$ (6)[c] | 232 | 6600 | 243 | 5940 | 290–2 | 6270 | | | | 3340 |
| 1,2,3-Trimethyl | B | 230 | 34600 | 279 sh | 5880 | 286 | 6630 | 293 | 6320 | 230 | 31200 |
| | BH$^+$ (6)[c] | 231 | 5140 | 238 | 4860 | 275 | 5520 | | | | 4850 |
| 5-Nitro | B | 254 sh | 15900 | 264 | 17400 | 322–4 | 8010 | | | 330 | 8350 |
| | BH$^+$ (12)[c] | 211 sh | 9970 | 277–8 | 9820 | | | | | | 1800 |
| 6-Nitro | B | 247–8 | 10600 | | | 324–7 | 8340 | 355–60 | 7500 | 350 | 7990 |
| | BH$^+$ (12)[c] | | | 254 | 1200 | | | | | | 630 |
| 2-Methyl-5-nitro | B | 204 | 19400 | 263–4 | 20400 | 328–9 | 8550 | | | 293 | 3050 |
| | | | | | | | | | | 340 | 8890 |
| | BH$^+$ (9)[c] | 212 | 10400 | 283–5 | 12500 | | | | | 293 | 10900 |
| | | | | | | | | | | 340 | 1100 |
| 1,2-Dimethyl-5-nitro | B | | | 260 sh | 18500 | 274 | 22500 | 333–7 | 9550 | 295 | 4920 |
| | | | | | | | | | | 350 | 9720 |
| | BH$^+$ (6)[f] | 212 sh | 12100 | 281 | 13100 | | | | | 295 | 10100 |
| | | | | | | | | | | 350 | 870 |

[a] Spectra of free bases (B) taken in 95% ethanol; those of conjugate acids (BH$^+$) in sulfuric acid solutions of molarity shown in parentheses. These spectra were determined with a Beckman DK-2 recording spectrophotometer. [b] Values of $\lambda_B$ and $\epsilon_B$ taken in water. Wave length chosen was slightly removed from maximum to increase the difference between $\epsilon_B$ and $\epsilon_{BH^+}$; these measurements were made with a Beckman DU except those for 2-methyl- and 1,2-dimethylindole, which were made with the DK-2. Values for $\epsilon_{BH^+}$ were taken at acid concentrations near but not usually the same as those given at left of table. [c] Solutions contained 0.5% ethanol (v./v.). [d] Contained 0.1% ethanol (v./v.). [e] Hydrochloric acid. [f] Contained 1% ethanol (v./v.). [g] Introduced as the hydrochloride. [h] Spectrum taken in water.

utility for studying solvation differences than for the somewhat uncertain purpose of determining thermodynamic acidity constants.[17]

Finally, it should be noted that to the extent that deviations of indicator ratio plots from parallelism are due to differences in solvation, it may be inferred that for two or more bases of *closely related structure* having parallel indicator ratio plots in regions of overlap, the solvation of each base–conjugate acid pair will be the same.[35] It follows that the measured pK difference ($\Delta \log I$) is a difference in *intrinsic* base strengths, that is, the difference of base strengths in the vapor phase. As required by this hypothesis, pK values and substituent effects of indoles are independent of medium in sulfuric and perchloric acids; acidity constants of Hammett bases are constant over much greater variations of solvent composition.[5]

This approach requires that the base strength differences between $H_1$ indoles and deviant indoles as predicted from substituent effects are differences in intrinsic base strengths. It implies that the difference between the measured value of $\Delta \log I$ at any acid concentration and that predicted by substituent effects is the amount by which the activity coefficient term in eq. 3 differs from zero at that concentration of acid. This relationship may afford a method for evaluating solvation effects in strongly acidic media.

