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A Model Study of the Intermolecular Interactions of Amino Acids in Aqueous Solution: The Glycine-Water System

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We have performed calculations of the glycine zwitterion surrounded by water molecules with the help of the mutually consistent field (MCF) method and perturbation theoretical expressions. Two different models for the hydration shell have been chosen, the glycine·$6H_2O$ and glycine·$12H_2O$ complexes, representing the most probable first and second solvation shell, respectively. To calculate the exchange and charge transfer energy contributions we have applied approximative expressions derived from perturbation theory for weakly overlapping subunits. For the sake of comparison we also calculated the interaction energy in the supermolecule approach for the smaller of the two solvation complexes. Furthermore, we have investigated the part of the potential energy surface which is determined by varying the lengths of the hydrogen bonds between glycine and water in the complex glycine·$12H_2O$ using the electrostatic approach. The exchange energy contribution to the interaction energy for different points on the surface was approximated with the help of an analytical expression fitted to three directly calculated points. For the charge transfer energy a polynomial expansion of second order was established on the basis of five values, computed with the aid of the perturbation theoretical expression. To get a more detailed insight in the relatively strong hydrogen bonds between the water molecules and the ionic hydrophilic parts of glycine *ab initio* model studies on $NH_4^+ \cdot 3H_2O$ and $HCOO^- \cdot 3H_2O$ systems are reported.

Key words: Mutually consistent field calculations – solvation energies – glycine-water-system.

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1. Introduction

In several recent publications [1–3] we have described a method which has been developed to calculate interaction energies between an arbitrary number of interacting molecules of medium to large size at intermolecular distances where overlap is small but not negligible. This approach, the mutually consistent field (MCF) method is based on the determination of the wave function for each component in the Coulomb field of all other molecules. Detailed investigations of different molecular complexes have shown [1–4] that the MCF-procedure contains significant advantages in comparison with a perturbation theoretical treatment. The interaction energies calculated with the help of the MCF-approach agree within about 10% with the results obtained in the framework of the supermolecule method and less computer time, especially in cases where the number and the size of molecules increase, is needed for the MCF-procedure.

In this study we have applied the MCF-method to the problem of hydration of amino acids, which have been represented by the simple model of the zwitterion of glycine. It seems reasonable to assume, especially in the case of ionic solutes that the first hydration shell and to a lesser extent the second one will have well-defined and highly ordered structures. The geometrical arrangement of the solvent molecules at larger distances will resemble very close to the structure of the bulk media. For this reason we were mainly interested in the investigation of the configuration and equilibrium positions of the neighboring water molecules which are assumed to interact strongly with the solute molecule. Our results for the structural parameters as well as the interaction energies of the hydrogen bond complexes can be compared with corresponding values of supermolecule calculations which are reported by Pullman et al. [5–10]. In their investigations the equilibrium positions of the water molecules on different favourable hydration sites were obtained separately for each solvent molecule, neglecting the mutual influence of the other ones. The solvation structure obtained in this way was then used without any change for different conformations of larger structurally similar molecules [11–13]. Since the pairwise interaction energies are much larger for hydrogen bonded systems involving an ionic component, this assumption seems to be not refined enough.

Two other partially empirical approaches are used to treat the solvation problem. In the continuum model which has been developed and applied to different solvents by Beveridge et al. [14] the total energy of a solvated molecule is given as the sum of the total energy of the solute in the free space approximation and the effective solvent-solute interaction energy. The second term is partitioned into electrostatic solute-solvent binding energy, the contribution due to dispersion forces and the energy which is necessary to form a cavity for the solute molecule in the solvent structure.

In the solvation shell model introduced by Hopfinger [15] it is assumed that in a hydration shell of certain radius around the different polar groups of the solute molecule a maximum of *n* solvent molecules can be arranged. The available volume of this hydration shell is described by van der Waals spheres of all the groups of the molecule and in this way depends on the conformation of the molecule. To calculate the total free energy for different conformations experimental values are used.

An efficient but expensive numerical treatment of the solvation problem has been developed and applied by Clementi et al. [16–19]. In this method the interaction energies of a large number of solute-solvent configurations created by a Monte-Carlo simulation are calculated with the help of interatomic pair functions given in analytical form and weighted at different temperatures by Boltzmann factors. This procedure yields solvation energies and the probability distribution of the solvent molecules around the solute as a function of temperature. Applications are reported for instance for glycine and serine zwitterion in water [16], for a tripeptide as a protein model in water [17], for the hydration of the constituent bases of DNA [18] and even for the interaction between one winding of DNA double helix with about five hundred water molecules [19].

