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Experimental and Computational Thermochemical Study of  $\alpha$ -Alanine (DL) and  $\beta$ -Alanine

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This paper reports an experimental and theoretical study of the gas phase standard ( $p^\circ = 0.1$  MPa) molar enthalpies of formation, at  $T = 298.15$  K, of  $\alpha$ -alanine (DL) and  $\beta$ -alanine. The standard ( $p^\circ = 0.1$  MPa) molar enthalpies of formation of crystalline  $\alpha$ -alanine (DL) and  $\beta$ -alanine were calculated from the standard molar energies of combustion, in oxygen, to yield  $\text{CO}_2(\text{g})$ ,  $\text{N}_2(\text{g})$ , and  $\text{H}_2\text{O}(\text{l})$ , measured by static-bomb combustion calorimetry at  $T = 298.15$  K. The vapor pressures of both amino acids were measured as function of temperature by the Knudsen effusion mass-loss technique. The standard molar enthalpies of sublimation at  $T = 298.15$  K was derived from the Clausius–Clapeyron equation. The experimental values were used to calculate the standard ( $p^\circ = 0.1$  MPa) enthalpy of formation of  $\alpha$ -alanine (DL) and  $\beta$ -alanine in the gaseous phase,  $\Delta_f H_m^\circ(\text{g})$ , as  $-426.3 \pm 2.9$  and  $-421.2 \pm 1.9$   $\text{kJ}\cdot\text{mol}^{-1}$ , respectively. Standard ab initio molecular orbital calculations at the G3 level were performed. Enthalpies of formation, using atomization reactions, were calculated and compared with experimental data. Detailed inspections of the molecular and electronic structures of the compounds studied were carried out.

## Introduction

$\alpha$ -Amino acids are among the most important building blocks in nature and are also believed to play key roles in interstellar chemistry as well as in the origin of life on Earth.<sup>1</sup> They are the building blocks of peptides, the backbones of proteins and, for this reason, they have been extensively studied.  $\alpha$ -Alanine, the second simplest proteinogenic amino acid, is a particularly important molecule because it is the smallest natural amino acid presenting a chiral  $\alpha$ -carbon atom. Furthermore,  $\alpha$ -alanine influences the conformational behavior of many other peptide residues.

On the contrary,  $\beta$ -amino acids, in spite of their biological importance, have received much less attention, but interest in  $\beta$ -amino acids has increased over the past several years, owing to their importance to multiple lines of research (combinatorial chemistry, medicinal chemistry, molecular design, proteomics, etc.).<sup>2</sup>  $\beta$ -Alanine, the simplest  $\beta$ -amino acid, plays an important role in a variety of biological processes. It is found in animal brain and liver tissue, as well as in plants, fruits, and insect cuticles.<sup>3</sup> In contrast to other neurologically active amino acids, the concentration of  $\beta$ -alanine in nerve tissue is low,<sup>4</sup> and from its broader distribution is probably more correctly designated a neurohormone rather than a neurotransmitter.<sup>5</sup> However,  $\beta$ -alanine is implicated as an actual neurotransmitter in the optic nerve of the mammalian visual system.<sup>6</sup>  $\beta$ -Alanine is found to be the

most abundant amino acid existing in CI chondrites, a type of carbonaceous meteorite.<sup>7</sup> It is one of the amino acids constituting the naturally occurring dipeptides anserine and carnosine,<sup>8</sup> and it also possesses pharmaceutical interest: derivatives of  $\beta$ -alanine have been proposed for treatment of epilepsy.<sup>9</sup> Recent experimental results indicate that  $\beta$ -alanine can be formed in the gas phase by ion–molecule reactions of smaller precursors in the interstellar medium, and that these reactions preferentially yield  $\beta$ -alanine over  $\alpha$ -alanine.<sup>10</sup> Also,  $\beta$ -alanine can be enzymatically converted to  $\alpha$ -alanine.<sup>11</sup>

Why did Nature choose  $\alpha$ -amino acids instead of  $\beta$ -amino acids as the essential building blocks of biological molecules such as proteins? We believe that thermodynamic data can provide useful information to answer this question. In particular, calorimetric measurements can render essential knowledge regarding the relative stability of  $\alpha$ - versus  $\beta$ -amino acid isomers. Furthermore, the determination of thermodynamic parameters in peptides constituted by  $\alpha$ - vis-a-vis  $\beta$ -amino acids is important in order to understand the contrasting properties between the natural ( $\alpha$ ) and the unnatural ( $\beta$ ) compounds. In this context, it should be interesting to compare the experimentally obtained calorimetric measurements with molecular modeling studies of the isomeric structures since such exercise should provide useful arguments to respond to the original question.

In this work, we have decided to study the thermochemical properties of  $\alpha$ -alanine (DL) as representative of  $\alpha$ -amino acids, and  $\beta$ -alanine as representative of  $\beta$ -amino acids, whose schematic formulas are presented in Figure 1.

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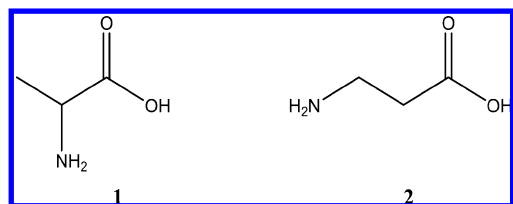


Figure 1. Schematic formulas of  $\alpha$ -alanine 1 and  $\beta$ -alanine 2.

Please note that the properties of a racemic chiral  $\alpha$ -amino acid (in this case  $\alpha$ -alanine (DL)) are not necessarily the same as those presented by enantiomerically pure compounds (D or L); that is, as demonstrated Destro et al.,<sup>12</sup> homochiral (DD or LL) intermolecular interactions may be different than heterochiral (DL) interactions.

As a consequence of the importance of  $\alpha$ -amino acids, a great number of thermochemical studies of  $\alpha$ -alanine (DL) have appeared in the literature.<sup>13–20</sup> It must be emphasized that the reported values of the enthalpies of formation in the condensed phase vary in a range of over 22.8 kJ mol<sup>−1</sup> (see below). Values for vapor pressures or for its enthalpy of sublimation have not been found in the literature. For  $\beta$ -alanine, the situation is even worse. There are only three values reported<sup>19,21,22</sup> for the enthalpy of formation in the condensed state but they spread in the range of ca. 248 kJ·mol<sup>−1</sup> (see below). There is one value for the enthalpy of sublimation of  $\beta$ -alanine, determined by Skoulika and Sabbah.<sup>21</sup>

The approach selected is a combination of experimental determinations of the enthalpy of formation, molecular structures, and high-level ab initio calculations.

## Experimental Procedures

**Materials and Purity Control.** Commercial samples of  $\alpha$ -alanine (DL) [CAS 302-72-7] (15.0 g, 168.4 mmol, Aldrich, cat. no. 13,522-4, mp 562 K, decomp.) and  $\beta$ -alanine [CAS 107-95-9] (15.0 g, 168.4 mmol, Aldrich, cat. no. 14,606-4, mp 475 K, decomp.) were placed in sublimators, which were evacuated to 0.5 mmHg and heated in an oil bath to 483–493 and 433–443 K, respectively, to afford 11.8 g (79% yield) of the sublimed  $\alpha$ -alanine (DL), mp 563–564 K (decomp.) and 6.0 g (40% yield) of the sublimed  $\beta$ -alanine, mp 477–478 K (decomp.). The standards used for DSC calibration were hexafluorobenzene, 99.9% purity, supplied by Aldrich; benzoic acid, NIST standard reference sample 39j; and high-purity indium (mass fraction > 0.999 99), tin and synthetic sapphire, supplied by Perkin-Elmer. The purity of the samples was checked by NMR and C, H, and N microanalysis: NMR analysis suggested at least 99.5% purity; calculated for C<sub>3</sub>H<sub>7</sub>NO<sub>2</sub>, 10<sup>2</sup>w(C) = 0.4044, 10<sup>2</sup>w(H) = 0.0791, 10<sup>2</sup>w(N) = 0.1572; found 10<sup>2</sup>w(C) = 0.4032, 10<sup>2</sup>w(H) = 0.0781, 10<sup>2</sup>w(N) = 0.1573, and 10<sup>2</sup>w(C) = 0.4054, 10<sup>2</sup>w(H) = 0.0775, 10<sup>2</sup>w(N) = 0.1575 for  $\alpha$ -alanine (DL) and  $\beta$ -alanine, respectively.

