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1 **Formate Dehydrogenases Mimics as Catalysts for Carbon Dioxide Reduction**

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8 9 **Abstract**

10 Formate dehydrogenases (FDH) catalyze reversibly the interconversion of CO₂ to formate.
11 They belong to the family of molybdenum and tungsten-dependent oxidoreductase. For
12 several decades, scientists have been synthesizing structural and functional model complexes
13 inspired by these enzymes. These studies not only allow for finding certain efficient catalysts,
14 but also in some cases to better understand the functioning of the enzymes. However, FDH
15 models for catalytic CO₂ reduction are less studied compared to the oxygen atom transfer
16 (OAT) reaction. Herein, we present recent results of structural and functional models of FDH.

17 **Keywords**

18 formate dehydrogenases, structural models, functional models, dithiolene complexes, carbon
19 dioxide Reduction

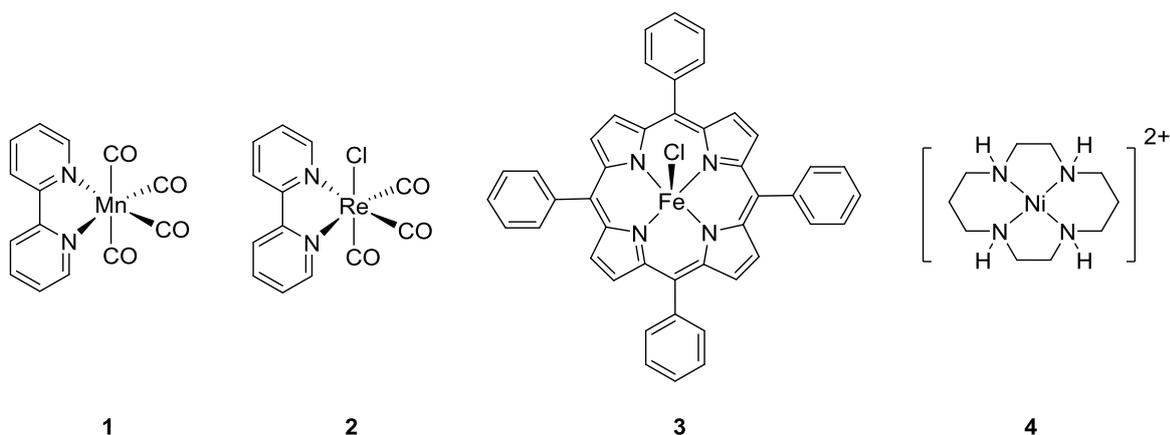
20 21 **I. Introduction**

22 Storage of diluted and intermittent sources of energy such as solar and wind energy is
23 a great challenge of the 21st century. It can be accomplished by the conversion of solar or
24 wind electricity into chemical energy, via formation of chemical bonds that can durably store
25 the energy. For this reason, the reduction of CO₂ is particularly appealing since, through its
26 transformation into a variety of energy-dense carbon compounds, it not only allows energy
27 storage but also gives access to fuels, allowing the use of renewable energy as a source of
28 energy without important shift of technology. The reduction of CO₂ can also be used as a

29 carbon feedstock to form precursors for organic synthesis, leading to valuable organic
30 compounds useful for the chemical industry [1, 2].

31

32 CO_2 is a thermodynamically stable molecule. Furthermore, its reduction implies multi-
33 electron and multi-proton transfers which results in very low kinetics. As a consequence
34 catalysts are absolutely needed. If heterogeneous materials are generally considered as more
35 stable and more efficient catalysts for CO_2 reduction, molecular metal complexes can offer
36 more tunability and selectivity [3]. For these reasons, the molecular approach has been
37 extensively developed over the last decades. Among the most remarkable and studied
38 complexes reported in the literature, one can mention Re- and Mn-bipyridine complexes (**1**
39 and **2**), metal complexes using N-based macrocycles, such as porphyrins **3**, phthalocyanins and
40 quaterpyridines, and Ni-cyclam complex **4** (Figure 1) [4]. Nevertheless, the library of
41 complexes able to catalyse the reduction of CO_2 efficiently and selectively remains narrow,
42 especially if we compare it with molecular complexes for hydrogen production.



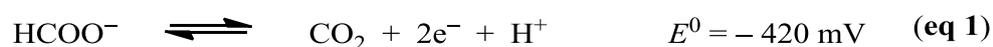
44 **Figure 1.** Some of the most known molecular catalysts for CO_2 reduction.

45 In order to expand this library and develop catalysts with non-noble metals the
46 bioinspired approach, yet at its infancy, is likely to be useful. In fact, while a number of
47 enzymes have shown the ability to catalyse the conversion of CO_2 into CO or formic acid,
48 using unique metal active sites, very little has been done to synthesize bioinspired complexes
49 mimicking these active sites and to evaluate their catalytic activity. In this review, we focus
50 on the models based on molybdenum- and tungsten-dependent formate dehydrogenases [5].
51 We show that this bioinspired approach can lead to new classes of interesting molecular
52 catalysts for CO_2 photo- and electro-reduction.

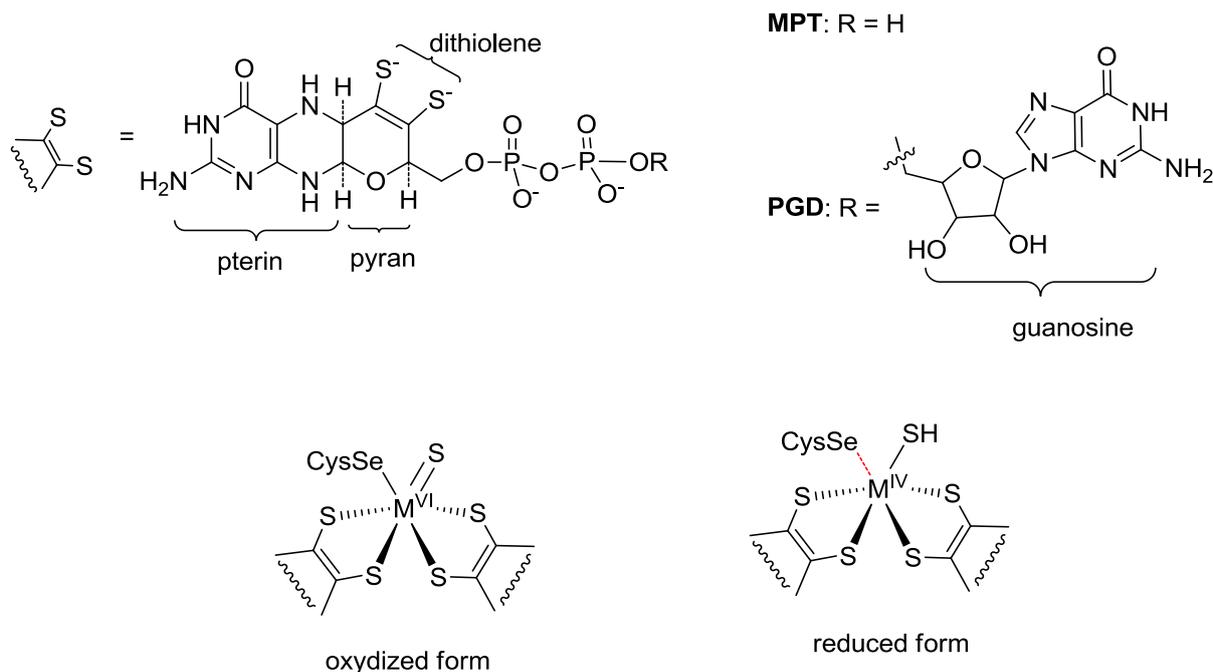
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II. Formate Dehydrogenases (FDHs)

FDHs catalyze the reversible transformation of CO₂ to HCOOH according to a two-electron redox process (eq. 1). There are two classes of FDHs: NAD-dependent ones that do not contain any metal ion and metal-dependent ones that possess a mononuclear molybdenum (or tungsten) center. Several excellent reviews described the different aspects of this enzyme in detail [5-8]. We will herein focus on the metal-dependent FDH and settle for a short summary.

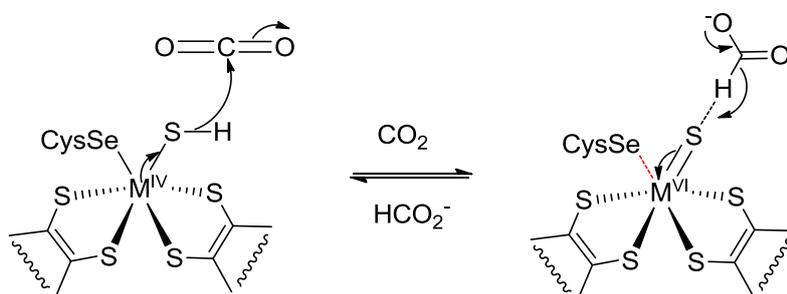


The structures of several FDHs from different organisms have been elucidated by X-ray diffraction [9-12]. The Mo (or W) atom is coordinated by two guanidine phosphate esterified pyranopterin cofactors called PGT (Figure 2, top). The [Mo(PGT)₂] (or [W(PGT)₂]) structure is well conserved in FDHs from different organisms and during the catalytic cycle. The cofactor without the guanosine moiety is called molybdopterin (**MPT**, Figure 2, top). **MPT** is a highly unstable organic molecule and has never been isolated without the protein backbone. It is composed of a pterin with a fused pyran ring carrying a dithiolene chelate (Figure 2, top). The redox state of the Mo (or W) atom varies from +VI to +IV during the catalytic cycle. Additional apical ligands are present; however, their exact coordination configuration remains controversial. It is generally admitted that, in the oxidized form, the Mo^{VI}/W^{VI} atom is coordinated by a selenocysteine (in a few cases a cysteine) residue and a terminal sulfido ligand (Mo/W=S) that is essential for catalytic activity. But at first and for a long time, this ligand was thought to be a terminal oxo ligand. It was only recently (2006) that this result was reinterpreted by Romão *et al.*, who determined it to be a sulfido ligand [12]. The reduced form of the enzyme is still a subject of controversy: the Mo^{IV}/W^{IV} center is presumably coordinated with a terminal hydrosulfido ligand (Mo/W-SH), along with the selenocysteine (or cysteine) residue (Figure 2, bottom). However, some publications suggest that the selenocysteine (or cysteine) residue is no longer present and the metal center is pentacoordinated with a SH ligand [12].



