Summary, Conclusions and Future Perspectives
9.1. Summary

The global aim of the research discussed in this thesis is the design, synthesis and characterization of suitable structural and functional models for the enzyme [NiFe] hydrogenase. Yet the thesis also describes models of other nickel-containing enzymes resulting from serendipitous findings along the main interest of the thesis.

The first part of Chapter 1 portrays a brief overview of nickel-containing enzymes with a special emphasis on the class of hydrogenases. The structural and functional properties of the enzymes and of specifically selected model complexes are also overviewed. Chapter 1 concludes with the scope of the thesis and a short summary of the strategies proposed for the structural and functional modeling of [NiFe] hydrogenases.

The design, syntheses and characterizations of new tetradeinate dithioether-dithiolate ($S_2S'$) ligands and bidentate thioether-thiolate (SS') ligands are presented in Chapter 2; schemes of the syntheses of the ligands and simplified code notations for the ligands and of their precursors, and intermediates have also been provided. The tetradeinate ligands are designed/selected in a way that they possess systematically varied steric and electronic properties. The ligands H$_2$ebss, H$_2$pbsss and H$_2$xbss have ethyl, propyl and xylyl bridging groups, respectively. Also, these three ligands are substituted with two electron-donating methyl groups on the $\beta$-carbons of ethylthiolate arms in order to vary the electronic properties (H$_2$ebsms, H$_2$pbsms and H$_2$xbssms).

The bidentate ligands possess different groups such as benzyl, 4-methylphenyl, 4-chlorophenyl, isobutyl and $n$-hexyl groups on the thioether sulfur, and have been prepared with or without the two methyl groups on the $\beta$-carbon of the ethylthiolate arm.

A library of new low-spin nickel complexes of new tetradeinate dithioether-dithiolate ligands is reported in Chapter 3. Two of these complexes, [Ni(ebsms)]$_2$ and [Ni(pbsms)], have been characterized by X-ray crystallography. [Ni(ebsms)]$_2$ is a coplanar dinuclear complex with two slightly distorted square-pyramidal NiS$_5$ units bridged together by two thiolates. A surprisingly short Ni–$S_{\text{thioether}}$ distance (2.139(3) Å) and interesting Ni⋯H$_{\text{Me}}$ interactions (2.66 and 2.74 Å) are also observed in the crystal structure. [Ni(pbsms)] is a mononuclear compound with square-planar structure, similar to the already reported structures of [Ni(pbss)] and [Ni(xbsms)]. The Ni–S$_{\text{thiolate}}$ distances in [Ni(pbsms)] are longer than the Ni–S$_{\text{thioether}}$ distances as exhibited by [Ni(pbss)], but which is in contrast to the usual observation. These low-spin nickel complexes were reacted with [Fe(Cp)(CO)$_2$I] to obtain [NiFe] complexes, including one reported complex; their electrocatalytic properties towards
proton reduction are also reported in Chapter 3. All the six [NiFe] complexes show electrocatalytic activity to produce dihydrogen in the presence of acetic acid as a source of protons. Catalytic reduction of $\text{H}^+$ is observed at potentials as low as $-1.19 \text{ V vs. Ag/AgCl}$ for [Ni(pbss)Fe(CO)Cp](PF$_6$) in acetonitrile. It was found that increased flexibility of the bridge of the ligands leads to electrocatalysts that need lower overpotentials whereas electron-donating dimethyl-substitution of the ligands leads to the need of higher overpotentials.

The lessons learned from Chapter 3 led to the use of two bidentate SS’-donor ligands instead of one tetradentate $S_2S'_2$-donor ligand, as an increase in flexibility in the NiS$_4$ coordination sphere favored the lower overpotentials in the proton reduction. Chapter 4 is devoted to analogous [NiFe] complexes based on new [Ni(SS’)$_2$] complexes. The [Ni(SS’)$_2$] complexes reported in this chapter were obtained by the reaction of Ni(acac)$_2$ with bidentate thioether-thiolate ligands reported in Chapter 2. The ligands substituted with two methyl groups yield stable mononuclear complexes whereas the ligands without methyl groups yield hexanuclear ([Ni$_6$(cpss)$_2$]) or insoluble oligonuclear ([Ni(mpss)]$_n$) complexes. These low-spin nickel complexes were reacted with [Fe(Cp)(CO)$_2$I] in dichloromethane with slow flow of argon gas, to obtain [NiFe] complexes; their electrocatalytic properties towards proton reduction are also reported in Chapter 3.

