AM1 Study of a β-Carboline Set. Part II: Pyrrole-*N* Deprotonated Species†

Carmen Carmona, José Hidalgo, Enrique Sánchez Marcos,* Rafael R. Pappalardo, María Muñoz and Manuel Balón
Department of Physical Chemistry, University of Sevilla, 41012 Sevilla, Spain

We report a semiempirical AM1 study of the structural properties and potential reactivity of several indole-*N* deprotonated β-carbolines with different degrees of aromaticity. The influence of methylation on the non-indole nitrogen atom has also been studied. Geometrical parameters, deprotonation enthalpies and static reactivity indices have been examined. In order to analyse the effect of annellation, some model compounds including those with only a few condensed rings have also been studied. The anionic data have then been used as ionic probes for the aromatic stabilizations of the annellated rings. Annellation effects are in general well reproduced by the AM1 semiempirical method.

The properties of the β-carboline ring (9*H*-pyrido[3,4-*b*]indole) have been the subject of extensive chemical and biochemical investigation because of their long recognized pharmacological interest.[1–6] β-Carboline derivatives possess a weakly acidic indole NH group, N-1, and a basic non-indole nitrogen atom, N-7 and, therefore, they can exist in aqueous solutions, at least, as three differently charged species. We have undertaken a series of studies on the prototropic equilibria of some β-carbolines[7–9] in concentrated acidic or basic media and we found it of interest to carry out a semiempirical AM1 study on the protonation of these molecules.[10] This study allowed us to rationalize the structural properties and general reactivity of the neutral and protonated species. Also, the influence of the degree of aromaticity of the β-carboline ring on molecular geometry, protonation equilibria, and some reactivity patterns was explored.

There was no theoretical data on the anionic forms of these β-carboline derivatives so, in relation to these studies, we carried out theoretical calculations on the N-1 deprotonated molecules using the AM1 method, which has recently proved to be a useful tool for computing deprotonation enthalpies.[11,12] Thus, the influence of the degree of aromaticity of the derivatives and the effect of N-7 methylation on the geometry and reactivity of the deprotonated molecules have been analysed.

The annellation effects of a benzene molecule on the protonation/deprotonation processes of different aromatic compounds have recently been reported.[11] The authors conclude that when these processes involve π-contributions, the annellation effects can be substantially larger or smaller than the roughly constant σ-polarization effect. In particular, for the pyrrole/indole system, the π-effect definitely favours the deprotonation of indole and contributes to an increase in the annellation effect. As some of the β-carbolines we are interested in can be formed by annellation of a pyridinic or benzenic ring to indole or azaindole, respectively, we decided to analyse these annellation effects. For this purpose, other related basic structures and the parent one- and two-ring systems have also been studied. All the molecules studied are shown in Fig. 1, reporting the numbering system employed hereafter.

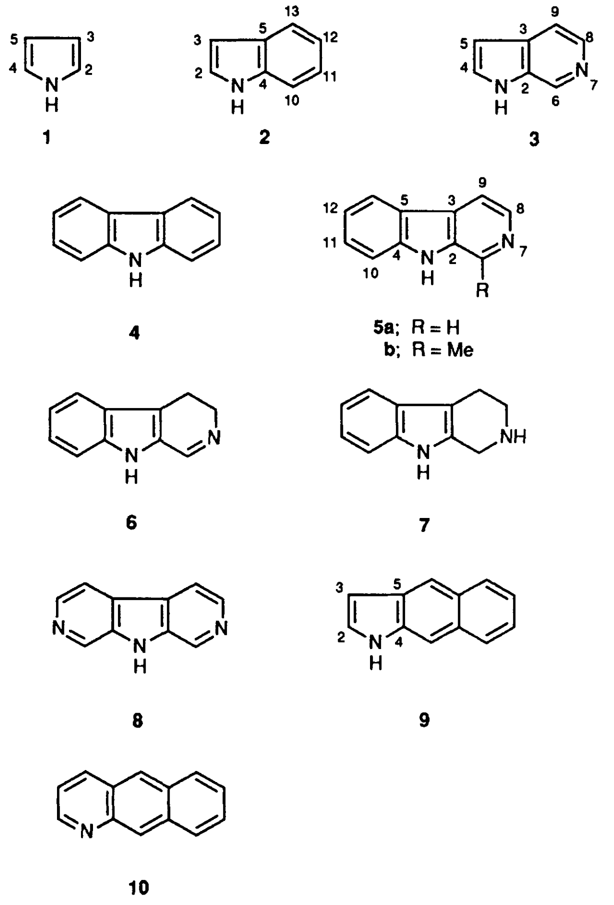


Fig. 1.

