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S–H bond cleavage in molecules of biological interest with CpFe(dppe)I†

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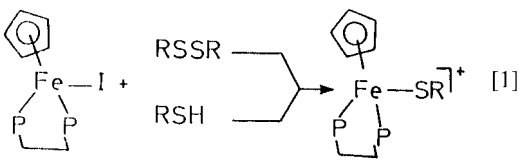
The reaction of CpFe(dppe)I (Cp, cyclopentadienyl; dppe, $Ph_2P(CH_2)_2PPh_2$) with biologically active RSH molecules (L-cysteine hydrochloride, dithiothereitol and 2-mercaptoethanol) in the presence of NH_4PF_6 and in methanol as solvent afforded the new iron(III) thiolate complexes [CpFe(dppe)SR]PF_6. The blue–black paramagnetic complexes were characterized by elemental analysis and IR, EPR and UV–visible spectroscopy. The selective S–H bond cleavage in the thiols suggests a possible utilization of the organometallic iron(II) complexes as inhibitors in some cysteine proteases. The spectroscopic properties of the new complexes have been compared with those of other Fe–S models as well as with Fe–S proteins. Copyright © 2000 John Wiley & Sons, Ltd.

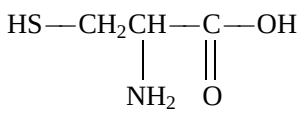
Keywords: bond cleavage; thiols; iron(III) complexes

INTRODUCTION

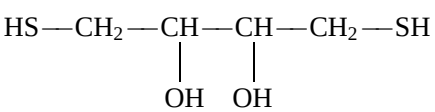
Biorganometallics is an emergent research field, which can be defined as the synthesis, reactions and applications of organometallic complexes with biogenic ligands.[1] Among the metal complexes with biologically important ligands are the metal–sulfur compounds, where the sulfur arises from compounds of biological interest.[2] Of these, the iron–sulfur metalloproteins are the most important and widely studied. These proteins contain active sites comprising tetrahedrally coordinated iron(II) and/or iron(III) ions with sulfido and S-bound cysteinato ligands. We have reported recently on oxidative additions of simple aliphatic and aromatic thiol and dithio ethers to the organometallic fragment $CpFe(dppe)^+$ (Eqn [1]).[3] (Cp, cyclopentadienyl; dppe, $Ph_2P(CH_2)_2PPh_2$).



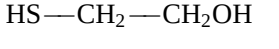
Now we present the similar behaviour of thiols of biological interest: L-cysteine hydrochloride (**1**), dithiothreitol (**2**) and 2-mercaptoethanol (**3**) (Fig. 1).



1 L-Cysteine



2 *three*-1,4-Dimercapto-2,3-butanediol (dithiothreitol)



3 2-Mercaptoethanol

Figure 1 The molecules of biological interest used in the formation of complexes.

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Table 1 IR[a] spectra (cm^{-1}) of complexes **4–6**

	CpFe(dppe)		Ligand				PF_6
Complex	Cp	dppe	ν(C=O)	ν(OH)	$\nu(NH_2)$	ν(SH)	$\nu(PF_6)$
4	1105	695	1612	3430	3269; 3269	—	841
5	1105	695	—	3428		2338	842
6	1103	695	—	3381		—	840

[a] In solid KBr.

RESULTS AND DISCUSSION

Thiols **1, 2** and **3** react with CpFe(dppe)I in methanol as solvent in the presence of NH_4PF_6 as halide abstractor, to give the iron(III) thiolate complexes **4, 5** and **6** respectively (Eqn [2]).

$$\text{CpFe(dppe)I} + \text{HSR} \xrightarrow[\text{CH}_3\text{OH}]{\text{NH}_4\text{PF}_6} [\text{CpFe(dppe)SR}]\text{PF}_6 \quad [2]$$

1–3 **4–6**

The complexes were characterized by elemental analysis and IR, UV–visible and EPR spectroscopic methods. The IR spectra (Table 1) show the typical bands of the PF_6 anion, $\nu(PF_6) \approx 840\ cm^{-1}$,[4] and of the CpFe(dppe) fragment,[5] $\delta(C_5H_5) \approx 1100\ cm^{-1}$; δ (out-of-plane C_6H_5) $\approx 690\ cm^{-1}$. Characteristic bands of the ligands were also observed: $\nu(NH_2)$ at 3425 cm^{-1} and 3269 cm^{-1}, ν(OH) at $\approx 3400\ cm^{-1}$ and $\delta(NH_2)$ at 1591 cm^{-1}. As expected, the ν(SH) band[3b,6] was not observed for complexes **4** and **6** but for 5 this vibration was observed at 2338 cm^{-1} due to the pendant uncoordinated S–H group of the ligand.

