Conformational Analysis of Be(II) and Mg(II) Complexes of *N*-Acetyl Alanine Methyl Ester

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Abstract

Conformational changes of *N*-acetyl alanine methyl ester upon binding of Be(II) and Mg(II) have been investigated by means of *ab initio* MO-SCF calculations with minimal basis set. Results obtained with single step optimized geometries are compared with those computed with full energy gradient optimization. The latter proved to be of far superior quality, but both methods lead to the same prediction towards the most stable complex structure, which are chelate complexes with simultaneous ion binding to peptide and ester group. This conformation involves drastic structural changes in the ligand molecule, hence indicating the ions' ability to induce some conformational changes also in biological macromolecules with similar functional groups.

Introduction

Reactive sites of proteins and enzymes interact strongly with metal ions [1]. These interactions can induce conformational changes and hence influence the structure and reactivity of the biomolecules. Studies of such ion–molecule interactions therefore provide valuable information even when conducted on smaller model systems, as long as they still contain the main features of the reactive sites of the macromolecule.

The model system *N*-acetyl alanine methyl ester [$CH_3CONHCH(CH_3)COOCH_3$] has already served this purpose in a previous study [2] proving that remarkable conformational changes are induced even by the weaker interacting alkali metal ions Li(I) and Na(I). The characteristic features of this compound are the peptide-like –CONHCHR– group and the existence of two carbonyl functions with one ester oxygen in close vicinity, providing therefore secondary binding sites for the metal ion, with or without conformational changes.

Experimental relevance of this compound has been found in studies on cationic hydrogen bonds of peptide-like molecules [3–5], in enzyme kinetics [6] and as elastase inhibitor [7]. *Ab initio* molecular orbital methods have been used for providing both energetic and structural data for the molecule and its metal ion complexes [2, 8].

In this work, these studies have been extended to the strongly interacting ions Be(II) and Mg(II) which could be expected to produce even stronger structural changes. Further, a methodical improvement has been introduced compared to the previous study [2] by fully optimizing all geometrical parameters and systematic comparison with the more simple commonly used stepwise optimization of a few single parameters.

Method

Ab initio MO-SCF calculations had to be performed with a minimal GLO basis set [9] due to the size of the system and the highly time consuming optimization procedure. Although absolute energies computed with the small basis set are considerably too high, relative differences could be expected to be satisfactory as already shown for comparable systems [10–12]. The geometry of the ligand in the single step optimization is the same as in our previous work [2]. The full geometry optimization of *N*-acetyl alanine methyl ester and its complexes was carried out by simultaneous energy gradient minimization, starting from the same conformation as in the single step process.

The single step optimizations were performed at the IBM 3031/08 computer of Chulalongkorn University while the simultaneous energy gradient minimizations were computed at the CDC Cyber 840 computer of the University of Innsbruck. The HONDO program [13] was used in all calculations.

Results and Discussion

The optimized geometries, total energies and binding energies of the ligand and its complexes with

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TABLE 1. Optimized geometrical parameters, total energies and binding energies of all system by single step optimization

System	Binding site	M(II)...O (Å)	$(\theta, \phi, \psi, \beta)$ (°)	Dihedral angle (°)	Total energies (a.u.)	Binding energies (kcal/mol)
Ligand			0, 0, 0, 0		−435.3040	
Be(II)					−12.5767	
Mg(II)					−185.6282	
Be(II) complex						
	O8	1.51	0, 0, 0, 0		−448.0472	−104.5
	O9	1.46	0, 0, 0. 0		−448.0908	−131.8
	O10	1.45	0, 0, 0, 0		−448.1432	−164.2
	O8–O9	1.78	0, 0, 180, 0		−448.0144	−83.9
	O8–O10	1.56	5, 129, 180, 0	C5O10O8C2 = 78.3	−448.1541	−171.6
	O9–O10	1.54	15, 124, 0, 0	C5O10O9C2 = 75.1	−448.1820	−189.1
Mg(II) complex						
	O8	1.88	0, 0, 0, 0		−621.0493	−73.5
	O9	1.81	0, 0, 0, 0		−621.0706	−86.9
	O10	1.68	0, 0, 0, 0		−621.1157	−115.2
	O8–O9	2.05	0, 0, 180, 0		−621.0493	−68.9
	O8–O10	1.95	2, 121, 180, 0	C5O10O8C2 = 84.0	−621.1359	−127.8
	O9–O10	1.90	14, 120, 0, 0	C5O10O9C2 = 78.0	−621.1532	−138.7

