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How tin metal prevents verdoheme ring opening? Comparative study of various nucleophiles

Mehdi D. Davari, Homayoon Bahrami, Mansour Zahedi *, Nasser Safari

Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, G.C., Evin, Tehran 19839-6313, Iran

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ABSTRACT

The inhibitory role of tin metal in the verdoheme ring opening mechanism has been investigated using B3LYP method. Nucleophilic additions of OH^-, NH_2^-, and CN^- to three possibly six, five, and four coordinate verdoheme complexes of tin(IV) have been employed as model reactions. The results of calculations suggest that nucleophilic attacks to tin(IV) verdohemes does not result in the opening of the macrocycle, being in excellent agreement with experimental reports. In six coordinate tin(IV) verdoheme complex the formation of open ring helical complexes is favorable thermodynamically but not kinetically. In this coordination state, tin has no coordination role. Thus, direct addition of nucleophiles to the positive oxo-carbon centers and formation of a closed ring hydroxy compound is proposed for blocking the conversion of verdoheme to biliverdin. Contrary to zinc and iron analogues, in five and four coordinate pathways, such addition to oxo-carbons does not proceed toward stable open chain helical products. This is because formation of these complexes is unfavorable both thermodynamically and kinetically. It has been determined that in the latter pathways a closed ring compound is formed as final product by adding nucleophiles to tin atoms. It has been thus shown that high affinity of ligands for binding to both the fifth and sixth coordination sites of the highly charged Sn(IV) center is responsible for inhibiting the conversion of verdoheme complexes to biliverdin compounds. Results indicate that high tendency of tin(IV) metal to increase coordination state plays a crucial role in preventing verdoheme ring opening. These key points have been corroborated with the results obtained from molecular orbital calculations.

1. Introduction

Degradation of heme is an important biological process that is carried out by O_2 and NADPH in the presence of heme oxygenase (HO) enzyme (Scheme 1) [1–3]. Heme degradation has received considerable attention in recent years from both experimental and theoretical viewpoints [4–9]. Even though verdoheme ring opening is considered as the rate-determining step to regulate HO enzyme activity, relatively little is known about mechanism of this controversial step in HO catalysis [10–12]. The process of coupled oxidation has been extensively used as a model for biological action of heme oxygenase [13–15]. Addition of nucleophile to Fe(II), Co(II), and Zn(II) verdohemes has shown that ring opening of the macrocycle yields the helical metal biliverdin complexes [16–19]. It has been proposed that these reactions are initiated by nucleophilic attack at one of the carbon atoms adjacent to the oxygen of verdoheme ring, where a tetrahedral carbon atom is initially formed followed by the ring opening process [19–21]. Although the latter process of metalloporphyrins has been observed to occur with metals such as Mn, Fe, Co, and Zn, some other metals like Sn prevent such action [22]. It is not clear why certain metals facilitate ring opening while others do not, nor is the reaction mechanism completely known. Furthermore, Sn porphyrins have been studied as potent inhibitors of HO activity and have been emerged as interventional agents for neonatal hyperbilirubinemia [23–30]. However, there are some ambiguities related to understanding the interaction of Sn porphyrin analogues with heme protein in heme cleavage process. Especially, the inhibition mechanism in the course of aforementioned process is not clear [29–31]. Also, the roles of the tin metals including coordination, and oxidation states in the course of ring opening mechanism of these verdoheme analogues have been obscured [32,33].

In our previous work on the conversion of zinc verdoheme into biliverdin, it became clear [34] that the presence of the zinc atom increases the positive charge on oxo-carbons in zinc verdoheme relative to 5-oxa-porphyrin. In accord to experimental report [20], it was determined that the intermediate which is initially formed by nucleophilic attack on one of aforementioned carbon atoms is then directly converted to a helical open ring complex of zinc biliverdin. Even though the most positive center for the nucleophilic attack was the zinc ion of zinc(II) verdoheme, it was shown that such addition did not lead to a stable intermediate.

* Corresponding author. Tel.: +98 21 22401765; fax: +98 21 22401765.
E-mail addresses: m-zahedi@cc.sbu.ac.ir, mansourzahedi@yahoo.com (M.Zahedi).

