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A New Method for the Preparation of Oxaporphyrins: Reaction of Metallo Porphyrins with IF

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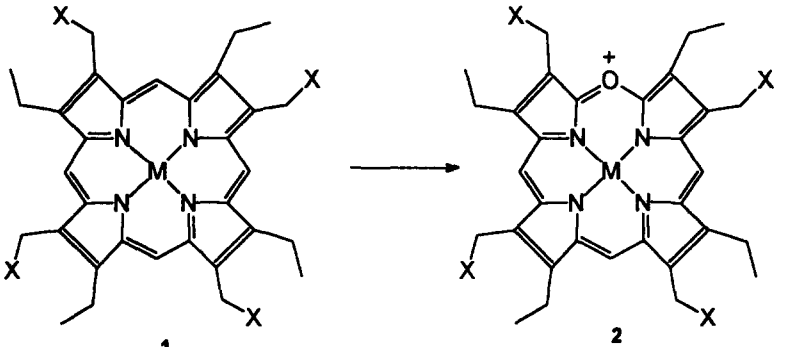
Abstract: Reaction of Co(II) or Cu(II) derivatives of etioporphyrin, octaethylporphyrin, coproporphyrin I tetramethyl ester and mesoporphyrin IX dimethyl ester with N-iodosuccinimide and triethylamine trihydrofluoride results in the formation of the oxaporphyrin (verdoheme) analog while the Ni analogs give mesofluoro and oxyporphyrin derivatives. © 1997 Elsevier Science Ltd.

The combination of N-halosuccinimide (NXS) and triethylamine trihydrofluoride (TEA.3HF) generates halogen fluoride, which is a convenient and effective reagent for the halofluorination of alkenes.[1] During our studies on the modification of porphyrins using this reagent, we observed an unusual reaction product identified as oxaporphyrin (verdoheme), in which one of the *meso* carbon atoms is replaced by an oxygen atom. Previously, such derivatives were obtained via a coupled oxidation procedure, involving air oxidation of haeme in pyridine solution in the presence of a reducing agent (ascorbic acid or hydrazine). This process readily produces a deep green, diamagnetic complex verdoheme which can be converted to linear tetrapyrrole (biliverdin), providing a model for the haeme oxidase reaction.[2-5] Preparation of the cobalt oxaporphyrin has also been achieved by modifying the coupled oxidation reaction conditions[6] and Zn oxaporphyrin analogs were obtained by photooxygenation of Zn oxyporphyrins in dry benzene/CH_2Cl_2.[7] Here we report a convenient, alternative method for the preparation of oxaporphyrins using IF as a reagent. The central metal ion of the porphyrin plays a key role in activating and guiding the oxidative attack on the *meso* position of the porphyrin periphery, resulting in the formation of either oxa- or oxy-porphyrin analogs.



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a: M=Cu; X=H, b: M=Co; X=H
c: M=Cu; X=CH_3 d; M=Co; X=CH_3

TEA.3HF (250 μL) was added to a solution of copper etioporphyrin (**1a**) (20 mg) containing N-iodosuccinimide (200 mg) in CH_2Cl_2 (20 mL) and the solution was stirred for 6 h at room temperature. The reaction mixture turned dark and was poured into water, extracted with CH_2Cl_2, concentrated and purified over a silica gel column. Elution with CH_2Cl_2 gave a dark brown material which was discarded. Further elution with 10-20% CH_3CN in CH_2Cl_2 gave a green colored eluate (60%, m.p. 210-212°C). The mass spectrum exhibited a cluster of peaks at 542 (100%) and 544 (51%), corresponding to the two natural isotopes of copper. The high resolution mass spectrum (HRMS) gave 542.2102 which corresponds to the formula $C_{31}H_{35}N_4O^{63}Cu$, suggesting that one of the *meso* carbon atoms of the porphyrin ring is replaced by an oxygen atom. The electronic spectrum of this material (Fig. 1) features peaks at λ_{max} 398 and 668 nm of nearly equal intensity, characteristic of oxaporphyrin derivatives and similar to the reported spectrum of $[(oeop)Fe^{++}(Py)_2]Cl$.[8] On the basis of these data Cu etiooxaporphyrin (**2a**) was assigned to the green compound.