83
 84 **Figure 2.** Structures of **PGD** and **MPT** (top) and active site of FDHs: M = Mo/W (bottom). The
 85 presence of the selenocysteine ligand in the reduced form is debated.

86



87
 88 **Scheme 1.** One of the possible proposed mechanisms of FDHs (M = Mo/W).

89

90 Recent studies show that there is no clear-cut experimental evidence that
 91 formate/carbon dioxide coordinates to the metal center during the catalytic
 92 oxidation/reduction process. Furthermore, the formation of a M(IV)-H hydride species could
 93 not be detected during the reduction of carbon dioxide process. Due to the fact that there are
 94 some ambiguities over the reduced form, the mechanism of this enzyme is not unanimously
 95 established. We herein show one mechanism among other proposals with M(IV)-SH for
 96 hydride transfer during the carbon dioxide reduction step (Scheme 1) [13]. More experimental
 97 studies are needed for unambiguously determine the mechanism.

98 **III. Structural models of FDH**

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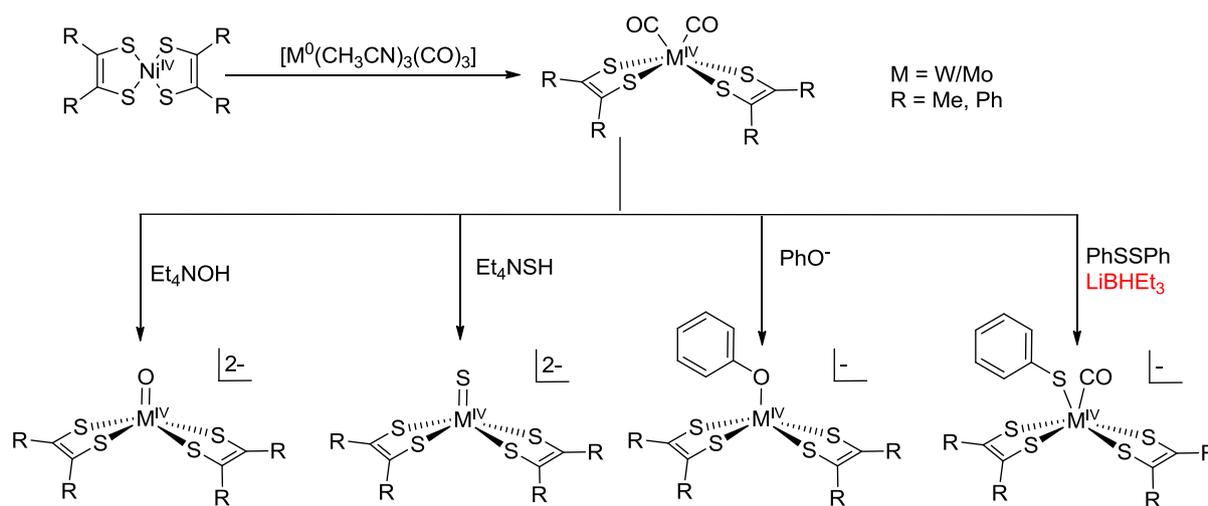
100 As mentioned earlier, the exact nature of the axial ligand and its role in the
101 mechanism has been only recently emphasized [7]. It was thought that FDHs catalyze oxygen
102 transfer reactions, as most molybdenum and tungsten enzymes do, which was compatible with
103 the first crystallographic structure of an enzyme of this family having $M^{VI}=O/M^{IV}-OH$ as the
104 axial ligands. This is probably why, so far, most models were synthesized with a terminal oxo
105 ligand.

106 As a result, very few $M^{VI}=S/M^{IV}-SH$ complexes have been developed ($M = Mo/W$).
107 The main challenges for the development of synthetic models of the active site of FDHs
108 resided in the stabilization of bis-dithiolene Mo/W-complexes. The first models of **MPT**
109 containing enzymes were synthesized as models of oxotransferases such as DMSO reductase
110 (DMSOR). Most of this work was done by the group of Richard Holm in the 90's [14], who
111 developed various synthetic routes to obtain bis-dithiolene Mo(W)-oxo complexes. Quite
112 simple dithiolene ligands were used. Other groups also contributed to this effort with simple
113 dithiolene ligands [15-18].

114 Two other challenges to be addressed for close mimics of FDHs regarded the nature of
115 the axial ligands and the structure of the dithiolene ligands.

116 **III.1. Variation of the axial ligands**

117 With simple dithiolene ligands ($R = Me, Ph$), Holm and *al.* developed a method
118 allowing the introduction of different axial ligand thanks to substitution of carbon monoxide
119 ligands on molybdenum or tungsten carbonyl complexes [19-23]. The precursors
120 $Mo/W(dithiolene)_2(CO)_2$ were prepared by a trans-metalation reaction from a Ni(IV)-
121 bisdithiolene complex. Unfortunately, the overall yields for the preparation of such complexes
122 are quite low, which is a strong limitation if one wants to use more elaborate ligands. It seems
123 that this methodology can only be applied to simple dithiolene ligands with Me and Ph
124 groups. More recently, Elvers *et al.* synthesized similar complexes thanks to the
125 photochemical deprotection of 1,3-Dithiol-2-ones and *in situ* complexation [24]. In this case,
126 the yields remained modest (max 20 %) and aliphatic dihiolenes ligands could also be used.



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128

129 **Scheme 2.** Synthetic route of bis-dithiolene Mo(W) complexes with different axial ligands
 130 developed by Holm and co-workers.

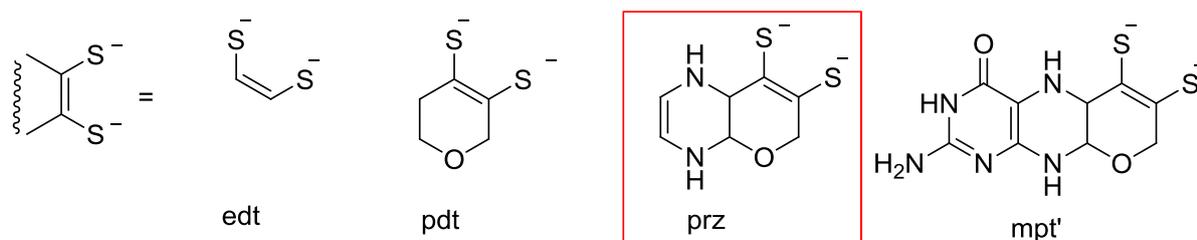
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132 III.2. Pyrazine containing ligands

133

134 However, the active site of FDH cannot be modeled only by its first coordination
 135 sphere, as the pterin part of the ligands plays an important role as a proton relay and also as a
 136 mediator of the red-ox properties of the active site. Schulzke and co-workers performed DFT
 137 calculations with model complexes Mo/W(O)(dithiolene)₂ and showed that in order to
 138 reproduce accurately the molecular/electronic properties of **MPT**, a simple dithiolene ligand
 139 was not appropriate even within a pyran ring and that the minimal ligand should be a fused
 140 pyran-tetrahydropyrazine-functionalized dithiolene, denoted **prz**. The third pyrimidine cycle
 141 seems not to be mandatory (Figure 3) [25].

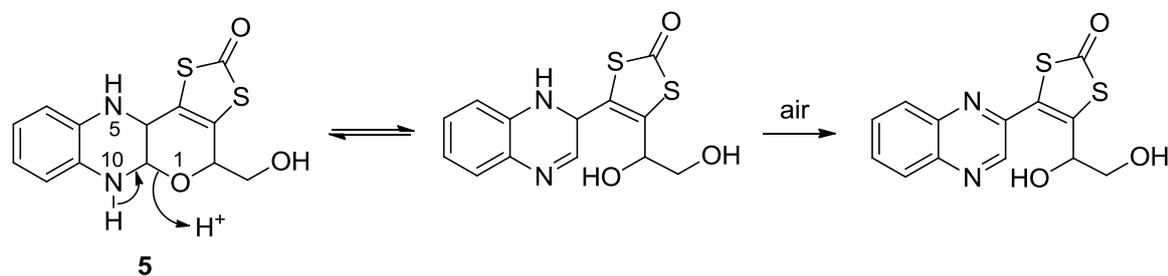
142 Hence, in the following paragraph we will describe only ligands bearing such a
 143 structure, with different oxidation states for the pyrazine cycle. The formation of a pyran
 144 cycle fused with a pyrazine unit represents the most challenging synthetic step.



145

146 **Figure 3.** Prz as minimum required ligand according to the DFT calculations.

147 One of the earliest and most elaborate syntheses of MPT-like ligands was developed
 148 by the groups of Joule and Garner at the end of the 90's [26-30]. It was specified that without
 149 the protection of the secondary amine N10, **5** was not stable and the pyran ring could open up
 150 in a proton assisted reaction (Scheme 3) [27]. In contrast, MPT is stable in the tricyclic form
 151 within FDHs, possibly because the active site does not contain a proton exchange site that
 152 favors pyran ring opening. One should note that, under very specific conditions, during
 153 protein crystallization for example, open forms of MPT have been obtained, reflecting the
 154 sensitivity of such pterin-pyran-dithiolene molecules [10, 31, 32]. However, the physiological
 155 relevance of these open forms is not established [33].



