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# Model for the *in vivo* transformation of cytochrome P-450 into "green pigments"

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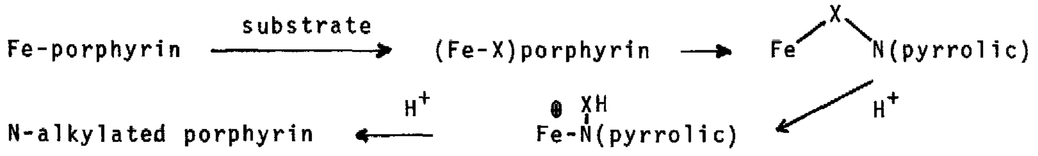
Summary: Alkyl transfer from the metal to a pyrrolic nitrogen of a metalloporphyrin is described as a model of heme modification during *abnormal metabolism of drugs*.

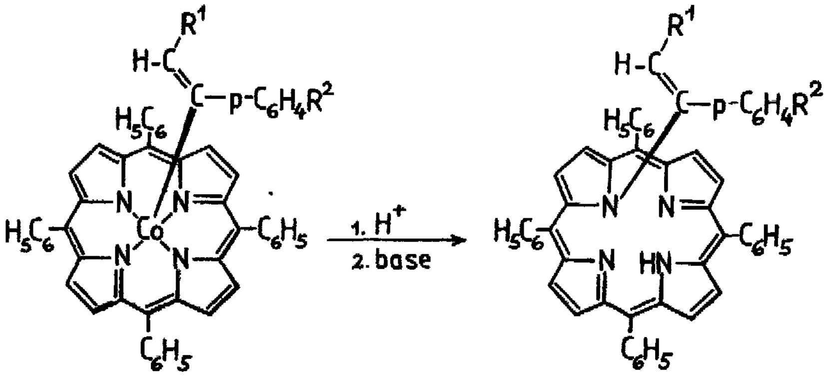
The abnormal metabolism of certain drugs and halogenated hydrocarbons cause loss of hepatic cytochrome P-450 activity. Allyl containing drugs transform the heme moiety into inactive modified "green pigments" for which a N-substituted porphyrin structure has been recently suggested [1]. Modification of the substrate with creation of an electrophilic center bound to the metal appears to be a determining step. Halogenated hydrocarbons may produce *in vivo* iron-carbene complexes as strongly supported by the isolation of model compounds like (Fe"=$CCl_2$)porphyrins [2,3].

Recent studies by ourselves and A.W. Johnson and coll. on diazoalcanes-metalloporphyrins reactions permitted the isolation of bridged compounds corresponding formally to the insertion of carbenes or nitrenes into the metal-pyrrolic nitrogen bond of metalloporphyrins [4]. These results suggested that the following sequence may explain the formation of alkylated hemes (X = electrophilic fragment) [5] :



In this communication we describe a model reaction in which we generate an electrophilic carbon bound to the metal of a metalloporphyrin and the transfer of the alkyl fragment from the metal to a pyrrolic nitrogen atom.

Styrylcobaltporphyrins 1 are easily prepared from acetophenones tosylhydrazones and cobalt(III)porphyrins in the presence of base [6]. Acid treatment ($CF_3COOH$) [7] and neutralization [7] give green compounds 2 :



| $\underline{1}$ | $R^1$ | $R^2$ | $\underline{2}$ | yield % | base |
|---|---|---|---|---|---|
| a | H | H | a | 16 | $NEt_3$ |
| b | $CH_3$ | H | b | 40 | aq. $NH_3$ |
| c | H | $NO_2$ | c | 47 | $NEt_3$ |

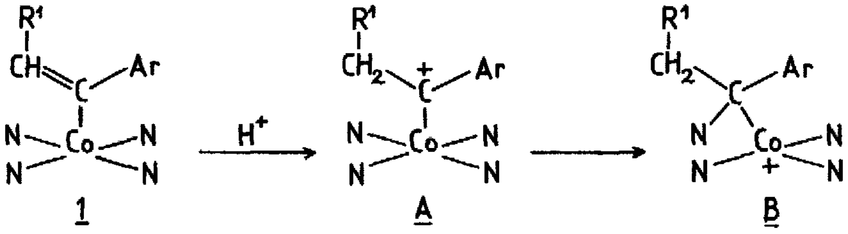
The n.m.r. spectra of 2a-c are typical for N-substituted porphyrins : large shifts of the styryl signals (see table) as well as 2:4 (AB system) :2 pattern for the pyrrolic protons. Chemical shifts [8] (ppm from TMS) :

|  | vinyl |  | phenyl |  |  |
|---|---|---|---|---|---|
|  | H | $R^1$ | ortho | meta | para |
| 2a | -1.81 | H at 1.18 | 5.55 | 6.85 | ca 7.1 |
| 2b | -1.36 | $CH_3$ at -1.36 | 5.61 | 7.1 | 7.1 |
| 2c | -1.70 | H at 1.22 | 5.58 | a | - |

a. masked by other phenyl resonances.

