Ab Initio Investigation of the Hydration of Deprotonated Amino Acids

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The complexation of five deprotonated anionic amino acids (glycine, L-alanine, L-valine, L-Aspartic acid, and L-glutamine) with one water molecule, has been investigated using a MP2/63-11++G(d,p) approach fully accounting for the basis set superposition errors. For each amino acid, several energetic minima have been identified, and we provide spectroscopic information allowing to discriminate them. Our results strongly suggest that two complexes should coexist under the experimental conditions for [Ala – H][–], [Val – H][–], and [Asp – H][–]. Comparisons with the experimental enthalpies, entropies, and Gibbs free energies recently obtained by Wincel [J. Am. Soc. Mass Spectrom. **2008**, *19*, 1091–1097] show that our simulation reproduces the most significant structure/energy experimental trends, though the entropic changes induced by hydration are slightly overestimated. (J Am Soc Mass Spectrom 2009, *20*, 632–638) © 2009 American Society for Mass Spectrometry

The most accurate measurements of the thermodynamic parameters related to complexation phenomena typically rely on mass spectrometry (MS) experiments [1]. The recent investigations by Wincel of the stepwise hydration of positively and negatively charged amino acids (AA) [2–4], clearly demonstrate the efficiency of such techniques. Nevertheless, the analysis of the experimental output remains a tough task, as MS does not deliver straightforward structural informations. To circumvent this drawback, it is possible to couple MS experiments to infrared (IR) spectra measurements, as illustrated by references [5, 6]. However, the interpretation of the vibrational signatures is often laborious, as several structures might coexist. In many instances, theoretical calculations can help extracting a maximal amount of information from the measurements. In a recent series of works [7–9], we have investigated the microhydration of three protonated AA: GlyH⁺, ProH⁺, and AlaH⁺, with modern and reliable quantum mechanical tools that deliver accurate enthalpies as well as Gibbs free energies (virtually within the experimental error bars or close to it), and also systematically come up with both structural and spectroscopic data. For instance, we managed to resolve most previous theory/experiment disagreements [7], while pinpointing relevant and easy-to-track IR peaks. For tri-hydrated Pro-H⁺ [8], we have shown that the experiment probably relates to a 33%/32%/18%/17% mixture of four complexes, showing how risky can be too simplistic interpretations of experimental thermodynamic data.

Here, we investigate a series of complexes made up of a deprotonated (anionic) AA and a single water molecule. Such species have recently been identified with MS [4], allowing meaningful comparisons between theoretical and experimental complexation energies. The selected systems are [Gly – H][–], [Ala – H][–], [Val – H][–], [Asp – H][–], [Gln – H][–], as well as the acetic acid as a model benchmark.

Computational Protocol

All calculations have been achieved with the Gaussian03 package [10]. We operated the computational protocol developed [11] and successfully applied for protonated AA [7–9], and details regarding the adequacy of the involved theoretical methodologies can be found in these previous works.

Analytic geometry optimizations and vibrational frequency calculations have been performed at the second-order Møller-Plesset (MP2) level, without resorting to any intermediate semiempirical stage, nor “cheap” ab initio optimization step. We have selected a basis set featuring both polarized and diffuse orbitals on each atom, namely 6-311++G(d,p), which is well-suited for investigating systems with delocalized charges. Such triple- ζ basis sets have been advocated to be efficient for modeling hydrogen bond energies in protein-like systems [12]. Similarly, the MP2 interaction energies obtained for H-bonded thymine–adenine structures agree very well with coupled-cluster [CCSD(T)] values [13]. We have performed test calculations for some of the smallest complexes herein investigated, and a perfect match between CCSD(T) and MP2 interaction energies was found. We are therefore convinced that such an approach is perfectly suitable for our purpose. To

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secure accurate enthalpies, the SCF convergence criterion has been systematically tightened to 10^{-9} a.u., and the force minimizations were carried out with the tight Gaussian03 optimization threshold, i.e., a minimum in the potential energy surface is granted only for a rms force smaller than 1×10^{-5} a.u.

The basis set superposition errors (BSSE) were corrected by using the well-established counterpoise (CP) procedure [14]. Note that these BSSE corrections have been applied not only to the complexation energies, but also to all the geometry optimizations and vibrational frequency calculations, following the procedure designed in reference [15]. Consequently, the values presented here are completely BSSE-free, including the vibrational contributions to the entropy. This is highly valuable as such BSSE effects are substantial for the water-AA geometrical and vibrational parameters [11].

