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Complexation of Sm^{3+} and pamidronate: A DFT study

Masoud Arabieh[1,*], Mohammad Hassan Khodabandeh[2], Mohammad Hossein Karimi-Jafari[3], Carlos Platas-Iglesias[4,*], Karim Zare[2]

(1. Computational Chemistry Laboratory, NSTRI, 11365-8486 Tehran, Iran; 2. Department of Chemistry, Faculty of Science, Shahid Beheshti University, G.C., Evin, 19839-63113 Tehran, Iran; 3. Department of Bioinformatics, Institute of Biochemistry and Biophysics, University of Tehran, 13145-1384 Tehran, Iran; 4. Departamento de Química Fundamental, Universidade da Coruña, Campus da Zapateira-Rúa da Fraga 10, 15008 A Coruña, Spain)

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Abstract: We reported a quantum mechanical study of the complexes formed between Sm^{3+} and the bisphosphonate ligand pamidronate in aqueous solution. According to available experimental pK_a values pamidronate was expected to exist in aqueous solution, at physiologically relevant pH, in its di- and tri-protonated forms (denoted by H_3L and H_2L). The most stable structures of the ligands and Sm^{3+} complexes were found by using a detailed analysis of the conformational space with semiempirical and DFT methods. The results showed that both H_2L and H_3L bisphosphonates acted as a tridentate ligands in their complexes with Sm^{3+}. The addition of explicit water molecules to the coordination sphere of the metal not only gave different coordination numbers for H_2L and H_3L complexes (CN=9 and 10), but also provided different trends in stabilization energies. The results highlighted the importance of considering not only an explicit first coordination shell, but also a second hydration shell, for an adequate description of this type of complexes in aqueous solution.

Keywords: samarium; radiopharmaceutical; bisphosphonates; solvent effects; rare earths

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Radiopharmaceuticals belong to a group of compounds containing a radionucleotide and one or more pharmaceutical ligands. These compounds are widely used in nuclear medicine for diagnosis and therapy applications[1]. Depending on the particular application of the radiopharmaceutical, a variety of metals such as Tc, Re or Sm are used as radionucleotides in their structures[2]. Another feature of these compounds is the role of the pharmaceutical ligand(s)[3]. Bisphosphonates (BPs), which are characterized by a P-C-P backbone structure and two phosphonic acid groups bound to the same carbon atom (Fig. 1(a)), are commonly used as ligands for pharmaceutical applications[4]. It has been shown that like inorganic pyrophosphate, a polyphosphate occurring naturally in the body, BPs have affinity for bone mineral and were found to prevent calcification both *in vitro* and *in vivo*, which leads them to inhibit the dissolution of hydroxyapatite crystals[5]. It has been found that the type of R1 and R2 side chain substituent in the structure of BPs controls their biological activity toward the antimineralization and also inhibition of bone resorption. For instance, when the R1 moiety is a hydroxyl group, the ability of BPs to prevent both crystal growth and dissolution is enhanced[6]. Moreover, bisphosphonates containing a basic primary nitrogen atom in an alkyl chain in R2 position, as in pamidronate (Fig. 1(b)), were found to be 10 to 100-fold more active than those that lack a nitrogen atom in the R2 moiety (as in etidronate and clodronate)[7,8]. It must be noticed that although the structure of the R2 side chain is the major determinant of the antiresorptive potency, both phosphonate groups, are also required for the drugs to be active[9].

BPs are not only used in direct treatment of a variety of bone diseases (such as Paget's disease, hypercalcimia, metastatic and osteolytic bone disease, etc.)[9,10], but also employed as appropriate ligands to coordinate radionuclides for both bone scanning imaging and bone pain palliation. For example, the complex of hydroxyl ethylene diphosphonate (HEDP) with Tc-99 is routinely used for bone scanning imaging, while the complexes of pamidronate and beta-emitter radionuclides such as Sm-153 are employed for bone pain palliation[11,12].

Although there are many individual reports on the structure and biological activity of BPs in the literature[10–12], there are few theoretical studies on complexes of these compounds with metal cations, especially with beta-emitter radionuclides. Rasanen et al. have modeled theoretically the complexation of methyl bisphosphonate (MBP) and Cl_2MBP with Ca^{2+} and Mg^{2+} both in the gas phase and in solution[13]. They have shown that the bisphosphonate ligands act as tridentate ligands when bound to Ca^{2+} and Mg^{2+}. Suzuki and co-workers, postu-

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* **Corresponding authors:** Masoud Arabieh, Carlos Platas-Iglesias (**E-mail:** Arabieh@gmail.com, Carlos.platas.iglesias@udc.es; **Tel.:** +98-2129902890, +34 981 167 00 (ext. 2050))

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lated BPs-Ca complexes models and calculated optimized geometries by using molecular mechanics methods[14]. Their results were not in agreement with those of Rsanen et al., most likely due to the poorer performance of molecular mechanics (MM) methods in comparison with quantum mechanics modeling. Naeves et al. have modeled the interaction of a variety of BPs-Sm complexes with hydroxyapatite both theoretically (MM method) and experimentally[15].

