acetonitrile and then acetonitrile. An additional 3.19 g. was obtained when the combined liquors were evaporated to about 20 ml. under reduced pressure. The ultraviolet spectrum of a solution of the salt in water was the same as an alkaline solution of phenylboronic acid.

Anal. Calcd. for $C_7H_{14}N_3BO_3$: C, 42.2; H, 7.04; N, 21.1; B, 5.43; formula wt., 199; mol. wt., 99. Found: C, 42.6; H, 7.11; N, 21.3; B, 5.64; mol. wt. (in water), 92.

B^{11} N.m.r. Chemical Shifts.—The nuclear magnetic resonance spectra were obtained using a Varian high resolution nuclear magnetic resonance spectrometer. The chemical shifts in Table I are relative to boron trifluoride etherate as zero reference. Because of the breadth of the resonance lines and the consequent uncertainty in fixing the exact position of the bands, the effect of the substituents on the chemical shielding of boron could not be delineated with assurance.

Ultraviolet Absorption Measurements.—The ultraviolet absorption studies were performed with a Cary automatic recording spectrophotometer, Model 11. The spectra of compounds VII, VIII, IX and XI (Table I) were obtained with alkaline solutions in order to retard changes in the spectra due from hydrolysis.

Solutions for hydrolysis studies were prepared by adding aqueous sodium hydroxide alone or together with an aqueous solution of the requisite boron acid to stock solutions of the cyclic borinides. The amount of biguanidinium ion, and hence the extent of hydrolysis, at equilibrium (Table II) was calculated from the equation

$$C_2 = (A_{231} - \epsilon_1 C_1)/(\epsilon_2 - \epsilon_1)$$

where C_1 represents the initial concentration of the heterocycle C_2 the concentration of biguanidinium ion, A_{231} the absorption in a 1-cm. cell, and ϵ_1 and ϵ_2 the molar extinction coefficient of the heterocycle of biguanidinium ion, respectively, at 231 mμ.

Acknowledgment.—The authors are indebted to Dr. J. A. Kuck for microanalyses, to N. Colthup for assistance in interpreting infrared spectra, and to Miss C. J. Kappes for naming the heterocyclic compounds.

[CONTRIBUTION FROM THE UNION CARBIDE RESEARCH INSTITUTE, UNION CARBIDE CORP., TARRYTOWN, N. Y.]

The Protonation of Indoles: Position of Protonation

BY R. L. HINMAN AND E. B. WHIPPLE

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The principal conjugate acid of an indole in strong aqueous acids is the 3-protonated isomer. This has been inferred from ultraviolet absorption spectra and confirmed by proton magnetic resonance measurements on a series of methylindoles. Deuterium exchange experiments show that exchange occurs generally at the 1- and 3-positions of the indole ring, and in some cases at the 2-position. Exchange at the 1- and 2-positions may occur by protonation of those positions. Some evidence for 1-protonation is provided by the infrared spectra of solid salts of indoles, which show the presence of 1- or 3-protonated species or both, depending on the indole, the acid and the method of isolation of the salt. In the conjugate acid of an indole, exchange in the 2-position takes place by protonation competitive with that at the 3-position, whereas exchange at the 1-position takes place by proton loss competitive with that at the 3-position. Diprotonation does not appear to be important in any of the exchange processes. The effects of methyl substituents in the hetero ring on the relative extents of 3- and 2-protonation are discussed.

The protonation of the indole nucleus has been of interest for many years from both theoretical and synthetic points of view. Although feebly basic, simple alkyl derivatives of indole form isolable salts with strong acids.[1] Moreover, a number of reactions of indoles are acid catalyzed. Dimerization and trimerization,[2] hydrogenation[3] and attack by molecular oxygen[3] fall in this group. The orientation and ease of reaction in electrophilic substitutions such as nitration will certainly be influenced by the extent of prior protonation.[4]

Two fundamental problems arise in a consideration of the protonation of the indole nucleus and its bearing on the reactions mentioned above. The first, which is the main subject of this paper, is the position of protonation. The second question, which will be treated in more detail in a subsequent paper, concerns the basicity of indole relative to other well-known bases, and the effect of substituents on the basicity.[5,6]

Every position of the hetero ring of indole has been suggested as the site of protonation.[2,4a,7] Some evidence which bears on this point was provided by Koizumi, who studied the acid-catalyzed exchange of deuterium in D_2O for ring hydrogens of indole and a number of its methyl derivatives.[7,8] With increasing concentration of acid, first the hydrogen on nitrogen and then both that hydrogen and the β-hydrogen underwent exchange. At still higher concentrations of acid (> 0.8 *N* HCl) further exchange occurred.[9] It

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(1) (a) P. Wagner, *Ann.*, **242**, 388 (1887); (b) K. A. Hofmann, A. Metzler and K. Hobold, *Ber.*, **43**, 1082 (1910); (c) B. Oddo. *Gazz. chim. ital.*, **43 I**, 385 (1913).