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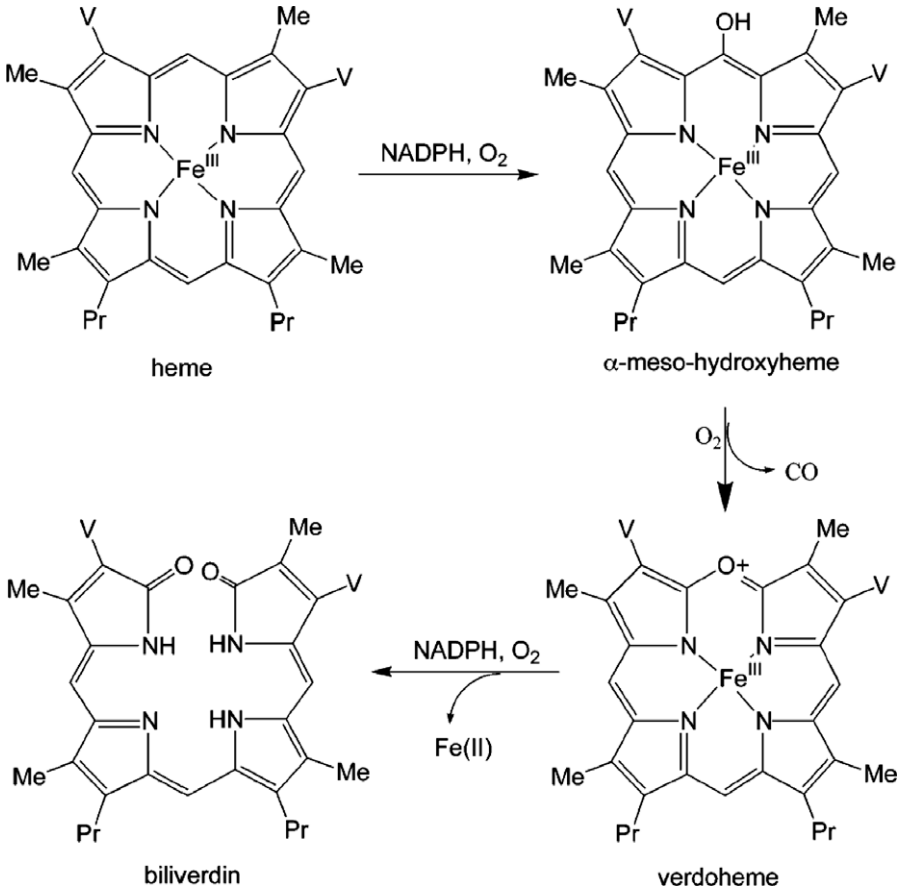

Scheme 1. Heme oxygenase reaction; V = vinyl, Me = methyl, Pr = propionate.

Thus, the zinc atom had no coordination role in transferring the nucleophiles to the oxo carbon, but it just had the effect of activating the oxo carbon for nucleophilic addition. Other works have shown that direct nucleophilic attack of OH^- on the five coordinate iron(II) verdoheme is in a fair accord with experimental report, making it a possible mechanism for conversion of verdoheme to biliverdin [35,36]. According to these results, the role of metal and ligand coordination in heme degradation is important.

In our recent study [37], first evidences of the ring opening prevention have been observed for the verdoheme complexes of tin through hydrolysis mechanism. However, investigating such behavior in the presence of other nucleophiles would shed more light on the preventive mechanism of verdoheme ring opening. To continue the work on the OH^- addition [37], we have focused on NH_2^- and CN^- nucleophilic attacks to variously coordinate tin(IV) verdoheme complexes using B3LYP method (Schemes 2 and 3). Computational results have been employed to obtain a comprehensive understanding of tin's inhibitory role in the ring opening process based on structural and energetic properties of tin verdoheme complexes. In addition, it has been illustrated that molecular orbital calculations satisfy the key findings.

2. Computational details

Molecular geometries of the model complexes were optimized without constraints via DFT calculations using the B3LYP functional [38–40]. All the calculations were performed using the Gaussian 98 program [41]. Imidazole, hydroxyl and porphyrin have been considered as models of ligand in meso- and proto-porphyrin IX. No side-chains were attached to the verdoheme models evaluated in this study in order to speed up the calculations. The 6-31G Pople basis set [42] was used for O, N, C, and H atoms, and 3-21G [43] was used for Sn, while single-point energies were calculated using the 3-21G for Sn and 6-31G(d) [44] for other atoms, namely O, N, C, and H atoms at the B3LYP level. Previous study [37] has demonstrated that these basis sets are effective in calculating reliable geometries and energy properties of tin verdoheme systems. Frequency calculations at the same level of theory were also performed to identify all the stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency). Zero point-energy corrections were taken into account for calculating the energetics of the reaction pathway. Basis set superposition errors (BSSE) were corrected using the counterpoise method [45]. The molecular orbital calculations were carried out on some species involved in nucleophilic additions to different tin(IV) verdohemes at the B3LYP level.

3. Results

Calculated atomic charges for optimized structure of six, five and four coordinate tin(IV) verdohemes revealed that the most positive sites of reactants (**1**s in Schemes 2 and 3) are centered on Sn and two carbon atoms adjacent to oxygen [37]. Thus, based on atomic charges [34–37], OH^-, NH_2^-, and CN^- nucleophiles are added to centered metal or to one of the carbon atoms adjacent to oxygen atom positions in all pathways.

3.1. Nucleophilic additions to six coordinate Sn(IV) verdoheme

Proposed mechanism of OH^-, NH_2^-, and CN^- nucleophilic additions to six coordinate Sn(IV) verdoheme with imidazole and hydroxyl as fifth and sixth axial ligands, $[Sn^{IV}(OP)(IM)(OH)]^{2+}$, (OP and IM are mono anion of 5-oxa-porphyrin and neutral imid-