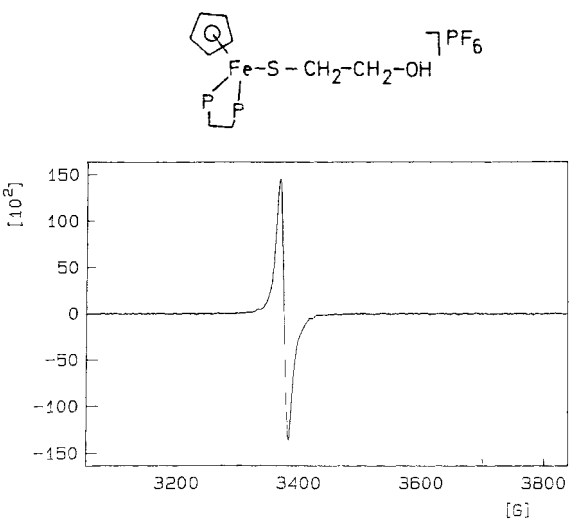

Figure 2 EPR spectrum of complex **6** in dichloromethane solution at room temperature.

As expected for d^5 low-spin iron(III) complexes the compounds are paramagnetic; EPR spectra at room temperature in CH_2Cl_2 exhibit one symmetrical singlet peak (Fig. 2). The g values (Table 2) are somewhat higher than the free electron value, as is usually observed for 17-electron iron(III) compounds having a single occupied HOMO with a predominantly metallic character.[7] Lacking hyperfine splitting, the spectra of these compounds cannot delineate the precise make-up of the simply occupied molecules orbital (SOMO), but they do indicate that the radical retains approximately octahedral symmetry, since lower symmetry would lead to a splitting of the g tensor. Thus the g values for complexes **4–6** are similar to those recently reported for iron(III) thiophenolate model complexes.[2]

The UV–visible spectra of complexes **4–6** exhibit the absorption pattern at *ca* 580 characteristic of compounds containing the Fe(III)-SR chromophore.[3] The spectrum for **6** is shown in Fig. 3.

It is interesting to note the high selectivity of the CpFe(dppe)I complex towards S–H bond cleavage, as well as towards S thiolate coordination, despite the other O–H, N–H and S–H bonds as well as the

Table 2 ESR[a] and UV–visible[b] data for complexes **4–6**

		$>\lambda_{max}(\varepsilon)$	
Complex	g (iso)	λ_1	λ_2
4	2.076	441(205)	553(820)
5	2.069	446(196)	573(790)
6	2.066	441(175)	583(700)

[a] In CH_2Cl_2.
[b] In CH_2Cl_2, λ in nm, ε in $(mol\ l^{-1})^{-1}$.

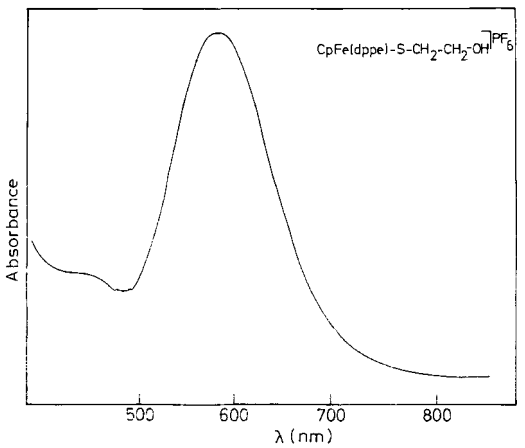

Figure 3 UV–visible spectrum of complex **6** in dichloromethane solution at room temperature.

other coordination sites present in the molecules (the latter selectivity being due to the low lability of the Fe–C_5H_5 and Fe–P bonds in the CpFe(dppe) fragment which preclude the generation of other coordination sites). Several examples of S–H activation of molecules of biological interest by metal complexes involve coordination of the NH_2 or C=O pendant group.[8] On the other hand, as noted previously,[8b] complexes with ligands like cysteine or other sulfur-containing molecules of biological interest are not very common; those with organometallic fragments are still very scarce.[1]

