ON THE DIFFERENTIAL HYDRATION OF VARIOUS FORMS OF GLYCINE IN DILUTED AQUEOUS SOLUTIONS: A MONTE CARLO STUDY

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Rigid-body Monte Carlo simulations were carried out in order to study the differential hydration of zwitterionic and neutral forms of glycine in water. To account for the solute polarization by the rather polar liquid environment, initial geometries were chosen as minima on the MP2/aug-cc-pVTZ potential energy surfaces of neutral and zwitterionic glycine continuously solvated by water, implementing the polarizable continuum model (PCM) within the integral equation formalism (IEFPCM). The dynamically changing hydrogen bonding network between the solute and solvent molecules was analyzed imposing distance, energy and angular distribution-based criteria. It was found that, on average, the zwitterionic form of glycine acts as an acceptor of 4.53 hydrogen bonds, while it plays the role of a proton donor in (on average) 2.73 hydrogen bonds with the solvent water molecules. In particular, we have found out that 2.73 solvent water molecules are involved in hydrogen bonding interaction with the ammonium group, acting as proton-acceptors. This is in excellent agreement with the recent experimental neutron diffraction studies, which have indicated that 3.0 water molecules reside in the vicinity of the NH_3^+ group of aqueous zwitterionic glycine. On the other hand, neutral form of aqueous glycine on average donates protons in 1.63 hydrogen bonds with the solvent water molecules, while at the same time it accepts 2.53 hydrogen bonds from the solvent molecules. The greater charge polarization in the zwitterionic form thus makes it much more exposed to hydrogen bonding interaction in polar medium such as water, which is certainly the main reason of the larger stability of this form of glycine in condensed media.

Key words: glycine; neutral and zwitterion; Monte Carlo simulations; hydration of biomolecules; hydrogen bonding in liquids; differential hydration; polarizable continuum model

ЗА ДИФЕРЕНЦИЈАЛНАТА ХИДРАТАЦИЈА КАЈ РАЗЛИЧНИТЕ ФОРМИ НА ГЛИЦИН ВО РАЗРЕДЕНИ ВОДНИ РАСТВОРИ: ИСПИТУВАЊА СО МЕТОДОТ МОНТЕ КАРЛО

Со цел да се изучи диференцијалната хидратација на цвитерјонската и неутралната форма на глицин во вода, изведени се симулации Монте Карло на системи составени од ригидни молекули. За опишување на поларизацијата на растворените видови, поради значително поларна околина во течна состојба, како почетни геометрии на неутралната и цвитерјонската форма на глицин се земени минимумите на хиперповршината на потенцијална енергија пресметана на MP2/aug-cc-pVTZ ниво на теорија на овие две молекули континуирано солватизирани во вода, имплементирајќи го моделот на поларизабилен континуум (PCM) во рамките на формализмот на интегрални равенки (IEFPCM). Мрежата на водородни врски помеѓу растворувачот и растворените супстанции, која постојано динамично се изменува, е анализирана при задавање определени ограничувања на меѓуатомските растојанија, енергијата, како и аголната распределба. Беше најдено дека цвитерјонските форми на глицинот во просек се јавуваат како акцептори со молекулите вода од растворувачот за 4,53

водородони врски, а како протондонори (во просек) за 2,73 водородни врски. Поконкретно, најдено е дека 2,73 молекули вода се вклучени како протон-акцептори во градење на водородни врски со амониум групата од оваа форма на глицин. Тоа е во одлична согласност со неодамнешните експериментални податоци од испитувањата со неутронска дифракција, кои покажуваат дека 3,0 молекули вода се наоѓаат во близина на групата NH_3^+ на хидратизираната цвитерјонска форма на глицинот. Од друга страна, неутралната форма на хидратизиран глицин во просек донира протони за образување на 1,63 водородни врски со молекулите од растворувачот. Во исто време таа гради 2,53 водородни врски со молекулите вода. Поголемата поларизација на цвитерјонската форма на глицинот го прави подостапен на водородно сврзување во поларен медиум како што е водата, што секако е главната причина за поголемата стабилност на оваа форма на глицинот во кондензирани медиуми.

1. INTRODUCTION

Hydration of biomolecules is a phenomenon of exceptional relevance to life itself [1]. Biomolecules, as organic parts of living organisms, are constantly interacting with water, the interaction strength varying from strongly attractive forces, up to almost complete repulsion. Despite the fact that not so long ago biochemists have considered water as being rather inert solvent, its rather active role in all biochemical properties has nowadays being constantly confirmed. One of the fascinating properties of water itself, which is responsible for the majority of its properties as a substance, is the ability of H_2O molecules to form networks of hydrogen bonds. However, water as a solvent, besides hydrogen bonds between H_2O molecules, forms network of hydrogen bonds with the solute molecules as well. This has been shown to be also of crucial importance for the behavior of biomolecules in their native surrounding, as well as for the influence of biomolecules on the structure of water as a solvent [1]. Analysis of hydrogen bonding networks in liquid water as well as in water solutions of biomolecules, is far from a "standardized" computational task. Thermal motions of molecules within the liquid cause constant formation and breaking of these noncovalent bonds, which have the right flexibility for the biochemical functioning of biomolecules, *i.e.* the hydrogen bonding networks themselves have a dynamical structure. It is not surprising that in certain cases the ex-

perimental data concerning this point cannot be unambiguously interpreted, even in the sense of determining the coordination numbers, *i.e.* the numbers of water molecules residing in various hydration shells. Therefore, analysis of these phenomena, in particular from theoretical side, is a very active area of research nowadays.

Among all molecular systems with biochemical relevance, the simplest amino-acid, glycine, has been a sort of a prototype for studying a vast variety of phenomena. Its solvation in water has been studied extensively, with numerous techniques, both theoretical and experimental [2–27], at various levels of sophistication. It is beyond the scope of the present manuscript to review all of the work related to this particular biomolecule, so the reader is referred to the original papers for much more details. However, despite very large number of studies, it seems that a thorough and systematic study of the hydrogen bonding networks formed between water as a solvent and various forms of glycine (neutral, zwitterionic etc.) is lacking. It is well known, on the other hand, that in gaseous phase the most stable form of glycine is the neutral molecule, while in condensed phases it is the zwitterionic form that corresponds to the absolute minimum on the potential energy hypersurface (PES) of this molecule. As the incorporation of glycine in aqueous solutions is certainly accompanied by the specific hydrogen-bonding interactions with the solvent molecules, the differences in

the stability between the neutral and zwitterionic forms in water would be expected to be closely related to the phenomena of formation of hydrogen bonding networks between the solute and solvent. The main aim of the present study is to contribute to further understanding of this point. We account explicitly for the thermal motions within the liquid by performing a statistical physics simulation of various forms of glycine in water solutions, and we analyze the (dynamical) hydrogen bonding networks between the solvent and solute molecules in an exact way, *i.e.* imposing a series of criteria according to which a given noncovalent interaction between the solute and solvent molecules should be classified as hydrogen bonding.

