Non-heme iron complexes as supramolecular oxidation catalysts

Klopstra, Marten

Chapter 7

Summary, Conclusions and Future Prospects

7.1 Introduction

In recent years non-heme iron complexes have been shown to be promising catalysts in the oxidation of alkanes and alkenes. These complexes are capable of mimicking iron oxygenases[1, 2, 3]. As was mentioned in Chapter 1 the aim of the research described in this thesis was the investigation of non-heme iron complexes as catalysts for oxidation reactions like epoxidation and dihydroxylation. Investigations have been carried out to combine the substrate binding site of cyclodextrin with the catalytic site of iron complexes in order to prepare a supramolecular catalyst with enhanced selectivity.
In this chapter, general conclusions will be drawn about the research discussed in Chapters 2 – 6 and future prospects are given for investigations based on the non-heme Fe-oxidation catalysts studied sofar.

7.2 Towards a Supramolecular Oxygenase Mimic

Chapters 2 and 4 deal with the design, synthesis and catalytic activity of artificial non-heme iron oxygenases. As mentioned in Chapter 2 the synthesis of a supramolecular catalyst based on the non-heme ligand N4Py has been undertaken. For this purpose different routes were examined in order to couple N4Py to β-cyclodextrin. The coupling was attempted by using a variety of activated esters of N4Py and N3Py in the reaction with hydroxyl groups at either the primary or secondary rim of β-cyclodextrin. Alternatively, halides were investigated as leaving groups in order to couple functionalized N4Py to cyclodextrin by an ether bond. In the coupling reactions problems arose as a result of the pyridine rings, the tertiary amine or the benzylic C-H moieties of N4Py, or by the specific features of β-cyclodextrin. However, alternative possibilities to prepare the target compounds remain to be investigated.
Whereas the *N*-hydroxysuccinic ester of TPA has been coupled to the amine group of an aminocyclodextrin[4], coupling of the *N*-hydroxysuccinic ester of N4Py using the same reaction conditions was unsuccessful. Here, the benzylic proton, which is present in N4Py but not in TPA, might be the origin of the instability of the ligand under the reaction conditions. The stability of N4Py under the reaction conditions might be increased by introduction of a methyl group at the benzylic position to eliminate the sensitive benzylic hydrogen. The ligand Me-N4Py (figure 1) has been synthesized in our laboratory[5] and the corresponding Fe(II) complex was found to be active in catalytic oxidation reactions indicating that successful coupling of this complex to β-cyclodextrin most probably will result in formation of an active supramolecular catalyst.

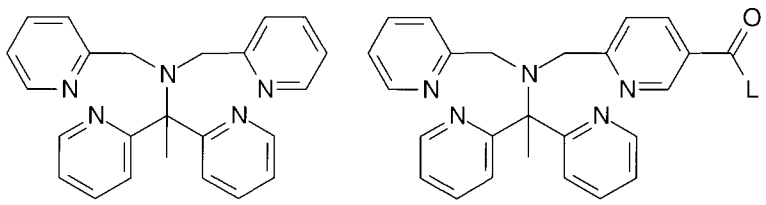
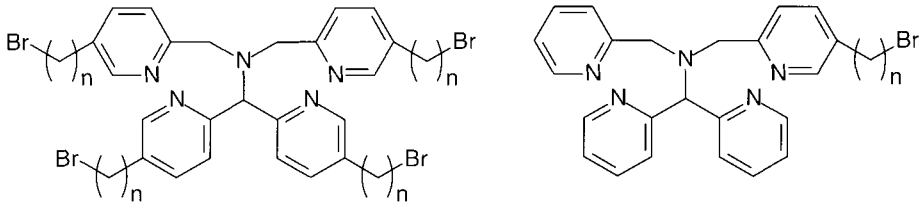


Figure 1 *Me-N4Py and a derivative for coupling with β-cyclodextrin.*

A promising method for the synthesis of the desired artificial oxygenase is the reaction of a bromoalkyl-substituted N4Py ligand with cyclodextrin. Reaction of **1** with cyclodextrin afforded a mixture of products with a high molecular mass indicating that coupling of **1** to cyclodextrin had occurred, although the desired product has not been isolated or indisputably characterized (§ 2.8). Further research in this field can be performed by using tetrabromo N4Py ligand **2**,[6] in which the bromine moieties are connected directly to the pyridine rings, or a monosubstituted bromoalkyl-N4Py **3** (figure 2). With a monosubstituted N4Py ligand fewer side products will be formed, which would result in a less troublesome purification of the product.

