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Original Scientific Paper

Gas-phase Basicity of Glycine*

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Abstract. The protonation thermochemistry of gaseous glycine is re-examined. The composite G3, G3MP2, G3B3, CBS-Q and CBS-QB3 methods have been used to estimate the enthalpy component *i.e.* the proton affinity of glycine, PA(Gly). The so called "protonation entropy", Δ_pS(Gly) = $S°$(GlyH$^+$) − $S°$(Gly), has been evaluated by calculating contributions to entropy of the internal rotations using the Pitzer hindered rotor model. The resulting theoretical gas-phase basicity, GB(Gly) = PA(Gly) − T[$S°$(H$^+$) − Δ_pS(Gly)] has been then calculated. These computations were done, either by considering only the most stable neutral and protonated conformers of glycine ("most stable conformer" values, denoted "msc") or a population of conformers based on a Boltzmann distribution at 298 K ("molar" values). An isodesmic procedure has been used by anchoring the computed data to the experimental proton affinities of isopropylamine. The results are the following: PA_{msciso}(Gly) = 889.2 kJ mol^{-1}, PA_{molar}(Gly) = 890.9 kJ mol^{-1}, Δ_pS_{msciso}(Gly) = 2.3 J mol^{-1} K^{-1}, Δ_pS_{molar}(Gly) = 1.2 [−6.2] J mol^{-1} K^{-1}, GB_{msciso}(Gly) = 857.5 kJ mol^{-1}, GB_{molar}(Gly) = 858.9 [856.6] kJ mol^{-1} [values in brackets correspond to data obtained by including the entropy of mixing]. Evaluated values of PA(Gly)= 889 kJ mol^{-1} and GB(Gly)= 856 kJ mol^{-1}, at 298 K, may be proposed after comparison with the available experimental data.

Keywords: proton affinity, gas-phase basicity, protonation entropy, aminoacids

INTRODUCTION

Proton affinity, PA(M), and gas phase basicity, GB(M), of a molecule M are the standard enthalpy and standard Gibbs free energy, respectively, of the deprotonation reaction (1), *i.e.* PA(M) = $\Delta_1H°$ and GB(M) = $\Delta_1G°$:

$$MH^+_{(gas)} \rightarrow M_{(gas)} + H^+_{(gas)} \quad (1)$$

Concerning the entropy change associated with reaction (1), it may be recalled that it is a custom to call "protonation entropy" the difference in absolute entropies between the protonated and the neutral forms of the species M:

$$\Delta_pS^\circ(M) = S^\circ(MH^+) - S^\circ(M) \quad (2)$$

This definition consequently leads to $\Delta_1S°$ = $S°$(H$^+$) − $\Delta_pS°$(M).

Determination of the gas-phase thermochemical parameters GB(M), PA(M) and $\Delta_pS°$(M) is of interest in several fundamental and applied aspects of chemistry and biochemistry. First, they represent the pure Brønsted basicity properties of the considered species since no solvent molecules or counter ions are involved.[1,2] Enthalpy and entropy changes associated with gas-phase protonation are thus intrinsic characteristics of the molecule. In line with this idea, these data may be also used to understand enzyme activity since it is known that the latter is determined by local acid-base properties of amino acid residues. Second, protonation is one of the major means to efficiently produce ions in a mass spectrometer in order to analyse chemical and biochemical molecules. The knowledge of the energies involved during the ionization process allows us to identify the protonation site and to understand the overall fragmentation processes.

Both experimental and theoretical methods of determination of the relevant thermochemical parameters have seen considerable improvements in the recent years.[3–6] Moreover, application to molecules of biochemical interest is an area of continuous progress.[7,8] In this short paper we intend to review and to update the structural and energetic aspects of the protonation of the simplest naturally occurring amino acid - glycine (Gly). Previous experimental and theoretical determinations are recalled and evaluated and new computational data

* Dedicated to Professor Zvonimir Maksić on the occasion of his 70th birthday.
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are provided by using state of the art quantum chemistry methods.

THEORETICAL PROCEDURES

Standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were carried out with the Gaussian03 computer program.[9] High level composite procedures including the latest formulation of (i) the Gn composite methods G3, G3B3 and G3MP2 [10] and (ii) the complete basis set CBS-Q and CBS-QB3 approach of Petersson *et al.*,[11] were used to determine accurate proton affinities at 298 K. These benchmark theoretical methods were compared to the less expensive hybrid DFT method using B3LYP/6-31+G(d,p) optimized geometries and single point calculations with the 6-311++G(3df,2p) basis set.

If we define $\Delta X_T(\mathrm{M})$ by the difference $X_T(\mathrm{M}) - X_T(\mathrm{MH}^+)$, the theoretical proton affinity of a molecule M, at a given temperature T is given by the sum:

$$\mathrm{PA}_T(\mathrm{M}) = \Delta E^\circ(\mathrm{M}) + \Delta\mathrm{ZPVE}(\mathrm{M}) + \Delta U_T^\circ(\mathrm{M})_{\mathrm{vib}} + \frac{5}{2}RT \qquad (3)$$

with $E°$ being the potential energy of the system relative to infinitely separated electrons and nuclei (*i.e.* the "total energy"), ZPVE the zero point vibrational energy, $U°_{T\mathrm{vib}}$ the contribution of vibration to the internal energy and the $5/2RT$ term arising from the sum of the translational and rotational contributions to the internal energy, not forgetting the PV contributions to enthalpy of the components of reaction (1). A good agreement is generally observed between proton affinity calculated using Eq. (3) at the G3's or CBS's levels and experiment since the standard deviation is close to 2 kJ mol^{-1}.[6]

In the Gaussian suite of programs,[9] standard statistical thermodynamic formulae are used in order to obtain the electronic, translational, rotational and vibrational contributions to entropy. The latter terms are estimated using the harmonic oscillator approximation. However, it is known that the lowest frequencies, particularly internal rotations, are generally highly anharmonic and are thus poorly described by the harmonic oscillator approximation. Unfortunately, the lowest frequencies are also those which give the largest contributions to the vibrational entropy. A means to more correctly estimate the vibrational entropy is to treat separately each internal rotation in the frame of a hindered rotor model. For this purpose we have chosen the model developed by Pitzer[12] which has proved to be successful when applied to monofunctional[13] or bifunctional[14] molecules containing up to four internal rotations. Briefly, this procedure involves calculation of the rotational energy barrier, $V_{0,}$ appearing in the variation of the potential energy with the dihedral angle ϕ of the considered internal rotation. The reduced moment of inertia, $I_{\mathrm{red,}}$ of the two rotating groups around the axis containing the bond is also required in order to calculate the partition function. In the present study, the rotational potential energy barriers, V_0, associated with rotations around the C−C, C−N and C−O bonds were obtained at the B3LYP/6-31+G(d,p) level. A relaxed rotation approach was adopted (*i.e.* all geometrical parameters were optimised except the dihedral angle considered). A complete scan of the dihedral angle, between 0 and 360° by steps of 20° to 5°, was explored for each torsional mode. The V_0 values used in the entropy calculations were equated with the difference between maxima and minima of the potential energy curves.

Note that, when the barrier V_0 is large enough, the rotational motion approaches that of a simple vibration which may be described by the harmonic oscillator model. Accordingly, if the potential energy is of the type $V_0(\phi) = V_0/2\ (1 - \cos n\ \phi)$, it reduces to the potential energy of a harmonic oscillator of fundamental frequency:

$$\nu_{\mathrm{harm.\ rot}} = (n/2\pi)(V_0/2I_{\mathrm{red}})^{1/2} \qquad (4)$$

Computation of entropy using this fundamental frequency in the harmonic oscillator approximation will be compared to the results given by the Pitzer model. The procedure described above leads generally to $\Delta_p S°(\mathrm{M})$ accurate to within ±2 J mol^{-1} K^{-1} per hindered rotation.[13,14]

RESULTS AND DISCUSSION

Experimental Gas-phase Protonation Thermochemistry of Glycine

Gas-phase Basicity from Equilibrium and Thermokinetic Measurement

The first determination of the gas phase basicity of glycine came from the measurement of proton transfer equilibrium constants, either by high pressure mass spectrometry[15] or by ion cyclotron resonance mass spetrometry.[16,17] The method is based on the determination of the equilibrium constant K_i of a proton exchange reaction (i) between the molecule of interest M and a reference base B_i:[3,6]

$$\mathrm{MH}^+ + \mathrm{B} \rightarrow \mathrm{M} + \mathrm{BH}^+ \qquad \text{(i)}$$

At a given temperature T, the standard Gibbs free energy of reaction (i) is equal to $\Delta_i G_T^\circ = -RT \ln K_i$ and,

considering the definitions of the gas-phase basicity and protonation entropy, the 298 K gas-phase basicity of M may be deduced from Eq. (5):

$$GB_{298}(M) = GB_{298}(B) + \Delta_i G^\circ_T - (T-298)\left[\Delta_p S^\circ_{298}(M) - \Delta_p S^\circ_{298}(B)\right] \quad (5)$$

if the variation of enthalpy and entropy with temperature may be neglected in the *T*/298 K range.

