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An Experimental and Theoretical Study on the Prototropic Equilibria of the Four Carboline Isomers

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We have determined the experimental pK_as for the pyridine protonation and pyrrole deprotonation equilibria of the four isomeric (α-, *β*-, *γ*-, and *δ*-) carbolines (pyridoindoles) and for the deprotonation of their *N*-pyrido methylated derivatives. HF 6-31+G* ab initio calculations have been carried out to obtain theoretically the magnitudes of the prototropic equilibria in gas phase and in solution. A cavity model of solvation has been employed. To analyze the influence of annelation and tautomerism, prototropic equilibria of azaindole isomers and *H*-pyrido tautomers of carbolines, respectively, have also been theoretically studied. Equilibria involving tautomeric species are always energetically unfavored against those of the normal forms. Solvation differently affects the relative gas phase values among isomers within the series and between the same isomers of related series. Solvent damps the magnitude of the gap among azaindole or carboline isomers and can even reverse the acidity sequence. The acidity sequence of theoretical free energies for the pyridine nitrogen deprotonation ($\gamma<\beta<\delta<\alpha$) and pyrrole nitrogen deprotonation ($\delta<\beta<\alpha<\gamma$) processes of the carboline normal forms in solution at 298 K are in quite reasonable agreement with those observed experimentally.

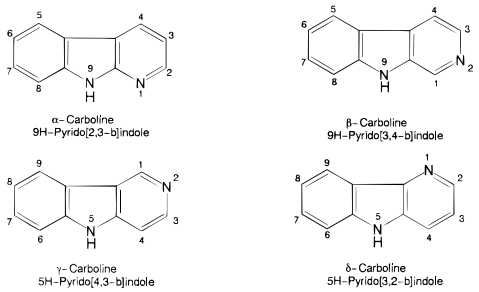
Introduction

In the last decades, the study of the prototropic equilibria of organic molecules has received considerable interest from both theoretical and experimental points of view.[1] This derives mainly from the fact that such studies in principle can provide a detailed insight into the intrinsic acidity or basicity of the molecules involved, and also they can highlight the influence of solvent effects on these equilibria.

Among the great variety of substrates to be investigated, N-heteroaromatic compounds possessing two or more nitrogen atoms are of great interest.[2] These compounds are ubiquitous in nature and constitute the basic elements of most of the macromolecules of biological interest. Usually, these heteroaromatic molecules can be structurally viewed as the condensation products of simpler individual N-heteroaromatic rings. As a general rule, the acidity/basicity of the nitrogen atoms in the condensed molecules greatly differs from that observed in the individual rings.[3] The changes in molecular structures and electronic charge distribution accompanying the annelation process can greatly affect the intrinsic acidity/basicity of these nitrogen centers as well as the solvation of the prototropic species. Furthermore, prototropic tautomerism can also profoundly influence the acid−base equilibria of these heteroaromatic compounds.[4]

Pyridoindoles,[5] trivially named carbolines, are convenient model compounds for the study of the mutual influence, in condensed systems, of N-heteroaromatic rings possessing different *π*-electronic characteristics. Thus, as shown in Scheme 1, carbolines are composed of a *π*-deficient pyridine ring fused to a *π*-sufficient indole ring. Annelation of these rings affects the acid−base properties of pyrrole and pyridine nitrogen atoms, respectively.[6] Carboline rings are, on the other hand, the structural units of numerous naturally occurring alkaloids which possess a wide range of biological and pharmacological properties.[7]

Scheme 1



The aim of this paper is to carry out an experimental and theoretical study of the prototropic equilibria of the four carboline isomers (CARB) shown in Scheme 1. The use of both theoretical and experimental methods will allow us to analyze separately the contribution of intrinsic and solvation effects on the prototropic processes. It is worthwhile to note that previous theoretical studies of a set of compounds derived from the *β*-carboline ring[8] proved to us that computation gives useful information on preferential sites and energetics of the prototropic processes. These studies showed that protonation on the

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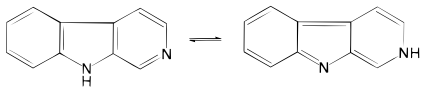
Scheme 2



pyridine nitrogen is always favored over protonation on the pyrrole nitrogen or the ring carbon atoms.[8a,9] Gas phase experiments have recently shown the same behavior for parent molecules.[10] A general conclusion was that a realistic description of the physicochemical properties of these compounds needs the inclusion of solvent effects, since the most interesting part of their chemistry occurs in solution and they discriminate among the different molecules and processes. In addition, the inclusion of correction terms to deal with the thermochemical energies (enthalpy and Gibbs free energy) is an important factor to obtain an acceptable degree of confidence in the estimation of the protonation and deprotonation energies.

