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Syntheses and investigations of metal complexes with tripodal and macrocyclic ligands

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Vorgelegt von

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"Die Neugier steht immer an erster Stelle eines Problems, das gelöst werden will."

- Galileo Galilei -

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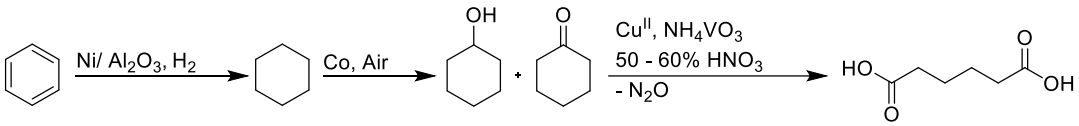
1. Introduction

1.1. Catalytic oxidation reactions in industry

Oxidation reactions are decisive in the chemical and pharmaceutical industries. In this context, about 20% of industrial processes are related to oxidation reactions, resulting in approximately 600 million tons of chemicals per year.[1,2] A notable example is the synthesis of adipic acid, a crucial precursor for the production of nylon. However, the current synthesis of adipic acid presents several challenges. One of them is that the process involves the use of oil-based chemicals, which creates a dependency on fossil fuels. Additionally, this process is energy-intensive, requiring both high pressure and high temperatures while it also significantly impacts greenhouse gas emissions.[3]



Scheme 1: Simplified reaction scheme for the production of adipic acid in industry.[4]

A simplified reaction scheme for the industrial production of adipic acid is shown in Scheme 1. The first step is the reduction of benzene to cyclohexane, followed by the oxygenation to cyclohexanol and cyclohexanone and in the final step, the catalytic reaction to adipic acid occurs.[4,5] On closer examination, it becomes apparent that the process itself is not effective due to the low conversion rate (4-8%) of cyclohexanol and cyclohexanone. Nevertheless, the process is responsible for 5 to 8% of the global emissions of the greenhouse gas nitrous oxide.[5] For this reason, extensive research is being carried out on potential alternatives. There are different approaches, including photochemical and continuous flow reactions.[4–6] Furthermore, a bioinorganic approach is another possible option. In the field of bioinorganic research, metal complexes that closely resemble the structure of active centers in enzymes are utilized.[7–10] The following chapter shows how metal complexes in enzymes and proteins, particularly copper proteins, play a significant role in biological systems.

1.2. Copper in biological systems

In general, copper is a trace element, and with a range of 80 to 120 mg per 70 kg body weight, it is the third most prevalent transition metal in the human body.[7,11] The most common oxidation states of copper ions are I and II. Furthermore, copper ions are a substantial factor in biochemically relevant processes, particularly in enzymes and proteins, as illustrated in Figure 1, which provides an overview of various enzymes that are involved.[7,12]

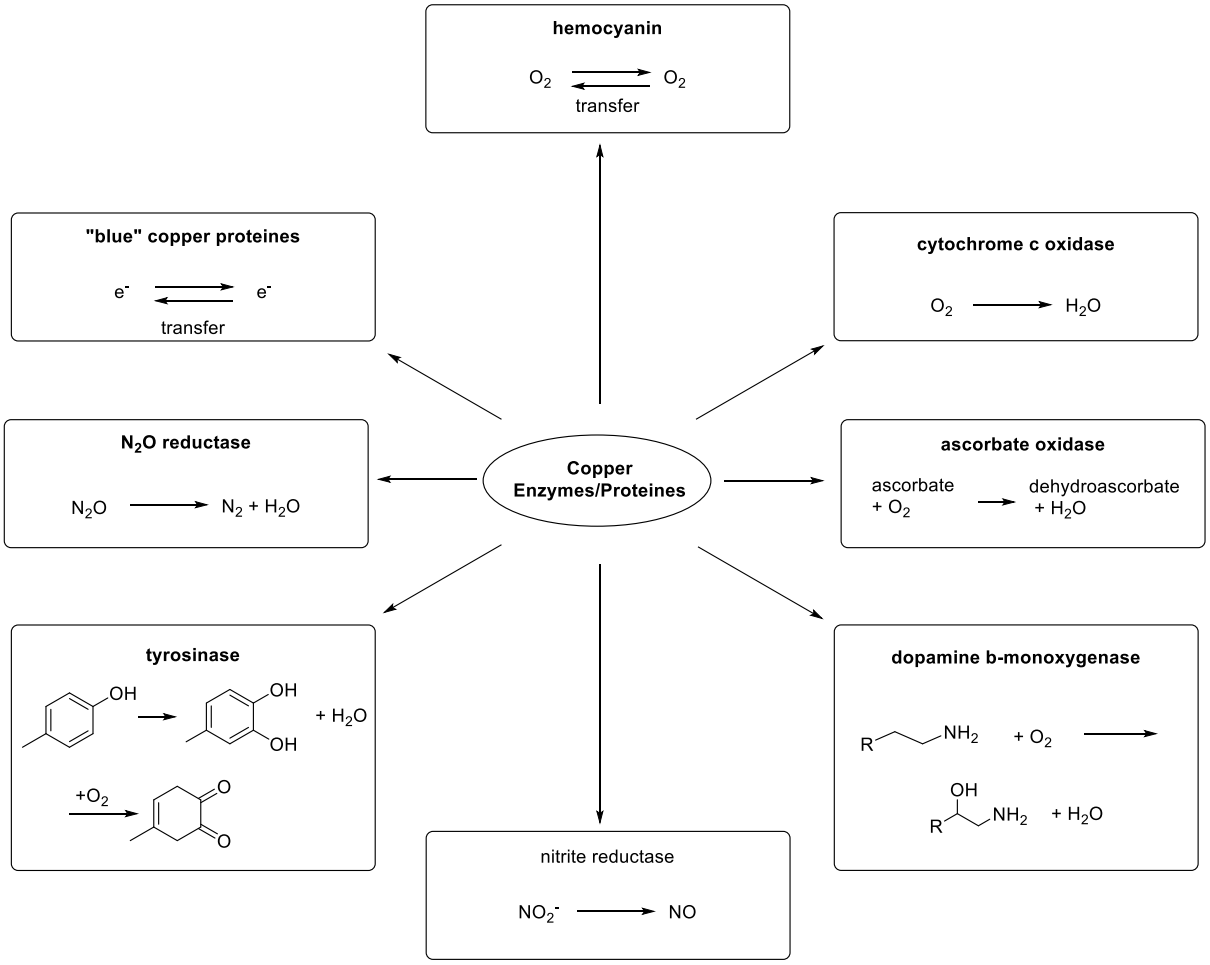


Figure 1: Overview of various copper enzymes involved in electron transfer, oxygen transfer, or oxidation reactions.[7,12]

In biological systems, a variety of copper enzyme types are identified, which perform a range of functions. The structural and spectroscopic properties of copper proteins enable their classification into three basic groups, designated as type 1, type 2, and type 3 copper proteins. Additionally, there are cases where multiple types of copper proteins coexist and

isolated proteins that do not align with the established classification system.[12–15]

The type 1 copper proteins or so-called "blue copper proteins", are primarily responsible for electron transfer. The absorption of these proteins is particularly strong at a wavelength of approx. 600 nm. This occurs here as a result of ligand-metal-charge-transfer interactions (LMCT) between the copper ion and the sulfur of the cysteinate residue.[13,16] Furthermore, it is noteworthy that these proteins show a small hyperfine splitting of the g∥-signal (^{63}Cu/^{65}Cu) in the EPR. Regarding their geometry, type 1 copper proteins usually contain a copper ion that is coordinated in a trigonal planar fashion by two histidines and a cysteine. However, there are different classes of copper type 1 proteins, and they are classified by the axially coordinated ligand. Examples of blue copper proteins include plastocyanin (whose active center is illustrated in Figure 2), azurin, and laccase.[7,13,17,18]

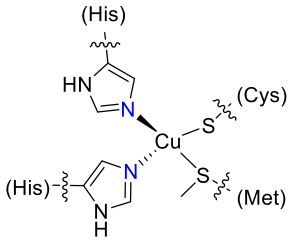


Figure 2: Structure of the active center of plastocyanin (type 1 copper protein) revealed by Monari et al..[18]

The second basic type consists of type 2 copper proteins, which are responsible for catalytic oxidation and reduction reactions. These proteins appear to have either a square planar or square-pyramidal geometry, and histidine or oxygen-containing ligands are mostly coordinated.[7,13,17] In comparison to type 1 copper proteins, the absorption is significantly weaker, which can be attributed to the absence of thiolate group ligands. As a result, the absorption is entirely due to forbidden d-d transitions. Additionally, the EPR spectrum does not exhibit any unusual characteristics compared to type 1 copper proteins. Examples of type 2 copper proteins include cytochrome c oxidase, amine oxidases, and galactose oxidase.[13,19] For instance, galactose oxidase is an extracellular enzyme that is present in certain fungal species. It serves as a catalyst for the oxidation of primary alcohols to aldehydes. The active center of galactose oxidase is shown in Figure 3. [7,13]

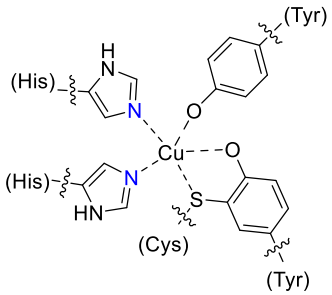
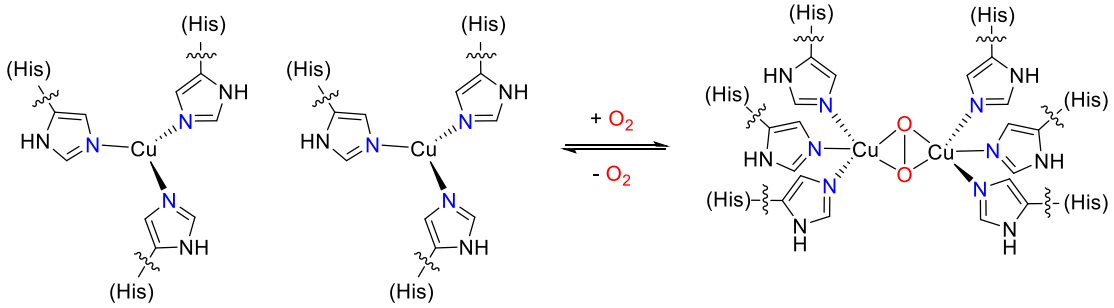


Figure 3: Structure of the active center of galactose oxidase (type 2 copper protein).[12]

Type 3 copper proteins are characterized by a binuclear copper center and are usually involved in activating dioxygen, either for the transport of dioxygen or for oxygenation reactions. In type 3 copper proteins, the copper centers are both coordinated in a trigonal planar fashion, involving three histidine-ligands. Moreover, an intense absorption of these complexes can be observed due to LMCT interactions. Hemocyanin as an example for a type 3 copper is found in arthropods and molluscs and is the analog to hemoglobin in the human body. Accordingly, it is responsible for the transport of oxygen.[7,13] The reversible binding of dioxygen to the active center of hemocyanin is shown in Scheme 2.[12,20]



Scheme 2: Binding of the type 3 copper protein hemocyanin with dioxygen.[12,20]

1.3. Catalytic reactions in nature

Type 3 copper proteins are not only responsible for the transport of dioxygen, but also for oxygenation reactions. One of the enzymes involved in oxygenation reactions is catechol oxidase. It is found in plants, insects, and crustaceans and catalyzes the oxidation of catechol to ortho-quinone. This reaction is followed by the subsequent auto-polymerization of the reactive quinone, leading to the formation of brown polyphenolic catechol melanin, which protects plants from pathogens and insects in the event of tissue damage. The active center is similar to that of tyrosinase. The difference is that tyrosinase is responsible for both the oxidation of monophenol (cresolase activity) and the oxidation of *o*-diphenol

(catecholase activity), whereas catechol oxidase only catalyzes the oxidation of *o*-diphenol.[14,21,22]

In Figure 5, a postulated catalytic cycle of catechol oxidase based on the spectroscopic data of Eicken *et al*. is shown. During a 4-electron oxidation, two catechols are oxidized to two equivalents of *o*-quinone and the following sequence describes this oxidation process: In the first step, the active center is present in the deoxy form. The catechol binds to the Cu(B) center and a copper dioxygen intermediate (a side-on-peroxido copper complex) forms in the presence of dioxygen (1). The catechol is oxidized to *o*-quinone, forming the met form of the active center (2). In the next step, a catechol coordinates to the Cu(B) center of the met form (3). After another oxidation to *o*-quinone, the enzyme reverts to its original state (4).[14,21]

Additionally, the enzyme catechol oxidase was isolated from a sweet potato, it was possible to characterize the “met form” of the active center by crystallization. Based on these findings, the previous shown catalysis cycle of catechol oxidase was assumed. [14,21,22,23]

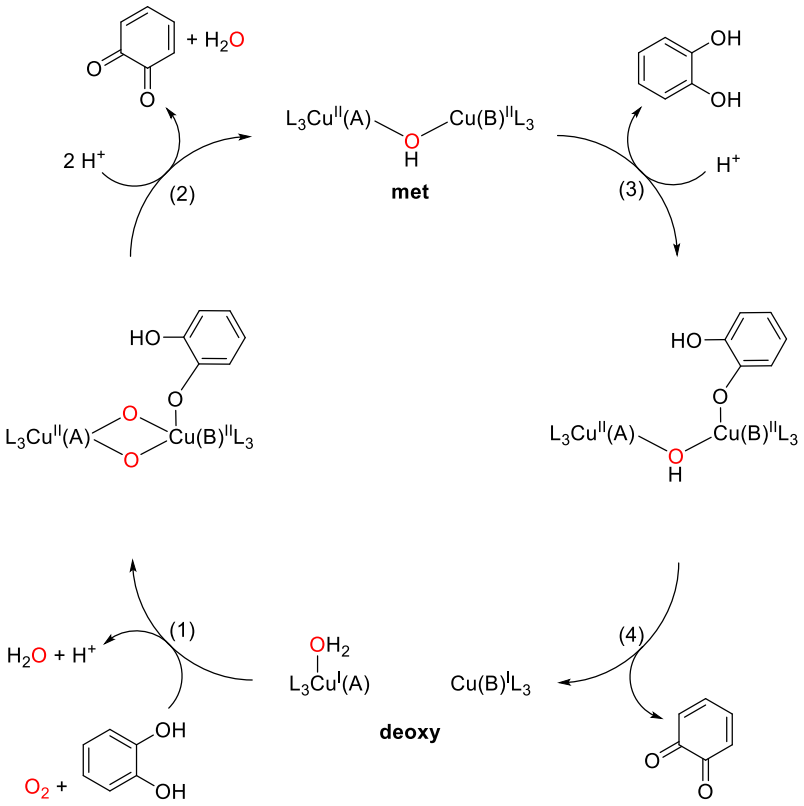
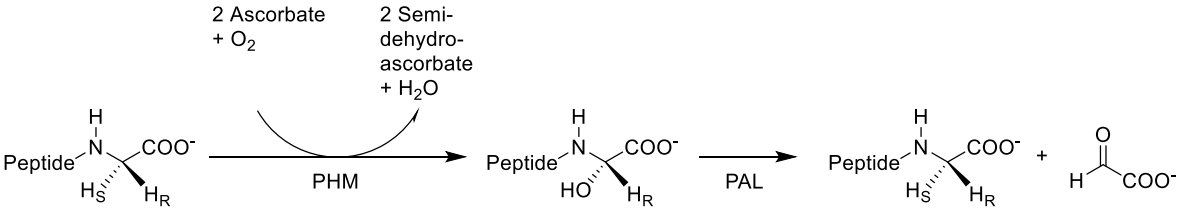


Figure 4: Proposed catalytic cycle for the oxidation of catechol with catechol oxidase. Both copper centers are coordinated by three histidins (L).[14,21]

Besides catechol oxidase and tyrosinase, which is responsible for the synthesis of melanin in the human organism, there are more monooxygenases, such as dopamine beta-monooxygenase (DβM) or peptidylglycine-*α*-hydroxylating monooxygenase (PHM).[24]

PHM is part of the bifunctional enzyme peptidylglycine α-amidating monooxygenase (PAM). In Scheme 3, the biosynthesis of a signaling molecule involving PAM is presented. First, PHM catalyzes the hydroxylation of the C*α*-position at the C-terminus of glycine, followed by the elimination of the hydroxylated glycine by PAL (peptidyl-alpha-hydroxyglycine alpha-amidating lyase).[24–27]



Scheme 3: Simplified reaction scheme for the biosynthesis of signal peptides with the bifunctional enzyme PAM.[25]

To better understand the catalytic hydroxylation, it is necessary to examine the active center and the mechanism in more detail. The active center contains two copper ions that are significantly distant from one another (approximately 11 Å) and devoid of any bridging ligands (noncoupled binuclear copper site).[28]

