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METAL SULPHUR COMPLEXES FOR MODELLING OF NITROGENASE ENZYMES

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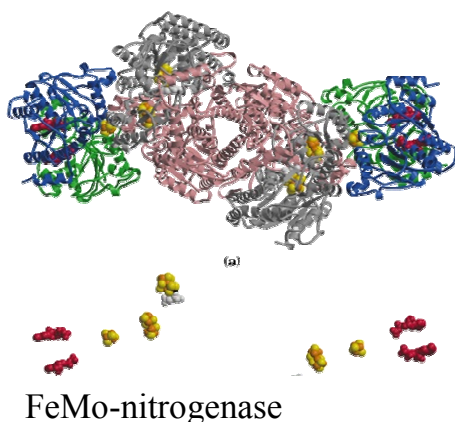
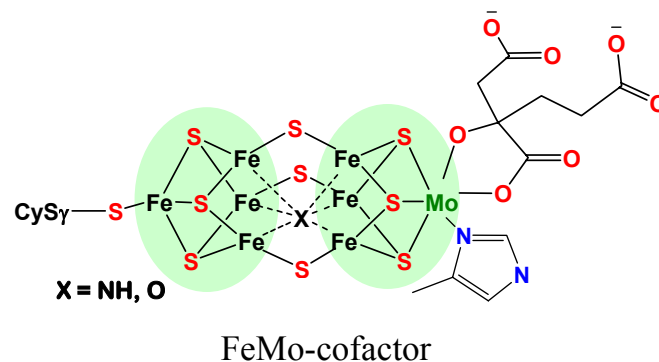
ABSTRACT

A new pyS_4 and $\text{pyN}_2\text{H}_2\text{S}_2$ -based iron and ruthenium complex have been synthesized and characterized in order to bind nitrogenase-relevant small molecules. These fragments were found to bind and stabilize the hydrazine small molecule which is a very important step in the nitrogenase fixation cycle. X-ray structural analysis of the hydrazine complexes deserve special interest because all types of hydrazine hydrogen atoms are involved in a system of inter- and intramolecular $\text{NH}\cdots\text{S}$ and $\text{NH}\cdots\text{N}$ hydrogen bonding with the sulfur donors (thiolate, thioether) as well as the solvate hydrazine N atoms.

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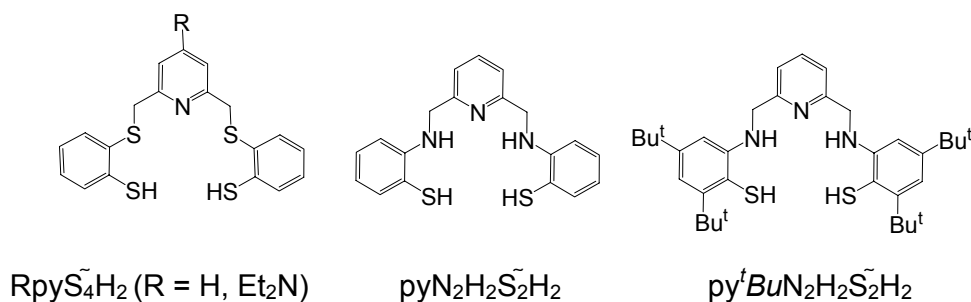
INTRODUCTION

Transition metals in sulfur-dominated coordination spheres form the active centres of numerous oxidoreductases such as nitrogenases, hydrogenases and CO dehydrogenases.^[1] In the search for low-molecular weight compounds that combine structural and reactivity features of nitrogenase enzymes, it was found that transition metal complexes containing [M(pyS₄)] fragments [pyS₄²⁻ = 2,6-bis(2-mercaptophenylthiomethyl) pyridine(2)] (M = Fe, Ru) bind many nitrogenase-relevant molecules such as CO, NO, N₂H₄, N₂H₂ and NH₃, although not N₂.^[2] As was pointed out earlier,^[3] a major factor for the binding of N₂ can be considered to be a high electron density at the metal centres.