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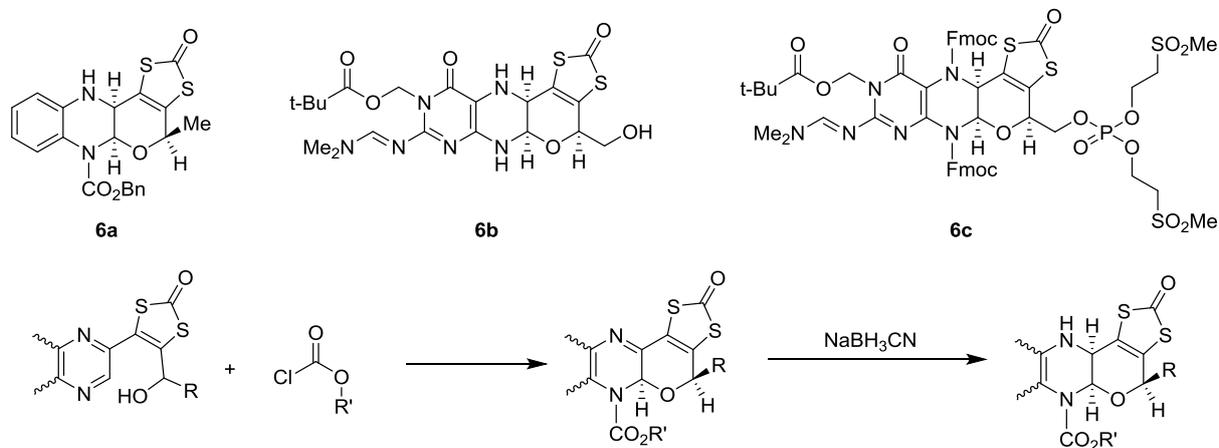
157 **Scheme 3.** Pyran ring scission according to Joule and co-workers.

158

159 In all the syntheses, the formation of the pyran ring was achieved by using a
 160 chloroformiate reagent to activate the nitrogen on the pyrazine cycle, after the protection of
 161 the dithiolene moiety. This activation also allowed the protection of the amine N10 and thus
 162 avoided an opening of the pyran cycle. The second imine of the cycle was then reduced and
 163 the resulting amine could be protected to prevent the reoxidation. In these remarkable
 164 syntheses, even the stereochemistry of the asymmetric carbons was matching with the natural
 165 ligand. **6a**, **6b** and **6c** were obtained (Scheme 4). Unfortunately, no molybdenum or tungsten
 166 complexes were described with these ligands. Nevertheless, CoCp(dithiolene) (Cp=

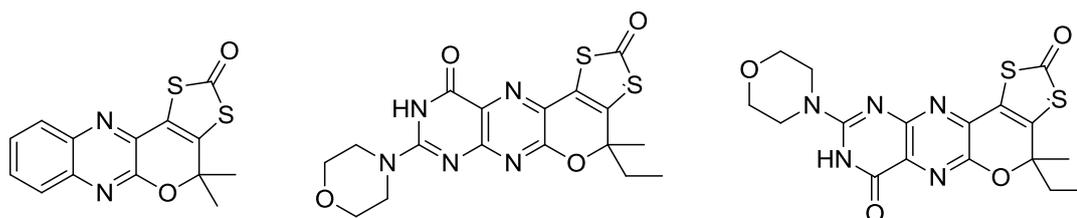
167 cyclopentadienyle) complexes were obtained proving the possibility for the molecules to
168 coordinate a metal center once deprotected (Scheme 4).

169



171 **Scheme 4.** MPT-like Ligands synthesized by Joule and co-workers.

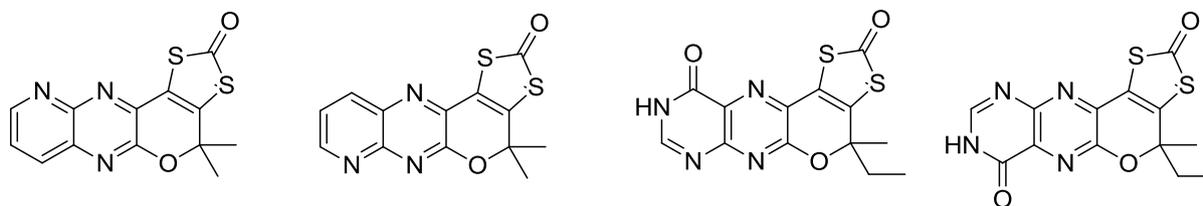
172 Later, Basu's group obtained a family of dithiolene ligand containing the **prz** moiety
173 **7a – 7g** (Scheme 5). Here again, after the protection of the dithiolene function in **8**, a
174 chloroformate activation through an intramolecular reaction between an amide and an alcohol
175 in **9** allowed the formation of the pyran cycle **7**. However, in these cases, the carbamate
176 derivatives were not obtained, and a fully oxidized pyrazine cycle was instead formed
177 (Scheme 5). The main drawback of this strategy was the relatively low global yield, especially
178 when the di-amine used in the Gabriel-Isay condensation was asymmetric due to the poor
179 regioselectivity of this step. Again, no tungsten or molybdenum complexes using these
180 ligands were reported [34, 35].



7a

7b

7c



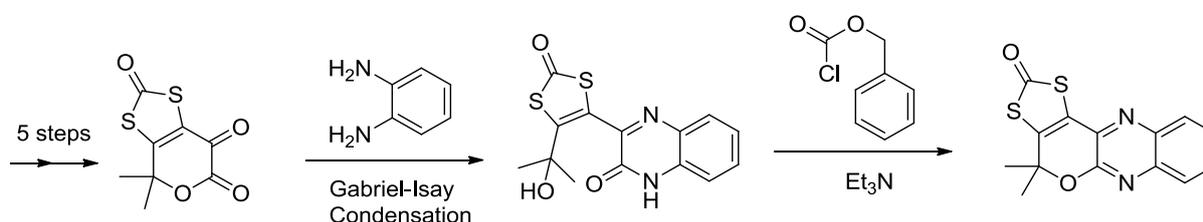
7d

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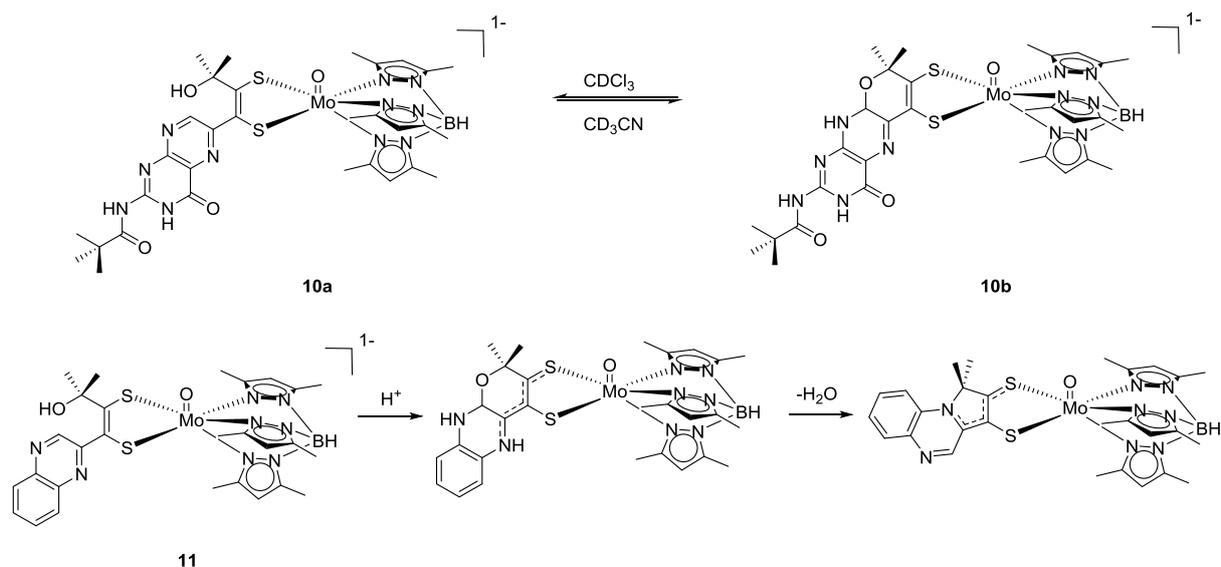
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183 **Scheme 5.** MPT-like Ligands synthesized by Basu and co-workers.

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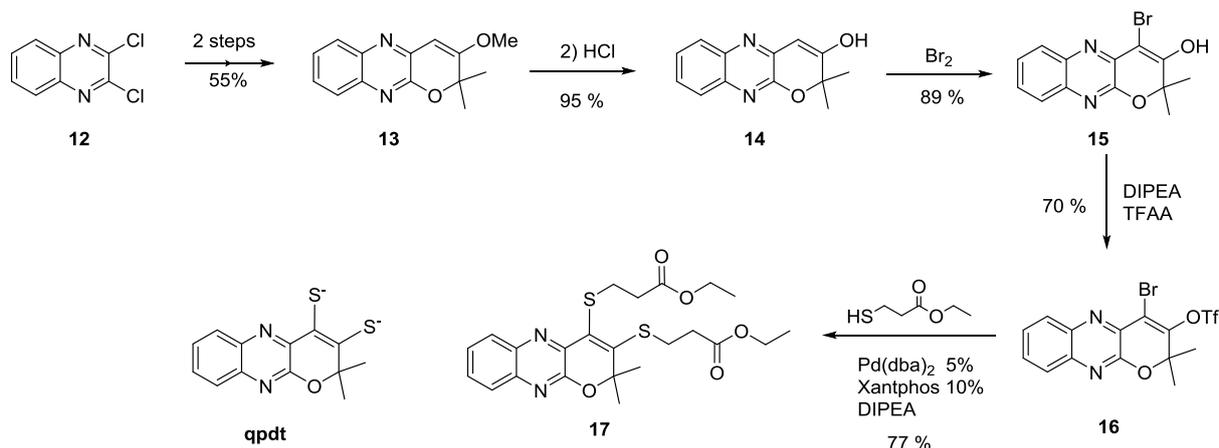
185 Burgmayer *et al.* used a rather original approach to prepare a closed pyran cycle. They
 186 observed a tautomerism between a closed and an open pyran cycle **10a** and **10b** directly on a
 187 molybdenum complex with a dithiolene ligand and a tris(3,5-dimethylpyrazolyl)hydroborate
 188 (Tp*) chelate (Scheme 6) [36, 37]. The spontaneous cyclisation depends upon the polarity of
 189 the solvent in which the complex was studied. This reaction was also studied with a simpler
 190 ligand **11** (Scheme 6) [38]. In this case, the cyclisation was not spontaneous but was promoted
 191 by the addition of trifluoroacetic acid (TFA). Unfortunately, the closed form was not stable,
 192 and dehydration of the ligand was observed yielding to a pyrrolo-quinoxaline ligand.

