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NEW IRON-PORPHYRIN COMPLEXES WITH METAL-CARBON BOND - BIOLOGICAL IMPLICATIONS

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Abstract - A study of the reactions of ferroporphyrins, in the presence of an excess of a reducing agent, with various polyhalogenated compounds, has led to a general method of preparation of iron-carbene complexes, Fe(porphyrin)(CRR'). It has thus been possible to obtain iron complexes of the dihalogenocarbenes CCl_2, CBr_2, CF_2, CFBr and CFCl, which are thermally stable (up to 100°C) and not dissociated in solution, but which react irreversibly with dioxygen and nucleophiles such as pyridine or primary amines. The corresponding Fe(porphyrin)(CI_2) complex has not been isolated since it reacts rapidly with another Fe^{II}(porphyrin) to give a heme dimer bridged by a carbon atom, Fe=C=Fe. Fungicides of the $RSCCl_3$ type are reduced by ferroporphyrins with formation of Fe-CClSR carbene complexes which are transformed into very stable thiocarbonyl-iron porphyrin complexes upon treatment by a Lewis acid. The insecticide DDT, $(pClC_6H_4)_2CHCCl_3$, forms, upon reaction with ferroporphyrins, very stable vinylidene carbene complexes Fe [porphyrin] [$C=C(pClC_6H_4)_2$].
These results strongly support the formation of cytochrome P 450-Fe^{II}-carbene complexes during reductive metabolism of various polyhalogenated compounds, as proposed previously. Cytochromes P 450-carbene complexes are also formed by in situ oxidation of the methylene group of 1,3-benzodioxole derivatives. This is strongly indicated by the spectral properties of the model complex Fe(tetraphenylporphyrin)(1,3-benzodioxol-2-carbene)($nBuS^-$) prepared by the general method here described, from 2,2-dichloro-1,3-benzodioxole.
The possible biological implications of the formation of these cytochrome P 450-iron-carbon bonds, are discussed.

INTRODUCTION

Until 1974, the only examples of metalloenzymes complexes involving a metal-carbon bond were the σ-alkyl-Co complexes of vitamin B_{12} (Note a). Is it possible that complexes involving a metal-carbon bond may be formed during the reactions of organic substrates with hemoproteins, since these metalloenzymes are widely distributed in living organisms ? Among the various known hemoproteins, cytochromes P 450, which are involved in the monooxygenases systems responsible for the detoxification of exogenous compounds by living organisms, are the best candidates for making organometallic chemistry with possible formation of iron-carbon bonds. The first reason for that is their readily accessible hydrophobic active site, near the heme, that almost any sufficiently hydrophobic organic compound may enter, and then interact with the iron-porphyrin and be metabolized. This is a distinctive feature for an enzymatic system. The second reason is the involvement of very reactive iron complexes in the catalytic cycle of these cytochromes (1). Thus, the "active oxygen" cytochrome P 450 complex, which has been depicted recently as a porphyrin-Fe^{V}=O or -Fe^{IV}-O· complex (2), is able to oxidize almost any organic compound including alkanes (1). The other reactive complex is cytochrome P 450-Fe^{II}, which contains an iron center considerably electron-enriched by the porphyrin and the endogenous axial thiolate ligand (1), and which is able to reduce various substrates like nitroarenes (3), tertiary amine-oxydes (4), carbon tetrachloride (5) and arene epoxydes (6). (Fig. 1)

Note a. If one excepts the complexes formed by interaction of iron - or copper - enzymes with ^-CN, CO or isocyanides.

