Selective metalloenzyme-inspired oxidations (Scientific report)

Biological oxidation reactions utilizing dioxygen, superoxides, peroxides or water as oxidants are amongst the most frequent reactions that occur in biology, where they are catalyzed by metalloenzymes belonging to the oxidoreductase class of enzymes. In biology, such reactions are catalyzed by oxidase, mono- and dioxygenase enzymes that activate dioxygen and effect catalytic oxidation of biological substrates under very mild conditions when compared to industrial catalysts. The majority of these metalloproteins exploit the oxidative power of dioxygen to catalyze a broad spectrum of oxidative reactions such as desaturations, oxidative cyclizations, mono- and dioxygenations, hydroperoxidations, *cis*-hydroxylations and epoxidations, which have medical, pharmaceutical, agricultural or commercial significance. Model chemistry in relevance to metalloenzymes has progressed remarkably in recent years, and contributed greatly to clarification of structure and mechanism of various enzymes. The other important contribution of the model systems to the progress in enzymatic studies is to obtain information about structures and reactivities of substrate-metal intermediates, and investigate how the model chemistry is related to development of efficient catalysis by metal complexes. Challenges ahead are to make industrial processes more "green" and more economically efficient with a higher productivity. The development of new catalysts for biologically relevant oxidation reactions is therefore of great importance.

This work focused on the mononuclear (as a continuity of our recent research, but by using novel chiral ligands) and dinuclear (with new (a)chiral ligands) non-heme Fe^{II} enzymes (mononuclear: Rieske dioxygenase, 1-aminocyclopropane-1-carboxylate oxidase, taurin dioxygenase, phenylalanine, tyrosine, and tryptophan hydroxylases; binuclear: soluble methane monooxygenase, ribonucleotide reductase deoxihipuszin hidroxiláz, and cyanobacterial aldehyde-deformylating oxygenase), which play important role in biological systems. The aim of this project was to work out structural and functional models for the non-heme Fe^{II} enzymes discussed above to elucidate the catalytic pathways, mechanisms, and expand of chemistry from bioinorganic chemistry to bioinspired catalysis by development of new homogeneous catalysts, that exhibit high chemo-, regio- or enantioselectivity in organic, and/or aqueous medium.

Synthetic models of nonheme monoiron enzymes [1]

A series of new asymmetric polypyridines (asN4Py, as1QN4Py, as2QN4Py) have been synthesized by classic organic, organometallic methods. Introduction of a chiral center into these unique ligands opens a new chapter for asymmetric oxidative catalysis with high-valent metal complexes. As a synthetic model of nonheme monoiron enzymes a new chiral pentadentate ligand and its Fe(II) complex were synthesized, characterized and used as precursor of chiral Fe(IV)-oxo species. The formation kinetics, characterization, reactivity and (enantio)selectivity of this intermediate in an OAT reaction was investigated in details and compared to a similar pentadentate ligand-containing system. Chiral N4Py-type ligand, *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine (asN4Py), was synthesized and characterized by nuclear magnetic resonance spectroscopy (NMR), electrospray ionization mass spectrometry (ESI-MS), and X-ray crystallography. The chiral separation of the racemic

ligand has been carried out by HPLC in a heptane/ethanol (50/50) mixture, and the electronic circular dichroism (ECD) were used to establish the absolute configurations (+)-(*S*) and (-)-(*R*) of asN4Py. Using the racemic mixture, asN4Py forms the monomeric Fe(II) complex $[Fe^{II}(asN4Py)(CH_3CN)]^{2+}$ (**1**). The structure of **1.(ClO$_4$)$_2$** was revealed by X-ray structure analysis. The oxidation of 4-MeO-PhSMe using CHP, TBHP and PhIO as terminal oxidants at ambient temperature (Fe:oxidant:substrate = 1:10:100) is catalyzed by both enantiomers of complex **1.(ClO$_4$)$_2$** (where the MeO-PhS(O)Me was formed in 13, 96 and 94% yields, respectively with particularly high *ee* values (93-98%), and very little overoxidation to the sulfone (<2-3%). The low amount of sulfone indicate that the *ee* values of MeO-PhS(O)Me originate from the enantioselective oxidation of sulfide rather than from kinetic resolution of the resulting chiral sulfoxide. To get direct evidence for the involvement of the high-valent Fe(IV)-oxo species in the enantioselective step, the Fe(IV)-oxo was generated by the reaction of either (*S*)-, or (*R*)-**1.(ClO$_4$)$_2$** with PhIO, and the reaction with 4-MeO-PhSMe was monitored by UV-visible spectroscopy, and the enantioselectivities were determined by chiral GC analysis. Similarly to the catalytic reactions, high enantioselectivities (up to 87 % *ee*) were observed in the stoichiometric reactions. These results demonstrate that the Fe(IV)-oxo complex with a chiral moiety can significantly affect the enantiomeric selectivity, therefore the oxidation must be bound to the metal-based oxidant. In conclusion, we have reported one of the first example of a chiral nonheme Fe(IV)-oxo intermediate that is capable of the stereoselective oxidation of PhSMe. **[2]**

Kinetics and mechanism of epoxidation of olefins by chiral tetrapyridyl oxoiron(IV) complex

High-valent oxoiron(IV) species play a key role in the catalytic cycle of mononuclear non-heme iron enzymes such as bleomycin and Rieske dioxygenases that are capable of a wide range of synthetically challenging oxidations such as hydroxylation, epoxidation etc.

