Investigation of Metal Ions Induced Conformational Changes in *N*-Acetyl Alanine Methyl Ester

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Abstract

The conformation of *N*-acetyl alanine methyl ester $CH_3CONHCH(CH_3)COOCH_3$ is determined by CNDO/2 and *ab initio* calculations with minimal GLO basis sets. The binding sites of small monovalent cations to the ligand are investigated by the *ab initio* method. The chelate geometry involving peptide and ester carbonyl groups was found to be the most preferential conformation.

Introduction

Numerous metal ions in living organisms are bound by proteins [1]. The nature and extent of metal-protein interaction is therefore a most important and fundamental question. Since proteins are complex macromolecules associated with many technical problems in their study, it is worthwhile to investigate simpler molecules still containing some of the essential features and reactive sites of the macromolecules. In previous papers [2–7], small peptides have been used as model compounds for metal complex formation.

In this work, we have investigated the metal ion influence on the conformation of another model compound, containing both peptide and ester functional groups, *N*-acetyl alanine methyl ester. This compound has been found to be biologically active in enzyme kinetics [8] and its protonation has been studied previously [9]. The conformation of the compound is characterized by the values of the angles $\theta = (COCH_3)$, $\phi = (NHCOCH_3)$ and $\psi = (COOCH_3)$ and will be denoted as (θ, ϕ, ψ) (Fig. 1). As metal ions forming complexes with the compound, we have chosen the small monovalent metal ions Li^+ and Na^+.

Method

Most geometrical parameters of $CH_3CONHCH(CH_3)COOCH_3$ were taken from refs. 10 and 11 and are listed in Table I. They were kept constant

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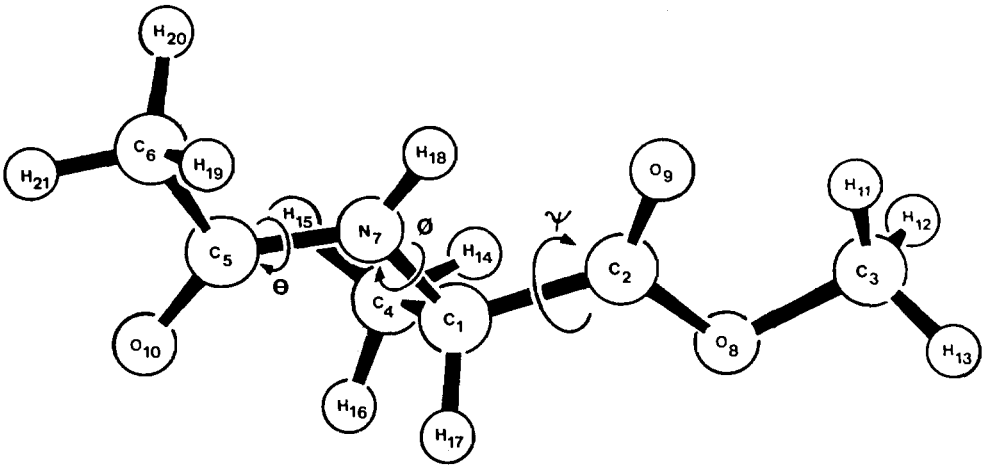

Fig. 1. Molecular structure of *N*-acetyl alanine methyl ester characterized by (ϕ, θ, ψ).

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TABLE I. Geometrical Parameters Used in the Calculations

Bond lengths	(Å)	Bond angles	(deg)
C1–C2	1.53	OCO	122
C1–C4	1.54	COC	104.5
C5–C6	1.53	CNH	116
C2–O8	1.43	CNC	121
C3–O8	1.47	NCO	125
N7–C5	1.32	NCC	114
C2–O9	1.24	tetrahedral angle	109.47
C5–O10	1.24		
N7–H18	1.00		
C–H	1.09		

throughout the calculations. The possible conformations of this compound were examined with regard to the angles θ, ϕ, and ψ by CNDO/2 [12] and by the *ab initio* LCAO–MO–SCF method with minimal GLO basis set [13]. The metal position has been optimized only by the *ab initio* method, as CNDO/2 had to be expected to fail in this procedure [13–16]. As already mentioned in a previous paper [17], the basis set superposition error leading to an overestimated stabilization energy will not influence significantly the relative order of stabilities, and the use of a minimal basis set is therefore an acceptable way to reduce the computational effort.