Moreover, if experiments are conducted at variable temperature, the enthalpy and entropy components of $\Delta_i G°_T$ may be disclosed by plotting ln K_i against $1/T$ following the well known van t'Hoff method. This procedure has been applied to the determination of the proton affinity and protonation entropy of glycine from high pressure mass spectrometry experiments.[15] The set of data coming from ICR experiments was obtained at only one temperature.[16,17]

Mautner *et al*.,[15] reported proton transfer experiments between glycine and aniline at variable temperature. They observed that, in the investigated temperature region 450−550 K, $\Delta_i H°$ and $\Delta_i S°$ are equal to zero. Assuming that $\Delta_i H° \approx \Delta_i H^\circ_{298}$ and $\Delta_i S° \approx \Delta_i S^\circ_{298}$, this means that $PA_{298}(\mathrm{Gly}) \approx PA_{298}(\mathrm{aniline})$ and $\Delta_p S^\circ_{298}(\mathrm{Gly}) \approx \Delta_p S^\circ_{298}(\mathrm{aniline})$ within the uncertainties limits. Since the tabulated proton affinity and protonation entropy of aniline[18] are equal to 882.5 kJ mol^{-1} and 2 J mol^{-1} K^{-1}, respectively, the experiments described in ref. 15 lead to PA(Gly) = 882.5 ± 4 kJ mol^{-1} and $\Delta_p S^\circ_{298}(\mathrm{Gly})$ = 2 ± 8 J mol^{-1} K^{-1}. In the same study, the proton transfer equilibrium constant involving 2-cyanopyridine and glycine has been determined at 500 K, thus leading to $\Delta_i G^\circ_{500} = 7.9$ kJ mol^{-1}. Introducing into Eq. (5) the following tabulated data[18] GB_{298}(2-cyanopyridine) = 841.0 kJ mol^{-1} and $\Delta_p S^\circ_{298}(2-\mathrm{cyanopyridine})$ = 2 J mol^{-1} K^{-1} but assuming $\Delta_p S^\circ_{298}(\mathrm{Gly})$ = 0 for the purpose of simplicity (the only experimental value is 2 ± 8 J mol^{-1} K^{-1}, as recalled above, but the "evaluated" value is −6 J mol^{-1} K^{-1} (ref. 18) and a theoretical estimate close to zero will be discussed in the last section of this paper) we derive GB_{298}(Gly) = 849.4 kJ mol^{-1}. A comparable treatment using the aniline data (*i.e.* GB_{298}(aniline) = 850.6 kJ mol^{-1} leads to GB_{298}(Gly) = 851.0 kJ mol^{-1}. In summary (Table 1), the Mautner *et al*.[15] results point to an average gas-phase basicity GB_{298}(Gly) = 850.2 ± 0.8 kJ mol^{-1} (assuming $\Delta_p S^\circ_{298}(\mathrm{Gly})$ = 0) and a resulting proton affinity of PA_{298}(Gly) = 882.6 kJ mol^{-1} in good agreement with the 882.5 ± 4 kJ mol^{-1} obtained from a van t'Hoff plot.

Locke *et al*.[16,17] determined equilibrium constants for proton transfer between glycine and four reference bases, namely methylamine, dimethylformamide, 2-fluoropyridine and aniline, in a pulsed ion cyclotron resonance mass spectrometer. Measurements were made at the temperature of 382 K and the resulting $\Delta_i G^\circ_{382}$ together with the data necessary to deduce GB_{298}(Gly) using Eq. (4) are summarised in Table 2. The average value of GB_{298}(Gly) = 856.6 ± 0.9 kJ mol^{-1} (assuming $\Delta_p S^\circ_{298}(\mathrm{Gly})$ = 0) and the resulting PA_{298}(Gly) = 889.0 kJ mol^{-1} are reported in Table 1.

A comparison between the two GB_{298}(Gly) estimates reveals a significant difference of 6.4 kJ mol^{-1}. It is not obvious to explain this difference but it should be remembered that the major sources of error in the equi-

Table 1. Summary of experimental and theoretical gas-phase protonation thermochemistry of glycine (in bold, this work)

Method	GB(M) / kJ mol^{-1}	PA(M) / kJ mol^{-1}	$\Delta_p S°$(M) / J K^{-1}mol^{-1}
Equilibrium	850.2±0.8[a]	882.6[a]	2±8[a]
	856.6±0.9[b]	(889.0)	(0)
Thermokinetic	855.1±1.9[c]	(887.5)	(0)
Simple kinetic	-	886.4[d]	-
	-	897.4[e]	-
		887.1[f]	-
Extended kinetic	855.4±3.6[f]	886.3±3.1[f]	2±6[f]
Theoretical (most stable conformers)		889[g] – 888.3[h]	
	857.5	**889.2**	**2.3**
Theoretical (molar)	851.4 [856.2][i]	883.2 [888.0][i]	(2.1)
	858.92	**890.9**	**1.2**
	856.6[j]	**890.9**	**−6.2**[j]

[a] From ref. 15. [b] From ref. 16 as adapted by Hunter & Lias in ref 18. [c] From ref. 19 using the ΔG_a correction proposed in ref. 22. [d] From ref. 24 corrected to the Hunter & Lias scale (ref. 22). [e] From ref. 25 corrected by anchoring the result to the Hunter & Lias (ref. 22) PA value of the closest reference base used by the authors (*i.e.* serine, for which $PA_{Hunter\&Lias}$(Serine) = 914.6 kJ mol^{-1} rather than 905.4 kJ mol^{-1} used in ref. 25). [f] From ref. 26. [g] G2MP2 calculation from ref 59. [h] G2 calculations, from ref. 61. [i] From ref. 62, into brackets, corrected by considering isodesmic reactions involving ammonia and methylamine. [j] when considering the entropy of mixing.

Table 2. Experimental data for proton transfer equilibrium: $GlyH^+ + B \rightarrow Gly + BH^+$

B	$\Delta_i G^\circ_T(T)$ / kJ mol^{-1}	$GB_{298}(B)^{(a)}$ / kJ mol^{-1}	$\Delta_p S^\circ_{298}(B)^{(b)}$ / J K^{-1}mol^{-1}	$GB_{298}(Gly)^{(b)}$ / kJ mol^{-1}
Methylamine[(c)]	−6.3 (382 K)	864.5	−7	857.6
Dimethylformamide[(c)]	0.8 (382 K)	856.6	5	857.0
2-Fluoropyridine[(c)]	3.3 (382 K)	852.7	2	856.2
Aniline[(c)]	4.8 (382 K)	850.6	2	855.6
Aniline[(d)]	0.0 (500 K)	850.6	2	851.0
2-Cyanoropyridine[(d)]	7.9 (570 K)	841.0	2	849.4

[(a)] Tabulated values, from ref. 18; [(b)] Calculated using Eq (4) *i.e.* $GB_{298}(Gly) = GB_{298}(B) + \Delta_i G°_T - (T - 298)\ \Delta_p S^\circ_{298}(Gly) - \Delta_p S^\circ_{298}(B)$], assuming $\Delta_p S^\circ_{298}(Gly) = 0$; [(c)] From ref. 16; [(d)] From ref. 15.

librium method appear to be associated with the measurement of the exact temperature of the experiments and of the pressure of the neutral reactants. The latter point is critical in the case of glycine since in both experiments it has been volatilized by heating the sample in a direct insertion probe close to the reacting region. The uncertainties associated with these difficulties, which may affect both ion cyclotron resonance and high pressure mass spectrometry experiments, may provide an explanation to the observed discrepancies.