The corresponding tautomeric forms of carbolines (CARB(T)), shown in Scheme 2 for the β-carboline isomer, have also been theoretically studied in order to clarify their possible role in the prototropic processes. Contributions of tautomeric forms have already been invoked to explain differences in gas phase and solution basicities of related compounds.[11] Thus, this study will allow the analysis of the influence of the pyridine nitrogen position on the acid−base properties of these molecules and to clarify the possible role of the mentioned tautomeric forms on the prototropic equilibria.

Likewise, two other sets of parent structures have been considered: azaindoles (AZA),[12] fused pyrrole−pyridine systems, and carbolines methylated in the pyridine nitrogen (NMe-CARB). Comparison among azaindoles and carbolines will allow the analysis of the influence of annelation of a benzene ring on the prototropic equilibria. The study of the NMe-CARB derivatives will afford the examination of the influence of the net charge on the reactants and the blocking of the pyridine nitrogen. It has previously been reported that methylation of this nitrogen atom to give the carbolinium ions increases the acidity of the pyrrole nitrogen.[13,14] These deprotonated molecules, usually called anhydrobases, have been thought to be a compromise between quinonoid and charge-separated dipolar structures.[5,13,14]

Computational Methods

HF calculations using the 6-31G* basis sets were carried out to obtain the optimized geometrical structure of the molecules of interest, both in gas phase and in solution. Later on, single point HF calculations with the previous basis sets augmented by diffuse functions, 6-31+G*, were carried out to get the SCF energies. To deal with enthalpy and Gibbs free energy, statistical formulas were added to the SCF energies. For this purpose, 6-31G* vibrational frequencies were calculated. As usual, these corrections (ZPE, zero point energy and ΔH (0 → 298 K), thermal correction) were scaled by an empirical factor of 0.89.[15] To test the influence of diffuse functions on geometrical relaxation, additional optimization geometries of anions with the 6-31+G* basis sets were carried out in gas phase. The changes were quite small, and the major changes in the energetics of the deprotonation processes (the corresponding neutral forms were also optimized with these basis sets) were 0.2 kJ/mol.

Solvent effects were taken into account by means of the continuum model of solvation.[16] In this type of model the solvent is represented by a polarizable continuum characterized by its dielectric permittivity, which in this work was setup to that of water $\epsilon = 78.5$, and the solute is represented by its charge distribution which is expanded as a series of multipole moments. The solute molecule is placed in a cavity prepared within the continuum, and the general expression for the free energy of solute−solvent long-range interactions is:

$$\Delta F^{\mathrm{sol}} = -\frac{1}{2}\sum_{l=0}^{\infty}\sum_{-l}^{l}\langle R_l^m\rangle\langle M_l^m\rangle \qquad (1)$$

where $\langle M_l^m\rangle$ is the m-th component of the multipole moment of order l of the solute charge distribution, and $\langle R_l^m\rangle$ is the corresponding component of the reaction field factor created by the polarized continuum (solvent) within the cavity. This reaction field is defined by

$$R_l^m = \sum_{k=0}^{\infty}\sum_{n=-k}^{k} f_{lk}^{mn}\langle M_k^n\rangle \qquad (2)$$

where f_{lk}^{mn} is an element of a reaction field tensor that depends on the dielectric permittivity of the solvent and on the geometry of the cavity. We have used the quantum chemical cavity model developed by Rivail and colleagues[17] which uses constant-coordinate cavities (spherical or ellipsoidal), which allows analytical expressions for the reaction factors,[18] and then the formulation of the corresponding Fock elements becomes

