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Experimental and Computational Study on the Molecular Energetics of 2-Pyrrolecarboxylic Acid and 1-Methyl-2-pyrrolecarboxylic Acid

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This paper reports a combined thermochemical experimental and computational study of 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid. Static bomb combustion calorimetry and Knudsen mass-loss effusion technique were used to determine the standard ($p° = 0.1$ MPa) molar enthalpies of combustion, $\Delta_c H^\circ_m$, and sublimation, $\Delta^g_{cr} H^\circ_m$, respectively, from which the standard ($p° = 0.1$ MPa) molar enthalpies of formation, in the gaseous phase, at $T = 298.15$ K, were derived. The values obtained were $-(286.3 \pm 1.7)$ and $-(291.6 \pm 1.7)$ kJ·mol for 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, respectively. For comparison purposes, the gas-phase enthalpies of formation of these two compounds were estimated by G3(MP2)//B3LYP and MP2 approaches, using a set of gas-phase working reactions; the results are in excellent agreement with experimental data. G3(MP2)//B3LYP computations were also extended to the calculation of N−H bond dissociation enthalpies, gas-phase acidities and basicities, proton and electron affinities and adiabatic ionization enthalpies. Moreover, the results are also discussed in terms of the energetic effects of the addition of a carboxylic and of a methyl groups to the pyrrole ring and compared with structurally similar compounds.

1. Introduction

Pyrrole derivatives are five-membered aromatic nitrogen heterocyclic compounds which are of extraordinary importance, being present in natural products, pharmaceuticals, and new materials. The 2-pyrrolecarboxylic acid is used in the synthesis of Ramipril {systematic name: 1-[2-(1-(ethoxycarbonyl)-3-phenylpropylamino)propionyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid},[1,2] which is an antihypertensive and cardiovascular protective drug, on the synthesis of benzopyran antihypertensive agents,[3] of azepinediones (used in the therapeutics of circulatory diseases, such as hypertension and congestive heart failure,[4,5]) and of cholecystokinin antagonists (potential therapeutic agents for appetitive disorders, anxiety, potentiation of opiate analgesia, and treatment of gastrointestinal, pancreatic, and possibly psychiatric disorders,[6]); its derivatives also show potential anticancer activity.[7] The 2-pyrrolecarboxylic acid also possesses anti-inflammatory activity[8] and hypocalcemic action.[9] Apart from the applications indicated above, 2-pyrrolecarboxylic acid has recently been used as a reducing agent in the preparation of gold colloids, which find applications in the fields of electronics, catalysis, and clinical diagnostics,[10] in the preparation of optically active atropisomers.[11] It is also an effective ligand for Cu-catalyzed monoarylation of anilines with aryl iodides and bromides, which is one of the main methods for obtaining the diaryl amine moiety, present in several biologically active pharmaceuticals, natural products, and materials.[12] 1-Methyl-2-pyrrolecarboxylic acid and its esters are used as starting materials for the synthesis of Netropsin and analogues, which are oligopeptides with antibiotic and antiviral activities.[13] Despite their important applications, reliable studies on the energetic properties of pyrrole derivatives are still scarce. The pyrrole derivatives scaffold is part of the structure of large biomolecules like tetra-pyrroles such as heme and vitamin B12, and therapeutic drugs. It is of great importance for the understanding of the activity and behavior of these large molecules, to know the molecular energetics of its fragments.

2-Pyrrolecarboxylic acid 1-Methyl-2-pyrrolecarboxylic acid

Figure 1. Structural formula of 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid.

The crystal and molecular structure of 2-pyrrolecarboxylic acid has been subject of experimental and theoretical investigations. Dubis et al. showed, using both infrared and Raman techniques, that 2-pyrrolecarboxylic acid forms cyclic dimers in the solid state and that this acid and its *N*-methyl derivative exist, in solution, in only one conformation, the syn form.[14] Later, Grabowski and co-workers determined, by single-crystal X-ray diffraction, the crystal structure of 2-pyrrolecarboxylic acid. This molecule has a unit cell with a monoclinic crystal system and a space group *C*2/*c*.[15]

The present work is part of a systematic study on the energetics of pyrrole derivatives, for which we recently reported a calorimetric and computational study of 2- and 3-acetylpyrroles.[16] Hence, we present here a thermochemical experimental and computational study of 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, whose structural formulas are depicted in Figure 1. The experimental investigation includes the measurement of the standard ($p° = 0.1$ MPa) massic energies of combustion, of the two title acids, in oxygen, at $T = 298.15$ K, using a static bomb combustion calorimetry, from which the standard ($p° = 0.1$ MPa) molar enthalpies of formation, in the condensed phase, were derived. The Knudsen mass-loss effusion technique allowed the determination of the standard molar

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enthalpies of sublimation, at $T = 298.15$ K, through the application of the Clausius−Clapeyron equation. From these experimental values, the standard molar enthalpies of formation, in the gaseous phase were derived and compared with values estimated by G3(MP2)//B3LYP and MP2/6-311+G(2d,2p) computations. G3(MP2)//B3LYP theoretical calculations were extended to the determination of N−H bond dissociation enthalpies, gas-phase acidities and basicities, proton and electron affinities, and adiabatic ionization enthalpies.

2. Experimental Section

2.1. Materials and Purity Control. The 2-pyrrolecarboxylic acid [CAS 634-97-9] and 1-methyl-2-pyrrolecarboxylic acid [CAS 6973-60-0] were purchased from Sigma-Aldrich Chemical Co. and from Alfa-Aesar with assessed minimum massic fraction purities of 0.99 and 0.98, respectively.

The two compounds, which are solids at room temperature, were purified by successive vacuum sublimations, and the purities were checked by gas−liquid chromatography and from the consistent results obtained after the combustion experiments, as well as by the closeness to unity of the carbon dioxide recovery ratios.

The average ratio of the mass of carbon dioxide recovered after combustion to that calculated from the mass of samples used in each experiment were 1.00007 ± 0.00096 for 2-pyrrolecarboxylic acid and 0.99973 ± 0.00229 for 1-methyl-2-pyrrolecarboxylic acid, where the uncertainties are twice the standard deviation of the mean.

The specific density used to calculate the true mass from the apparent mass in air of 2-pyrrolecarboxylic acid was $\rho = 1.458$ $\mathrm{g \cdot cm^{-3}}$;[15] for 1-methyl-2-pyrrolecarboxylic acid the value used, $\rho = 1.256$ $\mathrm{g \cdot cm^{-3}}$, was determined from the ratio mass/volume of a pellet of the compound (made in vacuum, with an applied pressure of 10^5 $\mathrm{kg \cdot cm^{-2}}$).

2.2. Combustion Calorimetry. The combustion experiments were performed with an isoperibol static bomb calorimeter, equipped with a Parr 1108 model twin valve bomb, made of stainless steel, and with an internal volume of 0.342 $\mathrm{dm^3}$.[17,18]

Benzoic acid NIST Thermochemical Standard 39j, with a certified massic energy of combustion, under bomb conditions of −26434 ± 3 $\mathrm{J \cdot g^{-1}}$,[19] was used for calibration of the bomb. The procedure described by Coops et al. was followed.[20] From six calibration experiments the value of the energy equivalent of the calorimeter was determined as $\varepsilon(\mathrm{calor}) = 16012.8 \pm 1.1$ $\mathrm{J \cdot K^{-1}}$, for an average mass of water added to the calorimeter of 3119.6 g; the quoted uncertainty is the standard deviation of the mean.

In all combustion experiments, the crystalline compounds were burnt in pellet form and 1.00 $\mathrm{cm^3}$ of deionized water was introduced into the bomb, which was purged twice to remove air, before being charged with 3.04 MPa of oxygen.