2. COMPUTATIONAL DETAILS

2.1. *Choice of initial geometries*

In the present study, we have carried out rigid-body Monte Carlo simulations of various conformers of neutral and zwitterionic glycine in diluted aqueous solutions. It is therefore of certain importance to choose properly the starting molecular/ionic geometries (which remain unaltered throughout the simulation). One straightforward choice would be to simply pick up gas-phase geometries and compute the charge distributions for such structures. However, if done so, then the overall polarizing effect that the water solvent has on the solute would be disregarded. Besides that, it is impossible to locate a stationary point that would correspond to zwitterionic glycine on any reliable PES of gas-phase glycine. This is, of course, in agreement with the fact that the neutral form is preferred energetically in gas phase, while zwitterion is the dominant form in solutions and solid state. We have therefore adopted the following "compromising" approach in the present study. We did certain explorations of the MP2/aug-cc-pVTZ PES of both neutral and zwitterionic glycine, solvated by water treated as a continual medium. For that purpose, we have

used the polarizable continuum model (PCM) within the integral equation formalism (IEF-PCM) [28]. Searches through the mentioned PES were done with the Schlegel's gradient optimization algorithm [29]. Upon location of a particular stationary point, analytical harmonic vibrational analysis has been performed for that particular structure. The absence of negative eigenvalues of the Hessian matrix was used as a confirmation that a true minimum on the PES is in question.

2.2. *Monte Carlo simulations*

To generate the structure of the studied liquid phases, first a series of Monte-Carlo (MC) simulations were performed, using the statistical mechanics code DICE [30]. All MC simulations were performed in the isothermal-isobaric (*NPT*) ensemble, implementing the Metropolis sampling algorithm, at $T = 298$ K, $P = 1$ atm, using the experimental density of liquid water of 0.9966 g cm^{-3} at these conditions. In each MC simulation, a single glycine molecule (*i.e.* a particular conformer thereof, in its neutral or zwitterionic form) was surrounded by 500 water molecules in a cubic box with side length of approximately 25 Å, imposing periodic boundary conditions. Long-range corrections (LRC) to the interaction energy were calculated for interacting atomic pairs between which the distance is larger than the cutoff radius defined as half of the unit cell length. The Lennard-Jones contribution to the interaction energy beyond this distance was estimated assuming uniform density distribution in the liquid (*i.e.* $g(r) \approx 1$), while the electrostatic contribution was estimated by the reaction field method involving the dipolar interactions. In all MC simulations carried out in the present study, intermolecular interactions were described by a sum of Lennard-Jones 12-6 site-site interaction energies plus Coulomb terms:

$$U_{ab} = \sum_{i}^{a} \sum_{j}^{b} 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \qquad (1)$$

where i and j are sites in interacting molecular systems a and b, r_{ij} is the interatomic distance between sites i and j, while e is the elementary charge. The following combination rules were used to generate two-site Lennard-Jones parameters ε_{ij} and σ_{ij} from the single-site ones:

$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j} \qquad (2)$$

$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j} \qquad (3)$$

For water we have used the SPC model potential parameters (Table 1) [31], while the charge distribution in the case of neutral and zwitterionic glycine was calculated by fitting the individual (atomic) charges, centered at atomic positions, to the molecular electrostatic potential computed from the QM wavefunction (MP2/aug-cc-pVTZ) at series of points selected by the CHELPG algorithm [32]. In the fitting procedure, the MP2 electronic density was used in all cases. As mentioned before, the geometries of various conformers of neutral and zwitterionic glycine that have been used throughout the MC simulations were those corresponding to the minima on the MP2/aug-cc-pVTZ potential energy surfaces (PESs) in the presence of water treated as a continual solvent modeled by the polarizable continuum model (PCM) within the integral equation formalism (*i.e.* IEFPCM).

T a b l e 1

The atomic (i.e. site) charges and Lennard-Jones parameters for the solvent water molecules used in the Monte Carlo simulations (see text for details)

Site	σ_{ii} / Å	ε_{ii} / (kcal mol^{-1})	q / e
H_w	0.0000	0.0000	0.41000
O_w	3.1650	0.1550	0.82000

The Lennard-Jones parameters for neutral and zwitterionic glycine were taken from the OPLS force field database (Tables 2 and 3) [33]. All simulations consisted of thermalization phase of at least $4.5 \cdot 10^7$ MC steps, which

was subsequently followed by averaging (simulation) phase of at least $4.5 \cdot 10^8$ MC steps.

T a b l e 2

The atomic (i.e. site) charges and Lennard-Jones parameters for the solute zwitterionic glycine molecules used in the Monte Carlo simulations (see text for details)

Site	σ_{ii} / Å	ε_{ii} / (kcal mol^{-1})	q / e
C1	3.5000	0.0660	0.003094
C2	3.7500	0.0660	0.801362
O3	2.9600	0.2100	0.761115
O4	2.9600	0.2100	0.799555
H5	0.0000	0.0000	0.070634
H6	0.0000	0.0000	0.070782
N7	3.2500	0.1700	0.330454
H8	0.0000	0.0000	0.284632
H9	0.0000	0.0000	0.330360
H10	0.0000	0.0000	0.330261

T a b l e 3

The atomic (i.e. site) charges and Lennard-Jones parameters for the solute neutral glycine molecules used in the Monte Carlo simulations (see text for details)

Site	σ_{ii} / Å	ε_{ii} / (kcal mol^{-1})	q / e
C1	3.5000	0.0660	0.375995
C2	3.7500	0.1050	0.685206
O3	2.9600	0.2100	0.609378
O4	3.0000	0.1700	0.700122
H5	0.0000	0.0000	0.022384
H6	0.0000	0.0000	0.022384
H7	0.0000	0.0000	0.485731
N8	3.2500	0.1700	1.031234
H9	0.0000	0.0000	0.374516
H10	0.0000	0.0000	0.374516

