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Comparing the ion affinity of two ionophores: Theoretical study of alkali earth metal ion–nano tubular cyclic peptide complexes

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ABSTRACT

The theoretical study of ion affinity of cyclic peptides containing L-proline (Cyclo(L-Pro)$_3$ and Cyclo(L-Pro)$_4$) with alkali earth metal ions has been carried out using the DFT methods. The metal binding affinity of these cyclic peptides has been evaluated using the binding energy. For both peptidic systems, the binding energies increased as $Be^{2+} > Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$ in the gas phase. The orbital nature of different interactions between the metal cations and the cyclic peptides has been analyzed by means of NBO. The ion affinity of both cyclic peptides in bulk water has been considered, too. In addition, the micro-solvation effect on the ion affinity of both cyclic peptides has been studied in the gas and bulk water phases. The dispersion corrected binding energies of complexes calculated and compared with uncorrected results.

1. Introduction

Ionophores are particular molecules that bind and transport ions selectively [1]. To design useful ionophores, various factors such as host-guest size complementarity, rigidity of host molecule, and ion dipolar moiety orientations in host-guest complexes are important [2].

Small cyclic peptides show a large class of biologically important molecules and have been found to be ion channel adapters, agonists and/or antagonists at specific receptor [3–7]. Compared to their linear precursors, they are more stable to degradative peptidases, more bio-available, and represent higher selectivity, potential diversity, and entropic advantages within molecular recognition [8–10].

Many of these compounds are antibiotic or antifungal that these properties also arise from the ability to bind and transport metals across biological membranes. Thus, the study of metal cation–cyclic peptide complexes is significant to understanding and predicting the bioactivity and distribution of metals in biological systems [11]. The understanding of stereochemical requirements is needed for the study of binding of cyclic peptides with metal ions and the determination of types of force and the factors responsible for coordination together with the type and mode in which it occurs [12]. The formation of metal cation–cyclic peptide complexes depends on the charge and size of cation. It also is affected by solvent and the conformation of cyclic peptide [13]. Most of the metal cation–cyclic peptide complexes play an important role in biological processes, for example, ion-transfer, enzyme catalysis and inhibition [14]. Although several experimental and theoretical studies about metal cation–cyclic peptide complexes were reported [15–20], no theoretical study containing alkali earth metal cation-Cyclo(L-Pro)$_3$ and alkali earth metal cation-Cyclo(L-Pro)$_4$ has been reported in the literature. Recently we have started a program to study of interaction of metal cations with cyclic peptides [21–24]. In our previous works, a more flexible scaffold containing 3 or 4 alanine molecules form the cyclic peptide structure. However, in the present study a more rigid platform constructed from 3 or 4 proline molecules have been used.

Peptide ligands for a target metal are applied for electrode surface modification [25]. It has been found experimentally that cyclic peptides selectively bind cations, too [16,26]. Furthermore, the choice of the appropriate ligands is important in selecting and transporting of metal cations. Thus, the present work should be useful to the synthesis of artificial ionophores for applications such as extractants or as synergists with the other extractants. The biomaterial applications of cyclic peptides provide the motivation for the present paper: to improve the transport of small molecules across a lipid bilayer with cyclic peptides and metal-coordination [27–29].

2. Computational methods

The geometries of all compounds were fully optimized with Gaussian 09 program package [30] using the methods B3LYP [31,32] and CAM-B3LYP [33,34] with 6–31 + G(d) basis set and their vibrational frequencies were calculated with same level. LANL2DZ was employed for heavy atoms Sr^{+2} and Ba^{+2}. The binding energies were calculated as the energy difference between the complexes and the isolated monomers. They were corrected by zero point energy (ZPE) and Grimme's dispersion [35,36] corrections; and the basis set superposition errors

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(BSSE) [37] were eliminated using the Boys–Bernardi counterpoise technique [38]. The B3LYP energies are close to the CAM-B3LYP energies. The natural bond orbital (NBO) analysis [39] at B3LYP/6–31 + G(d) level was performed to determine the nature of interactions in the formation of complexes. Solvent effects on the complexes were considered by using a relatively simple self-consistent reaction field (SCRF)