$$F_{\mu\nu} = F_{\mu\nu}^{\circ} + \sum_{l=0}^{\infty}\sum_{m=-l}^{l}\langle R_l^m\rangle\langle\mu|M_l^m|\nu\rangle = F_{\mu\nu}^{\circ} + F_{\mu\nu}^{\mathrm{sol}} \qquad (3)$$

where $F_{\mu\nu}^{\circ}$ denotes the matrix element for the free molecule, and the second term results from the inclusion in the hamiltonian of the electrostatic solute−solvent interactions. Due to the analytical form of the interaction energy, first derivatives for this perturbation energy have been written and combined with a cavity definition based on the inertia momenta of the solute.[19] In practice, the infinite series was truncated up to the sixth order since this guaranteed a good convergence of the interaction energy. Several applications dealing with solvation importance on physicochemical properties of organic molecules have recently appeared using this methodology.[20]

Computations were carried out with the GAUSSIAN-92 program.[21] The solvation model was implemented in this program as a set of independent links.[22] Energies and fully

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optimized geometries of all the molecules studied in this paper have been deposited as a Supporting Information.

Experimental Methods

α- and γ-carbolines were synthesized following the methods found in the bibliography.[23] β-carboline was purchased from Aldrich Química and δ-carboline was a gift from Dr. P. Rocca. NMe-CARB derivatives were prepared as the methosulfate salts by refluxing the parent carbolines with dimethyl sulfate in benzene.[24] Stock solutions of all the compounds (10^{-3} mol dm^{-3}) were prepared in methanol−water, and the final solutions had a methanol proportion less than 5%. Buffer solutions for UV-vis spectrophotometry (I = 0.01 mol dm^{-3}) were prepared as described in the bibliography,[25] and the pHs of the solutions were measured on a pH-meter Radiometer Copenhagen Model PHM82. All reagents used for buffer preparation were high purity chemical employed as received. Stock potassium hydroxide solution was prepared as described elsewhere.[26]

Ionization data, I(I = [acid]/[base]), necessary for determining the pK_a values, were obtained spectrophotometrically. Absorbance measurements were carried out on a Perkin-Elmer Lambda 5 UV-vis spectrophotometer with a thermostated cell holder maintained at 25 ± 0.1 °C. Ionization constants for the pyridine nitrogen protonation and for the deprotonation of the NMe-CARB derivatives, which take place in the pH region, were calculated using the Henderson−Hasselbach equation:

$$pK_a = pH + \log I \quad (4)$$

Ionization data for the pyrrole nitrogen deprotonation, outside the pH range, were analyzed by the excess acidity method (EA).[27] This method does not involve the use of any acidity function, although it does make use of the indicator overlap principle to determine the quantity $X = \log[f_{A^-}/(f_{HA}f_{OH^-})]$ for a reference compound. In this method, pK_a may be obtained from eq 5, where water activity, a_w, and the so-called

$$pK_w + \log[OH^-] - \log a_w + \log I = m \log X + pK_a \quad (5)$$

excess acidity function, X, were taken from the literature or calculated as elsewhere.[27] The plots of the first member of equation 5 *vs* log X give pK_a values as the intersect. This method has previously been shown to give reliable pK_a values for the deprotonation of indoles[28] and β-carboline derivatives.[6] Experimental pK_as for protonation and deprotonation equilibria of carboline derivatives have been recorded in Table 1. This table also collects literature data for the deprotonation of some NMe-CARB derivatives as well as data for the protonation of the four isomeric azaindoles.[29] Unfortunately, data for the deprotonation of azaindoles have not been reported.

Table 1. Experimental pK_a Values in Solution for the Pyridine and Pyrrole Nitrogen Deprotonation Processes, Eqs 6 and 10, Respectively, at 298 K

compound	pyridine nitrogen deprotonation	pyrrole nitrogen deprotonation
α-AZA	4.59[a]	
β-AZA	7.95[a]	
γ-AZA	8.26[a]	
δ-AZA	6.94[a]	
α-CARB	4.15 ± 0.11	14.70 ± 0.3
β-CARB	6.85 ± 0.03	14.53 ± 0.03
γ-CARB	7.53 ± 0.04	14.00 ± 0.02
δ-CARB	5.26 ± 0.07	15.10 ± 0.2
NMe-α-CARB		7.98 ± 0.03 (7.55)[b] (7.75)[c]
NMe-β-CARB		11.02 ± 0.27 (10.88)[b] (11.11)[c]
NMe-γ-CARB		10.79 ± 0.17 (10.54)[c]
NMe-δ-CARB		10.80 ± 0.20 (10.80)[b]

[a] Values taken from ref 29. [b] Values taken from ref 14. [c] Values taken from ref 13.