Another experimental approach of gas phase basicity is given by the "bracketing" technique.[3,6] Qualitatively, this method is based on the occurrence or non-occurrence of an ion-molecule reaction and the assumption that the reaction will be observed only if its Gibbs free energy change is negative. Quantification of the bracketing method has been proposed in an operational formalism called the "thermokinetic" method.[6] Briefly, the basis of the method is to consider a proton transfer reaction from MH^+ to B (reaction (i)) and to determine the corresponding bimolecular rate constant, k_{bim} from the MH^+ decay. By using the canonical thermodynamic formulation of the transition state theory it may be shown that k_{bim} can be related to the Gibbs free energy of reaction (i), $\Delta_i G°_T$. The thermokinetic method used consists of deducing the gas phase basicity $GB_{298}(M)$ by plotting k_{bim} values obtained for a series of reaction (i) involving bases B of known basicities, as a function of $GB_{298}(B)$ and by fitting the data with a parametric sigmoid function. This procedure has been applied to glycine[19] using experimental bimolecular rate constants obtained by Zhang *et al.*[20] and Wu and Lebrilla.[21] The gas-phase basicity value reported in Table 1, GB(Gly) = 855.1 kJ mol^{-1} is obtained using the correction factor proposed recently,[22] it is thus slightly at variance from the value quoted in the original ref. 19.

Kinetic Methods Measurements

The "kinetic method"[3,6,23] is one of the most widely used mass spectrometry technique for the determination of thermochemical quantities in the gas phase. This success mainly lies in the fact that no pressure measurement is needed, an ideal condition for molecules of low volatility such as glycine. In order to determine the protonation thermochemistry of a molecule M, the kinetic method considers the competitive dissociations of a series of proton bound dimers $[MHB_i]^+$, where B_i are reference bases. By using a tandem mass spectrometer, the proton bound dimers $[MHB_i]^+$ may be selected and its dissociations analysed by the second part of the instrument. It may be shown that the natural logarithm of the ratio of the two sets of products, $MH^+ + B$ and $M + BH^+$, is directly related to $[PA_{298}(M) - PA_{298}(B_i) - T\Delta_i S°_{298}]/RT$. A series of experiments using several bases B_i may be treated by plotting $\ln[MH]/[B_iH]$ *vs* $PA(B_i)$ and locating the *x*-intercept of the fitting line which provides the difference $[PA_{298}(M) - T\Delta_i S°_{298}]$. This means to handle the data corresponding to the so called "simple kinetic method". The determination of $PA_{298}(M)$ by this method is clearly possible only if the term $T\Delta_i S°_{298}$ may be neglected. In situations where $\Delta_i S°_{298}$ is not negligible a more elaborated method is needed. This is provided by the "extended kinetic method" which allows us to determine both parameters $PA_{298}(M)$ and $\Delta_i S°_{298}$. The extended kinetic method involves several sets of experiments corresponding to different temperatures T_j *i.e.* different ion activation conditions. The various $\ln[MH]/[B_iH]$ *vs* $PA(B_i)$ points obtained at different temperatures T_j are treated either graphically or statistically in order to derive the two parameters $PA_{298}(M)$ and $\Delta_i S°_{298}$. The glycine molecule has been studied by the "simple"[24,25] and the "extended"[26] kinetic methods, and the corresponding results are quoted in Table 1.

In 1993, Li and Harrison [24] generated $GlyHB_i^+$ adducts by chemical ionization of a mixture of glycine and reference base B_i (aliphatic amines) and studied their collision induced decompositions in a BEqQ mass spectrometer. At that time, the proton affinity scale was in the course of a re-evaluation. This led the authors to use

two proton affinity scales called the "Lias scale"[27] and the "Mautner scale".[28] The original data were reconsidered here in order to anchor PA(Gly) to the presently accepted proton affinity scale.[18] In a more recent study, Afonso *et al*.[25] explored the decompositions of adducts produced from various amino acids in an external electrospray source of an ion trap mass spectrometer by the simple kinetic method. Some of these amino acids were considered as reference bases and, in the case of glycine, even though not explicitly stated, it may be supposed that the reference base used was serine. Moreover, in their study, the authors used reference PA(B) values from the "Lias scale"[27] rather than the Hunter & Lias scale.[18] In order to correct the PA(Gly) value originally proposed by Afonso *et al*.,[25] we anchor its value to the proton affinity of serine as given in the Hunter & Lias scale.[18]

The extended kinetic method was applied to the determination of the protonation thermochemistry of glycine using a triple quadrupole mass spectrometer equipped with an electrospray source.[26] The centre of mass collision energies of the MHB^+ adducts was varied between zero and 4 eV and a large set of monofunctional molecules was used as reference bases. The statistical treatment of the data first demonstrates a negligible protonation entropy, $\Delta_p S^\circ_{298}(\mathrm{Gly}) = 2 \pm 6$ J mol^{-1} K^{-1}, and consequently confirms the observation made using the equilibrium method, and second, provides a proton affinity PA(Gly) close to 886 kJ mol^{-1}. It may be noted that, according to the fact that $\Delta_p S^\circ_{298}(\mathrm{Gly})$ is negligible, the PA value given by the extended kinetic method is close to that obtained by the simple kinetic method. This is confirmed for the values coming from references 24 and 26 but not for the PA(Gly) derived from ref. 25. A possible explanation of this discrepancy stems from the use of serine as a reference base. Accordingly, this molecule probably presents a negative, and perhaps significant, $\Delta_p S^\circ_{298}$ thus leading to an overestimate of the proton affinity determination by the simple kinetic method.

In conclusion, as summarized in Table 1, experiments demonstrate that glycine possesses a proton affinity situated between 883 and 889 kJ mol^{-1}, however most of the values fall in the restricted 886−889 window. The measured protonation entropy determined by two different methods is equal to 2 J K^{-1} mol^{-1}, but the uncertainties on these determinations are three to four times larger. One may thus conclude that $\Delta_p S^\circ_{298}(\mathrm{Gly})$ is close to zero. These enthalpic and entropic figures lead to gas-phase basicity in the range 850−857 kJ mol^{-1} with a more probable value of 856 kJ mol^{-1}. The significance of these quantities, at the molecular level, will be now examined by means of quantum chemistry calculations on the various conformers of neutral and protonated glycine.

Structures and Conformations of Neutral Glycine

The structure of isolated neutral glycine has attracted the interest of the researchers since more than four decades ago. The first question was to identify the most stable tautomer in the gas-phase, either the nonionized structure $H_2NCH_2CO_2H$ or the zwitterionic structure $H_3N^+CH_2CO_2^-$. The second concern was to characterise their various conformations and particularly those which were the most stable at room temperature and were consequently responsible for experimental observations in the gas phase.

It has been known for a long time that glycine in solution or in the crystalline state exists as a zwitterion but that, by contrast, isolated glycine exclusively exists in its nonionized tautomeric form. Accordingly, quantum chemistry calculations indicate that the zwitterionic structure $H_3N^+CH_2CO_2^-$ is not a minimum in the potential energy surface and evolves spontaneously by a 1,4-H shift toward its $H_2NCH_2CO_2H$ form, situated ≈70 kJ mol^{-1} below the zwitterions.[29–32] The obvious reason is that the zwitterionic structure may be more efficiently stabilized by charge-solvent electrostatic interactions. This is corroborated by computational results on the microsolvation process or using continuum models which clearly show that the increase in the number of water molecules stabilises the zwitterionic structure more efficiently.[30,33–36] It is worthy to note that the 1:1 glycine-water complex has been experimentally characterized by microwave spectroscopy[37] but that seven molecules of water are however necessary to produce isoenergetic neutral and zwitterionic glycine complexes.[36]

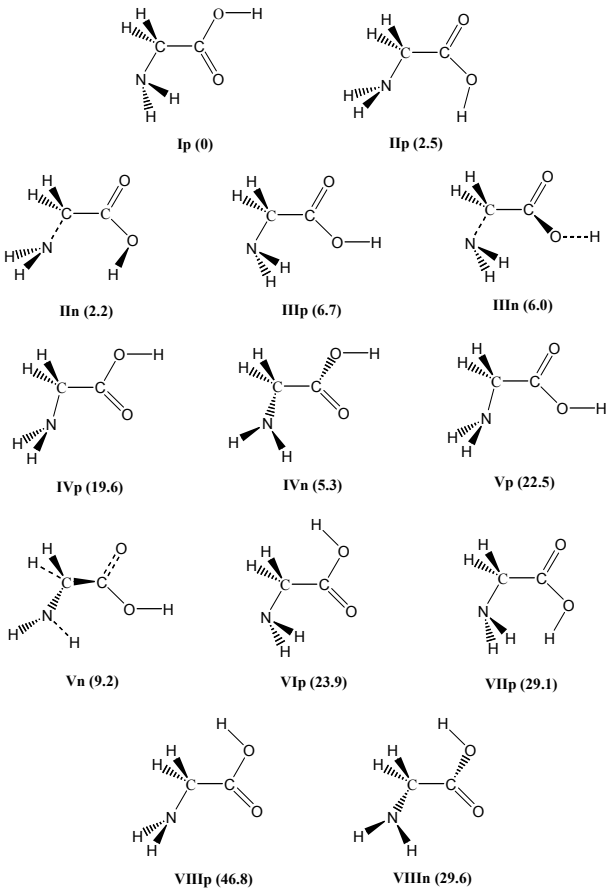
The largest stability of the nonionized tautomer of isolated neutral glycine is also attested by experiments. Accordingly, a number of experiments were designed to characterize neutral glycine in the gas phase, by microwave spectroscopy,[38–41] infrared spectroscopy in low-temperature argon matrices,[42,43] gas phase electron diffraction[44] and core binding energies determined by photoelectron spectroscopy.[45,46] All these studies conclude that gaseous glycine exists exclusively in its nonionized form. Moreover, these experiments, in conjunction with quantum chemistry calculations, allow the assignment of the sampled conformers' population.