As a functional model of Rieske dioxygenases, the reactivity of the previously reported low-spin (S = 1) oxoiron(IV) complex, $[Fe^{IV}(asN4Py)(O)]$ with chiral pentadentate ligand, asN4Py (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine), has been investigated in the oxidation reaction of various alkenes such as *cis*-cyclooctene and styrene derivatives. A linear free-energy relationship between the second-order rate constants (k_2) for the *para*-substituted styrene oxidations and the total substituent effect (TE) parameters has been established: ρ(TE) = +0.19. A comparison of this correlation for the corresponding oxoruthenium(IV)-mediated epoxidation reactions has revealed that the oxidation of aromatic alkenes mediated by $[Fe^{IV}(asN4Py)(O)]$ proceeds via the rate-limiting formation of a benzylic radical intermediate in a nonconcerted process. Based on these results above, similar mechanism with radicaloid intermediates can be proposed for other cyclic and acyclic alkenes. The moderate enantioselectivities for the oxidation of styrene derivatives (8-12% ee) can be explained by the rotation/collapse processes through C-C bond of the radicaloid species before the epoxide ring closure. **[3]**

Kinetics and enantioselectivity of the Baeyer-Villiger oxidation of cyclohexanones by chiral and achiral tetrapyridyl oxoiron(IV) complexes

Baeyer-Villiger (B.-V.) oxidation of ketones into esters or lactones by organic peroxyacids as stoichiometric oxidants has a wide range of application, from the synthesis of steroids, antibiotics, pheromones, and herbicides to the synthesis of intermediates for polymerization. *Baeyer-Villiger* monooxygenases (BVMO) are considered highly valuable catalysts for the synthesis of fine chemicals. Type III BVMOs are specific cytochrome P450s, which are involved in the synthesis of brassinosteroids, steroidal hormones essential for the growth and development of plants. These heme-containing monooxygenases are supposed to exploit the hydroperoxy heme intermediate ($Fe^{III}OOH$) as a "peracid catalyst". Since the classical B.-V. reaction lacks of the chemo-, regio-, and enantioselectivity, that are expected for organic synthesis, and the oxidants which are used are hazardous and expensive, these limitations led to the application of biomimetic systems.

Iron complexes of meso-tetraphenylporphyrin, $Fe^{III}(TPP)Cl$, and *N*,*N*‑bis(2‑pyridylmethyl)‑*N*‑bis(2‑pyridyl)methyl‑amine $[Fe^{II}(N4Py)(CH_3CN)]^{2+}$ proved to be efficient catalysts for the aerobic oxidation of cyclohexanone in the presence of various aldehydes as sacrificial reductants, wherein, contrary to the heme-containing monooxygenases, a high-valent iron porphyrin, $[Fe^{V}(TPP)(O)]Cl$ and $[Fe^{IV}(N4Py)(O)]^{2+}$ were proposed as key intermediates in the rate-determining oxygen atom transfer step to generate the ε-caprolactone. **[4]**

Oxoiron(IV) complex, $[Fe^{IV}(asN4Py)(O)]^{2+}$ with chiral pentadentate ligand, asN4Py (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine), is effective for the *Baeyer-Villiger* oxidation of cyclohexanone derivatives. The reaction is shown to be first order in both cyclohexanone and the oxoiron(IV) species. The second order rate constant is smaller by one order of magnitude than that obtained for the related achiral $[Fe^{IV}(N4Py)(O)]^{2+}$ complex. Oxidation of 4-substituted cyclohexanone derivatives by the chiral oxoiron (IV) complex attains moderate enantioselectivities up to 45% enantiomeric excess (ee). **[5]**

Oxidation of 2,6-di-tert-butylphenol by tetrapyridyl oxoiron(IV) complex

Phenols, which are typical substrates for the horseradish peroxidase (HRP), are oxidized to phenoxyl radicals. Mechanistic studies suggested that the oxidation process involves a rate determining electron transfer from the phenol to the oxo–heme species, in contrast to the biomimic $Fe^{IV}(T2MPyP)(O)$ (T2MPyP = tetra(2-*N*-methylpyridyl)porphyrin) containing system where oxidation occurs by hydrogen atom abstraction via simultaneous removal of a proton and an electron. Since phenols are one of the major water and soil pollutants, in addition to enzymatic systems, transition metal complexes have also been investigated as catalysts for phenol oxidations or degradations. On the other hand, the 2,6-di-*tert*-butylphenols are widely used as antioxidants and models of vitamin E in medicine.

