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Biomimetic Trispyrazolylborato Iron Complexes

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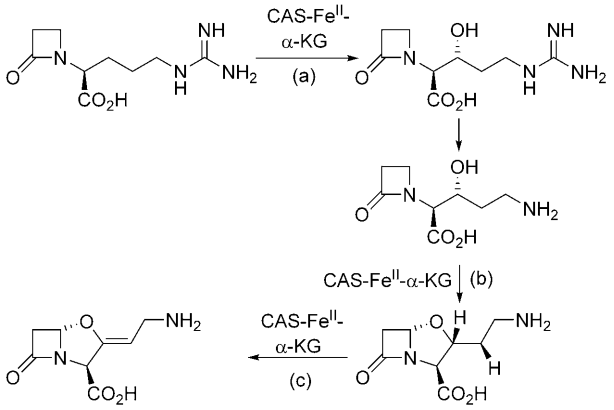
Many mononuclear iron oxygenases exhibit a common metal-binding motif, the so-called 2-His-1-carboxylate facial triad.[1] Among these, the family of α-ketoglutarate (α-KG)-dependent iron enzymes represents the biggest group. Usually, prior to a reaction with O_2, the Fe^{II} center that is bound by two histidine residues and an aspartate or glutamate of the triad coordinates one additional water molecule and a κ^2-O,O′-bound α-KG cosubstrate.[1] When this assembly binds oxygen, concomitant CO_2 cleavage and succinate formation result in an Fe^{IV}=O intermediate that is able to oxidize various substrates.[1] For taurine dioxygenase (TauD), probably the best-investigated α-KG-dependent iron enzyme,[1,2] a high-spin Fe^{IV}=O intermediate was confirmed.[2b]

α-KG-dependent enzymes are engaged in many biologically and physiologically relevant processes. These include collagen modification; the biosyntheses of antibiotics, β-lactamase inhibitors, and flavonoids; and DNA demethylation and repair. Furthermore, they are involved in oxygen sensing and erythropoetin (EPO) regulation.[1]

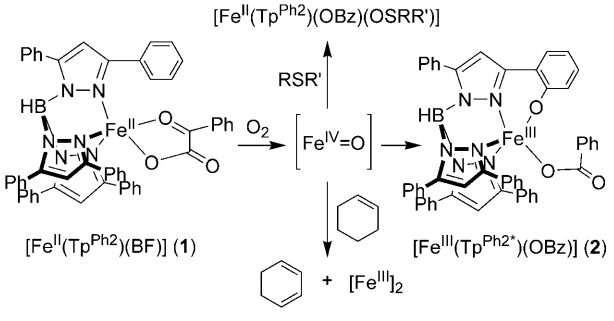
The reactivity of α-KG-dependent iron enzymes may be classified in three categories: Cleavage of aliphatic CH bond with a) subsequent hydroxylation by radical rebound, that is, recombination of the substrate radical and the hydroxyl radical, b) radical ring closure or ring expansion, or c) dehydrogenation. Examples of all three reaction categories can be observed in clavaminate synthase (CAS), an enzyme that catalyzes three steps in the biosynthetic pathway of clavaminate, either a hydroxylation, a ring-closure reaction, or a dehydrogenation reaction (Scheme 1), depending on the nature of the substrate.[3]

For more than 15 years, mononuclear iron trispyrazolylborato complexes have been applied as models for iron oxygenases, as the pyrazole donors mimic the imidazole groups of the 2-His-1-carboxylate facial triad. With [Fe(Tp^{Me2})(BF)] and [Fe(Tp^{Ph2})(BF)] (**1**), only a few of these models have shown any functional activity to date.[4–8] In 1995, Valentine and co-workers used [Fe(Tp^{Me2})(BF)] and O_2 to generate an oxidant in situ that was able to epoxidize *cis*-stilbene.[5] In contrast, the analogous complex



Scheme 1. CAS catalyzed steps in the clavaminate biosynthesis. See text for (a)–(c).