### Experimental[36]

**Materials.**—Compounds 1, 3, 16, 17, and 18 of Table I and compound 1 of Table II were purchased from the Fisher Scientific Co., compounds 2, 6, and 8 of Table I and 3 and 8 of Table II from the Aldrich Chemical Co., while 2 of Table II was obtained from the Regis Chemical Co. 3-Ethyl- and 3-*n*-propylindoles were gifts of Dr. Herbert Johnson, Union Carbide Chemicals Division, South Charleston, W. Va. The following known indoles were synthesized by the methods cited: 2-ethyl,[37a] 1,2,3-trimethyl,[37b] 1,3-dimethyl,[37b] 1-methyl,[37c] 1-ethyl,[37d] 1-methylindole-3-acetic acid,[37e] 6-nitro,[37f] 2-methyl-5-nitro,[37g] 1,2-dimethyl-5-nitro,[37g] 3-*t*-butyl.[37h] The last compound was obtained in 1% yield, and the recently reported method of synthesis from isatin[38] promises better results. Since no structure proof of 3-*t*-butylindole was given in the original report,[37h] the following evidence is provided here. The NH band at 2.99 μ in the infrared spectrum eliminates 1-*t*-butylindole, while the 2-isomer can be eliminated by the n.m.r. spectrum of the indole in 18 M sulfuric acid. A single low-field proton appears at 0.62 τ close to the position of a similar line in the conjugate acid of indole, and has a coupling constant of 7 c.p.s. in accord with the splitting observed for the conjugate acid of skatole.[3c] The very remote possibility of a 2-protonated 2-*t*-butylindole is eliminated because the low-field proton would now be at the 3-position. Coupling with the 1-proton would be small and coupling with the added proton at the α-position would also be small if not altogether absent because of the bond angles involved.[3c] In carbon tetrachloride the α-proton of 3-*t*-butylindole appeared at 3.50 τ with a 2 c.p.s. splitting, as compared to similar

lines at 3.35 τ for the α-proton of 3-methylindole and at 3.93 τ f or the β-proton of 2-methylindole.

**1,3-Diethylindole,** prepared by alkylation[37d] of 3-ethylindole, is a new compound, b.p. 92–93° (1 mm.), $n^{25}$D 1.5701. *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.03; H, 8.64; N, 8.29.

**The picrate,** reddish brown needles, after crystallization from 95% ethanol, melted at 96–97°. *Anal.* Calcd. for $C_{18}H_{18}N_4O_7$: C, 53.72; H, 4.51; N, 13.93. Found: C, 53.60; H, 4.67; N, 13.91.

All indoles were purified before use. Liquid samples were distilled under vacuum on an 18-in. spinning band column. A center cut was used for spectrophotometric measurements. Solids were brought to constant m.p. by repeated crystallization. Physical properties of known compounds agreed closely with literature values. The purity of the liquids and some of the lower melting solids was checked further by vapor phase chromatography using a Perkin–Elmer Type O column (silicone on diatomaceous earth).

Aqueous solutions of hydrochloric and sulfuric acids were prepared by dilution of Fisher reagent grade concentrated acids (36.5% min. and 95% min., respectively). Solutions of perchloric acid were prepared by dilution of Allied Chemical reagent grade acid, 70%. The concentrations of hydrochloric and perchloric acids were determined by titration against tris(hydroxymethyl)aminomethane. Concentrations of sulfuric acid were determined by titration or by density measurements. In the latter method calculations of the concentrations were based on data in the "International Critical Tables."

