Directing protonation in [FeFe] hydrogenase active site models by modifications in their second coordination sphere†

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Subtle changes in the second coordination sphere of [Cl_2bdtFe_2-$(CO)_4(Ph_2P–CH_2–X–CH_2–PPh_2)$] (bdt = benzene-1,2-dithiolate, X = NCH_3, NCH_2CF_3, CH_2) that do not influence the electronic character of the Fe_2 center can however direct protonation to three different sites: the *N* in the bis-phosphane, the Fe–Fe bond or the bdt-*S*.

X-Ray structure elucidation of [FeFe] hydrogenases (H_2ase) in the late 1990s[1,2] has revealed the molecular structure of their active sites (Chart 1a) which continue to fascinate bioinorganic chemists to date.[3,4] Apart from the structural modelling challenge,[5] particular focus has been given to the preparation of functional complexes that catalyze the reduction of protons to molecular hydrogen and thus offer an alternative to nobel metals that are currently used for this purpose. Over the last decade, more than 250 catalyst candidates have been examined and many of them have been shown to be homogenous electrocatalysts[6] or function even in photocatalytic schemes.[7–9]

Despite these efforts, bioinorganic models are still far from achieving similar high turnover rates and low overpotentials as the enzymes. This discrepancy suggests that it is insufficient to model only the primary coordination sphere, but that also the surrounding protein matrix has to be considered in the design of improved functional mimics. For this purpose, the second coordination sphere receives more and more attention in the modelling community.

It has been shown numerous times for [FeFe] H_2ase active site models that a given complex can lead to different protonation products depending on the conditions such as the counter anion of the used acid,[10,11] solvent[12] or temperature.[13,14] In contrast, systems in which the protonation behavior is programmed into the complex have not been reported. We have therefore prepared a series of electronically equivalent Fe_2 complexes **1–3** that differ solely in the second coordination sphere (Chart 1b). Whereas complexes **1** and **2** both contain an *N*-heteroatom in the bis-phosphane, complex **3** lacks such a potential protonation site. The *N* in **1** is expected to be more basic than that in **2** by 5 pK_a units in analogy to the difference in pK_as of the free amines.[15]

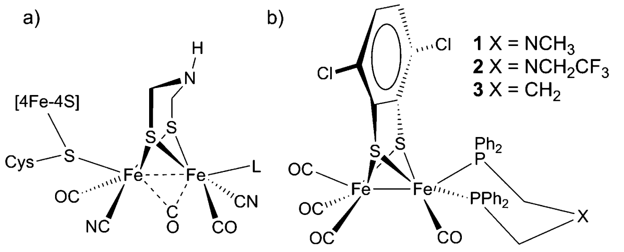

Chart 1

Complexes **1–3** were synthesized from [$Fe_2(Cl_2bdt)(CO)_6$][16] by stirring the latter in the presence of a slight excess of the bidentate phosphane in toluene or THF. All complexes were characterized by IR, ^1H NMR and ^{31}P NMR, elemental analysis and in the case of **1** by X-ray crystallography.† In the solid state structure of **1**, a π-stacking interaction between the bdt and a phenyl ring of the bis-phosphane leads to a mixed apical–basal (ap,ba) coordination of the latter.† RT ^{31}P NMR spectra of **1–3** (CH_2Cl_2) all feature exclusively one singlet at practically identical chemical shift of δ = 55.5, 55.6 and 55.6 ppm, respectively, indicating that each of the three complexes prevails in the same coordination mode.[14] At temperatures lower than -50 °C, the signal in the ^{31}P NMR spectra of **1** and **2** splits into two singlets.† The coalescence temperature for **3** is lower than those of **1** and **2**, preventing the observation of two signals even at -80 °C. This behavior is consistent with inversion barriers that are considerably smaller for cyclohexane compared to those of *N*-alkylated piperidines.[17] Since the bdt ligand in **1–3** is planar and thus cannot give rise to isomers in the same way as a more flexible propyldithiolate (pdt),[14] it is clear that the two signals stem from two dissimilar *P*-centers and that the bis-phosphane in **1–3** thus coordinates in an ap,ba fashion also in solution. The IR spectra of the three complexes are identical in the ν_{CO} region, indicating that the three bidentate phosphanes have an equal electronic impact on their respective Fe_2 sites and that the electron-density at the iron centers in **1–3** is equivalent. The IR pattern of **1–3** is similar to that reported for an analogue **4**[12,18] that is identical to **1** with the exception of a pdt instead of the bdt bridge in **1**.† The three major absorptions of **1–3** at 2032, 1965 and 1899 cm^{-1} are shifted by 13 cm^{-1} towards higher frequencies compared to those of **4** due to the electron-withdrawing character of the Cl_2bdt bridging ligand.[19] In other words, electron density in **1–3** is substantially lower compared to that in **4**, a situation that may impede the formation of hydride complexes as described for **4**. To study differences in the protonation behavior of **1–3** caused by their second coordination sphere, the three complexes were separately exposed to an equivalent acidic medium (CH_2Cl_2, $HBF_4·OEt_2$).

