ACID-BASE PROPERTIES OF 4-SUBSTITUTED INDOLES

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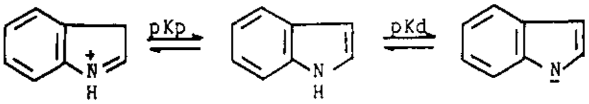
Abstract- The protonation and deprotonation equilibria of a set of 4-substituted indoles have been studied spectrophotometrically at 25 °C. Ionization data have been analyzed by the Hammett acidity function and the excess acidity methods. The existence of close relationships between the Hammett's σ_M constants of the substitutents and the ionization constants for both types of acid-base equilibria is reported.

The evaluation of the weakly acidic and basic properties of indoles (Scheme 1) has attracted interest since the beginning of the attempts to measure the strength of weak acids and bases.[1,2] This information is, on the other hand, of importance to the better knowledge of the reactivity and physicochemical properties of indole derivatives.[3] Although extensive data on dissociation constants of substituted indoles are now available,[2-5] those referred to 4-substituted indoles are practically non existent.



Scheme 1

In the course of our systematic investigations[6-9] on the acid-base properties of indole derivatives of biological and pharmacological importance, we deemed it of interest to study both, acid and basic dissociation equilibria of some representative 4-substituted indoles. The 4-substituted indole nucleus is, on the other hand, widespread in nature[10] (ergot alkaloids, tremorgenic mycotoxins, teleocidines) and most of its derivatives show pronounced pharmacological effects and a number of them are clinically useful.[11]

EXPERIMENTAL AND METHODS

4-Substituted indoles were commercial products of the best available quality and were used as received without further purification. Stock solutions in the concentration range 1×10^{-3}-10×10^{-3} M were prepared in methanol and further diluted with sulphuric acid or potassium hydroxide solution to finally contain not more than 2% v/v of methanol. Sulphuric acid solutions used as solvents were prepared from 96% v/v reagent analysis grade sulphuric acid (Merck) by dilution with distilled water. Aqueous potassium hydroxide solutions were prepared as described by Yagil.[2] All these solutions were standardized against appropriate solutions of acids or bases.

The solutions were spectrophotometrically stable during several hours and the reversibility of the spectra was confirmed. The more relevant characteristics of these spectra are collected in Table 1. The spectrophotometric procedure used to determine the ionization ratios I (I = [Acid]/[Base]) was basically the same as that employed previously.[6,7]

Table 1 - Absorption maxima (nm) of cationic (C), neutral (N) and anionic (A) species of 4-substituted indoles

	λmax(log ε)		
Substituent	C	N	A
OH	282(3.70)	262(3.70), 216(4.50)	299(3.92)
OMe	270(3.71)	262(3.74), 216(4.45)	298(3.87)
Me	315(4.15)	266(3.71), 215(4.43)	291(3.62)
NO_2	261(4.11)	386(3.67), 235(3.89)	502(4.03)
Cl	279(3.72)	268(3.76), 217(4.48)	296(3.39)
COOH	320(4.42)	309(3.67), 227(4.12)	340(3.47)

Table 2 - Ionization data of protonation and deprotonation equilibria at 25° C of 4-substituted indoles

		log I					
H_2SO_4 M	$-H_I$	OH	OMe	Me	NO_2	Cl	COOH
3.56	2.23	-0.94	-	-0.75	-	-	-
4.45	2.84	-0.53	-1.07	-0.33	-	-	-
5.34	3.46	-0.21	-0.64	+0.11	-	-	-
6.23	4.07	+0.06	-0.26	+0.58	-	-	-
6.91	4.54	+0.35	+0.16	+0.87	-	-0.49	-0.72
7.27	4.80	-	-	-	-	-0.28	-0.47
7.64	5.04	-	-	-	-	-0.11	-0.15
8.01	5.30	+0.64	+0.54	-	-1.05	+0.07	+0.10
8.90	5.91	+1.18	+0.96	-	-0.63	+0.47	+0.68
9.11	6.06	-	-	-	-0.45	+0.61	-
10.23	6.83	-	-	-	+0.17	-	-
10.68	7.14	-	-	-	+0.51	-	-
11.57	7.76	-	-	-	+0.91	-	-
KOH M	H_-						
1.21	14.31	-	-	-	+0.39	-	-
1.42	14.37	-	-	-	+0.22	-	-
2.10	14.56	-	-	-	+0.02	-	-
2.65	14.72	-	-	-	-0.16	-	-
3.21	14.88	-	-	-	-0.34	+0.89	-
5.41	15.52	-	-	-	-0.89	+0.32	+0.83
6.82	15.92	-	+0.51	-	-	-0.12	+0.45
7.25	16.05	-	+0.38	+0.78	-	-	+0.29
7.84	16.22	-	+0.22	-	-	-	+0.13
8.17	16.32	-	+0.11	+0.40	-	-0.42	-
9.15	16.58	+0.53	-0.12	+0.15	-	-0.71	-0.24
10.52	16.99	+0.17	-0.55	-0.28	-	-	-0.58
11.56	17.33	-0.16	-	-0.56	-	-	-
12.22	17.48	-0.32	-	-0.83	-	-	-
13.72	17.91	-0.71	-	-	-	-	-

