Isolation of σ-Alkyl-iron(III) or Carbene-iron(II) Complexes from Reduction of Polyhalogenated Compounds by Iron(II)-porphyrins: the Particular Case of Halothane $CF_3CHClBr$

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Fe^{II}(TPP) (TPP = tetraphenylporphyrin), in the presence of an excess of sodium dithionite, reacts with CF_3CCl_3 and halothane $CF_3CHClBr$, leading respectively to the carbene Fe^{II} (TPP)($CClCF_3$) and σ-alkyl-Fe^{III}(TPP)-($CHClCF_3$) complexes, the latter being the first isolated σ-alkyl-Fe^{III}(porphyrin) complex involving a halogen substituent on the carbon bound to iron.

Some polyhalogenated compounds, such as CCl_4 or the widely used anaesthetic halothane, $CF_3CHClBr$, are metabolically reduced in the liver by cytochrome P450-Fe^{II}, leading to stable complexes of this hemoprotein that involve an iron–carbon bond.[1–3] Such polyhalogenated compounds were found to react with iron(II)-porphyrins in the presence of an excess of reducing agent, leading to a rather general method of preparation of iron(II)-carbene complexes, equation (1) P = porphyrin.[4] Recent results suggest that σ-alkyl-iron complexes could be intermediates in the formation of these carbene complexes, equations (2)—(4).[5,6] Accordingly, reduction of compounds containing only one carbon–halogen bond, such as methyl iodide[7] or *p*-nitrobenzyl chloride,[8] by iron(II)-porphyrins, in the presence of an excess of reducing agent, was found to give stable σ-alkyl-Fe^{III} complexes.

$$R^1R^2CX_2 + (P)Fe^{II} \xrightarrow[-2X^-]{+2e^-} [R^1R^2C \rightarrow Fe^{II}(P)] \qquad (1)$$

$$R^1R^2CX_2 + (P)Fe^{II} \xrightarrow{-X^-} R^1R^2\dot{C}X + (P)Fe^{III} \qquad (2)$$

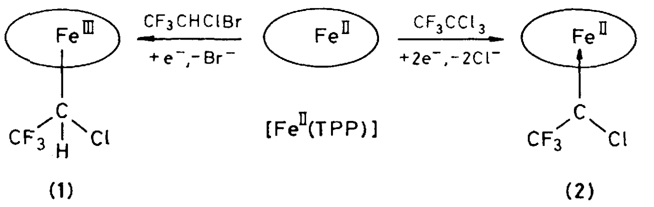
$$R^1R^2\dot{C}X + (P)Fe^{II} \longrightarrow [(P)Fe^{III}\text{—}CXR^1R^2] \qquad (3)$$

$$(P)Fe^{III} — CXR^1R^2 \xrightarrow[-X^-]{+e^-} [(P)Fe^{II} \leftarrow CR^1R^2] \qquad (4)$$

In this note, we report that reduction of halothane, $CF_3CHClBr$, by Fe^{II}(tetraphenylporphyrin) [Fe^{II}(TPP)], in the presence of an excess of reducing agent, leads to a complex exhibiting properties very different from those of the previously mentioned Fe^{II}-porphyrin carbene complexes, whereas reduction of its analogue CF_3CCl_3, under the same conditions, gives the expected [equation (1)] Fe(TPP)($CClCF_3$) carbene complex. These properties favour a σ-alkyl-Fe^{III} structure for the halothane-derived complex.

Reactions of $CF_3CHClBr$ and CF_3CCl_3 (1 mmol) with Fe(TPP)(Cl) (0.5 mmol) in 50 ml of C_6H_6 in the presence of 30 ml of water containing 10 mmol of sodium dithionite, at 20 °C and under argon, led, after 1 h of vigorous stirring, separation of the organic phase, washing with water, and pentane addition, to complexes (**1**) and (**2**), respectively, (yields > 90%). Both complexes exhibit visible spectra† very similar to those of low-spin Fe(TPP)(CR^1R^2) carbene complexes.[4] The elemental analysis (C,H,N,Cl) of complex (**2**) and its mass spectrum with a molecular peak at *m/e* = 784 (for ^{35}Cl) are indicative of a Fe(TPP)($CClCF_3$) structure. Its ^{1}H n.m.r. and i.r. spectra are in full agreement with this carbene structure, since they exhibit characteristics‡ very similar to those of low-spin iron(II)-porphyrin carbene complexes with axial symmetry,[4] such as Fe(TPP)(CClCN).

