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Comparisons of Computational and Experimental Thermochemical Properties of α-Amino Acids

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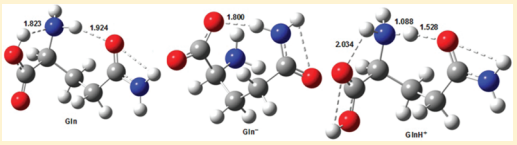
Supporting Information

ABSTRACT: This study provides comprehensive benchmark calculations for the thermochemical properties of the common α-amino acids. Calculated properties include the proton affinity, gas-phase basicity, protonation entropy, ΔH°_{acid}, ΔG°_{acid}, and enthalpies of formation for the protonated and deprotonated α-amino acids. In order to determine the performance at various levels of theory, including density functional methods and composite methods, the calculated thermochemical properties are compared to experimental results. For all the common α-amino acids investigated, the thermochemical properties computed with the Gaussian-n theories were found to be quite consistent with each other in terms of mean absolute deviation from experiment. While all Gaussian-n theory values can serve as benchmarks, we focus on the G3MP2 values as it is the least resource-intensive of the Gaussian-n theories considered.



1. INTRODUCTION

Proteins generally only contain α-amino acids while both D-α-amino acids and non-α-amino acids also occur in nature. Of the over 300 naturally occurring amino acids, the 20 common α-amino acids and their derivatives participate in diverse cellular functions and in biosynthetic reactions. The common α-amino acids are the basic monomer units from which the long polypeptide chains of proteins found in living species from bacteria to humans are formed.

Understanding the thermochemical properties of the α-amino acids is of great importance in applied chemistry and the understanding of biological systems, especially through biochemical process energetics. The gas-phase protonation thermochemistry of biomolecules will provide insight into intramolecular hydrogen bonds (H-bonds) and salt-bridges that may stabilize the structures. The gas-phase protonation/deprotonation thermochemistry of α-amino acids has been experimentally examined by the equilibrium method,[1−5] the bracketing method,[6,7] and the kinetic method.[8−11] Protonation enthalpies of amino acids are of importance in understanding proton transfer reactions in biological systems.[12] Of the common protonated α-amino acids, the imidazole group of histidine, the basic group of lysine, and the guanidine group of arginine exist as resonance hybrids with the positive charge distributed over all the nitrogen atoms.[8−10] It has been shown that protonation of several amino acids in small polypeptides by electrospray ionization give highly charged ions in mass spectrometry experiments.[13,14]

The intrinsic relative gas-phase acidities for α-amino acids depends on the relative strengths of the weak acid groups, −COOH and $-NH_3^+$:

$$R{-}COOH \leftrightarrows R{-}COO^- + H^+$$

$$R{-}NH_3^+ \leftrightarrows R{-}NH_2 + H^+$$

R−COOH is a far stronger acid than $R{-}NH_3^+$ in the solution phase, so at a physiological pH (i.e., pH = 7.4), carboxylic groups exist almost entirely as $R{-}COO^-$. However, in the gas phase, this order of acidity is reversed and carboxylic groups exist in the R−COOH form.

Thermodynamic properties such as the gas-phase basicity (GB), proton affinity (PA), ΔG°_{acid}, and enthalpy of formation for amino acids have been computed using various methods.[15−18] In addition, the comparison of experimental gas-phase IR spectra to calculated IR spectra using density functional theory (DFT) has been performed for several protonated and deprotonated amino acids.[19] In another recent work, certain thermochemical properties of glycine, alanine, valine, leucine, isoleucine, and proline were computed at the G3MP2B3 level.[20]

The gas-phase basicity (GB) and proton affinity (PA) of a molecule may be affected through intramolecular effects, substituent effects, and electronic and steric interactions. Experimental studies have investigated these effects.[21−24] The study of the gas-phase zwitterionic structure of α-amino acids is of fundamental importance as shown in Scheme 1. A number of factors are involved in the stability of the zwitterionic form of an amino acid as a function of the side chain.

The gas-phase basicity (−ΔG of protonation) and proton affinity (−ΔH of protonation) are defined for the protonation reaction: $AH + H^+ \rightarrow AH_2^+$, where AH is the conjugate base of an acid AH_2^+ (GB = −GA), and GA is the gas-phase ΔG°_{acid} of AH_2^+. The two quantities are related by using the following equation:

$$GB = PA + T\Delta S^\circ = PA + T[\Delta_p S^\circ - S^\circ(H^+)] \quad (1)$$

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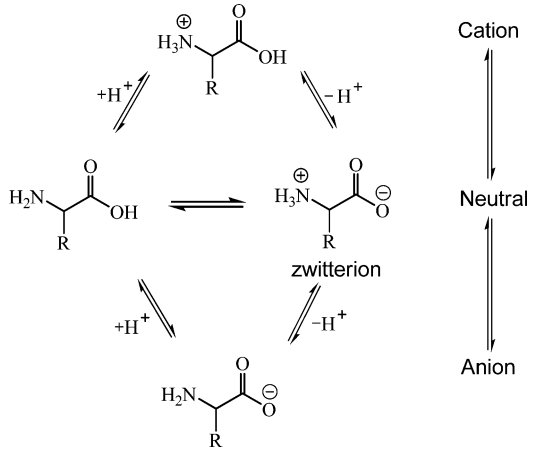
Scheme 1. Protonation and Deprotonation Reaction Equilibria for the α-Amino Acids



where $\Delta_p S^\circ = S^\circ(AH_2^+) - S^\circ(AH)$ and $S^\circ(H^+) = 108.8$ J mol^{-1} K^{-1} at 298 K, calculated using the Sackur−Tetrode equation. The protonation entropy can also be directly evaluated as the difference in calculated entropies of the protonated and neutral structures. The protonation entropy can be estimated by calculating the absolute third law entropy. Thermodynamic properties are then obtained via standard statistical mechanical treatments of the electronic, translational, rotational, and vibrational contributions to the property of interest.[25−27] Recently, Gronert et al.[28] computed the proton affinities of the α-amino acids at the G3MP2 level.

In this article, a detailed computational study of the thermochemical properties of the most stable conformations of the neutral, protonated, and deprotonated forms of all 20 α-amino acids are investigated with composite and density functional methods. Calculated thermochemical properties include the proton affinity, gas-phase basicity, protonation entropy, ΔH°_{acid}, ΔG°_{acid}, and enthalpies of formation for the protonated and deprotonated α-amino acids. The computed thermochemical properties of the amino acids and their protonation and deprotonation reactions are compared to the available experimental values. The variations in enthalpic and entropic factors will be explored, as well as the vital role of intramolecular hydrogen bonding. The overall goal is to provide a consistent set of thermochemical properties that can serve as benchmarks.

2. COMPUTATIONAL METHODS

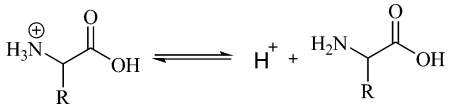
All calculations were performed with Gaussian09.[29] We have not performed an extensive conformational analysis for each amino acid, as such analyses have been extensively and elegantly performed in other works.[20,28,55] Instead, our approach has been to focus our calculations based on geometries as reported in the Supporting Information of works from Gronert,[28] Bouchoux,[20] and Poutsma.[55] Chemical intuition has then been used in determining other conformations that could potentially be more stable, yet might not be found from molecular mechanics based searches due to the highly variable nature of hydrogen bonding that may not be adequately accounted for in the force fields used.

We choose the lowest enthalpy structure as our criterion for selecting structures and not the lowest Gibbs energy. While authors of other works may feel that there is a stronger argument to be made for choosing structures based upon Gibbs energy due to the mass spectrometric techniques used in obtaining the experimental data, we feel the choice is not a valid one. First, the calculated entropy is the least reliable of the calculated thermodynamic properties, and so, the Gibbs energy is also subject to any errors that would result from entropy calculations. Additionally, as the geometry optimizations performed within computational chemistry software packages such as Gaussian do not occur in the Gibbs energy space. Claims to have found stationary points on the Gibbs energy surface, let alone a Gibbs energy global minimum are not warranted.

All computed thermodynamic values are based only on the single lowest enthalpy conformations. No distributions were considered. Also, hindered rotation contributions to the entropy were ignored in the expectation that the number of such rotations would be the same in both the neutral and protonated forms and cancel out in all computed thermodynamic properties.

The geometries of all reactants and products were fully optimized at the B3LYP level of theory using the 6-31G(d,p) and 6-31+G(d,p) basis sets, as well as with various composite methods (Gaussian-n theories). Frequency calculations ensured the absence of imaginary frequencies in the minima. From our previous work,[30−32] it was found that the activation energies and the enthalpies of reaction calculated using Gaussian-n theories (G1, G2, G2MP2, G3, G3MP2,[33] G3B3,[34] G3MP2B3,[34] G4MP2,[35,36] and CBS-QB3[37]) all agreed to within 10 kJ mol^{-1}. All of the optimized structures for the data presented here, as well as other explored conformations of neutral, protonated, and deprotonated forms and relative energies are provided in the Supporting Information (Tables SA1 to SA7 and Figures A1 to A7).

In this study, we evaluate the gas-phase basicity and proton affinity for the α-amino acids corresponding to the reaction



The gas-phase basicity and proton affinity for α-amino acids can be calculated from eqs 2 and 3, respectively,

$$GB = [\Delta G^\circ(AH) - \Delta G^\circ(AH_2^+)] + \Delta G^\circ(H^+) \quad (2)$$

$$PA = [\Delta H^\circ(AH) - \Delta H^\circ(AH_2^+)] + \Delta H^\circ(H^+) \quad (3)$$

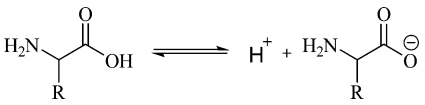
where $\Delta G^\circ(H^+) = -26.28$ kJ mol^{-1} and $\Delta H^\circ(H^+) = 6.19$ kJ mol^{-1} at 298 K.