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Exposure of complex **1** to these conditions gives rise to a new species that is characterized by IR absorptions at 2044, 1980 and 1908 cm^{-1} (Fig. 1a). Compared to the IR spectrum of **1** that of the protonated form is shifted by 12 cm^{-1} to higher frequencies, consistent with a protonation at the nitrogen (**[$1H_N$]**$^+$).[12] This assignment is confirmed by ^1H NMR data which show no signal in the hydride region.† The bis-phosphane in **[$1H_N$]**$^+$ presumably still resides in the ap,ba coordination mode as the signal in its ^{31}P NMR spectrum is only marginally shifted to 59 ppm. The presence of only one signal also suggests that the ring-flip of the *N*-protonated, six-membered metalloazaheterocycle either proceeds fast on the NMR time-scale or protonation occurs selectively either in the axial or the equatorial position. This behavior is in contrast to complex **4**, which showed two *N*-protonated species that differ in the stereochemistry at the *N*.[12]

In contrast to the IR spectrum of **[$1H_N$]**$^+$, protonation of complex **2** results in the formation of a species with ν_{CO} frequencies at 2106, 2058 and 1978 cm^{-1} (Fig. 1b). The much greater shift of 74 cm^{-1} towards higher energy compared to that of the non-protonated starting material is consistent with protonation of the Fe–Fe site and the formation of **[$2H_{Fe}$]**$^+$.[12,18] The ^1H NMR spectrum of **[$2H_{Fe}$]**$^+$ shows a doublet of doublet at −12.3 ppm (*J* = 7.5, 22.5 Hz, Fe*H*Fe) and a triplet at −10.2 ppm (*J* = 20 Hz, Fe*H*Fe). These two hydride signals correlate with an AB system and a singlet in the ^{31}P NMR as demonstrated in a 2-dimensional ^1H–^{31}P NMR correlation experiment (Fig. 2). There are thus two hydride isomers of **[$2H_{Fe}$]**$^+$ that differ in the orientation of the phosphane ligands (ba,ba and ap,ba). These results also prove that protonation of the Fe–Fe bond is still feasible under these conditions despite the electron-withdrawing character of the Cl_2bdt ligand compared to the pdt analogue **4**.