193 This study brings interesting insights for the catalytic site of FDH. However, the
 194 nature of the Tp* ligand is quite different from the natural ligand. Moreover, due to the
 195 equilibrium phenomenon, a mixture of two forms could be obtained, so it is hard to envisage
 196 organic reactions on the ligand to stabilize the pyran form once it is formed. Thus, these
 197 systems are not appropriate for catalytic studies.



199 **Scheme 6.** Solvent-dependent equilibrium between the open chain forms and the cyclized
 200 pyran forms.

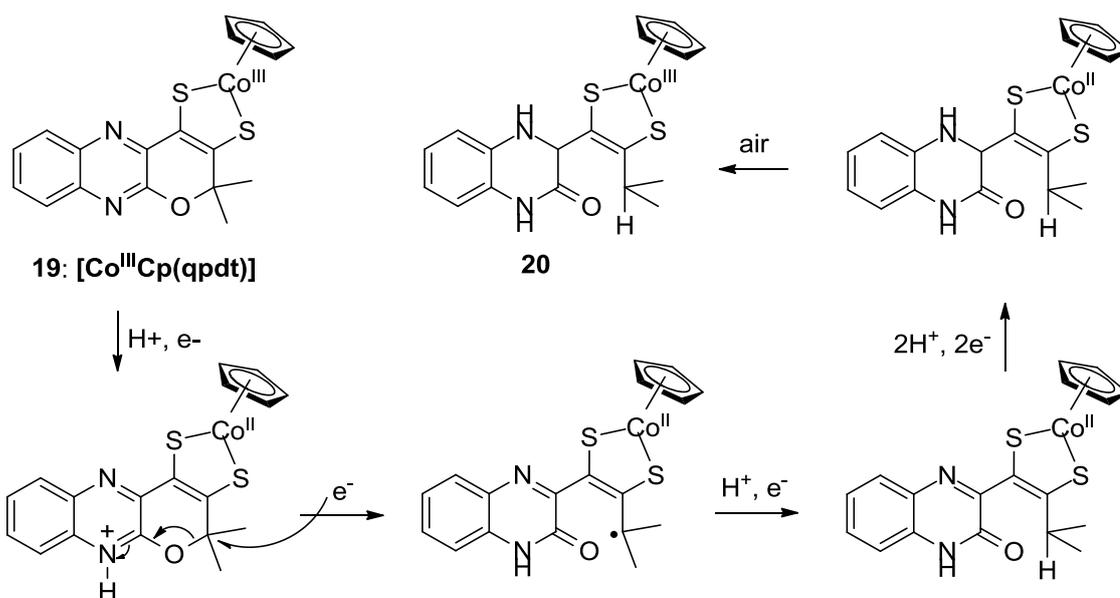
201
 202 In a quest for the bioinspired catalyst for CO₂ reduction, we developed a **prz**
 203 containing ligand with an oxidized pyrazine cycle similar to the one obtained by Basu *et al*
 204 (Scheme 5). However, we adopted a new synthetic strategy, wherein we chose to first prepare
 205 the tricyclic skeleton and then to introduce a protected dithiolene moiety [39, 40]. Starting
 206 from 2,3-dichloroquinoxaline **12**, the tricyclic molecule **13** was prepared in two steps according
 207 to a reported method [41]. The enol ether was hydrolyzed to the corresponding enol **14**, which
 208 was functionalized by bromination to **15** and activated by triflation to give **16**. Finally, a
 209 double cross-coupling reaction catalyzed by palladium allowed to introduce the protected
 210 dithiolene moiety. The protected ligand **17** was prepared in a straightforward and easily
 211 scalable way (Scheme).



212

213 **Scheme 7.** Synthesis of the protected ligand **17** and structure of ligand **qpdt**.

214 After deprotection of **17**, the quinoxaline-pyran-fused dithiolene ligand **qpdt** (Scheme
 215 7) could be obtained and directly used for complexation. The biomimetic complex
 216 $(\text{Bu}_4\text{N})_2[\text{Mo}^{\text{IV}}\text{O}(\text{qpdt})_2]$ (**18**) (Figure 5) was thus synthesized and fully characterized including
 217 via X-ray crystallography, showing that it is sharing a number of structural properties with the
 218 active site of FDHs. It proved to be a quite good catalyst for both electro- and photoreduction
 219 of protons into hydrogen [39]. However, further analysis showed that **18** was not the active
 220 catalyst, but a pre-catalyst. Indeed, under acidic and reductive conditions the ligand could
 221 undergo a ring opening of the pyran cycle [42]. This was unambiguously observed in the case
 222 of the $[\text{Co}^{\text{III}}\text{Cp}(\text{qpdt})]$ complex **19**, for which the product of electro-reduction **20** could be
 223 isolated and characterized. A possible mechanism is illustrated in Scheme 8. This reaction
 224 was promoted by the protonation of the quinoxaline cycle. A similar reaction was also
 225 observed when the protected ligand **17** was treated with sodium dithionite as a source of
 226 electrons.



227
228 **Scheme 8.** Electro-reduction of [Co^{III}Cp(qpdt)] resulting in an unusual ring scission.

229

230 These observations emphasized the necessity to better mimic MPT by reducing the

231 pyrazine cycles. In order to obtain such molecules, we decided to work with the tricyclic

232 skeleton previously described (Scheme 9). Indeed, we showed that obtaining such a motif was

233 the key step of the synthesis. Moreover, these molecules could be easily obtained on a 10 g

234 scale and as such constituted a good basis to develop new synthesis. Starting with molecule

235 **16**, the reduction of the first imine on the pyrazine cycle was possible by the activation of

236 N10 with a methylation reaction [43]. The iminium obtained **21** could be easily reduced by

237 NaBH(OAc)₃. Then, following the same methodology as for **qpdt**, the protected dithiolene

238 moiety was introduced, leading to molecule **23**, with a partially reduced pyrazine cycle. The

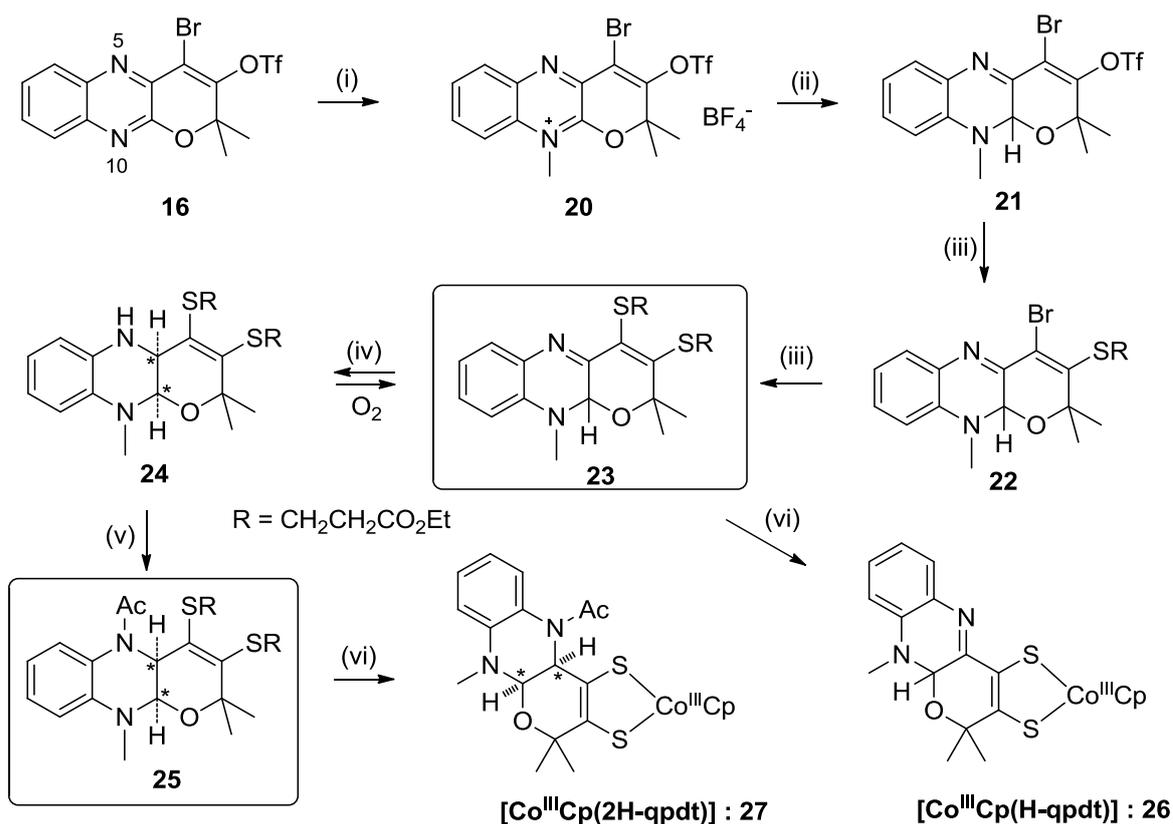
239 reduction was completed by treatment with NaBH₃CN to give the secondary amine **24**,

240 followed by acylation, in order to avoid reoxidation of the obtained amine, leading to **25**.