Previous conformational analysis of non-ionized neutral glycine, $H_2NCH_2CO_2H$, by quantum chemistry calculations revealed the existence of eight major minima in the potential energy surface.[47–56] The structures were originally classified into planar (p) and non-planar (n) depending on the spatial heavy atoms arrangements (Scheme 1, relative energies are MP2/6-311++G(d,p) values taken from the original work of Csaszar).[47] As expected, geometrical parameters and relative energies

of these conformers are obviously dependent on the theoretical level. It seems now firmly established that geometry optimization should be conducted at a correlated level in order to reproduce the subtle balance between stabilizing intramolecular H bonding and destabilizing steric or lone pair electron repulsion effects.[47–49,52,56] Since our goal was to attain accurate theoretical determination of the proton thermochemistry of glycine, we have investigated in detail the structures and the energies of the most stable conformers of glycine. We examined the five conformers, denoted GlyI to GlyV, which were previously predicted to lie in a ≈20 kJ mol^{-1} energy range. Conformational analysis was made at the HF, MP2 and B3LYP levels using the 6-31+G(d,p) basis set. Energies were computed by means of high level theoretical methods including the G3, G3B3, G3MP2, CBS-Q and CBS-QB3 composite techniques. For the purpose of comparison the energies were also computed at the more cheaper B3LYP/6-311++G(3df,2p)//B3LYP/6-31+G(d,p) level (denoted SP, for "single point", later on). Energies are presented in Table 3 and the conformers' geometries illustrated by Figure 1.

From examination of Table 3, it appears immediately that the seven levels of theory used here provide very close results since the mean standard deviation in relative 298 K enthalpies is only 0.4 kJ mol^{-1}, and the maximum deviation never exceeds 1.6 kJ mol^{-1}. From a structural point of view, conformers possessing a *syn* HOCO arrangement enhance internal hydrogen bonding interaction and are thus more stable than their *anti* counterpart. The most stable conformer GlyI (Figure 1) presents such a *syn* HOCO arrangement and a bifurcated $NH_2\cdots O{=}C$ hydrogen bonding type interaction. In agreement with previous findings,[47–49,52,56] the arrangement of the heavy atoms in GlyI is fully planar at all the levels of theory used in the present study (this conformer, also noted GlyIp,[47] pertains to the C_s point group of symmetry).

The second conformer, GlyII (Figure 1) is an exception of the aforementioned rule since it presents an *anti* HOCO arrangement. However this destabilizing situation is efficiently counterbalanced by the existence of a strong $OH\cdots NH_2$ hydrogen bond.[53] As a consequence, GlyII is almost as stable as GlyI since it is destabilized by only 4 kJ mol^{-1} ($\Delta H_{298}°$, Table 3). It may be emphasized that the data reported in Table 3 are related to the non planar structure denoted GlyIIn in the Csaszar nomenclature.[47] In fact the NCCO(H) dihedral angle varies from 7 to 17° depending upon the level of theory used. It is noteworthy that this range of values includes the most recent estimate of 11° which has been computed at a higher level of theory.[56] The planar structure GlyIIp represents the GlyIIn barrier to planarity.[56] This



Scheme 1.

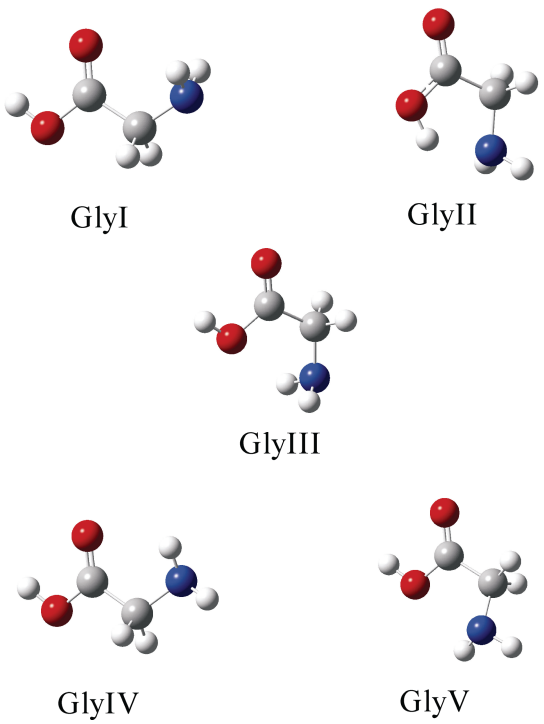


Figure 1. B3LYP/6-31+G(d,p) optimised geometries of the five most stable conformers of neutral glycine.

Table 3. Calculated 298 K enthalpies and free energies of glycine conformers in hartree (into parentheses, relative energies in kJ mol^{-1})

Species	Method	$\frac{H_{298}°}{\text{hartree}}$	$\frac{G_{298}°}{\text{hartree}}$	$\frac{G_{298}°(\text{Pitzer})^{(b)}}{\text{hartree}}$
GlyI(p)	B3LYP/6-31+G(d,p)	−284.370418 (0)	−284.406148	
	SP[(a)]	−284.461848 (0)	−284.497578	
	G3	−284.243476 (0)	−284.279030 (0)	−284.281286 (0)
	G3MP2	−284.047560 (0)	−284.083113	
	G3B3	−284.249694 (0)	−284.285486	
	CBS-Q	−284.021946 (0)	−284.057326	
	CBS-QB3	−284.024861 (0)	−284.060505	
GlyII(n)	B3LYP/6-31+G(d,p)	−284.369485 (2.5)	−284.404774	
	SP[(a)]	−284.460697 (3.0)	−284.495989	
	G3	−284.242130 (3.5)	−284.277075 (5.1)	−284.278431 (7.5)
	G3MP2	−284.045980 (4.1)	−284.080925	
	G3B3	−284.248430 (3.3)	−284.283299	
	CBS-Q	−284.020502 (3.8)	−284.055262	
	CBS-QB3	−284.023426 (3.8)	−284.058291	
GlyIII(p)	B3LYP/6-31+G(d,p)	−284.367976 (6.4)	−284.404627	
	SP[(a)]	−284.459154 (7.1)	−284.495805	
	G3	−284.240777 (7.1)	−284.277601 (3.8)	−284.279314 (5.2)
	G3MP2	−284.044807 (7.2)	−284.081631	
	G3B3	−284.247012 (7.0)	−284.283156	
	CBS-Q	−284.019193 (7.2)	−284.055970	
	CBS-QB3	−284.022079 (7.3)	−284.058078	
GlyIV(n)	B3LYP/6-31+G(d,p)	−284.368046 (6.2)	−284.403376	
	SP[(a)]	−284.460007 (4.8)	−284.495337	
	G3	−284.241562 (5.0)	−284.277001 (5.3)	−284.279963 (3.5)
	G3MP2	−284.045697 (4.9)	−284.081136	
	G3B3	−284.247929 (4.6)	−284.283460	
	CBS-Q	−284.019891 (5.4)	−284.055137	
	CBS-QB3	−284.023077 (4.7)	−284.058460	
GlyV(n)	B3LYP/6-31+G(d,p)	−284.366066 (11.4)	−284.401583	
	SP[(a)]	−284.457637 (11.1)	−284.493154	
	G3	−284.239386 (10.7)	−284.274912 (10.8)	−284.277673 (9.5)
	G3MP2	−284.043484 (10.7)	−284.079010	
	G3B3	−284.245755 (10.3)	−284.281423	
	CBS-Q	−284.017631 (11.3)	−284.052944	
	CBS-QB3	−284.020819 (10.6)	−284.056382	

[(a)] SP: single point energy calculation at the B3LYP /6-311++**G**(3df,2p)// B3LYP /6-31+**G**(d,p) level, $H_{298}°$ include $\Delta H_{298}°$ contributions calculated at the B3LYP /6-31+**G**(d,p) level.