The deprotonation enthalpy ΔH°_{acid} and acidity ΔG°_{acid} for α-amino acids can be calculated from eqs 4 and 5, respectively,

$$\Delta H^\circ_{acid} = [\Delta H^\circ(A^-) - \Delta H^\circ(AH)] + \Delta H^\circ(H^+) \quad (4)$$

$$\Delta G^\circ_{acid} = [\Delta G^\circ(A^-) - \Delta G^\circ(AH)] + \Delta G^\circ(H^+) \quad (5)$$

which correspond to the following reaction:



The gas-phase enthalpy of formation for protonated and deprotonated α-amino acids can be calculated from

$$\Delta H^\circ_{f(prot)}(AH_2^+) = \Delta H^\circ_{(PA)} + \Delta H^\circ_f(H^+) + \Delta H^\circ_f(AH) \quad (6)$$

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Table 1. Gas-Phase Basicities (GB)[a] of the α-Amino Acids (in kJ mol^{-1}) at 298.15 K

α-amino acid	B3LYP/6-31+G(d,p)	G3MP2[b]	G3MP2B3[b]	G4MP2	CBS-QB3	exptl[d]
glycine (Gly) [G]	855	853(−5)	855 (−7)[c]	854	854	848 (850)[e]
alanine (Ala) [A]	872	871 (−7)	870 (−6)[c]	870	868	864 (871)[e]
valine (Val) [V]	885	885 (−12)	884 (−11)[c]	884	883	873 (877)[f]
leucine (Leu) [L]	883	884 (−7)	883 (−6)[c]	882	881	877 (881)[f]
isoleucine (Ile) [I]	887	889 (−7)	886 (−4)[c]	888	885	882 (884)[f]
serine (Ser) [S]	879	881 (−12)	880 (−11)	880	878	869 (880)[g]
threonine (Thr) [T]	888	889 (−3)	887 (−1)	887	884	886
cysteine (Cys) [C]	872	873 (−10)	873 (−10)	873	870	863
methionine (Met) [M]	905	902 (−10)	901 (−9)	900	899	892 (898)[h]
aspartic (Asp) [D]	890	885 (−12)	884 (−11)	884	882	873
asparagine (Asn) [N]	912	905 (−15)	907 (−17)	906	905	890
glutamine (Gln) [Q]	940	937 (−41)	940 (−44)	939	937	896
glutamic (Glu) [E]	913	911 (−9)	909 (−7)	909	909	902 (904)[i]
lysine (Lys) [K]	963	960 (−32)	961 (−33)	960	960	928 (938)[j]
histidine (His) [H]	952	947 (−11)	947 (−11)	947	945	936 (941)[j]
arginine (Arg) [R]	1019	1014 (−22)	1011 (−19)	1012	1009	992 (1006)[k]
tyrosine (Tyr) [Y]	900	898 (−6)	897 (−5)	900	896	892 (895)[l]
phenylalanine (Phe) [F]	898	896 (−9)	895 (−8)	896	894	887 (892)[l]
tryptophan (Trp) [W]	909	910 (−6)	909 (−5)	907	906	904
proline (Pro) [P]	909	909 (−12)	908 (−11)[c]	909	905	897 (904)[m]

[a]The gas-phase basicity is calculated using eq 2. [b]The values in parentheses are the difference between the experimental (from ref 40) and the computed values (see Figure 1). [c]The values are identical with those of ref 20 (except Pro, 910 kJ mol^{-1}). [d]Reference 40. [e]Reference 1. [f]Reference 6b. [g]Reference 6a. [h]Reference 41. [i]Reference 52. [j]Reference 10. [k]Reference 44. [l]Reference 45. [m]Reference 46.

$$\Delta H^\circ_{f(deprot)}(A^-) = \Delta H^\circ_{acid} - \Delta H^\circ_f(H^+) + \Delta H^\circ_f(AH) \quad (7)$$

where $\Delta H^\circ_{(PA)}$ is the negative of the proton affinity of the amino acid, ΔH°_{acid} is the deprotonation enthalpy, and the enthalpy of formation for a gaseous proton $\Delta H^\circ_f(H^+) = 1536.4$ kJ mol^{-1} at 298 K.[38] For a neutral amino acid, $\Delta H^\circ_f(RCH(NH_2)COOH)$ has been determined from literature values for the enthalpy of formation for the crystalline amino acid ($\Delta H^\circ_{f(cr)}$) and its enthalpy of sublimation ($\Delta H^\circ_{(sub)}$).[4,39] The equation has the form $\Delta H^\circ_f = \Delta H^\circ_{f(cr)} + \Delta H^\circ_{(sub)}$. Unless otherwise stated, all calculated values given in the text are for the G3MP2 level of theory.

3. RESULTS AND DISCUSSION

Of the 40 structures we report at the G3MP2 level (20 protonated and 20 neutral amino acids), the lowest enthalpy (and Gibbs energy) structure we have found matches the Gronert[28] structure in 31 cases. We have found lower enthalpy structures (by 1.2 to 4.5 kJ mol^{-1}) for Thr, Cys, Gln, Lys, Tyr, Phe, Pro, GlyH$^+$, and LysH$^+$. In four cases, these structures also have lower Gibbs energy than the Gronert structures: Cys (1.6 kJ mol^{-1}), Gln (3.2 kJ mol^{-1}), Tyr (0.6 kJ mol^{-1}), and Pro (1.9 kJ mol^{-1}).

The results for the gas-phase basicity, proton affinity, protonation entropy, ΔH°_{acid}, ΔG°_{acid}, and enthalpies of formation for protonated and deprotonated amino acids at different levels of theory are given in Tables 1 to 8. Schematics of the protonation and deprotonation reactions of α-amino acids in this work are shown in Schemes 2 to 9.

3.1. Gas-Phase Basicities (GB) and Proton Affinities (PA) of α-Amino Acids. The gas-phase basicities and proton affinities calculated for the α-amino acids are listed in Tables 1 and 2. These tables also include the differences in the calculated and experimental values, which are also plotted in Figures 1 (ΔGB) and 2 (ΔPA).

It should be noted that the main source of experimental values is the review by Harrison,[40] which gives average values of experimental results for the GB and PA derived from different experimental methods. In some cases, Harrison has eliminated what he calls "suspect values" from this average value. We also include data from other experimental sources in Tables 1 and 2, but comparisons between calculated and experimental values are based on Harrison's work.[40]

In this study, α-amino acids may be represented as carboxyl derivatives (−COOH) of parent amines (R−NH$_2$) and the electron withdrawing −COOH group causes a decrease in the proton affinity of the amino group. Proton affinities of the amino acids are always close to those of the parent amines when protonation occurs on the amino nitrogen. The proton affinity of the amino acids can be increased by internal hydrogen bonding between the −NH$_3^+$ and −COOH, which tends to stabilize the protonated −NH$_3^+$ group. The zwitterionic forms are protonated at the carboxyl group, while nonionic forms are protonated at the amino group (Scheme 1).

The common α-amino acids can be classified into one of seven groups: aliphatic, hydroxylic, sulfur-containing, acidic or amides, basic, aromatic rings, and imino acid-containing. Our discussion of thermochemical properties will be generally organized within these groups. The aliphatic α-amino acids include Gly, Ala, Val, Leu, and Ile as shown in Scheme 2. The proton affinities and gas-phase basicities computed at the G3MP2, G3MP2B3, G4MP2, and CBS-QB3 levels of theory for this group are in excellent agreement with the experimental[1,6b,40] values (within 12 kJ mol^{-1} at most, but by about 7 kJ mol^{-1} on average) and differ by no more than 4 kJ mol^{-1} from each other for any specific amino acid of the group. Previously reported G3MP2[28] PAs for this group differ from those of Harrison[40] by no more than 8 kJ mol^{-1} (Val), where the largest difference with our G3MP2 PAs is 9 kJ mol^{-1} (Gly and Val). Additionally, we match the Gronert PAs for all members of this group to within 1 kJ mol^{-1}, except for Gly (3 kJ mol^{-1}).

Table 2. Gas-Phase Proton Affinities (PA)[a] of the α-Amino Acids (in kJ mol^{-1}) at 298.15 K

		G3MP2[b]					
α-amino Acid	B3LYP/6-31+G(d,p)	present work	Gronert[c]	G3MP2B3[b]	G4MP2	CBS-QB3	exptl[e]
Gly	888	890 (−9)	887 (−6)	888 (−7)[d]	889	886	881 (883)[f]
Ala	904	902 (−6)	902 (−6)	902 (−6)[d]	903	901	896 (900)[f]
Val	917	915 (−9)	914 (−8)	915 (−9)[d]	916	914	906 (911)[g]
Leu	917	915 (−5)	914 (−4)	916 (−6)[d]	916	914	910 (915)[g]
Ile	921	919 (−4)	918 (−3)	919 (−4)[d]	920	918	915 (917)[g]
Ser	913	913 (−13)	913 (−13)	914 (−14)	914	912	900 (921)[h]
Thr	920	919 (−1)	919 (−1)	918 (0)	919	916	918
Cys	903	903 (−8)	907 (−12)[p]	904 (−9)	904	902	895
Met	943	937 (1)	936 (2)	939 (−1)	939	937	938[e,i]
Asp	924	917 (−12)	916 (−11)	918 (−13)	919	916	905 (910)[j]
Asn	944	936 (0)	936 (0)	937 (−1)	938	936	936
Gln	977	972 (−31)	973 (−32)	975 (−34)	975	973	941
Glu	953	948 (−1)	948 (−1)	948 (−1)	948	948	947 (945)[k]
Lys	1000	998 (−12)	1000 (−14)	998 (−12)	997	997	986 (984)[l]
His	985	979 (2)	979 (2)	979 (2)	979	977	981 (979)[l]
Arg	1053	1047 (−23)	1046 (−22)	1046(−22)	1046	1044	1024 (1046)[m]
Tyr	931	926 (−2)	929 (−5)	927 (−3)	923	926	924 (935)[n]
Phe	928	924 (−4)	926 (−6)	925 (−5)	926	923	920 (931)[n]
Trp	941	941 (−4)	940 (−3)	942 (−5)	942	940	937
Pro	941	939 (−10)	942 (−13)	938 (−9)[d]	940	936	929 (937)[o]

[a]The gas-phase proton affinity is calculated using eq 3. [b]The values in parentheses are the difference between the experimental (from ref 40) and the computed values (see Figure 2). [c]Reference 28. [d]The values are identical with those of ref 20 (except Pro, 941 kJ mol^{-1}). [e]Reference 40. [f]Reference 1. [g]Reference 6b. [h]Reference 6a. [i]Reference 41. [j]Reference 56. [k]Reference 52. [l]Reference 10. [m]Reference 44. [n]Reference 45. [o]Reference 46. [p]Reference 28 reports this as 215.6 kcal mol^{-1} = 902.1 kJ mol^{-1}. However, using data provided in the Supporting Information of ref 28 actually gives the value we report here.

