

Anal. Calcd. $C_{18}H_{26}O_6$: C, 63.88; H, 7.75; O, 28.37. Found: C, 63.79; H, 7.89; O, 28.15.

This substance was also prepared from VIIb by treatment with methanol, hydrochloric acid and water (yield 40%) and by acetylation of XXVIIIa. Hydriodic acid at room temperature regenerated VIIb in 50% yield.

2-Methoxydehydrotetrahydrohelenalin.—Oxidation of 0.15 g. of XXVIIIa in 5 ml. of acetic acid with 0.1 g. of chromium oxide in 0.5 ml. of water and 2 ml. of acetic acid at room temperature for 1 hour, dilution with water and extraction with chloroform yielded 2-methoxydehydrotetrahydrohelenalin from the organic layer after washing and drying; m.p. 166–167° (from acetone-hexane), $[\alpha]_D -32.8^\circ$, λ_{max} 296 μ (ϵ 109).

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 65.29; H, 7.54; O, 27.17. Found: C, 65.13; H, 7.26; O, 27.19.

Rotatory Dispersion Curves.—Baldulin³² (in dioxane, c 0.116): $(\alpha)_{700} +29$, $(\alpha)_{589} +43^\circ$, $(\alpha)_{560} -612^\circ$, $(\alpha)_{277.5} +2890^\circ$; tetra-

hydrobaldulin³² (in methanol, c 0.0675): $(\alpha)_{700} -18^\circ$, $(\alpha)_{589} +28^\circ$, $(\alpha)_{515} +903^\circ$, $(\alpha)_{280} -732^\circ$, $(\alpha)_{264} -558^\circ$; allotetrahydrohelenalin³² (in methanol, c 0.117): $(\alpha)_{700} +77^\circ$, $(\alpha)_{589} +126^\circ$, $(\alpha)_{515} +1985^\circ$, $(\alpha)_{277.5} -1093^\circ$, $(\alpha)_{255} -488^\circ$; Neohelenalin³³ (in dioxane, c 0.679): $(\alpha)_{700} +51^\circ$, $(\alpha)_{589} +131^\circ$, $(\alpha)_{532.5} +1048^\circ$, $(\alpha)_{512.5} +779^\circ$, $(\alpha)_{280} +1600^\circ$; tetrahydromexicanin A³³ (in dioxane, c 0.059): $(\alpha)_{700} -22^\circ$, $(\alpha)_{589} -8^\circ$, $(\alpha)_{500} +12^\circ$, $(\alpha)_{512.5} -471^\circ$, $(\alpha)_{270} +402^\circ$, $(\alpha)_{265} +380^\circ$; tetrahydromexicanin A acetate³³ (in dioxane, c 0.050): $(\alpha)_{700} +4^\circ$, $(\alpha)_{589} +10^\circ$, $(\alpha)_{520} -816^\circ$, $(\alpha)_{275} +822^\circ$, $(\alpha)_{255} +730^\circ$; 2-methoxydihydrohelenalin acetate³³ (in dioxane, c 0.054): $(\alpha)_{700} +53^\circ$, $(\alpha)_{589} +72^\circ$, $(\alpha)_{517.5} +1231^\circ$, $(\alpha)_{280} -931^\circ$, $(\alpha)_{270} -452^\circ$; 2-methoxydihydrohelenalin³³ (in dioxane, c 0.050): $(\alpha)_{700} +42^\circ$, $(\alpha)_{589} +72^\circ$, $(\alpha)_{515} +1601^\circ$, $(\alpha)_{282.5} -428^\circ$, $(\alpha)_{270} +301^\circ$.

(32) We wish to express our appreciation to Dr. C. Djerassi and his group for determining these curves at Wayne State University.

(33) These curves were determined in the laboratories of Syntex S.A., Mexico, D.F.

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

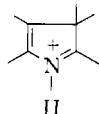
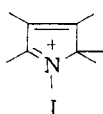
The Conjugate Acids of 2,5-Dimethylpyrrole

By E. B. WHIPPLE, Y. CHIANG AND R. L. HINMAN

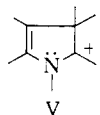
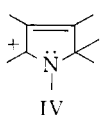
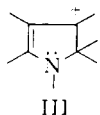
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While protonation of methylpyrroles normally occurs in the α -position, competitive β -protonation can be observed in the n.m.r. spectra of 2,5-dimethylpyrrole ($\sim 80\%$ β -protonation) and certain of its N-substituted derivatives. Separate bands can be identified in the electronic spectra of the isomeric salts in solution and used together with the n.m.r. data to determine pK_a 's toward protonation at each site. Observation over a varying medium of the distribution ratio between two conjugate acids derived from the same base permits direct verification that both are subject to parallel indicator acidity functions over the entire range of composition in aqueous sulfuric acid. The order of C-protonation rates of the bases in strong acids is shown to be opposite from that of stability of the conjugate acids.