3. RESULTS AND DISCUSSION

3.1. Differential hydration and hydrogen bonding of neutral and zwitterionic glycine from Monte Carlo simulations

As mentioned before, initial geometries of neutral and zwitterionic glycine that have been subsequently used in rigid-body Monte Carlo simulations have been obtained by geometry optimizations of various conformers of the two basis species continuously solvated by water as a solvent (using the polarizable continuum model (PCM) within the integral equation formalism (IEFPCM)). This was done in order to account for the polarization effects imposed on the solute by the medium. Though various solute conformers have indeed been considered, in the manuscript we will focus only on the lowest-energy conformers of both neutral and zwitterionic glycine. Geometries corresponding to the minimum-energy conformers of neutral and zwitterionic glycine, *i.e.* to global minima on the MP2/aug-cc-pVTZ PES of the corresponding continuously solvated species by water are shown in Figure 1.
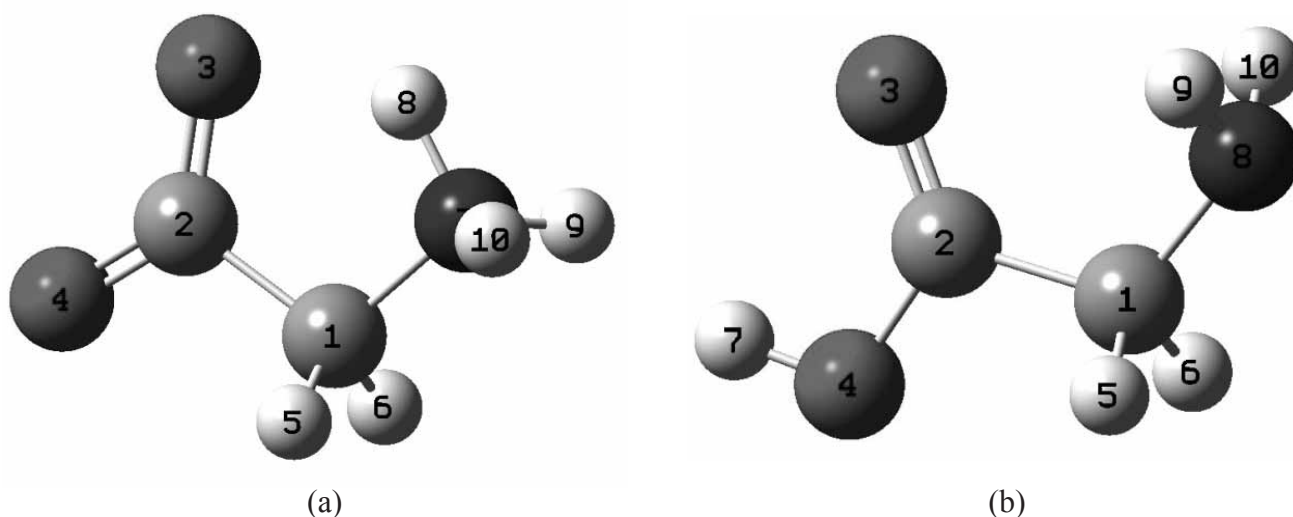
Note that the rigid-body approach to MC simulations implies neglecting the NH_2 group internal rotation barrier height which is roughly 3 kcal mol^{-1} in the case of neutral glycine, internal rotational barrier height of also approximately 3 kcal mol^{-1} in the case of the COO-group of zwitterionic glycine, barrier to internal rotation of COOH group in neutral glycine of approximately 2 kcal mol^{-1}, as well as somewhat higher NH_3 group internal rotation barrier height (> 4 kcal mol^{-1}) in the case of zwitterionic glycine.

In Figure 2, the radial distribution functions between the centers-of-mass of the solute and solvent computed from the equilibrated MC runs in the case of neutral and zwitterionic glycine are shown. As can be seen, in the case of zwitterionic glycine the first hydration shell spans up to about 5.05 Å, the total number of first-shell solvent molecules being 16.7. In the case of neutral glycine, on the other hand, the first shell extends up to 5.15 Å, accommodating about 17.0 first-shell waters. Though according to these two RDFs at first sight it may seem that the hydration behavior of the two forms of glycine is similar, the apparent situation is rather different, as we show below.
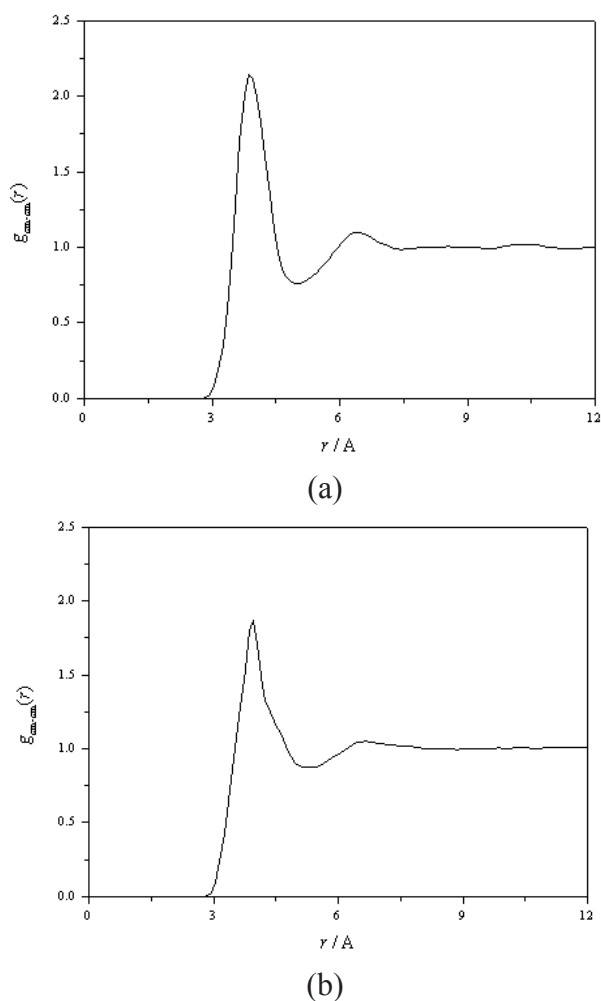

(a)

(b)

Fig. 1. Geometries corresponding to the minimum-energy conformers of neutral and zwitterionic glycine, *i.e.* to global minima on the MP2/aug-cc-pVTZ PES of the corresponding continuously solvated species, together with the atomic numbering schemes

(a)

(b)

Fig. 2. The radial distribution functions between the centers-of-mass of the solute and solvent species computed from the equilibrated MC runs in the case of neutral and zwitterionic glycine