(2) (a) G. F. Smith, *Chemistry & Industry*, 1451 (1954); (b) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960); (c) R. L. Hinman and E. Shull, *ibid.*, **26**, 2339 (1961).

(3) R. L. Hinman and P. Frost, in "Plant Growth Regulation," R. L. Klein, Ed., Iowa State Univ. Press, Ames, Iowa, 1961, p. 205; also unpublished work from this Laboratory. It has recently been suggested that reduction of indoles in acidic media may take place by way of a protonated indole (A. R. Bader, R. J. Bridgwater and P. R. Freeman, *J. Am. Chem. Soc.*, **83**, 3319 (1961)). In the pyrrole series the catalytic effect of acids on oxidation and hydrogenation (A. Treibs and H. G. Kolm, *Ann.*, **606**, 166 (1957)) and on trimerization (H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957)) has also been noted.

(4) (a) R. de Fazi, G. Berti and A. da Settimo, *Gazz. chim. ital.*, **89**, 2238 (1959); (b) W. E. Noland, Univ. of Minnesota, personal communication.

(5) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960).

(6) The basicities of a number of methylpyrroles and identification of the α-position as the site of protonation have recently been reported (R. J. Abraham, E. Bullock and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959)).

(7) (a) M. Koizumi, Y. Komaki and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 643 (1938); (b) A. Treibs, E. Herrmann, E. Meissner and A. Kuhn, *Ann.*, **602**, 153 (1957); (c) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957); (d) G. Berti, A. da Settimo and D. Segnini, *Gazz. chim. ital.*, **91**, 571 (1961).

(8) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); M. Koizumi, *ibid.*, **14**, 453 (1939).

(9) Exchange of the α-hydrogen was suggested to explain the results at the higher acid concentrations. Although exchange at this position occurs in some cases (see below), it is not clear that this was proved by the early work, the results of which were obscured by the occurrence

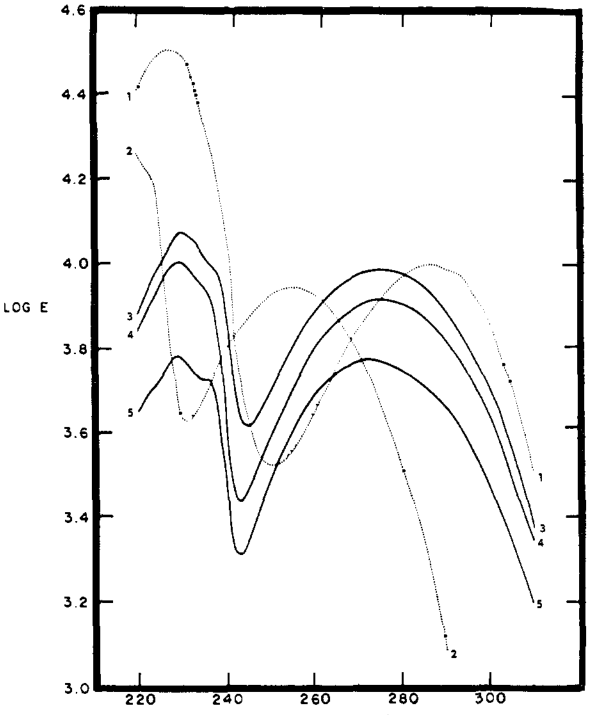


Fig. 1.—Ultraviolet absorption spectra of: 1, 1,2,3-trimethylindole in water; 2, 2,3,3-trimethylindolenine in 95% ethanol; 3, 1,2,3-trimethylindole in 3 *M* sulfuric acid; 4, 2,3,3-trimethylindolenine in 0.1 *N* hydrochloric acid; 5, 2,3,3-trimethylindolenine methiodide in water.

was assumed that protonation on nitrogen always occurred first and that exchange at other positions took place by means of acid-catalyzed tautomerization of the N-protonated species. It was not possible of course to determine the site of protonation when the ring positions were substituted by groups other than hydrogen.

Our initial attack on the question of the position of protonation was based on ultraviolet absorption spectra. In neutral solution indole and its mono-, di- and trialkyl derivatives exhibit a strong maximum near 220 mμ and a maximum of lower intensity near 280 mμ, usually flanked by two shoulders. When indoles of this type are dissolved in sufficiently strong acid to effect complete protonation, the peak near 220 mμ is replaced by two peaks of much lower intensity near 230 and 237 mμ. The detailed absorption at longer wave lengths is replaced by a very broad maximum near 275 mμ. The changes in the spectrum of 1,2,3-trimethylindole, shown in Fig. 1, are typical.