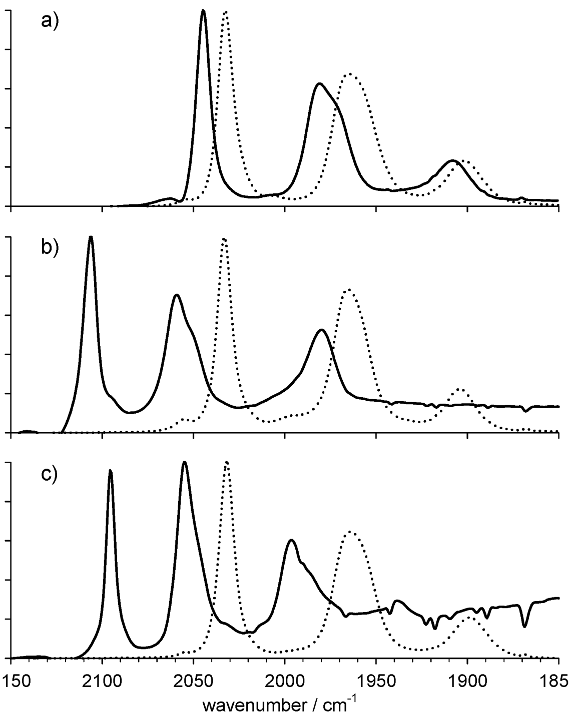


Fig. 1 Carbonyl region of the IR spectra obtained for solutions (3 mM) of **1** (a), **2** (b) and **3** (c) in CH_2Cl_2, before (dotted line) and after the addition of $HBF_4{\cdot}OEt_2$ (solid line).

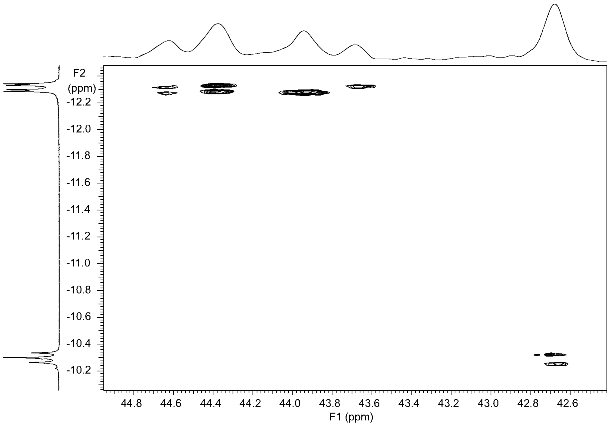
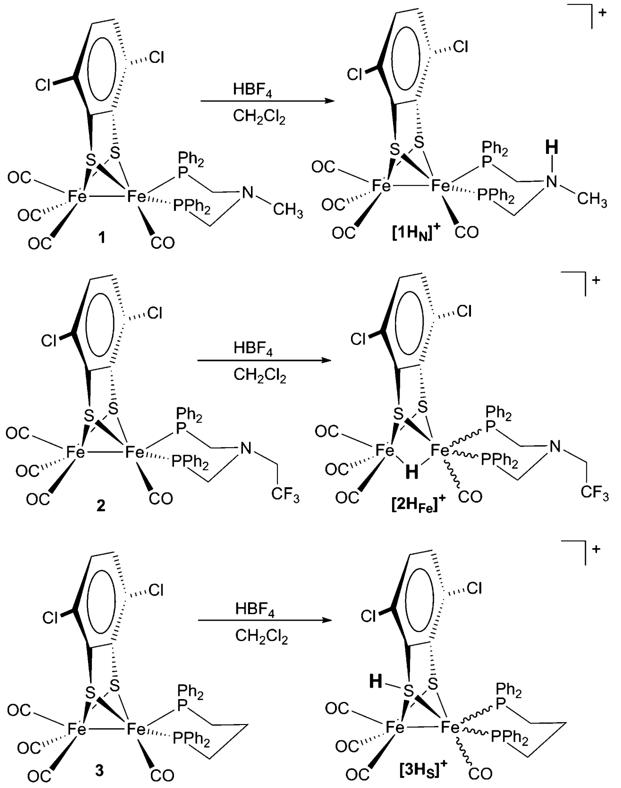


Fig. 2 2D ^1H–^{31}P HMBC NMR characterization of **[$2H_{Fe}$]**$^+$ in CH_2Cl_2.