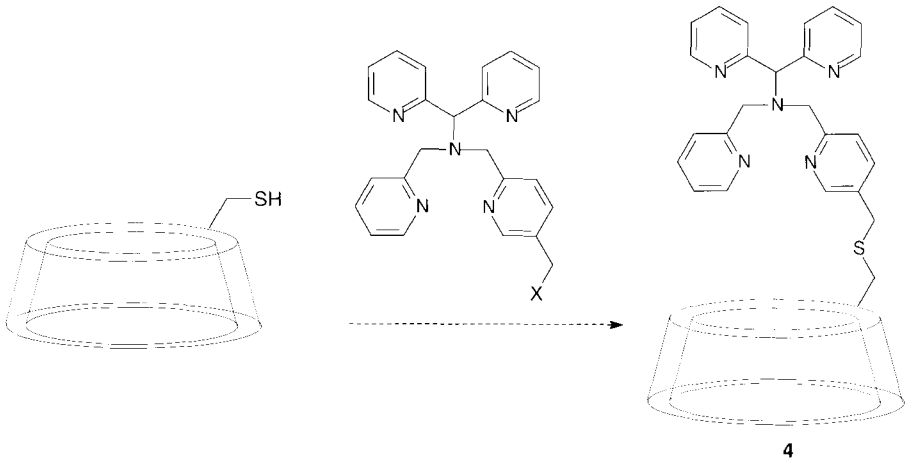


1 n = 3
2 n = 0

3

Figure 2 *Bromo-substituted-N4Py ligands for condensation with β-cyclodextrin.*

Another possible method for connecting N4Py to cyclodextrin consists of the synthesis of an active N4Py-triflate. Whereas coupling with tosyl ethers of N4Py was found to be unsuccessful, the use of the more active triflates might result in reaction with cyclodextrin[7].
In our group a dichloro substituted N4Py has been coupled to the cysteine residues of peptide chains[8]. Using the same concept an appropriate functionalized N4Py might be capable of coupling to 6-deoxy-6-mercapto-β-cyclodextrin[9] (Scheme 1). Since the iron complex of the N4Py-peptide system was found to be capable of oxidizing 2,2'-azidobis-(3-ethyl-benzothiazoline-6-sulphonic acid (ABTS) in water, also the iron complex of **4** is expected to be catalytically activity in oxidation reactions. However, catalytic oxidation by the iron complex of **4** might result in degradation of the ligand by oxidation of the thioether bond.



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Scheme 1 *Coupling of N4Py to 6-deoxy-6-mercapto-β-cyclodextrin.*

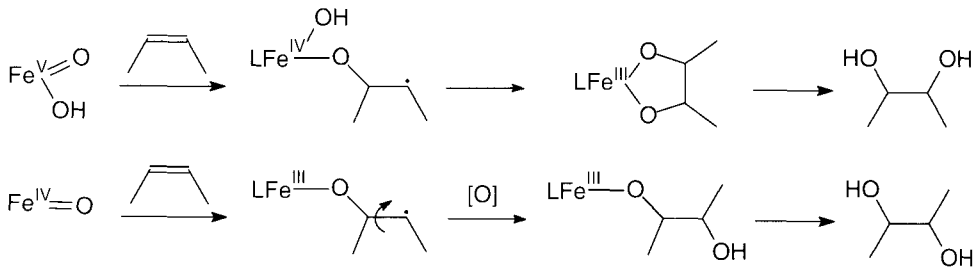
The synthesis of N4Py-based artificial oxygenases might be performed by using other receptor units. For this purpose molecules like cyclophanes[10], calixarenes[11], or the molecular 'clip' developed in the group of Nolte (Nijmegen)[4, 12, 13, 14] might be used.
The molecular clip was used as a receptor in an iron(II) TPA-based supramolecular catalyst as described in Chapter 4. This complex has been shown to be capable of oxidizing alkenes with hydrogen peroxide as terminal oxidant. Here, the presence of a receptor unit resulted in a higher catalytic activity of the complex in the epoxidation of norbornene with H_2O_2 compared to the parent complex. Since the activity of the iron complex was also almost twice as high as the physical mixture of the parent complex with the cyclodextrin receptor, the connection of the receptor unit results in the formation of a true supramolecular covalent catalyst. A comparable effect has been observed with the Fe(II) complex of a TPA-cyclodextrin ligand. Here, connecting a cyclodextrin unit to the catalyst also resulted in higher activities compared to using a physical mixture of cyclodextrin and the catalyst indicating the importance of the receptor to be in close proximity of the catalytic centre. In the group of Nolte research has been carried out to remove the protecting groups from the cyclodextrin moiety in order to obtain a water-soluble system[4]. With the corresponding iron complex of this TPA-cyclodextrin system catalytic oxidation in water might be performed, which would mimic oxidation with iron oxygenases.

