AM1 Study of a β-Carboline Set: Structural Properties and Potential Reactivity

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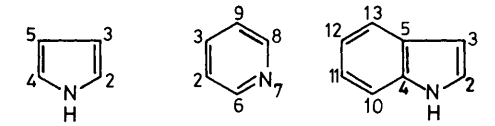
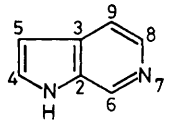
A set of β-carbolines derived from norharman and its corresponding dehydro and tetrahydro derivatives has been studied by means of the semiempirical AM1 method. Geometrical parameters, protonation affinities and static reactivity indices have been examined. Structural properties and protonation sites are well described by calculations. Orientation of electrophilic attack on different centres is only partially predicted by the frontier indices. The role of the protonated molecules as reactive species is also discussed.

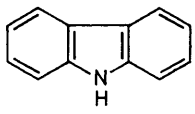
The β-carboline ring (9*H*-pyrido [3,4-*b*] indole), in a number of its different degrees of aromaticity, *eg.* (**6**), (**7**), and (**8**), is the basic structural unit of several alkaloids (*Rauwolfias*, *Peganum Harmala*) of biological and pharmacological interest.[1]



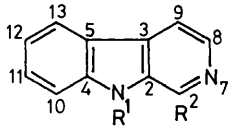
(**1**) Pyrrole (**2**) Pyridine (**3**) Indole



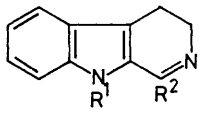
(**4**) Azaindole



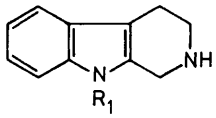
(**5**) Carbazole



(**6**) β-Carboline
a; $R_1 = R_2 = H$
b; $R_1 = H, R_2 = CH_3$
c; $R_1 = CH_3, R_2 = H$
d; $R_1 = R_2 = CH_3$



(**7**) Dehydro-β-carboline
$R_1 = R_2 = H$
$R_1 = H, R_2 = CH_3$
$R_1 = CH_3, R_2 = H$



(**8**) Tetrahydro-β-carboline
a; $R_1 = H$
b; $R_1 = CH_3$

Historically, β-carboline alkaloids have been used therapeutically for their hypotensive activity (*Reserpine*);[2] however, recent interest has been focussed on their neurological effects. These studies have demonstrated that β-carbolines interact with a number of neurotransmitter systems such as opiate, benzodiazepine, cholinergic, muscarinic, serotonine and dopamine receptors.[3] These properties coupled with the *in vivo* presence of those drugs in several human tissues and urine,[4,5] suggest that β-carboline derivatives may act as neurotransmitters or neuromodulators, themselves. In this sense, during the last few years important research on β-carboline participation in the mechanism of alcoholic intoxication has been undertaken.[6] More recently, the discovery that some β-carboline derivatives can destroy selectively and completely the proliferative capacity of various types of cancer cells *in vitro*, without affecting the normal cells has stimulated the interest in the β-carboline chemistry.[7,8]

Apart from the biochemical interest in β-carboline derivatives, this heterocyclic system possesses challenging chemical problems derived from its structural characteristics. The β-carboline ring is composed of a π-deficient pyridinic ring fused to a π-excessive indole ring. Although at first sight, it would be expected that each ring retains its individual character, their reactivities towards both electrophiles and nucleophiles can be modified in the β-carboline ring. The easy protonation at the pyridinic nitrogen atom[9–11] could be an additional factor which would change the reactivity of these compounds, especially with respect to the indole ring reactivity.

Theoretical calculations have proved to be a useful tool in the rationalization of the properties and reactivity of a great number of conjugated systems. In connection with our work on β-carboline chemistry we have deemed it of interest to carry out a theoretical study on a set of β-carboline derivatives. Semiempirical and *ab initio* calculation[12–16] on some model β-carbolines have been mainly centred on molecular structures and proton affinities. However, there is an almost complete lack of data on their protonated forms, which are the reactive species in the most typical reactions of these compounds.[17]

The principal aim of this work is to explore the influence of the aromaticity degree of the β-carboline ring on molecular geometry, protonation equilibria, reactivity of the protonated species and other reactivity patterns. In order to test the calculation procedures, as well as for comparative purposes, we have also included in this study other related basic structures with a minor number of condensed rings. All these compounds with the numbering system hereafter employed are shown above. The protonated species derived from these compounds are labelled with the neutral species' number and the protonation site in parentheses.