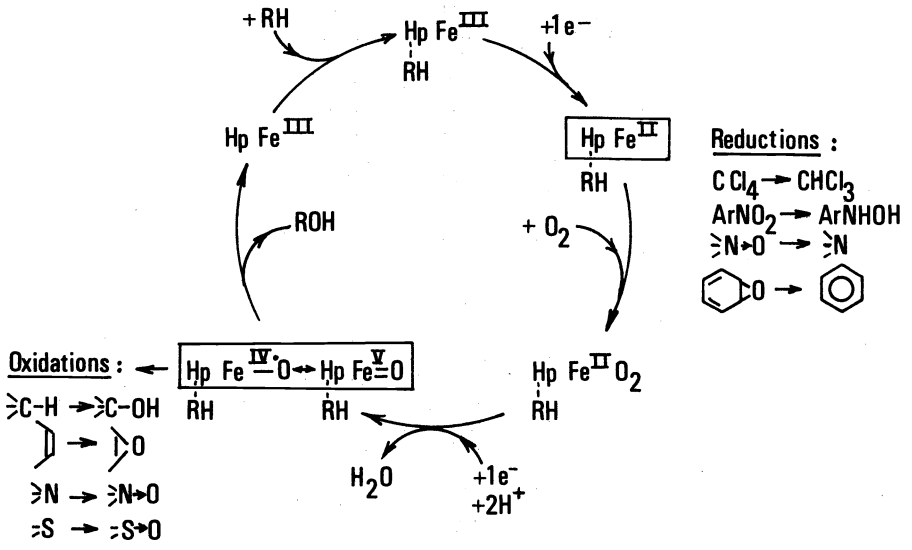


Fig. 1. The reactive iron complexes involved in the catalytic cycle of substrate hydroxylation by cytochrome P 450.

It seems likely that among all the reactions occurring between these two intermediate complexes and a wide range of organic susbtrates, iron-carbon complexes might be formed at least transiently. Accordingly, evidences have been presented recently in favor of the formation of cytochrome P 450-Fe^{II}-carbene complexes after reductive metabolism of polyhalogenated compounds such as carbon tetrachloride or the volatile anaesthetic halothane, $CF_3CHClBr$ (7, 8) :

$$\text{P 450 } Fe^{II} + CCl_4 \text{ (or } CF_3CHClBr) \xrightarrow{n\ e^-} \text{P 450 } Fe^{II}{\leftarrow}CCl_2 \text{ (or } CF_3CH)$$

The following study of the reactions of ferroporphyrins with various compounds of great environmental significance, which are widely used as solvents, aerosol propellants, insecticides or insecticides synergists, demonstrates the existence of porphyrin-iron-carbene complexes. Moreover, it describes a general method of preparation of iron complexes with carbene ligands which had not been previously stabilized by coordination to any transition metal complex.

I. PREPARATION AND PROPERTIES OF THE DICHLOROCARBENE COMPLEXES, $Fe(TPP)(CCl_2)(L)$

The iron-mesotetraphenyl porphyrin complex, $Fe^{II}(TPP)$, reacts with CCl_4 in the presence of an excess of a reducing agent (iron powder or sodium dithionite) affording rapidly and quantitatively the $Fe(TPP)(CCl_2)$ complex (9). The stoichiometry of the reaction has been found to be (10) :

$$Fe^{II}(TPP) + CCl_4 + 2\ e^- \longrightarrow Fe(TPP)(CCl_2) + 2\ Cl^- \qquad \text{(eq. 1)}$$

1

The pentacoordinated complex 1 readily binds various L ligands (alcohols, ethers, DMF, nitrogenous bases) in trans position to the carbene, explaining the occurrence of the equilibrium :

1 + L ⇌ Fe(TPP)(CCl_2)(L) 2 , in solution, and the formation of cystalline hexa- or pentacoordinated complexes 1 or 2, by crystallisation of complex 1 in the presence of coordinating solvents. As shown in table 1, the nitrogenous ligands have a considerably greater affinity for complex 1 than the oxygen-containing ligands such as alcohols (9,11). As expected, the hexacoordinated complexes 2 are low spin Fe(II) complexes as indicated by their magnetic susceptibility in solution and the shape of their ^1H and ^{13}C NMR spectra (11). It is noteworthy that this is also the case for the pentacoordinated complex 1, as for the Fe(TPP)(CO) complex (12). An X-ray analysis of a single crystal of the complex Fe(TPP)(CCl_2)(H_2O), 2 DMF definitely proved the presence of the coordinated carbene (11). The C-Cl distance (1.75 ± 0.03 Å) is as expected for a C_{sp2}-Cl bond and agrees with the IR frequency ν_{C-Cl} of complexes 1 and 2 (table 1). The L ligand exhibits a strong influence on some characteristics of the Fe-CCl_2 moiety (table 1).

TABLE 1. Influence of L on some characteristics of the Fe(TPP)(CCl_2)(L) complexes

complex	K_{eq} 1 + L ⇌ 2 ($l.mol^{-1}$) at 24°C (11)	ν_{C-Cl} (a) (cm^{-1}) (11)	$\delta^{13}C$ (CCl_2) (b) (ppm/TMS) (13)	t 1/2 O_2 (c) (h) (13)
1	-	872	225	3.5
2 (L = EtOH)	4	863	> 231	0.5
2 (L = C_5H_5N)	3500	854	242	0.8
2 (L = NMeIm)	75000	854	-	0.4

(a) - recorded in KBr under argon ; (b) - in $CDCl_3$. For 2 (L = EtOH), because of a rapid exchange, to the NMR time scale, between 1 and 2, even at - 40°C, one can only conclude to a downfield shift of the signal upon EtOH coordination ;
(c) - half-life of the complexes for O_2 oxidation leading to Fe^{III}(TPP)(Cl). conditions : complex 1 7.10^{-5} M in aerated C_6H_6 at 24°C + 10% EtOH (L = EtOH) or 10^{-2} M C_5H_5N (L = pyridine) or NMeIm (L = N-Me-imidazole).

