equatorial position at nitrogen. This would allow one proton on each β carbon atom to be in the axial position for which a large coupling constant would be expected, and the remaining β protons would be equatorial and would be expected to show a small coupling constant.[6] The spectrum of the morpholine derivative is shown in Figure 1 and shows a coupling to only two of the four possible β protons. In the pyrrolidine derivative, conformational interconversion at room temperature is apparently rapid enough to average the β-proton coupling constants, and as a result four equivalent β protons are seen. Evidence for a preferred tetrahedral geometry at nitrogen is found in the results of INDO calculations.[7] These calculations predict an amino nitrogen coupling constant of 12.01 G for the tetrahedral conformation of *N,N*-dimethylaminodicyanomethyl radical as compared with a 4.10-G coupling constant for the planar conformation. The cyano nitrogen coupling constants are predicted to be nearly the same for the tetrahedral model, 2.42 G, as for the planar model, 2.59 G. The calculation did not predict the proton coupling constants well (2.40 G predicted vs. 8.60 G observed). The tetrahedral model is calculated to be lower in energy than the planar conformation. MINDO/3 calculation allowing full optimization of the geometry predicts that the planar conformation should be more stable; however, the MINDO/3 method is known to predict incorrectly the geometry of tertiary amines.[7c]

The amino nitrogen hyperfine coupling constants are lower than those observed for other nitrogen centered radicals, CH_3N–O–t-Bu (a^N = 14.47 g),[8] $(CH_3)_2N\cdot$ (a^N = 14.78 g),[9] and $(CH_3)_2NO$ (a^N = 16.1 g).[10] This may result from the unpaired electron being delocalized over the dicyanomethyl system. The cyano nitrogen coupling constant observed here is slightly larger than that in tetracyanoethylene anion, 1.61 G,[11] suggesting that slightly more than half the electron density is in the dicyanomethyl portion of the molecule, and as a result the spin density on the amino nitrogen is smaller than in the nitrogen-centered radicals.

Acknowledgments. The author thanks The University of Mississippi Computer Center for a generous allotment of computing time, Dr. Robert M. Metzger for helpful discussion and assistance with the computer programs, and the National Science Foundation for a Departmental Instrument Grant to purchase the Varian E-4 EPR spectrometer.

Supplementary Material Available: The EPR spectra of the radicals for which coupling constants are given in Table I, except for the morpholine derivative (5 pages). Ordering information is given on any current masthead page.

Registry No.—Ia, 24380-79-8; Ib, 6667-19-2; Ic, 63533-62-0; Id, 63533-63-1; If, 4837-31-4; Ig, 19117-36-3; Ih, 63533-64-2; Ii, 29959-86-2; TCNE, 670-54-2.

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(3) EPR spectra were obtained on a Varian E-4 spectrometer and were still observable 1 day after formation. The hyperfine coupling constants are reported relative to the constants for anthracene cation which was taken as having hyperfine complex constants of 6.53, 3.06, and 1.38 G; J. R. Bolton and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 3307 (1964).
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Acid-Catalyzed Deuterium Exchange of the Indole Ring Protons in Tryptamine Derivatives

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Indole ring hydrogens, like those of other aromatic rings, undergo acid- and base-catalyzed proton exchanges. The rate of the acid-catalyzed proton exchange depends on basicity or nucleophilicity, which is reflected in the ground-state electronic structure of the molecule,[2] as well as on the stability of the protonated transition state,[3] a conjugated acid in terms of Brønsted.

Both acid- and base-catalyzed deuterium exchanges of hydroxyindole derivates have been observed,[4] but the results are qualitative and limited to the hydroxy derivatives. Furthermore, slow deuterium exchanges were not observed. In order to quantitatively assess the electronic structures of tryptamine derivatives and their ring-protonated conjugate acids, we have investigated acid-catalyzed deuterium ex-