241 Interestingly, the two protons of the junction of the pyrazine and pyran cycles in **25** adopt a

242 *cis* configuration (racemic mixture), as it is the case, with R, R absolute configuration, in

243 MPT.



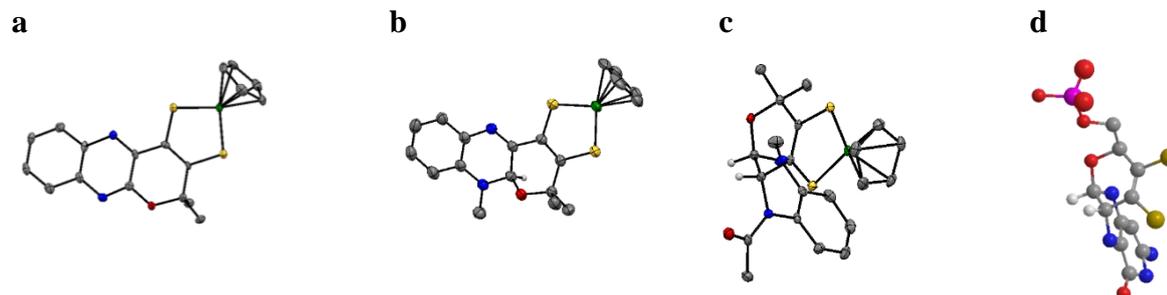
* relative stereochemistry is indicated

244
245

246 **Scheme 9.** Synthesis of dithiolene ligands **23**, **25** and complexes [Co^{III}Cp(H-qpdt)] (**26**) and
 247 [Co^{III}Cp(2H-qpdt)] (**27**). Conditions: i) (Me₃O)(BF₄); ii) Me₄NBH(OAc)₃; iii) Pd(dba)₂ (10
 248 %), Xantphos (10 %), HSCH₂CH₂CO₂Et, *i*Pr₂NEt; iv) Pd₂(dba)₃ (15 %), Xantphos (30 %),
 249 HSCH₂CH₂CO₂Et, *i*Pr₂NEt; (v) NaBH₃(CN), AcOH; (vi) AcCl, *i*Pr₂NEt; (vii) CoCpI₂(CO).

250 Since the two red-ox states of the pyrazine cycles of **23** and **25** could be found in
 251 nature, they were used for further complexation. Following Joule and Garner's methodology
 252 [26], [Co^{III}Cp(dithiolene)] complexes were first prepared in order to structurally characterize
 253 the ligands. Structures of the different complexes obtained are shown in Figure 4. As
 254 expected, the ligand went from a fully planar structure in **qpdt** to a bent structure with an
 255 significant angle between the pyrazine and the pyran cycle in **2H-qpdt**. As a comparison, a
 256 3D representation of ligand MPT in FDHs is shown in Figure 4d and underline the structural
 257 similarity between 2H-qpdt and MPT. Electronic properties were assessed thanks to NMR,
 258 UV-Visible spectroscopy and electrochemistry, which showed that with reduction of the
 259 pyrazine cycle the ligand has a more electron-donating effect onto the metal. In particular,
 260 2H-qpdt was much more donating than H-qpdt which in good agreement with the hypothesis

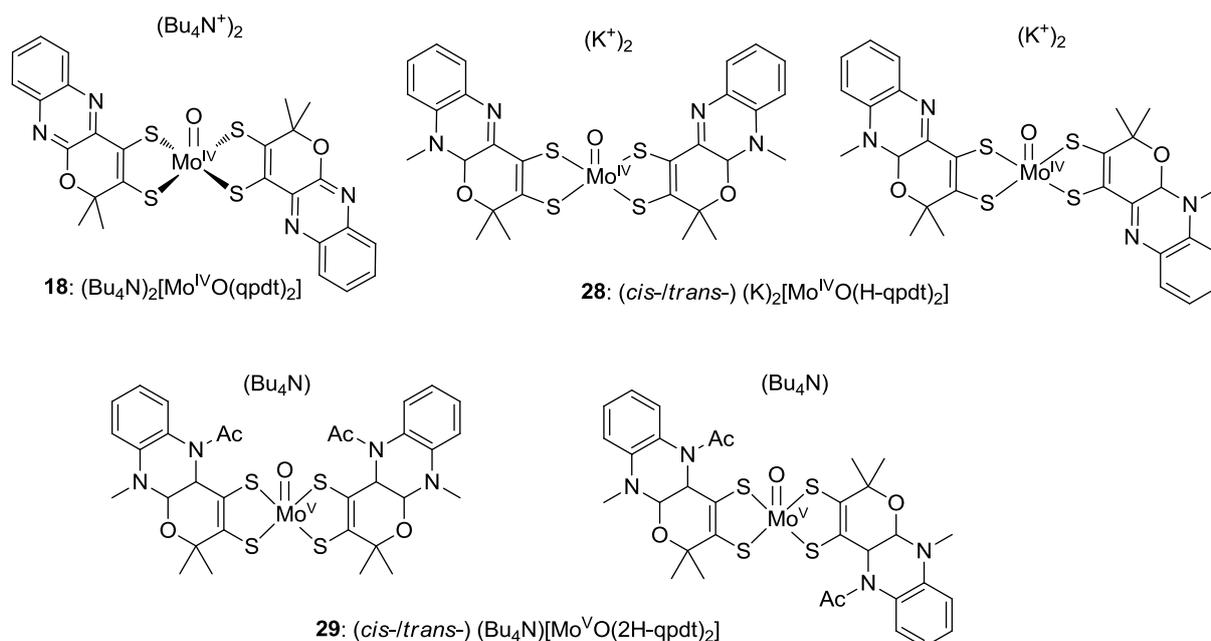
261 that the co-existence of both reduced states in natural active sites helps the modulation of their
262 red-ox activities.



263 **Figure 4.** Structure representations of (a) $[\text{Co}^{\text{III}}\text{Cp}(\text{qpdt})]$ **19**, (b) $[\text{Co}^{\text{III}}\text{Cp}(\text{H-qpdt})]$ **26**, (c)
264 $[\text{Co}^{\text{III}}\text{Cp}(\text{2H-qpdt})]$ **27** and (d) $\text{Mo}^{\text{IV}}(\text{MPT})_2$ 3D simplified representation of a MPT ligand in
265 FDHs.

266 More interestingly, both $\text{K}_2[\text{Mo}^{\text{IV}}\text{O}(\text{H-qpdt})_2]$ (**28**) and $(\text{Bu}_4\text{N})_2[\text{Mo}^{\text{V}}\text{O}(\text{2H-qpdt})_2]$
267 (**29**) (Figure 5) could be prepared, constituting the closest mimics of the FDH active site
268 obtained so far. $\text{K}_2[\text{Mo}^{\text{IV}}\text{O}(\text{H-qpdt})_2]$ (**28**) could be structurally characterized, confirming the
269 structure of the ligand found in the structure of $[\text{Co}^{\text{III}}\text{Cp}(\text{H-qpdt})]$ **26** (Figure 4b). Two
270 different structures were obtained, one with the dithiolene chelate in a *trans* orientation with
271 respect to MoS_4 core and one with a *cis* orientation. Unfortunately, no crystal structure of
272 $(\text{Bu}_4\text{N})_2[\text{Mo}^{\text{V}}\text{O}(\text{2H-qpdt})_2]$ (**29**) could be obtained, probably due to the existence of many
273 stereoisomers. Indeed, since 2H-qpdt exists in the form of a mixture of two enantiomers and
274 the two ligands could be *cis*- or *trans*-oriented with respect to the MoS_4 core, a mixture of
275 seven stereoisomers was expected. Nevertheless, indirect evidence led us to propose that the
276 structure of 2H-qpdt around the metal is similar to the one found in $[\text{Co}^{\text{III}}\text{Cp}(\text{2H-qpdt})]$ **27**
277 (Figure 4c). Additionally, $(\text{Bu}_4\text{N})_2[\text{Mo}^{\text{V}}\text{O}(\text{2H-qpdt})_2]$ (**29**) was well-characterized by other
278 techniques and we could confirm its red-ox state (Mo^{V}) thanks to UV-Visible and EPR
279 spectroscopy as well as cyclic voltammetry.

280



281
282

283 **Figure 5.** Structures of complexes **18**, **28** and **29**.

284 **IV. Functional models**

285

286 Until now most of dithiolene complexes studied for their catalytic activity have been
 287 tested for the reduction of protons into H_2 [40, 44-51]. In a first part, we will focus on the few
 288 examples of tungsten or molybdenum-bis(dithiolene) complexes that were shown to react
 289 with carbon dioxide. In a second part, we will discuss metal dithiolene complexes, with other
 290 metal ions than molybdenum or tungsten, which catalyze the reduction of CO_2 . Finally, we
 291 will also present those active complexes containing tungsten or molybdenum, but without
 292 sulfur-based ligands.