Computational Method

Semiempirical calculations at the AM1[18] level were carried out. Optimization of the molecular structure was done using the Fletcher–Powell algorithm.[19] The geometries of the fully aromatic rings were optimized assuming C_s symmetry. In the case of compounds (**7**) and (**8**) the dihedral angles of the

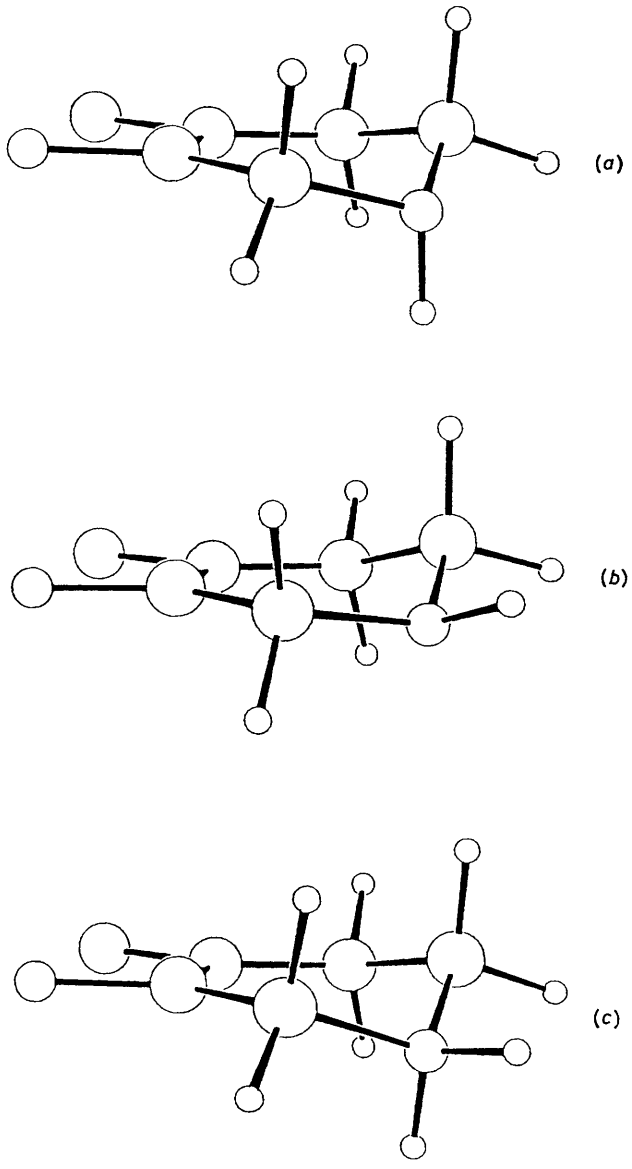


Figure 1. Preferred conformations of pyridinic ring in (**8a**) (*a*) and (*b*) and its protonated derivative (**8a**)(N-7) (*c*).

pyridinic ring were optimized. Different initial arrangements were considered in order to locate the minima. The method used to study the solvent effect was based on the cavity model derived by Kirkwood,[20] adapted to quantum chemical calculations[21] and extended to the use of ellipsoidal cavities.[22]

Results and Discussion

Geometries.—The fully optimized geometries of all the compounds reported in this paper are included as supplementary material.* A comparison between theoretical and experimental data in the cases where the latter are available[23–27] [(**1**)–(**3**), (**6a**), (**6b**), and (**8a**)] reveals a good agreement between them. Thus, the standard deviations are 0.025 Å and 2° for bond lengths and bond angles, respectively. Considering the recently reported STO-3G geometries of (**6a**) and (**6b**)[16] it is found that the average errors given by AM1 are similar to those corresponding to the *ab initio* calculations. [The standard deviations for (**6a**) are: 0.022 (AM1) and 0.015 Å (STO-3G) for bond lengths, and 0.51 (AM1) and 0.60° (STO-3G) for bond angles].