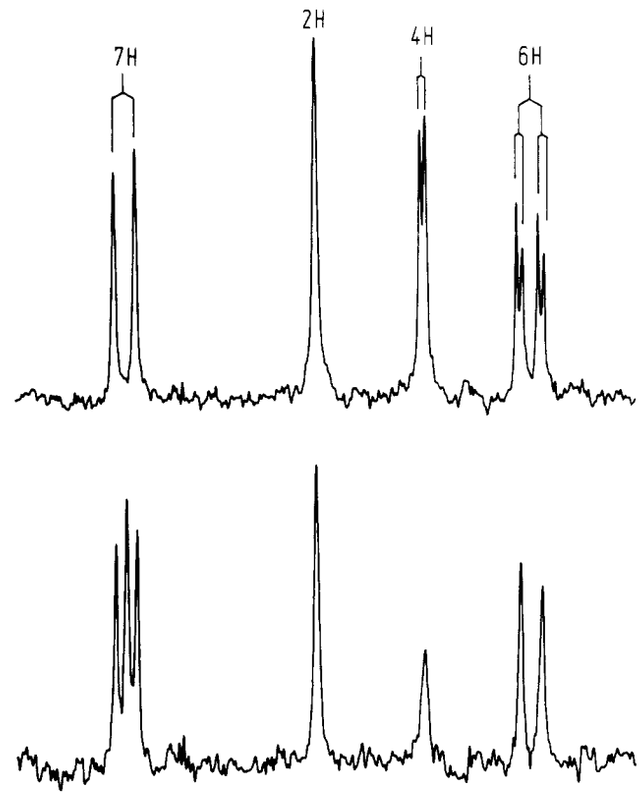

Figure 1. NMR spectra of the aromatic protons of 5-hydroxytryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1640–1563 Hz.

Table I. Chemical Shifts (ppm) of Aromatic Proton of Tryptamine Derivatives Relative to TSP as Zero at 220 MHz

Registry no.	Ring substitution	Solvent	Temp, °C	H-2	H-4	H-5	H-6	H-7
50-67-9	5-OH	1.0 N DCl	23	7.284	7.091		6.852	7.405
		D_2O/NaOD pD 9.9	23	7.222	7.045		6.835	7.372
1821-47-2	5-CH_3	1.0 N DCl	52	7.288	7.491		7.123	7.440
		Acetone/H_2O (5:1)	23	7.268	7.412		6.967	7.326
443-31-2	6-OH	0.4 N DCl	23	7.173	7.524	6.778		6.975
		D_2O/NaOH pD 10.5	23	6.926	7.370	6.547		6.617
61-54-1	H	1.0 N DCl	55	7.334	7.695	7.195	7.287	7.553

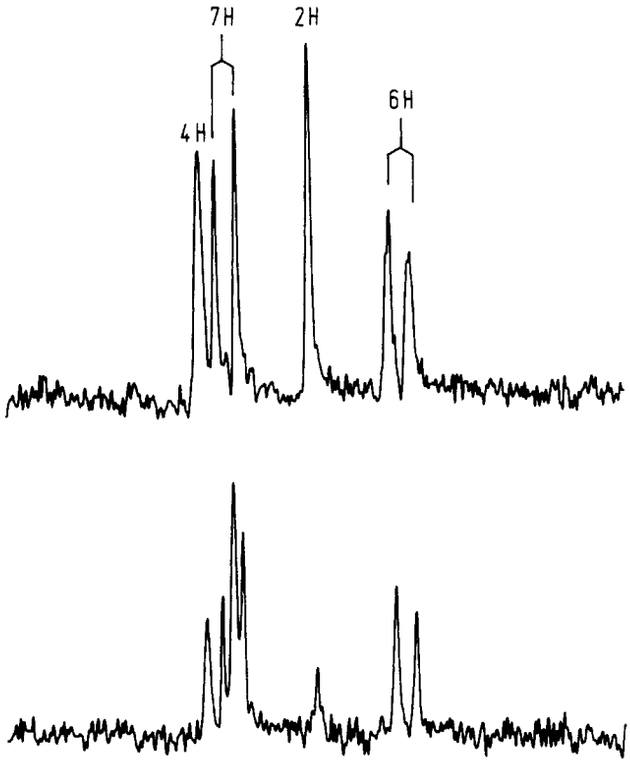

Figure 2. NMR spectra of the aromatic protons of 5-methyltryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1710–1491 Hz.