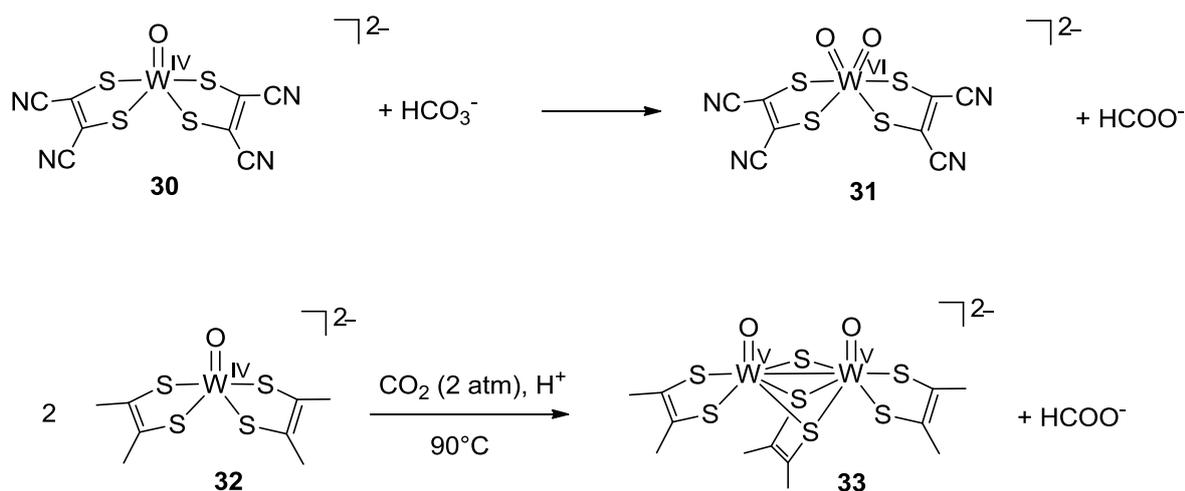
293

294 **IV.1. Mo/W-(dithiolene)₂ complexes**

295

296 **IV.1.a. Equimolar reaction with CO_2**

297 The first reaction between a tungsten bis-dithiolene complex and CO_2 was described
 298 by Sarkar and Das [52]. They reported that $[\text{W}^{\text{IV}}\text{O}(\text{mnt})_2]^{2-}$ (**30**) could slowly react with
 299 bicarbonate to give formate and $[\text{W}^{\text{VI}}\text{O}_2(\text{mnt})_2]^{2-}$ (**31**). The yield in formate was 55% based
 300 on **30** (Scheme 10).



301

302 **Scheme 10.** Non-catalytic reduction of CO₂ by tungsten bis-dithiolene complexes.

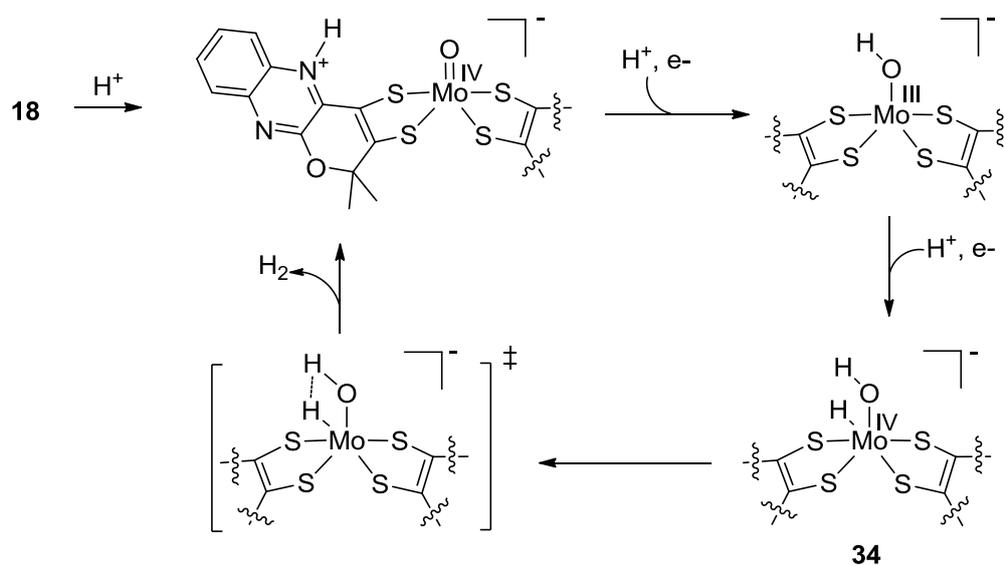
303 Kim and co-workers also described an equimolar reaction between the tungsten
 304 complex [W^{IV}O(Me₂C₂S₂)₂]²⁻ (**32**) and CO₂ which led to formate [53]. This reaction was
 305 accompanied by the formation of a triply bridged dinuclear W(V) complex (**33**) (Scheme 10).

306 IV.1.b. Catalytic reduction of CO₂

307 The three complexes [Mo^{IV}O(qpdt)₂]²⁻ (**18**), [Mo^{IV}O(H-qpdt)₂]²⁻ (**28**) and [Mo^VO(2H-qpdt)₂]²⁻
 308 (**29**) (Figure 5) were tested for the photocatalytic reduction of CO₂ [43]. Catalytic CO₂
 309 reduction activity was assessed under photochemical conditions, using [Ru(bpy)₃]₂⁺ as a
 310 photosensitizer (PS), BIH (1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzoimidazole) as the
 311 sacrificial electron donor and CH₃CN/TEOA (triethanolamine) in a 5:1 ratio as the solvent,
 312 saturated with CO₂. Complex **18** was highly selective for proton reduction into H₂, while
 313 complexes **28** and **29** showed ability to catalyze CO₂ reduction into a mixture of formic acid
 314 and carbon monoxide. The most selective complex was complex **29**, with a much larger
 315 proportion of CO₂-derived products accounting for almost 60 % (39 % formate and 19 % CO)
 316 and a total TON of 210 after 15 hours. Complex **28** was less active (TON= 95) and less
 317 selective (53 % H₂). Thus, the redox state of the central pyrazine ring seems to be determinant
 318 to selectively catalyze the reduction of CO₂ into formate. While FDHs are highly selective for
 319 CO₂ reduction and do not produce any H₂ during catalysis, the FDHs mimics discussed here
 320 are also good catalysts for proton reduction. DFT calculations suggested that the axial oxo
 321 ligand played a key role for driving this reaction (Scheme 11). Indeed, protonation of the
 322 reduced complex Mo(O) generates a doubly protonated intermediate Mo(OH)(H) **34**, in which
 323 one proton bound to the O ligand is very well positioned to react with the Mo-H hydride
 324 species, thus generating H₂, in competition with this hydride reacting with CO₂ to form formic

325 acid [40]. It is interesting to note that, in contrast, the enzyme has different mainly S-based
 326 axial ligands (Figure 2). We made the tentative proposition that this axial coordination is
 327 critical for controlling the selectivity. However this requires the functional characterization of
 328 appropriate mimics (as shown in Scheme 2) be functionally characterized.

329

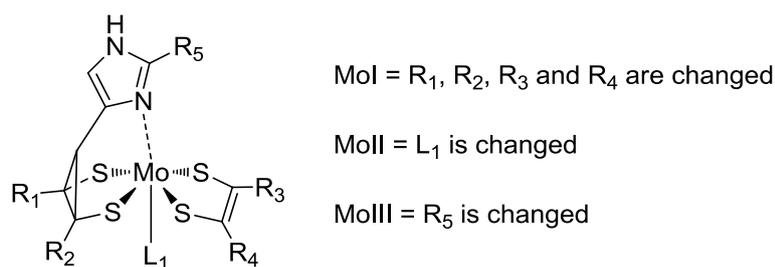


330

331 **Scheme 11.** Proposed catalytic cycle for proton reduction by complex **18**.

332 To date, these complexes which are the closest mimics of the active site of FDHs are
 333 the only Mo/W-dithiolene complexes able to catalyze the reduction of CO₂. It is quite
 334 interesting to note that not only formate could be obtained, but also that the most selective and
 335 active catalyst toward the formation of formate is the one bearing the closest mimic of the
 336 natural MPT-ligand.

337 Recently, Kumar *et al.* suggested, thanks to DFT calculations, that adding an
 338 imidazole moiety close to the axial position of the metal center could ease the reduction of
 339 CO₂ into formate (Figure 6) [54]. This could be an interesting modification, however in this
 340 purely theoretical work one of the ligand is not a dithiolene but only a disulfide chelate.

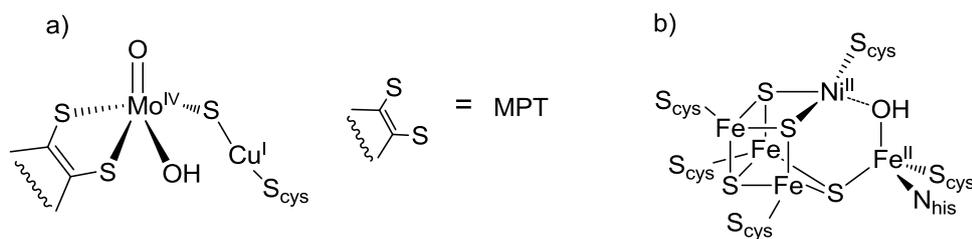


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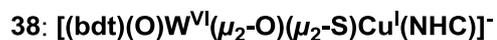
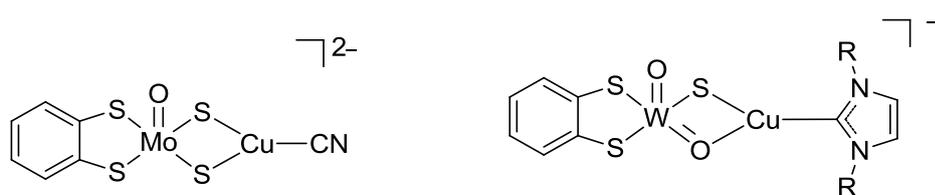
342 **Figure 6.** Some Mo-dithiolene complexes potentially interesting for CO₂ reduction according
 343 to the DFT calculations.

344 IV.2. Mo/W-Cu complexes, models of CO-dehydrogenases

345 Here, we describe bimetallic complexes containing a Mo/W-dithiolene subunit
 346 coupled to a mononuclear copper subunit. While the first component mimics FDH active site,
 347 the combination of both metal centers is reminiscent of the active site of CO-dehydrogenase
 348 (CODHs). CODH is another metalloenzyme able to reversibly reduce CO₂ into CO. There are
 349 two major families of CODHs: [Mo-Cu] [55] and [Ni-Fe] [56] CODHs. The former contains a
 350 heterobimetallic Mo-Cu active site in which the two metal ions are bridged by a sulfide ion,
 351 the Mo ion also being coordinated by the MPT ligand and an oxo/hydroxo moiety, and Cu(I)
 352 completing its coordination with a cysteinate from the polypeptide chain (Figure 7a); the latter
 353 contains a NiFe₄ cluster (Figure 7b), in which the Ni atom is used as the redox center and the
 354 pending Fe atom of the cluster is used exclusively as a Lewis acid to activate CO₂ and
 355 facilitate the cleavage of one of the C-O bonds.



