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Electronic and molecular structure of some heterocyclic bisphosphonates by MM and DFT calculations

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ABSTRACT

Bisphosphonate drugs have long been used for the treatment of bone disorders such as Paget's disease, cancer-related hypercalcemia, and postmenopausal osteoporosis, but the molecular mechanisms underlying their efficacy are only recently beginning to be understood.However, it is not yet clears the exact relationship between their molecular structure and pharmacologic activities. In this study, molecular geometries and physical-chemistry properties of zoledronate, risedronate and minodronate, differing only in the nature of the aliphatic chains, were predicted by molecular mechanics and their interactions with hydroxyapatite, the main bone mineral component, were examined. We report the synthesis and radiochemical characterization of ^{153}Sm complexes with pamidronate, alendronate and neridronate.

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General Terms
Computational chemistry, molecular modeling

Keywords
Hereocyclic Bisphosphonates, DFT, MM, cancer, interactions.

1. INTRODUCTION

Bisphosphonates are ideally suited for the treatment of bone disease because they bind avidly to bone mineral at sites of active bone metabolism, where they achieve therapeutic concentrations. Fleisch and all showed that bisphosphonates not only inhibit dissolution of hydroxyapatite crystals, but also affect osteoclast metabolism and function [1], [2] and [3]. Bone-bound bisphosphonates are released during bone resorption and are internalized by osteoclasts, leading to inhibition of osteoclast activity and induction of osteoclast apoptosis [4], [5] and [6]. These molecules are synthetic pyrophosphate analogs, in which the P–O–P group is replaced by the P–C–P bridge, where each P is a phosphonate group. The P–C–P bridge is resistant not only to chemical but also to enzymatic hydrolysis [7]. The

two phosphonate groups are essential both for binding to the mineral phase of bone and for cell-mediated antiresorptive activity. The properties of individual BPs depend on the two covalently bound sidechains, R1 and R2, attached to the central carbon atom (Scheme 1). R1 substituents which display additional capability to coordinate calcium, such as hydroxyl (OH) or amino (NH_2), provide enhanced chemisorptions to the mineral, most likely via tridentate binding to calcium [8]. The R2 side group predominantly determines the antiresorptive potency of the bisphosphonates. The presence of nitrogen atoms in the R2 side group is associated with the ability of an individual bisphosphonate to inhibit farnesyl pyrophosphate synthase (FPP) enzyme within the mevalonate pathway in osteoclasts [9]. Moreover, it can also influence overall bone affinity as a result of the ability of the nitrogen moiety to interact with the crystal surface of bone minera [10]. The nitrogen atom within the heterocyclic ring makes risedronate and zoledronate two of the most potent antiresorptive BPs [11].

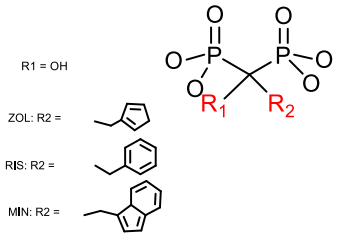

Fig1. Molecular structure of three studied amino-biphosphonates.

A few recent summaries of the chemistry of the nitrogen-containing clinical candidates have been published, while the series of heterocyclic compounds that ultimately culminated in the discovery of the pyridyl compound risedronate was thoroughly reviewed. In addition, a zoledronate-related series of compounds, studying the nitrogen orientation in the molecule, has been described which provided further evidence for the involvement of stereospecific recognition events [12].

This review proceeds as follows. In the first section, we analyze the electronic structure of three market heterocyclic bisphosphonates using DFT method. In the second section, we conduct an energy analysis using molecular mehcanic (MM) method. Finally, we summarize the interaction between currently on-market bisphosphates and FPPS in Protein Data Bank (PDB).

2. Materials and Methods

a. Quantum chemical calculations

The full geometrical optimization of the ligands (Figure 1) in the gas phase were carried out at the level of semi-empirical AM1 method [13], as well as density functional theory (DFT) [14] using a gradient technique [15,16] and 6-31G* [17,18] basis set. The DFT calculations were carried out with the B3LYP functional, in which Becke's nonlocal exchange [19,20] and the Lee-Yang-Parr correlation functional [21] semi-empirical and DFT calculations were performed using GAUSSIAN 03 for Windows program package [22].

b. MM calculations and force field parameters

Molecular mechanics calculations were used to obtain further information on the contribution of the various species to the observed behavior. The calculations of complexes were performed with the EMO program (Version 2010) [23], [24]. All the structures studied in our work were built using the program EMO (version 2010) by introducing the Allinger code of the atoms of the molecules studied, by the keyboard of the computer then the energy is minimized by using the semi-empirical parameters (Fig 3 and 4). The most stable conformation is obtained from various starting geometries, after optimization.