Experimental

Computational Method.—SCF calculations were carried out at the AM1 semiempirical level.[13] Previous workers have shown this method to give a good level of confidence in the description of heterocycles such as those studied in this work.[10,12,14] The geometries of the fully aromatic rings were optimized assuming planarity. In the case of those compounds with tetrahedral centres (**6** and **7**), the dihedral angles of the pyridinic ring were optimized. Different initial arrangements were considered in order to locate the minima. The entropy was computed using standard mechanical formulae and vibrational frequencies.[15,16]

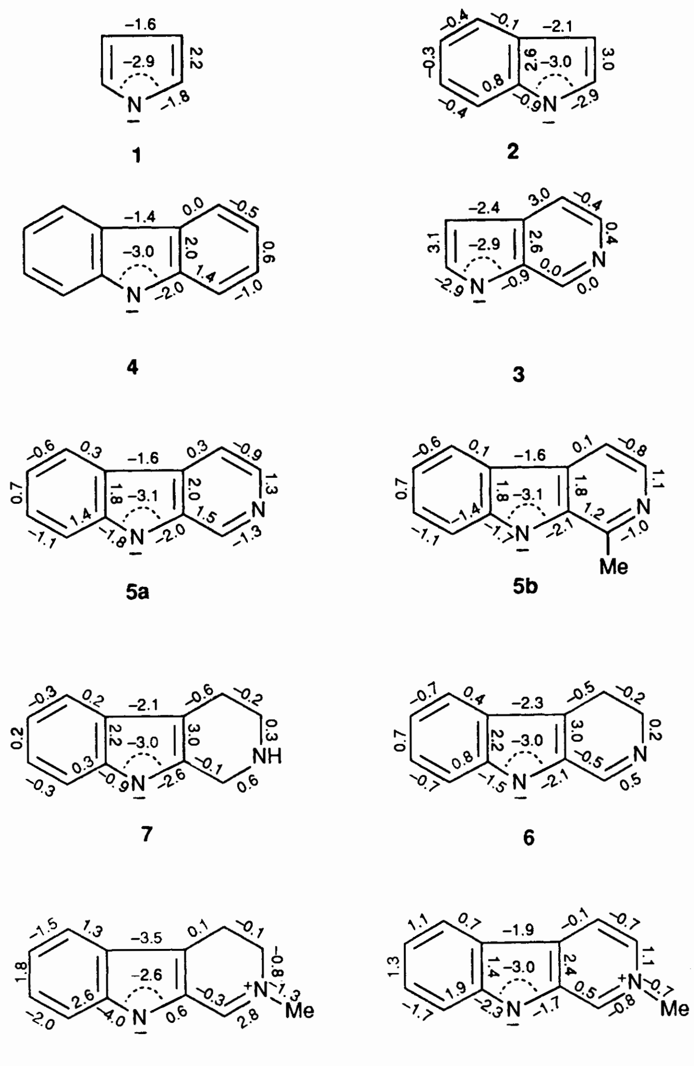
---

† Part I is ref. 10.

Results and Discussion

Geometries.—The fully optimized geometries of all the anionic forms studied in this paper have been deposited as supplementary material [Sup. No. 56794 (27 pp.)],* as have those of the neutral molecules.[10]

Fig. 2 shows the changes in the main geometrical parameters of compounds **1**–**7** produced by the deprotonation process. It is noted that for the partially aromatic compounds, the dihedral angles of the pyridinic ring after deprotonation are slightly distorted from those corresponding to the neutral molecules, *i.e.*, the changes are not greater than 2°. In Fig. 2 we have only considered the anionic forms which correspond to the deprotonation at N-1 assuming, *a priori*, that this should be the most acidic site of these molecules. The influence of annellation on the geometrical parameters of the neutral compounds was discussed in our last paper,[10] so this report focuses on the geometrical changes observed after the deprotonation process.