In relation to the conformation of the pyridinic ring for the partially aromatic compounds, in the case of the dehydro-β-carboline, (**7a**), the ring is almost planar with the dihedral angle C-13,C-5,C-3,C-9 = 1°. Optimization of the tetrahydro-β-carboline geometry, (**8**), yields two possible conformations where N-7 and C-8 atoms are twisted out of the molecular plane by *ca.* 10 and 35°, respectively (Figure 1). The preferred arrangement is (*a*), which corresponds to a more favourable staggered disposition of the hydrogen atoms attached to N-7 and C-8. The protonated form on N-7, (**8a**)(N-7), leads to the sole conformation drawn in Figure 1.

Figure 2 shows the main geometrical parameters of the most representative compounds. In Figure 2 we have exclusively considered the protonation on the pyridinic nitrogen, because this is the most basic site of these compounds (see below). As can be seen, the annellation effects of the indolic and pyridinic ring into β-carboline are reflected principally on the lengthening of the C(2)–C(3) and shortening of the C(3)–C(9) bonds, whereas the internal bond angles of both fused rings do not change significantly on annellation. On the other hand, the remaining geometrical parameters of the pyridinic ring are little distorted from those of pyridine itself. More significant modifications are observed in the benzenic bonds of the indolic fragment. As would be expected, for dehydro-, (**7**), and tetrahydro-β-carboline, (**8**), smaller modifications on annellation are observed. It is noteworthy that the magnitude of the C(6)=N(7) double bond of the dehydro-β-carboline reflects the strong localization of this bond. The angles involving the N-7 atom in these compounds are of the expected magnitude.

The geometrical changes induced by protonation deserve particular attention. In the case of the fully aromatic β-carbolines this process causes important geometrical changes. However, if the protonated form geometry is compared with those of the basic structures [(**3**) and (**2**)(N-7)], only the pyrrolic ring geometry is affected. A different situation is observed for the geometrical changes induced by protonation of the dehydro-β-carboline (**7a**). In this case, the lengthening and shortening of the N(7)–C(6) and C(6)–C(2) distances are transmitted to the whole of the indolic system the distances of which are alternately shortened and lengthened. This fact reflects a significant resonance interaction between the indolic π-system and the exocyclic double bond.

Finally, although the optimized structures of the methylated derivatives of β-carbolines are not shown in Figure 2, it should be indicated that methylation effects on geometries are, in general, the expected ones for this substituent. These are more important for N-7 methylation, the effects of which are very similar to those observed upon protonation.

Protonation Energies.—The calculated protonation enthalpies of the different β-carbolines are presented in Table 1. As these compounds have two preferential protonation sites N-1 and N-7, the proton affinities corresponding to both protonation processes have been recorded in Table 1. The level of the AM1 method gives reliable protonation enthalpies within 12–20 kJ mol^{-1}. Thus, the experimental proton affinity values for (**1**) and (**2**) are 875 and 922 kJ mol^{-1},[28] and the estimated ones are 865 and 900 kJ mol^{-1} respectively. As a result, the computed protonation enthalpies in Table 1 are reasonable compared with the experimental order of proton affinity increase. Also, AM1 correctly predicts the preferred protonation site of pyrrole[29] at C-2, indole[30] at C-3, azaindole[31] at N-7 and carbazole[32] at N-1.

The protonation enthalpies corresponding to the two dif-

* Available as Supplementary Publication No. 56769 (23 pp.). For details see Instructions for Authors in the January Issue.

