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The Influence of Na^+ on Neighbouring Hydrogen Bonds of Aliphatic Amino Acid

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Summary. The influence of Na^+ on hydrogen bonds of the OH $\cdots$ O and NH $\cdots$ O type between an aliphatic amino acid (glycine zwitterion) and water is investigated by *ab initio* calculations with minimal Gaussian basis sets. Distortion of the hydration shell caused by Na^+, and interaction energies contributing to the over-all stabilization are discussed.

Keywords. Glycine/Na^+ complex; Hydration.

Der Einfluß von Na^+ auf die benachbarten Wasserstoffbindungen in aliphatischen Aminosäuren

Zusammenfassung. Der Einfluß von Na^+ auf die Wasserstoffbindungen vom OH $\cdots$ O- und NH $\cdots$ O-Typ in aliphatischen Aminosäuren (Glycin-Zwitterion) und Wasser wurde mittels *ab initio* Berechnungen mit einem minimalen Gausschen Basissatz untersucht. Die durch Na^+-Ionen hervorgerufenen Verzerrungen der Hydratationsschale und die zur Gesamtstabilisierung beitragenden Wechselwirkungsenergien werden diskutiert.

Introduction

Considerable attention has recently been focused on the binding of metal ions in bioinorganic complexes [1–15]. The presence of the metal ion can influence the electronic and structural arrangement of a protein and thus affect its reactivity. The knowledge of the nature and the extent of metal ion/protein interaction is therefore most important for a large number of widely differing biological processes. These problems have been the subject of several papers using amino acids [10,15], amides [16], and small peptides [5–8, 12–13] as model compounds.

As most biological processes occur in aqueous solution, knowledge of the hydration of a metal complex is important for the understanding of metalloprotein hydration and the role of water in determining biological structures and functions.

The replacement of water coordinated to a metal ion by another ligand is a reaction of fundamental importance. Most of the aquocomplexes of the smaller alkaline and alkaline earth metals are six-coordinated in the first shell, with octahedral structure. The alkaline metals usually form complexes rapidly, but the complexes are weak and subject to rapid exchange, so that experimental studies must be carried out mostly at high concentrations. The glycine zwitterion/Na^+ complex in aqueous solution has not been studied yet, as it is difficult to design suitable experiments. Most studies have been retricted to transition metals which interact much more strongly with this type of ligand [11, 17–19].

In this work, we have investigated the structure of glycine zwitterion/Na^+ complex in aqueous solution and the effect of unsolvated Na^+ and solvated Na^+ on the neighbouring hydrogen bonds formed by the interaction between glycine zwitterion and its hydration water by means of *ab initio* calculation with minimal basis sets [20].

Method

The geometry of glycine zwitterion, denoted as gly, was taken from experimental data [21], as well as that of water [22]. All internal geometries were kept constant throughout the calculations. The *ab initio* LCAO-MO-SCF optimized energies were computed with the HONDO PROGRAM [23] at the IBM 3031/08 Computer Center of Chulalongkorn University.

Results and Discussion

Total energies, metal ion binding and hydrogen bond energies of all systems are collected in Table 1, and the optimized intermolecular geometrical parameters are reported in Table 2. The electronic density of the atoms for various systems evaluated by means of Mulliken Population Analysis are listed in Table 3.

Table 1. Total energy, metal ion binding energy and hydrogen bond energy

System	Total energy (Hartree)	Metal ion binding energy (kcal/mol)	Hydrogen bond energy (kcal/mol)
gly/Na^+	−389.33995	−67.1	–
gly	−240.08819	–	–
Na^+	−149.14481	–	–
gly · $5H_2O$	−562.85043	–	–
gly · $4H_2O/Na^+$	−647.55566	−66.4	–
gly · $4H_2O$	−498.30507	–	–
H_2O	−64.52139	–	–
$[Na(H_2O)_4]^+$	−407.37455	–	–
gly/W1	−304.63358	–	−15.1
gly/W2	−304.64795	–	−24.1
gly/W3	−304.64156	–	−20.1
gly/W4	−304.64309	–	−21.0
gly/W5	−304.64309	–	−21.0
gly/Na^+/W2	−453.90119	–	−25.0
gly/Na^+/W3	−453.88733	–	−16.3
gly/Na^+/W4	−453.91135	–	−31.4
gly/Na^+/W5	−453.91135	–	−31.4
$[(H_2O)_4Na(gly)]^+$	−647.52779	−40.8	–
$[(H_2O)_4Na(gly)]^+$/W2	−712.08308	–	−21.3
$[(H_2O)_4Na(gly)]^+$/W3	−712.07386	–	−15.5
$[(H_2O)_4Na(gly)]^+$/W4	−712.09038	–	−25.9
$[(H_2O)_4Na(gly)]^+$/W5	−712.09038	–	−25.9

