

Thermochemical and Theoretical Studies of Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,3-, Pyridine-2,5-, and Pyridine-2,6-dicarboxylic Acids

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The standard ($p^\circ = 0.1$ MPa) molar enthalpies of formation for gaseous pyridine-2,5-dicarboxylic acid, pyridine-2,6-dicarboxylic acid, and dimethylpyridine-2,6-dicarboxylate were derived from the standard molar enthalpies of combustion, in oxygen, at $T = 298.15$ K, measured by static bomb combustion calorimetry, and the standard molar enthalpies of sublimation, at 298.15 K, measured by Calvet microcalorimetry: pyridine-2,5-dicarboxylic acid, $-(580.6 \pm 5.0)$ kJ·mol⁻¹; pyridine-2,6-dicarboxylic acid, $-(608.0 \pm 6.1)$ kJ·mol⁻¹; dimethylpyridine-2,6-dicarboxylate, $-(562.4 \pm 4.2)$ kJ·mol⁻¹. The enthalpy of formation for crystalline pyridine-2,3-dicarboxylic acid was also derived from combustion calorimetry measurements as $-(733.1 \pm 2.0)$ kJ·mol⁻¹. In addition, theoretical calculations using the density functional theory and the B3LYP/6-311G** hybrid exchange-correlation energy functional have been performed for these molecules in order to obtain the most stable geometries and to access their relative stabilities. The good correlation obtained between experimental and theoretical results allowed the estimation of the enthalpy of sublimation for pyridine-2,3-dicarboxylic acid.

Introduction

The study of the thermochemical parameters of heterocyclic molecules, namely, pyridines,^{1,2} bipyridines,³ quinolines,⁴ diazines,⁵ and benzodiazines,⁶ has been a continuing interest in our laboratory. Besides, we have been looking for the energetic effect on the dissociation enthalpy of the (N–O) bond due to substituents on the ring of the nitrogen heterocycle *N*-oxides.⁷ It is our aim to enlarge the thermochemical data basis of these kinds of compounds as well as to provide credible correlations between structure and energetics in order to predict the thermochemical parameters for other compounds whose experimental study is impossible due to limitations of time to study the vast number of new compounds and/or to the impossibility to obtain pure samples of the compounds in the needed quantity.

In the present work, we report the standard molar enthalpies of formation of crystalline pyridine-2,3-dicarboxylic acid, pyridine-2,5-dicarboxylic acid, pyridine-2,6-dicarboxylic acid, and dimethylpyridine-2,6-dicarboxylate, which were obtained from measurements of the combustion energies of the crystalline species using a static bomb calorimeter. We report also the values of the enthalpies of sublimation of pyridine-2,5- and pyridine-2,6-dicarboxylic acids and dimethylpyridine-2,6-dicarboxylate, measured by Calvet microcalorimetry; these experimental

results together with those obtained from combustion calorimetry allow the calculation of the values for the gaseous standard molar enthalpies of formation for the corresponding compounds. In addition, theoretical calculations using the density functional theory and the B3LYP/6-311G** hybrid exchange-correlation energy functional have been performed for these molecules in order to obtain the most stable geometries and to access their relative stabilities.

Experimental Section

Materials. The crystalline dimethyl-2,6-pyridinedicarboxylate [5453-67-8], 2,6-Py(COOMe)₂, was purchased from Aldrich Chemical Co. and was purified by repeated vacuum sublimation.

The sample pyridine-2,3-dicarboxylic acid [89-00-9], 2,3-Py(COOH)₂, was purchased from Aldrich Chemical Co., >99.7%, and it was used without any treatment, as it suffers decomposition upon heating.

The pyridine-2,5-dicarboxylic acid [100-26-5], 2,5-Py(COOH)₂, was prepared by potassium permanganate oxidation of 5-acetyl-2-methylpyridine, as described by Binns et al.⁸ The sample was further purified by three crystallizations from water. The melting point of the purified sample was within 1 K of the published literature value. From elemental analysis, it was found for mass fractions: C, 0.5022; H, 0.0309; N, 0.0831, while the calculated values are C, 0.5031; H, 0.0302; N, 0.0838. The sample was submitted to further purification by repeated vacuum sublimation.

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Pyridine-2,6-dicarboxylic acid [499-83-2], 2,6-Py(COOH)₂, was a sample purchased from Aldrich Chemical Co. and purified by three crystallizations from water and repeated vacuum sublimation.

The purity of the compounds was assessed by differential scanning calorimetry (DSC) and confirmed by the average ratios of the mass of carbon dioxide recovered after combustion to that calculated from the mass of sample. For the studied compounds, the obtained ratios were the following: 2,6-Py(COOMe)₂, (1.0005 ± 0.0006); 2,3-Py(COOH)₂, (1.0003 ± 0.0008); 2,5-Py(COOH)₂, (0.9982 ± 0.0005); and 2,6-Py(COOH)₂, (0.9997 ± 0.0007), where the uncertainties are the standard deviation of the mean.