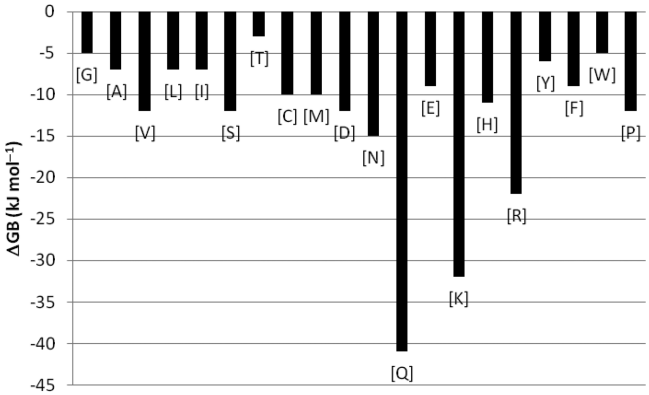

Figure 1. Plot of G3MP2 gas-phase basicity difference (ΔGB = GB$_{(exp)}$ − GB$_{(calcd)}$) in kJ mol^{-1} for the 20 amino acids.

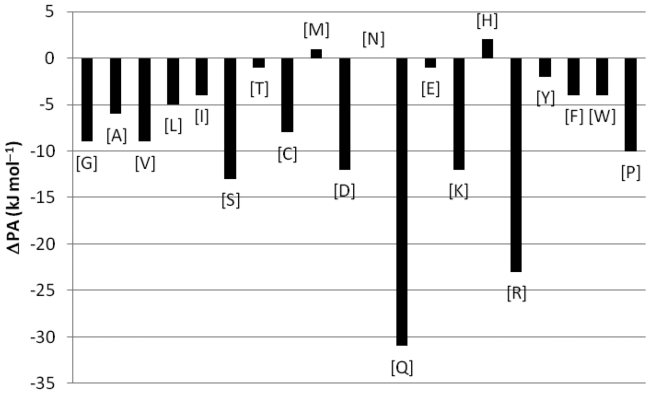

Figure 2. Plot of G3MP2 gas-phase proton affinity difference (ΔPA = PA$_{(exp)}$ − PA$_{(calcd)}$) in kJ mol^{-1} for the 20 amino acids.

The GBs and PAs of the aliphatic α-amino acids Gly, Ala, Val, Leu, and Ile are identical with the work of Bouchoux[20] at G3MP2B3 (Tables 1 and 2). The conformers of neutral and deprotonated glycine, as shown in Figure A1 and Table SA1 provided in the Supporting Information, are energetically similar to those reported by Cassady.[16b]

The hydroxylic amino acids include Ser (Scheme 3), Thr (Scheme 3), and Tyr (Scheme 7). However, we will discuss Tyr as an aromatic ring amino acid. The proton affinities and gas-phase basicities computed at the G3MP2, G3MP2B3, G4MP2, and CBS-QB3 levels of theory do not differ by more than 5 kJ mol^{-1}. Our GB and PA values of serine at G3MP2 are 881 and 913 kJ mol^{-1}, respectively, whereas the experimental[40] values are 869 and 900 kJ mol^{-1} (Table 1 and 2). Our G3MP2 PAs for this group match those of Gronert[28] except for Tyr, where they differ by 3 kJ mol^{-1}.

The sulfur containing amino acids include Cys (Figure 4) and Met (see Figure A3 of Supporting Information) as shown in Scheme 4. The GB and PA values of cysteine at G3MP2 are 873 and 903 kJ mol^{-1}, respectively. The experimental values[40] are 863 and 895 kJ mol^{-1}, respectively. The GBs and PAs of the other Gaussian-n theories are all within 3 kJ mol^{-1}. The PAs of the sulfur containing amino acids differ from experiment[40] by 1 kJ mol^{-1} for Met and 8 kJ mol^{-1} for Cys at G3MP2.

Calculations for different conformations of neutral methionine, as shown in Table SA3 and Figure A3, provided in the Supporting Information, show that the energy of conformer Met (NH_2···O=C) is slightly lower (4.2 kJ mol^{-1}) at G3MP2 than conformer Met_a (H_2N···HO). At B3LYP/6-31+G(d,p), both conformers are essentially energetically equivalent.[41] An investigation showed the NH_2···O=C hydrogen bonded conformer (Met) to be more stable.[42] Blieholder et al. studied[43]

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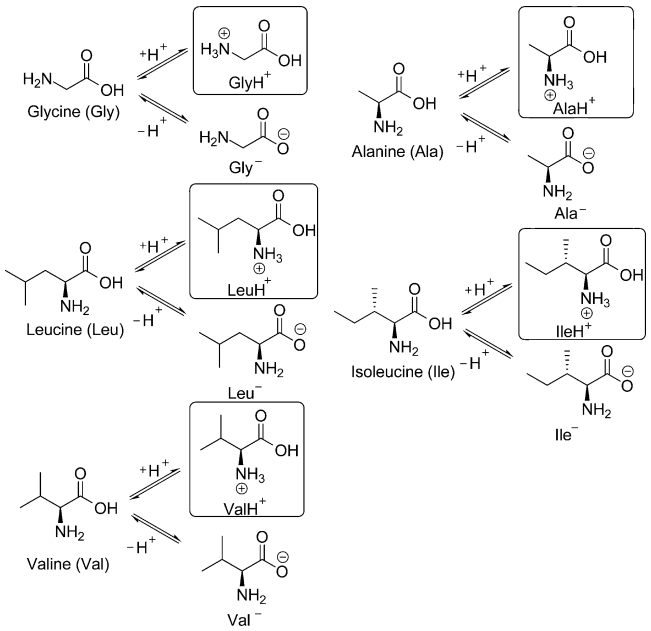
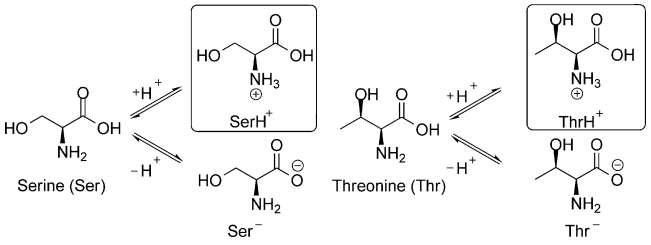
Scheme 2. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids Containing Aliphatic Side Chains[a]



[a]The box indicates the preferred protonation site.

Scheme 3. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids with Side Chains Containing Hydroxyl (−OH) Groups[a]



[a]The box indicates the preferred protonation site.

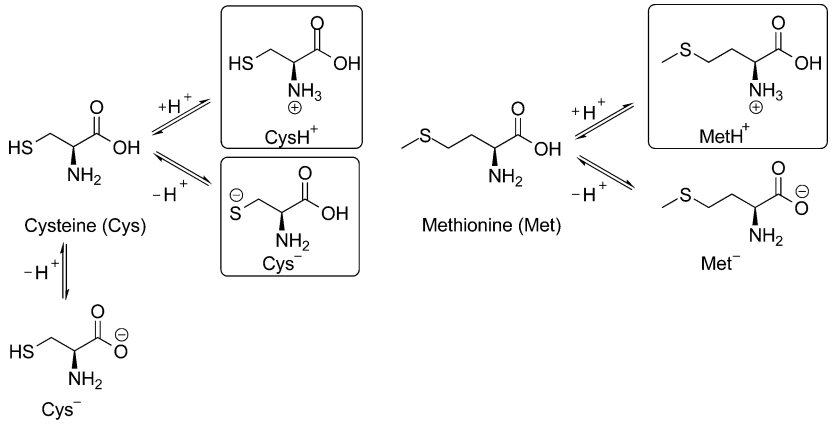
methionine with an AMBER force field and found the hydrogen-bonded conformer (Met) (OH···NH_2) to be more stable. Similarly, the protonated Met conformer ($MetH^+$) is more stable due to three strong intramolecular hydrogen bonds (CO···HO, NH···O, and NH···S). The PA of the Met conformer computed at G3MP2, G3MP2B3, G4MP2, and CBS-QB3 are found to be very close to the experimental[40,41] values, differing by no more than 2 kJ mol^{-1}.

The acidic/amidic amino acids include Asp, Asn, Glu, and Gln as shown in Scheme 5. The difference in proton affinity and gas-phase basicity calculated at G3MP2 for glutamic acid and aspartic acid (ΔPA = 31 kJ mol^{-1} and ΔGB = 26 kJ mol^{-1}, respectively) is smaller than for the corresponding amides glutamine and asparagine (ΔPA = 36 kJ mol^{-1} and ΔGB = 32 kJ mol^{-1}, respectively). Structurally, these amino acids differ by one methylene group in the side chain and energetically there is only a small difference between PA and GB. For glutamic acid and glutamine, the differences in their proton affinities and gas-phase basicities are 24 and 26 kJ mol^{-1}, respectively, at G3MP2. A comparison between aspartic acid and asparigine shows differences of 19 and 20 kJ mol^{-1}, respectively, for their PA and GB. The structural differences between these amino acids should account for these small differences in PA and GB. Scheme 5 (Figure A4, provided in Supporting Information) show the energetically most stable species of protonated asparagine ($AsnH^+$) and glutamine ($GlnH^+$) for the pyramidal N-terminal amino protonated forms. The protonated Asn conformer ($AsnH^+$) has the lowest energy due to stabilization by strong hydrogen bonding between the protonated amino group to the amidic oxygen $-NH_3^+\cdots O{=}C(NH_2)$, where the strong hydrogen bond forms in a six membered ring.

Figure A4, Supporting Information, shows that the $-NH_3^+\cdots O{=}C(NH_2)-$ hydrogen bridge bond of $GlnH^+$ may be similar to the $-NH_3^+\cdots O{=}C(OH)-$ H-bond of $GluH^+$. However, energetically, $GlnH^+$ is stabilized to a greater extent by the hydrogen bond, and as a result, Gln is less basic than Glu. Previous experimental[40] results have also found Gln to be less basic than Glu. Overall, our G3MP2 PAs of the acidic/amidic amino acids (Asp, Asn, Glu, and Gln) differ from experiment by 12, 0, 1, and 31 kJ mol^{-1}, whereas the values of Gronert[28] differ by 11, 0, 1, and 32 kJ mol^{-1} (Table 2).

The basic side chain amino acids include Arg, Lys, and His as shown in Scheme 6. The gas-phase basicities (GBs) and proton affinities (PAs) computed at G3MP2, G3MP2B3, G4MP2, and

Scheme 4. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids with Side Chains Containing Sulfur Atoms[a]



[a]The box indicates the preferred protonation and deprotonation (Cys^-) sites.