The strength of the C-Cl bond decreases with the σ-donor ability of the L ligand, as indicated by the variation of ν_{C-Cl} , while the ^{13}C chemical shift of the carbene carbon increases. With the strong σ-donating ligand P(nBu)$_3$, this ^{13}C NMR signal shifts up to 243 ppm ($J_{^{13}C-P}$ = 170 Hz) (13). The L ligand also influences the reactivity of the complex as shown by the increase of the rate of oxidation of complex 1 by O_2 in solution, in the presence of various ligands (table 1). This is confirmed by the faster oxidation of the Fe(TPP)(CCl_2)(pyridine) complex compared to complex 1, when exposed, as solids, to O_2 (13).

REACTIVITY OF THE Fe(TPP)(CCl_2) COMPLEX

In deaerated solvents such as benzene, the Fe-CCl_2 bond of complex 1 is very stable, exhibiting no dissociation even in dilute solution. The crystalline complex 1, heated in a sealed tube under 10^{-2} mm Hg, undergoes no dissociation up to 200°C ; above 200°C, it decomposes giving Fe(TPP) and tetrachloroethylene. As shown in Fig. 2, complex 1 fails to react with cyclohexene even for hours at 80°C ; similarly, poor nucleophiles such as alcohols are only able to bind to iron in position trans to the carbene. Stronger L nucleophiles like pyridine, N-methyl-imidazole and phosphines first bind to iron with formation of the corresponding complexes 2, but also lead slowly to the irreversible formation of the hemochromes, Fe(TPP)(L_2) (9,11). Primary amines, RNH_2, react with the bound carbene leading quantitatively to the corresponding isocyanide complexes Fe(TPP)(CNR)(RNH_2) (14).

Complex 1 does not react with electrophiles such as CH_3I or $(C_6H_5)_2CO$ in large excess even at 60°C. However it is oxidized quantitatively at room temperature by one equivalent of bromine, iodine or ferric chloride, to the corresponding Fe^{III}(TPP)(halide) complex (Fig. 2) (15).
Its reaction with two moles of Br_2 affords CBr_2Cl_2 almost quantitatively (15).