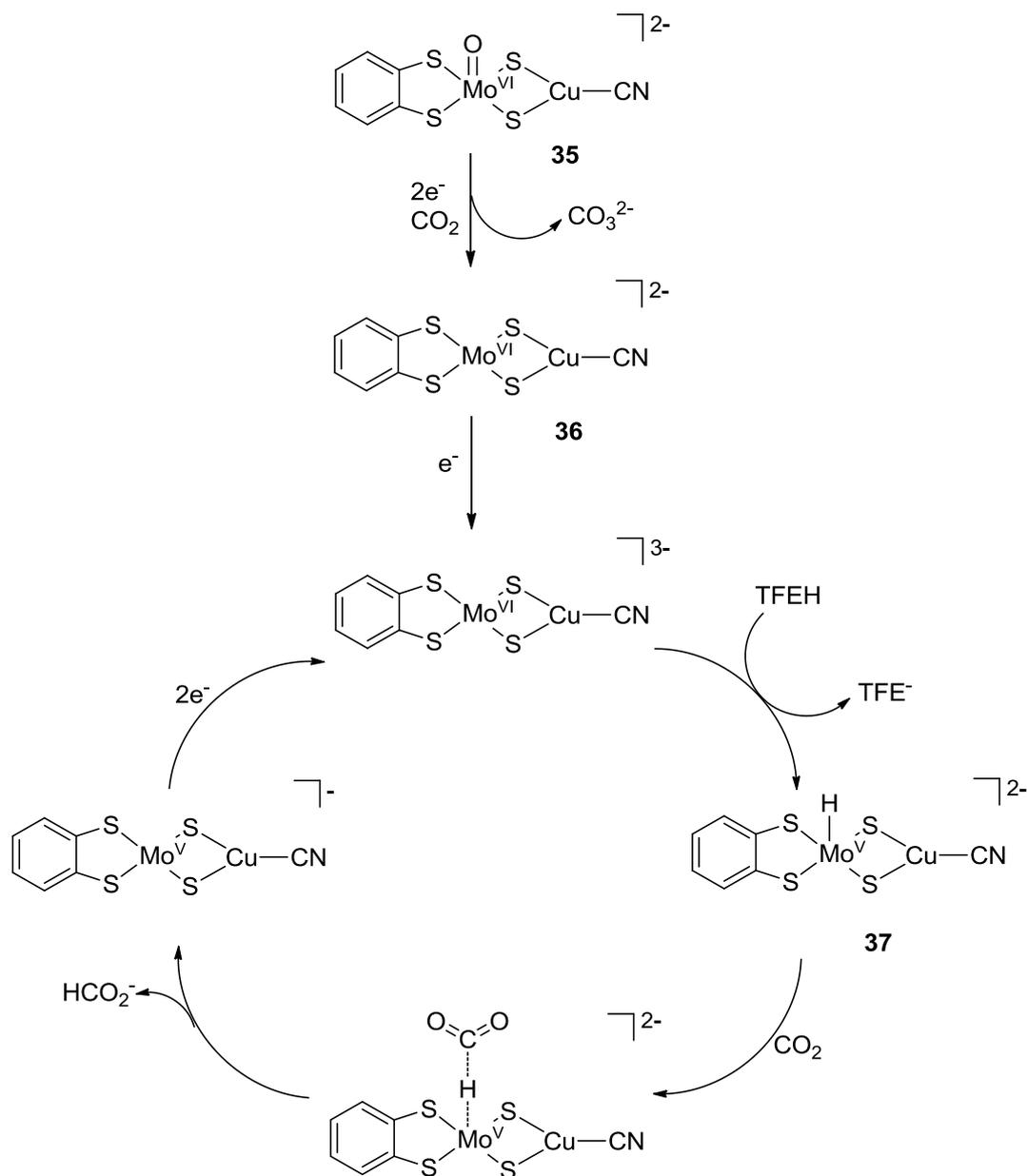
357 **Figure 7.** Active sites of (a) [MoCu]CODHs with M = Mo and (b) [NiFe]CODHs.



359 **Figure 8.** Two model complexes of [MoCu]CODHs.

360 Few synthetic dithiolene Mo/W dinuclear complexes have been explored as catalysts
 361 for catalytic CO₂ reduction. The complex $[(\text{bdt})\text{Mo}^{\text{VI}}(\text{O})\text{S}_2\text{Cu}^{\text{I}}\text{CN}]^{2-}$ (**35**, Figure 8, left) has
 362 been studied by our group as a catalyst for CO₂ electroreduction. As a result, complex **35**
 363 proved stable during CO₂ electroreduction in acetonitrile in the presence of a source of
 364 protons and formic acid was obtained as the major product (Faradic Efficiency: 70 – 75 %),

365 together with H₂ (20 %) and very small amounts of CO. Spectroscopic studies and DFT
 366 calculations (Scheme 12) proved that the complex was in fact just a pre-catalyst. Indeed, the
 367 first reaction was the loss of the oxo-ligand by a 2-electron reduction, via an efficient oxo-
 368 transfer to CO₂ leading to carbonate which eventually dissociates to give **36**, as shown by *in-*
 369 *situ* infra-red spectroelectrochemistry. The release of this coordination site allowed, after
 370 another reduction, the formation of a metal-hydride complex **37** which promoted the reduction
 371 of CO₂ into formate [57] (Scheme 12).



372

373 **Scheme 12.** Proposed mechanism of CO₂ electroreduction catalyzed by [Mo^{VI}(O)S₂(bdt) Cu^ICN]²⁻ **35**,
 374 based on spectroscopic studies and DFT calculations. TFEH= Trifluoroethanol.

375

376 This complex is so far the only mimic of [Mo-Cu]CODH to have the ability to
377 catalyze the reduction of carbon dioxide. However, the difference of selectivity between this
378 synthetic model (generating formate) and the enzyme (generating CO) still remains to be
379 explained.

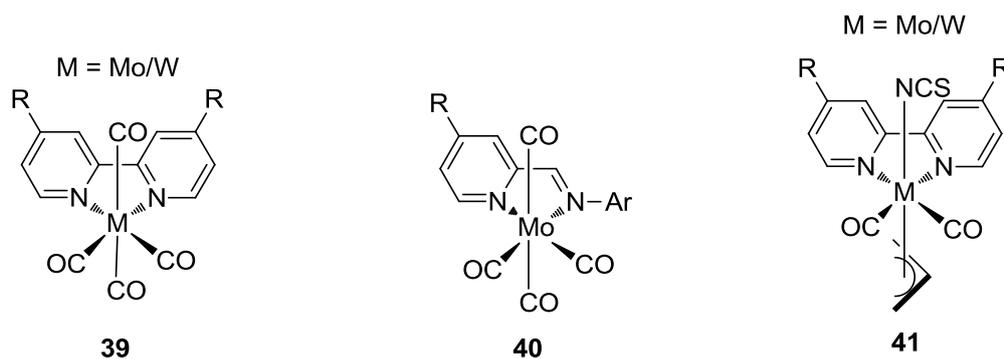
380 In that perspective, it is interesting to mention the work of Mankad's group [58]. They
381 synthesized the $[(\text{bdt})(\text{O})\text{W}(\mu_2\text{-S})(\mu_2\text{-O})\text{Cu}(\text{NHC})]^-$ complex (**38**, Figure 8) as a synthetic
382 model (NHC = N-heterocyclic carbene) (Figure 8, right). With this complex they failed to
383 detect any oxidation of carbon monoxide. Supported by DFT calculations they explained that
384 this absence of reactivity was due to the two $\mu_2\text{-O}$ and $\mu_2\text{-S}$ bonds between W and Cu. Indeed,
385 in the natural active sites, the backbone of the enzyme forces the two metals to be far apart
386 from each other, allowing only one $\mu_2\text{-S}$ bridge between the two atoms thus creating a
387 frustrated $\text{Mo}^{\text{VI}}/\text{Cu}^{\text{I}}$ Lewis pair. These features seemed to be mandatory to obtain CO
388 oxidation.

389

390 IV.3. Other Mo/W complexes

391 Several Mo/W complexes that do not contain any dithiolene ligand have been
392 described as catalysts for the reduction of CO_2 . Even if these complexes are structurally quite
393 different from the active site of FDH, they can bring interesting insights on the role of these
394 metal centers for the reduction of CO_2 .

395 Based on the previous work on manganese complexes, Kubiak's group studied the
396 bipyridine-Mo/W(CO)₄ complex **39** (Figure 9) [59]. After the loss of one carbon monoxide
397 ligand, the active catalyst was formed and could directly reduce CO_2 into CO. These
398 complexes were very selective toward the formation of CO with faradaic yield close to 100%.
399 However, their activity was low with an important overpotential. These results were
400 confirmed by cyclovoltammetry and spectroscopic studies by Tory *et al.* [60]. Other diamine
401 complexes such as **40**[61] and **41**[62] (Figure 9) have been tested but were too unstable to
402 efficiently catalyze the reduction of CO_2 . Finally, Grice and Saucedo showed that the
403 presence of a non-innocent ligand was not mandatory to promote the reduction of CO_2 , using
404 hexacarbonyl Mo and W complexes [63]. These complexes were functioning at a similar
405 overpotential to produce CO but were less selective with the formation of formate in the
406 presence of water.