Previous studies¹ by proton magnetic resonance of the hydrochloride salts of alkylpyrroles show a general preference for α -protonation, and indicate that α -methyl groups direct protonation to the opposite α -position while β -methyl substitution orients protonation to the adjacent α -site.² Both orientations are associated with a base strengthening effect at the position cited.¹ β -Protonation of the indole ring occurs with high specificity³ and methyl substitution in either the 1- or 2-positions is base strengthening.⁴ In both ring systems methyl substitution decreases basicity on the carbon atom bearing the methyl group. Less direct evidence points to a substantial base strengthening at the 2-position due to 3-methyl substitution on the indole ring.³ On the basis of the assumption that attached methyl groups stabilize in decreasing order carbonium ions, double bonds and tetrahedral carbon atoms, all of the above facts are consistent with the description of the conjugate acids in terms of the normal structures I or II and the "excited" structures III



through V. The β -protonation of indole would be a first-order effect arising from the fact that two Kekulé



(1) R. J. Abraham, E. Bullock and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959).

(2) The directive effects are indicated by single examples in the original work, and some of the proton resonance lines are improperly assigned (see subsequent text). The chemical structures assigned are nevertheless the correct ones, and a more extensive study of the methylpyrrole conjugate acids in this Laboratory confirms the directives.

(3) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(4) R. L. Hinman and J. Lang, A.C.S. Abstracts, Sept., 1961, p. 98 Q.

structures can be written in a fused benzene ring only in the case of II. In pyrrole, the orientation is determined by the presence of two excited structures III and IV opposed to the single structure V. Since this involves higher order structures, the specificity is less than for indole. As the heteroatom electronegativity increases, the weighting of the excited structures relative to the normal becomes greater, and this plus the fact that more singly charged excited structures (five vs. two) can be written for the α -protonated isomer when a fused aromatic ring is present accommodates the observation that electrophilic substitution in benzofuran occurs preferentially in the α -position.⁵

The orientation rules for methyl substituents follow directly from the positions of the charge in I through V and of the double bonds in the uncharged structures for the bases. One would predict from this argument that addition of a 2-methyl group to pyrrole would favor protonation at the 3- and 5-positions, have little effect at the 4-position and decrease basicity at the 2-position. A second methyl group at the 5-position would similarly increase basicity at positions 2 and 4, not further alter position 3, and oppose 5-protonation. There would hence be some cancellation of opposing effects of the α -positions, but only a net increase in basicity at the β -positions. It would therefore follow that in 2,5-dimethylpyrrole the C-methyl groups would have their greatest tendency to oppose the normal preference for α -protonation in the pyrrole ring. N-Methyl substitution should result in a further increase in relative basicity at the β -position due to a greater weighting of the normal structure II than of I.

The proton magnetic resonance spectrum of a solution of 2,5-dimethylpyrrole in 12 *M* sulfuric acid is shown in Fig. 1.⁶ The line positions indicated are

(5) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **72**, 4433 (1950).

(6) Abraham, Bullock and Mitra¹ reported a complex spectrum for hydrochloric acid solutions of this base. We observed similar patterns in sulfuric acid solutions unless air was excluded during sample preparation. With these precautions the patterns observed in Fig. 1 were stable over several days.

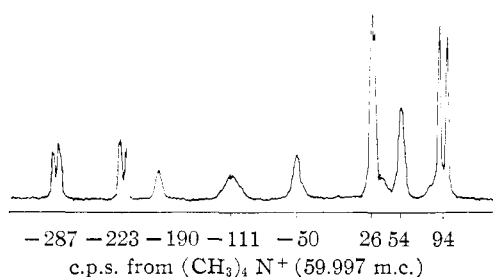
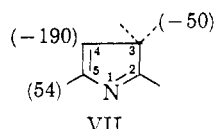
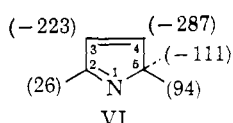


Fig. 1.—N.m.r. spectra (59.997 m.c.) of 2,5-dimethylpyrrole in 12 *M* H₂SO₄.

in c.p.s. from a tetramethylammonium ion internal reference which is not shown in the figure. The high-field doublet (94 c.p.s.) can be assigned¹ to an α -methyl group split by an adjacent proton, the latter appearing at -111 c.p.s. and having a broad, unresolved structure. The remaining protons are assigned to the lines indicated in VI. There still remain, however, peaks at +54, -50 and -190 c.p.s. which have in the order listed the intensity ratio 3:2:1. These are assigned as indicated by VII to the β -protonated form. The unassigned methyl group in VII is hidden in the strong line from VI at 26 c.p.s., as is verified by the fact that the integrated intensity of this line is just equal to the sum of the areas under the lines at 54 and 94 c.p.s.



