Justus-Liebig-Universität Gießen
Institut für Anorganische und Analytische Chemie
Fachbereich Biologie und Chemie

Activation of small molecules with iron(II)- and copper(I)-complexes

Kumulativ-Dissertation zur Erlangung
des Doktorgrades der Naturwissenschaften

vorgelegt von
Pascal Specht
aus Gießen

Selbstständigkeitserklärung

Ich erkläre: Ich habe die vorgelegte Dissertation selbstständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich stimme einer evtl. Überprüfung meiner Dissertation durch eine Antiplagiat-Software zu. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.

_____	_____
Ort, Datum	Pascal Specht

Erstgutachter: Prof. Dr. Siegfried Schindler

Zweitgutachter: Prof. Dr. Richard Göttlich

Danksagung

Ich möchte mich bei Prof. Dr. Siegfried Schindler für die Möglichkeit, in seiner Gruppe zu promovieren, und für die kontinuierliche Unterstützung bedanken. Außerdem möchte ich mich bei Prof. Dr. Richard Göttlich für die Zweitbegutachtung dieser Arbeit bedanken.

Weiterhin möchte ich mich bei Prof. Dr.-Ing. Michael Schlüter und den am DFG-Schwerpunktprogramm 1740 "Reaktive Blasenströmungen" beteiligten Gruppen für die tolle und interdisziplinäre Zusammenarbeit und die zahlreichen, anregenden Treffen und den regen Austausch bedanken. Ganz besonders möchte ich mich bei Dr. Martin Oßberger und Prof. Dr. Peter Klüfers von der LMU München für die hervorragende Zusammenarbeit bei der Untersuchung der Eisenkomplexe bedanken.

Danken möchte ich auch der studentischen Unterstützung während meiner Promotion durch Alexander Petrillo, Matthias Karl, Chloe McCumiskey, Rhona Lonergan, Diana Gallapeni und Chiara Mazzariol, deren Projekte ich betreut habe und deren Arbeit mir auch bei meiner eigenen Forschung weitergeholfen hat.

Ich möchte mich bei der gesamten Arbeitsgruppe Tim Brückmann, Florian Ritz, Lars Schneider, Thomas Rotärmel, Alexander Petrillo, Markus Lerch, Christopher Gawlig, Stefan Schaub und Frank Mehlich, sowie bei meinen ehemaligen Kollegen Dr. Miriam Wern und Dr. Andreas Miska für das gute Arbeitsklima, die tolle Zusammenarbeit und die wunderbaren Jahre während meiner Promotion bedanken. Außerdem möchte ich mich bei Lars Schneider und Dr. Miriam Wern für das Korrekturlesen meiner Arbeit bedanken.

Bei Dr. Jonathan Becker möchte ich mich für zahlreiche hilfreiche Diskussionen, aber auch für die Messung und Auswertung der Kristallstrukturen während meiner Promotion bedanken.

Außerdem möchte ich mich bei meinen ehemaligen Kommilitonen und Freunden bedanken, die mir immer mit Rat und Tat zur Seite standen.

Vor allem aber möchte ich mich bei meiner Familie bedanken, die mich in all den Jahren meines Studiums mit viel Unterstützung und Geduld begleitet hat.

„Lernen ist wie rudern gegen den Strom – wer aufhört, treibt zurück.“

– Laozi

Table of contents

1 Introduction

1.1 Metalloproteins

Metalloproteins are essential components for all living organisms and take part in a multitude of different functions as catalysts in biological processes, such as respiration, photosynthesis, water oxidation or binding and activation of small molecules, like molecular dioxygen or nitrogen oxides.[1–3] The elements copper and iron are particularly important here due to their unique properties and high bioavailability. In addition to zinc, these two elements are two of the three most common transition metals in the human body. As part of the active centers in enzymes they play a decisive role in many vital processes, especially in the binding and activation of molecular dioxygen and electron transfer reactions.[1,4,5]

1.1.1 Copper dioxygen proteins

Copper occurs as a trace element with about 150 mg in the human body and has already been observed in many enzymes of humans, animals, plants and microorganisms as part of the active center.[1,4,6,7] It is usually coordinated in the oxidation states +I, +II or as an intermediate also as +III. The biological functions of copper are mainly based on an easily accessible Cu^{I}/Cu^{II} redox transition in the positive potential range. Furthermore, some copper enzymes are able to bind molecular dioxygen reversibly or activate it and carry out one- or two-electron redox processes or catalyze oxygenation reactions on organic substrates. Figure 1 shows some examples for copper-containing proteins and their biological function.

In addition, to the classification according to their function (e. g. as oxidase or oxygenase), classic copper proteins are divided into type 1, type 2 and type 3 copper proteins based on their structural and spectroscopic properties.[1,3,4] Copper-containing proteins that do not correspond to this assignment are non-classical copper proteins.[8]

Type 1 copper proteins are also referred to as “blue” copper proteins due to their characteristic and intense blue color in the oxidized state.[3,8] Type 1 copper centers consist of a copper ion that is coordinated in a strongly distorted tetrahedral coordination geometry. It consists of two histidine and one cysteinate ligand in a distorted trigonal arrangement and a further weakly bound variable ligand, such as methionine, glutamine or leucine (Figure 2). The binding of the

cysteinate to the copper center and the resulting intensive ligand metal charge transfer absorption band at 600 nm leads to its distictive and eponymous blue color. The distorted geometry represents a compromise between the square-planar arrangement preferred by copper(II) and the tetrahedral arrangement preferred by copper(I) complexes. This enables a transition of the geometry and an increased speed of electronic transition of the two oxidation states. This property also leads to the frequent involvement of type 1 copper proteins in electron transfer processes. Examples of type 1 proteins are plastocyanin or azurin, which are involved in plant or bacterial photosynthesis as electron carriers.[9,10]

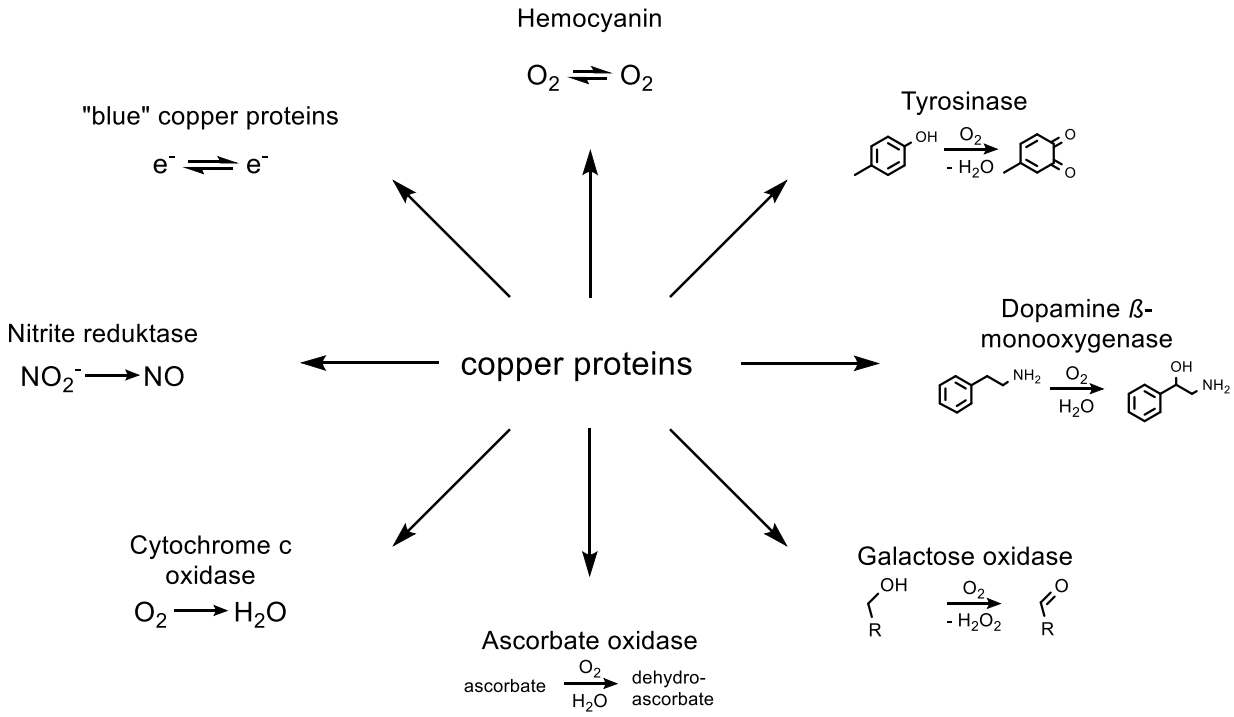


Figure 1: Several essential biological functions of copper-containing proteins.[11]

Type 2 copper proteins are also referred to as normal or non-blue copper proteins.[1,3,8] This is due to their usually slightly/weak blue color, which results from d-d transition states of orbitals of different symmetry of the copper ion, similar to common copper(II) complexes. The coordinative environment of the copper center usually has a square-planar or distorted tetrahedral geometry by four N and/or O donor atoms, e.g. two histidine residues, two tyrosine residues and one lable ligand such as water or a free coordination site (Figure 2). Type 2 copper proteins are mostly involved in catalysis as oxidase, oxygenase or superoxide dismutase. Examples are galactose oxidase, which catalyze the two-electron transfer reaction during the oxidation of primary alcohols to corresponding aldehydes[12] and dopamine β-monooxygenase, which is involved in the side chain hydroxylation of dopamine to norepinephrine.[8,13]

In contrast to type 1 and 2 copper proteins, type 3 copper proteins have an active center that consists of two copper ions coordinated by three histidine residues each (Figure 2).[1,3,8] This type of copper proteins plays an important role in binding and activation of molecular dioxygen. The molecular dioxygen is connected as a side-on peroxido ligand and the resulting complex has two characteristic absorption bands at 350 nm and 600 nm. The coordination geometry of the center change from a trigonal planar shape in the deoxy form to square pyramidal in the oxy form. Typical type 3 copper proteins are for example hemocyanin, tyrosinase and catechol oxidase.[8] Hemocyanin is responsible for the transport of dioxygen in molluscs and arthropods and also causes the blue colored blood, unlike the red blood of humans, of these organisms.[14,15] The enzyme tyrosinase catalyzes the hydroxylation of phenolic substrates to catechols and the further oxidation to ortho-quinones.[16,17]

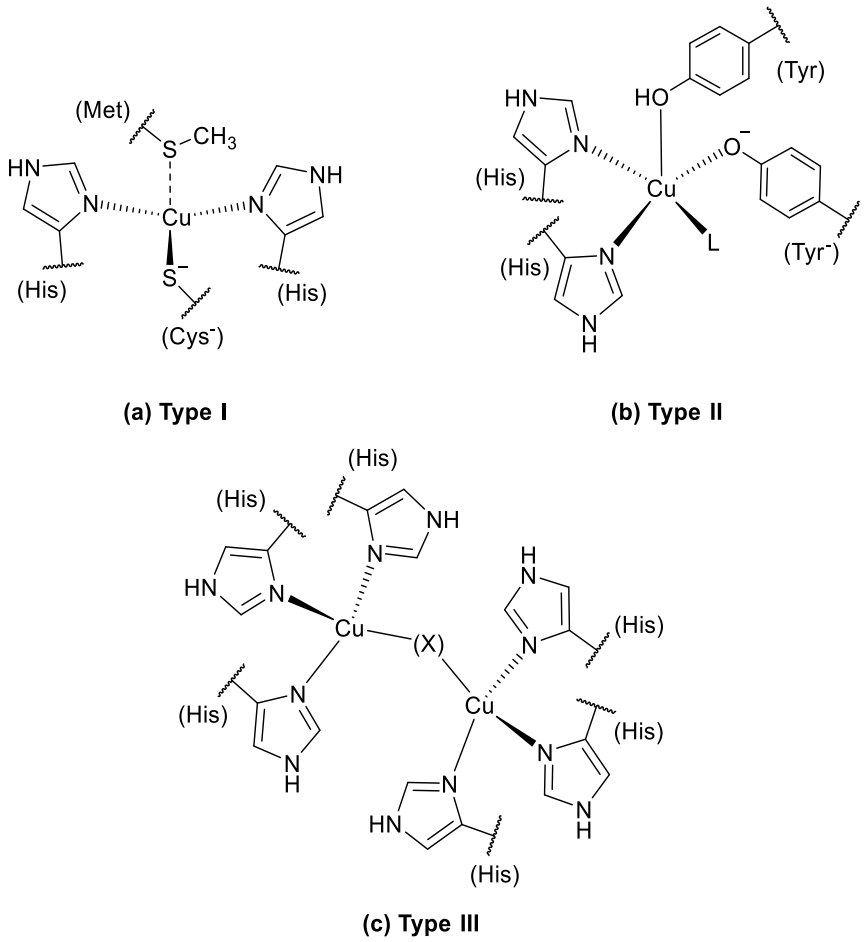


Figure 2: Active center of (**a**) type 1 (plastocyanin)[9], (**b**) type 2 (galactose oxidase)[12] and (**c**) type 3 (hemocyanin)[15] copper proteins.

Copper proteins that do not fit into this classification are called non-classical copper proteins and can be devided into further categories, which are referred to as copper centers of the type

(2+3), Cu_A, Cu_B or Cu_Z.[3,6,8] For example, type (2+3) copper proteins are part of the enzymes laccase or ascorbate oxidase, which contain a trinuclear unit consisting of a combination of type 2 and 3 copper centers and oxidize ascorbate to dehydroascorbate.[8,18] Examples for the other categories are cytochrome c oxidase (Cu_A and Cu_B), which catalyze the reduction of dioxygen to water in the respiratory chain and nitrous oxide reductase (Cu_Z), which reduce N_2O to N_2 in the nitrogen cycle.[8]

1.1.2 Iron nitrogen monoxide proteins and complexes

Iron ist the most common essential transition metal in the human body and is a central component of many proteins and enzymes. It usually occurs in the oxidation states +II, +III or +IV within a heme or non-heme protein framework (Figure 3).[1] The most famous and very important iron protein for humans and many other mammals is the dioxygen carrier protein hemoglobin, which can bind molecular dioxygen reversibly and is responsible for distributing dioxygen through the bloodstream as part of the red blood cells.[19,20] Another example is hemerythrin, which is a non-heme iron dioxygen transport protein and is found in various marine intervertebrates.[21] Iron enzymes can also occur in a catalytic function and, for example, catalyze redox or oxygenation reactions as cytochrome, catalase or peroxidase.[1,22]

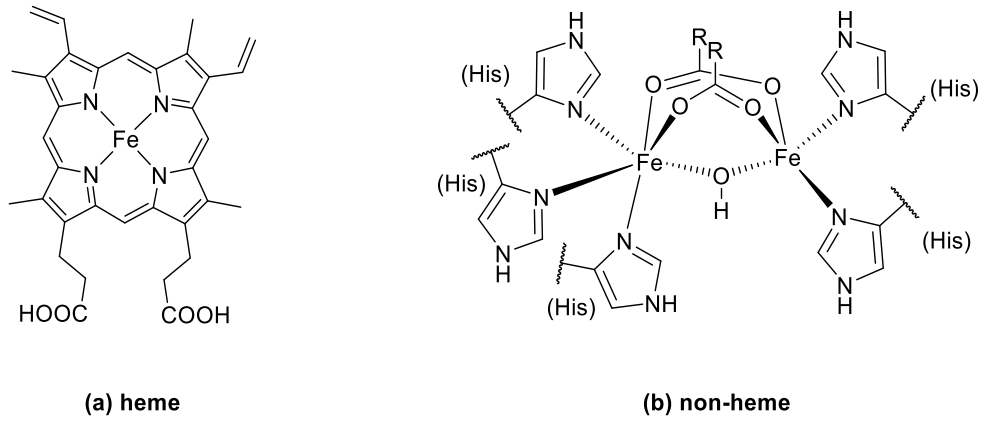


Figure 3: (**a**) Active site of heme proteins (e. g. hemoglobin and myoglobin)[23] and (**b**) active site of a non-heme protein (e. g. hemerythrin).[21]

In addition to the transport and activation of dioxygen as an oxidizing and oxygenating agent, another small molecule plays a crucial role in important biological processes in the human body: nitrogen monoxide (NO). For the discovery of the importance and role of NO in physiological and pathophysiological functions Murad, Furchgott and Ignarro were awarded with the Nobel Prize in physiology and medicine in 1998.[24–26] Nitrogen monoxide is a simple diatomic

molecule differing from dioxygen only by a single electron and in contrast to triplet dioxygen (diradical) occurs as a monoradical (Figure 4). NO is a colorless and highly reactive gas that reacts with a wide range of transition metals and, in presence of dioxygen, is converted to NO_2.[27] Due to this reactivity and the short half-life time in the human body and in aqueous solutions, NO as part of biological processes could not be proven for a long time.

The tasks that nitrogen oxide takes on here are blood pressure control, as a neurotransmitter and in immune response. In particular, the interaction of NO with iron-containing proteins and complexes is studied.[28,29] Examples are the ferro-heme enzyme soluble guanylyl cyclase,[30,31] regulatory [Fe-S]-proteins[32] or the vasodilating drug sodium nitroprousside.[33,34] The [Fe-S]-cluster of the [Fe-S]-proteins react with NO and form dinitrosyl iron complexes (DNICs) in order to control their transcription or translation activity.[32]

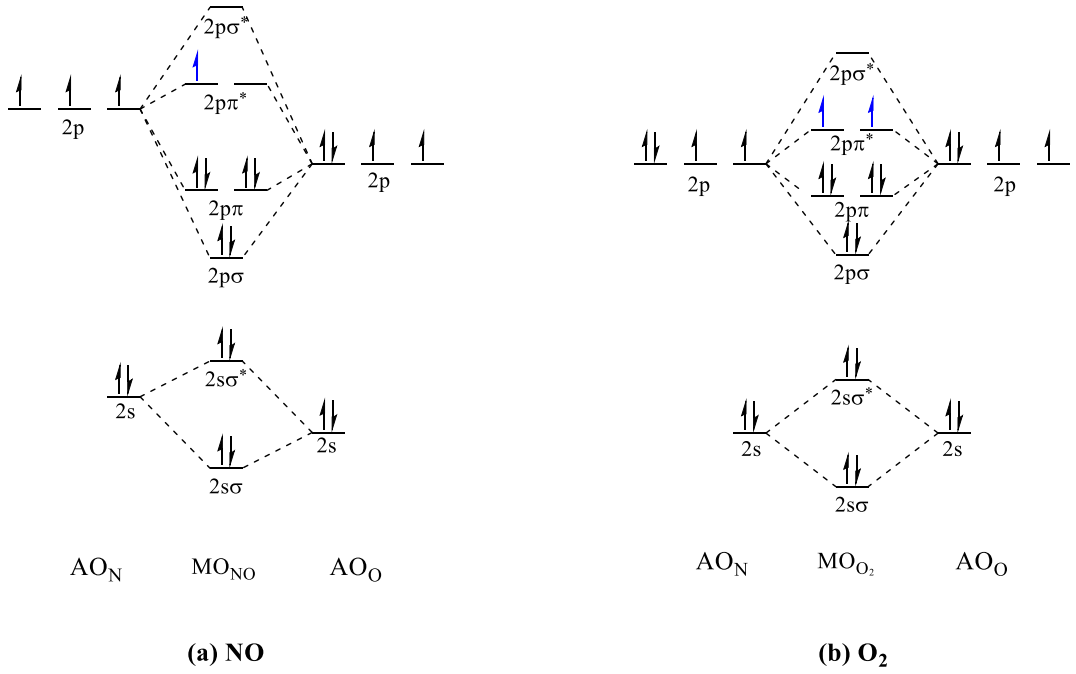


Figure 4: Comparison of the molecular orbital (MO) diagrams of (**a**) NO and (**b**) O_2.[20,35]

Tetracoordinate mononitrosyl iron complexes (MNICs) and their dinitrosyl homologues, DNICs, have been subject of research for decades.[36–39] Current research focuses primarily on thiolato- and sulfido-ligated nitrosyl-iron species, due to their importance in signalling and metabolic pathways.[36,38] Despite many years of research, the mechanisms for the formation of different iron-NO species and the dynamic of MNIC and DNIC formation or the occurrence of binuclear Roussin's red salt esters (RSEs) and their physiologicial roles are not fully understood (Figure 5). Recently, the equilibrium between low molecular weight DNICs from the direct

reaction among NO, Fe(II) and biothiols in aqueous solution were investigated and the simultaneous production of DNICs and thiyl radicals were shown, which represent a new way for in vivo formation of S-nitroso thiol species.[40]

In addition to its biological significance, NO also plays a special role in coordination chemistry. Here, NO occurs as a so-called non-innocent ligand and can bind to a metal center oxidized as NO^+ (isoelectronic to CO), as $NO^{\cdot}$ radical, reduced NO^- (isoelectronic to O_2) or even as $NO^{\cdot 2-}$ radical.[41,42] Thus enabling unclear oxidation states for the metal center. Even for a well known complex such as $[Fe(H_2O)_5(NO)]^{2+}$ (known from the qualitative analytical test of nitrate ("brown ring" test)), the oxidation state of the iron ion is discussed controversically and Fe(I), Fe(II) and Fe(III) are reported.[43–45] A possibility for a correct spelling of iron-NO complexes without specifying the oxidation state of iron is offered by the Enemark-Feltham notation, in which only the number of metal d electrons and the number of π* electrons are considered. An Fe(II)-NO complex would correspond to the notation $\{Fe(NO)\}^7$, resulting from the general notation $\{Fe(NO)_x\}^m$ with x = number of NO ligands and m = sum of metal d- and NO π*-electrons.[46] In the past, numerous reports on transition metal complexes with NO and their reactivity have been pubished.[47,48]

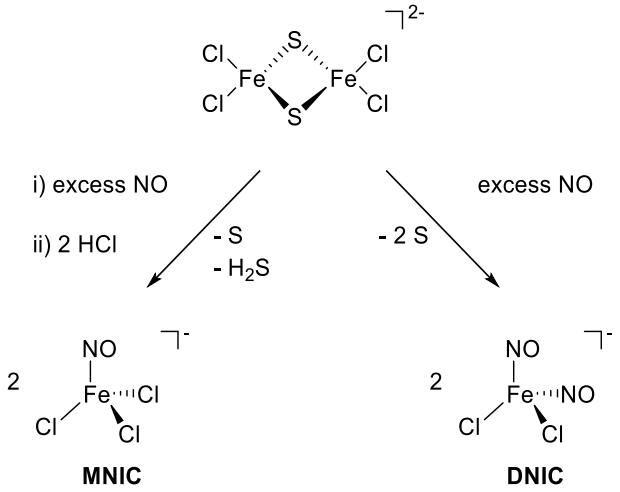


Figure 5: Control of the formation of MNIC and DNIC from $[FeS_2Cl_4]^{2-}$.[38]

The similarity of NO to other diatomic molecules, which are reinforced by its properties as a non-innocent ligand, also poses a challenge in biological processes for enzymes since molecular dioxygen or carbon monoxide can also occur in higher concentrations additionally and compete for binding to the active center (especially to iron centers).[28,49,50] This is particuarly important for dioxygen-binding enzymes in the respiratory chain, since all three molecules (O_2, NO and

CO) can bind reversibly and a high concentration of NO or CO can lead to asphyxiation. In general, NO and CO bind to an iron center much more strongly than dioxygen does.[49] In addition to the higher binding energy, however, the binding and dissociation rates must also be taken into account. NO has a comparatively high attachment rate and a very slow dissociation rate to iron heme centers, which complicate the role of NO as a signal molecule because, due to their biological function, the dissociation have to run very quickly.[28] In nature, for the protein myoglobin for example, this distinction is made by an interplay between inhibition of diatomic molecule binding by a water molecule and a preference for iron-dioxygen binding by a strong hydrogen bond of oxygen to a neighbouring histidine residue. This leads to a 100-fold increase in the overall affinity towards dioxygen binding compared to non-polar heme compounds.[51]

Kinetic studies provide an important method to observe the formation and reaction of transition metal-nitrosyl complexes and thereby offer a better understanding of pathways in which NO may participate and allow to evaluate the chemical processes that need to be considered in the interpretation of biological mechanisms.[29] Investigations with NO are a particular challenge as they require special working procedures under inert conditions due to its high reactivity towards dioxygen. Furthermore, since the reaction of NO with transition metals is generally very fast either cooling is required (which is usually difficult as most investigations are carried out in aqueous medium due to the better comparability with biological systems) or a suitable measuring system have to be used. Nevertheless, such investigations were carried out with natural, iron-based enzymes as well as with model systems.[29,52–54]

1.2 Model complexes

In bioinorganic chemistry there is a great interest in simulating the functions and reactivities of natural enzymes with the help of model compounds and thereby gaining a better understanding of the mechanisms in biological processes. This understanding could be used for example, in order to develop new drugs but also to use easily accessible systems to make reactivity functional for catalytic or synthetic application.

