Quantum Chemical Investigations on the Complexes of Ca^{2+} and Zn^{2+} with Aliphatic Dipeptides

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Several 1:1 complexes of Zn^{2+} with glycylglycine and of Ca^{2+} and Zn^{2+} with prolylglycine and glycylproline have been calculated within the Hartree–Fock method using a minimal GLO basis set. It was found that in spite of the fact that there are large differences in complex binding energy the relative stabilities of the different binding sites are the same in the case of Ca^{2+} and Zn^{2+} ions. Electronic density diagrams have been produced to illustrate the changes in electronic distribution caused by complex formation.

Introduction

In this work it was intended to gain more information about metal–dipeptide complexes by extending the study [1] in which we investigated the Ca^{2+} complexes of dipeptides consisting of glycyl and alanyl units and by expanding our recent experimental work [2, 3] with quantum chemical calculations. We were interested in obtaining information about coordination sites and geometries since these features are not available easily by experiment.

Experimental

Geometries of the Peptides and Complexes

The geometries of the peptides have been taken from refs. [4–6]. For glycylproline and prolylglycine the D-stereoisomeric forms have been used in the calculations. For the coordination of the metal ion to the dipeptide the following possibilities have been taken into account:

1) Coordination with both oxygens of the $-CO_2$ group.

2) Coordination with only one O of the carboxyl group.

3) Coordination with the oxygen of the peptide group.

4) Coordination with the peptide–oxygen and the amino group, if the peptide is in the anionic form.

5) Coordination with both oxygens of the $-CO_2$ group and the peptide – O.

6) Coordination with the NH_2 group, if the peptide is in the anionic form.

For a detailed geometrical description of the different coordination sites we refer to [1].

Technical Data

A minimal GLO basis set was used for all atoms [7, 1]. (For Ca: (8/4); for Zn: (8/4/2); both uncontracted). Since our systems are large from the viewpoint of quantum chemistry, it is not possible to use more extended basis sets.

For example, the glycylproline–Zn or the prolylglycine–Zn system consists of 60 electrons and 13 not-H-atoms and the calculation of the energy of one configuration requires about 150 minutes of CPU time on a Cyber 74 computer. The calculations were performed on the CDC Cyber 170/720 computer of the Interuniversitary Computing Center Vienna and the Cyber 74 computer of the University of Innsbruck. Details of the SCF program are given in ref. [8].

Results and Discussion

Zinc Complexes of Glycylglycine

In Table I the binding energies of the complexes are listed. Since it is known that the basis set superposition error leads to binding energies which are too high, the counterpoise method [10] was used to correct the energies of the complexes in the optimized geometries. Because this correction has only been performed at the optimized distances, the dis-

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TABLE I. Binding Energies of the Zinc Complexes of Glycylglycine.[a]

Complex	Zwitterionic		Anionic	
	Energy	Distance	Energy	Distance
1	−313.5	1.75	−439.2	1.74
2	−294.4	1.60	−398.7	1.58
3	−153.1	1.63	−327.6	1.62
4	–	–	−404.0	1.75
5	−324.2	1.85 2.05	−477.9	1.83 2.04
6	–	–	−300.1	1.69

[a]Distances in Å and energies in kcal/mol. Complexes 1, 2 and 3: Distance between Ca and O; Complex 4: The distance Ca–peptide-O is equal to the distance Ca–NH_2; Complex 5: First number: Ca–peptide-O, second number: Ca–CO_2 oxygens. 6: Distance between Ca and NH_2.

TABLE II. Energies of Protonation of the Zn Complexes of Glycylglycine (kcal/mol).

Complex	1	2	3	5
Energy	−142.74	−148.64	−84.19	−101.9

tance between Zn^{2+} and O is somewhat too small. Comparing our results with the Zn–O distances of another study [9] we estimate that our distances are about 0.15 Å too small.

As might be expected, the binding energies of the Zn–glycylglycine complexes are much higher than those of the corresponding Ca complexes [1]; the difference is about 150 kcal/mol. It should, however, be mentioned that some of this difference might be a consequence of the small distances. The order of the possible coordination sites is in principle the same. Complex 5, in which all three oxygens are coordinating, is the most stable one in both the zwitterionic and the anionic forms of the peptide. The next most stable one is the complex with bidentate coordination to the CO_2 group. Binding to the other possible sites gains less energy. The largest energetic difference between anionic and zwitterionic complexes can be found in the case of coordination to the peptide oxygen. This could be explained by the way that the zwitterionic form of the complex is destabilized in the close neighbourhood of the $-NH_3$ group and ion and profits most from the deprotonation.