**Differential Scanning Calorimetry.** The behavior of the samples as a function of temperature was studied by differential scanning calorimetry. A DSC Pyris 1 instrument from Perkin-Elmer equipped with an intracooler unit was used to study the fusion process and the possible existence of phase transitions in the temperature intervals where the thermochemical measurements were made. The DSC calorimeter was previously calibrated in temperature and energy with reference materials. Temperature and power scales were calibrated<sup>23–25</sup> at heating rates of 0.04 and 0.17 K·s<sup>−1</sup>. The temperature scale was calibrated by the melting temperature of the high-purity refer-

ence materials: hexafluorobenzene, tin, and indium.<sup>24</sup> The power scales were calibrated with high-purity indium.<sup>24</sup>

Thermograms of samples hermetically sealed in aluminum pans were recorded in a nitrogen atmosphere. All the pans with the samples were weighed on a Mettler AT21 microbalance with a detection limit of 1 × 10<sup>−6</sup> g, before and after the experiments to confirm that no product had volatilized.

Different scans at heating rates of 0.04 and 0.17 K·s<sup>−1</sup> were performed to determine the possible existence of phase transitions in the samples over the temperature range from  $T = 260$  to 563 K and 565 K for  $\alpha$ -alanine (DL) and  $\beta$ -alanine, respectively. A fresh sample was used for each run.

**Combustion Calorimetry.** The standard molar energies of combustion of  $\alpha$ -alanine (DL) and  $\beta$ -alanine were determined in a static bomb combustion calorimeter, in Porto University, already described in the literature.<sup>26</sup> The energy equivalent of the calorimeter was determined by combustion of benzoic acid, NIST Thermochemical Standard 39j, with a certified massic energy of combustion, under bomb conditions, of  $-26\,434 \pm 3$  J·g<sup>−1</sup>,<sup>27</sup> according to the procedure described by Coops et al.<sup>28</sup> The calibration results were corrected to give the energy equivalent of the calorimeter,  $\epsilon(\text{calor})$ , corresponding to the average mass of 3119.6 g of water added to the calorimeter. From six calibration experiments,  $\epsilon(\text{calor})$  was found to be  $15\,995.3 \pm 2.0$  J·K<sup>−1</sup>.

Samples in pellet form were ignited in oxygen at a pressure  $p = 3.04$  MPa, with 1.00 cm<sup>3</sup> of deionized water added to the bomb. The calorimeter temperatures were measured to  $\pm 1 \times 10^{-4}$  K, at time intervals of 10 s, with a quartz crystal thermometer (Hewlett Packard HP 2804 A), interfaced to a PC. The program LABTERMO was used for data acquisition and control of calorimeter temperatures.<sup>29</sup> 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 used, empirical formula CH<sub>1.686</sub>O<sub>0.843</sub>,  $\Delta_c u^\circ = -16\,240$  J·g<sup>−1</sup>,<sup>28</sup> a value which has been previously confirmed in our laboratory. *n*-Hexadecane (Aldrich, mass fraction > 0.999), stored under nitrogen, was used as combustion auxiliary of the two compounds, for the purpose of avoiding carbon soot residue formation. Its mass-related energy of combustion was found to be  $\Delta_c u^\circ = -47\,132.7 \pm 2.6$  J·g<sup>−1</sup>. The amount of nitric acid produced was determined by acid–base volumetry and corrections for it were based on  $-59.7$  kJ·mol<sup>−1</sup> for the molar energy of formation of 0.1 mol·dm<sup>−3</sup> HNO<sub>3</sub>(aq) from N<sub>2</sub>(g)/O<sub>2</sub>(g) and H<sub>2</sub>O(l).<sup>30</sup> The amount of substance 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 combustion of the cotton thread fuse and of the *n*-hexadecane. The average ratio of the mass of carbon dioxide recovered after combustion to that calculated from the mass of samples used in each experiment was  $(1.000\,04 \pm 0.004\,04)$  for  $\alpha$ -alanine (DL) and  $(1.0003 \pm 0.0054)$  for  $\beta$ -alanine, where the uncertainties are twice the standard deviation of the mean.

At  $T = 298.15$  K, a pressure coefficient of specific energy,  $(\partial u/\partial p)_T$ , was assumed to be  $-0.2$  J·g<sup>−1</sup>·MPa<sup>−1</sup>, a typical value for organic solids.<sup>31</sup> Corrections to the standard state were made following the procedure given by Hubbard et al.<sup>32</sup>

The atomic weights used were those recommended by the IUPAC Commission in 2007.<sup>33</sup> The specific densities, used to calculate the true mass from apparent mass in air were,  $\rho = 1.424$  g·cm<sup>−3</sup> for  $\alpha$ -alanine (DL) and  $\rho = 1.437$  g·cm<sup>−3</sup> for  $\beta$ -alanine.<sup>34</sup>

**Knudsen Effusion Technique.** The mass-loss Knudsen effusion technique was used to measure the vapor pressures of the crystals at several temperatures. A detailed description of the nine-cell Porto University Knudsen effusion apparatus, procedure, and technique, and the results obtained with five test substances have been reported before.<sup>35</sup> In this apparatus, the aluminum effusion cells are contained in cylindrical holes inside three aluminum blocks, each one maintained at a constant temperature, different from the other two blocks.

The vapor pressures were measured in the range 0.08–0.7 Pa for  $\alpha$ -alanine (DL) and 0.08–0.35 Pa for  $\beta$ -alanine, because these compounds suffer decomposition at higher temperature. The vapor pressure,  $p$ , of each compound in an effusion experiment, is calculated through eq 1, knowing the mass of sublimed compound,  $m$ , during a effusion time period,  $t$ , at the temperature  $T$  of the experiment, in a system evacuated to a pressure near  $1 \times 10^{-4}$  Pa:

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

where  $A_o$  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.

The exact areas and the transmission probability factors (Clausing factors) of the orifices of the effusion cells, made of platinum foil of 0.0125 mm thickness, are presented in the Supporting Information, Table S1.

**Computational Details.** Standard ab initio molecular orbital calculations<sup>36</sup> were performed with the Gaussian03 series of programs.<sup>37</sup> Energies were obtained using the Gaussian-3 theory, at the G3 level.<sup>38</sup>

G3 corresponds effectively to calculations at the QCISD(T)/G3large level, G3large being a modification of the 6-311+G(3df,2p) basis set, including more polarization functions for the second row (3d2f), less on the first row (2df), and other changes to improve uniformity. In addition, some core polarization functions are added.<sup>38</sup> Single-point energy calculations are carried out on MP2(full)/6-31G(d) optimized geometries, incorporating scaled HF/6-31G(d) zero-point vibrational energies, a so-called higher-level correction to accommodate remaining deficiencies, and spin-orbit correction for atomic species only.<sup>38</sup>

Due to the lack of symmetry and the internal rotational degree of freedom by the free rotation of the  $\text{NH}_2$ ,  $\text{COOH}$ , and  $\text{OH}$  groups with respect to the carbon skeleton,  $\alpha$ - and  $\beta$ -alanines exhibit a number of low-energy conformers. In this study, we have optimized the molecular structures of the lowest-energy conformers of  $\alpha$ -alanine and  $\beta$ -alanine, a total of 9 and 11, respectively. G3-calculated energies at 0 K, and enthalpies at 298 K, for all the conformers studied here are given in Tables 8 and 9. All of these structures are minima on the potential energy surface.

We have also reoptimized the geometries of the lowest-energy conformers of both alanines at the MP2(full)/6-31G(3df,2p) level to obtain more reliable molecular structures.