The calorimeter temperatures were measured to $\pm 1 \times 10^{-4}$ K, at time intervals of 10 s, with a quartz crystal thermometer (Hewlett Pachard HP 2804 A), interfaced to a PC. The ignition of the samples was made at $T = 298.150 \pm 0.001$ K, at least 100 readings after the start of the experiment, by the discharge of a 1400 μF capacitor through a platinum ignition wire of diameter 0.05 mm. After ignition, 100 readings were taken for each the main and the after periods. Data acquisition, control of the calorimeter temperature, and calculation of the adiabatic temperature change was performed using the program LABTERMO.[21]

The empirical formula and the massic energy of combustion of the cotton thread used as fuse in all the experiments are, respectively, $\mathrm{CH_{1.686}O_{0.843}}$ and −16240 $\mathrm{J \cdot g^{-1}}$;[22] this value has been previously confirmed in our laboratory. The nitric acid formed was determined by acid−base volumetry, and corrections for it were based on −59.7 $\mathrm{kJ \cdot mol^{-1}}$ for the molar energy of formation of 0.1 $\mathrm{mol \cdot dm^{-3}}$ $\mathrm{HNO_3(aq)}$ from $\mathrm{N_2(g)}$, $\mathrm{O_2(g)}$, and $\mathrm{H_2O(l)}$.[23] The amount of compound, m(cpd), used in each experiment and on which the energy of combustion was based, was determined from the total mass of carbon dioxide produced, taking into account that formed from the combustion of the cotton thread fuse.

At $T = 298.15$ K, $(\partial u/\partial p)_T$ for the two pyrrolecarboxylic acids studied was assumed to be −0.2 $\mathrm{J \cdot g^{-1} \cdot MPa^{-1}}$, a typical value for most organic solids.[24] For each compound, the corrections to the standard state to calculate the standard massic energy of combustion, $\Delta_c u°$, were made by the procedure given by Hubbard et al.[25] The atomic weights used throughout this paper were those recommended by the IUPAC Commission in 2005.[26]

2.3. Knudsen Effusion Technique. The vapor pressures of the two pyrrolecarboxylic acid derivatives were measured as a function of temperature, through the mass-loss Knudsen effusion method, using an apparatus and measuring procedure previously described.[27] This apparatus enables the simultaneous operation of nine aluminum effusion cells, which are placed in cylindrical holes inside three aluminum blocks, each one with three cells. Each block is maintained at a constant temperature, different from the other two blocks. There are three different groups of effusion cells according to their different areas of effusion orifices: series A (small orifices; $A_o \approx 0.5$ $\mathrm{mm^2}$), series B (medium orifices; $A_o \approx 0.8$ $\mathrm{mm^2}$), and series C (large orifices; $A_o \approx 1.1$ $\mathrm{mm^2}$). The exact areas and the transmission probability factors (Clausing factors) of each effusion orifice, made in platinum foil of 0.0125 mm thickness, are presented in the Supporting Information, Table S1.

The measurements were extended through a selected temperature interval of ca. 20 K, chosen to correspond to measured vapor pressures in the range of 0.1−1.0 Pa. In each effusion experiment, the mass loss of the crystalline samples, Δm, was measured by weighing the cells with the samples, within ±0.01 mg, before and after a convenient effusion time period, t, in a system evacuated to a pressure near 1×10^{-4} Pa. The vapor pressure, p, at each temperature, T, of the experiment, was calculated by means of the Knudsen equation

$$p = (\Delta m / A_o w_o t)(2\pi RT/M)^{1/2} \qquad (1)$$

in which A_o represents the area of the effusion orifice, w_o is the respective Clausing factor, R is the gas constant, and M is the molar mass of the effusing vapor.

3. Computational Details

All the computations have been performed by means of the composite G3(MP2)//B3LYP method,[28] through the Gaussian 03 computer code.[29]

This composite approach combines a series of separately performed standard ab initio calculations with the purpose of introducing successive corrections to the energy, initially calculated at a less expensive computational approach. In a first step, the B3LYP/6-31G(d) approach is used for the full-optimization and the calculation of the frequencies of the molecule. Then, keeping the B3LYP/6-31G(d) optimized geometry frozen, single-point calculations are carried out at higher levels of theory (QCISD(T)/6-31G(d) and MP2/GTMP2Large) with the aim of diminishing errors of the initial B3LYP/6-31G(d) energy, correcting correlation, and basis set deficiencies. This energy (with added zero-point vibrational energies scaled by 0.96 as usual with the G3(MP2)//B3LYP method), at $T = 0$ K, is corrected for $T = 298.15$ K by introducing the vibrational, the translational, the rotational, and the pV terms computed at the B3LYP/6-31G(d) level of theory. The enthalpies of formation, for the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, in the gas phase, were estimated by considering their atomization reactions as used with standard Gaussian-N theories. The following atomic experimental gas-phase enthalpies of formation were used: carbon, 716.67 kJ·mol^{-1}; hydrogen, 218.00 kJ·mol^{-1}; oxygen, 249.17 kJ·mol^{-1}; and nitrogen, 472.68 kJ·mol^{-1}.[30] In addition, the enthalpies of formation of the title compounds were estimated using a set of working reactions, for which the standard enthalpies of formation in the gas phase of all compounds, except those that we are interested in, are well-known and considered to be highly accurate.

N−H bond dissociation enthalpies, gas-phase acidities and basicities, proton and electron affinities, and adiabatic ionization enthalpies were also estimated for the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid by means of the G3(MP2)//B3LYP method. It is important to note that, by convention, gas-phase acidity ($\Delta G_{\mathrm{acidity}}$), proton affinity (PA) and electron affinity (EA) were calculated as

$$\mathrm{A} \rightarrow \mathrm{A}^- + \mathrm{H}^+ \quad \Delta G_{\mathrm{acidity}} = \Delta G_{\mathrm{r}} \tag{2}$$

$$\mathrm{A} + \mathrm{H}^+ \rightarrow \mathrm{AH}^+ \quad \mathrm{PA} = -\Delta H_{\mathrm{r}} \tag{3}$$

$$\mathrm{A} + \mathrm{e}^- \rightarrow \mathrm{A}^- \quad \mathrm{EA} = -\Delta H_{\mathrm{r}} \tag{4}$$

where A = 2-pyrrolecarboxylic acid or 1-methyl-2-pyrrolecarboxylic acid.

Additionally, for the sake of comparison, gas-phase enthalpies of formation calculations were also performed at the MP2/6-311+G(2d,2p) level of theory.

4. Results and Discussion

4.1. Condensed Phase and Phase Transition. Table 1 lists the combustion results for one experiment of each compound in which $\Delta m(\mathrm{H_2O})$ is the deviation of the mass of water added to the calorimeter from 3119.6 g, the mass assigned for ε(calor), ΔU_{Σ} is the correction to the standard state, and the remaining quantities are as previously described.[25,31] For the static bomb measurements, as samples were ignited at $T = 298.150 \pm 0.001$ K, the internal energy for the isothermal bomb process, ΔU(IBP), was calculated through

$$\Delta U(\mathrm{IBP}) = -\{\varepsilon(\mathrm{calor}) + C_p(\mathrm{H_2O(l)})\,\Delta m(\mathrm{H_2O}) + \varepsilon_{\mathrm{f}}\}\Delta T_{\mathrm{ad}} + \Delta U(\mathrm{ign}) \tag{5}$$

where ΔT_{ad} is the calorimeter temperature change corrected for the heat exchange and the work of stirring. Detailed results of each combustion experiment, for the compounds studied, are given in the Supporting Information, Tables S2 and S3.