Looking at the energies of protonation of the complexes (Table II) and comparing them with the calcium complexes [1], one can see that the order is exactly the same and the differences between

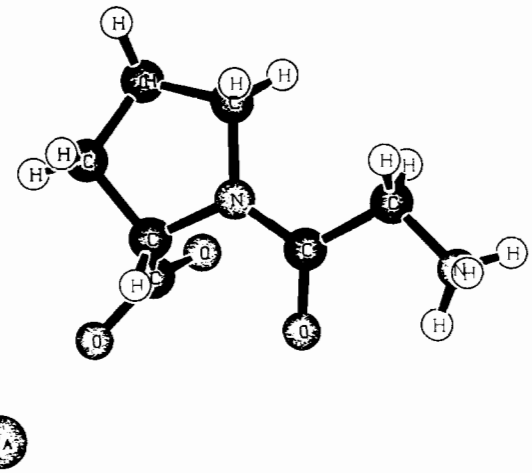


Fig. 1. Ca^{2+} coordinating to one oxygen of the carbonyl group of glycylproline.

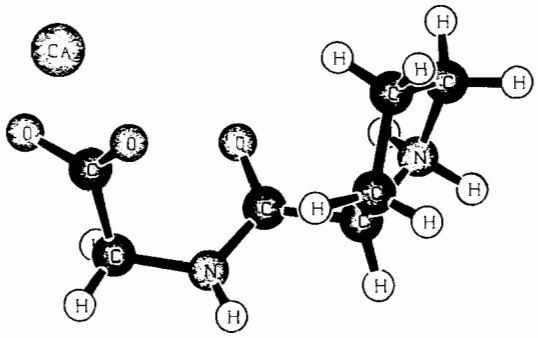


Fig. 2. Ca^{2+} coordinating to both CO_2 oxygens of prolylglycine.

the protonated and deprotonated complexes are always about 15 kcal/mol less in the case of the Zn complexes. That means that the zinc complexes are more acidic than the calcium complexes which are again more acidic than the peptides themselves. The experiment and also the high stabilisation energies of the calculated complexes show that zinc can also form a 1:2 complex with the peptide, which is dominating at high pH values. Although it would be interesting to investigate its differences in binding positions *etc.*, it has not yet been possible for us to perform calculations on these 1:2 complexes because of the size of the system.

Complexes of Glycylproline and Prolylglycine with Ca^{2+} and Zn^{2+}

In order to have some comparison with larger dipeptides, we also performed similar calculations on glycylproline and prolylglycine complexes. Figures 1 and 2 show examples of the complexes of the two

TABLE III. Binding Energies of the Complexes of Glycylproline and Prolylglycine with Ca and Zn.

Complex	Zwitterionic		Anionic	
	Ca^{2+}	Zn^{2+}	Ca^{2+}	Zn^{2+}
Glycylproline				
1				
Energy	−159.0	−315.3	−266.0	−443.8
Distance	2.37	1.85	2.34	1.85
2				
Energy	−145.2	−285.7	−242.9	−419.1
Distance	2.16	1.65	2.02	1.64
3				
Energy	−58.3	−157.8	−208.1	−330.1
Distance	2.22	1.62	2.13	1.61
4				
Energy	–	–	−244.7	NSC[a]
Distance			2.26	
6				
Energy	–	–	−173.3	NSC
Distance			2.16	
Prolylglycine				
Complex	Zwitterionic		Anionic	
	Ca^{2+}	Zn^{2+}	Ca^{2+}	Zn^{2+}
1				
Energy	−153.8	−312.7	−269.9	NSC
Distance	2.36	1.84	2.35	
2				
Energy	−145.3	−283.3	−220.0	−421.2
Distance	2.06	1.60	1.95	1.60
3				
Energy	NSC	−244.0	−226.2	−351.4
Distance		1.62	2.11	1.61
6				
Energy	–	–	−165.0	NSC
Distance			2.27	

[a]NSC: No convergence could be reached. 1–6: the same as in Table I.

peptides. In Table III, the binding energies of the complexes are listed. Again we applied the counterpoise method to correct the results. We have not taken into account the coordination type 5 (binding to all three oxygens, which is difficult in the case of glycylproline because of the rigid ring), but we have calculated the energies of position 6 where the ion is bound only to the $-NH_2$ group. Unfortunately, in some cases we could by no means reach convergency in the SCF procedure.

It can be seen that the binding energies are similar to those of the smaller dipeptides like glycylglycine, especially in the case of the calcium complexes. Also

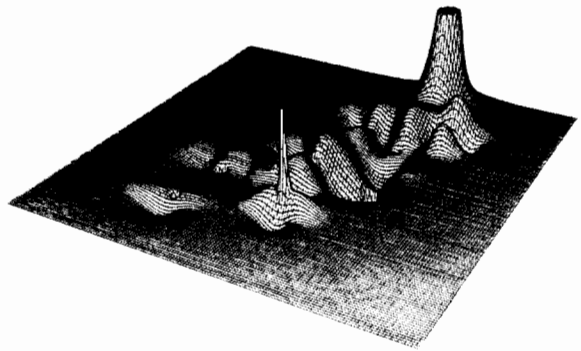


Fig. 3. Electronic density diagram of a Ca^{2+}–glycylglycine complex.

