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Preliminary communication

Control of axial ligation in mercaptide-chelated porphyrins by conformational and environmental effects: synthetic compounds for cytochrome P-450 *,**

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Abstract

Two models which reproduce the cytochrome P-450 spectra at room temperature, with iron porphyrins containing a thiolate chain grafted on highly cross-linked polystyrenes have been made.

The active site of cytochrome P-450 contains one iron porphyrin embedded in a large cleft of the apoprotein [1a], and there is strong evidence that the fifth ligand is a thiolate from a cysteine residue [1b]. The presence of this axial ligand induces Soret-band splitting (λ_{max} 380, 450 nm) of the visible spectrum when the sixth position on the metal center is occupied by carbon monoxide. Among the problems in designing a model system which would reproduce this special feature are (i) that of forcing coordination of the thiolate moiety to the iron(II) center, and (ii) that of preventing the oxidation of this thiolate residue into disulfide in the iron(III) "resting form" model complex [2]. A large excess of the thiolate [3], or a "tail" attached covalently at one [4] or two ends [5] of the porphyrin have both been used to hold the thiolate group on the metal center. Bimolecular reactions leading to the formation of disulfides have been avoided through site separation by using hindered porphyrins [3b,6] or by lowering the temperature [3b,7].

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* Dedicated to Prof. J. Tirouflet on the occasion of his retirement.

** *Editor's note*. This paper was judged suitable for publication in this Journal because although not concerned with organometallic compounds it forms part of a series in which organometallic derivatives are involved.

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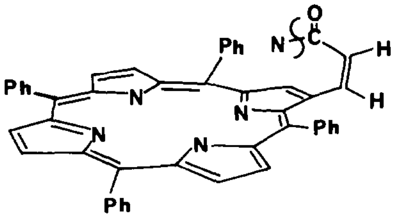
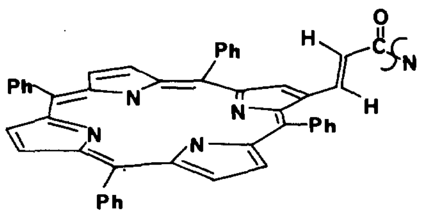


(1)



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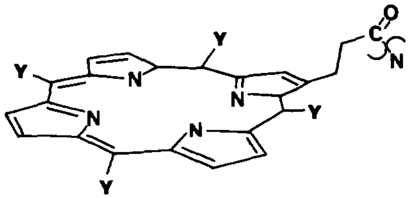
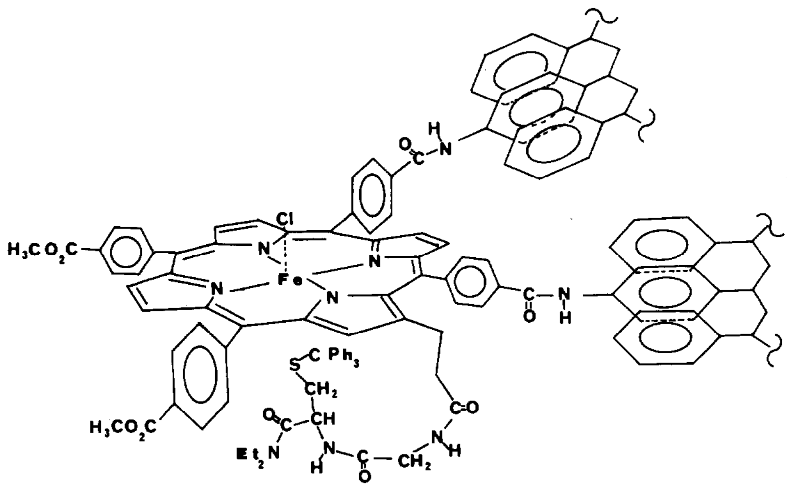


(3, Y = C_6H_5
4, Y = ($\underline{p}$-CO_2H)C_6H_4)

a, N = Gly-(SMe)-$\underline{L}$-Cys-OEt
b, N = Gly-(SBz)-$\underline{L}$-Cys-OMe
c, N = ½[Gly-(S-)-$\underline{L}$-Cys-OEt$]_2$
d, N = Gly-(STr)-$\underline{L}$-Cys-NEt_2
e, N = Gly-(S^-)-$\underline{L}$-Cys-NEt_2
f, N = Gly-(S^-)-$\underline{L}$-Cys-OMe
g, N = Gly-(S^-)-$\underline{L}$-Cys-OEt