The reactivity of the previously reported pentadentate low-spin (S = 1) oxoiron(IV) complex, $[Fe^{IV}(O)(asN4Py)]$ (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)-ethylamine), has been investigated in the oxidation reaction of 2,6-di-*tert*-butylphenol derivatives. Detailed kinetic, and mechanistic studies (kinetic isotope effect (KIE) of 4.52, and Hammett correlation with $\rho = -1.83$), lead to the conclusion that the rate-determining step in this reaction involves direct hydrogen-atom transfer (HAT) from the phenol by the oxoiron(IV) species, in contrast to the heme-type horseradish peroxidase (HRP) system. **[6]**

Oxoiron(IV)-mediated benzaldehyde oxidation as pterin-dependent hydroxylase mimics

Pterin-dependent hydroxylases, including phenylalanine (PheH), tyrosine (TyrH), and tryptophan (TrpH) hydroxylase are non-heme mononuclear iron enzymes with a 2-His-1-carboxylate platform, which are responsible for essential biological functions such as the biosynthesis of tyrosine (PheH), and various neurotransmitters like dopamine, norepinephrine, epinephrine (TyrH), and serotonin (TrpH). For such enzymes, catalytic oxoiron(IV) intermediates have been postulated to introduce a hydroxyl group on the aromatic ring via their electrophilic attack on the aromatic ring supported by inverse KIE and a NIH shift.

The present study describes the first example of the hydroxylation of benzaldehydes by synthetic nonheme oxoiron(IV) complexes, where the reactivity, chemoselectivity, and mechanism were strongly influenced by the ligand environment of the iron center. We have reported the comparison of the stoichiometric oxidation of benzaldehyde to benzoic acid and/or salicylic acid by $[Fe^{IV}(N4Py)(O)]^{2+}$ (**1**) and $[Fe^{IV}(asN4Py)(O)]^{2+}$ (**2**) complexes (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine). Interestingly, the aromatic hydroxylation does not occur in the reaction of **1** but does with **2**, which may be explained by the replacement of one of the pyridyl moiety by a more labile 2-pyridylmethyl arm on the N4Py ligand. In summary, it is possible that there is a mixed mechanism, but both the benzylic and arene oxidation can be drawn with the two different resonances of the intermediate benzoyl radical. Since the redox properties of **1** and **2** complexes are almost identical ($E_{1/2}$ = 1.01 V and 0.95 V vs. SCE, respectively), the difference in the mechanisms can be explained by different geometries around the iron centers. Similarly to the recently published results, the aromatic ring oxidation occurs only in the presence of **2**, which has two *cis*-labile sites for the formation of a six-membered-ring transition state. The benzylic oxidation by **1** and **2** can be drawn by an intermolecular tunneling-like HAT processes in both cases. **[7]**

Structural and functional models of alpha-ketoglutarate-dependent flavone synthase

Due to the antioxidant or putative anticancer activities of certain flavonoids, they also nutritional values and medicinal benefits to humans. For example, naringenin has been reported to be a good inhibitor of aromatase as a major strategy in the treatment of breast cancer. The introduction of the C^2-C^3 double bond into flavanones to form flavones is an important reaction in the biosynthesis of flavonoids. The therapeutic potential of flavones makes these compounds also valuable targets for drug design, including DNA approaches.

As a synthetic alpha-ketoglutarate-dependent flavone synthase model, where high-valent oxoiron(IV) species has been proposed as active oxidant, we have carried out a detailed mechanistic studies on the $[Fe^{II}(N4Py)(CH_3CN)](ClO_4)_2$, $[Fe^{II}(asN4Py)(CH_3CN)](ClO_4)_2$, and $[Fe^{II}(asN2Py2Quin)(CH_3CN)](ClO_4)_2$-catalyzed oxidative desaturation reaction of flavanone to flavone with MCPBA, including the kinetics on the reactivity of the trapped and spectroscopically characterized oxoiron(IV) intermediates. In this study we have demonstrated, that iron(II) complexes with N4Py-type ligands are active and selective catalysts in the oxidation of flavanone. The experimental and computational results clearly indicated the formation of a high-valent metal-oxo intermediate ($Fe^{IV}O$), and its role in the oxidation process, including a rebound mechanism with the formation of 2-hydroxyflavanone

contrary with the dissociation process suggested by Nam for substrates with stronger C-H bonds. This system is the first biomimics of FS enzymes. **[8]**

1-Aminocyclopropane-1-carboxylic acid oxidase (ACCO) mimics

Metal coordinated amino acids (AA) are important due to their involvement in a number of biochemical and catalytic systems, such as oxygen conveyer, electron transfer and oxidation. For example, 1-aminocyclopropane-1-carboxylate (ACC) oxidase (ACCO) is a key enzyme that catalyzes the final step in the biosynthesis of the plant hormone ethylene. ACCO has been classified as a member of a family of non-heme iron proteins, and suggested that the substrate oxidation proceeds through two successive monoelectronic oxidation steps including the formation of peroxoiron(III) and oxoiron(IV) intermediates. However, there are only few reported functional models of ACCO. These are mainly using iron and copper ions.