The electrocatalytic proton reduction potential of these [NiFe] compounds, $E_{\text{HER}}$ is indeed found to be lower than that of the complexes with tetradentate ligands reported in Chapter 3 ($\sim -0.9 \text{ V vs. Ag/AgCl}$). However, the stability of these [Ni(SS’)$_2$Fe(C$_5$H$_5$)(CO)][PF$_6$] complexes is lower than that of the [Ni(S$_2S'_2$)Fe(C$_5$H$_5$)(CO)][PF$_6$] complexes in the presence of protic acids; the complexes [Ni(bsms)$_2$Fe(C$_5$H$_5$)(CO)][PF$_6$] and [Ni(cpsms)$_2$Fe(C$_5$H$_5$)(CO)][PF$_6$] are readily decomposed in the presence of acid. This is likely due to the fact that the thioether sulfurs of the [Ni(SS’)$_2$Fe(C$_5$H$_5$)(CO)][PF$_6$] complexes are easily protonated, which leads to the decomposition.

In order to make more stable and improved electrocatalysts the [Ni(S$_2S'_2$)] complexes were reacted with the [Ru(bpy)$_2$(EtOH)$_2$] moiety and a new class of complexes with the general formula [Ni(S$_2S'_2$)Ru(bpy)$_2$](PF$_6$)$_2$ have been obtained in good yield; their structures and proton reducing abilities are presented in Chapter 5. The complex [Ni(pbss)Ru(bpy)$_2$](PF$_6$)$_2$ has been characterized by X-ray crystallography, whereas all the three [Ni(S$_2S'_2$)Ru(bpy)$_2$](PF$_6$)$_2$ complexes reported in Chapter 5 have been characterized using 1D and 2D NMR techniques; the complex [Ni(pbsms)Ru(bpy)$_2$](PF$_6$)$_2$ is found to have two conformers in solution due to the dynamical motion of the dimethylethylene arms. These three complexes are also found to be active in proton
reduction (−1.43 to −1.01 V vs. Ag/AgCl) and are stable in the presence of protic acids such as trifluoroacetic acid for months.

A serendipitously obtained hexanuclear Ni₆-thiolate metallacrown, its reactivity with iodine, protonation studies and the proton reduction abilities are presented in Chapter 6. Two square-pyramidal NiS₅ units and four NiS₄ square-planar units are bridged together via thiolates of the Hcpps ligands in the solid state structure, whereas all the six nickel(II) centers are found to have NiS₅ square-pyramidal geometry in solution as studied by ¹H NMR spectroscopy.

The hexanuclear metallacrown [Ni₆(cpss)₁₂] has been demonstrated to functionally resemble the [NiFe] hydrogenases. Protonation of the [Ni₆L₁₂] cluster was studied employing ¹H NMR spectroscopy and ESI-MS by the sequential additions of dichloroacetic acid or p-toluenesulfonic acid monohydrate into solutions of [Ni₆L₁₂] in CD₂Cl₂ and DMF-d₇, respectively; protonation takes place on the thioether sulfurs available in the metallacrown. The electrochemical properties of both the parent and protonated [Ni₆L₁₂] species have been studied using cyclic voltammetry. Protonated [Ni₆L₁₂] shows an interesting electrocatalytic property as it catalyses the reduction of protons into molecular hydrogen in the presence of protic acids, such as dichloroacetic acid and chloroacetic acid at −1.5 and −1.6 V vs Ag/AgCl in DMF, respectively. A catalytic cycle has been proposed based on the observations from the NMR spectroscopic and electrochemical studies of the metallacrown. The behavior of this electrocatalyst was further studied by its immobilization on the surface of a pyrolytic graphite electrode; reduction of a dichloroacetic acid solution in acetonitrile on the surface of the modified electrode occurs at 220 mV more positive potential compared to the unmodified electrode.