In order to avoid the local minima corresponding to unstable conformers, we carried out it with the option ‘‘SCAN’’ which makes it possible to sweep the surface of potential energy (PES). This enabled us to eliminate the geometries having little chance to generate the most stable conformers. Energies of the found conformers are optimized by the semi empirical method. The most stable conformations have the lower energies. For each structure we have done the energies: E_{EMO}, $E_{stretching}$, $E_{bending}$, $E_{torsion}$, $E_{Van\ der\ Waals}$.

c. Analysis of protein-ligand interactions:

For analysing the interactions of docked protein-ligand complexes, the Ligplot^{+}programme [25] was used to check the hydrogen bond and hydrophobic interactions between receptor and ligand atoms within a range of 5 Å. Also PyMOL (V-1.3) [26] were used to visualize the interactions and to prepare figures. The IDs of the PDB files used in the LigPlot^{+} calculation are 2F8C (zoledronate), 1YQ7 (risedronate) and 3B7L (minodronate).

3. Results and discussion:

a. Electronic properties

The most important orbitals in a molecules are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).

These orbitals determine the way the molecule interacts with other species. The frontier orbital gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule [27].The HOMO–LUMO energy gap values increases in the following order: **ZOL < MIN < RIS**. This demonstrate that The lower value for frontier orbital gap in case of **ZOL** than other ligands makes it slightly more reactive and less stable (Table 1).The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor.

Table. 1: HOMO and LUMO energies, HOMO-LUMO gaps, Dipole moment M, Ionization energy I, Energy(HF) for ZOL, RIS and MIN.

LIGANDS	HOMO	LUMO	Energy Gap	Dipole-M	I	Energy (u.a)
ZOL	-0.24846	-0.00443	-0.24403	1.8520	0.24846	-1515.43530
RIS	-0.21922	-0.03778	-0.18144	4.4560	0.21922	-1660.06960
MIN	-0.24807	-0.02314	-0.22493	6.5838	0.24807	-1537.50582

The 3D plots of the frontier orbitals HOMO and LUMO and the molecular electrostatic potential map (MEP) figures for four molecules are shown in Fig 2.The MEP map shows that oxygen and nitrogen atoms represent the most negative potential region but the nitrogen atom seems to exert comparatively small negative potential as compared to oxygen atom.

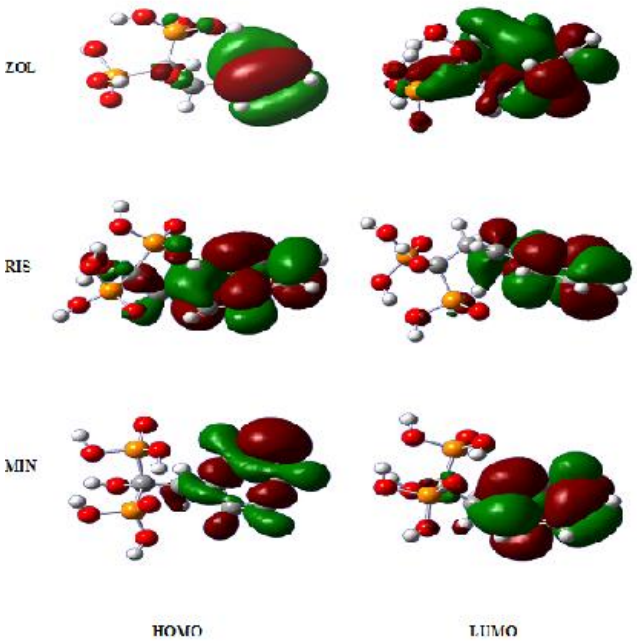

Fig. 2. The highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals of Ligands.

The analysis of the Mulliken charge atoms given in Table 2 show that the **O_1**, **O_2** and **O_3**atoms in the case of **ZOL** positions are characterized by the lowest value of the Mulliken charge atoms this means that the **ZOL**has more reactivity than other than other ligands. This result is agreed with experimental.

Table 2: Mulliken charge atoms of the three sites O_1, O_2 and O_3in neutral systems, respectivelyfor L_{1-3} systems.

Ligands	P---O_1 P—O_2	C—O_3	
ZOL	-0.638	-0.649	-0.662
RIS	-0.587	-0.586	-0.540
MIN	-0.667	-0.644	-0.608

a. ***MM calculations***

An optimized geometry and minimized steric energy (stretching energy +angle bending energy + rotation energy +Van der Waals energy + electrostatic energy) for all three ligands were determined by molecular modeling which carried out by the EMO program using the molecular mechanics (MM2). This program uses the relaxation method (single step method) for calculations.