1.2.1 Iron NO complexes and NO donor drugs

In case of iron NO complexes, the focus is primarily on the investigation of biologically active DNIC species, which can occur in a monomeric DNIC and a dimerized form as Roussin’s red

salt ester (RSE, Figure 6), but also in NO donor drug development, in which molecular carriers for NO-releasing are investigated for medical applications.

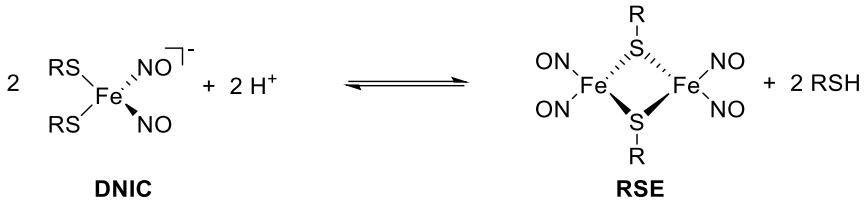


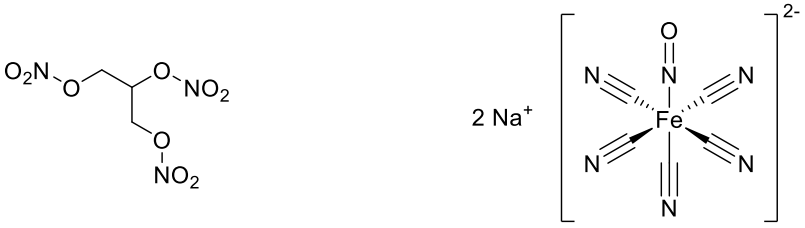
Figure 6: Equilibrium between DNIC and RSE.[40]

In the formation of DNICs, a distinction is made by the anionic, paramagnetic DNIC form $\{Fe(NO)_2\}^9$, whose iron center is usually coordinated by thiolate ligands, and the neutral, diamagnetic form $\{Fe(NO)_2\}^{10}$ of DNICs that are coordinated by CO, PPh_3 or N-containing ligands.[55,56] It could be shown that this property helps in the characterization and prediction of active DNIC species in biological systems and offers the possibility of differentiating between different types of $\{Fe(NO)_2\}^9$ (anionic, neutral) and RSEs species by using EPR (electron paramagnetic resonance) in combination with IR spectroscopy (infra-red spectroscopy) and the relative position of the ν_{NO} stretchting frequencies.[57,58]

This distinction is also important for a better understanding of different processes that are influenced by NO, in addition to its natural, biological function. In this context, NO-realeasing NO donor drugs play an important role in the medical field (Figure 7). For decades, despite intensive research, mainly two types of NO donor drugs found in clinical application. These are organic nitrates such as nitroglycerin which is mainly used to relieve pain in connection with angina pectoris and the already mentioned sodium nitroprusside which is used for the short-term reduction of blood pressure.[59,60] In the development of new drugs, the focus is primarily on stabilisation, transport and and control of NO release as this could for example, release smaller amounts of NO over a longer period of time.[61,62] Current approaches pursue the binding of NO to macromolecules,[63] metal-organic frameworks[64,65] or nanoparticles[61,66] as with higher molecular weights the payload can be increased and released in a more controlled and effective manner compared to low molecular weight NO donors.[67] It has been shown that therapies with NO-releasing macromolecular materials can be used to treat cardiovascular diseases, cancer, bacterial infections or to support wound healing.[67]

However, reactions of NO with iron complexes are not only studied in the medical or biological field, but also in bioinorganics or complex chemistry. As already mentioned, NO is very similar

to molecular dioxygen (Figure 4), but usually much more reactive. Therefore, it is not surprising that NO is used when dioxygen shows no or only a very slow reaction rate with iron(II) complexes to learn more about the binding situation and the mechanisms.[68]



(a) nitroglycerin **(b) sodium nitroprusside**

Figure 7: Chemical structure of NO donor drugs (**a**) nitroglycerin and (**b**) sodium nitroprusside.

Iron-NO model complexes are also used to study local mass transfer phenomena in reactive bubble columns. Processes in gas-liquid systems in the chemical industry are often optimized by trial and error, which is time-consuming and costly. For the investigation of the influence of hydrodynamic interactions, such as bubble bounce or coalescence on mass transport, the strong color difference in the reaction of the complexes with NO is of particular importance. The reaction is tracked with UV/Vis spectroscopy or high-speed cameras and evaluated by sophisticated experimental analysis.[69]

1.2.2 Model compounds for copper proteins and enzymes

In contrast to iron-nitrosyl compounds which are involved in a wide variety of different processes and whose role is mainly in the distribution and release of NO, copper-containing proteins (mainly type 2 and type 3 copper proteins) are characterized primarily by their ability to bind and activate dioxygen and their role in numerous substrate oxidation and oxygenation processes.[70,71] The focus in bioinorganic chemistry is therefore mainly on mimicking natural systems by suitable model systems. On the one hand, this is to gain a better understanding of the mechanisms and reactivities in biological processes, but also, on the other hand, to use simplified systems to make the reactivities of enzymes usable for synthetic applications or catalyzes.[72] In this context, it is particularly important to distinguish between the possibilities of dioxygen binding to mononuclear copper centers, such as η^1- (end-on) or η^2- (side-on) superoxido complexes, and to dinuclear copper centers in the form of trans-μ-1,2- (end-on) peroxido and μ-η^2 : η^2- (side-on) peroxido complexes and bis(μ-oxido) complexes, whose

existence has already been demonstrated and characterized with model systems or, in the case of η^1-superoxido and μ-η^2 : η^2-peroxido species, even in natural systems (Figure 8).

The investigation of copper-dioxygen intermediates with model systems and the design of the ligand system is very important, as even minor changes in the electronic or steric properties of a ligand can lead to the formation or observation of a different copper-dioxygen intermediate or none at all.[73] The type and number of donor atoms, the chelate ring size, or the steric size of the ligands are all parameters for the ligand design which can lead to different results in dioxygen activation.[70] In the case of dioxygen binding to copper complexes ligands with nitrogen donors, analogous to the biological priority in the form of pyrazoles, pyridines, imidazoles or amines are used. However, binding via sulfur and phosphorus donors is also possible although ligands with these donors often form very stable copper(I) complexes with low reactivity toward dioxygen. The change in denticity and steric hindrance has a very large influence on the stability and reactivity of the copper(I) complex toward dioxygen, since these factors primarily affect the coordination geometry. Thus, oxygenation reactions of mononuclear copper(I) complexes with bidentate or tridentate ligands often proceed via a superoxido intermediate, which in solution tend to form binuclear copper-dioxygen species with another copper(I) complex.

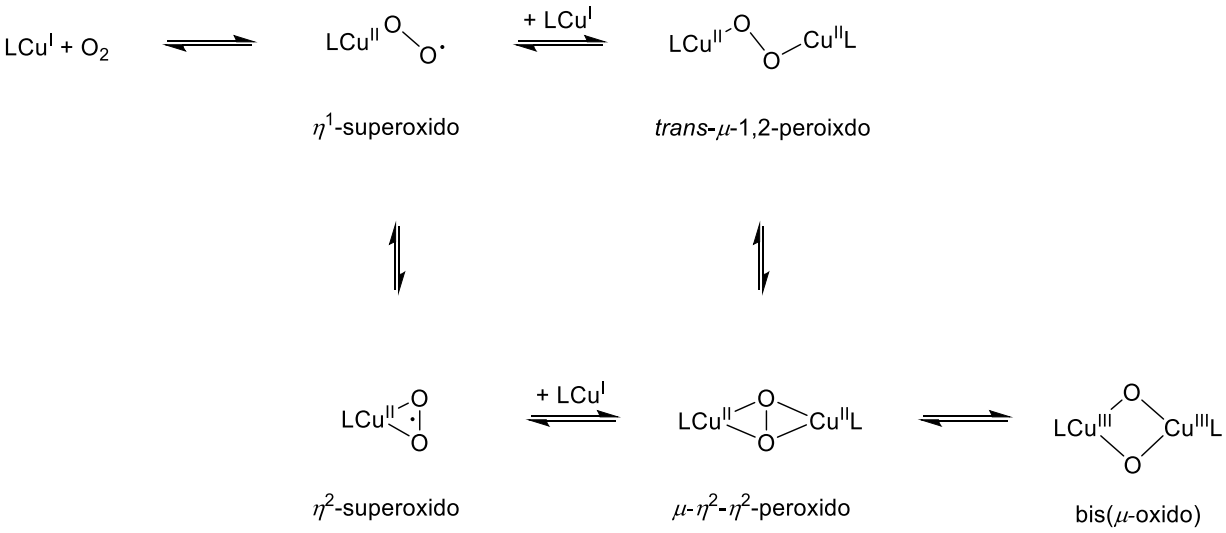


Figure 8: Copper-dioxygen species formed by reaction of copper(I) complexes with O_2 including possible pathways of different binding modes in equilibrium.[72,74]

The various copper-dioxygen species can generally be described as being in equilibrium, since only relatively small structural changes are formally required for the transformation (Figure 8). For example, for the formation of a peroxido species, the prior formation of a superoxido

species is inevitable, but its formation or transformation is rarely observed due to a rapid onward reaction to a dinuclear species. It is shown, however, that the property of dimerization can be suppressed by an increased number of donor atoms or an increase in the steric demand of the ligand so that mononuclear copper-dioxygen species can be stabilized. The characterization of η^1-superoxido complexes with different ligands (tet b, tmpa, Me_6tren or TMG_3tren) has already been done crystallographically or by UV/Vis spectroscopy.[74–77] η^1-superoxido complexes have an intense, characteristic charge-transfer band at 400 nm and two further, weaker absorption bands at 600 nm and 750 nm. Characterization of η^2-superoxido complexes could be performed crystallographically with the sterically demanding ligand $Tp^{tBu,iPr}$(Figure 9a, R^3 = *t*Bu, R^5 = *i*Pr).[78]

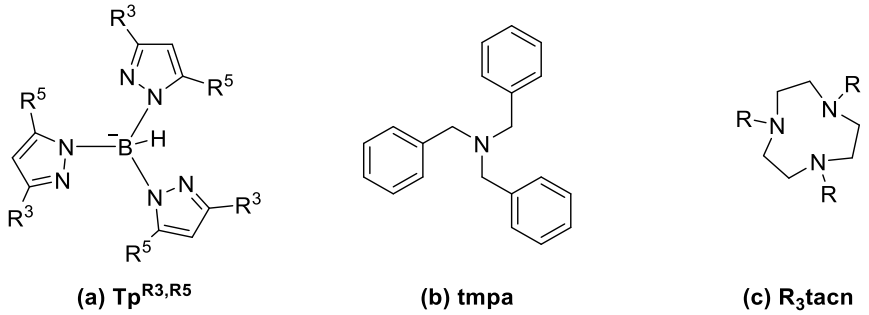


Figure 9: Shown are selected ligands that were used for crystallization and characterization of different copper-dioxygen species (**a**) $Tp^{R3,R5}$ (= tris(pyrazolyl)borates, R^3, R^5 = Me, *i*Pr, *t*Bu), (**b**) tmpa (= tris[(2-pyridyl)methyl]amine) and (**c**) R_3tacn (= N,N',N''-trisubstituted 1,4,7-triazacyclononane, R = Me, *i*Pr, Bz, Py).

Besides the species that have been mentioned above copper hydroperoxido species also have biological relevance and a role as intermediate active species in various enzymes, such as dopamine β-monooxygenase (DβM) and peptidylglycine α-hydroxylating monooxygenase (PHM).[13,79] Mononuclear hydroperoxido species can also be formed by protonation of peroxido species or the direct use of hydrogen peroxide.[80–82] Copper hydroperoxido species have already been detected crystallographically and spectroscopically with various model systems, usually by an intesive band at about 400 nm and another weaker band at about 650 nm.[80,83]

Dinuclear copper species are of particular interest because of the ability of their natural representatives (tyrosinase, catechol oxidase and hemocyanin) to reversibly bind and activate dioxygen. The stability of dinuclear copper-dioxygen species is primarily related to the increased thermodynamic stability of the peroxide species (2 e^-) relative to the superoxide species (1 e^-), so that more model complexes of dinuclear copper-dioxygen species have tended

to be characterized and detected in the past.[70] The common binding modes have been mentioned previously and are shown in Figure 8. However, dioxygen binding can be influenced by the choice of ligand. For example, trans-μ-1,2-peroxido species have been detected in the past mainly with tetradentate ligands, whereas μ-η^2 : η^2-peroxido and bis(μ-oxido) complexes have been detected with bidentate, tridentate and tetradentate ligands. All dinuclear copper-dioxygen species could already be detected spectroscopically or crystallographically using model complexes.

In biological systems, only μ-η^2 : η^2-peroxido copper species have been detected so far, but it is still discussed in the literature if the bis(μ-oxido) species is the active species of enzymes. The spectroscopic characterization of bis(μ-oxido) species is based on an intense charge-transfer band at 340 nm and another weaker absorption band at 530 nm and was first demonstrated by Moro-oko and co-workers in 1988 with a model system (ligand used shown in Figure 9a, $R^3 = R^5 =$ Me).[84] The first crystal structure and characterization of an trans-μ-1,2-peroxido complex was published by Karlin and co-workers in 1988 with the ligand tmpa (Figure 9b).[85] With the copper(I) complex $[(i\text{Pr}_3\text{tacn})\text{Cu(MeCN)}]^+$ ($i\text{Pr}_3$tacn = 1,4,7-triisopropyl-1,4,7-triazacyclononane, Figure 9c, R = *i*Pr) even both copper-dioxygen species, the μ-η^2 : η^2-peroxido and the bis(μ-oxido) species, could be detected simultaneously in equilibrium by Tolman and co-workers. By varying the solvent, the ratio of the isomers could be shifted to the side of the peroxido species (favored in dichloromethane) or to the side of the bis(μ-oxido) species (favored in tetrahydrofuran).[86,87]

The bis(μ-oxido) species was first detected spectroscopically in 1993, characterized crystallographically in 1996 (ligand used shown in Figure 9c, R = Bz) and has been detected with numerous other different ligands over the years.[88,89] Crystallographically, a bis(μ-oxido) complex can be distinguished by a shorter Cu-Cu distance and an increased O-O distance compared to the μ-η^2 : η^2-peroxido complex. Spectroscopically, the characterization can be performed by two very intense absorption bands at about 300 nm and 400 nm.[70]

1.3 Model compounds for synthetic and catalytic application

The enzyme tyrosinase stands out as a model for a synthetic and catalytic application of copper(I) model complexes. Tyrosinase is a type 3 copper protein and catalyzes the selective ortho-hydroxylation of L-tyrosine to L-DOPA and further oxidation to L-DOPAquinone

(catalytic cycle shown in Figure 10), which in further subsequent reactions leads to the formation of melanin in biosynthesis. Melanin is responsible for the browning of skin, hair, fruits or vegetables, but also supports immune reactions.[17,90,91] In particular, the crystal structure published by Matoba *et al*. led to a detailed understanding of the tyrosinase mechanism.[92] The activation of dioxygen at the tyrosinase occurs, as previously suspected on the basis of spectroscopic studies, via a the μ-η^2 : η^2-peroxido complex. Through these findings, the already generally accepted mechanism proposed by Solomon was refined by Tuczek and co-workers.[16,17,93]

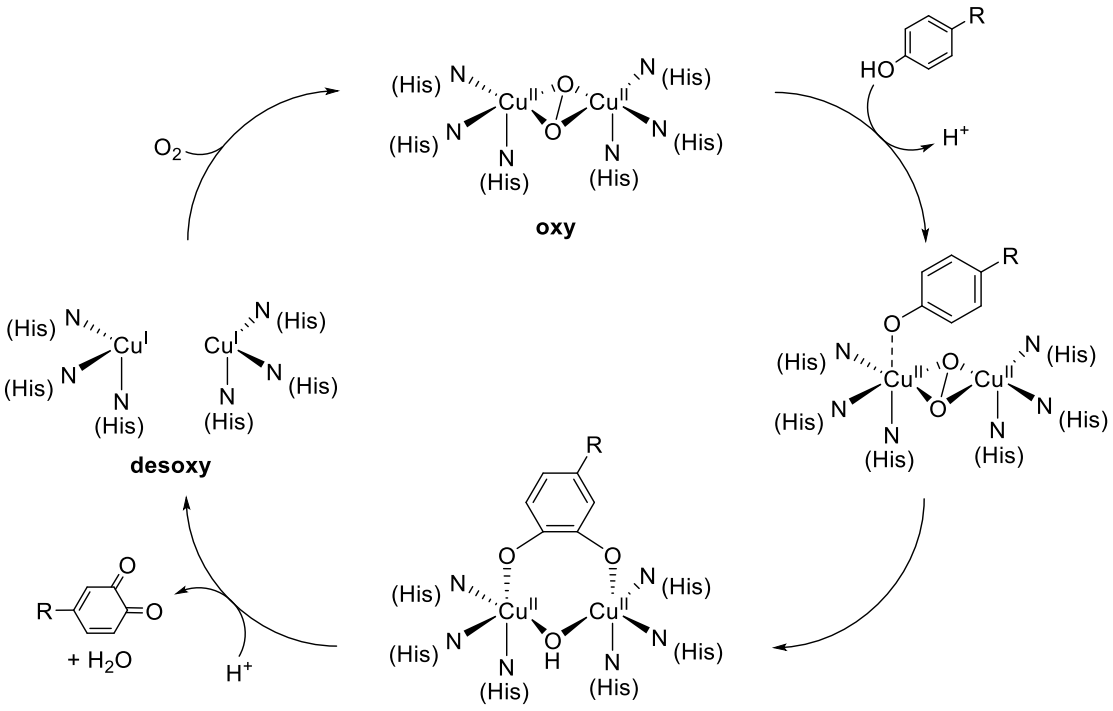
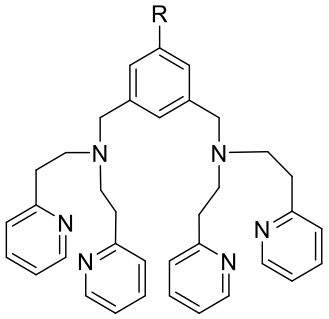


Figure 10: Catalytic cycle of Tyrosinase.[17]

Although the reactivity of tyrosinase has been widely known for years, it is still a challenge to develop suitable model systems that can activate dioxygen and show tyrosinase-like activity. For the first model systems that showed tyrosinase-like activity, *m*-xylyl-brigded ligands were used (Figure 11, R = H). Complexes with these types of ligands are able to bind two copper ions with three nitrogen donors each, which are linked together by a xylyl spacer. In 1981, Karlin and co-workers demonstrated that a copper(I) complex with the ligand Py2-*m*-xyl^H performs selective hydroxylation upon reaction with dioxygen, resulting in a dinuclear hydroxide- and phenolate-bridged copper(II) complex.[94] Further detailed studies with differentially substituted *m*-xylyl-based ligands could show that electron-releasing substituents increase the rate of hydroxylation, thus enhancing the assumption that the active copper-

dioxygen intermediate is a peroxidic electrophile, which could be demonstrated spectroscopically.[95] It was also observed that a change in chelate ring size from a six-membered chelate ring to a five-membered chelate ring resulted in stabilization of the copper(I) complex and no hydroxylation reaction occurred.[96] In contrast to tyrosinase, with this type of ligand and also with many other model complexes, copper-dioxygen species could be detected but no catalytic activity was observed. Despite a stable copper-dioxygen intermediate, either no reaction took place at all or, at most, only stoichiometric conversions could be obtained.[97,98]



Py2-*m*-xyl^{R}

Figure 11: Ligand Py2-*m*-xyl^{H} (= N,N,N',N'-tetra-(2-pyridyl)-*α*,*α*'-diaminoxylene, R = H, *t*Bu, F, CN, NO_2) that was used for a model system with tyrosinase-like activity.

Model systems of tyrosinase that are capable of stoichiometric or even catalytic reactions mostly use external monophenolic substrates and perform intermolecular oxygenation or oxidation reactions to the ortho-quinone.[99] Examples are the model systems published in the early 1990s by Réglier *et al*. and Casella *et al*. which for a long time were the only model systems with catalytic tyrosinase-like activity.[100,101] The next catalytic tyrosinase model system, which was also the first system based on a mononuclear copper(I) complex, was published about 20 years later by Tuczek and co-workers.[102] In the meantime, a number of other model systems with tyrosinase-like and catalytic reactivity exist, which have been published in recent years by further development and variation of known ligands or by the development of new ligands by Lumb and Ottenwaelder,[75–77] Tuczek[99] and Herres-Pawlis.[106,107]

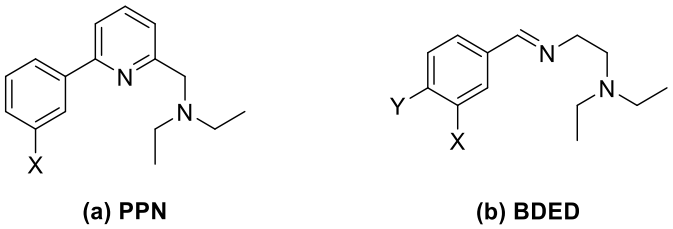
1.4 Intramolecular hydroxylation reactions with copper(I) complexes

1.4.1 Aromatic ligand hydroxylation

Aromatic hydroxylation reactions are much more common in the literature than aliphatic hydroxylations. This is partly due to the better comparability of the well-studied native model tyrosinase, but also to the significantly lower dissociation energy of allylic C-H bonds (~90 kcal/mol) compared to aliphatic equivalents (~100 kcal/mol).[108] Furthermore, it was observed that in the case of unsaturated hydrocarbons, pre-activation of the C-H bond already occurs due to the attachment of the substrate to the metal center, which does not occur in the case of aliphatic adducts.[109] In intramolecular ligand hydroxylation, in contrast to intermolecular hydroxylation, a reaction at the ligand is desired explicitly. The previously described model system of Karlin (chapter 1.3) is the first model system in which selective hydroxylation of the ligand at the bridging *m*-xylyl unit (Figure 11) by a μ-η^2 : η^2-peroxido complex could be observed.