**Indicator Measurements.**—Stock solutions of each indole were prepared in 95% ethanol (except for tryptamine·HCl, which was prepared in distilled water) in concentrations ranging from 4 × $10^{-3}$ to 4 × $10^{-3}$ M and were kept in a constant temperature bath at 25.0 ± 0.1°. Aliquots of 0.05 ml. were pipetted into 10-ml. volumetric flasks and diluted to the mark with the appropriate acid. The solutions thus prepared contained 0.5 vol. % ethanol. With 2-methyl-5-nitroindole, 1,2-dimethyl-5-nitroindole, and 1,3-diethylindole, where the solubility of the compound in water or acid was particularly low, additional alcohol was used to make the final concentration 1 vol. %. The stock solution was so chosen that the final concentration of indole yielded an absorbance reading of 0.1 to 0.8 at the wave length studied. Absorbance readings of less than 0.1 were taken with 2-methyl-5-nitroindole (340 mμ), 6-nitroindole, 1,2-dimethyl-5-nitroindole (295 and 350 mμ), and 4-chloro-2-nitroaniline (420 mμ), which were more insoluble or for which the extinction coefficient of the acidic or basic form was near zero. The absorption spectra of most of the neutral indoles and their conjugate acids have not been reported previously and are given in Table VI. The wave lengths used for absorbancy measurements (Table VI) were in most cases at or near those of the maxima of the free bases, though in the cases of the nitroindoles, maxima of the conjugate acids were used also. Absorbancies of the perchloric acid solutions and most of the sulfuric acid solutions were measured in 1-cm. quartz cells on a Beckman DU spectrophotometer, with the cell compartment maintained at 25.0 ± 0.1° by means of double thermospacers. The slit was set at 0.15 to 0.3 mm. Measurements were made 1 to 1.5 min. after mixing. In general no attempt was made to exclude air at any stage except for indole (see below). For those compounds which were most susceptible to dimerization or oxidation in acid, especially indoles unsubstituted in the hetero ring, several measurements were made during a period from 4 to 15 min. after the initial reading and the results were extrapolated back to the time of mixing. Measurements of 1,2-dimethylindole and 2-methylindole in hydrochloric acid and sulfuric acid were made on a Beckman DK-2 spectrophotometer using a thermostated cell compartment maintained at the above temperature. These solutions contained 95% ethanol in amounts increasing from 0.2 to 1.0 vol. % with increasing acidity and increasing indole concentration. Similar measurements in perchloric acid yielded results identical with those made on the Beckman DU spectrophotometer. Measurements at the wave lengths studied were made of many of the indoles at varying concentrations of both indole and acid to verify the validity of Beer's law. For calculation of ionization ratios $\epsilon_B$ was chosen as the extinction coefficient of the indole in pure water and $\epsilon_{BH^+}$ as the extinction coefficient of the indole in a concentration of acid such that no further change in $\epsilon$ occurred with increasing acid strength (Table VI). Ionization ratios of representative indoles are given in Table VII. Plots of log $I$ vs. $C_{H_2SO_4}$ (Fig. 3) were made by a

(35) Although observations of this type cannot normally be made in dilute aqueous solution because the activity coefficient ratio is held constant, H. K. Hall, Jr. (*J. Am. Chem. Soc.*, **79**, 5441 (1957)) has shown that when $pK_a$ is plotted against $\Sigma\sigma^*$, aliphatic amines are separated into classes according to the number of substituents on nitrogen. The class distinctions were ascribed to the common mode of solvation of members of each class in a medium of fixed composition.

(36) Melting points and boiling points are uncorrected.

(37) (a) F. T. Tyson, *J. Am. Chem. Soc.*, **63**, 2024 (1941); (b) J. T. Fitzpatrick and R. D. Hiser, *J. Org. Chem.*, **22**, 1703 (1957); (c) P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949); (d) K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960); (e) H. R. Snyder and E. L. Eliel. *J. Am. Chem. Soc.*, **70**, 1703 (1948); (f) A. P. Terent'ev and M. N. Preobrazhenskaia, *Proc. Acad. Sci., U.S.S.R. Chem.*, **118**, 50 (1958); (g) W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, **28**, 2262 (1963); (h) G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 940 (1961).

(38) M. Bettembourg and S. David, *Bull. soc. chim. France*, 772 (1962).

<div align="center">

TABLE VII

IONIZATION RATIOS OF REPRESENTATIVE INDOLES IN
SULFURIC ACID[a]