N-acetyl alanine methyl ester has three reactive sites available for binding metal ions as illustrated in Fig. 2.

The CNDO/2 calculations were performed at the IBM 3010 computer of Chulalongkorn University while the *ab initio* data were computed at the CDC Cyber 730 computer of the University of Innsbruck.

Results

I. Conformation of the Ligand

The conformation of *N*-acetyl alanine methyl ester was investigated by rotating the angles θ, ϕ and ψ. Both CNDO/2 and *ab initio* optimized energies show that the conformation with $(\theta, \phi, \psi) = (0, 0, 0)$ is the most favoured one, for which CNDO/2 gives a total energy of -118.02928 a.u. and *ab initio* -435.27883 a.u. This optimum conformation is expected to result due to partial double bonds and a weak H-bond between NH and O9.

II. Metal Ion Complexes

The results of the *ab initio* binding energies for several possible Li^+ and Na^+ complexes are presented in Table II.

II.1 Li^+-complex

The binding energies for the Li^+–O8, Li^+–O9 and Li^+–O10 complexes are -21.1, -26.8 and -41.4 kcal/mol, respectively, showing that the O10 site is favoured over the others. The optimized distance for $Li^+\cdots$O10 is 1.76 Å (Fig. 2). Rotation of the OCH_3 group of the Li^+–O10 complex gives a binding energy of -24.3 kcal/mol, and the rotation barrier with and without Li^+ remains almost identical ($\sim$17 kcal/mol).

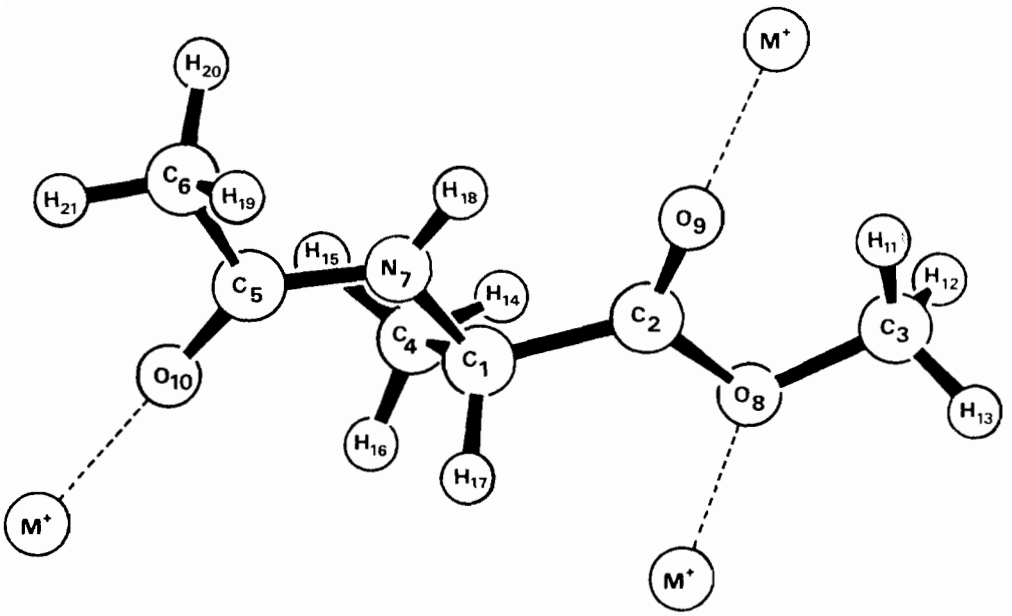

Fig. 2. Coordination at the ester oxygen (O8) of the OCH_3 group (denoted as M^+–O8 complex), at the carbonyl oxygen (O9) of the ester group only (denoted as M^+–O9 complex), and at the carbonyl oxygen (O10) of the peptide group (denoted as M^+–O10 complex).