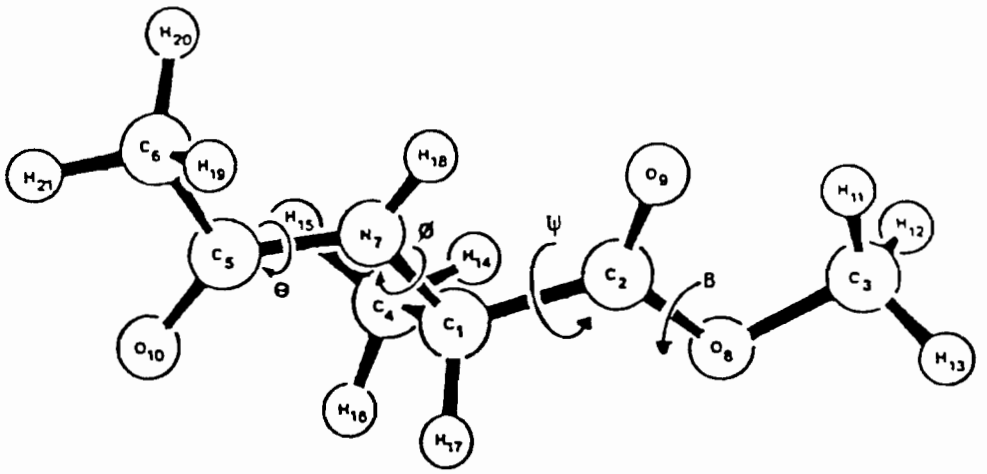

Fig. 1. *N*-Acetyl alanine methyl ester with conformation $(\theta, \phi, \psi, \beta) = (0, 0, 0, 0)$.

Be(II), Mg(II) by single step optimization and simultaneous energy gradient minimization are summarized in Tables 1 and 2, respectively. The atom numbering and the notation of geometrical parameters are shown in Fig. 1.

Single Step Optimization

The total energy of *N*-acetyl alanine methyl ester calculated for the previous conformation [2] is −435.3040 a.u. This value differs slightly from that of ref. 2, due to the use of the HONDO program instead of the previously used SCF program.

When the metal is located near O8, O9 or O10 (Fig. 2), the results are similar to those for alkali ion

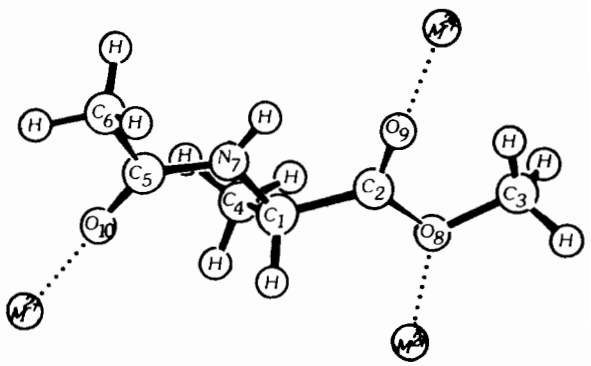

Fig. 2. Metal ion binding to O8, O9 or O10.

TABLE 2. Optimized geometrical parameters, total energies and binding energies of all system by simultaneous energy gradient minimization

System	Binding site	M(II)...O (Å)	$(\theta, \phi, \psi, \beta)$ (°)	Dihedral angle (°)	Total energies (a.u)	Binding energies (kcal/mol)
Ligand			−2.0, −1.9, −2.8, 1.5		−435.9208	
Be(II) complex						
	O8	1.60	−2.8, −1.7, −3.4, 2.0		−448.6704	−108.5
	O9	1.45	−1.9, −1.9, 1.7, 1.4		−448.6902	−120.9
	O10	1.45	−1.9, −2.3, −6.3, 1.7		−448.5934	−60.2
	O9–O10	Be...O9 = 1.57 Be...O10 = 1.53	16.3, 122.4, −3.1, 1.6	C5O10O9C2 = 82.0	−448.7767	−175.2
Mg(II) complex						
	O8	1.90	−2.7, −1.7, −3.4, 1.9		−621.6700	−75.9
	O9	1.81	−1.8, −1.9, −1.8, 1.4		−621.6738	−78.3
	O10	1.68	−2.0, −2.0, −4.9, 1.7		−621.6559	−67.1
	O8–O10	Mg...O8 = 2.26 Mg...O10 = 2.15	10.4, 119.1, 179.7, 1.0	C5O10O8C2 = 91.5	−621.7122	−102.4
	O9–O10	Mg...O9 = 1.91 Mg...O10 = 1.87	16.2, 118.9, −2.2, 1.0	C5O10O9C2 = 87.0	−621.7561	−130.0

complexes [2]. The oxygen of the peptide linkage (O10) is the preferred binding site for metal ions. The optimized distance for Be(II)...O10 is 1.45 Å and the corresponding binding energy is −164.2 kcal/mol whereas the Mg(II)...O10 distance is 1.81 Å and the ion binding energy is −115.2 kcal/mol (see Table 1).