The charge distribution has been analyzed using a population partition technique, the natural bond orbital (NBO) analysis of Reed and Weinhold.<sup>39</sup> The NBO analysis has been performed using the NBO program<sup>40</sup> implemented in the Gaussian 03 package.<sup>37</sup>

## Results

**Experimental Determination of the Enthalpies of Formation in the Gas Phase.** The samples of  $\alpha$ -alanine (DL) and  $\beta$ -alanine were studied by DSC over the temperature range from

**TABLE 1: Typical Combustion Results, at  $T = 298.15$  K, for the Compounds Studied<sup>a</sup>**

	$\alpha$ -alanine (DL)	$\beta$ -alanine
$m(\text{CO}_2, \text{total})/\text{g}$	1.42097	1.19276
$m(\text{cpd})/\text{g}$	0.62515	0.58861
$m(\text{fuse})/\text{g}$	0.00245	0.00284
$m(n\text{-hex})/\text{g}$	0.15777	0.10159
$\Delta T_{\text{ad}}/\text{K}$	1.17893	0.97358
$\varepsilon_f/\text{J} \cdot \text{K}^{-1}$	16.75	16.43
$\Delta m(\text{H}_2\text{O})/\text{g}$	−0.8	0.1
$-\Delta U(\text{IBP})^b/\text{J}$	18872.00	15588.22
$\Delta U(\text{fuse})/\text{J}$	39.79	46.12
$\Delta U(n\text{-hex})/\text{J}$	7435.91	4788.01
$\Delta U(\text{HNO}_3)/\text{J}$	45.64	34.26
$\Delta U(\text{ign})/\text{J}$	1.14	0.89
$\Delta U_{\Sigma}/\text{J}$	10.19	8.95
$-\Delta_c u^\circ/\text{J} \cdot \text{g}^{-1}$	18140.40	18196.90

<sup>a</sup>  $m(\text{CO}_2, \text{total})$  is the mass of  $\text{CO}_2$  recovered in each combustion;  $m(\text{cpd})$  is the mass of compound burnt in each experiment;  $m(\text{fuse})$  is the mass of the fuse (cotton) used in each experiment;  $m(n\text{-hex})$  is the mass of  $n$ -hexadecane used as auxiliary of combustion;  $\Delta T_{\text{ad}}$  is the corrected temperature rise;  $\varepsilon_f$  is the energy equivalent of the contents in the final state;  $\Delta m(\text{H}_2\text{O})$  is the deviation of mass of water added to the calorimeter from 3119.6 g;  $\Delta U(\text{IBP})$  is the energy change for the isothermal combustion reaction under actual bomb conditions;  $\Delta U(\text{fuse})$  is the energy of combustion of the fuse (cotton);  $\Delta U(n\text{-hex})$  is the energy of combustion of  $n$ -hexadecane used as auxiliary of combustion;  $\Delta U(\text{HNO}_3)$  is the energy correction for the nitric acid formation;  $\Delta U(\text{ign})$  is the electric energy for the ignition;  $\Delta U_{\Sigma}$  is the standard-state correction;  $\Delta_c u^\circ$  is the standard massic energy of combustion. <sup>b</sup>  $\Delta U(\text{IBP})$  includes  $\Delta U(\text{ignition})$ .

$T = 260$  to  $563$  K and  $565$  K, respectively, and no transitions in the solid state were observed for both compounds.

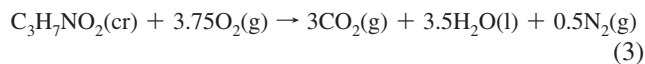
Table 1 lists the typical combustion results for one experiment of each amino acid, in which  $\Delta m(\text{H}_2\text{O})$  is the deviation of the mass of water added to the calorimeter from 3119.6 g, the mass assigned to  $\varepsilon(\text{calor})$ ,  $\Delta U_{\Sigma}$  is the correction to the standard state and the other quantities are as previously described.<sup>32,41</sup>

The internal energy associated to the isothermal bomb process,  $\Delta U(\text{IBP})$ , was calculated through

$$\Delta U(\text{IBP}) = -\{\varepsilon(\text{calor}) + c_p(\text{H}_2\text{O}, \text{l}) \cdot \Delta m(\text{H}_2\text{O}) + \varepsilon_f\} \Delta T_{\text{ad}} + \Delta U(\text{ign}) \quad (2)$$

where  $\Delta T_{\text{ad}}$  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.

All the  $\Delta_c u^\circ$  values, together with the mean value  $\langle \Delta_c u^\circ \rangle$ , and its standard deviation of the mean are presented in Table 2. These results are referred to the hypothetical combustion reaction, represented by eq 3:



In Table 3, the derived standard molar values for the energy,  $\Delta_c U_m^\circ(\text{cr})$ , and enthalpy,  $\Delta_c H_m^\circ(\text{cr})$ , of combustion reaction 3, as well as the standard molar enthalpies of formation in the crystalline phase,  $\Delta_f H_m^\circ(\text{cr})$ , at  $T = 298.15$  K, are presented. According to Rossini<sup>42</sup> and Olofsson,<sup>43</sup> the uncertainty assigned to the molar enthalpy of combustion is twice the overall standard deviation of the mean, including the uncertainties in calibration and in the values of the auxiliary quantities used.



**TABLE 2: Individual Values of Standard ( $p^\circ = 0.1$  MPa) Massic Energies of Combustion,  $\Delta_c u^\circ$ , of the Compounds, at  $T = 298.15$  K**

$-\Delta_c u^\circ / \text{J} \cdot \text{g}^{-1}$	
$\alpha$ -alanine (DL)	$\beta$ -alanine
18125.86	18196.90
18136.91	18199.55
18132.37	18207.93
18146.07	18204.04
18140.40	18187.71
18160.00	18187.27
18123.06	
$-\langle \Delta_c u^\circ \rangle / (\text{J} \cdot \text{g}^{-1})$	
$\alpha$ -alanine (DL) (18137.8 $\pm$ 4.8) <sup>a</sup>	$\beta$ -alanine (18197.2 $\pm$ 3.4) <sup>a</sup>

<sup>a</sup> 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	$-\Delta_c U_m^\circ(\text{cr}) / (\text{kJ} \cdot \text{mol}^{-1})$	$-\Delta_c H_m^\circ(\text{cr}) / (\text{kJ} \cdot \text{mol}^{-1})$	$-\Delta_f H_m^\circ(\text{cr}) / (\text{kJ} \cdot \text{mol}^{-1})$
$\alpha$ -alanine (DL)	1616.0 $\pm$ 1.0	1616.6 $\pm$ 1.0	564.3 $\pm$ 1.1
$\beta$ -alanine	1621.2 $\pm$ 0.8	1621.8 $\pm$ 0.8	559.1 $\pm$ 0.9

The standard molar enthalpies of formation of  $\text{H}_2\text{O}(\text{l})$ ,  $-285.830 \pm 0.042 \text{ kJ} \cdot \text{mol}^{-1}$ ,<sup>44</sup> and  $\text{CO}_2(\text{g})$ ,  $-393.51 \pm 0.13 \text{ kJ} \cdot \text{mol}^{-1}$ ,<sup>44</sup> were used to calculate the  $\Delta_f H_m^\circ(\text{cr})$  from  $\Delta_c H_m^\circ$ , at  $T = 298.15$  K.

The standard molar enthalpies of sublimation at the mean temperature of the experimental temperature range of both amino acids studied were obtained from the integrated form of the Clausius–Clapeyron equation,  $\ln(p/\text{Pa}) = a - b(T/\text{K})^{-1}$ , where  $a$  is a constant and  $b = \Delta_{\text{cr}}^{\text{H}} H_m^\circ(T)/R$ . The results of the Knudsen effusion experiments are summarized in Table 4, in which we present, for each compound and for each effusion orifice used, the values of the vapor pressures obtained from each effusion experiment during the effusion time period  $t$  at the temperature  $T$ , together with the residuals of the Clausius–Clapeyron equation  $\{10^2 \Delta \ln(p/\text{Pa})\}$ , derived from least-squares treatment. The detailed parameters of the Clausius–Clapeyron equation, together with the calculated standard deviations, the standard molar enthalpies of sublimation at the mean temperature of the experiments  $T = \langle T \rangle$ , the equilibrium pressure at this temperature,  $p(\langle T \rangle)$ , and the entropy of sublimation, at equilibrium conditions,  $\Delta_{\text{cr}}^{\text{S}} S_m^\circ(\langle T \rangle, p(\langle T \rangle))$ , are given in Table 5. The plots of  $\ln(p/\text{Pa})$  against  $1/T$  for the global results obtained for the two amino acids studied are shown in Figure 2.