We describe herein a systematic study of the influence of the pyridine ring substituents as well as the substitution of σ -donor- π -acceptor thioether functions by σ -donor amine functions on the electron density at the metal centres and the reactivity of the resultant complexes and the applications for nitrogenases functions. We focus on the syntheses of the new $Et_2Npy\tilde{S}_4H_2$ ligand and the related iron and ruthenium complexes of the two ligands $Et_2Npy\tilde{S}_4H_2$ and $pyN_2H_2S_2\tilde{H}_2$ ^[4] [pyN₂H₂S₂²⁻ = 2,6-bis(2-mercaptophenylamino methyl)pyridine(2)] are also described.

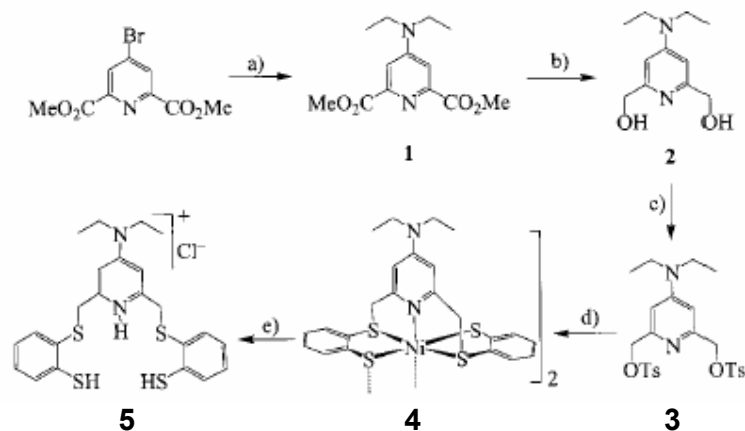
The synthesis of the new steric $py^tBuN_2H_2S_2\tilde{H}_2$ ligand in order to solve the solubility problem as well as to decrease the tendency of dimer formation via $\tilde{M}\tilde{S}\tilde{M}$ thiolate bridged bonds which blocks the free coordination sites of the metal centers will also be discussed.^[5] Efforts are underway to investigate the coordination chemistry of the new steric ligand towards different metal ions.



Scheme 1.

