

Dramatic Medium Effects on Reactivity. The Ionization Sites of Pyrrole and Indole Carboxylic Acids

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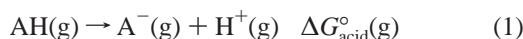
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Received July 9, 1998

Abstract: The intrinsic (gas phase) acidities of pyrrole- and indole-2- and 3-carboxylic acids as well as those of methyl indole-3-carboxylate and 1-methyl indole-3-carboxylic acid have been measured by means of Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry. Ab initio molecular orbital and DFT calculations were performed at several levels of theory on all the relevant species. This study was extended to the same species in aqueous solution by means of the continuum model implemented in the SCRFPAC program. The calculated acidities, both in the gas phase and in solution, are in very good agreement with the experimental data and conclusively show that (i) pyrrole- and indole-3-carboxylic acids behave as NH acids in the gas phase, (ii) in the gas phase, pyrrole- and indole-2-carboxylic acids are deprotonated at the COOH group, although competing ionizations possibly take place, and (iii) these four compounds behave in aqueous solution as OH acids.

Introduction

The gas-phase acidity of an acid, AH, is given by the standard Gibbs energy change, $\Delta G_{\text{acid}}^{\circ}(\text{g})$, pertaining to reaction 1:



Several experimental techniques are available nowadays¹ that allow the quantitative study of the thermodynamics of reaction 1. An important consequence is the possibility of quantitatively assessing the influence of the solvent on the relative strengths of the potential acidic sites of a molecule. It is known, for example, that in aqueous or methanolic solution, hydroxamic acids essentially act as OH acids,^{2a} while in DMSO^{2a} and in the gas phase^{2b} they act as NH acids. In the case of 4-[(2,4,6-trinitrophenyl)amino]benzoic acid, the preferred ionization sites in DMSO and in a 60:40 DMSO–water mixture are the amino and the carboxylic groups, respectively.^{2c} These are clear examples of medium dependence of the relative strength of the acidic sites of a molecule. Here we report an extremely large effect of this sort involving two paradigmatic acidic function-

alities, namely, the OH group of carboxylic acids and the NH group of simple azoles.³

In aqueous solution, the pK_{a} 's of benzoic acid, pyrrole, and indole are respectively 4.20,⁴ 17.51,⁵ and 16.97.⁵ It follows that the ionization of an isolated COOH group is favored over that of an isolated NH group by about 12 pK_{a} units ($\sim 16 \text{ kcal mol}^{-1}$ at 298 K). Unless exceptionally strong interactions are assumed, the most acidic site of pyrrole- and indolecarboxylic acids in water is thus expected to be the carboxylic functionality.

Indole- and pyrrolecarboxylic acids are of biological and pharmaceutical significance,^{6–10} and this triggered our interest in these compounds. Pyrrole-2-carboxylic acid presents anti-inflammatory activity⁸ and hypocalcemic action.⁷ Indole-2-carboxylic acid is an antagonist of potentiation by glycine at the NMDA (*N*-methyl-D-aspartate) receptor.⁹ Indole-2-carboxylic acids are hypoglycemic compounds⁶ and potent type-2 specific inhibitors of human steroid 5 α -reductase.¹⁰

The acidity of these compounds was studied in aqueous solution by Cativiela et al.,¹¹ but hitherto no study seems to have

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(1) Bartmess, J. E. In *Advances in Gas-Phase Ion Chemistry*; Adams, N. G., Babcock, L. M., Eds.; JAI Press: Greenwich, 1996; Vol. 2, pp 193–217.

(2) (a) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330–3336. (b) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Org. Chem.* **1990**, *55*, 3980–3981. (c) Bagno, A.; Dorigo, F.; McCrae, P.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2163–2168.

(3) Catalán, J.; Abboud, J.-L. M.; Elguero, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. L., Ed.; Academic Press: New York, 1987; Vol. 41, pp 187–274.

(4) *Handbook of Chemistry and Physics*, 1995–1996, 76th ed.; CRC Press: Boca Raton, 1995.

(5) Yagil, G. *Tetrahedron* **1967**, *23*, 2855–2861.

(6) Bauman, N.; Gordon, S.; Pease, B. S. *Biochem. Pharmacol.* **1969**, *18*, 1241–1243.

(7) Fang, V. S. *Arch. Int. Pharmacodyn.* **1973**, *202*, 183–193.

(8) Davis, J. S.; Waters, J. A.; Parmar, S. S. *Pharmacology* **1981**, *23*, 287–292.

(9) Huettner, J. E. *Science* **1989**, *243*, 1611–1613.

