Coordination Chemistry Reviews 257 (2013) 381–393

Contents lists available at SciVerse ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Intrinsic properties and reactivities of mononuclear nonheme iron–oxygen complexes bearing the tetramethylcyclam ligand

Sam P. de Visser[a,*], Jan-Uwe Rohde[b,*], Yong-Min Lee[c,d], Jaeheung Cho[c,d], Wonwoo Nam[c,d,**]

[a] Manchester Interdisciplinary Biocenter and School of Chemical Engineering and Analytical Science, University of Manchester, 131 Princess Street, Manchester M1 7DN, United Kingdom
[b] Department of Chemistry, The University of Iowa, Iowa City, IA 52242, United States
[c] Department of Bioinspired Chemistry, Ewha Womans University, Seoul 120-750, South Korea
[d] Department of Chemistry and Nano Science, Ewha Womans University, Seoul 120-750, South Korea

Contents

ARTICLE INFO

Article history:
Received 17 April 2012
Received in revised form 5 June 2012
Accepted 8 June 2012
Available online 7 July 2012

Dedicated to Prof. Edward I. Solomon on the occasion of his 65th birthday.

Keywords:
Metalloenzymes
Biomimetics
Oxygen activation
Iron-oxo
Intermediates
Macrocyclic ligands

ABSTRACT

Iron–oxygen species, such as iron(IV)-oxo, iron(III)-superoxo, iron(III)-peroxo, and iron(III)-hydroperoxo complexes, are key intermediates often detected in the catalytic cycles of dioxygen activation by heme and nonheme iron enzymes. Our understanding of the chemistry of these key intermediates has improved greatly by studies of the structural and spectroscopic properties and reactivities of their synthetic analogues. One class of biomimetic coordination complexes that has proven to be particularly versatile in studying dioxygen activation by metal complexes is comprised of Fe^{IV}=O and Fe^{III}—O_2(H) complexes of the macrocyclic tetramethylcyclam ligand (TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane). Several recent advances have been made in the synthesis and isolation of new iron–oxygen complexes of this ligand, their structural and spectroscopic characterization, and elucidation of their reactivities in various oxidation reactions. In this review, we summarize the chemistry of the first structurally characterized mononuclear nonheme iron(IV)-oxo complex, in which the Fe^{IV}=O group was stabilized by the TMC ligand. Complexes with different axial ligands, $[Fe^{IV}(O)(TMC)(X)]^{n+}$, and complexes of other cyclam ligands are discussed as well. Very recently, significant progress has also been reported in the area of other iron–oxygen intermediates, such as iron(III)-superoxo, iron(III)-peroxo, and iron(III)-hydroperoxo complexes bearing the TMC ligand. The present results demonstrate how synthetic and mechanistic developments in biomimetic research can advance our understanding of dioxygen activation occurring in mononuclear nonheme iron enzymes.

* Corresponding authors.
** Corresponding author at: Ewha Womans University. Tel.: +82 2 3277 2392; Fax: +82 2 3277 4441.
E-mail addresses: sam.devisser@manchester.ac.uk (S.P. de Visser), jan-uwe-rohde@uiowa.edu (J.-U. Rohde), wwnam@ewha.ac.kr (W. Nam).

0010-8545/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ccr.2012.06.002

1. Introduction

The cytochromes P450 (CYP 450) are a versatile group of heme-based monooxygenases with vital functions for human health, including the biodegradation and metabolism of toxic compounds in the body as well as the biosynthesis of hormones [1–7]. They utilize molecular oxygen at a heme center and react via oxygen atom transfer to substrates, leading to C—H hydroxylation, C=C epoxidation, aromatic hydroxylation, and heteroatom oxidation [8,9]. The CYP 450s contain a central heme active site that is linked to the protein via a thiolate bridge from a cysteinate residue [10,11]. The catalytic cycle of the CYP 450s starts from the resting state (Fig. 1A) [12–14], where a water molecule fills the sixth binding position of the metal. Upon substrate binding into the active site, the water molecule is released and a five-coordinate high-spin ferric species with a vacant coordination site for dioxygen binding is formed (Fig. 1B). After the reduction of the ferric heme by reduced putidaredoxin to a five-coordinate high-spin ferrous heme (Fig. 1C), dioxygen binds to the heme in a ferric-superoxo form (Fig. 1D) and picks up another electron and proton to form a ferric-hydroperoxo species (Fig. 1E) that is protonated to give an iron(IV)-oxo heme π-cation radical oxidant (Fig. 1F), which is the active species of the enzyme and also known as Compound I (Cpd I). Due to the high reactivity and short lifetime of Cpd I, it has been difficult to trap and characterize it with spectroscopic methods, but recently Rittle and Green collected the first pieces of evidence from Mössbauer and UV–vis spectroscopic experiments [15]. However, its participation as active oxidant in the catalytic cycle was inferred from indirect evidence [16,17] and high-level computational studies [18–22] for a long time. Until recently, therefore, there was considerable discussion in the literature regarding the active oxidant in CYP 450 enzymes, where some site-directed mutation studies seemed to implicate the ferric-hydroperoxo species as active oxidant [23]. A series of computational and experimental biomimetic studies, however, contradicted this conclusion and reasoned that Cpd I is a superior oxidant over the ferric-hydroperoxo species at least in heme enzymes and iron porphyrin models [24–27]. In CYP 450 enzymes, the second reduction step is rate-determining and dioxygen-bound intermediates are short-lived (see Fig. 1). As a consequence, biochemical studies into the mechanism and reactivity of Cpd I have been hampered by its short lifetime, and research has been redirected to biomimetic model complexes instead.

