Quantum chemical analysis of the deferiprone–iron binding reaction

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Abstract: To prevent side effects of excessive accumulation of iron in the body, chelation therapy is recommended in transfusion-dependent patients. The reaction between deferiprone and iron to form a complex red substance can be described as 3 molecules of the chelator, deferiprone, reacting with a molecule of iron. However, the actual mechanism of the deferiprone–iron binding reaction is not well understood. A quantum chemical analysis of the deferiprone–iron binding reaction was performed, focusing on the reaction between 1 molecule of deferiprone and 1 molecule of iron. The two main alternative pathways for the deferiprone–iron binding reaction were shown to be C-C cleavage and C-O cleavage. The required energy for complex formation in C-C cleavage was less than for C-O cleavage. The total energy requirement for C-C cleavage was negative, implying that this reaction can occur without any external energy source. The resulting complex fits the reported tertiary structure model for the deferiprone–iron complex

Keywords: deferiprone, complex, iron, quantum analysis, energy

Introduction

To prevent the side effects of excessive accumulation of iron in the body, chelation therapy is recommended in transfusion-dependent patients (Ceci et al 2003; Marx 2003). Pharmacologically, the tight binding of chelators to iron blocks the iron's ability to catalyze redox reactions (Ceci et al 2003). Consequently, a chelator that binds to all binding sites of the iron completely inactivates the free iron.

The two common iron-chelating agents available for the treatment of iron overload are deferoxamine and deferiprone (Ceci et al 2003). Deferiprone is the only orally active iron-chelating drug to be used therapeutically in conditions of transfusional iron overload (Nagarajan et al 2005). It is indicated as a second-line treatment in patients with thalassaemia major, for whom deferoxamine therapy is contraindicated, or in patients with serious toxicity to deferoxamine therapy (Ceci et al 2003).

The reaction between deferiprone and iron to form a complex red substance can be described as three molecules of the chelator, deferiprone, reacting with one molecule of iron. However, the actual mechanism of the deferiprone–iron binding reaction is not well described. This paper reports a quantum chemical analysis of the deferiprone–iron binding reaction.

Materials and methods

Alternative pathways for deferiprone–iron binding reaction

Deferiprone is a bidentate chelator: a single molecule can interact with only two of the coordination sites on iron (Figure 1). Therefore, 3 molecules are required for complete binding. This study focused on the reaction between 1 molecule of deferiprone and 1 molecule of iron. The two main alternative pathways for the deferiprone–iron binding reaction are C-C cleavage and C-O cleavage.

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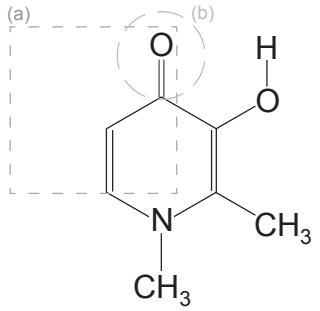
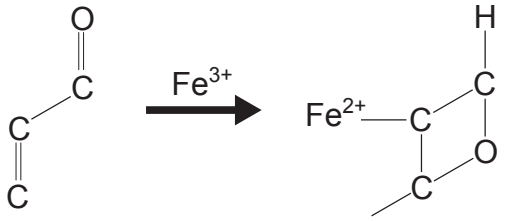


Deferiprone molecule

(a) C–C cleavage



(b) C–O cleavage

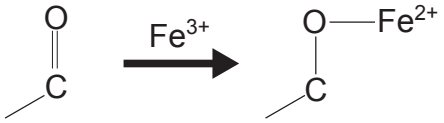


Figure 1 The alternative pathways for the deferiprone–iron binding reaction.

Quantum chemical analysis for bonding energy

The quantum chemical analysis for bonding energy of deferiprone ($C_7H_9NO_2$) was performed according to classical bonding theory (Goldberg 1989). The resulting complexes between deferiprone and iron from each alternative reaction pathway were analyzed, and the required energy for complex formation by each pathway was compared.

Results

The details and the required energy for complex formation in C-C cleavage and C-O cleavage pathways are presented in Table 1. The required energy for complex formation in C-C cleavage was less than for C-O cleavage.

Discussion

The recommended treatment for many congenital hematological disorders, especially for thalassaemia major, is regular blood transfusions. These transfusions lead to the harmful accumulation of iron in the body and subsequent hemochromatosis (Ceci 2003). Iron chelation is required in these cases. Deferiprone is a new oral iron-chelating agent which is effective in removing iron from the heart, which is the target organ of iron toxicity and mortality in iron-loaded thalassaemia patients (Kontoghiorghes et al 2003). Biochemically, deferiprone is a bidentate chelator. Because a single molecule can interact with only 2 of the coordination sites on iron, 3 molecules are required for complete binding (Merson and Oliver 2002; Kontoghiorghes et al 2003). The crystal structure of deferiprone is orthorhombic (Chan et al 1992). In each molecule, the OH group and the CO oxygen are insignificantly intramolecularly hydrogen-bonded (Chan et al 1992). The fundamental intermolecular and insignificant intramolecular hydrogen-bonded dimer structure of deferiprone is maintained, but is distorted and supplemented by hydrogen bonds between the CO oxygen of each deferiprone molecule and the OH group of one formic acid molecule (Chan et al 1992).

Tam et al (2003) noted that future chelator research would focus on the application of chelators for other diseases and the development of new effective chelators. Evidence on the differences in the mode of action of chelators, and molecular structure–activity correlations, is valuable for future metallopharmacological studies (Kontoghiorghes et al 2004). Therefore, research on the biochemical reaction in deferiprone–iron complex formation can provide useful information for further bio-iron research. In the present study, 2 possible mechanisms are proposed for deferiprone–iron complex formation. The energy required for C-C cleavage was much less than for C-O cleavage. In addition, the total energy requirement for C-C cleavage was negative, implying that this reaction can occur without any external energy source. The resulting complex fits the reported tertiary structure model for the deferiprone–iron complex (Wiwanitkit 2005).

Table 1 Details and required energy for complex formation in C-C cleavage and C-O cleavage pathways

Items	C-C cleavage	C-O cleavage
Bond breaking*	1 C=C, 1 C=O	1 C=O
Bond forming†	2 C-O, 1 C-H, 1 C-C, 1 C-Fe^{2+}	1 C-O, 1 C-Fe^{2+}
Accumulated energy	146 kcal/mol + 177 kcal/mol	177 kcal/mol
Released energy	(2 × 83 kcal/mol) + 100 kcal/mol + 80 kcal/mol + 1 eV	83 kcal/mol + 1 eV
Required energy‡	−23 kcal/mol − 1 eV	94 kcal/mol − 1 eV

* bond-breaking accumulated energy
† bond-forming released energy
‡ required energy = accumulated energy − released energy
Abbreviations: eV, electron volt.

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