Except when noted, all the thermodynamic functions have been computed for $T = 298.15$ K and $P = 1012.95$ mbar, using the standard thermochemistry package in Gaussian03. The usual MP2 scaling factor of 0.95 has been used to determine the thermodynamic contributions [16, 17]. In our previous works [7–9], we demonstrated that the ΔS and ΔG shifts are negligible when going from room-temperature to the experimental (~ 300 – 400 K depending on the AA) conditions. From the results of reference [7, 11] our computed ΔH and ΔG are as close as 1 kcal/mol to the best theoretical models (i.e., including anharmonic effects, considering higher-order electron correlation effects, striving towards the basis set limit, . . .), whereas for the ΔS , this theoretical inaccuracy is about 2 cal/mol · K.

Results and Discussion

In the following, we initially present calculations on acetic acid (a small molecule with a carboxylic moiety) and the smallest AA (namely, glycine), as these tiny structures allow for extensive test calculations. We then proceed to L-alanine and L-valine. These are (much) larger but their lateral chain is unable to directly interact with the complexed water molecule. Eventually, L-aspartic acid and L-glutamine, featuring “reactive” and flexible lateral groups have been treated. Supplementary data, which can be found in the electronic version of this article, contain all XYZ Cartesian coordinates of the investigated complexes.

Acetic Acid and Glycine

For the deprotonated acetic acid (I), we have found three possible stable complexes (see Figure 1). The closely related deprotonated formic acid has been previously investigated using the MP2 method but with smaller basis sets and energy-only-BSSE corrections [CP-MP2/6-31+G(d)//MP2/6-31G(d)], and three similar complexes were unraveled [18]. Amongst the structures of Figure 1, I-a is the most stable. Indeed, I-b (I-c) presents relative G of 0.2 kcal/mol (1.7 kcal/mol) above it, under standard conditions. Consequently, I-a and I-b are predicted to coexist in a 60%/40% ratio at room temperature, and in a 56%/44% ratio under the experimental conditions (see Table 1), and I-c will be virtually absent. It is worth pointing out that the I-b (I-c) relative

Figure 1. Representation of the possible complexes between deprotonated acetic acid (I), deprotonated glycine (II), and one water molecule. The values between brackets are the relative Gibbs free energies. The hydrogen bond distances are given in Å, the energies in kcal/mol.

Table 1. Comparisons between the gas-phase hydration enthalpies (in kcal/mol) and entropies (cal/mol · K) of [AA – H][–] obtained by the MS experiment, and by the CP-MP2/6-311++G(d,p) theory

Anion	Structure	Theory			Experiment [4]		
		–ΔH	–ΔS	–ΔG	–ΔH	–ΔS	–ΔG
MeCO ₂ ^a	I-a (56%) ^b	16.2	28.2	7.8	16.4 ± 0.8	25.4 ± 2.0	9.0 ± 1.4
	I-b (44%) ^b	13.3	19.1	7.6			
	Total ^c	14.9	24.2	7.7			
[Gly – H] [–]	II-a (100%)	15.4	28.0	7.0	16.0 ± 0.3	26.6 ± 0.4	8.2 ± 0.4
	Total	15.4	28.0	7.0			
[Ala – H] [–]	III-a (58%) ^b	15.3	27.9	7.0	15.3 ± 0.4	25.6 ± 1.2	7.8 ± 0.8
	III-b (42%) ^b	15.1	27.9	6.7			
	Total	15.2	27.9	6.9			
[Val – H] [–]	IV-a (70%) ^b	14.8	27.8	6.5	14.3 ± 0.4	24.2 ± 1.0	7.2 ± 0.7
	IV-b (30%) ^b	14.1	27.8	5.8			
	Total	14.6	27.8	6.3			
[Asp – H] [–]	V-a (67%) ^b	11.1	27.0	3.1	12.3 ± 0.5	27.0 ± 1.9	4.4 ± 1.1
	V-b (33%) ^b	10.7	27.0	2.6			
	Total	11.0	27.0	2.9			
[Gln – H] [–]	VII-a (100%)	13.0	27.4	4.8	14.4 ± 0.4	30.8 ± 1.2	5.4 ± 0.8
	Total	13.0	27.4	4.8			

^aExperimental temperature is missing in reference [4]. Glycine's average T (400 K) has been used to compute the ratio of I-a and I-b.