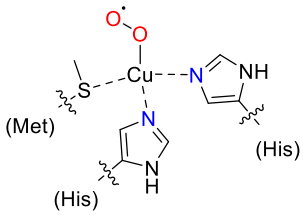


Figure 5: Molecular structure of the end-on superoxido copper complex in PHM. [26]

The formation of the copper dioxygen species, as well as the catalytic reaction itself, occurs only at one of the two copper ions (Cu_B-center). The formed copper-dioxygen species is an end-on superoxido copper complex (Figure 5). This evidence was provided by Prigge *et al*., who were able to identify it crystallographically. It was achieved by reacting a frozen crystal of the protein with a slow substrate and ascorbate in the presence of dioxygen.[26] Furthermore, the complex was confirmed by computational studies of Chen *et al*.[28]

1.4. Model compounds of copper enzymes and proteins

Apart from the end-on superoxido copper complex observed in the case of PHM, additional dioxygen intermediates could be observed in nature or in synthetic model complexes. Dioxygen can bind to the copper center in a number of ways, so it is important to know which dioxygen intermediates exist and to determine which of these intermediates are reactive. The nature of binding is contingent on various factors, including the external conditions and the ligands bound to the copper center. As a mononuclear copper complex, the dioxygen or the peroxide forms an end-on or side-on complex.[29,30] These types of binding can be explained through the concept of hapticity η, which is defined as the number of ligand atoms directly bonded to the metal ion. In a side-on complex, two ligand atoms are directly bonded, while an end-on complex, only one ligand atom is bonded. Besides mononuclear complexes, there are binuclear complexes. The binuclear form can occur because of the presence of an additional copper complex. On one hand, a peroxido copper complex (trans-μ-1,2-peroxido or μ-η^2:η^2-peroxido) and on the other hand a bis-μ-oxido complex can occur. In some cases, trinuclear intermediates are possible as well.[29,31]

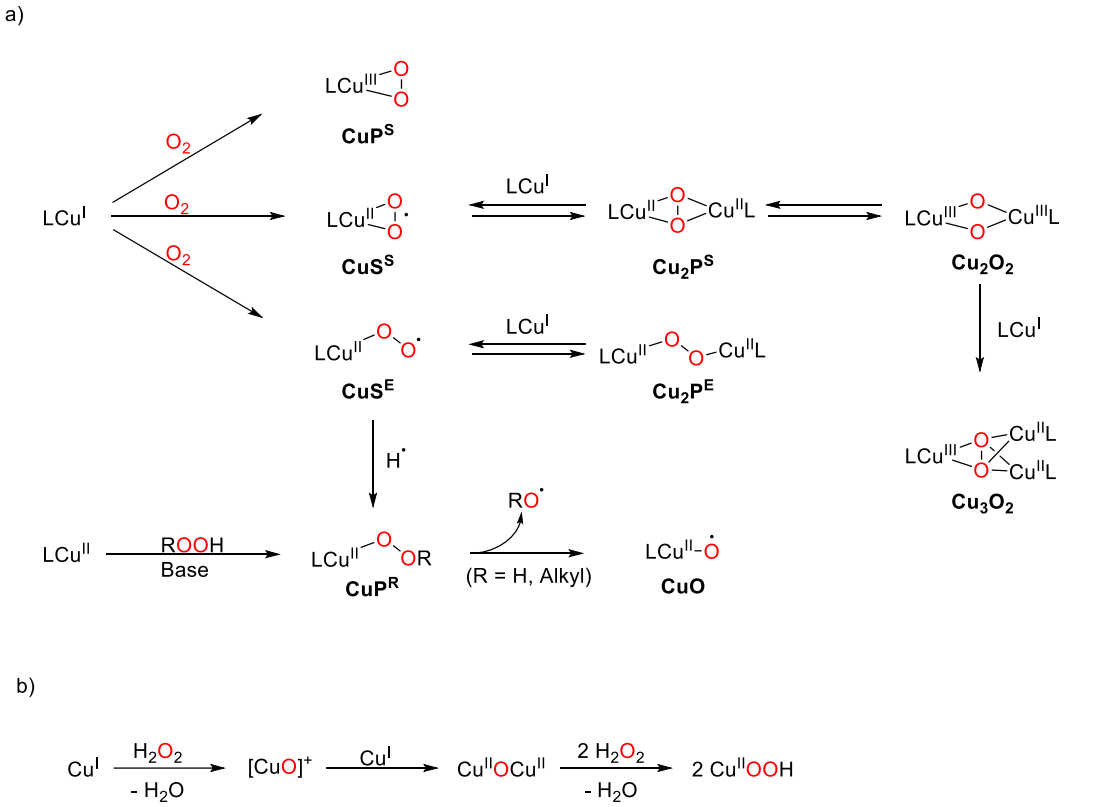


Figure 6: a) Various known oxygen intermediates involved in the reaction of copper(I) and copper(II) complexes with molecular oxygen and peroxides (L = Ligand, P = Peroxido, S = Superoxido, E = End-on, S = Side-on). Redrawn from Itoh et al..[29] b) Proposed mechanism for a reaction of a copper(I) complexes and hydrogen peroxide to a $[CuOOH]^+$ species.[9,32]

The various copper dioxygen complexes are partially in equilibrium. In Figure 6, a variety of reaction pathways involving copper-dioxygen intermediates are shown, particularly in the context of the reactions of copper(I) and copper(II) complexes with dioxygen and peroxides.[29] The following chapters (1.5, 1.6) present a selected range of model complexes developed to better understand the mechanisms as well as reactivity in the active center of enzymes regarding dioxygen and to examine catalysts for oxygenation reactions.

1.5. Copper complexes with tripodal ligand systems

Model complexes play a key role in understanding the reactivity of active centers of enzymes and in the development of environmentally friendly catalysts. An important group of ligands used for copper-oxygen complexes are tripodal ligands.[8,9,33] In the case of tripodal ligands, the metal center is coordinated by three donor atoms in a trigonal pyramidal fashion, and the reactivity depends on the properties of the ligand (steric effects, aromaticity, etc.). In Figure 7, examples of tripodal ligands that have made a significant contribution to the study of tripodal ligands are shown. All shown ligands are distinguished by a particular characteristic, with the ligand tren (tris(2-aminoethyl)amine) providing the fundamental framework.

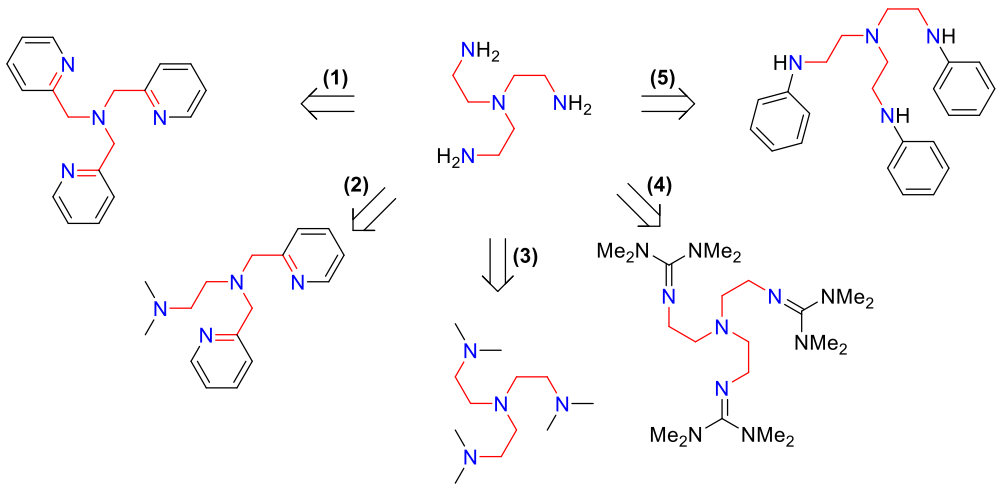


Figure 7: Tripodal tetradentate ligands tmpa (1), Me_2uns-penp (2), Me_6tren (3), TMG_3tren (4), and Bn_3tren (5).[34–38]

In a study by Jacobsen *et al*., the ligand tmpa (tris(2-pyridylmethyl)amine) was used for the investigation of copper-dioxygen complexes. Notably, this investigation led to the successful crystallographic characterization of the first copper-dioxygen complex as a result of the reaction of a copper(I) complex and dioxygen. In this case, a trans-μ-1,2-peroxido copper complex was formed, which crystallized at −90 °C in EtCN. Both copper center ions were

distorted trigonal bipyramidal coordinated by tmpa as well as dioxygen, and the distance between the two copper centers was found to be 4.359 Å. In addition to the crystallographic characterization, UV-Vis measurements were performed at −80 °C in EtCN (propionitrile), in which characteristic bands at 440, 525, and 590 nm were observed.[34,39] Furthermore, Raman vibrations were detected at 832 cm^{-1} and 561 cm^{-1}.[40] Besides the characterization, Lukas *et al*. described the use of the trans-*μ*-1,2-peroxido copper complex for the oxidation of toluene to benzaldehyde and benzyl alcohol. However, a yield of only 8% was obtained, determined by GC-MS measurements. Nevertheless, Lukas *et al*. were able to obtain a conversion of up to 40% determined via GC-MS using a derivative. In this case, an “ethylpyridine” arm is exchanged with an anisole-containing substituent.[41] As a result of the successful characterization of a copper-dioxygen complexes, a series of studies was made on copper(I) complexes, along with a variety of tmpa derivatives.[9,33,42]

Another tmpa derivative demonstrates the impact of ligand substitution on the reactivity with dioxygen. In this instance, the pyridine residues of the ligand tmpa have been substituted with dimethylamine groups (-NMe_2) in para-position.[42,43]. In the subsequent step, the initial complex (a copper carbon monoxide complex) reacted with dioxygen, resulting in the formation of a copper-dioxygen species. The species had been identified as an end-on superoxido copper complex (shown in Figure 8), confirmed by absorbance bands at 418, 615, and 767 nm in CO-saturated THF at −85 °C using UV-Vis spectroscopy. In addition, resonance Raman measurements showed a stretching frequency that corresponds to the characteristics of an end-on superoxido copper complex. Due to the promising reactivity, oxidation reactions of phenol derivatives (*p*-MeO-2,6-DTBP, DTBP: Di-tert-butylphenole); 2,6-DTBP; and 2,4,6-TTBP, TTBP: Tri-tert-butylphenol) with the end-on superoxido copper complex were examined. Conversions of up to 40% were revealed via GC (gas chromatography) and GC-MS (MS: mass spectrometry).[43]

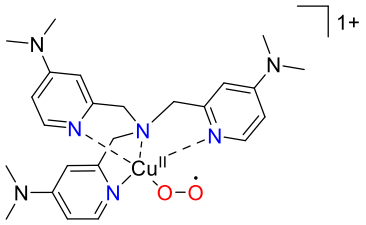


Figure 8: Structure of an end-on superoxido copper complex with the ligand Me_2N-tmpa.[42]

Another noteworthy ligand is Me_6tren (Tris(2-dimethylaminoethyl)amine; Figure 7). In comparison to tmpa, Me_6tren has a higher steric demand and a different nature of the donor atoms. These differences can be explained by looking at the interaction of the ligand with a copper center. In the case of tmpa, the copper ion is mostly coordinated by the N-donor atoms

of the pyridine ring (aromatic properties). In contrast, the N-donor atoms of Me_6tren exhibit aliphatic characteristics.

Becker *et al*. investigated copper(I) complexes with Me_6tren and dioxygen. Interestingly, two copper-dioxygen species were identified by UV-Vis absorption spectroscopy. In particular, time-dependent measurements via stopped-flow technique were taken at a temperature of −60 °C in a solution of propionitrile. Initially, a band at 412 nm was observed, indicating the presence of a superoxido copper complex.[35] Subsequently, a high absorption was identified at 560 nm, indicating the formation of the trans-*μ*-1,2-peroxido copper complex. Compared to the formed trans-*μ*-1,2-peroxido copper complex with the ligand tmpa, the absorption bands reveal a slight shift, which can be explained in part by small differences in the geometry of the copper centers. The formation of the copper-dioxygen intermediates was additionally confirmed via resonance Raman spectroscopy (Measurement in propionitrile at −90 °C). While a peak at 1122 cm^{-1} indicated a superoxido copper complex, the trans-*μ*-1,2-peroxido copper complex was identified with peaks at 825 cm^{-1} ($^{16}O_2$) and 777 cm^{-1} ($^{18}O_2$). [35,44]

Related to the ligand tmpa, it can be noted that the end-on superoxido copper complex was found to be more stable and the peroxido copper complex less stable.[35,44,45] Noteworthy, Würtele *et al*. successfully revealed the molecular structure of a trans-*μ*-1,2-peroxido copper complex with Me_6tren a decade later (Figure 9). The exchange of an anion greatly enhanced the stabilization of the complex, and as a result, it was possible to crystallize the complex.[46]

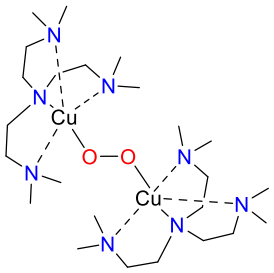


Figure 9: Molecular structure of $[Cu_2(Me_6tren)_2(O_2)]^{2+}$ obtained by Würtele et al..[46]

Derivatives of uns-penp ((aminoethyl)bis(2-pyridylmethyl)amine, shown in Figure 11) represent another ligand system of interest. These derivatives feature two pyridyl substituents and an ethylamine substituent that is also susceptible to substitution. Weitzer *et al*. investigated copper(I) complexes with the derivative Me_2-uns-penp ((2-dimethylaminoethyl)bis(2-pyridylmethyl)amine)). In this instance, time-resolved absorption measurements via stopped-flow technique were conducted in propionitrile at −90°C. During the investigation, the formation of both the end-on superoxido copper complex (λ_{max}: 412 nm) and the trans-*μ*-1,2-peroxido copper complex (λ_{max}: 528 nm) was observed. The formation of the end-on superoxido copper complex occurred too rapidly at these low temperatures to be observed completely, whereas

the formation of the trans-*μ*-1,2-peroxido copper complex could be traced fully. Weitzer *et al*. also determined that the trans-*μ*-1,2-peroxido copper complex showed higher longevity at higher temperatures than the trans-*μ*-1,2-peroxido copper complex with the coordinating ligands tmpa and Me_6tren.[35,36,39] Interestingly, Würtele *et al.* enabled the preservation of a trans-*μ*-1,2-peroxido copper complex as a stable solid at ambient temperature by using the anion BPh_4^- (tetraphenylborate anion) for their copper(I) complexes with Me_2-uns-penp. Due to this achievement, investigations have been conducted to examine the catalytic conversion of toluene to benzaldehyde and benzyl alcohol at ambient temperature utilizing the trans-*μ*-1,2-peroxido copper complex. In this instance, a conversion of around 15% was obtained.[46]

Building upon the findings of Weitzer and Würtele's published works, Brückmann *et al*. studied copper(I) complexes of symmetrical and asymmetrical uns-penp derivatives (Figure 11 shows an example of a symmetrical and an asymmetrical ligand of their work). The objective of Brückmann *et al.* was to obtain a trans-*μ*-1,2-peroxido copper complex in a solid state. Therefore, a copper(I) complex with an uns-penp derivative and the anion BPh_4 was prepared and reacted with dioxygen. As part of it, a trans-*μ*-1,2-peroxido copper complex was obtained with the asymmetrical ligand Et-*i*Prop-uns-penp and identified crystallographically. The molecular structure is illustrated in Figure 10. Furthermore, Brückmann *et al*. were able to show that complexes with symmetrical ligands exhibit suppressed oxygen reactivity. In contrast, complexes with asymmetrical ligands were reactive with dioxygen.[47]

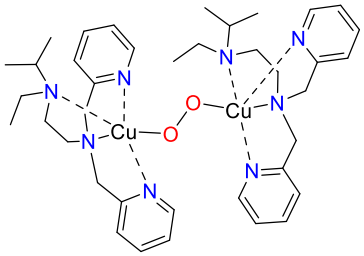
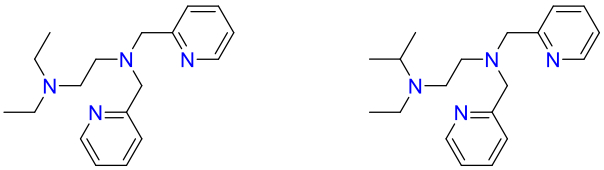


Figure 10: Molecular structure of $[Cu_2(Et\text{-}iProp\text{-}uns\text{-}penp)_2(O_2)]^{2+}$ obtained by Brückmann et al..[47]

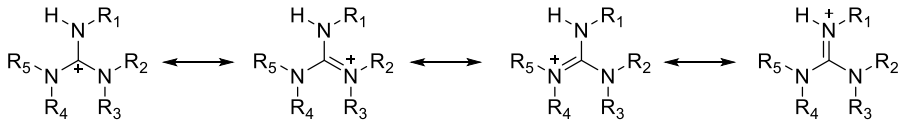
Meanwhile, Brückmann *et al*. investigated the immobilization of the ligand Me_2-uns-penp on silica and mesoporous silica. Besides the successful immobilization, a comparable reactivity with dioxygen was observed, similar to that seen in the non-immobilized copper(I) complex with Me_2-uns-penp. However, the stability in solid state was found to be lower. Nevertheless, catalytic oxidation experiments with toluene were carried out and the received conversions were comparable to those reported by Würtele *et al*.[46,48]



(1) Et_2-uns-penp (2) Et-*i*Prop-uns-penp

Figure 11: The tripodal tetradentate derivatives Et_2-uns-penp (1, with symmetrical amine redidues) and Et-iProp-uns-penp (2, with asymmetrical amine residue).[47]

Another relevant ligand is TMG_3tren, which was described by Raab *et al*..[37] This ligand has a higher steric demand than tmpa and Me_6tren, and it has also improved donor properties. The positive properties of the donor groups are a result of the high basicity of the guanidine residues, which is due to resonance stabilization.[49] The stabilization is shown in Scheme 4.