2. Method

As a first step in the study of conformational problems and solvation effects of macromolecules, with special emphasis on biochemical systems like proteins, two complexes of the glycine zwitterion with water molecules (attached in such a way to represent the first and second hydration shell, respectively) were investigated by means of the MCF-method [1–3]. Glycine as the smallest of the amino acids, was chosen because it usually serves as a model both in the treatment of solvation effects in peptides [16, 17] and (in the form of polyglycine) in crystal orbital calculations of proteins [20–25].

For the geometry of the investigated glycine zwitterion with six and twelve water molecules, respectively, standard bond lengths and bond angles for the components were used. In the glycine·$6H_2O$ complex, illustrated in Fig. 1, one cluster of three water molecules (cluster *B* in Fig. 1) is attached to the ammonium group and each of the oxygen atoms of the water molecules falls in the straightline defined by one of the N—H bonds of glycine. For the distance of the N—H···O hydrogen bond the experimental value of 1.81 Å was taken. Another cluster of three water molecules (cluster *C* in Fig. 1) is bound to the carboxylate group of glycine. One of these water molecules lies in the plane of the carboxylate group with O···H distances of 2.63 Å. The two additional water molecules are attached to each of the oxygen atoms of the carboxylate group in such a way, that it lies under the plane of this group with an O···H distance of 1.79 Å. Our chosen configuration differs from the energy minimized geometry given by Pullman [6] in the way that we have rotated the two water molecules bound to the oxygen atoms around the C—O bonds by 90 degrees (as spacefilling molecular models show the original configuration leads to strong steric hindrance when we take a second hydration shell, which is described below, into account). As Clementi pointed out [26], in the case of a glycine zwitterion a small hydrophobic group is between two strongly hydrophilic charged groups. Therefore the effect of the methylene group which would push away the water molecules from this

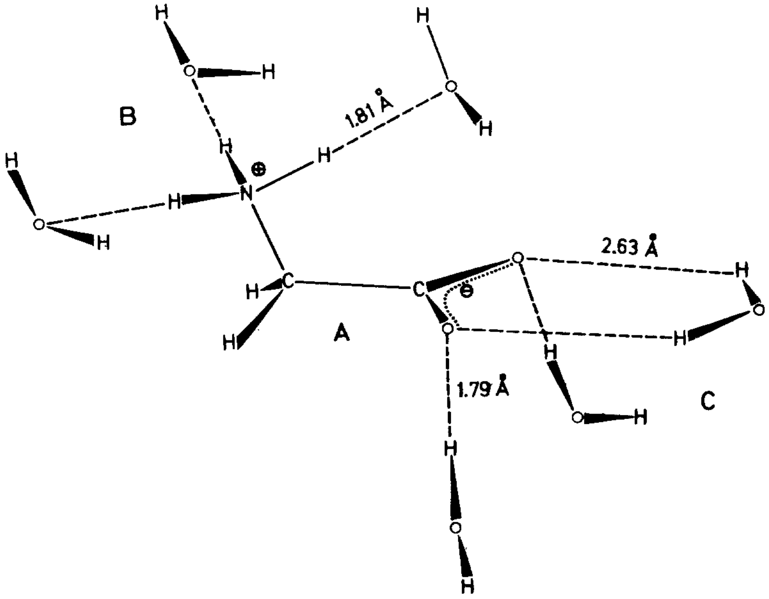

Fig. 1. The geometry of the glycine·$6H_2O$-complex

hydrophobic site is very much diminished. Because of this, we neglected the solvation of the methylene group.

In the glycine·$12H_2O$ complex, which is shown in Fig. 2, the solvation of the carboxylate group (cluster *D* in Fig. 2) remains unchanged, but two additional water molecules form hydrogen bonds (with a distance of 1.79 Å for the

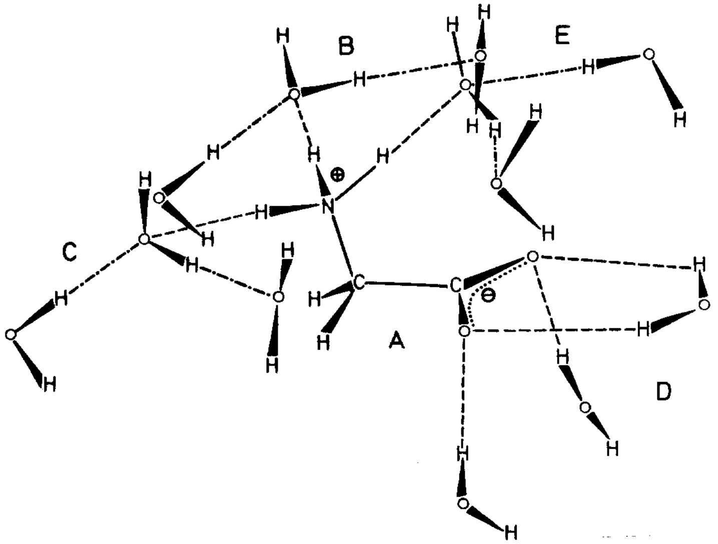

Fig. 2. The geometry of the glycine·$12H_2O$-complex

O—H···O bonds) with each of the water molecules attached to the ammonium group. In this way we obtained three clusters each consisting of three water molecules (cluster *B*, *C* and *E* in Fig. 2) representing the second hydration shell. Using this configuration the space around glycine is completely filled as can be seen with the help of CPK molecular models. As mentioned above the cluster *D* solvates the carboxylate group in and under the plane of this group. The two additional water molecules of cluster *E* are placed near the carboxylate group and complete the solvation of this hydrophilic group above its plane (the O···H distance is 2.72 Å).