The enthalpies of sublimation, at  $T = 298.15$  K, were derived from the same thermodynamic parameter, at the mean temperature,  $\langle T \rangle$ , of the experiment, by means of eq 4

$$\Delta_{\text{cr}}^{\text{H}} H_m^\circ(298.15 \text{ K}) = \Delta_{\text{cr}}^{\text{H}} H_m^\circ(\langle T \rangle) + \Delta_{\text{cr}}^{\text{S}} C_{p,m}^\circ(298.15 \text{ K} - \langle T \rangle) \quad (4)$$

The values of  $\Delta_{\text{cr}}^{\text{S}} C_{p,m}^\circ$  for both compounds were estimated from the respective molar heat capacities, in the crystalline phase,  $C_{p,m}^\circ(\text{cr})$ , taken from the literature<sup>45,46</sup> and the values of the gas phase molar heat capacities,  $C_{p,m}^\circ(\text{g})$ , at  $T = 298.15$  K, were derived in this work from statistical thermodynamics using the vibrational frequencies from HF/6-31G(d) calculations.

**TABLE 4: Knudsen Effusion Results for the  $\alpha$ -Alanine (DL) and  $\beta$ -Alanine**

$T/\text{K}$	$t/\text{s}$	orifices	$p/\text{Pa}$		$10^2\Delta \ln(p/\text{Pa})$	
			medium	large	medium	large
$\alpha$ -Alanine (DL)						
397.14	21778	B4–C7	0.0899	0.0813	11.8	1.6
399.14	21778	B5–C8	0.103	0.0941	4.8	−4.3
401.15	21778	B6–C9	0.129	0.114	6.4	−6.1
403.11	18931	B4–C7	0.143	0.131	−2.5	−11.8
405.09	18931	B5–C8	0.173	0.157	−3.5	−13.5
407.15	18931	B6–C9	0.212	0.230	−3.8	4.5
409.13	15123	B4–C7	0.290	0.267	8.1	0.0
411.08	15123	B5–C8	0.343	0.314	6.1	−2.8
413.15	15123	B6–C9	0.419	0.378	6.1	−4.3
415.13	11053	B4–C7	0.507	0.471	6.4	−1.1
417.08	11053	B5–C8	0.604	0.555	5.4	−3.0
419.16	11053	B6–C9	0.721	0.640	3.7	−8.2

$T/\text{K}$	$t/\text{s}$	orifices	small	
			$p/\text{Pa}$	$10^2\Delta \ln(p/\text{Pa})$
$\beta$ -Alanine				
388.14	27321	A1	0.0798	−2.1
389.14	22042	A1	0.0886	−1.3
390.18	27321	A2	0.103	1.0
391.18	22042	A2	0.116	3.4
392.15	27321	A3	0.122	−2.7
393.15	22042	A3	0.142	2.8
394.15	21586	A1	0.153	0.0
395.18	21586	A2	0.175	2.2
396.16	21586	A3	0.189	−0.3
397.15	19638	A1	0.208	−0.7
398.18	19638	A2	0.231	−1.1
399.15	19638	A3	0.248	−3.9
400.15	17549	A1	0.291	1.9
401.18	17549	A2	0.320	0.7
402.15	17549	A3	0.351	0.1

For  $\alpha$ -alanine (DL),  $C_{p,m}^\circ(\text{g}) = 102.1 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$  and  $C_{p,m}^\circ(\text{cr}) = 121.6 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ ,<sup>45</sup> yielding a value of  $\Delta_{\text{cr}}^{\text{S}} C_{p,m}^\circ = -19.5 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ . For  $\beta$ -alanine,  $\Delta_{\text{cr}}^{\text{S}} C_{p,m}^\circ = -17.6 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ , calculated from  $C_{p,m}^\circ(\text{g}) = 98.5 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$  and  $C_{p,m}^\circ(\text{cr}) = 116.1 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ .<sup>46</sup>

The standard molar enthalpies, entropies and Gibbs energies of sublimation, at  $T = 298.15$  K, are presented in Table 6.

The standard molar enthalpies of formation in the gaseous phase at  $T = 298.15$  K obtained by the sum of the respective standard molar enthalpies of formation in crystalline phase and the standard molar enthalpies of sublimation, given in Tables 3 and 6, respectively, are summarized in Table 7. Also included in the table are all the experimental data for  $\alpha$ -alanine (DL) and  $\beta$ -alanine available in the literature. As it can be observed, our value for the standard molar enthalpy of formation in the condensed state for  $\alpha$ -alanine (DL),  $-564.3 \pm 1.1 \text{ kJ} \cdot \text{mol}^{-1}$  agrees with the values measured by Huffman et al.,<sup>17</sup>  $-563.6 \pm 0.6 \text{ kJ} \cdot \text{mol}^{-1}$ , and Kamaguchi et al.,<sup>18</sup>  $-562.4 \pm 0.7 \text{ kJ} \cdot \text{mol}^{-1}$ . In the case of  $\beta$ -alanine, our value,  $-559.1 \pm 0.9 \text{ kJ} \cdot \text{mol}^{-1}$ , agrees with that obtained by Skoulika and Sabbah,<sup>21</sup>  $-558.0 \pm 0.3 \text{ kJ} \cdot \text{mol}^{-1}$ ; our standard molar enthalpy of sublimation is slightly larger than the value reported by that authors. It would be useful here to note that similar behavior has been observed with other systems.

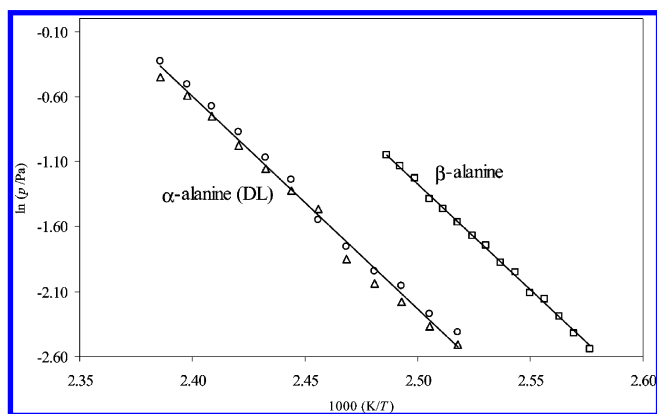
**Molecular and Electronic Structures.**  $\alpha$ - and  $\beta$ -alanine molecules, as other amino acids, exist as zwitterions in the crystalline state<sup>47</sup> as well as in aqueous solution, stabilized by electrostatic, polarization, and hydrogen-bonding interactions with their environment. Several crystal structure determinations have been reported<sup>12,48</sup> (orthorhombic space groups  $Pna21$  and

**TABLE 5: Experimental Results for  $\alpha$ -Alanine (DL) and  $\beta$ -Alanine Where  $a$  and  $b$  Are From Clausius–Clapeyron Equation,  $\ln(p/\text{Pa}) = a - b(T/\text{K})$  and  $b = \Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^{\circ}(\langle T \rangle)/R$ ;  $R = 8.314\,472\text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$** 

orifices	$a$	$b$	$\langle T \rangle / (\text{K})$	$p(\langle T \rangle) / (\text{Pa})$	$\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^{\circ}(\langle T \rangle) / (\text{kJ}\cdot\text{mol}^{-1})$	$\Delta_{\text{cr}}^{\text{g}}S_{\text{m}}^{\circ}(\langle T \rangle, p(\langle T \rangle)) / (\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1})$
$\alpha$ -Alanine (DL)						
B4–B5–B6	$38.65 \pm 0.87$	$16338 \pm 354$			$135.8 \pm 2.9$	
C7–C8–C9	$38.61 \pm 0.94$	$16355 \pm 384$			$136.0 \pm 3.2$	
global results	$38.63 \pm 0.80$	$16346 \pm 325$	408.15	0.243	$135.9 \pm 2.7$	$333.0 \pm 6.6$
$\beta$ -Alanine						
A1–A2–A3	$39.70 \pm 0.51$	$16386 \pm 200$	395.15	0.171	$136.2 \pm 1.7$	$344.7 \pm 4.3$