(10) Holt, D. A.; Yamashita, D. S.; Konialian-Beck, D. L.; Luengo, J. I.; Abell, A. D.; Bergsma, D. J.; Brandt, M.; Levy, M. A. *J. Med. Chem.* **1995**, *38*, 13–15.

(11) Cativiela, C.; Dejardin, J.-L.; Elguero, J.; García, J. I.; González, E.; Mayoral, J. A. *Collect. Czech. Chem. Commun.* **1990**, *55*, 72–79.

Table 1. pK_a Values Measured in Water for **1–4** and a Series of Reference Compounds

compd	pK_a	ref
1	4.36	11
2	5.01	11
3	3.82	11
4	5.29	11
benzoic acid	4.20	4
pyrrole	17.51	5
indole	16.97	5
indole-2-carboxylate anion	17.13	5
indole-3-carboxylate anion	15.59	5

been carried out on the intrinsic (gas phase) acidity of heterocyclic carboxylic acids. We have studied in this work the intrinsic acidities of indole- and pyrrole-2- and 3-carboxylic acids (see Scheme 1).

As indicated above, comparison of the pK_a values of **1–4** in aqueous solution (see Table 1) with those for a series of reference compounds suggests that **1–4** behave as carboxylic acids (loss of the proton from the COOH group). But, is the behavior similar in the gas phase? This question is important, as it is not always certain that the environment of biological receptors behaves as bulk water and the gas phase provides the ultimate example of a solvent-free environment.

Experimental Section

Indole-3-carboxylic acid was synthesized according to Doyle et al.¹² Pyrrole-3-carboxylic acid was synthesized according to Cativiela and García.¹³ 1-Methylindole-3-carboxylic acid was synthesized from methyl indole-3-carboxylate according to a standard procedure by Kikugawa and Miyake.¹⁴ All other products used in this work were commercial from Aldrich. Their purity was assessed by standard methods.

The gas-phase acidities were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer.^{15–18}

Working conditions were similar to those already described.¹⁹ The average cell temperature is ca. 333 K. FT-ICR measurements provide the standard Gibbs energy change, $\delta\Delta G_{\text{acid}}^{\circ}(\text{g})$, for the proton-exchange reaction 2:



where AH_{ref} is a reference acid.

For this equilibrium:

$$\delta\Delta G_{\text{acid}}^{\circ}(\text{g}) = -RT \ln K_p \quad (3)$$

In every case, the reversibility of reaction 2 was confirmed by means of double resonance-like experiments.

AH and AH_{ref} were initially deprotonated by iso- $\text{C}_5\text{H}_{11}\text{O}^{-}$, generated *in situ* by electron ionization of isoamyl nitrite (ionization energy of ca. 3.5 eV).

(12) Doyle, F. P.; Ferrier, W.; Holland, D. O.; Mehta, N. D.; Naylor, J. H. C. *J. Chem. Soc.* **1956**, 2853–2857.

(13) Cativiela, C.; García, J. I. *Org. Prep. Proced. Int.* **1986**, 18, 283–285.

(14) Kikugawa, Y.; Miyake, Y. *Synthesis* **1981**, 461–462.

(15) FT-ICR/MS: *Analytical Applications of Fourier Transform Ion Cyclotron Resonance Mass Spectrometry*; Asamoto, B., Ed.; VCH: Weinheim, 1991.

(16) Marshall, A. G.; Verdun, F. R. *Fourier Transforms in NMR, Optical and Mass Spectrometry*; Elsevier: Amsterdam, 1990.

(17) *Fourier Transform Mass Spectrometry. Evolution, Innovation and Applications*; Buchanan, M. V., Ed.; ACS Symp. Ser. 359; American Chemical Society: Washington, DC, 1987.

(18) *Gas-Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vols. 1 and 2; 1984; Vol. 3.

(19) Abboud, J.-L. M.; Herreros, M.; Notario, R.; Esseffar, M.; M6, O.; Yáñez, M. *J. Am. Chem. Soc.* **1996**, 118, 1126–1130.

The pressure readings for the various neutral reagents, as determined by the Bayard-Alpert gauge of the FT-ICR spectrometer, were corrected by means of the gauge sensitivity for each reactant. The gauge sensitivities relative to N_2 (S_i) have been estimated according to Bartmess and Georgiadis²⁰ using the average molecular polarizabilities, $\alpha(\text{ahc})$, calculated according to Miller.²¹

Computational Details

Standard ab initio molecular orbital and density functional calculations were performed with the Gaussian 94 series of programs.²²

For all the species included in this study, full geometry optimizations were carried out at the HF/6-31G(d) level. The corresponding harmonic vibrational frequencies were evaluated at the same level of theory to confirm that the optimized structures found correspond to minima of the potential energy surface and to evaluate the corresponding zero-point vibrational energies, ZPE, thermal corrections at 298 K, and entropy values. ZPE values were scaled by the empirical factor 0.9135, recently suggested by Scott and Radom.²³ All the minima found at the HF/6-31G(d) level were again fully reoptimized at the HF/6-31+G(d) level (in some cases, reoptimization was also carried out at the MP2/6-31+G(d) level).