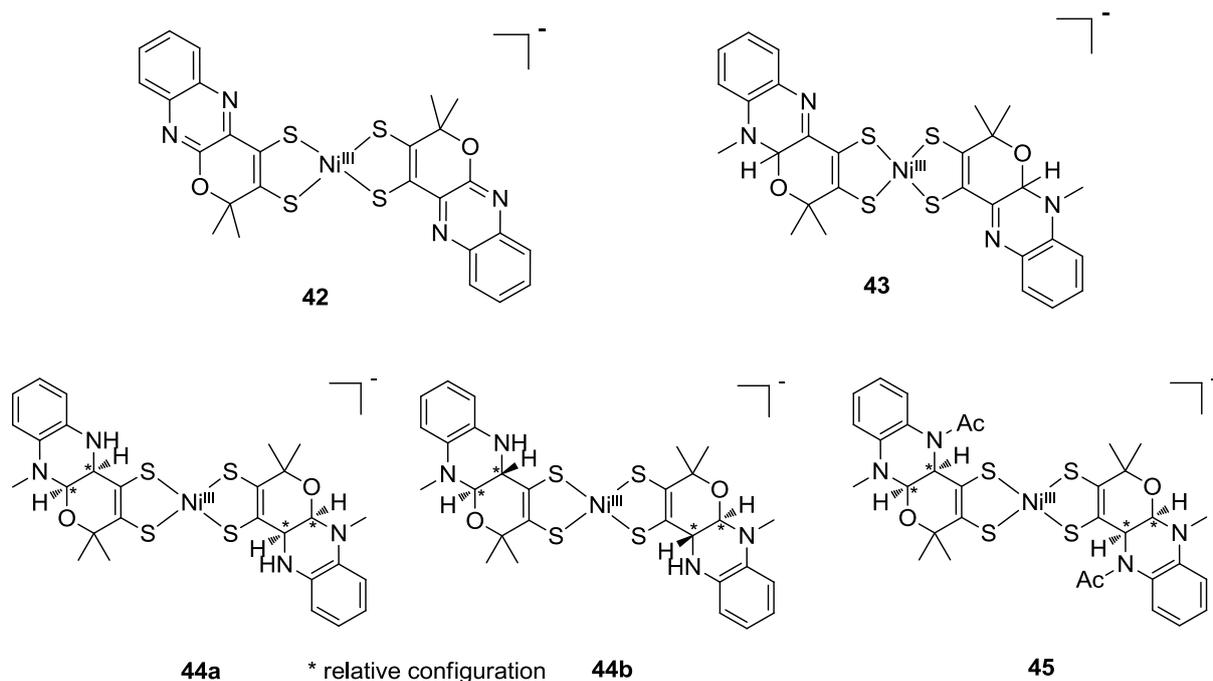
407

408 **Figure 9.** Some Mo/W based complexes active for CO₂ reduction.

409

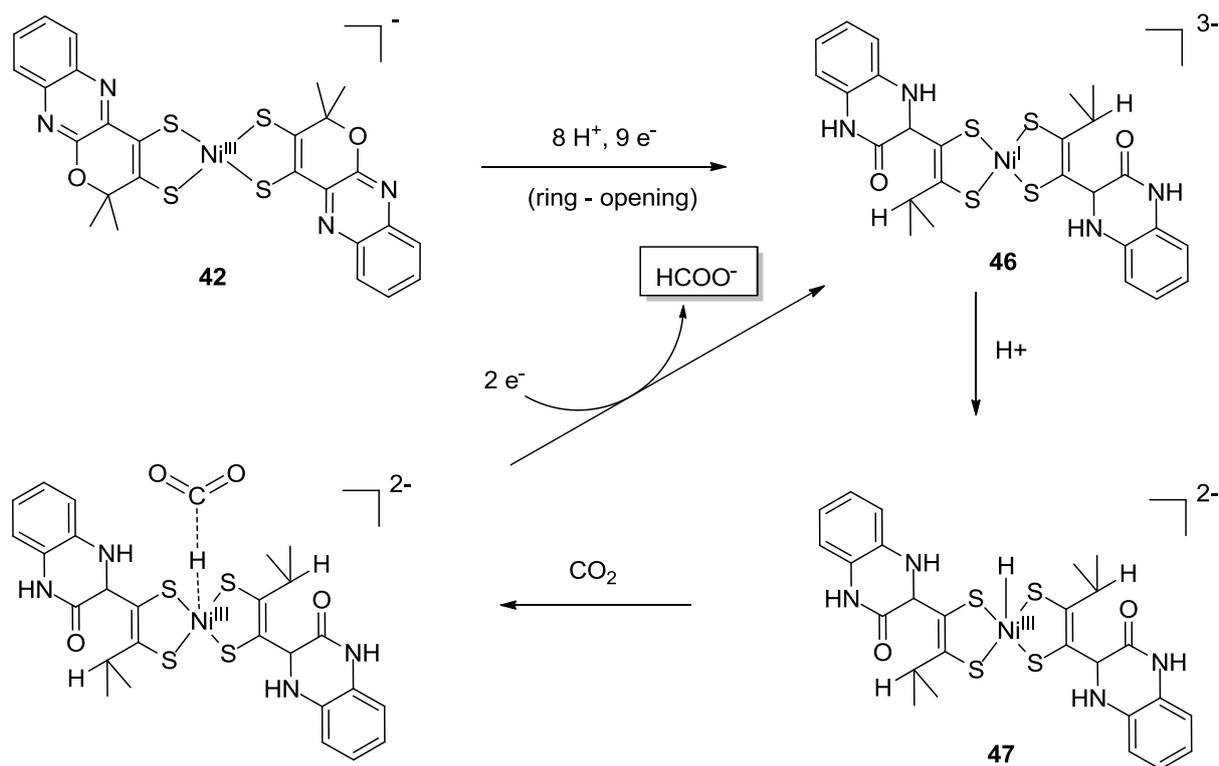
410 **IV.4. Ni(dithiolene)₂ complexes**

411 As mentioned earlier, the Ni center of [Ni-Fe]-CODH, in a tetra-sulfur environment, is
 412 the only redox active metal in the cluster (Figure 7). For this reason, we considered
 413 [Ni(dithiolene)₂] complexes as a reasonable bioinspired complex for mimicking this active
 414 site. The availability of the **qpdt** ligand afforded the possibility to prepare the complex
 415 (Bu₄N)[Ni^{III}(qpdt)₂] (**42**) in which the Ni ion is tetracoordinated in a S₄ environment with a
 416 square planar geometry (Figure 10) [64]. We showed by electrolysis that in the presence of
 417 trifluoroethanol as a proton source, this complex was able to promote the reduction of CO₂
 418 into formate as the major product (60%), together with small amounts of CO and H₂.
 419 However, these results could only be obtained on a mercury electrode. This observation was
 420 reminiscent of the case of [Ni(cyclam)]²⁺, and this might originate from favourable transient
 421 interactions between the complex and the Hg surface. However, it is very likely that this
 422 complex was only a pre-catalyst and that ligand pyran ring opening occurred during electro-
 423 reduction. For this reason we also assessed Ni-bisdithiolene complexes with dithiolene
 424 versions having a fully reduced pyrazine ring (Figure 10) [65]. (Bu₄N)[Ni^{III}(H-qpdt)₂] (**43**)
 425 was first prepared. **44a** and **44b** were obtained *via* chemical and electrochemical reduction of
 426 **42** respectively. (Bu₄N)[Ni^{III}(2H-qpdt)₂] (**45**) was also obtained using the ligand 2H-qpdt. All
 427 these complexes catalyzed the reduction of CO₂ to formate as the major product. **44b** proved
 428 to be the most active (larger TONs) and the most selective (FY for formate 70%) among all
 429 Ni(bis-dithiolene) complexes studied. This was quite surprising, especially knowing that the
 430 only difference between **44a** and **44b** resided in the configuration of the ring junction, *cis* vs.
 431 *trans*. It is very likely that this is also the consequence of using a Hg electrode. Thus, we
 432 postulate that noncovalent interactions between the complexes and the Hg surface are strong
 433 enough to affect the activity of stereoisomers differently.



434
 435 **Figure 10.** Structures of complexes $[\text{Ni}^{\text{III}}(\text{qpdt})_2]^-$ (**42**), $[\text{Ni}^{\text{III}}(\text{H-qpdt})_2]^-$ (**43**) and $[\text{Ni}^{\text{III}}(2\text{H-}$
 436 $\text{qpdt})_2]^-$ (**45**); chemical reduction of **43** gave **44a** and electroreduction of **43** gave **44b**.

437 The mechanism of CO_2 reduction by complex **42** was studied by the DFT calculations. **42** was
 438 the pre-catalyst and under electrolysis, the ring-opening reaction first took place to furnish
 439 **46**, which gave after protonation the key intermediate $\text{Ni}^{\text{III}}\text{-H}$ **47**. After the departure of
 440 formate, **47** was regenerated by a 2-electron reduction process (Scheme 13).



443 **Scheme 13.** Proposed reaction mechanisms of CO₂ reduction by complex **42** to formate.

444
445 **V. Conclusion**

446
447 CO₂ reduction remains a challenging reaction, and a variety of strategies has been
448 followed in order to optimize both solid and molecular catalysts. However, there is still
449 progress to be made, in terms of selectivity, efficiency and stability. The bio-inspired
450 approach, consisting in the design of metal complexes mimicking enzyme active sites, is an
451 original approach that has been exploited only very recently and is still at its infancy. FDHs
452 and CODHs are a family of enzymes that represent remarkable targets for understanding CO₂
453 binding, activation and transformation into formate and CO respectively. Unfortunately, these
454 enzymes are difficult to study structurally and mechanistically, in particular because of their
455 extreme sensitivity towards O₂. Bioinspired complexes might thus be ideal to understand CO₂
456 reduction mechanisms by natural active sites as well as to discover novel catalysts. The very
457 first studies described here nicely demonstrate that FDHs and CODHs mimics can display
458 interesting catalytic activities. However, more work is needed to better incorporate key
459 components of the active sites, such as S-based axial ligands in FDH mimics, single S bridges
460 in Mo-Cu complexes as well as Ni-(S)_n sites in NiFe clusters. This research might result in
461 fascinating synthetic challenges as well as in novel efficient catalysts.

463

464

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