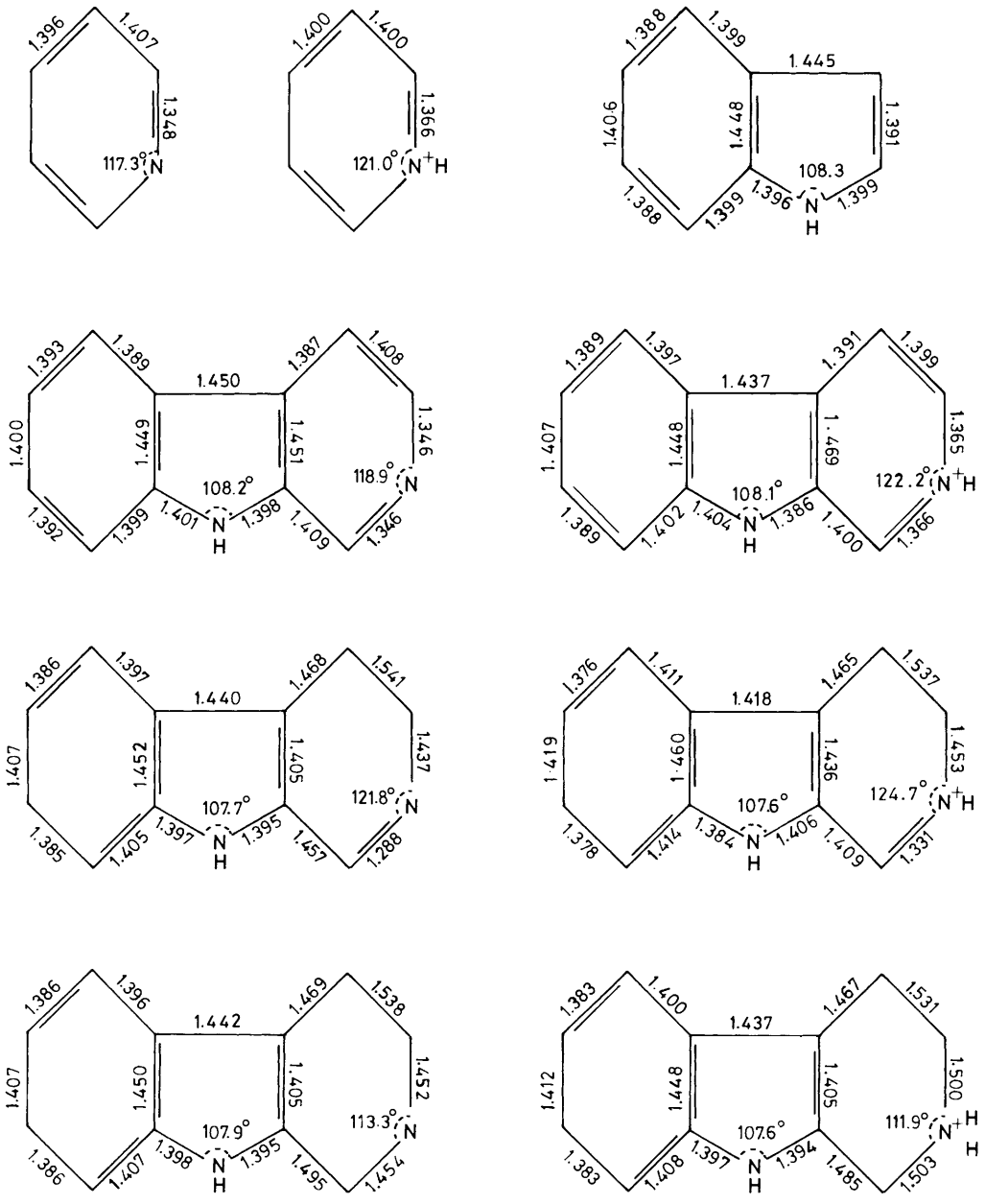


Figure 2. Main geometrical parameters of β-carbolines and model compounds. (Bond lengths in Å and bond angles in degrees).

ferent nitrogen atoms in the β-carboline ring show that N-7 protonation is always favoured over N-1 protonation, independently of the degree of aromaticity and of methyl substitution. This fact agrees with the experimental trends observed in solution[9–11] and suggests that the protonation orientation does not change from gas phase to solution. Unfortunately, the lack of experimental information on gas-phase basicity of β-carbolines precludes the confirmation of the theoretical results.

The fact that β-carbolines protonate on pyridinic rather than on pyrrolic nitrogen reflects that protonation is most favourable at a σ- than at a π-lone-pair which is entirely or partially delocalized over the β-carboline ring.