Table 2. The orientation of the first hydration shell of glycine zwitterion upon unsolvated and solvated Na^+ effect including the hydrogen bond energy

System	Optimized geometrical parameters							
	$O_1 \cdots O_L$ (Å)	$C_2\hat{O}_1O_L$ (degrees)	$O_1\hat{O}_LH_{L1}$ (degrees)	$O_2 \cdots O_L$ (Å)	$C_2\hat{O}_2O_L$ (degrees)	$O_2\hat{O}_LH_{L1}$ (degrees)	$NH \cdots O_L$ (Å)	H-bond energy (kcal/mol)
$[(H_2O)_4Na(gly)]^+/W2$	2.55	128	40	–	–	–	–	−21.3
gly/W2	2.55	132	20	–	–	–	–	−24.1
gly/Na^+/W2	2.55	132	70	–	–	–	–	−25.0
$[(H_2O)_4Na(gly)]^+/W3$	–	–	–	2.70	100	12.0	–	−15.5
gly/W3	–	–	–	2.70	108	0.0	–	−20.1
gly/Na^+/W3	–	–	–	2.65	105	10.0	–	−16.3
$[(H_2O)_4Na(gly)]^+/W4$	–	–	–	–	–	–	2.62	−25.9
gly/W4	–	–	–	–	–	–	2.64	−21.0
gly/Na^+/W4	–	–	–	–	–	–	2.70	−31.4
$[(H_2O)_4Na(gly)]^+/W5$	–	–	–	–	–	–	2.62	−25.9
gly/W5	–	–	–	–	–	–	2.64	−21.0
gly/Na^+/W5	–	–	–	–	–	–	2.70	−31.4

Table 3. The electronic density of the atoms for various systems calculated by means of Mulliken population analysis

Atom	gly · 5H_2O	gly/Na^+	gly · 4H_2O/Na^+		$[(H_2O)_4Na(gly)]^+$
H_1	0.589	0.585	0.576		0.592
H_2	0.583	0.591	0.578		0.602
H_3	0.583	0.591	0.578		0.602
N	7.890	7.721	7.900		7.717
H_4	0.757	0.717	0.736		0.730
H_5	0.757	0.717	0.736		0.730
C_1	6.449	6.461	6.417		6.477
C_2	5.594	5.665	5.643		5.656
O_1	8.436	8.479	8.485		8.457
O_2	8.374	8.421	8.470		8.401
Na^+	–	10.053	10.055		10.118
W1 O_L	8.482	–	–		8.445
H_{L1}	0.784	–	–	axial water	0.770
H_{L2}	0.791	–	–		0.765
W2 O_L	8.518	–	8.397		8.445
H_{L1}	0.732	–	0.762	axial water	0.770
H_{L2}	0.784	–	0.782		0.765
W3 O_L	8.498	–	8.484		8.445
H_{L1}	0.773	–	0.777	equatorial water	0.767
H_{L2}	0.823	–	0.815		0.767
W4 O_L	8.404	–	8.416		8.446
H_{L1}	0.747	–	0.743	equatorial water	0.767
H_{L2}	0.750	–	0.746		0.767
W5 O_L	8.404	–	8.416		–
H_{L1}	0.747	–	0.743		–
H_{L2}	0.751	–	0.746		–

The Conformation of Glycine Zwitterion/Na^+ *Complex*

From our previous work [24] based on semiempirical calculations (CNDO/2), the most stable conformation of glycine zwitterion is predicted to be $(\theta, \varphi) = (o, o)$ as illustrated in Fig. 1.