The NH protons are not observed in either species, being broadened by quadrupole relaxation and also obscured by the solvent.⁷ However, the spectrum of 1,2,5-trimethylpyrrole in strong acids shows two lines due to N-methyl groups in the α - and β -protonated species, the remainder of the spectrum being similar to Fig. 1. The spectrum of a fresh solution of 1,2,5-trimethylpyrrole in 15 *M* D₂SO₄ shows no line corresponding to that at -111 c.p.s., a weaker and broader line around -50 c.p.s., and no doublet structure in the lines near 94 c.p.s. and 26 c.p.s. This latter observation points to the fact that the doublet structure in the 26 c.p.s. line of Fig. 1 is due to spin coupling with a single proton rather than to a partial resolution of overlapping methyl group lines from the two conjugate acids. The exchange experiments illustrated in Fig. 4 reveal this fact quite clearly, and further show that a proton on the nitrogen atom is not responsible. Since no quartet structure with the required 3.1 c.p.s. splitting is apparent in either of the vinyl proton multiplets in Fig. 1, the splitting must be between the 2-methyl group and the acidic proton in the 5-position of the conjugate acid. Similar splittings observed in a number of cases by Abraham, *et al.*,¹ were erroneously attributed to coupling between the acidic proton and methyl groups on carbon atoms one removed from the site of protonation. Since this voids the logical argument on which some of their structural assignments were based, it becomes necessary to assign structures to the other methylpyrrole conjugate acids on a somewhat different basis. Starting from 2,5-dimethylpyrrole and using both chemical shifts and multiplet patterns as a guide, one reaches the same structural conclusions as before, the only change being to permute the assignments of methyl groups in the 2- and 4-position of the 5-protonated examples considered previously.⁸

(7) In a number of related compounds, e.g., 2,4-dimethylpyrrole and 2,3,4,5-tetramethylpyrrole, a broad low-field NH resonance has been observed in 18 *M* H₂SO₄ solutions.

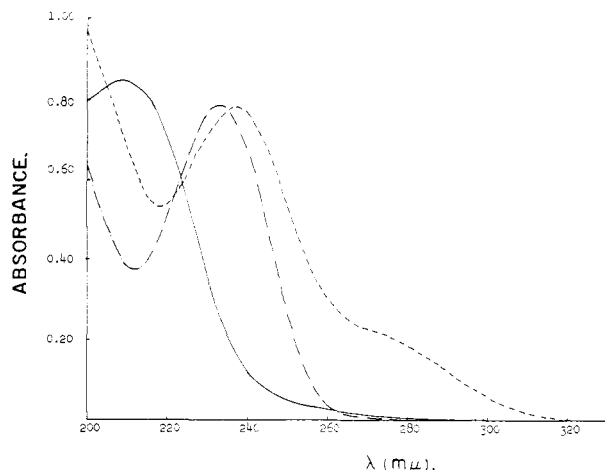


Fig. 2.—Ultraviolet spectra of: (—) 2,5-dimethylpyrrole in H₂O (1.1×10^{-4} *M*); (---) 2,5-dimethylpyrrole in 2.5 *M* H₂SO₄ (2.7×10^{-4} *M*); (-·-) 2-methylpyrrole in 4.3 *M* H₂SO₄ (1.74×10^{-4} *M*).