The protonation enthalpy sequence in gas phase (dehydro > fully aromatic > tetrahydro), seems to reveal the aforementioned resonance stabilization of the cations. Although the absence of comparable experimental data on liquid-phase pyridinic protonation of the different β-carboline rings prevents a qualitative comparison, it is interesting to note that harmaline [11-OCH_3(**7b**) derivative] is more basic than harmine [11 OCH_3(**6b**) derivative] by 1.8 pK_a units.[10–11]

Whereas the experimental results were obtained in solution, the above calculations consider the process in the gas phase. The protonation of molecules is highly influenced by the solvent and as a consequence, the thermodynamic quantities associated with the equilibrium change to a large extent from gas phase to solution. At first sight, one may expect that the electrostatic solute–solvent interactions would be important in this equilibrium involving charged species. The solvation contribution must be dependent on the molecular volume, which is essentially determined by the number of condensed rings in the molecule. Then, within the β-carboline molecules set it may be assumed that this contribution, although important, will almost remain constant. However, in order to compare molecules with a different number of rings, the solvation contribution must be calculated. Table 2 shows the result of the solvation energy

Table 1. AM1 proton affinities for compounds (**1**)–(**8**). The protonation site is indicated in parentheses. If there is a second protonation its site will be indicated by the second atom in parentheses.

Compound	Proton affinity/ kJ mol^{-1}
Monocycle	
(**1**)(N-1)	814.0
(**1**)(C-2)	865.0
(**2**)(N-7)	900.0
(**2**)(C-3)	745.4
Bicycle	
(**3**)(N-1)	857.1
(**3**)(C-3)	902.1
(**4**)(N-1)	828.7
(**4**)(N-7)	933.8
(**4**)(C-5)	876.8
Tricycle	
(**5**)(N-1)	882.4
(**5**)(C-12)	862.8
(**6a**)(N-1)	861.1
(**6a**)(N-7)	931.2
(**6a**)(N-7,N-1)	492.0
(**6a**)(N-7,C-12)	512.2
(**6b**)(N-1)	871.0
(**6b**)(N-7)	943.6
(**6b**)(N-7,N-1)	504.2
(**6b**)(N-7,C-12)	524.1
(**7a**)(N-1)	854.9
(**7a**)(N-7)	938.0
(**8a**)(N-1)	866.0
(**8a**)(N-7)	896.2
(**8a**)(N-7, N-1)	549.9
(**8a**)(N-7,C-3)	543.2

Table 2. Thermodynamic parameters of the protonation process in the continuum model.

Compound	V_m/Å^3	Proton affinity/ kJ mol^{-1}	ΔG_{solv}/ kJ mol^{-1}	$-\Delta G_{prot,solv}$ Theor.[a]	$-\Delta G_{prot,solv}$ expt.[b]
(**2**)	147.3	900.0	208.0	18.1	12.8
(**4**)	203.6	933.8	187.1	31.0	19.7
(**6a**)	287.3	931.2	182.7	24.0	17.8

[a] Theoretical values calculated using $\Delta G_{solv}(H^+) = -1\,089.9$ kJ mol^{-1}. [b] See refs. 9 and 31.

contribution [$\Delta G_{solv} = \Delta G_{solv}(B) - \Delta G_{solv}(BH^+)$] and the basicity in gas phase, proton affinity, and in solution, $\Delta G_{prot,solv}$ for a monocycle (**2**), a bicycle (**4**), and a tricycle (**6**). The monopole and dipole terms and an ellipsoidal cavity shape have been considered. It has been assumed that the entropy term is negligible compared with the computational error inherent in the AM1 method. The molecular volume has been calculated by the method described.[33] The comparison between theoretical and experimental basicities is satisfactory especially considering the inherent error of the calculated proton affinity values. The quantification of electrostatic solute–solvent interactions indicates that severe changes in the relative order of basicity of molecules containing a different number of fused rings are not observed. In fact, the order of proton affinity is retained in solution. This conclusion seems to support the assumption that for the β-carboline set the order obtained in the gas phase is a good basis for the discussion of the protonation process in solution.

Recently, it has been suggested that N-7 protonated β-carboline cations can be protonated further in highly concentrated sulphuric acid solution.[34] The site of this second protonation is a striking problem of theoretical interest. Bearing in mind that protonated β-carbolines could behave as indole (**3**) or carbazole (**5**), which protonate, in highly acidic media, on carbon and nitrogen atom respectively,[30,32] protonation of β-carbolines could then occur either on a carbon or on atom N-1. To study this particular point we have evaluated the corresponding protonation enthalpies for both carbon and nitrogen protonation of β-carbolines.