Copper models:

Copper(II) chloride and novel bis(1-amino(cyclo)alkane-1-carboxylato-kappa N-2,O)copper(II) complexes as catalysts were studied in relation with enzymatic oxidation of amino acids. The oxidation of aminophosphonate derivative: (1-amino-l-methyl)ethylphosphonic acid was also investigated. Two bis(1-aminocycloalkane-1-carboxylato-kappa N-2,O)copper(II) complexes were structurally characterized. Surprisingly, while the 1-aminocyclobutane-1-carboxylate complex has square planar (SP-4) copper(II) center with trans-orientated ligands, the 1-aminocyclohexane-l-carboxylate complex has mu-carboxylato dimeric structure with square pyramidal (SPY-5) sites, one with cis- and one with trans-orientated ligands. Redox behavior of the bis(1-amino(cyclo)alkane-1-carboxylato-kappa N-2,O)copper(II) complexes was also investigated. Catalytic oxidations were carried out in alkaline DMF-water mixtures using H_2O_2 as oxidant and the complexes as catalysts. The observed potentials for the irreversible current peaks associated with the Cu(II) to Cu(I) reduction and the rates of the amino acid oxidations show inverse trend. This suggests that the Cu(II)/Cu(I) redox cycling due to the presence of H_2O_2 plays important role in the peroxide/copper activation that in turn provides the observed products. **[9]**

Copper(II)-amino acid (AA) complexes that contain 2,2'-bipyridine (bpy) as supporting ligand were investigated. X-ray structural analysis of three new bpy-based complexes revealed a bidentate coordination of the AAs on the copper(II) centers similar to that proposed for the substrate on the iron(II) center of the 1-aminocyclopropane-1-carboxylic acid oxidase (ACCO). Similar complexes with two aminophosphonic acids (APAs), 1-aminocyclopropane-1-phosphonic acid (ACP) and (1-amino-1-methyl)ethylphosphonic acid (AMEP), were also investigated, and the latter complex was structurally characterized. This structure reveals the bidentate coordination of -aminophosphonate on the copper(II) ion. The oxidation of the bound amino acids (AAs) and aminophosphonates (APAs), which model the reaction catalyzed by ACCO, was investigated. The complexes react with H_2O_2 and give oxidation products that were identified by gas chromatography. Reduction of Cu^{II} to Cu^{I} was detected by UV/Vis spectroscopy upon reaction with H_2O_2 or ascorbate. This reduction is proposed to be the initial step for the peroxide/copper activation prior to the oxidation of the AA and APA ligands by means of a radical mechanism. **[10]**

As a continuity of the $[Cu^{II}(AIB)(bpy)(H_2O)](ClO_4)_2$-containing ACCO (1-aminocyclopropane-1-carboxylate oxidase) model, two new copper(II)–amino acid complexes $[Cu^{II}_2(AIB)_2(PBI)_2(CH_3OH)(ClO_4)]ClO_4$ and $[Cu^{II}_2(AIB)_2(PBT)_2(H_2O)](ClO_4)_2.CH_3OH$ with a modified hetero-bidentate ligands (PBT = 2-pyridin-2-yl-benzothiazole and PBI = 2-pyridin-2-yl-1H-benzoimidazole) have been synthesized, characterized by various techniques including IR, UV–Vis, electrochemical and X-ray measurements, and investigated their reactivity toward H_2O_2 with respect to the redox behavior compare to $[Cu^{II}(AIB)(bpy)(H_2O)](ClO_4)_2$. **[11]**

Solid-state stereochemistry and mobility of paramagnetic copper(II) complexes formed by aliphatic amino acids (*L*-alanine, *D,L*-alanine, 1-amino-2-methyl-alanine) and 1-amino(cyclo)alkane-1-carboxylic acids (alkane = propane, butane, pentane, hexane) as bidentate ligands has been studied by ^{13}C and ^{2}H solid-state fast magic angle spinning (MAS) NMR spectroscopy. We examined the prospective method to characterize solid-state paramagnetic compounds in a routine way. Both ^{13}C and ^{2}H MAS spectra can distinguish D,L and *L,L* diastereomers of natural and polydeuterated bis([Dn]alaninato)copper(II) (n = 0, 2, 8) complexes with axial and/or equatorial methyl positions (conformations) primarily due to different Fermi-contact (FC) contributions. The three-bond hyperfine couplings clearly show Karplus-like dependence on the torsional angles which turned out to be a useful assignment aid. Density functional theory calculations of the FC term and crystal structures were also used to aid the final assignments. The correlations obtained for bis(alaninato-κ2N,O)copper(II) complexes were successfully used to characterize other complexes. The usefulness of the ^{2}H MAS spectra of the deuterated complexes was underlined. Even the spectra of the easily exchangeable amine protons contained essential stereochemical information. In the case of a dimer structure of bis(1-aminohexane-1-carboxylato-κ2N,O)copper(II) both the ^{13}C and ^{2}H resolutions were good enough to confirm the presence of the cis and trans forms in the asymmetric unit. With regard to the internal solid-state motions in the crystal lattice, the obtained quadrupolar tensor parameters were similar for the *D,L*- and *L,L*-alaninato isomers and also for the *cis*−*trans* forms suggesting similar crystal packing effects, static amine deuterons involved in hydrogen bonding, and fast rotating methyl groups. **[12]**