In recent years there has been an intensive development of density functional theory (DFT) and its applications to various chemical problems.²⁴ Among the various proposed functionals, the combination of Becke's three-parameter hybrid exchange functional²⁵ with the Lee, Yang, and Parr (LYP) correlation functional²⁶ (denoted B3LYP²⁷) has been widely used and Smith and Radom²⁸ have calculated acidities using different functionals and shown that the B3LYP method best reproduces the experimental data.

This has prompted us to also use DFT in this work. Full geometry optimizations were carried out at the B3LYP/6-31G(d) level, and the corresponding harmonic vibrational frequencies were evaluated at the same level of theory, scaling ZPE values by the empirical factor of 0.9806.²³ All the minima found at the B3LYP/6-31G(d) level were again fully reoptimized at the B3LYP/6-31+G(d) level.

Calculations on chemical species in solution have been carried out by considering the continuum model^{29–31} that has been successfully used in several studies on tautomerism²⁹ and acid/base equilibria.^{32–38}

(20) Bartmess, J. E.; Georgiadis, R. M. *Vacuum* **1983**, 33, 149–153.

(21) Miller, K. J. *J. Am. Chem. Soc.* **1990**, 112, 8533–8542.

(22) Gaussian 94, Revision E.2; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; González, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1995.

(23) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, 100, 16502–16513.

(24) *Density Functionals in Chemistry*; Labanowski, J. K., Andzelm, J. W., Eds.; Springer-Verlag: New York, 1991.

(25) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648–5652.

(26) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev., B* **1988**, 37, 785–789.

(27) Stevens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, 98, 11623–11627.

(28) Smith, B. J.; Radom, L. *Chem. Phys. Lett.* **1995**, 245, 123–128.

(29) Cramer, D. J.; Truhlar, D. G. In *Solvent Effects and Chemical Reactivity*; Tapia, O., Bertrán, J., Eds.; Kluwer Academic Press: The Netherlands, 1996; pp 1–80.

(30) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, 94, 2027–2094.

(31) Rivail, J.-L.; Rinaldi, D. In *Computational Chemistry: Reviews of Current Trends*; Leszczynski, J., Ed.; World Scientific: Singapore, 1996; pp 139–174.

(32) Tuñón, I.; Silla, E.; Tomasi, J. *J. Phys. Chem.* **1992**, 96, 9043–9048.

(33) Tuñón, I.; Silla, E.; Pascual-Ahuir, J.-L. *J. Am. Chem. Soc.* **1993**, 115, 2226–2230.

(34) Wiberg, K. B.; Castejón, H.; Keith, T. A. *J. Comput. Chem.* **1996**, 17, 185–190.

(35) Richardson, W. H.; Peng, C.; Bashford, D.; Noodleman, L.; Case, D. A. *Int. J. Quantum Chem.* **1997**, 61, 207–217.

(36) Kallies, B.; Mitzner, R. *J. Phys. Chem. B* **1997**, 101, 2959–2967.

(37) Topol, I. A.; Tawa, G. J.; Burt, S. K.; Rashin, A. A. *J. Phys. Chem. A* **1997**, 101, 10075–10081.

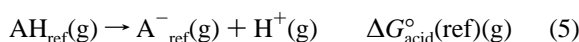
The application of this model to the study of the acidity of a variety of carboxylic acids in solution^{34,35} has yielded satisfactory results. Computations were carried out by using the SCRFPAC program³⁹ updated to the Gaussian 94 environment.²² According to this methodology, described elsewhere,³¹ the solute is placed in a general-shaped cavity embedded in a polarizable continuum whose permittivity is taken to be equal to that of water at 25 °C (78.4). The wave function of the solute is relaxed in this environment by considering a solute–solvent interaction obtained from a multipole expansion. Terms up to sixth order have been used. Other solvation terms are also included in the total energy. The B3LYP/6-31+G(d) geometries optimized in the gas phase were used for single point calculations of solvated structures. Previous work^{33–35,37,38} supports this methodology because of the modest changes observed, both in geometric parameters and in energy contributions, when single point calculations on gas-phase geometries are compared with full geometric optimizations in the presence of the reaction field.