If protonation occurred predominantly at the 3-position, the product would have the indolenine structure Ia. The ultraviolet spectrum of Ia would be expected to resemble closely those of the conjugate acid Ib and methiodide Ic of 2,3,3-trimethylindolenine. The anticipated relationship was verified by experiment (Fig. 1).[10] Although this is good evidence for 3-protonation, it does not rule out protonation at the other positions because models of these protonated forms were not available for comparison.

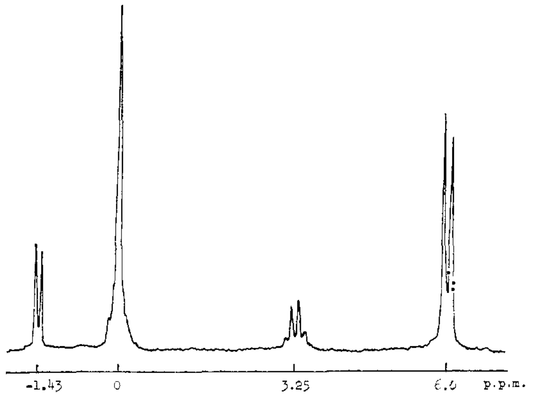
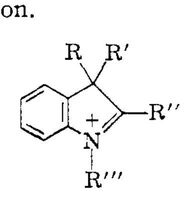


Fig. 2.—Proton magnetic resonance spectrum of skatole at 60 mc. in 18 *M* sulfuric acid solution.



Ia, R = H; R′ = R″ = R‴ = CH_3
b, R = R′ = R″ = CH_3; R‴ = H
c, R = R′ = R″ = R‴ = CH_3
d, R = R″ = R‴ = H; R′ = CH_3

Proton magnetic resonance spectra provide unequivocal proof that the 3-protonated species (Ia) is predominant in strong acids. The 60 mc. spectrum of skatole in 18 *M* sulfuric acid (Fig. 2) is illustrative. The resonance of the methyl hydrogens can be positively identified as the doublet at 6.0 p.p.m. higher applied field than the aromatic proton line. The methyl doublet differs from the methyl proton line in the free base[2c,11,12] both in the 7.5 c.p.s. splitting and in its shift of 1.2 p.p.m. to higher field. Both effects would result from the presence of an added proton at the 3-position and the resultant change of hybridization of that carbon. The quartet fine structure and 7.5 c.p.s. splitting of the 3.25 p.p.m. line[12] require its assignment to the added proton in the 3-position. The broadening of the quartet with concurrent disappearance of the methyl group splitting on dilution of the acid with water, and the absence of a 3.25 p.p.m. line from the spectrum of skatole in D_2SO_4 solution confirm the assignment.

The doublet split by 6 c.p.s. at −1.43 p.p.m. is assigned to the ring hydrogen at the 2-position. Its splitting results from spin coupling with the otherwise undetected single proton on the nitrogen atom. The corresponding line in the spectrum of the conjugate acid of 1,3-dimethylindole is a singlet. The absence of spin coupling between the protons in the 2- and 3-positions is understandable

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of extensive dimerization, the failure of the α-hydrogen of N-methylindole to undergo exchange, and the apparent exchange of five hydrogens in skatole in 3.0 *N* acid.

[10] A similar approach has recently been used to show that a number of 2-phenylindoles undergo 3-protonation (M. J. Kamlet and J. C. Dacons, *J. Org. Chem.*, **26**, 220 (1961)).

[11] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).

[12] For purposes of direct comparison with the spectra of the free bases, chemical shifts are referenced internally with respect to the aromatic proton line(s) of the dissolved indole. The positive direction is that of increasing external field.

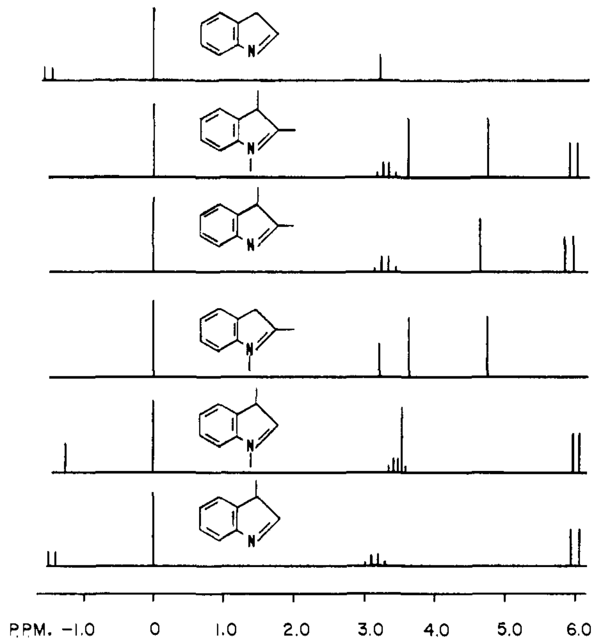

Fig. 3.—Proton magnetic resonance spectra of conjugate acids of indoles in sulfuric acid (12–18 *M*).

in terms of the bond angles,[13] and the failure to observe an N–H proton resonance is not unexpected.[14]

The normalized line intensities are compatible with these assignments, and all details of the spectra of the methyl-substituted indoles summarized in Fig. 3 are in complete agreement.