*Pbca*, respectively, and both enantiomers in the crystal). In the  $\alpha$ -alanine (DL), no phase transition has been detected when the temperature<sup>12</sup> is lowered to 19 K. However, twinning crystals (space group *P1* at room temperature and 100 K) were obtained when crystallizing the racemic sample in the presence of optically active  $\alpha$ -amino acids to obtain the spontaneous resolution of the sample.<sup>49</sup>

In both compounds (Figure 3), the crystal cohesion is mainly due to  $\text{N}^+ - \text{H} \cdots \text{O}$  intermolecular interactions where one oxygen atom of the carboxylate group is involved in one hydrogen bond

**Figure 2.** Plots of  $\ln(p/\text{Pa})$  against  $1/T$  for  $\alpha$ -alanine (DL) and  $\beta$ -alanine:  $\square$ , small holes;  $\circ$ , medium holes;  $\triangle$ , large holes.**TABLE 6: Values of the Standard ( $p^{\circ} = 0.1\text{ MPa}$ ) Molar Enthalpies,  $\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^{\circ}$ , Entropies,  $\Delta_{\text{cr}}^{\text{g}}S_{\text{m}}^{\circ}$ , and Gibbs Energies  $\Delta_{\text{cr}}^{\text{g}}G_{\text{m}}^{\circ}$  of Sublimation at  $T = 298.15\text{ K}$  for  $\alpha$ -Alanine (DL) and  $\beta$ -Alanine**

compound	$\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^{\circ} / (\text{kJ}\cdot\text{mol}^{-1})$	$\Delta_{\text{cr}}^{\text{g}}S_{\text{m}}^{\circ} / (\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1})$	$\Delta_{\text{cr}}^{\text{g}}G_{\text{m}}^{\circ} / (\text{kJ}\cdot\text{mol}^{-1})$
$\alpha$ -alanine (DL)	$138.0 \pm 2.7$	$241.2 \pm 6.6$	$66.1 \pm 3.3$
$\beta$ -alanine	$137.9 \pm 1.7$	$248.4 \pm 4.3$	$63.8 \pm 2.1$

**TABLE 7: Experimental Values for Standard ( $p^{\circ} = 0.1\text{ MPa}$ ) Molar Enthalpies of Formation, in Crystalline and Gaseous Phases, and Standard Molar Enthalpy of Sublimation, at  $T = 298.15\text{ K}$** 

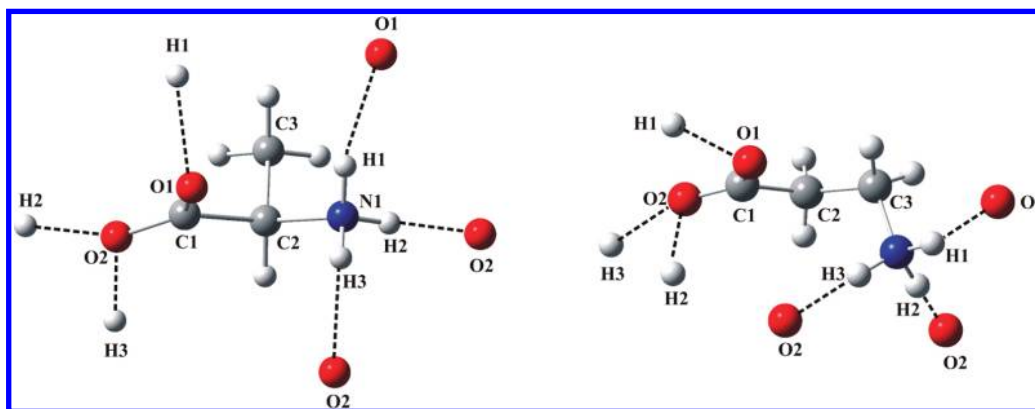
amino acid	$\Delta_{\text{f}}H_{\text{m}}^{\circ}(\text{cr}) / (\text{kJ}\cdot\text{mol}^{-1})$	$\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}^{\circ} / (\text{kJ}\cdot\text{mol}^{-1})$	$\Delta_{\text{f}}H_{\text{m}}^{\circ}(\text{g}) / (\text{kJ}\cdot\text{mol}^{-1})$	reference
$\alpha$ -alanine (DL)	$-559.0 \pm 8.0^a$	—	—	Stohmann (1890) <sup>13</sup>
	$-559.8 \pm 8.0^a$	—	—	Stohmann, Langbein (1891) <sup>14</sup>
	$-556.1 \pm 4.0^a$	—	—	Fischer et al. (1904) <sup>15</sup>
	$-560.7 \pm 4.0^a$	—	—	Wrede (1911) <sup>16</sup>
	$-563.6 \pm 0.6$	—	—	Huffman et al. (1937) <sup>17</sup>
	$-562.4 \pm 0.7$	—	—	Kamaguchi et al. (1975) <sup>18</sup>
	$-578.9 \pm 2.9$	—	—	Contineanu et al. (1984) <sup>19</sup>
	$-557.9 \pm 2.7^b$	—	—	Diaz et al. (1992) <sup>20</sup>
	$-564.3 \pm 1.1$	$138.0 \pm 2.7$	$-426.3 \pm 2.9$	This work
	$-558.0 \pm 0.3$	$134 \pm 2$	$-424 \pm 2$	Skoulaka, Sabbah (1982–3) <sup>21</sup>
$\beta$ -alanine	$-310 \pm 1.5$	—	—	Contineanu et al. (1984) <sup>19</sup>
	$-547.1 \pm 1.1$	—	—	Gerasimov et al. (1988) <sup>22</sup>
	$-559.1 \pm 0.9$	$137.9 \pm 1.7$	$-421.2 \pm 1.9$	This work

<sup>a</sup> Value adjusted by the application of various corrections so as to bring them to a common basis. See ref 20. <sup>b</sup> Value derived from experimental enthalpies of formation of alanine containing dipeptides.

(O1) and the other in a bifurcated hydrogen bond (O2). In spite of this fact, significant differences in the C–O lengths in  $\alpha$ -alanine (DL) are observed. This may be due to the conformation of the molecule which is more extended in  $\alpha$ -alanine (DL) than in  $\beta$ -alanine, the longer bond being the one involved in the bifurcated interaction.

In the gas phase, where the intermolecular interactions have no effect, amino acids are intrinsically flexible systems, existing as their nonionized forms. Like other amino acids,  $\alpha$ - and  $\beta$ -alanine molecules exhibit significant internal rotational degrees of freedom due to free rotation of the  $\text{NH}_2$ ,  $\text{COOH}$ , and  $\text{OH}$  groups with respect to the carbon skeleton, and a number of low-energy conformers. Intramolecular hydrogen bonding becomes important in conformations in the gas phase. The energy barriers that separate different conformers are typically rather small for many conformations so that thermal energy at room temperature enables the molecule to freely change from one conformation to another. Therefore, it is not generally feasible to isolate a specific conformer experimentally at room temperature.<sup>50</sup> Iijima and Beagley<sup>51</sup> carried out in 1991 an electron diffraction study of gaseous  $\alpha$ -alanine, and in 1999, a reinvestigation of molecular structure and conformation of gaseous  $\alpha$ -alanine by joint analysis using electron diffraction data and rotational constants was made by Iijima and Nakano,<sup>52</sup> determining the molecular parameters of two species. To our knowledge, there has not been any experimental study on the gaseous molecular structure of  $\beta$ -alanine.

