

PROTONATION OF FULLY AROMATIC BETACARBOLINES IN HIGHLY CONCENTRATED SULPHURIC ACID MEDIA

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The monocation–dication equilibria of 6-nitro and 6-sulphonic acid derivatives of betacarboline (9*H*-pyrido[3,4-*b*]indole) were investigated mostly by UV-visible absorption spectroscopy. Dications are formed in very highly concentrated sulphuric acid solutions (>15 M). Ionization constants, pK_a values and solvation parameters obtained from the excess acidity method are reported. The unusually high m^* parameters are discussed and compared with other related data.

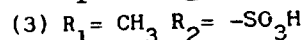
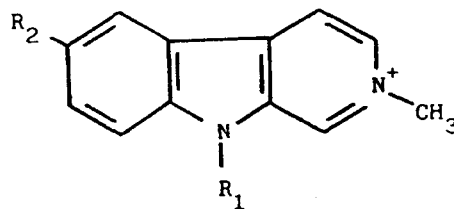
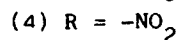
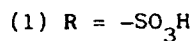
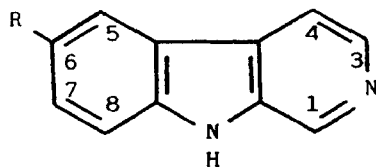
INTRODUCTION

Betacarboline (9*H*-pyrido[3,4-*b*]indole) is the parent compound of an important class of heterocycles that are the basic structural unit of some indole alkaloids possessing potent and varied biological activity.¹ In addition to their biological importance, betacarbolines offer challenging thermodynamic and structural problems in relation to their different acid and basic sites. In recent years, we have undertaken a series of experimental and theoretical studies on the acid–base equilibria of these compounds.^{2,3}

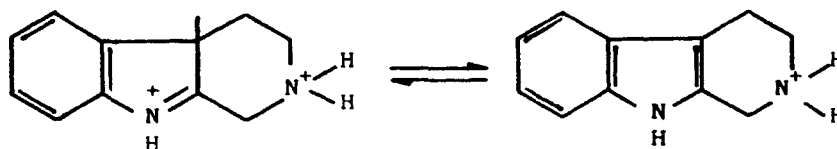
In the context of these studies, it was observed that the piperidinic monoprotonated cations of the less aromatic members of the series, 1,2,3,4-tetrahydrobetacarbolines, protonated in highly concentrated H_2SO_4 solution as typical indoles, yielding

indoleninium dications (Scheme 1).² However, dehydro and fully aromatic monoprotonated cations (betacarbolines are protonated on the N–2 pyridine atom in diluted acidic media³) experience sulphonation on the C–6 atom of the benzene ring in these media, which hinders the study of their aromatic ring protonation processes.⁴

Since the basicity and protonation site of the aromatic betacarboline ring in highly concentrated sulphuric acid media are problems of theoretical and practical interest mainly in connection with aromaticity and basicity in heterocyclic systems, we decided to extend our previous work to study the second protonation equilibria of fully aromatic betacarboline ring. To do this, we investigated the influence of increasing sulphuric acid concentration on the absorption spectra of the betacarboline derivatives 1–4. The presence of the electron-withdrawing sulphonic and nitro groups in



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Scheme 1

these compounds makes them little prone to sulphonation reactions and renders stable their solutions in highly concentrated H_2SO_4 media.

EXPERIMENTAL

Compounds **1** and **4** and the sulphate salts of **2** and **3** were prepared as previously described.^{3,4} Stock solutions of about 1×10^{-3} M were prepared in methanol and further diluted with appropriate sulphuric acid solutions to contain finally 5% v/v of methanol. Sulphuric acid solutions employed as solvents were prepared from 98% (w/w) reagent analysis grade sulphuric acid (Merck) by dilution with distilled water and were standardized against appropriate standard potassium hydroxide solutions.