As it has been well-recognized that it is the zwitterionic form of glycine which is much more stable in condensed phases (liquid and solid) in comparison to the neutral one, we aim to seek for an intermolecular solvent-solute interaction basis for this observation. We therefore further analyze in details the hydrogen bonding between glycine and solvent water molecules. Both the proton-donating and the proton-accepting abilities of the solvent and solute molecules are considered. However, being able to count (on average) the number of hydrogen bonding interactions in which each center within the solute molecule takes part is far from a trivial task. To avoid any arbitrariness, and also to correctly account for all fundamental criteria for this noncovalent interaction in solution, we adopt the following multistep procedure,

which we illustrate through the particular example of the O3 center within zwitterionic glycine. One parameter which certainly is of importance for establishing whether a hydrogen-bonding interaction (X-H···Y) between a given proton-donor (X-H) and proton-acceptor (Y) occurs is the XY distance. The radial distribution function between the O3 center within zwitterionic glycine and the O atom of the solvent water molecules (O_w) is shown in Figure 3. The first sharp peak seen in this RDF implies an existence of well-defined population of first-shell water molecules closely-positioned to the O3 center. However, ascribing a given solvent water molecule as being "hydrogen bonded" to the solute species only by analysis of the pair-wise atom-atom RDFs is merely equivalent to imposing only a single criterion for a definition of hydrogen bond – the distance criterion. This simply means that if the O3···O_w distance is smaller than a threshold value (*e.g.* the minimum between the first and second-shell RDF peaks) the solvent and solute species would be considered to be hydrogen bonded. However, this is obviously not always the case. Due to the thermal motions in the liquid, although certain solvent molecules may approach closely the solute species, their orientation may not be favorable from either energetic of orientational, *i.e.* geometric aspect (characteristic of the hydrogen bond interaction). It is therefore necessary to impose two additional criteria to define precisely the hydrogen bond within a liquid (thermally fluctuating medium).
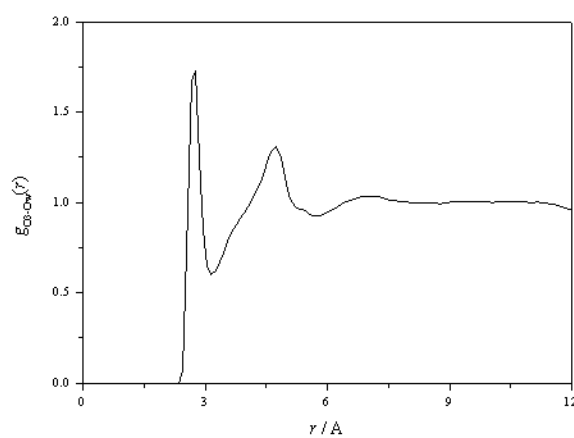

Fig. 3. The radial distribution function between the O3 center within zwitterionic glycine and the O atom of the solvent water molecules (O_w)

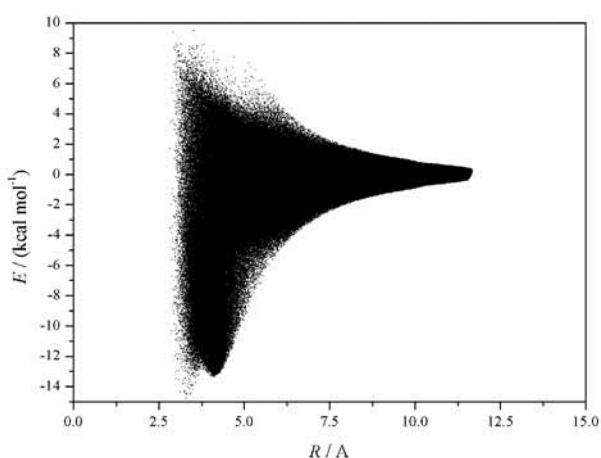The necessity for imposing the energetic criterion can be clearly seen from Figure 4, where the solute-solvent pair-wise interaction energies are plotted against the distances between the centers of masses of the solute and solvent molecules. Obviously, even for very small R_{cm-cm} values, the pairwise intermolecular interaction energies may be zero or positive. To select the energy cut-off criterion, we constructed the histogram of solute-solvent pair-wise interaction energies as computed from the MC potential (Figure 5).
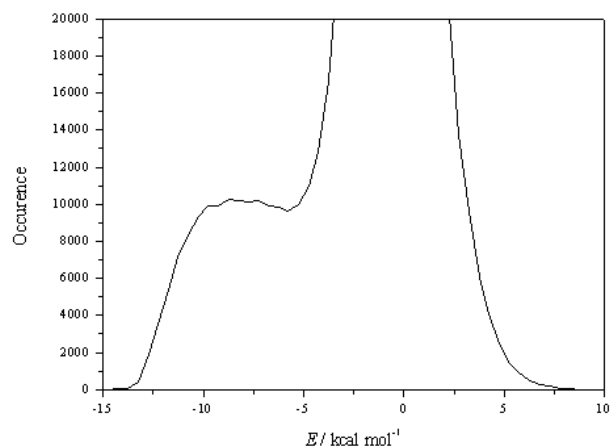
Fig. 5. The histogram of solute-solvent pair-wise interaction energies as computed from the MC potential for zwitterionic form of aqueous glycine

Fig. 4. The solute-solvent pair-wise interaction energies plotted against the distances between the centers of masses of the solute and solvent molecules

The singularity at $E = 0$ is due to the large number of weak ion-dipolar pair interactions at large solute-solvent distances, with the solvent molecules which are, at these distances, irregularly distributed due to thermal motions within the liquid. However, the additional, albeit much smaller peak at lower-energy values (with a maximum appearing somewhat below –10 kcal mol^{-1}), corresponds to a particular population of more strongly interacting solvent molecules with the solute. In order to cut off what is out of this particular population, we impose an energy criterion of –5.0 kcal mol^{-1} (the value that roughly corresponds to the minimum between the two bell-shaped curves in the histogram on Figure 5).