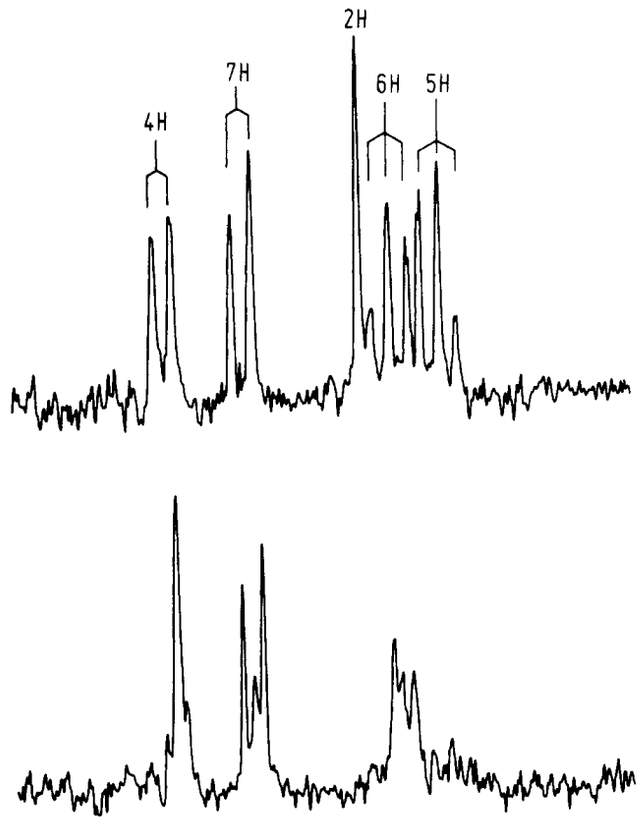

Figure 3. NMR spectra of the aromatic protons of tryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1755–1504 Hz.

change of 5-hydroxytryptamine, 6-hydroxytryptamine, 5-methyltryptamine, and tryptamine. Because these compounds exhibit widely different solubilities and exchange rates, comparison of exchange rate constants under identical experimental conditions is difficult. Only evaluation of thermodynamic parameters and acidity function dependence permit such a comparison through an extrapolation.

Chemical Shift Assignments. The benzenoid protons of 5- and 6-substituted tryptamines constitute an AMX spin system at 220 MHz, and their peak assignments are straightforward. In the case of 5-hydroxytryptamine (Figure 1), H-6 appears as a doublet of doublets, being ortho coupled to H-7 ($J_{6,7}$ = 8.0 Hz), and meta coupled to H-4 ($J_{4,6}$ = 2.3 Hz) (Table I). Additional couplings are not observed, so both H-4 and H-7 appear as doublets and H-2 is a singlet.

The proton splitting pattern of 6-hydroxytryptamine is identical with that of 5-hydroxytryptamine, with H-5 being ortho coupled to H-4 ($J_{4,5}$ = 8.6 Hz) and meta coupled to H-7 ($J_{5,7}$ = 2.1 Hz). Again H-2 is a singlet and long-range couplings are not observed. Proton chemical shifts for 5- and 6-hydroxytryptamine are in the same order as previously reported.[4]

The NMR spectrum of 5-methyltryptamine is similar to that of the 5-hydroxy derivative, except that the meta coupling is smaller and poorly resolved ($J_{4,6} \approx 1$ Hz) (Figure 2).

The benzenoid protons of tryptamine constitute an ABCD system, and their assignments are more complicated. Both H-4 and H-7 appear as doublets ($J_{4,5} = J_{6,7}$ = 7.0 Hz), but H-5 and H-6 further split each other ($J_{5,6}$ = 7.0 Hz) and appear as pseudo triplets (i.e., overlapping double doublets). Smaller coupling constants (meta) are <1 Hz, and could not be measured with accuracy. From the analysis of 5-methyltryptamine (Figure 2) and 7-methyltryptamine,[5] the downfield doublet can be assigned to H-4, and the remaining doublet to H-7. This agrees with the previous reports[6,7] that H-4 always appeared at lower field than H-7 in ring-substituted indoles, and is further confirmed by a recent NMR study of tryptophan.[8] Assignment of the H-4 and H-7 doublets (and the H-2 singlet) permits straightforward identification of the remaining resonances. Assignment of H-5 is based upon the observation that coalescence of the H-4 doublet is associated with deuterium exchange of the upfield "triplet" (Figure 3); the re-