1 **2** **4** **3** **5a** **5b** **7** **6** **6** (N - 7 - Me) **5a** (N - 7 - Me)

Fig. 2. Main geometrical parameter changes of β-carbolines and model compounds. A minus sign means a decrease of the parameter value in the deprotonated form. (Bond lengths in 10^{-2} Å and bond angles in degrees).

Table 1. Enthalpy and free-energy changes (kJ mol^{-1}) for the process $AH \rightleftharpoons A^- + H^+$.

Compound	$\Delta H_{acid}^{298\,K}$ [a]	$\Delta G_{acid}^{298\,K}$ [b]
1	1487.0	1457.8
2	1448.5	1418.9
3	1422.3	1392.3
4	1431.8	1402.1
5a	1408.0	1378.7
5b	1411.0	1381.6
5a (N-7-CH_3)	1043.9	1014.7
6	1413.6	1386.8
6 (N-7-CH_3)	1035.0	1003.9
7	1431.2	1402.1
8	1383.6	—
9	1430.6	—
10	1611.1	—

[a] $\Delta H_f^{298\,K}(H^+) = 1536.4$ kJ mol^{-1}. [b] $\Delta G_f^{298\,K}(H^+) = 1504.0$ kJ mol^{-1}.

As can be seen in Fig. 2, the general effect of this process is to decrease the C(4)N(1)C(2) angle by *ca.* 3°. As expected, the pyrrolide fragment of the molecule shows the most significant variations in bond length. Thus, the deprotonation process produces a decrease in the C(4)–N(1) and C(2)–N(1) distances and the rest of the bonds of the pyrrolide fragment of the molecule are alternately lengthened or shortened. The changes in the C(2)–N(1) and C(4)–N(1) distances reflect the importance of the π-electron redistribution for the deprotonation process. In fact, these bonds should be lengthened owing to the location of the electron pair in the σ-plane. However, these changes are not generally observed, except for the methylated dehydro derivative **6** (N-7-Me), in which the C(2)–N(1) bond is longer in the deprotonated molecule. The dehydro derivatives show other significant differences with respect to the fully aromatic molecules which are mainly apparent for compound **6** (N-7-Me). While C(2)–C(6) and C(6)–N(7) bonds are lengthened and shortened, respectively, after deprotonation of the fully aromatic derivatives, the opposite is found for the dehydro compounds. The greatest variations in the bond lengths are observed in the deprotonation of **6** (N-7-Me). Also, on deprotonating this compound, the N-7-Me distance is considerably shortened compared with the corresponding bond in compound **5a** (N-7-Me).

Deprotonation Enthalpies.—The calculated deprotonation enthalpies and free energies of the different compounds for the N-1 deprotonation processes are presented in Table 1. AM1 calculations give reliable deprotonation enthalpies; thus, the errors with respect to experimental values[11] for compounds **1** and **2** are 21 and 22 kJ mol^{-1}, respectively. Unfortunately, the lack of experimental information on gas phase acidity of β-carbolines precludes any comparison of the theoretical results for these compounds.

The entropic contributions to these processes are roughly constant along the series. This implies that the relative acidity order obtained from the enthalpy or the free-energy values is the same. The entropic term contributes to the free energy of deprotonation by *ca.* 30 kJ mol^{-1}, in good agreement with the value for pyrrole reported by Bartmess and McIver from pulsed ICR experiments (32 kJ mol^{-1}).[17]

For compounds **1**–**7**, the theoretical deprotonation enthalpy sequence obtained in the gas phase is the same as the acidity sequence observed in solution. In fact, β-carbolines have been shown[9] to be stronger acids than indoles and their acidities increase with the degree of aromaticity of the compounds. Thus, in solution the following sequence of pK_a values holds: pyrrole

---

* For details of the supplementary material deposition scheme, see 'Instructions for Authors (1990)', *J. Chem. Soc., Perkin Trans. 2*, 1990 issue 1.