The reaction of the mononuclear complex [Ni(mpsms)₂] with Cul yielded a heterooctanuclear cage of formula [{Ni(mpsms)₂}₂(Cul)₆], possessing interesting structural features including Ni⋯H anagostic interactions, which is reported in Chapter 7. The molecular structure of the [Ni₂Cu₆] cluster is determined by X-ray crystallography, which shows two distorted square-planar NiS₄, four trigonal-planar CuI₂S and two tetrahedral CuI₂S₂ sites; the tetrahedrally distorted NiS₄ units resemble the nickel centre of the [NiFe] hydrogenase and the Ni–S–Cu–I cage structure is compared with the bifunctional enzyme carbon monoxide dehydrogenase/acetyl-coenzyme A synthase (CODH/ACS). Furthermore, novel anagostic Ni⋯H interactions are observed in the X-ray crystal structure of the molecular cage and have been confirmed to pertain in solution, employing variable temperature ¹H NMR spectroscopic studies. These Ni⋯H interactions have been observed for the first time in a complex of NiS₄ coordination sphere.
A light-induced C–S bond cleavage in a nickel thiolate complex with relevance to the function of methyl-coenzyme M reductase (MCR) is presented in Chapter 8. The dinuclear complex [Ni(ebsms)]$_2$ is found to be light-sensitive; the yield of the complex was drastically improved when it was synthesized in dark. Upon stirring a toluene solution of the complex [Ni(ebsms)]$_2$ in the presence of UV light, it yields another dinuclear complex [Ni(S$_2$S')]$_2$ and oligoisobutylene sulfide through a C–S bond cleavage reaction, proposedly provoked by the light-induced formation of a Ni(I)-S' radical species in solution. The presence of Ni(I)-S' radical character in [Ni(ebsms)]$_2$ is indicated by the unusual disorder and the short Ni–S distance (2.139(3) Å) as observed in the X-ray crystal structure of [Ni(ebsms)]$_2$, the broad signals observed in the $^1$H NMR spectra of [Ni(ebsms)]$_2$, and the products obtained from the light-induced C–S bond cleavage reaction. The results are discussed in the light of the function of methyl coenzyme M reductase.

9.2. General Discussion, Conclusions and Future Perspectives

In contrast to the many stable nickel(II), [NiFe] and [NiRu] complexes that are reported to have tetradentate N$_2$S$_2$-donor or bidentate NS-donor ligands, the complexes reported in this thesis have been synthesized using tetradentate S$_2$S'_2-donor and bidentate SS'-donor ligands.$^{1-5}$ The thiouronium salts of both tetradentate S$_2$S'_2-donor and bidentate SS'-donor ligands have been synthesized in good yield. These thiouronium salts are found to be air stable and odorless crystalline solids, which can be stored for many months without noticeable changes; this helped to circumvent the synthesis and manipulation of oxidation sensitive, unstable and pungent smelly thiol compounds. The synthesis route followed in this thesis may be employed to make a whole range of new ligands and their complexes. Even though all the [Ni(S$_2$S')]$_2$ complexes could be synthesized in toluene, some complexes have been obtained in better yield when using different solvents such as THF ([Ni(ebss)] and [Ni(xbss)]). Likewise, the [Ni(SS')$_2$] complexes could be formed in ethanol or in toluene; however, the synthesis in toluene showed better yields and needed no further purifications.

Although not all of the X-ray crystal structures of the [Ni(S$_2$S')]$_2$ and [Ni(SS')$_2$] complexes are known, in general it is assumed that these complexes acquire slightly distorted square-planar NiS$_4$ coordination spheres. The [Ni(S$_2$S')]$_2$ complexes possess enforced cis orientation of thiolates and thioether donors whereas the [Ni(SS')$_2$] complexes possess highly preferred trans orientation.$^6$ However, the trans oriented [Ni(SS')$_2$] complexes acquire cis orientation upon reaction with other moieties such as FeX$_2$, ZnX$_2$ (X = Cl, Br, I), CuI, [Fe$_2$(CO)$_9$], [Fe(CO)$_2$(NO)$_2$], [Fe(CO)$_4$I$_2$], [Fe(CO)$_5$] and [Fe(C$_5$H$_5$)(CO)]$^7$. Even though the new [Ni(S$_2$S')Fe(C$_5$H$_5$)(CO)](PF$_6$) and
[Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes are not structurally characterized, the combination of data obtained from various techniques such as ESI-MS spectrometry, FTIR spectroscopy and elemental analysis, and the reported structure of [Ni(pbss)Fe(C₅H₅)(CO)](PF₆) are helpful in understanding the structures of these complexes.¹ The ¹H NMR spectroscopy and the known X-ray crystal structure of [Ni(pbss)Ru(bpy)₂](PF₆)₂ were very helpful in elucidating the structure of the three [Ni(SS')₂Ru(bpy)₂](PF₆)₂ complexes in solution.