Scheme 4: Resonance stabilization of positive charge by guanidine residues.

Schatz *et al.* investigated a copper(I) complex with TMG_3tren and dioxygen. Through UV-Vis spectroscopy, the presence of two bands at 442 nm and 690 nm was revealed in acetone and propionitrile. Furthermore, measurements in acetone at −70 °C with resonance Raman spectroscopy showed peaks at 1117 cm^{-1} (with $^{16}O_2$) and 1059 cm^{-1} (with $^{18}O_2$). Both indicated the presence of a copper-dioxygen complex. In further analysis, DFT calculations were conducted for both an end-on-superoxido copper complex and a side-on-superoxido copper complex, and furthermore, theoretical values for resonance Raman measurements were determined, which were compared with the measured results. These results represented a clear indication of the formation of an end-on superoxido copper complex.[45] In 2006, Würtele *et al*. confirmed this indication and published the first crystallographic evidence of an end-on superoxido copper complex as a result of the reaction of a copper(I) complex and dioxygen. As shown in Figure 12, the molecular structure of the copper ion is coordinated in a trigonal bipyramidal fashion by TMG_3tren and dioxygen coordination. A comparison of the O_1-O_2 bond (1.280 Å) and the Cu_1-O_1-O_2 angle reveals parallels with the crystallographic results of the copper-dioxygen complex of PHM.[50]

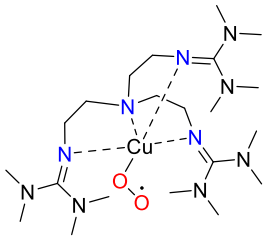
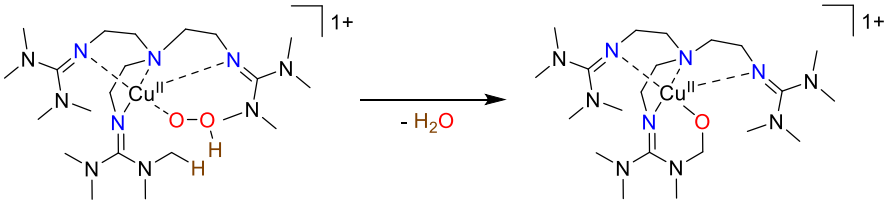


Figure 12: Molecular structure of [TMG$_3$trenCu(O$_2$)]$^+$ obtained by Würtele et al..[50]

Due to the high stability of the complex and the observed high reversibility, oxygenation experiments with copper(I) complexes and the ligand TMG$_3$tren were performed. Different exogenous phenolic substrates were used for oxygenation reactions, and oxygenation products were identified successfully. In addition to the expected product, a hydroxylation reaction of ligand was observed. Specifically, a methylene group of the ligand is hydroxylated, resulting in the formation of an alkoxide. The alkoxide is coordinated to the copper ion and deactivates the copper complex for further oxygenation reactions. The hypothesis of Maiti *et al.* (Scheme 5) was that the end-on superoxido complex is formed, initially. Then the copper-dioxygen complex reacts to form a hydroxido copper complex via an H-abstraction reaction. Subsequently, the hydroxide copper complex lead to the oxygenation of the methyl group of the ligand, generating water as a side-product. The hypothesis was confirmed through investigations involving H-donors, such as Tempo-H.[51]



Scheme 5: Assumed sub-step of the oxygenation of the ligand TMG$_3$tren by Maiti et al..[51]

1.6. Copper complexes with macrocyclic ligand systems

Another group of ligands was used in extensive research related to copper-dioxygen complexes.[8,9] These are macrocyclic ligands, which are able to stabilize complexes due to their characteristic macrocyclic effect.[52] Some examples of macrocyclic ligands include the cyclam derivative tet b, 12-TMC, and derivatives of 1,4,7-triazacyclonane (Shown in Figure 13 and Figure 15), which can stabilize copper-dioxygen complexes.[53–57]

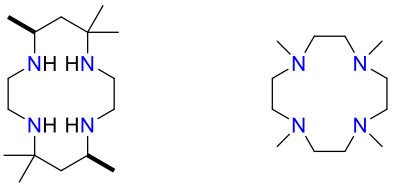


Figure 13: The macrocyclic ligands tet b (left) and 12-TMC (right).

Although cyclam derivatives are frequently used as ligands for bioinspired dioxygen activation, they are rarely employed in the copper-dioxygen activation process.[58] Nevertheless, it has been known since 1979 that copper complexes with tet b are reactive with dioxygen. Nappa *et al*. were able to spectroscopically confirm the presence of a superoxido copper complex in solution by reacting a copper(II) complex with potassium superoxide and [18]crown-6 in DMSO.[59] Hoppe *et al*. (2013) took a different approach by investigating the reaction of the copper(I) complex with the ligand tet b and dioxygen. Time-resolved absorbance measurements were carried out, and absorbance bands at 395 and 669 nm were observed, indicating an end-on superoxido copper complex. These observations are in line with the results reported by Nappa *et al*., who also identified the formation of an end-on superoxido copper complex.[57]

Additionally, Hoppe *et al*. observed the formation of a trans-*μ*-1,2-peroxido copper complex, confirmed by infrared spectroscopy and resonance Raman spectroscopy. Furthermore, the trans-*μ*-1,2-peroxido copper complex was crystallized at low temperatures, and its molecular structure was successfully solved by XRD spectroscopy. The molecular structure is illustrated in Figure 14.[57]

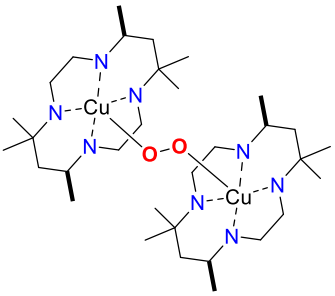


Figure 14: Molecular structure of $[Cu_2(tet\ b)_2(O_2)]^{2+}$ obtained by Hoppe et al..[57]

Besides copper complexes with the ligand tet b, the reactivity with dioxygen was also observed for copper complexes with the cyclam derivative 12-TMC. Garcia-Bosch *et al*. were able to identify spectroscopically a side-on superoxido copper complex at temperatures between −90 and −135 °C. By UV-Vis measurements, absorbance bands at

364, 450, and 635 nm, as well as a Raman Shift via resonance Raman spectroscopy at 544 cm^{-1} ($^{16}O_2$) and 515 cm^{-1} ($^{18}O_2$), provide confirmation. Additionally, DFT studies show evidence for the formation of a side-on superoxido copper complex. Furthermore, a series of oxidation reactions were conducted with various substrates by using the side-on superoxido copper complex, including phenol derivatives and PPh_3. However, no reactivity was observed towards these substrates. Garcia-Bosch *et al*. explained the low reactivity as a result of the copper ion being fully coordinated by the ligand 12-TMC and the superoxide, which could potentially prevent substrate binding.[56]

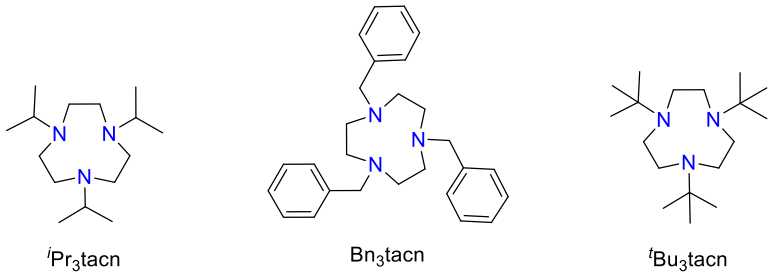
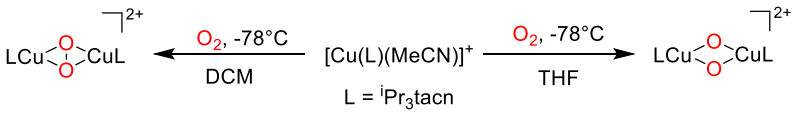


Figure 15: The macrocyclic ligands $^{i}Pr_3$tacn (left), Bn_3tacn (center), and $^{t}Bu_3$tacn (right).

An example of a derivative of a 1,4,7-triazacyclononane is $^{i}Pr_3$tacn (1,4,7-triazacyclononane ligand with three iso-propyl groups). Mahapatra *et al*. investigated copper(I) complexes with the ligand $^{i}Pr_3$tacn and treated them with dioxygen at −78 °C in dichloromethane. In this case, UV-Vis spectroscopy was used to identify characteristic bands at wavelengths of 365 and 510 nm. Furthermore, resonance Raman measurements showed distinctive peaks at 722 cm^{-1} (with $^{16}O_2$) and 680 cm^{-1} (with $^{18}O_2$). As a result of the analysis, a copper dioxygen adduct was identified, which was determined to be a μ-η^2:η^2-peroxido copper complex.[60] Interestingly, Halfen *et al*. showed that the solvent affects the formation of specific copper dioxygen species. By changing the solvent from dichloromethane (DCM) to tetrahydrofuran (THF), a bis-μ-oxido copper complex was observed. The different reactivity of copper(I) complexes with $^{i}Pr_3$tacn is illustrated in Scheme 6.[54]



Scheme 6: Reaction of copper(I) complexes with the ligand ^{i}Prtacn and dioxygen in DCM and THF. A formation of a bis-μ-oxido complex copper is obtained in DCM, and a μ-η^2:η^2-peroxido copper complex is obtained in THF.

The identification of the bis-μ-oxido copper complex was accomplished by measuring the absorption bands at 324 nm as well as 448 nm and resonance peaks at 600 cm^{-1} (with $^{16}O_2$) and 580 cm^{-1} (with $^{18}O_2$). Furthermore, it was ascertained that the bis-μ-oxido and the μ-η^2:η^2-peroxido copper complex could be successfully transferred to the other intermediate by adding an excess of the respective solvent.[54,61,62]

Interestingly, Halfen *et al*. studied copper(I) complexes with the ligand Bn_3tacn (1,4,7-triazacyclononane ligand with three benzyl groups) as well. At low temperatures of −75°C in DCM, the observation of a particular oxido copper complex with distinctive absorption bands at 318 and 430 nm was made using UV-Vis spectroscopy. In this case, a bis-μ-oxido copper complex was formed, and the change of solvent did not affect the intermediate formation.[54,61] However, an observation was made during the reaction of these complexes with dioxygen which is the dealkylation of the respective ligand after reacting. As a result of the dealkylation, the complex was ineffective as a catalysts.[54,61,63]

In 2016, Karahalis *et al*. investigated copper(I) complexes with ^{t}Bu$_3$tacn, a 1,4,7-triazacyclononane ligand with three tert-butyl groups (as a result of the simplified synthesis of this ligand by Thangavel *et al*.).[55,64] Karahalis *et al*. published a noteworthy method for a synthesis of a copper-dioxygen intermediate. In this method, a μ-η^2:η^2-peroxido copper complex was formed as a crystalline solid through a reaction with air at room temperature. The molecular structure of the formed μ-η^2:η^2-peroxido copper complex is shown in Figure 16. Interestingly, the demanding synthesis of the copper complex with the ligand does not involve the use of acetonitrile because the presence of acetonitrile during the complex formation can lead to its inactivation.[55]

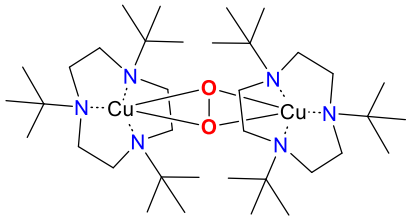
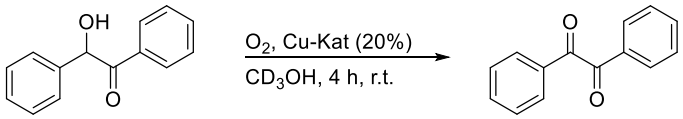


Figure 16: Molecular structure of $[Cu_2(^tBu_3tacn)_2(O_2)]^{2+}$ obtained by Karahalis et al..[55]

The measurement of the bond distance in the molecular structure revealed a separation of 3.6349(8) Å between the copper cores and an oxygen-oxygen bond length of 1.475(4) Å. In addition, Karahalis *et al*. were able to conduct stability tests in a variety of solvents and demonstrate the stability of the copper dioxygen intermediate in protic solvents, such as methanol and water. For instance, the half-life of the μ-η^2:η^2-peroxido complex in an aqueous Na_2HPO_4 solution was 9.6 days. In comparison to methanol ($t_{1/2}$ of 14.2 h) or acetonitrile ($t_{1/2}$ of 2.5 h), the half-life in the aqueous solution was significantly higher. Due

to the high stability of the μ-η^2:η^2-peroxido copper complex in solution, oxygenation reactions were performed with various substrates, including phenol and electron-rich phenolic substrates. In addition, Karahalis *et al*. were able to conduct catalytic oxidation reactions at various temperatures in deuterated methanol with phenolic substrates, such as 2,4-di-tert-butylphenol or benzoin (illustrated in Scheme 7) The yield was determined using nuclear magnetic resonance (NMR) spectroscopy and an internal standard like 1,3,5-trimethoxybenzene or 1,3,5-tri-tert-butylbenzene.[55]



Scheme 7: Catalysed oxidation of benzoin with $[Cu_2(^tBu_3tacn)_2(O_2)OTf_2$.[55]

2. Research Goals

As shown in chapters 1.5 and 1.6, current research is focusing on the development of model complexes that imitate the reactivity of active centers of enzymes such as peptidyl-α-hydroxylating monooxygenase (PHM). For the synthesis of these model complexes, tripodal ligands, like TMG_3tren, have demonstrated remarkable potential. The first end-on superoxide copper complex was successfully synthesized and characterized with TMG_3tren (a model complex for PHM).[50,51] However, the catalytic activity fell short of initial expectations. In contrast, ligands with aliphatic residues, such as Me_6tren, do not provide enough stability for the end-on superoxido copper complex.[35,36,65]

For this reason, a possible missing link, the imine ligand tris(2-(propan-2-ylideneamino)ethyl)amine ($imine_3$tren), was developed (illustrated in Figure 17). The present ligand exhibits characteristics that resemble both aliphatic ligands, like Me_6tren, and guanidine-type ligands, such as TMG_3tren. Consequently, it may serve as a suitable system for stabilizing an end-on superoxido copper complex. In order to accomplish this goal, the tripodal ligand was synthesized, and in addition, several metal complexes were prepared, with a particular focus on copper complexes.

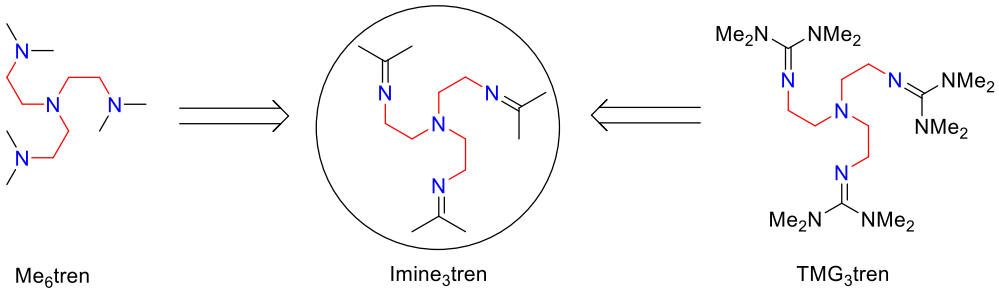
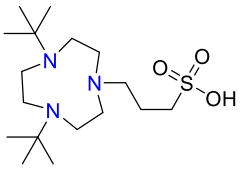


Figure 17: Ligand influences on the development of $imine_3$tren.