Table II. First-Order Rate Constant (k) of Deuterium Exchange of Indole Ring Hydrogens of Tryptamine Derivatives as a Function of Temperature and Acid Concentration[a]

Ring substitution	DCl Concn, N	Temp, °C	H-2	H-4	H-5	H-6	H-7
5-OH	0.05	32.0		5.4×10^{-3}			
	0.10	32.0		1.0×10^{-2}			
	0.15	32.0		1.7×10^{-2}			
	0.50	32.0	9.6×10^{-4}			2.7×10^{-3}	
	1.0	20.5		3.5×10^{-2}			
	1.0	23.0	6.7×10^{-4}	5.0×10^{-2}		1.9×10^{-3}	
	1.0	27.5	1.3×10^{-3}	9.5×10^{-2}		3.7×10^{-3}	
	1.0	32.0	2.6×10^{-3}	1.8×10^{-1}		6.9×10^{-3}	
	1.0	33.5	3.2×10^{-3}			8.6×10^{-3}	
	2.0	23.0	2.2×10^{-3}			7.1×10^{-3}	
	2.0	32.0	7.7×10^{-3}			2.1×10^{-2}	
5-CH_3	1.0	52.0	2.2×10^{-2}	1.4×10^{-2}		8.3×10^{-3}	
	1.0	64.0	9.3×10^{-2}	6.2×10^{-2}		3.6×10^{-2}	
6-OH	0.1	28.0	2.6×10^{-3}		2.2×10^{-3}		4.8×10^{-3}
	0.2	28.0	5.1×10^{-3}		4.3×10^{-3}		9.6×10^{-3}
	0.4	28.0	1.1×10^{-2}		9.1×10^{-3}		2.1×10^{-2}
	0.6	28.0	1.7×10^{-2}		1.4×10^{-2}		3.2×10^{-2}
	0.4	23.0	5.2×10^{-3}		4.1×10^{-3}		1.0×10^{-2}
H	1.0	55.0	3.7×10^{-2}	3.7×10^{-4}	1.1×10^{-2}	1.9×10^{-3}	1.5×10^{-3}
	1.0	65.0	1.2×10^{-1}	1.2×10^{-3}	3.3×10^{-2}	6.5×10^{-3}	4.7×10^{-3}

[a] k is given in units of min^{-1}.

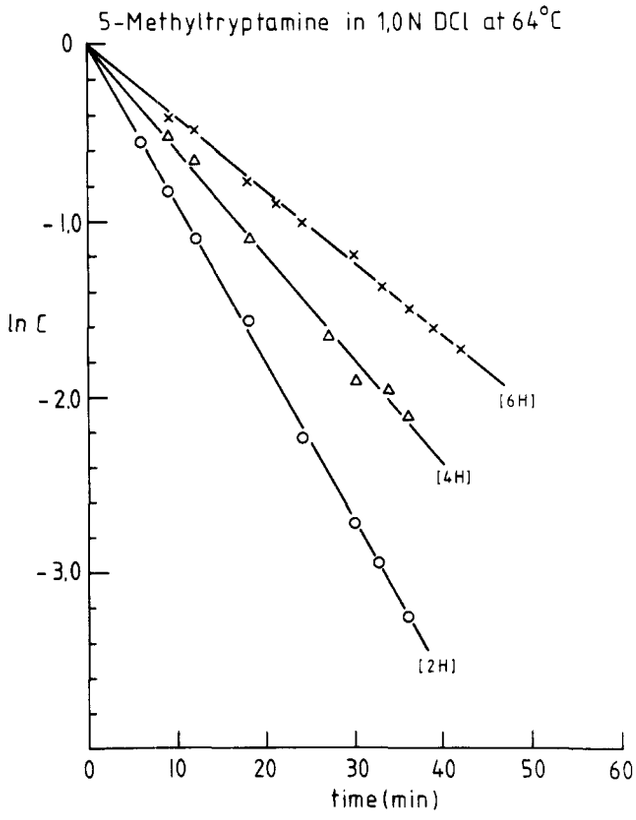

Figure 4. Exponential decay of the aromatic protons of 5-methyltryptamine as a function of time.