$\alpha$ -Alanine has been the subject of numerous theoretical calculations.<sup>53–64</sup> Before the 1990s, Schäfer and co-workers<sup>53</sup> examined two conformers at the HF/4–21G level. In 1993, Godfrey et al.<sup>54</sup> studied six conformers at the HF/6-31G(d,p) level and registered the rotational spectra of  $\alpha$ -alanine using Stark-modulated free-expansion jet spectrometry. They experimentally identified two different conformers with a ratio of relative abundances to be about 8:1. In 1995, Császár,<sup>55</sup> Gronert



**Figure 3.** Molecular structures of  $\alpha$ -alanine (DL) (left) and  $\beta$ -alanine (right) at room temperature showing the conformation of the molecules and the N–H...O intermolecular interactions (C1–O1/O2 = 1.240(2)/1.254(2) Å, N1C1C2O1 = 16.3(2)°, N1–H...O1 = 2.865(2), H...O1 = 2.00 Å, N1–H...O1 = 165°; N<sup>+</sup>–H...O2: 2.804(2), 1.92 Å, 173 and 2.817(2), 1.96 Å, 160° for the  $\alpha$ -alanine (DL); C1–O1/O2 = 1.252(2)/1.257(2) Å, O1C1C2C3 = 12.6(2), C1C2C3N1 = 83.2(1)°, N1–H...O1 = 2.756(3), 1.83 Å, 164° and N<sup>+</sup>–H...O2: 2.833(8), 1.91 Å, 174°/2.795(8), 1.89 Å, 159° for the  $\beta$ -alanine).

and O'Hair,<sup>56</sup> and Cao et al.<sup>57</sup> used MP2 correlated methods to study the conformers of  $\alpha$ -alanine, but in the two first studies the authors located only 5 and 10 conformers while in the last study the authors identified for the first time the set of 13 conformers commonly accepted for  $\alpha$ -alanine. One year later, Császár<sup>58</sup> carried out again a detailed theoretical study on the complete set of conformers of gaseous  $\alpha$ -alanine at different DFT and ab initio methods, with different basis sets. Also, Godfrey et al.<sup>59</sup> repeated their theoretical work studying the 13 conformers at the MP2/6-31G(d,p) level. The full set of conformers have also been studied by Selvarengan and Kolan-daivel<sup>60</sup> at different DFT methods with 6-311++G(d,p) basis set. The five lowest-energy conformers were studied by Stapanian et al.<sup>61</sup> using B3LYP and MP2 methods with aug-cc-pVDZ basis set, combined with an experimental study by matrix-isolation IR spectroscopy. A similar experimental and theoretical study was carried out by Lambie et al.<sup>62</sup> at the B3LYP/6-31++G(d,p) level. And more recently, Upadhyay et al.<sup>63</sup> have carried out an ab initio and density functional study of L- and D-forms of  $\alpha$ -alanine, and Yang et al.<sup>64</sup> have studied the 5 lowest-energy conformers at the MP2 and B3LYP/6-31++G(d,p) levels.

There have been several theoretical studies on the conformers of  $\beta$ -alanine since 1990.<sup>65–73</sup> Ramek<sup>65</sup> showed via HF/4-31G level calculations that as many as 38 stable conformers of the neutral species of  $\beta$ -alanine may exist, which include 20 conformational isomers with unique intrinsic geometry, disregarding optical isomers. These conformers involve a number of intramolecular interactions of different chemical nature that have been characterized in detail by Ramek et al.<sup>65</sup> McGlone and Godfrey<sup>66</sup> studied the rotational spectrum of  $\beta$ -alanine from the 20 conformational isomers obtained by Ramek et al.<sup>65</sup> They found that one of them was not a local minimum on the HF/6-31G(d,p) potential energy surface. They identified two conformers by using a Stark-modulated free-expansion jet spectrometer. Heal et al.<sup>67</sup> analyzed the family of 20 stable conformations in terms of their shape similarities, using the topological shape group method, using the 6-31G(d,p) basis set. Several high-level ab initio studies have been recently published. Galano and Alvarez-Idaboy<sup>68</sup> investigated 12 conformers using the MP2 method with 6-311G(d,p) and 6-311++G(d,p) basis sets. Tian<sup>69</sup> has studied 10 low-lying conformers by the hybrid density functional B3LYP/aug-cc-pVDZ method. Sanz et al.<sup>70</sup> have identified two new conformers using the combination of Fourier transform microwave spectroscopy in a pulsed supersonic jet with laser ablation. They also carried out calculations

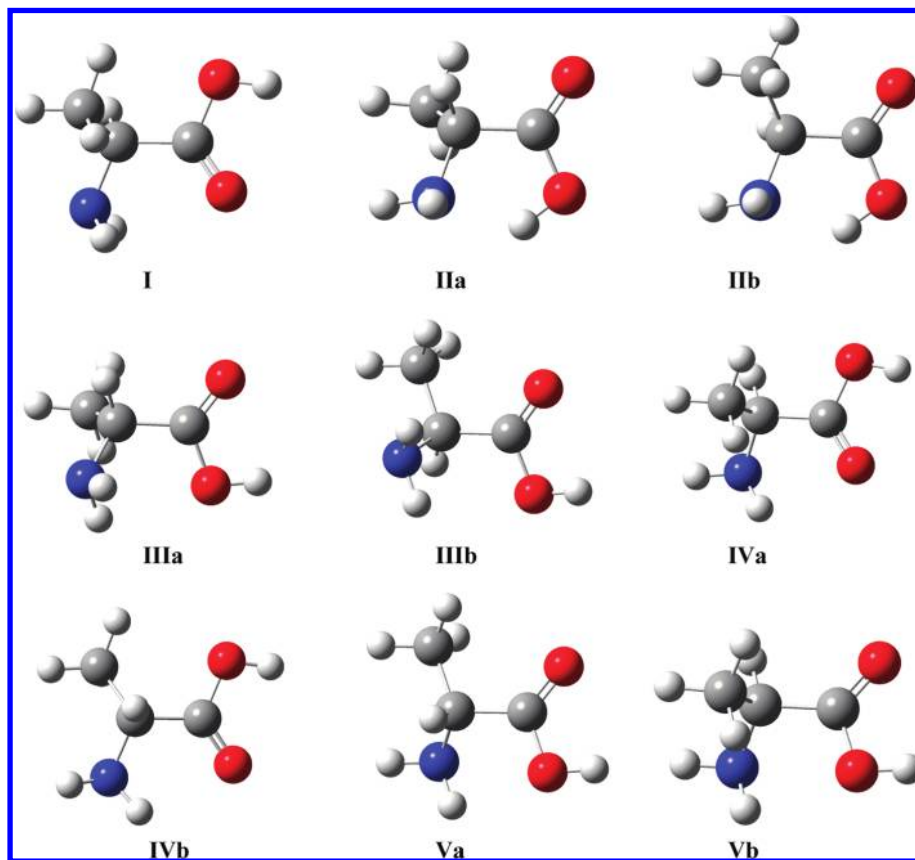
at the MP2/6-311++G(d,p) level on the 20 structures previously reported. More recently, Dobrowolski et al.<sup>71</sup> have recorded for the first time the argon-matrix low-temperature FTIR spectra of  $\beta$ -alanine. They revealed a quite complicated spectral pattern which suggests the presence of several conformers in the matrix. To interpret the spectra, the authors investigated 18 conformers at B3LYP and MP2 levels, combined with the aug-cc-pVDZ basis set, and reoptimizing the 10 low-energy structures at the QCISD/aug-cc-pVDZ, and B3LYP and MP2 levels by using the aug-cc-pVTZ basis set. The authors demonstrated the presence of at least three  $\beta$ -alanine conformers, and the possible presence of five additional conformers. Zhang et al.<sup>72</sup> have reported a photoionization and dissociative photoionization study of  $\beta$ -alanine using IR laser desorption combined with synchrotron vacuum ultraviolet (VUV) photoionization mass spectrometry. They studied the four most stable conformers and their cations at the G3//B3LYP level. And very recently, Dorofeeva and Ryzhova<sup>73</sup> have carried out a theoretical study at the G4 level on the enthalpy of formation of  $\beta$ -alanine, optimizing 11 conformers at the MP2/6-311++G(2df,p) level.