Although the n.m.r. spectra establish directly that the predominant protonation of the indole ring occurs in the 3-position,[15] they do not exclude the possibility of protonation to a limited extent in other positions.[16] Indirect evidence bearing on this point was obtained by observing exchange at the various ring positions in D_2SO_4–D_2O mixtures. The spectrum of skatole in 18 *M* D_2SO_4, for example. first observed about two minutes after mixing, showed a singlet for the 2-proton signal which disappeared gradually over a period of about 30 minutes. Rapid exchange of the NH proton is therefore followed by slow exchange of the proton on the 2-carbon. For the former the mean lifetime can be estimated as $0.20 \leq \tau_1 \leq 60$ sec. by assuming that a minimum of three half-lives had elapsed between the D_2SO_4 addition and the first observation; the lower limit is that below which dynamic effects from the exchange would have been observed in H_2SO_4 solutions. With 1,3-dimethylindole in D_2SO_4 a half-life on the order of several days was observed for the 2-proton.[17] For both 1,3-dimethylindole and skatole the rates of 2-proton exchange increased as the solvent acid was diluted with D_2O, thereby eliminating any exchange mechanism involving diprotonation. This evidence for α-protonation is consistent with the observations that electrophilic substitution of the α-position of an indole may occur when the β-position is occupied by alkyl groups, as in the dimerization of skatole.[2c]

Evidence for 1-protonation was obtained from the infrared spectra of salts of indoles and strong acids, prepared by precipitation with ether. The position of protonation can be determined by the presence of absence of bands corresponding to the groups ammonium ($R_3\overset{+}{N}H$, 2400–2600 cm.$^{-1}$), immonium ($=\overset{+}{N}H$—, ~2000 cm.$^{-1}$) and $>C=\overset{+}{N}<$ (1630–1640 cm.$^{-1}$). (Salts containing the immonium group also show the band(s) of the general ammonium group.)

As shown in Table I, the added proton can be attached to the nitrogen or to the 3-carbon, depending on the acid, the indole and the method of isolation of the salt. All perchlorates examined were 3-protonated. The acid sulfate of 1,2,3-trimethylindole showed only an ammonium band. indicating 1-protonation. When the acid sulfate of 1,2-dimethylindole was prepared by instantaneous precipitation from ether during dropwise addition of concentrated sulfuric acid, the product showed bands corresponding to the ammonium and $>C=\overset{+}{N}<$ groupings, but not the immonium group. This indicates that both 1- and 3-protonated species were present, the methiodide of 2.3.3-trimethylindolenine serving as a model for the 3-protonated salt. When the salt was prepared in sulfuric acid solution identical to that in which only the n.m.r. spectrum of the 3-protonated species was observed, and then precipitated with ether. the product showed ammonium bands of about the same strength as those in the preparation above. but only a very weak band for the $>C=\overset{+}{N}<$ group. The infrared spectra of the sulfate and perchlorate of 2-methylindole have bands in all three regions of interest corresponding to those in the hydrochloride of 2,3,3-trimethylindolenine (Ib), indicating the presence of the 3-protonated salt, but not excluding the 1-protonated type. From these results it is clear that 1- or 3-protonation may occur in solution. The 1-protonated isomer can be isolated in certain cases probably because it is the less soluble species.[18]

The exchange of hydrogen on the indole nitrogen observed by n.m.r. when skatole was dissolved in D_2SO_4 may therefore have taken place by protona-

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(13) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(14) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 80; see also ref. 2c, footnote 18.

(15) The present study includes only indole and its methyl derivatives. However, the evidence cited in footnote 10 together with experiments in this Laboratory on a variety of substituted indoles including 5- and 6-nitroindole, indole-3-acetic acid, tryptophan, tryptamine and other alkylindoles, show that 3-protonation is a very general phenomenon. Certain 2-phenylindoles[10] and 3-acylindoles are apparently exceptions. The latter undergo protonation mainly on the acyl oxygen (G. Berti and A. da Settimo, *Gazz. chim. ital.*, **91**, 728 (1961)).

(16) The sensitivity of the n.m.r. measurements is estimated to be about 5% of the total indole concentration, or ~0.07 *M*.

(17) Koizumi[17a] reported that the α-hydrogen of N-methylindole would not undergo exchange at hydrochloric acid concentrations up to 3 *N*.

(18) In analogous fashion C-protonation of pyrroles is observed in solution, but the isolated salts appear to be N-protonated (E. Bullock. *Can. J. Chem.*, **36**, 1686 (1958); also ref. 6). Evidence has been presented for protonation of simple vinylamines on nitrogen as well as on carbon in chloroform solution (A. J. Speziale and R. C. Freeman, *J. Am. Chem. Soc.*, **82**, 909 (1960)).