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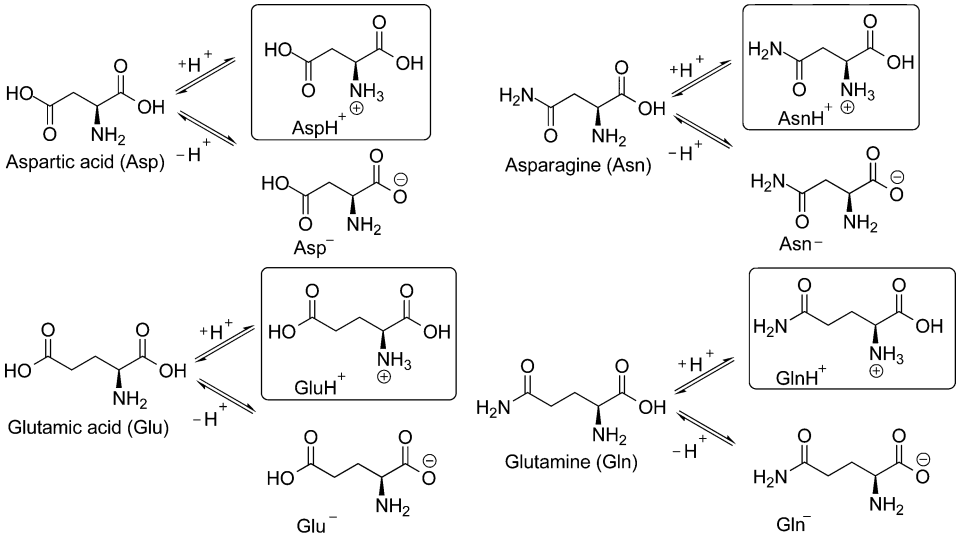
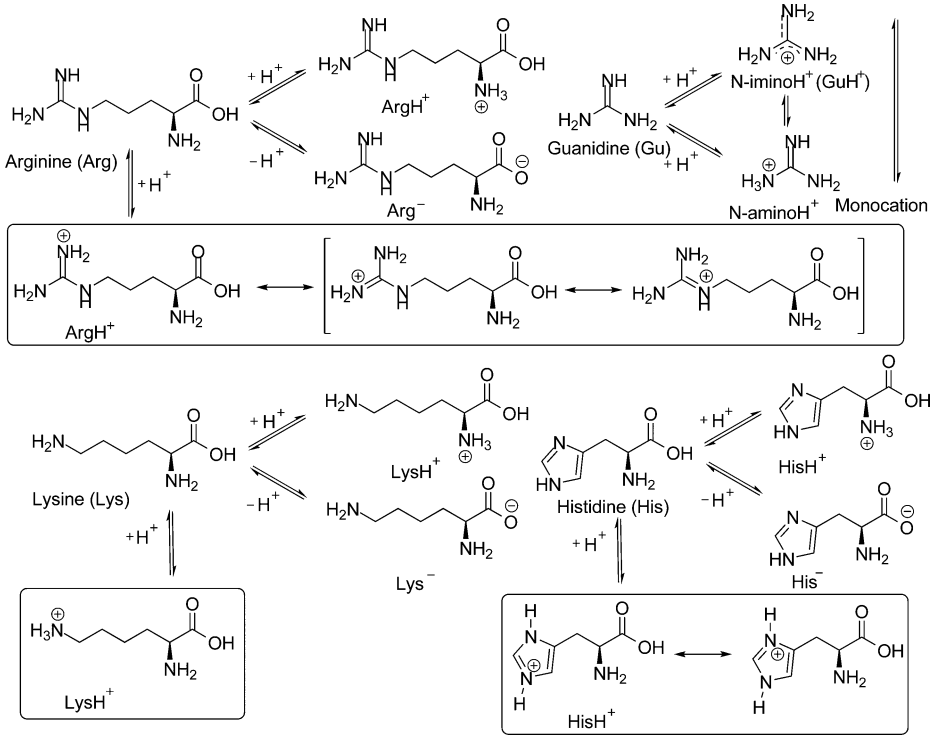
Scheme 5. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids with Side Chains Containing Acidic or Amide Groups[a]



[a]The box indicates the preferred protonation site.

Scheme 6. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids with Side Chains Containing Basic Groups[a]



[a]The box indicates the preferred protonation site.

CBS-QB3 differ by no more than 5 and 3 kJ mol^{-1}, respectively, and are given in Table 1 and 2. The strongly basic guanidino group present in the side chain of protonated arginine can be described through three resonance structures, each with a positive charge possessed by one of the three nitrogen atoms. The stabilization one expects to see from several resonance forms (Scheme 6) should increase the likelihood of protonation (the basicity) at the side chain N-imino group compared to protonation at the N-amino atom (Figure A5 of Supporting Information). In fact, the most stable protonated arginine conformer (protonated N-imino ArgH$^+$) is a result of an intramolecular hydrogen bond that is significantly stronger. The proton affinities of these two forms also show a similar large discrepancy due to stabilized intramolecular hydrogen bonding. This supports the notion that protonation at the N-imino group is much more likely than at the amino nitrogen. For the PAs of the basic side chain amino acids (Lys, His, and Arg), our G3MP2 values differ from experiment[40] by 12, 2, and 23 kJ mol^{-1},

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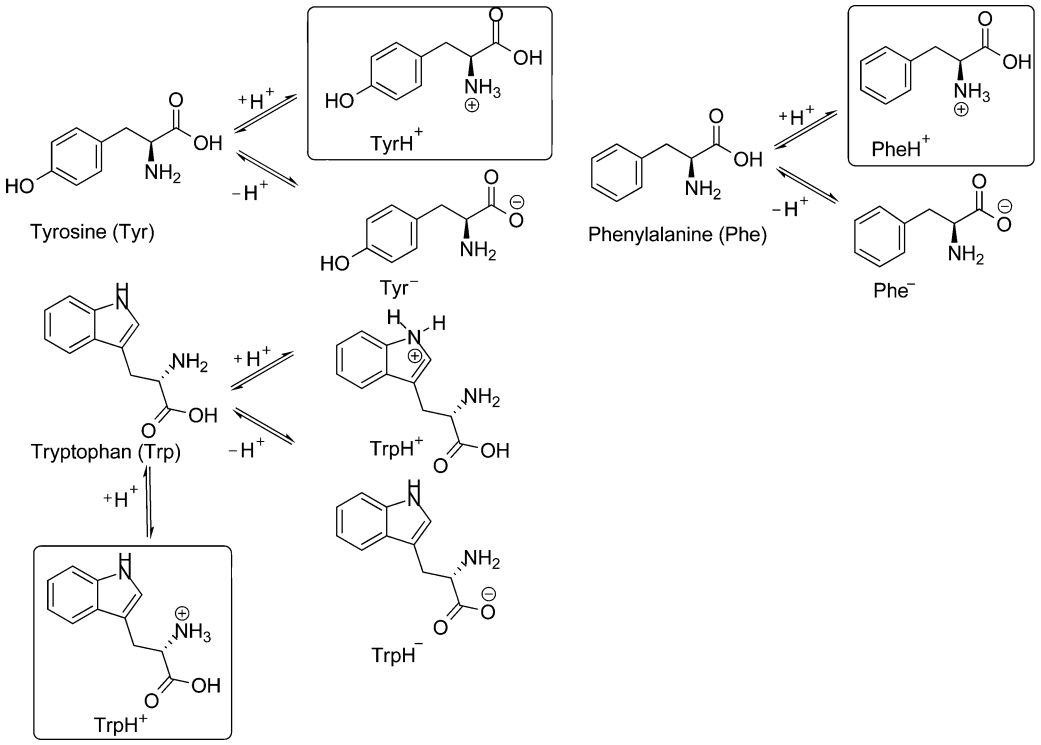
Scheme 7. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids Containing Aromatic Rings[a]



[a]The box indicates the preferred protonation site.

whereas the values of Gronert[28] differ by 14, 2, and 22 kJ mol^{-1} (Table 2).

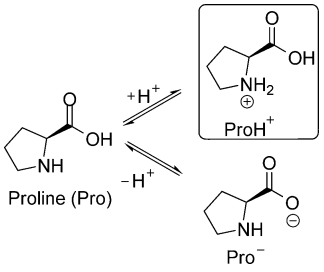
The computed PA and GB of histidine are close to the experimental[10] results and differ by less than 11 kJ mol^{-1}. Protonation of histidine appears to be energetically more favorable on the imidazole ring compared to the amino nitrogen. Once again, this can be explained through resonance stabilization (two resonance structures, Scheme 6) of the protonated imidazole ring compared to a single resonance structure when protonation occurs at the imidazole ring amino nitrogen.

The structures of the neutral and protonated forms of lysine are shown in Scheme 6 (see Figure A5, provided in Supporting Information). This amino acid has four methylene (−CH_2) groups in the side chain, which allows for conformational flexibility. Protonation can occur at the side chain amino group ($LysH^+$) and the backbone amino group ($LysH^+$_a), but a salt-bridge (Lys_b) form also exists where protonation occurs on the side chain amino group, while the carboxyl group donates its proton to the backbone amino group. Protonation at the side chain amino group ($LysH^+$) leads to an intramolecular hydrogen-bonded (−H_2N−H^+···NH_2−) form that is energetically more stable than the backbone protonation and salt-bridge forms. A comparison of the GB (960 kJ mol^{-1}) of Lys shows that it is significantly more basic than His (GB of 947 kJ mol^{-1}), which agrees with experimental results obtained through the kinetic method.[10]

The aromatic ring amino acids include His (discussed previously), Phe, Tyr, and Trp as shown in Scheme 7. The proton affinities and gas-phase basicities computed at G3MP2, G3MP2B3, G4MP2, and CBS-QB3 are found to be similar to experimental[40] results, with differences of no more than 11 kJ mol^{-1}. For this group, the G3MP2 PAs are all in good agreement with experiment,[40] differing by no more than 4 kJ mol^{-1} (Table 2).

Proline contains a five membered pyrrolidine ring as shown in Scheme 8. The PA and GB values of proline at G3MP2 are

Scheme 8. Structures for the Neutral, Protonated, and Deprotonated α-Amino Acids with an Imino Acid Ring[a]



[a]The box indicates the preferred protonation site.

