

THE ACID-BASE PROPERTIES OF PYRROLE AND ITS BENZOLOGS INDOLE AND
CARBAZOLE. A REEXAMINATION FROM THE EXCESS ACIDITY METHOD.

M. Balón*, M.C. Carmona, M.A. Muñoz and J. Hidalgo

Departamento de Química Física, Facultad de Farmacia, Universidad

Sevilla, 41012 Sevilla, Spain.

(Received in UK 8 September 1989)

Abstract.- The acid-base equilibria of protonation and deprotonation of pyrrole and its benzologs indole and carbazole have been reexamined using the Excess Acidity Method (E.A.M.).

The pyrrole ring has very weak acid and very weak basic properties¹. Protonation of pyrrole and indole^{2,3} derivatives takes place in concentrated acidic media on carbon atoms (α -carbon in pyrrole and β -carbon in indole), whereas carbazole⁵ protonates in these media, on nitrogen. The acidity constants for these protonation equilibria in sulfuric acid solutions have been measured and expressed using different acidity functions. Values of pK_a of -3.80 ², -3.50 ⁴ and -4.94 ⁵ have been reported at 25°C for pyrrole, indole and carbazole, respectively.

The pyrrolic NH group deprotonation in all these compounds takes place in highly basic media and pK_a values of 17.51 and 16.97 have been reported for deprotonation equilibria of pyrrole and indole in concentrated hydroxide solutions⁶, and 23.05 and 20.95 in pure DMSO⁷, respectively. To our knowledge, the direct experimental pK_a value of carbazole deprotonation in aqueous media has not been reported. It has been indirectly estimated as 17.06 at 20°C by an extrapolative method⁸ and as 21.1 from fluorimetric titration and the Förster-Weller cycle⁹. This equilibrium has a pK_a value of 19.9 in pure DMSO⁷.

It is worth to note that all these protonation and deprotonation equilibria take place out of the pH range and, therefore, the reported pK_a values did not represent the true thermodynamic pK_a , since no adherence of the ionization data to any acidity function was observed in any case. Thus, the significance and utility of these apparent pK_a s are very restricted.

Nowadays, it is well established that the acid-base behaviour of weak acids and bases in non-ideal aqueous media might be described, at least, by two parameters which must reflect the internal and external stabilizations of the acid-base conjugate pairs due to the molecular structure itself and the solvation process, respectively^{10,11}. The approach based in the Excess Acidity Methods (E.A.M.)¹²⁻¹⁵ has proved to be very useful for this purpose. These methods give the thermodynamic pK_a value, which is referred

to a standard state, and a second m^* or ϕ parameter, which are related with the solvation requirements of the acid-base conjugate pair. In this paper we have used the E.A.M. as developed by Marziano -Cimino-Passerini¹³ and Cox-Yates^{14,15} to reexamine the ionization equilibria of protonation and deprotonation of pyrrole, indole and carbazole.

EXPERIMENTAL

Indole and carbazole were commercial products of the best available quality and were used as received. Pyrrole was freshly distilled immediately before its use. Preparation of solutions and spectrophotometric measurements were carried out as previously described^{14,17,20}. Ionization ratios I , ($I = |\text{Acid}| / |\text{base}|$) were obtained by spectrophotometric titration or from literature where suitable data were available (pyrrole, indole, 1-methylpyrrole and 1-methylindole protonations)^{3,5}. All these experimental measurements were carried out using thermostated solutions at a temperature of $25 \pm 0.1^\circ\text{C}$. Ionization data may be obtained from the authors upon request. Ionization constants and solvation m^* parameters were obtained from eqs. (1) and (2) which were derived from the application of the E.A.M. to protonation¹⁵ and deprotonation equilibria¹⁴, respectively:

$$\log I - \log C_{\text{H}^+} = m^*_p x_p + \text{p}K_p \quad (1)$$

$$\text{p}K_v + \log C_{\text{OH}^-} - \log a_v + \log I = m^*_d x_d + \text{p}K_d \quad (2)$$

where water activities and x functions were taken from elsewhere^{11,20,21}.