Whereas the difference in reactivity between **1** and **2** can easily be explained by a simple difference in basicity, *i.e.* the amine in **1** is a more basic site than that in **2** which is thus protonated at the Fe–Fe site instead, the protonation behavior of **3** is not expectable. Treatment of complex **3** with $HBF_4{\cdot}OEt_2$ in CH_2Cl_2 affords a species with IR absorptions at 2095, 2055 and 1996 cm^{-1} that are thus shifted by 63 cm^{-1} compared to those of **3** (Fig. 1c). Furthermore, no signal in the typical hydride region of its ^1H NMR spectrum can be found.

In the absence of a nitrogen in the bis-phosphane bridge, the only remaining basic sites are the bdt sulfur ligands. Although suggested by DFT calculations to be a potential intermediate in catalysis,[20] it is only the second time that *S*-protonation is experimentally observed in [FeFe] H_2ase models. Interesting to note are the similarities between the two systems. *S*-Protonation was first observed in a $Fe_2(CO)_4(PMe_3)_2$ system which contains a strongly electron withdrawing azadithiolate (adt) ligand.[21] It thus seems that electron deficient Fe_2 sites are a general prerequisite for this unusual reactivity. Protonation of bdt-based *S*-ligands has furthermore been described almost 20 years ago by Sellmann *et al.* for $[Fe^{II}(bdt)_2]^{2-}$.[22] The observed shift of the ν_{CO} IR-frequencies upon *S*-protonation of **3** (63 cm^{-1}) lies between that observed for *S*-protonation of the above mentioned $[(adt)Fe_2(CO)_4(PMe_3)_2]$ (130 cm^{-1})[21] and that of a *S*-ethylated $[(pdt)Fe_2(CO)_4(PMe_3)_2]$ (40 cm^{-1}).[23] The ^{31}P NMR spectrum of **[$3H_S$]**$^+$ shows one singlet at 9.6 ppm, suggesting a rapid proton exchange between the two *S* ligands. Prontonation of the bdt-*S* greatly weakens the Fe–S bond which results in a low stability of **[$3H_S$]**$^+$ and rapid decomposition under ambient conditions.

Since the electronic content of the $Cl_2bdtFe_2(CO)_4(Ph_2PR)_2$ cores in **1–3** are identical, their different protonation behavior has to be explained by their second coordination spheres (Scheme 1). In the presence of a *N*-base in the bis-phosphane bridge in **1** and **2**, protonation occurs at the most basic site of the complexes, *i.e.* at the *N* in complex **1** and the Fe–Fe bond in complex **2**. The basicity of the Fe–Fe bond in **1–3** thus has to lie between that of the two *N*-containing bis-phosphane ligands in **1** and **2**. Since complex **2** is not protonated at the bdt-*S*, the basicity of this site has to be lower than that of the



Scheme 1 Complexes **1–3** and their different protonation products.

Fe–Fe bond. Complex **3** which lacks the *N*-base possesses sufficient electron density at the Fe_2 site to allow for protonation is however protonated at the bdt-*S* instead. Complex **3** thus does not follow the order of protonation site preferences that is deduced from the protonation behavior of **1** and **2**, and **[3H$_S$]$^+$** has to be assigned as a kinetic protonation product. This assignment in turn implies that complex **2** contains a structural feature that allows the system to find its thermodynamic minimum, *i.e.* the Fe–Fe site. The *N* in the bisphosphane of **2** is the only difference compared to **3** and thus has to be made responsible for assisting protonation of the Fe–Fe bond, presumably by shuttling protons from the surrounding medium to the metal site. This behavior is in accordance to that described for related diiron[12,13] and nickel[24] complexes.

In this work, we could demonstrate that protons can be directed to three different sites of a Fe_2 complex by careful design of the second coordination sphere. Since perfect control of the second coordination sphere can be assumed in the enzyme, it is interesting to hypothesize if similar kinetic products may be intermediates in the enzymatic catalytic cycle, thereby providing higher-energy pathways that may look unfavorable from a purely thermodynamic viewpoint.

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