939 (942 kJ mol^{-1} for Gronert) and 909 kJ mol^{-1}, while the experimental values[46] are 937 and 904 kJ mol^{-1}, respectively. The G3MP2B3 value (938 kJ mol^{-1}) is also very close to the G3MP2B3 PA[20] (941 kJ mol^{-1}) and our G4MP2 (940 kJ mol^{-1}) and CBS-QB3 (936 kJ mol^{-1}) values. Overall, our PAs and GBs values for Pro are in good agreement with the experimental values.[46]

As there are several different sources of experimental data available for the proton affinity of the amino acids, Table 3 shows the relative order of proton affinity for these experimental methods[8−10,40] as compared to the order provided by G3MP2. In some cases (e.g., Asp and Leu), the order of the calculated proton affinity does not match the order for the different experimental methods, yet the experimental methods

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Table 3. Comparison of the Order of the Computed Proton Affinities (PA) of the α-Amino Acids with Order Derived from Different Experimental Methods

G3MP2	exptl[a]	exptl[b]	exptl[c]	exptl[d]
Gly (890)	Gly	Gly	Gly	Gly
Ala (902)	Cys	Ala	Ala	Ala
Cys (903)	Ala	Cys	Cys	Cys
Ser (913)	Ser	Ser	Ser	Ser
Val (915)	Asp	Val	Asp	Val
Leu (915)	Val	Asp	Val	Asp
Asp (917)	Leu	Leu	Leu	Leu
Thr (919)	Ile	Thr	Thr	Thr
Ile (919)	Thr	Ile	Ile	Ile
Phe (924)	Phe	Phe	Phe	Phe
Tyr (926)	Asn	Met	Met	Tyr
Asn (936)	Tyr	Tyr	Tyr	Met
Met (937)	Met	Asn	Glu	Asn
Pro (939)	Gln	Pro	Asn	Glu
Trp (941)	Pro	Glu	Trp	Pro
Glu (948)	Glu	Trp	Pro	Trp
Gln (972)	Trp	Gln	Gln	Gln
His (979)	His	Lys	Lys	Lys
Lys (998)	Lys	His	His	His
Arg (1047)	Arg	Arg	Arg	Arg

[a]Reference 40. [b]Reference 8. [c]Reference 9. [d]Reference 10.

show significant variability. Because the Gaussian-n theory based calculations are within 5 kJ mol^{-1} of each other, we conclude that very similar orders are obtained between the calculated and experimental proton affinities once experimental errors have been taken into account.

Finally, the mean absolute deviation (MAD) between experimental[40] and the G3MP2 proton affinities is 7.8 kJ mol^{-1}. Similarly, the MAD for the gas-phase basicities of the six amino acids with aliphatic side chains at G3MP2B3 is 6.8 kJ mol^{-1}, similar to those reported by Bouchoux.[20] As the different sources of experimental data can vary by ∼2% relative to each other, G3MP2 calculations of these properties can be claimed to give results that are very consistent to experimental results. Additionally, the different Gaussian-n theory results (G3MP2, G3MP2B3, G4MP2, and CBS-QB3) agree with each other to within ∼1% or less in terms of relative difference (5 kJ mol^{-1}). These differences fall within the range of experimental error and can likely be considered to be random in nature.

3.2. Evaluation of Protonation Entropy Differences of α-Amino Acids. The entropy of protonation $\Delta_pS°$ of an amino acid can be calculated from its proton affinity and gas-phase basicity using eq 1. The protonation entropy can also be calculated as the direct difference of the calculated entropy values for lowest enthalpy structures of the protonated and neutral forms. As indicated in the computational methods section, hindered rotations were not considered, as the number of such rotations was likely to be the same in both the protonated and neutral forms and therefore would cancel out in the calculated entropy difference. This assumption was found to be true for fourteen of the amino acids. For the remainder (Cys, Asn, Gln, His, Arg, and Phe), the number of hindered rotors differed by 1.

Table 4 shows the calculated total gas-phase entropy and the translational, rotational, and the vibrational contribution to the protonation entropy. The table also compares these to the experimental[40] gas-phase protonation entropy. In general, the calculated and experimental values are in good agreement. However, in some cases (e.g., Met, Lys and His), there are some large discrepancies. There are several factors that can account for this difference. First, as has already been discussed, the protonation entropy ($\Delta_pS°$) is affected by the relative stability of all the conformers of the amino acid. LysH$^+$ (Figure A5 of Supporting Information) is the most stable conformer due to cyclization through intramolecular hydrogen bonding. Such hydrogen bonding will play a significant role in altering both the rotational and vibrational entropy contributions to the overall gas-phase entropy and protonation entropy.

The computed $\Delta_pS°$ of LysH$^+$ is −18.5 J mol^{-1} K^{-1}, while the experimental[40] value of Harrison (−85.0 J mol^{-1} K^{-1}) has been estimated. Since the experimental determination of the proton affinity often relies on the estimate of the gas-phase entropy change[40] of the protonation reaction, experimental PA values could be significantly in error due to errors in the entropy estimate. For example, it is stated[6,47,48,59] that the entropy of cyclization for lysine should be similar to that of 1,5-diaminopentane (1,5-DAP) (ΔS_{cyc} = −86 J mol^{-1} K^{-1}),[6] and so, the reported experimental PA value reflects that estimate. This is justified by the measured difference in gas-phase basicity of lysine and leucine (47 ± 13 kJ mol^{-1}) as compared to the measured difference between the GB of 1,5-DAP and *n*-pentylamine (1-aminopentane), 45 ± 6 kJ mol^{-1}.[6] Our difference for the GB of lysine and leucine at G3MP2 is 76 kJ mol^{-1}. However, the $\Delta_pS°$ results of 1,5-DAP show that the computed value, −16.5 J mol^{-1} K^{-1}, differs significantly from the experimental[48] range of −70.0 to −96.0 J mol^{-1} K^{-1}. In G3MP2 calculations, the entropy change of cyclization of 1,5-DAP (−16.5 J mol^{-1} K^{-1}) can be considered to be of the same magnitude as for lysine (−18.5 J mol^{-1} K^{-1}) but is of a much smaller magnitude than is estimated by Harrison.[40]

A similar argument can be made for histidine. Using the experimental protonation entropy (−50 J mol^{-1} K^{-1})[59] of 1,3-diaminopentane (1,3-DAP) as a comparable, Harrison estimates the protonation entropy to be −42.8 J mol^{-1} K^{-1}. However, calculated protonation entropies for 1,3-DAP and His are found to be consistent with each other (−13.8 and 0.3 J mol^{-1} K^{-1} respectively), but of a much smaller magnitude than the estimated value used.

Additionally, for Arg, estimated entropies of protonation range from −0.7 to −25.4 J mol^{-1} K^{-1} based on a comparison to guanidine in its N-imino and N-amino forms (Figure A6 of Supporting Information). Calculations once again show the protonation entropy (−0.4 J mol^{-1} K^{-1}) for arginine does match well with the protonation entropy calculated for the two forms of guanidine, but the calculated protonation entropy values are positive and have magnitudes around 12 J mol^{-1} K^{-1}, while the experimental results are negative but of similar magnitudes.

We believe that the calculated protonation entropies are likely more reliable than experimentally derived entropies. As justification, we point to the discussion and conclusions of several works.[48,59,54] Bouchoux[59] concludes for the extended kinetic method that random errors in PA and protonation entropies can be significant (if not unacceptable) if not enough experimental points are considered. Therefore, he concludes that the GB values are the more reliable experimental results than PA or protonation entropy.

In the thermokinetic method, Bouchoux[59] points out that approximations are sometimes made in experimentally determining protonation entropies, which can fail as the true

Table 4. Comparison of G3MP2, G3MP2B3, and Experimental Values of Gas-Phase ($\Delta S°$) and Protonation Entropies ($\Delta_p S°$) of the α-Amino Acids and Comparable Amines in J mol^{-1} K^{-1} at 298.15 K[a]

α-amino acid/comparable amine	$\Delta S°$	$\Delta_p S°$	$\Delta_p S°$ (expt[b])
Gly	−122.7 (−109.6)	−13.9 (−0.8)	−0.7 (−1.9)[c]
Ala	−105.0 (−109.3)	3.8 (−0.5)	−0.7 (11.5)[c]
Val	−101.4 (−105.5)	7.4 (3.3)	−0.7 (−5.3)[d]
Leu	−104.9 (−109.7)	3.9 (−0.9)	−0.7 (−5.3)[d]
Ile	−102.7 (−110.6)	6.1 (−1.8)	−0.7 (−1.9)[d]
Ser	−109.2 (−113.5)	−0.4 (−4.7)	−0.7 (−28.8)[e]
Thr	−99.6 (−103.6)	9.2 (5.2)	−0.7
Cys	−101.2 (−104.1)	7.6 (4.7)	−0.7
Met	−116.1 (−126.6)	−7.3 (−17.8)	−42.8 (−25.4)[f]
Asp	−107.9 (−114.1)	0.9 (−5.3)	−0.7
Asn	−104.4 (−103.1)	4.4 (5.7)	−0.7
Gln	−119.9 (−118.5)	−11.1 (−9.7)	−42.8
Glu	−124.2 (−130.3)	−15.4 (−21.5)	−42.8 (−28.8)[g]
Lys	−127.3 (−122.6)	−18.5 (−13.8)	−85.0 (−45.6)[h]
1,5-diaminopentane	−125.3	−16.5	(−70 to −96)[i]
1,3-diaminopentane	−122.6	−13.8	−50[j]
His	−108.5 (−109.0)	0.3 (−0.2)	−42.8 (−18.7)[h]
Arg	−109.2 (−117.9)	−0.4 (−9.1)	−0.7 (−25.4)[k]
guanidine (N-imino)	−101.0	7.8	−15.4[l]
guanidine (N-amino)	−96.3	12.5	−15.4[l]
Tyr	−96.1 (−100.4)	12.7 (8.4)	−0.7 (−25.4)[m]
Phe	−95.5 (−99.7)	13.3 (9.1)	−0.7 (−22.1)[m]
Trp	−104.9 (−109.2)	3.9 (−0.4)	−0.7
Pro	−103.0 (−103.0)	5.8 (5.8)	−0.7 (−1.9)[n]

[a]The gas-phase ($\Delta S°$) and protonation entropies ($\Delta_p S°$) relate the proton affinity and gas-phase basicity (see eq 1) and $S° = S°_{trans\text{-}indist} + S°_{rot} + S°_{vib}$. Calculated values are at G3MP2, while the values in parentheses are calculated at G3MP2B3. [b]Reference 40. [c]Reference 1. [d]Reference 6b. [e]Reference 6a. [f]Reference 41. [g]Reference 52. [h]Reference 10. [i]Reference 48. [j]Reference 59. [k]Reference 44. [l]Reference 53. [m]Reference 45. [n]Reference 46.

