IONIZATION CONSTANTS OF CARBONYL DERIVATIVES OF PYRROLE

M. I. Struchkova, G. G. Dvoryantseva,
Yu. E. Sklyar, and R. P. Evstigneeva

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The indicator ratios of 22 carbonyl derivatives of pyrrole in sulfuric acid solutions were determined by spectrophotometry. The investigated compounds are divided into three groups with respect to the magnitude of the slope of the dependence of the indicator ratio on the molar concentration of the acid (d log I°/dC_c). Carbethoxypyrroles are characterized by a medium d log I°/dC_c value (0.70), which is the same as that observed for a number of indoles (0.70). For 2- and 3-formyl- and 3-acetylpyrroles this value (0.53) is close to the value obtained for Hammett bases (0.48). 2-Acetylpyrroles form a separate group. The ionization constants of the investigated compounds were determined with the aid of the corresponding acidity functions (H_1 and H_0). The effects of substitution on the basicity of the pyrrole ring are discussed.

The structures of the protonated forms of carbonyl derivatives of pyrrole were previously studied by means of electronic and PMR spectra [1, 2]. In the present research we measured the ionization constants of 22 compounds of this type spectrophotometrically.

Pyrrole and its derivatives are members of a class of weak aromatic bases. In order to estimate the relative acidities of such compounds it is sufficient to compare the acid concentrations at which the same degree of protonation is observed, for example, at the half-protonation point, where log I° = log $[BH^+]/[B] = 0$. The titration curves constructed for this purpose characterize the protolytic equilibrium directly in the nonideal medium. The Hammett method [3, 4], which makes it possible to measure the pK_a values on a scale that is an extension of the pH scale to the higher acidity region, is usually employed to determine the ionization constants. However, when this approach is used a certain amount of subjectivity in the selection of the acidity functions is possible, and this leads to variations in the pK_a values for the same substance over rather broad limits. In this connection, the relative basicities of the investigated compounds expressed in terms of the molar acid concentration at the half-protonation point were examined in addition to the pK_a values. We adopted the magnitude of the slope of the dependence of the indicator ratio on the molar acid concentration (d log I°/d C_c) as the fundamental criterion of the selection of the acidity functions.

The characteristic spectra of the bases and conjugate acids of carbethoxy-, acetyl-, and formylpyrroles, the titration curves obtained from them, and the graphs of the dependence of the indicator ratios on the molar acid concentration are presented in Figs. 1-3. The experimental data used for the construction of these dependences are presented in Tables 1 and 2.

All of the examined 2- and 3-carbethoxypyrroles (Table 1, compounds I-X) form a single group with respect to the slopes of the linear portions of the graphs of the dependences of log I° on C_c, and the average d log I°/dC_c value (0.70) is identical to the value found previously for indole and its derivatives (0.70) [5]. This makes it possible to correctly use the acidity function H_1 for the determination of the ionization constants of carbethoxypyrroles. It follows from the PMR spectra [1] that the structure of the conjugate acids of

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M. V. Lomonosov Moscow Institute of Fine Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 364-369, March, 1975. Original article submitted April 25, 1974.