Experimental Results

The Gibbs energy change for reaction 1, $\Delta G_{\text{acid}}^{\circ}(\text{g})$, is given by $\Delta G_{\text{acid}}^{\circ}(\text{g})_{\text{av}}$, the average of the $\Delta G_{\text{acid}}^{\circ}(\text{g})$ values obtained through eq 4:

$$\Delta G_{\text{acid}}^{\circ}(\text{g}) = \delta \Delta G_{\text{acid}}^{\circ}(\text{g}) + \Delta G_{\text{acid}}^{\circ}(\text{ref})(\text{g}) \quad (4)$$

wherein $\Delta G_{\text{acid}}^{\circ}(\text{ref})(\text{g})$ pertains to reaction 5:



Values of $\Delta G_{\text{acid}}^{\circ}(\text{ref})(\text{g})$ are taken from ref 40 unless stated otherwise.

Experimental results are shown in Scheme 1.

Notice that the uncertainties reported for the acidities are rather small, as far as the overlaps with the references are concerned. The “absolute” values are obviously less precise, perhaps by as much as 1 or 2 kcal mol⁻¹.

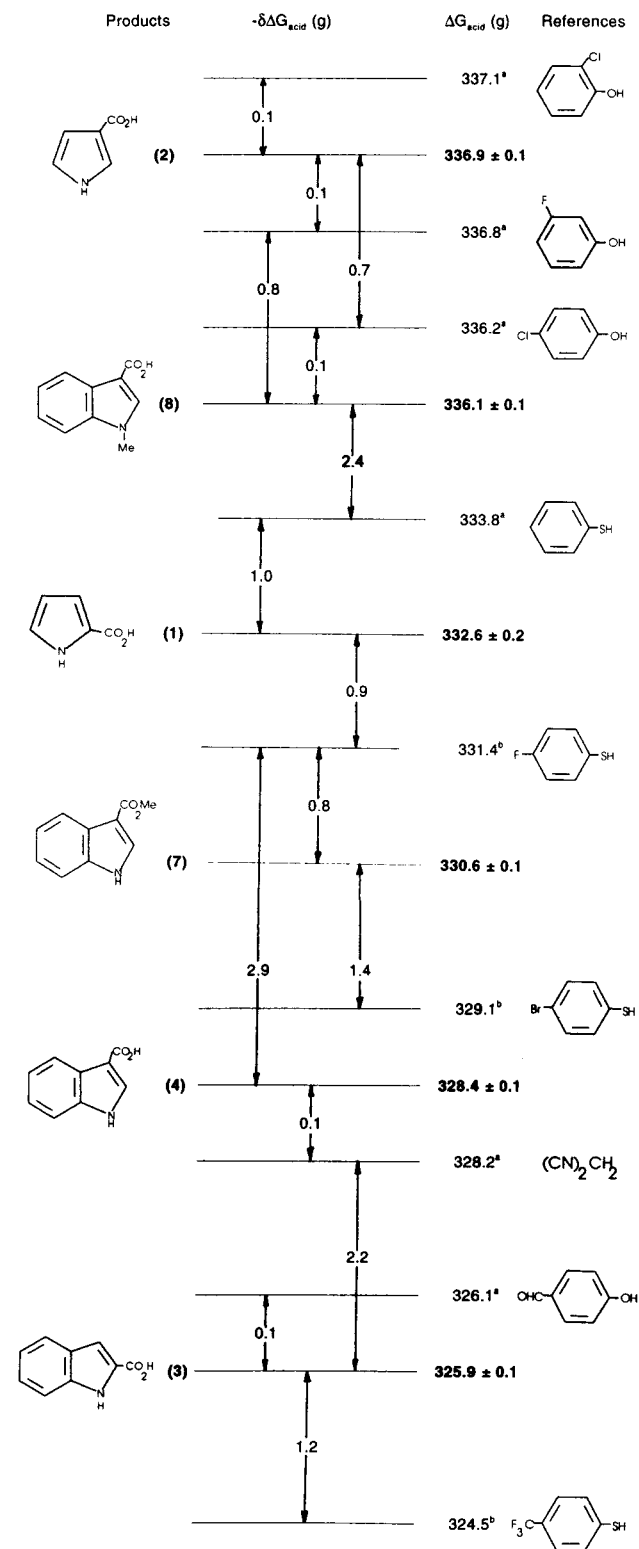
The experimental acidity values of **1–4** (see Scheme 1) say little about the origin of the acidic hydrogen of the molecules (possible sites being the COOH or NH groups). To answer this question it is necessary to carry out a theoretical study of the intrinsic acidities of **1–4**.