The chelate conformation in which Be(II) or Mg(II) are simultaneously bound to O9 and O10 (Fig. 3(c)), after geometry optimization concerning angles $\theta, \phi, \psi, \beta$ and metal–ligand distance, is predicted to be the most favourable one, as for Li(I) and Na(I) complexes. The optimized chelate geometry of the Be(II) complex is characterized by $(\theta, \phi, \psi, \beta) \approx (15, 124, 0, 0)$ and the dihedral angle C5O10O9C2 ≈ 75.1°. The Be(II)...O9 and Be(II)...O10 distances

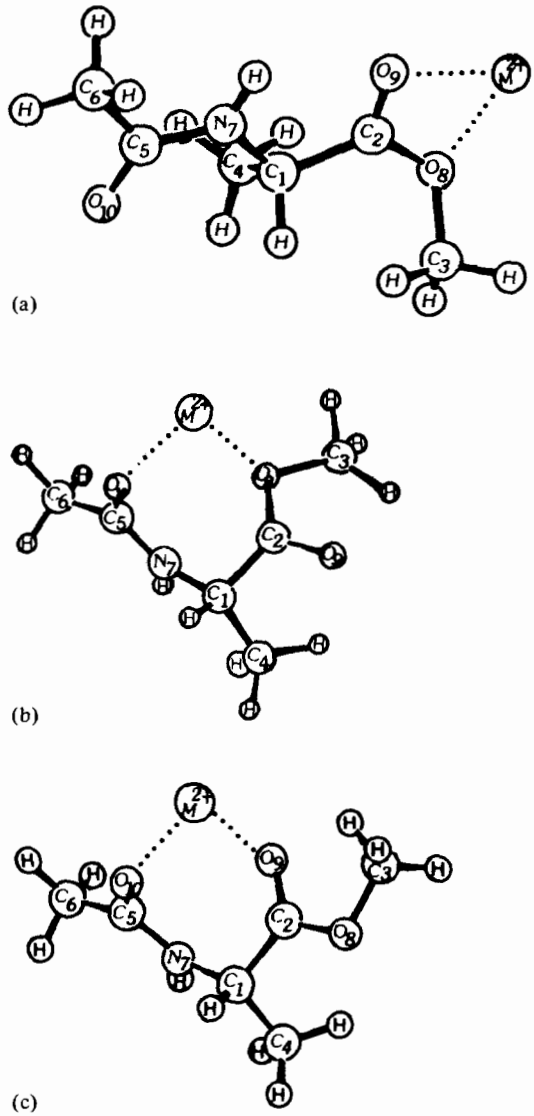

Fig. 3. Chelate conformations in which metal ion is binding to: (a) O8 and O9, (b) O8 and O10, (c) O9 and O10.

are both 1.54 Å (Table 1). The corresponding binding energy is −189.1 kcal/mol.

The optimized chelate geometry of the Mg(II) complex is characterized by angles $(\theta, \phi, \psi, \beta) = (14, 120, 0, 0)$ and the dihedral angle C5O10O9C2 of 78.0°. Mg(II)...O9 and Mg(II)...O10 are both 1.90 Å, the corresponding binding energy is −138.7 kcal/mol.

The relative order of binding energies to the different sites is identical to the one found for Li(I) and Na(I) complexes, and the relationship between optimized binding distance of ions to the ligand and the ionic radii of the metal ions is linear, indicating that the binding of all ions is essentially based on the same mechanism.

Simultaneous Energy Gradient Minimization

In this part, the ligand *N*-acetyl alanine methyl ester and its complexes were optimized by the forces relaxation method. The angles characterizing the conformation did not change significantly (only about +2–3°) (cf. Table 2) compared to the single step optimized geometry, but the total energy of free ligand decreases to −435.9208 a.u., which is 387 kcal/mol lower than obtained with the single step optimization procedure. This clearly indicates that the relaxation of the molecule is a most relevant procedure in order to find the energy minimum within a given basis set.