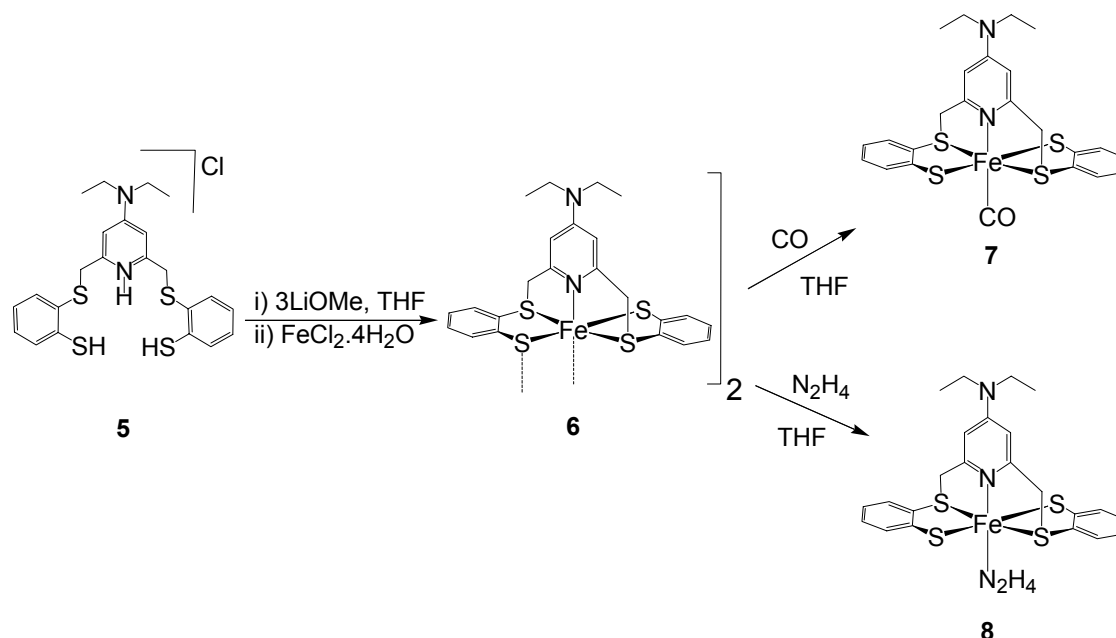
RESULTS AND DISCUSSIONS

The synthesis of the new $\text{Et}_2\text{NpyS}_4\text{H}_2 \cdot \text{HCl}$ (**5**) ligand has been described in details in our previous paper starting from Celedamic acid (Scheme 2).^[6]



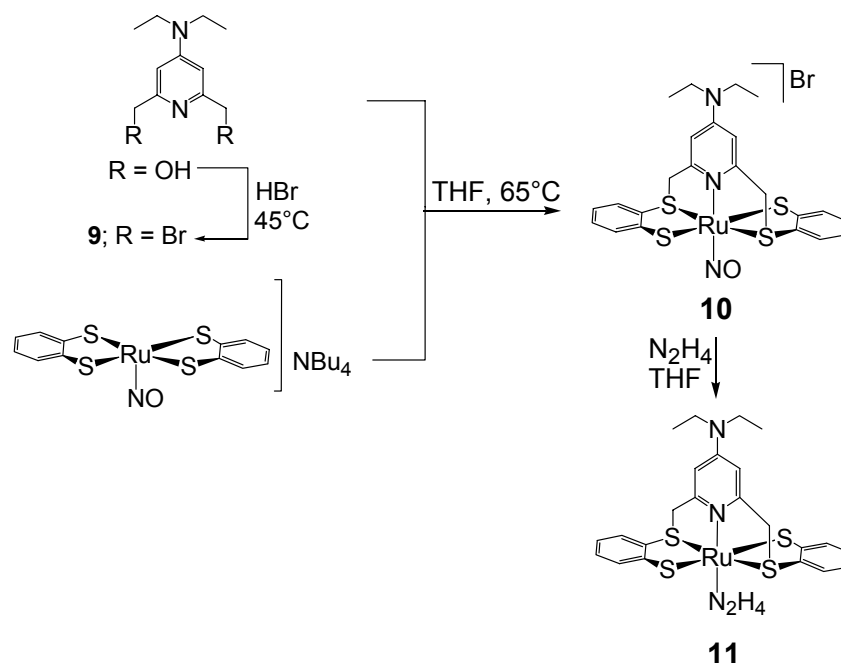
Scheme 2.

The reaction between $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and the dianion $\text{Et}_2\text{NpyS}_4^{2-}$ resulting from deprotonation of **5** with three equivalents of LiOMe afforded yellow paramagnetic $[\{\text{Fe}(\text{Et}_2\text{NpyS}_4)\}_x]$ (**6**) [μ_{eff} (293 K) = 5.15 μB]. The solidstate structure of **6** has not yet been determined but from the mass spectrum as well as the solubility; x is probably 2. Dinuclear **6** readily coordinates CO to give the C_2 symmetric and diamagnetic mononuclear $[\text{Fe}(\text{CO})(\text{Et}_2\text{NpyS}_4)]$ complexes (**7**) indicating that **6** partially dissociates in solution into two unsaturated monomers. Alternatively, complex **7** could also be obtained directly from $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{Et}_2\text{NpyS}_4^{2-}$ in the presence of CO. Complexes **7** exhibits characteristic $\nu(\text{CO})$ (1948 cm^{-1}) bands in its IR (KBr) spectrum. The $\nu(\text{CO})$ of **7** is low when compared with that of $[\text{Fe}(\text{CO})(\text{pyS}_4)]$ (1963 cm^{-1}),^[7] indicating a high electron density at the Fe centre which in turn results in a strong FeCO bond.


Scheme 3.