As can be seen in Table 1, our results predict that for the fully aromatic β-carbolines, this process takes place on C-12 atom. Unfortunately the available experimental studies, carried out in concentrated sulphuric acid solutions, indicate that a sulphonation on atom C-12 prevents the second protonation process.[35,36] However, using a medium without a proton donor available for a substitution process, it would be expected that theoretical suggestions hold up. In the case of tetrahydro-β-carbolines the theoretical results do not allow the unambiguous prediction of the most favourable second protonation site, due to the similarity of the proton affinity values for N-1 and C-3 protonation (see Table 1).

Table 3. Charge and frontier reactivity indices for compounds (**6**)–(**8**).

	Net atomic charge/e	f_r
(**6a**)	N-1 = −0.23	N-1 = 0.50
	C-12 = −0.17	C-6 = 0.25
	C-10 = −0.17	C-12 = 0.25
(**6b**)	N-1 = −0.23	N-1 = 0.48
	C-15 = −0.17[a]	C-6 = 0.27
	C-12 = −0.17	C-8 = 0.25
	C-10 = −0.17	
(**6c**)	N-1 = −0.19	N-1 = 0.54
	C-12 = −0.17	C-6 = 0.23
	C-10 = −0.16	C-12 = 0.23
(**7a**)	N-1 = −0.19	N-1 = 0.49
	C-12 = −0.16	C-6 = 0.36
	C-10 = −0.16	C-12 = 0.22
(**7b**)	N-1 = −0.19	C-3 = 0.49
	C-15 = −0.18[a]	C-2 = 0.36
	N-7 = −0.17	C-13 = 0.22
	C-12 = −0.16	
(**7c**)	N-7 = −0.17	C-3 = 0.50
	C-12 = −0.16	C-2 = 0.30
	C-10 = −0.15	N-1 = 0.24
(**8a**)	N-7 = −0.27	C-3 = 0.54
	N-1 = −0.20	C-12 = 0.49
	C-12 = −0.16	C-2 = 0.36
(**8b**)	N-7 = −0.27	C-3 = 0.55
	C-12 = −0.16	C-2 = 0.30
	N-1 = −0.16	N-1 = 0.27

[a] C-15 Is the atom in group R^2.

Reactivity.—The net atomic charges and frontier electron densities, [$f_r = 2(C_r^{HOMO})^2$], computed for the basic β-carboline rings under study and their corresponding N-7 protonated or methylated cations are presented in Tables 3 and 4. The discussion below is limited to electrophilic substitution reactions since nucleophilic attack on β-carbolines does not seem to be important unless deprotonation of the pyrrolic NH group takes place.[17] The aim of this section is to try to relate the reactivity static indices with the known experimental features of these compounds.

Let us start with the analysis of the protonation site on the neutral molecules. As it has been reported, experimental