Uv-vis electronic absorption spectra were carried out on a Perkin Elmer Lambda-5 spectrophotometer whose cell compartment was thermostated at 25.0±0.1°C. All measurements were made against blanks of the appropriate solvents.

Ionization ratios obtained by the spectrophotometric method are shown in Table 2. These data were analyzed using eqs (1)-(3) which derive from the Hammett acidity function method (HAFM) and the excess acidity method (EAM).[12-14]

$$\log I = mH + pK_{HAFM} \qquad (1)$$

$$\log I - \log C_{H^+} = m^*_P X_P + pK_P \ (EAM) \qquad (2)$$

$$pK_w + \log C_{OH^-} - \log a_w + \log I = m^*_D X_D + pK_D \ (EAM) \qquad (3)$$

In the first of these approaches, HAFM, it seemed reasonable to use the H_I and H- acidity functions previously established for protonation and deprotonation of indole derivatives, respectively.[4,5] EAM, which is based on free energy relationships and does not make use of any acidity function, gives the pK_A values referred to infinite dilution in water as the standard state and a second term, m^*, related with the stabilization of the acid-base conjugated pair by solvation. Water activities, a_w, and X functions were calculated as previously described.[8,9-15,16]

RESULTS AND DISCUSSION

The results of the ionization data analysis from HAFM and EAM are shown in Table 3. From a perusal of these data the following conclusions can be drawn;

1) A comparison of the pK_A's obtained from EAM with the appropriate HAFM $(H)_{1/2}$ acidity values derived from HAFM reveals a satisfactory correspondence within the error margins inherent to both types of treatments. It seems, therefore, evident that EAM is a suitable method for determining pK_A values of 4-substituted indoles.

2) The non uninformity of m^* values for the protonation equilibria indicates that these ionization processes do not fit any common acidity function.[14] On

Table 3 - Ionization data analysis of protonation and deprotonation equilibria of 4-substituted indole derivatives at 25°C

	Protonation			Deprotonation		
Substituent	$(H_{1/2})^{(a)}$	pK_p	m (b)	$(H_{1/2})^{(a)}$	pK_d	m (b)
H (c)	- 2.38	-2.43± 0.3	0.95±0.17(0.968)	16.56	16.72±0.16	1.06±0.16(0.995)
OH	- 2.16	-2.20± 0.2	0.72±0.06(0.995)	17.21	17.02±0.07	0.89±0.06(0.990)
OMe	- 2.70	-2.82± 0.1	0.88±0.04(0.996)	16.50	16.58±0.08	0.94±0.07(0.994)
Me	- 2.43	-2.36± 0.3	1.01±0.07(0.990)	16.80	17.08±0.2	1.17±0.11(0.985)
Cl	- 3.15	-3.48± 0.2	0.87±0.06(0.998)	15.77	15.81±0.04	0.87±0.05(0.990)
NO_2	- 5.42	-5.04± 0.2	1.06±0.10(0.998)	14.61	14.55±0.04	0.85±0.09(0.991)
COOH (d)	- 5.06	-4.86± 0.1	1.37±0.05(0.999)	16.30	16.39±0.05	1.02±0.06(0.990)