Calorimetric Measurements. The combustion experiments for 2,6-Py(COOMe)₂ and 2,6-Py(COOH)₂ were performed with a static bomb calorimeter (twin valve bomb, type 1108, Parr Instrument Company); the apparatus and technique have been described.^{9,10} Benzoic acid (Bureau of Analysed Samples, Thermochemical Standard, BCS-CRM-190n) was used for calibration of the bomb. Its massic energy of combustion is $-(26\,432.3 \pm 3.8) \text{ J}\cdot\text{g}^{-1}$, under certificate conditions. The calibration results were corrected to give the energy equivalent $\epsilon(\text{calor})$ corresponding to the average mass of water added to the calorimeter: 3119.6 g . From six calibration experiments, $\epsilon(\text{calor}) = (16\,007.3 \pm 0.7) \text{ J}\cdot\text{K}^{-1}$, where the uncertainty quoted is the standard deviation of the mean. For all experiments, ignition was made at $T = (298.150 \pm 0.001) \text{ K}$. Combustion experiments were performed in oxygen at $p = 3.04 \text{ MPa}$, with 1.00 cm^3 of water added to the bomb. The electrical energy for ignition was determined from the change in potential difference across a capacitor when discharged through the platinum ignition wire. For the cotton-thread fuse, empirical formula $\text{CH}_{1.686}\text{O}_{0.843}$, $\Delta_c u^\circ = -16\,250 \text{ J}\cdot\text{g}^{-1}$.¹¹ The corrections for nitric acid formation were based on $-59.7 \text{ kJ}\cdot\text{mol}^{-1}$,¹² for a molar energy of formation of $0.1 \text{ mol}\cdot\text{dm}^{-3} \text{ HNO}_3(\text{aq})$ from N_2 , O_2 , and $\text{H}_2\text{O}(\text{l})$.

The measurements for the energy of combustion of pyridine-2,3-dicarboxylic acid were also performed in the static combustion equipment previously described; however, a different twin valve bomb (Parr Instrument Company type, 1105) was used. From 10 calibration experiments with benzoic acid (BDH Thermochemical Standard, batch 693976/01, having a massic energy of combustion under standard bomb conditions of $-(26\,435.1 \pm 3.5) \text{ J}\cdot\text{g}^{-1}$), the energy equivalent of the calorimeter, $\epsilon(\text{calor}) = (15\,908.7 \pm 1.3) \text{ J}\cdot\text{K}^{-1}$, was determined. To have a complete reaction, *n*-hexadecane [$\Delta_c u^\circ = -(47\,161.9 \pm 3.2) \text{ J}\cdot\text{g}^{-1}$] was used as an auxiliary in the combustion experiments.

The energy of combustion of pyridine-2,5-dicarboxylic acid was also determined with an isoperibol static bomb calorimeter, with a twin valve bomb of internal volume of 0.290 dm^3 , that has been used formerly at the National Physical Laboratory, Teddington,¹³ and in Manchester.¹⁴ This calorimeter has been transferred from Manchester to Porto and was used mainly as previously described but with a few changes in technique because of the different auxiliary equipment used.¹⁵ The electrical energy for ignition was determined from the change in potential across a $1400 \mu\text{F}$ condenser on discharge through the platinum ignition wire. The calorimeter temperature was measured to $\pm 10^{-4} \text{ K}$ with an S10 four-wire calibrated ultrastable thermistor probe (Thermometrics, standard serial no. 1030) and recorded by a high sensitivity nanovolt/microohm meter (Agilent 34420 A) interfaced to a micro-computer programmed to compute the adiabatic temperature change. The calorimetric system was calibrated using

benzoic acid (BDH Thermochemical Standard, batch 693976/01) having a massic energy of combustion under standard bomb conditions of $-(26\,435.1 \pm 3.5) \text{ J}\cdot\text{g}^{-1}$. The calibration results were corrected to give the energy equivalent $\epsilon(\text{calor})$ corresponding to an average mass of water added to the calorimeter of 2900.0 g . One set of seven calibration experiments was made in oxygen at $p = 3.04 \text{ MPa}$, with 1.00 cm^3 of water added to the bomb, leading to an energy equivalent of the calorimeter of $\epsilon(\text{calor}) = (15\,551.6 \pm 2.6) \text{ J}\cdot\text{K}^{-1}$, where the uncertainty quoted is the standard deviation of the mean. As it was very difficult to purify pyridine-2,5-dicarboxylic acid and the amount of sample available was small, *n*-hexadecane, $\Delta_c u^\circ = -(47\,164.3 \pm 3.6) \text{ J}\cdot\text{g}^{-1}$, was used as an auxiliary in the combustion experiments, to get an appropriate temperature change.

The amount of substance used in each experiment was determined from the total mass of carbon dioxide produced after allowance for that formed from the cotton-thread fuse and auxiliary of combustion. The densities at $T = 298.15 \text{ K}$ for the compounds were estimated: dimethylpyridine-2,6-dicarboxylate, $\rho = 1.2$; pyridine-2,6-dicarboxylic acid, $\rho = 0.94$ (taken as similar to the pyridine-2,4-dicarboxylic acid density¹⁶); pyridine-2,5-dicarboxylic acid, $\rho = 1.0$; and pyridine-2,3-dicarboxylic acid, $\rho = 1.2$. An estimated pressure coefficient of massic energy of $(\partial u/\partial p)_T = -0.2 \text{ J}\cdot\text{g}^{-1}\cdot\text{MPa}^{-1}$ at $T = 298.15 \text{ K}$, a typical value for most organic compounds, was assumed. For each compound, the massic energy of combustion $\Delta_c u^\circ$ was calculated by the procedure given by Hubbard et al.¹⁷

The standard molar enthalpies of sublimation for pyridine-2,5- and pyridine-2,6-dicarboxylic acids and dimethylpyridine-2,6-dicarboxylate were measured by Calvet microcalorimetry, using the "vacuum sublimation" drop method,¹⁸ on a SETARAM HT 1000 apparatus. From the observed enthalpies of sublimation, the standard molar enthalpies of sublimation, at $T = 298.15 \text{ K}$, were calculated using $\Delta_{298.15 \text{ K}}^T H_m^\circ$ estimated by a group method based on the values of Stull et al.¹⁹

The microcalorimeter was calibrated *in situ* for these measurements by making use of the reported molar enthalpy of sublimation, at $T = 298.15 \text{ K}$, of naphthalene, C_{10}H_8 : $(72.51 \pm 0.01) \text{ kJ}\cdot\text{mol}^{-1}$.²⁰