Table 2. Energies (kJ/mol) Relative to the β-Derivative of AZA and CARB Isomers

	α	β	γ	δ
AZA	−24.4	0.0	−7.1	−1.8
CARB	−30.2	0.0	-12.1	−6.0

Results

Table 2 collects the theoretical energies in solution of the neutral molecules of azaindole and carboline series relative to the β-isomer. Curiously, in spite of the predominance of the β-carboline derivative in nature, this isomer is the least stable within the series. Evidently, this fact should be related with the greatest natural abundance of β-carboline precursors such as tryptophan, tryptamine, serotonin, etc.[5] We have also calculated the energy differences between tautomeric and neutral forms of each carboline derivative. Tautomers are less stable than the corresponding carbolines, the differences being around 40 and 80 kJ/mol for the pairs α/γ and β/δ, respectively.

Before discussing the energetics of the prototropic processes, we will make a brief comment on the geometrical changes observed after the protonation or the deprotonation processes of carboline derivatives. The analysis of these geometrical changes shows slight modifications in distances and bond angles. These modifications are similar for protonation or deprotonation processes. Figure 1 shows for the NMe-CARB derivatives the changes in distances associated to the deprotonation process. These systems show the greatest changes. They can be clearly differentiated into two groups. Thus, after deprotonation of NMe-α-CARB or NMe-γ-CARB, the distances in the two rings of the azaindole fragment change while the benzene ring retains its geometry. However, for NMe-β-CARB and NMe-δ-CARB the changes are distributed along the whole tryciclic ring system. These results qualitatively agree with the proposal of Gray et al.[13] on the greater participation of quinonoid canonical forms on the electronic structures of the deprotonated NMe-β-CARB and NMe-δ-CARB derivatives. Aihara et al.[30] have also carefully examined this point using quantum chemical methods for the β-carboline anhydrobase derivatives.

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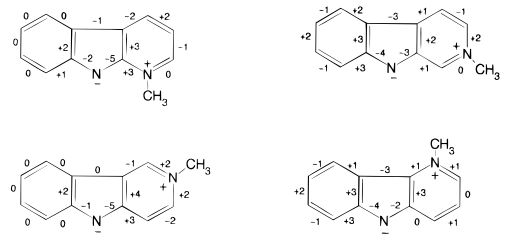

Figure 1. Changes of the distances (in 10^{-2} Å units) due to the deprotonation process of the NMe-CARB. (A negative value indicates that in the deprotonated form the distance is shorter than in the normal form).

Table 3. Thermodynamic Parameters for Processes of Eq 6 in Gas Phase and Solution (ϵ = 78.5) and Differences between the Solvation Free Energy of the Neutral and Protonated Molecules ΔF^{sol} (Energy values in kJ/mol)

compound	PA	GB	ΔG^{sol}	ΔF^{sol}
α-AZA	951.9 (931)[a]	919.9	10.0	180.0
β-AZA	989.4	956.9	37.6	170.6
γ-AZA	994.9	962.3	41.3	168.9
δ-AZA	987.4	954.6	31.4	166.6
α-CARB	956.6	924.5	7.2	172.6
β-CARB	985.3	952.4	24.8	162.3
γ-CARB	996.8	964.0	37.6	163.4
δ-CARB	976.6	943.2	12.8	159.4
α-CARB(T)	1018.0	985.9	56.2	160.2
β-CARB(T)	1078.7	1045.8	95.2	139.2
γ-CARB(T)	1059.0	1026.2	78.6	142.3
δ-CARB(T)	1080.3	1046.9	95.5	138.4

[a] Experimental value in gas phase, taken from reference 41.