Table 2. Annellation effects[b] on gas-phase acidities derived from AM1-derived E_{dp}.

Species	ΔE_{dp}/kJ mol^{-1}
1/**2**	38.5
1/**3**	64.7
1/**4**	55.2
1/**8**	103.4
2/**4**	16.7
2/**5a**	40.5
2/**9**	17.8
3/**5a**	14.3
Quinoline[a]/**10**	14.4

[a] The E_{dp} value of this compound has been taken from ref. 11. [b] ΔE_{dp} $(\Delta/2) = E_{dp}(1) - E_{dp}(2)$.

(17.25)[18] < indole(16.72)[18] < tetrahydro(16.09)[8] < dehydro (15.34)[9] < fully aromatic (14.43)[9] derivatives.

The presence of a pyridinic instead of a benzenic ring leads to a decrease in the theoretical deprotonation enthalpy. This is also observed in solution: norharmane **5a** is more acidic than carbazole **4**, by about 0.73 pK_a units. The large decrease in the deprotonation enthalpy after N-7 methylation is also noteworthy. From this pronounced substituent effect, unobserved upon C-6 methylation **5b**, it is evident that the positively charged quaternary nitrogen has an additional stabilizing effect on the anions. In solution, N-7 methylated β-carboline **5a** (N-7-Me), is also a stronger acid (pK_a ~10.9)[19] than the corresponding unsubstituted compound.

The fact that the order of gas-phase acidity as given by AM1 is maintained in solution, seems to indicate that the solvation contribution, although important, is almost constant among the β-carbolines. Variation of the number of fused rings does not give rise to severe changes in the relative order of acidity of the molecules studied. This behaviour has already been observed in the protonation of these molecules.[10]

Table 3. Net atomic charge from Mulliken population analysis for compounds **1**–**7** and their respective anions.

	Neutral		Anion	
Compound	Atom	Charge	Atom	Charge
1	N-1	−0.18	N-1	−0.24
	C-2	−0.14	C-2	−0.26
	C-3	−0.20	C-3	−0.29
			C-5	−0.29
2	N-1	−0.22	N-1	−0.25
	C-3	−0.20	C-3	−0.33
3	N-1	−0.20	N-1	−0.24
	C-5	−0.20	C-5	−0.33
	N-7	−0.13	N-7	−0.21
4	N-1	−0.24	N-1	−0.27
	C-8	−0.16	C-8	−0.23
	C-12	−0.16	C-12	−0.23
5a	N-1	−0.23	N-1	−0.25
	N-7	−0.12	N-7	−0.17
	C-12	−0.17	C-12	−0.23
5a (N-7-CH_3)	N-1	−0.20	N-1	−0.18
	N-7	−0.02	N-7	−0.05
	C-12	−0.14	C-12	−0.17
5b	N-1	−0.23	N-1	−0.25
	N-7	−0.12	N-7	−0.16
	C-12	−0.17	C-12	−0.23
6	N-1	−0.19	N-1	−0.20
	N-7	−0.16	N-7	−0.26
	C-12	−0.16	C-3	−0.23
6 (N-7-CH_3)	N-1	−0.17	N-1	−0.11
	N-7	−0.15	N-7	−0.25
	C-2	−0.16	C-2	−0.19
7	N-1	−0.20	N-1	−0.23
	N-7	−0.27	N-7	−0.28
	C-3	−0.15	C-3	−0.29

Annellation Effects.—The annellation effects on protonation or deprotonation have been extensively reported in the literature from both theoretical and experimental points of view.[11,20] In particular, Meot-Ner *et al.*[11] have recently studied the carbon acidities of a wide range of aromatic compounds with different numbers of fused rings. By symmetry considerations and substituent effects, these authors conclude that the annellation of a benzene ring has an effect, ΔE_{dp}, assigned to the polarization of the σ-system, of 28 kJ mol^{-1} on the deprotonation energy: $\Delta E_{dp} = E_{dp}(\text{parent}) - E_{dp}(\text{annellated})$. Larger annellation effects are observed when the parent molecule is pyrrole. In this case ΔE_{dp} becomes 38 kJ mol^{-1}, the extra annellation effects being ascribed to a π-contribution. However, the simultaneous annellation of two benzene rings to the pyrrole molecule [pairs **1**/**4** in Table 2] gives a value of *ca.* 28 kJ mol^{-1} per benzene molecule.