[(b)] Using the entropies calculated within the Pitzer 's model of hindered rotations (Table 4).

saddle point is situated only 0.2 kJ mol^{-1} above GlyIIn[56] and it is expected that the ground vibrational state of GlyIIn surmounts this barrier thus explaining the experimental observation of an apparent *C*s symmetry for this conformer.[20]

Structure GlyIII is structurally comparable to GlyI in that sense that it is also characterized by a *syn* HOCO arrangement and a bifurcated hydrogen bonding. GlyIII however involves as H-bond acceptor the hydroxylic oxygen rather than the carbonyl one (Figure 1). A second similarity with GlyI is that GlyIII presents a planar heavy atoms arrangement and thus corresponds to GlyIIIp in ref 47. Accordingly, for the GlyIII structures corresponding to Table 3, the NCCO(H) dihedral angle is equal to 0 ± 1°. In fact, when using HF, MP2 or B3LYP methods with the 6-31G(d) or 6-31G(d') basis set, all the tentatives of geometry optimization of a non-planar GlyIIIn structure collapsed to the planar GlyIIIp conformer. The same phenomenon arises at the B3LYP/6-31+G(d,p) level but not at the HF or MP2/6-31+G(d,p) levels. In these latter cases, the planar conformer is a maximum in the potential energy surface and corresponds to a transition structure. This situation is reminiscent of the GlyIIn case examined above. Similarly, the barrier for planarity of GlyIIIn is sufficiently small (0.3 kJ mol^{-1} at the /MP2/6-31+G(d,p) level) to be easily surmounted at room temperature. Whether GlyIIIn or GlyIIIp is the true local minimum does not alter the fact that GlyIII is predicted to be situated 7 kJ mol^{-1} above GlyI on the 298 K enthalpy scale (Table 3).

Table 4. Entropy calculations (J K^{-1} mol^{-1}) at 298 K for neutral glycine conformers

GlyI		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.6
Rotational	$S°$				106.5
Vibrational (without internal rotations)	$S°$				17.5
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	10.0	20.0	55.0	
	ν (cm^{-1})[a]	27	125	300	
	$S°_{free}$	31.6	21.8	18.7	72.1
	$S°_{harm\ osc}$	25.2	12.6	5.9	43.7
	$S°_{Pitzer}$	26.9	13.3	6.3	46.5
Total					333.1

GlyII		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.6
Rotational	$S°$				106.2
Vibrational	$S°$				15.1
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	38.0	45.0	55.0	
	ν (cm^{-1})[a]	52	191	292	
	$S°$free	31.7	21.7	18.9	72.3
	$S°$harm osc	19.8	9.3	6.1	35.2
	$S°$Pitzer	19.9	9.5	6.5	35.9
Total					319.8

GlyIII		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.6
Rotational	$S°$				106.5
Vibrational	$S°$				17.3
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	3.5	11.3	(55.0)	
	ν (cm^{-1})[a]	16	95	299	
	$S°_{free}$	31.5	21.7	18.8	72.0
	$S°_{harm\ osc}$	29.4	14.9	6.0	50.3
	$S°_{Pitzer}$	30.4	16.3	6.4	53.1
Total					339.5

GlyIV		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.6
Rotational	$S°$				106.3
Vibrational	$S°$		-		16.7
Internal rotation (Pitzer)	V° (kJ mol^{-1})	3.3	13.3	(55.0)	-
	ν (cm^{-1})[a]	16	102	300	-
	$S°_{free}$	31.6	21.8	18.7	72.1
	$S°_{harm\ osc}$	29.8	14.3	5.9	50.0
	$S°_{Pitzer}$	30.5	15.9	6.3	52.7
Total					338.3

GlyV		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.6
Rotational	$S°$				106.1
Vibrational	$S°$				16.1
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	3.5	7.6	55.0	
	ν (cm^{-1})[a]	16	109	300	
	$S°_{free}$	31.5	18.9	18.7	69.1
	$S°_{harm\ osc}$	29.5	13.7	5.9	49.1
	$S°_{Pitzer}$	30.5	15.7	6.3	52.5
Total					337.3

[a] Harmonic frequency associated with the rotation, following Eq. (4): $\nu_{harm.rot} = (n / 2\pi) (V_0 / 2I_{red})^{1/2}$, see text.

Conformers GlyIV and GlyV are close in structure to their respective CN rotamers GlyIp and GlyIIIp. The two structures GlyIV and GlyV present unambiguously a non planar arrangement of their heavy atoms (NCCO(H) dihedral angles are in the 158/161° and 36/47° ranges for GlyIV and GlyV , respectively) in agreement with previous observation that GlyIVn and GlyVn were ≈15 kJ mol^{-1} below their planar counterparts GlyIVp and GlyVp.[47] The 298 K enthalpies of GlyIV and GlyV, relative to GlyI, are 5 and 11 kJ mol^{-1}, respectively. We note that it places conformer GlyIV as the third position in decreasing stability order, after GlyI and GlyII.

The remaining conformers GlyVI–GlyVIII (not examined here but reported in Scheme 1) are the *anti* HOCO homologues of GlyI, GlyIII and GlyIV. They do not enjoy a favourable interaction between the hydrogen and the carbonyl oxygen of the HOCO moiety in its *syn* arrangement and consequently lose benefit of the corresponding extra stabilization of ≈ 25 kJ mol^{-1}. This high energy gap renders very unlikely the participation of GlyVI–GlyVIII to the conformer population at room temperature and, for this reason, they were not included in our investigation.

The second thermochemical parameter of interest is entropy. As explained in the theoretical procedure section, entropy calculations have been done in the present study by using the standard statistical functions in the harmonic oscillator approximation except for internal rotations which were treated as hindered rotors. The summary of the entropy calculations concerning neutral glycine are gathered in Table 4. Figure 2 displays the three calculated potential energy curves *vs*. dihedral angles used for the estimate of the rotational barriers introduced in the entropy calculations for GlyI.

A general comparison between the third law entropy of the five conformers of glycine (Table 4) shows that GlyII is the species of lower entropy. Its third law entropy is calculated to be ≈13 J K^{-1} mol^{-1} below that of GlyI whereas GlyIII–GlyV exhibit $S°$ larger than that of GlyI by *ca* 5 J K^{-1} mol^{-1}. This observation is in line with the results of Miller and Clary[55] who studied the conformational space of GlyI–GlyV and the relevant thermodynamic by a Monte-Carlo technique. Accordingly, the authors found relative vibrational entropies of 0, −3.7, +4.6, +5.2 and +7.7 J K^{-1} mol^{-1} at 300 K for GlyI–GlyV, respectively, thus pointing to a lower vibrational entropy for GlyII. The lowest entropy of GlyII is essentially due to the very efficient internal hydrogen bonding [53] which noticeably increases the C−C and C−N rotational barriers V_0 (Table 4) and thus reduces the corresponding entropy contribution. It may be underlined that this effect is not reproduced by the standard procedure used in Gaussian since the entropy contributions of the internal rotation are identical for GlyI and GlyII.

Having in hand enthalpies and entropies, the 298 K Gibbs free energies $G°$ may be calculated. This has been done using the entropies corrected by considering internal rotations as hindered rotors. The results are given in the last column of Table 3. These data allowed us to calculate the glycine conformer population since, assuming a Boltzmannn distribution, the individual populations (molar fractions) x_i are given by:

$$x_i = \exp(-G_i / RT) / \sum_1^N \exp(-G_i / RT) \qquad (6)$$

Consideration of the conformational equilibrium between neutral glycine structures GlyI to GlyV at 298 K leads to 69.5 % of GlyI, 3.5 % of GlyII, 8.5 % of GlyIII, 17 % of GlyIV and 1.5 % of GlyV. By comparison with comparable estimates based on Gibbs free energies calculated using standard harmonic oscillator approximation [57] our results show an identical participation of GlyI but a larger weight for conformer GlyIV to the detriment of GlyII. This observation parallels one based on computations based on a Monte-Carlo technique providing an anharmonic and quantum mechanical description of the conformational free energy at the MP2/6-311++G(d,p) level[55] which predict a percentage of GlyIV close to 15 %. It may be also underlined that experiments designed to identify the conformers of neutral isolated glycine[37−46] were interpreted by populations involving conformers GlyI in *ca* 75 % of the overall conformer population in the 200 K−300 K temperature range. The remaining 25 % contribution was attributed to a mixture of conformers GlyII and GlyIII and the question of the possible existence of conformer GlyIV has been recently raised.[55]