Table 3. Steric energies (KJ/mol) of copper(II) complexes in octahedral coordination mode

N-BP	Stretching	Bending	Torsion	V.d.W	Electro statics	Total
ZOL	5.76	65.21	-2.38	45.23	-81.77	**32.043**
RIS	4.59	29.54	-25.11	49.49	-83.43	-24.921
MIN	3.69	79.40	-38.81	42.17	-83.31	-3.144

The table 3 shows that steric energy of the minimized structures for cupric complexes increases in the order: **RIS< MIN< ZOL**. The results obtained shows that **RIS** is more stable compared to other aminobisphosphonates.

C. ***Analysis of protein-ligand interactions:***

Fig.3 shows schematic representations summarizing the binding of the N-BPs zoledronate, risedronate, minodronate to FPPS. Images were created using the program LigPlot^{+} v.1.0, which generates schematic 2-D representations of protein-ligand complexes from the PDB file input. The IDs of the PDB files used in the LigPlot calculation are 3B7L (minodronate), 2F8C (zoledronate), 1YQ7 (risedronate).

As shown in Fig. (**3**), all N-BPs havecommon P-C-P structures and their interactions are the same,wherein the bisphosphonate moiety of the N-BP binds to atrinuclear Mg^{2+} cluster, and all three magnesiumions are octahedral coordination and linked with the carboxylate groups of the side chains of Asp103 and Asp107 for ZOL and Min but for RIS are linked to Asp257 and Asp121. Two of three magnesium ions form rather symmetrical six-membered rings, with the bisphosphonate acting as a bidentate chelate, while one magnesium ion forms an additional single chelate. It is reported that the OH group on the carbon atom in the P-C-P structure in N-BPs, together with the two phosphate groups in this structure, is responsible for the N-BPs high affinity to bone minera. However, the OH group also contributes to FPPS binding *via* the polar interaction with Asp243 for ZOl and Min and Asp for Ris257. Also shows the hydrophobic contacts between FPPS and N-BPs. As shown in the figure, minodronate, which has a bulky bicyclic ring have a large number of hydrophobic contacts (Fig. 3) compared with the other N-BPs.

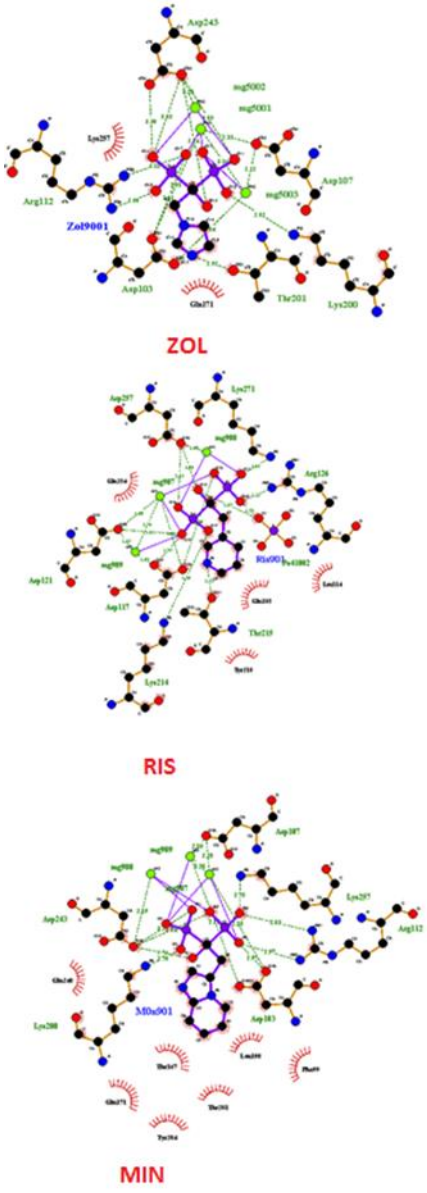

Fig3: Ligplot for screened ligands

Conclusion

Three heterocyclic bisphosphonates were investigated by both theoretical methods (MM: molecular mechanics and MQ: molecular quantum) .MQ used for calculated the Fukui functions values,f_k^-, locals nucleophilicity indexes N_k, HOMO and LUMO energies, HOMO-LUMO gaps and other reactivity descriptors for found the governing nucleophilic attack. In our study the distribution of the electron density shows that the compounds studied had many active centers in nucleophilicity. The areas containing the nitrogen and oxygen atoms have more opportunity to form bonds with the metal Mg.

The site analysis can provide deep insights into the binding between protein/ligand, although its prediction of relative binding free energies is not particularly accurate. Combinational use with QM and MM may be desirable. In this paper, we show a detailed analysis of the energetic basis of molecular recognition between FPPS and N-BPs. It is expected that similar research on the analysis of interactions between BP drugs and FPPS will increase in the future, and facilitate further drug research.

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