The results obtained by simultaneous energy gradient minimization for local binding minima near O8, O9 or O10 differ from the single step optimization data. O9 is found to be the most stable binding site followed by O8 and O10, and there is no obvious relationship between binding energy and metal–ligand distance. The optimized Be(II)...O9 distance is 1.45 Å and $\theta, \phi, \psi, \beta$ change by −1.9, −1.9, 1.7, 1.4° compared to the free ligand. The corresponding binding energies are −120.9, −108.5 and −60.2 kcal/mol for O9, O8 and O10 respectively, which is considerably less than those obtained in single step optimization. The Mg(II) complex gives similar results. The favoured binding site is O9 with the metal–ligand distance 1.81 Å. The angles $\theta, \phi, \psi, \beta$ change by −1.8, −1.9, −1.8, 1.4° and the binding energy is −78.3 kcal/mol.

Similar to the results of monovalent and divalent cation complexes in the single step optimization, the forces relaxation method predicts a simultaneous binding of ions to O9 and O10 forming a chelate complex to be the most preferential conformation (Fig. 3(b)). The chelate Be(II) complex gives Be(II)...O9 and Be(II)...O10 distances of 1.57 and 1.53 Å, respectively, and $\theta, \phi, \psi, \beta$ are equal to 16.3, 122.4, −3.1, 1.6° and the dihedral angle C5O10O9C2 is 82.0°. The corresponding binding energy is −175.2 kcal/mol. The angles differ only by about ±2° from the single step optimized conformation but several bonding distances become longer due to the molecular backbone relaxation (cf. Table 3). The Mg(II) complex gives Mg(II)...O9 and Mg(II)...O10 distances as 1.91 and 1.87 Å, respectively, and $\theta, \phi, \psi, \beta = 16.2, 118.9, -2.2, 1.0$. The dihedral angle is 87.0° and the corresponding binding energy is −130.0 kcal/mol.

TABLE 3. Optimized bond lengths, bond angles of Be(II) and Mg(II) chelate complexes after simultaneous energy gradient minimization

	Be(II) complex	Mg(II) complex
Bond lengths (Å)		
C1–C2	1.70	1.70
C1–C4	1.73	1.73
C1–N7	1.57	1.56
C2–C3	2.21	2.20
C2–O8	1.45	1.44
C2–O9	1.33	1.36
C3–O8	1.65	1.64
C3–H11	1.31	1.31
C5–C6	1.65	1.66
C5–N7	1.47	1.48
C5–O10	1.46	1.46
O9–M(II)	1.57	1.91
O10–M(II)	1.53	1.87
Bond angles (°)		
C2–C1–N7	107.4	108.3
C4–C1–N7	104.4	111.1
C2–C1–C4	108.6	108.6
C1–C2–O8	103.9	105.1
C1–C2–O9	117.6	115.1
O8–C2–O9	138.3	139.5
C6–C5–N7	107.3	106.3
C6–C5–O10	124.0	125.4
N7–C5–O10	128.6	128.1
C1–N7–C5	114.2	113.4
C2–O9–M(II)	119.7	121.2
C5–O10–M(II)	110.6	113.8
O9–M(II)–O10	108.2	88.6

Conclusions

Both single step optimization and simultaneous energy gradient minimization lead to the same prediction of the optimized conformation of ligand and its divalent cation complexes, namely that the chelate geometry in which the metal ion binds to both O9 and O10 is the absolute minimum of the interaction surface. The result indicates the findings of our previous study [2] to be reliable in this aspect too, and confirms that the metal ions have a strong affinity to both peptide bond and a second functional group, like the ester carbonyl in this model

compound. Such a chelate conformation, however, implies serious changes in structure. It can be concluded, therefore, that metal ion binding can be the reason for severe changes in conformation of macromolecules as well.

From the methodical viewpoint, our study allows also some relevant conclusions. Although it seems, that the commonly used single step optimization procedure allows qualitative predictions of the complex conformation with highest stability, already relative ordering of intrinsic affinities to the various binding sites can be erroneous.

Further, stabilization energy values obtained after the energy gradient minimization are considerably lower and hence more realistic than the ones obtained by single parameter optimization. Thus the binding energies usually strongly overestimated by small basis set calculations due to basis set superposition error, become rather similar to those obtained with much more extended basis sets. This seems to be another reason to justify the higher computational effort needed for the full geometry optimization and to provide more reliability for calculations even with minimal basis sets as used in this work.

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