Structures and Conformations of Protonated Glycine

Glycine presents three evident sites for protonation, the nitrogen and the two oxygen atoms, with possible intramolecular hydrogen bond in the various protonated forms. A number of theoretical calculations has been devoted to the isomeric structures and conformations of protonated glycine[8,20,21,26,50−52,54,57−66] as well as its microhydrated counterparts.[67−69] All the authors conclude that the most basic site is the amino nitrogen, followed by the carbonyl oxygen and, further, by the hydroxyl oxygen. Protonation of the oxygen atoms of the carbonyl and the hydroxyl functions lead to structures which are situated ≈110−130 and ≈160 kJ mol^{-1}, respectively, above the most stable conformer of the N-protonated form. Since we are dealing with protonation thermochemistry in the room temperature region, we

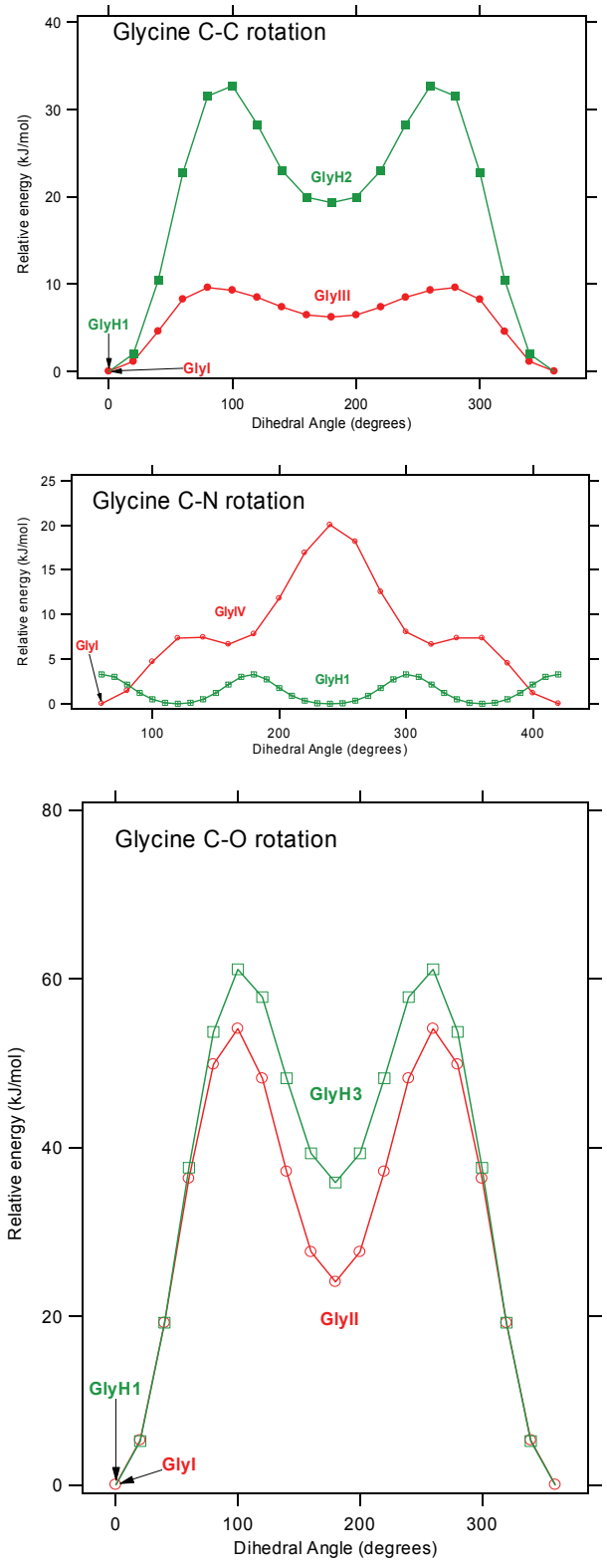


Figure 2. Schematic potential energy profile (B3LYP/6-31+G(d,p) level) associated with rotations around the three internal rotation modes of neutral glycine (red circles) and protonated glycine (green squares), only the curves involving the most stable conformers GlyI and GlyH1 are represented.

will consequently consider protonation exclusively at the nitrogen atom.

Three conformers of the N-protonated glycine were located as minima on the potential energy surface and all of them present a planar arrangement of their heavy atoms. The most stable form is conformer GlyH1 where a single intramolecular hydrogen bond is created between one N−H hydrogen and the oxygen of the carbonyl group (Figure 3). The second conformer, GlyH2, is less stable by ≈20 kJ mol^{-1} since the amino hydrogens are under the effect of the less basic hydroxyl oxygen. Moreover, a bifurcated $NH_2\cdots OH$ hydrogen bonding allows a steric decompression with the CH_2 group, a situation in contrast with that encountered with conformer GlyH1. As observed with neutral glycine, the *syn* HOCO arrangement contributes to the stability of the corresponding protonated forms, thus favouring conformations GlyH1 and GlyH2. It is noteworthy that the energy difference between the *syn* and *anti* conformers appears to be amplified in the protonated species as indicated by the relative energy of the third conformer, GlyH3, with respect to GlyH1 (≈32 kJ mol^{-1}). The 298 K enthalpies, relative to GlyH1, calculated at the SP, G3, G3MP2, G3B3, CBS-Q and CBS-QB3 levels agree within ≈1 kJ mol^{-1}. When we included in the comparison the result obtained at the simple B3LYP/6-31+G(d,p) level, the standard deviation falls to 1.4 kJ mol^{-1}, a value which is still satisfactory.

Third law entropy calculations for the three conformers GlyH1−GlyH3 are summarized in Table 6. The rotational barriers associated with rotation around the C−C, C−O and C−N bonds used in the calculation of the hindered rotors entropies of GlyH1, are illustrated by Figure 2. If the third law entropies of GlyH1 and GlyH3 are close together, $S°$(GlyH2) is larger by *ca.* 7 J mol^{-1} K^{-1}. This difference is essentially due to the reduced CC rotational barrier associated with this latter conformer. The enthalpy and entropy estimates given in Tables 5 and 6 allow for the computation of the corresponding Gibbs free energies and individual populations. The gap in Gibbs free energy between the most stable form, GlyH1 and the two others GlyH2 and GlyH3 is

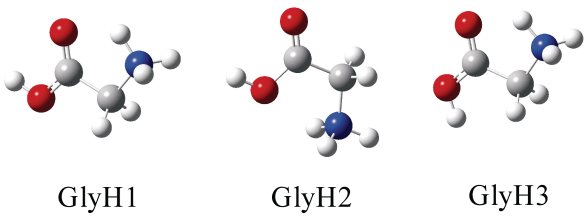


Figure 3. B3LYP/6-31+G(d,p) optimized geometries of the three conformers of N-protonated glycine.

Table 5. Calculated 298 K enthalpies and free energies of protonated glycine conformers in hartree (into parentheses, relative energies in kJ mol^{-1})

Species	Method	$\frac{H_{298}^{\circ}}{\text{hartree}}$	$\frac{G_{298}^{\circ}}{\text{hartree}}$	$\frac{G_{298}^{\circ}(\text{Pitzer})^{(b)}}{\text{hartree}}$
GlyH1	B3LYP/6-31+G(d,p)	−284.706140 (0)	−284.741869	
	SP[(a)]	−284.797260 (0)	−284.832989	
	G3	−284.580287 (0)	−284.614271 (0)	−284.618358 (0)
	G3MP2	−284.384205 (0)	−284.418189	
	G3B3	−284.585630 (0)	−284.621388	
	CBS-Q	−284.357818 (0)	−284.391666	
	CBS-QB3	−284.360093 (0)	−284.395644	
GlyH2	B3LYP/6-31+G(d,p)	−284.698492 (20.1)	−284.735406	
	SP[(a)]	−284.788471 (23.1)	−284.825385	
	G3	−284.571978 (21.8)	−284.608286 (15.7)	−284.610810 (19.8)
	G3MP2	−284.375911 (21.8)	−284.412219	
	G3B3	−284.578181 (19.6)	−284.615543	
	CBS-Q	−284.349279 (22.4)	−284.385409	
	CBS-QB3	−284.352244 (20.6)	−284.388645	
GlyH3	B3LYP/6-31+G(d,p)	−284.692969 (34.6)	−284.728433	
	SP[(a)]	−284.785994 (29.6)	−284.821458	
	G3	−284.568175 (31.8)	−284.602311 (31.4)	−284.606292 (31.7)
	G3MP2	−284.372172 (31.6)	−284.406308	
	G3B3	−284.573601 (31.6)	−284.609239	
	CBS-Q	−284.345779 (31.6)	−284.379777	
	CBS-QB3	−284.348020 (31.7)	−284.383440	

[(a)] SP: single point energy calculation at the B3LYP/6-311++G(3df,2p)// B3LYP /6-31+G(d,p) level, H_{298}° include ΔH_{298}° contributions calculated at the B3LYP /6-31+G(d,p) level.
[(b)] Using the entropies calculated within the Pitzer 's model of hindered rotations (Table 6).