Table 5. Gas-Phase Deprotonation Enthalpies ($\Delta H°_{acid}$)[a] of the α-Amino Acids in kJ mol^{-1} at 298.15 K

α-amino acid	B3LYP/6-31+G(d,p)	G3MP2[b]	G3MP2B3[b]	G4MP2	CBS-QB3	exptl[d,e]
Gly	1424	1435 (−1)	1435 (−1)[c]	1435	1430	1434 (1433)[f]
Ala	1422	1432 (−2)	1432 (−2)[c]	1433	1428	1430 (1425)[f]
Val	1416	1425 (6)	1424 (7)[c]	1425	1419	1431 (1420)
Leu	1417	1427 (−8)	1427 (−8)[c]	1427	1422	1419
Ile	1414	1424 (−1)	1423 (0)[c]	1423	1418	1423 (1418)
Ser	1381	1392 (−1)	1391 (0)	1392	1385	1391 (1392)
Thr	1379	1390 (−2)	1390 (−2)	1390	1385	1388 (1390)
Cys	1384	1399 (−4)	1395 (0)	1398	1392	1395[g](1393)
Met	1422	1430 (−23)	1431 (−24)	1432	1432	1407 (1405)
Asp	1326	1349 (−4)	1345 (0)	1346	1339	1345 (1340)[h]
Asn	1380	1388 (−3)	1388 (−3)	1389	1383	1385 (1388)
Gln	1385	1385 (0)	1383 (2)	1383	1379	1385 (1388)
Glu	1334	1347 (1)	1345 (3)	1346	1338	1348 (1350)[h]
Lys	1415	1417 (−1)	1416 (0)	1417	1412	1416 (1412)
His	1384	1399 (−14)	1398 (−14)	1398	1393	1385 (1375)
Arg	1390	1390 (−1)	1394 (−5)	1394	1390	1389 (1381)
Tyr	1409	1415 (−2)	1416 (−3)	1417	1415	1413 (1408)
Phe	1410	1416 (2)	1416 (2)	1417	1412	1418 (1408)
Trp	1413	1419 (2)	1420 (1)	1417	1416	1421 (1410)
Pro	1422	1428 (3)	1428 (3)[c]	1428	1423	1431 (1430)

[a]Calculated using eq 4. [b]The values in parentheses are the difference between the experimental and calculated values (see Figure 3). [c]The values are identical with those of ref 20 (except Leu, 1424 kJ mol^{-1}). [d]Reference 55. [e]The values in parentheses from ref 49. [f]Reference 4b. [g]Reference 18. [h]Reference 50.

entropy change deviates from zero. He also states that the full entropy analysis method used in deriving PA and protonation entropies only gives part of the protonation entropy difference, not the true entropy difference. Such a statement agrees with that of Poutsma[48] for the extended kinetic method where the graphical intercept used to evaluate the protonation entropy may not be related to a thermodynamic quantity but rather a difference in entropy of

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the microcanonical density of states at the given activation energy.

3.3. Gas-Phase Deprotonation Enthalpy ($\Delta H°_{acid}$) of α-Amino Acids. The gas-phase deprotonation enthalpies ($\Delta H°_{acid}$) for α-amino acids were calculated at the B3LYP/6-31+G(d) level of theory, as well as with the Gaussian-n theories (G3MP2, G3MP2B3, G4MP2, and CBS-QB3). Results are given in Table 5. As seen before in the calculated proton affinities and gas-phase basicities, the $\Delta H°_{acid}$ of amino acids computed at G3MP2, G3MP2B3, G4MP2, and CBS-QB3 are in reasonable agreement with the experimental results.[4,18,20,28,49,50,55]

The calculated $\Delta H°_{acid}$ of amino acids such as Gly, Ala, Val, Leu, and Ile computed at G3MP2 are 1435, 1432, 1425, 1427, and 1424 kJ mol^{-1}, respectively, while the difference ($\Delta\Delta H°_{acid}$) between the experimental[4,49,55] and calculated values differ by no more than 8 kJ mol^{-1}. For this group, our $\Delta H°_{acid}$ values at G3MP2B3 and those of Bouchoux[20] are identical (except Leu) and all in good agreement with experiment, differing by no more than 8 kJ mol^{-1} (Table 5). Figure 3 illustrates that theoretical methods (G3MP2) show excellent agreement with experimental $\Delta H°_{acid}$.

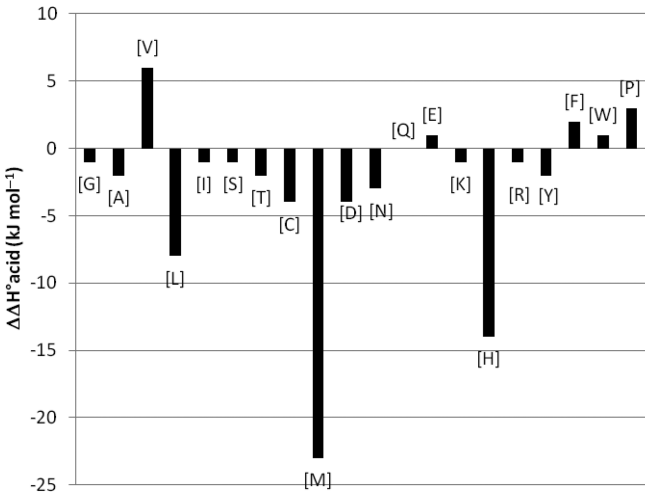

Figure 3. Plot of G3MP2 $\Delta\Delta H°_{acid} = \Delta H°_{acid\,(exp)} - \Delta H°_{acid\,(calcd)}$ in kJ mol^{-1} for the 20 amino acids.

The $\Delta H°_{acid}$ of the amino acids with aromatic rings (Tyr, Phe, and Trp) computed at G3MP2 are 1415, 1416, and 1419 kJ mol^{-1}, respectively, while the experimental values again differ by no more than 2 kJ mol^{-1}. The hydroxylic amino acids (Ser and Thr) have $\Delta H°_{acid}$ computed at G3MP2 of 1392 and 1390 kJ mol^{-1}, respectively, and are found to be close to those obtained using G3MP2B3, G4MP2, and CBS-QB3 and differ by no more than 7 kJ mol^{-1} from each other. The deviation from the experimental results, differ by no more than 2 kJ mol^{-1} for G3MP2.

The conformer of neutral Cys is more stable than both Cys_a and Cys_b and has three strong intramolecular H-bonds (OH···N, NH···S, and SH···O═C), as shown in Figure 4. The deprotonation of Cys to produce a thiolate Cys^- ion is more likely than that of deprotonation to carboxylate Cys^-_a (Figure 4), as the enthalpy of thiolate Cys^- is significantly lower (9.2 kJ mol^{-1}) than Cys^-_a (see Table SA3 of Supporting Information). This matches previous experimental and computational work indicating that deprotonation of Cys yields a thiolate ion.[19,57] Previous calculations at G3B3 show the energetic difference between deprotonation of the carboxyl and thiol groups yield similar values (12.6 kJ mol^{-1}).[18,58] For this group (Cys) our $\Delta H°_{acid}$, at G3MP2B3 and G3B3[18] (1395 kJ mol^{-1}), are all in good agreement with experiment. Overall, the G3MP2 $\Delta H°_{acid}$ of the sulfur containing amino acids (Cys and Met) are computed as 1399 and 1430 kJ mol^{-1}, respectively, while the experimental values (1395 and 1407 kJ mol^{-1}, respectively) show good agreement differing by no more than 23 kJ mol^{-1}. Similarly, the computed $\Delta H°_{acid}$ (G3MP2) for the acidic/amidic amino acids (Asp, Asn, Gln, and Glu) are 1349, 1388, 1385, and 1347 kJ mol^{-1}. The G3MP2 $\Delta H°_{acid}$ are found to be close to those obtained using G3MP2B3 (1345, 1388, 1383, and 1345 kJ mol^{-1}, respectively) and differ by approximately 4 kJ mol^{-1}, with a difference of at most 4 kJ mol^{-1} with experiment.

The basic amino acids (Lys, His, and Arg) have $\Delta H°_{acid}$ computed at G3MP2 of 1417, 1399, and 1390 kJ mol^{-1}, in good agreement with experimental values differing by no more than 14 kJ mol^{-1} (His).

Finally, the calculated $\Delta H°_{acid}$ of proline computed at the G3MP2 is found to be close to the other Gaussian-n theory computed values (5 kJ mol^{-1} difference at most) and differs by 3 kJ mol^{-1} compared to the experimental value. Our G3MP2B3 value (1428 kJ mol^{-1}) is identical to that reported by Bouchoux.[20]

As in the case of the calculated proton affinities and gas-phase basicities, calculated $\Delta H°_{acid}$ can show some large absolute differences compared to experimental values (i.e., 23 kJ mol^{-1} for Met), but when these are considered as relative differences, the agreement with experimental results is within 1.6%. Overall, the MAD in our G3MP2 $\Delta H°_{acid}$ (4.0 kJ mol^{-1}) shows good agreement with experiment.[4,18,49,50,55] Previous G3MP2B3 results[20] of the corresponding $\Delta H°_{acid}$ of the six amino acids is identical with our work (with a MAD of 3.5 kJ mol^{-1}), as shown in Table 5.

The average difference between experimental and G3MP2 $\Delta H°_{acid}$ is −2.6 kJ mol^{-1} and examination of Figure 3 confirms that the calculated values are consistent with the experimental values. Additionally, the different Gaussian-n theory results (G3MP2, G3MP2B3, G4MP2, and CBS-QB3) agree with each other to within 10 kJ mol^{-1} (or ∼1% or less in terms of relative difference).

3.4. Gas-Phase Acidity ($\Delta G°_{acid}$) of α-Amino Acids. The computed gas-phase acidities for α-amino acids are listed in Table 6 along with the experimental results, while the difference between the G3MP2 values and the experimental values is shown in Figure 5.

The $\Delta G°_{acid}$ of the aliphatic amino acids (Gly, Ala, Val, Leu, and Ile) computed at G3MP2 are 1403, 1401, 1394, 1395, and 1393 kJ mol^{-1}, respectively. The G3MP2 values are close to the experimental results[4,16,17,49] and differ by no more than 5 kJ mol^{-1}. Our G3MP2B3 values are identical to those reported by Bouchoux.[20]

The gas-phase $\Delta G°_{acid}$ of the acidic/amidic amino acids (Asp, Asn, Gln, and Glu) computed at G3MP2 are 1319, 1359, 1361, and 1324 kJ mol^{-1}, respectively, which agrees very well with G4MP2, in that they differ by no more than 4 kJ mol^{-1} (see Table 6). The G3MP2 values are close to the experimental results and differ by no more than 7 kJ mol^{-1}.