Glycine zwitterion has only one negatively charged group which is the most favourable site for metal binding. In similar systems 4-member rings are readily formed in which both oxygen atoms are bound to the metal ion [25]. In agreement with this finding, the most preferred binding site for Na^+ at the glycine zwitterion is located in the bisectrix of the $O_1C_2O_2$ angle, with optimized $O \cdots Na^+$ distances of $2.20\,\text{Å} \pm 0.05$ (Fig. 2). The corresponding stabilization energy is -67.1 kcal/mol.

The Influence of Unsolvated Na^+ *on the First Hydration Shell of Glycine Zwitterion*

As a first step to estimate whether or not a stabilized complex is formed in aqueous solution, one can compare the metal/ligand interaction energy with the data for

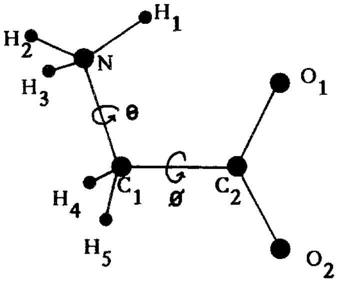

Fig. 1. Glycine zwitterion with conformation $(\theta, \varphi) = (o, o)$, one H-atom of $-NH_3^+$ and N, C_1, C_2, O atoms are in the same plane

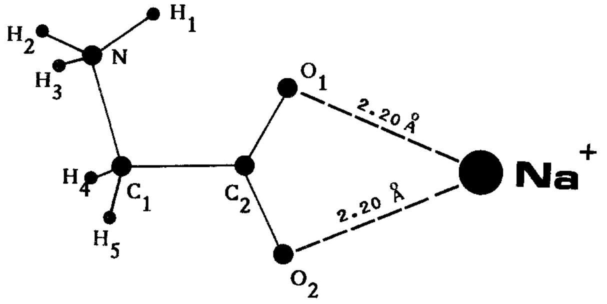

Fig. 2. The conformation of glycine zwitterion/Na$^+$ complex

hydration. The metal ion is supposed to bind to the ligand whenever the metal/ligand binding energy is larger than the ligand interaction with water. The binding of Na$^+$ to the COO$^-$ group of hydrated glycine zwitterion leads to a stabilization energy of -66.4 kcal/mol which compares favourably to the ligand's binding to water W1 (cf. Fig. 3), stabilized by -15.1 kcal/mol.

According to our previous studies [26, 27], the first hydration shell of glycine zwitterion is proposed to consist of five water molecules interacting through H-bonds (Fig. 3). When Na$^+$ is bound to glycine zwitterion at the COO$^-$ group, the

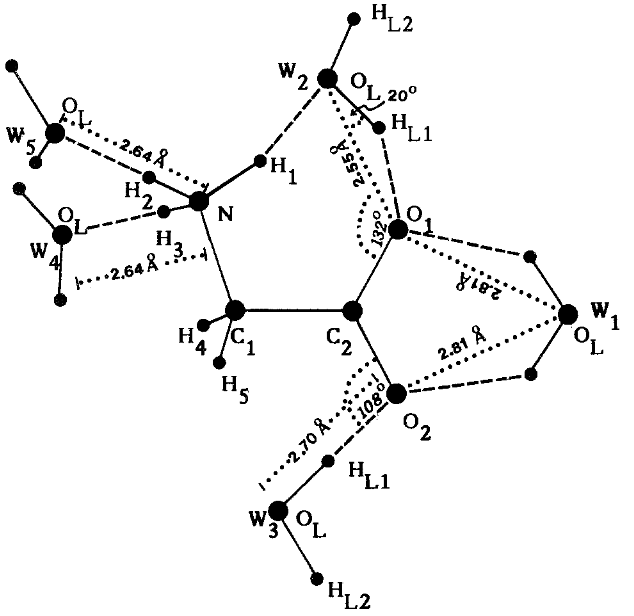

Fig. 3. The orientation of the first hydration shell of glycine zwitterion (W1, W2, W3, W4 and W5)