A preliminary study, at the ab initio HF/3-21G(d) level, was performed to determine the structure of the most stable conformers of compounds **1–4**, because there are four possible conformers of the neutral compounds and other four NH-deprotonated conformers, depending on the orientation of the COOH group within the molecule. In the case of deprotonation of the COOH group there is only one possible structure.

The most stable structures of compounds **1–4** and their OH- and NH-deprotonated forms are presented as part of the Supporting Information. As can be seen there, all the structures are planar. In the case of anions **1(N⁻)** and **3(N⁻)** there is an intramolecular hydrogen bond between the OH group and the N atom of the ring. Theoretical structures of compounds **1–4** and their corresponding anions, optimized at HF/6-31+G(d), B3LYP/6-31+G(d), and in some cases MP2/6-31+G(d) levels, are presented as part of the Supporting Information. To our knowledge, there are no experimental data on the structures of these compounds.

The standard Gibbs energies at 298 K, evaluated at several levels of ab initio and DFT theories, for the most stable structures of compounds **1–4** are given in Table 2. The electronic

Scheme 1



energy values and the corresponding zero-point vibrational energies, thermal corrections to enthalpies, and entropies, evaluated at several levels of ab initio and DFT theories, are collected in Tables S1 and S2 (see Supporting Information).

Discussion

The data reported in Table 2 indicate that in the cases of pyrrole-3-carboxylic acid, **2**, and indole-3-carboxylic acid, **4**, NH-deprotonation is clearly favored relative to COOH-depro-

(38) Li, G.-S.; Ruiz-López, M. F.; Maigret, B. *J. Phys. Chem. A* **1997**, *101*, 7885–7892.

(39) Pappalardo, R. R.; Rinaldi, D. SCRFPAC, QCPE No. 622; Indiana University, Bloomington IN, 1992. Updated version for Gaussian 94 by Rinaldi, D.

Table 2. Gibbs Energy Values Obtained at Different Computational Levels for Compounds **1–4** and Their Corresponding NH- and OH-Deprotonated Forms^a (All Values in Hartrees)

compd		B3LYP/6-31+G(d)	HF/6-31+G(d)	MP2/6-31+G(d) //HF/6-31+G(d)	MP2/6-31+G(d)
1	pyrrole-2-carboxylic acid	-398.70405	-396.38399	-397.54155	-397.54755
1(N⁻)	pyrrole-2-carboxylic acid, pyrrolide anion	-398.16788	-395.83699	-397.01231	-397.01838
1(O⁻)	pyrrole-2-carboxylate anion	-398.17039	-395.84065	-397.01490	-397.02058
2	pyrrole-3-carboxylic acid	-398.70062	-396.38262	-397.53843	-397.54429
2(N⁻)	pyrrole-3-carboxylic acid, pyrrolide anion	-398.15905	-395.82975	-397.00211	-397.00796
2(O⁻)	pyrrole-3-carboxylate anion	-398.15490	-395.82592	-396.99871	-397.00398
3	indole-2-carboxylic acid	-552.31273	-549.00095	-550.66474	
3(N⁻)	indole-2-carboxylic acid, indolide anion	-551.78426	-548.45936	-550.14491	
3(O⁻)	indole-2-carboxylate anion	-551.78894	-548.46693	-550.14808	
4	indole-3-carboxylic acid	-552.31241	-549.00272	-550.66542	
4(N⁻)	indole-3-carboxylic acid, indolide anion	-551.78299	-548.46168	-550.14221	
4(O⁻)	indole-3-carboxylate anion	-551.77342	-548.45337	-550.13332	

^a The Gibbs energy values, at 298 K, have been obtained from electronic energies by using scaled zero-point vibrational energies, thermal corrections, and entropies, computed at B3LYP/6-31G(d) and HF/6-31G(d) levels.

Table 3. Calculated Acidities from Isodesmic Reactions 6 and 7 for NH- and OH-Deprotonations, Respectively. Differences between Calculated and Experimental Acidities Are Indicated in Parentheses (All Values in kcal mol⁻¹)

