

A theoretical study on the $[\text{Al}(\text{DFX})_2]^{3-}$, $[\text{Fe}(\text{DFX})_2]^{3-}$ and $[\text{Ga}(\text{DFX})_2]^{3-}$ complexes

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Abstract

In this work, density functional theory (DFT) study on the electronic structures and binding energies of deferasirox coordinated to Al^{3+} , Fe^{3+} and Ga^{3+} metal ions was carried out, using the CAM-B3LYP/6-31G(d) level of the theory in the water. The results indicate that deferasirox has the most stable complex with Fe^{3+} metal ion, because of maximum interaction of Fe^{3+} metal ion with oxygen and nitrogen atoms of the deferasirox. Because of the importance of the charge transfer in the complex formation, donor-acceptor interaction energies were evaluated. Finally, the probable correlation between the binding energy values and electronic chemical hardness was analyzed.

Keywords: Binding energy, Deferasirox, NBO, Electronic chemical hardness

Introduction

Because humans are enabled to remove iron from the body, a clinically relevant state can occur if toxic levels of iron accumulate. Excess iron deposited in the liver, spleen and myocardium, which this iron accumulation leads to progressive organ dysfunction and finally death [1]. Iron-chelating agents slowly mobilize iron by binding of iron present in a transit pool, which is in equilibrium with the insoluble iron deposits. Then iron chelate is excreted in the urine.

4-[3,5-Bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl] benzoic acid, known as deferasirox (DFX) is a promising drug approved for the oral treatment of iron overload in patients suffering from chronic anemia such as β -thalassemia [2]. DFX is highly selective for Fe^{3+} metal ion, which forms a stable complex in a 2:1 molar ratio at physiological pH [3]. Furthermore, DFX increases aluminium and other toxic metal absorption such as gallium [4]. Despite the fact that theoretical investigations have been performed for metal ion uptake by biomolecules, but a few theoretical studies have been performed on the metal-DFX complexes [5].

Computational methods

The geometry of the complexes have been optimized at the CAM-B3LYP level [6] using the 6-31G(d) basis set. Solvent effects were taken into account by the conductor like polarizable continuum model (CPCM) [7]. In order to estimate the main donor-acceptor interactions, natural bond orbital (NBO) analysis was performed on the optimized structures. Finally, molecular orbital analysis was also done to evaluate the difference between the HOMO and LUMO energies and electronic chemical hardness, at the same level of theory.

Results and Discussion

After optimizing the complex and ligand, separately (Figure 1), metal-ligand binding energy (E_b) have been computed according to Eq. 1.

$$E_b = \frac{-(E_{\text{complex}} - E_{\text{metal}} - 2 E_{\text{ligand}})}{2} \quad (1)$$

Where E_{complex} , E_{metal} and E_{ligand} are the energies of the complex, corresponding metal ion and ligand components, respectively. Theoretical metal-ligand binding energies have been calculated and the metal-ligand binding energy trend is accordance to: $\text{Fe}^{3+} > \text{Al}^{3+} > \text{Ga}^{3+}$.

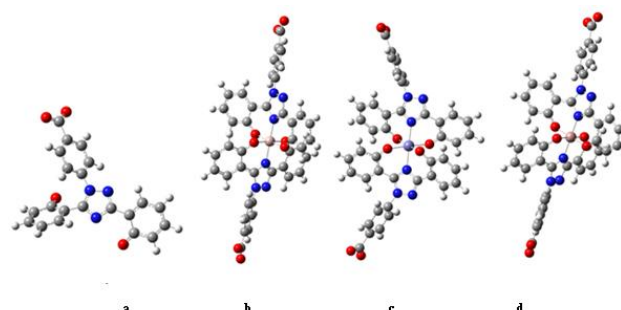


Fig. 1: Optimized structures of a) DFX, b) $[\text{Al}(\text{DFX})_2]^{3-}$, c) $[\text{Fe}(\text{DFX})_2]^{3-}$ and d) $[\text{Ga}(\text{DFX})_2]^{3-}$.

Natural bond orbital (NBO) analysis indicates the charge transfer from the oxygen and nitrogen atoms of the DFX to the metal ions. The important donor-acceptor interaction energies of the complexes are related to the interaction of the lone pair (LP) electrons of the oxygen and nitrogen atoms of the DFX and nonbonding orbital of the metal ion (LP^*_M). According to data, it is confirmed that $[\text{Fe}(\text{DFX})_2]^{3-}$ complex is more stable than $[\text{Al}(\text{DFX})_2]^{3-}$ and $[\text{Ga}(\text{DFX})_2]^{3-}$ complexes.

According to the frontier molecular orbital (FMO) theory, electronic chemical hardness (η) can be defined on the basis of the energy gap between the highest energy occupied molecular orbital (HOMO) and lowest energy

unoccupied molecular orbital (LUMO), according to Eq. 2.

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (2)$$

HOMO-LUMO energies and electronic chemical hardness of the metal-DFX complexes in the aqueous solution have been calculated. Based on the data, $[\text{Fe}(\text{DFX})_2]^{3+}$ has the maximum chemical hardness among the studied metal-ligand complexes. Moreover, there is a linear correlation between the binding energy and the electronic chemical hardness.

Conclusion

DFT calculations have been employed to investigate the complexation of Al^{3+} , Fe^{3+} and Ga^{3+} metal ions and DFX. From the energy view point, DFX is the best receptor for Fe^{3+} metal ion. NBO analysis indicated charge transfer from oxygen and nitrogen atoms of the DFX to the metal ions. Finally, according to calculations of HOMO-LUMO energy gap, a linear correlation between the binding energy and the electronic chemical hardness was obtained.

References

- [1] Y. Kohgo, K. Ikuta, T. Ohtake, Y. Torimoto, J. Kato, Body iron metabolism and pathophysiology of iron overload, *International journal of hematology*, 88 (2008) 7-15.
- [2] E. Nisbet-Brown, F.N Olivieri, P.J. Giardina, R.W. Grady, E.J. Neufeld, R. Sechaud, A.J. Krebs-Brown, J.R. Anderson, D. Alberti, K.C Sizer, *The Lancet*, 361 (2003) 1597-1602.
- [3] H. Nick, P. Acklin, R. Lattmann, P. Buehlmyer, S. Hauffe, J. Schupp, D. Alberti, Development of tridentate iron chelators: from desferrithiocin to ICL670, *Current medicinal chemistry*, 10 (2003) 1065-1076.
- [4] G.J. Kontoghiorghes, *Hemoglobin*, 32 (2008) 608-615.
- [5] S. Salehi, A.S. Saljooghi, M. Izadyar, *Computational Biology and Chemistry*, 64 (2016) 99-106.
- [6] T. Yanai, D.P. Tew, N.C.A. Handy, *Chemical Physics Letter*, 393 (2004) 51-57.
- [7] V. Barone, M. Cossi, *The Journal of Physical Chemistry A*, 102 (1998) 1995-2001.