All *ab initio* calculations have been performed with a standard LCAO SCF program using the STO-3G minimal basis set [27].

The basic idea of the MCF-method consists in including the Coulomb potential of all the partner molecules in the Fock operator of the molecule under consideration and to change the charge distributions iteratively until mutually consistent solutions are obtained. In this way the electrostatic as well as the polarization energy contributions to the interaction energy are obtained in one step. The Coulomb potential of the molecule is represented by a point charge distribution of the Hartree–Fock Coulomb potential. To determine this distribution, the Hartree–Fock SCF-orbitals are transformed to localized orbitals using Boy's criterion [28]. Then the exact Hartree–Fock Coulomb potential $V_l^I(\boldsymbol{r}_{il}^I)$ for each localized orbital Ψ_l^I of the Ith molecule is calculated at points $\boldsymbol{r}_{il}^I$, situated on spheres with different radii around the center of charge of the orbital Ψ_l^I. These radii cover the short, medium and long range parts of the molecular potential field. These potentials are then fitted by a number of point charges using a method to minimize the least square sum [29]

$$F_l^I = \sum_{i=1}^{m_l^I} \left[\sum_{j=1}^{M^I} \frac{q_{jl}^I}{\boldsymbol{r}_{il}^I - \boldsymbol{r}_{jl}^I} - V_l^I(\boldsymbol{r}_{il}^I) \right]^2 \qquad l = 1, 2, \ldots, n^{I^*},$$

where M^I is the number of point charges for each localized orbital m_l^I is the number of calculated potential points, n^{I^*} is the number of occupied localized orbitals in the Ith molecule and q_{jl}^I, $\boldsymbol{r}_{jl}^I$ are the parameters which are to be determined. The total interaction energy for N molecules in the MCF-scheme is then given by

$$\Delta E_{\text{MCF}}^{\text{corr}} = \Delta\tilde{E} + \sum_{I=1}^{N} \sum_{\substack{J=1 \\ (I \neq J)}}^{N} (\Delta\tilde{E}_{\text{ep}}^{IJ} + \Delta\tilde{E}_{\text{ex}}^{IJ} + \Delta\tilde{E}_{\text{Ch.tr.}}^{IJ})$$

with

$$\Delta\tilde{E} = \sum_{I=1}^{N} (\tilde{E}^I - E^I).$$

Here E^I and $\tilde{E}^I$ are the total energies of the molecule I, calculated with the Hartree–Fock and the polarized MCF-orbitals, respectively. $\Delta\tilde{E}_{\text{ep}}^{IJ}$ stands for the electrostatic and polarization energy contribution between the Ith and the Jth subsystem and can be written in the form

$$\begin{aligned}\Delta\tilde{E}_{\mathrm{ep}}^{IJ} &= \sum_{j=1}^{M^J}\sum_{l=1}^{n^J}\sum_{k=1}^{M^I}\sum_{l'=1}^{n^I}\frac{q_{kl'}^{I}(\boldsymbol{r}_{kl'}^{I})q_{jl}^{J}(\boldsymbol{r}_{jl}^{J})}{|\boldsymbol{r}_{kl'}^{I}-\boldsymbol{r}_{jl}^{J}|}\\ &+\sum_{k=1}^{M^I}\sum_{l'=1}^{n^I}\sum_{\alpha=1}^{L^J}\frac{q_{kl'}^{I}(\boldsymbol{r}_{kl'}^{I})Z_{\alpha}^{J}(\boldsymbol{R}_{\alpha}^{J})}{|\boldsymbol{r}_{kl'}^{I}-\boldsymbol{R}_{\alpha}^{J}|}\\ &+\sum_{j=1}^{M^J}\sum_{l=1}^{n^J}\sum_{\beta=1}^{L^I}\frac{q_{jl}^{J}(\boldsymbol{r}_{jl}^{J})Z_{\beta}^{I}(\boldsymbol{R}_{\beta}^{I})}{|\boldsymbol{r}_{jl}^{J}-\boldsymbol{R}_{\beta}^{I}|}+\sum_{\alpha=1}^{L^J}\sum_{\beta=1}^{L^I}\frac{Z_{\alpha}^{J}(\boldsymbol{R}_{\alpha}^{J})Z_{\beta}^{I}(\boldsymbol{R}_{\beta}^{I})}{|\boldsymbol{R}_{\alpha}^{J}-\boldsymbol{R}_{\beta}^{I}|}.\end{aligned}$$

Where Z_{γ}^{I} and $\boldsymbol{R}_{\gamma}^{I}$ is the charge and position vector, respectively, of the γth atom in the Ith molecules and L^I is the number of atoms in it.