Because the compounds studied in the present work have the pyrrole ring as the parent molecule, we deemed it of interest to analyse the annellation effects of a pyridine or a benzene ring on the deprotonation energy. Table 2 shows the effects of annellation derived from the AM1 calculations. The pyridine ring has an annellation effect greater than that of the benzene ring by *ca.* 26 kJ mol^{-1}. This value is derived from the ΔE_{dp} difference between **1**/**3** and **1**/**2** and from half of the ΔE_{dp} difference between **1**/**4** and **1**/**8**. Using the ΔE_{dp} value given by Meot-Ner for the benzene ring annellation, a pyridine effect of *ca.* 54 kJ mol^{-1} can be derived. However, the value obtained from the annellation of the **1**/**3** pair is larger by *ca.* 11 kJ mol^{-1}. Again an extra annellation effect is found when the pyrrole ring is the parent compound instead of the pyridinic or the benzenic rings. Because this larger effect has been assigned to a π-contribution, the effects of changes in the π-electron distribution on the deprotonation process have been examined. From this analysis, a large increase in the electron density on C-3 or C-5 of the pyrrolic fragment of **2** or **3** is observed.* This electron redistribution is not found in the deprotonation of pyridine containing annellated rings, where a hydrogen is removed from a carbon atom. Thus, the pair pyridine/quinoline, reported by Meot-Ner, shows the annellation effects expected from the σ-polarization of a benzene ring.

Going further by symmetrically fusing another aromatic ring to a two-ring system, it is found that this extra effect disappears. Thus, it might be expected that the annellation effects of the pairs **3**/**5a** and **2**/**4** have the same value. This can be calculated as the difference between the simple σ-polarization of the benzene ring and the additional π-contribution due to the C-5 or C-3 atom, respectively (*ca.* 28 − 11 = 17 kJ mol^{-1}). As can be seen in Table 2, a mean value of *ca.* 16 kJ mol^{-1} is obtained for these pairs. When a pyridine ring is annellated to the two-ring system a similar effect is observed. The ΔE_{dp} value of 41 kJ mol^{-1} for **2**/**5a** (Table 2) agrees quite well with that predicted, *i.e.* 54 − 11 = 43 kJ mol^{-1}. In contrast, the annellation of a benzene ring to the quinoline molecule to form acridine only has an effect assigned to the σ-polarization (28 kJ mol^{-1}).[11]

Finally, in order to test the assumption that the pyrrolide

---

* 0.15 and 0.14, respectively.

fragment is involved in the extra π-effect, the ΔE_{dp} values for compounds **9** and **10** have been calculated. In these cases, the benzene ring is asymmetrically annellated. As shown in Table 2, the addition of the benzene ring contributes by nearly the same amount to the deprotonation process (14.4 kJ mol^{-1} for quinoline/**10** and 17.8 kJ mol^{-1} for **2**/**9**).

Reactivity.—The net atomic charges, obtained from Mulliken Population Analysis, for compounds **1**–**7** and their N-1 deprotonated forms are collected in Table 3. The atom bearing the most negative charge varies with the molecule. Thus, in all the aromatic three-ring systems, compounds **4**, **5a**, **5b** and **5a** (N-7-Me), N-1 has the higher negative charge. However, in the anions of indole, azaindole and pyrrole, the charge is preferentially located on a carbon atom. On the other hand, N-7 is the atom bearing the most negative charge in the dehydro derivatives and a compromise situation between N-7 and C-3 is observed for the tetrahydro molecules.