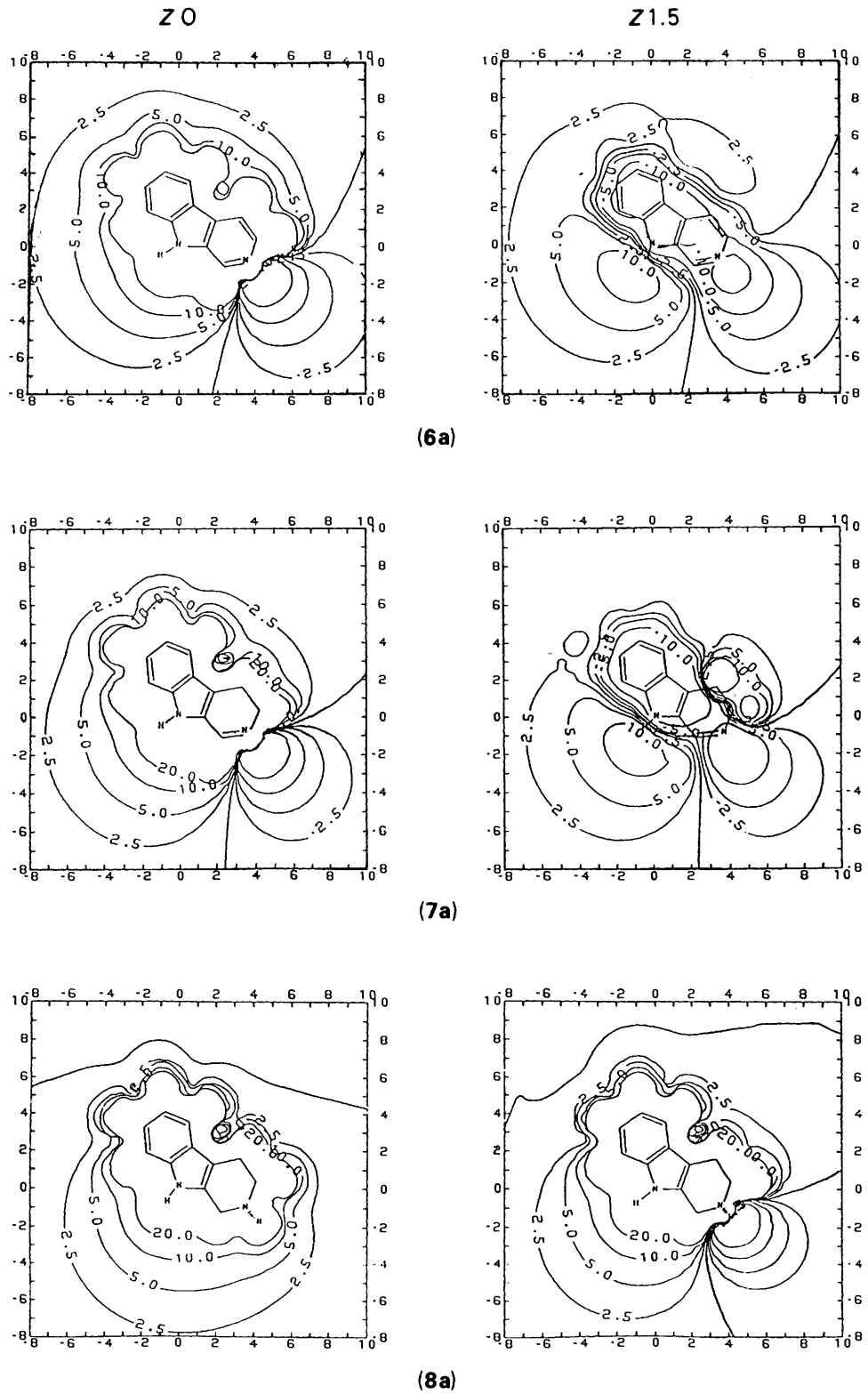


Figure 3. Electrostatic potential maps for (**6a**), (**7a**), and (**8a**) in (*Z* 0 Å) and above (*Z* 1.5 Å) the molecular plane (contours in kcal mol^{-1}).

evidence always indicates N-7 as the preferred protonation site. Although data in Table 3 show that the atom bearing the most negative charge is not N-7 in all the cases, it is well known that electrostatic potential maps (EPM) rather than the net charge on the atom give the preferred protonation site. Figure 3 shows the EPM for (**6a**), (**7a**), and (**8a**) in the molecular plane and at 1.5 Å above this plane. For the fully aromatic β-carboline, (**6a**), the EPM in the molecular plane shows a clearly defined well around the N-7. Although at 1.5 Å the π-system of the ring defines an attractive region over the whole molecule, the minimum on N-7 is still kept. This indicates that protonation on N-7 has a wide approach channel. A similar situation is found for the dehydro-β-carboline, (**7a**), but the minimum on N-7 in the EPM at 1.5 Å is less deep and wide, due to the proximity to

Table 4. Charge and frontier reactivity indices for N-7-protonated and methylated cations of compounds (**6**–**8**).