Treatment of an equimolar amount of **6** with N_2H_4 in THF afforded the hydrazine complex $[\text{Fe}(\text{N}_2\text{H}_4)(\text{Et}_2\text{NpyS}_4)]$ (**8**). Complex **8** is stable and could be isolated as a solid and completely characterised. This is in contrast to the analogous $[\text{Fe}(\text{N}_2\text{H}_4)(\text{pyS}_4)]^{[2a]}$ which is highly labile towards N_2H_4 elimination and could be isolated in crystalline form only in the presence of excess N_2H_4 . One possible reason for this high stability could be that all N_2H_4 hydrogen atoms are involved in both intra- and intermolecular hydrogen bonding as found for solid **8** in the solid state (Figure 1).

The coordination of the $\text{Et}_2\text{NpyS}_4\text{H}_2$ ligand has been also investigated towards ruthenium which could be expected to be less labile (Scheme 4). As a first target complex $[\text{Ru}(\text{NO})(\text{Et}_2\text{NpyS}_4)]\text{Br}$ (**10**) was prepared. It was obtained by template alkylation of $\text{Bu}_4\text{N}[\text{Ru}(\text{NO})(\text{S}_2\text{C}_6\text{H}_4)_2]^{[8]}$ with $\text{Et}_2\text{Npy}(\text{CH}_2\text{Br})_2$ (**9**) in boiling THF. Complex **10** exhibits a low $\nu(\text{NO})$ frequency (1858 cm^{-1} in KBr) compared with the related complex $[\text{Ru}(\text{NO})(\text{pyS}_4)]\text{Tos}$ (1892 cm^{-1}).^[2e] This further indicates a higher electron density at the ruthenium centre.



Scheme 4.

When a red brown THF suspension of **10** was treated with N₂H₄, a green solution was formed from which the hydrazine complex [Ru(N₂H₄)(Et₂NpyS₄)] (**11**) was isolated. Complex **11** is stable over prolonged periods of time in both the solid state and solution. The high stability is also because of both intra- and intermolecular hydrogen bonding as found for solid **11** in the solid state (Figure 1).

The coordination chemistry of the sulphur amine pyN₂H₂S₂-H₂ has been also investigated in order to have a high electron density at the metal center by substitution of the π-donor-π-acceptor thioether functions by the only π-donor amine functions. Treatment of [RuCl₂(py)₄] with pyN₂H₂S₂-H₂ in the presence of two equivalents of LiOMe (for deprotonation of the thiol S-H functions) afforded a red [Ru(py)(pyN₂H₂S₂)] (**12**). The pyridine coligand in complex **12** proved to be labile and could be replaced by DMSO at room temperature to afford [Ru(DMSO)(pyN₂H₂S₂)] (**13**). Complex **13** proved also substitution inert towards CO, N₂H₄, N₂ or NO ligands. It could not be reacted with CO at room temperature at pressures ranging from 1 to 100 bar.