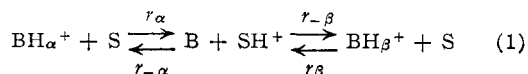
Figure 2 shows the ultraviolet spectrum from 200 to 320 μ of 2,5-dimethylpyrrole in various water-sulfuric acid solutions. In addition to the band around $\lambda_{\max} \approx 237$ μ which can be assigned to the α -protonated form,⁹ there is an additional band or broad shoulder with $\lambda_{\max} \approx 275$ μ which we assign to the β -protonated form. This band is also present in acidic solutions of 1,2,5-trimethylpyrrole and N-phenyl-2,5-dimethylpyrrole, both of which show β -protonation in their n.m.r. spectra, but is absent in the corresponding solutions of pyrrole, N-methylpyrrole and 2-methylpyrrole which undergo α -protonation only. Broad ultraviolet bands with $\lambda_{\max} \approx 275$ μ are observed in acidic solutions of indoles^{3,4} and 1,4-dihydropyridinium salts¹⁰ which undergo β -protonation. As a model for α -protonation, 2-methylpyrrole is particularly apt, since it undergoes virtually complete 5-protonation and its conjugate acid (λ_{\max} 233 μ , ϵ_{\max} 4500, ϵ_{238} 4140 in 4.3 *M* H₂SO₄) differs from α -protonated 2,5-dimethylpyrrole only by a methyl group on the tetrahedral carbon of the ring. The substantially lower intensity of absorption (ϵ_{238} 2900) observed in the spectrum of the latter is indicative of incomplete α -protonation. Taking the perchlorate of 1,4,4-trimethyl-1,4-dihydropyridine¹⁰ (ϵ_{238} 800) as a model for absorption by β -protonated 2,5-dimethylpyrrole, one can estimate the concentrations of α - and β -protonated species from the maximum absorbance in the spectrum of the mixture according to $800x_{\beta} + 4140(1-x_{\beta}) = 2900$, obtaining a value of 0.37 for the mole fraction of β -protonation compared with the value 0.29 derived from the n.m.r. intensities (Table II). Alternatively, beginning with the n.m.r. data and using the molar absorbancies of 2-methylpyrrole (ϵ_{275} 29) and 2,5-dimethylpyrrole (ϵ_{275} 740) at 275 μ , one derives a value ϵ_{275} 2490 for the β -protonated form to compare with ϵ_{274} 2300 in the model.¹⁰

The overlap of ultraviolet absorption bands from three species in the acid-base system (1) introduces added complications in the measurement of the base strengths

(8) One can immediately conclude that the assigned structure for 2,4-dimethylpyrrole is correct. In the case of 2,3,5-trimethylpyrrole, the distinction between 2- and 5-protonation must be made on the basis of more detailed analogies than before. In certain other cases, such as in 2-methylpyrrole, the 3 c.p.s. triplet structure we observe in the methyl group would lead to assignment of 3-protonation by the original argument, but to 5-protonation by the present one. Details of the spectra of about ten methylpyrrole salts will be published separately.

(9) E. Bullock, *Can. J. Chem.*, **36**, 1686 (1958).

(10) E. M. Kosower, Abstracts of Papers, Chicago, Ill., ACS Meeting, Sept., 1961, p. 54-Q. The authors are indebted to Dr. Kosower for a preprint of this paper.



by indicator methods.¹¹ Since both protonated forms are always present simultaneously, the measurement of the extinction coefficients for their absorption bands requires an independent determination of their concentration ratio. This may be obtained from the n.m.r. spectrum at high acid concentrations where exchange rates are slow, but not in the region where the protonated and unprotonated base are present in comparable amounts which is of interest in the base-strength determinations. Also the base is generally present in much larger concentration in the n.m.r. measurements ($\sim 0.1M$) than in the indicator experiments ($\sim 10^{-4}M$). However, the ratio of absorbancies at 238 and 280 $m\mu$ differs by no more than 10% between 2,5-dimethylpyrrole concentrations of $\sim 10^{-4}M$ and $10^{-1}M$ in 12 M sulfuric acid (Table I), leading one to expect only minor error from this source. The lack of generality in the deviations from ideal laws, as reflected in the variety of indicator "acidity functions,"^{4,11,12} make it improper to assume outrightly

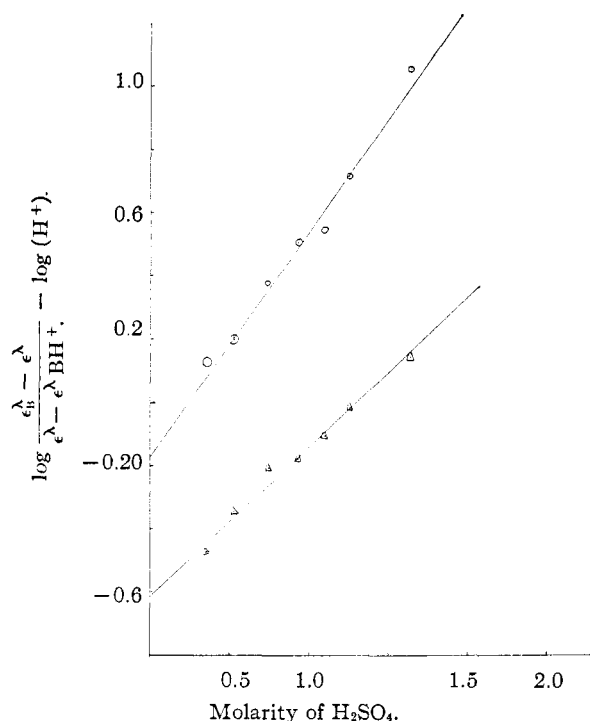


Fig. 3.—Indicator ratio plots of: (a) 1,2,5-trimethylpyrrole and (b) 2,5-dimethylpyrrole in aqueous sulfuric acid solutions.