Protonation Processes. The energetics of the pyridine nitrogen protonation processes formulated by equation:

$$BH^+ \leftrightarrows B + H^+ \quad (6)$$

have been calculated in gas phase, gp, and in solution, sol, by the following formulas:

$$\Delta H^{gp}(298\ K) = \Delta E_{SCF} + \Delta ZPE + \Delta H(0 \rightarrow 298\ K) + 6.19 \quad (7)$$

$$\Delta G^{gp}(298\ K) = \Delta H^{gp}(298\ K) - 298.15\Delta S - 32.5 \quad (8)$$

$$\Delta G^{sol}(298\ K) = \Delta G^{gp}(298\ K) + \Delta F^{sol} - 1089.9 \quad (9)$$

where the Δ symbol denotes the difference between the values for the corresponding magnitude of B and BH^+ for the process in eq 6. The constant term for each equation comes from the thermodynamic correction term and the proton contribution. Constant values correspond to the case in which variables are expressed in kJ/mol.

Table 3 collects the main thermodynamical data, i.e. proton affinity, PA = ΔH^{gp}(298 K); gas phase basicity, GB = ΔG^{gp}(298 K), and free energy in solution, ΔG^{sol}(298 K); likewise to show the different solvent effect, the gap between the solvation free energies of neutral and protonated forms, ΔF^{sol}, has also been included. At this point, it is worth mentioning that within the continuum model this energy is a Helmholtz free energy and not a Gibbs free energy, but for a charge process in condensed phase it is well known that these two values for a given solute should not differ too much. In addition, since we are interested in dealing with relative differences among quite similar chemical structures, our approach assumes that the difference $\Delta G^{sol} - \Delta F^{sol}$ remains constant within each series.[20]

Table 4. Thermodynamic Parameters for Processes of Eq 10 in Gas Phase and Solution (ϵ = 78.5) and Differences between the Solvation Free Energy of the Basic and Acid Forms, ΔF^{sol} (energy values in kJ/mol)

compound	APA	$\Delta G^{gp}{}_{acid}$	$\Delta G^{sol}{}_{acid}$	ΔF^{sol}
α-AZA	1488.7	1457.4	138.1	−229.5
β-AZA	1457.4	1426.4	131.8	−204.7
γ-AZA	1461.5	1430.4	135.9	−204.6
δ-AZA	1467.6	1436.9	136.8	−210.2
α-CARB	1473.7	1442.7	139.2	−213.6
β-CARB	1450.0	1420.1	142.9	−187.3
γ-CARB	1445.1	1414.4	137.2	−187.3
δ-CARB	1458.5	1429.1	147.7	−191.5
α-CARB(T)	1412.4	1381.4	90.7	−200.8
β-CARB(T)	1356.9	1327.0	73.5	−163.6
γ-CARB(T)	1383.1	1352.4	93.4	−169.1
δ-CARB(T)	1354.9	1325.6	66.1	−169.6
NMe-α-CARB	1027.9	995.8	60.7	154.8
NMe-β-CARB	1090.1	1057.2	99.8	132.5
NMe-γ-CARB	1071.6	1038.9	86.5	137.5
NMe-δ-CARB	1087.8	1054.5	96.9	132.4

Let us start analyzing the gas phase results for these processes. The proton affinity sequence is the same for the set of azaindoles and carbolines, i.e. the acidity increases within the series: $\gamma > \beta > \delta \gg \alpha$. The addition of the entropic term to obtain the gas phase basicity, GB, implies an almost linear displacement around 30 kJ/mol for all compounds. Therefore, the consideration of the relative protonation energies in terms of enthalpy or Gibbs free energy is similar. As expected from eq 9, when the processes are considered in solution the values for Gibbs free energies, ΔG^{sol}, are highly reduced with respect to those in gas phase. Solvent effect does not alter the acidity sequence but rather it reduces the gap among the different isomers, since the most acid form, i.e. α, is that having the largest solvent contribution, ΔF^{sol}.

At this point, there is an interesting fact to be realized when the two sets of isomers, azaindoles and carbolines, are compared. Thus, PA and GB values predict that α- and γ-azaindoles should be more acidic than the corresponding carbolines while the opposite is true for the β- and δ-derivatives. However, inclusion of solvent effects eliminates these differences. Thus, according to ΔG^{sol} values all carboline isomers should be more acidic than their corresponding azaindoles, that is, solvation decreases the acidity of azaindoles.