In 1999, another model system was presented by Holland *et al*. to investigate if such a hydroxylation could also proceed via a bis(μ-oxido) intermediate complex. In previous hydroxylation reactions of natural copper proteins and also model systems mainly μ-η^2 : η^2-peroxido species as copper-dioxygen intermediates were observed.[110] For this purpose, the bidentate ligand PPN (2-(diethylaminoethyl)-6-phenylpyridine) instead of the tridentate *m*-xylyl-based ligand was used (Figure 12a). For the copper(I) complex of the ligand PPN and variously substituted derivatives a bis(μ-oxido) complex was found to be the active species by spectroscopic studies at low temperatures. The lack of other absorption bands that could be assigned to peroxido- or superoxido species indicates that this type of dioxygen binding mode can only exist via a rapid equilibrium. These observations could be confirmed by DFT (density functional theory) calculations.[111] Furthermore, it was shown that the hydroxylation and degradation of the bis(μ-oxido) complex occurs via a 1,2-H shift and the formation of an intermediate dienone, resulting in the hydroxylated product. After the reaction of the copper(I) complex with dioxygen, a conversion of up to 40% to the hydroxylated ligand was detected, depending on the substituents. This corresponds to a conversion of 80% (based on the maximum conversion) because bis(μ-oxido) complexes are monooxygenases and therefore only one of two ligands forming the complex can be hydroxylated. However, the hydroxylated product was

not isolated, but the yield was estimated by GC/MS and ^{1}H-NMR. By inserting electron withdrawing groups such as NO_2 and CF_3 a deactivating effect was shown. By inserting electron donor groups such as OCH_3 an activating effect on the rate determining step and hydroxylation yield was shown.



(a) PPN **(b) BDED**

Figure 12: The ligands (**a**) PPN (= 2-(diethylaminoethyl)-6-phenylpyridine, X = H) and (**b**) BDED (= *N*'-benzylidene-*N*,*N*-diethylethylenediamine X = Y = H). For the substitution effects studies, substituents were attached at position X and Y, respectively.

With regard to a possible application in organic synthesis, the system with PPN has the disadvantage that the synthesis and isolation of the ligand is relatively time-consuming, partly requires starting materials that are no longer commercially available and, due to the ligand structure, the possibility of substrate variability is relatively inflexible. Therefore, Becker *et al*. developed the ligand BDED (*N*'-benzylidene-*N*,*N*-diethylethylenediamine, Figure 12b, X = Y = H).[111] The ligand BDED is structurally very similar to the ligand PPN but can be prepared by a simple Schiff base reaction with high yields, high purity and with inexpensive starting materials (benzaldehyde and *N*,*N*-diethylethylenediamine). The copper(I) complex with the ligand BDED can activate dioxygen as a bis(μ-oxido) complex in the same way as the complex with the ligand PPN and an intramolecular and selective hydroxylation can be carried out on the aromatic substrate (Figure 13). The mechanism and the occurrence of a bis(μ-oxido) intermediate were also confirmed by DFT calculations.[111] Because of the simple binding of the substrate via an imine bond, it is also possible to vary the substrate and instead of benzaldehyde any other substrate with an aldehyde or ketone function can be bound to the ligand. After the hydroxylation reaction the hydroxylated substrate can easily be separated from the ligand by acidic imine cleavage. Because of this easy binding and cleavage of the substrate to the ligand, this concept is also referred to as the "clip-and-cleave concept".[112] Thus, hydroxylation of the ligand BDED (Figure 13) and subsequent work-up already resulted in a conversion of almost 50% salicylaldehyde (detected by GC-MS), which, due to the limiting conversion of monoxygenases, already corresponds to the maximum possible conversion of 100%. However, only 8% salicylaldehyde could be isolated by flash chromatography, which of

course still offers potential for improvement due to the much higher conversion. The investigations of the substitution effects on the substrate with the ligand BDED were similar to the results with ligand PPN.

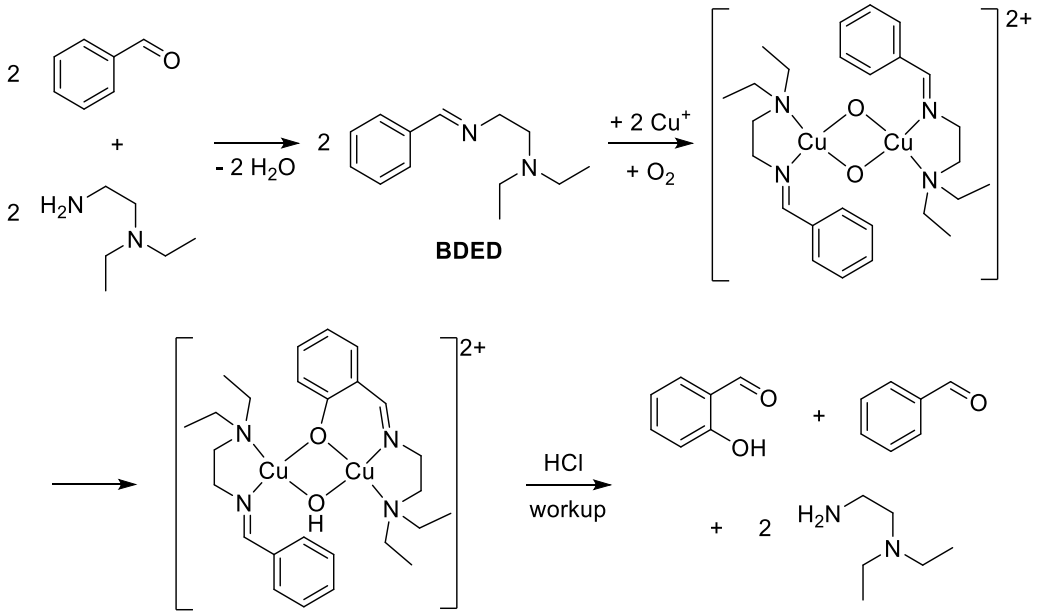


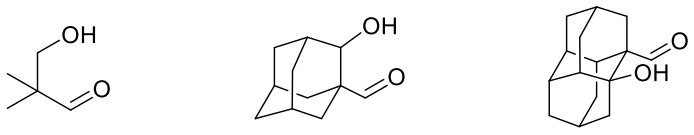
Figure 13: Intramolecular hydroxylation of copper(I)-BDED complex with dioxygen.[111]

1.4.2 Aliphatic ligand hydroxylation

Aliphatic ligand hydroxylation is particularly challenging due to the quite high C-H dissociation energy (~100 kcal/mol) and the non-activated nature of these bonds.[108] Therefore, it is not surprising that few examples of selective hydroxylation of aliphatic substrates are available in the literature compared to aromatic hydroxylation reactions. Moreover, in many reactions whose oxygenation mechanism proceeds via a metal oxo species, the involvement of radical intermediates is frequently observed, which can complicate the selectivity but also the study of the mechanism.[113] Nevertheless, some intramolecular, selective hydroxylation reactions on non-activated aliphatic C-H bonds using dioxygen-activating copper(I) complexes have been observed in the past. One of the first model systems of this kind was presented by Réglier and co-workers in which a mixed bis(μ-oxido) Cu(II)/Cu(III) intermediate is assumed to be the active species and hydroxylation occurs at propyl and cyclopentyl groups in the β-position.[114]

Based on the work with the BDED ligand by Becker *et al*. (clip-and-cleave concept, chapter 1.4.1), the ligand system BDED was extended by the use of new substrates and the successful regioselective hydroxylation at non-activated aliphatic C-H bonds of aldehydes.[112] Thus, the

ligand DPDen, in which trimethylacetaldehyde (hydroxylated product shown in Figure 14a) was attached to the ligand backbone, was also hydroxylated successfully and, analogous to the ligand BDED, a bis(μ-oxido) complex was observed as the intermediate copper-dioxygen species at low temperatures.[111,112] Even though an efficient separation of the product was not possible, but a nearly quantitative conversion could be detected by GC/MS. Also of particular relevance is the selective hydroxylation of adamantane-1- and diadamantane-1-carbaldehyde at the β-position, whose hydroxy-functionalization at this position is otherwise difficult to achieve (Figure 14b and Figure 14c).[115,116]



(a) (b) (c)

Figure 14: Selectively hydroxylated products of (**a**) trimethylacetaldehyde, (**b**) adamantane-1-carbaldehyde and (**c**) diadamantane-1-carbaldehyde.

A very similar ligand system was published by Schönecker and co-workers in the early 2000s. Here, the substrate was attached via an amine or imine function to the ligand scaffold, which usually consists of an ethylene or methylene linked pyridine (Figure 15).[117–120] Chiral steroids and camphor were used as substrates, the functionalization of which, mainly due to regioselectivity, is generally not very easy to carry out and are therefore also of interest for applications in organic synthesis. It was shown that different positions can be hydroxylated depending on the linkage of the ligand to the substrate. When linked via an amine, the 16β-position is hydroxylated and the stereoselectivity of the hydroxy group can be controlled depending on the residue on the amine. When using imino pyridyl ligands and spatial fixation by the C=N bond in an anti-arrangement occurs, the 12β-position is hydroxylated. Of particular interest is that in one case there is a β-hydroxylation and in the other case a hydroxylation at the γ-position occurs (Figure 15).[117] For the hydroxylation reaction, unlike the clip-and-cleave concept, the copper(II) complex was assumed to be reduced with an excess of reducing agent before the addition of dioxygen. The repeated reduction of the copper(II) complexes allows the higher conversions compared to the direct use of copper(I) complexes without reducing agent. The disadvantage, however, is a very long reaction time of several days, a costly work-up and the yields, which were still relatively low despite the use of reducing agent excess.

Based on the ligand system published by Schönecker for the hydroxylation of steroids and camphor derivatives, further investigation to optimize the reaction conditions and increase the yield was first carried out by Baran and co-workers and based on these findings in more detail by Garcia-Bosch and co-workers.[121–123]

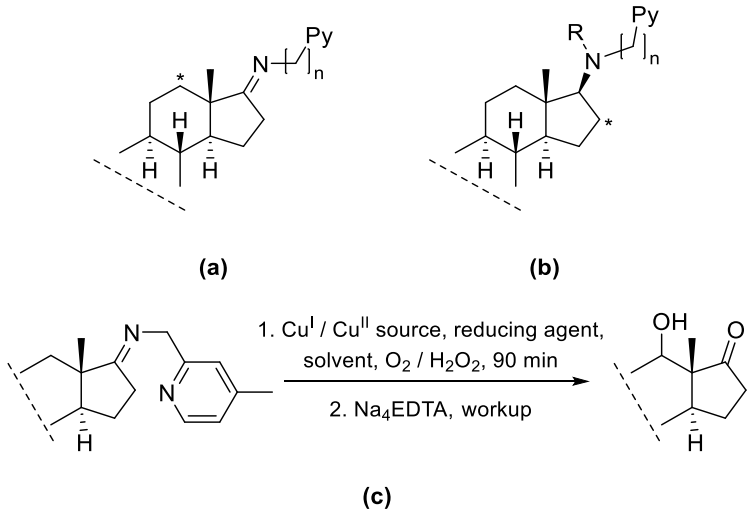


Figure 15: The used ligand systems of Schönecker with (**a**) imine and (**b**) amine linkage (R = Me, Et, n = 1, 2). With * the preferred sites for hydroxylation (**a**) at the 12β- and (**b**) at the 16β-position are marked.[117] (**c**) Experimental conditions of the ligand hydroxylation published by groups of Baran and Garcia-Bosch.[121,122]

Baran and co-workers were able to develop a method in which, by using reducing agents to reactivate copper(II) to copper(I) and minor changes to the reaction conditions, hydroxylation yields for steroid and camphor ligands of over 90% were achieved.[121] These results represent the first ligand system to achieve selective hydroxylation with such high yields. Crucial for the high yield is mainly the use of the right reducing agent, but also the choice of solvent, minor variations on the ligand backbone and the choice of the right copper(I) salt had an influence on the conversion.

The very detailed investigations by Garcia-Bosch and co-workers based on Schöneckers ligand system showed that the mechanism of hydroxylation when using imino pyridine ligands does not proceed via a bis(μ-oxido) complex, as first assumed, but very probably via a hydroperoxido complex as the active species.[122,124] In the proposed mechanism, which is shown in Figure 16, the copper(I) complex first reacts with dioxygen to form copper(II) and a superoxide, which directly reacts further to form hydrogen peroxide. Subsequently, the copper(II) complex reacts with hydrogen peroxide to form the copper hydroperoxido intermediate, which then carries out the hydroxylation on the ligand.[122]. This finding allowed a more targeted approach for improving the reaction conditions. Starting with the copper(II) complex and hydrogen peroxide

as oxidant, yields of hydroxylated product in the range of 70-99% were obtained. On the one hand, this allows working at atmospheric conditions, since dioxygen-sensitive copper(I) complexes are no longer used, and on the other hand, costs can be reduced, through less expensive copper(II) salts and external reducing agents no longer required to be used. Further work with this ligand system has shown that the optimized reaction conditions are suitable for the hydroxyl-functionalization of a variety of different ketone or aldehyde substrates. However, it has also been shown that very different results can be expected in terms of conversion depending on the substrate.[123]

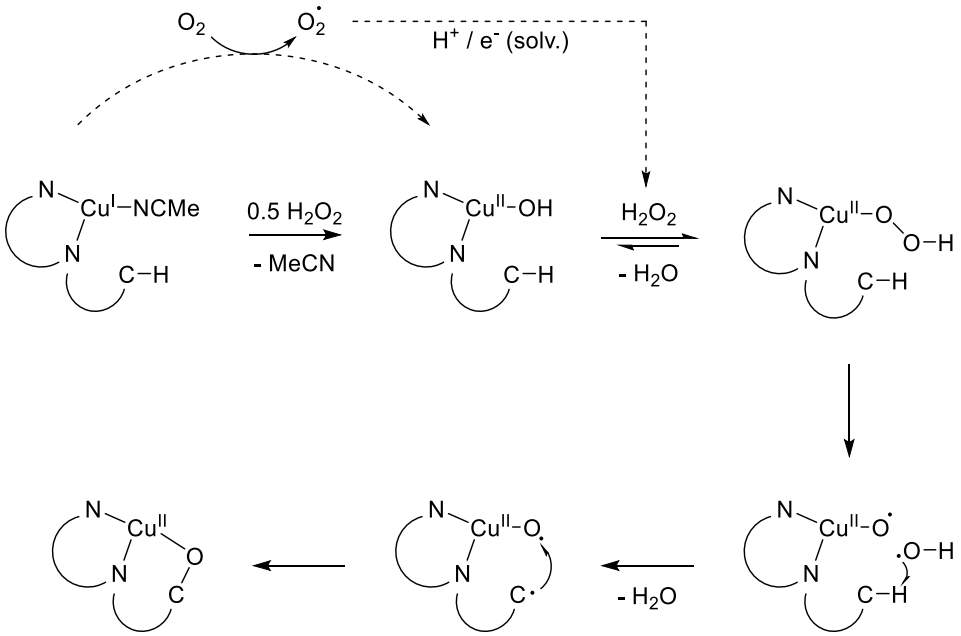


Figure 16: Proposed reaction mechanism for the intramolecular γ-hydroxylation of C-H bonds with $LCu^{II}(OOH)$ as the active intermediate.[123]

1.5 Research goals

The activation of small molecules plays a crucial role in many processes in the human body, but also in the chemical industry. Nitrogen monoxide and dioxygen represent two of these molecules whose electron configurations are very similar (monoradical vs. diradical) but whose properties and roles in science are nevertheless different. While research on nitrogen monoxide is mainly studied with regard to biological processes and the use of NO releasing drugs with many open questions regarding to the potential of possible applications and the exact mechanisms, the role of dioxygen in the human body is much more intensively researched and better understood. Therefore, the focus here is mainly on the development of new model systems with transition metals on the model of nature to perform catalytic or stoichiometric reactions, which can either replace complex and expensive synthesis routes by simple, selective and cheap methods or catalyze reactions at mild conditions on an industrial scale to save enormous amounts of energy and material costs.

With regard to gaining a better understanding of the formation of iron-NO complexes, one goal of this research work was the kinetic investigation of a series of iron complexes in order to obtain detailed information on the mechanism of these reactions. For this purpose, the formation of the complexes shown in Figure 17 was studied using low temperature stopped-flow techniques.

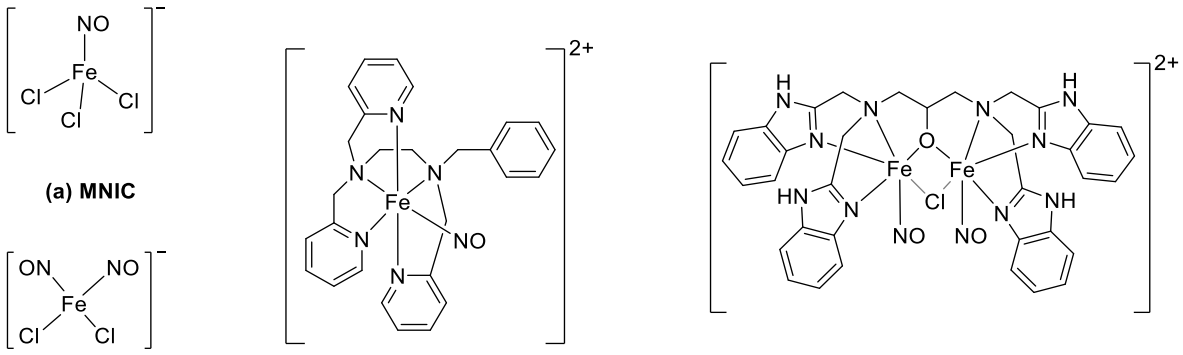


Figure 17: Investigated iron-nitrosyl complexes (**a**) MNIC and (**b**) DNIC and complexes with ligands (**c**) bztpen and (**d**) HPTB.

The iron complexes differed fundamentally in their coordination environment starting with simple iron(II) chloride in methanol (MNIC/DNIC system, Figure 17a and Figure 17b), via the mononuclear iron complex with the chelating ligand bztpen (= N-benzyl-N,N',N'-tris(2-pyridylmethyl)-ethylenediamine, Figure 17c) to the binuclear complex with the chelate ligand

HPTB (= N,N,N',N'-tetrakis(2-benzimidazolylmethyl)-2-hydroxy-1,3-diaminopropane, Figure 17d). Details of this study are described in chapter 2 and have been published in the Journal Dalton Transactions.

As shown in the introduction, copper-based oxygenation reactions offer unique possibilities for the functionalization of substrates. The aim was therefore to optimize the clip-and-cleave concept published by Becker *et al.*,[111,112] which allows selective and intramolecular hydroxylations to be carried out and to make it usable for applications in organic synthesis. For this purpose, modifications on the ligand scaffold and changes in the reaction conditions were used to increase the hydroxylation conversion and to solve problems in the solubility of the copper(I) complexes. A general scheme for the intramolecular ligand hydroxylation with benzaldehyde as a substrate is shown in Figure 18. In addition, the versatility of the ligand system was investigated by hydroxylating additional substrates to provide simple routes to functionalize hard-to-reach positions and thereby facilitating the synthesis of expensive specialty chemicals. The study of the active copper-dioxygen intermediate, in case of successful hydroxylation, should then lead to further insights into the hydroxylation mechanism. The detailed investigations and results are described in chapter 3 and have been published in the European Journal of Inorganic Chemistry.

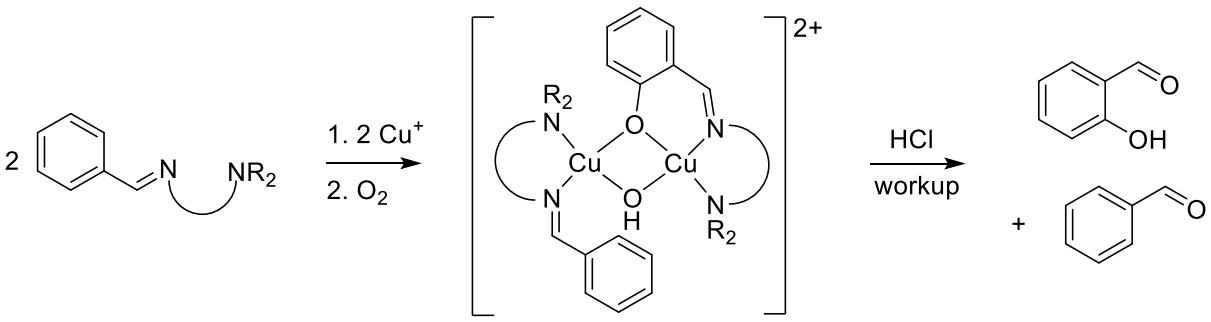


Figure 18: General scheme of an intramolecular ligand hydroxylation. NR_2 can be an amine (R = Et, *i*Pr) or a pyridine.

2 Iron(II) nitrogen monoxide complexes

2.1 Kinetic studies on the reaction of NO with iron(II) complexes using low temperature stopped-flow techniques

This article has been published in the Journal Dalton Transaction

Pascal Specht, Martin Oßberger, Peter Klüfers and Siegfried Schindler

Dalton Trans., **2020**, *49*, 9480-9486

© The Royal Society of Chemistry 2020

Dalton Transactions

ROYAL SOCIETY OF CHEMISTRY

PAPER

Cite this: *Dalton Trans.*, 2020, **49**, 9480

Kinetic studies on the reaction of NO with iron(II) complexes using low temperature stopped-flow techniques†‡

Pascal Specht,[a] Martin Oßberger,[b] Peter Klüfers [b] and Siegfried Schindler [a]*

Low temperature stopped-flow techniques were used to investigate the reaction of three different iron(II) complexes with nitrogen monoxide. The kinetic studies allowed calculation of the activation parameters from the corresponding Eyring plots for all three systems. The reaction of iron(II) chloride with NO leading to the formation of **MNIC** (mononitrosyl-iron-complex) and **DNIC** (dinitrosyl-iron-complex) led to activation parameters of $\Delta H^{\ddagger}$ = 55.4 ± 0.4 kJ mol^{-1} and $\Delta S^{\ddagger}$ = 13 ± 2 J K^{-1} mol^{-1} for **MNIC** and $\Delta H^{\ddagger}$ = 32 ± 6 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −193 ± 21 J K^{-1} mol^{-1} for **DNIC**. Formation of **MNIC** turned out to be much faster in comparison with **DNIC**. In contrast, activation parameters for the formation of monocular [Fe(bztpen)(NO)](OTf)$_2$ (bztpen = *N*-benzyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-ethylenediamine) $\Delta H^{\ddagger}$ = 17.8 ± 0.8 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −181 ± 3 J K^{-1} mol^{-1} supported an associative mechanism. Interestingly, [Fe(bztpen)(CH$_3$CN)](OTf)$_2$ does not react with dioxygen at all. Furthermore, activation parameters of $\Delta H^{\ddagger}$ = 37.7 ± 0.7 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −66 ± 3 J K^{-1} mol^{-1} were obtained for the reaction of NO with the dinuclear iron(II) H-HPTB complex (H-HPTB = *N*,*N*,*N*′,*N*′-tetrakis(2-benzimidazolylmethyl)-2-hydroxy-1,3-diaminopropane), [Fe$_2$(H-HPTB)(Cl)$_3$]. The kinetic data allowed postulation of the mechanisms for all of these reactions.