The pairwise intermolecular exchange and charge transfer energy terms are calculated with the help of perturbation theoretical expressions, whose explicit form are given in Ref. [30] (Eqs. (I.4) and (I.5)). These equations are derived from the perturbation theory for weakly overlapping subsystems given by Murrell et al. [31] using the Mulliken approximation for the two-electron integrals.

In the supermolecule approach which we have applied also in the case of the glycine$\cdot$6H_2O complex for reasons of comparison with the MCF-results, the total interaction energy for smaller model systems which contain parts of the glycine zwitterion (like $NH_4^+\cdot 3H_2O$ and $HCO_2^-\cdot 3H_2O$) were calculated using the expression for N interacting components

$$\Delta E_{SM}=E^{SM}-\sum_{I=1}^{N}E^{I}.$$

In the case of the glycine$\cdot$12H_2O complex a part of the two-dimensional potential energy map around the equilibrium geometry was calculated by varying the O···H distances between the glycine and the four water complexes in the linear hydrogen bonded arrangement. To calculate the new interaction energies the electronic point charge distribution and the nuclei have been shifted in the case of the water clusters B, C and E in the direction of the N—H bonds of the glycine by different values ΔR. With these charge distributions $\Delta\tilde{E}_{\mathrm{ep}}$ was recalculated. For the exchange and charge transfer energy terms extrapolation formulae have been applied (for more detail see below). This can be justified by the fact that the deviation from the equilibrium position was smaller than the region of validity of the fitted analytical functions.

3. Results and Discussion

The different interaction energy contributions in the MCF-scheme for both hydrated glycine complexes, glycine$\cdot$6H_2O and glycine$\cdot$12H_2O, are given in Table 1 together with the supermolecule results for the glycine$\cdot$6H_2O system. Convergence in the interaction energy of about one per cent relative to the total interaction energy is reached after performing two MCF iteration cycles in both cases. The total interaction energy between the glycine zwitterion and the three

Table 1. The interaction energies in the glycine·$6H_2O$-, and the glycine·$12H_2O$-complex (for $\Delta R = 0$), calculated with the MCF-method, the exchange and charge transfer contributions, and the supermolecule result for the glycine·$6H_2O$-complex (in kcal/mole)

	glycine·$6H_2O$	glycine·$12H_2O$
$\Delta\tilde{E}$	6.5	7.5
$\Delta\tilde{E}_{ep}^{AB}$	−68.1	−19.2
$\Delta\tilde{E}_{ep}^{AC}$	−39.7	−19.6
$\Delta\tilde{E}_{ep}^{AD}$	—	−40.1
$\Delta\tilde{E}_{ep}^{AE}$	—	−40.7
$\Delta\tilde{E}_{ep}^{W.W.}$ [a]	−4.1	6.4
$\Delta\tilde{E}_{ep}$	−111.9	−113.2
$\Delta\tilde{E}_{MCF}$	−105.4	−105.7
$\Delta\tilde{E}_{ex}$	49.2	38.5
$\Delta\tilde{E}_{CT}$	−29.5	−38.0
$\Delta E_{MCF}^{corr.}$ [b]	−85.7 [c]	−105.2
ΔE_{SM}	−79.9	—

[a] Total water-water-interaction.

[b] Total interaction energy, including exchange and charge-transfer contributions.

[c] 107% ΔE_{SM}.