	Net atomic charge/e	f_r
(**6a**)(N-7)	N-1 = −0.20	C-12 = 0.41
	C-10 = −0.15	N-1 = 0.38
	C-12 = −0.14	C-10 = 0.34
(**6b**)(N-7)	C-15 = −0.20	N-1 = 0.39
	N-1 = −0.20	C-12 = 0.38
	C-10 = −0.15	C-11 = 0.34
	C-12 = −0.14	
(**6a**)(N-7-CH_3)	N-1 = −0.20	C-12 = 0.41
	C-10 = −0.15	N-1 = 0.39
	C-12 = −0.14	C-10 = 0.33
(**6c**)(N-7-CH_3)	N-1 = −0.16	N-1 = 0.45
	C-10 = −0.15	C-12 = 0.35
	C-12 = −0.14	C-10 = 0.32
(**6d**)(N-7-CH_3)	C-15 = −0.21[a]	N-1 = 0.46
	N-1 = −0.15	C-12 = 0.31
	C-10 = −0.15	C-10 = 0.31
	C-12 = −0.14	
(**7a**)(N-7)	N-7 = −0.20	C-10 = 0.44
	C-2 = −0.17	C-13 = 0.38
	C-10 = −0.17	N-1 = 0.37
(**7a**)(N-7-CH_3)	N-1 = −0.17	C-10 = 0.43
	C-2 = −0.17	C-13 = 0.37
	C-10 = −0.17	N-1 = 0.36
(**7b**)(N-7)	C-15 = −0.24	C-10 = 0.43
	N-7 = −0.21	C-13 = 0.37
	N-1 = −0.17	N-1 = 0.37
(**7c**)(N-7-CH_3)	C-10 = −0.17	N-1 = 0.41
	C-2 = −0.17	C-10 = 0.39
	N-7 = −0.15	C-13 = 0.33
(**8a**)(N-7)	N-1 = −0.17	C-10 = 0.43
	C-10 = −0.14	C-13 = 0.41
	C-2 = −0.13	C-3 = 0.35
(**8a**)(N-7-CH_3)	N-1 = −0.17	C-10 = 0.42
	C-10 = −0.14	C-13 = 0.40
	C-12 = −0.13	C-3 = 0.36
(**8b**)(N-7-CH_3)	C-10 = −0.14	C-10 = 0.39
	C-12 = −0.13	C-3 = 0.38
	C-3 = −0.13	C-13 = 0.37

[a] C-15 Is the atom in group R^2.

this plane of the hydrogen atoms bonded to C-8 and C-9. In the case of tetrahydro-β-carboline, (**8a**), it is noteworthy that the well only appears in the EPM at 1.5 Å. Thus, the approach channel in the molecular plane is prevented in this case.

On the other hand, if softer electrophilic reagents are considered, orbital-controlled reactivity will be expected, and the atom with the highest coefficient on the HOMO should be used as the reactivity index. As can be seen in Table 3, this index predicts that the preferred orientation of electrophilic attack is at N-1 for the fully aromatic β-carbolines, (**6**), and C-3 for tetrahydro-β-carbolines, (**8**). Therefore, the latter compounds behave as typical indoles which is in agreement with the experimental pattern of the more characteristic reactions of tetrahydro-β-carboline derivatives. Unsubstituted dehydro-β-carbolines behave as fully aromatic while the methylated ones behave as tetrahydro compounds.

It is also interesting to analyse the potential reactivity of the protonated derivatives since these are the most reactive species in weakly acidic media. Frontier orbital indices in Table 4 suggest that for (**6a**)(N-7) and (**6a**)(N-7-CH_3), the electrophilic substitution reactions occur preferentially on atom C-12. The change in electrophilic attack position upon protonation reflects the polarization induced by the positive charge on the pyridinic ring. This electronic redistribution activates the benzenic fragment for electrophilic attack. Although unfortunately there are not extensive and systematic studies concerning the electrophilic substitution reactions of β-carbolines, some pieces of evidence support these predictions experimentally. Nitration[37–38] of aromatic β-carbolines is known to occur in the benzene ring, mainly at the *para* position, C-12, of the pyrrole nitrogen. The halogenation[39] and sulphonation[35–36] reactions follow the same orientation. In some cases there is also evidence for a smaller yield of the C-10 derivatives. Although this experimental behaviour is also observed for the carbon methylated derivatives, data in Table 4 show that for these compounds N-1 is the atom bearing the highest coefficient on the HOMO. This controversy can be explained by considering that this orientation is probably unfavoured by the steric hindrance of the methyl groups. This reflects the fact that static indices are only a first approach to the reactivity problem and that it is necessary to include other factors to improve the description of the possible pathways.

Unfortunately, the lack of comparable experimental results for protonated dehydro- and tetrahydro-β-carbolines precludes any comparison with the theoretical results. In this sense, further work on reactivity pattern of protonated partially aromatic β-carbolines is in progress.

Acknowledgements

We gratefully acknowledge financial support from the Direccion General de Investigacion Cientifica y Tecnica (PB86-0236) and (PB86-0140) and Dr. A. Criado for his help on searching for the crystallographic data.

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Paper 9/00615J
Received 8*th February* 1989
Accepted 20*th July* 1989