It has been impossible to select a convenient temperature to measure the enthalpy of sublimation of pyridine-2,3-dicarboxylic acid, since the compound decomposes upon heating, as is described in the literature.^{21,22}

Results

Table 1 lists the results for a typical combustion experiment on each compound; $\Delta m(\text{H}_2\text{O})$ is the deviation of the mass of water added to the calorimeter from 3119.6 g or 2900.0 g , with the mass assigned for $\epsilon(\text{calor})$ depending of the apparatus used, ΔU_Σ is the correction to the standard state, and the remaining terms are as previously described.¹⁷ As samples were ignited at $T = 298.15 \text{ K}$, $\Delta U(\text{I.B.P.}) = -\{\epsilon(\text{calor}) + c_p(\text{H}_2\text{O}, \text{l})\Delta m(\text{H}_2\text{O}) + \epsilon_{\text{f}}\Delta T_{\text{ad}} + \Delta U(\text{ign})\}$, where ΔT_{ad} is the calorimeter temperature change corrected for heat exchange and the work of stirring. The individual values of $-\Delta_c u^\circ$, together with the mean and its standard deviation, are given in Table 2. Table 3 lists the derived standard molar energies and enthalpies of combustion and the standard molar enthalpies of formation for the compounds in the condensed state, at $T = 298.15 \text{ K}$. In accordance with normal thermochemical practice, the uncertainties assigned to the standard molar enthalpies of combustion and formation are twice the overall standard deviation of the mean and include the

Table 1. Typical Combustion Experiments for Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,3-, Pyridine-2,5-, and Pyridine-2,6-dicarboxylic Acids at $T = 298.15$ K^a

	2,6-Py(COOMe) ₂	2,3-Py(COOH) ₂	2,5-Py(COOH) ₂	2,6-Py(COOH) ₂
$m(\text{CO}_2)/\text{g}$	1.888 52	1.702 58	1.676 55	2.264 44
$m'(\text{cpd})/\text{g}$	0.928 21	0.717 30	0.522 25	1.225 81
$m''(\text{fuse})/\text{g}$	0.002 97	0.003 21	0.004 03	0.002 96
$m'''(n\text{-hexadecane})$		0.120 63	0.227 18	
$\Delta T_{\text{ad}}/\text{K}$	1.239 13	1.101 78	1.243 05	1.255 76
$\epsilon_{\text{calor}}/(\text{J}\cdot\text{K}^{-1})$	16 007.3	15 908.3	15 551.6	16 007.3
$\epsilon_{\text{f}}/(\text{J}\cdot\text{K}^{-1})$	16.28	16.10	16.22	16.19
$\Delta m(\text{H}_2\text{O})/\text{g}$	0.0	-0.1	0.0	0.0
$-\Delta U(\text{I.B.P.})/\text{J}$	19 854.71	17 544.08	19 350.43	20 120.63
$-\Delta U(\text{ign})/\text{J}$	0.59	1.20	1.21	1.03
$-\Delta U(\text{HNO}_3)/\text{J}$	33.91	29.23	25.29	40.48
$-\Delta U(n\text{-hexadecane})/\text{J}$		5689.11	10 728.07	
$-\Delta U(\text{fuse})/\text{J}$	48.23	52.13	65.45	48.07
$\Delta U_{\text{f}}/\text{J}$	17.06	15.11	12.66	24.02
$-\Delta_{\text{c}}u^\circ/(\text{J}\cdot\text{g}^{-1})$	21 283.45	16 392.62	16 311.99	16 322.32

^a $m'(\text{cpd})$ is the mass of compound burnt in the experiment; $m''(\text{fuse})$ is the mass of fuse (cotton) used in the experiment; $m'''(n\text{-hexadecane})$ is the mass of n -hexadecane burnt in the experiment; ΔT_{ad} is the corrected temperature rise; ϵ_{calor} is the energy equivalent of the calorimeter; ϵ_{f} is the energy equivalent of bomb contents in the initial state; $\Delta m(\text{H}_2\text{O})$ is the deviation of the mass of water added to the calorimeter from the mass used for calibration; $\Delta U(\text{I.B.P.})$ is the energy change for the isothermal combustion reaction under actual bomb conditions; $\Delta U(\text{I.B.P.})$ includes the ignition energy, $\Delta U(\text{ign})$; $\Delta U(\text{HNO}_3)$ is the energy correction for the nitric acid formation; $\Delta U(n\text{-hexadecane})$ is the energy of combustion of the n -hexadecane; $\Delta U(\text{fuse})$ is the energy of combustion of the fuse (cotton); ΔU_{f} is the energy correction to the standard state; and $\Delta_{\text{c}}u^\circ$ is the standard massic energy of combustion.

Table 2. Individual Values of the Massic Energy of Combustion $\Delta_{\text{c}}u^\circ$ for Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,3-, Pyridine-2,5-, and Pyridine-2,6-dicarboxylic Acids at $T = 298.15$ K

2,6-Py(COOMe) ₂	2,3-Py(COOH) ₂	2,5-Py(COOH) ₂	2,6-Py(COOH) ₂
$-\Delta_{\text{c}}u^\circ/(\text{J}\cdot\text{g}^{-1})$			
21 265.63	16 391.48	16 311.99	16 319.67
21 283.45	16 388.01	16 293.67	16 322.32
21 282.13	16 385.09	16 352.91	16 301.49
21 281.52	16 396.97	16 308.15	16 314.60
21 272.60	16 399.39	16 351.13	16 308.41
21 284.67	16 376.04		16 342.89
	16 392.62		
$-(\Delta_{\text{c}}u^\circ)^{\text{a}}/(\text{J}\cdot\text{g}^{-1})$			
21 278.3 ± 3.1	16 389.9 ± 3.2	16 323.6 ± 12.0	16 318.2 ± 5.8

^a Mean value and standard deviation of the mean.