</div>

| $H_2SO_4$, $M$ | log $I$ | $H_2SO_4$, $M$ | log $I$ | $H_2SO_4$, $M$ | log $I$ |
|---|---|---|---|---|---|
| | | | | 1,2-Dimethyl-5- | |
| 1,2-Dimethylindole | | 2,3-Dimethylindole | | nitroindole | |
| 0.80 | +0.55 | 1.00 | −0.93 | 3.44 | −0.73 |
| 0.90 | .68 | 1.25 | − .84 | 3.44 | − .84 |
| 1.00 | .76 | 1.48 | − .71 | 3.92 | − .47 |
| 1.25 | .97 | 1.73 | − .47 | 3.92 | − .45 |
| 1.50 | 1.14 | 1.97 | − .31 | 4.47 | − .13 |
| 1.75 | 1.35 | 2.47 | + .03 | 4.47 | − .07 |
| 2.00 | 1.46 | 2.96 | .36 | 4.88 | + .23 |
| | | 3.46 | .68 | 4.88 | .13 |
| 2-Methylindole | | 3.96 | .97 | 5.51 | .73 |
| 1.25 | +0.36 | | | 5.51 | .57 |
| 1.50 | .55 | 1-Methylindole | | 5.93 | 1.02 |
| 1.75 | .73 | 2.96 | −0.56 | 5.93 | 0.89 |
| 2.00 | .91 | 2.96 | − .44 | | |
| 2.50 | 1.19 | 3.44 | − .21 | 3-Methylindole | |
| | | 3.46 | − .12 | 5.92 | −0.74 |
| 1,2,3-Trimethylindole | | 3.92 | + .18 | 6.53 | − .34 |
| 1.51 | +0.21 | 3.95 | .12 | 6.90 | + .05 |
| 1.75 | .34 | 4.47 | .57 | 6.99 | .07 |
| 2.02 | .55 | 4.88 | .79 | 7.41 | .28 |
| 2.25 | .71 | 4.93 | .84 | 7.50 | .39 |
| 2.52 | .87 | | | 7.89 | .68 |
| 2.95 | 1.22 | | | 7.92 | .67 |
| | | | | 8.88 | 1.43 |
| Indole-3-acetic acid | | Tryptamine | | 1,3-Dimethylindole | |
| 8.20 | −0.74 | 8.47 | −0.83 | 4.03 | −0.81 |
| 8.71 | − .43 | 8.87 | − .51 | 4.03 | − .94 |
| 9.22 | + .02 | 9.16 | − .30 | 4.11 | − .82 |
| 9.74 | .35 | 9.46 | − .04 | 4.11 | − .78 |
| 10.25 | .66 | 9.81 | + .20 | 4.47 | − .59 |
| 5-Nitroindole | | 9.91 | .27 | 4.52 | − .46 |
| 8.91 | −0.93 | 10.27 | .60 | 4.52 | − .51 |
| 8.91 | − .82 | 10.27 | .61 | 4.82 | − .23 |
| 9.77 | − .69 | 10.87 | .97 | 4.82 | − .25 |
| 9.77 | − .59 | Indole | | 4.88 | − .27 |
| 9.88 | − .53 | 3.92 | −0.67 | 4.88 | − .30 |
| 10.35 | − .39 | 4.10 | − .84 | 5.04 | − .07 |
| 10.35 | − .33 | 4.47 | − .38 | 5.04 | − .05 |
| 11.28 | + .16 | 4.61 | − .30 | 5.11 | − .04 |
| 11.28 | .00 | 4.88 | − .19 | 5.11 | − .09 |
| 11.63 | .40 | 5.10 | − .23 | 5.39 | + .13 |
| 12.50 | .79 | 5.51 | − .07 | 5.39 | .17 |
| | | 5.64 | − .01 | 5.51 | .29 |
| | | 5.93 | + .27 | 5.51 | .26 |
| | | 6.15 | .25 | 5.93 | .56 |
| | | 6.40 | .43 | 5.93 | .96 |
| | | 6.89 | .68 | 5.97 | .66 |
| | | | | 6.03 | .74 |
| | | | | 6.03 | .74 |
| | | | | 6.40 | .99 |
| | | | | 6.40 | .96 |

[a] Measurements used for plots like those of Fig. 3, for determining d log $I$/d$C_{H_2SO_4}$. Measurements were made at wave lengths given in Table VI. Where more than one measurement is recorded for one concentration of acid, it indicates that separate determinations were made at one wave length, or if several wave lengths are indicated in Table VI, the results are from one experiment only.