that the equilibrium ratio of α - to β -protonation is independent of the acid. For dilute solutions of bases, it is customary¹¹ to group the various deviations from ideal behavior into an indicator acidity function defined by (2) where $I_\alpha = C_\alpha/C_\beta$ is the measured ratio of α -protonated to free base, and $pK_\alpha = -\log K_\alpha$ is thermodynamically defined from 1 and 3 in terms of an aqueous solution reference state. Since a similar set of

$$pK_\alpha = H_\alpha + \log I_\alpha \quad (2)$$

$$K_\alpha = a_{\text{B}}a_{\text{H}^+}/a_{\alpha\text{B}} \quad (3)$$

definitions applies to β -protonation, one obtains 4 by

$$pK_\beta = pK_\alpha = (H_\beta - H_\alpha) + \log (C_\beta/C_\alpha) \quad (4)$$

subtracting equations of the form 2. Hence, the condition that the ratio C_β/C_α is independent of acid con-

centration implies that protonation at each position is subject to parallel acidity functions, or that the ratio of activity coefficients, f_β/f_α , is constant. Values of the distribution ratio determined from the n.m.r. spectra in the range 9 M to 18 M H_2SO_4 are listed in Table I. The variations noted are on the order of the reproducibility of the area measurements in the n.m.r. spectra. The variations in this ratio to be expected from eq. 4 if α - and β -protonation followed different known acidity functions are also indicated in the table, and are seen to be well outside the differences in observed values. It is further apparent that the ratio of intensities at the absorption maxima of the overlapping ultraviolet bands from the conjugate acids is nearly constant over the whole acidity range where protonation is virtually complete. Since H_α and H_β by definition have the same lower limit, parallel behavior extending to very low acidities would require that they be equal. Although this limiting case is not realized in Table I, the inference is strong that the

TABLE I

SOLVENT EFFECT ON DISTRIBUTION BETWEEN CONJUGATE ACIDS OF 2,5-DIMETHYLPYRROLE

Solvent H_2SO_4 , M	A_{280}/A_{238}^a	C_β/C_α^b	$h_I/h_0 = 10(H_0 = H_I)$	$h_R'/h_0 = 10(H_0 - H_R')$
18		0.42		
15	0.249	.41		
12	.240	.40	83	42700
12	.224 ^c			
9	.225	.42	22	3720
6.5	.248			
4.3	.255			
2.7	.241			

Trifluoroacetic acid

^a Absorbance ratio from ultraviolet spectra at $3.2 \times 10^{-4}M$ base concentration, except where otherwise noted. ^b Concentration ratio from n.m.r. spectra at 15% wt. base concentration. ^c Pyrrole concentrations 7.7% wt. ($\sim 0.1M$).

acidity functions do not anywhere differ appreciably. The assumption of a constant line shape for the ultraviolet absorption band of the total protonated base thus appears justified, permitting the determination in Fig. 3 of a composite pK defined by eq. 5.

$$pK = \left(\frac{1}{K_\alpha} + \frac{1}{K_\beta} \right) = \lim_{C_H \rightarrow 0} \left\{ \log \frac{C_\alpha + C_\beta}{C_\beta} \right\} \quad (5)$$

Values of the composite pK of 2,5-dimethylpyrrole at several wave lengths and in two solvent acids are listed in Table II. The constancy of the pK values give a further indication of the confidence to be placed in the assumptions leading to eq. 5. Inserting the distribution ratio $R = C_\beta/C_\alpha = K_\alpha/K_\beta$ into eq. 4 and 5, one obtains

$$pK_\alpha = pK - \log (1 + R) \quad (6)$$

$$pK_\beta = pK_\alpha + \log R \quad (7)$$

permitting pK_α values for protonation at each position to be determined using the n.m.r. value of the distribution ratio. The results for three bases are listed in Table III.¹³

The data for 2,5-dimethylpyrrole leads to the conclusion that the ratios of activity coefficients $f_{\text{BH}^+}/f_{\text{B}}$ for both the α - and β -protonated conjugate acids describe virtually the same function of the medium over its entire range of composition from water to sulfuric acid. While this supports the assumptions underlying

(11) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

(12) N. Deno, P. Groves and G. Saines, *J. Am. Chem. Soc.*, **81**, 5790 (1959).

(13) The indicator ratio plots of 1,2,5-trimethylpyrrole show more experimental scatter and are less reproducible than those for 2,5-dimethylpyrrole, and the pK_α 's determined in H_2SO_4 and HClO_4 solutions differ by about 0.15 unit. The distribution coefficients at high acid concentrations are reproducible and constant over variations in the medium, however. The source of difficulty in the lower region is not clear.