Table 3. Derived Standard ($p^\circ = 0.1$ MPa) Molar Energies of Combustion $\Delta_{\text{c}}U_{\text{m}}^\circ$, Standard Molar Enthalpies of Combustion $\Delta_{\text{c}}H_{\text{m}}^\circ$, and Standard Molar Enthalpies of Formation $\Delta_{\text{f}}H_{\text{m}}^\circ$ for Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,3-, Pyridine-2,5-, and Pyridine-2,6-dicarboxylic Acids at $T = 298.15$ K

	$-\Delta_{\text{c}}U_{\text{m}}^\circ(\text{cr})$ kJ·mol ⁻¹	$-\Delta_{\text{c}}H_{\text{m}}^\circ(\text{cr})$ kJ·mol ⁻¹	$-\Delta_{\text{f}}H_{\text{m}}^\circ(\text{cr})$ kJ·mol ⁻¹
2,6-Py(COOMe) ₂	4152.5 ± 1.4	4151.9 ± 1.4	675.9 ± 1.8
2,3-Py(COOH) ₂	2739.1 ± 1.1	2736.0 ± 1.1	733.1 ± 1.8
2,5-Py(COOH) ₂	2728.0 ± 4.1	2724.9 ± 4.1	744.2 ± 4.2
2,6-Py(COOH) ₂	2727.1 ± 2.0	2724.0 ± 2.0	745.1 ± 2.2

uncertainties in calibration and in the auxiliary quantities used. To derive $\Delta_{\text{f}}H_{\text{m}}^\circ$ from $\Delta_{\text{c}}H_{\text{m}}^\circ$, the standard molar enthalpies of formation ($\text{H}_2\text{O}(\text{l})$, $-(285.83 \pm 0.04)$ kJ·mol⁻¹; $\text{CO}_2(\text{g})$, $-(393.51 \pm 0.13)$ kJ·mol⁻¹) were used.²³

Table 4 presents the values, determined from six experiments, for the observed enthalpies of sublimation, the estimated corrections for temperature, as well as the standard molar enthalpies of sublimation, at 298.15 K. Table 5 lists the derived standard molar enthalpies of formation for the compounds in the gaseous state, at $T = 298.15$ K.

Theoretical Calculations. The most stable conformations of all pyridinemonocarboxylic and -dicarboxylic acids and of dimethylpyridine-2,6-dicarboxylate were obtained

from density functional theory (DFT) calculations based on the Becke three-parameter hybrid exchange²⁴ and the Lee–Yang–Parr²⁵ correlation density functional (B3LYP) with Pople's split-valence 6-31G* extended basis set.^{26,27} We report in Table 6 the relevant geometrical parameters thus obtained (see Figure 1 for the atom numbering).

Harmonic vibrational frequencies were then calculated at the optimum conformations which, after being scaled by the appropriate factors of 0.9613,²⁸ were used to obtain estimates of the thermal factors, at $T = 298$ K, properly corrected for the anharmonicity.

More accurate energies were also obtained from single-point calculations using second-order Møller–Plesset perturbation theory (MP2) with the 6-31G* basis set and using density functional theory with the 6-311G** extended basis set.^{26,27,29}

The total molecular energies obtained from all calculations as well as the corresponding thermal corrections are collected in Table 7. All calculations were performed at the most stable B3LYP/6-31G* geometries using the U.K. version of GAMESS.^{30,31}

Discussion

Most Stable Conformations. The most stable conformations of the studied systems should result from a compromise between several conflicting interactions which occur involving the pyridinic aromatic ring and the π electron acceptor $-\text{COOH}$ substituents. Indeed, in the absence of other interactions, the allowance of extended π electron delocalization between the aromatic ring and the substituents leads us to expect that the mutual coplanar orientation of those fragments should contribute to stabilize the molecular systems. On the other hand, for the isomers substituted at contiguous sites (2,3- and 3,4-), sterical repulsions arise between the close substituents opposing the above stabilizing tendency, thus favoring the non-planarity of one or both substituents. It is the balancing of these opposing tendencies that should finally determine the optimum conformation. In addition, for 2- and 6-substituted isomers, there is also the possibility of the occurrence of hydrogen-bond-type interactions, $\text{O}-\text{H}\cdots\text{N}$, which further stabilize these molecules and, in pyridine-2,3- and pyridine-3,4-dicarboxylic acids, a further $\text{O}-\text{H}\cdots\text{O}$ hydro-

Table 4. Standard ($p^\circ = 0.1$ MPa) Molar Enthalpies of Sublimation $\Delta_{\text{cr}}^{\text{g},T}H_{\text{m}}^\circ$, Determined by Microcalorimetry at Various Temperatures T for Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,5- and Pyridine-2,6-pyridinedicarboxylic Acids

	no. of expts	T K	$\Delta_{\text{cr}}^{\text{g},T}H_{\text{m}}^\circ$ kJ·mol ⁻¹	$\Delta_{298.15\text{ K}}^T H_{\text{m}}^\circ$ kJ·mol ⁻¹	$\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^\circ(298.15\text{ K})$ kJ·mol ⁻¹
2,6-Py(COOMe) ₂	7	385	130.0 ± 3.8	16.5	113.5 ± 3.8
2,5-Py(COOH) ₂	6	492	194.4 ± 2.7	30.8	163.6 ± 2.7
2,6-Py(COOH) ₂	6	494	168.2 ± 5.7	31.1	137.1 ± 5.7