The aromatic ring amino acids (Phe, Tyr, and Trp) gas-phase acidities determined at G3MP2 are 1384, 1383, and 1386 kJ mol^{-1} and in good agreement with experimental values (Figure 5)

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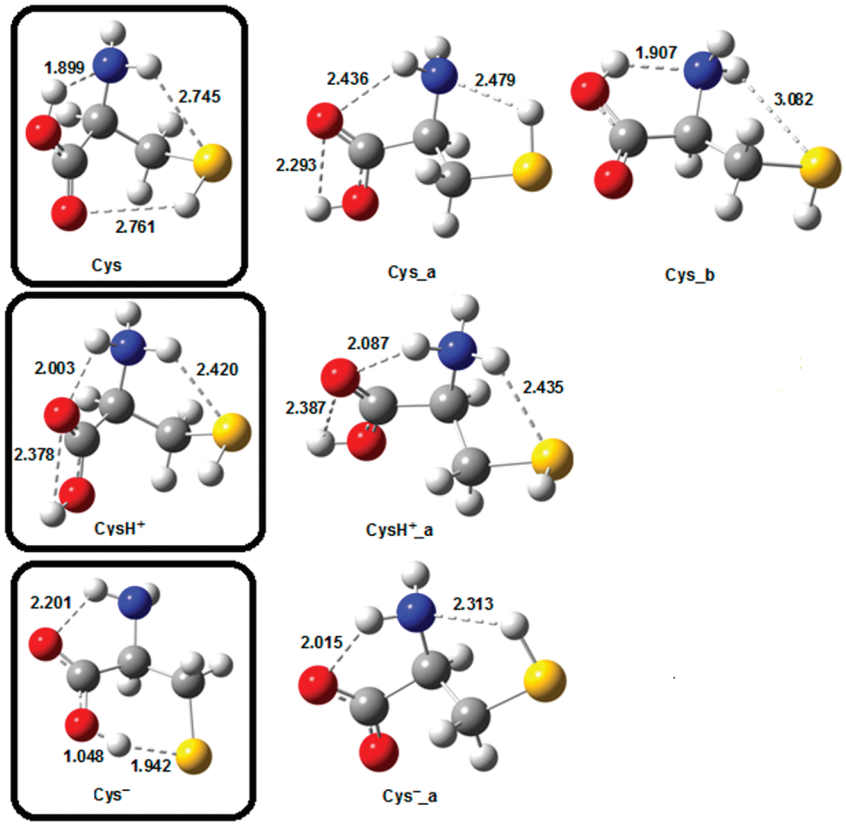

Figure 4. Optimized structures for the neutral, protonated, and deprotonated cysteine. The box indicates the most stable conformer. Bond distances are in angstroms.

Table 6. Gas-Phase Acidity ($\Delta G°_{acid}$)[a] of the α-Amino Acids in kJ mol^{-1} at 298.15 K

α-amino acid	B3LYP/6-31+G(d,p)	G3MP2[b]	G3MP2B3[b]	G4MP2	CBS-QB3	exptl[e]
Gly	1394	1403 (1)[c]	1405 (−1)[d]	1406	1400	1404 (1400)[f]
Ala	1392	1401 (−4)	1403 (−6)[d]	1404	1398	1397[g]
Val	1385	1394 (−3)	1394 (−3)[d]	1393	1388	1391
Leu	1387	1395 (−5)	1397 (−7)[d]	1398	1393	1390
Ile	1385	1393 (−4)	1394 (−5)[d]	1393	1389	1389
Ser	1353	1363 (0)	1363 (0)	1364	1356	1363
Thr	1349	1359 (2)	1359 (2)	1360	1355	1361
Cys	1355	1368 (−4)	1366 (−2)	1369	1362	1364
Met	1389	1399 (6)	1401 (4)	1402	1395	1405
Asp	1298	1319 (0)[c]	1318 (1)	1320	1312	1319[c] (1340)[h]
Asn	1349	1359 (0)	1358 (1)	1358	1353	1359
Gln	1359	1361 (−2)	1357 (2)	1357	1353	1359
Glu	1312	1324 (7)[c]	1324 (7)	1324	1316	1331[c,h]
Lys	1381	1386 (−3)	1385 (−2)	1386	1380	1383
His	1353	1367 (−11)	1367 (−11)	1367	1362	1356
Arg	1363	1362 (−3)	1368 (−9)	1367	1363	1359
Tyr	1377	1383 (−4)	1384 (−5)	1384	1382	1379
Phe	1377	1384 (−5)	1384 (−5)	1385	1380	1379
Trp	1381	1386 (−6)	1388 (−8)	1384	1384	1380
Pro	1389	1396 (−1)	1396 (−1)[d]	1396	1391	1395

[a]Calculated using eq 5. [b]The values in parentheses are the difference between the experimental and calculated values (see Figure 5). [c]The values are identical with those of ref 16b (except Glu, 1319 kJ mol^{-1}). [d]The values are identical with those of ref 20 (except Ile, 1395 kJ mol^{-1}). [e]Reference 49. [f]Reference 4b. [g]Reference 4b. [h]Reference 17b.

and differ by no more than than 6 kJ mol^{-1} (Trp). Similarly, the hydroxylic amino acids (Ser and Thr) calculated at G3MP2 are 1363 and 1359 kJ mol^{-1}, respectively, which agree quite well with experimental values (deviating by 0 and 2 kJ mol^{-1}, respectively).

The sulfur containing amino acids (Cys and Met) computed at G3MP2 are 1368 and 1399 kJ mol^{-1}, respectively, which are in excellent agreement with the G4MP2 level of theory (all within 3 kJ mol^{-1}) though the G3MP2Met value differs from the experimental value by 6 kJ mol^{-1}.

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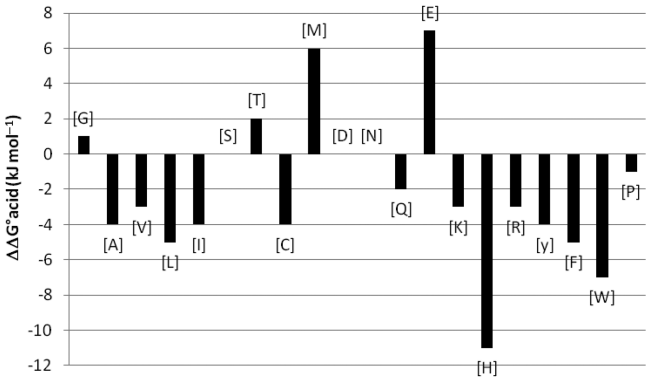

Figure 5. Plot of G3MP2 $\Delta\Delta G^{\circ}_{acid} = \Delta G^{\circ}_{acid\ (exp)} - \Delta G^{\circ}_{acid\ (calcd)}$ in kJ mol^{-1} for the 20 amino acids.

The basic amino acids (Arg, Lys, and His) gas-phase acidities calculated at G3MP2 are 1362, 1386, and 1367 kJ mol^{-1}, respectively, which are in reasonable agreement with experimental values (1359, 1383, and 1356 kJ mol^{-1}).

Finally, the calculated gas-phase ΔG°_{acid} of proline computed at G3MP2 is 1396 kJ mol^{-1} and is in good agreement with the experimental value (1395 kJ mol^{-1}). The average difference between experimental and G3MP2 gas-phase acidities is −2.0 kJ mol^{-1}, indicating it is likely that the differences are random. Overall, the MAD between the experimental and our G3MP2 gas-phase ΔG°_{acid} is 3.6 kJ mol^{-1}.

3.5. Exploring the Gas-Phase Enthalpy of Formation for Protonated α-Amino Acids. The gas-phase enthalpy of formation for protonated α-amino acids can be calculated using eq 6, where $\Delta H^{\circ}_{(PA)}$ is the negative of the proton affinity, and the enthalpies of formation of the neutral amino acids in the gas-phase have been reported from additive group contributions, though a value for Arg is not available.[39]

In this study, the enthalpies of formation for protonated amino acids are calculated from the enthalpy for reaction $RCH(NH_2)COOH + H^+ \rightarrow RCH(NH_3^+)COOH$. The calculated enthalpies of formation of the protonated amino acids ($\Delta H^{\circ}_{f(prot)}$) are given in Table 7. The plot of the difference between the experimental[4,51] and calculated values ($\Delta\Delta H_{f(prot)} = \Delta H^{\circ}_{f(exp)} - \Delta H^{\circ}_{f(calcd)}$) is shown in Figure 6.

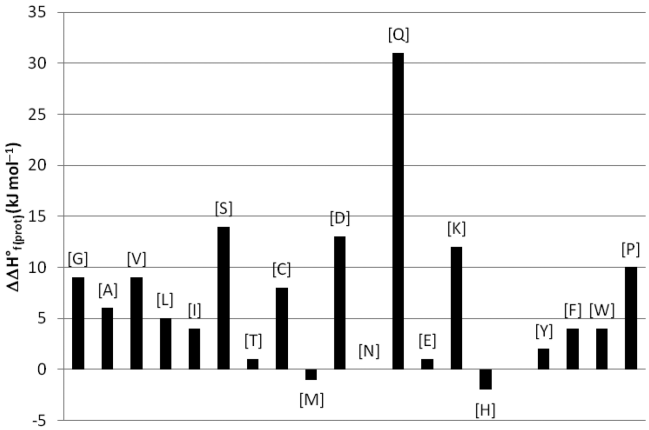

Figure 6. Plot of G3MP2 gas-phase enthalpy of formation ($\Delta\Delta H^{\circ}_{f\ (prot)} = \Delta H^{\circ}_{f(prot)\ (exp)} - \Delta H^{\circ}_{f(prot)\ (calcd)}$) in kJ mol^{-1} for the protonated 20 amino acids.

This shows that the calculated enthalpies of formation of the protonated amino acids differ from experimental values by no more than 31 kJ mol^{-1}. Overall, the MAD for our G3MP2, $\Delta H^{\circ}_{f(prot)}$ (7.2 kJ mol^{-1}), shows good agreement with experiment. For previous G3MP2B3 results[20] of the corresponding enthalpies of formation of these six protonated amino acids, the MAD is 15.8 kJ mol^{-1} compared to 6.7 kJ mol^{-1} for our results, as shown in Table 7.