remaining hydration sites are W2, W3, W4 and W5. The effect of Na^+ on the orientation of these water molecules has been investigated and the results are summarized in Table 2. Na^+ does not effect the hydrogen bond distance of W2, but one hydrogen atom of W2 is rotated away from O_1 by 50°, due to the repulsion between Na^+ and the hydrogen of W2. The electronic charge of O_1 is increased but the positive charge of hydrogen of W2 (H_{L1}) decreases (see Table 3). Therefore, Na^+ stabilizes this hydrogen bond by only 0.9 kcal/mol. In contrast to this, for W3 the hydrogen bond distance is shortened by 0.05 Å. The oxygen of W3 is displaced to the region of the CH_2 group by 3°, probably due to the increasing protonic charge at H_5. The increasing electronic density at O_2 and the small decrease of positive charge at H_{L1} of W3 would enhance the stabilization of this hydrogen bond. However, our result shows that the hydrogen bond energy is reduced by 3.8 kcal/mol. This could be explained by the distortion of the linearity of the hydrogen bond $O_2 \cdots H_{L1}O_L$.

The remarkable increase of the hydrogen bond energies of W4 and W5 (10.4 kcal/mol) also can be rationalized by considering the atomic population of the NH-hydrogens and the oxygen of water molecules. The increasing positive charge at NH-hydrogens, i.e. the increasing of proton donor ability indicates that the Na^+ effect is transferred through the molecular backbone to the amino group and further to the water molecules W4, W5.

The Structure of Glycine Zwitterion/Na^+ Complex in Aqueous Solution

Na^+ forms an octahedral first hydration shell with water molecules [28]. When a ligand is placed into the solution containing metal ions, the ions are supposed to bind to the ligand whenever the metal/ligand binding energy exceeds the binding energy of replaced water molecules. At least one water molecule is released from the ion's hydration shell. In the case of the gly/Na^+ complex, Na^+ binds to the oxygen atoms of the COO^- group and, therefore, Na^+ must release two water molecules from its octahedral shell. The metal/ligand interaction energy with −40.8 kcal/mol overcomes the hydration energy for two coordinated water molecules (−30.8 kcal/mol) [28]. This indicates the possibility of complex formation between Na^+ and gly in aqueous solution forming $[(H_2O)_4Na(gly)]^+$ (see Fig. 4).

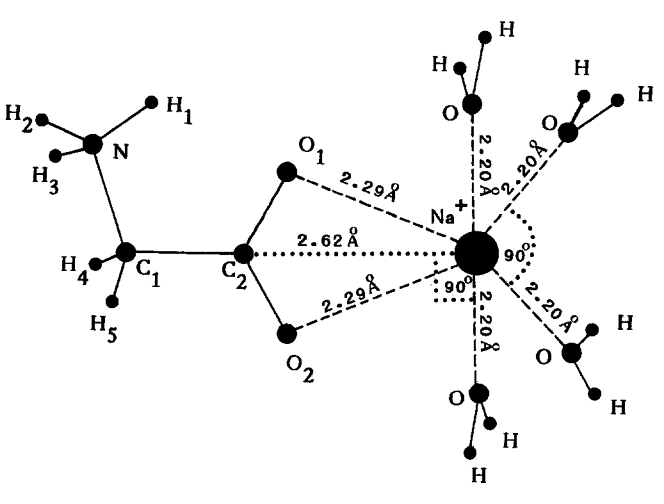

Fig. 4. The conformation of $[(H_2O)_4Na(gly)]^+$

The calculated $Na^+ \cdots OH$ bond lengths in $[(H_2O)_4Na(gly)]^+$ are all equal to 2.29 Å ± 0.02 and the optimized octahedral angles are 90° ± 5°.

The optimized distance of carboxylate oxygen atoms to Na^+ is 0.09 Å longer than in the unsolvated complex. The elongation of this intermolecular distance also leads to the lowering of metal/ligand interaction by 26.3 kcal/mol (from -67.1 kcal/mol to -40.8 kcal/mol). Besides steric effects, this can also be explained by considering the change of atomic population (cf. Table 3). The decrease of electronic charge at O_1, O_2 and the decrease of the positive charge of Na^+ due to the influence of hydration reduce electrostatic interaction between gly and Na^+.