Besides tripodal ligands, macrocyclic ligands play a pivotal role in the activation of dioxygen, as described in chapter 1.6. Especially the previously mentioned 1,4,7-triazacyclononane derivatives have been demonstrated to be a suitable system. Karahalis *et al*. have demonstrated that the ligand $^{t}Bu_3$tacn is capable of forming a stable μ-η^2:η^2-peroxido copper complex, showing remarkable stability in solvents, such as methanol and water.[55]

An essential objective of the second part of the project was the development of an environmentally friendly catalyst that is efficient under mild conditions. To achieve this objective, the 1,4,7-triazacyclononane ligand system was modified to enhance its solubility and reactivity protic solvents like water and methanol. One common strategy is the

implementation of carboxylic acid, phosphonic acid, or sulphonic acid substituents. In this context, a particular focus was on the synthesis of a 1,4,7-triazacyclononane derivative with a sulphonic acid substituent (illustrated in Figure 18). Furthermore, the reactivity of a copper(I) complex with dioxygen, as well as copper(II) complexes with hydrogen peroxide, was investigated, examining the suitability as a potential catalyst for oxygenation reactions.[66]



(^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn

Figure 18: Structure of the investigated water-soluble ligand (^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn.

3. Investigations of metal complexes with the tripodal tetradentate ligand tris(2-(propan-2-ylideneamino)ethyl) amine (imine$_3$tren)

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Lars Schneider, Dr. Jonathan Becker, Prof. Dr. Siegfried Schindler

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ARTICLE

Investigations of metal complexes with the tripodal tetradentate ligand tris(2-(propan-2-ylideneamino)ethyl) amine (imine$_3$tren)

Lars Schneider,[a] Jonathan Becker,[a] and Siegfried Schindler*[a]

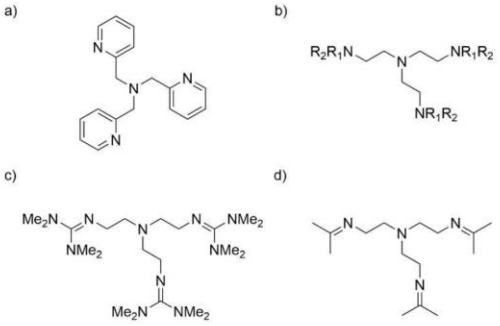
Dedicated to Prof. Kaim, 70th birthday.

The imine ligand tris(2-(propan-2-ylideneamino)-ethyl)amine (imine$_3$tren) had been prepared and characterized. The complexes [Na(imine$_3$tren)(C_3H_6O)]BPh_4, [Cu(imine$_3$tren)]BPh_4, [Zn(imine$_3$tren)(CH_2Cl_2)$_2$]$(BPh_4)_2$ and [Ni(imine$_3$tren)Br]BPh_4 were synthesized and structurally characterized. In contrast to copper(I) complexes with related tripodal ligands [Cu(imine$_3$tren)]BPh_4 reacted quite slowly with dioxygen in solution and no "dioxygen adduct" complex could be spectroscopically detected. Cyclic voltammetry of this complex only showed an irreversible oxidation to a copper(II) species.

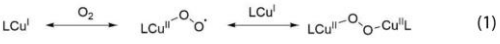
Introduction

Copper dioxygen complexes play an essential role in biological systems.[1,2] In enzymes such as e.g. peptidylglycine-α-hydroxylating monooxygenase (PHM), they are responsible for selective oxygenation of organic substrates.[1,3,4] The catalytic species in PHM consists of an end-on superoxido copper complex and in general "dioxygen adduct" copper complexes are formed in the active sites of the enzymes.[3,5,6] Oxygenation reactions are not only important in biology but furthermore, in industrial applications (e.g. oxygenation of toluene). Therefore, to obtain a better understanding of copper "dioxygen adduct" complexes, model compounds have been developed that resemble the active site of the enzymes.[7] In the past, tripodal ligands have proven to be suitable systems for these investigations.[5,8,9]

Jacobsen *et al.* described the first crystallographic characterized copper "dioxygen adduct" complex, an end-on peroxido copper system that had been studied in great detail based on the ligand tris(2-pyridylmethyl)amine (tmpa, Scheme 1).[10] Similar reactivities have been observed with tren (tris(2-aminoethyl) amine, Scheme 1) based ligands, e.g. tris-(2-dimethylaminoethyl)amine (Me_6tren, Scheme 1, $R_1 = R_2 = CH_3$).[11,12] Copper(I) complexes with this ligand system react with dioxygen according to equation 1. While the dinuclear peroxido complexes are quite persistent at low temperatures the mononuclear superoxido complexes normally can be observed only briefly spectroscopically in stopped-flow measurements.[9,11,13]



Scheme 1. Tripodal ligands tmpa (a), tren, $R_1 = R_2 = H$ (b), TMG_3tren (c) and imine$_3$tren (d).



(1)

Still it was possible for the first time to obtain a resonance Raman spectrum of the *end-on* superoxido complex [Cu(Me_6trenO_2)]$^+$ (characteristic peak at 1122 cm^{-1} for the vibration frequency of ^{16}O–^{16}O).[11] In contrast, a guanidine derivative of tren (tris(tetramethylguanidino)tren = TMG_3tren, Scheme 1) allowed (due to the electronic and steric features of this ligand) to finally isolate and structurally characterize the first example of such a species.[14] The reaction with dioxygen is reversible and [Cu(TMG_3tren)]$^+$ can be regarded as a model compound for the active center in PHM, however it lacks its catalytic properties.[15]

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Introducing sterically more demanding alkyl groups into the tren ligand e.g. isoprop$_3$tren (Scheme 1, R_1 = H, R_2 = isopropyl), also suppresses the formation of dinuclear peroxido complexes according to eq. 1. However, the mononuclear superoxido complexes observed are not stable over time and could not be isolated as solids.[16,17] Obviously alkyl groups in tren alone seem not capable to stabilize the copper superoxido complexes enough for thorough investigations while guanidine groups stabilize it too much to afford catalytic oxygenation reactions. Therefore, it seemed likely that the imine ligand tris(2-(propan-2-ylideneamino)ethyl)amine (imine$_3$tren, Scheme 1), in a way an intermediate ligand type between isoprop$_3$tren and TMG$_3$tren, might be a suitable candidate for optimization of the stability as well as the reactivity of the corresponding copper superoxido complex. Here we now report the synthesis, characterization and reactivity of the copper complex $[Cu(imine_3tren)]^+$ together with a series of other metal complexes with this ligand.

Results and Discussion

Despite the fact that it was quite easy to obtain the ligand isoprop$_3$tren by an in situ reduction of imine$_3$tren (Scheme 1),[16] it turned out to be extremely difficult to synthesize the imine itself in pure form. Previously, imine$_3$tren was synthesized in a template reaction with different iron salts, however, we did not succeed to obtain the free ligand that way.[18] While it was possible to prepare and structurally characterize some iron(II) complexes such as $[Fe(imine_3tren)(OAc)_2]$, different attempts to optimize the reaction with regard to higher yields failed and side reactions turned out to be a big problem. However, these iron complexes did not show any reactivity towards dioxygen. Furthermore, experiments to exchange the central ion or to remove it had failed. An additional problem were the limited yields and side reactions that led to the formation of iron complexes with a macrocyclic ligand (formed during the template reaction).[18,19] During our efforts to obtain pure iron complexes in better yields with this ligand and different iron salts, we synthesized a sodium complex instead. Later on we obtained suitable crystals of $[Na(imine_3tren)]BPh_4$ (**1**) for XRD characterization and the molecular structure of the cation of this complex is presented in Figure 1 (crystallographic data are reported in the Supporting Information) which is coordinated in a distorted trigonal bipyramidal geometry.

Finally, after a large number of experiments it turned out that the ligand can be synthesized using pyrrolidine as an assisting reagent. According to Scheme 2 it was used to activate the ketone acetone and thus promoted the imine formation.[20] The purification was performed by Kugelrohr distillation under an argon atmosphere. Still, it turned out that the product contained a small amount of impurities that could not be removed. However, the product was pure enough to finally allow the preparation of the copper(I) complex by reacting it with $[Cu(MeCN)_4]PF_6$ followed by an anion exchange with sodium tetraphenylborate. The complex $[Cu(imine_3tren)]BPh_4$ (**2**) was obtained as a light yellow crystalline product that could be structurally characterized.

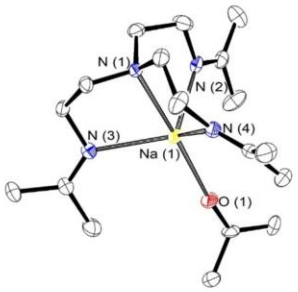
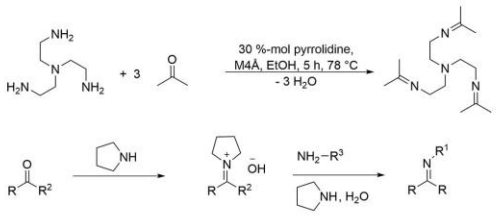


Figure 1. The molecular structure of **1** (the anion and H atoms are omitted for clarity), an acetone molecule is coordinated as an additional ligand.



Scheme 2. Top: Synthesis of the ligand imine$_3$tren with pyrrolidine as a catalyst; bottom: Activation of a substrate by pyrrolidine in general.[20]

The molecular structure of the cation of **2** is presented in Figure 2 (crystallographic data are reported in Tables 1 and 2). Furthermore, it was possible to synthesize and structurally characterize $[Cu(imine_3tren)]OTf$ (see Supporting Information). In **2**, the copper(I) ion is coordinated in a distorted trigonal pyramidal geometry by four N-Donor atoms. No additional acetonitrile molecule is coordinated as an additional ligand that has been observed for some copper(I) complexes with tripodal ligands. Bond lengths and angles (Table 1) are averaged over

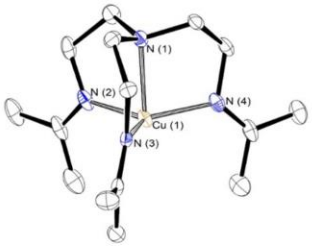


Figure 2. The molecular structure of the cation of **2** (only one of the two complexes in the asymmetric unit is presented).

Table 1. Selected average interatomic distances/Å and angles/° for complex **2**.

Cu(1)–N(1)	2.153	N(1)–Cu(1)–N(2)	85.36
Cu(1)–N(2)	2.006	N(1)–Cu(1)–N(3)	85.26
Cu(1)–N(3)	2.018	N(1)–Cu(1)–N(4)	85.26
Cu(1)–N(4)	1.998	N(3)–Cu(1)–N(2)	123.95
		N(4)–Cu(1)–N(2)	118.5
		N(4)–Cu(1)–N(3)	115.81

Table 3. Selected interatomic distances/Å of [Cu(TMG_3tren)]SbF_6 (a), [Cu(isoprop$_3$tren)]BPh_4 (b), [Cu(imine$_3$tren)]BPh_4 (c) for comparison.[16,21]

	a	b	c
Cu(1)–N(1)	2.175	2.209	2.153
Cu(1)–N(2)	2.048	2.089	2.006
Cu(1)–N(3)	2.048	2.058	2.018
Cu(1)–N(4)	2.048	2.087	1.998

two independent copper(I) complexes in the asymmetric unit. In comparison to the related copper complexes with the tripodal ligands TMG_3tren and isoprop$_3$tren (Table 3), the Cu–N bond lengths in **2** are shorter.

Unfortunately, and in contrast to the complexes [Cu(TMG_3tren)]SbF_6 and [Cu(isoprop$_3$tren)]BPh_4, **2** showed only sluggish reactivity towards dioxygen. Intensive investigations with this complex only led to a simple slow oxidation to a copper(II) complex according to the UV/vis spectrum presented in Figure 3.

Stopped-flow measurements at different temperatures (and under different conditions) did not provide spectroscopic evidence for the formation of the expected *end-on* superoxido copper complex. Neither did other oxidants such as hydrogen peroxide led to any kind of a "dioxygen adduct" complex. This was furthermore supported by cyclic voltammetry: no reversible

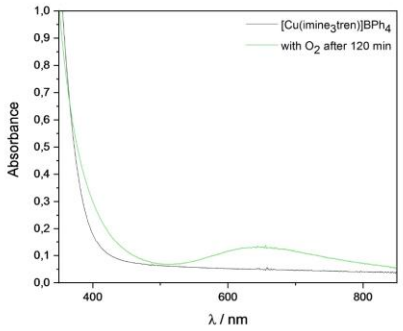


Figure 3. UV/Vis spectra of **2** ([complex] = 1 mmol/L) before and after the reaction with dioxygen in methanol at room temperature.

Table 2. Crystallographic data and structure refinement for **2**, **3** and **4**.

	2	**3**	**4**
CCDC No	2051597	2051598	2051599
Empirical formula	$C_{39}H_{50}BCuN_4$	$C_{65}H_{74}B_2Cl_4N_4Zn$	$C_{39}H_{50}BBrN_4Ni$
M_t	649.18	1140.07	724.26
Crystal size [mm]	0.284×0.107×0.008	0.210×0.152×0.138	0.137×0.104×0.022
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space Group	$P2_1/c$	$P2_1/n$	$P2_1/n$
a [Å]	15.9849(8)	20.0415(10)	16.760(5)
b [Å]	14.7006(8)	11.9321(6)	13.546(3)
c [Å]	29.4309(15)	25.2090(12)	16.843(4)
α [°]	90°	90°	90°
β [°]	90.4444(14)°	104.101(2)°	109.596(10)°
γ [°]	90°	90°	90°
V [Å^3]	6915.7(6)	5846.8(5)	3602.2(16)
Z	8	4	4
F(000)	2768	2400	1520
ρ_{calc} [Mg m^{-3}]	1.247	1.295	1.335
μ [mm^{-1}]	0.665	0.647	1.681
Reflections collected	105479	69940	73231
Independent reflections	13123	10321	6587
R[int]	0.0992	0.0819	0.0947
Scan range θ_{max} [°]	2.330 to 25.681	1.489 to 25.026	1.977 to 25.350
Completeness to θ_{max} [°]	99.9	100.0	100.0
Index ranges	$-19 \le h \le 19$ $-17 \le k \le 17$ $-39 \le l \le 35$	$-23 \le h \le 23$ $-14 \le k \le 14$ $-30 \le l \le 30$	$-20 \le h \le 20$ $-16 \le k \le 16$ $-20 \le l \le 20$
Data/restraints/parameters	13123/0/823	10321/4915/1538	6587/2325/807
R1, wR2 [$I > 2\sigma(I)$]	0.0463, 0.0821	0.0641, 0.1553	0.0383, 0.0799
R1, wR2 [all data]	0.0839, 0.0924	0.1151, 0.1841	0.0696, 0.0921
Goodness-of-fit on F^2	1.023	1.011	1.047
Max./min. el. Dens [eA^{-3}]	0.306, −0.515	0.590, −0.526	0.450, −0.442

oxidation of copper(I) to copper(II) could be observed. See Supporting Information for details on these measurements.

In a way this was not completely unexpected due to the fact that copper(II) complexes with tripodal ligands with imine groups proved to be unstable even as a regular copper(II) complex. For example, imine ligands obtained from tren and benzaldehyde decomposed over time in the presence of air and moisture when coordinated to copper(II) ions.[22] Furthermore, no dioxygen adduct complex was detected when the copper(I) complex with this imine ligand was reacted with dioxygen in contrast to the reaction with Bz_3tren or Bz_3Me_3tren as a ligand that allowed observation of the dinuclear end-on peroxido as well as the mononuclear end-on superoxido copper complex as reactive intermediates.[17,22,23]

With nearly pure $imine_3$tren at hand it furthermore was possible to obtain the corresponding zinc complex by reacting $ZnCl_2$ with $imine_3$tren followed by an anion exchange with sodium tetraphenylborate. The molecular structure of the cation of **3** is depicted in Figure 4 (crystallographic data are reported in Table 2 and 4). A comparison of the molecular structure between the zinc and the copper complex shows similarities in terms of bond angles and lengths and the same coordination geometry (distorted trigonal pyramidal) of both complexes. Cyclic voltammetry of **3** that contains redox inactive Zn(II) was performed in the presence of ferrocene to obtain an idea about the redox behaviour of the ligand system (see Supporting Information). An irreversible oxidation of the ligand in this complex was observed at 1.32 V vs. ferrocene.

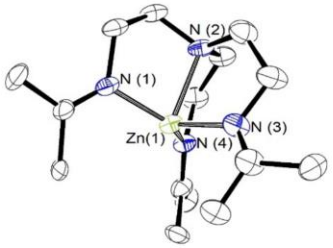


Figure 4. The molecular structure of **3** (anion, solvent molecules and hydrogen atoms are omitted for clarity).

Table 4. Selected interatomic distances/Å and angles/° for complex 3.

Zn(1)–N(1)	1.965(16)	N(1)–Zn(1)–N(2)	86.8(6)
Zn(1)–N(2)	2.141(13)	N(1)–Zn(1)–N(3)	125.1(9)
Zn(1)–N(3)	1,953(14)	N(1)–Zn(1)–N(4)	116.2(10)
Zn(1)–N(4)	2.042(15)	N(2)–Zn(1)–N(3)	85.8(5)
		N(2)–Zn(1)–N(4)	83.1(6)
		N(3)–Zn(1)–N(4)	116.7(9)

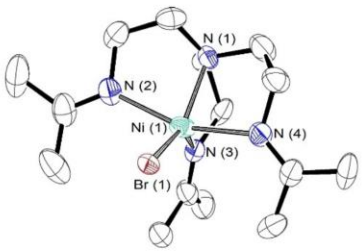


Figure 5. The molecular structure of **4** (not coordinated anion and hydrogen atoms are omitted for clarity).