The individual values of $-\Delta_{\mathrm{c}}u°$, together with the mean value, $\langle\Delta_{\mathrm{c}}u°\rangle$, and its standard deviations are given in Table 2. The values of $\Delta_{\mathrm{c}}u°$ refer to the combustion reaction, represented by

$$\mathrm{C}_a\mathrm{H}_b\mathrm{O}_c\mathrm{N}_d(\mathrm{cr}) + \left(a + \frac{b}{4} - \frac{c}{2}\right)\mathrm{O_2(g)} \rightarrow a\mathrm{CO_2(g)} + \frac{b}{2}\mathrm{H_2O(l)} + \frac{d}{2}\mathrm{N_2(g)} \tag{6}$$

In Table 3, the derived standard molar values for the energy, $\Delta_{\mathrm{c}}U^{\circ}_{\mathrm{m}}(\mathrm{cr})$, and enthalpy, $\Delta_{\mathrm{c}}H^{\circ}_{\mathrm{m}}(\mathrm{cr})$, of combustion reaction (6), as well as the standard molar enthalpies of formation, $\Delta_{\mathrm{f}}H^{\circ}_{\mathrm{m}}(\mathrm{cr})$, in the crystalline phase, at $T = 298.15$ K, are presented.

According to Rossini[32] and Olofsson,[33] the uncertainty assigned to the molar enthalpy of combustion is twice the overall standard deviation of the mean and includes the uncertainties in calibration and in the values of the auxiliary quantities used.

To derive $\Delta_{\mathrm{f}}H^{\circ}_{\mathrm{m}}(\mathrm{cr})$, at $T = 298.15$ K, from $\Delta_{\mathrm{c}}H^{\circ}_{\mathrm{m}}(\mathrm{cr})$, the standard molar enthalpies of formation of $\mathrm{H_2O(l)}$, -285.830 ± 0.042 kJ·mol^{-1}, and $\mathrm{CO_2}$ (g), -393.51 ± 0.13 kJ·mol^{-1}, were used.[34]

The integrated form of the Clausius−Clapeyron equation, $\ln(p/\mathrm{Pa}) = a - b(T/\mathrm{K})^{-1}$, where a is a constant and $b = \Delta^{\mathrm{g}}_{\mathrm{cr}}H^{\circ}_{\mathrm{m}}(\langle T\rangle)/R$, was used to derive the standard molar enthalpies of sublimation at the mean temperature of the experimental

TABLE 1: Typical Combustion Results, at $T = 298.15$ K ($p° = 0.1$ MPa), for the Studied Compounds[a]

	2-pyrrolecarboxylic acid	1-methyl-2-pyrrolecarboxylic acid
$m(\mathrm{CO_2,total})$/g	1.16988	1.15716
m(cpd)/g	0.58807	0.54618
m'(fuse)/g	0.00316	0.00280
ΔT_{ad}/K	0.76412	0.81492
$\varepsilon_{\mathrm{f}}/(\mathrm{J \cdot K^{-1}})$	15.26	15.62
$\Delta m(\mathrm{H_2O})$/g	0	0
$-\Delta U(\mathrm{IBP})$ [b]/J	12246.60	13061.06
ΔU(fuse)/J	51.32	45.47
$\Delta U(\mathrm{HNO_3})$/J	32.69	28.43
ΔU(ign)/J	0.76	0.82
ΔU_{Σ}/J	10.82	9.65
$-\Delta_{\mathrm{c}}u°/(\mathrm{J \cdot g^{-1}})$	20663.82	23760.50

[a] $m(\mathrm{CO_2,total})$ is the mass of $\mathrm{CO_2}$ recovered in each combustion; m(cpd) is the mass of compound burnt in each experiment; m'(fuse) is the mass of the fuse (cotton) used in each experiment; ΔT_{ad} is the corrected temperature rise; ε_{f} is the energy equivalent of the contents in the final state; $\Delta m(\mathrm{H_2O})$ is the deviation of mass of water added to the calorimeter from 3119.6 g; ΔU(IBP) is the energy change for the isothermal combustion reaction under actual bomb conditions and includes the energy for ignition; ΔU(fuse) is the energy of combustion of the fuse (cotton); $\Delta U(\mathrm{HNO_3})$ is the energy correction for the nitric acid formation; ΔU(ign) is the electric energy for the ignition; ΔU_{Σ} is the standard-state correction; $\Delta_{\mathrm{c}}u°$ is the standard massic energy of combustion. [b] ΔU(IBP) includes ΔU(ign).

TABLE 2: Individual Values of Standard ($p° = 0.1$ MPa) Massic Energies of Combustion, $\Delta_{\mathrm{c}}u°$, of the Compounds, at $T = 298.15$ K

	2-pyrrolecarboxylic acid	1-methyl-2-pyrrolecarboxylic acid
$-\Delta_{\mathrm{c}}u°/(\mathrm{J \cdot g^{-1}})$	20670.74	23760.50
	20663.82	23750.03
	20675.44	23776.57
	20641.05	23752.90
	20653.16	23747.82
	20671.66	23772.85
		23765.00
$-\langle\Delta_{\mathrm{c}}u°\rangle/(\mathrm{J \cdot g^{-1}})$	20662.6 ± 5.4[a]	23760.8 ± 4.2[a]

[a] Mean value and standard deviation of the mean.

TABLE 3: Derived Standard ($p^\circ = 0.1$ MPa) Molar Energies of Combustion, $\Delta_c U_m^\circ$, Standard Molar Enthalpies of Combustion, $\Delta_c H_m^\circ$, and Standard Molar Enthalpies of Formation, $\Delta_f H_m^\circ$, for the Crystalline Compounds, at T = 298.15 K

compound	$-\Delta_c U_m^\circ$(cr)/ (kJ·mol^{-1})	$-\Delta_c H_m^\circ$(cr)/ (kJ·mol^{-1})	$-\Delta_f H_m^\circ$(cr))/ (kJ·mol^{-1})
2-pyrrolecarboxylic acid	2295.6 ± 1.3	2295.0 ± 1.3	387.1 ± 1.5
1-methyl-2-pyrrolecarboxylic acid	2973.1 ± 1.3	2973.7 ± 1.3	387.8 ± 1.5

temperature range. The experimental results obtained from each effusion cell, together with the residuals of the Clausius–Clapeyron equation $\{10^2\Delta\ln(p/\text{Pa})\}$, derived from least-squares adjustments are summarized in Table 4 for the two pyrrolecarboxylic acids studied.

Table 5 presents for each orifice used and for the global treatment of all the (p,T) points obtained for each studied compound the detailed parameters of the Clausius–Clapeyron equation, together with the calculated standard deviations and the standard molar enthalpies of sublimation at the mean temperature of the experiments, $T = \langle T\rangle$. For each compound, the calculated enthalpies of sublimation obtained from each individual orifice are in consonance within experimental error. The equilibrium pressure at this temperature $p(\langle T\rangle)$ and the entropies of sublimation, at equilibrium conditions, are also presented with the latter calculated as

$$\Delta_{cr}^{g}S_m(\langle T\rangle, p(\langle T\rangle)) = \Delta_{cr}^{g}H_m^\circ(\langle T\rangle)/\langle T\rangle \tag{7}$$

The plots of ln $p = f(1/T)$ for the global results of the two compounds studied are shown in Figure 2. The (p,T) values, calculated from the (p,T) equations for the crystalline compounds, within the experimental range of pressures used, 0.1–1.0 Pa, are given in Table 6. The values of the enthalpies of sublimation, at T = 298.15 K, $\Delta_{cr}^{g}H_m^\circ(T = 298.15K)$, were calculated through eq 8, from the enthalpies of sublimation, at the mean temperature $\langle T\rangle$ of the experiment:

$$\Delta_{cr}^{g}H_m^\circ(T = 298.15\text{K}) = \Delta_{cr}^{g}H_m^\circ(\langle T\rangle) + \Delta_{cr}^{g}C_{p,m}^\circ(298.15 - \langle T\rangle) \tag{8}$$

For each compound studied, the value of $\Delta_{cr}^{g}C_{p,m}^\circ$ was assumed as being -50 J·K^{-1}·mol^{-1}, resembling estimations made by other authors,[35] a value that our research group has already used for other organic compounds.[16,36–40]

Table 7 presents, for each compound, the values, at T = 298.15 K, of the standard molar enthalpies, entropies, and Gibbs energies of sublimation.