Tautomers of carboline molecules are much less acid than their corresponding normal forms in the range 60−100 and 40−80 kJ/mol in gas phase and in solution, respectively. The acidity sequence is $\delta \approx \beta > \gamma \gg \alpha$.

Experimental pK_a values in solution, shown in Table 1, indicate that carboline isomers are always more acidic than the corresponding azaindoles and also that the sequence of increasing acidity, $\gamma > \beta > \delta > \alpha$, is the same within each series.

Deprotonation Processes. The energetics of the pyrrole deprotonation processes formulated by eq 10

$$AH \leftrightarrows A^- + H^+ \quad (10)$$

has been calculated using eqs 7−9 were the Δ symbol denotes the difference between the values for the corresponding magnitudes of A^- and AH. Table 4 collects the main thermodynamical values, i.e. anion proton affinity

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enthalpy, APA = ΔH^{gp}(298 K), gas phase acidity, ΔG^{gp}_{acid} (298 K), and free energy in solution, ΔG^{sol}_{acid}(298 K); likewise to show the role of solvent effects, the gap between the solvation free energies of anionic and neutral forms, ΔF^{sol}, has also been included. It should be noticed that for the NMe-CARB derivatives the species which is deprotonated is a cation and, therefore, the solvation gap defined as ΔF^{sol} is a positive value instead of the negative values obtained for the rest of the systems. In contrast to the protonation processes, deprotonations are not thermodynamically favored. For azaindoles the acidity increases in the series: $\alpha < \delta < \gamma < \beta$ and this sequence is the same when solvent effects are considered. However, this acidity sequence is not kept for the carboline isomers. Furthermore, it changes if the processes are considered in gas phase, ΔG^{gp}_{acid}, or in solution, ΔG^{sol}_{acid}. Thus, anion proton affinities and gas phase acidities predict an increase of acidity in the sequence $\alpha < \delta < \beta < \gamma$, while the sequence $\delta < \beta < \alpha < \gamma$ is obtained when the solvent effects are included.

Interestingly, although the consideration of solvent effects reduces the gap among isomers of a given molecular system, i.e. azaindoles or carbolines, this effect is specially pronounced for the α-derivatives. Deprotonation of the α-isomers is the most unfavored process in gas phase, but the most stabilizing solvent contribution is associated with these derivatives. In fact, the position of α-CARB in the acidity sequence changes depending on the consideration of ΔG^{gp}_{acid} or ΔG^{sol}_{acid} values.

On the other hand, if azaindole and carboline isomers are compared, data in gas phase predict that all the carbolines are more acidic than their azaindole counterparts. However, consideration of solvent effects reverses this prediction. In this case, solvation increases the acidity of azaindoles, the solvent effect being more pronounced than in the protonation processes.

Tautomers of carbolines are more acidic than their analogous compounds by about 60−100 kJ/mol. The acidity sequence in solution is quite different from that of the normal carbolines, $\gamma < \alpha < \beta < \delta$. As it may be expected for the deprotonation process of a cation, the NMe-CARB derivatives show APA much smaller (ca. 400−500 kJ/mol) than the rest of the series. For these derivatives, the acidity increases in the series: $\beta \leq \delta < \gamma < \alpha$. Consideration of Gibbs free energy instead of enthalpy of processes does not change the order, given that an almost constant displacement of the values of about −30 kJ/mol is obtained. In solution, the acidity sequence is maintained, but the inclusion of solvent effects reduces the gap among different isomers again. However, different from the behavior of azaindole and carboline series, within the NMe-CARB derivatives, NMe-α-CARB is the most acidic isomer and the least favored in the deprotonation process in solution.

Experimental pK_a values recorded in Table 1 show that the acidity of carbolines increases in the sequence $\delta < \alpha \approx \beta < \gamma$ and the sequence for the NMe-CARB derivatives is $\beta \approx \delta \approx \gamma < \alpha$.