TABLE I

INFRARED SPECTRA OF INDOLE SALTS

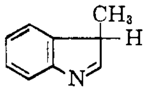
Base	Acid	Medium[a]	Ammonium $\overset{+}{\gt NH}$[b]	Immonium $=\overset{+}{N}H-$[b]	$>C=\overset{+}{N}<$[b]
2-Methylindole	H_2SO_4[c]	N	2490(m)	1975(w)	1644(s)
	$HClO_4$[c]	N	.....	2080(w)	1640(s)
1,2-Dimethylindole	H_2SO_4[c]	K	2390–2480(m); 2570–2600(m)	.....	1632(s)
	H_2SO_4[d]	K	2360–2480(m); 2600(m)	.....	1632(v.w.)
	$HClO_4$[e]	K	.....	.....	1630(s)
1,2,3-Trimethylindole	H_2SO_4[c,f]	K	2390–2460(m); 2570(m)	.....	....
	$HClO_4$[c]	K	.....	.....	1632(s)
2,3,3-Trimethylindolenine	HCl	K	2400–2430(s); 2590(s)	1978(m); 2060(w)	1640(s)
2,3,3-Trimethylindolenine methiodide		N or K	.....	.....	1635(s)

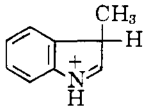
[a] N = Nujol, K = KBr. [b] References for assignments of bands: B. Witkop, J. B. Patrick and H. M. Kissman, *Ber.*, **85,** 949 (1952); B. Witkop, *J. Am. Chem. Soc.*, **78,** 2873 (1956). [c] Product isolated by rapid precipitation from ether solution during dropwise addition of concd. acid. [d] Product isolated by addition of ether to solution of indole in concd. acid. [e] Spectra the same whether product isolated by method *c* or *d*. [f] Salt was an oil.

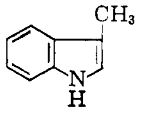
tion (deuteronation) of nitrogen. Exchange by this mechanism has been proposed previously for aqueous solutions in the range from 3.0 *N* acids to *p*H 7.0.[7a,8] We have found that in neutral dioxane–D_2O mixtures, exchange of the indole NH can be followed by the disappearance of the NH band in the infrared, a process which obeys a first-order rate law. Acid accelerates the exchange: $2 \times 10^{-6}M$ sulfuric acid more than doubled the rate. However, base *also* catalyzes the exchange, indicating that in neutral solution exchange may occur by removal of a proton from the indole nitrogen by a molecule of solvent, rather than by protonation, as previously suggested.[8]

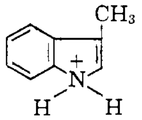
The experiments described above indicate that in acidic media exchange at the three hetero ring positions in the neutral indole may occur by competitive protonation of the neutral base. In the conjugate acid of an indole the situation is somewhat different. By adding skatole to 18 *M* sulfuric acid and then diluting with 18 *M* D_2SO_4, it was possible to observe simultaneously by n.m.r. the proton exchange at all three indole ring positions in the conjugate acid (Id). The doublet structure in the 2-proton resonance had disappeared during the two minutes which elapsed before the first scan, but about one-half the total intensity in the methyl group pattern still showed doublet structure. This disappeared rapidly, and was followed by a slow decay of the 2-proton signal.[19] Disappearance of the doublet structure in the 3-methyl group and the 3-proton signal took place at a rate which was an order of magnitude greater than the disappearance of the 2-proton signal. This experiment suggests, but does not prove, that exchange of the 2-proton occurs by a competitive protonation of the free base. It demonstrates unequivocally that exchange of the NH proton does not *depend* on this mechanism (although concurrent N-protonation is not excluded). Two alternative mechanisms for NH proton exchange in the conjugate acid which satisfy the criterion of not requiring an initial deprotonation of the 3-position are either diprotonation or proton loss from the 1-position to yield the tautomeric indolenine. The latter process should correspond generally to that for 3-proton exchange, while diprotonation would be expected to follow a rate law which has a dependency on acidity inverse of that for the deprotonation of the 3-position. Also, the activation energies for proton loss at alternate sites might reasonably be similar, while a higher value would be expected for addition of a second proton to the positive ion. By observing the collapse of the two doublets in protonated skatole at elevated temperatures (~75°) and different concentrations of solvent acid, it was found that both exchange rates increase with decreasing solvent acidity, and that both processes have activation energies of about 16 kcal. mole^{-1}. Therefore, deprotonation to the indolenine is the mechanism required to explain the faster rate of NH *vs.* β-CH proton exchange in the conjugate acid. The faster deprotonation to the stronger base (indolenine) is an interesting example of the kinetically-controlled reaction type more often encountered in the competitive protonation of an ambident anion.[20] These facts collectively give strong support to the over-all reaction scheme