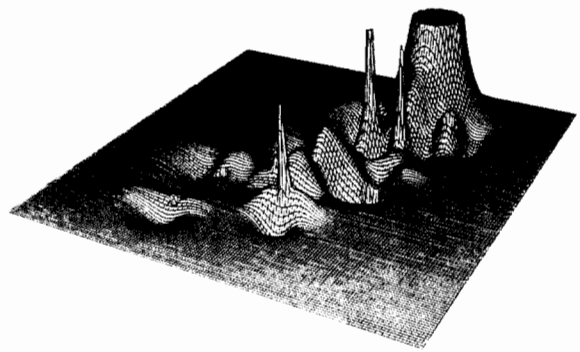
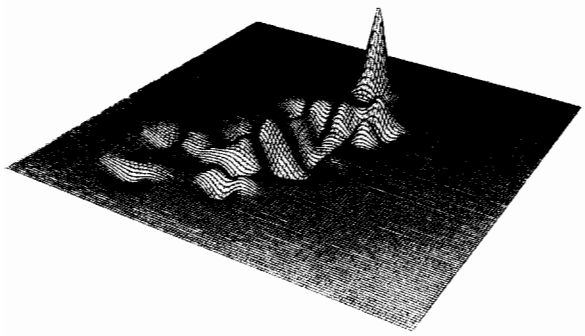


Fig. 4. Electronic density diagram of a Zn^{2+}–glycylglycine complex.

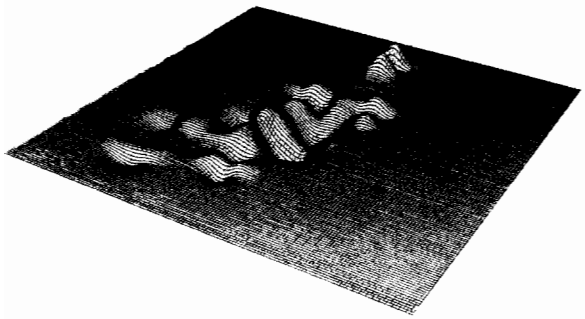
the differences between the peptides are not large. This can be compared with experimental data [2, 3], indicating the different positions of glycylproline and prolylglycine on the scale of stability of aliphatic dipeptide complexes. The numerical differences in the experimental stability constants are rather small. (pK values: Ca–glycylproline –2.57; Ca–prolylglycine –1.50; Zn–glycylproline –4.03; Zn–prolylglycine –3.58). The small calculated differences also seem to indicate that some of the experimental differences are due to sterical effects, as discussed in [2].

Electronic Density Diagrams

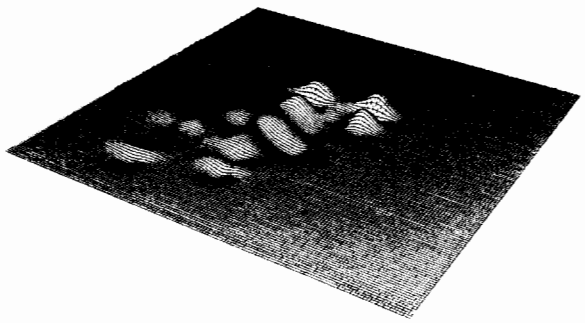
To illustrate the changes in electronic density arising upon complex formation we have used the Hartree–Fock wavefunction to plot perspective diagrams showing the density differences between the two components and the complex. It is known that the electronic density is an observable which can be calculated with good accuracy even with small basis sets [11]. As dipeptide we used glycylglycine since it is advantageous to have a planar molecule to get an illustrative diagram. The peptide in all plots has been oriented in such a way that the amino-N



(a)



(b)



(c)

Fig. 5. Electronic density differences for Ca–glycylglycine. The three diagrams correspond to distances of (a): 2.5, (b): 3.5, (c): 5.0 A between the ion and the coordinating oxygens of the CO_2 group.

is situated near the left lower edge of the plane, the peptide-O near the right lower and one carboxyl-O near the right upper edge.

Figure 3 shows the density differences when a Ca^{2+} ion coordinates to both CO_2 oxygens. In Fig. 4 the same is shown for Zn^{2+} instead of Ca^{2+}. One can see that the influence of Zn^{2+} on the whole peptide molecule is much stronger. In both pictures the peaks of the ions have been cut off. In Fig. 5 we calculated the density differences for different distances of Ca^{2+} to the coordinating CO_2 group to be larger than the equilibrium distance. It can be seen that even at 5 Å where there is no considerable charge transfer to calcium, the twofold positive ion already has a strong polarisation effect on the peptide.

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