A mononuclear Fe^{IV}=O species is also believed to be the key oxidant of nonheme iron enzymes that activate dioxygen at a mononuclear Fe^{II} site. These enzymes carry out substrate hydroxylation, halogenation, and other reactions involving C—H bond activation for a variety of purposes, including biosynthetic functions, DNA repair, and cellular oxygen sensing. Many of these enzymes, including several α-ketoglutarate- (αKG) and pterin-dependent oxygenases for which such a high-valent Fe intermediate has been trapped in recent years, contain a 2His/1carboxylate ligand motif that links the metal to the protein. The catalytic cycle of one representative enzyme, taurine:α-ketoglutarate dioxygenase (TauD) [7,28–34], is shown in Fig. 2 and starts from a resting state where the three remaining Fe coordination sites are occupied by water molecules, and upon co-substrate binding, namely αKG, two water molecules are replaced and the third water molecule is released when substrate (taurine) enters the binding site (Fig. 2A′). Subsequently, molecular oxygen binds the metal in the ferric-superoxo form (Fig. 2B′), which is an elusive intermediate that has been proposed by computational modeling to attack the α-keto position of αKG to form a bicyclic ring-structure (Fig. 2C′) [35,36]. Decarboxylation then leads to a high-valent iron(IV)-oxo species with succinate bound (Fig. 2D′), which reacts with substrate via hydrogen atom (H-atom) abstraction from the substrate to give a ferric-hydroxo complex (Fig. 2E′). Rebound of the hydroxyl group finally leads to the alcohol product (Fig. 2F′). The iron(IV)-oxo species, in contrast to Cpd I of the CYP 450s, appears to have a lifetime that is long enough to enable spectroscopic characterization, and work by Hausinger, Krebs, and Bollinger provided compelling evidence of its spectroscopic and catalytic properties [37–39]. In particular, D′ was characterized by spectroscopic techniques as a high-spin Fe^{IV}=O species, and its kinetics were followed spectroscopically. Further studies with deuterated substrate gave evidence of an elevated kinetic isotope effect for the reaction and implicated a rate determining H-atom abstraction reaction in the process. To gain further insights into nonheme iron(IV)-oxo species, a range of biomimetic model complexes was studied and characterized, which revealed considerable differences in activity between nonheme iron and heme complexes.

One of the first biomimetic model systems where an iron(IV)-oxo species was trapped and characterized structurally was a mononuclear nonheme iron(IV)-oxo complex of the tetraaza-macrocyclic TMC ligand (TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) [40]. This iron complex has since been intensely studied, and valuable insights into its physical properties, axial ligand influences, and reactivities with substrates have been gained from this work. Furthermore, reactivity studies of several $[Fe^{IV}(O)(TMC)(X)]^{n+}$ complexes (X = a neutral or anionic ligand), $[Fe^{III}(O_2)(TMC)]^{+}$, and $[Fe^{III}(O_2H)(TMC)]^{2+}$ have unveiled consid-

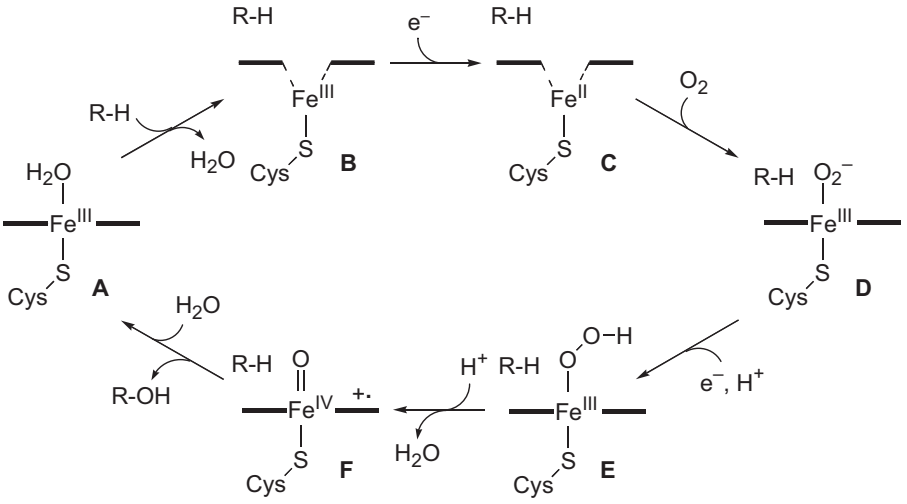

Fig. 1. Proposed catalytic cycle of cytochrome P450 enzymes.