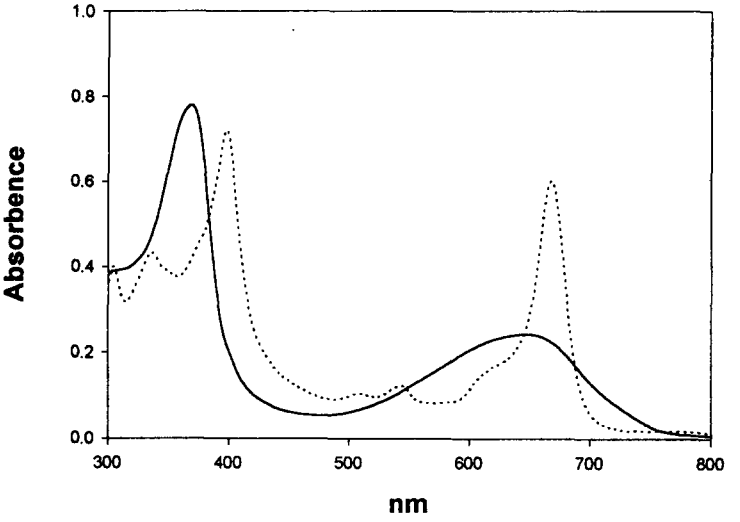
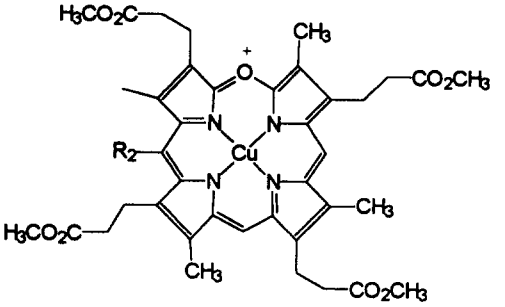


Figure 1. Electronic spectra in $CHCl_3$ of (---) Cu etiooxaporphyrin (**2a**) and (—) etiobiliverdin.

When the reaction was performed under strict anhydrous condition and an atmosphere of nitrogen, the formation of **2a** was almost completely suppressed. Similar treatment of Cu octaethylporphyrins (**1c**) gave **2c** as a green colored compound with absorption peaks at λ_{max} 398 and 669 nm ($CHCl_3$) and HRMS corresponding to $C_{35}H_{43}N_4O^{63}Cu$. Similarly, Cu coproporphyrin I tetramethyl ester gave **3** with absorption maxima at λ_{max} 398 and 664 nm whereas Cu mesoporphyrin XI dimethyl ester gave a mixture of Cu mesoverdohemochrome IX dimethyl esters in low yield, as green colored compounds with absorption maxima at λ_{max} 398 and 663 nm. Hydrolysis of the green complex **2a** with methanolic KOH followed by acidification gave a blue compound with

UV-vis maxima at λ_{max} 368 and 642 nm, characteristic for a biliverdin analog (Fig. 1). Likewise **2c** gave octaethylbilatriene-abc (λ_{max} 367 and 646 nm and HRMS 554.3621 corresponding to $C_{35}H_{46}N_4O_2$).[9] This conversion further supports the proposed structure for the Cu etiooxaporphyrin (**2a**). This method represents the first example for the synthesis of a copper oxaporphyrin. Previous attempts to prepare such a complex using H_2O_2 in pyridine failed.[9]



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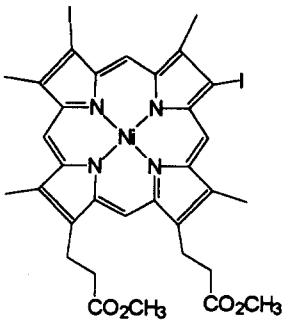