In contrast, the characteristics of complex (**1**) differ markedly from those expected for the Fe(TPP)($CHCF_3$) carbene complex that should be formed according to equation (1). The elemental analysis (C,H,N,Cl,F) of a sample containing 1 mol of C_6H_6 of crystallization [as determined by g.l.c.] corresponds to the formula Fe(TPP)($CHClCF_3$),C_6H_6. This is confirmed by the mass spectrum of (**1**) (70 eV, 250 °C) which shows a molecular ion at 785—787 (785 for ^{35}Cl) as expected for Fe(TPP)($CHClCF_3$) and fragments at 750 (M^+ – Cl), 703 [Fe(TPP)(Cl)], and 687 [Fe(TPP)(F)]; in addition, above 200 °C, one notes the appearance of the peaks of $CF_2{=}CHCl$, a decomposition product of complex (**1**). The ^{1}H n.m.r. spectrum of (**1**) ($CDCl_3$, Me_4Si, 20 °C) displays broad peaks at δ 6.2 (8H), 5.1 (12H), and –14 (4H) and –14.4 (4H) for the porphyrin protons. The upfield shifted signal consisting of two peaks at –14 and –14.4 p.p.m., was assigned to the pyrrole protons since it is the only signal appearing in the spectrum of complex (**1**) prepared from {*meso*-tetra([$^2H_5$]-phenyl)porphyrin}Fe^{II}. This spectrum is completely different from those of low-spin diamagnetic Fe^{II}(TPP)(carbene) complexes,[4] but looks like those of low-spin (S = 1/2) Fe^{III}(TPP) complexes[9] and particularly those of low-spin σ-alkyl-Fe^{III} complexes, Fe(TPP)(R), recently prepared by reaction of electrochemically generated Fe^{I}(TPP) with alkyl halides (R = Me, Et, or Bu^n).[10] These results suggest a σ-alkyl-Fe^{III} (TPP)($CHClCF_3$) structure for complex (**1**)§ which would be in agreement with (i) its decomposition under mass spectrometry conditions into Fe(TPP)(F) and $CF_2{=}CHCl$, (ii) its reaction with Br_2 leading quantitatively to Fe(TPP)(Br) and $CF_3CHClBr$, and (iii) the chemical shift of its pyrrole protons which is similar to those reported for low-spin σ-alkyl-Fe^{III} complexes Fe(TPP)(R),[10] the appearance of two peaks of equal intensity for these protons in the particular case of (**1**) being related to the presence of a chiral carbon bound to



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† $\lambda(\epsilon)$ = 410 (1.1×10^5), 521 (1.05×10^4) nm for (**1**), 410 (1.8×10^5), 528 (1.07×10^4) nm for (**2**), in C_6H_6.

‡ ^{1}H N.m.r.: δ 8.7 (s, 8H, pyrrole), 8.03 (m, 8H), and 7.73 (m, 12H); i.r. ν_{C-Cl} 845 cm^{-1} as compared with 865 cm^{-1} for Fe(TPP)(CClCN) (ref. 4b).

§ Preliminary results from e.s.r. spectroscopy (100 K) are in agreement with a low-spin Fe^{III} state for (**1**) with *g*-values of 1.6, 2.3, and 3.0: H. Ruf, V. Ullrich, J. P. Battioni, and D. Mansuy, unpublished results.

iron.¶ Moreover, the visible spectrum of (**1**) is nearly superimposable on those of previously described low-spin σ-alkyl complexes $Fe^{III}(TPP)(R)$.[8,10] It is noteworthy that the visible and e.s.r. spectra of (**1**) are completely different from those of the intermediate-spin $Fe^{III}(TPP)(C{=}CAr_2)(Cl)$ complexes which have a carbene moiety inserted between the iron and one pyrrole nitrogen,[11] which spectra are characteristic of the highly distorted geometry of the latter complexes.[11d] This excludes a possible $Fe^{III}(TPP)(CHCF_3)(Cl)$ structure, with a $CHCF_3$ moiety inserted into an Fe–N bond, for complex (**1**).

Complex (**1**) is the first isolated σ-alkyl-Fe^{III}(porphyrin) complex involving a halogen substituent on the carbon bound to iron. The aforementioned results indicate that, depending critically upon the nature of their R^1 and R^2 substituents, certain compounds $R^1R^2CX_2$ containing at least two reactive halogen substituents on the same carbon may be reduced by $Fe^{II}(TPP)$ in the presence of an excess of reducing agent to give either an $Fe^{II}(CR^1R^2)$ carbene complex as is most often encountered,[4] or a σ-alkyl-$Fe^{III}(CXR^1R^2)$ complex, as final stable products. In the case where $Fe^{II}(CR^1R^2)$ carbene complexes are finally isolated, the intermediate formation of the σ-alkyl-$Fe^{III}(CXR^1R^2)$ complexes seems likely, equations (2)—(4), but remains to be established.

Further studies are necessary to determine the structure of the 470 nm absorbing cytochrome P450 complex formed upon anaerobic reduction of halothane by liver microsomes in the presence of an excess of NADPH or sodium dithionite.[1–3] The present results suggest, in addition to the previously proposed carbenic structure $[Fe^{II} \leftarrow CHCF_3]$,[2] a σ-alkyl $[Fe^{III} — CHClCF_3]$ structure. This seems to be supported by very recent data on the microsomal halothane reduction.[12]

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¶ We were not able to detect any signal for the proton of the CF_3CHCl ligand presumably because of its close proximity to the paramagnetic Fe^{III} centre. Similarly, no signal was detected for the protons of the σ-alkyl ligand that are close to iron in various σ-alkyl Fe(TPP)(R) complexes (ref. 10).

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