Received 15th May 2020,
Accepted 13th June 2020

DOI: 10.1039/d0dt01764g

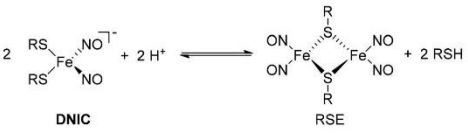
rsc.li/dalton

Introduction

Nitrogen monoxide became well known as a pollutant (one component of nitrogen oxides NO_x) in 2015, the beginning of the Volkswagen emissions scandal with regard to the exhaust system of Diesel engines. While ammonia can be used at higher temperatures in industry and in cars (formed from a urea solution, called AdBlue) iron chelate complexes, *e.g.* iron(II) edta, can be applied for gas purification under ambient conditions.[1,2] However, despite the bad image due to its known toxicity, NO was chosen molecule of the year by Science magazine in 1992.[3] This was a consequence of the identification of NO as a signalling molecule in the cardiovascular system, a finding that led to the award of the Nobel prize (in physiology or medicine) in 1998 to Furchgott, Ignarro and Murad. Consequently, interest in the solution-phase reactions of NO increased since understanding of the reactivity of this molecule could provide new insights into its physiological role. The reactions of NO with transition metal ions in the active site of metalloproteins, mainly iron enzymes, are particularly interesting.[4] Furthermore, better understanding was gained on the reactivity of sodium nitroprusside ($Na_2[Fe(CN)_5(NO)] \times 2\ H_2O$) that is used as a vasodilator during surgery due to the release of NO.[5,6]

Since about 30 years it is known that NO can modify a number of iron sulphur proteins leading to monomeric dinitrosyl iron complexes (**DNIC**s) as one of the commonly observed products.[7–9] However, formation of multinuclear complexes such as the dinuclear Roussin's red salt esters (RSEs) can also occur (Scheme 1).

An excellent study on the dynamics of the formation of several **DNIC**s from the direct reaction of NO with iron(II) and thiols in aqueous solution has been reported recently.[10] Quite complex kinetic behavior was observed due to a series of equilibria involved. However, the final step of the formation of **DNIC** could be kinetically analyzed and activation parameters



DNIC RSE

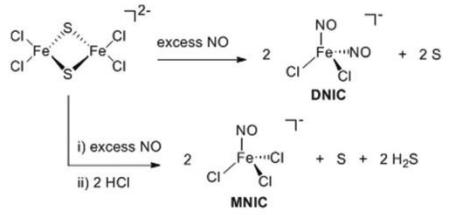
Scheme 1 Equilibrium between **DNIC** and RSE.[10]

[a]*Institut für Anorganische und Analytische Chemie, Justus-Liebig-Universität Gießen, Heinrich-Buff-Ring 17, 35392 Gießen, Germany. E-mail: siegfried.schindler@ac.jlug.de*
[b]*Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, 81377 München, Germany*

† Dedicated to Prof. Rudi van Eldik on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: Details on kinetic measurements/data. See DOI: 10.1039/d0dt01764g

This journal is © The Royal Society of Chemistry 2020



Scheme 2 Formation of **MNIC** (**1**) and **DNIC** (**2**) from the reaction of $[FeS_2Cl_4]^{2-}$ (redrawn from J. Fitzpatrick *et al.*).[8]

were obtained ($\Delta H^{\ddagger}$ = +56 ± 3 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −61 ± 5 J K^{-1} mol^{-1}). The results supported the mechanism described previously for the nitrosylation of biomimetic rubredoxin: the **DNIC** is generated *via* a mononitrosyl iron complex (**MNIC**) that was extremely air- and light-sensitive.[7,11]

When the influence of an acidic environment was investigated, it turned out that depending on the reaction conditions the two quite stable iron nitrogen monoxide complexes **MNIC** (**1**), $[FeCl_3(NO)]^-$, and **DNIC** (**2**), $[FeCl_2(NO)_2]^-$, formed (Scheme 2).[8,12]

However, besides the importance of NO in biochemical reactions it is quite interesting as a non-innocent ligand in coordination chemistry and several reports have been published on transition metal complexes with NO ligands and their reactivity in the past.[13–15] Indeed the three different ligand assignments as NO^+ (isoelectronic to CO), $NO^{\bullet}$, and NO^- (isoelectronic to O_2) leads to difficulties in the correct description of the oxidation states of the transition metal ion. Thus, even the simple complex $[Fe(H_2O)_5NO]^{2+}$, well known since many years from the qualitative analytical test on nitrate ("brown ring" test) had caused a lot of discussion on the oxidation state of the iron ion (Fe^{I}, Fe^{II} and Fe^{III} has been reported).[16,17] To keep track of the oxidation states of transition metal NO complexes the Enemark-Feltham notation $\{Fe(NO)_x\}^m$ with x = number of NO ligands and m = sum of metal (d) and NO (π^*) electrons) has been introduced leading for Fe^{II} + NO to $\{FeNO\}^7$.[18]

Quite surprisingly little is known about the kinetics and mechanisms of the reaction of NO with transition metal complexes.[4,19,20] The reasons for this are based on (a) the difficult handling of NO, (b) the extreme fast reaction rates and (c) related to b: mechanistic studies were performed mainly in aqueous solutions that did not allow cooling to slow down reaction rates. In here, we now present kinetic data and mechanistic interpretation for the formation of three different iron NO complexes that had been investigated in methanol using low temperature stopped-flow techniques.

Results and discussion

MNIC/DNIC

Reactions of nitrogen monoxide with iron(II) complexes usually are extremely fast. For example, the reversible reaction of NO with $[Fe(H_2O)_6]SO_4$ in an acetate buffered aqueous solution has a rate constant of k_{on} = (1.42 ± 0.04) × 10^6 L mol^{-1} s^{-1} at 25 °C and had to be measured by T-jump or flash photolysis.[16] From the temperature and pressure dependence activation parameters were calculated to $\Delta H^{\ddagger}$ = +37.1 ± 0.5 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −3 ± 2 J K^{-1} mol^{-1} and $\Delta V^{\ddagger}$ = +6.1 ± 0.4 cm^3 mol^{-1} thus supporting a dissociative interchange (I_d) mechanism. With iron(II) chelate complexes, *e.g.* $[Fe(edta)(H_2O)]^{2-}$ the reaction with NO was even faster, however, followed the same I_d ligand substitution mechanism.[20] In contrast an associative interchange mechanism was assigned for the related complex $[Fe(nta)(H_2O)_2]^-$. A much slower reaction rate was observed for the formation of $[Fe(CN)_5(NO)]^{2-}$ from $[Fe(CN)_5(H_2O)]^{2-}$ with a reaction rate k_f of 250 ± 10 L mol^{-1} s^{-1} at 25 °C (activation parameters $\Delta H^{\ddagger}$ = +70 ± 1 kJ mol^{-1}, $\Delta S^{\ddagger}$ = +34 ± 4 J K^{-1} mol^{-1} and $\Delta V^{\ddagger}$ = +17.4 ± 0.3 cm^3 mol^{-1}).[21] Based on these results a dissociative mechanism was proposed with rate-controlling dissociation of coordinated water and subsequent fast coordination of NO.

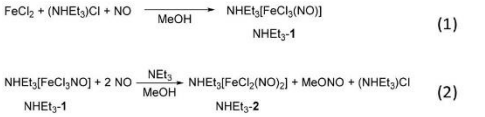
MNIC (**1**) and **DNIC** (**2**) can be synthesized in a different way and Klüfers and co-workers have reported their physical and chemical properties recently.[6] However, despite the importance of these complexes no kinetic investigation had been performed so far on the formation of these two complexes. According to Scheme 3 iron(II) chloride reacts – depending on reaction conditions – with nitrogen monoxide to form either $NHEt_3$-**1** or $NHEt_3$-**2**. Both complexes have been structurally characterized previously.[6]

1 is formed in a fast reaction (eqn (1)) without base and is stable under these conditions. In the presence of a base **2** is formed in a consecutive reaction (eqn (2)), however, at a much slower rate. The two complexes can be easily distinguished by their UV-vis spectra as shown in Fig. 1 ($FeCl_2$ does not absorb under these conditions in that wavelength range).

A big advantage in the investigation of these complexes is based on the redox-innocent ligand chloride that simplifies the system in contrast to non-innocent sulphur ligands in the natural systems described in the introduction.[12]

Kinetic investigation of MNIC formation

The formation of **1** can be followed spectroscopically easily between −87.0 °C and −34.0 °C. The time resolved UV-vis spectra are presented in Fig. 2 with characteristic absorbance maxima at 464 nm and 587 nm. As described above **1** is stable under these conditions and did not react further. However,



Scheme 3 Reaction of iron(II) chloride with nitrogen monoxide in methanol leads to the formation of **1** (eqn (1)). In presence of a base and with higher excess of nitrogen monoxide **2** is formed (eqn (2)).

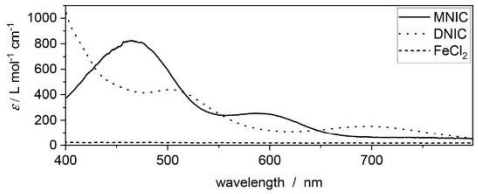


Fig. 1 UV-vis spectra of **MNIC** ($c_{Fe^{II}} = 2 \times 10^{-3}$ mol L^{-1}), **DNIC** ($c_{Fe^{II}} = 1 \times 10^{-3}$ mol L^{-1}) and complex solution before the reaction ($c_{Fe^{II}} = 1 \times 10^{-3}$ mol L^{-1}) in methanol.

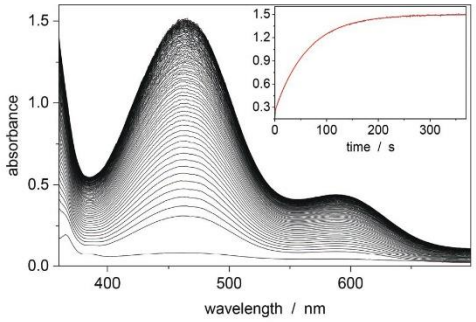


Fig. 2 Time resolved stopped-flow UV-vis spectra of **MNIC** formation at −81.9 °C in methanol ($c_{complex} = 2 \times 10^{-3}$ mol L^{-1}, $c_{NO} = 7.25 \times 10^{-3}$ mol L^{-1}, after mixing). Inlay (time trace): absorbance *vs.* time at 464 nm (black: experimental, red: exponential fit).

time of formation and rate constants change fast when the temperature is varied.

At −81.9 °C formation of **1** is complete within 300 s and the absorbance *vs.* time trace can be perfectly fitted with a one exponential fit. With NO concentration in excess and with the rate law $v = k_{obs} \times c_{complex}$ (complex = $[FeCl_2(MeOH)_2]$, see below) a first order rate constant $k_{obs} = 15.8 \times 10^{-3}$ s^{-1} could be calculated. It turned out that the reaction rate is independent with regard to NO concentration thus leading to zero order of NO concentration (see ESI, Fig. S1‡). The obtained first order rate constants were used for obtaining an Eyring plot (see ESI, Fig. S2 and S3‡) and activation parameters were calculated to $\Delta H^{\ddagger} = +55.4 \pm 0.4$ kJ mol^{-1} and $\Delta S^{\ddagger} = +13 \pm 2$ J K^{-1} mol^{-1}. The positive activation entropy indicates a dissociative or dissociative interchange mechanism.

When $FeCl_2$ is dissolved in methanol it forms $[FeCl_2(MeOH)_2]$ as reactant that in consecutive reactions is transformed into $NHEt_3$-**1**. Based on the results of our kinetic study a reaction mechanism according to Scheme 4 is proposed.

The first step is rate determining and the dissociation of a methanol ligand that is followed by the reaction with NO/Cl^-. This accounts for the independence of the rate on the NO concentration. Furthermore, the mechanism is supported by the fact that the reaction rate is independent on chloride concentration.

$$[FeCl_2(MeOH)_2] \longrightarrow [FeCl_2(MeOH)] + MeOH \quad (3)$$

$$[FeCl_2(MeOH)] + NO + Cl^- \longrightarrow \underset{\mathbf{1}}{[FeCl_3(NO)]^-} + MeOH \quad (4)$$

Scheme 4 Proposed mechanism for the formation of **1**.

In general, such a dissociative mechanism should be observed in the biological systems as well (Scheme 2), however – as pointed out by Ford and co-workers[10] – things are much more complicated in the natural systems due to complex equilibria and non-innocent ligands.

Kinetic investigation of DNIC formation

1 reacted with nitrogen monoxide to **2** in a much slower reaction. Absorbance maxima of **1** and **2** overlap in large parts (Fig. 1), however, it was still possible to separate the two reactions. **2** has two characteristic absorbance maxima at 520 nm and 700 nm. With only a small absorbance of **2** at 700 nm this wavelength was used for data fitting. The reaction follows first order kinetics and a good one exponential fit to the absorbance *vs.* time trace is possible. Kinetic studies were performed in a temperature range between −5.0 °C and 40.0 °C. The formation of **2** under the applied conditions took 1.5 h with a rate constant of $k_{obs} = 6.5 \times 10^{-4}$ s^{-1} at 20.0 °C (Fig. 3). Further experiments with dependence on nitrogen monoxide concentration were not carried out because a pseudo first kinetic could not be guaranteed anymore with lower concentrations of nitrogen monoxide.

Activation parameters could be calculated to $\Delta H^{\ddagger} = +32 \pm 6$ kJ mol^{-1} and $\Delta S^{\ddagger} = -1.9 \pm 0.2 \times 10^2$ J K^{-1} mol^{-1} (see ESI, Fig. S4‡). In comparison with the formation of **1** there is a huge difference in rate. From the Eyring plot the rate constant for the formation of **1** can be calculated to $k_{obs} = 5.0 \times 10^5$ s^{-1}

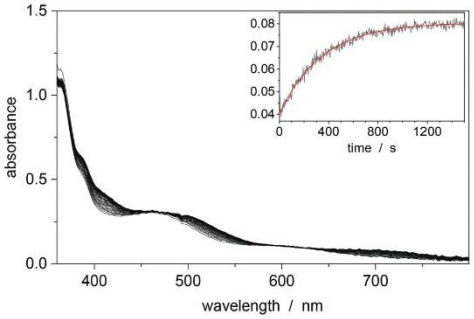


Fig. 3 Time resolved stopped-flow UV-vis spectra of **DNIC** formation at 40.0 °C in methanol ($c_{complex} = 1 \times 10^{-3}$ mol L^{-1}, $c_{NO} = 7.25 \times 10^{-3}$ mol L^{-1}, after mixing). Inlay (time trace): absorbance *vs.* time at 700 nm (black: experimental, red: exponential fit).

This journal is © The Royal Society of Chemistry 2020

at 20.0 °C. So, the reaction rates differ by a factor of 10^9. This huge difference most likely is caused by electron transfer during the reaction of **1** to **2**. The mononitrosyl iron complex of $\{FeNO\}^7$-type turns into a $\{Fe(NO)_2\}^9$-species, where the latter receives two electrons. Two NO molecules as ligands and a reducing agent, contribute one electron respectively. The remaining NO binds to methanolate forming methyl nitrite. With regard to the large negative value of $\Delta S^{\ddagger}$ an associative mechanism could be suggested. However, this for sure is not referring to a simple reaction step especially not for the simple substitution of another chloride ligand in **1**. Here we observe a complex reaction system and not just one reaction.

The iron bztpen system

In contrast to most other iron(II) complexes [Fe(bztpen)(CH_3CN)][$OTf)_2$ (bztpen = *N*-benzyl-*N*,*N*′,*N*′tris(2-pyridylmethyl)-ethylenediamine, Scheme 5) does not react with dioxygen.[22,23] Only when a large excess of hydrogen peroxide is used (together with a base) the complex can be oxidised to an iron(III) peroxido complex. Using iodosobenzene, formation of an iron(IV) oxido complex can be observed, however, none of these species could be crystallized and therefore have only been spectroscopically characterized.[24] In contrast, reacting the complex with nitrogen monoxide did allow crystallization and structural characterization of the corresponding nitrosyl complex.[22] Therefore, a kinetic analysis of this reaction was possible, without an interference of a side reaction of the complex with dioxygen.

When [Fe(bztpen)(CH_3CN)][$OTf)_2$ was reacted with NO an absorbance increase is observed with a maximum at 550 nm and a decrease of the absorbance maximum at 380 nm (Fig. 4). The increase as well as the decrease follow first order kinetics in complex concentration and were fitted with a one exponential fit (inlay in Fig. 4). The formation time of the NO complex at −47.8 °C is around 40 s with rate constant $k_{obs} = 0.136\ s^{-1}$.

A plot of k_{obs} *vs.* nitrogen monoxide concentration shows a linear correlation (see ESI, Fig. S5‡) and thus confirms first order dependence in nitrogen monoxide concentration leading to the second order rate law:

$$v = k_{obs} \cdot c_{complex} \cdot c_{NO} \quad (5)$$

From the slope a second order rate constant k = 19.3 L mol^{-1} s^{-1} can be derived at −47.8 °C. With measurements in the temperature range between −47.8 °C and −18.4 °C an Eyring plot allowed calculation of the activation parameters to

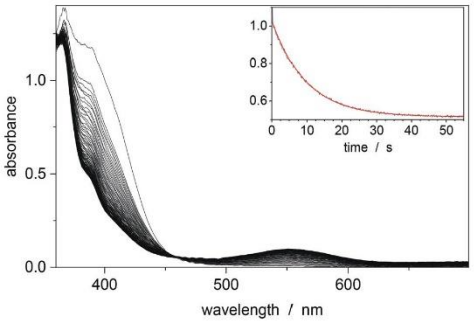


Fig. 4 Time resolved stopped-flow UV-vis spectra of [Fe(bztpen)(CH_3CN)][$OTf)_2$ with nitrogen monoxide at −47.8 °C in methanol ($c_{complex}$ = 0.5 × 10^{-3} mol L^{-1}, c_{NO} = 7.25 × 10^{-3} mol L^{-1}, after mixing). Inlay (time trace): absorbance *vs.* time at 384 nm (black: experimental, red: exponential fit).

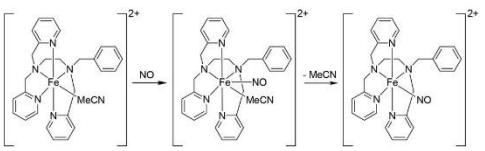
$\Delta H^{\ddagger}$ = +17.8 ± 0.8 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −181 ± 3 J K^{-1} mol^{-1} (see ESI, Fig. S6‡). The large negative value for activation entropy indicates an associative mechanism for the formation of the nitrosyl complex. The postulated mechanism is presented in Scheme 5.

NO is approaching and binding to the complex while acetonitrile is still coordinated, the rate determining step. Then acetonitrile dissociates and [Fe(bztpen)(NO)][$OTf)_2$ is formed.

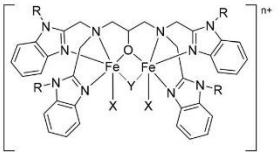
The iron HPTB system

Activation of dioxygen at metal ion sites is important with regard to selective oxygenation of organic substrates in organic synthesis as well as for the reactivity of metalloenzymes.[25–28] Where dioxygen complex products are not readily accessible, nitrogen monoxide, as a related diatomic molecule to dioxygen, and its metal complexes may provide a better understanding of dioxygen binding patterns.[29,30]

The dinuclear iron(II) complex with the ligand Et-HPTB (*N*,*N*,*N*′,*N*′-tetrakis(2-(1-ethylbenzimidazolyl)methyl)-2-hydroxy-1,3-diaminopropane ([Fe_2(R-HPTB)$(X)_2$Y](anion); see Scheme 6, a deprotonated ligand with R = Et in the corresponding iron complex) has been used as a model compound for the oxygen carrier protein hemerythrin (as well as related metalloenzymes).

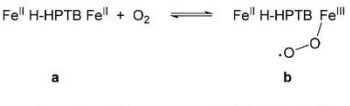


Scheme 5 Postulated mechanism of the formation of the iron nitrosyl complex of [Fe(bztpen)(MeCN)]$^{2+}$.

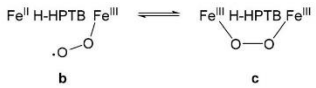


Scheme 6 The iron(II) R-HPTB complex ([Fe_2(R-HPTB)$(X)_2$Y]) with R = H or Et, X = NO or Cl^-, Y = benzoate or Cl^-.

The reaction of dioxygen with $[Fe_2(Et\text{-}HPTB)(benzoate)](BF_4)_2$ in nitrile solvents has been investigated in great detail using low temperature stopped-flow methods.[31] More recently some of us investigated the related complex $[Fe_2(H\text{-}HPTB)(Cl)_3]$ in methanol and obtained $\Delta H^{\ddagger}$ = +15.0 ± 0.4 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −146 ± 1 J K^{-1} mol^{-1} as activation parameters.[32] These values are identical (in the range of error) with the ones derived from the measurements in propionitrile for $[Fe_2(Et\text{-}HPTB)(benzoate)](BF_4)_2$ ($\Delta H^{\ddagger}$ = +15.4 ± 0.6 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −121 ± 3 J K^{-1} mol^{-1}). While the reaction most likely must proceed in two steps according to the following equations only the formation of the peroxido complex (c) could be observed in one step. This easily can be explained by assuming that the formation of the iron superoxido complex (b) is rate determining and the consecutive reaction to the peroxido complex is much faster.



(6)



(7)

Reacting NO instead of dioxygen with the iron(II) Et-HPTB complex showed an NO molecule coordinated to each of the two iron ions (Scheme 6, anions = 2 BF_4^-, X = NO, Y = benzoate) in the product. The molecular structure of this complex has been characterized previously.[33,34] More recently an iron HPTB complex with only one NO ligand coordinated has been reported, however, not by using NO itself as a reactant.[35] So far no kinetic studies have been performed with this system that could give more details on the reactivity of the iron(II) R-HPTB complexes.

When $[Fe_2(H\text{-}HPTB)(Cl)_3]$ in methanol was reacted with NO a fast reaction was observed. The time resolved UV-vis spectra are reported in Fig. 5.

To slow down the reaction it has been studied in a temperature range between −81 °C and −40 °C. The nitrosyl complex is observed with absorbance maxima at 452 nm and at 600 nm. A perfect one exponential fit of absorbance *vs.* time (inlay in Fig. 5) with nitrogen monoxide concentration in excess leads to the rate constant k_{obs} = 0.133 s^{-1} at −78.2 °C. Activation parameters were calculated from an Eyring plot to $\Delta H^{\ddagger}$ = +37.7 ± 0.7 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −66 ± 3 J K^{-1} mol^{-1} (see ESI, Fig. S7‡). These values are somewhat different with regard to activation parameters obtained for the analogous reaction with dioxygen, however, here the product contains a peroxide bridge leading to a highly ordered system instead of the two NO ligands coordinated separately to each iron cation. However, similar findings were reported for an iron(II) complex system with the tripodal ligand 6-Me$_3$TPA (6-Me$_3$-TPA = tris(6-methyl-2-pyridylmethyl)amine.[30] Activation parameters of $\Delta H^{\ddagger}$ = +29 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −77 J K^{-1} mol^{-1} for the reaction of this complex with NO are in good agreement with our data.