Recent results on site separation control by the use of polymers demonstrated that iron(II) porphyrins covalently bound to highly cross-linked polystyrenes enable efficient separation of the macrocycles and mimic the reversible fixation of molecuar oxygen by myoglobine [8]. Moreover, the use of these macroporous polymers also afforded the hydrophobic environment required for the active site of the enzyme. In this communication we report our attempts to reproduce the hyperporphyrin absorption spectrum by constraining the coordination to iron(II) of a cysteinate residue covalently bound to porphyrin rings, either by a conformational effect in solution or by an "environmental" effect on highly cross-linked polystyrene.

The syntheses of the substituted porphyrins **1**H_2–**3**H_2 have been described previously [9]. Metallation by zinc has shown that axial binding of the protected (*S*-Me) residue of the cysteine is observed only for **1a**Zn^{II} [10]. Refluxing **1b**H_2, **3b**H_2 or **3c**H_2 in THF with iron(III) chloride affords the corresponding **1b**$Fe^{III}Cl$ or **3**$Fe^{III}Cl$ complex. Both **3b**$Fe^{III}Cl$ and **3c**$Fe^{III}Cl$ are reduced in DMSO by the complex of 18-crown-6 with sodium dithionite [4]. The corresponding **3**$Fe^{II}(dmso)_2$ or **3**Fe^{II}(CO)(dmso) complexes respectively are formed under argon (λ_{max} 427, 530, 556 nm) or carbon monoxide (λ_{max} 418, 536 nm). Removal of the protecting group is brought about by further addition of sodium hydride [4]. However, under carbon



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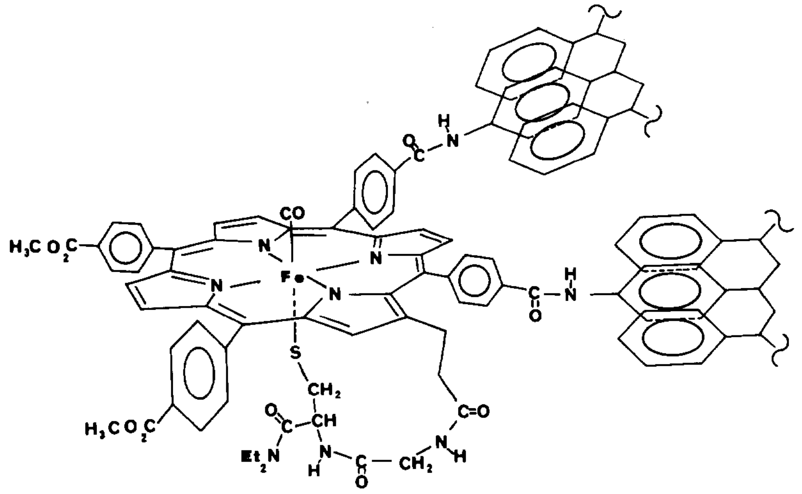

(6)

monoxide the expected splitting of the Soret band is not observed and only bands assigned to $3Fe^{II}$(dimsyl) (λ_{max} 447, 578, 621 nm), $3Fe^{II}$(CO)(dimsyl) (λ_{max} 420, 540 nm) and $3Fe^{II}$(CO)(dmso) are present. The absence of coordination of the cysteinate residue to the iron(II) center may arise from the presence of a large excess of solvent and dimsyl sodium. Several authors have pointed out the inherent difficulties in approach of the appended ligand to the metal center [4–6]. An exact balance of factors such as geometric disposition and electronic character of the incipient thiolate is important in promoting this ligation. The use of the so-called '*cis-endo*' tail porphyrin **1bH**$_2$ [10] might enforce the coordination of the *S*-cysteinate. Indeed, the reduction of **1bFe**^{III}Cl under the above mentioned conditions (dmso/$Na_2S_2O_4$/18-crown-6) gives **1bFe**^{II}(CO)(dmso) (Fig. 1a, λ_{max} 425, 542 nm).

