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N-Substituted Porphyrins Formation from Carbene Iron-porphyrin Complexes : a Possible Pathway for Cytochrome P450 Heme Destruction.

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Abstract : N-substituted porphyrins are formed in high yields upon treatment by CF_3CO_2H or $FeCl_3$ of the iron-porphyrin complexes obtained by one-electron oxidation of iron-porphyrin-vinylidene carbene complexes.

After metabolic activation, several organic compounds containing halo, nitrile, nitro or vinyl groups, selectively degrade hepatic cytochrome P450 in vitro [1]. CCl_4, $CF_3CHClBr$ and various ethylenic compounds have been shown to lead to this degradation reactions also in vivo [1]. In the case of the ethylenic substrates, the cytochrome P450 heme is converted into "green pigments" for which a N-alkyl-porphyrin structure has been recently demonstrated [2].

Cytochrome P450-Fe(II)-carbene complexes are formed either by metabolic reduction of polyhalogenated compounds such as CCl_4 [3] or $CF_3CHClBr$ [4] or by oxidative metabolism of 1,3-benzodioxole derivatives [5]. Iron-porphyrin models of these carbene complexes have been prepared in our laboratory [6] and it has been recently shown that the one-electron oxidation of the carbenic complex $[Fe(TPP)^7(C{=}C(pClC_6H_4)_2)]^8$, 1, by $FeCl_3$ leads to the $[Fe^{III}(TPP)(C{=}C(pClC_6H_4)_2)(Cl)]^9$ complex, 2, where the vinylidene group is inserted into a Fe-N (pyrrolic) bond [10] (scheme 1). In this communication, we show that reactions of complex 2 with acids or one-electron oxidants lead to N-substituted tetraphenylporphyrins, indicating that compounds able to form iron-porphyrin-carbene complexes may lead to irreversible heme N-alkylation by the route indicated in scheme 1.

This formation of N-substituted porphyrins from bridged complexes such as 2 is without precedent in the iron-porphyrin series, but has been suggested as a general reaction of metalloporphyrins [11c,d] and established in the case of Ni-, Zn- and Co- porphyrin complexes [11, 12].

Table 1

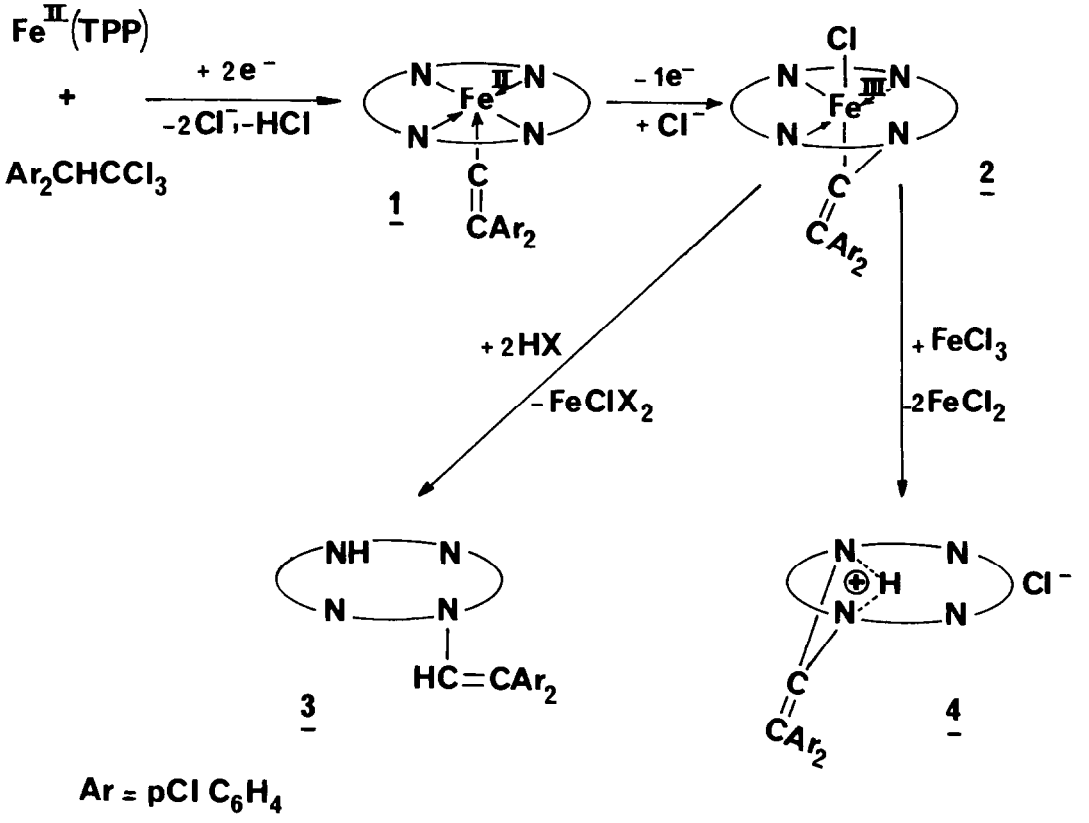
	Compound 3	Compound 4
UV-visible spectrum $\lambda(\varepsilon)$ in C_6H_6 at + 24° C.	435(22×10^4), 497(sh), 529(12×10^3), 569(15×10^3), 622(4.1×10^3) and 684(5×10^3)nm.	430(14×10^4), 509(7.7×10^3), 549(12×10^3), 585(15.5×10^3) and 631(7.1×10^3)nm.
RMN ^{1}H : 250 MHz solvent $CDCl_3$ at 24° C. δ in ppm/TMS	Porphyrin signals : 8.22(s,2H), 8.39(AB System,4H), 7.51(s,2H) (H pyrroles), 8.14(m,8H), 7.64 (m,12H)(H phenyls). - N-Substituent signals :-1.96 (s,1H)(H vinyl), 2.84(d,4H) 5.6(m,4H).	Porphyrin signals :9.34(d,2H,J=4Hz) 9.14(d,2H,J=4Hz),9.05(d,2H,J=4Hz), 8.51(d,2H,J=4Hz)(H pyrroles), 8.36(m,2H)8.0 — 7.68(m,16H) (H phenyls). - N-Substituent signals: 6.21(d, 4H,J=8Hz),2.73(very broad *,4H) - Acidic protons : ~ 2 ppm(3H).
RMN ^{13}C : 22.63MHz, Solvent $CDCl_3$ at 24° C. δ in ppm/TMS	156.4, 153.3, 150.0, 141.8, 139.1, 137.4, 134.2, 133.5, 132.6, 129.6, 128.3, 127.6 126.8, 126.6, 126.0 and 120.2.	150.1, 147.4, 144.0, 142.6, 137.1, 135.8, 135.2, 134.1, 133.8, 131.6, 129.2, 128.2, 127.7, 126.9, 125.4, 124.7, 124.3, 121.4 and 118.0.
Mass spectrometry 70 eV, 200° C.	M^+= 860 for ^{35}Cl(5%), $[M-C_{14}H_8Cl_2]^+$ = 614 (100%) $C_{14}H_8Cl_2$ corresponds to C=C ($pClC_6H_4$)$_2$.	$[M-Cl^-]^+$= 859 for ^{35}Cl (1%) $[M-Cl^--C_{14}H_8Cl_2+1]^+$=614(10%) and a peak (100%) with an isotopic cluster corresponding to $C_{14}H_{10}Cl_2$ (CH_2=C($pClC_6H_4$)$_2$. m/e= 248 for ^{35}Cl).