[Fe^{II}(Tp^{3tBu,5iPr})(BF)] proved to be unreactive, as Hikichi et al. reported, probably owing to steric hindrance by the ligand.[6] This hindrance seems to be smaller in the complex [Fe^{II}(Tp^{Ph2})(BF)] (**1**), and in 1999 Que and co-workers observed conversion of **1** with O_2 to form the complex [Fe^{III}(Tp^{Ph2*})(OBz)] (**2**) within 1 h at 25 °C. This reaction was explained by formation of an Fe^{IV}=O species by oxidative decarboxylation and subsequent hydroxylation of one phenyl substituent of the Tp^{Ph2} ligand (Scheme 2).[7] A Tp^{Ph2} complex exhibits an



Scheme 2. Reactions of **1** with O_2 in benzene at 25 °C.

almost identical reaction with phenylpyruvate,[8] a substrate of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) that acts as both substrate and cosubstrate.[9]

The reaction of [Fe^{II}(Tp^{Ph2})(BF)] (**1**) with O_2 has now been revisited by Münck, Que, and co-workers, who used

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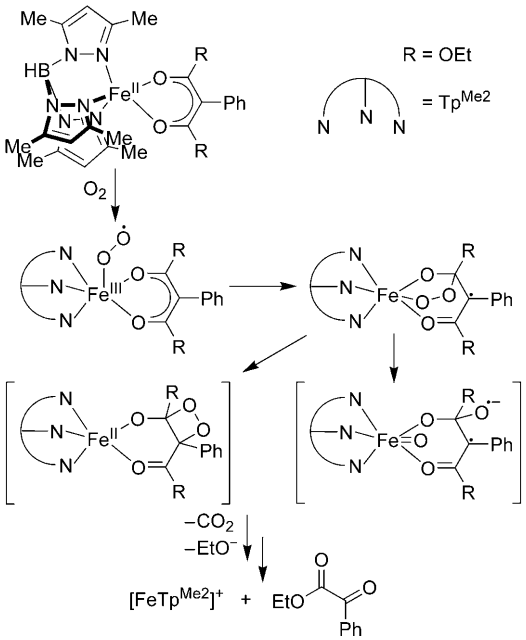
interception reactions to further investigate the system.[10] With an excess of MeSPh, the formation of complex **2** was completely suppressed in favor of the sulfoxide complex [$Fe^{II}(Tp^{Ph2})$(OBz)(OSMePh)] (Scheme 2). Using protein crystallography of the enzyme isopenicillin N synthase (IPNS), Baldwin et al. confirmed analogous interception of an Fe^{IV}=O species in a sulfoxidation reaction.[11] The MeSPh concentration has no significant effect on the reaction time of **1** with O_2, thus indicating that formation of the Fe^{IV}=O species is the rate-determining step. The presence of a sufficient amount of MeSPh substrate suppresses the self-hydroxylation of the biomimetic Tp^{Ph2} complexes. Again, this result highlights an analogy to the α-KG-dependent iron enzymes. Only when the substrate is present in the active site and one coordinated water molecule has been displaced from the Fe^{II} center is an Fe^{IV}=O species formed by reaction with O_2. Thus, the oxidant is only formed when enough substrate is present to avoid any self-hydroxylation of the enzyme.

Further interception reactions were performed with 9,10-dihydroanthracene (DHA), fluorene, cyclohexene, toluene, ethylbenzene, diphenylmethane, cyclopentane, cyclooctane, and cyclohexane. DHA and cyclohexene were able to intercept 75–80% of the Fe^{IV}=O oxidant by forming anthracene and cyclohexadiene, respectively. This reaction resembles a dehydrogenation according to category (c). In the case of cyclohexene, attack of the Fe^{IV}=O oxidant first causes the formation of a cyclohexenyl radical, which then reacts further with the resulting Fe^{III}–OH species to yield the dehydrogenated product.[10] The success of this interception reaction seems to be less dependent on the strength of the C–H bond to be cleaved than on the shape of the substrate. To date, the field of biomimetic oxidations of hydrocarbons with Fe^{IV}=O species has been dominated by hydroxylations (a). In oxygenases, substrate hydroxylation is closely related to dehydrogenation. Discrimination between these two transformations is usually based on the shape of the substrate and the enzyme pocket of the active site, as discussed above in case of CAS (Scheme 1). Que et al. are the first to report similar discrimination in a biomimetic model. Interestingly, formation of neither 2-cyclohexenol nor 2-cyclohexenone was observed (Scheme 2). Instead, UV/Vis and Mössbauer spectroscopy indicate a side reaction to a dinuclear Fe^{III}-μ-O-Fe^{III} complex, which can easily be explained by reaction of the [$Fe^{II}(Tp^{Ph2})$(OBz)] product with the Fe^{IV}=O species.[10]