TABLE II
COMPOSITE pK VALUES FOR 2,5-DIMETHYLPYRROLE

Acid	λ	Slope ^a	pK
H ₂ SO ₄	237	0.498	-0.58
H ₂ SO ₄	240	.450	-.55
HClO ₄	240	.565	-.49
HClO ₄	280	.618	-.50

^a $d \log (I/C_{H^+})/dC_{acid}$ where C = molarity.

TABLE III
BASE STRENGTHS OF N-SUBSTITUTED DERIVATIVES OF 2,5-DIMETHYLPYRROLE^a

N-Substitution	pK	$R = C_\beta/C_\alpha$	$pK_\alpha = pK - \log (1 + R)$	$pK_\beta = pK_\alpha + \log R$
-H	-0.55	0.42	-0.70	-1.07
-CH ₃	-0.05	.56	-0.24	-0.49
-C ₆ H ₅	-1.93	.191	-2.01	-2.73

^a Measured in aqueous sulfuric acid solution.

the use of generalized acidity functions, the methylpyrroles as a class¹⁴ appear to define a self-consistent function intermediate between those for arylelefins¹² and methylindoles.⁴ Since bases in different classes would by hypothesis be differently solvated in the reference medium, differences in pK_a can at best measure differences in proton affinity which are independent of the environment when taken between members of the same class. While there is some basis for correlating pK_a 's with deductions based on molecular properties as implied in I through V among different substituted pyrroles and/or different protonation sites,¹⁵ comparisons between pyrroles and indoles would, for example, necessarily involve differences in solvation.

One might expect either on intuitive grounds (e.g., structures I through V), simple molecular orbital calculations or empirical correlations with the chemical shifts and/or methyl substituent effects that the π -electron distributions in the α - and β -protonated salts of methylpyrroles would differ appreciably. The implication of the present study would then be that the acidity function was not particularly sensitive to the details of charge delocalization. It is difficult in particular to attribute the different class behaviors of indoles and pyrroles to this property. While more dramatic cases have been cited¹² to advance the argument, the present example has the advantage that the molecules compared are in other respects more similar, and the range of medium composition accessible to experiment is considerably greater.

The tendency of an N-phenyl group to decrease basicity in the pyrrole ring is the expected result of cross-conjugation, the presumption being that the α -methyl groups on the pyrrole ring are not highly effective in hindering resonance in the base. In order to explain similarly the effect of N-phenyl substitution on the β/α protonation ratio it becomes necessary to include doubly charged excited structures in the resonance argument. Of interest in this connection is that a p -carboxyl group on the aromatic ring further decreases the β/α protonation ratio.

The n.m.r. spectra also show that the rates of protonation in 2,5-dimethylpyrrole and its N-substituted derivatives are greater in the β -position than in the thermodynamically preferred α -position. This rests on the observation (Fig. 4) that as the solvent acid is diluted the n.m.r. peaks due to the β -protonated form broaden and then merge, while the lines identified

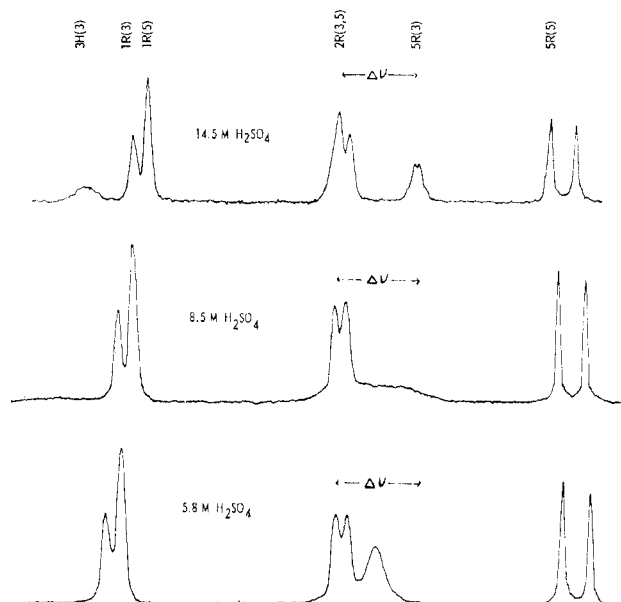
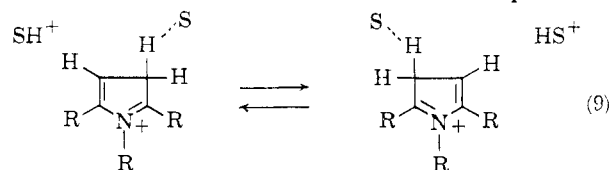