≈20 and 32 kJ mol^{-1}, respectively (in relatively close agreement with estimates based on entropy calculation in the harmonic oscillator approximation (*ca*. 16 and 31 kJ mol^{-1} at 298 K in Table 5, fourth column, and ref. 50). The Gibbs free energy difference reported in Table 5 leads to a population of conformers containing more than 99.97 % of GlyH1 and less than 0.03 % of GlyH2 and GlyH3 at 298 K. We can thus make the approximation that the population of protonated glycine at 298 K consists exclusively of the GlyH1 conformer.

Theoretical Gas-phase Protonation Thermochemistry of Glycine

Since the 1990's, the proton affinity of glycine has been calculated at various theoretical levels.[8,57−64,20,26] However, only limited data is of direct significance because either (i) the considered structures were not the most stable,[60,63,64] (ii) correction to the temperature of 298 K has not been considered[58,63,64] or (iii) these information are not specified.[8] In fact only three high level *ab initio* studies provide correct computation of 298 K proton affinity of glycine using the most stable conformers GlyI and GlyH1.[59,61,62] In a study devoted to the thermochemistry of radicals and ions of glycine, Yu *et al*.[59] calculated a proton affinity value of 889 kJ mol^{-1} using G2MP2 computed $\Delta_f H°$ of GlyI and GlyH1 and the experimental $\Delta_f H°(H^+)$ of 1530.0 kJ mol^{-1}. Topol *et al*.[61] confirmed this estimate by calculating, at the G2 level, PA(Gly) = 888.3 kJ mol^{-1}. Finally, Zhang and Chung-Philips[62] estimated the proton affinity of glycine using a method based on an additive procedure called "MP4/6-311G(2d,2p)" which include thermal and BSSE (basis set superposition error) corrections. They obtained a PA(Gly) value of 883.2 kJ mol^{-1}. We noted that, at the same level, the proton affinity of ammonia and methylamine were underestimated by 5.1 and 4.5 kJ mol^{-1} respectively. Consequently, an isodesmic correction (see below) would provide a PA value close to 888 kJ mol^{-1}, in agreement with the above mentioned G2MP2 and G2 estimates.

Concerning the gas-phase basicity, GB(Gly), and the associated protonation entropy, $\Delta_p S_{298}^{\circ}(\text{Gly})$, the information are even more scarce. Zhang and Chung-Philips[62] used entropy values as given by Gaussian without correction to computed entropies and Gibbs free energies for neutral and protonated glycine. However, as seen in the previous section, significant discrepancies may occur for low frequency vibrations calculation using the harmonic oscillator approximation and consequently affect the resulting entropy and Gibbs free energy terms. The authors took into account a distribution of conformers GlyI/GlyII/GlyIII/GlyIV in the ratio 68/8/18/6 in order to correct their PA and GB estimates (883.2 and 851.4 kJ mol^{-1} corrected to 888.0 and 856.2

Table 6. Entropy calculations (J K^{-1} mol^{-1}) at 298 K for N-protonated glycine conformers

GlyH1		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.8
Rotational	$S°$				107.0
Vibrational	$S°$				15.9
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	32.7	3.3	61.1	
	ν (cm^{-1})[(a)]	47	42	325	
	$S°_{free}$	32.0	23.4	18.5	73.9
	$S°_{harm\ osc}$	20.7	21.6	5.4	47.7
	$S°_{Pitzer}$	20.8	22.4	6.5	49.7
Total (Pitzer)					335.4

GlyH2		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.8
Rotational	$S°$				106.7
Vibrational	$S°$		-		17.3
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	12.6	3.3	89.3	-
	ν (cm^{-1}) [(a)]	29	410	386	-
	$S°_{free}$	32.0	23.5	18.6	74.1
	$S°_{harm\ osc}$	240.7	21.7	4.2	50.6
	$S°_{Pitzer}$	26.0	22.7	6.6	55.3
Total	-		-		342.1

GlyH3		CC rotation	CN rotation	CO rotation	Total
Translational	$S°$				162.8
Rotational	$S°$				107.1
Vibrational	$S°$				14.9
Internal rotation (Pitzer)	$V°$ (kJ mol^{-1})	85.5	3.3	26.5	
	ν (cm^{-1}) [(a)]	75	42	214	
	$S°_{free}$	32.0	23.4	18.5	73.9
	$S°_{harm\ osc}$	16.8	21.6	8.4	46.8
	$S°_{Pitzer}$	19.2	22.6	9.2	51.0
Total (Pitzer)					335.8

[(a)] Harmonic frequency associated with the rotation, following Eq. (4): $\nu_{harm.rot} = (n / 2\,\pi)\,(V_0 / 2I_{red})^{1/2}$, see text.

kJ mol^{-1} respectively if the proton affinity is anchored to those of ammonia and methylamine, Table 1).

We have computed proton affinity of glycine using the 298 K calculated enthalpies reported in Tables 3 and 5. A "most stable conformers" (denoted "msc") proton affinity may be first defined by considering reaction (1) involving exclusively conformer GlyI for neutral glycine and conformer GlyH1 for protonated glycine. These crude estimates presented in Table 7 show PA_{msc}(Gly) ranging from 886.3 to 890.4 kJ mol^{-1}. In order to test the validity of the various levels of theory to predict accurate proton affinity we also examined isopropylamine at the same levels. The results are given in Table 7 and demonstrate a PA_{calc}(isopropylamine) range limited by 921.2 and 923.9 kJ mol^{-1}, if we exclude the simplest B3LYP/6-31G(d,p) level value of 926.7 kJ mol^{-1}. The tabulated experimental proton affinity of isopropylamine is equal to 923.8 kJ mol^{-1}, in clear agreement with the computations, particularly with the G3 and G3MP2 results. To fully exploit these data, an isodesmic procedure may be used to deduce a more confident theoretical "most stable conformer" proton affinity of glycine. This quantity may be defined by $PA_{msciso}(Gly) = PA_{msc}(Gly) - PA_{calc}$(isopropylamine) + 923.8 kJ mol^{-1}. Using the SP, G3, G3MP2, G3B3, CBS-Q and CBS-QB3 data (Table 7) a mean value of $PA_{msciso}(Gly)$ = 889.2 ±1.0 (standard deviation) kJ mol^{-1} is obtained.

A molar proton affinity may be now defined by considering the population of neutral and protonated glycine conformers at 298 K, and this quantity, PA_{molar}, is given by:

$$PA_{molar} = \sum_{1}^{N} x_i PA_i \qquad (7)$$

where PA_i and x_i are the "most stable conformer" proton affinities and the molar fractions respectively, of each of the N conformers. When using the x_i values reported in the preceding discussion, and the PA_i (calculated at the G3 level) anchored to $PA(GlyI) = PA_{msciso}(Gly)$ = 889.2 kJ mol^{-1}, it follows that $PA_{molar}(Gly)$ = 890.9 kJ mol^{-1}.

Table 7. Calculated proton affinities of isopropylamine and glycine (kJ mol^{-1})

Method	$PA_{mono}(\text{isopropylamine})^{(a)}$ / kJ mol^{-1}	$PA_{mono}(\text{Gly})^{(a)}$ / kJ mol^{-1}	$PA_{mono}(\text{Gly})_{iso}^{(b)}$ / kJ mol^{-1}
B3LYP/6-31+G(d,p)	926.7	887.6	884.7
SP	922.9	-	-
G3	923.9	890.4	890.3
G3MP2	923.5	890.0	890.3
G3B3	923.2	888.1	888.7
CBS-Q	922.5	888.0	889.3
CBS-QB3	921.2	886.3	888.9

[(a)] Monoconformer proton affinity, $PA_{mono}(M) = H_{298}°$ (most stable conformer M) – $H_{298}°$ (most stable conformer MH^+) + 6.2 kJ mol^{-1}. [(b)] Isodesmic proton affinity anchored on the experimental proton affinity of isopropylamine (923.8 kJ mol^{-1}, ref 18), $PA_{mono}(Gly)_{iso} = PA_{mono}(Gly) - PA_{calc}(\text{isopropylamine}) + 923.8$ kJ mol^{-1}.