The Influence of Solvated Na$^+$ *on the First Hydration Shell of Glycine Zwitterion*

The changes of the orientation of W2, W3, W4 and W5 influenced by solvated Na^+ have been investigated. The results (Table 2) show that the H-bond distances for W2 and W3 are not affected compared to gly/W2 and gly/W3, but the positions of W2 and W3 are relocated more distant from the area occupied by hydrated Na^+ (Fig. 5). The energies for both now nonlinear-H-bonds are thus decreased by 2.8 and 4.6 kcal/mol, respectively. The H-bond distance between $[(H_2O)_4Na(gly)]^+$ and W4/W5 is not significantly different form that of gly/W4 and gly/W5 but the bond energy is increased by 4.9 kcal/mol, due to the interaction with solvated Na^+.

The overall effect of solvated Na^+ leads to a smaller stabilization for the whole hydration shell, compared to the calculation employing the unsolvated Na^+; Namely to a net stabilization of -2.4 kcal/mol only, as most of the energy gain by ion influence is compensated by the loss of W1 in the ligand's hydration shell ($+15.1$ kcal/mol). The net effect of -2.4 kcal/mol is within the methodical limits.

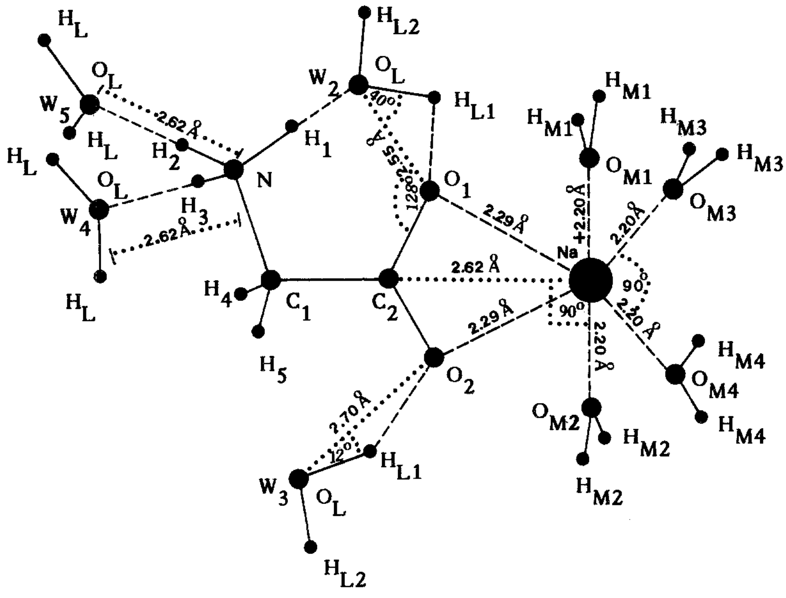

Fig. 5. The orientation of the first hydration shell of gly/Na$^+$ complex (W2, W3, W4 and W5)

However, looking into the details one can clearly see, that the ion stabilizes the NH_3^+ group's hydration to a significant extent. This can be considered as a kind of spill-over effect of the cation towards the cationic functional group of the zwitterion.

These results also show, that any evolution of ion effects in solution has to include at least a part of the ion's solvation shell. In our case, consideration of unsolvated Na^+ only would have led to quite erroneous conclusions about stabilization data. Considering finally the possibility of Na^+ complex formation with gly in water, our calculations indicate that a gain by Na^+/ligand binding of -40.8 kcal/mol and an additional stabilization of -2.4 kcal/mol for the hydration shell stand against the dehydration energies of $+30.8$ kcal/mol for the ion and $+15.1$ kcal/mol for the ligand. The balance of $+2.7$ kcal/mol is within methodical limits again. It is impossible, therefore, to decide from these energy data, whether complex formation should occur or not. If it occurs, however, it is to be expected that the complex will be a rather weak one.

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