water molecules attached to the ammonium group in the glycine·$6H_2O$ complex is −68.1 kcal/mole. Due to the symmetry of the amino-acid in its zwitterionic form two of the three water molecules are in equivalent geometrical position relative to the C—NH_3 group and point away from the glycyl part. The third one has a different configuration with respect to the amino acid. If we assume equal amount of interaction energies between each of the water molecules and glycine we get a stabilization of the complex by one hydrogen bond of the type N—H···O of 22.7 kcal/mole. Pullman [5] reports for a similar interaction between the ammonium group of histamine and a water molecule a stabilization of 28 kcal/mole but mentions, that this value is too high by about 5 kcal/mole. To get a comparable supermolecule result to the MCF value we calculated the $NH_4^+ \cdot 3H_2O$ complex, placing the water molecules in the same relative configuration to the ammonium group as in the glycine·$6H_2O$ case. The result is an overall stabilization of 66.6 kcal/mole or 22.2 kcal/mole per hydrogen bonded water molecule which is in good agreement with the MCF result. The solvation of the carboxylate group by three water molecules (cluster *C* in Fig. 1) leads to an attractive interaction of 39.7 kcal/mole. A supermolecule calculation for the model complex $HCOO^- \cdot 3H_2O$ taking the same geometrical arrangement as in the glycine·$6H_2O$ system leads to 47.1 kcal/mole stabilization energy. The calculated interaction in the MCF scheme (electrostatic and polarization contributions) is by −21.9 kcal/mole stronger than the supermolecule result ($\Delta E^{SM} = -79.9$ kcal/mole) which shows that exchange and charge transfer energy contributions cannot be neglected in this case. The pairwise exchange energies calculated with the help of the approximate perturbation theoretical expression is 22.5 kcal/mole for the glycine-water cluster *B* and 26.7 kcal/mole for the glycine-water cluster *C*, respectively. The exchange energy between the two water clusters (*B* and *C*) is less than 0.01 kcal/mole and can be neglected. The MCF interaction energy is reduced to -58.6 kcal/mole by including the total exchange energy and is now lower than the supermolecule result. But in the case of charged species the stabilization by the charge transfer energy is as it is expected of the same order of magnitude as the other energy terms and has to be taken into account. For the total charge transfer energy we calculated again with the help of an approximate perturbation theoretical expression the value of -29.5 kcal/mole which leads to the final MCF energy of -85.2 kcal/mole being about 7% above the SM result.

In the case of the glycine$\cdot 12H_2O$ complex the interaction energies between glycine and the water clusters *B* and *C*, respectively, are equivalent because the two water clusters are symmetry equivalent with respect to the symmetry plane of the glycine molecule. These interaction energies are smaller than the energy obtained by the supermolecule calculation for the $NH_4^+\cdot 3H_2O$ complex, because the additional water molecule attached to those which are directly hydrogen bonded to the ammonium group lead to an overall small destabilization of the complex due to steric hindrance with the glycine residue. The interaction between the zwitterion and the water cluster which solvates both the ammonium group and the carboxylate group (cluster *E* in Fig. 2), yields a stabilization of 40.1 kcal/mole. This is due to the solvation of the ammonium group which gives about 20 kcal/mole attraction as the interaction of glycine with the clusters *B* and *C* show, and the solvation of the carboxylate group which contributes about -20 kcal/mole. From these results we can conclude that the solvation of the ammonium group, including the second hydration shell yields about 60 kcal/mole stabilization energy, which is about 7 kcal/mole smaller than the energy given by the supermolecule calculation for the $NH_4^+\cdot 3H_2O$ complex which is a model for the first hydration shell. The interaction between the zwitterion and the water molecules attached to the carboxylate group (cluster *D*) gives a stabilization of 40.7 kcal/mole, so that the solvation of the carboxylate group yields a total stabilization of about 60 kcal/mole. If one includes the repulsive interaction among the four water clusters, one ends up with the same amount of interaction energy ΔE_{MCF} as for the glycine$\cdot 6H_2O$ complex.

The total exchange energy between the glycine and the three water clusters at the ammonium group (23.7 kcal/mole) has about the same value as the comparable exchange contribution in the glycine$\cdot 6H_2O$ complex. The reason for this is that the additional water molecules are too far from the glycine part of exert an essential influence. The exchange energy between the glycine and the water cluster at the carboxylate group (cluster *D*) is 14.8 kcal/mole which is about 10 kcal/mole smaller than the corresponding value in glycine$\cdot 6H_2O$ probably due to the different polarization of the charge distribution in the two complexes. Since the exchange energy between the individual water clusters is less than 0.1 kcal/mole we have neglected this contribution. Including the charge transfer energy (−38.0 kcal/mole), computed with the help of the perturbation theoretical expression, the total interaction energy in the MCF scheme totaled to −105.2 kcal/mole. This value can be compared with a result given by Clementi [32], which is calculated as an average over 1,000,000 configurations with the help of Monte-Carlo computer simulation. If one adds up the water-water and the water-glycine zwitterion interaction energies, given there, one ends up with a total interaction energy of −106.4 kcal/mole, which differs only by 1.2 kcal/mole from our result.

The additional stabilization of about 20 kcal/mole of the larger complex compared to the smaller one indicates that our model chosen in such a way as to represent the first hydration shell is incomplete. This means that the additional water molecules of cluster *E* should be taken into account in the case of conformational studies of a molecule in aqueous solution even if one constructs the solvation shell only by strongly interacting water molecules.