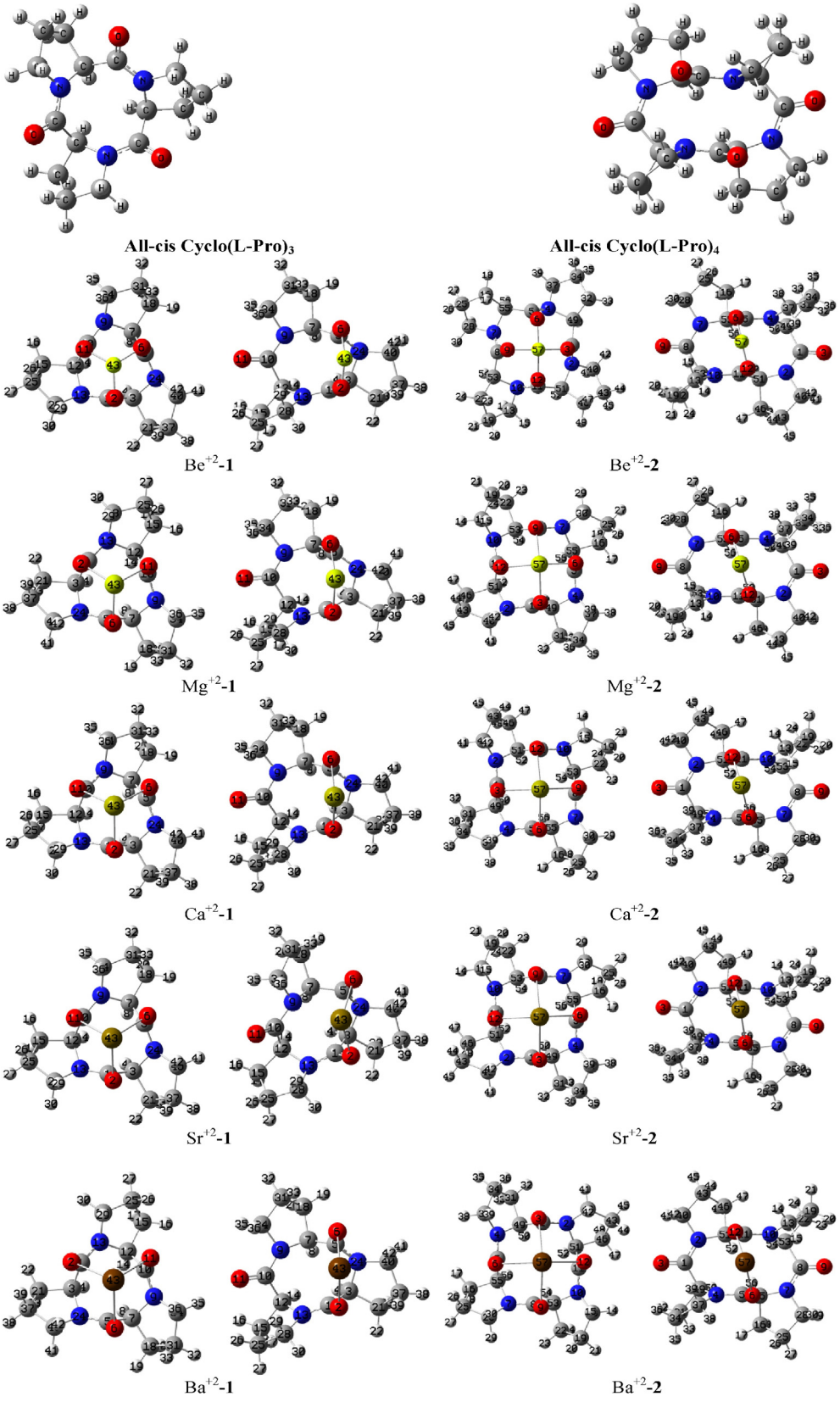

Fig. 1. The optimized structures of M^{+2}-Cyclo(L-Pro)$_3$ (bi and tridentate) and M^{+2}-Cyclo(L-Pro)$_4$ (bi- and tetradentate) complexes calculated at B3LYP/6–31 + G(d) level.