In addition, a nickel(II) complex could be prepared with nickel(II)bromide and $imine_3$tren followed by an anion exchange with sodium tetraphenylborate. The molecular structure of $[(imine_3tren)NiBr]BPh_4$, **4** (Figure 5) shows a distorted trigonal bipyramidal geometry and the bond angles and lengths are reported in Table 5.

Prior to the successful preparation described herein by applying the free ligand all our attempts to isolate a nickel complex with this ligand had ended with the crystallization of nickel tren complexes instead.[18,19] Furthermore, we did not succeed to crystallize nickel(II) $imine_3$tren complexes with other anions. The molecular structure of **4** is similar to the corresponding iron complex [Fe ($imine_3$tren)(OAc)]OTf reported previously.[18] There is nothing unusual about the UV-vis spectrum of **4** and the cyclic voltammogram is complex as expected (Supporting Information).

Conclusions

Finally, after many attempts (over years) it was possible to obtain the ligand $imine_3$tren in nearly pure form that allowed us to synthesize and structurally characterize zinc, nickel and two copper(I) complexes with this ligand. While the zinc and the nickel complex as redox inactive complexes have been prepared to investigate the coordination behavior with this ligand additionally to iron complexes reported previously,[18] the copper(I) complexes were synthesized to investigate their reactivity towards dioxygen. With a ligand that can be classified in between the pure aliphatic tren alkyl ligands and the guanidine derivatives we had hoped to obtain a copper complex that would form a quite stable but still reactive *end-on* superoxido complex. Unfortunately, this was not the case and in contrast to our expectations no "dioxygen adduct" copper

Table 5. Selected interatomic distances/Å and angles/° for complex **4**.

Ni(1)–N(1)	2.025(6)	N(1)–Ni(1)–N(2)	80.9(3)
Ni(1)–N(2)	2.147(7)	N(1)–Ni(1)–N(3)	87.6(3)
Ni(1)–N(3)	1.984(6)	N(1)–Ni(1)–N(4)	82.2(3)
Ni(1)–N(4)	2.102(6)	N(1)–Ni(1)–Br(1)	134.6(2)
Ni(1)–Br(1)	2.418(3)	N(2)–Ni(1)–N(3)	96.1(4)
		N(2)–Ni(1)–N(4)	158.1(4)
		N(2)–Ni(1)–Br(1)	91.3(4)
		N(3)–Ni(1)–N(4)	97.3(3)
		N(3)–Ni(1)–Br(1)	137.8(2)
		N(4)–Ni(1)–Br(1)	90.4(2)

complex was observed with different oxidants. This might be a consequence of the instability in general of tren imine ligands in combination with copper(II) ions as observed by us and others previously.[22] However, even these negative results are important in obtaining a better understanding for optimizing these copper complex systems in general towards their ability to perform selective oxygenation reactions. We have observed several times that within these complexes only slight ligand modifications can have a dramatic effect on their reactivity and therefore needed to be tested.

Experimental Section

Material and Methods

The used reagents and solvents have the degree of purity p.a and were bought from AcrosOrganics, Alfa Aesar, Merck and Sigma Aldrich or were synthesized as described below. The solvents were distilled over a drying agent under an argon atmosphere and stored in the glove box. Experiments were performed under inert conditions. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using an Avance II 400 MHz WB (Bruker BioSpin GmbH). The measurements were performed at room temperature and the program MestReNova 14.1.2 was used for data analysis. The UV-Vis measurements were carried out at room temperature with an Agilent 8543-spectrometer. Time resolved stopped-flow measurements at low temperatures were performed on a SF-61SX2 and a CSF-61DX2 instrument (Hi-Tech, Salisbury, UK, now TgK Scientific, Bradford-on-Avon, UK). The quartz cell had a diameter of 1 cm and the spectral range is between 300 and 700 nm. For GC-MS measurements a MS 5977B with a 7820A GC-system by Agilent Technologies was used. The IR measurements were perfomed with a FT/IR-4100 instrument (JASCO Deutschland GmbH, Pfungstadt, DE). Details of X-Ray crystal structure determination are reported in the Supporting Information. Electrochemical data were recorded with an e-corder 410 by edaq (eDAQ, Colorado Springs, US) and the program eChem. For cyclic voltammetry a glassy carbon electrode as working electrode, a platinum/titanium electrode (counter electrode) and an Ag/AgCl reference electrode were used. The solvent was acetone or acetonitrile and NBu_4PF_6 or NBu_4BF_4 as conducting salt (0.1 M) was applied. The complex concentrations were adjusted to 1×10^{-3} M and ferrocene was used as an internal standard ($E^0 = 0.49$ V was measured under these conditions).

Synthesis of imine$_3$tren: Tris(2-aminoethyl)amine (1.5 mL, 10 mmol) and molecular sieve 4 Å (5,0 g) was added to ethanol (10 mL) under inert conditions. Pyrrolidine (0.25 mL, 3.0 µmol) and acetone (2.3 mL, 30 mmol) were added dropwise and the solution was heated to reflux for 5 h. The yellow coloured suspension was filtered and the solvent and the pyrrolidine was removed under reduced pressure. After purification, the product could be obtained as a yellow coloured oily liquid with a yield of 40 %. ^{1}H-NMR (δ/ppm): 3.33 (m), 2.83 (m), 1,96 (m), 1,80 (m); ^{13}C-NMR: 167.75, 55.44, 49.70, 29.07, 18.44; GC-MS: 25.353 min.

Synthesis of [Na(imine$_3$tren)(acetone)]BPh$_4$ (1): A solution of imine$_3$tren (79.9 mg, 0.300 mmol), $NaBPh_4$ (103 mg, 0.300 mmol) and acetone (1 mL) was stirred overnight. The next day, the solution was filtered and added dropwise to diethyl ether (18 mL). After 1 day at −40 °C colourless crystals could be obtained, which were suitable for X-Ray analysis. Yield: 83.1 mg (42 %) Anal. Calc. for $C_{42}H_{56}BN_4NaO$: C 75.66 %, H 8.47 %, N 8.40 % found: C 75.58 %, H 8.64 %, N 8.51 %. IR data are reported in the SI.

Synthesis of [Cu(imine$_3$tren)]BPh$_4$ (2): A solution of imine$_3$tren (133 mg, 0.500 mmol) in acetone (1 mL) was added dropwise to a suspension of $[Cu(MeCN)_4]PF_6$ (186 mg, 0.500 mmol) in acetone (1 mL). After stirring for 2 h, the suspension was filtered and solid $NaBPh_4$ (171 mg, 0.500 mmol) was added. The next day the solution was filtered and added dropwise to diethyl ether (18 mL). After one day at −40 °C, yellow crystals could be obtained, which were washed with diethyl ether and dried. The crystals were suitable for X-Ray analysis. Yield: 73°%. Anal. Calc. for $C_{39}H_{59}BCuN_4$: C 72.15 %, H 7.76 %, N 8.63 % found: C 72.12 %, H 7.78 %, N 8.16 %. IR data are reported in the SI.

Synthesis of [Zn(imine$_3$tren)](CH$_2$Cl$_2$)$_2$(BPh$_4$)$_2$: A solution of imine$_3$tren (60,0 mg, 0.225 mmol) in acetone (1 mL) was added dropwise to a suspension of $ZnCl_2$ (30.7 mg, 0.225 mmol) in acetone (1 mL). After stirring for 2 h, solid $NaBPh_4$ (154 mg, 0.450 mmol) was added and it was stirred for overnight at room temperature. The next day, the solution was filtered and added dropwise to diethyl ether (18 mL). After 1 day at −40 °C, a light yellow coloured solid could be obtained. The solvent was removed and the solid was washed with diethyl ether. Then it was dried and dissolved in CH_2Cl_2. The solvent was slowly evaporated in a vial with a cannula inside the glove bove and after a few days light yellow crystals could be obtained, which were suitable for X-Ray analysis. Yield: <1 %. However, the small batch of the non crystalline product turned out to contain impurities and no correct elemental analysis could be obtained. The IR data are reported in the SI.

Synthesis of [Ni(imine$_3$tren)(Br)]BPh$_4$: A solution of imine$_3$tren (79.9 mg, 0.300 mmol) in acetone (2 mL) was added dropwise to a suspension of $NiBr_2$ (65.5 mg, 0.300 mmol) in acetone (1 mL). After stirring for 2 h, solid $NaBPh_4$ (205 mg, 0.600 mmol) was added and it was stirred for overnight at 65 °C. On the next day, the solution was filtered and the solvent was slowly removed. After a few days, a few dark green crystals (which were suitable for X-Ray analysis) together with a powder in an overall yield of 15.9 % could be obtained. The powder contained additionally a small amount of $Ni(BPh_4)_2$ and dichloromethane from washing the sample. Anal. Calc. for $(C_{39}H_{50}BBrN_4Ni)(C_{48}H_{40}B_2Ni)_{1/6}(CH_2Cl_2)_{1/6}$: C 66.29 %, H 6.72 %, N 6.56 % found: C 66.10 %, H 7.05 %, N 6.86%. The IR data are reported in the SI.

Acknowledgments

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Keywords: Copper · nickel · zinc · complexes · dioxygen activation · tripodal ligand

[1] E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 7, 3659–3853.
[2] D. A. Quist, D. E. Diaz, J. J. Liu, K. D. Karlin, *J. Biol. Inorg. Chem.* **2017**, *22*, 2–3, 253–288.

[3] S. T. Prigge, B. A. Eipper, R. E. Mains, L. M. Amzel, *Science* **2004**, *304*, 5672, 864.
[4] P. Chen, J. Bell, B. A. Eipper, E. I. Solomon, *Biochemistry* **2004**, *43*, 19, 5735–5747.
[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*, 3, 2059–2107.
[6] S. Fukuzumi, Y.-M. Lee, W. Nam, *Dalton Trans.* **2019**, *48*, 26, 9469–9489.
[7] a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 8, 6234–6458; b) H. R. Lucas, L. Li, A. A. N. Sarjeant, M. A. Vance, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2009**, *131*, 9, 3230–3245; c) C. Würtele, O. Sander, V. Lutz, T. Waitz, F. Tuczek, S. Schindler, *J. Am. Chem. Soc.* **2009**, *131*, 22, 7544–7545.
[8] a) L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 2, 1013–1045; b) S. Schindler, *Eur. J. Inorg. Chem.* **2000**, *11*, 2311–2326.
[9] S. Itoh, *Acc. Chem. Res.* **2015**, *48*, 7, 2066–2074.
[10] a) R. R. Jacobson, Z. Tyeklar, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 11, 3690–3692; b) Z. Tyeklar, R. R. Jacobson, N. Wei, N. N. Murthy, J. Zubieta, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 7, 2677–2689.
[11] M. Weitzer, S. Schindler, G. Brehm, S. Schneider, E. Hörmann, B. Jung, S. Kaderli, A. D. Zuberbühler, *Inorg. Chem.* **2003**, *42*, 6, 1800–1806.
[12] a) M. Becker, F. W. Heinemann, S. Schindler, *Chem. Eur. J.* **1999**, *5*, 11, 3124–3129; b) Y. J. Choi, K.-B. Cho, M. Kubo, T. Ogura, K. D. Karlin, J. Cho, W. Nam, *Dalton Trans.* **2011**, *40*, 10, 2234–2241.
[13] C. X. Zhang, S. Kaderli, M. Costas, E.-I. Kim, Y.-M. Neuhold, K. D. Karlin, A. D. Zuberbühler, *Inorg. Chem.* **2003**, *42*, 6, 1807–1824.
[14] a) C. Würtele, E. Gaoutchenova, K. Harms, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2006**, *45*, 23, 3867–3869; b) M. Schatz, V. Raab, S. P. Foxon, G. Brehm, S. Schneider, M. Reiher, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2004**, *43*, 33, 4360–4363.
[15] D. Maiti, D.-H. Lee, K. Gaoutchenova, C. Würtele, M. C. Holthausen, A. A. Narducci Sarjeant, J. Sundermeyer, S. Schindler, K. D. Karlin, *Angew. Chem.* **2008**, *120*, 1, 88–91.
[16] J. Will, C. Würtele, J. Becker, O. Walter, S. Schindler, *Polyhedron* **2019**, *171*, 448–454.
[17] K. Komiyama, H. Furutachi, S. Nagatomo, A. Hashimoto, H. Hayashi, S. Fujinami, M. Suzuki, T. Kitagawa, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1, 59–72.
[18] J. Will, L. Schneider, J. Becker, S. Becker, A. Miska, C. Gawlig, S. Schindler, *Isr. J. Chem.* **2020**, *60*, 999–1003.
[19] K. I. Alexopoulou, L. Schneider, A. Miska, C. Würtele, S. Schindler, *Z. Anorg. Allg. Chem.* **2018**, *644*, 14, 759–762.
[20] S. Morales, F. G. Guijarro, J. L. García Ruano, M. B. Cid, *J. Am. Chem. Soc.* **2014**, *136*, 3, 1082–1089.
[21] Christian Würtele, *End-on "copper dioxygen adduct complexes"*, Dissertation, Gießen, **2008**.
[22] M. Schatz, M. Becker, O. Walter, G. Liehr, S. Schindler, *Inorg. Chim. Acta* **2001**, *324*, 1–2, 173–179.
[23] D. Walther, K. Hamza, H. Görls, W. Imhof, *Z. Anorg. Allg. Chem.* **1997**, *623*, 1135–1143.

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4. Investigations on Water-Soluble Copper Complexes with the Sterically Demanding Triazacyclononane Derivative (^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn

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Investigations on Water-Soluble Copper Complexes with the Sterically Demanding Triazacyclononane Derivative (^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn

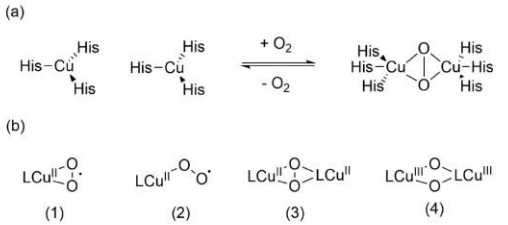
Lars Schneider,[a] Christian Würtele,[a] and Siegfried Schindler*[a]

Related to environmentally friendly productions in the industry, the synthesis of catalysts with designed ligands for solubility in protic solvents and reactivity under mild conditions becomes important. Thus, copper complexes were synthesized with a ligand system that was designed for better solubility in protic solvents. The reactivity of copper complexes with hydrogen peroxide under ambient conditions was investigated in water and in methanol. The formation of a μ-η^2:η^2-peroxide copper complex with a stability of a few minutes was observed in contrast to most related complexes reported in the literature. A kinetic analysis was performed, leading to activation parameters of $\Delta H^{\neq}$: 66 ± 4 kJ·mol^{-1} and $\Delta S^{\neq}$: −5 ± 12 J·K^{-1}·mol^{-1} (in water), a strong indication of an interchange mechanism.

Introduction

Selective oxygenation and oxidation reactions of organic substrates play a key role in industry and nature.[1,2] In industry, for example, the oxygenation of toluene or the production of adipic acid (oxygenation of cyclohexane), a precursor for the synthesis of nylon, are important.[3] In nature, oxidations can occur in active sites of enzymes such as e.g. peptidyl glycine α-hydroxylating monooxygenase (PHM).[4] The copper-mediated enzyme activates dioxygen, followed by hydroxylation of glycine. Another copper-based protein is hemocyanin which is responsible for the oxygen transport in arthropods and mollusks. Here and in the related monooxygenase tyrosinase, copper forms a μ-η^2:η^2-peroxido complex with dioxygen (Scheme 1, (a)).[2] Depending on the system/enzyme, dioxygen can bind differently to the copper center; examples are shown in Scheme 1 (b).[5,6]

These intermediates are generally short-lived and crucial for activating and transferring dioxygen. Model complexes have been developed to investigate these intermediates.[2,5,6] In the past, macrocyclic ligands have proved to be suitable systems for stabilizing copper dioxygen intermediates such as tet b (*rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane), or derivatives of 1,4,7-triazacyclononane (tacn, Figure 1).[7–9]



Scheme 1. (a) Binding of dioxygen by hemocyanin and tyrosinase; (b) examples of known copper complexes obtained by a reaction with dioxygen (charges are omitted; His = histidine, (1) copper side-on superoxido, (2) copper end-on superoxido, (3) dicopper side-on peroxido, (4) dicopper bis-μ-oxido).

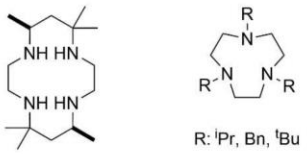


Figure 1. The macrocyclic ligand tet b and derivatives of 1,4,7- triazacyclononane (tacn).