In this work, we have first identified a set of conformers of  $\alpha$ - and  $\beta$ -alanine at low levels of theory, and then the most stable ones were reoptimized at higher levels. Finally, for the set of conformers within  $\sim 10$  kJ·mol<sup>−1</sup> range (9 and 11 conformers for  $\alpha$ - and  $\beta$ -alanine, respectively) we have obtained their energies at the G3 level. The structures of the most stable conformers of both alanines obtained in this work, optimized at the MP2(Full)/6-31G(d) level, are shown in Figures 4 and 5, respectively. Their Cartesian coordinates are collected in the Supporting Information.

The nine conformers of  $\alpha$ -alanine optimized in this work match with the nine lowest-energy conformers located by Császár,<sup>58</sup> and we have followed the same nomenclature (see Figure 4). All investigations agree that conformer I is the most stable form of  $\alpha$ -alanine.

In the case of  $\beta$ -alanine, we have located 11 conformers; 10 of them are included in the set of 20 conformers located initially by Ramek,<sup>65</sup> and we have followed the same nomenclature. One of the conformers located by us is not included in the set of 20 conformers previously established, but matches with conformer V in the paper of Galano and Alvarez-Idaboy.<sup>68</sup> We have named it as conformer A (see Figure 5). All investigations agree that conformer I is the most stable form of  $\beta$ -alanine.

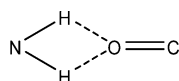
The lowest-energy conformer, for both alanines, has been reoptimized at the MP2(full)/6-31G(3df,2p) level to obtain a



**Figure 4.** MP2(full)/6-31G(d)-optimized structures of the nine lowest-energy conformers of  $\alpha$ -alanine.

more reliable molecular structure, and it is shown in Figures 6 and 7, respectively.

The most stable conformer of  $\alpha$ -alanine (see Figure 6) presents a bifurcated  $\text{N}-\text{H}\cdots\text{O}$  hydrogen bond between the oxygen of the carboxylic group and the two hydrogen atoms of the amino group, but the bifurcated  $\text{H}\cdots\text{O}$  interactions are not equal (2.59 and 2.83 Å) due to the chirality of the  $\alpha$ -carbon atom.



The most stable conformer of  $\beta$ -alanine (see Figure 7) is stabilized by  $\text{N}-\text{H}\cdots\text{O}$  hydrogen bond (2.36 Å). The hydrogen bond is now established between the oxygen atom of the carboxylic group and only one of the hydrogens of the amino group, presumably because a bifurcated interaction imposes too close a distance between the atoms involved. Therefore, two conformers can arise in  $\beta$ -alanine, depending on the H atom involved in the intramolecular interaction.<sup>70</sup>

The optimized geometrical parameters for the most stable conformers of  $\alpha$ - and  $\beta$ -alanine have been collected in Tables S4 and S5 of the Supporting Information. As it can be observed in Table S4, there is a very good agreement between the optimized structure of  $\alpha$ -alanine and the experimental molecular structure in the gas phase determined by Iijima and Nakano.<sup>52</sup>

A population analysis using the natural bond orbital (NBO) analysis to obtain the natural atomic charges (the nuclear minus summed populations of the natural atomic orbitals on the atoms) that characterize the ground electronic state of the compounds studied has also been carried out. The calculated NBO charges located at all the atoms for the most stable structures of  $\alpha$ - and  $\beta$ -alanine are reported in Tables S4 and S5 of the Supporting

Information. In  $\alpha$ -alanine, all the heavy atoms are negatively charged except the C atom of the carboxylic group, with a charge of 0.967. Partial negative charges are located at the N atom (−0.914), the two O atoms (−0.716 the O atom of the carbonyl group, and −0.792 the O atom of the OH group), and the C atoms of the CH (−0.138) and  $\text{CH}_2$  (−0.642) groups. In  $\beta$ -alanine, the behavior is very similar, with similar charges on the heavy atoms.

#### Theoretical Determination of the Enthalpies of Formation.

G3-calculated energies at 0 K, enthalpies at 298 K, and entropies for the nine lowest-energy conformers of  $\alpha$ -alanine and for the eleven lowest-energy conformers of  $\beta$ -alanine are given in Tables 8 and 9, respectively.

The standard procedure to obtain enthalpies of formation in Gaussian-*n* theories is through atomization reactions.<sup>74</sup> The G3-calculated enthalpies of formation of the studied conformers of  $\alpha$ -alanine and  $\beta$ -alanine, using atomization reactions, are shown in Tables 8 and 9, respectively.

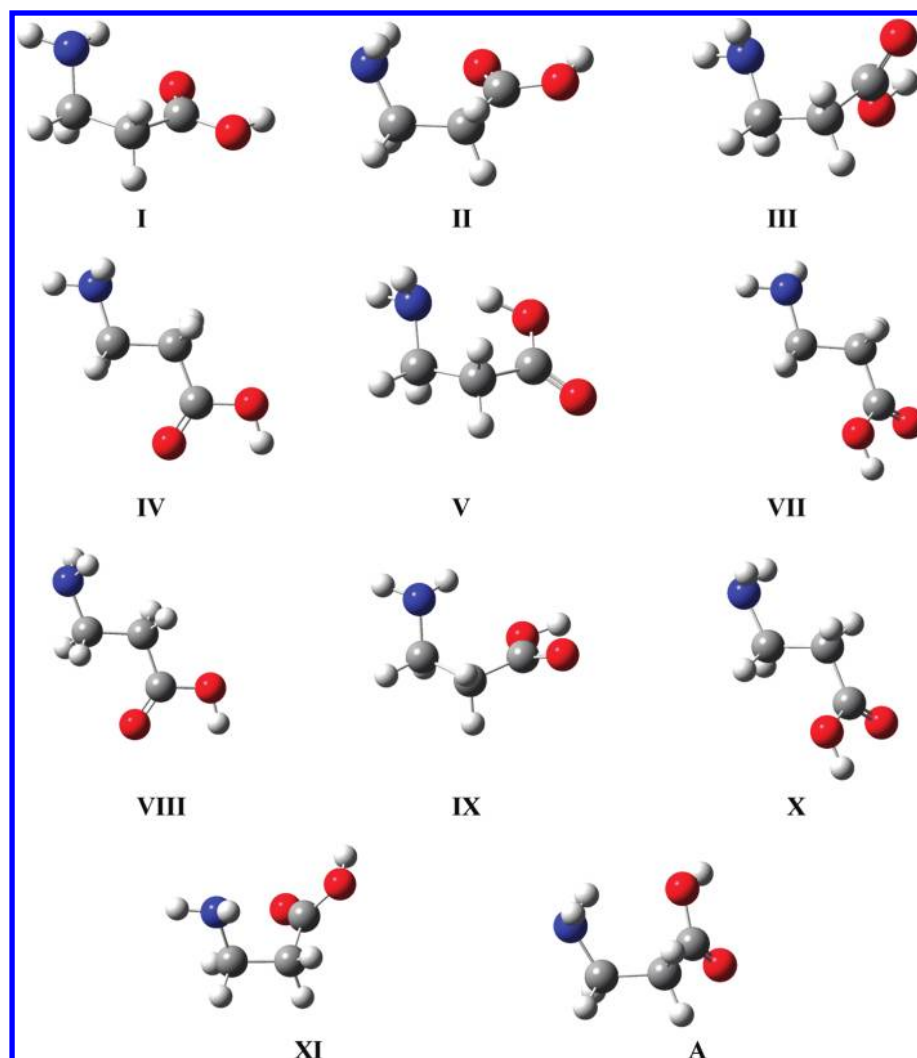
To obtain the conformational composition of both alanines in the gas phase, at 298 K, the  $\Delta_f G_m^\circ$  values are needed. They can be calculated through eq 5

$$\Delta_f G_m^\circ(i) = \Delta_f H_m^\circ(i) - T[S^0(i) - \sum S^0(\text{el})] \quad (5)$$

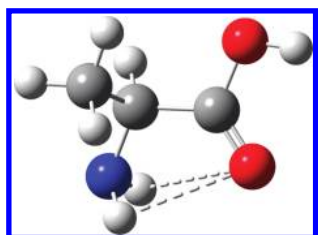
where the sum of the entropy of the elements, in the case of the compounds studied, is calculated as

$$\sum S^0(\text{el}) = 3S^0(\text{C}, \text{s}) + \frac{7}{2}S^0(\text{H}_2, \text{g}) + \frac{1}{2}S^0(\text{N}_2, \text{g}) + S^0(\text{O}_2, \text{g}) \quad (6)$$

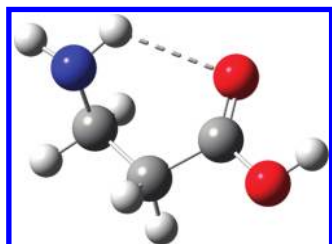




**Figure 5.** MP2(full)/6-31G(d)-optimized structures of the eleven lowest-energy conformers of  $\beta$ -alanine.



**Figure 6.** MP2(full)/6-31G(3df,2p)-optimized structure of the lowest-energy conformer of  $\alpha$ -alanine.



**Figure 7.** MP2(full)/6-31G(3df,2p)-optimized structure of the lowest-energy conformer of  $\beta$ -alanine.

Using for the elements the entropy values at 298 K taken from ref 75,  $\Delta_f G_m^\circ$  values have been obtained for all the conformers and collected in Tables 8 and 9.