For the two compounds studied experimentally, the standard molar enthalpies of formation in the gaseous state, at T = 298.15 K, were derived from the calculated standard molar enthalpies of formation in the crystalline state and the standard molar enthalpies of sublimation, given in Tables 3 and 7, respectively, and are presented in Table 8.

No experimental data for the enthalpies of combustion and formation of the title compounds have been found in the literature for comparison with our results. For 2-pyrrolecarboxylic acid, the enthalpy of sublimation was previously determined by Bradley and Care, by measuring the vapor pressures in the range of temperatures of 349.73–353.57 K, as 126.82 kJ·mol^{-1}, which corrected to T = 298.15 K yields 129.50 kJ·mol^{-1}.[41] This result is in disagreement with the corresponding value determined in this work (100.8 ± 0.9 kJ·mol^{-1}); a similar discrepancy has also been reported by Roux et al. for 2-thiophene-[42] and 2-furancarboxylic acids.[43]

4.2. Gas-Phase–Molecular Structures. The molecular structure of 2-pyrrolecarboxylic acid was determined by Dubis and co-workers using the density functional theory (DFT) at the B3LYP/6-311+G(d) level,[14] and by Grabowski and collaborators using single-crystal X-ray diffraction, DFT calculations at the B3LYP/6-311++G(d,p) level, and ab initio calculations at the MP2/6-311++G(d,p) level;[15] the results suggest that the syn conformer is more stable than the anti conformer, by ca. 4.1 kJ·mol^{-1}.

The calculated molecular structures of the two compounds studied, optimized at the B3LYP/6-31G(d) level of theory (G3(MP2)//B3LYP calculations), are shown in Figure 3. Bond distances and bond angles obtained in this work with B3LYP/6-31G(d) and MP2/6-311+G(2d,2p) approaches for the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid are collected in Table S4 in the Supporting Information and are compared with the available experimental and computational data. There is a very good agreement between the experimental and calculated geometric parameters for 2-pyrrolecarboxylic acid. No structural data for the 1-methyl-2-pyrrolecarboxylic acid has been found in the literature for comparison with our results. The geometrical parameters of the two acids studied agree well with the corresponding ones found for pyrrole, previously reported by us.[16]

The calculated molecular structure of 2-pyrrolecarboxylic acid is planar, pertaining to the symmetry point group C_s, whereas 1-methyl-2-pyrrolecarboxylic acid is almost planar, with symmetry point group C_1.

At the G3(MP2)//B3LYP level, the N–H,O-syn is the preferred conformation for 2-pyrrolecarboxylic acid (Figure 3) and has the carbonyl oxygen syn to the NH(N–H,O=syn). The N–H,O-anti conformation is 4.7 kJ·mol^{-1} less stable than the N–H,O-syn, which is in very good agreement with results previously reported by Grabowski et al.[15] For 1-methyl-2-pyrrolecarboxylic acid, the N–CH$_3$,O=syn is also the most stable conformation (Figure 3), and, at the same level, the differences between both types of structures is ca. 8.9 kJ·mol^{-1}.

The C$_5$NH angle in 2-pyrrolecarboxylic acid is larger that the C$_2$NH one (127.8° vs 122.4°, respectively), suggesting that the H atom from the N–H group of this acid is slightly tilted in the direction of the -COOH group, which has already been found for 2-acetylpyrrole.[16] For comparison purposes, the molecular structure of 3-pyrrolecarboxylic acid was also calculated at the same level; the preferred conformation is the N–H,O=anti and the G3(MP2)//B3LYP 2→3 isomerization enthalpy is ≈7.1 kJ·mol^{-1}, being with the 2-isomer more stable than the 3-isomer (results not shown in this work).

4.3. Gas-Phase Experimental and Theoretical Enthalpies of Formation. The experimental results reported in this work, combined with other values published earlier in the literature, enable us to determine the enthalpic increments for the insertion of a -COOH group in the thiophene, furan, and pyrrole rings. The standard molar enthalpies of formation, in the gaseous phase, at T = 298.15 K, are for thiophene, 115.0 ± 1.0 kJ·mol^{-1},[44] 2-thiophenecarboxylic acid, −259.2 ± 1.9 kJ·mol^{-1},[42] furan, −34.8 ± 0.7 kJ·mol^{-1},[45] 2-furancarboxylic acid, −410.3 ± 2.1 kJ·mol^{-1},[43] pyrrole, 108.3 ± 0.5 kJ·mol^{-1},[46] and 2-pyrrolecarboxylic acid, −286.3 ± 1.7 kJ·mol^{-1}, as shown in the scheme of Figure 4. This figure clearly shows, from the

TABLE 4: Knudsen Effusion Results for the 2-Pyrrolecarboxylic Acid and 1-Methyl-2-pyrrolecarboxylic Acid[a]

T/K	t/s	orifices	p/Pa small	p/Pa medium	p/Pa large	$10^2\Delta\ln(p/\mathrm{Pa})$ small	$10^2\Delta\ln(p/\mathrm{Pa})$ medium	$10^2\Delta\ln(p/\mathrm{Pa})$ large
			2-Pyrrolecarboxylic acid					
331.12	21946	A1-B4-C7	0.106	0.110	0.102	1.5	5.3	−1.8
333.09	21946	A2-B5-C8	0.134	0.132	0.128	4.3	2.3	−0.8
335.29	21946	A3-B6-C9	0.181	0.163	0.157	10.9	0.2	−3.5
337.12	18917	A1-B4-C7	0.204	0.188	0.188	3.5	−4.5	−4.6
339.16	18917	A2-B5-C8	0.243	0.237	0.231	−0.1	−2.7	−5.3
341.19	18917	A3-B6-C9	0.298	0.288	0.281	−0.4	−3.9	−6.4
343.12	16036	A1-B4-C7	0.366	0.360	0.354	0.6	−1.2	−2.7
345.16	16036	A2-B5-C8	0.450	0.441	0.428	0.8	−1.2	−4.3
347.18	16036	A3-B6-C9	0.579	0.537	0.516	5.8	−1.7	−5.5
349.13	11141	A1-B4-C7	0.706	0.668	0.655	6.8	1.3	−0.7
351.16	11141	A2-B5-C8	0.838	0.817	0.796	4.3	1.7	−0.9
353.19	11141	A3-B6-C9	1.008	0.992	0.957	3.3	1.6	−1.9
			1-Methyl-2-pyrrolecarboxylic acid					
305.12	23364	A1-B4-C7	0.104	0.0985	0.0971	6.3	0.9	−0.5
307.19	23364	A2-B5-C8	0.128	0.126	0.124	2.0	0.1	−1.7
309.21	23364	A3-B6-C9	0.164	0.157	0.154	2.4	−2.3	−4.1
311.12	20089	A1-B4-C7	0.207	0.198	0.196	2.5	−1.6	−2.5
313.17	20089	A2-B5-C8	0.256	0.250	0.246	−0.4	−2.7	−4.2
315.20	20089	A3-B6-C9	0.322	0.311	0.305	−0.7	−4.3	−6.2
317.11	10465	A1-B4-C7	0.435	0.412	0.409	7.3	1.8	1.3
319.16	10465	A2-B5-C8	0.535	0.513	0.505	4.9	0.6	−0.9
321.20	10465	A3-B6-C9	0.688	0.640	0.615	7.2	0.0	−4.0
323.11	11125	A1-B4-C7	0.832	0.794	0.778	5.1	0.4	−1.6
325.15	11125	A2-B5-C8	1.016	0.981	0.952	2.9	−0.6	−3.7
327.20	11125	A3-B6-C9	1.265	1.210	1.172	2.7	−1.7	−4.9

[a] Detailed data of the effusion orifices (diameter and Clausing factors) of the Knudsen effusion apparatus are presented in the Supporting Information.