TABLE 1. Ionization Constants of Carbethoxy-, Acetyl-, and Formylpyrroles

No.	Compound	λ anal., nm	ε_B	ε_{BH^+}	H_2SO_4 molarity, where log $I^\circ = 0$	$\frac{d \lg I^\circ}{d C_{H_2SO_4}}$	pK_a	Range of H_2SO_4 concentrations over which the slopes were measured, M
I	2,4-Dimethyl-3-carbethoxypyrrole	233	9300	3040	4,02	0,78	−2,6	2,6—5,8
II	2,4,5-Trimethyl-3-carbethoxypyrrole	233	9450	2520	5,17	0,73	−3,5	4,2—6,2
III	2,4-Dimethyl-5-ethyl-3-carbethoxypyrrole	234	19300	5150	4,30	0,69	−2,7	3,2—5,2
IV	1,2,4-Trimethyl-3-carbethoxypyrrole	243	9400	2860	3,47	0,62	−2,1	1,0—4,4
V	3,4-Dimethyl-2-carbethoxypyrrole	278	14300	5100	9,81	0,70	−6,5	8,8—10,8
VI	3,4,5-Trimethyl-2-carbethoxypyrrole	288	18800	3170	5,54	0.72	−3,6	4,5—6,5
VII	3,5-Dimethyl-4-ethyl-2-carbethoxypyrrole	287	19100	3640	5,83	0,72	−3,7	4,5—6,5
VIII	3,5-Dimethyl-2-carbethoxypyrrole	280	19750	2800	7,23	0,63	−4.7	6,2—8,2
IX	1,3,5-Trimethyl-2-carbethoxypyrrole	280	18400	3740	4,93	0,68	−3,1	2,6—4,2
X	1,3,4,5-Tetramethyl-2-carbethoxypyrrole	288	16870	4800	2,60	0,78 0,70	−1,6	1,6—3.6
XI	4-Methyl-3-acetylpyrrole	276	4500	20300	3,79	0,50	−1,9	0,7—4.2
XII	2,4-Dimethyl-3-acetylpyrrole	276	7550	19500	1.97	0,59	−0,8	1,0—3,0
XIII	2,4,5-Trimethyl-3-acetylpyrrole	278	3580	19800	1.46	0,66	−0,5	1,0—2,2
XIV	2,4-Dimethyl-5-ethyl-3-acetylpyrrole	278	3850	**20800**	1,46	0,66	−0,5	1,0—2,2
XV	2,4-Dimethyl-3-formylpyrrole	271	7550	19600	2,42	0.47	−1,1	0,3—3,6
XVI	1-Ethyl-2,5-dimethyl-3-formylpyrrole	281	8100	21000	2,34	0,47	−1,0	0,8—3.2
XVII	3,5-Dimethyl-2-formylpyrrole	309	21600	17600	1,98	0,48	−0,9	1,0—3,0
XVIII	3,4-Dimethyl-2-formylpyrrole	292	12950	19450	2,85	0,42	−1,3	0,5—4,4
XIX	3,4,5-Trimethyl-2-formylpyrrole	319	19600	9400	0,61	0.47 0,53	+0.1	0,8—1,5
XX	3,5-Dimethyl-2-acetylpyrrole	320	11700	22700	0.93	1,1	—	0,1—2,0
XXI	3,4,5-Trimethyl-2-acetylpyrrole	317	19800	16730	0.63	1.3	—	0,1—2,0
XXII	3,5-Dimethyl-4-ethyl-2-acetylpyrrole	316	20100	16700	0,63	1,3	—	0,1—2,0

3-carbethoxypyrroles I-IV corresponds to the addition of a proton to the α-carbon atom of the pyrrole ring (5-C). Protonation of 2-carbethxoypyrroles V-VIII under the same conditions occurs through the formation of an intermediate form of the conjugate acid, which in the course of a few hours is converted to a stable form with a different structure. The stable form of 3,4-dimethyl-2 -carbethoxypyrrole (V) has an α-pyrrolene structure, which corresponds to the addition of a proton to the 5-C atom. The N-protonated form is the stable form for 2-carbethoxypyrroles with a methyl group in the 5 position (VI-VIII). The ionization constants and the molar acid concentrations at the half-protonation point of V-VIII, which are presented in Table 1, pertain to the formation of intermediate forms of the conjugate acids. On the basis of the PMR and UV spectra it may be concluded that the sole and stable form of the cations of N-methyl derivatives of 2-carbethoxypyrroles IX and X is similar in structure to the intermediate unstable form of the cations of V-VIII. Thus the ionization constants of an entire series of 2-carbethoxypyrroles (V-X) probably characterize the basicity of the same center. It was established from the PMR spectra that this process is not associated with protonation of molecules of V-X at the carbon atoms of the pyrrole ring in the 3, 4, and 5 positions. The addition of a proton initially to the ring-nitrogen atom is excluded in V-VIII and is unlikely in IX and X. It has been assumed [1] that the formation of the intermediate form of the conjugate acids of 2-carbethoxypyrroles occurs as a result of the addition of a proton to the oxygen atom of the carbonyl group. However, one cannot exclude the possibility that the protonation center in this process is the carbon atom of the pyrrole ring bonded to the carbethoxy group (2-C). Evidence in favor of this structure is the fact that V-X are subject to the same acidity function as 3-carbethoxypyrroles (I-IV), which form 5-C cations, whereas formyl- and acetylpyrroles, for which protonation at the carbonyl oxygen atom has been established [2], form a different series.