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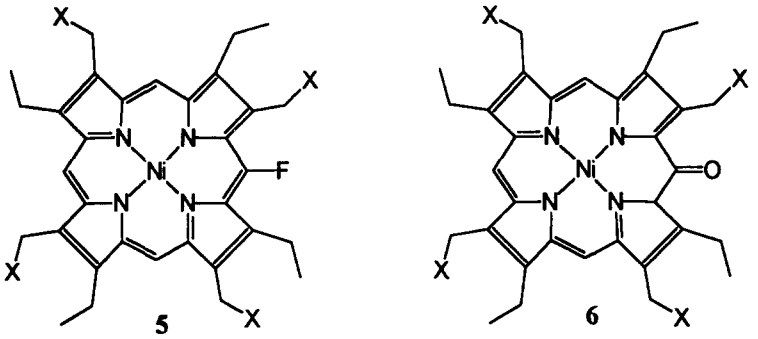
Cobalt etioporphyrin (**1b**) was similarly treated with IF and the crude product was purified. The first eluting band represented a violet colored minor product, with absorption peaks at λ_{max} 395 and 692 nm in a ratio of 1:2. The second major band was a blue-violet colored compound with λ_{max} 394 and 633 nm in a ratio of 40:60. In the presence of air the color of the solution changed to blue and the peaks in the UV-vis shifted to $\lambda_{max}(CH_2Cl_2)$ 397 and 671 nm (mass spectrum (*m/z*) $M^+ = 538$). The spectral shift was attributed to changes in the oxidation state of the central ion (Co^{++} to Co^{+++}). Similar observations were recently reported by Chang *et al.*[10] for **2b**. In this study the latter compound was obtained by an alternate procedure via oxygenation of a Co(II) porphyrinyl naphthoic acid. Using the above reaction condition, Co octaethylporphyrin (**1d**) reacts similarly with IF and gave the corresponding oxaporphyrin analogue[6] **2d** ($\lambda_{max}(CH_2Cl_2)$ 395 and 671 nm; *m/z* $M^+ = 594$). However, upon changing the central metal to Ni, the reactivity of the Ni octaethylporphyrin towards IF decreased and oxaporphyrin could no longer be detected in the reaction mixture. During silicagel column chromatography a small amount of pink material eluted before the starting material. The HRMS gave 608.2825 which corresponds to $C_{36}H_{43}N_4{}^{58}NiF$ and the ^{1}HNMR spectrum confirmed the presence of a fluorine atom at the *meso* position since only two singlets were detected at δ 9.62 and 9.56 accounting for 3 protons (**5b**). A second, more polar compound was eluted and assigned to Ni α-oxyoctaethylporphyrins (**6b**, 30%) (HRMS 606.2868 corresponding to $C_{36}H_{44}N_4{}^{58}NiO$). Similar products were obtained from Ni etioporphyrin (**5a** and **6a**). Treatment of Zn etioporphyrin gave a small amount of Zn oxaporphyrin (5%, λ_{max} 394 and 661 nm) and a major orange product with λ_{max} 542, 575 and 409 nm. The latter was unstable and the spectrum changed to λ_{max} 434 and 542 nm, with a mass *m/z* 606 suggesting that all four *meso* positions were substituted with oxygen atoms. Zn oxyporphyrins are reported quite unstable and prone to air oxidation.[7,11] Similar products were obtained with the Zn octaethylporphyrin. The reaction of Ni deuteroporphyrin results in iodination at the β-position[12] to yield 4 (40-50%) without affecting the *meso* position. The assigned structure

was based on mass and ^1H NMR spectral data which showed the absence of β-protons. The reaction of Fe(II) $(Py)_2OEP$ with IF did not give any oxaporphyrin analog.



a:X=H; b:CH_3

The reaction of etioporphyrin Ni or Cu with ClF and BrF in CH_2Cl_2 yields mono through tetra *meso*-chlorinated or brominated derivatives as the principal products (unpublished results). In summary, our data show that oxidation of metal porphyrins with IF constitutes an efficient alternative method to prepare oxaporphyrins.

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