TABLE 5: Experimental Results for 2-Pyrrolecarboxylic Acid and 1-Methyl-2-pyrrolecarboxylic Acid, Where a and b Are from the Clausius−Clapeyron Equation, $\ln(p/\mathrm{Pa}) = a - b(\mathrm{K}/T)$, and $b = \Delta_{\mathrm{cr}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ}(\langle T\rangle)/R$ ($R = 8.314472$ J·K^{-1}·mol^{-1})

orifices	a	b	$(\langle T\rangle)$/K	$(p(\langle T\rangle))$/Pa	$\Delta_{\mathrm{cr}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ}(\langle T\rangle)$/(kJ·mol^{-1})	$\Delta_{\mathrm{cr}}^{\mathrm{g}}S_{\mathrm{m}}(\langle T\rangle,p(\langle T\rangle))$/(J·K^{-1}·mol^{-1})
			2-Pyrrolecarboxylic Acid			
A1-A2-A3	33.60 ± 0.50	11865 ± 170			98.7 ± 1.4	
B4-B5-B6	33.41 ± 0.43	11811 ± 146			98.2 ± 1.2	
C7-C8-C9	33.61 ± 0.30	11889 ± 102			98.9 ± 0.8	
global results	33.54 ± 0.32	11855 ± 110	342.16	0.330	98.6 ± 0.9	288.2 ± 2.6
			1-Methyl-2-pyrrolecarboxylic Acid			
A1-A2-A3	35.46 ± 0.37	11520 ± 116			95.8 ± 1.0	
B4-B5-B6	35.27 ± 0.24	11474 ± 77			95.4 ± 0.6	
C7-C8-C9	34.99 ± 0.29	11391 ± 91			94.7 ± 0.8	
global results	35.24 ± 0.27	11462 ± 84	316.16	0.363	95.3 ± 0.7	301.4 ± 2.2

increments presented, that the substitution of a hydrogen atom by a -COOH group produces a significant stabilization in the three aromatic rings, which can be explained by the favorable interaction and electronic delocalization between this group and the rings. However, the introduction of the carboxylic group in the 2-position of pyrrole causes a greater stabilization (ca. 19 kJ·mol^{-1}) than in thiophene and furan rings, in which the resulting enthalpic effects are similar (≈ -375 kJ·mol^{-1}). These results suggest that, in the case of 2-pyrrolecarboxylic acid, the large enthalpic stabilization upon the introduction of the -COOH group may be due to internal hydrogen bonding, as was already reported for 2-acetylpyrrole.[16] From the discussion in the previous section, the computational structure of 2-pyrrolecarboxylic acid has the hydrogen atom of the N−H group slightly moved to the carbonyl oxygen atom, indicating the formation of an intramolecular N−H···O bond. This fact was confirmed through a topological analysis with the Topmod program,[47] aiming at the location of critical points in the electronic charge density distribution in the region between the H and O atoms, that revealed a bond critical point with electron localization function, $\eta = 0.026$, electron density, $\rho = 0.0090$, and Laplacian of the electron density, $\nabla^2\rho = 0.0347$, calculated at the B3LYP/6-311+G(2d,2p) level of theory. However, there is an extra stabilization in 2-pyrrolecarboxylic acid, when compared with the other two cyclic species, besides this stabilizing intramolecular N−H···O bond, since the enthalpic difference between the 2- and 3-pyrrolecarboxylic acids is 7.1 kJ·mol^{-1} (in the latter the intramolecular N−H···O bond is nonexistent) and the enthalpic increment due to the insertion of the -COOH group in pyrrole is ca. 19 kJ·mol^{-1} more negative than in the other two compounds. The heteroatoms sulfur (in thiophene), oxygen (in furan) and nitrogen (in pyrrole) bear one delocalized lone electron pair, which is found in a p orbital, contributing to the aromatic sextet. However, for furan and thiophene, there is a second lone electron pair, which is placed into one sp^2 hybrid orbital, in the plane of the ring, and does not contribute to the delocalization. Thus, the lower stabilization due to the insertion of a -COOH group into the thiophene and furan rings, when compared with pyrrole, can be also assigned to a probable repulsion between the sp^2 lone electron pair and the adjacent acid group, producing a destabilizing effect. Pyrrole, in contrast to thiophene and furan, has a hydrogen attached to the nitrogen,

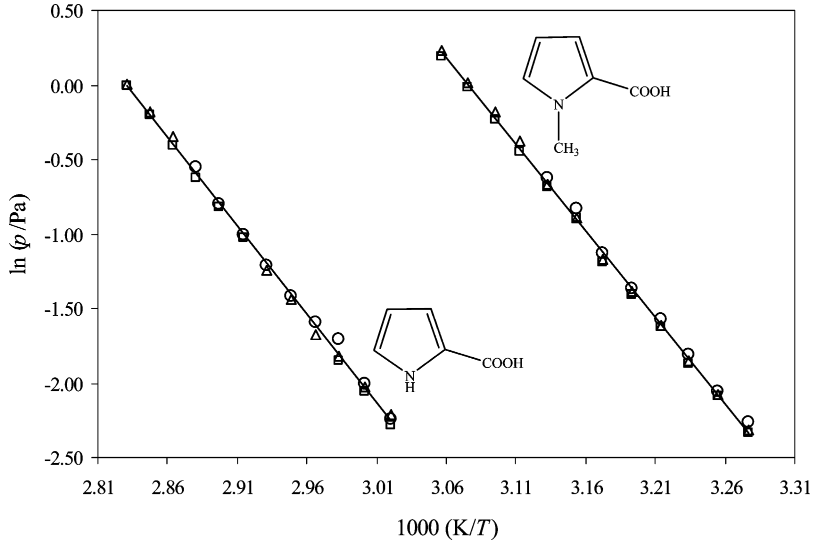

Figure 2. Plots of ln(p/Pa) against 1/T for 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid: ○, small holes; △, medium holes; □, large holes.

TABLE 6: Calculated (p,T) Values from the Vapor Pressure Equations for the Compounds Studied

	T/K									
	p/Pa = 0.1	p/Pa = 0.2	p/Pa = 0.3	p/Pa = 0.4	p/Pa = 0.5	p/Pa = 0.6	p/Pa = 0.7	p/Pa = 0.8	p/Pa = 0.9	p/Pa = 1.0
2-pyrrolecarboxylic acid	330.8	337.3	341.2	344.1	346.3	348.2	349.7	351.1	352.4	353.5
1-methyl-2-pyrrolecarboxylic acid	305.3	311.0	314.5	317.0	319.0	320.6	322.0	323.2	324.3	325.3

TABLE 7: Values of the Standard (p° = 0.1 MPa) Molar Enthalpies, $\Delta_{cr}^{g}H_m^\circ$, Entropies, $\Delta_{cr}^{g}S_m^\circ$, and Gibbs Energies $\Delta_{cr}^{g}G_m^\circ$, of Sublimation, at T = 298.15 K, for the Compounds Studied

compound	$\Delta_{cr}^{g}H_m^\circ$/ (kJ·mol^{-1})	$\Delta_{cr}^{g}S_m^\circ$/ (J·K^{-1}·mol^{-1})	$\Delta_{cr}^{g}G_m^\circ$/ (kJ·mol^{-1})
2-pyrrolecarboxylic acid	100.8 ± 0.9	190.1 ± 2.6	44.1 ± 1.2
1-methyl-2-pyrrolecarboxylic acid	96.2 ± 0.7	200.2 ± 2.2	36.5 ± 1.0

