Preparation of a Cobalt Analogue of Verdoheme by Coupled Oxidation of Cobalt(II) Octaethylporphyrin

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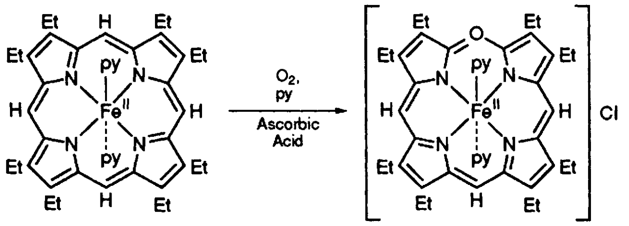
Conditions are reported which allow octaethylporphyrin cobalt(II) to be oxygenated to form the verdoheme analogue, octaethyloxaporphyrincobalt(III) dichloride, which has been isolated and characterized by X-ray diffraction.

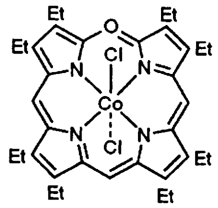
Oxidation of pyridine solutions of iron(II) porphyrins by molecular oxygen in the presence of a reducing agent such as ascorbic acid (coupled oxidation) produces verdoheme (Scheme 1) which can be converted into biliverdin.[1,2] This process has been widely used as a model for the metabolic destruction of haem that is catalysed by haem oxygenase.[3] Since cobalt(II) porphyrins, like iron(II) porphyrins, are capable of binding dioxygen, there has been considerable interest in the behaviour of cobalt porphyrins in these oxidative processes. While it was initially reported that cobalt haem was oxidized by haem oxygenase,[4] later reports suggested otherwise.[5,6] *In vitro*, cobalt porphyrins are inhibitors of haem oxygenase but *in vivo* they induce haem oxygenase formation.[7] Cobalt substituted myoglobin and haemoglobin form biliverdin when treated with dioxygen and ascorbate, but only the Co^{II}, not the Co^{III}, form reacts. In pyridine solution, attempts to effect coupled oxidation of cobalt porphyrins have not yielded the cobalt analogue of either verdoheme or biliverdin.[6,8] Under typical coupled oxidation conditions it appears that ascorbate is unable to reduce Co^{III} to Co^{II}, and we, like others,[6,8] found that Co^{II} porphyrins in pyridine are simply oxidized to their Co^{III} form.

By modifying the reaction conditions, we find that it is possible to obtain a cobalt analogue of verdoheme by a coupled oxidation route. A suspension of 400 mg of ascorbic acid and 100 mg of [(oep)Co^{II}] in a mixture of 80 ml of dichloromethane and 10 ml of tetrahydrofuran (THF) was cooled in a liquid-nitrogen bath until it partly froze. Dioxygen was vigorously bubbled through the slurry, and the mixture was stirred and allowed to warm to room temperature under an atmosphere of dioxygen. After 2 h, when the initially red solution had become green, the solution was evaporated, redissolved in dichloromethane, and filtered to remove ascorbic acid. The solution was stirred in air for 24 h. The resulting solution was concentrated, and chromatographed on a silica gel column. Elution with dichloromethane produced first a pink band, due to unreacted [(oep)Co^{II}], and then a red-green band that was collected to give a 64% yield of microcrystals of [(oeop)$Co^{III}Cl_2$] **3**, from dichloromethane-*n*-



1 [(oep)$Fe^{II}(py)_2$]   **2** [(oeop)$Fe^{II}(py)_2$]Cl

Scheme 1 oep = dianion of octaethylporphyrin; oeop = monoanion of octaethyloxaporphyrin; py = pyridine



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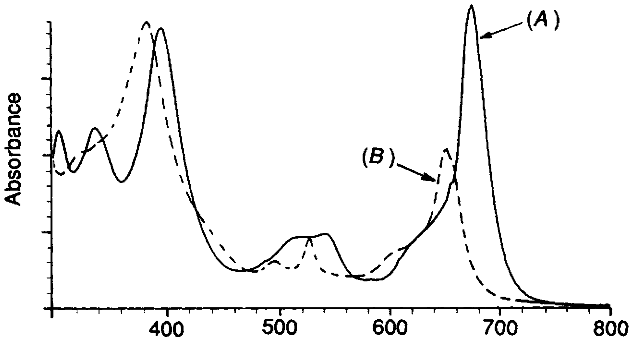

Fig. 1 Absorption spectra of chloroform solutions of (*A*), [(oeop)-$Co^{III}Cl_2$] **3**: λ_{max}/nm (ε/cm^{-1} dm^3 mol^{-1}): 338 (5.3 × 10^4), 398 (8.2 × 10^4), 514 (2.0 × 10^4), 540 (2.1 × 10^4), 620 sh (1.8 × 10^4) and 678 (8;8 × 10^4); (*B*), [(oeop)$Fe^{II}(py)_2$]Cl **2**, with 5% pyridine (from ref. 2)