Discussion

The literature is full of interesting, sound studies where the acid−base properties of organic molecules are obtained from theoretical models. Their predicted results are either compared to experimental gas-phase data or extrapolated to the expected behavior in solution.[9,31,32] In view of the influence that solvent has on a large number of physicochemical properties, it is of interest to include models of solvation to the quantum chemical schemes in order to try a more quantitative description of these properties. Thus, the acid−base equilibria involve magnitudes associated to the charge process which strongly depends on the nature of the solvent. However, a direct comparison of the experimental pK_a values and the ΔG^{sol}(298 K) is not possible in all cases, since the solvation model usually refers to infinite dilute solution for the different species in the prototropic equilibria. The model takes into account only the solute−solvent interactions, but not the interactions of solute with other species present in the medium. Thus, experimental determination of deprotonation process of carbolines is performed in drastic basic media, so that a nonconventional pH scale is employed. As shown below, this does not affect the relative values within a set of isomers given that the use of such a scale causes only a linear displacement in the energy difference due to the change of the thermodynamic reference state.

Table 5. Experimental and Calculated pK_a Differences (ΔpK_a) for the Pyridine and Pyrrole Nitrogen Deprotonation Processes, Eqs 6 and 10, Respectively

	pyridine nitrogen deprotonation		pyrrole nitrogen deprotonation	
compound	exptl	calcd	exptl	calcd
α-AZA	0.0	0.0		1.1
β-AZA	3.4	4.8		0.0
γ-AZA	3.7	5.5		0.7
δ-AZA	2.4	3.8		0.9
α-CARB	0.0	0.0	0.7	0.4
β-CARB	2.7	3.1	0.5	1.0
γ-CARB	3.4	5.3	0.0	0.0
δ-CARB	1.1	1.0	1.1	1.8
α-CARB(T)		0.0		4.3
β-CARB(T)		6.8		1.3
γ-CARB(T)		3.9		4.8
δ-CARB(T)		6.9		0.0
NMe-α-CARB			0.0	0.0
NMe-β-CARB			3.0	6.9
NMe-γ-CARB			2.8	4.5
NMe-δ-CARB			2.8	6.4

Table 5 gives the experimental and calculated relative pK_a values among isomers for each type of compound. The theoretical values have been calculated from equation:

$$\Delta pK_a = \frac{(\Delta G^{sol})_i - (\Delta G^{sol})_j}{2.303RT} \qquad (11)$$

where isomer "j" is the less basic one for protonation or deprotonation processes, respectively. There is a reasonable agreement at the qualitative and even quantitative level (standard deviations of ΔpK_a are 1.5 and 2.5, for protonation and deprotonation processes, respectively). Bearing in mind error bars for the experimental values and the intrinsic small differences, it may be concluded that the theoretical approach employed is able to highlight the differential prototropic properties of isomers within a family of compounds.

In the chemistry of azaindoles and carbolines, as well as other molecular systems, where pyrrole and pyridine nitrogens are both present, tautomerism has been usually

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invoked to explain properties not well-understood on the basis of normal structure.[33−36] Catalán et al.[11] in a pioneer ab initio study of gas-phase basicity of azaindoles suggest that the influence of tautomeric forms is partially responsible for the protonation process in solution. This might explain the partial disagreement between the calculated gas-phase PAs and the pK_a values observed in solution. The results presented here do not support this interpretation either for azaindoles or for carbolines. For the latter, the tautomeric forms have been calculated in gas phase and in solution. Table 5 indicates a poor correlation between the experimental ΔpK_a and the values predicted from tautomeric equilibria, whereas the correlation from equilibria of normal forms is quite satisfactory.