linear least-squares treatment. Corrections for medium effects on $\epsilon$ have been discussed in the text. Acidity constants determined by the overlap method are all based on the thermodynamic $pK_a$ of 2-methylindole taken as the average of values obtained by the customary extrapolation procedure in sulfuric, hydrochloric, and perchloric acids (Table I). The average deviation of these results was ±0.01. Ultraviolet spectra of 1,2-dimethylindole, 1,3-dimethylindole, 2-methylindole, 2-methyl-5-nitroindole, and several other indoles in solutions of increasing acidity showed isosbestic points, indicating no lateral solvent shifts within the range of acid concentrations used. Examination of the stability of the methylindoles in various concentrations of acid gave results in complete accord with those of Berti who has discussed this point in detail.[2] A Hammett indicator, 4-chloro-2-nitroaniline, supplied by Aldrich Chemical Co., was used to test the validity of the method. The slope and $pK_a$ obtained were in agreement with previous work[4] and were not affected by the use of 0.5 vol. % ethanol. Moreover, measurements at 420 m$\mu$ with absorbancies of < 0.1 were consistent with those made at 232 m$\mu$.

**Measurement of Indicator Ratio of Indole in Sulfuric Acid. A. Under Nitrogen.**—A 2.04 × 10$^{-2}$ $M$ stock solution of indole in 95% ethanol was prepared using 0.1194 g. of indole and adding 95% ethanol to 50 ml. A second solution, 4.08 × 10$^{-3}$ $M$, was prepared by diluting a 5-ml. aliquot of the first solution to 25 ml. with 95% ethanol. About 10 ml. of each solution was transferred to erlenmeyer flasks, which were stoppered with serum caps, and flushed with nitrogen through glass capillary tubes for 1 hr.; 25-ml. portions of the aqueous sulfuric acid solutions previously prepared and standardized were also flushed with nitrogen. All the solutions were immediately placed in a glove box under a positive pressure of nitrogen. Solutions of indole in sulfuric acid were prepared by pipetting 50 $\mu$l. aliquots of the appropriate stock solution into a 10-ml. volumetric flask about half filled with acid and adding acid to the mark. After mixing, a few ml. was transferred to a Beckman 1-cm. silica cuvette and stoppered with a serum cap. The cuvette was removed from the glove box and absorption of the solution at 215 m$\mu$ was measured on a Beckman DU spectrophotometer whose cell compartment was maintained at 25 ± 0.1° by means of double thermospacers. The first measurement was taken 2-3 min. after mixing and several measurements were taken for 3-7 min. thereafter. In cases where the absorption showed changes with time, the results were extrapolated back to the time of mixing. The final concentration of indole was 2.05 × 10$^{-5}$ $M$ in 7.7 $M$ H$_2$SO$_4$ and 1.02 × 10$^{-4}$ $M$ in 7.7-14.8 $M$ H$_2$SO$_4$. The measured absorption ranged from 0.05 to 0.82. The average value of d log $I$/d(H$_2$SO$_4$) from several experiments of this type was 0.38.

**B. In Very Dilute Solution.**—Two stock solutions of indole in 95% ethanol were prepared by dissolving 3.16 and 14.48 mg. of indole in 100 ml. of ethanol to yield solutions 2.70 × 10$^{-4}$ and 1.24 × 10$^{-3}$ $M$, respectively. Aliquots of 0.20 ml. were diluted to 50 ml. with aqueous sulfuric acid solutions previously prepared and standardized. Final concentration of indole was 1.08 × 10$^{-6}$ $M$ in 7.01 $M$ acid and 4.96 × 10$^{-6}$ $M$ in 7.0-9.8 $M$ H$_2$SO$_4$. Absorption of the solutions was measured at 215 m$\mu$ on a Beckman DU spectrophotometer using 10-cm. Beckman cylindrical cells with fused-on silica windows. The cell compartment was maintained at 25.0 ± 0.1° by means of double thermospacers. The value for $\epsilon_{BH^+}$ was taken from previous measurements in H$_2$SO$_4$ using 1-cm. path length cells. The first measurement was taken 2-3 min. after mixing. Little or no change occurred for 5 min. Value of d log $I$/d$C_{H_2SO_4}$ = 0.54.