Of all first-shell water molecules which satisfy both the distance and energetic criterion for the h-bond definition, we also considered their actual orientation with respect to the solute species, which also has to be an appropriate one in the case of h-bonding arrangement. To define this orientation quantitatively, we consider the distribution of the $O3O_wH_w$ angle for all of the first-shell waters satisfying the previous two criteria. The corresponding first-shell selected angular distribution function is given in Figure 6.
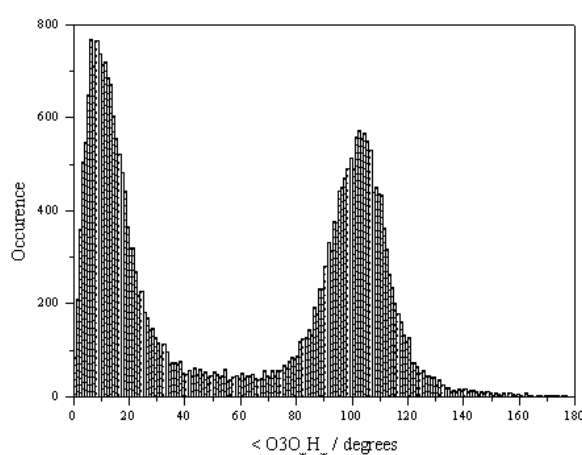
Fig. 6. The first-shell $O3O_wH_w$ angular distribution function (computed considering all molecules satisfying the distance and energetic criterion)

As obvious from Figure 6, the pronounced peak at very low angles corresponds to favorable h-bonding arrangements of the first shell water molecules around the solute species. The minimum between the two most pronounced peaks in the considered angular distribution function is therefore a natural angular criterion for the h-bond existence (60° in the presently studied case). Imposing these three criteria, leads to a total number of 1.67 hydrogen bonds in which, on average, the O3 center participates as a proton-acceptor. Repeating the same procedure for the O4 center, for which the $O4$-O_w RDF and the angular distribution are given in Figure 7 leads to an average number of 2.84 hydrogen bonds in which this center participates as a proton-acceptor in the liquid. Such difference between the O3 and O4 centers in the zwitterionic glycine is actually logical, as the O4 center is, so to say, much more exposed to interactions with the solvent molecules, while the O3 one is sterically more crowded (and, furthermore, it participates in an intramolecular noncovalent interaction with the N7H8 bond as a proton-acceptor). Similar analysis for the N center in zwitterionic glycine has shown that it practically does not act as a proton acceptor (the average number of h-bonds being 0.02), in line with the intuitive expectation and the purely "chemical" logic.

On the other hand, the NH bonds in zwitterionic glycine may also act as proton donors interacting with the oxygen atom of solvent waters. Performing the analogous analysis for the NH8 bond (see Figure 8), leads to 0.39 hydrogen bonds with solvent water molecules in which this bond participates on average with a role of proton donor. Such a small number is due to the already existing intramolecular weak h-bond with the O3 center within zwitterionic glycine. NH9 and NH10 bonds, on the other hand, participate in, on average, 1.17 hydrogen bonds as proton donors (Figure 8).

All these data are pictorially presented in Figure 9. Thus, the whole zwitterionic glycine molecule acts as an acceptor of (on average) 4.53 hydrogen bonds, while it plays the role of a proton donor in (on average) 2.73 hydrogen bonds with the solvent water molecules. Recent experimental neutron diffraction studies [2] have indicated that 3.0 water molecules reside in the vicinity of the NH_3^+ group of aqueous zwitterionic glycine. This is in excellent agreement with the data that we obtain (2.73 waters being involved in hydrogen bonding interaction with the ammonium group as proton-acceptors). Other *ab intio*-based studies have led to similar results [2,3].
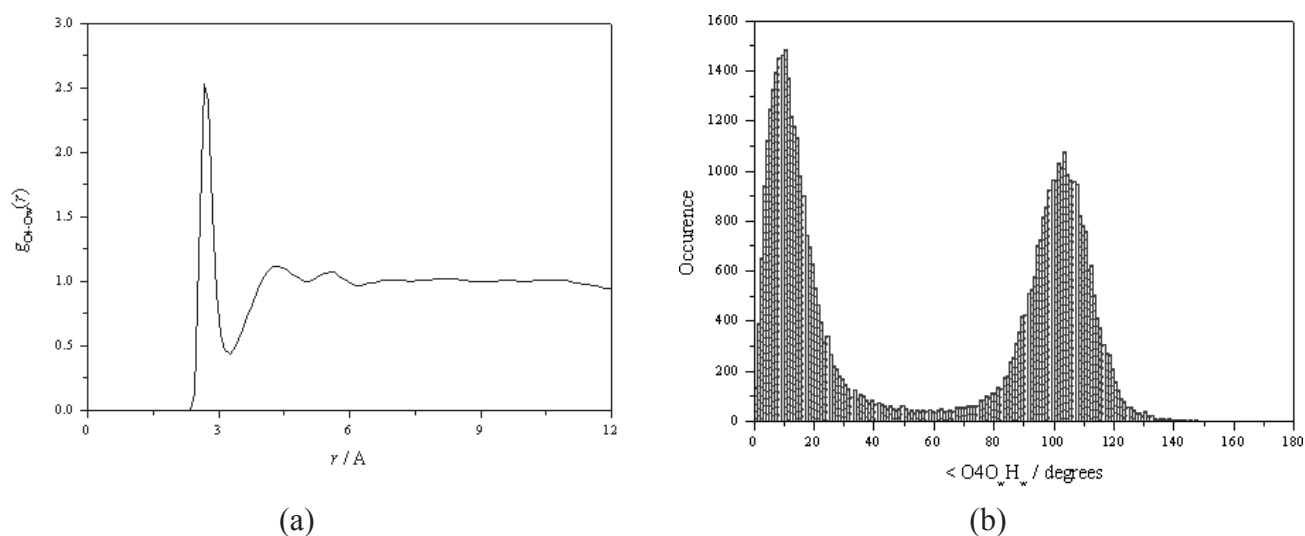

(a)

(b)

