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QUANTUM CHEMICAL INVESTIGATIONS ON ION-DIPEPTIDE COMPLEX FORMATION

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Abstract

The binding of cations to aliphatic dipeptides is studied at the example of glycylglycine and Na^+ ion by means of ab initio LCAO-MO-SCF calculation using a minimal GLO basis set. Information gained about various reactive sites and geometries are presented. It was found that the simultaneous binding of metal ion to both oxygens of CO_2^- group in the zwitterionic form of the ligand is the most favourable form. The data on Na^+ complexation are discussed in relation to the ion's hydration energy.

The influence of metal ions on structure and molecular properties of proteins and their transport through membranes are of great importance in a wide range of biological and chemical systems[1,2]. This has led to a number of experimental and theoretical studies on model compounds capable of describing these phenomena[3-7]. Aliphatic dipeptides are considered as the most simple model systems containing the peptide bond fundamental for the protein structure.

Informations concerning metal complexes of dipeptides should hence give insight into principle structures and their reactivities in more complex biological systems.

Cooperative experimental and quantum chemical research has been recently reported by us[8-11]. In continuation of this work on cation binding to biomolecules, we present here an ab initio investigation on the interaction of Na^+ with glycylglycine.

All calculations were performed by the ab initio LCAO-MO-SCF method using well tested minimal gaussian basis sets.[12-14] The geometries of the ligand were taken from refs. 16-18 and kept constant throughout the calculation, as it is known that the minimal basis set is suitable for the optimization of the intermolecular but less for the intramolecular geometrical parameter.[19] The molecular structure of the ligand and its binding sites available for metal binding are illustrated in Fig. 1.

Table 1 summarizes the *ab initio* binding energies for all systems considered, together with the optimized geometrical parameters.

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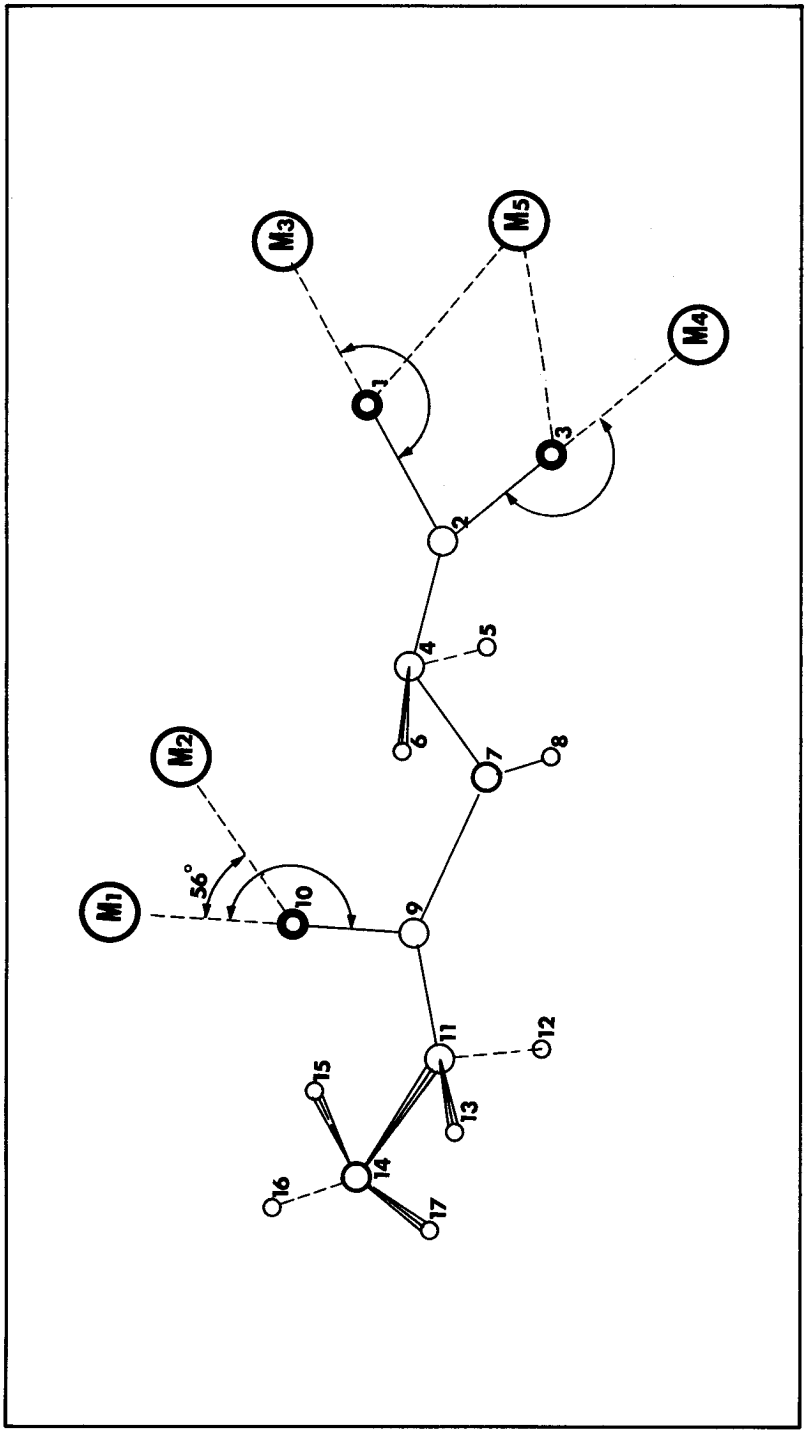