^bThe relative concentrations of each isomer are computed using the average experimental temperature. See reference [4] for more details.

^cThe total values are calculated as weighted average of the results of each isomer.

stability is 3.0 kcal/mol (2.8 kcal/mol) on the H scale, and 3.2 kcal/mol (3.0 kcal/mol) on the U scale, with respect to the most stable I-a. The difference between the stabilities of I-a and I-b, which is sizable in terms of internal energy (3.0 kcal/mol), is almost negligible in terms of Gibbs free energies (0.2 kcal/mol, see above): this exemplifies the importance of the entropic contribution. This factor undergoes large modifications of its vibrational component (S_{vib}) when going from the bidentate to the monodentate structures, the former presenting fewer low-frequency modes centered on the methyl group. Using only total energies, which is U, similar differences have been unraveled for the formic acid anion, 2.9 kcal/mol (3.5 kcal/mol) [18], while B3LYP/6-31G(d) yields a 2.5 kcal/mol disparity between bidentate and monodentate complexes in dialanine [19]. In the present case, considering only total energy results gives an overstabilization of I-a, and incorrectly leads to undetectable I-b conformers. The hydrogen bond lengths are 2.08 Å for I-a and 1.81 Å for I-b, so that two longer hydrogen bonds could provide a larger total strength than a single shorter bond. The Merz-Singh-Kollman charges borne by the two oxygen atoms of the MeCO₂ (–0.87 |e|, each) are slightly modified by complexation: –0.82 |e| for I-a, –0.89/–0.81 |e| for the oxygen atom that bonded/not bonded to the water molecule for I-b. Recording the IR spectra should allow to easily discriminate between I-a and I-b, as the intense OH stretching appears at higher energies for the former (3751 versus 3457 cm^{–1} in the unscaled harmonic model). We emphasize that the hydrogen bonds stretching frequencies are very sensitive to anharmonic factors (see reference [11]), so that the relative, rather than the absolute vibrational frequencies are meaningful. The comparison between ex-

perimental and theoretical hydration energies of MeCO₂ is given in Table 1, and Wincel's experimental values for MeCO₂ are in the line of previous experiments on the same system [20, 21]. Our thermodynamic parameters compare with experiments, as ΔS and ΔG are within the reported error bars, though ΔH is slightly too small. The ΔS are very different for I-a and I-b, and only the average fits the measurements, hinting (but not proving) that our calculations achieved a correct balance between the two structures.

Before studying the hydration process of [Gly – H][–], we operated a conformational search for this deprotonated structure to identify the potentially numerous favorable sites on the potential energy surface of this AA that shows a flexible main chain. In general, for AA, such an analysis is carried out by varying the dihedral angles, t1 (N-Cα-C-O) and t2 (H-N-Cα-C) [22, 23]. Fully relaxed MP2/6-311++G(d,p) scans using 5° steps have been performed for these two angles (Figure 2). As can be seen, the compound presents an almost coplanar N-C-COO[–] structure, with the minimum for t1 close to 17°. Whilst the complete rotation of the carboxylic moiety is impossible in the experimental conditions (temperature between 370 and 420 K), variations of ±20° around the minimum are expected. For the t2 angle, one obtains an even smoother potential in the 0 to 120° region, while a full rotation of the NH₂ group would require more than 10 kcal/mol. In other words, as long as the nitrogen lone pair points towards the CH₂ group and that an intramolecular hydrogen bond takes place between the amino and ketone groups, an iso-energetic regime is reached. Consequently, significant thermal movements are likely, especially on the amine side of the [Gly – H][–]. Note that these effects were

Figure 2. Conformational energy profile of $[\text{Gly} - \text{H}]^-$ as a function of the t_1 (left) and t_2 (right) dihedral angles. The graph is symmetric around 0 degree for t_1 . The horizontal line indicates the thermal energy in the experimental conditions.

accounted for in our computed entropy only through the harmonic approximation, which remains a rough approximation.