RESULTS AND DISCUSSION

The results of the ionization data analysis are collected in Table 1. In this Table, and for comparison purposes, we have also included data from the literature for other structurally related compounds. A first inspection of these data reveals that the revised E.A.M. $\text{p}K_a$ s are, in most of the cases, only slightly changed with respect to those previously reported and obtained using other methods. The more relevant difference is observed in the case of indole protonation, whose E.A.M. $\text{p}K_a$ of -2.43 is a $\text{p}K_a$ unity greater than that previously reported⁴. It is interesting to note that the actual $\text{p}K_a$ is in very good agreement with that of -2.5 predicted from theoretical procedures²². On the other hand, the m^* values are not substantially equal in each type of ionization equilibria, and therefore, all the compounds under study do not follow any common acidity functions¹⁴.

Data in Table 1 reveal several qualitative correlations between structure and acidity. Thus, from the comparison of the protonation parameters of the carbon bases pyrrole and indole, a clear trend towards an increase in $\text{p}K_a$ and a decrease in m^* on annelation is observed. The substantially higher m^* value for pyrrole protonation than for indole protonation is indicative of a weaker solvation of the former. This difference between m^* values is also of interest since it implies an inversion of the basicity of pyrrole and indole going from diluted to concentrated acidic aqueous solutions. In wholly aqueous solutions indole is a stronger base than pyrrole but, above 40% w/w sulfuric acid solutions, the reverse is true. Similar inversions of acidities have been reported¹¹.

TABLE 1: Ionization data analysis of the protonation and deprotonation equilibria at 25°C of pyrrole, indole and carbazole and other related compounds.

Protonation equilibria	pK_a	m^*	r^a	pK_a (other methods)
Pyrrole ^b	-3.57±0.10	1.66±0.06	0.999	-3.80 ²
1-methylpyrrole ^b	-3.15±0.15	1.99±0.12	0.999	-2.90 ²
Indole ^b	-2.43±0.30	0.95±0.17	0.968	-3.50 ⁴ ; -2.50 ²²
1-methylindole ^b	-2.56±0.21	1.77±0.18	0.993	-2.32 ⁵
Carbazole	-4.87±0.15	1.07±0.04	0.999	-4.94 ⁵
9-methylcarbazole	-5.89±0.46	1.35±0.12	0.997	-5.60 ⁵
Diphenylamine ¹⁵	0.765±0.002	1.07±0.03	0.992	0.78 ²³
<u>Deprotonation equilibria</u>				
Pyrrole	17.25±0.23	0.91±0.13	0.992	17.51 ⁶ ; 23.05 ⁷
Indole	16.72±0.16	1.06±0.13	0.995	16.97 ⁶ ; 20.95 ⁷
Carbazole	15.16±0.08	1.45±0.18	0.994	19.97 ⁶ ; 21.1 ⁹ ; 17.6 ⁸
Diphenylamine ¹⁴	23.39	1.20	0.9999	22.44 ²⁴

a) Correlation coefficient, b) Ionization data taken from ref. 2 and 4

Although pyrrole and indole protonate on carbon^{2,3}, the structures of their protonated cations have often been supposed to involve a large localization of their positive charges on the nitrogen atoms. In this sense it seems reasonable to suspect that the different m^* values for protonation of these compounds can be interpreted as a measure of the relative localization of the positive charge on the nitrogen atom, or as it is equivalent, its delocalization into the aromatic ring. The more delocalized the positive charge, the weaker the solvation and the higher the m^* values will be. Thus, the m^* value for pyrrole protonation which is close to those of typical carbon bases⁷, seems to imply a greater delocalization of the positive charge of the pyrrole cation into the ring. In contrast, the smaller m^* value for indole protonation can be taken as indicative of the minor delocalization of the positive charge of its cation.

Certainly, the m^* value of indole is rather distant from the typical values of carbon bases (usually between 1.7 and 2.2)^{7,15} being, on the contrary, close to those of nitrogen bases such as anilines (around to 1.0)^{7,15}. This somewhat exceptional behaviour of the carbon base indole strongly suggests the possibility of the positive charge of its protonated cation being almost completely localized on the nitrogen atom. In this connection, it is interesting to note that equilibria between N-1 and C-3 protonated cations of several indole derivatives have been substantiated in concentrated sulfuric acid solutions⁹.