TABLE 8: Standard (p° = 0.1 MPa) Molar Enthalpies of Formation, in Both Crystalline and Gaseous Phases, and Standard Molar Enthalpies of Sublimation, at T = 298.15 K

compound	$-\Delta_fH_m^\circ$(cr)/ (kJ·mol^{-1})	$\Delta_{cr}^{g}H_m^\circ$)/ (kJ·mol^{-1})	$-\Delta_fH_m^\circ$(g)/ (kJ·mol^{-1})
2-pyrrolecarboxylic acid	387.1 ± 1.5	100.8 ± 0.9	286.3 ± 1.7
1-methyl-2-pyrrolecarboxylic acid	387.8 ± 1.5	96.2 ± 0.7	291.6 ± 1.7

instead of a second lone electron pair, and this effect does not occur. This leads us to conclude that the higher stabilization in pyrrole due to the introduction of a -COOH group in the 2-position of the ring, with respect to thiophene and furan, can be partly ascribed by the stabilizing intramolecular N−H···O bond and also by the absence of the destabilizing effect referred to above.

The introduction of a methyl group both in pyrrole and in 2-pyrrolecarboxylic acid produces exactly the same stabilizing effects, as it is shown in Figure 5. In both compounds, the entrance of this group slightly stabilizes the rings, by ≈5 kJ·mol^{-1}, since the methyl group is an inductive electronic density donor.

To estimate the enthalpies of formation of the two pyrrolecarboxylic acids studied experimentally, the G3(MP2)//B3LYP approach and the MP2 method with the 6-311+G(2d,2p) basis set have been used. For 2-pyrrolecarboxylic acid, five different working reactions were considered. Two other equations were used to estimate the enthalpies of formation of 1-methyl-2-pyrrolecarboxylic acid. For both compounds, the reaction of atomization was also applied. The results are reported in Table 9. The calculated enthalpies of reactions 1−9 have been combined with the experimental standard gas-phase enthalpies of formation of the species considered in these reactions: thiophene, 2-thiophenecarboxylic acid, pyrrole, furan, and 2-furancarboxylic acid (data already cited above); benzene, 82.6 ± 0.7 kJ·mol^{-1};[45] benzoic acid, −294.0 ± 2.2 kJ·mol^{-1};[45] methane, −74.4 ± 0.4 kJ·mol^{-1};[45] acetic acid, −432.8 ± 2.5 kJ·mol^{-1};[45] ethane, −83.8 ± 0.3 kJ·mol^{-1};[45] 2-methylpyrrole, 74.91 kJ·mol^{-1};[48] ammonia, −45.90 kJ·mol^{-1};[30] 2-pyrrolecarboxylic acid, −286.3 ± 1.7 kJ·mol^{-1} (determined experimentally in this work); methylamine, −23.4 ± 1.0 kJ·mol^{-1};[45] 1-methylpyrrole, 103.1 ± 0.5 kJ·mol^{-1};[45] and the atoms considered in the atomization reactions (eqs 6 and 9), already presented in section 3, allowing the estimation of the enthalpies of formation of 2-pyrrolecarboxylic acid (eqs 1−6) and 1-methyl-2-pyrrolecarboxylic acid (eqs 7−9).

The theoretical results obtained are in very good agreement with the experimental derived gas-phase enthalpies of formation. For 2-pyrrolecarboxylic acid, the maximum deviations from the experimental results are 3.8 and 10.1 kJ·mol^{-1} for the G3(MP2)//B3LYP and MP2 approaches, respectively. However, for the MP2/6-311+G(2d,2p) method, the other reactions provide better results. For 1-methyl-2-pyrrolecarboxylic acid, the maximum deviations from the experimental results are 3.0 and 8.2 kJ·mol^{-1} for G3(MP2)//B3LYP and MP2 approaches, respectively. Comparison of the calculated $\Delta_fH_m^\circ$(g) values, both at G3(MP2)//B3LYP and MP2 level with the experimental ones, shows that the values obtained with G3(MP2)//B3LYP level are closer to the experimental ones. The estimates based on

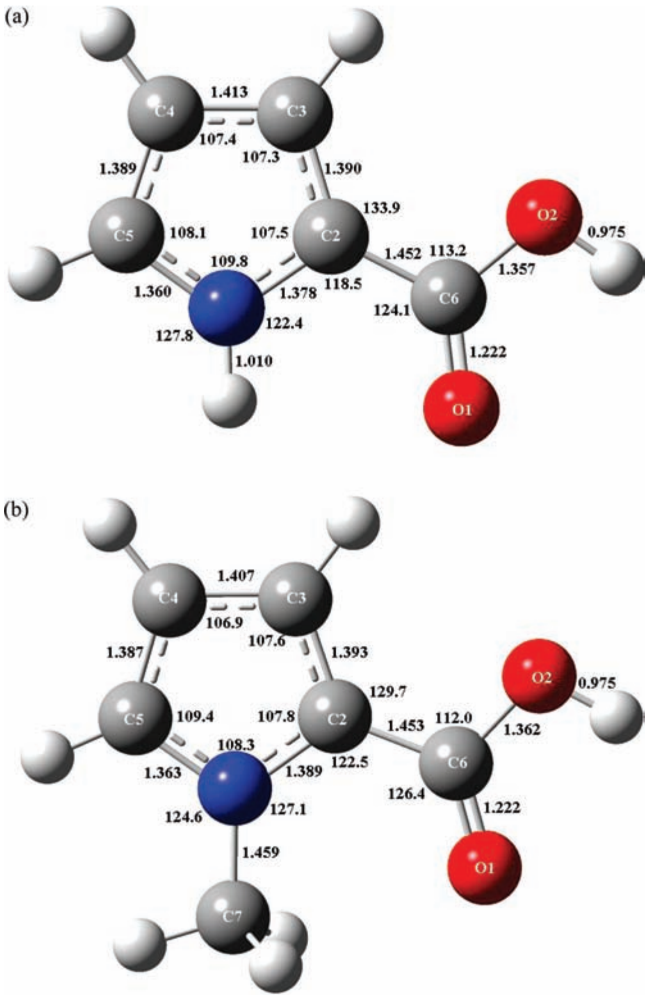

Figure 3. Optimized most stable configurations for the 2-pyrrolecarboxylic acid (syn) (a) and 1-methyl-2-pyrrolecarboxylic acid (syn) (b). Distances are in angstroms and angles in degrees.

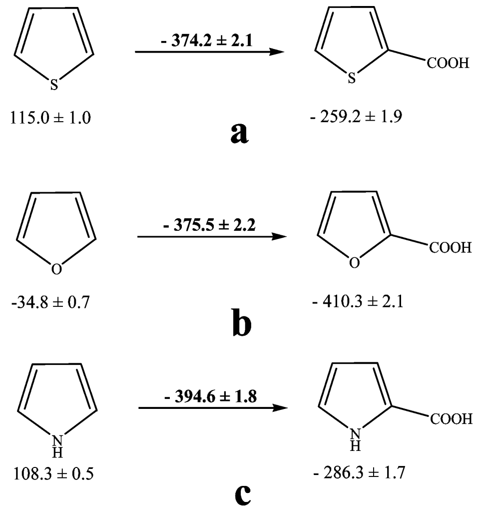

Figure 4. Enthalpic increments ($kJ\cdot mol^{-1}$) of the introduction of a -COOH group in the 2-position of (a) thiophene, (b) furan, and (c) pyrrole.