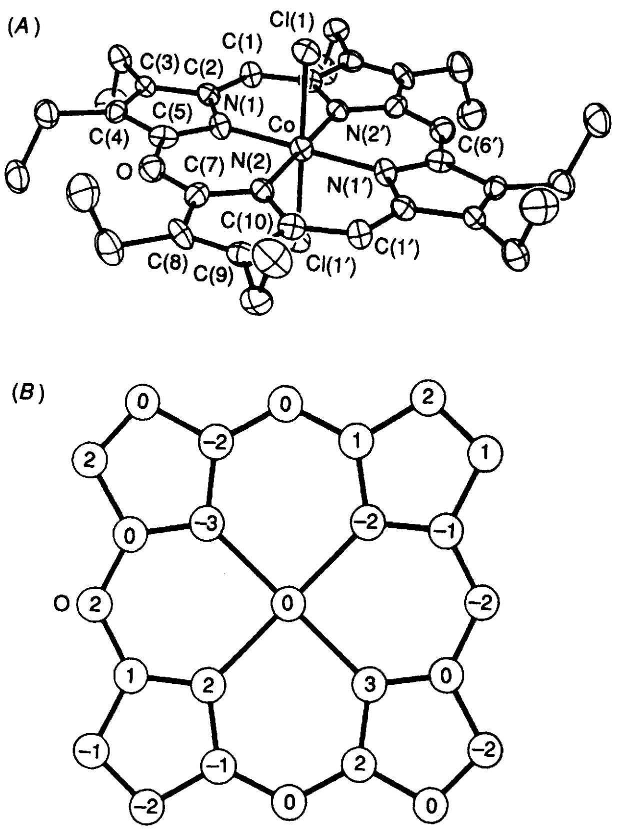

Fig. 2 (*A*) A perspective view of [(oeop)$Co^{III}Cl_2$] with 50% thermal contours for all atoms. (*B*) Out-of-plane displacements (in units of 0.01 Å) of the core atoms of the oxaporphyrin from the mean plane of the macrocycle.

hexane. The electronic absorption spectrum of the product is shown in Fig. 1. This spectrum, with nearly equally intense features at 398 and 678 nm, is similar to the spectrum of [(oeop)Fe^{II}(py)$_2$]Cl (trace B).[2] The ^{1}H NMR spectrum of **3** is characteristic of a diamagnetic complex [δ 9.71 (2 H) and 9.70 (1 H), *meso*-H; 3.68 (16 H) complex m, methylene-H; 1.85, 1.83, 1.82, 1.79 (24 H) overlapping triplets, methyl-H; in $CDCl_3$ at 24 °C].

The results of an X-ray diffraction study of **3** are shown in Fig. 2.† The cobalt ion is six-coordinate with two axial halide ligands. The Co–N distances [1.964(5), 1.956(5) Å] are in the range observed for cobalt(III) porphyrins.[9] The macrocycle is planar as Fig. 2(*B*) shows. The cobalt ion sits at a crystallographic inversion centre, and there is disorder in the location of the oxygen bridge. The oxygen atom is equally distributed between the site shown in Fig. 2 and the opposite site labelled C(6′).

The conditions used for the preparation of [(oeop]Co^{III}Cl$_2$] are particularly crucial to its successful synthesis. Ascorbic acid is insufficiently soluble in dichloromethane alone to let it act as a solvent. THF was added to increase the solubility of the ascorbic acid. However, in THF alone the reaction is less well controlled and further bleaching of the porphyrin and its oxidation products occurs. Dichloromethane also reacts to supply the axial ligands of the product. The cooling of the solution in a dinitrogen bath presumably serves to increase the dioxygen concentration to a level that facilitates the oxidation. The yield of the cobalt verdoheme analogue **3** obtained by this procedure (64%) actually exceeds that of verdoheme itself where the best yield reported is only 50%.[2]

Further studies to identify any other products of this coupled oxidation process and its mechanism are in progress.

We thank the National Institute of Health (GM 26226) for financial support.

Received, 21st September 1993; Com. 3/05712G

Footnote

† *Crystal data*: dark-green needles of [(oeop)CoCl$_2$]·2CH$_2$Cl$_2$ that were obtained by diffusion of *n*-hexane into a dichloromethane solution of the complex crystallize in the monoclinic space group $P2_1/c$ with a = 12.702(5), b = 8.125(3), c = 19.327(5) Å, β = 101.23(2)° at 130 K with $Z = 2$ using graphite-monochromated Mo-Kα (λ = 0.71073 Å) radiation. Refinement of 1803 reflections with $F > 4.0\sigma(F)$ and 218 parameters yielded $R = 0.057$; $R_w = 0.054$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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