TABLE 2. Indicator Ratios of Carbethoxy-, Acetyl, and Formylpyrroles

Compound	$c_{H_2SO_4}$	lg I°	Compound	$c_{H_2SO_4}$	lg I°	Compound	$c_{H_2SO_4}$	lg I°
III	2,84	−1,03	XI	0,79	−1,48	XVIII	0,95	−0,79
	3,82	−0,33		1,75	−1,01		1,36	−0,62
	4,40	+0,02		3,98	+0,12		2,15	−0,31
	4,58	+0,20		4,75	+0,42		2,72	−0,05
	4,95	+0,49	XII	1,15	−0,49		3,22	+0,20
	5,42	+0,67		1,33	−0,40		3,84	+0,44
V	8,15	−0,82		1,75	−0,13		4,60	+0,74
	8,56	−0,75		1,98	+0,01			
	9.20	−0,36		2,46	+0,28			
	9,75	−0,02	XVI	0,95	−0,66			
	10,20	+0,27		1,48	−0,41			
	10,70	+0,75		1,95	−0,17			
	11,00	+1,05		2,16	−0,06			
	11.10	+1,20		2.57	+0,09			
VI	4,53	−0.63		3,12	+0,36			
	5,0	−0.37		3,20	+0.43			
	5,43	−0,12	XVII	1.0	−0,42			
	5,62	+0,02		1,95	−0,04			
	5,90	+0,22		2,28	+0,13			
	6,13	+0,55		2,82	+0,37			
	6,53	+0,76		3,79	+0,71			

The examination of the changes in the electronic spectra observed on passing from neutral molecules to cations and the comparison of the titration curves and the slopes of the dependences of the indicator ratio on the acid concentration require division of the formyl- and acetylpyrroles into two groups. One series, for which the average d log I°/dC$_c$ value (0.53) is close to the value obtained for the Hammett indicators (0.48) [6], includes 2- and 3-formyl- and 3-acetylpyrroles (XI-XIX). Consequently, the H_0 function can be used for the determination of the pK_a values of these compounds. 2-Acetylpyrroles XX-XXII, which form a separate group for which the slopes of the dependence of log I° on C$_c$ do not correspond to any of the known acidity functions, do not fit into this series. In addition, according to the PMR and UV spectral data the oxygen atom of the acetyl group is the preferred protonation center for these compounds under normal conditions [2].* The observed anomaly is apparently associated with the peculiarities of the mechanism of protonation of 2-acetylpyrroles rather than with a change in the cationoid center. With respect to the character of the changes in the electronic spectra of XXI and XXII, the formation of a monocation can be represented in two steps (see Fig. 1). On passing from aqueous solutions to 2 M H_2SO_4 a bathochromic shift ($\Delta\lambda$ = 25 nm) and an increase in the intensity of the short-wave transition are observed. The position of the absorption maximum of the long-wave transition does not change over this acidity range, but its intensity falls appreciably. An increase in the acid concentration to 16 M leads to a small shift ($\Delta\lambda$ = 9 mm) and a further decrease in the intensity of the long-wave band, as well as to a certain increase in the intensity of the short-wave transition. The complete coincidence of the spectrum of 3,4,5-trimethyl-2-acetylpyrrole (XXI) in 16 M H_2SO_4 with the spectrum of the cation of 3,4,5-trimethyl-2-formylpyrrole (XIX), for which protonation at the carbonyl oxygen atom follows unambiguously from the PMR spectrum [2], should be noted. Inflection points are observed on the titration curves of 2-acetylpyrroles in 2 M H_2SO_4. It follows from an examination of these curves that the protolytic equilibrium in 2 M H_2SO_4 is shifted by ~80% to favor the protonated form. The molar acid concentration at the half-protonation point, which corresponds to this pseudoequilibrium for XXI (0.63), is in good agreement with the value found for 3,4,5-trimethyl-2-formylpyrrole (0.61).

