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THE POSITION OF PROTONATION AND BASICITIES OF INDOLES

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The weakly basic character of the indole nucleus has been a subject of continuing interest with regard to both the base strengths of the nuclei and the positions of protonation. Protonation of positions 1[1a] and 3[1b,c] have received the most support, but it has also been shown[2] that substitution of the 2-position by electrophilic species may take place when the 3-position is occupied, as in skatole.

We have obtained direct spectroscopic evidence that indole and a number of its methyl derivatives are protonated predominantly at the 3-position in strongly acidic media. In the 60 mc. n.m.r. spectrum[3] of 2,3-dimethylindole the 3-methyl resonance is split and shifted to higher fields (507 cps. relative to solvent as internal standard) than that of the 2-methyl (431 cps.). A quartet at 349 cps. is assigned to the 3-hydrogen of formula I. The coupling constant of the doublet and the quartet is ~ 7.6 cps., in accord with the

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[1a] E.g. R. de Fazi, G. Berti and A. daSettimo, Gazz. chim. ital. 89, 2238 (1959).

[1b] A. Treibs, E. Herrmann, E. Meissner and A. Kuhn, Ann. 602, 153 (1957).

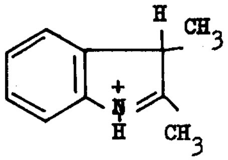
[1c] H. F. Hodson and G. F. Smith, J. Chem. Soc. 1957, 3544.

[2] W. E. Noland and D. N. Robinson, Tetrahedron 3, 68 (1958).

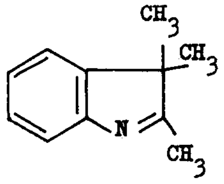
[3] The authors are indebted to Dr. Earl Whipple of the Union Carbide Research Institute for obtaining and interpreting the N.M.R. spectra.

structural feature > $CHCH_3$. The spectra of skatole and 1,2,3-trimethylindole in acid show similar splitting of the 3-methyl resonance, whereas the spectrum of 1,2-dimethylindole shows three lines at 338 (CH_2), 364 (1-methyl), and 429 cps. (2-methyl) with relative areas of 2:3:3. In 6 M sulfuric acid, where the proton exchange rate is greater, the 3-methyl resonance in 1,2,3-trimethylindole was not shifted from its position in 12 M acid, but was no longer split, showing that it is the proton from the strong acid which causes the spliting.

Further evidence for 3-protonation was obtained from the ultraviolet spectra of indole and its 1-, 2-, and 3-mono-, di-, and trimethyl derivatives in strong acid. These spectra resemble closely those of 2,3,3-trimethylindolenine (II) in 0.1 N hydrochloric acid (λ_{max} 229, 235, 275 mμ, log ϵ 4.00, 3.95, 3.91) and of the methiodide of II in water (λ_{max} 229, 236, 273 mμ, log ϵ 3.78, 3.73, 3.77). In 3 M sulfuric acid, for example, the spectrum of 1,2,3-trimethylindole shows λ_{max} 230, 237, 275 mμ (log ϵ 4.07, 3.99, 3.98).



I



II

While protonation occurs predominantly at the 3-position[4] in aqueous

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[4] It has been shown by deuterium exchange studies (M. Koizumi and coworkers, Bull. Chem. soc. Japan 13, 307, 643 (1938); 14, 453 (1939)) that 3-protonation of indole occurs in mild acid and both 2- and 3-protonation take place when pH < 0.5. A very low concentration of 2-protonated indole would explain the results of the exchange experiments, which lasted at least five hours, and would be compatible with our results. The exchange work naturally did not show that protonation of the 3-position occurs even when an alkyl group is present.

acid, in solid salts of methylindoles protonation of the 1- or 3-position may take place. Thus the infrared spectrum of the salt of 2-methylindole and sulfuric acid in Nujol had a band of medium strength at 1644 cm^{-1}, indicating the presence of $>C{=}\overset{+}{N}H$. Bands at 2490 and 1995 cm^{-1} showed the presence of immonium and ammonium bands, respectively.[5] However, the acid sulfates of 1,2-dimethylindole and 1,2,3-trimethylindole showed bands of medium intensity near 2500 cm^{-1}, indicating formation of the ammonium group by protonation of the indole nitrogen.

The shifts in the ultraviolet spectra on protonation were also used to estimate the relative basicities of indole and some of its methyl derivatives. The spectrum of 2-methylindole is shifted completely to the protonated form in 4 *M* sulfuric acid. 1-Methylindole requires 6 M acid, while the spectrum of skatole shows similar changes in 9 M acid, the methyl group in the 3-position actually exerting a striking base-weakening effect, as shown in the following series of basicities: 1,2 > 1,2,3; 2 >2, 3 >1 >1,3 > indole > 3. Preliminary *p*Ka' measurements show that *2-methylindole is several thousand times more basic than skatole*. The reason for this difference is under study. 2-Methylindole-3-acetic acid is much more basic than indole-3-acetic acid, and in general the biologically significant indoles derived from skataole fall in the least basic group. This pronounced difference in basicities is also shown by the fact that all 2-alkylindoles studied (2-methyl-, 1,2-dimethyl-, 1,2,3-trimethyl-, 2,3-dimethyl- and tetrahydrocarbazole) were successfully titrated potentiometrically in nitromethane with 0.1 N perchloric acid in acetic acid as titrant. Indoles which lack the alkyl group in the 2-position could not be titrated. Analysis

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[5] B. Witkop, J. B. Patrick, and H. M. Kissman, *Ber.* **85**, 949 (1953).

for 2-methylindole in the presence of 3-methylindole was effected by this method. Previous unsuccessful attempts[6] to titrate the indole nucleus were limited to indole itself, which is not basic enough to give a satisfactory end-point.

Quantitative measurements of the *p*Ka's of indoles using the Hammett H_0 function are in progress.

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[6] J. S. Fritz and G. S. Hammond, Quantitative Organic Analysis, John Wiley, New York, 1957, p. 34.