Fig. 4.—Methyl group n.m.r. lines from 1,2,5-trimethylpyrrole in various dilutions of aqueous sulfuric acid; number in parentheses refers to the site of protonation. The ring positions are numbered as in VI and VII.

with the α -protonated system retain their fine structure. Equilibration of the methyl lines in the β -protonated salt thus occurs during an average lifetime (τ_α) of the α -protonated species. Since the chemical shift between methyl groups in the former is 30 c.p.s. at the operating frequency, then their merger requires that $2\pi\tau_\beta < 0.033$ sec. From the retention of fine structure in the 2-methyl group of the 5-protonated species ($J = 3$ c.p.s.) one has the further condition $2\pi\tau_\alpha > 0.33$ sec., or $\tau_\alpha/\tau_\beta >> 10$. Since in the dynamic equilibrium 1 one has the condition $r_\alpha = r_{-\alpha}$ and $r_\beta = r_{-\beta}$, then

$$\frac{\tau_\alpha}{\tau_\beta} = r_\beta C_\alpha / C_\beta r_\alpha = R^{-1}(r_{-\beta}/r_{-\alpha}) >> 10 \quad (8)$$

or inserting $R = 0.56$ from Table III, $r_{-\beta} >> 5.6r_{-\alpha}$. That the equilibration of methyl lines in the β -protonated salt is a solvolytic process is apparent from the fact that the averaging process for the ring protons includes the solvent protons; i.e., no narrowing of the ring proton lines is observed. It is not possible to conclude from the present experiment if a concerted exchange process such as in 9 is involved since the qualitative



rate law that the exchange is facilitated by dilution is satisfied so long as the concentration of "free" solvent increases faster than that of protonated solvent decreases in the process of dilution.¹⁶

In conclusion, the extent of β -protonation in 2,5-dimethylpyrrole affords a possible explanation of several earlier observations in the literature. The failure to obtain a crystalline salt from this base in the preparative experiments of Treibs and Kolm¹⁷ is suggestive of a mixture, and the reported mixture of Δ^3 - and Δ^1 -pyrrolines in a 4:1 ratio from the reduction of the base in zinc and hydrochloric acid¹⁸ would sug-

(14) In addition to the bases in Table III, the class so far includes 2-methylpyrrole, N-methylpyrrole and pyrrole.

(15) Whether N-protonation follows an acidity function similar to that for α - and β -protonation is an open question, however.

(16) Deuterium exchange experiments with N-methylpyrrole show, however, that the initial protonation of the base in strong acids is faster in the β -position. Interestingly, the opposite order of rates is observed in weak acids.

(17) A. Treibs and H. G. Kolm, *Ann.*, **606**, 166 (1957).

(18) G. C. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

gest that an initial protonation determines the structure of the reduction products. Indirect evidence for significant basicity in the β -position of the pyrrole ring has been inferred from reaction products with other electrophilic reagents, *e.g.*, nitration.¹⁹ This is also apparent in the fact that all the hydrogen atoms in pyrrole are readily exchanged with deuterium in acid solutions.¹ Finally, the mechanism proposed²⁰ for the trimerization of pyrrole, which assumes β -protonation, is indirectly supported by our direct observation of this step in a closely related system.

Experimental^{21,22}

Materials.—2,5-Dimethylpyrrole was prepared by passing a slow stream of dry ammonia gas through a refluxing solution of 10 g. of acetonylacetone in 30 ml. of benzene; water was removed azeotropically. The pure product, b.p. 164–166° (755 mm.) (reported²³ b.p. 165°), weighed 7.6 g. (92%); v.p.c. analysis at 150° showed a single sharp peak, retention time 6.5 min. The infrared spectrum (pure liquid) had bands at 2.98 μ (NH) and 6.25 μ (double bonds).

1,2,5-Trimethylpyrrole, prepared by the above method with methylamine instead of ammonia, was a colorless liquid, b.p. 168–170° (755 mm.) (reported²⁴ b.p. 173° (746 mm.)); v.p.c. analysis at 150° showed a single sharp peak with a retention time of 9 min.

2,5-Dimethyl-1-phenylpyrrole was prepared by the method of Yanovskaya.²⁵

Fisher certified reagent sulfuric acid and perchloric acids were used for all measurements. Concentrations were determined by titration with 0.2 *N* sodium hydroxide (standardized against potassium acid phthalate) using phenolphthalein as indicator.

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(22) The authors are indebted to Mr. Spyros Theodoropoulos for the syntheses of the pyrroles.