7.3 Non-Heme Iron Complexes as Catalysts in Oxidation Reactions

The research described in Chapters 3, 5, and 6 deals with the catalytic oxidation of alkanes and alkenes with the iron(II) complexes of several tetradentate nitrogen ligands. In Chapter 3 the iron(II) complex of N3Py-Me, which was originally developed by Roelfes in our group[15], was further examined as a catalyst in the oxidation of alkenes affording the corresponding epoxides and diols. Labeling studies in acetonitrile as solvent showed that oxygen from water is incorporated in the epoxidation and *cis*-dihydroxylation products. Based on these results a

mechanism is proposed that is in correspondence with the mechanism proposed for $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$. In this mechanism oxidation occurs by an active $(HO)Fe^{V}=O$ species (Scheme 2), which contains oxygen atoms derived both from hydrogen peroxide and water (Chapter 6, Scheme 5). By using ketone-based solvents like acetone the selectivity of the catalyst was changed. In these solvents a preference for epoxidation and *trans*-dihydroxylation was observed; however also more side products were formed. Labeling studies in acetone suggested incorporation of oxygen from the solvent in the final products. For catalytic oxidation in these solvents an additional mechanism has been proposed in which an active Fe(IV) species is involved, and oxygen atoms from both hydrogen peroxide and acetone are present in the active species. The formation of *trans*-diols in this solvent is explained by the formation of a carbon centered radical species, which is formed by reaction of the Fe(IV) species with the substrate. This species is expected to undergo isomerization affording the thermodynamically favored *trans*-diol (Scheme 2)[16]. Further proof for incorporation of oxygen in the products would be achieved by using labeled acetone as solvent in the oxidation reaction. If an acetonyl peroxide intermediate, originating from acetone and an iron species, is involved in the oxidation labeled oxygen from acetone will incorporate into the final products.

In the catalysis experiments described in this thesis usually 50 equivalents of H_2O_2 with respect to the catalyst were used. However, Jacobsen and coworkers showed that the iron complex of BPMEN is capable of oxidizing alkenes to the corresponding epoxides on a preparative scale[17]. By using SbF_6^- as a counterion and acetic acid as additive 1.4 g of 1-deceen was epoxidized in 85 % yield with 3 mol % of catalyst. Using analogous conditions $[(N3Py\text{-}Me)Fe(CH_3CN)_2](ClO_4)_2$ is expected to be capable of performing epoxidations with comparable results.



Scheme 2 *Proposed cis- and trans-dihydroxylation with iron(V) and iron(IV) species.*

In Chapter 5 the synthesis of chiral tetradentate ligands including a chiral N3Py ligand was described. The corresponding iron(II) complexes did show catalytic activity in the oxidation of olefins. However, no enantioselectivity was observed in these experiments although iron complexes of BPMCN and 6-Me_2-BPMCN have been reported in the literature to be capable of enantioselective dihydroxylation reactions[18].

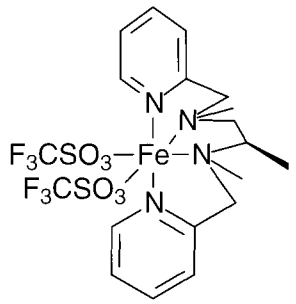


Figure 3 *Example of an iron complex with a chiral ligand*[19].

A possibility to perform oxidation reactions enantioselectively using a chiral N3Py ligand might be achieved by coupling of a dinaphthyl group at the *ortho*-position of one of the pyridine rings of N3Py (figure 3). In this way the chiral moiety will be situated in close proximity of the active site of the catalyst which might result in catalytic asymmetric oxidation by the corresponding complex. Related systems have been reported by the groups of Maruyama[20] and Salvadori[21] in which dinaphthyl groups were connected to a porphyrin ring. The epoxidation of styrene with Fe-complexes of such chiral porphyrins using iodosobenzene has been reported to provide up to 89 % ee.

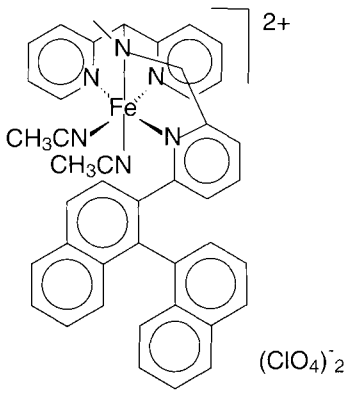


Figure 3 *Introducing chirality in N3Py-Me by a dinaphthyl moiety.*

Chapter 6 deals with the benzylic oxidation of C-H bonds using an automatic parallel screening approach. A series of non-heme iron complexes of tri-, tetra-, penta-, and hexadentate ligands was screened for the oxidation of the model substrates ethylbenzene and 4-methoxy-1-ethylbenzene with H_2O_2, O_2 or *tert*-butylhydroperoxide as the terminal oxidants affording the corresponding alcohol and ketone. With O_2 as oxidant the reactions occur by autoxidation as shown by the low A/K-ratios (typically <1) found in the oxidation of ethylbenzene, whereas with H_2O_2 the catalysts are directly involved in the oxidation reaction