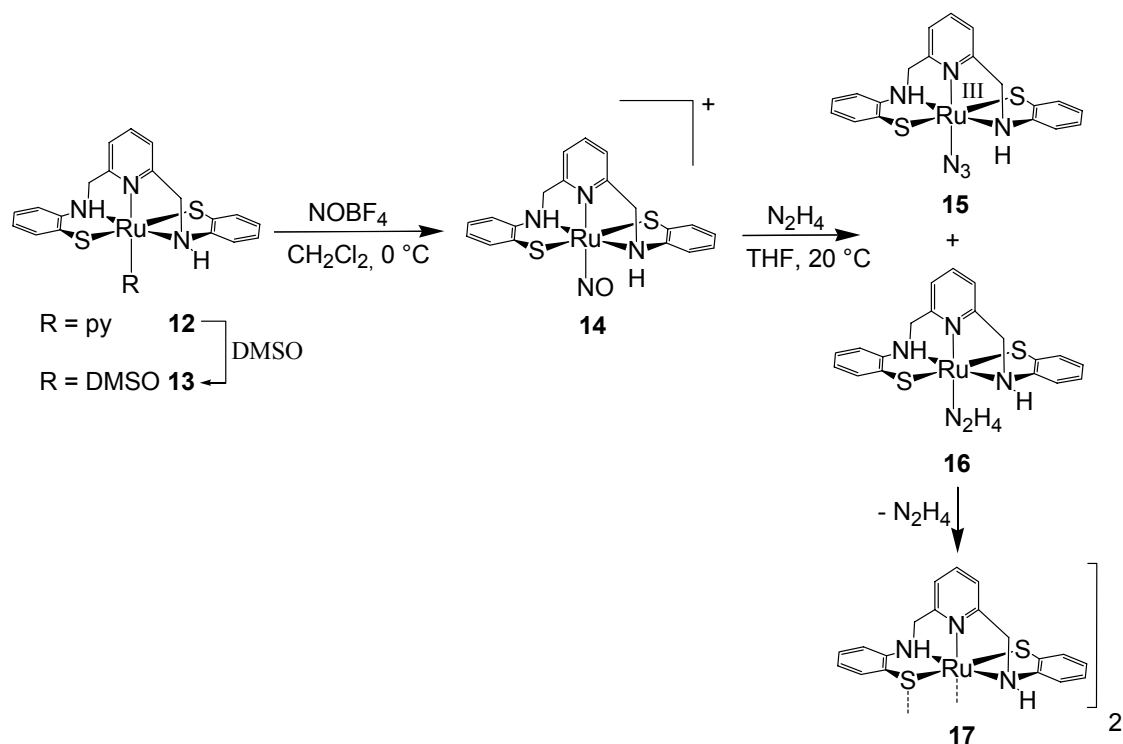
When a CH₂Cl₂ suspension of [Ru(DMSO)(pyN₂H₂S₂)] (**13**) was treated with an equimolar amount of NOBF₄, a brown [Ru(NO)(pyN₂H₂S₂)]BF₄ ([**14**]BF₄) was produced.^[9] It was surprising to observe such reaction of **13** with NOBF₄ under normal conditions. However, complex [**14**]BF₄ showed a ν(NO) frequency at 1858 cm⁻¹ in KBr and 1870 cm⁻¹ in MeOH and this made the cation [**14**]⁺ a candidate for attempts to convert the NO into N₂ ligand by addition of nitrogen nucleophiles to the nitrosyl N atom.^[10] For this reason, complex [**14**]BF₄ was treated with N₂H₄.

When a brown THF suspension of [14]BF₄ was treated with excess of anhydrous N₂H₄, gas was evolved and a red-brown solid was formed, which exhibits a strong band in its IR (KBr) spectrum at around 2037 cm⁻¹, consistent with the formation of a bound azide complex **15**. However, this product was so insoluble in all common solvents that it could not be adequately characterized. An orange solid was formed upon addition of ether to the filtrate, which was isolated and characterized as hydrazine complex [Ru(N₂H₄)(pyN₂H₂S₂)] (**16**). Complex **16** demonstrates that the [Ru(pyN₂H₂S₂)] fragment can bind "hard" coligands. However, **16** proved too labile to be used as a starting material. All efforts to oxidize **16** or to get a N₂ species by the reaction of N₂ with **16** remained as yet unsuccessful, instead dinuclear [{Ru(pyN₂H₂S₂)}₂] (**17**) was formed. The dinuclear **17** was found not to react with boiling DMSO, pyridine, or with CO in these solvents.

In order to reduce the M-S-M bridging capacity of the ligand and hence the tendency of the complexes to oligomerize, efforts are now underway to insert a bulky group in the ortho position to the sulphur donors.