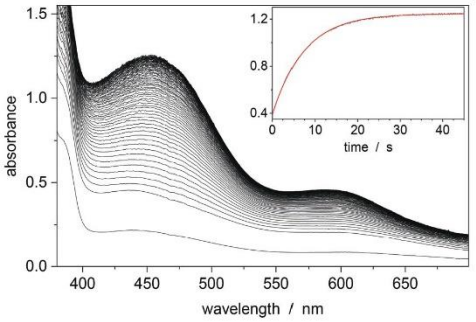


Fig. 5 Time resolved stopped-flow UV-vis spectra of $[Fe_2(H\text{-}HPTB)(Cl)_3]$ reacting with nitrogen monoxide at −78.2 °C in methanol ($c_{complex}$ = 1 × 10^{-3} mol L^{-1}, c_{NO} = 7.25 × 10^{-3} mol L^{-1}, after mixing). Inlay (time trace): absorbance *vs.* time at 452 nm (black: experimental, red: exponential fit).

Furthermore, activation parameters for the reaction of this complex with dioxygen ($\Delta H^{\ddagger}$ = +17 ± 2 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −175 ± 20 J K^{-1} mol^{-1}) also fit quite well our data for the $[Fe_2H\text{-}HPTB(Cl)_3]$ complex ($\Delta H^{\ddagger}$ = +15.4 ± 0.6 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −121 ± 3 J K^{-1} mol^{-1}) taking the large errors of the values for the activation entropy into account. Comparing the activation parameters of these reactions we can now support the suggestion made earlier, that both the nitrosylation and oxidation of these complexes share a similar associative mechanism with a somewhat later transition state in the reaction with NO, leading to a partial compensation effect between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.[30]

Experimental

Materials and methods

Complexes and ligands H-HPTB and bztpen were prepared and characterized as previously described.[36,37] Solvents and reagents used were of commercially available reagent quality. ^{13}C-NMR and ^{1}H-NMR spectra were measured on a Bruker Avance II 400 MHz and Avance III 400 MHz HD spectrometer. Electrospray-ionization MS (ESI-MS) measurements were performed on a Bruker micro-TOF mass spectrometer. All measurements under inert conditions were carried out in argon or nitrogen atmosphere by standard Schlenk techniques or working in a glove box (MBraun, Garching, Germany). For these experiments extra dry solvents were distilled under argon atmosphere with a drying agent and transferred into the glove box. For reactions with nitrogen monoxide a gastight syringe was filled with methanol only and saturated with *in situ* prepared nitrogen monoxide (see below) by bubbling a gas stream through the solvent for 15 min (14.5 × 10^{-3} mol L^{-1}).[38] Different concentrations of nitrogen monoxide were achieved by mixing a saturated nitrogen monoxide solution with argon saturated pure methanol, thus achieving lower concentrations. Due to the mixing of complex and nitrogen monoxide solution

 This journal is © The Royal Society of Chemistry 2020

in the stopped-flow instrument, the maximum nitrogen monoxide concentration is 7.25×10^{-3} mol L^{-1}.

Low-temperature stopped-flow measurements

For low-temperature stopped-flow measurements HI-TECH Scientific CSF-61DX2 and SF-61SX2 instruments (TgK Scientific, Bratford on Avon, UK) were used. Setup and kinetic measurements procedure already were described in detail previously.[39] The kinetic data were analysed with the integrated software Kinetic Studio (Version 5.02 Beta, TgK Scientific). For the investigation of **MNIC** formation a 4×10^{-3} mol L^{-1} iron(II) chloride tetrahydrate solution with 2.5 times excess of triethylammonium chloride (10×10^{-3} mol L^{-1}) was prepared. To check the NO dependency of **MNIC** formation, these experiments were also carried out with a 0.6×10^{-3} mol L^{-1} complex solution (0.6×10^{-3} mol L^{-1} iron(II) chloride tetrahydrate, 1.5×10^{-3} mol L^{-1} triethylammonium chloride) in order to obtain better conditions for pseudo first order with higher nitrogen monoxide excess. For the investigation of **DNIC** formation a 2×10^{-3} mol L^{-1} iron(II) chloride tetrahydrate with five times excess (10×10^{-3} mol L^{-1}) triethylammonium chloride and triethylamine (2×10^{-3} mol L^{-1}) was prepared (to avoid formation of iron precipitation triethylamine was added at the end). The complex solutions were prepared in a glove box and filled into gastight syringes. For the reaction of the iron(II) bztpen complex with nitrogen monoxide a 1×10^{-3} mol L^{-1} solution with bis(acetonitrile)iron(II) triflate and bztpen in a ratio of 1 : 1 was prepared. For the reaction of the diiron(II) H-HPTB complex with nitrogen monoxide a 2×10^{-3} mol L^{-1} complex solution was prepared with anhydrous iron(II) chloride in a 2 : 1 ratio of iron salt to ligand.

In situ preparation of nitrogen monoxide

A suspension of 90 g (0.32 mol) iron(II) sulphate heptahydrate in 200 ml (2.04 mol) sulphuric acid was filled in a dropping funnel and added in small portions to 140 g (2.03 mol) sodium nitrite in a Schlenk flask. Before starting to prepare nitrogen monoxide the whole apparatus was flushed with nitrogen to remove oxygen. The gas stream was then passed through wash bottles filled with concentrated sodium hydroxide solution to remove nitric dioxide and solid sodium hydroxide was used for drying.

$$2\ FeSO_4 + 3\ H_2SO_4 + 2\ NaNO_2 \rightarrow 2\ NO + 2\ H_2O + Fe_2(SO_4)_3 + 2\ NaHSO_4$$

Conclusions

Reactions of iron(II) complexes, for example iron aminocarboxylate derivatives (*e.g.* $[Fe(edta)]^{2-}$ complexes and derivatives) react extremely fast with nitrogen monoxide.[20,40] For applications in industry there is high interest in gaining better understanding of mass transfer in reactive bubbly flows and detailed kinetic studies are necessary for high level calculations.[2,41] However, reactivity studies with these complexes were performed in water and it was necessary to use fast measurement techniques such as laser flash photolysis to obtain rate constants and activation parameters. To the best of our knowledge there are nearly no reports of the kinetics of NO binding to iron(II) complexes in organic solvents. Using methanol as a solvent and working with a different group of iron(II) compounds we were able to study the kinetics of iron NO complex formation in methanol using low temperature stopped-flow techniques. Activation parameters of $\Delta H^{\ddagger} = +37.7 \pm 0.7$ kJ mol^{-1} and $\Delta S^{\ddagger} = -66 \pm 3$ J K^{-1} mol^{-1} for the reaction of the iron H-HPTB complex are similar to the data obtained for an iron 6-Me_3TPA complex ($\Delta H^{\ddagger} = +29$ kJ mol^{-1} and $\Delta S^{\ddagger} = -77$ J K^{-1} mol^{-1} in dichloromethane) described previously.[30] This is the only report we are aware of, in which such a reaction has been described in the past. Furthermore, activation parameters for the reaction of this complex with dioxygen ($\Delta H^{\ddagger} = +17 \pm 2$ kJ mol^{-1} and $\Delta S^{\ddagger} = -175 \pm 20$ J K^{-1} mol^{-1}) also fit quite well our data for the $[Fe_2(H\text{-HPTB})(Cl)_3]$ complex ($\Delta H^{\ddagger} = +15.4 \pm 0.6$ kJ mol^{-1} and $\Delta S^{\ddagger} = -121 \pm 3$ J K^{-1} mol^{-1}) taking the large errors of the values for the activation entropy into account. In general, it is quite difficult to compare the activation parameters for the formation of iron NO complexes because they have been obtained under quite different reaction conditions.

Understanding the mechanisms of these reactions is not only important for the biological systems described in the introduction but furthermore for industrial setups, such as reactions in bubble flow columns. Knowing kinetic parameters for these reactions, *e.g.* for the formation of **MNIC**, allows further optimization for future applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge financial support from the German Research Foundation (DFG, Deutsche Forschungsgemeinschaft) received within the scope of SPP 1740 (Influence of local transport processes in chemical reactions in bubble flows), SCHI 377/13-1 and KL 624/18-1.

References

1 J. F. Demmink, I. C. F. van Gils and A. A. C. M. Beenackers, *Ind. Eng. Chem. Res.*, 1997, **36**, 4914–4927.
2 M. W. Hlawitschka, M. Oßberger, C. Backes, P. Klüfers and H.-J. Bart, *Oil Gas Sci. Technol.*, 2017, **72**, 1–11.
3 D. E. Koshland Jr., *Science*, 1992, **258**, 1861–1861.
4 P. C. Ford and I. M. Lorkovic, *Chem. Rev.*, 2002, **102**, 993–1017.
5 F. Roncaroli, J. A. Olabe and R. van Eldik, *Inorg. Chem.*, 2002, **41**, 5417–5425.

6 A. In-Iam, M. Wolf, C. Wilfer, D. Schaniel, T. Woike and P. Klüfers, *Chem. – Eur. J.*, 2019, **25**, 1304–1325.
7 M.-L. Tsai, C.-C. Tsou and W.-F. Liaw, *Acc. Chem. Res.*, 2015, **48**, 1184–1193.
8 J. Fitzpatrick and E. Kim, *Acc. Chem. Res.*, 2015, **48**, 2453–2461.
9 A. Buet and M. Simontacchi, *Ann. N. Y. Acad. Sci.*, 2015, **1340**, 39–46.
10 D. R. Truzzi, O. Augusto, A. V. Iretskii and P. C. Ford, *Inorg. Chem.*, 2019, **58**, 13446–13456.
11 T.-T. Lu, S.-J. Chiou, C.-Y. Chen and W.-F. Liaw, *Inorg. Chem.*, 2006, **45**, 8799–8806.
12 C. T. Tran and E. Kim, *Inorg. Chem.*, 2012, **51**, 10086–10088.
13 R. Eisenberg and C. D. Meyer, *Acc. Chem. Res.*, 1975, **8**, 26–34.
14 J. A. McCleverty, *Chem. Rev.*, 1979, **79**, 53–76.
15 J. C. Fanning, *Coord. Chem. Rev.*, 1991, **110**, 235–273.
16 A. Wanat, T. Schneppensieper, G. Stochel, R. van Eldik, E. Bill and K. Wieghardt, *Inorg. Chem.*, 2002, **41**, 4–10.
17 G. Monsch and P. Klüfers, *Angew. Chem., Int. Ed.*, 2019, **58**, 8566–8571.
18 J. H. Enemark and R. D. Feltham, *Coord. Chem. Rev.*, 1974, **13**, 339–406.
19 K. A. Pearsall and F. T. Bonner, *Inorg. Chem.*, 1982, **21**, 1978–1985.
20 T. Schneppensieper, A. Wanat, G. Stochel and R. van Eldik, *Inorg. Chem.*, 2002, **41**, 2565–2573.
21 F. Roncaroli, J. A. Olabe and R. van Eldik, *Inorg. Chem.*, 2003, **42**, 4179–4189.
22 T. Nebe, A. Beitat, C. Würtele, C. Dücker-Benfer, R. van Eldik, C. J. McKenzie and S. Schindler, *Dalton Trans.*, 2010, **39**, 7768–7773.
23 A. Hazell, C. J. McKenzie, L. P. Nielsen, S. Schindler and M. Weitzer, *J. Chem. Soc., Dalton Trans.*, 2002, 310–317.
24 D. Wang, K. Ray, M. J. Collins, E. R. Farquhar, J. R. Frisch, L. Gómez, T. A. Jackson, M. Kerscher, A. Waleska, P. Comba, M. Costas and L. Que Jr., *Chem. Sci.*, 2013, **4**, 282–291.
25 Y. Liang, J. Wei, X. Qiu and N. Jiao, *Chem. Rev.*, 2018, **118**, 4912–4945.
26 A. L. Feig and S. J. Lippard, *Chem. Rev.*, 1994, **94**, 759–805.
27 P. P. Chandrachud and D. M. Jenkins, *Tetrahedron Lett.*, 2015, **56**, 2369–2376.
28 M. E. Sosa Torres, J. P. Saucedo-Vázquez and P. M. H. Kroneck, Sustaining Life on Planet Earth: Metalloenzymes Mastering Dioxygen and Other Chewy Gases. Metal Ions in Life Sciences, in *The Magic of Dioxygen*, ed. P. Kroneck and M. Sosa Torres, Springer, Cham, 2015, vol. 15.
29 L. M. Blomberg, M. R. A. Blomberg and P. E. M. Siegbahn, *J. Inorg. Biochem.*, 2005, **99**, 949–958.
30 S. V. Kryatov, E. V. Rybak-Akimova, V. L. MacMurdo and J. Que Jr., *Inorg. Chem.*, 2001, **40**, 2220–2228.
31 A. L. Feig, M. Becker, S. Schindler, R. van Eldik and S. J. Lippard, *Inorg. Chem.*, 1996, **35**, 2590–2601.
32 A. Miska, D. Schurr, G. Rinke, R. Dittmeyer and S. Schindler, *Chem. Eng. Sci.*, 2018, **190**, 459–465.
33 A. L. Feig, M. T. Bautista and S. J. Lippard, *Inorg. Chem.*, 1996, **35**, 6892–6898.
34 Y. Jiang, T. Hayashi, H. Matsumura, L. H. Do, A. Majumdar, S. J. Lippard and P. Moënne-Loccoz, *J. Am. Chem. Soc.*, 2014, **136**, 12524–12527.
35 A. Majumdar and S. J. Lippard, *Inorg. Chem.*, 2013, **52**, 13292–13294.
36 V. McKee, M. Zvagulis, J. V. Dagdigian, M. G. Patch and C. A. Reed, *J. Am. Chem. Soc.*, 1984, **106**, 4765–4772.
37 L. Duelund, R. Hazell, C. J. McKenzie, L. P. Nielsen and H. Toftlund, *J. Chem. Soc., Dalton Trans.*, 2001, 152–156.
38 M. D. Lim, I. M. Lorković and P. C. Ford, *Methods Enzymol.*, 2005, **396**, 3–17.
39 M. Weitzer, M. Schatz, F. Hampel, F. W. Heinemann and S. Schindler, *J. Chem. Soc., Dalton Trans.*, 2002, 686–694.
40 M. Wolak and R. van Eldik, *Coord. Chem. Rev.*, 2002, **230**, 263–282.
41 D. Merker, L. Böhm, M. Oßberger, P. Klüfers and M. Kraume, *Chem. Eng. Technol.*, 2017, **40**, 1391–1399.

This journal is © The Royal Society of Chemistry 2020

3 Selective Ligand Hydroxylation

3.1 Aerobic C-H hydroxylation by copper imine complexes: The clip-and-cleave concept – versatility and limits

This article has been published in the European Journal of Inorganic Chemistry

Pascal Specht, Alexander Petrillo, Jonathan Becker and Siegfried Schindler

Eur. J. Inorg. Chem., **2021**, 1961-1970

© 2021 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

Aerobic C–H Hydroxylation by Copper Imine Complexes: The Clip-and-Cleave Concept – Versatility and Limits

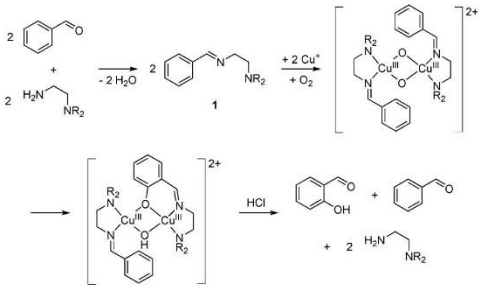
Pascal Specht,[a] Alexander Petrillo,[a] Jonathan Becker,[a] and Siegfried Schindler*[a]

The intramolecular ligand hydroxylation of a series of copper(I) imine complexes during their reaction with dioxygen had been systematically studied. The so-called clip-and-cleave concept offers a facile way to oxygenate aldehydes or ketones. A copper(I) complex for example, with an imine ligand derived from an ethylenediamine derivative and cyclohexanone was oxidized. Decomposing the complex after the reaction with hydrochloric acid showed a 50% conversion of the cyclohexanone to 2-hydroxycylohexanone. Depending on the ligand system, three different reaction pathways have been identified that can cause hydroxylation reactions. While the radical based mechanisms are more difficult to identify, the reactions that go through a copper bis(μ-oxido) complex as active species can be analyzed by low temperature stopped-flow techniques. In an ideal case the formation and decomposition of this reactive intermediate can be spectroscopically observed. It was shown that this depends strongly on the ligand system: steric effects, chelate ring size and coordination number play an important role for the mechanism and the outcome of the reaction.

Introduction

Copper monooxygenases such as e.g. tyrosinase or methane monooxygenase are important enzymes for the oxygenation of organic substrates (tyrosine to L-DOPA and methane to methanol).[1] Besides the interest in a better understanding of the biological function, these enzymes demonstrate that it is possible to perform selective oxidation reactions under ambient conditions (aqueous solutions, room temperature) using dioxygen from air as the sole oxidant.[2] Due to the importance of catalytic selective oxidation reactions in industry,[3] low molecular weight complexes have been "designed" to model the reactivity of the copper enzymes.[4,5]

In that regard we recently developed a so called "clip-and-cleave" system that allows stoichiometric C–H hydroxylation in the γ-position of aromatic and aliphatic aldehydes utilizing a copper imine complex system,[6,7] similar to the initial oxygenation step of tyrosinase, which catalyzes the *ortho*-hydroxylation of L-tyrosine to L-DOPA prior to the further oxidation to L-DOPA quinone in melanin biosynthesis.[8] In contrast to our previous work, the nomenclature has been adapted to the nomenclature of Garcia-Bosch and co-workers for the carbon that is hydroxylated.[9] In Scheme 1 the general reaction mechanism is presented using benzaldehyde as a substrate. In a first step the imine ligand is prepared, here from benzaldehyde and *N*,*N*-diethylethylenediamine, leading to *N*'-benzylidene-*N*,*N*-diethylethylenediamine (BDED, **1**). BDED was then reacted with a copper(I) salt e.g. $[Cu(CH_3CN)_4]OTf$, to form the copper(I) complex [Cu(**1**)]OTf in situ (most likely one or two CH_3CN molecules are coordinated as ligands additionally). Reaction with dioxygen caused formation of a copper bis(μ-oxido) complex as an intermediate followed by intramolecular ligand hydroxylation. Yields of salicylaldehyde were close to the limiting 50% (theoretical maximum yield in this reaction)[6,7] and the formation and decomposition of the intermediate, the copper bis(μ-oxido) complex, could be followed spectroscopically by low temperature stopped-flow measurements. Copper bis(μ-oxido) complexes have been investigated in great detail during the last years with regard to ligand variation, reaction conditions etc.[5,10]



Scheme 1. Intramolecular hydroxylation of $[Cu^{I}(\mathbf{1})]^{+}$ complex (R = Et) with dioxygen. The hydroxylation proceeds via a copper bis(μ-oxido) intermediate.[6]

More recently an excellent extensive study on intramolecular ligand hydroxylation was reported by Garcia-Bosch and co-workers, using camphor derivatives and steroids as

[a] P. Specht, A. Petrillo, Dr. J. Becker, Prof. Dr. S. Schindler
Institut für Anorganische und Analytische Chemie
Justus-Liebig-Universität Gießen
Heinrich-Buff-Ring 17, 35392 Gießen, Germany
E-mail: siegfried.schindler@anorg.chemie.uni-giessen.de
https://www.uni-giessen.de/fbz/fb08/Inst/iaac/schindler

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejic.202100185

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

substrates.[11] This work is based on results obtained earlier by Schönecker and later by Baran and co-workers.[12–15] In contrast to the mechanism described above (Scheme 1), they did not observe formation of a copper bis(μ-oxido) complex at all. Their detailed kinetic analysis showed that for these reactions obviously a different mechanism takes place.[9,11] Their proposed reaction mechanism for the hydroxylation of sp^2 C–H bonds is presented in Scheme 2. Here, using imino pyridine ligands, they assigned a hydroperoxido complex ($LCu^{II}(OOH)$) as active species. By optimizing the reaction conditions, they were able to achieve yields close to 100% of hydroxylated product.

With regard to the importance of selective oxidation reactions we were interested to learn more about the occurrence of the two different mechanisms and investigated these reactions in more detail.

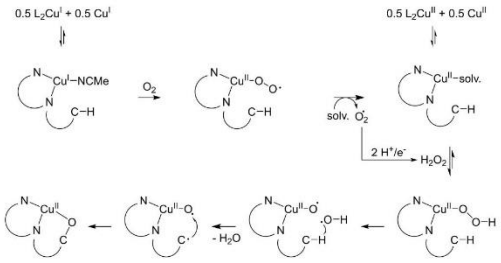
Results and Discussion

Influence of solvent and ligand backbone

Many of the reactions leading to selective oxygenation reactions rely on the formation of a mononuclear copper complex in a 1:1 ratio of copper(I):ligand.[6,7,9,11,16] However, when ligands are utilized that do not provide necessary sterically features/hindrance a strong tendency is observed that a complex in a copper(I) to ligand ratio of 1:2 forms. These complexes often are nearly unreactive towards dioxygen. This problem was observed for the copper BDED system described above as well.[6] Depending on the conditions, the unreactive complex $[Cu(\mathbf{1})_2]X$ (X = different anions) is easily formed leading herewith to complete suppression of the hydroxylation reaction. Often these complexes exhibit a more intensive color and furthermore decreased solubility. Figure 1 shows the difference between solutions containing [Cu(**1**)]OTf and $[Cu(\mathbf{1})_2]$OTf in acetone.

To avoid this problem, it was decided to modify the ligand system e.g. by introducing sterically more demanding, bulkier groups into the ethylenediamine unit. Therefore, the ligands **L** presented in Scheme 3 were prepared. Furthermore, due to the fact that the formation of the $[Cu(\mathbf{L})_2]$OTf complex is also depending on the solvent used, the influence of different solvents was tested. While being used successfully in the past, acetonitrile (or propionitrile) and methanol had to be excluded for our studies because no hydroxylation reaction was observed using these two solvents. Methanol can be a problem because it is a protic solvent, thus leading to decomposition of intermediates prior to a reaction with the ligand and nitrile solvents might suppress any further reaction because nitriles coordinate strongly to the copper(I) ion (blocking it against dioxygen activation).[17] Acetone so far proved to be the best solvent for the investigations described herein, however it was also possible to use dichloromethane, despite some problems described earlier (low yield and ligand decomposition at low temperatures), that can occur with this solvent.[6]

Ligands **1** to **7** were investigated under the same conditions that were applied previously for the hydroxylation reaction using [Cu(**1**)]OTf. The results obtained according to Scheme 1 are presented in Table 1 together with the original findings for this complex (entry 1) for which a ligand conversion to the hydroxylated product, salicylaldehyde, of almost 50% were achieved. In our new measurements we had some more problems with the precipitation of a yellow/orange solid discussed above in combination with some formation of



Scheme 2. Proposed mechanism for the intramolecular hydroxylation of sp2C–H bond. Redrawn from Trammell *et al.*[11]

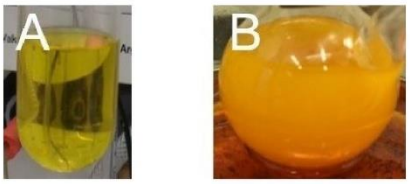
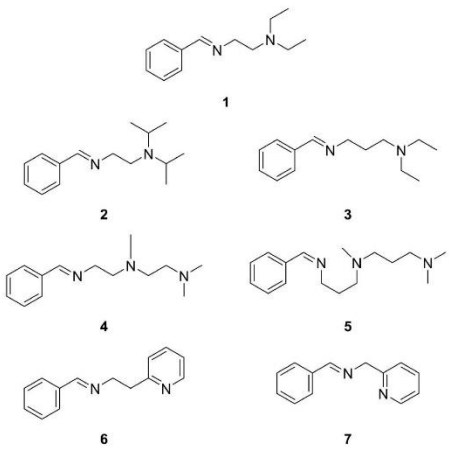


Figure 1. (A) The 1:1 [Cu:L] complex [Cu(**1**)]OTf in acetone and (B) the 1:2 [Cu:L_2] complex $[Cu(\mathbf{1})_2]$OTf in acetone.