G3(MP2)//B3LYP enthalpies, together with working reactions 2, 5, and 6 for 2-pyrrolecarboxylic acid and reactions 7 and 8 for 1-methyl-2-pyrrolecarboxylic acid almost match the experimental results presented here, with deviations smaller than the uncertainty intervals associated with the experimental values. It is important to point out that the calculated $\Delta_f H_m^\circ(g)$ values of 2-pyrrolecarboxylic acid strongly support the experimental result obtained in this work; thus, this experimental value was used to estimate the $\Delta_f H_m^\circ(g)$ of 1-methyl-2-pyrrolecarboxylic acid in reaction 7, with a high degree of confidence, and the calculated value only differs by 0.8 $kJ\cdot mol^{-1}$ from the experimental one.

The computed G3(MP2)//B3LYP and MP2/6-311+G(2d,2p) enthalpies for the compounds studied, auxiliary molecules and atoms used in the working reactions are listed in Table S5 in the Supporting Information.

4.4. Other Gas-Phase Thermodynamic Properties. The G3(MP2)//B3LYP calculations have also been extended to the determination of other thermodynamic properties of the title compounds, namely, N−H (for 2-pyrrolecarboxylic acid) and NCH_2−H (for 1-methyl-2-pyrrolecarboxylic acid) bond dissociation enthalpies (BDE), gas-phase acidities, $\Delta G_{acidity}$ (N−H and -COOH deprotonations), and basicities ($\Delta G_{basicity}$), proton (PA) and electron affinities (EA), and adiabatic ionization enthalpies (IE).

The validity of the G3(MP2)//B3LYP approach for the determination of these thermodynamic properties was tested, in a previous work, for pyrrole, and the values obtained compare very well with the experimental or calculated data found in the literature.[16] Therefore, one expects that this theoretical method would be also a good choice for the calculation of the thermodynamic properties of other substituted pyrroles. The calculated values for the two pyrrolecarboxylic acids studied are presented in Table 10. Here, are also presented the values of those thermodynamic properties, cited above, for pyrrole, determined in a previous work, for comparison purposes.[16]

Thermodynamic data for these two compounds are scarce in the literature; only the $\Delta G_{acidity}$ values (possible deprotonations sites, N−H and -COOH groups) for 2-pyrrolecarboxylic acid, determined by Notario and collaborators, through ab initio molecular orbital theory and DFT calculations performed at several levels of theory were found.[49] The calculated acidity of 2-pyrrolecarboxylic acid, when the deprotonation takes place at the -COOH group, obtained in this work (1391.6 $kJ\cdot mol^{-1}$) is in excellent agreement with $\Delta G_{acidity}$ values computed by Notario et al.,[49] (average value ≈ 1392 $kJ\cdot mol^{-1}$) and with an experimental value reported in that work (1391.6 $kJ\cdot mol^{-1}$). $\Delta G_{acidity}$ of 2-pyrrolecarboxylic acid when the deprotonation takes place at the N−H group is very close to that computed for 2-acetylpyrrole (ca. 1420 $kJ\cdot mol^{-1}$),[16] although our calculated value indicates that the deprotonation of 2-pyrrolecarboxylic acid at the N−H group ($\Delta G_{acidity} = 1422.7\ kJ\cdot mol^{-1}$) would be more difficult than predicted by Notario et al.,[49] ($\Delta G_{acidity} \approx 1392\ kJ\cdot mol^{-1}$) by means of several theoretical methods. By comparing the $\Delta G_{acidity}$ values obtained for the possible deprotonation sites of 2-pyrrolecarboxylic acid, the data reported in Table 10 indicate that the -COOH deprotonation is clearly favored relative to N−H deprotonation, by 31.1 $kJ\cdot mol^{-1}$, showing that this compound behaves as a carboxylic acid (loss of proton from the -COOH group) in the gas phase. Notario et al. suggested that this acid is also deprotonated at -COOH group, but that the difference between the two deprotonation sites is very small (ca. 3 $kJ\cdot mol^{-1}$); the -COOH and N−H deprotonated structures have a similar stability, and it is expected that a prototropic equilibrium between the two possible deprotonation structures is established. It was also shown that, in solution, 2-pyrrolecarboxylic acid behaves as OH acid. For 2-indolecarboxylic acid, the -COOH deprotonation is also favored relative to the N−H deprotonation by ca. 13.8 $kJ\cdot mol^{-1}$.[49]

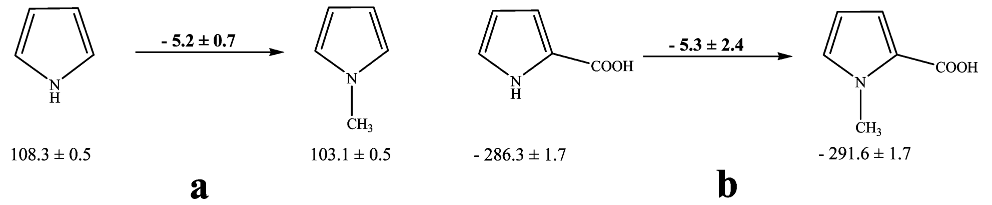

Figure 5. Enthalpic increments (kJ·mol^{-1}) of the introduction of a -CH$_3$ group in the N-position of (a) pyrrole and (b) 2-pyrrolecarboxylic acid.

TABLE 9: Comparison between the Experimental and Computed G3(MP2)//B3LYP and MP2/6311+G(2d,2p) Gas-Phase Enthalpies of Formation of 2-Pyrrolecarboxylic Acid and 1-Methyl-2-pyrrolecarboxylic Acid, at *T* = 298.15 K[a]

	$-\Delta_f H_m^\circ(g)/(kJ \cdot mol^{-1})$		
Reaction/compound[b]	G3(MP2)//B3LYP	MP2/ 6-311+G(2d,2p)	expt
(1) $2PyrCOOH + Tph \rightarrow 2TphCOOH + Pyr$	282.5 (−3.8)	282.2 (−4.1)	286.3 ± 1.7
(2) $2PyrCOOH + Fur \rightarrow 2FurCOOH + Pyr$	287.4 (1.1)	288.3 (2.0)	
(3) $2PyrCOOH + Bz \rightarrow BzCOOH + Pyr$	283.2 (−3.1)	285.6 (−0.7)	
(4) $2PyrCOOH + CH_4 \rightarrow Pyr + CH_3COOH$	289.0 (2.7)	296.4 (10.1)	
(5) $2PyrCOOH + C_2H_6 \rightarrow 2MePyr + CH_3COOH$	287.5 (1.2)	291.3 (5.0)	
(6) $2PyrCOOH \rightarrow 5C + 5H + N + 2O$	285.0 (1.3)	---	
(7) $1MePyrCOOH + NH_3 \rightarrow 2PyrCOOH + CH_3NH_2$	292.4 (0.8)	298.7 (7.1)	291.6 ± 1.7
(8) $1MePyrCOOH + CH_4 \rightarrow 1MePyr + CH_3COOH$	292.3 (0.7)	299.8 (8.2)	
(9) $1MePyrCOOH \rightarrow 6C + 7H + N + 2O$	288.6 (−3.0)	---	

[a] Enthalpic differences between the experimental and computed values are given in parentheses. All values are in kilojoules per mole. [b] 2PyrCOOH = 2-pyrrolecarboxylic acid, 2TphCOOH = 2-thiophenecarboxylic acid, 2FurCOOH = 2-furancarboxylic acid, BzCOOH = benzoic acid, 1Me2PyrCOOH = 1-methyl-2-pyrrolecarboxylic acid, 1MePyr = 1-methylpyrrole, 2MePyr = 2-methylpyrrole, Pyr = pyrrole, Tph = thiophene, Fur = furan, and Bz = benzene.