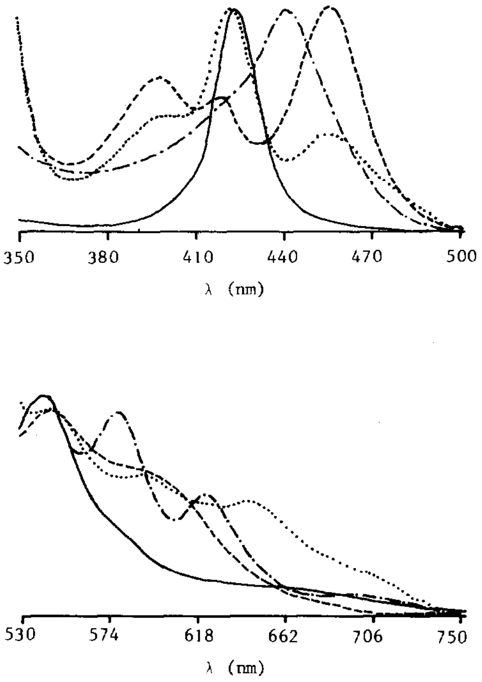

Fig. 1. UV-visible spectra in dmso of (a, ———) **1b**Fe^{II}(CO)(dmso), (b, ·–·–·) **1b**Fe^{II}(CO)(dimsyl), (c, ······) **1f**Fe^{II}(CO), and (d, ------) of Fe[T(*p*-CO_2CH_3)PP](CO)(PhS^-) in toluene with a large excess of PhSK-18-crown-6.

Cleavage of the *S*-benzoyl group with dimsylpotassium affords first the dimsyl complex **1f**Fe^{II} (dimsyl) (Fig. 1b, λ_{max} 447, 581, 626 nm), then a mixture of the expected complex (Fig. 1c), which exhibits a splitted Soret band (λ_{max} 402, 457 nm), and its substitution product with dmso **1f**Fe^{II}(CO)(dmso). This spectrum is very similar to that of the product obtained from the reaction of Fe(Cl)T(*p*-CO_2CH_3)PP with a large excess of potassium thiophenate, in the presence of 18-crown-6 (Fig. 1d).

The appropriate balance between geometric and electronic effects for the control of axial ligation is also achieved when **4d**Fe^{III}Cl is grafted onto a styrene-*p*-aminostyrene copolymer cross-linked with 30% of divinylbenzene [8a]. Cleavage of the *S*-trityl group of species **5** by TFA, followed by reduction of a toluene suspension with 0.1 *M* 18-crown-6-sodium dithionite in methanol, gave a material which was characterized by UV-visible reflectance spectroscopy (Fig. 2b) under carbon monoxide (760 torr). The conversion of the thiol into the thiolate residue is best carried out with potassium acetanilide-18-crown-6 [6]. Figure 2c featured a new absorption at λ_{max} 456 nm but the tail of the sodium dithionite adsorption prevents the observation of a band at λ_{max} ~ 400 nm. However, the reflectance spectrum resulting from the reaction of potassium thiophenate-18-crown-6 with grafted Fe(Cl)T(*p*-CO_2H)PP [8] strongly supports the presence of the model species **6** (Fig. 2d). This species is easily decarbonylated, either by pumping off the CO atmosphere or by sweeping with argon. After five carbonylation–decarbonylation cycles the spectroscopic features remain unchanged. Therefore, linking the iron porphyrin to

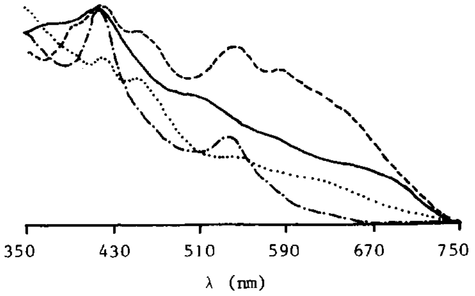

Fig. 2. Reflectance UV-visible spectra under carbon monoxide of (a, ———) species **5** after removal of the *S*-trityl group, (b, ·–·–·) this species after reduction (c, ······) this species after reaction with potassium acetanilide, and (d, ------) the reaction product of grafted Fe(Cl)T(p-CO_2H)PP with PhSK-18-crown-6.

the appropriate polymer also allows control of the axial coordination of a thiolate ligand. We believe that in this case external coordination is prevented by (i) the weak complexing behaviour of the reaction medium and the non-polar and hydrophobic character of the copolymers, and (ii) the preferential conformation of the thiolate chain associated with steric interactions within the polymer pore containing the covalently-bound porphyrin, which enforces the thiolate ligand to stay above the iron(II) center.

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