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N.m.r. Spectra.—Samples (0.2 g.) of the freshly distilled pyrrole and 1.0 ml. of aqueous sulfuric acid of the concentration specified containing a few crystals of tetramethylammonium chloride were degassed separately and mixed under vacuum. Sealed 5-mm. o.d. precision ground thin wall sample tubes containing the mixed solutions were examined using a Varian HR-60 spectrometer (59.997 m.c.) and Hewlett-Packard 200-J audio-oscillator calibrated against a 524-C frequency counter. The frequency separation between the tetramethylammonium ion internal reference and tetramethylsilane is 198.7 c.p.s., the latter occurring at higher field. Areas were determined with a H. A. Philbrick model UPA-2 integrator using an ac-lock in detector operating at 1200 c.p.s. according to the circuit described by Johnson.²⁶

pK_a Measurements.—Stock solutions (10^{-2} *M*) of the freshly distilled pyrrole in 95% ethanol were prepared immediately before each determination. In the indicator measurements, 0.1 ml. of the stock was pipetted into 10-ml. volumetric flasks and diluted to volume with the appropriate acid. Ultraviolet measurements were conducted at 25° in 1-cm. silica cells in a Beckman DU spectrophotometer equipped with double thermo-spacers except for preliminary work carried out on a Beckman model DK-2 recording spectrophotometer. All bases and conjugated acids were found to obey Beer's law. The reversibility of the spectra was demonstrated by approaching intermediate acid concentrations either from neutral or strongly acidic media. Indicator ratio determinations were made about 2 minutes after mixing the pyrrole and acid, and readings rechecked 4 minutes later showed less than 1% change in absorbance. The pK_a 's listed were determined at 237, 242 and 275 μ , respectively, for 2,5-dimethyl-, 1,2,5-trimethyl- and 1-phenyl-2,5-dimethylpyrrole. In the first two cases, direct extrapolation using the eq. 10

$$pK_{BH^+} = \lim_{C_a \rightarrow 0} [\log (C_{BH^+}/C_B) - \log C_{H^+}] \quad (10)$$

was possible, the value for C_{H^+} being corrected for the second ionization of sulfuric acid using a constant of 0.02.²⁷ A least squares technique assuming the linearity of the equation above was used to obtain pK_{BH^+} from the experimental points. The extrapolation of the data for 1-phenyl-2,5-dimethylpyrrole was based on the indicator ratio plot for 2,5-dimethylpyrrole, the two curves being parallel in the region of overlap; 50% protonation of 1-phenyl-2,5-dimethylpyrrole occurs in 2.83 *M* H_2SO_4 , and the slope of $\log I$ vs. molarity of H_2SO_4 is 0.80 at the 50% protonation point.

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Acylium Ion Formation in the Reactions of Carboxylic Acid Derivatives. III. The Hydrolysis of 4-Substituted-2,6-dimethylbenzoyl Chlorides¹

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The kinetics of hydrolysis of five 4-substituted-2,6-dimethylbenzoyl chlorides in 99% acetonitrile-water were determined. The hydrolysis of mesitoyl chloride was shown to be subject to both hydronium ion (the first instance of acid catalysis of an acid chloride) and hydroxide ion catalysis. Tetra-*n*-butylammonium chloride depresses the rate presumably due to a common-ion rate effect. Other salts have relatively little effect on the reaction. Electron-donating 4-substituents accelerate the neutral and acid-catalyzed hydrolysis but depress the base-catalyzed hydrolysis. The Hammett ρ -constants for the neutral, acid-catalyzed and base-catalyzed reactions are -3.85 , -3.73 and $+1.20$, respectively, the former two obtained from plots employing σ^+ -constants and the latter one obtained from a plot employing σ -constants. In neutral and acid-catalyzed hydrolysis, no carbonyl oxygen exchange was found to accompany the reaction. On the basis of the above evidence it is postulated that two distinct pathways occur in the hydrolysis of these acid chlorides: (1) in neutral and acid-catalyzed hydrolysis, a unimolecular heterolytic fission occurs, with the formation of an acylium ion in the rate-determining step; and (2) in base-catalyzed hydrolysis, addition of hydroxide ion to the carbonyl group occurs, with the formation of a tetrahedral addition intermediate in the rate-determining step.

Introduction

Previous papers in this series have presented experimental evidence for the formation of acylium ion intermediates in two reactions, the diazotization of benzamide³ and the hydrolysis of methyl mesitoate in sulfuric acid.⁴ The present paper attempts to pre-

sent evidence concerning an analogous reaction, the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides.

The nucleophilic reactions of acid halides differ from those of esters principally in the speed of reaction, presumably because of the smaller resonance stabilization in the ground state of acid chlorides than of esters and of the ready ionization of the carbon-halogen bond. Acid chlorides may react with nucleo-

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