The relative basicities of the cationoid centers of different nature in pyrrole derivatives can be estimated from the molarity of the acid at log I° = 0. It is seen from the data in Table 1 that the basicity of the carbonyl oxygen atom in 3-acetylpyrroles XII-XIV ($M_{H_2SO_4}$ = 1.46-1.97) considerably exceeds the basicity of the α-carbon atom of the pyrrole ring in the corresponding 3-carbethoxy derivatives (I-III) ($M_{H_2SO_4}$ = 4.02-5.17). The sharp

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*The possibility of protonation at 4-C is not excluded in strongly acidic media for 4-unsubstituted 2-acetyl- and 2-formylpyrroles.

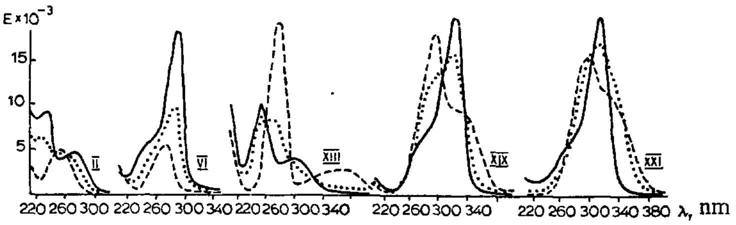

Fig. 1. Electronic spectra of the bases (——) and conjugate acids (----) of carbonyl derivatives of pyrrole.

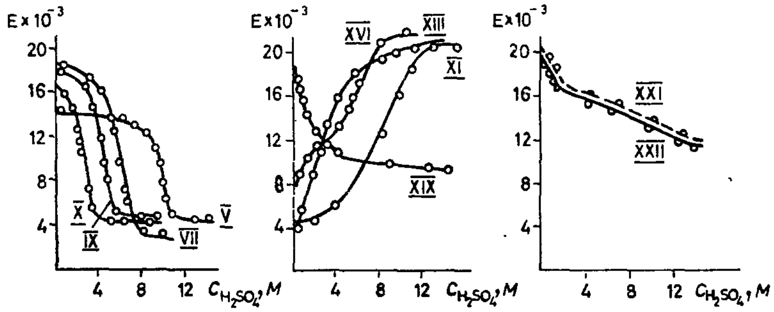

Fig. 2. Titration curves of carbonyl derivatives of pyrrole.

decrease in the basicity of the pyrrole ring when a carbethoxy group is introduced follows from a comparison of I-IV with alkylpyrroles, which add a proton at the same center (5-C). Thus the acid molarities at the half-protonation points of 2,4-dimethylpyrrole [7] and 2,4-dimethyl-3-carbethoxypyrrole (I) are 0.008 and 4.02, respectively. This difference corresponds to a decrease of several orders of magnitude in the basicity of the α center in the case of 3-carbethoxy substitution. The introduction of a carbethoxy group into the 2 position leads to a further decrease in the basicity. The acid molarity is 7.23 at the half-protonation point of 3,5-dimethyl-2-carbethoxypyrrole (VIII). Moreover, the basicity of 2-carbethoxypyrroles V, VI, and VIII ($M_{H_2SO_4}$ = 5.54-9.81) proved to be even lower relative to the corresponding 2-formylpyrroles (XVIII, XIX and XVII) $M_{H_2SO_4}$ = 0.61-2.85). This result is in better agreement with the structure of the intermediate forms of the conjugate acids of V-VIII, which corresponds to the addition of a proton to the 2-C atom rather than to the oxygen atom of the carbonyl group.