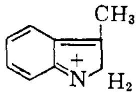
$$\begin{tikzcd}
 & & B'H^+ + S \arrow[d, shift left, "k_1"] & \\
B'' + SH^+ \arrow[r, shift left, "k_{-4}"] & B'''H^+ + S \arrow[l, shift left, "k_4"] \arrow[r, shift left, "k_3"] & B + SH^+ \arrow[l, shift left, "k_{-3}"] \arrow[u, shift left, "k_{-1}"] \arrow[r, shift left, "k_{-2}"] & B''H^+ + S \arrow[l, shift left, "k_2"]
\end{tikzcd}$$


B''


B'''H$^+$


B


B'H$^+$


B''H$^+$

and at the same time offer support for the sug-

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[19] In order to minimize the time interval between recording the 2-proton signal and that of the methyl group, a side band of the latter was actually observed after presetting the spectrometer for the optimum modulating frequency and amplitude.

[20] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 565.

gestion[21] that the introduction of deuterium into the methyl groups of 1,1-diphenyl-2-methylpropene by D_2SO_4 takes place by the closely analogous sequence below, the terminal olefin corresponding to

$$(C_6H_5)_2\overset{+}{C}{-}CH(CH_3)_2 \rightleftarrows (C_6H_5)_2C{=}C(CH_3)_2 \rightleftarrows$$
$$(C_6H_5)_2CH\overset{+}{C}(CH_3)_2 \rightleftarrows (C_6H_5)_2CHC(CH_3){=}CH_2$$

the indolenine in our series. A general parallel between the exchange rates at the 3-position and the pK_a's of the bases[22] supports our assumption that proton transfers at the 3-position occur through the acid–base reactions to which the equilibrium data are applicable. Thus the 3-proton in the weakest conjugate acid of the series, that of 1,2-dimethylindole, has a mean lifetime of about 0.15 second in 8.7 M sulfuric acid, but shows negligible exchange over a period of several days in 18 M acid. The strongest conjugate acid of the series, that of skatole, has a mean 3-proton half-life of several minutes in 18 M acid. Conjugate acids of intermediate strength, including 1,3-dimethyl-, 2,3-dimethyl- and 1,2,3-trimethylindole, show intermediate exchange rates, all of which increase as the concentration of solvent acid is decreased.

Although a quantitative treatment of the rate and/or equilibrium laws cannot be based on anything as simple as a second-order exchange process involving a single solvent species of definite composition, a qualitative approach of this type is possible.[23] Using the equilibria indicated above, and assuming that every "protonation" introduces deuterium and that no isotope effects are involved, the rate of introduction of deuterium at the α-position of *the conjugate acid* $B'''H^+$ (the only species observed directly) can be expressed by

$$r\alpha = (1/2)\left(\frac{k_{-2}}{k_{-2} + k_{-3}}\right) k_3 C_{B'''H^+} C_S$$

and the rate of deuterium introduction at the β-position as

$$r\beta = \left(\frac{k_{-3}}{k_{-2} + k_{-3}}\right) k_3 C_{B'''H^+} C_S$$

Since $k_{-2}/2k_{-3} = r\alpha/r\beta$, which is $\ll 1$

and $K_3 = k_3/k_{-3}$, then

$r\alpha \cong {}^1/_2 k_{-2} K_3 C_{B'''H^+} C_S$, and

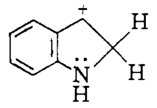
$r\beta \cong k_3 C_{B'''H^+} C_S$

Comparing the conjugate acids of skatole and 1,3-dimethylindole, when $C_{B'''H^{+(3)}} = C_{B'''H^{+(1,3)}}$, and C_S is the same in both cases

$$\frac{r\alpha^{(3)}}{r\alpha^{(1,3)}} = \frac{k_{-2}{}^{(3)}}{k_{-2}{}^{(1,3)}} \times \frac{K_3{}^{(3)}}{K_3{}^{(1,3)}} \qquad (1)$$

Then insofar as K_3 can be replaced by K_{a3} and the k_{-2}'s are equal, the ratio of 2-proton exchange rates between skatole and 1,3-dimethylindole will approach a value of about 15, the ratio of the known K_a values.[22] (The increasing exchange rates with increasing concentration of water are correctly accounted for in the first two equations.)