Table 5. Derived Standard ($p^\circ = 0.1$ MPa) Molar Enthalpies of Formation $\Delta_f H_{\text{m}}^\circ$ of Dimethylpyridine-2,6-dicarboxylate and Pyridine-2,5- and Pyridine-2,6-dicarboxylic Acids at $T = 298.15$ K

	$\Delta_f H_{\text{m}}^\circ(\text{cr})$ kJ·mol ⁻¹	$\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^\circ$ kJ·mol ⁻¹	$\Delta_f H_{\text{m}}^\circ(\text{g})$ kJ·mol ⁻¹
2,6-Py(COOMe) ₂	-675.9 ± 1.8	113.5 ± 3.8	-562.4 ± 4.2
2,5-Py(COOH) ₂	-744.2 ± 4.2	163.6 ± 2.7	-580.6 ± 5.0
2,6-Py(COOH) ₂	-745.1 ± 2.2	137.1 ± 5.7	-608.0 ± 6.1

gen-bond-type interaction between both substituents can come into play in the stabilization process. The occurrence of the last H-bond-type interaction depends crucially on the coplanarity or near coplanarity of both substituents, thus opposing the tendency resulting from the mutual steric repulsions.

The net result of all the mentioned interactions is the coplanarity between the -COOH substituents and the pyridinic ring for all the studied systems, with the exception of pyridine-3,4-dicarboxylic acid. For the 2- and 6-substituted isomers, the hydrogen atom of the ortho carboxyl group is found to be oriented *cis* relative to the nitrogen atom of the ring, thus allowing the occurrence of O-H···N hydrogen-bond-type stabilizing interactions.

In addition, a further H-bond-type stabilizing interaction, involving both -COOH substituents, is found to occur for the isomers with contiguous substituents. The occurrence of this interaction creates a second closed ring of atoms for pyridine-2,3- and pyridine-3,4-dicarboxylic acid isomers, thus qualifying itself as a resonance assisted H-bond (RAHB),^{32,33} which is one of the strongest H-bond-type interactions.^{32,33} The qualification of these O-H···O interactions as RAHBs can be supported by the observed equalization of the bond lengths in the second ring of pyridine-2,3- and pyridine-3,4-dicarboxylic acid isomers when compared with the corresponding bond lengths in the remaining isomers.

Indeed, the O-H and C=O bond lengths in pyridine-2,3-dicarboxylic acid (0.999 Å and 1.222 Å, respectively) and in pyridine-3,4-dicarboxylic acid (0.991 Å and 1.226 Å, respectively) show a substantial increase over the corresponding average values of 0.980 Å and 1.212 Å found for the remaining disubstituted isomers, while the C-O bond length (1.321 Å and 1.327 Å, respectively, for the 2,3- and 3,4-isomers) evidences a corresponding decrease over the average value (1.345 Å) of the remaining disubstituted isomers. Also, the (O)H···O distance amounts to 1.582 Å (2,3-) and 1.625 Å (3,4-) as compared to the average bond length of similar intramolecular H-bonds in the methoxyphenol isomers³⁴ (2.079 Å), while the O-O distance displays very short values of 2.574 Å and 2.591 Å for the 2,3- and 3,4-isomers. Thus, the proton involved in this interaction tends to occupy a more central and symmetric position relative to the hydrogen bond in pyridine-2,3- and pyridine-3,4-dicarboxylic acids.

In addition, more detailed insight into the nature of this O-H···O interaction can be obtained from a topological analysis of the electron density obtained from the B3LYP/6-31G* wave functions using the theory of atoms in

molecules (AIM).³⁵⁻³⁷ In this way, a bond line is found for each H-bond-type interaction, with the electron density at the corresponding bond critical point being much larger for the O-H···O interactions in pyridine-2,3- and pyridine-3,4-dicarboxylic acids (0.0616 and 0.0547 au, respectively) as compared with the corresponding values found for the similar O-H···O interactions in ortho-substituted methoxyphenols³⁴ whose average values amount to a mere 0.0214 au.

More detailed insight of the individual orbital interactions involved in the stabilization of those systems can be obtained by conducting a natural bonding orbital (NBO)³⁸⁻⁴⁰ study of the corresponding wave functions. This analysis reveals that the delocalization energy, obtained by suppression of all interactions between the filled natural bonding orbitals (NBOs) and the corresponding antibonding NBOs in the Fock matrix, is much larger by ~125–250 kJ·mol⁻¹ for pyridine-2,3-dicarboxylic acid and pyridine-3,4-dicarboxylic acid than for the remaining systems. This large increase in the delocalization energy results mainly from the interactions between the two close substituents, as can be asserted from similar calculations on the conformers with the relevant O-H bond rotated by 180° about the C-O bond (this conformation suppresses the O-H···O interaction and is called the open conformation). These calculations give delocalization energies for the pyridine-2,3-dicarboxylic and pyridine-3,4-dicarboxylic acids which are now about the same magnitude as for the remaining systems or even slightly lower, in the case of pyridine-3,4-dicarboxylic acid. Additionally, inspection of the individual orbital interactions through the second-order perturbation theory analysis of Fock matrix in the framework of the NBO method enabled us to verify that for the conformers which have the O-H···O hydrogen bond the interactions involving the lone electronic pair of the proton acceptor oxygen atom and the antibonding O-H orbital of the proton donor group assume a very important role, while such interactions have no measurable effect for the open conformers.