A similar treatment may be applied to the protonation entropy $\Delta_p S^\circ_{298}(\text{Gly})$. First a "most stable conformer" value of $\Delta_p S^\circ_{298}(\text{Gly}) = 2.3$ J K^{-1} mol^{-1} is easily deduced from absolute entropies of GlyI and GlyH1 quoted in Tables 4 and 6. Correction to this estimate should be however introduced since, rigorously, the total entropy of one mole of a mixture of N components with molar fractions x_i is given by:

$$S_T°_{\text{molar}} = \sum_1^N x_i \left(S_T°\right)_{\text{molar}} - R\sum_1^N x_i \ln x_i \qquad (8)$$

where the second term is the entropy of mixing. Separate computation of the two components of this equation is possible for neutral and protonated glycine using the figures included in Tables 4 and 6. For neutral glycine, the results are $S^\circ_{298}(\text{Gly})_{\text{molar}} = 334.1$ J K^{-1} mol^{-1}, or 342.0 J K^{-1} mol^{-1} when including the entropy of mixing. For protonated glycine the existence of 99.97 % of the conformer GlyH1 at 298 K leads to the approximation $S^\circ_{298}(\text{GlyH}^+)_{\text{molar}} \approx S^\circ_{298}(\text{GlyH1}) = 335.4$ J K^{-1} mol^{-1}. The averaged $\Delta_p S^\circ_{298}(\text{Gly})_{\text{molar}}$ is consequently equal to 1.3 J K^{-1} mol^{-1}, or −6.2 J K^{-1} mol^{-1} when including the entropy of mixing.

Finally, the gas phase basicity of glycine may be calculated from the relationship $GB(M) = PA(M) - T\Delta_1 S°$ and, again, two definitions may be used - a "most stable conformer" gas phase basicity, $GB_{msc}(Gly) = 857.5$ kJ mol^{-1} and a molar value averaged over the 298 K distribution of conformers, $GB_{molar}(Gly) = 858.9$ kJ mol^{-1}, or 856.6 kJ mol^{-1} when including the entropy of mixing.

Comparison of these theoretical figures with experimental values (Table 1) is satisfactorily. The most evident is protonation entropy which is conclusively predicted by computation to be close to zero with an upper limit given by the "most stable conformer" value of 2 J K^{-1} mol^{-1} and a lower limit provided by the averaged value including the entropy of mixing *i.e.* −6 J K^{-1} mol^{-1}. It is gratifying that this range of values matches the $\Delta_p S^\circ_{298}(\text{Gly})$ experimentally determined by the equilibrium method at variable temperature[15] and by the extended kinetic method.[26] One may note also that the accuracy of the theoretical protonation entropy is probably close to ±6 J K^{-1} mol^{-1}. Concerning proton affinity and gas phase basicity, a general comparison reveals a slight shift of *ca.* 2−3 kJ mol^{-1} between experiment and theory pointing to a slight overestimate given by the latter. One reason of this shift may be the overestimate of the experimental proton affinity of isopropylamine, the reference value in our isodesmic evaluation of the proton affinity. It may be emphasized however that, in addition to the fact that there is no particular reason to suspect this value, a difference of 2−3 kJ mol^{-1} in proton affinity or gas phase basicity is close to the accuracy limit of the present computational methods as recalled in the theoretical section.

CONCLUSION

The present study contains new theoretical data relevant to the protonation thermochemistry of glycine. Conformational analysis has been conducted at the B3LYP/6-31+G(d,p) level on neutral and protonated glycine and the corresponding rotational barriers have been determined. Our results confirm the previous finding that five neutral conformers lie below 20 kJ mol^{-1} and may participate in the description of glycine in the 0−500 K temperature range. In contrast, only one conformer of

protonated glycine, namely GlyH1, should be considered in this temperature range.

The two essential thermochemical parameters, enthalpy and entropy, were carefully examined. The first by using total energies and 298 K corrections calculated using the state of the art G3, G3MP2, G3B3, CBS-Q, CBS-QB3 composites methods and a less expensive single point (SP) B3LYP/6-311++G(3df,2p)//B3LYP/6-31+G(d,p) + B3LYP/6-31+G(d,p) at the 298 K correction level, the second by considering each internal rotation as a hindered rotor and by computing the corresponding entropy contribution in the frame of the Pitzer model. This approach allows for the estimation of the Gibbs free energies of each conformer and further to their molar fraction assuming a Boltzmann distribution at 298 K.

Following this line, the protonation entropy of glycine *i.e.* $\Delta_p S^\circ_{298}(\mathrm{Gly}) = S^\circ_{298}(\mathrm{GlyH}) - S^\circ_{298}(\mathrm{Gly})$ has been calculated. It falls in the range −6/+2 (with a probable uncertainty of ±6) J K^{-1} mol^{-1} in correct agreement with the available experimental data of 2±6 J K^{-1} mol^{-1} (Table 1). Proton affinity, PA(Gly), has been predicted by calculation to be of the order 889.2/890.9 kJ mol^{-1}, and the comparison with experimental values is also satisfactory since most of the experimental determination fall in the 886−889 kJ mol^{-1} range. Theoretical gas phase basicity, GB(Gly), is equal to 857−859 kJ mol^{-1} whereas experiments point to a value close to 856 kJ mol^{-1}. The comparison is consequently correct even if both theoretical PA(Gly) and GB(Gly) present a slight overestimate. By considering the experimental and theoretical data reported in Table 1, the evaluated values for PA(Gly) = 889 kJ mol^{-1} and GB(Gly) = 856 kJ mol^{-1} may be proposed. This suggests a slight reevaluation of the presently tabulated values of PA(Gly) = 886.5 kJ mol^{-1} and GB(Gly) = 852.2 kJ mol^{-1}.[18,70]

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70. The Hunter and Lias tabulation (ref. 18) lies *inter alia* , as anchoring point, on a proton affinity value of ammonia equal to $PA(NH_3)$ = 853.6 kJ mol^{-1}. Very recently, using the highest level theoretical methods to date, a value of $PA(NH_3)$ = 852.6 kJ mol^{-1} has been proposed in: G. Czako, E. Matyus, A. C. Simmonett, A. G. Csaszar, H. F. Schafer III, and W. D. Allen, *J. Chem. Theory Comput.* **4** (2008) 1220−1229.

SAŽETAK

Bazičnost glicina u plinskoj fazi

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Termokemija protoniranja plinovitog glicina je ponovno istraživana. Kompozitne G3, G3MP2, G3B3, CBS-Q i CBS-QB3 metode su korištene za određivanje entalpijske komponente, tj. protonskog afiniteta glicina, PA(Gly). Takozvana "entropija protoniranja", $\Delta_p S(\mathrm{Gly}) = S°(\mathrm{GlyH^+}) - S°(\mathrm{Gly})$, je određena računanjem doprinosa entropiji interne rotacije korištenjem Pitzerovog modela ometanog rotora. Dobivena teorijska bazičnost u plinskoj fazi, $\mathrm{GB(Gly)} = \mathrm{PA(Gly)} - T[S°(\mathrm{H^+}) - \Delta_p S(\mathrm{Gly})]$ je nakon toga računana. Ovi računi su napravljeni, uzimajući u obzir najstabilniji neutralni protonirani konformer glicina ("najstabilniji protonirani konformer" vrijednost je označena sa "msc") ili populaciju konformera bazirajući se na Boltzmannovu distribuciju na 298 K ("molarne" vrijednosti). Izodezmička procedura je korištena fiksiranjem računskih podataka sa eksperimentalnim protonskim afinitetom izopropilamina. Rezultati su slijedeći: $\mathrm{PA_{msciso}(Gly)}$ = 889,2 kJ mol^{-1}, $\mathrm{PA_{molar}(Gly)}$ = 890,9 kJ mol^{-1}, $\Delta_p S_{\mathrm{msciso}}(\mathrm{Gly})$ = 2,3 J mol^{-1} K^{-1}, $\Delta_p S_{\mathrm{molar}}(\mathrm{Gly})$ = 1,2 [−6,2] J mol^{-1} K^{-1}, $\mathrm{GB_{msciso}(Gly)}$ = 857,5 kJ mol^{-1}, $\mathrm{GB_{molar}(Gly)}$ = 858,9 [856,6] kJ mol^{-1} [vrijednosti u zagradama odgovaraju podacima koji uključuju entropiju miješanja]. Vrijednosti dobivene za PA(Gly)= 889 kJ mol^{-1} i GB(Gly)= 856 kJ mol^{-1}, na 298 K, su predložene nakon usporedbe sa eksperimentalno dostupnim podacima.