In 18 M D_2SO_4 the observed exchange rate at the α-position increases in the order 1-methyl < 1,3-dimethyl < 3-methylindole. Exchange in the first case is negligible,[17] and the difference of the other two rates deviates significantly from the value of 15 called for in eq. 1. These deviations would be ascribed to the non-equivalence of the k_{-2} values. If the changes in the basicity of the β-position,[22] which differ in magnitude with the point of methyl substitution in the hetero ring, operate in a similar but not corresponding way at other protonation sites, substituents may have an even greater effect on the α/β protonation ratio than on the pK_a of the β-position. Hence the observation that appreciable α-proton exchange is observed only when 3-methyl groups are present appears to depend not only on a negative effect on the pK_a for β-protonation, as expressed by equations having the form of (1), but also on an enhancement of basicity at the α-position. The former effect is to be expected because stabilization by the methyl groups would be greater on the sp² carbon of the base than on the sp³ carbon of the conjugate acid. On a similar basis, a 3-methyl group should lower the energy of the benzyl carbonium ion structure II relative to the free base, and hence increase the basicity at the α-position to the extent that this structure describes the ground state of the conjugate acid. The decrease in α-proton exchange rate caused by the presence of a 1-methyl group, which is more than would be expected from eq. 1 on the basis of the increase in pK_a at the β-position, suggests that valence-bond structures with positive charge on the nitrogen atom are relatively less important in the α-protonated conjugate acid than in the free base.



II

Acknowledgment.—The authors are indebted to Dr. Verner Schomaker for helpful discussions.

Experimental[24]

2,3,3-Trimethylindolenine was prepared by refluxing for 2.5 hr. a solution of the phenylhydrazone of methyl isopropyl ketone in glacial acetic acid.[25] The product was a pale yellow liquid, b.p. 58° (0.45 mm.), n^{22}_D 1.5440. Ultraviolet spectrum of a $10^{-4}M$ solution in 95% ethanol showed λ_{max} 222.5, 255, ϵ_{max} 16700, 8780. In 0.1 N hydrochloric acid, the spectrum showed λ_{max} 229, 235, 275; ϵ_{max} 10, 100, 8900, 8150.

The product formed a picrate, m.p. 158–159° (from 95% ethanol) (reported[26] m.p. 158°), and a hydrochloride, m.p. 185–187° dec. after recrystallization from ethanol–ether. The hydrochloride rapidly turned red when exposed to air.

Anal. Calcd. for $C_{11}H_{14}NCl$: N, 7.16. Found: N, 7.54.

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[21] N. C. Deno, P. T. Groves and G. Saines, *J. Am. Chem. Soc.*, **81**, 5790 (1959).

[22] R. L. Hinman and J. Lang, Abstracts of Papers, 140th National Meeting of the American Chemical Society, September 8, 1961, p. 98-Q.

[23] Log-log plots of the 3-proton exchange rate in the conjugate acid of 1,2-dimethylindole against the activity of water in sulfuric acid solution (N. C. Deno and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **76**, 244 (1954)) over the concentration range 6 M–10 M in sulfuric acid fail to show a linear dependence, and the slopes fall between 2.0 and 3.0. Insofar as the rate laws for protonation in the 2- and 3-positions do not differ in form, the qualitative conclusions of this treatment are not affected.

[24] Melting points and boiling points are uncorrected. Ultraviolet spectra were determined with a Beckman DK-2 spectrophotometer equipped with silica cells of 1-cm. light path. Infrared spectra were obtained with a Perkin-Elmer model 21 spectrophotometer equipped with sodium chloride optics.

[25] K. H. Pausacker, *J. Chem. Soc.*, 621 (1950).

[26] G. Plancher, *Ber.*, **31**, 1488 (1898).

TABLE II

PHYSICAL PROPERTIES OF INDOLE SALTS

			Analyses, %							
			Calcd.				Found			
Compound	M.p., °C.	Formula	C	H	N	Cl or S	C	H	N	Cl or S
2-Methylindole perchlorate	129–131 d.	$C_9H_{10}NO_4Cl$	...	..	6.06	15.15	...	..	5.91	15.48
Hydrosulfate	[a]	$C_9H_{11}NO_4S$	...	..	6.10	13.92	...	..	5.51	14.56
1,2-Dimethylindole perchlorate	112–114 d.	$C_{10}H_{12}NO_4Cl$	48.89	4.93	5.70	14.43	48.48	5.14	5.94	14.22
Hydrosulfate	[a]	$C_{10}H_{13}NO_4S$	...	..	5.76	13.18	...	..	5.20	13.62
1,2,3-Trimethylindole perchlorate	123–125 d.	$C_{11}H_{14}NO_4Cl$	50.87	5.44	5.39	13.65	50.53	5.44	5.34	13.43

[a] Melted over a wide range beginning at about 50°.

2,3,3-Trimethylindolenine methiodide was obtained from the reaction of 0.005 mole of 2,3,3-trimethylindolenine and 0.01 mole of methyl iodide in 20 ml. of benzene, at 5°. After 30 hr. the yellow crystals were isolated by filtration and recrystallized twice from absolute ethanol. The resulting pale yellow crystals melted at 256–258° dec. (reported[27] m.p. 253° d.) and turned red when exposed to air. The ultraviolet absorption spectrum of a 5×10^{-5} solution in 95% ethanol (determined with 5×10^{-5} M potassium iodide in 95% ethanol in the reference cell) showed λ_{max} 219, 237, 278; ϵ_{max} 19,900, 6800, 13050.

