ACID-BASE PROPERTIES OF INDOLYLGLYOXAL AND SOME ACETYLINDOLES

A. L. Vereshchagin, N. N. Pogodaeva,
and A. A. Semenov

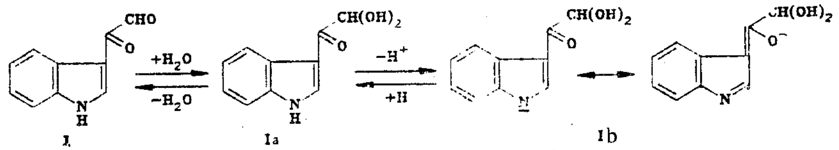
UDC 541.132:547.441'756:543.422

A spectrophotometric study of the acid-base properties of 3-acylindoles showed that they were stronger acids than the alkylindoles. It was found that protonation of these compounds occurs at the carbonyl group. For indolylglyoxal, 3-acetylindole, and 1-methyl-3-acetylindole the pK_b was determined; the pK_a for indolylglyoxal and 3-acetylindole was measured in 50% aqueous methanol.

The physicochemical characteristics of indolylglyoxal (I) have been widely studied because of interest in its biological properties. In the present work, the acid and base dissociation constants of the indole I have been determined spectrophotometrically, and these values have been compared with analogous parameters for other acylindoles. In order to overcome the difficulty in measuring the pK_a of compound I, which has a low solubility in water, we dissolved it in 50% aqueous methanol. The starting solution of indole I was diluted with aqueous-methanol solutions of potassium hydroxide, and the optical densities of these solutions, which had a range of pH values, were determined. As the absorption density of the ionized forms and non-ionized forms of compound I were known, the pK_a could then be calculated.

The basic properties of indoles are difficult to study because they are not stable in acid solutions, and therefore we first examined the stability of compounds I-III in solutions of sulfuric acid of different concentrations. The change in the UV spectrum of 3-acetylindole (II) in 65% sulfuric acid over the course of a few days was negligible; 1-methyl-3-acetylindole (III) in 58% sulfuric acid solution was optically stable for one day, but the spectrum of compound I began to change within 30 minutes after solution in concentrated H_2SO_4; moreover, a decrease in the acid concentration to 60% markedly increased the rate of change. Earlier attempts [1] to avoid errors caused by the instability of indoles in acid solution were ineffective, because measurements were difficult to take in the short time available (20 min) between preparation of the solutions and measurement of their optical density. This, naturally was reflected in the accuracy of the measurement of pK_b.

When studying the UV spectra of alkaline solutions of compound I it was obeerved that at pH ∿ 10 the point of inflection at 275 nm disappears and the optical density at 330-340 nm decreases. This observable weak change, and also tendency of the ketoaldehydes to form hydrates, in all probability, indicates that in this pH range the aldehyde group of compound I undergoes hydration to give the hydrate Ia. The spectra of compounds I and Ia are not well differentiated and there is no isobestic point in the spectra of weakly alkaline solutions of compound I, so that UV spectroscopy cannot be used for the measurement of the hydration constant. A further increase in the alkalinity of the solution of compound I leads to the formation of the anion Ib and is accompanied by the appearance of new absorption bands at greater wavelengths with higher molar extinction coefficients. Absorption curves at pH values from 12 to 14.5 (Fig. 1) have an isobestic point, which indicates that the total concentration of compounds Ia and Ib is constant, and consequently the pK_a can be determined (Table 1).



I Ia Ib

The acidic properties of the acylindoles have been widely studied. However, it is impossible to compare our data with existing data, since, because of the low solubility of

---

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskhikh Soedinenii, No. 12, pp. 1621-1624, December, 1987. Original article submitted October 30, 1985; revision submitted March 20, 1986.

TABLE 1. Acid and Base Dissociation Constants for Some Acylindoles

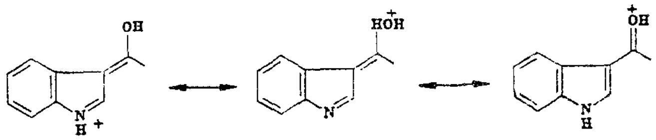
Compound	λ_{max}, nm		$\varepsilon \cdot 10^3$		pK_a	pK_b
	B	BH^+	B	BH^+		
Indole [1]	216	233	34,8	3,92	16,97	−3,6
	266	238	5,72	3,81		
	276	279	5,78	4,81		
	287		4,75			
I	248	240	9,7	8,39	13,26±0,05*	−4,6
	259	270	8,4	13,01		
	276	352	6,5	6.38		
	304		9,4			
II	241	235	14,5		13.79±0.06*;	−1,74±0,05
	260	260	10,2	23,43	12,99 [7]	
	297	340	14,1	26,33		
III	246	241	21,67	17.0		−1,53±0,09
	305	270	24,0	26,33		
		340		20,17		

*Measured in 50% methanol.

the indole I, measurements were made in 50% methanol. To obtain comparable results, the acetylindole (II) was studied using the same solvent. It was found that indole Ia was a stronger acid than II. In all probability, this is because of the presence of two hydroxyl groups, which strengthens the electron-acceptor properties of the substituent, thus weakening the N–H bond and favoring the loss of a proton. Judging from the acid dissociation constant, dissociation of the gem-diol Ia does not make a significant contribution to the pK_a value.