In recent years, the development of Fe^{IV}=O models with long lifetimes and a high ($S=2$) spin state similar to that of the enzyme Fe^{IV}=O intermediate has been an unfulfilled goal of bioinorganic coordination chemistry. For the Fe^{IV}=O oxidant formed from **1**, irrefutable evidence of such a high spin state remains elusive.[10] However, in another very recent publication Que et al. report that a high spin state has now been confirmed for a model complex with the tetradentate tripod ligand TMG_3tren.[12] The $S=2$ iron(IV) oxo complex cation $[Fe^{IV}(O)(TMG_3tren)]^{2+}$ can be generated by reaction of 2-(*tert*-butylsulfonyl)iodosobenzene ($tBuSO_2C_6H_4IO$) with [$Fe^{II}(TMG_3tren)$(OTf)]OTf. It was characterized by resonance Raman and Mössbauer spectroscopy as well as by EXAFS spectroscopy and corresponding DFT calculations.[12] In this complex, the authors take advantage of the steric hindrance of the TMG_3tren ligand, which suppresses intermolecular decomposition processes. Furthermore, the ligand in $[Fe^{IV}(O)(TMG_3tren)]^{2+}$ enforces a trigonal-bipyramidal geometry with local C_{3v} symmetry and thus a $S=2$ ground state, which arises from degenerate d_{xy} and $d_{x^2-y^2}$ orbitals.[12] In contrast, DFT calculations on the Fe^{IV}=O species of TauD, backed by spectroscopic data, favor an octahedral geometry of the Fe^{IV}=O species with a κ^2-coordinated carboxylate donor.[2c] Such a geometry should also be accessible with heteroscorpionate and scorpionate ligands such as Tp^{Ph2}.

For the enzyme acetylacetone dioxygenase,[13] in which the Fe^{II} cofactor is coordinated by three histidine residues, Limberg and Siewert very recently reported a structurally similar, functional model bearing a Tp^{Me2} ligand (Scheme 3).[14] In this case, an intercepting reaction was not



Scheme 3. Proposed mechanism for the oxidative cleavage of diethylphenylmalonate.[14]

used. Instead, diethylphenylmalonate was used as substrate analogue.[14] Exposure to O_2 leads to formation of ethylbenzoylformate and release of CO_2 in a reaction that is even catalytic. The authors suggest a mechanism involving dioxetane formation or O–O bond cleavage.

These very recent examples of biomimetic iron trispyrazolylborato complexes show that this chemistry, even after more that 15 years, is always good for a surprise. The detection of Fe^{IV}=O species by interception as well as the application of substrate-analogous compounds are approaches that have long been neglected in the field of biomimetic model complexes. It seems promising to extend these concepts to iron complexes with N,N,O ligands that mimic the 2-His-1-carboxylate facial triad more closely, such as sterically hindered bis(pyrazol-1-yl)acetato or bis(imidazol-2-yl)propionato ligands.[1a,d]

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[4] Abreviations: α-KG = α-ketoglutarate, BF = benzoylformate, Bz = benzoyl, DHA = 9,10-dihydroanthracene, EXAFS = extended X-ray absorption fine structure, OTf = CF_3SO_3, TauD = taurine:α-ketoglutarate dioxygenase, TMG_3tren = tris(tetramethylguanidino)tren (tren = tris(2-aminoethyl)amine), Tp^{Me2} = hydrotris(3,5-dimethylpyrazol-1-yl)borate, $Tp^{3tBu,5iPr}$ = hydrotris(3-*tert*-butyl-5-isopropylpyrazol-1-yl)borate, Tp^{Ph2} = hydrotris(3,5-diphenylpyrazol-1-yl)borate.

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