* Split into two signals - at 2.61 and 2.85 ppm- at 90 MHz (24°C).

Compound 3 is a N-substituted tetraphenylporphyrin as shown by its characteristic electronic spectrum, almost identical to those of N-CH_3 [14] or N-CH_2COOEt-[12a] TPPH, and ^{1}H NMR spectrum exhibiting a characteristic 2H(s)/4H(AB system)/2H(s) pattern for the pyrrolic protons [11d] and large upfield shifts for the protons of the N-vinyl group. Elemental analysis and mass spectrometry agree with the N-vinyl-TPPH structure for compound 3 (vinyl =HC=C(p ClC$_6$H$_4$)$_2$).

Compound 4 exhibits a UV-visible spectrum almost identical to that of cis-21, 22 CHCOOEt-meso-tetraphenylporphyrin hydrochloride where two adjacent pyrrolic nitrogens are bridged by the CHCOOEt group [12a]. As the latter porphyrin, compound 4 was only isolated as a monocationic salt (hydrochloride in our conditions). It involves a similar structure with the C=C(p Cl C_6H_4)$_2$ group bridging two adjacent pyrrolic nitrogens, as shown by its elemental analysis corresponding to: TPP + C=C($pClC_6H_4$)$_2$ + HCl + H_2O (hydrate : 1 mole of H_2O determined by ^{1}H NMR), and its ^{1}H NMR spectrum which displays four doublets (J=4Hz) for

Scheme 1



Reaction of complex 2 with CF_3CO_2H and $FeCl_3$: reaction of complex 2 (20 ml of a 10^{-2} M solution in CH_2Cl_2) with CF_3CO_2H (10 eq.) or $FeCl_3$ (1.1 eq.) is complete within 30 min. at 20° C as shown by visible spectroscopy. After washing with water and chromatography of the crude product on silica gel (eluent : CH_2Cl_2 for reaction of complex 2 with CF_3CO_2H, CH_3COCH_3/CH_2Cl_2 75/25 for reaction with $FeCl_3$), a new compound is obtained (compound 3 for reaction with CF_3CO_2H, compound 4 for reaction with $FeCl_3$- 80 % yield for both products after crystallization from CH_2Cl_2/pentane). Compound 4 was also obtained from electrooxidation (+0,8V, DMF+ LiCl)of complex 2, indicating that $FeCl_3$ acts as an oxidant in the reaction of formation of 4[13]. The different characteristics of compounds 3 and 4 are reported table 1.

the pyrrolic protons as expected from the symmetry, if one assumes a rapid exchange (versus the NMR time scale) of the acidic proton between the two adjacent nitrogen atoms. Formation of compound 3 from complex 2 involves the rupture of the Fe-C bond by acids, a well known reaction of transition metal σ-complexes, and demetalation of the intermediate iron-N-substituted porphyrin [11, 12]. Formation of compound 4 could be seen as a reductive elimination of the σ-vinyl and one nitrogen ligands of the intermediate Fe^{IV} complex formed by one-electron oxidation of complex 2, followed by demetalation since the iron is then only bound to two of the four pyrrolic nitrogens. A similar reaction has been reported in the case of a Co^{III}-porphyrin complex with the CHCOOEt group inserted into a Co-N-bond [12].

Iron-porphyrin-carbene complexes may thus lead irreversibly to N-substituted porphyrins in two steps (scheme 1). It is therefore tempting to speculate that similar reactions may occur with cytochrome P450-carbene complexes formed during the reductive metabolism of CCl_4 or $CF_3CHClBr$ [3,4] or the oxidative metabolism of the 1,3-benzodioxole derivatives [5]. This could be at the origin of the in vivo degradation of cytochrome P450 observed after administration of these compounds.

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7 TPP and $TPPH_2$ are the abbreviations respectively used for the dianion and the free base of meso-tetraphenylporphyrin.

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