Using the point charge distribution obtained with the MCF procedure for the four clusters, respectively, it is possible to calculate ΔE_{ep} as a function of the intermolecular distance between the glycine molecule and the hydrogen bond lengths. The parameter ΔR denotes that the four water clusters are simultaneously shifted by a vector of length ΔR from the assumed equilibrium distances. The direction of the translation vectors are the direction of the hydrogen bonds $N^{+}—H\cdots O$ for the water clusters *B*, *C* and *E* and the direction of the C—C bond of glycine for the water cluster *D* at the carboxylate group. The numerical results of these calculations for the glycine·$12H_2O$ complex together with the exchange and charge transfer energies are given in Table 2

Table 2. The interaction energies in the glycine·$12H_2O$-complex, calculated with the MCF-method ($\Delta\tilde{E}^{IJ}_{\mathrm{ep}}$), the interaction energies, including the exchange and charge transfer contributions ($\Delta\bar{E}^{IJ}$), and the total interaction energies (ΔE_{ep}, $\Delta\bar{E}$), including water-water interactions, as a function of a simultaneous translation of the water clusters by translation-vectors of length ΔR

ΔR (a.u.)	$\Delta\tilde{E}^{AB}_{\mathrm{ep}}$	$\Delta\tilde{E}^{AD}_{\mathrm{ep}}$	$\Delta\tilde{E}^{AE}_{\mathrm{ep}}$	$\Delta\tilde{E}_{\mathrm{ep}}$	$\Delta\bar{E}^{AB}$ (kcal/mole)	$\Delta\bar{E}^{AD}$	$\Delta\bar{E}^{AE}$	$\Delta\bar{E}$
−0.5	−22.4	−41.9	−60.0	−137.9	−9.1	−41.6	−49.9	−109.7
−0.3	−21.2	−41.0	−50.9	−126.5	−15.4	−40.4	−47.4	−118.6
−0.1	−19.9	−40.4	−43.7	−117.2	−18.3	−39.5	−43.8	−119.9
0.0	−19.3	−40.1	−40.7	−113.2	−19.1	−39.0	−41.8	−119.0
0.1	−18.7	−40.0	−58.0	−109.5	−19.4	−38.7	−39.8	−117.3
0.3	−17.6	−39.7	−33.3	−102.9	−19.2	−38.1	−35.7	−112.2
0.5	−16.5	−39.4	−29.3	−97.2	−18.3	−37.4	−31.6	−105.6
1.0	−14.1	−38.2	−21.8	−84.8	−15.2	−34.9	−23.2	−88.6
1.5	−12.1	−35.5	−16.6	−73.6	−12.3	−31.2	−17.0	−72.8
2.0	−10.4	−31.5	−12.7	−63.1	−10.4	−27.3	−12.8	−60.9
3.0	−7.9	−22.4	−7.7	−44.8	−7.9	−19.2	−7.7	−42.7
4.0	−6.2	−14.9	−4.8	−31.3	−6.2	−12.7	−4.8	−29.9
5.0	−4.9	−9.8	−3.1	−22.1	−4.9	−8.3	−3.1	−21.2

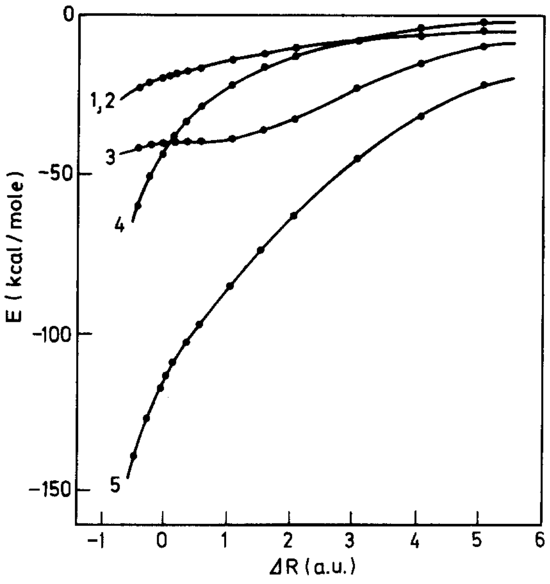

Fig. 3. The interaction energies $\Delta\tilde{E}_{ep}^{AB}$ (curve 1), $\Delta\tilde{E}_{ep}^{AC}$ (curve 2), $\Delta\tilde{E}_{ep}^{AD}$ (curve 3), $\Delta\tilde{E}_{ep}^{AE}$ (curve 4), and the total interaction energy $\Delta\tilde{E}_{ep}$ (curve 5), as a function of a simultaneous translation of the water clusters *B*, *C*, *D*, and *E* by translation-vectors of length ΔR, in the glycine·$12H_2O$-complex

and the pairwise as well as the total potential curves corresponding to the ΔE_{ep} results are drawn in Fig. 3. Since exchange and charge transfer energy contribution are not included, we find a steep descent of the attractive energy terms in the range $\Delta R = 0$. To estimate the exchange energy for a larger range of intermolecular distances we tried to fit an analytical expression