On the basis of the $[\text{Gly} - \text{H}]^-$ conformer corresponding to the joint t_1/t_2 minimum, a large number of hydrated structures have been considered. Eventually, we have found six possible $[\text{Gly} - \text{H}]^- - (\text{H}_2\text{O})$ buildings (II in Figure 1). The most stable structure is the bidentate complexation on the carboxylic side (II-a), followed by the mono-dentate complexes (II-b, II-c, and II-d) that lie between 1.2 and 1.4 kcal/mol higher on the Gibbs free-energy (G) scale. The II-e and II-f assemblies, which correspond to a bridging structure and to the complexation with the nitrogen lone pair, are even less probable with relative G of 1.8 and 3.7 kcal/mol, respectively, compared with II-a. On top of that, no structure with the oxygen atom of the water molecule bonded to one of the two hydrogen atoms of the amino group of the $[\text{AA} - \text{H}]^-$ could be obtained, despite numerous trials. This result strongly contrasts with the computation on zwitterionic [24] or protonated glycine [7]. Indeed, in the former case, the most stable complex (in gas phase) is alike II-e, the bidentate structure being ~ 4 kcal/mol higher in energy, whereas in the latter case, bonding to the ammonium group is favored by 8.4 kcal/mol over an interaction with the carboxylic moiety. For the neutral glycine, the first water molecule interacts with the COOH group through a joint bond between, on the one hand, the oxygen atom of the water and the acidic hydrogen of glycine and, on the other hand, one hydrogen atom of the water with the “free” oxygen atom of glycine [24]. In short, by modifying the charge distribution on the AA, one obtains totally different results, and it is not possible to extrapolate the behavior of the anionic species from the properties of the cationic, zwitterionic, or neutral compounds. By coupling IR measurements to the MS experiments, it

would be in principle easy to discriminate II-a from the other structures. Indeed, its vibrational spectrum shows two peaks located at 3756 cm^{-1} and 3780 cm^{-1} in the usually measured region [5], whereas the other structures only have one significant absorption at lower frequency: 3490 cm^{-1} for II-b, 3445 cm^{-1} for II-c, 3490 cm^{-1} for II-d, 3431 cm^{-1} for II-e, and 3403 cm^{-1} for II-f. These harmonic frequencies only provide qualitative trends, similarly to acetic acid. The hydrogen bond lengths are much longer in II-a (2.11 and 2.08 Å) than in the five other structures, for which it lies between 1.75 Å and 1.89 Å. These values are also totally comparable to those obtained for the corresponding acetic acid structures. The same conclusion holds for the partial atomic charges borne by the two oxygen atoms in $[\text{Gly} - \text{H}]^-$: -0.81 and -0.86 in II-a. Our CP-MP2 hydration energies are compared with experiment in Table 1, where only one complex should pertain in the experimental conditions, that is the very one deduced from experimental data by Wincel [4]. Given the estimated theoretical inaccuracies, the computed ΔH , ΔS , and ΔG agree with experiments, though we slightly overestimate ΔS (and thus underestimate ΔG), as already noted for the cationic case [7]. Note that incorrectly using II-b as the reference complex would have led to much larger errors, with, for instance, an unacceptable ΔG of 5.8 kcal/mol. This brings additional compelling evidence that our procedure unravels the correct structures and accurately yields the hydration energies, even for anions. For $\text{Gly} - \text{H}^+$, the experimental ΔH is 15.4 ± 0.7 kcal/mol [3], i.e., 0.6 kcal/mol above the $[\text{Gly} - \text{H}]^-$ value, a difference that we nicely estimate with CP-MP2: 1.0 kcal/mol. Subsequently, we can state that our theoretical approach correctly and consistently models the hydration process of deprotonated glycine.