Anal. Calcd. for $C_{12}H_{16}N$ I: C, 47.85; H, 5.36; N, 4.65. Found: C, 48.11; H, 5.54; N, 4.65.

Salts of Indoles.—Salts of 2-substituted indoles and strong acids were prepared either by adding concd. sulfuric or perchloric acid dropwise to an ethereal solution of the indole at ice-bath temperatures or by adding ether to a solution of the indole in concd. acid. The products which separated were purified by repeated triturations with dry ether. The salts were all hydrolyzed immediately by water and turned red on exposure to air. The perchlorates, which by infrared analysis were always 3-protonated, were readily purified. The hydrosulfates were difficult to purify and melted over wide ranges. The hydrosulfate of 1,2,3-trimethylindole was an oil. Analyses of the hydrosulfates were not entirely satisfactory but were sufficient to show that the salts formed were 1:1 adducts of acid and base. Results are summarized in Table II.

Exchange Experiments Followed by Infrared Spectroscopy.—The disappearance of the NH band at 3350 cm.$^{-1}$ was followed, using a 0.76 M solution of skatole in freshly purified dioxane containing 1.67 M D_2O. The rate of disappearance of NH followed a first-order plot with a half-life of 86.6 min. at 22°. In solutions containing $2 \times 10^{-6} M$ sulfuric acid the reaction rate was more than doubled over somewhat more than 50% of reaction, after which a marked decrease in rate occurred. In solutions containing 5×10^{-5} M sulfuric acid or $2 \times 10^{-4} M$ sodium hydroxide the rate of disappearance of NH was too rapid to measure. In indole the NH band only began to decrease when the sulfuric acid concentration reached $10^{-4} M$. No deuterium was introduced on carbon at this acid concentration, confirming previous observations.[8]

N.m.r. spectra were determined with a Varian HR-60 spectrometer operating at a frequency of 59.9967 mc. and equipped with a variable temperature probe. Chemical shifts were measured with a Hewlett-Packard model 200 J audio oscillator and model 524 C frequency counter. Concentrations of indoles were 5–10% by weight. Solutions were prepared in a nitrogen atmosphere, as the protonated indoles are rapidly oxidized. Dynamic effects from proton exchange were generally observed in 6–10 M sulfuric acid, while the slower rates in more concentrated acid were followed by isotopic exchange.

Stability of Indoles in Concd. Sulfuric Acid.—With the exception of that of skatole the n.m.r. spectra of solutions of indoles in concd. sulfuric acid, including that of indole itself, showed only minor changes over periods as long as a week, providing that air was excluded. It can be inferred that the completely protonated species show little tendency to react with themselves or to undergo sulfonation. The stability of indole in concd. sulfuric acid is particularly noteworthy, because of its well-known and pronounced reactivity with more dilute mineral acids. The stability of indole and some of its methyl derivatives have recently been studied by means of ultraviolt spectrophotometry over a wide range of acid concentrations.[7d] Over a period of 30 minutes solutions of indole in concd. sulfuric acid were stable, while its solutions in lower concentrations of acid were not stable. Over a period of 28 hours, however, an increase in absorption of as much as 186% was noted in concd. sulfuric acid. We cannot explain this great difference from our n.m.r. results which show only minor changes during a 4-day period. However, the indole concentration was about $10^{-4} M$ in the previous work and about 1 M in the present work.

The n.m.r. spectrum of skatole in concd. sulfuric acid contained additional lines of very low intensity, close to the quartet and methyl doublet. The lines increased markedly with time. The change was faster in 12 M acid than in 18 M, and was also brought about by 12 M perchloric acid, thereby eliminating sulfonation. After standing for several days in 12 M perchloric acid skatole was at least 50% converted to the unknown product. The spectrum of the product was not that of skatole dimer[20] or of a protonated skatole dimer, as observed with an authentic sample[20] in 18 M sulfuric acid. However, when skatole dimer was warmed with 70% perchloric acid, the n.m.r. spectrum of the supernate resembled that of the unknown product formed from the monomer.

Several attempts to isolate the product responsible for the observed spectrum were made by letting a solution of 2.6 g. of skatole in 12 ml. of concd. sulfuric acid stand at room temperature under nitrogen for periods of 24–72 hours. The red solutions were diluted with ice-water, made basic with 40% sodium hydroxide and extracted with ethyl acetate. In each case a yellow solid melting from 215–225° dec. was obtained in low yield, but its n.m.r. spectrum in concd. acid did not resemble that of the reaction product of skatole in acid. It seems pertinent that solutions of 1,3-dimethylindole in 18 M sulfuric acid were completely stable.

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[27] E. Fischer and A. Steche, *Ann.*, **242**, 348 (1887).