Effects of stereochemistry, polymorphism, crystal packing, and solid phase mobility on the 2H magic-angle spinning (MAS) NMR spectra of the paramagnetic Cu(II) glycinato complexes have also been investigated. The reliability of information obtained from the spectra, such as symmetry relations within a molecule, number of chemical sites or molecules found in the asymmetric units, was confirmed by previously published X-ray crystal and molecular structures. From the ^{2}H MAS spectra, complemented with powder diffractograms of the synthetized bis(glycinato-d4)copper(II) complexes, we could identify three solid phases, namely the cis aqua and non-aqua forms and the trans non-aqua crystals. A fourth sample was identified as octahedral copper(II) complex chain with bidentate glycine and NO_3 ligands in the octahedral building units. Correlations between the sign and magnitude of the observed paramagnetic shifts and the number of bonds and/or the dihedral angles connecting the actual ^{2}H nucleus and the paramagnetic center, useful in structural assignments, were revealed. The agreement of the ^{2}H MAS NMR spectral information with the available crystal diffraction data forecast their applicability in NMR crystallographic works too. **[13]**

Iron models:

We have carried out a detailed kinetic, mechanistic and computational studies of the H_2O_2 oxidation of 1-aminocyclopropane-1-carboxylic acid (ACCH) to ethylene by heme, [Fe(III)(TPP)Cl] (TPP = meso-tetraphenylporphyrin), and nonheme-type iron complex, $[Fe(II)(CH_3CN)(N4Py)](ClO_4)_2$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)-methylamine), as biomimics of 1-aminocyclopropane-1-carboxylic acid oxidase (ACCO). **[14]**

Series of dichloroiron(III) complexes of 1,3-bis(2'-arylimino)isoindoline have been used as catalysts for the oxidative decarboxylation and deamination reaction of acyclic [alpha-aminoisobutyric acid (AIBH)] and cyclic amino acids [1-aminocyclohexane-1-carboxylic acid (ACHH), 1-aminocyclopentane-1-carboxylic acid (ACPH), 1-aminocyclobutane-1-carboxylic acid (ACBH), 1-aminocyclopropane-1-carboxylic acid (ACCH)] to ethylene or the corresponding carbonyl compounds. We have found that the title complexes are very efficient and selective as catalysts, and linear correlations were observed between the reaction rate and the oxidation potential, $E\text{pa}^{o'}$, of the iron complexes, and the endocyclic bond angle of the substrates used. **[15]**

Catecholase and catechol dioxygenase mimics:

The biodegradation of aromatic hydrocarbons is mediated by a great number of metalloenzymes, metalloproteins. They are able to utilize dioxygen from the air to convert biologically harmful compounds into useful carbon sources. Catecholase and catechol dioxygenases are the member of oxidoreductases family. Catechol dioxygenases split into two subgroups the intradiol- and the extradiol-cleaving enzymes. Members to be mentioned of the first group are catechol 1,2-dioxygenase and protocatechuate 3,4-dioxygenase. They are both Cu(II) or Fe(III)-dependent biocatalysts.

A series of new mixed ligand copper complexes $Cu^{II}(PBI)(O_2Ncat)$ (PBI = 2-(2-pyridyl)-benzimidazole), $Cu^{II}(DMPBI)(O_2Ncat)$ (DMPBI = 5,6-dimethyl-2-(2-pyridyl)-benzimidazole), $Cu^{II}(PBO)(O_2Ncat)$ (PBO = 2-(2-pyridyl)-benzoxazole), $Cu^{II}(PBT)(O_2Ncat)$ (PBT = 2-(2-pyridyl)-benzothiazole), and $Cu(TBA)(O_2Ncat)$ (TBA = 4-(1*H*-1,3-benzodiazol-2-yl)-1,3-thiazole) have been synthesized by classic organic, bioinorganic methods. The complexes have been found to mimic catechol oxidase and catechol dioxygenase activity depending on the oxidant used. Triplet state dioxygen activates the complex leading to intradiol cleavage product, 2-nitromuconic acid while sterically more demanding *tert*-butyl hydroperoxide (TBHP) oxidizes the 4-nitrocatechol (O_2NcatH_2) ligand into 4-nitrobenzoquinone. We have also found that the electron density on the copper center significantly increase the reactivity toward the oxidant used. **[16]**

Phenoxazinone synthase mimics:

The multicopper oxidase phenoxazinone synthase (PHS) catalyzes the oxidative coupling of two molecules of a substituted 2-aminophenol (OAPH) to the phenoxazinone chromophore in the penultimate step of the biosynthesis of the antibiotic *actinomycin D* by *Streptomyces antibioticus*. This naturally occurring antibiotic is used clinically for the treatment of Wilm's tumor, gestational chlorocarcinoma and other tumors. Aminophenols are also widely used as reducing agents, as intermediates in chemical synthesis, bleaching, and

hair dyes, and as materials for photography. It is well known that 2-aminophenol causes toxic methemoglobinemia in human erythrocytes, where oxy and methemoglobin are involved, resulting in the production of 2-aminophenoxazinone-3-one. Thus, it appears that iron containing enzymes are also capable of oxidative dimerization of 2-aminophenol.

As a mimics series of dichloroiron(III) complexes of 1,3-bis(2′-arylimino)isoindoline, including a new structurally characterized ligand 1,3-bis(5′-methyl-2′-thiazolylimino)-isoindoline and its complex, have been used as catalysts for the oxidative coupling of 2-aminophenol (OAPH) to 2-aminophenoxazine-3-one (APX) in DMF solution at ambient temperature. The complexes were suitable as catalyst, and depending on the oxidant used, two different mechanisms can be proposed, namely a metal-based oxidation for dioxygen, and a hydroxyl radical mediated process, including zero-order dependence on the concentration of the substrate, for H_2O_2. In the former case a mechanism on the basis of kinetic data was proposed assuming ternary complex formation between catalyst, substrate and dioxygen, and a nice correlation was found between the reaction rate and the oxidation potential, E'_{pa} of the iron center in the precursor complexes. **[17]**

Structural and functional models of non-heme diiron oxidoreductases:

Metalloenzymes with non-heme diiron centers have emerged as important class of enzymes. Several members of them are now structurally characterized. This review summarizes recent investigations with non-heme diiron oxidoreductases (Ribonucleotide reductase (R2), soluble methane monooxygenase (sMMO), stearoyl-acyl carrier protein (ACP) Δ9-desaturase (Δ9D), human deoxyhypusine hydroxylase (hDOHH) and hemerythrin (Hr), via their synthetic models focusing specifically on the synthesis, characterization, and spectral behavior of well-defined peroxo-diiron(III) intermediates. Fundamental biochemical processes are catalyzed by these enzymes, such as biodegradation of hydrocarbons, or synthesis of essential biomolecules including DNA building blocks. Better understanding on biologically determinant reactions may lead scientists to the discovery of crucial drugs and even “green solutions” in industrial applications. A brief overview on reaction kinetics, that has afforded useful insights into the mechanism of dioxygen activation and substrate oxidation by diiron centers, is also included in this paper. **[18]**

Deoxyhypusine hydroxylase mimics:

Deoxyhypusine hydroxylase is the key enzyme in the biosynthesis of hypusine containing eukaryotic translation initiation factor 5A (eIF5A). The biosynthesis of eIF5A involves a posttranslational modification of the eIF5A precursor, where a lysine residue is firstly modified to deoxyhypusine (Dhp) by deoxyhypusine synthase (DHS) and then the nascent Dhp is hydroxylated by deoxyhypusine hydroxylase (DOHH) to form hypusine (Hpu). The importance of hypusine and these 2 enzymes has been shown by several studies where depletion of spermidine or inhibition of either DHS or DOHH leads to a decrease of hypusine-containing eIF5A [eIF5A(Hpu)] and inhibition of eukaryotic cell growth. Consequently, these results suggest that eIF5A and DOHH could be promising targets for antitumor and anti- HIV-1 therapies. The diiron center of human DOHH (hDOHH) forms a peroxo-diiron(III) intermediate (hDOHHperoxo) when its reduced form reacts with O_2. In our

research the precursor complexes was synthesized from the reaction of different nitrogen-containing heterocyclic ligands, and Fe(II) salts. They have been characterized by X-ray crystallography and several spectroscopic techniques. The precursor complexes are suitable catalyst for oxidation reactions, where the in situ formed peroxidodiiron(III) intermediates were isolated as key species. We isolated two types of peroxo-diiron(III) intermediates, (μ-oxido)(μ-1,2-peroxo)diiron(III) and (μ-1,2-peroxo)diiron(III). The peroxo-diiron(III) intermediate undergoes O-O bond scission to generate a high-valent oxidant capable for C-H, O-H bond activation and oxygen transfer.