COMPARISON WITH OTHER IRON–SULFUR MODELS

It is interesting to compare the results obtained for the complexes **4–6** with those obtained for other iron–sulfur models. The active sites of proteins usually involve iron(II) or iron(III) ions coordinated to *S*-cysteinate and/or *N*-macrocyclic ligands, where the iron atoms can be in low- or high-spin configuration.[1,2] The EPR parameter values obtained for the complexes **4–6** compare well with *g* values for other iron–sulfur models ($[LFe^{III}MFe^{III}L]^{n+}$ (L = 1,4,7-Tris(4-t-butyl-2-mercaptobenzyl)-1,4,7-triazacyclononane; M = Cr, Co, Fe, Ni, Sn), g = 2.1,[9a] and Fe(III)–N_4 macrocyclic complexes, g = 2.06[10a]) but they are somewhat lower than those obtained for some iron–sulfur proteins ; *g* values of *ca* 2.2 have been measured for the proteins CoA(*Rhodospirillum rubrum*)[11] and P450CAM(*Pseudomonas putida*).[11]

Most interestingly the UV–visible absorption patterns of the complexes **4–6** are close to that reported for the $[LFe^{III}]$ model[9a] and for some iron–sulfur proteins.[10a] The band around 570 nm has previously been assigned tentatively to a *d–d* transition in $[CpFe(dppe)SR]PF_6$ complexes.[3] However, in some iron–sulfur model[9b,10b] and in iron–sulfur proteins[2,10a] a band around 770 and 819 nm, respectively, has been associated with a thiolate S–iron charge-transfer transition.

POSSIBLE BIOCHEMICAL APPLICATIONS

Cysteine proteases are an important class of enzymes in which the reactive group at the active site involved in catalysis is the thiol group.[12,13] They are ubiquitous in Nature and play vital roles in numerous physiological processes, including arthritis, osteoporosis, Alzheimer's disease and cancer cell invasion.[13] Although several organic compounds have been used as inhibitors of cysteine proteases,[13] to our knowledge organometallic complexes have not been used. The above results show that the S–H bond is cleaved selectively in molecules of biological interest by the organometallic reagent CpFe(dppe)I leaving unaltered the other coordinating groups of the sulfur-containing compounds **1–3**, namely OH, NH_2 and C=O. The use of Reaction [2] determine the inhibitor activity of some cysteine proteases is under investigation.

EXPERIMENTAL

Infrared spectra were recorded on an FT-IR Perkin-Elmer 2000 spectrophotometer. Visible absorption spectra were measured on a Varian DMS-90 spectrophotometer in cuvettes 1 cm long. EPR spectra were run on a Brucker ECS 106 spectrometer using a rectangular mode cavity with 50 Hz field modulation. The measurements were made with the microwave band X (9.79 GHz) using dichloromethane as solvent. Elemental analyses were performed with a Perkin-Elmer 240 microanalyser.

All reactions were carried out under nitrogen by standard Schlenk techniques. Solvents were purified by standard procedures. CpFe(dppe)I was

prepared by previously reported methods.[14] L-Cysteine (Riedel–de Haenag) dithiothreitol (Sigma) and 2-mercaptoethanol (Sigma) were used as received.

General procedures for synthesis of the complexes

CpFe(dppe)I [0.14 g (0.22 mmol), 0.15g (0.23 mmol) or 0.13 g (0.2 mmol) respectively] was stirred with the corresponding stoichiometric amount of RSH: **1**, 0.038 g (0.21 mmol); 2, 0.026 g (0.172 mmol); **3**, 0.0158 g (0.2 mmol) in the presence of NH_4PF_6 (0.08 g (0.56 mmol) in methanol (30 ml) for 24 h at room temperature. The solvent was evaporated under vacuum, the black–blue solid residue was extracted with dichloromethane (15 ml) and filtered through Celite, and the filtrate was concentrated under reduced pressure to a volume of *ca* 10 ml. Upon addition of an n-hexane–diethyl ether (1:1) mixture, blue–black microcrystals were precipitated and were washed several times with diethyl ether and with n-hexane and dried under reduced pressure.

Yields and microanalysis were as follows.

Complex 4
Yield 0.0979 g (53.8%). Analysis: Found. C, 51.85; H, 4.35; S, 1.6. Calcd for $C_{34}H_{36}F_6O_2NSP_3Fe$:C, 50.88; H, 4.48; S 1.7%.

Complex 5
Yield 0.1172 g (66.21%). Analysis: Found: C, 50.59; H, 4.49; S, 5.43. Calcd for $C_{35}H_{39}F_6O_2S_2P_3Fe$: C, 51.34; H, 4.64; S 5.5%.

Complex 6
Yield 0.098 g (57.65%). Analysis: Found: C, 51.66; H, 4.75; S, 5.91. Calcd for $C_{33}H_{35}F_6OSP_3Fe$: C, 51.25; H, 4.01; S 5.87%.

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