X-ray Crystal Structure Determinations

The crystal structures of the complexes [Fe(N₂H₄)(Et₂NpyS₄)] (**8**), [Ru(N₂H₄)(Et₂NpyS₄)] (**11**) and [Ru(N₂H₄)(Et₂NpyS₄)]·N₂H₄ (**11**·N₂H₄) were determined by X-ray crystallography. Figures 1 depict the molecular structures of the complexes. The Et₂NpyS₄ ligand acts as a square-pyramidal coordination cap and the overall geometry around the iron centre is pseudo-octahedral. The pyridine N1 donor and the coligand L or the bridging S donor of a second Fe fragment as well as the two thiolate and the two thioether donor atoms of the Et₂NpyS₄²⁻ ligand occupy corresponding *trans* positions and thus provide the steric rigidity of the py(CH₂)₂ backbone. A comparison of the geometrical parameters of the structures demonstrates that the Fe₋donor distances in all cases lie in the usual range observed for diamagnetic [FeNS₄] cores.^[2a,2b,2e,6] The Fe[~]S(thiolate) distances (average 230 pm) are slightly longer than the Fe[~]S(thioether) distances (average 223 pm).



Scheme 4.

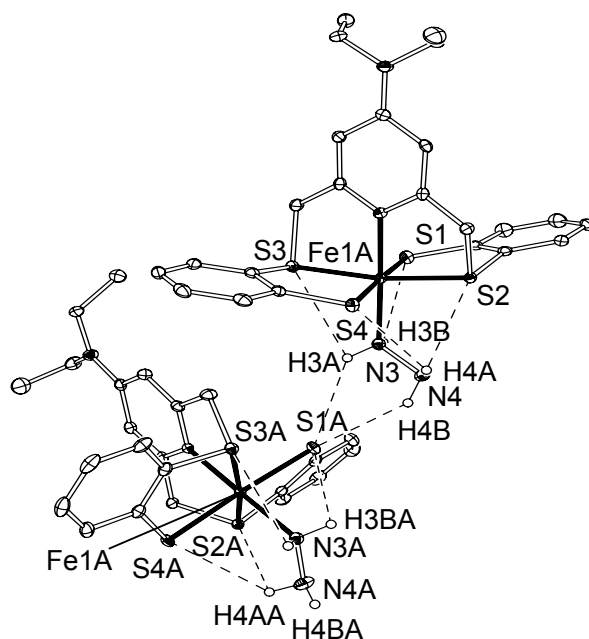
The crystal structures of the complexes **8**, **11** and **11**·N₂H₄ deserve special interest because all types of hydrazine hydrogen atoms are involved in a system of inter- and intramolecular $\tilde{\text{N}}\text{H}\cdots\text{S}$ and $\tilde{\text{N}}\text{H}\cdots\text{N}$ hydrogen bonding with the sulfur donors (thiolate, thioether) as well as the solvate hydrazine N atoms. The hydrogen bonds are indicated by both the $\tilde{\text{N}}\text{H}\cdots\text{S}$ and $\tilde{\text{N}}\text{H}\cdots\text{N}$ vectors as well as the distances which are shorter than the sum of the corresponding van der Waals radii ($r_{\text{H}} = 120$ pm, $r_{\text{S}} = 185$ pm).^[11] Figure 3 shows the molecular structures and the hydrogen bonding geometry for **8** and **11**·N₂H₄.

The crystal lattices of **8** and **11** contain chains of molecules which are connected by intermolecular $\tilde{\text{N}}\text{H}\cdots\text{S}$ (thiolate) hydrogen bonds and each molecule exhibits additional intramolecular $\tilde{\text{N}}\text{H}\cdots\text{S}$ hydrogen bonds. The type of bonds, bond lengths and bond angles in the two complexes are very similar, only **8** contains an additional $\tilde{\text{N}}\text{H}\cdots\text{S}$ bond. The crystal lattice of **11**·N₂H₄ additionally contains intermolecular $\tilde{\text{N}}\text{H}\cdots\text{N}$ hydrogen bonds between the solvate hydrazine and the coordinated hydrazine. This system of hydrogen bonds is of interest because it contributes significantly to the stabilisation of the N₂H₄ coligand and a similar effect may stabilise the intermediate diazene complex which is assumed to be essential for N₂ fixation.^[2c]