(a) Acidity function value at half ionization. (b) The figures between parentheses are the correlation coefficients. (c) Data taken from ref.4 (d) Carboxylic group deprotonates in the pH region (ref.10). Protonation of this group takes place at higher acidities than indolic ring protonation.

the contrary, the closest proximity of m^* values for the deprotonation equilibria (mean value of $m^* = 0.97\pm0.12$) reflects the existence of a common acidity function for these ionization equilibria of all the studied compounds. Indeed, all the slopes of log I vs H_- are sufficiently close to unity to be assumed that the deprotonation equilibria follow this acidity function. In this sense it is interesting to realize that although the deprotonation of the indole-4-carboxylate anion gives a dianionic species, this compound does not follow the $H_=$ acidity function developed by Yagil for this type of ionization equilibria. This behaviour has previously been observed for other similar compounds and discussed in a previous paper.[17]

3) Finally, data in Table 3 reveal the existence of quantitative correlations between structure and basicity or acidity, Figure 1 shows that $pK_{p(EAM)}$ and $pK_{d\ (EAM)}$ values satisfactory correlate with the σ^o_M constants of the substituents.[18] Both relationships can be expressed by means of eqns (4) and (5).

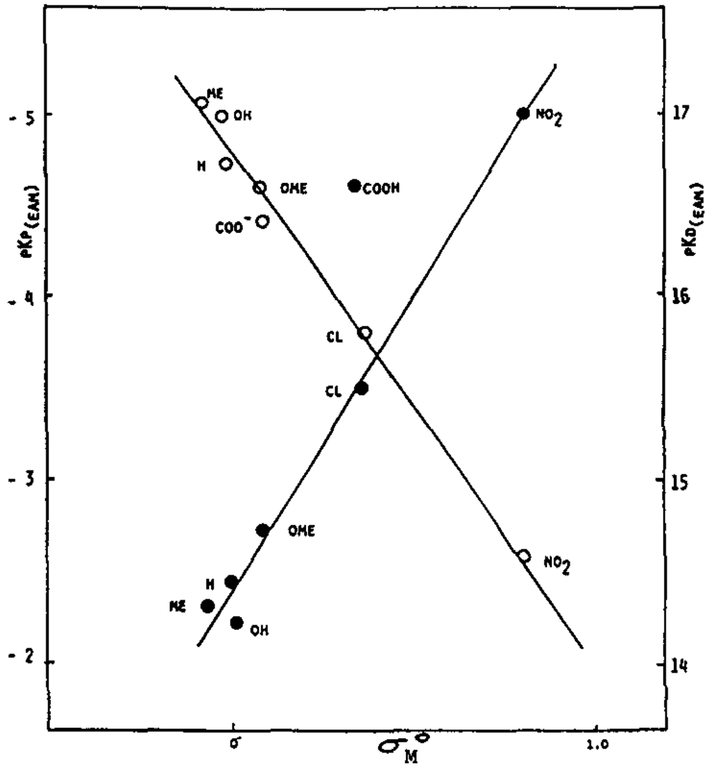


Figure 1 - Correlation of Hammett σ^{o}_{M} substituent with pK's$_{(EAM)}$ of protonation (●) and deprotonation (○) equilibria of 4-substituted indoles

$$pKp = -0.69\ \sigma^{o}_{M} - 2.48 \qquad (r^2 = 0.96) \qquad (4)$$

(excluding the indole-4-carboxylic acid value)

$$pKd = -3.18\ \sigma^{o}_{M} + 16.86 \qquad (r^2 = 0.98) \qquad (5)$$

From the above correlations two interesting points may be brought out. Firstly, the same mechanism for the transmission of the electronic effects of the substituents in 4-position of the indole ring seems to opperate in both type of ionization processes. However, the protonation equilibrium is less sensitive as given by the value of the slope, (ρ = 0.69) to these effects Than the deprotonation process (ρ = 3.18). It is also noteworthy that the ρ value for the deprotonation process is about 1.5 units greater than the previously obtained for 5-substituted indoles.[5] Secondly, the apparent correlations with σ^{o}_{M} values reveal that strong conjugative interactions due to the substituents in 4-position of the indole ring must be relatively unimportant.

ACKNOWLEDGEMENTS

We thank DGYT (PB 89- 0643) and Junta de Andalucia for financial support.

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Received, 19th February, 1991