For example, copper complexes with 1,4,7-triazacyclononane derivatives can form different intermediates when reacted with dioxygen, such as μ-η^2:η^2-peroxido or bis-μ-oxido compounds. Even the variation of substituents on the 1,4,7-triazacyclononane is decisive for the reactivity of the respective copper complex.[8–11] Halfen *et al.* were able to detect both a μ-η^2:η^2-peroxido and a bis-μ-oxido complex by investigating [Cu(^{i}Pr$_3$tacn)]OTf with dioxygen at −78 °C. The formation was dependent on the solvent. In dichloromethane the formation of a side-on-peroxido and in THF a bis-μ-oxido complex was favored.[8] In contrast, a [Cu(^{t}Bu$_3$tacn)]OTf complex forms preferably a μ-η^2:η^2-peroxido copper complex with a particular

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stability.[9] As a result, this complex could be crystallized and was structurally characterized. Furthermore, Karahalis *et al.* performed stability tests in different solvents, showing that the copper-dioxygen intermediate was also stable in the protic solvent methanol as well as in water for a certain time. Catalytic oxidation reactions were performed with electron-rich compounds such as 3,5-di-tert butyl catechol.[9]

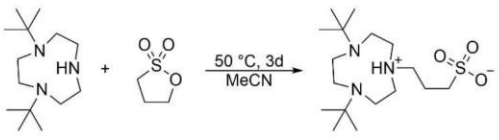
Concerning green/sustainable chemistry, our focus was on modifying the 1,4,7-triazacyclononane system for high solubility and high reactivity in water (or methanol) to develop an environmentally friendly catalyst that could work under mild conditions. The modification of ligands to increase water solubility is not unknown and usually, phosphonic acid, sulphonic acid or carboxylic acid substituents have been used.[12,13] Pasachenik *et al.*, as well as Clegg *et al.*, already investigated the pH dependence of 1,4,7-triazacyclononane derivatives with phosphonic acid substituents. Pasachenik *et al.* measured the pH dependence as a part of the characterization of the copper(II) complexes, while Clegg *et al.* performed NMR studies on small macrocycles with methylenephosphonates.[13,14] Furthermore, soluble 1,4,7-triazacyclononane derivatives are applied in bleaching or in medicine where these ligands function as chelators for copper radioisotopes (radiotracers) for positron emission tomography (PET), as a contrast agent in pH-responsive magnetic resonance imaging or emission computed tomography (SPECT).[15]

Results and Discussion

Synthesis of the Ligand and Characterization of the Complexes

To achieve solubility in protic solvents, one of the *tert*-butyl groups was substituted with a sulphonic group attached through a propyl spacer. For the synthesis of the target ligand, a precursor ligand with two *tert*-butyl groups (^{t}Bu$_2$tacn) was prepared according to Pickel *et al.*[11] This compound was reacted with 1,3-propane sultone to obtain the final ligand (Scheme 2). The synthesis of (^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn **1** required a reaction time of about 3 days and the conditions for this reaction were selected according to a similar reaction in the literature.[16] **1** was obtained as a white powder with a yield of 54%. ^{1}H-NMR and ^{13}C-NMR spectroscopy confirmed the purity of the ligand.

In Figure 2 the molecular structure of **1** is presented. Interestingly, the sulphonic group is fully deprotonated, and one nitrogen is protonated (see SI for further details). The O–S distances and the O–S–O angles confirmed the assumption of a full deprotonation of the sulphonic group. This ligand represented the starting point for the synthesis of several complexes.



Scheme 2. Synthesis of **1**.

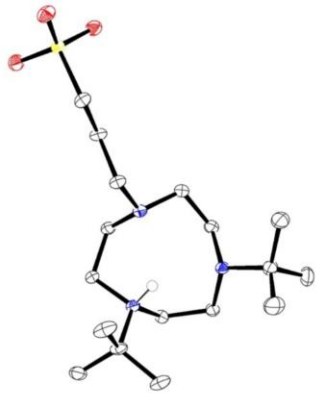


Figure 2. ORTEP Plot of the molecular structure of **1**. Ellipsoids are drawn at 50% probability. Selected bond length (°): S(1)–O(1): 1.4568; S(1)–O(2): 1.4558; S(1)–O(3): 1.4545. Selected bond angles (Å): O(1)–S(1)–O(2): 112.69; O(1)–S(1)–O(3): 112.61; O(2)–S(1)–O(3): 113.31. The N–H hydrogen interacts with the other nitrogen compounds in the ring, these are also shown in Table S4.

Synthesis and Characterization of the Copper (I)/(II) Complexes with 1

The copper(I) complex [Cu(**1**)(MeCN)]OTf (**2**) was synthesized by stirring [Cu(MeCN)$_4$]OTf and **1** for 3 h in dichloromethane at room temperature. The formation of the copper(I) complex could be confirmed by elemental analysis, while, attempts to obtain crystals for structural characterization failed. However, the molecular structure of the closely related complex [Cu(^{t}Bu$_3$tacn)(MeCN)]PF$_6$ was reported previously and supports our formulation.[17a] Furthermore, ^{1}H-NMR spectroscopy confirmed the formation of **2**, but some disproportionation was observed (Figure S14).

The synthesis of the copper(II) complex took 3 d stirring the reactants (**1** and Cu(OTf)$_2$) in dichloromethane. A small unknown precipitate was observed during the synthesis, which was removed by filtration. The main product, obtained as a green solid, was characterized by elemental analysis. The results revealed a formation of a copper complex in a metal cation-to-ligand ratio of 1:2 that we assigned as [Cu(**1**)$_2$(H$_2$O)](OTf)$_2$ (**3**). This has been observed for several copper complexes in the past, but here, it was assumed that the sterically demanding ligand would suppress it. However, one of the sterically demanding *tert*-butyl groups had been replaced by a somewhat less demanding sulfonate group. Furthermore, and most likely the main reason, the ligand was protonated at one nitrogen of the macrocycle, thus making coordination of all nitrogen atoms unlikely. With this the ligand is only coordinated through two

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nitrogen atoms of each ligand and most likely a water molecule (or a triflate anion) as a fifth ligand.

In contrast, it was possible to obtain the molecular structure of a copper(II) complex with **1**, when $Cu(OAc)_2$ was used instead of $Cu(OTf)_2$ under different conditions. The molecular structure of compound [Cu(**1**)]OAc (**4**) is presented in Figure 3. The deprotonated ligand and one acetate are the anions. The copper ion is coordinated in a distorted square pyramidal geometry by the ligands (τ: 0.3) and such a five-coordinated copper(II) complex is in accordance with the literature.[8,17]

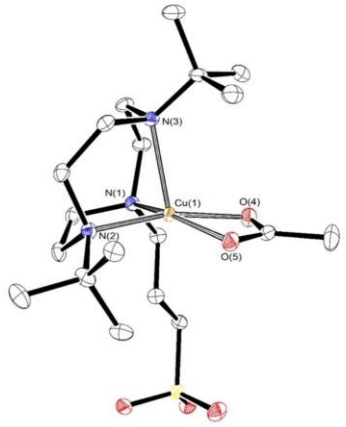

Figure 3. ORTEP Plot of the molecular structure of [Cu(**1**)]OAc, **4**. Ellipsoids are drawn at 50% probability. Selected bond length (Å): Cu(1)–N(1): 2.002; Cu(1)–N(2): 2.044; Cu(1)–N(3): 2.273; Cu(1)–O(4): 2.038; Cu(1)–O(5): 2.020. Selected bond angles (°): N(1)–Cu(1)–N(2): 87.74; N(1)–Cu(1)–N(3): 87.03; N(2)–Cu(1)–N(3): 87.18; N(1)–Cu(1)–O(4): 96.62; N(1)–Cu(1)–O(5): 158.26; N(2)–Cu(1)–O(4): 166.82; N(2)–Cu(1)–O(5): 108.21; N(3)–Cu(1)–O(4): 105.41; N(3)–Cu(1)–O(5): 107.90 ; O(4)–Cu(1)–O(5): 64.67.

Electrochemistry

The redox potentials of the complexes [Cu(**1**)(MeCN)]OTf (**2**) and $[Cu(\mathbf{1})_2(H_2O)](OTf)_2$ (**3**) were investigated by cyclic voltammetry. In protic solvents, we could not observe a redox reaction at all for complex **2** (SI, Figure S1). In contrast, **2** in acetone showed a quasi-reversible redox behavior with an $E_{1/2}$ potential of −0.001 V (Figure 4 and Table 1).

Complex **3** was investigated in H_2O, MeOH, and MeCN and showed quasi-reversible behavior in all three solvents. The cyclic voltammogram of **3** in water is presented in Figure 5, and data are reported in Table 1. The redox potential of complex **3** in methanol is shifted to a much higher positive value compared to the measurement in acetonitrile. The results of the measurements in water were compared with one of the few other examples in which the electrochemistry of a related copper complex (a derivative of tacn as a ligand) was investigated in an aqueous solution.[18] Experiments with the conducting salt $LiClO_4$ were performed with **3** and **4**, but the CVs turned out to be featureless (Figures S4 and S5). In contrast, when KCl was applied as an electrolyte, the excess of chloride anions obviously stabilized the electrochemical system. While

Table 1. Potentials of the copper(I) complex **2** in acetone and the copper(II) complex **3** in water (a), methanol (b, Figure S2) and acetonitrile (c, Figure S3) in comparison with their reference substances $K_3[Fe(CN)_6]$ in H_2O (d) and ($[Fe(Cp)_2]$ in acetone (e) and in MeCN (f) (In V vs. Ag/AgCl).

	E_p^{red} [V]	E_p^{ox} [V]	$E_{1/2}$ [V]	ΔE [V]
2	−0.049	0.047	−0.001	0.096
(a) **3**	−0.193	−0.041	−0.117	0.152
(b) **3**	0.322	0.416	0,369	0.094
(c) **3**	−0.060	0.172	0.056	0.230
(d) $K_3[Fe(CN)_6]$	−0.154	−0.028	−0.091	0.126
(e) $[Fe(Cp)_2]$	0.352	0.422	0.387	0.070
(f) $[Fe(Cp)_2]$	0.382	0.467	0.425	0.085

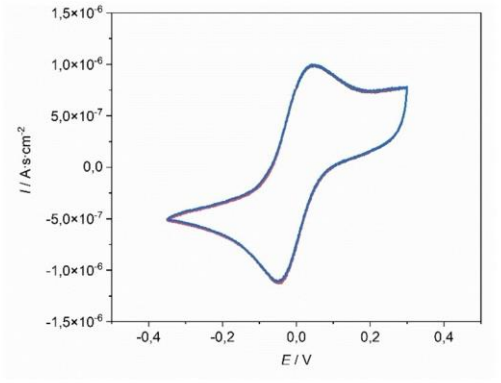

Figure 4. Cyclic voltammogram of the **2** in acetone at 25.0 °C ([complex] = 0.9 mmol/L, $[nBu_4NBF_4]$ = 0.1 mol/L, scan rate: 100 mV/s, cycle number: 3). Ag/AgCl was used as a reference electrode.

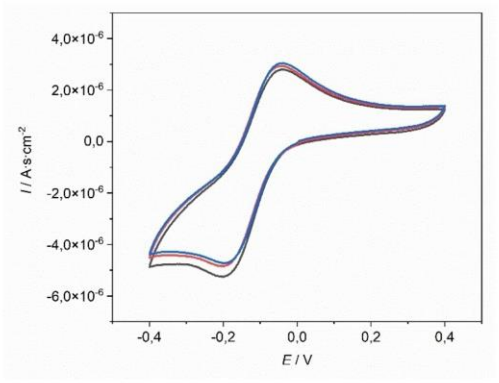

Figure 5. Cyclic voltammogram of **3** in H_2O at 25.0 °C ([complex] = 0.7 mmol/L, ([KCl] = 0.1 mol/L, scan rate: 100 mV/s, cycle number: 3). Ag/AgCl was used as a reference electrode.

the $E_{1/2}$ values of the two complexes cannot be compared to the reported systems due to different reaction conditions, the overall behavior is quite similar. Thus, in principle, it might also be possible to prepare the copper(I) complex by electrolysis.

Reactivity of the Copper complex 2 Towards Dioxygen

Our original hope to spectroscopically observe the formation of a "dioxygen adduct" complex as an intermediate when **2** would be reacted with dioxygen in a protic solvent unfortunately was not fulfilled. Reacting **2** with dioxygen in the protic solvent methanol led to a slow unspecified oxidation of the complex (Supporting Information, Figure S6) to the corresponding copper(II) complex. However, this was not completely surprising because up to now only very few copper(I) complexes are known that react with dioxygen in protic solvents leading to "dioxygen adduct" complexes that can be spectroscopically observed.[19] To the best of our knowledge no copper complex is known so far that reacts in such a way in water in contrast to the copper proteins e.g. hemocyanin.[20] Mainly, this is a problem caused by the kinetics of the reaction. While most likely such a "dioxygen adduct" copper complex is formed, this reaction is rate determining while the consecutive reactions of its decomposition are much faster and thus do not allow the detection of this species. This is often also the case for studies in protic solvents.[21] Furthermore, even the μ-η^2:η^2-peroxido copper complex obtained from [Cu(^{t}Bu$_3$tacn)]OTf complex, while stable for some time in aqueous solutions, cannot be formed directly by reacting the copper(I) complex with dioxygen in water.[9]

To test if a "dioxygen adduct" complex as an intermediate would form in organic solvents, we switched to the non-protic solvent acetone. Here, it was possible to observe the slow formation of a μ-η^2:η^2-peroxido copper complex with characteristic absorbance maxima at 390 and 520 nm that is stable for several hours (Figure 6).

Reactivity of the Copper(II) Complexes with Hydrogen Peroxide in Protic Solvents

Since the reaction of the copper(I) complex **2** with dioxygen in a protic solvent only showed the slow formation of a species that so far could not be characterized, we switched to the reaction of the corresponding copper(II) complex with hydrogen peroxide (an oxidant that can be regarded as an environmentally friendly compound). Therefore, reactions of **3** with hydrogen peroxide in the protic solvents water and methanol were performed. While, in principle, being more interested in the reactions in water, methanol allows us – if necessary – to study these reactions at temperatures as low as −80 °C, thus having a chance to observe short-lived reactive intermediates spectroscopically.

When **3** was reacted with H_2O_2 in water at 25 °C, two absorbance maxima at 380 and 520 nm were observed (Figure 7), clearly indicating the formation of a μ-η^2:η^2-peroxido copper complex. The complex is quite stable at room temperature and a buffer system was not needed. With regard to DNA cleavage the reaction of hydrogen peroxide with copper complexes with pyridyl ligands were investigated in phosphate buffered aqueous solutions by Zhu *et al.*[22] Herein, again not all complexes showed the formation of an intermediate that could be spectroscopically observed. However, especially the reaction behavior of the reported mononuclear complex is quite similar to our system.

In Figure 8 the reaction of **3** with H_2O_2 in methanol is presented. No low-temperature measurements were necessary. Two bands could be observed at 378 nm and 520 nm indicating again the formation of a μ-η^2:η^2-peroxido copper complex at room temperature.

Furthermore, the reactivity of **4** with hydrogen peroxide at 25 °C was investigated in water, and likewise, the formation of a μ-η^2:η^2-peroxido copper complex could be observed (Supporting Information, Figure S8). This clearly shows that complexes **3**

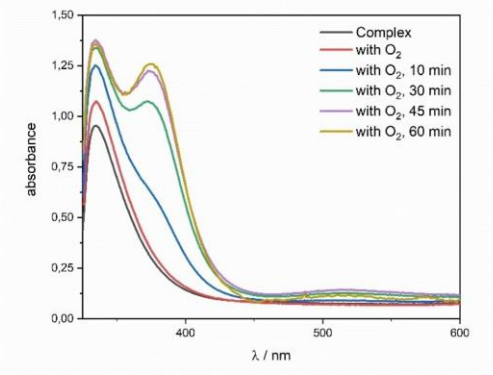

Figure 6. UV-Vis spectra of **2** ([complex] = 0.9 mmol/L) with and without dioxygen in acetone at −30 °C.

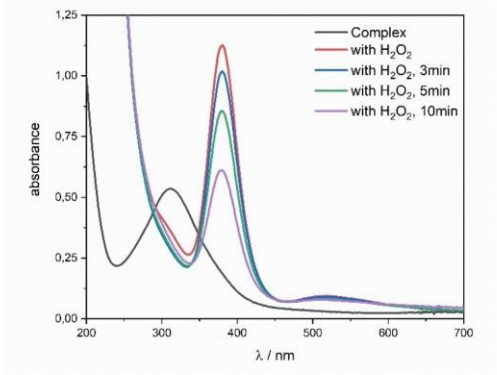

Figure 7. UV-Vis spectra of **3** before and after the reaction with H_2O_2 in water at 25 °C ([complex] = 0.3 mmol/L).