Table III. Arrhenius Activation Energy (kcal/mol) of Deuterium Exchange of Indole Ring Hydrogens of Tryptamine Derivatives

Ring substitution	H-2	H-4	H-5	H-6	H-7
5-OH	26.1	25.3		27.1	
5-CH_3	26.6	26.6		26.5	
6-OH	25.7		27.4		24.4
H	26.1	25.9	26.1	26.9	25.6

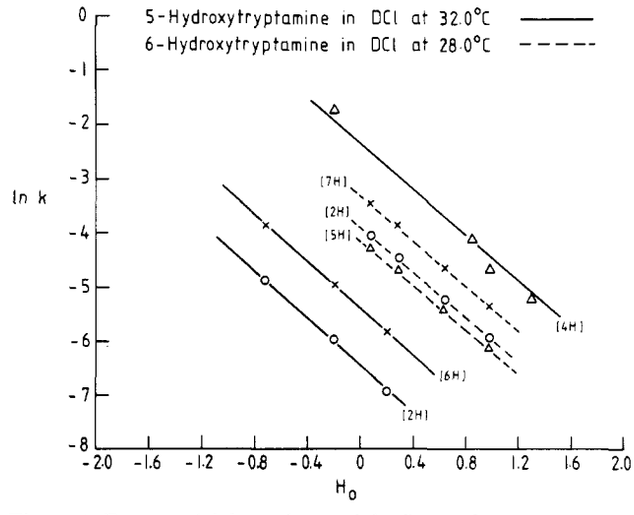

Figure 5. Exponential dependence of the first-order rate constants of deuterium exchange on the acidity function, H_0.

maining "triplet" is therefore H-6. These assignments for tryptamine are identical with those of tryptophan.[8]

It was observed that the aromatic proton resonances shift downfield upon protonation at the side chain alkylammonium group (Table I), but that the chemical shifts in an acidic medium were relatively independent of the acid concentration.

Deuterium Exchange of the Indole Ring Protons. The rate of disappearance of the ring protons of tryptamine derivatives in deuterium chloride (lower parts of Figures 1–3) is first order in the concentration of the ring proton, obeying the equation $A = A_0e^{-kt}$ (Figure 4). Because the deuterium exchange rate constants vary widely depending on the proton position, and because tryptamine derivatives show a wide range of solubilities, it is rather difficult to make a quantitative comparison under identical conditions. However, two parameters make such a comparison possible by extrapolation; one is the dependence of the rate constant on the DCl concentration, and the other is the temperature coefficient of the rate constant, i.e., the Arrhenius activation erergy, k =

Table IV. Calculated Deuterium Exchange Rate Constant (min^{-1}) of Indole Ring Hydrogens of Tryptamine Derivatives[a]

Ring substitution	H-2	H-4	H-5	H-6	H-7
5-OH	9.4×10^{-4}	6.5×10^{-2}		2.5×10^{-3}	
5-CH_3	5.4×10^{-4}	3.6×10^{-4}		2.0×10^{-4}	
6-OH	1.9×10^{-2}		1.5×10^{-2}		3.5×10^{-2}
H	6.4×10^{-4}	6.6×10^{-6}	1.8×10^{-4}	3.4×10^{-5}	2.6×10^{-5}

[a] In 1.0 N DCl at 25 °C.