TABLE II. Optimized Values of Parameters Calculated with *ab initio* Method Using Minimal GLO Basis Set[a]

System (θ, ϕ, ψ)	Binding site of metal ion	Optimized distance $M^+ \cdots O$ (Å)	Total energy (a.u.)	Binding energy (kcal/mol)
Li^+-complex				
(0, 0, 0) Fig. 2	O8	1.85	−441.72234	−21.1
(0, 0, 0) Fig. 2	O9	1.80	−441.73157	−26.8
(0, 0, 0) Fig. 2	O10	1.76	−441.75476	−41.4
(7, 115, 0) Fig. 3	O9–O10	1.90	−441.75810	−43.5
(0, 0, 0) as Fig. 4	O10	1.76	−441.72756	−24.3
(0, 0, 0) as Fig. 4	O8–O9	2.05	−441.70305	−8.9
(0, 180, 0) Fig. 3	O9–O10	2.00	−441.24653	destabilized
Na^+-complex				
(0, 0, 0) Fig. 2	O10	2.09	−584.45939	−33.2
(4, 115, 0) Fig. 2	O9–O10	2.18	−584.46758	−38.3

[a]The total energies of Li^+ and Na^+ are −6.40997 and −149.12772 a.u., respectively.

The chelate geometry in which Li^+ is simultaneously bound to O8 and O9, with the conformation (0, 0, 0) (Fig. 4) gives a binding energy of only −8.9 kcal/mol.

The simultaneous binding of Li^+ to O9 and O10 after optimization of (θ, ϕ, ψ) and the distance between Li^+ and both O9 and O10 is predicted to be the most preferential conformation. This chelate geometry has the conformation (7, 115, 0), where C2, O9, O10, C5 and Li^+ are in the same plane and the $O9 \cdots Li^+$ and $O10 \cdots Li^+$ distances are both 1.90 Å (Fig. 3). The corresponding energy is −43.5 kcal/mol. The simultaneous binding to both O9 and O10 at the conformation (0, 180, 0), with the rotation of the OCH_3 group was also investigated. The result indicates that this conformation is not well stabilized.

II.2 Na^+-complex

Since all possible binding sites have been studied for the Li^+-complex, it seemed unnecessary to do so for the Na^+-complex, too. Only the previously most stabilized chelate conformation and the Na^+–O10 complex have been studied, therefore.

Similar to the Li^+-complex, the optimization predicts the chelate geometry as the more stable one, characterized by the angles (4, 115, 0). The C2, O9, O10, C5 and Na^+ are located in one plane; the

