Quantum Chemical Investigations on the Bonding of Calcium(II) to Aliphatic Dipeptides

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Several 1:1 complexes of calcium(II) with glycylglycine, glycyl-L-alanine and L-alanyl-L-alanine have been calculated within the Hartree-Fock method using a minimal GLO basis set. It was found that there are no significant differences in the stability of the complexes between the three peptides but large differences as far as the several possibilities of coordination are concerned.

Introduction

This work was intended to supply some information about the applicability of quantum theoretical calculations of main group metal complexes of dipeptides, being of interest within the context of our recent work on the properties of peptides and related substances and their metal complexes with experimental methods. This work deals with calcium complexes for several reasons. Calcium has 20 electrons, thus allowing *ab initio* calculations without difficulties, if minimal basis sets are used. Further, it forms mainly 1:1 complexes with peptides, as can be proved by experiment [7]. Thus the complexes dominating in nature can be calculated within an acceptable amount of computing time. Dipeptides are the simplest substances containing a peptide linkage and are therefore good subjects for the study of general properties of peptides. Finally, theoretical treatment is desirable for obtaining information about coordination sites and preferred geometries because these features cannot be ascertained easily by experiment.

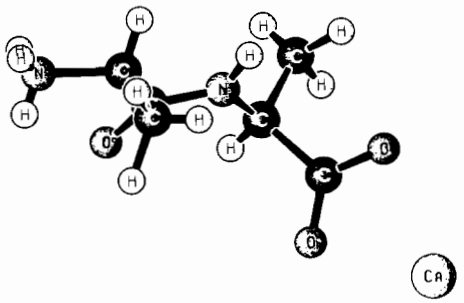

Fig. 1. Coordination of alanylalanine with both oxygens of the CO_2 group.

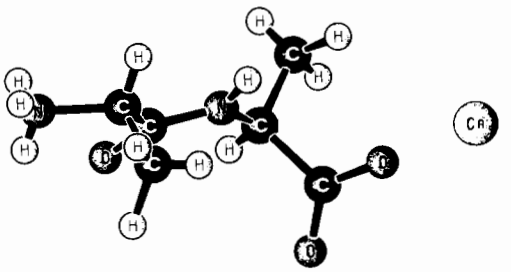

Fig. 2. Coordination with one CO_2 oxygen.

Ab initio calculations of calcium–peptide complexes have not been performed up to now. Some publications dealing with scf calculations of peptides are: [12], [11], [9], [10]. (Most of them deal with the characteristics of the peptide bond or with the conformation of glycylglycine.)

In some publications complex formation constants have been determined by either acid–base titrations or NMR investigations. Examples are [4], [6], [7], [15] and [16]. (Calcium complexes: only [7] and [16].)

Geometries of the Peptides and of the Complexes

The geometry of the peptides has been taken from the references [1], [2], and [3]. It was assumed that the calcium ion has the following possibilities to coordinate to the peptide:

1) coordination with both oxygen atoms of the $-CO_2$ group (Fig. 1). The distance of the metal ion from the O atoms was optimized by moving the Ca along a line defined by the condition that it always has the same distance from both oxygens.

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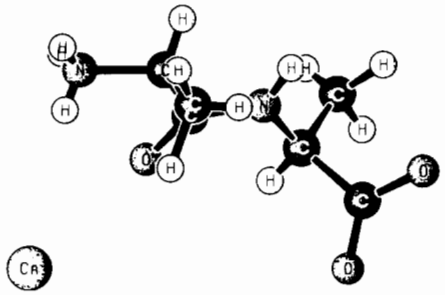

Fig. 3. Coordination with the oxygen of the peptide group.

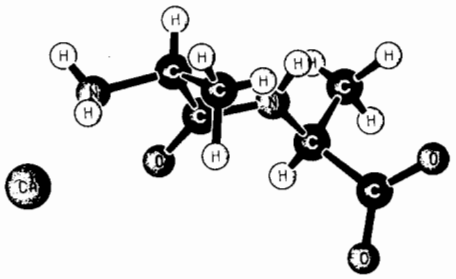

Fig. 4. Coordination at the peptide oxygen and at the NH_2 group.