We can thus suppose that the occurrence of the second hydrogen-bond-type interaction in the pyridine-2,3- and pyridine-3,4-dicarboxylic acid isomers, allowing extended cyclic electron delocalization across the second ring, is the main factor which preserves their stability, which otherwise will be seriously decreased by the sterical repulsion between the close substituents. In the case of pyridine-3,

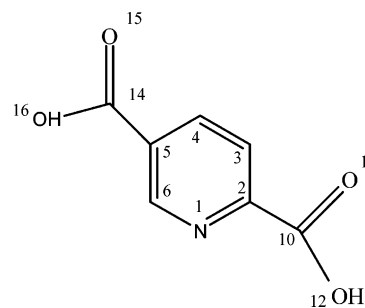
**Figure 1.** Atom numbering for pyridinedicarboxylic acids.

Table 6. Calculated B3LYP/6-31G* Bond Lengths (Å), Bond Angles (deg), and Dihedral Angles (deg) (See Figure 1 for Atom Numbering)^a

	R_{1-2}	R_{1-6}	R_{r-10}	R_{r-14}	R_{10-11}	R_{10-12}	R_{14-15}	R_{14-16}	θ_{r-r-10}	θ_{r-r-14}	$\Phi_{r-r-10-12}$	$\Phi_{r-r-14-16}$	$\Phi_{r-10-12-H}$	$\Phi_{r-14-16-H}$
Py	1.339	1.339												
2-Py(COOH)	1.342	1.336	1.511		1.210	1.342			115.6	–	0.0		0.0	
3-Py(COOH)	1.337	1.339	1.486		1.214	1.356			122.9	–	0.0		180.0	
4-Py(COOH)	1.338	1.340	1.492		1.213	1.354			123.0	–	0.0		180.0	
2,3-Py(COOH) ₂	1.348	1.329	1.522	1.540	1.222	1.323	1.215	1.321	110.2	131.2	–0.1	–0.2	0.1	0.0
2,4-Py(COOH) ₂	1.341	1.337	1.511	1.496	1.209	1.342	1.212	1.350	115.8	122.8	0.0	0.0	0.0	180.0
2,5-Py(COOH) ₂	1.343	1.334	1.512	1.489	1.209	1.341	1.213	1.353	115.6	118.7	0.0	180.0	0.0	180.0
2,6-Py(COOH) ₂	1.337	1.338	1.511	1.500	1.210	1.341	1.214	1.346	115.6	118.5	0.0	180	0.0	180.0
3,4-Py(COOH) ₂	1.331	1.338	1.487	1.539	1.226	1.344	1.213	1.327	116.4	130.8	18	–21.5	–177.5	6.8
3,5-Py(COOH) ₂	1.337	1.337	1.488	1.488	1.213	1.355	1.213	1.355	122.9	118.8	0.0	180.0	180.0	180.0
2,6-Py(COOCH ₃) ₂	1.337	1.337	1.505	1.505	1.217	1.340	1.217	1.340	118.9	117.6	0.0	180.0	180.0	180.0

^a 1, nitrogen; 2–3–4–5–6, C–C–C–C–C; 10, carbon atom of lowest numbered substituent; 14, carbon atom of highest numbered substituent; 11, oxygen atom doubly bonded to C10; 12, oxygen atom singly bonded to C10; 15, oxygen atom doubly bonded to C14; 16, oxygen atom singly bonded to C14. In angles r–r–10–12 and r–r–14–16, r symbolizes ring carbon atoms, and they appear in increasing ordering; the first r has a lower numbering and the second a higher numbering.

Table 7. Calculated Total Energies (hartrees) at the Most Stable Geometries and Thermal Corrections E_{TOT} (kJ·mol^{–1})

	MP2/6-31G*	B3LYP/6-31G*	B3LYP/6-311G**	E_{TOT}
Py	–247.482 456	–248.284 973	–248.349 817	236.233
2-Py(COOH)	–435.580 863	–436.859 380	–436.984 557	281.625
3-Py(COOH)	–435.577 332	–436.856 863	–436.981 628	281.625
4-Py(COOH)	–435.577 606	–436.855 389	–436.980 119	281.506
2,3-Py(COOH) ₂	–623.666 624	–625.424 658	–625.608 948	325.380
2,4-Py(COOH) ₂	–623.674 085	–625.427 848	–625.613 070	326.588
2,5-Py(COOH) ₂	–623.674 158	–625.429 116	–625.614 349	326.721
2,6-Py(COOH) ₂	–623.673 347	–625.427 386	–625.612 517	326.370
3,4-Py(COOH) ₂	–623.659 589	–625.416 688	–625.600 597	326.220
3,5-Py(COOH) ₂	–623.670 264	–625.426 827	–625.611 691	326.682
2,6-Py(COOCH ₃) ₂	–701.975 810	–704.036 103	–704.229 887	477.111
CH ₄	–40.332 526	–40.518 371	–40.534 248	121.891
CH ₃ CH ₃	–79.494 688	–79.830 414	–79.857 273	191.157
HCOOCH ₃	–228.396 400	–229.063 011	–229.133 662	169.829
CH ₃ COOCH ₃	–267.572 989	–268.388 482	–268.470 249	244.369
C ₆ H ₆	–231.457 732	–232.248 666	–232.311 529	266.103
C ₆ H ₅ COOH	–419.555 137	–420.822 139	–420.944 499	311.772
C ₆ H ₅ COOCH ₃	–458.709 808	–460.128 713	–460.255 656	387.364
C ₆ H ₅ OH	–306.490 935	–307.464 887	–307.555 477	279.422

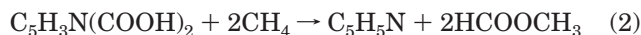
4-dicarboxylic acid, this repulsion still dominates to a large extent and the molecule adopts a conformation with the substituents, even though interacting among themselves through the cited H-bond interaction, orienting themselves out of the plane of the pyridinic ring.