TABLE 10: G3(MP2)//B3LYP Computed X−H Bond Dissociation Enthalpies (BDE), Gas-Phase Acidities ($\Delta G_{acidity}$) and Basicities ($\Delta G_{basicity}$), Proton (PA) and Electron Affinities (EA), and Adiabatic Ionization Enthalpies (IE), at *T* = 298.15 K, for Pyrrole,[16] 2-Pyrrolecarboxylic Acid, and 1-Methyl-2-pyrrolecarboxylic Acid[a]

		$\Delta G_{acidity}$					
compound	X−H BDE [b]	N−H deprotonation	-COOH deprotonation	$\Delta G_{basicity}$	PA	EA	IE
pyrrole	398.1[16]	1470.0[16]	–	841.1[16]	872.9 (C2)[16]	−184.3[16]	798.5[16]
2-pyrrolecarboxylic acid	421.6	1422.7	1391.6	813.2	844.2 (O1)	−41.7	833.0
		1391.2[c]	1394.5[c]				
		1393.7[d]	1390.3[d]				
		1391.6[e]	1392.0[e]				
		1391.6[f]	1391.6[f]				
			1391.6[g]				
1-methyl-2-pyrrolecarboxylic acid	396.7	–	1403.1	826.2	857.8 (O1)	−38.2	811.8

[a] All values are in kilojoules per mole. [b] X = N for pyrrole and 2-pyrrolecarboxylic acid; X = NCH$_2$ (C7, according to Figure 3) for 1-methyl-2-pyrrolecarboxylic acid. [c] Value obtained by B3LYP/6-31+G(d).[49] [d] Value obtained by HF/6-31+G(d).[49] [e] Value obtained by MP2/6-31+G(d)//HF/6-31+G(d).[49] [f] Value obtained by MP2/6-31+G(d).[49] [g] Experimental value cited in ref 49.

With regard to 1-methyl-2-pyrrolecarboxylic acid it is more difficult to remove a proton than in 2-pyrrolecarboxylic acid ($\Delta G_{acidity}$ = 1403.1 kJ·mol^{-1} vs 1391.6 kJ·mol^{-1}, respectively). The introduction of a methyl group in the N-position of 2-pyrrolecarboxylic acid decreases its acidic character by 11.5 kJ·mol^{-1}. The same behavior occurs in 3-indolecarboxylic acid; it is much easier to deprotonate this acid than its *N*-methyl derivative.[49]

The computed N−H BDE for 2-pyrrolecarboxylic acid is 23.5 kJ·mol^{-1} larger than for pyrrole. A higher enthalpy is required for N−H bond scission, which supports the interaction between the -COOH group and the N−H group from the pyrrole ring referred above. This was also noticed for 2-acetylpyrrole.[16] The NCH_2−H bond dissociation enthalpy for 1-methyl-2-pyrrolecarboxylic acid is compared with the C−H BDE of methylamine. Computationally, Wayner et al.,[50] using G2(MP2) method, obtained C−H BDEs for methylamine of 388 and Leroy et al.[51] using ab initio (MP4=STDQ 6-31+G**2df//MP2/6-31G**) obtained 391.6 kJ·mol^{-1}; Burkey et al.[52] reported an experimental value of 393.3 kJ·mol^{-1}. Our theoretical result, 396.7 kJ·mol^{-1}, is in good agreement with the previously reported results for methylamine.

Both title pyrrolecarboxylic acids protonate preferentially on the carbonyl oxygen atom (O1), which was already observed for 2-acetylpyrrole (the preferred protonation site is in the oxygen of the acetyl group).[16] For 2-nitropyrrole (the preferred protonation site is in the oxygen of the nitro group).[53] For the two 2-pyrrolecarboxylic acids studied, as well as for pyrrole and 2-acetyl- and 2-nitropyrroles, the N atom is the least favorable protonation site. When a -COOH group is introduced in the 2-position of the pyrrole ring, the proton affinity decreases by 28.7 kJ·mol^{-1}. However, the introduction of a methyl group into the N-position of 2-pyrrolecarboxylic acid increases the proton affinity by 13.6 kJ·mol^{-1}. The computed values also show that O1-protonation is easier for 1-methyl-2-pyrrolecarboxylic acid than for the 2-pyrrolecarboxylic acid. All the computed proton affinity values of each protonation site of the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid are reported in Table S6, in the Supporting Information.

As it can be seen in Table 10, the addition of an electron to the pyrrole ring is much more unfavorable than when an electron is added to 2-pyrrolecarboxylic acid or 1-methyl-2-pyrrolecarboxylic acid. The same behavior has been already verified for 2-acetylpyrrole, relative to pyrrole; in this acetyl derivative, the electron affinity is higher than in the 2-pyrrolecarboxylic acid (EA = −16.6 kJ·mol^{-1} vs −41.7 kJ·mol^{-1}, respectively). The capacity of a compound to act as electron-donor species is measured through the ionization enthalpy. The energy required to remove an electron from 2-pyrrolecarboxylic acid is found to be 21.2, 34.5, and 14.3 kJ·mol^{-1} higher than that obtained for 1-methyl-2-pyrrolecarboxylic acid, pyrrole, and 2-acetylpyrrole, repectively.[16]

5. Conclusions

In the present work, the combination of an experimental and computational study, together with data available in the literature, allowed the determination of the gas-phase standard molar enthalpies of formation, at $T = 298.15$ K, of 2-pyrrolecarboxylic acid and its *N*-methyl- derivative.

Static bomb combustion experiments and Knudsen effusion experiments have been performed, and the standard molar enthalpies of formation, in the crystalline phase, and the standard molar enthalpies of sublimation, have been derived, at $T = 298.15$ K, respectively. Combining these two values, the experimental standard molar enthalpies of formation, in the gas phase, at $T = 298.15$ K, have been obtained.

G3(MP2)//B3LYP and MP2 approaches have been also used to estimate the gas-phase enthalpies of formation of the title compounds, at $T = 298.15$ K. It was found that both methods yielded results which are in excellent agreement with experimental data, although the values obtained with the G3(MP2)//B3LYP composite approach are closer to the experimental ones. This composite method has also been applied to determine the molecular structures and the structural parameters of the two compounds studied. For 2-pyrrolecarboxylic acid, it was found, computationally, the formation of a N−H···O bond similarly to that previously observed for 2-acetylpyrrole.[16] The G3(MP2)//B3LYP calculations have been extended to calculate other gas-phase thermodynamic parameters of the two 2-pyrrolecarboxylic acid derivatives, namely, N−H bond dissociation enthalpies, gas-phase acidities and basicities, proton and electron affinities, and adiabatic ionization enthalpies. For these two acids, no results were found in the literature to compare with the ones obtained in this work, except for the $\Delta G_{\text{acidity}}$ of 2-pyrrolecarboxylic acid. Since the computed results obtained for pyrrole, with this approach, are in very good agreement with the available experimental and computational data found in the literature,[16] we believe it is possible to trust that the computed thermodynamic properties that appear in Table 10, for the two title acids, are accurate enough to be used in future compilations.

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Supporting Information Available: Detailed data of the effusion orifices (diameter and Clausing factors) of the Knudsen effusion apparatus, the data and the details of all the combustion calorimetry experiments for the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, comparison of selected experimental and calculated structural parameters for 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, G3(MP2)//B3LYP and MP2 enthalpies (energies plus thermal corrections for $T = 298.15$ K) for the 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid, for the auxiliary molecules, and for the atoms used in the several working reactions, and G3(MP2)//B3LYP computed proton affinities, PA, at $T = 298.15$ K for 2-pyrrolecarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid.This material is available free of charge via the Internet at http://pubs.acs.org.

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