Alanine and Valine

L-Alanine and L-Valine can be considered as simple “extensions” of the glycine case as, on the one hand, only the apolar alkyl side groups differ, and, on the other hand, the measured thermodynamical parameters for $[\text{Ala} - \text{H}]^- - \text{H}_2\text{O}$, $[\text{Val} - \text{H}]^- - \text{H}_2\text{O}$ and $[\text{Gly} - \text{H}]^- - \text{H}_2\text{O}$ are similar enough to suggest that no significant changes in the complexation process should occur. Therefore, only the two dominant hydrated $[\text{Ala} - \text{H}]^-$ and $[\text{Val} - \text{H}]^-$ are depicted in Figure 3, i.e., though identified, we did not use the mono-dentate complexes. For the deprotonated alanine, two bi-dentate structures (III-a and III-b) differing only by the relative orientation of the amino group, co-exist under standard conditions, the monodentate complexes being too unstable to be experimentally detected. Indeed, the most stable mono-dentate $[\text{Ala} - \text{H}]^-$, that is similar to the II-c of $[\text{Gly} - \text{H}]^-$, is 0.9 kcal/mol above III-a in G terms. Consequently, for $[\text{Val} - \text{H}]^- - \text{H}_2\text{O}$, we only searched after bi-dentate complexes. It turns out that two of them, with an opposite orientation of the isopropyl side-chain, are predicted to be experimentally detectable (IV-a and IV-b on Figure 3). For both $[\text{Ala} - \text{H}]^-$ and $[\text{Val} - \text{H}]^-$, the hydrogen bond lengths are in the line with $[\text{Gly} - \text{H}]^-$ (~ 2.10 Å), and the IR spectra also show two strong absorption bands corresponding to stretching modes (between 3750 and 3790 cm^{-1}) associated to the water molecule. As the relative intensities and positions of these two peaks are almost independent of the orientation of the amino/isopropyl groups, it is very likely that for both AA, vibrational spectroscopy could not allow any easy discrimination between a and b structures.

In Table 1, the theoretical thermodynamical parameters related to the hydration are listed with their experimental counterparts. For both amino acids, our theoretical ΔH are on a par with the experimental data, and, similarly to $[\text{Gly} - \text{H}]^-$, CP-MP2 predicts ΔS to be

Figure 3. The two most stable $[\text{Ala} - \text{H}]^- - \text{H}_2\text{O}$ (III) and $[\text{Val} - \text{H}]^- - \text{H}_2\text{O}$ (IV) complexes. The values between brackets are the relative Gibbs free energies. The hydrogen bond distances are given in Å, the energies in kcal/mol.

too large by $\sim 10\%$, and subsequently slightly too small ΔG . The evolutions of the energies with the nature of the considered AA are, in practice, as important as the absolute complexation energies. Choosing glycine as a reference, one experimentally observes a decrease of the binding energies for alanine and valine, what our approach nicely reproduces. In fact, we correctly predict the ordering of the ΔH , ΔG , and ΔS for all these three amino acids, though the decrease of the ΔS when increasing the size of the lateral chain is significantly underestimated.

Aspartic Acid and Glutamine

L-Aspartic acid has two carboxylic groups with similar acidity (within two pKa units), and, at the B3LYP/cc-pVDZ level [25]; three minima have consequently been identified for unhydrated $[\text{Asp} - \text{H}]^-$: one with a deprotonated side-chain, one with the COO^- unit on the main chain, and one with a cyclic pattern with the two carboxylic group sharing the hydrogen atom. In this work, the latter conformer is clearly the most stable, as also advocated by other recent DFT calculations [26]. These results are consistent with our MP2/6-311++G(d,p) calculations, that yield a shared-proton conformer more stable by 4.8 (10.4) kcal/mol than its main (side) counterpart. We investigated the hydrated complexes on the basis of these three conformers. In Figure 4, we report some of the reached minima (all structures have not been displayed, but just some representative examples). The four most stable hydrated $[\text{Asp} - \text{H}]^-$ belong to the cyclic hydrogen family: V-a (relative G = 0.0 kcal/mol), V-b (G = +0.4 kcal/mol), V-c (G = +0.9 kcal/mol) and V-d (G = +1.2 kcal/mol). Therefore, we predict a two-third/one-third ratio of V-a/V-b in the experimental conditions, in good agreement with Wincel who foresaw a majority of V-a [4]. The most stable main chain (V-e) and side-chain (V-f) structures lie significantly higher in terms of Gibbs free-energy: +2.9 and +6.5 kcal/mol, respectively. Note that the difference in stability between main chain, side-chain and cyclic $[\text{Asp} - \text{H}]^-$ tends to decrease upon hydration. Would such effect pertains when more water molecules surround the aspartic acid, then solvated $[\text{Asp} - \text{H}]^-$ might not adopt a shared-hydrogen conformation; though such a statement has still to be checked. The most stable conformer structure presents a strong 2037 cm^{-1} absorption that corresponds to the exchange of the hydrogen between the oxygen atoms of the two carboxylic groups. Experimentally tracking this strong IR signature upon hydration should certainly help in discriminating V-a (2472 cm^{-1} : +435 cm^{-1}) from V-b (2178 cm^{-1} : +141 cm^{-1}). The intermolecular hydrogen bond lengths with the water molecule are 2.15 ± 0.06 Å for both V-a and V-b, that is slightly larger than the values in the corresponding bi-dentate glycine I-a, and indicates a weaker interaction between water and the amino acids, as the COO^- groups are already stabilized by “half a proton.” Indeed, in Table 1, we