Experimental X-ray diffraction studies evidence the existence of an intramolecular hydrogen bond between the adjacent carboxyl groups in the crystalline 2,3-isomer⁴¹ but not in the crystalline 3,4-isomer.⁴²

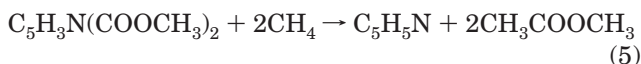
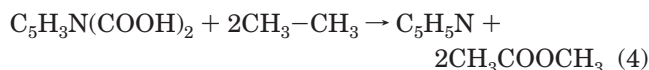
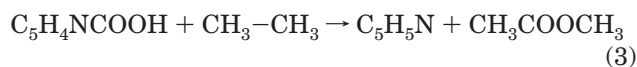
Energetic Stability. The stabilizing effect of the O–H···N and O–H···O hydrogen-bond-type interactions can be estimated as the difference in energy between the most stable conformation of each isomer and the corresponding conformation optimized with the restriction that the relevant O–H bond remains frozen at the trans orientation relative to the proton acceptor fragment. In this way, we have obtained the O–H···N bond strengths: 14.0 kJ·mol^{–1}, 11.8 kJ·mol^{–1}, 12.4 kJ·mol^{–1}, and 13.9 kJ·mol^{–1}, respectively, for pyridine-2-carboxylic acid, pyridine-2,4-dicarboxylic acid, pyridine-2,5-dicarboxylic acid, and pyridine-2,6-dicarboxylic acid. These values indicate a considerably weaker interaction than that occurring in 2-hydroxypyridine for which we have recently⁴³ estimated a value of 24.2 kJ·mol^{–1}. For pyridine-2,3-dicarboxylic acid, our estimate of 25.3 kJ·mol^{–1} indicates a much stronger interaction. On the other hand, for the O–H···O interaction in pyridine-2,3- and pyridine-3,4-dicarboxylic acids, we find the values 40.8 kJ·mol^{–1} and 29.5 kJ·mol^{–1}, respectively. These estimates support the greater importance of this hydrogen-bond-type interaction, as mentioned above. In

fact, this interaction has a strength almost comparable to the 56.9 kJ·mol^{–1} value which we have reported for the O–H···O hydrogen bond of 2-hydroxypyridine-*N*-oxide.⁴³

To study the energetic stability of these systems, we have considered several types of isodesmic reactions. The choice of the particular isodesmic reactions is of course conditioned to the existence of good experimental energetic data concerning all the auxiliary molecules involved, whose geometries and energies have also been calculated using the same methods mentioned above. The first set of reactions, denoted by I in Table 8, involves the following reactions:



and the second set (II) consists of the following reactions:



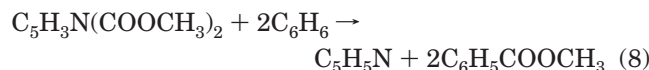
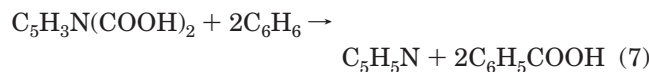
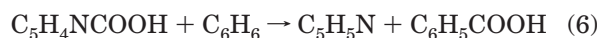
As can be seen from the results in Table 8, reaction sets I and II are very consistent in reproducing the experimen-

Table 8. Theoretical Estimates of the Standard Molar Enthalpies of Formation in the Gas Phase (kJ·mol⁻¹) at T = 298.15 K

		MP2/6-31G*	B3LYP/6-31G*	B3LYP/6-311G**	experimental
2-Py(COOH)	I; II	-240.4; -238.4	-227.9; -228.5	-242.5; -242.8	-243.0 ± 2.6 ⁴⁴
	III; IV	-239.4; -243.1	-239.3; -242.4	-241.5; -242.4	
3-Py(COOH)	I; II	-231.1; -229.1	-221.3; -221.9	-234.8; -235.1	-221.5 ± 1.5 ⁴⁵
	III; IV	-230.2; -235.5	-232.7; -238.8	-233.8; -239.8	
4-Py(COOH)	I; II	-232.0; -230.0	-217.5; -218.2	-231.0; -231.2	-234.8 ± 4.7 ⁴⁴
	III; IV	-231.0; -227.4	-228.9; -223.4	-229.9; -223.9	
2,3-Py(COOH) ₂	I; II	-589.7; -585.7	-573.9; -575.1	-599.9; -600.4	
	III; IV	-587.7; -591.3	-596.6; -599.7	-597.8; -598.7	
2,4-Py(COOH) ₂	I; II	-608.0; -604.0	-581.0; -582.3	-609.5; -610.0	
	III; IV	-606.1; -609.7	-603.8; -606.9	-607.4; -608.3	
2,5-Py(COOH) ₂	I; II	-608.1; -604.1	-584.2; -585.5	-612.7; -613.2	-580.6 ± 5.0
	III; IV	-606.2; -609.8	-607.0; -610.1	-610.6; -611.5	
2,6-Py(COOH) ₂	I; II	-606.3; -602.3	-580.0; -581.3	-608.2; -608.8	-608.0 ± 6.1
	III; IV	-604.4; -608.0	-602.8; -605.9	-606.2; -607.1	
3,4-Py(COOH) ₂	I; II	-570.3; -566.3	-552.1; -553.3	-577.1; -577.6	
	III; IV	-568.4; -573.8	-574.8; -581.0	-575.0; -581.1	
3,5-Py(COOH) ₂	I; II	-597.9; -593.9	-578.3; -579.5	-605.7; -606.3	
	III; IV	-596.0; -601.3	-601.0; -607.2	-603.7; -609.7	
2,6-Py(COOCH ₃) ₂	II	-567.5	-563.5	-556.1	-562.4 ± 4.2
	III	-537.4	-542.2	-544.2	
	V	-569.4	-586.5	-551.5	