FIG. 1 Molecular structure of Na^+/glycylglycine in a series of significant positions numbered 1 to 5. More detailed information on the binding energy is given in Table 1. Circles represent H(○), C(◯), N (◯) , O (◯) and Na^+ (Ⓜ).

Table 1. BINDING ENERGIES OF Na^+ TO GLYCYLGLYCINE

Sites of[a] Cation Binding	O....Na^+ Optimized Distance (Å)	Total Energy (Hartree)	Binding Energies (kcal/mol)
M1	2.10	-564.6313	-20.1
M2	2.19	-564.6674	-42.7
M3	2.03	-564.7207	-76.1
M4	2.03	-564.6984	-62.1
M5	2.18	-564.7457	-91.9

[a] The numbering is indicated in Fig 1.

TABLE 2. CALCULATED HYDRATION ENERGY PER WATER MOLECULE OF THE FIRST ($\triangle$E (I)) AND SECOND ($\triangle$E (II)) HYDRATION SHELL.

Ion	1st hydration shell $\triangle E$ (I)	2nd hydration shell $\triangle E$ (II)	Hydration energies for one coordination site $\triangle E^{hy} = \triangle E(I) + 2\triangle E(II)$
Li^+	-25.7	-9.8	-45.3
Na^+	-17.3	-7.6	-32.5
Mg^{++}	-59.4	-21.6	-102.5
Ca^{++}	-47.1	-19.9	-86.9

The binding of the metal ion to O_1, O_3 and O_{10} has been investigated along bond directions forming an angle of 180° with C_2-O_1, C_3-O_3 and C_9-O_{10}, respectively. The maximum binding energies obtained along these directions are -76.2 kcal/mol for O_1, -62.1 kcal/mol for O_3 and -20.1 kcal/mol for O_{10}, corresponding to the optimized ligand-cation distances of 2.03 Å, 2.03 Å and 2.10 Å, respectively. The region around O_1 seems to exert a strong attraction towards the Na^+ ion. The interaction energy decreases, however, when the metal ion moves towards C_4. Binding to the oxygen of the peptide group (O_{10}) of glycylglycine gains less energy and even decreases when the metal ion turns around the peptide oxygen towards the $-NH_3^+$ group.

The most stable binding site is located in the bisectrix of the $O_1C_2O_3$ angle. The distances between both anionic oxygens (O_1 and O_3) and the metal ion have been optimized in this direction with respect to total binding energy. The most stable arrangement results at the distance 2.18 Å for Na^+, and the corresponding energy is -91.9 kcal/mol. This equilibrium distance is 0.1 Å shorter than Na.....O in Na^+-H_2O. It should be mentioned, however that this value agrees very well with the Na-O distances found in some biological systems.[20]

The absolute stabilization energies can be assumed to be too high, as an inevitable basis set superposition error occurs, due to the use of small basis sets. However, this error will not influence significantly the relative order. As only the relative order was of interest, a counterpoise correction seemed to be unnecessary. Comparison with calculation on smaller systems near HF-level indicates, that this correction would decrease the binding energies by a factor of about 0.75.

It was also intended to investigate how stable the peptide complex is compared to the ion's stabilization by its hydration energy.

It is clear that the use of the metal ligand interaction energy only is not sufficient to predict correctly whether or not a complex is formed in aqueous solution. It was pointed out[21] that in order to explain most of the properties of the hydrated ion correctly, one should consider at least two hydration shells. The calculated hydration energies per water molecule are shown in Table 2.

The metal ion is supposed to bind to the glycylglycine whenever the metal-ligand binding energy is greater than its binding to the water, which should be released from the ion's hydration shell. This should concern at least one water in the first and two of the second hydration shell. An important result of our investigation is, therefore, that binding of Na^+ to glycylglycine (at O_1 and O_3) appears more favourable than its binding to water, indicating the possibility of at least partial dehydration of the cation in favour of a binding to glycylglycine at O_1, O_3 or both oxygens of the COO^- group. However, towards the oxygen at the peptide group, Na^+ is not supposed to bind to the ligand.

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บทคัดย่อ

ได้ศึกษาการจับกันระหว่างไดเปปไทด์ glycylglycine กับ ไอออนของ Na^+ โดยใช้ ab initio LCAO-MO-SCF calculation พบว่าไอออนของโลหะมีแนวโน้มที่จะจับกับอะตอมออกซิเจนทั้งสองของกลุ่ม COO^- ในสภาพ zwitterion