Scheme 3. Ligands used in this study: BDED (**1**), BDiPED (**2**), BDPD (**3**), BTED (**4**), BTPD (**5**), BEP, (**6**) and BMP (**7**).

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

Table 1. Conversion of the substrate into hydroxylated products using ligands **1**–**7** (Scheme 3) with benzaldehyde as substrate.

Entry	Ligand	Acetone[a] Conversion [%]	Dichloromethane
1[b]	BDED (**1**)	Close to 50	–
2[c]	BDED (**1**)	34	33
3	BDiPED (**2**)	45	41
4	BDPD (**3**)	0	0
5	BTED (**4**)	0	0
6	BTPD (**5**)	0	0
7	BEP (**6**)	5	8
8	BMP (**7**)	5	3

[a] Traces of diisopropylamine after hydroxylation experiment detected. [b] J. Becker *et al.*[6] [c] Reproduced results of Entry 1.

diisopropylamine in acetone. Nevertheless, hydroxylation conversions of 34% in acetone and 33% in dichloromethane were observed. The occurrence of diisopropylamine had been puzzling at first, however it can be explained by a reaction with the solvent acetone according to the mechanism presented in Figure S53 (see Supporting Information). In an imine equilibrium free benzaldehyde can react with acetone followed by a 1,3-H-shift. Cleavage of the imine allows the reaction with a second acetone molecule and through a hydride transfer, similar to a Cannizzaro type reaction, diisopropylamine is formed. The additionally formed side products were most likely extracted during the aqueous work-up and therefore could not be detected in GC-MS measurements.

A look at Table 1 immediately shows two important aspects that are essential for the intramolecular ligand hydroxylation under these conditions:

1.) Here "wrong" chelate ring sizes seem to completely suppress ligand hydroxylation. With ligand **3** a six-membered chelate ring size is achieved in contrast to ligand **1** and **2** that form 5-membered chelate rings. Six-membered chelate rings are well known to often stabilize copper(I) complexes better and that might be one of the reasons for the completely suppressed hydroxylation reaction.[18] However, this is not generally the case because hydroxylation reactions also can be observed with copper(I) complexes with ligands in six-membered chelate rings.[19]
2.) Independent of chelate ring sizes it seems that tridentate ligands such as e.g. **4** and **5** are not suitable here as well. For copper(I) complexes with these ligands no hydroxylation was observed at all. Our intention to avoid formation of $[Cu(\mathbf{L})_2]X$ complexes by using tridentate ligands obviously was counterproductive. Most likely a bidentate ligand is necessary (at least in our reactions) to keep the coordination sites open for their reactivity towards hydroxylation. Further investigations with these two ligands were not carried out due to the lack of a hydroxylation reaction as well as due to the high cost and time-consuming preparation of the reactants for ligand syntheses.

Our approach to introduce more bulky groups to suppress the 1:2 copper:ligand formation was valid because copper(I) complexes with ligand **2** showed higher hydroxylation conversions in comparison to complexes with ligand **1** in both solvents under our conditions. Still, it is possible to achieve a conversion of up to 50% with both ligands **1** (entry 1 in Table 1) and **2** but it is obviously more difficult with **1**. Furthermore, despite the slightly higher conversion in acetone, small amounts of diisopropylamine were again detected, indicating that dichloromethane is the better solvent to perform these reactions.

However, quite surprisingly and despite the structural similarity of **2** with **1**, no copper bis(μ-oxido) complex could be spectroscopically detected as an intermediate during the reaction of its copper(I) complex with dioxygen (see Supporting Information). Two possibilities could account for that: a) if the formation of the copper bis(μ-oxido) complex (or another "dioxygen adduct" complex) is rate determining then consecutive hydroxylation is fast and there is no chance to observe the intermediate or b) hydroxylation occurs according to the mechanism proposed by Garcia-Bosch and co-workers (Scheme 2).[11] From our data we cannot really say which of the two cases is more likely here.

In contrast to the formation of a quite stable copper bis(μ-oxido) complex with ligand **1**, the sterically more demanding isopropyl groups in **2** could lead to some shielding and thus exclude formation of such a binuclear unit. To some extent this is supported by the molecular structure of the copper(I) complex [Cu(**2**)]Cl (Figure 2, crystallographic data are reported in the Supporting Information and selected bond lengths and angles are reported in Table 2) in which the two isopropyl groups definitely require some space. This steric shielding furthermore allowed us to crystallize this complex in a 1:1 copper to ligand ratio. With ligand **1** it only had been possible to crystallize the 1:2 complex $[Cu(\mathbf{1})_2]SbF_6$.[6] In general, it is not easy to crystallize and structurally characterize copper(I) com-

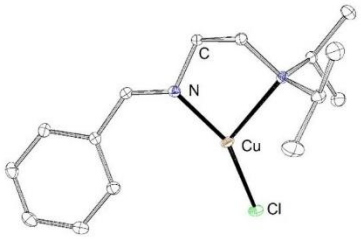


Figure 2. ORTEP plot of molecular structure of [Cu(**2**)Cl]. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 2. Selected bond length [Å] and angles [°] for complex [Cu(**2**)Cl] (Figure 2).

Cu(1)–N(1)	1.9415(9)	N(1)–Cu(1)–Cl(1)	153.44(3)
Cu(1)–Cl(1)	2.1577(3)	N(1)–Cu(1)–N(2)	84.09(3)
Cu(1)–N(2)	2.3727(9)	Cl(1)–Cu(1)–N(2)	122.17(2)
Cu(1)–C_{oxid}	3.263(1)	Dihedral angle[a]	158.8

[a] C_{oxid}–Cu(1)–N(2) angle.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

plexes of this type. Therefore, chloride or iodide as co-ligands have been used.[20]

[Cu(**2**)]Cl shows a trigonal coordination of copper by the imine and amine nitrogen atoms and chloride. Whether the amine-copper bond is a strong coordinative bond is worth discussing, since the bond length is relatively long. The copper-amine nitrogen distance is 2.3727(9) Å, whereas the distance between imine nitrogen and copper is 1.9415(9) Å. In the copper(I) BDED complex, the largest distance between nitrogen and copper is 2.239(3) Å. Cu–N amine distances higher than 2.37 Å are less common, nevertheless, similar bond lengths were determined with structurally very similar ligands and also the Cu–N imine distances fit very well.[21]

Only low reactivity was achieved with ligands **6** and **7** (entry 7 and 8 in Table 1). Here a pyridyl group with an ethylene respectively a methylene bridge was introduced instead of the ethylene diamine backbone. The conversion is well below that of **1** and **2**, however, See *et al.* have shown that higher yields with copper(I) complexes with this type of imino pyridine functionalized ligands (steroids) were possible under slightly different reaction conditions.[15] We also tried to apply these reaction conditions, using a reducing agent and dioxygen as oxidant, but instead of a clean hydroxylation reaction with high yields we observed overoxidation of the aromatic substrate and the formation of various by-products.

Recently, Trammell *et al.* reported the molecular structure of the copper(I) complex with **7** as a ligand ([(**7**)Cu(CH_3CN)]PF_6).[9] The complex shows a trigonal planar coordination geometry which is comparable to the molecular structure of the copper(I)-**2** complex with chloride (Figure 2). Within estimated standard deviation there is no difference of the N–Cu–N angles (84.09(3)° vs. 84.4(4)°). Also, the Cu–$C_{oxid.}$ distance is very similar (3.263(1) Å vs. 3.243(13) Å), only the dihedral angle ($C_{oxid.}$–Cu–N) is slightly more angled (158.8° vs. 178.8°) in case of the copper(I)-**2** complex.

The hydroxylation of benzaldehyde with this complex was performed using hydrogen peroxide instead of dioxygen. In comparison with their other investigated systems the conversion of 39% was quite low but still significantly higher than in our experiment with dioxygen (entry 8 in Table 1). Stopped-flow measurements of the reaction of dioxygen with the copper(I) complexes with the ligands **6** and **7** did not indicate the formation of a "dioxygen adduct" complex as an intermediate and only showed a slow oxidation to corresponding copper(II) complexes.

Aliphatic hydroxylation

A particular challenge is the hydroxylation of aliphatic substrates (non-activated C–H bonds), which already has been described by Réglier *et al.*[22] In comparison to a selective aromatic hydroxylation, very few examples for selective aliphatic hydroxylations are known in the literature. Based on the BDED ligand, Becker *et al.* reported the selective hydroxylation of trimethylacetaldehyde, an adamantane carboxaldehyde as well as of an diadamantane-1-carboxaldeyde.[7]

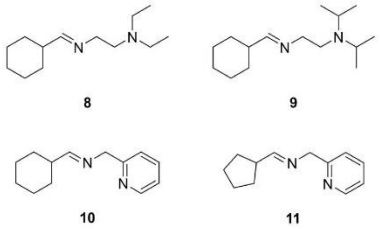
Cyclohexane is an important basic chemical in industry, e.g. for the manufacturing of polymers such as 6,6 nylon where it is oxidized in a first reaction sequence to cyclohexanol and cyclohexanone. With regard to this, new possibilities for the derivatization of cyclohexane could become interesting. Therefore, experiments with cyclohexane derivatives, cyclohexane carboxaldehyde as well as cyclopentane carboxaldehyde and cyclohexanone (see further below) were carried out to expand the range of substrates and to investigate reaction parameters for possible selective hydroxylation reactions. Ligands **8**, **9**, **10** and **11** (Scheme 4) were synthesized in good yields and applied in analogy to the aromatic systems described above. However, in contrast to these systems investigations with the ligands **8**, **9**, **10** and **11** turned out to be much more problematic.

While the copper(I) complex with ligand **11** did not seem to react at all with dioxygen copper(I) complexes with ligands **8**, **9** and **10** at least showed some reactivity. However, GC-MS results of the product mixtures only showed cyclohexane carboxaldehyde (the substrate) while the expected product, 2-hydroxycyclohexane-1-carboxaldehyde was not detected at all. Instead, formation of some other products was observed which could not be identified so far. Most likely this is caused by decomposition reactions during the oxidation process, either directly or of the hydroxylated product (if it actually was formed in the process). Aspects that control C–C cleavage versus C–H bond hydroxylation by copper complexes was previously discussed by Schoenebeck and co-workers.[23]

Efforts to crystallize copper(I) complexes with ligands **8**, **9**, **10** and **11** only were successful with ligand **9** and chloride as a co-ligand. However, in contrast to our expectations that [Cu(**9**)Cl] would be obtained, the molecular structure revealed that [Cu(**9**)$_2$][$CuCl_2$] formed instead (Figure 3, crystallographic data are reported in the Supporting Information).

Despite the fact that the molecular structure in the solid state might not represent the actual molecule in solution, it gives an idea why no hydroxylation reaction was observed. A chelate complex, necessary at least for the formation of a copper bis(μ-oxido) complex, obviously is avoided.

In addition, it was tried to obtain single crystals of the corresponding copper(II) complexes with ligands **8**, **9**, **10** and **11**. Again, we only succeeded with ligand **9** by reacting it with copper(II) chloride dihydrate in either acetone or in acetonitrile.



Scheme 4. Ligands CyDED (**8**), CyDiPED (**9**) and CyMPy (**10**), substrate: cyclohexane carboxaldehyde and ligand CypMPy (**11**), substrate: cyclopentane carboxaldehyde.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

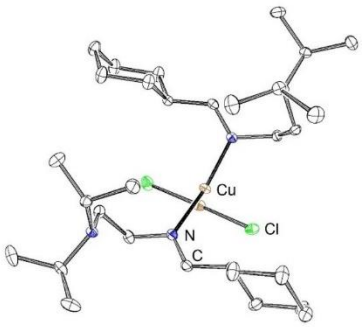


Figure 3. ORTEP plot of the molecular structure of $[Cu(\mathbf{9})_2][CuCl_2]$. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Dark green crystals were obtained in both solvents after a few days with the same orthorhombic unit cell. The molecular structure of the complex $[Cu_2(O–CyDiPED)_2Cl_2]$ that crystallized in the orthorhombic space group *Pba*2 in a 2:2 copper to ligand ratio with two coordinated chloride anions is presented in Figure 4 (crystallographic data are reported in the Supporting Information and selected bond lengths and angles are reported in Table 3).

This result is surprising in so far, that obviously a β-hydroxylation of the ligand had occurred under ambient conditions (presence of air and moisture) during the crystallization process. Reactions of copper(II) complexes with dioxygen and water are well known (a few selected examples are given in the references)[24] and according to these previous results we propose the mechanism presented in Scheme 5 for this hydroxylation reaction.

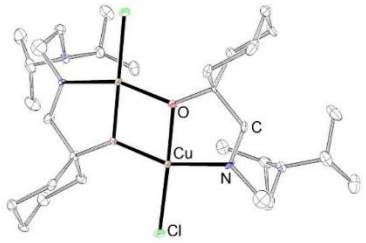


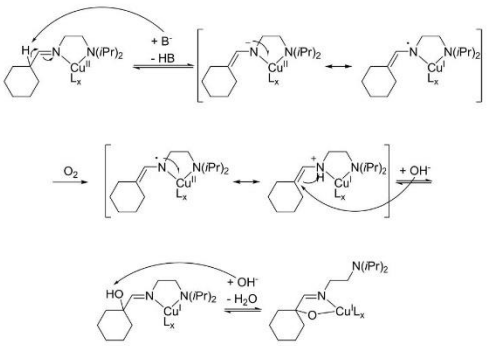
Figure 4. ORTEP plot of molecular structure of $[Cu_2(O–CyDiPED)_2Cl_2]$. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 3. Selected bond length [Å] and angles [°] for complex $[Cu_2(O\text{-}\mathbf{9})_2Cl_2]$ (Figure 4).

Cu(1)–O(1)#1	1.921(3)	O(1)#1–Cu(1)–O(1)	76.15(12)
Cu(1)–Cl(1)	1.925(3)	O(1)#1–Cu(1)–Cu(1)#1	38.13(8)
Cu(1)–N(4)	1.977(3)	O(1)#1–Cu(1)–N(4)	81.78(12)
Cu(1)–Cl(5)	2.2185(11)	O(1)–Cu(1)–N(4)	157.78(13)
Cu(1)–Cu(1)#1	3.0274(9)	O(1)#1–Cu(1)–Cl(5)	176.98(17)
		O(1)–Cu(1)–Cl(5)	102.79(8)

Furthermore, this reaction also can give a hint, why the expected reaction of a β-hydroxylation with a copper(I) complex and oxygen (see general hydroxylation procedure) does not result in the expected product. In contrast to all the other aliphatic substrates, which can be hydroxylated with a BDED based ligand system, the substrates do not have a hydrogen at the β-carbon (e.g. adamantane carboxaldehyde or trimethylacetaldehyde).

To investigate this further and by avoiding this kind of β-hydroxylation we switched from cyclohexane carboxaldehyde to cyclohexanone as a substrate. Therefore, ligands **12**, **13**, **14** and **15** were synthesized (Scheme 6). It turned out that the synthesis of these imine ligands starting from a ketone as a substrate are much more difficult than expected. The imine condensation could not be performed under the same mild conditions as described for the ligands above: reaction temperature needed to be elevated, a change of solvent was necessary, and *p*-toluene sulfonic acid was added in catalytic amounts. Furthermore, it turned out that these imine ligands



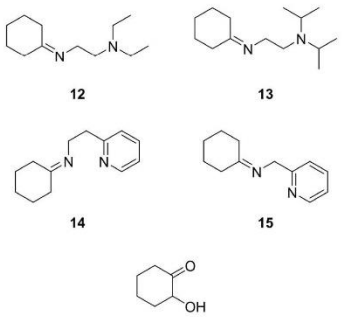
Scheme 5. Proposed mechanism for β-hydroxylation of **9** with copper(II).

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing



Scheme 6. Ligands CyonDED (**12**), CyonDiPED (**13**), CyonEPy (**14**), and CyonMPy (**15**), bottom: hydroxylated product 2-hydroxycyclohexanone.

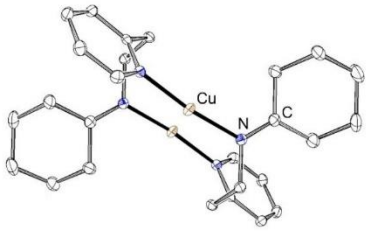


Figure 5. ORTEP plot of molecular structure of $[Cu_2(\mathbf{14})_2](OTf)_2$. Hydrogen atoms and counter ions are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 4. Selected bond length [Å] and angles [°] for complex $[Cu_2(\mathbf{14})_2](OTf)_2$ (Figure 5).

Cu(1)–N(2)	1.9074(12)	N(2)–Cu(1)–N(1)#1	172.95(5)
Cu(1)–N(1)#1	1.9164(13)		
Cu(1)–Cu(1)#1	3.284		

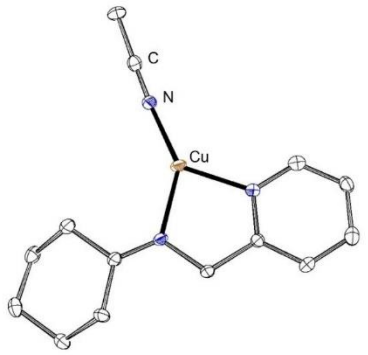


Figure 6. ORTEP plot of the molecular structure of the cation of [Cu-(**15**)(MeCN)]OTf. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

were extremely sensitive towards water which led to a back reaction to the reactants despite applying a drying agent. Thus, working under inert conditions together with a drying agent was essential to prepare these ligands. Furthermore, all ligands were purified by "Kugelrohr" distillation. Caused by these problems, only decent yields of all four of these ligands were obtained.

With ligands **14** and **15** we succeeded in crystallizing the corresponding copper(I) complexes that turned out to be quite different with regard to their molecular structures. The binuclear complex $[Cu_2(\mathbf{14})_2](OTf)_2$ in which two copper(I) are bridging two ligands is shown in Figure 5 (Crystallographic data are reported in the Supporting Information and selected bond lengths and angles in Table 4).

In contrast, the copper(I) complex with ligand **15** crystallized as expected. The molecular structure of the cation of [Cu-(**15**)(MeCN)]OTf is presented in Figure 6 (Crystallographic data are reported in the Supporting Information). The molecular structure shows the same trigonal planar coordination geometry of copper(I) which was also observed with similar ligands (see Figure 2 and Trammel *et al.* 2019).[9] The N–Cu–N angle is very similar with 84.01° (average of both angles), the dihedral angle 178.5° and the Cu–$C_{oxid.}$ distance is 3.267 Å and has a comparable length towards the other molecular structures.

Despite the problems with the ligand handling described above, no changes were necessary for the experiments of the intramolecular ligand hydroxylation and they could be carried out according to our general procedure in acetone and dichloromethane. The hydroxylation of the substrate cyclohexanone to 2-hydroxycyclohexanone (Scheme 6) could be carried out successfully with the copper(I) complexes of all four ligands and conversions are presented in Table 5.

It was observed that with imine amine-based ligands **12** and **13** higher conversion to the hydroxylated product (close to the limiting 50% if a copper bis(μ-oxido) complex is the reactive intermediate; see below under kinetic measurements) were achieved in comparison with the imino pyridyl ligands (**14** and **15**). Furthermore, acetone turned out to be the better solvent compared to conversions in dichloromethane. Again, as discussed above, diisopropylamine was detected after the hydroxylation reaction in acetone (as well as some other small amounts of by-products).

So far, we did not manage to obtain 2-hydroxycyclohexanone in pure form from the reaction mixtures. Therefore, trying to increase the conversion/yield, hydroxylation experi-

Table 5. Conversion of the substrate into hydroxylated products using ligands **12**–**15** with cyclohexanone as substrate.

Entry	Ligand	Acetone[a] Conversion/%	Dichloromethane
1	CyonDED (**12**)	47	35
2	CyonDiPED (**13**)	46	21
3	CyonEPy (**14**)	22[b]	7
4	CyonMPy (**15**)	16	3[b]

[a] Traces of diisopropylamine detected. [b] Blue precipitate after oxygen treatment.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

ments were performed with copper(II) complexes with **12** and **13** as ligands and hydrogen peroxide as the oxidant according to the reaction conditions reported by Trammell *et al.*[4,11] However, in both cases only the non-hydroxylated substrate, cyclohexanone, could be detected and no conversion to a hydroxylated product was observed. This is particularly interesting with regard to our observations by UV-vis spectroscopy (see kinetic investigations below).

Kinetic investigations

The reaction of dioxygen with the copper(I) complexes with ligands **12** and **13** in acetone and dichloromethane was investigated with low temperature stopped-flow measurements.

The reaction of dioxygen with the copper(I) complex with ligand **12** is very fast in both solvents. Time resolved spectra at −93.0 °C in acetone are shown in Figure 7. An absorbance increase is observed with maxima at 405 nm and at 490 nm. The spectrum fits perfectly well to a copper bis(μ-oxido) complex as an intermediate and is in line with our previous observations for the copper(I) complex with ligand **1** (Scheme 1).[6] The formation of this intermediate is complete in about 7 s with a rate constant $k_{obs} = 2 \cdot 10^{-3}\ s^{-1}$ under these conditions (calculated from the absorbance time trace shown as an inset in Figure 7). Analysis of the same reaction in dichloromethane gave the same result, however only half of the height of the absorbance maxima was observed (see Supporting Information). Therefore, a kinetic analysis herein is only reported for the reaction in acetone.

Stopped-flow measurements in the temperature range between −94 °C and −55 °C allowed to obtain activation parameters of $\Delta H^{+} = +24.2 \pm 0.2\ kJ\,mol^{-1}$ and $\Delta S^{+} = -115 \pm 1\ JK^{-1}mol^{-1}$, calculated from an Eyring plot (see Supporting Information). These data are well in line with the results reported previously for the hydroxylation of trimethylacetaldehyde as a substrate.[7] The negative activation entropy indicates an associative mechanism, the formation of a copper superoxido complex as the rate-determining step and a fast consecutive reaction to the copper bis(μ-oxido) complex.[16]

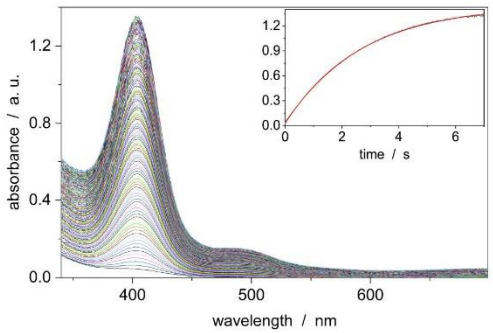


Figure 7. Time resolved stopped-flow UV-vis spectra of the formation of copper(I) bis(μ-oxido) complex with ligand **12** in acetone ($c_{complex} = 0.50 \cdot 10^{-3}\ mol\,L^{-1}$, $c_{O2} = 5.7 \cdot 10^{-3}\ mol\,L^{-1}$, after mixing) at −93.0 °C. Inlay (time trace): Absorbance vs. time at 405 nm (black: experimental, red: exponential fit).