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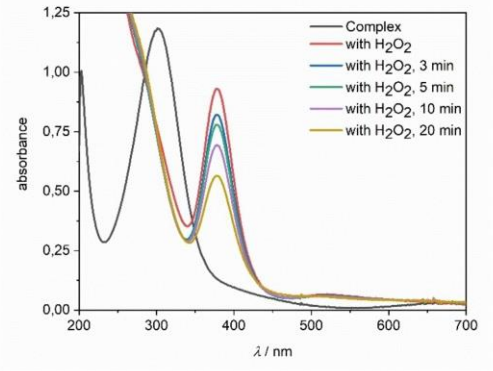


Figure 8. UV-Vis spectra of **3** before and after the reaction with H_2O_2 in methanol at room temperature ([complex] = 0.3 mmol/L).

and **4** will form copper complexes L–Cu–OH_2 in aqueous solutions, which accounts for the identical behavior.

To determine the activation parameters and, thus the mechanism of the copper dioxygen adduct formation, the reaction of **3** with hydrogen peroxide in water was analyzed in more detail. The plot absorbance vs. time (Figure S9) under pseudo-first-order conditions ($[H_2O_2] \gg [\mathbf{3}]$) could be fitted to a single exponential function. Accordingly, it is a first-order reaction in terms of the copper complex concentration. In the next step, the concentration dependence of H_2O_2 was investigated with a plot of k_{obs} vs. the concentration of hydrogen peroxide (Figure 9). The obtained linear correlation without an intercept leads to a first-order reaction related to the H_2O_2 concentration and overall to a rate law of (v = rate of formation of the peroxido complex):

$$v = k\,[\mathbf{3}] \times [H_2O_2]$$

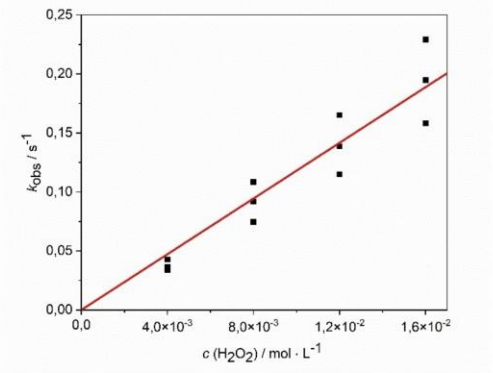


Figure 9. k_{obs} vs. $c(H_2O_2)$ at 15 °C for the reaction of **3** with hydrogen peroxide in water.

To get more detailed information about the reaction mechanism, time-resolved UV-Vis measurements were performed in a temperature range of 10.0 to 35.0 °C under first-order conditions. The activation parameters of the second order rate constant were calculated to $\Delta H^{\ddagger}$: 66 ± 4 kJ·mol^{-1} and $\Delta S^{\ddagger}$: −5 ± 12 J·K^{-1}·mol^{-1} from an Eyring plot (Figure 10).

Despite the large error of the activation entropy, its value close to zero clearly indicates an interchange mechanism of substituting a water molecule with hydrogen peroxide followed by deprotonation and formation of the dinuclear peroxido copper complex according to Scheme 3.

The overall reaction is quite similar to the formation of a peroxido iron complex investigated previously. Here as well the activation entropy is close to 0 and most likely both reactions follow the same mechanism.[23]

Subsequently, first investigations of catalytic oxidation reactions with **3** and hydrogen peroxide with different substrates and in different solvents were made. Herein electron-rich substrates such as 2,4-di-*tert*-butylphenol similar to Karahalis *et al.* were used because of their successful oxidation with the catalyst [Cu(^{t}Bu$_3$tacn)]OTf and dioxygen.[9] Unfortunately, an oxidation of a substrate under our conditions could not be observed.

Conclusions

The results obtained showed that it is possible to develop copper complexes that can form peroxido complexes in aqueous solutions similar to copper enzymes, e.g., tyrosinase. While so far, we have not achieved this formation by the

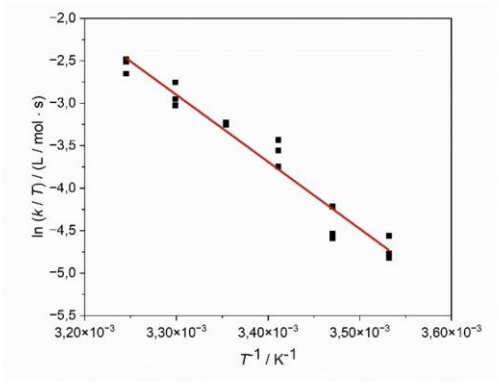
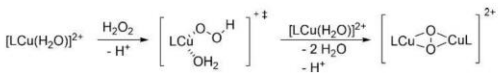


Figure 10. Eyring plot for the reaction of **3** with H_2O_2 between 10 to 35 °C.



Scheme 3. Proposed mechanism for the formation of the μ-η^2:η^2-peroxido copper complex (L:(^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn (anions were omitted for clarity).

reaction of a copper(I) complex with dioxygen, ligand design should lead to this in the near future. Furthermore, despite the fact that we could not observe catalytic activity for our system, again, this will be only a question of time and appropriate ligand design. The complexes reported here might be too stable for performing oxygenation, similar to a copper superoxido complex we reported in the past.[24] However, the quite high stability of these complexes allowed us to study the kinetics of the reaction of the copper(II) complexes with hydrogen peroxide and to postulate a reasonable interchange mechanism. In general, the results imply a step forward in the development of a more environmentally friendly catalyst in the future.

Experimental Section

The used reagents and solvents have the degree of purity p.a. and were bought from Acros Organics, Alfa Aesar, Merck and Sigma Aldrich or were synthesized as described below. The solvents were distilled over a drying agent under an argon atmosphere and stored in the glove box. $[Cu(MeCN)_4]OTf$ and $^tBu_2Htacn$ were prepared according to the literature. Oxygen and water-sensitive experiments were performed under inert conditions. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using an Avance III 400 MHz HD (Bruker BioSpin GmbH, Rheinstetten). The measurements were performed at room temperature and the program MestReNova 14.1.2 was used for data analysis. The UV-Vis measurements were carried out at certain temperatures with an Agilent 8543-spectrometers. For GC-MS measurements a MS 5977B with a 7820A GC-system by Agilent Technologies was used. Electrospray-ionization MS (ESI-MS) were performed with a Bruker Mikro-TOF. For elemental analysis the CHN-Analysator Thermo FlashEA – 1112 Series was used. Electrochemical data were recorded with an e-corder 410 by edaq (eDAQ, Colorado Springs, US) and the program eChem. For cyclic voltammetry, a glassy carbon electrode as a working electrode, a platinum/titanium electrode (counter electrode) and an Ag/AgCl reference electrode were used. As a conducting salt NBu_4BF_4, KCl or $LiClO_4$ (0.1 M) was applied dependent on the solvent. The complex concentrations were adjusted to $1 \cdot 10^{-3}$ M and ferrocene or prussian red were used as an internal standard. Details of X-Ray crystal structure determination are reported in the Supporting Information. CCDC- 2299680 (1) and CCDC- 2299681 (4) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/ products/csd/request/ (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Synthesis of $(^tBu)_2(^nPrSO_3)$Htacn: $(tBu)_2$tacn (400 mg, 1.66 mmol) and 1,3-Propane sultone (204 mg, 1.67 mmol) were added to 25 mL acetonitrile and was heated to 70 °C for 2 d. Afterward, the solvent was removed under reduced pressure and the received solid **1** was recrystallized in acetonitrile/water (324 mg, 0.891 mmol, Yield: 54 %). ^{1}H-NMR(δ/ppm): 3.31–3.15 (m, 4H); 3.00–2.94 (m, 2H), 2.86–2.82 (m, 10H), 1.30 (s, 18H); ^{13}C-NMR (δ/ppm): 64.18, 59.17, 54.81, 53.90, 51.68, 51.12, 30.27, 26.85. Anal. Calc. (%) for $C_{17}H_{37}N_3O_3S$: C 56.16, H 10.16, N 11.56, found: C 55.89, H 10.29, N: 11.53. ESI-MS (m/z) calculated $(C_{17}H_{37}N_3O_3Na^+)$ 386.245; found 386.237 $[M+Na]^+$.

Synthesis of [Cu(**1**)(MeCN)]OTf, **2**: $[Cu(MeCN)_4]OTf$ (15.2 mg, 0.0403 mmol) and **1** (15.0 mg, 0.0412 mmol) were stirred in 4 mL dichloromethane for 3 h and afterward the solvent was removed under reduced pressure. It was received a colourless solid (24.5 mg, 0.0396 mmol, Yield: 98 %). Anal. Calc. (%) for $C_{20}H_{40}CuF_3N_4O_6S_2$: C 38.92, H 6.53, N 9.08, found: C 38.77, H 6.41, N: 8.39.

Synthesis of $[Cu(\mathbf{1})_2(H_2O)](OTf)_2$, **3**: $Cu(OTf)_2$ (36.2 mg, 0.105 mmol) and **1** (38.2 mg, 0.105 mmol) were stirred in 8 mL dichloromethane for 3 days. The resulting green suspension was filtered, and the solvent was removed under reduced pressure. It was received a green solid (49.5 mg, 0.0448 mmol, Yield: 43 %). Anal. Calc. (%) for $C_{36}H_{76}CuF_6N_6O_{13}S_4$: C 39.07, H 6.92, N 7.59, found: C 38.78, H 6.45, N: 7.09.

Synthesis of [Cu(**1**)]OAc, **4**: $Cu(OAc)_2$ (7,5 mg, 0.041 mmol) and **1** (15 mg, 0.041 mmol) were stirred in 1 mL methanol. After 2 h, the resulting turquoise solution was filtered and the solvent was removed. It was received a turquoise solid (18,4 mg, 0,034 mmol, Yield: 82 %). The slow diffusion of Et_2O in the complex solution at −35 °C led to the formation of a crystalline solid 4.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Copper · Water soluble · Hydrogen Peroxide · Kinetics · Time-resolved spectroscopy

[1] a) D. A. Quist, D. E. Diaz, J. J. Liu, K. D. Karlin, *J. Biol. Inorg. Chem.* **2017**, *22*, 253; b) K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, Wiley, **2003**.
[2] E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659.
[3] a) C. Gawlig, S. Schindler, S. Becker, *Eur. J. Inorg. Chem.* **2020**, *2020*, 248; b) C. Würtele, O. Sander, V. Lutz, T. Waitz, F. Tuczek, S. Schindler, *J. Am. Chem. Soc.* **2009**, *131*, 7544; c) H. R. Lucas, L. Li, A. A. N. Sarjeant, M. A. Vance, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2009**, *131*, 3230; d) K. Sato, M. Aoki, R. Noyori, *Science* **1998**, *281*, 1646; e) K. C. Hwang, A. Sagadevan, *Science* **2014**, *346*, 1495; f) U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R. S. Da Cruz, M. C. Guerreiro, D. Mandelli, E. V. Spinacé, E. L. Pires, *Appl. Catal. A* **2001**, *211*, 1.
[4] a) P. Chen, J. Bell, B. A. Eipper, E. I. Solomon, *Biochemistry* **2004**, *43*, 5735; b) S. T. Prigge, B. A. Eipper, R. E. Mains, L. M. Amzel, *Science* **2004**, *304*, 864.
[5] L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013.
[6] 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.
[7] T. Hoppe, S. Schaub, J. Becker, C. Würtele, S. Schindler, *Angew. Chem.* **2013**, *125*, 904.
[8] 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.

[9] G. J. Karahalis, A. Thangavel, B. Chica, J. Bacsa, R. B. Dyer, C. C. Scarborough, *Inorg. Chem.* **2016**, *55*, 1102.
[10] a) S. Mahapatra, S. Kaderli, A. Llobet, Y.-M. Neuhold, T. Palanché, J. A. Halfen, V. G. Young, T. A. Kaden, L. Que, A. D. Zuberbühler, W. B. Tolman, *Inorg. Chem.* **1997**, *36*, 6343; b) J. Cahoy, P. L. Holland, W. B. Tolman, *Inorg. Chem.* **1999**, *38*, 2161; c) W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227.
[11] T. C. Pickel, G. J. Karahalis, C. T. Buru, J. Bacsa, C. C. Scarborough, *Eur. J. Org. Chem.* **2018**, *2018*, 6876.
[12] a) C. F. G. C. Geraldes, M. P. M. Marques, B. d. Castro, E. Pereira, *Eur. J. Inorg. Chem.* **2000**, *2000*, 559; b) W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem. Int. Ed.* **1993**, *32*, 1524.
[13] M. P. Pasechnik, S. P. Solodovnikov, B. K. Shcherbakov, I. B. Goryunova, Y. M. Polikarpov, E. I. Matrosov, M. I. Kabachnik, *Russ. Chem. Bull.* **1992**, *41*, 1377.
[14] W. Clegg, P. B. Iveson, J. C. Lockhart, *J. Chem. Soc. Dalton Trans.* **1992**, 3291.
[15] a) K. Shastri, E. W. C. Cheng, M. Motevalli, J. Schofield, J. S. Wilkinson, M. Watkinson, *Green Chem.* **2007**, *9*, 996; b) J. Kubinec, V. Širůčková, J. Havlíčková, J. Kotek, V. Kubíček, P. Lubal, P. Hermann, *Eur. J. Inorg. Chem.* **2022**, *2022*; c) X. Shen, Y. Pan, G. Liang, *Eur. J. Inorg. Chem.* **2023**, 26, e202200786.
[16] L. Sonnenschein, A. Seubert, *Tetrahedron Lett.* **2011**, *52*, 1101.
[17] a) A. Thangavel, M. Wieliczko, J. Bacsa, C. C. Scarborough, *Inorg. Chem.* **2013**, *52*, 13282; b) R. Haidar, M. Ipek, B. DasGupta, M. Yousaf, L. J. Zompa, *Inorg. Chem.* **1997**, *36*, 3125; c) A. G. Blackman, E. B. Schenk, R. E. Jelley, E. H. Krenske, L. R. Gahan, *Dalton Trans.* **2020**, *49*, 14798.
[18] M. Le Fur, M. Beyler, N. Le Poul, L. M. P. Lima, Y. Le Mest, R. Delgado, C. Platas-Iglesias, V. Patinec, R. Tripier, *Dalton Trans.* **2016**, *45*, 7406.
[19] a) J. E. Bol, W. L. Driessen, R. Y. N. Ho, B. Maase, L. Que, J. Reedijk, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 998; b) T. N. Sorrell, W. E. Allen, P. S. White, *Inorg. Chem.* **1995**, *34*, 952; c) M. Lerch, M. Weitzer, T.-D. J. Stumpf, L. Laurini, A. Hoffmann, J. Becker, A. Miska, R. Göttlich, S. Herres-Pawlis, S. Schindler, *Eur. J. Inorg. Chem.* **2020**, *2020*, 3143.
[20] H.-D. Projahn, S. Schindler, R. van Eldik, D. G. Fortier, C. R. Andrew, A. G. Sykes, *Inorg. Chem.* **1995**, *34*, 5935.
[21] a) M. Becker, F. W. Heinemann, F. Knoch, W. Donaubauer, G. Liehr, S. Schindler, G. Golub, H. Cohen, D. Meyerstein, *Eur. J. Inorg. Chem.* **2000**, *2000*, 719; b) M. Becker, S. Schindler, R. van Eldik, *Inorg. Chem.* **1994**, *33*, 5370.
[22] Q. Zhu, Y. Lian, S. Thyagarajan, S. E. Rokita, K. D. Karlin, N. V. Blough, *J. Am. Chem. Soc.* **2008**, *130*, 6304.
[23] a) L. Westerheide, F. K. Müller, R. Than, B. Krebs, J. Dietrich, S. Schindler, *Inorg. Chem.* **2001**, *40*, 1951; b) T. Nebe, A. Beitat, C. Würtele, C. Dücker-Benfer, R. van Eldik, C. J. McKenzie, S. Schindler, *Dalton Trans.* **2010**, *39*, 7768.
[24] a) D. Maiti, D.-H. Lee, K. Gaoutchenova, C. Würtele, M. C. Holthausen, A. A. Narducci Sarjeant, J. Sundermeyer, S. Schindler, K. D. Karlin, *Angew. Chem.* **2008**, *120*, 88; b) C. Würtele, E. Gaoutchenova, K. Harms, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2006**, *45*, 3867; c) M. Schatz, V. Raab, S. P. Foxon, G. Brehm, S. Schneider, M. Reiher, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2004**, *43*, 4360.