We have carried out a detailed mechanistic studies on the $[Fe^{II}(IndH)(CH_3CN)_3](ClO_4)_2$-catalyzed (IndH = 1,3-bis(2-pyridylimino)isoindoline) oxidation of various hydrocarbons with H_2O_2, including the kinetics on the reactivity of the trapped and spectroscopically characterized μ-1,2-peroxo-diiron(III) intermediate. Comparison of the catalytic and stoichiometric results, based on Hammett correlations and kinetic isotope effects, supports the direct metal-based oxidation process, that may serve as one of the first functional model of the deoxyhypusine hydroxylase. **[under submission]**

The spectroscopic characterisation of the (μ-1,2-peroxido)diiron(III) species formed transiently upon reaction of $[Fe(II)(NN)_3]^{2+}$ complexes with H_2O_2 by UV/vis absorption and resonance Raman spectroscopy is reported. The intermediacy of such species in the disproportionation of H_2O_2 is demonstrated. **[19]**

The reactivity of the previously reported peroxo adducts $[Fe_2(\mu\text{-}O_2)(L^1)_4(CH_3CN)_2]^{2+}$, and $[Fe_2(\mu\text{-}O_2)(L^2)_4(CH_3CN)_2]^{2+}$, ($L^1$ = 2-(2'-pyridyl) benzimidazole and L^2 = 2-(2'-pyridyl)-N-methylbenzimidazole) towards H_2O_2 as catalase mimics, and towards various phenols as functional RNR-R2 mimics, is described. Kinetic, mechanistic and computational studies gave direct evidence for the involvement of the (μ-1,2-peroxo) diiron(III) intermediate in the O-H activation process via formation of low-spin oxoiron(IV) species. **[20, 21]**

To get direct evidence for the involvement of a peroxo-diiron(III) species in the *Baeyer-Villiger* oxidation, the reaction of $[Fe_2(\mu\text{-}O_2)(L^1)_4(CH_3CN)_2]^{2+}$ (L^1 = 2-(2'-pyridyl)benzimidazole) with various cycloketone derivatives was investigated. The peroxo-diiron(III) complex was generated by the reaction of Fe(II) complex with PhIO, and the rate of the decay of the absorption band at 760 nm with cyclohexanones was measured as a function of the concentration of added cyclohexanone derivatives. It was found that the nucleophilic peroxo-diiron(III) species is able to oxidize the cyclohexanone derivatives to the corresponding *ε*-caprolactones, including it's nucleophile attack on the carbonyl group. The relative reactivity of substrates is in the following order: 4^tBu-cyclohexanone > cyclohexanone > 2Me-cyclohexanone > 3Me-cyclohexanone > 4Me-cyclohexanone. The oxidation of other cyclic ketones like cyclopentanone and cyclobutanone was also examined. Their relative reactivity shows the following order: cyclohexanone > cyclopentanone > cyclobutanone, and correlates very well with their endocyclic bond angles. Since no reaction has been observed for benzophenone, this indicates clearly that the conjugation of the carbonyl group decreases the reactivity of the ketone. In order to get some mechanistic information about the peroxo-diiron(III)-mediated Baeyer-Villiger reaction we subsequently measured pseudo first-order rate constants (k_{obs}) for a series of para-substituted acetophenone derivatives (p-R-PhC(O)Me, R = H, Me, NO_2) . A second order rate constants (k_{ox}) were

calculated and the Hammett plot ($\log k_{rel} = \log {}^{R}k_{ox}/{}^{H}k_{ox}$) vs σ_p gave a ρ-value of zero (all substrates gave the same k_{ox}), excluding the nucleophilic attack of peroxo-diiron(III) as rate-determining step. These results are in good agreement with the *Baeyer-Villiger* oxidations, where the rate-determining step is not nucleophilic attack of the peroxide on the electrophilic carbonyl, which is reversible, but is a *Crieege*-like rearrangement. The cationic transition state can be stabilized by electron rich a-carbon-containing substrates. Thus cyclohexanones display high reaction rates, whereas acetophenones with electron poor a-carbons show much slower rates. **[under submission]**

The reactivity of our previously reported peroxo adducts $[Fe_2(\mu\text{-}O_2)(L^1)_4(CH_3CN)_2]^{2+}$, and $[Fe_2(\mu\text{-}O_2)(L^2)_4(CH_3CN)_2]^{2+}$, ($L^1$ = 2-(2'-pyridyl)benzimidazole and L^2 = 2-(2'-pyridyl)-N-methylbenzimidazole) towards various aldehydes as functional cADO mimics has been described. To get direct evidence for the involvement of a peroxo-diiron(III) species in the oxidative deformylation reaction, the reaction of $[Fe_2(\mu\text{-}O_2)(L^1)_4(CH_3CN)_2]^{2+}$ with various phenylacetaldehyde derivatives has been investigated. The peroxo-diiron(III) complex was generated by the reaction of Fe(II) complex with PhIO, and the rate of the decay of the absorption band at 760 nm with aldehyde was measured as a function of the concentration of added phenylacetaldehyde derivatives. It was found that the nucleophilic peroxo-diiron(III) species is able to oxidize the phenylacetaldehyde derivatives to the corresponding alkanes and their hydroxy and oxo derivatives, including it's nucleophile attack on the carbonyl group. (**Komplexkémiai Kollokvium, under submission**)

Catalytic oxidation of alcohols and sulfides with hydrogen peroxide using isoindoline and phthalazine-based diiron complexes