$$\Delta E_{ex}^{IJ}(\Delta R) = \Delta E_{ex}^{IJ}(0)\exp(\alpha\Delta R)$$

for three values calculated at different ΔR around the equilibrium distance ($\Delta R = 0$). A linear regression calculation was performed for each pair exchange energy contribution and the following functions (energies in kcal/mole, ΔR in a.u.) were obtained,

$$\Delta E_{ex}^{AB} = 8.44\exp(-2.27\,\Delta R); \qquad a^2 = 1.0000$$

$$\Delta E_{ex}^{AC} = 7.87\exp(-2.29\,\Delta R); \qquad a^2 = 1.0000$$

$$\Delta E_{ex}^{AD} = 14.15\exp(-0.44\,\Delta R); \qquad a^2 = 0.9758$$

$$\Delta E_{ex}^{AE} = 7.46\exp(-2.30\,\Delta R); \qquad a^2 = 1.0000,$$

where *a* is the correlation coefficient.

For the charge transfer energy of each pair of interacting systems a polynomial of second order as a function of ΔR has been fitted to five values calculated for different ΔR. The sum of the squared deviations given as the difference between the directly computed value and the one obtained from the analytical expression was in all cases less than 10^{-4}. In Fig. 4 the pair interaction energy curves and their sum is drawn as a function of ΔR for the complex glycine·$12H_2O$. The calculated energy minima for the two equivalent clusters at the ammonium group and for the cluster at the carboxyl group for $\Delta R = 0$ and $\Delta R = +0.5$ a.u., respec-

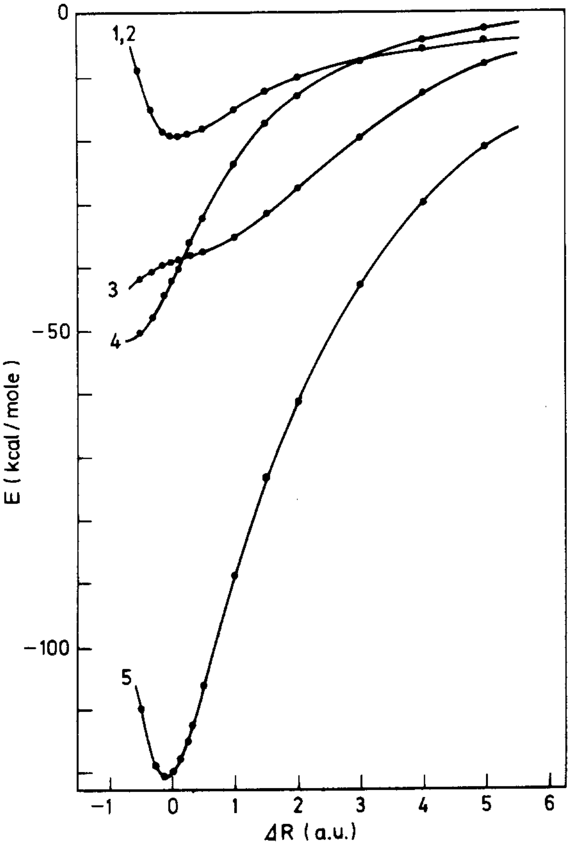

Fig. 4. The interaction energies $\Delta\bar{E}^{AB}$ (curve 1), $\Delta\bar{E}^{AC}$ (curve 2), $\Delta\bar{E}^{AD}$ (curve 3), $\Delta\bar{E}^{AE}$ (curve 4), and the total interaction energy $\Delta\bar{E}$ (curve 5), including exchange and charge transfer contributions in the glycine·$12H_2O$-complex, as a function of ΔR (see Fig. 3)

tively, whereas the slope of the potential curve for cluster E suggests a minimum for $\Delta R < -1.0$, which has no physical meaning. This behaviour can be explained by the experience that for small intermolecular distances the calculation of the electrostatic interaction energy with the help of a point charge distribution as well as the application of the perturbation theoretical expressions derived for weakly overlapping systems are no longer valid. As can be seen from Fig. 4 the total interaction curve exhibits a sharp minimum at ΔR about -0.10 a.u., which means that the equilibrium hydrogen bond lengths occurring in the cluster are decreased by this distance relative to the corresponding isolated ones due to the mutual interaction of the water molecules.