Table 7. Gas-Phase Enthalpies of Formation for Protonated α-Amino Acids ($\Delta H^{\circ}_{f\ (prot)}$)[a] in kJ mol^{-1} at 298.15 K

			G3MP2B3[b]				exptl	
$\Delta H^{\circ}_f(AH^+)$	B3LYP/6-31+G(d,p)	G3MP2[b]	present work	Bouchoux[b,c]	G4MP2	CBS-QB3	present work[d]	previous work
$\Delta H^{\circ}_f(GlyH^+)$	259	256 (9)	259 (6)	256 (9)	258	260	265 (263)	244[e]
$\Delta H^{\circ}_f(AlaH^+)$	216	218 (6)	218 (6)	210 (14)	218	220	224 (220)	208[e]
$\Delta H^{\circ}_f(ValH^+)$	153	155 (9)	155 (9)	146 (18)	154	156	164 (159)	
$\Delta H^{\circ}_f(LeuH^+)$	132	135 (5)	134 (6)	124 (16)	133	135	140 (135)	
$\Delta H^{\circ}_f(IleH^+)$	128	130 (4)	130 (4)	123 (11)	129	132	134 (132)	
$\Delta H^{\circ}_f(SerH^+)$	56	55(14)	55 (14)		55	57	69 (48)	54[f]
$\Delta H^{\circ}_f(ThrH^+)$	13	14 (1)	14 (1)		14	17	15	16[f]
$\Delta H^{\circ}_f(CysH^+)$	255	255 (8)	255 (8)		254	257	263	263[f]
$\Delta H^{\circ}_f(MetH^+)$	182	187 (−1)	186 (0)		186	188	186	181[f]
$\Delta H^{\circ}_f(AspH^+)$	−174	−168 (13)	−168 (13)		−169	−167	−155 (−160)	−163[f]
$\Delta H^{\circ}_f(AsnH^+)$	2	10 (0)	8 (2)		8	10	10	22[f]
$\Delta H^{\circ}_f(GlnH^+)$	−52	−47 (31)	−50 (34)		−50	−48	−16	
$\Delta H^{\circ}_f(GluH^+)$	−224	−219 (1)	−219 (1)		−219	−219	−218	
$\Delta H^{\circ}_f(LysH^+)$	93	95 (12)	95 (12)		96	96	107 (109)	
$\Delta H^{\circ}_f(HisH^+)$	330	335 (−2)	335 (−2)		335	337	333 (335)	
$\Delta H^{\circ}_f(TyrH^+)$	124	128 (2)	128 (2)		132	129	130 (119)	
$\Delta H^{\circ}_f(PheH^+)$	306	310 (4)	310 (4)		309	311	314 (303)	
$\Delta H^{\circ}_f(TrpH^+)$	381	380 (4)	380 (4)		379	380	384	
$\Delta H^{\circ}_f(ProH^+)$	223	224 (10)	225 (9)	207 (27)	224	227	234 (226)	

[a]The gas-phase enthalpy of formation for protonated α-amino acids is calculated using eq 6. [b]The values in parentheses are the difference between the experimental and the calculated values (see Figure 6). [c]Reference 20. [d]Calculated using eq 6 as well as the two experimental values of −PA given in Table 2 and $\Delta H^{\circ}_{f(g)} = \Delta H^{\circ}_{f(cr)} + \Delta H^{\circ}_{(sub)}$. [e]Reference 4. [f]Reference 51.

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Table 8. Gas-Phase Enthalpies of Formation for Deprotonated α-Amino Acids ($\Delta H°_{f\,(deprot)}$)[a] in kJ mol^{-1} at 298.15 K

			G3MP2B3[b]				exptl	
$\Delta H_f°(A^-)$	B3LYP/6-31+G(d,p)	G3MP2[b]	present work	Bouchoux[b,c]	G4MP2	CBS-QB3	present work[d]	previous work
$\Delta H°_f(Gly^-)$	−502	−492 (0)	−491 (−1)	−494 (2)	−491	−496	−492 (−493)	−505[e]
$\Delta H°_f(Ala^-)$	−530	−520 (−2)	−520 (−2)	−519 (−3)	−519	−524	−522 (−527)	−536[e]
$\Delta H°_f(Val^-)$	−587	−578 (7)	−578 (7)	−588 (17)	−578	−583	−571 (−582)	
$\Delta H°_f(Leu^-)$	−606	−596 (−8)	−596 (−8)	−609 (5)	−596	−601	−604	
$\Delta H°_f(Ile^-)$	−609	−599 (−1)	−600 (0)	−607 (7)	−600	−605	−600 (−605)	
$\Delta H°_f(Ser^-)$	−723	−713 (0)	−713 (0)		−712	−719	−713 (−712)	
$\Delta H°_f(Thr^-)$	−761	−750 (−2)	−750 (−2)		−750	−755	−752 (−750)	
$\Delta H°_f(Cys^-)$	−530	−516 (−3)	−519 (0)		−517	−523	−519 (−521)	
$\Delta H°_f(Met^-)$	−526	−518 (−23)	−518 (−23)		−517	−523	−541 (−543)	
$\Delta H°_f(Asp^-)$	−998	−974 (−4)	−978 (0)		−977	−984	−978 (−983)	
$\Delta H°_f(Asn^-)$	−747	−739 (−3)	−739 (−3)		−738	−743	−742 (−739)	
$\Delta H°_f(Gln^-)$	−763	−762 (0)	−765 (3)		−765	−768	−762 (−760)	
$\Delta H°_f(Glu^-)$	−1010	−997 (1)	−999 (3)		−998	−1006	−996 (−994)	
$\Delta H°_f(Lys^-)$	−565	−563 (−1)	−563 (−1)		−563	−568	−564 (−568)	
$\Delta H°_f(His^-)$	−374	−359 (−14)	−361 (−12)		−361	−365	−373 (−383)	
$\Delta H°_f(Tyr^-)$	−609	−603 (−2)	−602 (−3)		−602	−603	−605 (−610)	
$\Delta H°_f(Phe^-)$	−429	−422 (2)	−422 (2)		−421	−426	−420 (−430)	
$\Delta H°_f(Trp^-)$	−339	−332 (2)	−331 (1)		−334	−335	−330 (−341)	
$\Delta H°_f(Pro^-)$	−488	−482 (3)	−482 (3)	−497 (18)	−482	−487	−479 (−480)	

[a]The gas-phase enthalpy of formation for deprotonated α-amino acids is calculated using eq 7. [b]The values in parentheses are the difference between the experimental and the calculated values (see Figure 7). [c]Reference 20. [d]Calculated using eq 7 as well as the two experimental values of the $\Delta H°_{acid}$ given in Table 5. [e]Reference 4.

3.6. Exploring the Gas-Phase Enthalpy of Formation of Deprotonated α-Amino Acids. In this study, the gas-phase enthalpy of formation for deprotonated α-amino acids can be calculated using eq 7 based on the reaction $RCH(NH_2)COOH \rightarrow RCH(NH_2)COO^- + H^+$. The calculated enthalpies of formation for the deprotonated amino acids ($\Delta H°_f$ (A^-)) are given in Table 8. The plot of the difference between the experimental and calculated values ($\Delta\Delta H_{f(deprot)} = \Delta H°_{f(exp)} - \Delta H°_{f(calcd)}$) is shown in Figure 7 and indicates that the calculated enthalpies of formation of the deprotonated amino acids differ from experimental values by no more than 23 kJ mol^{-1}. It should be emphasized that only two of the experimental[4] values were actually measured, while all other experimental values are based on calculations involving Sagadeev's additive group contribution values.[39]

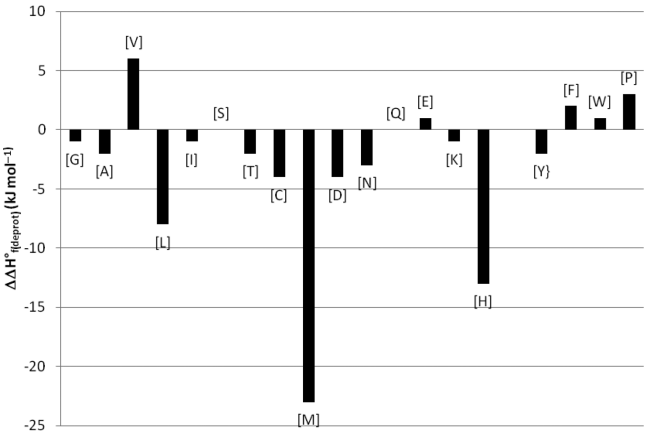
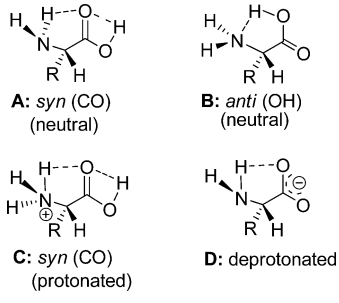


Figure 7. Plot of G3MP2 gas-phase enthalpy of formation ($\Delta\Delta H°_{f(deprot)} = \Delta H°_{f(deprot)\,(exp)} - \Delta H°_{f(deprot)\,(calcd)}$) in kJ mol^{-1} for the deprotonated 20 amino acids.

Within the Gaussian-n theories, the enthalpies of formation of the deprotonated amino acids differ at most by 10 kJ mol^{-1}. The average difference between experimental and G3MP2 enthalpies of formation for deprotonated amino acids is −2.5 kJ mol^{-1} and examination of Figure 7 confirms that it is likely that the calculated values are somewhat systematically larger than the experimental values. In fact, the source of this systematic difference can be traced back to $\Delta H°_{acid}$. Of the three terms on the right-hand side of eq 7, only the $\Delta H°_{acid}$ has shown a systematic difference between experimental and calculated results. Overall, the MAD in our G3MP2, $\Delta H°_{f(deprot)}$ (4.1 kJ mol^{-1}), shows good agreement with experiment. Finally, the MAD between the experimental and our G3MP2B3 shows that $\Delta H°_{f(deprot)}$ is 3.5 kJ mol^{-1} and 8.7 kJ mol^{-1} at G3MP2B3 for Bouchoux[20] of the six amino acids (Table 8).

In summary, the general conformers for the neutral (A and B), protonated (C), and deprotonated (D) α-amino acids are shown in Scheme 9. In this study, the computed thermochemical

Scheme 9. General Conformers for the Neutral (A and B), Protonated (C), and Deprotonated (D) α-Amino Acids



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properties of the twenty α-amino acids are in close agreement with available experimental values.

4. CONCLUSIONS

Computations were carried out in order to compare high level computational theories with the experimental values of the thermochemical properties of the α-amino acids. The thermochemical properties calculated using Gaussian-n theories are generally in good agreement with experimental values. The present study also demonstrates the importance of theoretical studies in locating the favored protonation site and the effects of conformational changes in the evaluation of the thermochemical properties of amino acids. This work provides a consistent database of thermochemical properties to be used in biochemical evaluation of protonation/deprotonation reactions and comparison to experimental PA and GB determination.

Overall, G3MP2 calculations are consistent with the more resource intensive G3MP2B3, G4MP2, and CBS-QB3 calculations and generally show small relative differences compared to experimental thermochemical properties. As such, in cases where experimental results cannot be found (e.g., enthalpies of formation of protonated and deprotonated amino acids), calculated thermochemical properties of the α-amino acids can be used with confidence.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full geometries and energies of all structures are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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