2) Coordination with only one of the oxygen atoms of the CO_2 group (Fig. 2).

3) Coordination with the oxygen of the peptide group (Fig. 3).

In this and in the former case Ca···O-C was assumed to be linear.

4) Coordination at the peptide oxygen and at the amino group (Fig. 4). For this purpose the peptides were assumed to be in a conformation where the atoms N–C–C–O are in *cis*-configuration and in one plane with Ca and each other, calcium having the same distance from N and O (and from the 2 hydrogens in the NH_2 group). This complex is only possible if the peptide is in the anionic form.

5) A conformation in which calcium can interact with all three oxygen atoms of the peptide. A conformation of the peptide was chosen where the two $-CO_2$ oxygens have the same distances from the carbonyl O. The calcium is above the center of the so formed triangle (Fig. 5).

Quantum Mechanical Calculations

A minimal GLO basis set was used in all calculations. For Ca^{2+} a (8/4) basis set, optimized on the ion was taken, the exponents being (5141.0, 806.0, 312.0, 86.25, 11.55, 5.23, 0.942, 0.277/13.581, 2.902, 0.707). The basis sets of the other atoms were taken from ref. [5].

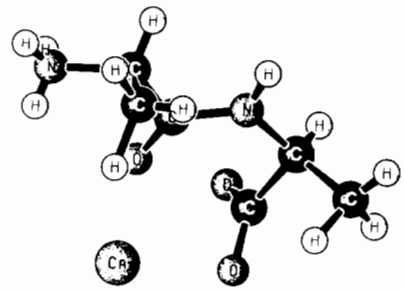

Fig. 5. Calcium coordinates with all three oxygens.

Because of the considerable size of the system (glycylglycine: 17 atoms, 9 not-H-atoms, 70 electrons; alanylalanine: 23 atoms, 11 not-H-atoms, 86 electrons) calculations with extended basis sets or CI calculations are not possible.

Even with our minimal basis the calculation of one alanylalanine–Ca conformation took about 200 minutes of CPU time which makes it unreasonable to calculate a complete energy surface.

All calculations were performed at the CYBER 120/720 computer of the Technical University of Vienna, using an SCF program of Ahlrichs, Lischka and Staemmler [8].

The distances of calcium from the peptides were optimized with a step width of 0.1 Å.

Results and Discussion

While there can be found only small and not significant stability differences between the peptides under investigation, the energies for the various coordination sites differ considerably (Table I). Assuming that differences of more than 5 kcal/mol are significant, the following can be stated:

a) Complexes with the NH_3 form of the peptide: The most stable geometry is the one in which Ca is coordinated to all 3 oxygen atoms.

About the same energy is gained when calcium coordinates only with the two CO_2 oxygens (both about 190 kcal/mol). The conformational change within the peptide leads only to a small energetic difference.

Bonding is weaker if monodental complexation to the CO_2 group occurs.

By far the lowest energy results from bonding of Ca to the carbonyl oxygen.

b) Complexes with the anionic forms of the peptides:

In general there exists the same order as stated above, but the complex with coordination to all three oxygens is now by far the most stable one. The geometry 4) which is only possible in peptides with NH_2 amino group is more stable than one with

TABLE I. Binding Energies of the Complexes.*

	Gly-Gly	Gly-Ala	Ala-Ala	Gly-Gly	Gly-Ala	Ala-Ala
Form	$-NH_3$	$-NH_3$	$-NH_3$	$-NH_2$	$-NH_2$	$-NH_2$
Complex a)	−164.6	−158.2	−163.1	−258.9	−266.0	−260.8
Distance 1)	2.36	2.36	2.34	2.36	2.38	2.30
Complex b)	−144.6	−138.9	−135.1	−232.8	−241.2	−234.3
Distance 2)	2.11	2.10	2.11	2.08	2.07	2.08
Complex c)	−41.2	−54.2	−48.2	−196.4	−199.9	−195.6
Distance 2)	2.20	2.20	2.21	2.13	2.12	2.14
Complex d)	–	–	–	−218.9	−218.4	−211.4
Distance 3)	–	–	–	2.33	2.35	2.34
Complex e)	−160.6	−154.3	−152.9	−302.7	−286.6	−291.6
Distance 4)	2.49/2.33	2.54/2.36	2.48/2.32	2.46/2.31	2.49/2.30	2.44/2.28