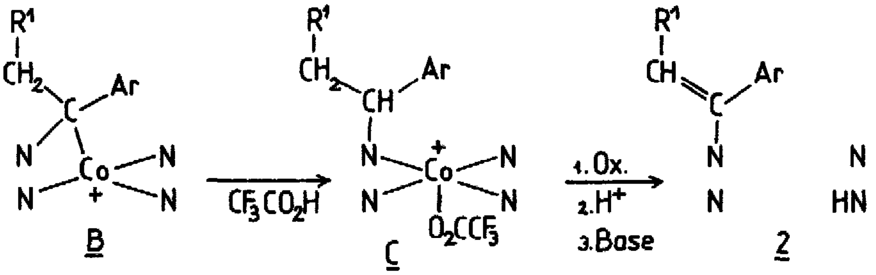
The $^{13}C$ n.m.r. spectrum of 2b shows for the 3-carbon side chain : 10.5 ($CH_3$), 118.0 (quaternary C) and 121.5 (tertiary C) (ppm from TMS).

The reaction $\underline{1} \longrightarrow \underline{2}$ is best explained by the following sequence :



a) protonation to form a benzylic cation A (the electron-rich porphyrin may contribute to its stabilisation).

b) attack of a pyrrolic N to form a bridged compound B.



c) cleavage ($H^+$) of the Co-C bond to form cation C.

d) rapid intramolecular oxidation of C (benzylic position) by cobalt(III), followed by acid catalyzed demetallation to 2. A similar oxidation of a side-chain ($N\text{-}CH_2\text{-}CO_2Et \longrightarrow N\text{-}CHCl\text{-}CO_2Et$), catalyzed by cobalt(III) was described by Johnson [4b].

We conclude that generation of an electrophilic center bound to the metal of a metalloporphyrin is sufficient to initiate an alkyl migration to a pyrrolic nitrogen atom. A similar pathway may operate *in vivo* from various precursors (iron porphyrins ; carbon, nitrogen or oxygen [9] containing electrophilic species bound to the metal).

## References

1. "Green pigments" from allyl-substituted drugs : F. De Matteis and L. Cantoni, Biochem. J., 183, 99 (1979) and references cited therein.
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3. Oxidation of one of these carbene complexes give a product possessing a $\mathrm{Fe{-}\underset{\wedge}{C}{-}N}$ arrangement : B. Chevrier, R. Weiss and D. Mansuy, personal communication.
4. a) H.J. Callot, Th. Tschamber, B. Chevrier and R. Weiss, Angew. Chem., 87, 545 (1975) ; b) A.W. Johnson and coll., J. Chem. Soc. Perkin I, 2076 (1975), 720 and 1623 (1977) ; c) H.J. Callot, B. Chevrier and R. Weiss, J. Amer. Chem. Soc., 100, 4733 (1978) ; d) H.J. Callot, Tetrahedron, 35, 1455 (1979) ; e) K. Ichimura, Bull. Chem. Soc. Japan, 51, 1444 (1978).
5. H.J. Callot and E. Schaeffer, Nouv. J. Chim. (in the press).
6. E. Schaeffer, Thesis, Université Louis Pasteur, Strasbourg, 1979. H.J. Callot and E. Schaeffer, submitted for publication. See also : H.J. Callot and E. Schaeffer, J. Organomet. Chem., 145, 91 (1978).
7. The reaction is very sensitive to the nature of acid and base used. Trifluoroacetic acid/$NEt_3$ or aq. $NH_3$ (2b) proved to give the best reproducible yields.
8. Ambiguities due to superimposition of signals are eliminated by the following experiments : 1) 2b was transformed into its ZnCl complex which showed a doublet at -1.33 ($R^1=CH_3$) and a quartet at -1.86 (vinyl H) ; 2) 2c was transformed into 2d ($R^2=NHCOCH_3$ ; $NaBH_4$-$Cuacac_2$ then $Ac_2O$). 2d showed the expected two doublets at 5.52 and 6.92 for the phenyl protons.
9. Formation of porphyrin N-oxides can be postulated since the corresponding model (octaethylporphyrin-N-oxide) is known : see R. Bonnett, R.J. Ridge and E.H. Appelman, J.C.S. Chem. Comm., 310 (1978).

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