Although there is little information on the reactivity of the anionic molecules studied in the present paper, there is some evidence to support the theoretical results. Thus, alkylation of the anions of pyrrole and its benzo analogues, indole and carbazole, with halogenoalkanes gives N-1-alkylated derivatives as the major products.[21] However, reactions involving the heteroaryl Grignard reagents yield the *C*-alkylated compound.[21] Usually, the pyrrole ring is preferentially alkylated at the C-2 position but 3-alkylpyrroles are also frequently formed in high yield. Indolylmagnesium halides are also alkylated at the 3-position.[21]

In the case of the aromatic β-carbolines, N-1 alkylation with alkyl halides can be achieved after forcing deprotonation with, for example, sodamide.[2] Moreover, the N-1 deprotonated N-7 methyl-substituted derivative undergoes protonation and alkylation at the N-1 atom.[2]

Finally, although alkylation at the N-1 atom of the tetrahydro derivative has been carried out with alkyl halide after treatment with sodamide, acylation seems to take place preferentially at the N-7 atom.

Acknowledgements

We gratefully acknowledge financial support from the *Dirección General de Investigación Científica y Técnica* of Spain (PB86-0236) and (PB86-0140).

References

1 V. Sniecks, in *The Alkaloids*, ed. R. H. F. Manske, Academic Press, New York, 1968, vol. 11.
2 R. A. Abramovitch and I. D. Spencer, *Adv. Heterocycl. Chem.*, 1964, **3**, 79.
3 B. T. Ho, W. M. McIsaac, K. E. Walker and V. Estevez, *J. Pharm. Sci.*, 1968, **57**, 269, 1368.
4 N. S. Buckholtz and W. O. Boggan, *Life Sci.*, 1977, **20**, 2093.
5 M. Beljanski and M. S. Meljanski, *IRCS Med Sci.*, 1984, **12**, 587.
6 F. Bloom and R. Alan, in *Betacarbolines and Tetrahydroisoquinolines*, eds. F. Bloom and R. Alan, Liss, New York, 1982.
7 M. Balón, C. Carmona and D. González, *Tetrahedron*, 1985, **41**, 4706.
8 J. Hidalgo, M. Balón, M. A. Muñoz and C. Carmona, *Tetrahedron*, 1986, **42**, 1497.
9 M. A. Muñoz, C. Carmona, J. Hidalgo and M. Balón, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1573.
10 J. Hidalgo, M. Balón, C. Carmona, M. A. Muñoz, R. Pappalardo and E. Sánchez Marcos, *J. Chem. Soc., Perkin Trans. 2*, 1990, 65.
11 M. Meot-Ner (Mautner), J. F. Liebman and S. A. Kafafi, *J. Am. Chem. Soc.*, 1988, **110**, 5937.
12 M. Meot-Ner (Mautner) and S. A. Kafafi, *J. Am. Chem. Soc.*, 1988, **110**, 6297.
13 M. J. S. Dewar, E. G. Zoelisde, E. F. Heady and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
14 J. Anguiano, J. Fernández Sanz and J. Vilarrasa, *J. Org. Chem.*, 1988, **53**, 3900.
15 D. MacQuarrie, *Statistical Mechanics*, Harper and Row, New York, 1976.
16 M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.*, 1977, **99**, 7822.
17 J. E. Bartmess and R. T. McIver, Jr., in *Gas Phase Ion Chemistry*, ed. M. T. Bowers, Academic Press, New York, 1979, vol. 2, ch. 11.
18 M. Balóm, C. Carmona, M. A. Muñoz and J. Hidalgo, *Tetrahedron*, 1989, **45**, 7501.
19 R. Sakuros and K. P. Ghiggino, *J. Photochem.*, 1982, **18**, 1.
20 J. Catalán, R. M. Claramunt, J. Elguero, J. Laynez, M. Menéndez, F. Anvia, J. H. Quian, M. Taagepera and R. W. Taft, *J. Am. Chem. Soc.*, 1988, **110**, 4105.
21 D. J. Chadwick, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky, C. W. Rees, C. W. Bird and G. W. H. Cheeseman, Pergamon Press, Oxford, 1987, vol. 4.

Paper 0/01801E
Received 23rd *April* 1990
Accepted 3rd *July* 1990