PMR spectroscopic data indicates that protonation of 3-acylindoles occurs at the carbonyl group [2]. We confirmed this by UV spectroscopy, and were able to follow the process of the addition of a proton quantitatively.

The spectra of the protonated forms of indole and the acylindoles differ considerably (Table 1), while the appearance of the long-wave maximum is due to the increase in conjugation of the system. The pK_b values for the indoles II and III are very similar, whereas the pK_b values for indole is 1.5 times less than that for 1-methylindole [1]. The acylindole II is considerably more basic than indole itself, in agreement with the protonization of 3-acylindoles at the carbonyl oxygen. Such a proton addition leads to stabilization of the resulting cation through resonance.



This also explains the increased basicity of compound II. The substitution of the methyl group of acetylindole II by the aldehyde in indolylglyoxal I leads to partial destabilization of the cation, which causes I to become less basic.

Consequently, both protonization, and deprotonization of acylindoles leads to the formation of ions stabilized by resonance. This occurs because of the presence of conjugated groups with opposite electronic effects (electron-donor NH and electron-acceptor CO), which causes the characteristic behavior of these compounds.

EXPERIMENTAL

Compounds I-III were prepared by the method given in [3, 4]. Acid and base dissociation constants were determined by standard methods [5]. Starting solutions were prepared by dissolving the required amounts of compounds II and III in 60-65% H_2SO_4, and of indolylglyoxal I in concentrated H_2SO_4. These were then transferred to volumetric flasks and diluted with H_2SO_4 solutions of different normalities and, after determining the optical density, the exact concentration of acid in the samples was determined by potentiometric titration. From the data obtained, pK_b was calculated. The concentration of the solutions did not

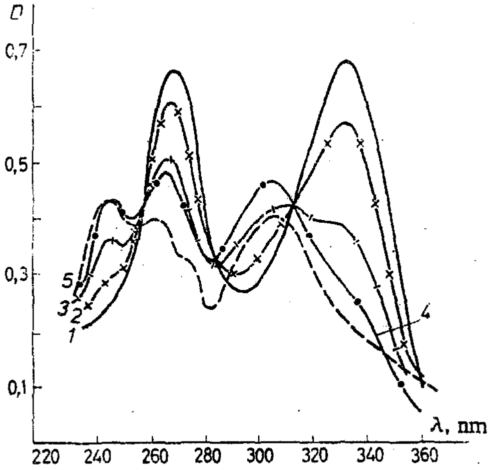


Fig. 1. UV spectra of indolylglyoxal in 50% aqueous methanol. 1) In 0.5 N KOH solution; 2) in 0.25 N KOH solution; 3) in 0.1 N KOH solution; 4) in 0.05 N KOH solution; 5) in neutral solution.

exceed $5 \cdot 10^{-5}$ M. The optical density was measured on Specord and SF-16 automatic double-beam spectrophotometers using 1 cm quartz cells. In determining the acid dissociation constant, the ionic strength of working solutions was kept constant by the addition of KCl; analytical wavelengths used were 333, 296, 269, and 243 nm for compound I, and 330, 295, 267, and 240 nm for compound II. For the determination of the base dissociation constant, analytical wavelengths of 270, 300, 350, 365 (for I), 330, 340, 345 (for II), and 270, 308, 342 nm (for III) were used.

The concentration of hydrogen ions was determined using a universal EV-74 ionomer with a glass-silver chloride electrode. Potentiometric titrations for the measurement of the base dissociation constant were carried out at 25 ± 1°C. Constants were calculated from the formula given in [5]; the accuracy of the experimental pK values was evaluated by the mean squares error method, and the confidence interval from a 95% probability calculation using the formula in [6].

LITERATURE CITED

man and J. Lang, J. Am. Chem. Soc., 86, 3796 (1964).
ylin, E. D. Matveeva, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 9, 1235

agietu, V. A. Budylin, and A. N. Kost, Preparative Indole Chemistry [in Russian], Shtiintsa, Kishinev, (1975).
4. A. L. Vereshchagin, O. V. Bryanskii, and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 1, 46 (1983).
5. I. Ya. Bernshtein and Yu. L. Kaminskii, Spectrophotometric Analysis in Organic Chemistry [in Russian], Moscow, Khimiya, 143 (1975).
6. K. Doerffel, Statistik in der Analytischen Chemie; Deut. Verlag Grudstoffind, Leipzig (1966).
7. G. Yagil, Tetrahedron, 23, 2855 (1967).