To the best of our knowledge, there are no experimental or theoretical reports in the literature on the complexation between bisphosphonates and heavy metal ions such as the lanthanides. The lack of work in this area is probably related to the inherent difficulties associated with the computational treatment of heavy elements. For instance, no accurate parameters for semiempirical or empirical methods are available for these metals. Moreover, the computational modeling of compounds containing such heavy atoms requires an adequate treatment of relativistic effects[16]. Although the emergence of different computational approaches, such as the methods based on density functional theory (DFT), and the development of relativistic and quasi-relativistic effective core potentials for elements below the third period of the periodic table, has facilitated the growth of theoretical studies in this area, many computational difficulties for working with systems containing these atoms still exist. Moreover, the tendency of BPs as ligands to form polymeric metal complexes makes their isolation and characterization often complicated.

In this work, the formation, structure, and stability of complexes of pamidronate (3-amino-1-hydroxylpropyliden-1,1-bisphophonate) with Sm^{3+} have been studied theoretically for the first time. The results of this study will be useful for designing new force fields required to perform molecular dynamics simulations on the interactions of BPs with other moieties. As seen in Fig. 1(b), pamidronate has four ionizable OH groups attached on phosphorus atoms and one amino ($-NH_2$) group that might be protonated in the form of a positive acidic moiety ($-NH_3^+$). Successive deprotonation of this pentaprotic acid (referred as H_5L) results in other protonation states of pamidronate, that is H_3L, H_2L and HL. It has been found experimentally that the forms resulting from the first and the second ionizations of the four P–OH groups, H_2L and H_3L, are the most abundant structures in aqueous medium at about neutral pH according to the experimental pK_a values[17,18]. Furthermore, the tendency of phosphonates to undergo protonation while coordinating lanthanide(III) ions is well known[19]. Thus, in this study we have focused on the coordination of the di- and tri-protonated forms of the ligand H_2L and H_3L to Sm^{3+} in aqueous solution.

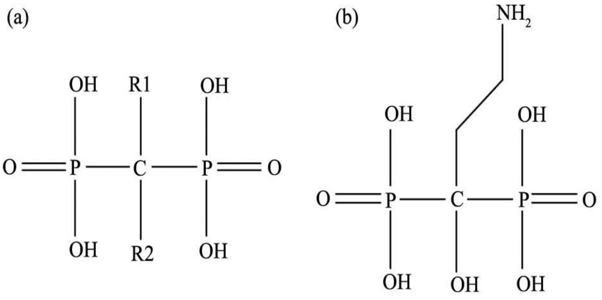

Fig. 1 General structure of bisphosphonates (a) and pamidronate (H_4L) (b)

In the first part of present study we reported a systematic semiempirical and DFT conformational search to find the most stable conformers of ligands H_2L and H_3L in solution. Subsequently, the most stable forms of the complexes formed between Sm^{3+} and ligands H_2L/H_3L were obtained by using a variety of initial structures that allowed exploring the conformational space using a DFT level of theory. In the second part, several explicit water molecules were added to each of the complexes to find out the number of water molecules that complete the metal coordination environment in aqueous solution. Furthermore, the role of the second-sphere solvation shell on the structure energetics of the systems has also been examined. Finally, different approaches were investigated to evaluate the degree of metal-to-ligand charge transfer in complexes during the addition of water molecules to the coordination sphere of the metal.

1 Computational details

The semiempirical PM6 Hamiltonian in conjunction with Conductor-Like Screening Model (COSMO) was applied for prescreening of the conformational space of the ligands. PM6 is the most recent member of the NDDO family of semiempirical methods and is understandably the most accurate[20]. This method recently has been successfully used in theoretical studies on rare elements[21]. COSMO is a computationally efficient continuum approach for modeling solvent effects which generates a conducting polygonal surface around the solute at the Van der Waals distance[22]. The most stable PM6/COSMO structures were then subjected to further optimizations at the B3LYP/6-311++G(d,p) level of theory. In all metal-ligand structures and subsequent hydrated complexes Sm^{3+} was described by a quasi-relativistic effective core potential (RECP) developed by the Stuttgart group (ECP51MWB)[23]. According to this model, 46 core electrons and all 4f electrons of Sm (5 electrons in the case of Sm^{3+}) are replaced by a core potential that implicitly incorporates the relativistic effects. Replacement of 4f electrons in this ECP is supported by the fact that the f-orbitals do not play an important role in metal-ligand bonding in lanthanide complexes[24]. Another practical advantage of this ECP is the replacement of an odd number of electrons (51 electrons in the case of Sm^{3+}) that allows treating the system in a pseudo-closed-