In contrast, during the reaction of dioxygen with the copper(I) complex with ligand **13** in acetone (measurements in dichloromethane were excluded due to disproportionation of the complex), no copper bis(μ-oxido) complex as an intermediate was spectroscopically observed (see Supporting Information). However, while the mechanism is not quite clear for the reaction of the copper(I) complex with the ligand **2** as described above, the situation is different here. The lack of reactivity of the copper(II) complex with ligand **13** towards H_2O_2 speaks against the hydroxylation mechanism described in Scheme 2.[11,15] Instead and most likely here the formation of the copper bis(μ-oxido) complex is rate determining while the consecutive hydroxylation is fast and therefore does not allow to observe the intermediate.

No kinetic studies were performed with the copper(I) complexes of ligands **14** and **15**. Here the formation of a solid during the reaction with dioxygen precluded the stopped-flow measurements.

Conclusions

Over time, different new findings have helped a lot to gain better understanding of stoichiometric or catalytic oxygenation reactions with copper complexes either in the active site of enzymes or applied in form of their model complexes in the lab. For a long time, it was thought that only ligands preorganized for the formation of binuclear copper complexes were suitable for these reactions, however, Tolman and coworkers could demonstrate that this is not required and that mononuclear copper complexes can self-organize themselves to form a binuclear copper bis(μ-oxido) complex.[25] While the ligand system by Tolman was excellent as proof of concept it was not suitable for synthetic applications. By introducing our clip-and-cleave concept it became possible to perform hydroxylation reactions of different aldehydes and ketones.[6,7] We believe that this concept has a great potential for future applications due to the easy handling and the mild reaction conditions. However, one of the problems that comes with this approach is the formation of copper(I) complexes in a copper to ligand ratio of 1:2 that can completely suppress the hydroxylation reaction. Our systematic study on ligand modification to avoid this (reported in here) showed how difficult it is to optimize such a system. Furthermore, the formation of the binuclear copper bis(μ-oxido) complex limits the maximum yield of the hydroxylation to 50%. Based on earlier work by Schönecker[12–14] with the same limitations Baran, Garcia-Bosch and coworkers could increase the yields in their synthetic applications on steroids close to 100% by applying an additional reducing agent (e.g. ascorbate) or working with copper (II) complexes and hydrogen peroxide.[9,11,15] While it seemed that this problem was solved we now could show that this only

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

might work if a radical mechanism takes place (as reported by Trammell *et al.*)[11] but not if a copper bis(μ-oxido) complex is formed. Furthermore, with two different mechanisms at place for ligand hydroxylation we now would like to add a third possible reaction pathway starting from simple copper(II) complexes in the presence of air and moisture. While this type of reaction is well known since a long time, to the best of our knowledge it has not been really applied in the context of selective ligand hydroxylation. Our results show how sensitive the oxygenation reaction is towards small changes in the whole system that can lead either (depending on the mechanism) to β- or γ- hydroxylation of the substrate or completely suppress the reaction. With the new findings we now hope to design a system that would allow its application in synthetic chemistry. Once such a complex system is identified it could be optimized e.g. by immobilization (and chemical reactivation) or by reactivating it through electrochemistry or photochemistry. Our goal still remains to identify simple copper complexes that can be used to selectively oxidize organic substrates in good yields with dioxygen from air. That this is possible has been demonstrated previously by Lumb and co-workers who showed that they could catalytically oxidize phenols and derivatives with dioxygen.[26]

Experimental Section

Materials and methods

Solvents and reagents used were of commercially available reagent quality. ^{13}C-NMR and ^{1}H-NMR spectra were measured on a Bruker Avance II 400 MHz and Avance III 400 MHz HD spectrometer. Electrospray-ionization MS (ESI-MS) measurements were performed on a Bruker micro-TOF mass spectrometer. All measurements under inert conditions were carried out in argon or nitrogen atmosphere by standard Schlenk techniques or working in a glove box (MBraun, Garching, Germany). For these experiments extra dry solvents were distilled under an argon atmosphere with a drying agent and transferred into the glove box. For gas chromatography with coupled mass spectrometry (GC-MS) a HP-GC 5890 Series II with coupled HP 5972 Series mass detector and Agilent Technologies 5977B MSD with 7820 A GC system was used. For gas chromatography (GC) a 5890 Series II GC was used. For low-temperature stopped-flow measurements HI-TECH Scientific SF-61SX2 instrument (TgK Scientific, Bratford on Avon, UK) was used. Setup and kinetic measurements procedure were described in detail previously.[27] Kinetic data were analysed with the integrated software Kinetic Studio (Version 5.02 Beta, TgK Scientific). For the reactions of copper(I) complex solutions with dioxygen a gastight syringe was filled with argon saturated solvent and saturated with dioxygen by bubbling a dioxygen stream through the solvent for 15 min ($c_{max}(O_2) = 11.44$ mmol L^{-1} in acetone, $c_{max}(O_2) = 11.08$ mmol L^{-1} in dichloromethane).[28] Due to the mixing of the complex and dioxygen solutions in the stopped-flow instrument, the maximum concentrations have to be divided by two resulting in $c(O_2) = 5.72$ mmol L^{-1} in acetone and $c(O_2) = 5.54$ mmol L^{-1} in dichloromethane. Diffraction data for all samples were collected at low temperatures (100 K) using ϕ- and ω-scans on a BRUKER D8 Venture system equipped with dual IμS microfocus sources, a PHOTON100 detector and an OXFORD CRYOSYSTEMS 700 low temperature system. Mo–Kα radiation with a wavelength of 0.71073 Å and a collimating Quazar multilayer mirror were used. Semi-empirical absorption correction from equivalents was applied using SADABS-2016/2[29] and the structures were solved by direct methods using SHELXT2014/5.[30] Refinement was performed against F^2 on all data by full-matrix least squares using SHELXL2018/3.[31] All non-hydrogen atoms were refined anisotropically and C–H hydrogen atoms were positioned at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2× or 1.5× (CH_3) the U_{eq} value of the atoms they are linked to.

Ligand syntheses

General procedure for the syntheses of ligands 1–15: The substrate (aldehyde or ketone functionalized) and the ligand backbone (amine functionalized) were dissolved in diethyl ether and stirred over sodium sulfate for one hour at room temperature and were kept for another hour under reflux. After the reaction mixture was filtered the solvent was removed using a rotary evaporator. Finally, the product was dried under oil pump vacuum. The general procedure is based on the ligand synthesis of BDED (**1**) published previously.[6] Amounts of reactants, yields, analyses and notes (in case that ligand synthesis deviates from the general procedure) are listed for each ligand in the supporting information.

Ligand hydroxylation

General procedure for ligand hydroxylation: Depending on the ligand 1.00 mmol (**1**–**3** and **6**–**15**) or 0.10 mmol of ligand (**4**–**5**) were dissolved in 5–10 ml solvent (absolute dichloromethane, acetone, methanol or acetonitrile) and added to a solution of 377 mg (1.00 mmol, for **1**–**3** and **6**–**15**) or 37.7 mg (0.10 mmol, for **4**–**5**) [Cu(MeCN)$_4$]OTf in 5–10 ml solvent in a Schlenk tube. Subsequently dioxygen was passed through the solution for 15 min. For the workup 10 ml hydrochloric acid (1 mol L^{-1}) were added and stirred for one hour at room temperature and additionally for one hour under reflux. After cooling the organic solvent was removed and the remaining reaction mixture extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated using a rotary evaporator for GC-MS analysis. The conversion rate was estimated on the basis of the integrals of the different fractions of hydroxylated product and reactant.

Low-temperature stopped-flow measurements

[Cu(CyonDED)]OTf with dioxygen in acetone: 96 mg (0.25 mmol) [Cu(MeCN)$_4$]OTf and 50 mg (0.25 mmol) CyonDED (**12**) were dissolved in 10 ml of absolute acetone. The solution was diluted to a complex concentration of 0.50 mmol L^{-1} and filled into a gastight syringe. Measurements were performed between −94 °C and −55 °C

[Cu(CyonDED)]OTf with dioxygen in dichloromethane: 107 mg (0.283 mmol) [Cu(MeCN)$_4$]OTf and 56 mg (0.28 mmol) CyonDED (**12**) were dissolved in 10 ml absolute dichloromethane. The solution was diluted to a complex concentration of 0.56 mmol L^{-1} and filled into a gastight syringe. Measurements were performed between −93 °C and −39 °C.

[Cu(CyonDiPED)]OTf with dioxygen in acetone: 92 mg (0.24 mmol) [Cu(MeCN)$_4$]OTf and 55 mg (0.24 mmol) CyonDiPED (**13**) were dissolved in 10 ml absolute acetone. The solution was diluted to a complex concentration of 0.96 mmol L^{-1} and filled in a gastight syringe. Measurements were performed between −92 °C and −49 °C.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

Single crystals

[Cu(BDiPED)Cl]: 23 mg (0.10 mmol) BDiPED (**2**) and 9.9 mg (0.10 mmol) copper(I) chloride were dissolved in acetonitrile each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 30 min. After a few days at room temperature crystals were obtained.

[Cu_2(O–CyDiPED)$_2$$Cl_2$]: 119 mg (0.500 mmol) CyDiPED (**9**) and 85.2 mg (0.500 mmol) copper(II) chloride dihydrate were dissolved in 3 ml acetone (or acetonitrile) each. Under stirring the ligand solution was added to the copper(I) salt solution dropwise. Subsequently a few drops of diethyl ether were added, and the solution was stirred for 30 min. After three days at room temperature dark green crystals were obtained. Crystals with the same orthorhombic unit cell and molecular structure of the complex were obtained, but the co-crystallized solvent was acetonitrile instead of acetone.

[Cu(CyDiPED)$_2$][$CuCl_2$]: In a glovebox 119 mg (0.500 mmol) CyDiPED (**9**) and 49.5 mg (0.500 mmol) copper(I) chloride were dissolved in 3 ml dry acetonitrile (or dichloromethane) each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for 30 min. After a few days at room temperature crystals were obtained. Crystals with the same triclinic unit cell and molecular structure of the complex were obtained, just with dichloromethane instead of acetonitrile.

[Cu_2(CyonEPy)$_2$](OTf)$_2$: 20.2 mg (0.100 mmol) CyonEPy (**14**) and 37.7 mg (0.100 mmol) [Cu(MeCN)$_4$]OTf were dissolved in THF each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 30 min. After a few days at room temperature crystals were obtained.

[Cu(CyonMPy)(MeCN)]OTf: 18.8 mg (0.100 mmol) CyonMPy (**15**) and 37.7 mg (0.100 mmol) [Cu(MeCN)$_4$]OTf were dissolved in methanol each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 15 min. After a few days at room temperature colourless crystals were obtained.

Deposition Numbers 2050690 (for [Cu(**2**)Cl]), 2050691 (for [Cu(**9**)$_2$][$CuCl_2$]), 2050692 (for [Cu_2(**14**)$_2$](OTf)$_2$), 2050693 (for [Cu(**15**)(MeCN)]OTf), and 2050694 (for [Cu_2(O-**9**)$_2$$Cl_2$]) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Copper · Dioxygen activation · Kinetics · Selective hydroxylation · Stopped-flow

[1] a) E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. F. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659–3853; b) M. H. Sazinsky, S. J. Lippard in *Metal Ions in Life Sciences. Sustaining Life on Planet Earth: Metalloenzymes Mastering Dioxygen and Other Chewy Gases.* Methane Monooxygenase: Functionalizing Methane at Iron and Copper (Eds.: A. Sigel, H. Sigel, R. K. O. Sigel, P. M. H. Kroneck, M. E. S. Torres), Vol.15, Springer, Cham, Switzerland, **2015**, pp. 205–256; c) D. A. Quist, D. E. Díaz, J. J. Liu, K. D. Karlin, *J. Biol. Inorg. Chem.* **2017**, *22*, 253–288; d) M. O. Ross, F. MacMillan, J. Wang, A. Nisthal, T. J. Lawton, B. D. Olafson, S. L. Mayo, A. C. Rosenzweig, B. M. Hoffman, *Science* **2019**, *364*, 566–570.

[2] a) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333–340; b) S. D. McCann, S. S. Stahl, *Acc. Chem. Res.* **2015**, *48*, 1756–1766.

[3] a) J. l. van der Vlugt, F. Meyer in *Organometallic Oxidation Catalysis* (Eds.: F. Meyer, C. Limberg), Vol. 22, Springer, Berlin Heidelberg, **2007**, pp. 191–240; b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234–6458; c) M. E. Ali, M. M. Rahman, S. M. Sarkar, S. B. A. Hamid, *J. Nanomater.* **2014**, *2014*, 1–23.

[4] R. Trammell, K. Rajabimoghadam, I. Garcia-Bosch, *Chem. Rev.* **2019**, *119*, 2954–3031.

[5] C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee, W. B. Tolman, *Chem. Rev.* **2017**, *117*, 2059–2107.

[6] J. Becker, P. Gupta, F. Angersbach, F. Tuczek, C. Näther, M. C. Holthausen, S. Schindler, *Chem. Eur. J.* **2015**, *21*, 11735–11744.

[7] J. Becker, Y. Y. Zhyhadlo, E. D. Butova, A. A. Fokin, P. R. Schreiner, M. Förster, M. C. Holthausen, P. Specht, S. Schindler, *Chem. Eur. J.* **2018**, *24*, 15543–15549.

[8] a) A. Bijelic, M. Pretzler, C. Molitor, F. Zekiri, A. Rompel, *Angew. Chem. Int. Ed.* **2015**, *54*, 14677–14680; b) M. M. Del Garcia-Molina, J. L. Muñoz-Muñoz, F. Garcia-Molina, P. A. García-Ruiz, F. Garcia-Canovas, *J. Agric. Food Chem.* **2012**, *60*, 6447–6453; c) J. N. Hamann, B. Herzigkeit, R. Jurgeleit, F. Tuczek, *Coord. Chem. Rev.* **2017**, *334*, 54–66.

[9] R. Trammell, L. D'Amore, A. Cordova, P. Polunin, N. Xie, M. A. Siegler, P. Belanzoni, M. Swart, I. Garcia-Bosch, *Inorg. Chem.* **2019**, *58*, 7584–7592.

[10] a) M. Paul, M. Teubner, B. Grimm-Lebsanft, C. Golchert, Y. Meiners, L. Senft, K. Keisers, P. Liebhäuser, T. Rösener, F. Biebl, et al., *Chem. Eur. J.* **2020**, *26*, 7556–7562; b) W. Keown, T. A. G. Large, L. Chiang, E. C. Wasinger, T. D. P. Stack, *Chem. Commun.* **2019**, *55*, 7390–7393.

[11] R. Trammell, Y. Y. See, A. T. Herrmann, N. Xie, D. E. Díaz, M. A. Siegler, P. S. Baran, I. Garcia-Bosch, *J. Org. Chem.* **2017**, *82*, 7887–7904.

[12] B. Schönecker, T. Zheldakova, Y. Liu, M. Kötteritzsch, W. Günther, H. Görls, *Angew. Chem. Int. Ed.* **2003**, *42*, 3240–3244.

[13] B. Schönecker, T. Zheldakova, C. Lange, W. Günther, H. Görls, M. Bohl, *Chem. Eur. J.* **2004**, *10*, 6029–6042.

[14] B. Schönecker, C. Lange, T. Zheldakova, W. Günther, H. Görls, G. Vaughan, *Tetrahedron* **2005**, *61*, 103–114.

[15] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776–13779.

[16] A. Hoffmann, M. Wern, T. Hoppe, M. Witte, R. Haase, P. Liebhäuser, J. Glatthaar, S. Herres-Pawlis, S. Schindler, *Eur. J. Inorg. Chem.* **2016**, 4744–4751.

[17] K. D. Karlin, D. H. Lee, S. Kaderli, A. D. Zuberbühler, *Chem. Commun.* **1997**, 475–476.

[18] M. Schatz, M. Becker, F. Thaler, F. Hampel, S. Schindler, R. R. Jacobson, Z. Tyeklár, N. N. Murthy, P. Ghosh, Q. Chen, et al., *Inorg. Chem.* **2001**, *40*, 2312–2322.

[19] O. Sander, A. Henß, C. Näther, C. Würtele, M. C. Holthausen, S. Schindler, F. Tuczek, *Chem. Eur. J.* **2008**, *14*, 9714–9729.

[20] O. Bienemann, A. Hoffmann, S. Herres-Pawlis, *Rev. Inorg. Chem.* **2011**, *31*, 83–108.

[21] O. Bienemann, R. Haase, A. Jesser, T. Beschnitt, A. Döring, D. Kuckling, I. Dos Santos Vieira, U. Flörke, S. Herres-Pawlis, *Eur. J. Inorg. Chem.* **2011**, 2367–2379.

[22] I. Blain, M. Giorgi, I. de Riggi, M. Réglier, *Eur. J. Inorg. Chem.* **2000**, *2000*, 393–398.

[23] A. S.-K. Tsang, A. Kapat, F. Schoenebeck, *J. Am. Chem. Soc.* **2016**, *138*, 518–526.

[24] a) E. C. Constable, *Metals and Ligand Reactivity. An Introduction to the Organic Chemistry of Metal Complexes*, VCH Verlagsgesellschaft mbH, Weinheim, **1996**; b) M. Schatz, M. Becker, O. Walter, G. Liehr, S. Schindler, *Inorg. Chim. Acta* **2001**, *324*, 173–179; c) T.-D. J. Stumpf, M. Steinbach, C. Würtele, J. Becker, S. Becker, R. Fröhlich, R. Göttlich, S. Schindler, *Eur. J. Inorg. Chem.* **2017**, 4246–4258.

[25] P. L. Holland, K. R. Rodgers, W. B. Tolman, *Angew. Chem. Int. Ed.* **1999**, *38*, 1139–1142.

[26] a) K. V. N. Esguerra, Y. Fall, L. Petitjean, J. P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668; b) Z. Huang, J. P. Lumb, *Angew. Chem. Int. Ed.* **2016**, *55*, 11543–11547; c) K. V. N. Esguerra, J. P. Lumb, *Angew. Chem. Int. Ed.* **2018**, *57*, 1514–1518; d) Z. Huang, O. Kwon, H. Huang, A. Fadli, X.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

Marat, M. Moreau, J.-P. Lumb, *Angew. Chem.* **2018**, *130*, 12139–12143; e) M. S. Askari, L. A. Rodríguez-Solano, A. Proppe, B. McAllister, J.-P. Lumb, X. Ottenwaelder, *Dalton Trans.* **2015**, *44*, 12094–12097.
[27] M. Weitzer, M. Schatz, F. Hampel, F. W. Heinemann, S. Schindler, *J. Chem. Soc. Dalton Trans.* **2002**, 686–694.
[28] H. Sterckx, B. Morel, B. U. Maes, *Angew. Chem. Int. Ed.* **2019**, *58*, 7946–7970.
[29] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *J. Appl. Crystallogr.* **2015**, *48*, 3–10.
[30] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2015**, *71*, 3–8.
[31] G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8.

Manuscript received: March 4, 2021
Revised manuscript received: March 31, 2021
Accepted manuscript online: April 1, 2021

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH

4 Summary

The studies on the reactivity of dioxygen and nitrogen monoxide with transition metal model complexes provide important insights for a better understanding of similar processes in biological environments. Due to its short-lived nature in the human body the physiological significance of nitrogen monoxide compared to dioxygen has only been known for a relatively short time. Accordingly, there are still many unanswered questions regarding the reaction mechanisms of nitrogen monoxide in biological processes, as well as its potential as a drug and for treating various diseases. Dioxygen, on the other hand, is already well studied due to its importance as an oxidizing and oxygenating agent in the human body. Therefore, the focus is to mimic the reactivities of enzymes by model systems to perform selective and catalytic/stoichiometric oxygenation reactions under mild reaction conditions in the laboratory or for an application in industry.

During this research, various iron complexes were kinetically investigated for their reactivity towards nitrogen monoxide in methanol using low temperature stopped-flow technique to gain a better understanding of the mechanisms of such reactions. The used systems had different complex coordination environments, starting with the "simple" iron(II) chloride, via the mononuclear complex iron-bztpen to the dinuclear iron-HPTB. It was shown that in the MNIC/DNIC system the reaction to the mononitrosyl complex (MNIC) is, as expected, very fast, independent of the nitrogen monoxide concentration and proceeds via a dissociative interchange mechanism. The further reaction to the dinitrosyl complex (DNIC) proceeds very slowly, also in comparison to the other complexes studied (reaction rate to MNIC differs by a factor of 10^9). This is most likely related to the fact that not simply a second nitrogen monoxide molecule coordinates, but at the same time electron transfers take place and a conversion from $\{FeNO\}^7$- to $\{Fe(NO)_2\}^9$-species occurs. In the study of the iron(II) complexes with the ligands bztpen and HPTB, it was shown that the reaction proceeds via an associative mechanism. In the case of the iron-HPTB complex, the activation parameters are in accordance with data from a similar complex in the literature.

The activation of dioxygen by means of copper(I) complexes modelled on natural systems offers the possibility of replacing time-consuming or expensive synthetic routes by simple methods. The clip-and-cleave concept, which was already introduced by Becker *et al.*, provide a pathway for a selective and intramolecular ligand hydroxylation.[111,112] During these studies,

this concept was examined and optimized by modifications on the ligand scaffold, changes in reaction conditions, and investigations of the hydroxylation mechanism. This investigation could show that even small changes on the ligand scaffold have a great influence on the reactivity of the complex and can lead to an increase, but also to a complete suppression of the hydroxylation reactivity. It was shown that hydroxylation of the different ligands (even with small differences) leads to the formation of different copper-dioxygen intermediates or even shows no intermediate at all despite successful ligand hydroxylation. Using cyclohexanecarbaldehyde as a substrate, it could be shown that in addition to the two known mechanisms for copper-mediated hydroxylation (via a bis(μ-oxido) or hydroperoxido complex), there is a third possibility for ligand hydroxylation starting from a copper(II) complex, which represents a promising, alternative and facile pathway for further oxygenation reactions. Hydroxylation of these substrates and also the various hydroxylation methods provide the opportunity for a stoichiometric and easy preparation of specialty chemicals or functionalization of difficult to access sites of substrates.

