A theoretical study on the electronic structures and equilibrium constants evaluation of Deferasirox iron complexes

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Elemental iron is essential for cellular growth and homeostasis but it is potentially toxic to the cells and tissues. Excess iron can contribute to tumor initiation and tumor growth. Obviously, in iron overload issues using an iron chelator in order to reduce iron concentration seems to be vital. This study presents the density functional theory calculations of the electronic structure and equilibrium constant for iron-deferasirox (Fe-DFX) complexes in the gas phase, water and DMSO. A comprehensive study was performed to investigate the Deferasirox-iron complexes in chelation therapy. Calculation was performed in CAMB3LYP/6-31G(d,p) to get the optimized structures for iron complexes in high and low spin states. Natural bond orbital and quantum theory of atoms in molecules analyses was carried out with B3LYP/6-311G(d,p) to understand the nature of complex bond character and electronic transition in complexes. Electrostatic potential effects on the complexes were evaluated using the CHARMM calculations. The results indicated that higher affinity for Fe(III) is not strictly a function of bond length but also the degree of Fe-X (X=O,N) covalent bonding. Based on the quantum reactivity parameters which have been investigated here, it is possible reasonable design of the new chelators to improve the chelator abilities.

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1. Introduction

Human bodies require iron (Fe) for the variety of the important biological processes, including energy generation, oxygen transport and DNA synthesis [Kalinowski and Richardson, 2005]. Iron is able to switches between two stable redox states, the ferric and ferrous forms, allowing it to act as an electron donor/acceptor. Although, Iron is an essential element for the majority of the organisms and functions in a variety of cell reduction and enzymatic processes, iron overload is a particularly sever condition [Kontoghiorghes et al., 2005].

Potentially toxic iron-catalyzed reactive oxygen species (ROS) are unavoidable in an oxygen-rich environment [Frey and Reed, 2012]. So far Iron and ROS are increasingly familiar as the significant initiators and the mediators of the cell death in a different kind of organisms and pathological conditions. The origin of the toxicity of extra Fe is related to the oxidative stress resulting from so called Fenton chemistry where Fe catalysis the interruption of hydrogen peroxide to hydroxyl radicals (Lambeth and Neish, 2014; Wang et al., 2010; Arvapalli et al., 2010) (Fig. 1).

Because the human body lacks a physiological mechanism for actively evacuating iron so, Iron overload needs to be cured by administration of an appropriate chelating agent transforming the excess body iron into an excretal form (Flaten et al., 2016; Liu and Hider, 2002; Schier et al., 2003). Iron chelators are useful drugs for clinical treatment of the excretion iron overload [Richardson, 2002; Chantrel-Groussard et al., 2006] and could be used cure the neurodegenerative procedures such as Alzheimer’s, Parkinson’s, and prion diseases, where the iron plays a significant role (Manus et al., 2011).

Obviously a chelator must show a genuine activity to lower the Fe levels. To do this, the chelator must gain access to tissues where Fe loading occurred and be able to bind Fe competitively and to be excreted as an intact Fe complex (Brard et al., 2006; Yu et al., 2006; Kalinowski et al., 2007; Triantafyllou et al., 2007; Gharagozloo et al., 2008). Nowadays, there are several kinds of chelating agents used extensively for the clinical treatment of the transfusion-induced iron overload (Cappellini, 2009; Porter, 2009) (Fig. 2), the gold standard being Desferal (desferrioxamine B, DFO) (Blatt and Stittely, 1978). Two oral alternatives to DFO now available are Exjade(deferasirox, ICL670) (Bergeron et al., 1991; Lescoat et al.,

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