Using eq 7

$$x_i = \frac{e^{-\left[\frac{\Delta_f G_m^\circ(i)}{RT}\right]}}{\sum_{i=1}^n e^{-\left[\frac{\Delta_f G_m^\circ(i)}{RT}\right]}} \quad (7)$$

we have obtained the compositions in the gas phase at 298 K for  $\alpha$ - and  $\beta$ -alanines, as they are shown in Tables 8 and 9. As it can be observed that the most stable conformer of  $\alpha$ -alanine, conformer I, accounts for 43.2% of the composition in the gas phase. For  $\beta$ -alanine, conformer I accounts for 44.6% of the gas-phase composition.

Using eq 8

$$\Delta_f H_m^\circ(X) = \sum_{i=1}^n x_i \Delta_f H_m^\circ(i) \quad (8)$$

the final value for the enthalpy of formation of  $\alpha$ -alanine (DL) is calculated as  $-424.8 \pm 4.4 \text{ kJ} \cdot \text{mol}^{-1}$ , and a value of  $-419.1 \pm 4.4 \text{ kJ} \cdot \text{mol}^{-1}$  is obtained for  $\beta$ -alanine. The estimated error of G3 calculations is taken from the mean absolute deviation for the G3-calculated enthalpies of forma-

TABLE 8: G3 Results for  $\alpha$ -Alanine Conformers

conformer	$E_0^a$	$H_{298}^a$	$\Delta\Delta H^b$	$S^c$	$\Delta_f H_{298K}^0$	$\Delta_f G_{298K}^0$	$\chi$
I	-323.525411	-323.517445	0.0	333.93	-426.47	-294.83	0.432
IIa	-323.524679	-323.516961	1.3	328.15	-425.19	-291.83	0.129
IIb	-323.524242	-323.516557	2.3	327.59	-424.13	-290.60	0.078
IIIa	-323.523596	-323.515625	4.8	337.09	-421.69	-290.99	0.092
IIIb	-323.523670	-323.515720	4.5	338.82	-421.94	-291.76	0.125
IVa	-323.523708	-323.515762	4.4	332.98	-422.05	-290.13	0.065
IVb	-323.523460	-323.515572	4.9	331.86	-421.55	-289.29	0.046
Va	-323.522806	-323.514929	6.6	331.43	-419.86	-287.48	0.022
Vb	-323.522103	-323.514149	8.7	332.99	-417.81	-285.89	0.012

<sup>a</sup> In hartrees. <sup>b</sup> In kJ·mol<sup>-1</sup>. <sup>c</sup> In J·mol<sup>-1</sup>·K<sup>-1</sup>.TABLE 9: G3 Results for  $\beta$ -Alanine Conformers

conformer	$E_0^a$	$H_{298}^a$	$\Delta\Delta H^b$	$S^c$	$\Delta_f H_{298K}^0$	$\Delta_f G_{298K}^0$	$\chi$
I	-323.523469	-323.515730	0.0	331.70	-421.96	-289.66	0.446
II/VI <sup>d</sup>	-323.522411	-323.514652	2.8	333.14	-419.13	-287.26	0.169
III	-323.520860	-323.513052	7.0	333.13	-414.93	-283.05	0.031
IV	-323.521201	-323.513235	6.6	338.12	-415.41	-285.02	0.069
V	-323.522596	-323.515173	1.5	324.08	-420.50	-285.92	0.099
VII	-323.520500	-323.512517	8.4	339.39	-413.53	-283.52	0.037
VIII	-323.520540	-323.512696	8.0	336.74	-414.00	-283.20	0.033
IX	-323.519841	-323.511872	10.1	340.57	-411.83	-282.17	0.022
X	-323.519717	-323.511748	10.5	341.97	-411.51	-282.27	0.023
XI	-323.519511	-323.511642	10.7	340.23	-411.23	-281.47	0.016
A	-323.520878	-323.513019	7.1	338.21	-414.85	-284.49	0.055

<sup>a</sup> In hartrees. <sup>b</sup> In kJ·mol<sup>-1</sup>. <sup>c</sup> In J·mol<sup>-1</sup>·K<sup>-1</sup>. <sup>d</sup> The structures of conformers II and VI converged to the same minimum.

tion obtained by Curtiss et al.<sup>76</sup> using the G3/99 test set that includes 222 experimental values. Our calculated values are in very good agreement with the experimental values measured in this work,  $-426.3 \pm 2.9$  and  $-421.2 \pm 1.9$  kJ·mol<sup>-1</sup>, respectively, and also the value calculated for  $\alpha$ -alanine coincides with the experimental value recommended for  $\alpha$ -alanine (L) by Dorofeeva and Ryzhova,<sup>77</sup>  $-424.8 \pm 2.0$  kJ·mol<sup>-1</sup>. These last authors have calculated a value of  $-427.6 \pm 4.0$  kJ·mol<sup>-1</sup> for  $\alpha$ -alanine (L), at the G3X level, and very recently<sup>73</sup> have calculated a value of  $-419.0$  kJ·mol<sup>-1</sup> for  $\beta$ -alanine, at the G4 level.

Since calculated entropies of formation for  $\alpha$ - and  $\beta$ -alanine are essentially identical,  $-442.7$  and  $-442.4$  J·mol<sup>-1</sup>·K<sup>-1</sup>, respectively, this means that the difference in Gibbs energies of formation arises from the difference in enthalpies of formation; that is, the intrinsic relative stability is of enthalpic origin. Values of  $-292.8$  and  $-287.2$  kJ·mol<sup>-1</sup> have been calculated in this work for the Gibbs energies of formation of  $\alpha$ - and  $\beta$ -alanine, respectively.

The isomerization enthalpy between  $\alpha$ - and  $\beta$ -alanine, corresponding to reaction



is calculated as  $4.5$  kJ·mol<sup>-1</sup> (using only the lowest-energy conformer) or  $5.7$  kJ·mol<sup>-1</sup> (using all the conformers), in very good agreement with the value derived from the experimental enthalpies of formation measured in this work,  $5.1 \pm 3.5$  kJ·mol<sup>-1</sup>. It is also of interest to point out that the experimental and calculated enthalpies of formation determined in the present work indicate that the more branched amino acid ( $\alpha$ -alanine) is intrinsically more stable than the linear  $\beta$ -amino acid,  $\beta$ -alanine. This observation is in line with the well-established stability of branched alkanes relative to linear  $n$ -alkanes.<sup>78</sup>

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**Supporting Information Available:** Table S1 presents the exact areas and transmission probability factors for the platinum orifices of the Knudsen effusion apparatus. Tables S2 and S3 list the details of all the combustion calorimetry experiments at  $T = 298.15$  K for  $\alpha$ -alanine (DL) and  $\beta$ -alanine. Tables S4 and S5 collect the optimized geometrical parameters and the calculated NBO charges for the most stable conformers of  $\alpha$ - and  $\beta$ -alanine. Also are included the Cartesian coordinates for all the lowest-energy conformers of  $\alpha$ - and  $\beta$ -alanine, optimized in this work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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