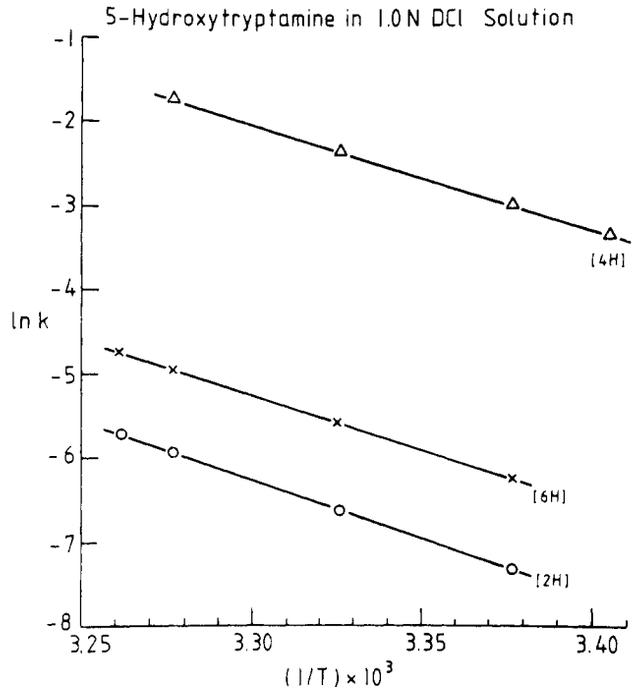

Figure 6. Arrhenius plot of the first-order rate constants of deuterium exchange of 5-hydroxytryptamine.

$Ae^{-\Delta E^{\ddagger}/RT}$ (Table II). It has been observed in these experiments that the first-order rate constants exponentially increase with increasing negative acidity function, $-H_0$,[9-12] of deuterium chloride, yielding the relationship, $k = k_0 e^{-H_0 x}$, where χ is a slope giving the value 2.45, and k_0 is the rate constant at the zero acidity function (Figure 5). It has been shown in these experiments that χ is independent of both ring proton species and temperature. The Arrhenius activation energy, $\Delta E^{\ddagger}$, for the deuterium exchange of the indole ring protons also shows a constant value of about 26 kcal/mol (Figure 6 and Table III). The constant values of these two parameters ($\chi = 2.45$ and $\Delta E^{\ddagger} = 26$ kcal/mol) for all species investigated ensure the validity of the temperature-independent Brønsted catalysis law ($\ln k = \alpha + \beta \ln K$),[13-15] where k and K represent the rate constant and equilibrium constant, respectively. Under these two conditions the logarithm of the rate constants then should be proportional to the stability of the ring-protonated aromatic conjugate acids.

Structural analysis shows that the deuterium exchange rate constants correlate with the stability of the resonance structure of the indole ring protonated conjugate acid (Table IV). These observations provide a basis for the validity of the Brønsted catalysis law in the protonation of the indole ring.

Experimental Section

5-Hydroxytryptamine creatine sulfate, 5-hydroxytryptamine bioxalate, 6-hydroxytryptamine creatine sulfate, 5-methyltryptamine, and tryptamine hydrochloride were purchased from Sigma Chemical Co., and used without further purification. Deuterium oxide and deuterium chloride were obtained from ICN Isotope and Nuclear Division. Throughout the experiments, 0.05 M solutions were prepared by dissolving the sample in DCl/D_2O solution of a known concentration, transferred quickly to the NMR tube, and equilibrated for few minutes in thermostated sample holder. When the temperature of measurement is significantly different from the room temperature, the samples were prepared in a water bath of desired temperature.

The 220-MHz NMR spectra were obtained in Fourier transform mode using a Varian HR 220 spectrometer equipped with a variable temperature unit and Nicolet Technology Corp. (NTC) pulse and Fourier transform accessories. A single 90° pulse was used to obtain each spectrum (2500 Hz sweep width and 8192 computer data points). There was sufficient time between successive spectral acquisitions to allow for proton relaxation. Chemical shifts are reported in parts per million (ppm) relative to internal TSP [3-(trimethylsilyl-2,2,3,3,-d_4)propionic acid sodium salt), and peak integrations were determined with the aid of the NTC NMR program. The collected data were analyzed using a simple regressional analysis method.

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Pyridinium *p*-Toluenesulfonate. A Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols

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Tetrahydropyranylation of hydroxyl groups has been recognized as the useful and representative method for the protection of alcohols.[2] In addition, it has recently been shown that 2-tetrahydropyranyl (THP) ethers are important pre-