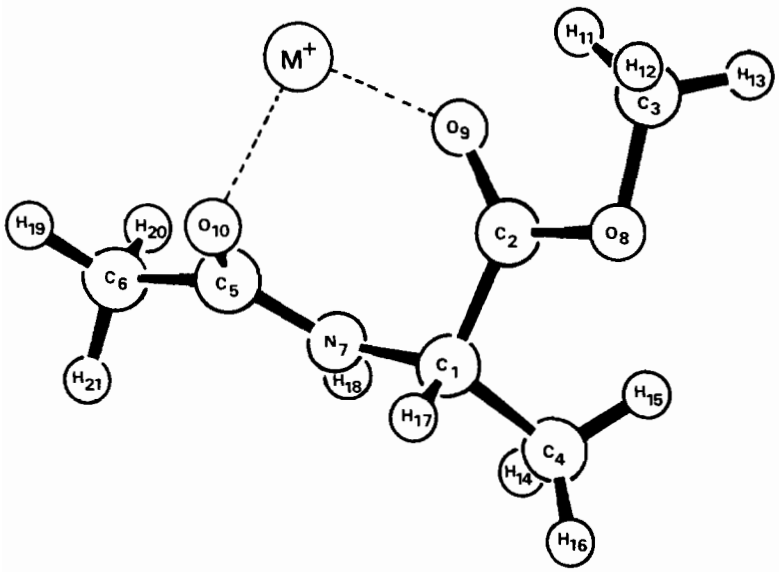

Fig. 3. Chelate conformation in which the metal ion is simultaneously binding to both carbonyl groups (09 and O10) (denoted as chelate complex).

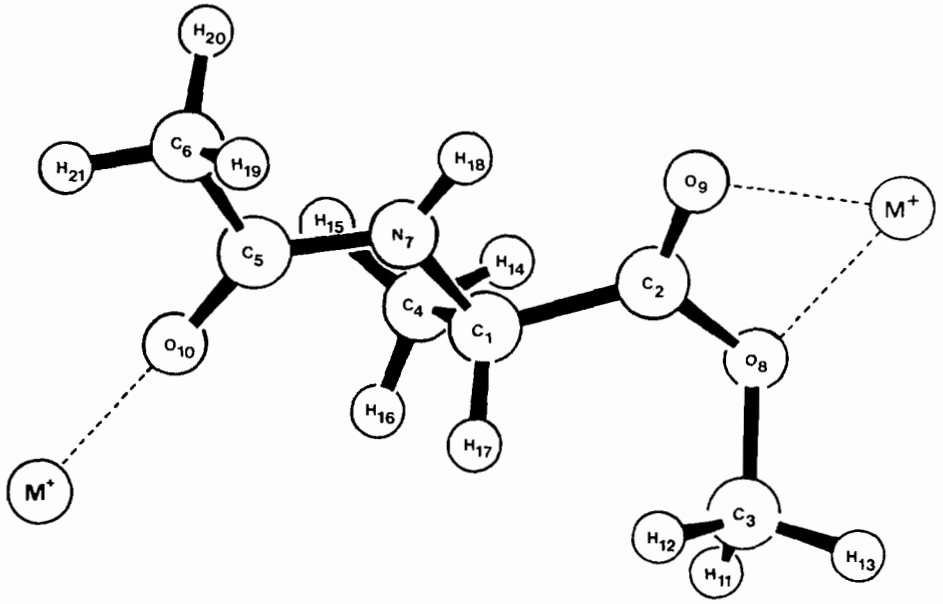

Fig. 4. The metal ion is simultaneously binding to the carbonyl oxygen (O9) of the ester group and the ester oxygen (O8) of the OCH_3 group with the OCH_3 group rotated 180°.

distances O9···Na^+ and O10···Na^+ are 2.18 Å (Fig. 3). The corresponding binding energy is −38.3 kcal/mol, whereas the binding energy for the Na^+–O10 complex is only −33.2 kcal/mol with a O10···Na^+ distance of 2.09 Å (Fig. 2).

Discussion

The results show that the amido group is clearly favoured over an ester group for the binding of small monovalent cations. It is to be expected, therefore, that in larger biomolecules the affinity of metals is also larger for the peptide bonds compared to the ester functional groups. Similar results have been obtained by Pullman and co-workers [18]. One of the most interesting results, however, is the finding that a second functional group, like the ester carbonyl in this model, in the vicinity of the peptide bond can lead to a chelate binding, which is associated with a conformation change. One can conclude, therefore, that even small monovalent cations can alter significantly the conformation of biomolecules provided there exists a suitable functional group near the peptide binding site of the metal.

Our results also seem to confirm conclusions drawn from studies on the reaction of *N*-acetyl alanine methyl ester with H^+ and $RH_3NH_3^+$, in which it has been postulated [9] that the structure of the reaction product should be a chelate conformation, similar to those found by us for Li^+ and Na^+ complexes.

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