Zusammenfassung

Die Untersuchungen der Reaktivität von Sauerstoff und Stickstoffmonoxid mit Übergangsmetall-Modellkomplexen liefern wichtige Erkenntnisse zum besseren Verständnis ähnlicher Prozesse in biologischen Umgebungen. Die physiologische Bedeutung von Stickstoffmonoxid ist, aufgrund seiner Kurzlebigkeit im menschlichen Körper, im Vergleich zu Sauerstoff erst seit relativ kurzer Zeit bekannt. Dementsprechend gibt es noch viele unbeantwortete Fragen zu den Reaktionsmechanismen von Stickstoffmonoxid in biologischen Prozessen sowie zu seinem Potenzial als Medikament und zur Behandlung verschiedener Krankheiten. Sauerstoff hingegen ist aufgrund seiner Bedeutung als Oxidations- und Oxygenierungsmittel im menschlichen Körper bereits gut erforscht. Daher liegt der Fokus darauf, die Reaktivitäten von Enzymen durch Modellsysteme zu imitieren, um selektive und katalytische/stöchiometrische Oxygenierungsreaktionen bei milden Reaktionsbedingungen im Labor oder für eine Anwendung in der Industrie durchzuführen.

Im Rahmen dieser Forschungsarbeit wurden verschiedene Eisenkomplexe auf ihre Reaktivität gegenüber Stickstoffmonoxid in Methanol mittels Tieftemperatur-Stopped-Flow-Technik kinetisch untersucht, um ein besseres Verständnis für die Mechanismen solcher Reaktionen zu erlangen. Die verwendeten Systeme wiesen unterschiedlich komplexe Koordinationsumgebungen auf, beginnend mit dem "einfachen" Eisen(II)-chlorid, über den einkernigen Komplex Eisen-bztpen bis hin zum zweikernigen Eisen-HPTB. Es wurde gezeigt, dass beim MNIC/DNIC-System die Reaktion zum Mononitrosyl-Komplex (MNIC) erwartungsgemäß sehr schnell und unabhängig von der Stickstoffmonoxid-Konzentration und über einen dissoziativen Austauschmechanismus abläuft. Die weitere Reaktion zum Dinitrosylkomplex (DNIC) verläuft, auch im Vergleich zu den anderen untersuchten Komplexen, sehr langsam (Reaktionsgeschwindigkeit zu MNIC unterscheidet sich um den Faktor 10^9). Dies hängt höchstwahrscheinlich damit zusammen, dass nicht nur ein zweites Stickstoffmonoxid-Molekül koordiniert, sondern gleichzeitig ein Elektronentransfer stattfindet und eine Umwandlung der $\{FeNO\}^7$- zu einer $\{Fe(NO)_2\}^9$-Spezies erfolgt. Bei der Untersuchung der Eisen(II)-Komplexe mit den Liganden bztpen und HPTB wurde gezeigt, dass die Reaktion über einen assoziativen Mechanismus abläuft. Im Falle des Eisen-HPTB-Komplexes stimmen die Aktivierungsparameter mit Daten eines ähnlichen Komplexes aus der Literatur überein.

Die Aktivierung von Sauerstoff mittels Kupfer(I)-Komplexen nach dem Vorbild natürlicher Systeme bietet die Möglichkeit, zeitaufwendige oder teure Syntheserouten durch einfache Methoden zu ersetzen. Das Clip-and-Cleave-Konzept, das bereits von Becker *et al*.[111,112] vorgestellt wurde, bietet einen Weg für eine selektive und intramolekulare Ligandenhydroxylierung, welches durch Modifikationen am Ligandengerüst, Änderungen der Reaktionsbedingungen und Untersuchungen des Hydroxylierungsmechanismus weiter untersucht und optimiert wurde. Dabei konnte gezeigt werden, dass bereits kleine Änderungen am Ligandengerüst einen großen Einfluss auf die Reaktivität des Komplexes haben und zu einer Erhöhung, aber auch zu einer vollständigen Unterdrückung der Hydroxylierungsreaktivität führen können. Es konnte außerdem gezeigt werden, dass die Hydroxylierung der verschiedenen Liganden (auch mit nur kleinen Unterschieden) zur Bildung unterschiedlicher Kupfer-Sauerstoff-Intermediate führt oder sogar, trotz erfolgreicher Ligandenhydroxylierung, überhaupt kein Intermediat zeigt. Anhand von Cyclohexancarbaldehyd als Substrat konnte gezeigt werden, dass es neben den beiden bekannten Mechanismen für die kupfervermittelte Hydroxylierung (über einen Bis(μ-oxido)- oder Hydroperoxido-Komplex) eine dritte Möglichkeit der Ligandenhydroxylierung ausgehend von einem Kupfer(II)-Komplex gibt, die einen vielversprechenden, alternativen und einfachen Weg für weitere Oxygenierungsreaktionen darstellt. Die Hydroxylierung dieser Substrate und auch die verschiedenen Hydroxylierungsmethoden bieten die Möglichkeit einer stöchiometrischen und leichten Herstellung von Spezialchemikalien oder Funktionalisierung schwer zugänglicher Stellen von Substraten.

5 References

[1] W. Kaim, B. Schwederski, *Bioanorganische Chemie* **2005**, *4. Auflage*, Vieweg+Teubner.

[2] J. Liu, S. Chakraborty, P. Hosseinzadeh, Y. Yu, S. Tian, I. Petrik, A. Bhagi, Y. Lu, *Chem. Rev.* **2014**, *114*, 4366–4369.

[3] R. H. Holm, P. Kennepohl, E. I. Solomon, *Chem. Rev.* **1996**, *96*, 2239–2314.

[4] W. Kaim, J. Rall, *Angew. Chem. Int. Ed.* **1996**, *35*, 43–60.

[5] X. Huang, J. T. Groves, *Chem. Rev.* **2018**, *118*, 2491–2553.

[6] M. Pascaly, I. Jolk, B. Krebs, *Chemie unserer Zeit* **1999**, *33*, 334–341.

[7] E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. F. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659–3853.

[8] I. A. Koval, P. Gamez, C. Belle, K. Selmeczi, J. Reedijk, *Chem. Soc. Rev.* **2006**, *35*, 815–840.

[9] P. M. Colman, H. C. Freeman, J. M. Guss, M. Murata, V. A. Norris, J. A. M. Ramshaw, M. P. Venkatappa, *Nature* **1978**, *272*, 319–324.

[10] H. B. Gray, B. G. Malmström, R. J. P. Williams, *J. Biol. Inorg. Chem.* **2000**, *5*, 551–559.

[11] P. Gamez, I. A. Koval, J. Reedijk, *Dalt. Trans.* **2004**, 4079–4088.

[12] N. Ito, S. E. V. Phillips, C. Stevens, Z. B. Ogel, M. J. McPherson, J. N. Keen, K. D. S. Yadav, P. F. Knowles, *Nature* **1991**, *350*, 87–90.

[13] J. P. Klinman, *Chem. Rev.* **1996**, *96*, 2541–2561.

[14] A. Volbeda, W. G. J. Hol, *J. Mol. Biol.* **1989**, *206*, 531–546.

[15] A. Volbeda, W. G. J. Hol, *J. Mol. Biol.* **1989**, *209*, 249–279.

[16] H. Decker, T. Schweikardt, F. Tuczek, *Angew. Chem. Int. Ed.* **2006**, *45*, 4546–4550.

[17] M. Rolff, J. Schottenheim, H. Decker, F. Tuczek, *Chem. Soc. Rev.* **2011**, *40*, 4077–4098.

[18] A. Messerschmidt, A. Rossi, R. Ladenstein, R. Huber, M. Bolognesi, G. Gatti, A.

Marchesini, R. Petruzzelli, A. Finazzi-Agró, *J. Mol. Biol.* **1989**, *206*, 513–529.

[19] M. F. Perutz, *Trends Biochem. Sci.* **1989**, *14*, 42–44.

[20] M. Momenteau, C. A. Reed, *Chem. Rev.* **1994**, *94*, 659–698.

[21] M. A. Holmes, I. Le Trong, S. Turley, L. C. Sieker, R. E. Stenkamp, *J. Mol. Biol.* **1991**, *218*, 583–593.

[22] A. Franke, C. Fertinger, R. Van Eldik, *Angew. Chem. Int. Ed.* **2008**, *47*, 5238–5242.

[23] A. Riccio, L. Vitagliano, G. Di Prisco, A. Zagari, L. Mazzarella, *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 9801–9806.

[24] F. Murad, *Angew. Chem. Int. Ed.* **1999**, *38*, 1856–1868.

[25] R. F. Furchgott, *Angew. Chem. Int. Ed.* **1999**, *38*, 1870–1880.

[26] L. J. Ignarro, *Angew. Chem. Int. Ed.* **1999**, *38*, 1882–1892.

[27] H. Tsukahara, T. Ishida, M. Mayumi, *Nitric Oxide - Biol. Chem.* **1999**, *3*, 191–198.

[28] C. E. Cooper, *Biochim. Biophys. Acta* **1999**, *1411*, 290–309.

[29] P. C. Ford, I. M. Lorkovic, *Chem. Rev.* **2002**, *102*, 993–1017.

[30] J. N. Burstyn, A. E. Yu, E. A. Dierks, B. K. Hawkins, J. H. Dawson, *Biochemistry* **1995**, *34*, 5896–5903.

[31] S. Kim, G. Deinum, M. T. Gardner, M. A. Marletta, G. T. Babcock, *J. Am. Chem. Soc.* **1996**, *118*, 8769–8770.

[32] J. C. Crack, J. Green, A. J. Thomson, N. E. Le Brun, *Curr. Opin. Chem. Biol.* **2012**, *16*, 35–44.

[33] F. Roncaroli, J. A. Olabe, R. van Eldik, *Inorg. Chem.* **2002**, *41*, 5417–5425.

[34] P. G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai, A. J. Janczuk, *Chem. Rev.* **2002**, *102*, 1091–1134.

[35] C. Mortimer, U. Müller, *Chemie: Das Basiswissen der Chemie* **2019**, *13.Auflage*, Stuttgart: Thieme.

[36] M.-L. Tsai, C.-C. Tsou, W.-F. Liaw, *Acc. Chem. Res.* **2015**, *48*, 1184–1193.

[37] A. Buet, M. Simontacchi, *Ann. N. Y. Acad. Sci.* **2015**, *1340*, 39–46.

[38] J. Fitzpatrick, E. Kim, *Acc. Chem. Res.* **2015**, *48*, 2453–2461.

[39] A. In-Iam, M. Wolf, C. Wilfer, D. Schaniel, T. Woike, P. Klüfers, *Chem. Eur. J.* **2019**, *25*, 1304–1325.

[40] D. R. Truzzi, O. Augusto, A. V. Iretskii, P. C. Ford, *Inorg. Chem.* **2019**, *58*, 13446–13456.

[41] W. Kaim, A. Das, J. Fiedler, S. Záliš, B. Sarkar, *Coord. Chem. Rev.* **2020**, *404*, 213114.

[42] M. Wolak, R. van Eldik, *Coord. Chem. Rev.* **2002**, *230*, 263–282.

[43] A. Wanat, T. Schneppensieper, G. Stochel, R. van Eldik, E. Bill, K. Wieghardt, *Inorg. Chem.* **2002**, *41*, 4–10.

[44] H. Y. Cheng, S. Chang, P. Y. Tsai, *J. Phys. Chem. A* **2004**, *108*, 358–361.

[45] G. Monsch, P. Klüfers, *Angew. Chem. Int. Ed.* **2019**, *58*, 8566–8571.

[46] J. H. Enemark, R. D. Feltham, *Coord. Chem. Rev.* **1974**, *13*, 339–406.

[47] J. C. Fanning, *Coord. Chem. Rev.* **1991**, *110*, 235–273.

[48] J. A. McCleverty, *Chem. Rev.* **1979**, *79*, 53–76.

[49] C. Rovira, K. Kunc, J. Hutter, P. Ballone, M. Parrinello, *Int. J. Quantum Chem.* **1998**, *69*, 31–35.

[50] L. M. Blomberg, M. R. A. Blomberg, P. E. M. Siegbahn, *J. Inorg. Biochem.* **2005**, *99*, 949–958.

[51] J. S. Olson, G. N. Phillips, *J. Biol. Inorg. Chem.* **1997**, *2*, 544–552.

[52] K. A. Pearsall, F. T. Bonner, *Inorg. Chem.* **1982**, *21*, 1978–1985.

[53] M. Hoshino, M. Maeda, R. Konishi, H. Seki, P. C. Ford, *J. Am. Chem. Soc.* **1996**, *118*, 5702–5707.

[54] T. Schneppensieper, A. Wanat, G. Stochel, R. van Eldik, *Inorg. Chem.* **2002**, *41*, 2565–2573.

[55] M. C. Hung, M. C. Tsai, G. H. Lee, W. F. Liaw, *Inorg. Chem.* **2006**, *45*, 6041–6047.

[56] Z. J. Tonzetich, L. H. Do, S. J. Lippard, *J. Am. Chem. Soc.* **2009**, *131*, 7964–7965.

[57] M. L. Tsai, W. F. Liaw, *Inorg. Chem.* **2006**, *45*, 6583–6585.

[58] B. D'Autréaux, O. Horner, J. L. Oddou, C. Jeandey, S. Gambarelli, C. Berthomieu, J. M. Latour, I. Michaud-Soret, *J. Am. Chem. Soc.* **2004**, *126*, 6005–6016.

[59] M. R. Miller, I. L. Megson, *Br. J. Pharmacol.* **2007**, *151*, 305–321.

[60] L. Grossi, S. D'Angelo, *J. Med. Chem.* **2005**, *48*, 2622–2626.

[61] T. Yang, A. N. Zelikin, R. Chandrawati, *Adv. Sci.* **2018**, *5*, 1701043.

[62] Z. Ma, B. Moulton, *Coord. Chem. Rev.* **2011**, *255*, 1623–1641.

[63] J. Cheng, K. He, Z. Shen, G. Zhang, Y. Yu, J. Hu, *Front. Chem.* **2019**, *7*, 1–8.

[64] A. C. McKinlay, J. F. Eubank, S. Wuttke, B. Xiao, P. S. Wheatley, P. Bazin, J. C. Lavalley, M. Daturi, A. Vimont, G. De Weireld, et al., *Chem. Mater.* **2013**, *25*, 1592–1599.

[65] E. D. Bloch, W. L. Queen, S. Chavan, P. S. Wheatley, M. Joseph, R. Morris, C. M. Brown, C. Lamberti, S. Bordiga, J. R. Long, et al., *J. Am. Chem. Soc.* **2015**, *137*, 3466–3469.

[66] R. J. Soto, L. Yang, M. H. Schoenfisch, *ACS Appl. Mater. Interfaces* **2016**, *8*, 2220–2231.

[67] A. W. Carpenter, M. H. Schoenfisch, *Chem. Soc. Rev.* **2012**, *41*, 3742–3752.

[68] S. V. Kryatov, E. V. Rybak-Akimova, V. L. MacMurdo, L. Que Jr., *Inorg. Chem.* **2001**, *40*, 2220–2228.

[69] M. W. Hlawitschka, M. Oßberger, C. Backes, P. Klüfers, H.-J. Bart, *Oil Gas Sci. Technol.* **2017**, *72*, 1–11.

[70] L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013–1045.

[71] S. Schindler, *Eur. J. Inorg. Chem.* **2000**, 2311–2326.

[72] C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee, W. B. Tolman, *Chem. Rev.* **2017**, *117*, 2059–2107.

[73] L. Q. Hatcher, K. D. Karlin, *J. Biol. Inorg. Chem.* **2004**, *9*, 669–683.

[74] C. Würtele, E. Gaoutchenova, K. Harms, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2006**, *45*, 3867–3869.

[75] M. Nappa, J. S. Valentine, A. R. Miksztal, H. J. Schugar, S. S. Isied, *J. Am. Chem. Soc.*

1979, *101*, 7744–7746.

[76] M. Becker, F. W. Heinemann, S. Schindler, *Chem. Eur. J.* **1999**, *5*, 3124–3129.

[77] C. X. Zhang, S. Kaderli, M. Costas, E. Kim, Y.-M. Neuhold, K. D. Karlin, A. D. Zuberbühler, *Inorg. Chem.* **2003**, *42*, 1807–1824.

[78] K. Fujisawa, M. Tanaka, Y. Moro-oka, N. Kitajima, *J. Am. Chem. Soc.* **1994**, *12*, 12079–12080.

[79] S. T. Prigge, R. E. Mains, B. A. Eipper, L. M. Amzel, *Cell. Mol. Life Sci.* **2000**, *57*, 1236–1259.

[80] A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa, H. Einaga, *Angew. Chem. Int. Ed.* **1998**, *37*, 798–799.

[81] T. Osako, S. Nagatomo, Y. Tachi, T. Kitagawa, S. Itoh, *Angew. Chem. Int. Ed.* **2002**, *41*, 4325–4328.

[82] P. Chen, K. Fujisawa, E. I. Solomon, *J. Am. Chem. Soc.* **2000**, *122*, 10177–10193.

[83] M. Kodera, T. Kita, I. Miura, N. Nakayama, T. Kawata, K. Kano, S. Hirota, *J. Am. Chem. Soc.* **2001**, *123*, 7715–7716.

[84] N. Kitajima, Y. Moro-oka, *J. Am. Chem. Soc. Chem. Commun.* **1988**, 151–152.

[85] R. R. Jacobson, Z. Tyeklar, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 3690–3692.

[86] E. A. Lewis, W. B. Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076.

[87] J. Cahoy, P. L. Holland, W. B. Tolman, *Inorg. Chem.* **1999**, *38*, 2161–2168.

[88] K. D. Karlin, N. Wei, B. Jung, S. Kaderli, P. Niklaus, A. D. Zuberbühler, *J. Am. Chem. Soc.* **1993**, *115*, 9506–9514.

[89] J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, L. Que, A. D. Zuberbühler, W. B. Tolman, *Science* **1996**, *271*, 1397–1400.

[90] G. Prota, *Med. Res. Rev.* **1988**, *8*, 525–556.

[91] H. Decker, E. Jaenicke, *Dev. Comp. Immunol.* **2004**, *28*, 673–687.

[92] Y. Matoba, T. Kumagai, A. Yamamoto, H. Yoshitsu, M. Sugiyama, *J. Biol. Chem.* **2006**, *281*, 8981–8990.

[93] E. I. Solomon, P. Chen, M. Metz, S.-K. Lee, A. E. Palmer, *Angew. Chem. Int. Ed.* **2001**, *40*, 4570–4590.

[94] K. D. Karlin, P. L. Dahlstrom, S. N. Cozzette, P. M. Scensny, J. Zubieta, *J. Am. Chem. Soc. Chem. Commun.* **1981**, 881–882.

[95] K. D. Karlin, M. S. Nasir, B. I. Cohen, R. W. Cruse, S. Kaderli, A. D. Zuberbühler, *J. Am. Chem. Soc.* **1994**, *116*, 1324–1336.

[96] K. D. Karlin, J. C. Hayes, J. P. Hutchinson, J. Zubieta, *Inorganica Chim. Acta* **1983**, *78*, L45–L46.

[97] M. Kodera, K. Katayama, Y. Tachi, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *J. Am. Chem. Soc.* **1999**, *121*, 11006–11007.

[98] Z. Hu, R. D. Williams, D. Tran, T. G. Spiro, S. M. Gorun, *J. Am. Chem. Soc.* **2000**, *122*, 3556–3557.

[99] J. N. Hamann, B. Herzigkeit, R. Jurgeleit, F. Tuczek, *Coord. Chem. Rev.* **2017**, *334*, 54–66.

[100] L. Casella, M. Gullotti, R. Radaelli, P. Di Gennaro, *J. Chem. Inf. Model.* **1991**, 1611–1612.

[101] M. Réglier, C. Jorand, B. Waegell, *J. Chem. Soc. Chem. Commun.* **1990**, 1752–1755.

[102] M. Rolff, J. Schottenheim, G. Peters, F. Tuczek, *Angew. Chem. Int. Ed.* **2010**, *49*, 6438–6442.

[103] M. S. Askari, L. A. Rodríguez-Solano, A. Proppe, B. McAllister, J. P. Lumb, X. Ottenwaelder, *Dalt. Trans.* **2015**, *44*, 12094–12097.

[104] K. V. N. Esguerra, Y. Fall, J. P. Lumb, *Angew. Chem. Int. Ed.* **2014**, *53*, 5877–5881.

[105] Z. Huang, O. Kwon, H. Huang, A. Fadli, X. Marat, M. Moreau, J.-P. Lumb, *Angew. Chem. Int. Ed.* **2018**, *57*, 11963–11967.

[106] M. Paul, M. Teubner, B. Grimm-Lebsanft, C. Golchert, Y. Meiners, L. Senft, K. Keisers, P. Liebhäuser, T. Rösener, F. Biebl, et al., *Chem. Eur. J.* **2020**, *26*, 7556–7562.

[107] M. Paul, A. Hoffmann, S. Herres-Pawlis, *J. Biol. Inorg. Chem.* **2021**, *26*, 249–263.

[108] S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.

[109] A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

[110] P. L. Holland, K. R. Rodgers, W. B. Tolman, *Angew. Chem. Int. Ed.* **1999**, *38*, 1139–1142.

[111] J. Becker, P. Gupta, F. Angersbach, F. Tuczek, C. Näther, M. C. Holthausen, S. Schindler, *Chem. Eur. J.* **2015**, *21*, 11735–11744.

[112] J. Becker, Y. Y. Zhyhadlo, E. D. Butova, A. A. Fokin, P. R. Schreiner, M. Förster, M. C. Holthausen, P. Specht, S. Schindler, *Chem. Eur. J.* **2018**, *24*, 15543–15549.

[113] C. Limberg, *Angew. Chem. Int. Ed.* **2003**, *42*, 5932–5954.

[114] I. Blain, M. Giorgi, I. De Riggi, M. Réglier, *Eur. J. Inorg. Chem.* **2000**, *2000*, 393–398.

[115] R. Hrdina, F. M. Metz, M. Larrosa, J. P. Berndt, Y. Y. Zhygadlo, S. Becker, J. Becker, *European J. Org. Chem.* **2015**, *2015*, 6231–6236.

[116] B. J. K. Chakrabarti, D. M. Rackham, D. E. Tupper, C. Limited, E. W. Manor, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1893–1900.

[117] B. Schönecker, T. Zheldakova, Y. Liu, M. Kötteritzsch, W. Günther, H. Görls, *Angew. Chem. Int. Ed.* **2003**, *42*, 3240–3244.

[118] B. Schönecker, T. Zheldakova, C. Lange, W. Günther, H. Görls, M. Bohl, *Chem. Eur. J.* **2004**, *10*, 6029–6042.

[119] B. Schönecker, C. Lange, T. Zheldakova, W. Günther, H. Görls, G. Vaughan, *Tetrahedron* **2005**, *61*, 103–114.

[120] B. Schönecker, C. Lange, *J. Organomet. Chem.* **2006**, *691*, 2107–2124.

[121] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776–13779.

[122] R. Trammell, Y. Y. See, A. T. Herrmann, N. Xie, D. E. Díaz, M. A. Siegler, P. S. Baran, I. Garcia-Bosch, *J. Org. Chem.* **2017**, *82*, 7887–7904.

[123] R. Trammell, L. D'Amore, A. Cordova, P. Polunin, N. Xie, M. A. Siegler, P. Belanzoni, M. Swart, I. Garcia-Bosch, *Inorg. Chem.* **2019**, *58*, 7584–7592.

[124] P. Gupta, M. Diefenbach, M. C. Holthausen, M. Förster, *Chem. Eur. J.* **2017**, *23*, 1427–1435.