All the six [Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes are found to be active as electrocatalysts in proton reduction and also found to be relatively stable in higher concentrations of acetic acid. The increase in the flexibility of the NiS₄ coordination sphere favors the lower negative $E_{\text{HER}}$ values whereas the electron-withdrawing dimethyl groups tend to shift the $E_{\text{HER}}$ values to higher negative. All the three active [Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes reduce protons around −0.9 V vs. Ag/AgCl; this less potential ($E_{\text{HER}}$) is negative than that of the [Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes. It appears – according to the available observations – that the [Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes readily undergo protonation on the thioether sulfurs of the bidentate SS'-donor ligands; this protonation is advantageous, as this behavior assists in reducing the complexes easily; on the other hand it is disadvantageous because it leads to the decomposition of the complexes [Ni(bsms)₂Fe(C₅H₅)(CO)](PF₆) and [Ni(cpsms)₂Fe(C₅H₅)(CO)](PF₆).

As it was found that increased flexibility of tetradeptate ligands favors proton reduction at lower potentials, but bidentate ligands are too flexible leading to decomposition, future studies should be directed to the synthesis of more flexible tetradeptate ligands comprising electron-withdrawing groups. In this view tetradeptate P₂S₂-donor ligands also may be useful, as the electronic and steric properties of phosphine ligands in general are easily modified.

The three active [NiRu] complexes are found to work at −1.01, −1.06 and −1.43 V vs. Ag/AgCl with promising stability in the presence of protic acids. Surprisingly, all three [Ni(SS')₂Ru(bpy)₂](PF₆)₂ complexes are stable in the presence of 20 equivalents of trifluoroacetic acid for months as determined by ESI-MS spectrometry, showing the high acid tolerance of the complexes. A preliminary study yielded the complexes [Ni(pbss)Ru(tpa)₂](PF₆)₂ and [Ni(pbsms)Ru(tpa)₂](PF₆)₂ (Fig. 9.1). The tripicolylamine (tpa) ligand may dissociate one of the pyridyl rings, opening a catalytic site at the ruthenium center.¹² These [NiRu] complexes open a new avenue as they comprise both redox-active and photo-active moieties directly connected together. Future studies including the photoelectrocatalytic properties of these complexes may be highly interesting, especially in view of the development of a hydrogen economy.
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Fig. 9.1. Perspective views of new [Ni(S₂S')₂Ru(tpa)](PF₆)₂ complexes synthesized as models for [NiFe] hydrogenases.¹

Owing to the stability of the [Ni₆(cpss)₁₂] and the simple ¹H NMR spectra as compared to the other reported complexes, protonation studies were successfully performed shedding light on the mechanism of electrocatalytic proton reduction. The thioether sulfurs of the ligands Hcpss in the complex [Ni₆(cpss)₁₂] were found to be readily protonated; this observation explains both the electrocatalytic properties of this hexanuclear complex and the acid induced decomposition of the [Ni(SS')₂Fe(C₅H₅)(CO)](PF₆) complexes.

The heterooctanuclear cage [{Ni(mpsms)₂}₂(CuI)₆] proved the robustness of the [Ni(SS')₂] complexes reported in this thesis in view of the synthesis of suitable models for hydrogenases and as well for other nickel containing enzymes. Further investigation and utilization of the secondary contacts such as Ni···H interactions observed in this cage structure may pave the way for the synthesis of future mimics with self-stabilizing intra or intermolecular frameworks.

9.3. References

Chapter 9