compd	B3LYP/6-31+G(d)	HF/6-31+G(d)	MP2/6-31+G(d)// HF/6-31+G(d)	MP2/6-31+G(d)	exptl ^a
1(N)	332.5	333.1	332.6	332.6	
1(O)	333.3 (0.7)	332.3 (-0.3)	332.7 (0.1)	332.6 (0.0)	332.6
2(N)	335.8 (-1.1)	336.8 (-0.1)	337.1 (0.2)	337.0 (0.1)	336.9
2(O)	340.9	340.7	340.9	340.9	
3(N)	327.6	329.7	328.6		
3(O)	327.1 (1.2)	326.4 (0.5)	326.4 (0.5)		325.9
4(N)	328.2 (-0.2)	329.4 (1.0)	328.8 (0.4)		328.4
4(O)	336.6	336.1	336.1		
7	332.3 (1.7)	332.7 (2.1)	332.3 (1.7)		330.6
8	334.8 (-1.3)	335.3 (-0.8)	335.3 (-0.8)		336.1
9	342.7 (0.8)	344.2 (2.3)	342.1 (0.3)		341.9
10	347.5 (1.1)	347.7 (1.3)	347.1 (0.7)		346.4
11	342.1 (-0.7)	342.0 (-0.8)	341.4 (-1.4)		342.8
12	329.7 (-0.3)	329.7 (-0.3)	329.4 (-0.6)		330.0
13	321.9 (1.1)	321.9 (1.1)	322.6 (1.8)		320.8
14	324.3 (-1.5)	325.3 (-0.5)	325.4 (-0.4)		325.8
15	335.4 (1.6)	334.4 (0.6)	334.0 (0.2)		333.8
dev ^b	(0.9)	(0.9)	(0.7)		

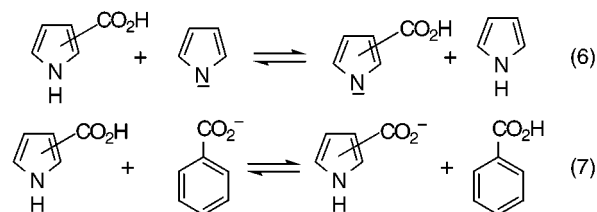
^a Values taken from ref 40. ^b |dev| are the mean absolute deviations between theory and experiment taking into account OH-deprotonation in the case of **1** and **3** and NH-deprotonation in the case of **2** and **4**.

tonation. In the other two cases, COOH-deprotonation may be slightly more favorable but, in any case, the COOH- and NH-deprotonated structures have quite comparable stabilities, and the computed gap becomes even narrower when correlation effects are included. Thus, for **1(N⁻)/1(O⁻)** the gaps at the HF/6-31+G(d), MP2/6-31+G(d)//HF/6-31+G(d), MP2/6-31+G(d), and B3LYP/6-31+G(d) levels are respectively 2.3, 1.6, 1.4, and 1.6 kcal mol⁻¹ and for **3(N⁻)/3(O⁻)** the gaps are 4.8, 2.0, and 2.9 kcal mol⁻¹ at the HF/6-31+G(d), MP2/6-31+G(d)//HF/6-31+G(d), and B3LYP/6-31+G(d) levels, respectively. Use of isodesmic reactions (see below) further reduces these gaps.

How does this result compare to the experimental data? We have to obtain now reliable theoretical acidities of **1–4**.

The size of the molecules studied in this work does not allow us to calculate the “absolute” acidities at the G2 or G2(MP2) levels, which are the most suitable to obtain theoretical acidities close to the experimental values.^{28,41} An alternative procedure to improve the accuracy is to calculate “relative” acidities through the use of isodesmic reactions⁴² in which there is an important cancelation of errors.

We have calculated the acidities of the relevant compounds using isodesmic reactions 6, for NH-deprotonation, and 7, for deprotonation of the COOH group:



taking pyrrole (**5**) and benzoic acid (**6**), respectively, as reference compounds and using their experimental acidities.⁴³ Calculated values are collected in Table 3, together with the differences with the experimental acidities.

As shown in this table, the NH-acidities of **2** and **4** are very close to the experimental values and very far from those calculated assuming deprotonation of the carboxylic group. As mentioned earlier, the situation of **1** and **3** is not so clear-cut.

(41) Smith, B. J.; Radom, L. *J. Phys. Chem.* **1991**, *95*, 10549–10551.

(42) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.

(43) Experimental $\Delta G_{\text{acid}}(\text{g})$ values for pyrrole and benzoic acid are 351.8 and 332.9 kcal mol⁻¹, respectively, taken from ref 40.

(40) NIST Chemistry Webbook, NIST Standard Reference Database Number 69, March 1998 Release; Negative Ion Energetics data compiled by Bartmess, J. E. (<http://webbook.nist.gov/chemistry/>).