Moreover, for the set of azaindoles, comparison of PA values predicted by Catalán et al.[11] and those of Table 3 shows that the sequence is the same, but the absolute values, as well as the energy gap among isomers, differ for about 50 kJ/mol. It seems that the small differences found by Catalán et al.[11] among the gas-phase PAs of azaindoles must be attributed to the indirect calculation method used by these authors. They predict azaindole PAs by interpolating the 1s orbital energy of the pyridine nitrogen using a correlation between PAs and core-binding energies previously established for 3- and 4-substituted pyridine derivatives.[37,38]

Similar relationships between PAs and core-binding energies proved to be useful for a variety of protonation sites including oxygen, nitrogen, carbon, phosphorus, and sulfur atoms. These relationships based on the formal analogy between the core-level ionization reaction and the protonation process[39,40] are valid provided the relaxation energy involved in the removal of a core-electron is practically the same for all the compounds in the series. Thus, calculation of azaindole PAs using the correlation for pyridines actually assumes that this condition holds up for these compounds. However, in azaindoles, as well as in carbolines, the influence of pyrrole and indole annelation to the pyridine ring, respectively, should be important. In fact, Catalán et al.[41] state further that this correlation may be not adequate for systems whose basic center is located in an azole ring, given that such a simple and general linear relationship hardly accounts for details of local bonding at the nitrogen site.

The attractive idea of a correlation between PA and 1s orbital energy of the nitrogen atom involved in the prototropic processes of azaindoles and carbolines has been revisited by us and results are shown in Figure 2. It can be seen that for the protonation process, α-isomers are excluded from the correlation, whereas for the deprotonation process, two parallel series result (error bars of these linear correlations are ±3 kJ/mol). The lack of generality observed for these groups of isomers confirms, as expected, that annelation effects introduce more involved factors that are not reflected on the core-orbital energies.

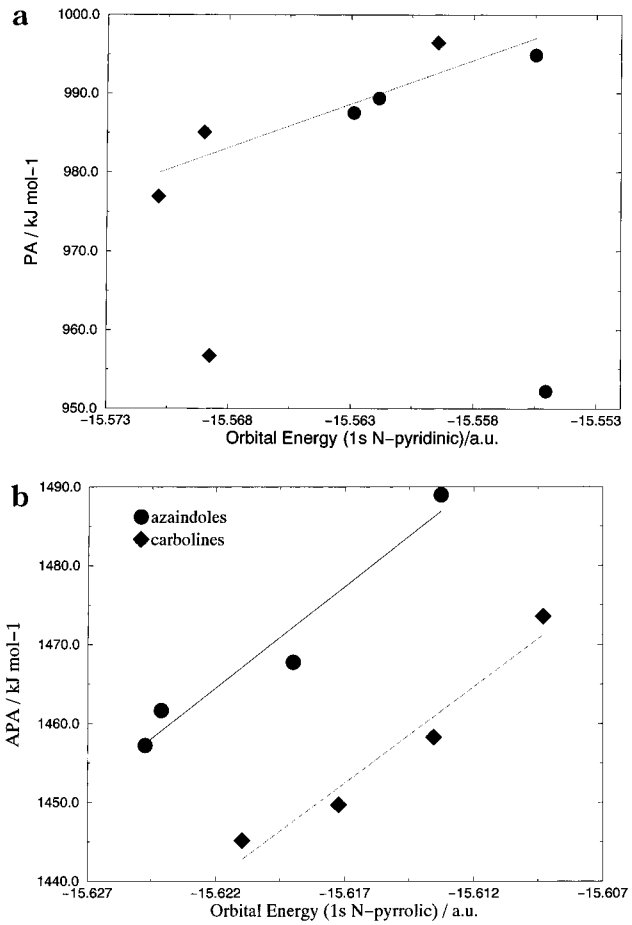

Figure 2. (a) Correlation of calculated PA and the N_{1s} (pyridine) orbital energy for azaindole and carboline isomers. The points outside linear correlation correspond to the α isomers. (b) Correlation of calculated APA and the N_{1s} (pyrrolic) orbital energy for azaindole and carboline isomers.

Also, our results demonstrate that there is not direct correlation between gas phase and solution acidity. Solvation differently affects the relative GB and ΔG^{gp}_{acid} values among isomers within the series and between the same isomers of related series. Solvent damps the magnitude of the gap among azaindole isomers or carboline isomers and can even reverse the acidity sequence when the two series, azaindoles and carbolines, are compared. Thus, the results obtained in the present work point to the paramount importance of solvent effect in the realistic description of the energetics of the prototropic equilibria.

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Supporting Information Available: Total molecular energies, zero point vibrational energies, thermal corrections and entropies of the considered molecules, as well as their corresponding optimized geometrical structures in cartesians coordinates (58 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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