Ionization data I ($I = [\text{acid}]/[\text{base}]$) at $25 \pm 0.1^\circ\text{C}$ were obtained spectrophotometrically as in previous work.^{2,3} For the sake of brevity these data are only reported in mathematical form (Table 1). Analysis of the ionization data was performed using equations (1) and (2), which are derived from the Hammett acidity function (HAF) and excess acidity (EA) methods:

$$\log I = -mH + pK_a \quad (1)$$

$$\log I - \log C_{H^+} = m^*X + pK_a \quad (2)$$

where H represents the acidity function and X the excess acidity function. These parameters were taken from the literature.⁵⁻⁷

^{13}C -NMR spectra were measured at 50.2 MHz on a Varian XL-200 spectrometer. The ^{13}C chemical shifts were measured relative to benzene as an external standard (coaxial tube) and converted to the Me_4Si

scale. Proton decoupled spectra were recorded to assist signal assignments.

RESULTS AND DISCUSSION

The spectra shown in Figure 1 and the data in Table 2 illustrate the modifications produced in the absorption spectra of the betacarbolines **1-4** by increasing the H_2SO_4 concentration. In 0.1 M H_2SO_4 the spectra are those of the pyridinic monoprotonated cations.³ These spectra do not show any appreciable change with increasing H_2SO_4 concentration up to ca 14 M H_2SO_4 . In more concentrated H_2SO_4 solutions the absorption bands of the monocations undergo a hyperchromic shift with a slight change in position, and a new absorption band emerges around 300–320 nm. These spectral modifications are fairly stable and reversible.

The plots of the absorbances measured at the wavelength of maximum absorption at 300–320 nm against sulphuric acid concentration were sigmoid curves indicative of prototropic equilibria involving the formation of diprotonated cations. Full protonation of the monocations is reached at ca 16–17 M, therefore these compounds are expected to have extremely low basicities. In fact, we have tested several other derivatives of **1** possessing halogen and methoxy substituents and they showed none or incomplete protonation in these media.

To obtain information concerning the basicity of the fully aromatic betacarboline ring with respect to this second protonation process, we selected **1** and **4** as model compounds. Bearing in mind the structural relation of betacarboline with indole and carbazole, the

Table 1. Ionization data analysis for monocation-dication equilibria of **1** and **4** at 298 K^a

Compound	$\text{dlog } I/\text{d}[\text{H}_2\text{SO}_4]$	$[\text{H}_2\text{SO}_4]_{1/2}^b$	HAF				EA	
			H_0		H_1		m^*	pK_a
			m	pK_a	m	pK_a		
1	2.1 ± 0.1 (0.999)	15.3	3.5 ± 0.1 (0.998)	-29 ± 2	3.0 ± 0.1 (0.999)	-31 ± 2	3.3 ± 0.1 (0.999)	-24 ± 1
4	1.1 ± 0.1 (0.997)	14.6	1.8 ± 0.2 (0.997)	-13.6 ± 1	1.5 ± 0.1 (0.997)	14.9 ± 0.2	1.7 ± 0.2 (0.997)	-12 ± 1

^a Figures in parentheses are correlation coefficients.

^b Sulphuric acid concentration corresponding to half protonation.

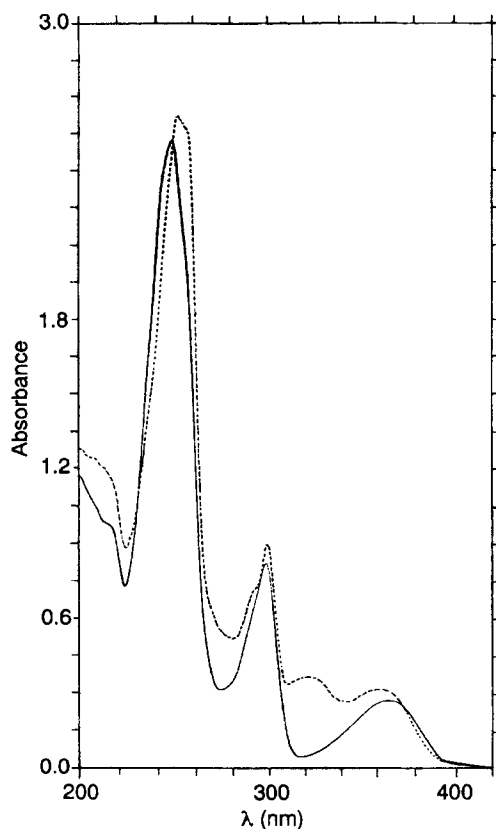


Figure 1. Absorption spectra of **1** in 0.1 M (solid line) and 18 M (dotted line) sulphuric acid solutions

ionization data for these dications were first analysed by the HAF method by using the H_0 and H_1 acidity functions, which are known to correlate the protonation equilibria of carbazoles⁸ and indoles,⁶ respectively. However, since our bases did not show adherence to these acidity functions (the slopes of $\log I$ vs H plots are markedly different from unity), the ionization data were subsequently analysed by using the EA method.