A series of diiron(III) complexes of 1,3-bis(2′-arylimino)isoindoline, $[(Fe(L)Cl)_2O]$ and 1,4-di-(2′-aryl)aminophthalazine, $[Fe_2(\mu\text{-}OMe)_2(H_2L)Cl_4]$, including new structurally characterized ligands, 1,4-di-(4′-methyl-2′-thiazolyl)aminophthalazine and 1,4-di-(2′-benzthiazolyl)-aminophthalazine, have been characterized, and used as catalysts for the oxidation of *para*-substituted phenyl methyl sulfides and benzyl alcohols. *Hammett* correlations and kinetic isotope effect experiments support the involvement of electrophilic metal-based oxidants. In case of $[(Fe(L^{1,2})Cl)_2O]$ catalysts, direct correlation has been found between the oxidative and catalase-like activity. **[22]**

A new sterically hindered isoindoline-based 1,3-bis(5'-methyl-4'-phenyl-2'-thiazolylimino) isoindoline was synthesized by fusion method with satisfyingly good yield. The structure of the newly synthesized compound was identified by FT-IR, UV-Vis, ^{1}H-NMR, ^{13}C-NMR and X-ray analysis. **[23]**

Isoindoline-derived ligands and applications: During the past decade isoindoline-based ligands became subject of growing interest due to their modular set-up. In this review the structure and reactivity of these ligands and their transition metal complexes are covered. Beyond the discussion of the structural properties particular attention is paid to the expanding fields of applications of these compounds. **[24]**

Synthesis of Chiral Copper Catalysts for HAT and OAT Reactions

In order to extend the number of chiral transition metal complexes suitable for mimicking HAT or OAT enzymatic reactions a mononuclear copper complex

$[Cu^{II}(asN4Py)(MeCN)](O_3SCF_3)_2$ and its mixed mono- and trinuclear $[Cu(pic)_2(ClO_4)_2][Cu_3(asN4Py)_2(pic)_2(ClO_4)_2](ClO_4)$ derivatives were synthesized containing N,N-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)-ethylamine (asN4Py) chiral ligands and 2-picolinate (pic) bridges. The structures were elucidated using single crystal X-ray diffraction and spectroscopic methods. Due to the non-trivial assignments of the formal Cu oxidation states, the d-electron count and the location of electron holes were assigned by broken-symmetry electronic structure calculations using a spectroscopically validated, hybrid density functional theory with saturated basis set. The ground state description of the mononuclear complexes is trivial; thus, they were used to validate the computational level of theory and the modelling approach. The experimental structure of the trinuclear complex can only be described by considering two asymmetric resonance structures in the crystal structure containing Cu^{II}-Cu^{II}-Cu^{I}/Cu^{I}-Cu^{II}-Cu^{II} metal centres. **[25]**

Flavin coenzyme mimics:

A 1,3,2-oxazaphosphole picks up triplet dioxygen in 1 : 1 stoichiometry similar to flavin organic co-factors. 1,3,2-Oxazaphosphole catalyzes the oxygenation of triphenylphosphine to triphenylphosphine oxide. The reaction obeys an overall third order rate equation. In a radical pathway, organic hydroperoxide is formed from the catalyst and $^3O_2$, which oxygenates PPh_3, similar to flavin cofactors. **[26]**

1,3,2-Oxazaphospholes are able to catalyze the oxidation of 3,5-di-*tert*-butylcatechol with $^3O_2$ to the corresponding *o*-quinone, and 2-aminophenol to 2-aminophenoxazine-3-one in methanol. In both cases, an overall third order reaction rate equation and a new type of biomimetic organocatalyst for oxidation reactions was found. A one electron transfer of the phenolate, which is formed through the deprotonation of the substrates by the catalyst, to dioxygen seems to be rate-determining step. **[27]**

2,3-Dihydro-2,2,2-triphenylphenanthro[9,10-d]-1,3,2-l5-oxazaphosphole serves as good catalyst for the oxidation of thiophenol, cysteine and glutathione to their disulfides by molecular oxygen. The kinetics of the reactions unveiled an overall second order rate equation for all reactions and pure dioxygen chemistry for all three substrates. The formation of an unstable hydroperoxide from the catalyst is assumed to be a key step during the reaction. **[28]**

The reactions of 2,3-dihydro-2,2,2-triphenylphenantro[9,10-d]-1,3,2-λ^5-oxazaphospholes with aromatic aldehydes lead to the corresponding 2-substituted phenanthro[9,10-d][1,3]oxazoles via an aza-*Wittig* reaction in good yields. **[29]**

2,3-Dihydro-2,2,2-triphenylphenanthro[9,10-d]-1,3,2-λ^5-oxazaphospholes react with carbon dioxide in an overall second order reaction at room temperature to give 3H-phenanthro[9,10-d]oxazol-2-ones and triphenylphosphine oxide in good yields. Nucleophilic attack of the phenolate on CO_2 and formation of Ph3P=O was found. **[30]**

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