To further clarify the situation, we have also measured the intrinsic acidities of two other compounds, methyl indole-3-carboxylate (**7**) and 1-methylindole-3-carboxylic acid (**8**), for which there is only one possibility of deprotonation. The experimental results are collected in Scheme 1. It is important to point out that the methylation of the carboxylic group in **4** decreases the acidity by only 2.2 kcal mol⁻¹, while the *N*-methylation decreases the acidity by 7.7 kcal mol⁻¹.

Also carried out were the calculations at several ab initio levels for the corresponding neutral and deprotonated structures of **7** and **8** (see Supporting Information). The calculated acidities of **7** and **8**, from isodesmic reactions 6 and 7, are in good agreement with the experimental values (see Table 3).

For the very purpose of allowing a more strict comparison of experimental and computed acidities, we have studied seven compounds corresponding to NH acids, indole (**9**), pyrazole (**10**), and imidazole (**11**), and carboxylic acids, 4-fluoro- (**12**), 4-cyano- (**13**), 4-formyl- (**14**), and 4-methoxy- (**15**) benzoic acids. The calculated Gibbs energy values, at 298 K, for the ionization of all these compounds are given in Table S3 (see Supporting Information), and the corresponding calculated acidities using isodesmic reactions 6 and 7 are shown in Table 3.

The experimental and computed values for compounds **5** to **15** (those having a single, unambiguous ionization site) obey the excellent linear relationship, eq 8:

$$\Delta G_{\text{acid}}(\text{calc}) = 12(11) + 0.965(0.033)\Delta G_{\text{acid}}(\text{exp}) \quad (8)$$

$$n = 11; r = 0.995; \text{sd} = 0.98 \text{ kcal mol}^{-1}$$

Ninety-five percent confidence intervals for the intercept and the slope^{44a} are given in parentheses. At this level, the equation $\Delta G_{\text{acid}}(\text{calc}) = \Delta G_{\text{acid}}(\text{exp})$ remains essentially within the confidence limits of eq 8.

Figure 1 is a plot of ΔG_{acid} values calculated at the MP2/6-31+G(d)//HF/6-31+G(d) level vs the experimental values for compounds **1–4**. OH- and NH-deprotonation are represented by up and down triangles, respectively. The line drawn is that defined by eq 8, and the dotted lines limit the 99% confidence interval for individual values (the dispersion band).^{44b}

It is clear that deprotonation in pyrrole- and indole-3-carboxylic acids, **2** and **4**, respectively, occurs at the NH group with 99% confidence. In the case of pyrrole- and indole-2-carboxylic acids, **1** and **3**, respectively, both possibilities are within the dispersion band. In the case of **1**, an equilibrium very likely exists between both anionic structures in the gas phase.

Last, we go back to our initial consideration of the ionization of compounds **1–4** in water. It was assumed all through this study that these compounds ionize in water as carboxylic acids. To our knowledge, no direct experimental evidence seems to support this concept. Thus, we have examined the ionization of these species, as well as that of benzoic acid and pyrrole, by means of a continuum solvation model³⁹ (see computational details).

This kind of model is known to reproduce relative basicities of amines within 0.7 pK units.³⁶ As previous studies have shown, electronic correlation must be included to properly account for structural effects on the acid–base behavior of azoles.³⁷ This was done here, using single point DFT calculations (see

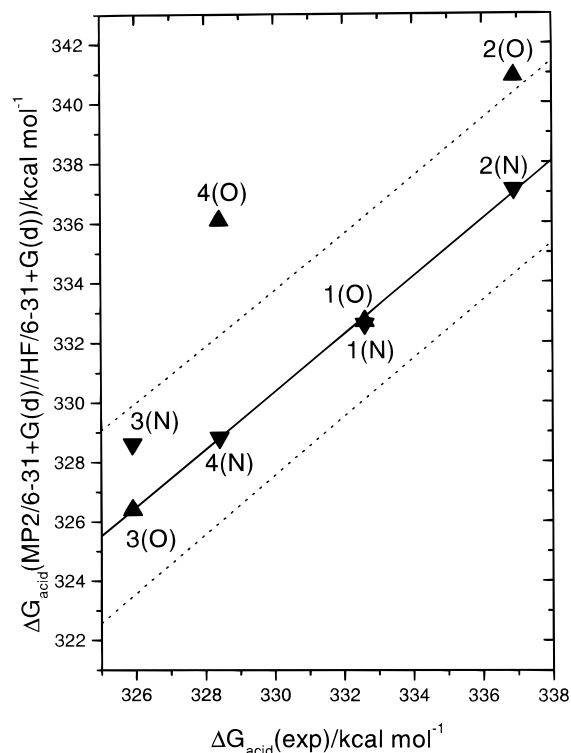


Figure 1. MP2/6-31+G(d)//HF/6-31+G(d)-calculated versus experimental ΔG_{acid} values for pyrrole- and indolecarboxylic acids (compounds **1** to **4**). OH- and NH-deprotonation are represented by up and down triangles, respectively. The solid line is that defined by eq 8 (see Text) and the dotted lines limit the 99% confidence interval for individual values.