CONCLUSION

The new pentadentate $\text{Et}_2\text{NpyS}_4\text{-H}_2$ ligand has been synthesised with the aim of preparing transition metal complexes which exhibit electron-rich metal centres, possess a core configuration with thiolate, thioether and amine donors and bind biologically relevant small molecules. This goal was achieved as evidenced by the low $\nu(\text{CO})$ frequency of $[\text{Fe}(\text{CO})(\text{Et}_2\text{NpyS}_4)]$ (1948 cm^{-1}) compared with the analogous $[\text{Fe}(\text{CO})(\text{pyS}_4)]$ (1963 cm^{-1}). The $[\text{M}(\text{Et}_2\text{NpyS}_4)]$ fragments ($\text{M} = \text{Fe}, \text{Ru}$) were found to bind and stabilise many nitrogenase-relevant molecules such as CO , NO , and N_2H_4 .

The X-ray structural analyses of $[\text{Fe}(\text{N}_2\text{H}_4)(\text{Et}_2\text{NpyS}_4)]$ and $[\text{Ru}(\text{N}_2\text{H}_4)(\text{Et}_2\text{NpyS}_4)]$ revealed that such complexes can form intra- and intermolecular $\text{NH}\cdots\text{S}$ and $\text{NH}\cdots\text{N}$ hydrogen bonds. This stabilises the hydrazine complex $[\text{Fe}(\text{N}_2\text{H}_4)(\text{Et}_2\text{NpyS}_4)]$ and makes it isolable and stable in the solid state. This is in contrast to the parent complex $[\text{Fe}(\text{N}_2\text{H}_4)(\text{pyS}_4)]$ which was highly labile with respect to elimination of the N_2H_4 coligand and could not be isolated. The results also revealed that the $[\text{Ru}(\text{pyN}_2\text{H}_2\text{S}_2)]$ fragment can bind "hard" coligands such as N_2H_4 but still unstable enough to oxidise to the diazine intermediate. Further modifications are underway in order to reduce the $\text{M}\cdots\text{M}$ bridging capacity of the ligand and hence the tendency of the complexes to oligomerize, efforts are now underway to insert a bulky group in the ortho position to the sulphur donors.



MHz): δ = 0.85 (t, 6 H, 2CH₂CH₃), 2.90 (br., N₂H₄), 3.32 (m, 4 H, 2CH₂CH₃), 4.50 (m, 4 H, 2CH₂), 6.56 (s, 2 H, H_β, pyridine), 7.44 (m, 2 H, C₆H₄), 7.94 (m, 2 H, C₆H₄), 9.72 (m, 4 H, C₆H₄) ppm. IR (KBr): ν = 3318, 3285, 3237 (m, $\tilde{\text{N}}\text{H}$) cm⁻¹. MS (FD⁺, THF): m/z = 512 [Fe(Et₂NpyS₄)]⁺, 1024 [{Fe(Et₂NpyS₄)₂}]⁺. C₂₄H_{30.5}FeN₄OS₄ (563.13): calcd. C 51.19, H 5.46, N 9.95; found C 50.82, H 5.71, N 9.55.

[Ru(N₂H₄)(Et₂NpyS₄)] (11): N₂H₄ (0.5 mL, 16 mmol) was added to a red-brown suspension of **10**·0.3THF (110 mg, 0.16 mmol) in THF (10 mL). Gas evolved and a red solution formed which was concentrated in volume to 3 mL. Addition of MeOH (10 mL) led to precipitation of a red microcrystalline solid which was separated, washed with MeOH (10 mL) and ether (20 mL) then dried in vacuo. Yield 40 mg of **11** · 0.3N₂H₄ · 0.6H₂O (41%). ¹H NMR ([D₆]DMSO, 269.60 MHz): δ = 1.02-0.83 (t, 6 H, 2CH₂CH₃), 3.10-2.99 (m, 4 H, 2CH₂CH₃), 3.30 (m, 1 H, NH₂), 4.24-4.22 (d, 1 H, NH₂), 4.31-4.28 (d, 2 H, CH₂), 4.37 (d, 2 H, CH₂), 4.42 (d, 1 H, NH), 6.19 (s, 2 H, H_β, pyridine), 6.67-6.59 (m, 4 H, C₆H₄), 7.37-7.35 (m, 2 H, C₆H₄), 7.50-7.47 (m, 2 H, C₆H₄) ppm. ¹³C{¹H} NMR (DMF-d₇, 67.83 MHz): δ = 12.02 (CH₂CH₃), 43.25 (CH₂CH₃), 56.69 (CH₂), 102.93, 119.93, 130.61, 132.19, 132.98, 149.98, 158.28 [C(aryl)] ppm. IR (KBr): ν = 3318, 3242, 3100 (m, $\tilde{\text{N}}\text{H}$) cm⁻¹. MS (FD⁺, CH₂Cl₂): m/z = 558 [Ru(Et₂NpyS₄)]⁺, 590 [Ru(N₂H₄)(Et₂NpyS₄)]⁺, 1116 [{Ru(Et₂NpyS₄)₂}]⁺. C₂₃H_{29.7}N_{3.3}O_{0.6}RuS₄ (611.5): calcd. C 45.17, H 4.89, N 10.69, S 20.97; found C 45.16, H 5.07, N 10.53, S 20.63.