Fig. 7. **(a)** The radial distribution function between the O4 center within zwitterionic glycine and the O atom of the solvent water molecules (O_w); **(b)** the first-shell $O4O_wH_w$ angular distribution function (computed considering all molecules satisfying the distance and energetic criterion)
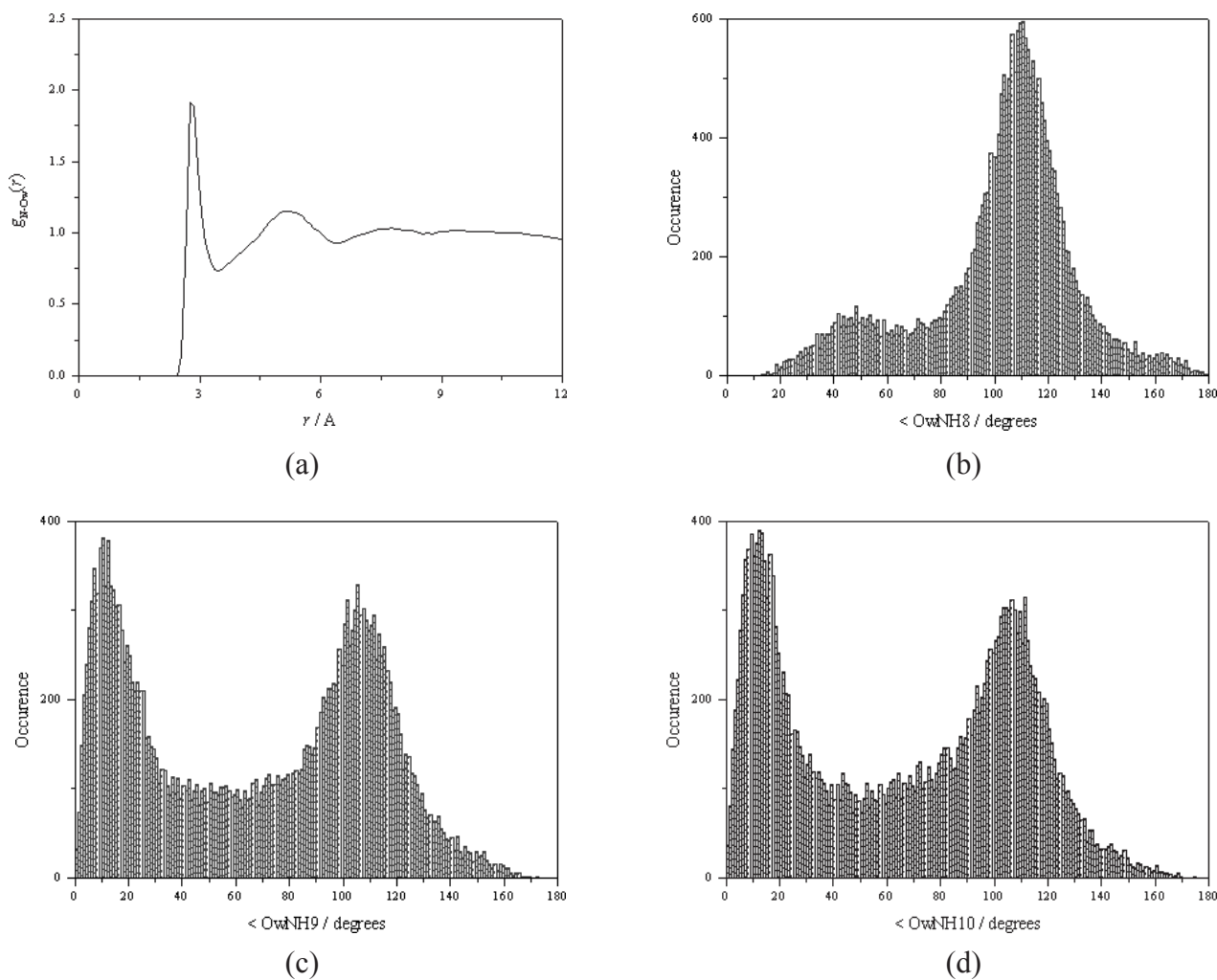
(a)

(b)

(c)

(d)

Fig. 8. **(a)** The radial distribution function between the N center within zwitterionic glycine and the O atom of the solvent water molecules (O_w); **(b)** the first-shell O_wNH8 angular distribution function (computed considering all molecules satisfying the distance and energetic criterion); **(c)** the first-shell O_wNH9 angular distribution function (computed considering all molecules satisfying the distance and energetic criterion); **(d)** the first-shell O_wNH10 angular distribution function (computed considering all molecules satisfying the distance and energetic criterion).
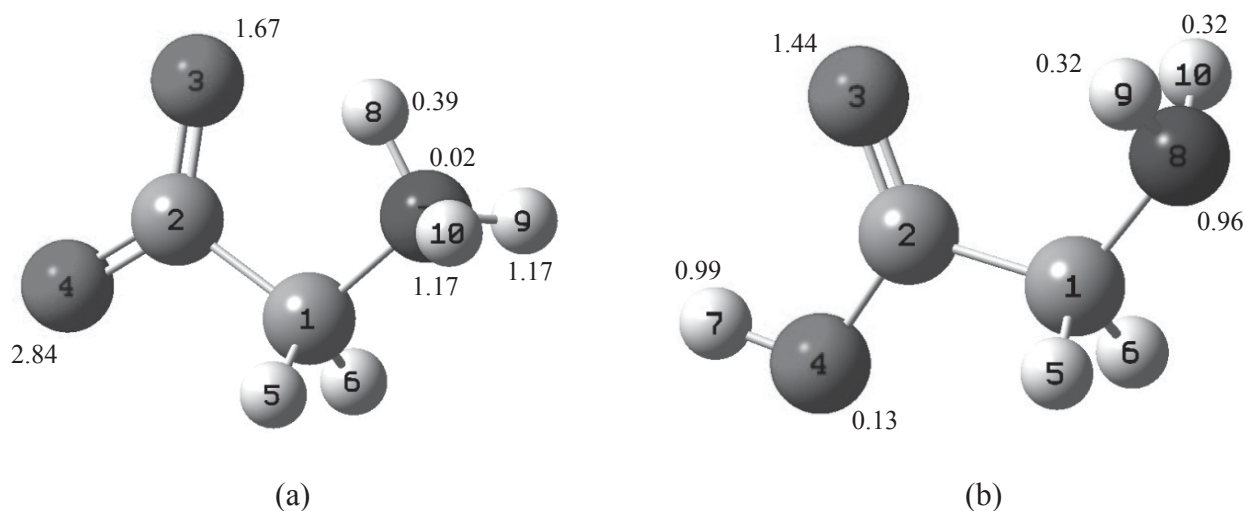

(a)

(b)

Fig. 9. The total number of h-bonds donated or accepted (on average) by the zwitterionic **(a)** and neutral **(b)** forms of glycine
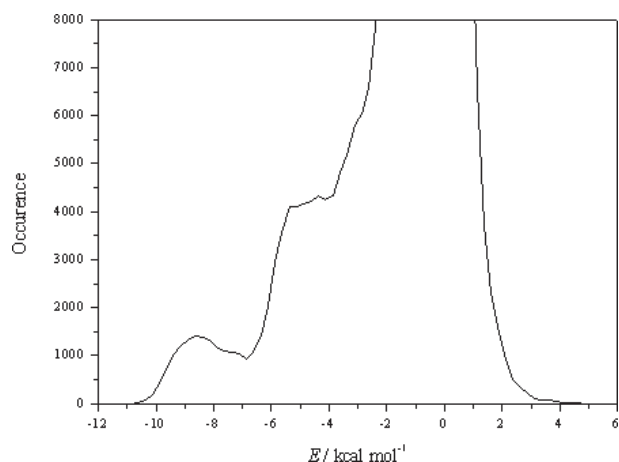
Fig. 10. The histogram of solute-solvent pair-wise interaction energies as computed from the MC potential for neutral form of aqueous glycine

We have carried out analogous anasis for each center in the neutral glycine as well. For this form of glycine, the histogram of solute-solvent pair-wise interaction energies as computed from the MC potential is presented in Figure 10. As can be seen, besides the singularity at $E = 0$, two populations of favorably interacting species appear, with maxima in the distributions around -9.0 and -5.0 kcal mol^{-1}. The two populations here are due to the greater diversity in the possibilities for hydrogen bonding in the case of neutral aqueous glycine. In order to account for each of the species involved in these two populations, we impose the energy cutoff criterion of 3.0 kcal mol^{-1} in our further analysis of the hydrogen bonding in the liquid.