Table 4. Calculated ΔG and ΔpK_a Values for Reactions 6 and 7 in Aqueous Solution, at the B3LYP/6-31+G(d) Level (See Text) (All Values in kcal mol⁻¹)

compd	ΔG	$\Delta pK_a(\text{calc})$	$\Delta pK_a(\text{exp})$
reaction 6 ^a			
1	-0.2	-0.1	-13.1
2	2.8	2.1	-12.5
3	-0.8	-0.6	-13.7
4	0.7	0.5	-12.2
reaction 7 ^b			
1	-0.2	-0.1	0.2
2	2.7	2.0	0.8
3	-2.3	-1.7	-0.4
4	2.9	2.1	1.1

^a Taking pyrrole ($pK_a = 17.51$) as reference. ^b Taking benzoic acid ($pK_a = 4.20$) as reference.

computational details). The results are summarized in Table S4 (see Supporting Information).

Notice that, although specific solvation through hydrogen bonding is not included, the treatment takes it implicitly into account, as these interactions are largely electrostatic in nature.⁴⁶ Using these results, we have reexamined the proton-exchange reactions 6 and 7 in aqueous solution, taking as before pyrrole and benzoic acid as reference compounds. Data are summarized in Table 4.

These results are remarkable and rewarding in various respects: (i) the conceptual self-consistency of our approach as compounds **1–4** are shown in all cases to ionize in water as

(44) (a) The 95% confidence intervals of the intercept and the slope of the regression equation $y = a + bx$ have been calculated through the following equations: $a \pm t_{n-2}^{0.05} \{(1/n + x^2/\sum(x_i - x)^2)S_{y,x}^2\}^{1/2}$ and $b \pm t_{n-2}^{0.05} \{S_{y,x}^2/\sum(x_i - x)^2\}^{1/2}$, taken from ref 45. (b) The 99% confidence interval for individual values has been calculated through the equation $y_0 \pm t_{n-2}^{0.01} \{(1 + 1/n + (x_0 - x)^2/\sum(x_i - x)^2)S_{y,x}^2\}^{1/2}$, taken from ref 45.

(45) Massart, D. L.; Vandeginste, B. G. M.; Deming, S. N.; Michotte, Y.; Kaufman, L. *Chemometrics: A Textbook*; Elsevier: Amsterdam, 1988.

(46) Solà, M.; Lledós, A.; Bertrán, J.; Abboud, J.-L. M. *J. Am. Chem. Soc.* **1991**, *113*, 2873–2879.

carboxylic acids (this confirms our initial contention regarding the fundamental, and so far unnoticed, role played by solvation in the ionization of these compounds) and (ii) the excellent quantitative agreement between the experimental and calculated values both in gas-phase and solution systems.

Conclusions

The combination of FT-ICR experimental data with ab initio calculations of substantial level leads to the following conclusions:

- (1) In aqueous solution, compounds **1–4** behave as OH acids.
- (2) In the gas phase, pyrrole 3-carboxylic acid, **2**, and indole 3-carboxylic acid, **4**, behave as NH acids.
- (3) In the cases of pyrrole- and indole-2-carboxylic acids, **1** and **3**, in the gas phase, a prototropic equilibrium between the two possible deprotonated structures is expected to occur.

Acknowledgment. This paper is dedicated to Prof. J. Elguero. We are very grateful to Centro de Supercomputación de Galicia (CESGA) for computing facilities. This work was

supported by Grants PB93-0289-C02-02 of the Spanish D.G.I.-C.Y.T. and PB96-0927-C02-01 of the Spanish D.G.E.S. L.S. thanks the European Communities for work contract No. ERBFMBICT960938 corresponding to a postdoctoral grant from the program "Training and Mobility of Researchers". Work by H.H. was supported by the Moroccan Ministry of Education and CSIC. Profs. C. Foces-Foces, M. F. Ruiz-López, M. Rico, and J. Elguero are acknowledged for helpful comments.

Supporting Information Available: Calculated structures of compounds **1–4** and their OH- and NH-deprotonated forms evaluated at several ab initio and DFT levels and Tables S1 to S4, including electronic energy values, zero-point vibrational energies, thermal corrections to enthalpies, entropies, and Gibbs energies for the compounds used in this work, evaluated at several levels of ab initio and DFT theories (19 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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