Figure 4. Representative structures for [Asp - H]⁻ (V) and [Gln - H]⁻ (VI) complexes with a single water molecule. The values between brackets are the relative Gibbs free energies. The hydrogen bond distances are given in Å, the energies in kcal/mol.

notice that, consistently with experiment, the computed ΔH and ΔG are significantly smaller for [Asp - H]⁻ than for all [Gly - H]⁻, [Ala - H]⁻ and [Val - H]⁻. If our ΔH and ΔG are slightly too low (as awaited), the entropic value is, this time, correctly estimated.

For unhydrated L-glutamine, we discerned two deprotonated species, both with an extra stabilizing interaction between the amino group in the side-chain and the COO⁻ on the main chain, but contrasting in the orientation of the NH₂ on the main chain. Both conformers present an intramolecular H-bond distance of 1.71 Å, and a characteristic IR absorption around 3066 cm⁻¹ in the harmonic approximation. For the hydrated structure, we have performed an extensive search starting with these two favorable conformers. Six representative minima were located and are depicted in Figure 4. The bidentate structure VI-a is the most stable, followed by VI-b (relative G = +1.2 kcal/mol) for which only the orientation of the NH₂ group on the main chain has been modified. Both are vibrationally characterized by a blue-shifted intramolecular NH stretching mode at 3194 cm⁻¹. As for the other deprotonated amino acids, the mono-dentate structures, VI-c, VI-d, and VI-e are higher in energy, with relative G of +2.5, +4.2, and +4.5 kcal/mol, respectively. We have also detected a minimum for which the water molecule is in interaction

with the oxygen atoms of both the main and side chains (VI-f), but it presents a very large relative G of +11.8 kcal/mol. Note that VI-f does not display the very strong NH stretching vibration and could therefore be detected, if present under peculiar experimental conditions. Though contrasting with reference [4], which proposed a direct interaction between the water molecule and the oxygen atom of the side chain, our results correctly reproduce the experimental hydration ΔG and ΔH , as demonstrated by Table 1.

Conclusions

Using a MP2/6-311++G(d,p) approach including full counterpoise corrections, the structures and energetics of the complexes between [Gly - H]⁻, [Ala - H]⁻, [Val - H]⁻, [Asp - H]⁻, and [Gln - H]⁻ and water have been investigated. In any cases, structures featuring a double charged-reinforced hydrogen bonding between the water molecule and the carboxylic moiety is favored, though two conformers could coexist under standard conditions for [Ala - H]⁻, [Val - H]⁻ and [Asp - H]⁻. Such bidentate entities could be experimentally detected by the typical signatures in the IR spectra. Additionally for [Gln - H]⁻, we have demonstrated that the structure anticipated from experiment

(that is, with a water molecule in between the amide and carboxylic groups) is very unlikely. The thermodynamic parameters computed with our CP-MP2 approach agree very well with experiment, though the entropy variations related to hydration can be overestimated. The chemically induced variations closely follow the measured trends; for instance, the variations of hydration ΔG from $[\text{Gly} - \text{H}]^-$ to $[\text{Ala} - \text{H}]^-$, $[\text{Val} - \text{H}]^-$, $[\text{Gln} - \text{H}]^-$, and $[\text{Asp} - \text{H}]^-$ are experimentally (theoretically) -0.4 ± 1.0 (-0.1), -1.0 ± 1.1 (-0.7), -2.8 ± 1.2 (-2.2), -3.8 ± 1.5 (-4.1) kcal/mol, respectively. As proposed before [27], there is a (qualitative) relationship between the measured gas-phase acidities [26, 28] and the binding energies. Also, the fact that hydration energies are larger for protonated than deprotonated amino acids appears to be well reproduced by theory. We are currently performing microhydration investigations on other families of molecules.

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