Further analysis of the O3-O$_w$ RDF and the distribution function of the O3O$_w$H$_w$ angle (Figure 11) has led us to a conclusion that the O3 center in neutral glycine accepts 1.44 hydrogen bonds on average from the solvent water molecules (the imposed R and $<$ O3O$_w$H$_w$ cutoffs were 4.15 Å and 50º, respectively). Similar analysis for the O4 center (the detailed figures are available from the authors upon request) gives a total number of 0.13 hydrogen bonds accepted on average by this center. The proton-accepting abilities of these two centers in the liquid are, thus, lower compared to the corresponding sites in the case of the zwitter-

ionic form. The N8 center, on the other hand, as intuitively expected can now serve much more efficiently as proton acceptor, accepting 0.96 hydrogen bonds on average. As for the proton-donating abilities of the O4H7, N8H9 and N8H10 bonds (the detailed figures are available from the authors upon request), they participate on average in 0.99, 0.32 and 0.32 hydrogen bonds with the solvent molecules.
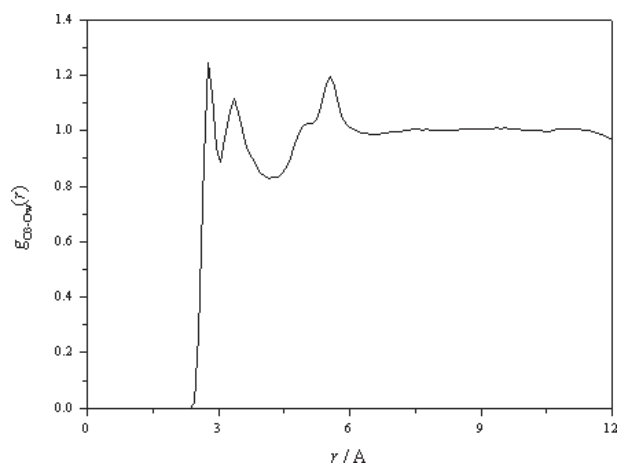
(a)
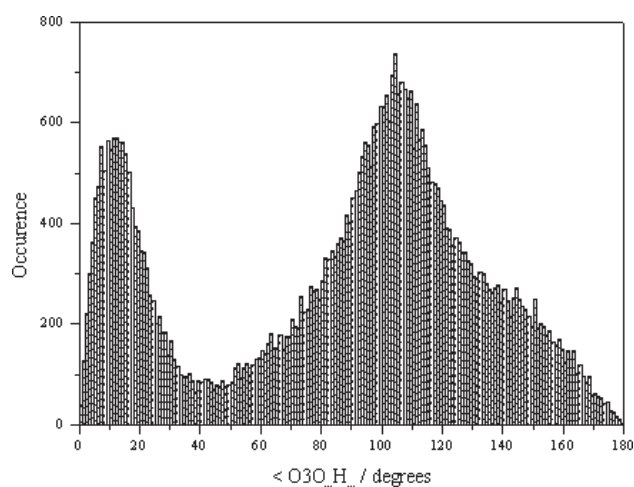
(b)

Fig. 11. **(a)** The radial distribution function between the O3 center within neutral glycine and the O atom of the solvent water molecules (O$_w$); **(b)** The first-shell O3O$_w$H$_w$ angular distribution function (computed considering all molecules satisfying the distance and energetic criterion)

All in all, the neutral form of aqueous glycine on average donates protons in 1.63 hydrogen bonds with the solvent water molecules (compared to 2.73 in the case of zwitterionic

form), while at the same time it accepts 2.53 hydrogen bonds from the solvent molecules (compared to 4.53 in the case of zwitterion). The greater charge polarization in the zwitterionic form thus makes it much more exposed to hydrogen bonding interaction in polar medium such as water, which is certainly the main reason of the larger stability of this form of glycine in condensed media.

4. CONCLUSIONS

We have carried out Monte-Carlo statistical physics simulations to study the hydration behavior of neutral and zwitterionic forms of glycine in diluted aqueous solutions. Though being based on rigid molecular geometries, the current simulations have incorporated explicitly the solvent-induced solute polarization, as the geometries used throughout the simulations corresponded to the minima on the MP2/aug-cc-pVTZ potential energy surfaces of neutral and zwitterionic glycine continuously solvated by water, computed implementing the polarizable continuum model (PCM) within the integral equation formalism (IEF-PCM). The solute-solvent hydrogen bonding interactions were thoroughly analyzed, on the basis of a set of criteria (distance, energy and angular distribution-based). We have found out that, on average, the zwitterionic form of glycine acts as an acceptor of 4.53 hydrogen bonds (the corresponding number being 2.53 in the case of neutral glycine), while it plays the role of a proton donor in (on average) 2.73 hydrogen bonds with the solvent water molecules (1.63 in the case of neutral aqueous form). The greater charge polarization in the zwitterionic form thus makes it much more exposed to hydrogen bonding interaction in polar medium such as water, which is certainly the main reason of the larger stability of this form of glycine in condensed media. We have also found out that 2.73 solvent water molecules are involved in hydrogen bonding interaction with the ammonium group of aqueous zwitterionic glycine, acting as proton-acceptors –

this number is in excellent agreement with the results from recent experimental neutron diffraction studies, which have indicated that 3.0 water molecules reside in the vicinity of the NH_3^+ group of the aqueous zwitterion.

REFERENCES

[1] T. Wyttenbach, M. T. Bowers, Hydration of biomolecules, *Chem. Phys. Lett.*, **480**, 1–16 (2009).

[2] M. G. Campo, Molecular dynamics simulation of glycine zwitterions in aqueous solution, *J. Chem. Phys.*, **125**, 114511 (2006).

[3] J. Sun, D. Bousquet, H. Forbert, D. Marx, Glycine in aqueous solution: solvation shells, interfacial water, and vibrational spectroscopy from *ab initio* molecular dynamics, *J. Chem. Phys.*, **133**, 114508 (2010).