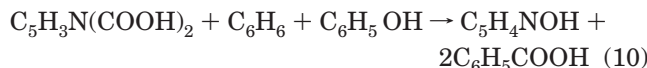
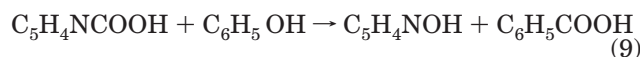
tal standard enthalpies of formation. However, the results obtained from B3LYP/6-31G* calculations indicate a lower stability than that observed experimentally. The largest deviations (for pyridine-2,5-dicarboxylic acid) amount to 27.8 kJ·mol⁻¹ (MP2/6-31G*) and 32.2 kJ·mol⁻¹ (B3LYP/6-311G**) for reaction set I and to 23.5 kJ·mol⁻¹ (MP2/6-31G*) and 32.6 kJ·mol⁻¹ (B3LYP/6-311G**) for reaction set II. However, excluding B3LYP/6-31G*, a reasonable agreement is found between the experimental standard enthalpies of formation and our theoretical estimates, with these being in most cases within the experimental uncertainty.

Set III involves benzoic acid:

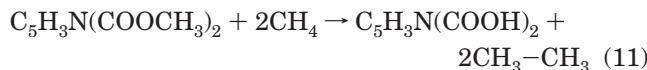


The values for the enthalpy variation for these reactions represent the effect of the carboxylic group on the stability of the pyridine ring as compared to its effect on benzene. Also, in this case, a consistent description is obtained for all levels of calculation. The largest deviations (for pyridinedicarboxylic acid) amount to 25.6 kJ·mol⁻¹ (MP2/6-31G*), 26.4 kJ·mol⁻¹ (B3LYP/6-31G*), and 30.0 kJ·mol⁻¹ (B3LYP/6-311G**). The unacceptably large deviations of 25.0 kJ·mol⁻¹ (MP2/6-31G*), 20.2 kJ·mol⁻¹ (B3LYP/6-31G*), and 18.2 kJ·mol⁻¹ (B3LYP/6-311G**) for dimethylpyridine-2,6-dicarboxylate can perhaps be accounted for by noting that the two experimental standard enthalpies of formation of methyl benzoate (C₆H₅COOCH₃) reported in NIST tables,⁴⁶ -269.3 ± 5.1 kJ·mol⁻¹⁴⁷ and -299.8 kJ·mol⁻¹,⁴⁸ span a very large energy range, also allowing our estimates of the standard enthalpy of formation of dimethylpyridine-2,6-dicarboxylate to vary in a corresponding range which would then clearly contain the experimentally observed values.

The last set (IV) of isodesmic reactions is constituted by the following reactions involving hydroxypyridines:



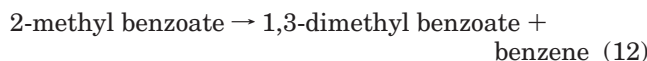
for the pyridine carboxylic acids. For pyridine-2,6-dimethylcarboxylate, the following reaction was chosen instead:



The resulting estimates of the enthalpies of formation in Table 8 show again a very good agreement with experiment, with the largest deviations (for pyridine-2,5-dicarboxylic acid) amounting to 29.2 kJ·mol⁻¹ (MP2/6-31G*), 29.5 kJ·mol⁻¹ (B3LYP/6-31G*), and 30.9 kJ·mol⁻¹ (B3LYP/6-311G**).

The results for the enthalpies of formation reported in the present work for pyridine-2,6-dicarboxylic acid and dimethylpyridine-2,6-dicarboxylate show the same trend as the recent result for methyl benzoate relative to benzoic acid.⁴⁹ Actually, the methylation of benzoic acid means an enthalpic increment of 18.0 ± 4.6 kJ·mol⁻¹, which is in perfect agreement with the increments associated with the transformations: acetic acid/methyl acetate, ΔH = 20.9 ± 2.2 kJ·mol⁻¹; and hexanoic acid/methyl hexanoate, ΔH = 19.3 ± 2.6 kJ·mol⁻¹, as referred by Roux et al.⁴⁹

From our work, we can calculate the increment for the dimethylation of the pyridine-2,6-dicarboxylic acid as 46.0 ± 7.3 kJ·mol⁻¹. Using the following process:



and the literature values for the enthalpies of formation of the involved species,⁴⁹⁻⁵¹ we can calculate an enthalpy of reaction of 7 kJ·mol⁻¹, which means the destabilization effect caused by the second methylation of benzene in the meta position relative to the first methylation. As in dimethylpyridine-2,6-dicarboxylate acid, the -COOMe groups are in relative meta positions, and we can estimate

for the energy of the exchange of two $-\text{COOH}$ groups by two $-\text{COOMe}$ groups the value $(46.0 - 7) = 39 \text{ kJ}\cdot\text{mol}^{-1}$; thus, for each exchange, we obtain $39/2 = 20 \text{ kJ}\cdot\text{mol}^{-1}$, in good agreement with the values presented by Roux et al.⁴⁹

Considering the mean value of all of the 12 theoretical estimates of the standard molar enthalpy of formation for gaseous pyridine-2,3-dicarboxylic acid, resumed in Table 8 as $-(591 \pm 10) \text{ kJ}\cdot\text{mol}^{-1}$, and using the standard molar enthalpy of crystalline pyridine-2,3-dicarboxylic acid, reported in this work, we can estimate the value $142 \pm 10 \text{ kJ}\cdot\text{mol}^{-1}$ for the correspondent standard molar enthalpy of sublimation, which seems to be a reasonable value when compared with the experimental value measured for the enthalpy of sublimation of pyridine-2,6-dicarboxylic acid.

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