Let us examine the effect of alkyl substituents in various positions of the ring on the basicities of the pyrrole derivatives. Within the limits of each series of the compounds this effect can be quantitatively characterized by the pK_a values. In 3-carbethoxypyrroles the effects of the methyl group are similar in character to those observed in a number of methyl derivatives of pyrrole [7] and indole [5]. A methyl group in the 5 position lowers the basicity of the 5-C carbon atom bonded to it by almost an order of magnitude ($\Delta pK_a = -0.9$). The effect of an ethyl group in the same ring position proved to be much weaker ($\Delta pK_a = -0.1$). N-Methylation leads to an increase of 0.5 pK_a units in the basicity of the α center. Acetyl- and formylpyrroles also differ appreciably from 3-carbethoxy derivatives and from alkylpyrroles and indoles with respect to the effect of methyl groups on the basicities. It is seen from a comparison of the ionization constants of XII-XIV, XVIII, and XIX that the basicity increases on passing from 5-unsaturated 3-acetyl- and 2-formylpyrroles to the corresponding 5-methyl derivatives, whereas the effects of CH_3 and C_2H_5 groups are of the same magnitude. The effect of methyl groups on the basicity depends on the position of the carbonyl group in the pyrrole ring. A methyl group in the 2 position in 3-acetylpyrroles XI-XIII increases the basicity considerably more strongly than a methyl group in the 5 position (ΔpK_a = 1.1 and 0.3, respectively). A considerably greater effect of a CH_3 group in the 5 position is observed in 2-formylpyrroles XVIII and XIX ($\Delta pK_a = 1.4$). These data are in complete agreement with the protonation of the acetyl- and formylpyrroles at the oxygen atom of the carbonyl group. A methyl group in the 4 position increases the basicity of 2-formylpyrroles by one order of magnitude (XVII and XIX).

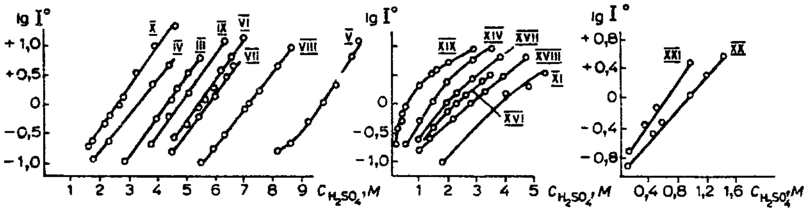

Fig. 3. Graphs of the dependence of the indicator ratio on the acid concentration of carbonyl derivatives of pyrrole.

The increase in the ionization constants of 2-carbethoxypyrroles when a methyl group is introduced into the 1, 4, and 5 positions indicates, regardless of the results of other investigative methods, the absence of protonation in these ring positions. In addition, the electron-donor effect of the methyl group in these compounds increases sharply as compared with the effect in 2-formylpyrroles. The pK_a values increases successively by 1.1-1.5, 1.6-2.0, and 2.9 units in the case of 4, 1, and 5 substitution.

EXPERIMENTAL

The electronic spectra of the investigated compounds were measured with a Hitachi EPS-3T spectrophotometer. The starting solution of the base (10^{-3} M) was prepared in 96% ethanol, after which 1-ml samples of the starting solution were removed and diluted to 10^{-5} M with distilled water (for the spectrum of the base) and with sulfuric acid solutions. The acid concentration was determined by titration or from the specific gravity with the aid of the tables in [8]. The slopes of the dependences of the indicator ratio on the molar acid concentration were calculated by the method of least squares. The stability of the investigated compounds with respect to acid was monitored from the reversibility of the spectra of the cations and neutral molecules. For an accurate comparison with the PMR data the electronic spectra of the cations of some of the investigated compounds were measured at solution concentrations of 10^{-1} M, and the identical character of their spectra and the spectra obtained under normal conditions was established.

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