[4] A. White, S. Jiang, Local and bulk hydration of zwitterionic glycine and its analogues through molecular simulations, *J. Phys. Chem.*, *B* **115**, 660–667 (2011).

[5] K. Leung, S. B. Rempe, Ab initio molecular dynamics study of glycine intramolecular proton transfer in water, *J. Chem. Phys.*, **122**, 184506 (2005).

[6] N. Vyas, A. K. Ojha, A. Materny, Simulation of the Raman spectra of zwitterionic glycine + nH_2O (n = 1, 2, …, 5) by means of DFT calculations and comparison to the experimentally observed Raman spectra of glycine in aqueous medium, *Vibrat. Spectrosc.*, **55**, 69–76 (2011).

[7] T. Yoshikawa, H. Motegi, A. Kakizaki, T. Takayanagi, M. Shiga, M. Tachikawa, Path-integral molecular dynamics simulations of glycine·$(H_2O)_n$ (n = 1–7) clusters on semi-empirical PM6 potential energy surfaces, *Chem. Phys.*, **365**, 60–68 (2009).

[8] K. T. Lee, K. Y. Han, I. Oh, S. K. Kim, Barierless pathways in the neutral-zwitterion transition of amino-acid: Glycine-$(H_2O)_9$, *Chem. Phys. Lett.*, **495**, 14–16 (2010).

[9] F. Lelj, C. Adamo, V. Barone, Role of Hartree-Fock exchange in density functional theory. Some aspects of the conformational potential energy surface of glycine in the gas phase, *Chem. Phys. Lett.*, **230**, 189–195 (1994).

[10] L. F. Pacios, P. C. Gómez, Atomic charges in conformers of gaseous glycine, *J. Mol. Struct.* (*THEOCHEM*), **544**, 237–251 (2001).

[11] P. Selvarengan, P. Kolandaivel, Potential energy surface study of glycine, alanine and their zwitter-ionic forms, *J. Mol. Struct.* (*THEOCHEM*), **671**, 77–86 (2004).

[12] M. Kieninger, S. Suhai, O. N. Ventura, Glycine conformations: gradient-corrected DFT-studies, *J. Mol. Struct. (THEOCHEM)*, **433**, 193–201 (1998).

[13] R. A. Cormanich, L. C. Ducati, R. Rittner, Are hydrogen bonds responsible for glycine conformational preferences?, *Chem. Phys.*, **387**, 85–91 (2011).

[14] A. G. Császár, Conformers of gaseous glycine, *J. Am. Chem. Soc.*, **114**, 9568–9575 (1992).

[15] P. Palla, C. Petrongolo, J. Tomasi, Internal rotation potential energy for the glycine molecule in its zwitterionic and neutral form. A comparison among several methods, *J. Phys. Chem.*, **84**, 435–442 (1980).

[16] R. Bonaccorsi, P. Palla, J. Tomasi, Conformational energy of glycine in aqueous solutions and relative stability of the zwitterionic and neutral forms. An ab initio study, *J. Am. Chem. Soc.*, **106**, 1945–1950 (1984).

[17] M. T. Parsons, Y. Koga, Hydration number of glycine in aqueous solutions: An experimental estimate, *J. Chem. Phys.*, **123**, 234504 (2005).

[18] T. Watanabe, K. Hashimoto, H. Takase, O. Kikuchi, Monte Carlo simulation on the conformation and interaction of the glycine zwitterions in aqueous solution, *J. Mol. Struct.* (*THEOCHEM*), **397**, 113–119 (1997).

[19] C. Alagona, C. Ghio, P. A. Kollman, Monte Carlo simulation studies of the salvation of ions. 2. Glycine zwitterion, *J. Mol. Struct.* (*THEOCHEM*), **166**, 385–392 (1988).

[20] C. Alagona, C. Ghio, Monte Carlo simulation of the salvation of ions. 3. The non intramolecularly h-bonded form of glycine zwitterion, *J. Mol. Liq.*, **47**, 139–160 (1990).

[21] Yu. I. Khurgin, V. A. Kudryashova, V. A. Zavizion, Study of intermolecular interactions in aqueous solutions by millimeter spectroscopy, *Russ. Chem. Bull.*, **46**, 1248–1250 (1997).

[22] M. Tschapek, C. Wasowski, The hydration of a zwitterion, glycine, as a function of pH, *Biochim. Biophys. Acta*, **582**, 548–550 (1979).

[23] C. Espinoza, J. Szczepanski, M. Vala, N. C. Polfer, Glycine and its hydrated complexes: A matrix isolation infrared study, *J. Phys. Chem. A*, **114**, 5919–5927 (2010).

[24] B. Yogeswari, R. Kanakaraju, A. Abiram, P. Kolandaivel, Molecular dynamics and quantum chemical studies on incremental solvation of glycine, *Comp. Theor. Chem.* **967**, 81–92 (2011).

[25] R. M. Balabin, The first step in glycine solvation: The glycine-water complex, *J. Phys. Chem. B*, **114**, 15075–15078 (2010).

[26] J. Chang, A. M. Lenhoff, S. I. Sandler, Solvation free energy of amino acids and side-chain analogues, *J. Phys. Chem. B*, **111**, 2098–2106 (2007).

[27] C. M. Liegener, A. K. Bakhshi, R. Chen, J. Ladik, Theoretical Auger spectra of the glycine ion in solution, *J. Chem. Phys.*, **86**, 6039–6045 (1987).

[28] J. Tomasi, B. Mennucci, R. Cammi, Quantum mechanical continuum solvation models, *Chem. Rev.*, **105**, 2999–3093 (2005).

[29] C. Peng, P. Y. Ayala, H. B. Schlegel, M. J. Frisch, Using redundant internal coordinates to optimize equilibrium geometries and transition states, *J. Comp. Chem.*, **17**, 49–56 (1996).

[30] K. Coutinho, S. Canuto, *DICE: A Monte Carlo program for molecular liquid simulation*, University of São Paulo, Brazil, 1997.

[31] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, J. Hermans, *Intermolecular Forces*, edited by B. Pullmam (Reidel, Dordrecht, 1981), pp.331.

[32] C. M. Breneman, K. B. Wiberg, Determining atom-centered monopoles from molecular electrostatic potentials - the need for high sampling density in formamide conformational-analysis, *J. Comp. Chem.*, **11**, 361–73 (1990).

[33] W. L. Jorgensen, D. S. Maxwell, J. Tirado-Rives, Development and testing of the OPLS all-atom force field on conformational energetic and properties of organic liquids, *J. Am. Chem. Soc.*, **118**, 11225–11236 (1996).