The results of these analyses are summarized in Table 1. As can be seen, the X excess acidity function correlates satisfactorily the ionization data for **1** and **4** ($r > 0.99$).

Our previous studies on the protonation equilibria of indoles^{9,10} and betacarbolines^{2,3} demonstrated that the EA method consistently provides better results than the HAF method. On the other hand, the EA method also affords a more rational insight into the structural and solvent factors influencing the acid–base behaviour. Hence it is nowadays well established that the acid–base behaviour of weak acids or bases in non-ideal aqueous media must be described by at least two parameters. These parameters reflect the internal and external stabilizations of the acid–base conjugated pair as a consequence of the molecular structure itself and solvation. Hence the EA method gives the pK_a value, which is referred to the standard state, usually infinite dilution in water, and an m^* parameter related to the stabilization of the acid–base conjugate pair by solvation.⁷

The substantially higher m^* value for protonation of **1** than for protonation of **4** is indicative of a weaker solvation of the former dications. Particularly, the exceptionally high m^* value obtained for **1** strongly suggests the possibility of the positive charge of its dication being almost completely delocalized into the aromatic system and, therefore, solvation through hydrogen bonding as negligible.

Also, the differences between these pK_a and m^* values are interesting, since they imply an inversion of the basicity of **1** and **4** on going from dilute to concentrated acidic aqueous solutions. In dilute acidic aqueous solutions the monocation of **4** is a stronger base than that of **1** but above 16 M sulphuric acid the reverse is true. Similar inversions of basicities for other compounds have been reported previously.^{7,11}

On the other hand, the unusually high m^* values obtained for **1** and **4** protonations seem distant from those of typical nitrogen bases, being more closely related to those of carbon bases such as indoles. In fact, the pK_a and m^* values for **4** are comparable to those of -14 and 2 , respectively, obtained previously for the

Table 2. UV–visible absorption spectra of compounds **1–4** in 0.1 and 18 M H_2SO_4

Compound	$[H_2SO_4]$ (M)	λ_{max} (nm) ($\log \epsilon$)
1	0.1	366 (3.56), 298 (4.11), 244 (4.32)
	18	364 (3.58), 324 (3.62), 299 (4.13), 248 (~4.60)
2	0.1	364 (3.48), 302 (4.08), 248 (4.29)
	18	361 (3.50), 320 (3.60), 300 (3.59), 251 (~4.56)
3	0.1	362 (3.47), 303 (4.10), 250 (4.30)
	18	360 (3.50), 319 (3.59), 301 (3.58), 252 (~4.55)
4	0.1	350 (3.70), 280 (4.17), 236 (4.20)
	18	358 (3.76), 306 (4.16), 282 (4.18)

indoleninic dications of 1-methyl-6-nitro-1,2,3,4-tetrahydrobetacarboline.² Similarly, the m^* value of **1** is comparable to that of 3.11 for the protonation of 1-methyl-2-phenylindole.¹²

However, in relation to the protonation site, we have shown in a previous paper¹³ that the formation of the indoleninic dications of the tetrahydrobetacarboline derivatives is accompanied by significant and diagnostically useful shifts in their ¹³C NMR spectra. In particular, in 18 M sulphuric acid, the signal of the C-4a atom, the protonation site, changes its multiplicity and it is shielded by about 50 ppm.

Conversely, the results of similar ¹³C NMR experiments carried out with **1–3** show that, on increasing the sulphuric acid concentration from 0.1 to 18 M, the multiplicities of the ¹³C NMR signals of **1–3** remain unchanged. Further, most of these signals experience only slight downfield shifts (ca 2–3 ppm), except those of the methyl groups in **2** and **3**, which are shifted by about 7–8 ppm. Although these results indicate N-9 protonation, we cannot on this basis establish unambiguously the structure of the dications. Hence, as suggested by one of the referees, it is possible that these extremely weak bases could not attain the slow exchange conditions required on the NMR time-scale. Therefore, the determination of the structure of the fully aromatic betacarboline dications requires more extensive experimental work, which will be the subject of future research.

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