as indicated by A/K-ratios that are higher than 1. Catalytic oxidation of ethylbenzene with O_2 as oxidant was found to be accelerated by increasing the temperature to 80 °C. Higher turnovers might be found by further increasing the temperature of the reaction mixture. This can be achieved by performing the reaction in the absence of solvent avoiding the restrictions to the reaction temperature caused by the boiling temperature of acetonitrile. A temperature effect on the activity of heme iron catalysts in benzylic autooxidation reactions has been reported, in which the reaction time for oxidation decreased from 24 h at 40 °C to 4 h at 120 °C[22]. Catalysts that were found to be almost inactive in the benzylic oxidation at 30 °C might be capable of performing oxidation reactions at higher temperatures. Using the automatic screening approach the scope of the catalysts can be further investigated for oxidation of alkenes[2, 23], sulfides[24] or ketones[25] with either H_2O_2 or O_2 as terminal oxidants.

The highest activities in the oxidation with H_2O_2 as terminal oxidant were found for pentadentate pyridine-based ligands like N4Py and trispicen. Coordination of iron to oxygen atoms in the ligand results in a lower activity of the complex. When N4Py ligands have substituents on the *ortho*-position of the two picolinic moieties, usually similar activity of the corresponding iron complex is observed.

In the benzylic oxidation of ethylbenzene with O_2 at 80 °C the highest turnover numbers were found for the complexes of the ligands N3Py and TPA. Apparently, tetradentate ligands, without substituents on the *ortho*-position of the pyridine rings, afford the most active iron catalysts for benzylic oxidation with O_2 as terminal oxidant.

The complexes of the imines **1** – **3** (figure 4) showed relatively high activities in benzylic oxidation both with H_2O_2 and O_2 at 30 °C. In the oxidation of ethylanisole with H_2O_2 as terminal oxidant these complexes showed the highest selectivities for alkohol formation with A/K-ratios as high as 6. On account of these results the oxidizing properties of the complexes deserve to be investigated in more detail. Here, the enantiomers of the chiral ligand **2** might be capable of performing benzylic oxidation enantioselectively. The iron(II) complex of the related ligand BPMCN has already been reported to be capable of performing asymmetric catalytic oxidation of alkenes affording the corresponding *cis*-diols in 30 % ee[18]. Regarding the similarities in structure compared to the imines **1** – **3** the compounds BPMCN and BPMEN might also be suitable ligands for the benzylic oxidation reaction.

Eventually, non-heme iron catalysts with higher activity and selectivity should be formed that are capable of performing the benzylic oxidation reaction with H_2O_2 or O_2 as terminal oxidant. In the ideal situation only alcohol or ketone would be formed as oxidation product.

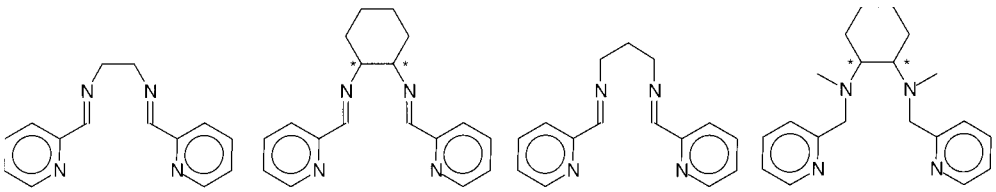


Figure 4 *Imine based ligands for oxidation catalysis and the BPMCN ligand.*

7.4 Final Conclusions

Although in the attempted coupling reactions of N4Py with functionalized cyclodextrin the target molecule was not isolated, the principle of using a supramolecular non-heme iron catalyst has been proven by the Fe(II) complexes of a TPA-cyclodextrin ligand and a TPA-substituted molecular clip. However, further research has to be done toward highly active and selective functional iron oxygenase mimics. As discussed in this chapter, there are still possibilities to achieve the coupling of N4Py to cyclodextrin.

Iron(II) complexes of tetradentate non-heme ligands have been shown to be promising catalysts in oxidation reactions like epoxidation and *cis*-dihydroxylation of alkenes and benzylic oxidation of alkylarenes. Both hydrogen peroxide and oxygen were used as terminal oxidants in these catalytic oxidation reactions. Chiral ligands were synthesized and the corresponding iron complexes were tested in oxidation reactions affording new information about the restrictions of the ligands with respect to enantioselective oxidation catalysis. Mechanisms for the catalytic oxidation by $[(N3Py\text{-}Me)Fe(CH_3CN)_2](ClO_4)_2$ in different solvents have been proposed. Here, the catalytic behavior of the iron complex depended on the nature of the solvent. Eventually, the results discussed above might help to create new, commercially applicable non-heme iron catalysts and new models for non-heme iron oxygenases.

7.5 References

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