The pK_a and m^* values of carbazole are in very good agreement with its behaviour as a nitrogen base. Thus, the lower basicity of carbazole, as compared with the carbon bases pyrrole and indole and the nitrogen base diphenylamine, is clearly a consequence of the greater aromaticity disruption involved in the process of carbazole protonation. On the other hand, in view of the similar structures of carbazole and diphenylamine protonated cations, similar m^* values for the protonation of both bases would be expected and were, in fact, found.

Finally, in relation with the protonation equilibria, it is also noticeable that methylation on nitrogen increases the m^* values for all the compounds under study. As it has been previously pointed out^{7,19}, this is consistent with a less efficient solvation of the methylated nitrogens. Moreover, the greater increase of m^* observed for indole methylation, as compared with that of pyrrole methylation, is in agreement with the above hypothesis of the positive charge localization on nitrogen in their respective cations.

We may now turn our attention to the deprotonation equilibria. The increase of acidity and m^* values going from pyrrole to indole and carbazole, follows a rational order consistent with the resonance stabilization of their anions. On annelation, the negative charge of the deprotonated anions is progressively stabilized by resonance delocalization, which in turn causes a decrease of the interaction with the solvent. Therefore, annelation causes two contrasting effects on acidity, increasing internal and decreasing external stabilizations of the anions.

Acknowledgments: We are grateful to the Dirección General de Investigación Científica y Técnica (PB86-0236) for financial support of this work.

REFERENCES

- For a recent review on pyrrole, indole and carbazole chemistry see: D.J.Chadwick "Comprehensive Heterocyclic Chemistry" Eds.A.R. Katritzky, C.W.Rees, C.W.Bird and G.W.H.Cheeseman, vol 4, Pergamon Press, (1984).
- Y. Chiang and E.B. Whipple, J. Am. Chem. Soc., **85**, 2763, (1963).
- R.L. Hinman and E.B. Whipple, J. Am. Chem. Soc., **84**, 2534, (1962).
- R.L. Hinman and J. Lang, J. Am. Chem. Soc., **86**, 3796, (1964).
- H.J. Chen, L.E. Hakka, R.L.Hinman, A.J. Kresge and E.B. Whipple, J. Am. Chem. Soc., **93**, 5102, (1971).
- G. Yagil, Tetrahedron, **23**, 2861, (1967).
- F.G.Bordwell, G.E.Drucker and H.E.Fried, J. Org. Chem., **46**, 632, (1981).
- R. Gaboriaud, J.C. Halle and P. Lefellier, Bull. Soc. Chim. Fr., **78**, 1093, (1976).
- S.G. Schulman and A.C.Capomacchia, Anal. Chim. Acta, **59**, 471, (1972).
- R.A. Cox and K.Yates, Can. J. Chem., **61**, 2225, (1983).
- A.Bagno, G.Scorrano and R.A. More O'Ferral, Rev. Chem. Intermed., **7**, 313, (1987).
- J.F. Bunnett and P. Olsen, Can. J. Chem., **44**, 1899, (1966).
- N.C. Marziano, G.M. Cimino and R.C. Passerini, J. Chem. Soc. Perkin Trans 2, 1915, (1973).
- R.A. Cox and R. Stewart, J. Am. Chem. Soc., **98**, 488, (1976).
- R.A. Cox and K. Yates, J. Am. Chem. Soc., **100**, 3861, (1978).
- G. Yagil, J. Phys. Chem., **71**, 1034, (1967).
- M. Balón, C. Carmona and D.González, Tetrahedron, **41**, 4703, (1985).
- J.Hidalgo, M.Balón, M.Muñoz and C.Carmona, Tetrahedron, **42**, 1497, (1986).
- M.Muñoz, M.C.Carmona, J.Hidalgo and M.Balón, J. Chem. Soc. Perkin Trans 2, 1573, (1986).
- M.Balón, M.A.Muñoz, M.C.Carmona and J.Hidalgo, J. Chem. Soc. Perkin Trans 2, 1165, (1988).
- T.J.Hannigan and W.J.Spillane, J. Chem. Soc. Perkin Trans 2, 851, (1982).
- J.Catalán, P.Pérez and M.Yáñez, Tetrahedron, **38**, 3693, (1982).
- D.Dolman and R.Stewart, Can. J. Chem., **45**, 903, (1967).
- A.Albagli, A.Buckley, A.M.Last and R.Stewart, J. Am. Chem. Soc., **95**, 4711, (1973).