4. Conclusions

We have investigated different hydration shell models representing the first and second solvation shell, respectively, of the simplest amino acid, glycine, in its zwitterionic form as it occurs in aqueous solution. The computations were carried out in a comparative way with the help of the SM approach on one side and the MCF method including perturbation theoretical expressions for the exchange and charge transfer energy contributions on the other side. The numerical results for the solvated glycine complexes and the simplified models of these systems indicate that the MCF method is suitable to describe interaction energies between strongly hydrogen bonded systems as long as the intermolecular distances are in the range where the overlap between the interacting subunits of the potential surface near the equilibrium configuration can easily be determined with considerable less amount of CPU time compared to the corresponding SM treatment of this problem. In addition to this we obtain detailed qualitative as well as quantitative informations about the character of the different interactions which contribute to the energy and about the effective changes due to the presence of additional water molecules. For the system under consideration we find that the difference in the total interaction energy is relatively large (about 20 kcal/mole) going from the assumed first hydration shell to the second one. This result suggests that one has to include those water molecules which are responsible for this effect, namely the water molecules which link the ammonium group with the carboxyl group of glycine in the first hydration shell due to their strong interaction with the solute. We also may conclude from the data that another shell of water molecules arranged in a proper manner around each of the clusters will not play a significant role with respect to the equilibrium configuration of the solute-solvent system but rather act as a constant potential representing the bulk water.

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References

1. Otto, P., Ladik, J.: Chem. Phys. **8**, 192 (1975)
2. Otto, P., Ladik, J.: Chem. Phys. **19**, 209 (1977)
3. Otto, P.: Chem. Phys. **33**, 407 (1978)
4. Otto, P.: Chem. Phys. Lett. **62**, 538 (1979)
5. Pullman, B.: Adv. Quant. Chem. **10**, 251 (1977)
6. Port, G. N. J., Pullman, A.: Int. J. Quant. Chem. **QBS 1**, 21 (1974)
7. Pullman, A., Pullman, B.: Quart. Rev. Biophys. **7**, 505 (1975)
8. Port, G. N. J., Pullman, A.: FEBS Letters **31**, 70 (1973)
9. Dreyfus, M., Maigret, B., Pullman, A.: Theoret. Chim. Acta (Berl.) **17**, 109 (1970)
10. Berthold, H., Pullman, B.: Biochem. Biophys. Acta **232**, 595 (1971)
11. Diner, S., Malrieu, J. P., Claverie, P.: Theoret. Chim. Acta (Berl.) **13**, 1 (1969)
12. Malrieu, J. P., Claverie, P., Diner, S.: Theoret. Chim. Acta (Berl.) **13**, 18 (1969)
13. Diner, S., Malrieu, J. P., Jordan, F., Gilbert, M.: Theoret. Chim. Acta (Berl.) **15**, 110 (1969)
14. Beveridge, D. L., Kelly, M. M., Radna, R. J.: Int. J. Quant. Chem. Soc. **96**, 3769 (1974)
15. Hopfinger, A. J.: Conformational properties of macromolecules. New York: Academic Press 1973

16. Carozzo, L., Corongiu, G., Petrongolo, C., Clementi, E.: J. Chem. Phys. **68**, 787 (1978)
17. Rugassi, M., Ferro, D. R., Clementi, E.: J. Chem. Phys. **70**, 1040 (1979).
18. Clementi, E., Corongiu, G.: J. Chem. Phys. **72**, 3979 (1980)
19. Clementi, E., Corongiu, G.: Int. J. Quant. Chem. **16**, 897 (1979); Clementi, E.: Computational aspects for large chemical systems. Lecture Notes in Chemistry, Vol. **19**, p. 152. Heidelberg New York: Springer Verlag 1980
20. Ladik, J.: Electronic structure of polymers and molecular crystals. Ed. André, J.-M., Delhalle, J., Ladik, J., p. 663. New York: Plenum Press 1975
21. Ladik, J.: Int. J. Quant. Chem. **QBS 1**, 5 (1974)
22. Suhai, S., Ladik, J.: Acta Chim. Acad. Sci. Hung. **82**, 67 (1974)
23. Suhai, S.: Biopolymers **13**, 1731 (1974)
24. Beveridge, D. L., Jano, I., Ladik, J.: J. Chem. Phys. **56**, 4744 (1972)
25. Suhai, S., Kaspar, J., Ladik, J.: Int. J. Quant. Chem. **17**, 995 (1980)
26. Clementi, E.: Computational aspects for large chemical systems. Lecture Notes in Chemistry, Vol. 19, p. 102. Springer Verlag, Heidelberg-New York, 1980
27. Hehre, W., Stewart, R. F., Pople, J. A.: J. Chem. Phys. **51**, 2657 (1969)
28. Boys, S. F.: Rev. Mod. Phys. **32**, 306 (1966)
29. Gaissmaier, B., Hohecker, W., Unbehauen, R., Wehrhahn, W.: Frequenz Bd **29**, No. 5 (1975)
30. Sohalski, W. A., Chojnacki, H.: Int. J. Quant. Chem. **13**, 679 (1978)
31. Murrel, J. N., Randic, M., Williams, D. R.: Proc. Roy. Soc. A **284**, 566 (1965)
32. See Ref. [26], p. 101

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