*All distances in Å and all energies in kcal/mol. 1) Between the Ca and each one of the two CO_2 oxygens. 2) Between Ca and the coordinating O. 3) Distance between Ca and the peptide O and the NH_2 N. 4) First number: Ca–peptide O; second number: Ca–CO_2 oxygens. a) Coordination with both CO_2 oxygens. b) Coordination with one CO_2 O. c) Coordination with the O of the peptide group. d) The Ca is coordinating with the amino N and the peptide O. e) Calcium interacts with all three oxygens.

coordination at the carbonyl O and less than one with monodental CO_2 coordination.

Regarding the energies of protonation of the peptides and complexes in the various geometries used (Table II), it can be seen that the stabilisation energy values differ strongly, with alanylalanine having the lowest.

Accuracy of the Calculations and Comparison to Experimental Results

Though we know that the use of a minimal basis set cannot lead to very accurate energies, especially in the case of complex formations, no better SCF is calculation can be performed with systems of such size at this time. If no exact energies are expected, minimal basis sets lead in general to good geometries and relative energies within one series.

TABLE II. Energies of Protonation of the Peptides and Complexes (kcal/mol).

	glycylglycine	glycylalanine	alanylalanine
peptide in geometry a), b) and c)*	−258.3	−286.8	−167.7
peptide in geometry d)	−271.1	−168.7	−62.9
peptide in geometry e)	−210.3	−269.4	−170.5
complex a)	−158.3	−163.5	−64.9
complex b)	−166.9	−139.7	−66.8
complex c)	−99.6	−130.9	−73.4
complex e)	−115.1	−132.0	−27.6

*a), b), c), d), e): same as in Table I.

To avoid the main disadvantage of small basis sets, the superposition error which leads to an overestimated bonding energy, we used the counterpoise method [19] (*i.e.* the complex formation energy is calculated as the difference between the complex (calculated as usual) and the sum of peptide and calcium (both calculated with all the functions of the complex)). These values are given in Table I. To allow comparisons, we have added the uncorrected vaues in Table III.

The calculated energies of stabilisation are about half of the hydration energy of Ca(II) [18] (that is the binding energy of two water molecules of the first and four of the second shell) in the case of the NH_3 forms of the complexes (a, b, and e) and about 50 per cent higher if the NH_2 forms of the complexes are considered (Table I). Thus it is indicated that only weak complexes exist in aqueous solution and those mainly in basic solutions. These conclusions are in good agreement with the experimentally determined [7] small complex formation constants, (GlyGly: pK = −2.04; GlyAla: pK = −2.02; AlaAla: pK = −2.15) which are also close in value.

Our results confirm that a conformation where Ca is coordinated only to oxygen atoms is most probable, in agreement with the conclusions drawn from experimental data [14, 17, 7].

Acknowledgements

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TABLE III. Binding Energies of the Complexes without Correction of the Basis Set Superposition Error.*

	Gly-Gly	Gly-Ala	Ala-Ala	Gly-Gly	Gly-Ala	Ala-Ala
Form	$-NH_3$	$-NH_3$	$-NH_3$	$-NH_2$	$-NH_2$	$-NH_2$
Complex a)	−195.1	−191.0	−194.7	−295.1	−300.5	−297.6
Complex b)	−169.2	−165.9	−160.6	−260.6	−269.2	−261.5
Complex c)	−57.8	−70.0	−56.9	−216.5	−212.1	−214.1
Complex d)	–	–	–	−246.9	−246.6	−235.9
Complex e)	−201.1	−192.9	−192.6	−346.4	−329.7	−335.5

*a)–e): the same as in Table I.

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