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5. Summary

Oxidation reactions play an important role in the chemical and pharmaceutical industries.[1] However, these processes (see Chapter 1) are still very inefficient due to the use of environmentally harmful catalysts and solvents. Today, efforts are made to improve the efficiency and environmental compatibility of these processes. The reactivities of active enzymes can serve as a valuable model. In these enzymes, oxygenation reactions are selective, occur under mild conditions and transition metals are involved. The peptidyl glycine-α-hydroxylating monooxygenase is an example of these, which is responsible for the hydroxylation of glycine.[26] Inspired by the reactivities observed in these enzymes, model complexes have been developed to imitate their behavior. For instance, the synthesis of copper(I) complexes with TMG_3tren, which enabled the formation of an end-on superoxido complex that exhibits a structural similarity to the copper dioxygen species in the active center of PHM.[50,51] In general, the development of model complexes facilitates the observation, characterization, and examination of the reactivity of diverse copper-dioxygen complexes.

In the first part of this research study, the tripodal tetradentate ligand $imine_3$tren was synthesized, and a variety of metal complexes were examined. This investigation focused on zinc, sodium as well as nickel complexes and a particular interest in copper(I) complexes. The development of $imine_3$tren as a ligand was driven by generating an intermediate form between the known ligands Me_6tren and TMG_3tren. It was anticipated as the missing link between these two ligands and the development of a stable copper complex for oxygen activation. Consequently, it was expected that this ligand would exhibit enhanced reactivity due to the modifications made to the system.

A synthesis of the ligand and the respective copper(I) complex was successfully achieved. However, when the reactivity with dioxygen was investigated, there was no evidence of a copper dioxygen intermediate. A possible explanation may be attributed to the instability of the imine group, a characteristic that has been previously observed in analogous systems.[67]

In the second part of this research study, a ligand system (($^{t}Bu)_2(^{n}PrSO_3$)Htacn) was developed that showed high solubility in water and methanol. Additionally, the reactivity of copper(I) complexes with dioxygen and of copper(II) complexes with hydrogen peroxide in protic solvents was investigated successfully. The ligand was synthesized from the fundamental system 1,4,7-triazacyclononane, with the integration of two tert-butyl groups and a propyl-bridged sulfonic acid group for enhanced solubility in protic solvents. In the following study on the activation of dioxygen with copper(I) complexes, only a copper-

dioxygen species in the form of a μ-η^2:η^2-peroxido copper complex was identified in aprotic solvents. In contrast, the use of copper(II) complexes and hydrogen peroxide also led to the identification of a μ-η^2:η^2-peroxido copper complex in protic solvents, such as water and methanol. Furthermore, the kinetics of the reaction between the copper(II) complex and hydrogen peroxide were examined, which led to the postulation of an interchange mechanism. In summary, it was possible to obtain a copper dioxygen intermediate with the ligand ((^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn) under mild conditions and in environmentally friendly solvents such as water and methanol, which may possess potential for catalyzed oxygenation reactions.

6. Zusammenfassung

Oxidationsreaktionen spielen in der chemischen und pharmazeutischen Industrie eine wichtige Rolle.[1] Diese Prozesse (siehe Kapitel 1) sind jedoch noch sehr ineffizient aufgrund der Verwendung von umweltschädlichen Katalysatoren und Lösungsmittel. Heute wird nach Möglichkeiten gesucht, diese Prozesse effizienter und umweltfreundlicher zu gestalten. Als Vorbild kann die Reaktivität aktiver Zentren von Enzymen dienen, in denen Oxidations-und Oxygenierungsreaktionen selektiv unter milden Bedingungen ablaufen und ein zumeist ein Übergangsmetall involviert ist. Ein Beispiel hierfür ist das Teilenzym Peptidylglycin-*α*-hydroxylierende Monooxygenase, das für die Hydroxylierung von Glycin verantwortlich ist.[26] Nach dem Vorbild des aktiven Zentrums wurden Modellkomplexe entwickelt, die die Reaktivität nachahmen sollen. Ein Beispiel sind Kupfer(I)-Komplexe mit TMG_3tren, mit dem es möglich war einen end-on Superoxido Kupfer-Komplex herzustellen, der in seiner Struktur mit der Sauerstoff-Spezies im aktiven Zentrum von PHM vergleichbar ist.[50,51] Insgesamt ermöglicht die Entwicklung von Modellkomplexen die Beobachtung, Charakterisierung und Untersuchung der Reaktivität verschiedener Kupfer-Sauerstoff-Komplexe.

Im ersten Teil dieser Forschungsarbeit wurde der tripodale tetradentate Ligand $imine_3$tren hergestellt und verschiedene Metallkomplexe untersucht. Neben Zink-, Natrium- und Nickel-Komplexen lag der Hauptfokus hierbei auf Kupfer(I)-Komplexen. Die Entwicklung des Liganden $imine_3$tren erfolgte mit der Intention, eine Zwischenform der bekannten Liganden Me_6tren und TMG_3tren zu schaffen. Es wurde antizipiert, dass dieser Ligand das fehlende Intermediat ist und den entscheidenden Durchbruch bei der Entwicklung eines stabilen Kupferkomplexes für Sauerstoff-Aktivierung bringen würde. Dementsprechend wurde aufgrund der Änderung des Systems eine verbesserte Reaktivität erwartet.

Nach intensiver Forschung gelang die Synthese des Liganden und des entsprechenden Kupfer(I)-Komplexes. Jedoch konnte bei der Untersuchung der Reaktivität mit Sauerstoff kein Sauerstoff-Intermediate nachgewiesen werden. Eine mögliche Erklärung könnte in der Instabilität des Imins liegen, die bereits in anderen Systemen in der Vergangenheit beobachtet wurde.[67]

Im zweiten Teil dieser Forschungsarbeit wurde der Ligand ($(^tBu)_2(^nPrSO_3)$Htacn) entwickelt, welcher sich durch eine hohe Löslichkeit in Wasser und Methanol auszeichnet. Darüber hinaus wurde die Reaktivität von Kupfer(I)-Komplexen mit Sauerstoff sowie von Kupfer(II)-Komplexen mit Wasserstoffperoxid erfolgreich in protischen Lösungsmitteln untersucht. Für den Liganden wurde das Grundsystem 1,4,7-Triazacyclononan genutzt, welches mit zwei tert-Butyl-Gruppen und einer propyl-verbrückten Sulphonsäuregruppe

substituiert war. Die Sulfonsäure-Gruppe diente hierbei der Erhöhung der Löslichkeit in protischen Lösungsmitteln. Im Rahmen der Untersuchung zur Aktivierung von Sauerstoff in Verbindung mit Kupfer(I)-Komplexen des Liganden konnte lediglich eine Kupfer-Sauerstoff-Spezies, in Form eines μ-η^2:η^2-peroxido Kupfer-Komplexes, in aprotischen Lösungsmitteln nachgewiesen werden. Demgegenüber konnte bei der Verwendung von Kupfer(II)-Komplexen und Wasserstoffperoxid ein μ-η^2:η^2-peroxido Kupfer-Komplex in den protischen Lösungsmitteln Wasser und Methanol nachgewiesen werden. Es wurde außerdem die Kinetik der Reaktion des Kupfer(II)-Komplexes mit Wasserstoffperoxid untersucht. Dabei konnte ein Interchange-Mechanismus postuliert werden. Zusammenfassend lässt sich festhalten, dass mit dem Liganden ((^{t}Bu)$_2$(^{n}PrSO$_3$)Htacn) ein Kupfer-Sauerstoff-Intermediate unter milden Bedingungen und in umweltfreundlichen Lösungsmitteln wie Wasser und Methanol nachgewiesen werden konnte, der das Potential für katalytische Oxygenierungsreaktionen haben kann.

7. References

[1] U. Bornscheuer, R. W. Fischer, L. J. Gooßen, R. S. Schlögl, R. S. Schomäcker, S. Schunk, *Katalytische Oxidationsreaktionen als Schlüsseltechnologie*, *Positionspapier*, DECHEMA Gesellschaft für Chemische Technik und Biotechnologie e.V. **2015**.

[2] a) F. Cavani, J. H. Teles, *ChemSusChem* **2009**, *2*, 508; b) A. Gabrič, Ž. Hodnik, S. Pajk, *Pharmaceutics* **2022**, *14*; c) J. N. Armor, *Catalysis Today* **2011**, *163*, 3.

[3] a) C. Gawlig, S. Schindler, S. Becker, *Eur. J. Inorg. Chem.* **2020**, *2020*, 248; b) U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R. S. Da Cruz, M. C. Guerreiro, D. Mandelli, E. V. Spinacé, E. L. Pires, *Appl. Catal. A-Gen.* **2001**, *211*, 1; c) K. C. Hwang, A. Sagadevan, *Science* **2014**, *346*, 1495.

[4] S. van de Vyver, Y. Román-Leshkov, *Catal. Sci. Technol.* **2013**, *3*, 1465.

[5] K. C. Hwang, A. Sagadevan, *Science* **2014**, *346*, 1495.

[6] Y. Wen, X. Wang, H. Wei, B. Li, P. Jin, L. Li, *Green Chem.* **2012**, *14*, 2868.

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

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

[9] 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.

[10] S. Fukuzumi, Y.-M. Lee, W. Nam, *Dalton Trans.* **2019**, *48*, 9469.

[11] M. Pascaly, I. Jolk, B. Krebs, *Chem. Unserer Zeit* **1999**, *33*, 334.

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

[13] J. T. Rubino, K. J. Franz, *J. Inorg. Biochem.* **2012**, *107*, 129.

[14] I. A. Koval, P. Gamez, C. Belle, K. Selmeczi, J. Reedijk, *Chem. Soc. Rev.* **2006**, *35*, 814.

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

[16] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563; b) E. I. Solomon, R. K. Szilagyi, S. DeBeer George, L. Basumallick, *Chem. Rev.* **2004**, *104*, 419.

[17] K. I. Tishchenko, E. K. Beloglazkina, A. G. Mazhuga, N. V. Zyk, *Ref. J. Chem.* **2016**, *6*, 49.

[18] A. Monari, T. Very, J.-L. Rivail, X. Assfeld, *Comput. Theor. Chem.* **2012**, *990*, 119.

[19] I. S. MacPherson, M. E. P. Murphy, *Cell. Mol. Life. Sci.* **2007**, *64*, 2887.

[20] M. E. Cuff, K. I. Miller, K. E. van Holde, W. A. Hendrickson, *J. Mol. Biol.* **1998**, *278*, 855.

[21] C. Eicken, B. Krebs, J. C. Sacchettini, *Curr. Opin. Struc. Biol.* **1999**, *9*, 677.

[22] T. Klabunde, C. Eicken, J. C. Sacchettini, B. Krebs, *Nat. Struct. Biol.* **1998**, *5*, 1084.

[23] a) C. Gerdemann, C. Eicken, B. Krebs, *Acc. Chem. Res.* **2002**, *35*, 183; b) S. K. Dey, A. Mukherjee, *Coordin. Chem. Rev.* **2016**, *310*, 80.

[24] J. P. Klinman, *J. Biol. Chem.* **2006**, *281*, 3013.

[25] S. T. Prigge, A. S. Kolhekar, B. A. Eipper, R. E. Mains, L. M. Amzel, *Science* **1997**, *278*, 1300.

[26] S. T. Prigge, B. A. Eipper, R. E. Mains, L. M. Amzel, *Science* **2004**, *304*, 864.

[27] P. Chen, E. I. Solomon, *J. Am. Chem. Soc.* **2004**, *126*, 4991.

[28] P. Chen, J. Bell, B. A. Eipper, E. I. Solomon, *Biochemistry* **2004**, *43*, 5735.

[29] S. Itoh, *Acc. Chem. Res.* **2015**, *48*, 2066.

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

[31] a) D. A. Quist, D. E. Diaz, J. J. Liu, K. D. Karlin, *J. Biol. Inorg. Chem.* **2017**, *22*, 253; b) A. Hoffmann, M. Wern, T. Hoppe, M. Witte, R. Haase, P. Liebhäuser, J. Glatthaar, S. Herres-Pawlis, S. Schindler, *Eur. J. Inorg. Chem.* **2016**, *2016*, 4744.

[32] S. Kim, C. Saracini, M. A. Siegler, N. Drichko, K. D. Karlin, *Inorg. Chem.* **2012**, *51*, 12603.

[33] W. Keown, J. B. Gary, T. D. P. Stack, *J .Biol. Inorg. Chem.* **2017**, *22*, 289.

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

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

[36] M. Weitzer, M. Schatz, F. Hampel, F. W. Heinemann, S. Schindler, *J. Chem. Soc., Dalton Trans.* **2002**, 686.

[37] V. Raab, J. Kipke, O. Burghaus, J. Sundermeyer, *Inorg. Chem.* **2001**, *40*, 6964.

[38] K. Komiyama, H. Furutachi, S. Nagatomo, A. Hashimoto, H. Hayashi, S. Fujinami, M. Suzuki, T. Kitagawa, *B. Chem. Soc. Jpn.* **2004**, *77*, 59.

[39] Z. Tyeklar, R. R. Jacobson, N. Wei, N. N. Murthy, J. Zubieta, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 2677.

[40] P. Gamez, I. A. Koval, J. Reedijk, *Dalton Trans.* **2004**, 4079.

[41] H. R. Lucas, L. Li, A. A. N. Sarjeant, M. A. Vance, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2009**, *131*, 3230.

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

[43] D. Maiti, J. S. Woertink, A. A. Narducci Sarjeant, E. I. Solomon, K. D. Karlin, *Inorg. Chem.* **2008**, *47*, 3787.

[44] M. Weitzer, S. Schindler, G. Brehm, S. Schneider, E. Hörmann, B. Jung, S. Kaderli, A. D. Zuberbühler, *Inorg. Chem.* **2003**, *42*, 1800.

[45] M. Schatz, V. Raab, S. P. Foxon, G. Brehm, S. Schneider, M. Reiher, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2004**, *43*, 4360.

[46] C. Würtele, O. Sander, V. Lutz, T. Waitz, F. Tuczek, S. Schindler, *J. Am. Chem. Soc.* **2009**, *131*, 7544.

[47] T. Brückmann, J. Becker, C. Würtele, M. T. Seuffert, D. Heuler, K. Müller-Buschbaum, M. Weiß, S. Schindler, *J. Inorg. Biochem.* **2021**, *223*, 111544.

[48] T. Brückmann, J. Becker, K. Turke, B. Smarsly, M. Weiß, R. Marschall, S. Schindler, *Z. anorg. allg. Chem.* **2021**, *647*, 560.

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

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

[51] D. Maiti, D.-H. Lee, K. Gaoutchenova, C. Würtele, M. C. Holthausen, A. A. N. Sarjeant, J. Sundermeyer, S. Schindler, K. D. Karlin, *Angew. Chem. Int. Ed.* **2008**, *47*, 82.

[52] R. D. Hancock, A. E. Martell, *Comment. Inorg. Chem.* **1988**, *6*, 237.

[53] A. P. Cole, V. Mahadevan, L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Inorg. Chem.* **2005**, *44*, 7345.

[54] 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.

[55] G. J. Karahalis, A. Thangavel, B. Chica, J. Bacsa, R. B. Dyer, C. C. Scarborough, *Inorg. Chem.* **2016**, *55*, 1102.

[56] I. Garcia-Bosch, R. E. Cowley, D. E. Díaz, M. A. Siegler, W. Nam, E. I. Solomon, K. D. Karlin, *Chem. Eur. J.* **2016**, *22*, 5133.

[57] T. Hoppe, S. Schaub, J. Becker, C. Würtele, S. Schindler, *Angew. Chem. Int. Ed.* **2013**, *52*, 870.

[58] a) K. Ray, F. F. Pfaff, B. Wang, W. Nam, *J. Am. Chem. Soc.* **2014**, *136*, 13942; b) J. Cho, R. Sarangi, W. Nam, *Acc. Chem. Res.* **2012**, *45*, 1321.

[59] M. Nappa, J. S. Valentine, A. Miksztal, H. J. Schugar, S. S. Isied, *J. Am. Chem. Soc.* **1979**, *101*, 7744.

[60] S. Mahapatra, J. A. Halfen, E. C. Wilkinson, L. Que, W. B. Tolman, *J. Am. Chem. Soc.* **1994**, *116*, 9785.

[61] W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227.

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

[63] S. Mahapatra, J. A. Halfen, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11575.

[64] A. Thangavel, M. Wieliczko, J. Bacsa, C. C. Scarborough, *Inorg. Chem.* **2013**, *52*, 13282.

[65] J. Will, C. Würtele, J. Becker, O. Walter, S. Schindler, *Polyhedron* **2019**, *171*, 448.

[66] a) C. F. G. C. Geraldes, M. P. M. Marques, B. d. Castro, E. Pereira, *Eur. J. Inorg. Chem.* **2000**, *2000*, 559; b) M. P. Pasechnik, S. P. Solodovnikov, B. K. Shcherbakov, I. B. Goryunova, Y. M. Polikarpov, E. I. Matrosov, M. I. Kabachnik, *Russ. Chem. Bull.* **1992**, *41*, 1377; c) W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem. Int. Ed.* **1993**, *32*, 1524.

[67] M. Schatz, M. Becker, O. Walter, G. Liehr, S. Schindler, *Inorg. Chim. Acta* **2001**, *324*, 173.