[Ru(N₂H₄)(pyN₂H₂S₂)] (16): A mixture of anhydrous N₂H₄ (0.5 ml, exc. 1.5 mmol) and [Ru(NO)(pyN₂H₂S₂)]BF₄ (250 mg, 0.44 mmol) in CH₂Cl₂ (15 ml) was stirred at 20 °C for 24 h. The resultant red-brown solid was removed by filtration. Subsequent addition of Et₂O (40 ml) to the filtrate led to the precipitation of an orange solid, which was separated, washed with MeOH (10 ml) and Et₂O (20 ml) and dried in vacuo. Yield: 38 mg of **16** · 1.8CH₂Cl₂ · CH₃CN (14%). ¹H NMR ([D₆]DMSO, 269.7 MHz): δ = 7.54 (m, 3H, 2NH + H□, pyridine), 7.32–7.26 (m, 5H, Ar–H), 6.78–6.72 (m, 5H, Ar–H), 4.91–4.86 (dd, 2H, CHH), 4.53–4.47 (d, 2H, CHH), 3.23 (s, 2H, NH₂), 2.13 (d, 2H, NH₂). ¹³C{¹H} NMR ([D₆]DMSO, 100.4 MHz): δ = 157.44, 151.61, 150.47, 134.28, 130.69, 125.90, 125.27, 119.97, 119.55, (C[Aryl]), 69.1 (CH₂). IR (KBr): $\tilde{\nu}$ = 3232, 3141 (w, N–H). MS (FD⁺, CH₂Cl₂): m/z = 452 [Ru(pyN₂H₂S₂)]⁺, 484 [Ru(N₂H₄)(pyN₂H₂S₂)]⁺, 904 [{Ru(pyN₂H₂S₂)₂}]⁺. Calc. for C_{22.8}H_{27.6}Cl_{3.6}N₆RuS₂ (679.97): C, 40.25; H, 4.09; N, 12.33. Found: C, 40.16; H, 4.16; N, 12.25%.

[{Ru(pyN₂H₂S₂)₂}]⁺ (17): A yellow suspension of pyN₂H₂S₂H₂ (284 mg, 0.8 mmol), LiOMe (1.6 ml, 1.6 mmol of 1 N solution in MeOH) and [RuCl₂(CH₃CN)₄] (270 mg, 0.8 mmol) in MeOH (30 ml) was heated at 65 °C for 3 h. The resulting fine red crystals were separated, washed with MeOH (20 ml) and Et₂O (30 ml) and dried in vacuo. Yield: 230 mg of **17** · MeOH (62%). IR (KBr): $\tilde{\nu}$ = 3252, 3242 (w, N–H). MS (FD⁺, DMSO): m/z = 904 [{Ru(pyN₂H₂S₂)₂}]⁺. Calc. for C₃₉H₃₈N₆ORu₂S₄ (937.17): C, 49.98; H, 4.09; N, 8.97; S, 13.69. Found: C, 49.81; H, 3.82; N, 8.94; S, 13.54%.

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