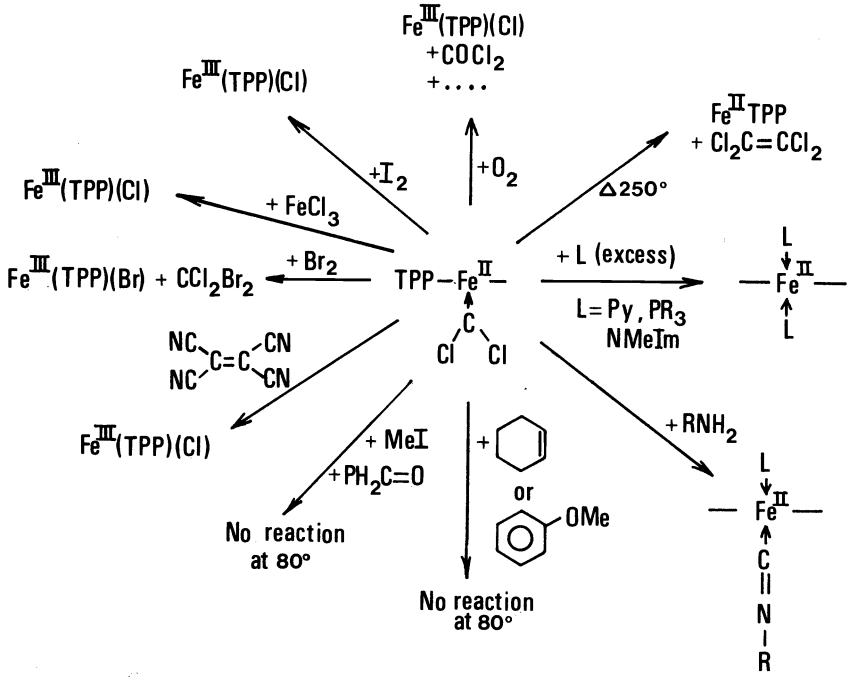


Fig. 2. Some reactions of the Fe(TPP)(CCl_2) complex

Complex 1 also reacts with dioxygen leading quantitatively to Fe^{III}(TPP)(Cl) (9,11). When the reaction with dioxygen is performed in the presence of pyrocatechol, pyrocatecholcarbonate is formed (≃ 60% yield) indicating that phosgene is the major product derived from the carbene moiety during the oxidation (15). It is noteworthy that the oxidation by dioxygen goes faster in the presence of ligands trans to the carbene (table 1), which suggests that dioxygen does not react after coordination to iron in trans position to the carbene, but on the opposite side, with the Fe-CCl_2 moiety (13).

II. GENERALIZATION OF THE REACTION :

II. A. PREPARATION AND COMPARATIVE PROPERTIES OF IRON-PORPHYRIN COMPLEXES OF VARIOUS DIHALOGENO-CARBENES

The preparation method of complex 1 has been easily used for the obtention of similar CCl_2 complexes of various iron-porphyrins (11) including protoporphyrin IX which is present in the active site of several hemoproteins. It also allowed the preparation of iron complexes of other carbenes :

$$RR'CX_2 + Fe^{II}(P) + S_2O_4^{2-} \text{ (or } Fe^0) \longrightarrow Fe(P)(CRR') + 2X^- \quad \text{(eq. 2)}$$

P = porphyrin , X = halogen

The CFCl, CFBr and CBr_2 complexes of Fe(TPP) have thus been obtained in the crystalline state, their structures being established from analytical and spectral data (16). The formation of the Fe(TPP)(CF_2) complex from CF_2Br_2 (eq. 2) has also been shown to occur from

visible and ^1H NMR spectroscopy. However, the complex is difficult to purify completely because of its great instability to dioxygen and even weak nucleophiles. Table 2 compares some characteristics of these dihalogenocarbene complexes of Fe(TPP) (16).

TABLE 2. Comparative properties of the dihalogenocarbene complexes, Fe(TPP)(CRR')

CRR'	$CRR'X_2$ (a)	K_{py} (b) ($l.mol^{-1}$)	t 1/2 O_2 (c) (h)	t 1/2 Py (d) (s)
CF_2	CF_2Br_2		< 0.04	< 5
CFCl	$CFCl_3$	14000	0.25	300
CFBr	$CFBr_3$		0.5	< 5
CCl_2	CCl_4	3500	3.5	5400
CBr_2	CBr_4	1600	10	120

(a) - starting compound for the preparation of the complex ; (b) - equilibrium constant at 24°C for the binding of pyridine in trans position to the carbene ; (c) - half-lives of the complexes for oxidation by O_2 leading to Fe^{III}(TPP)(halide) or $[Fe^{III}(TPP)]_2O$ in the case of CF_2 (for conditions, see table 1) ; (d) - half-lives of the complexes in the presence of 1 M pyridine, at 24°C, leading to $Fe(TPP)(Py)_2$.

This table underlines the following main points :

- The ability of the halogen substituent to stabilize the carbene complex towards oxidation by dioxygen, increases in the order : Br > Cl > F.

- The presence of a fluorine substituent on the carbene markedly increases the binding affinity of the complex for pyridine. This could be related to its greater electronegativity which also favors the irreversible reaction of the corresponding complexes with nucleophiles like pyridine leading to $Fe(TPP)(Py)_2$.

- Replacement of Cl by Br on the carbene ligand, also markedly enhances the rate of its formal replacement by pyridine.

II. B. THE REACTION OF Fe(TPP) WITH CI_4

The complex, 3, isolated after reaction of tetraiodomethane with Fe^{II}(TPP) in the presence of a reducing agent in excess, in conditions identical to those used for the preparation of complex 1 from CCl_4, is not the expected $Fe(TPP)(CI_2)$ complex (17). Complex 3 is stable for months to dioxygen in the solid state or in solution. Moreover, it fails to give $Fe(TPP)(Py)_2$ or $Fe(TPP)(RNC)(RNH_2)$ upon treatment with pyridine or a primary amine RNH_2 in conditions where all the carbene complexes of table 2 react in a few seconds. Its elemental analysis, molecular weight and magnetic susceptibility measurements, ^1H NMR and IR spectra indicate a structure $[Fe(TPP)]_2C$ for complex 3 with two Fe(TPP) bridged by a carbon atom (17). This complex is the carbon analog of the previously described $[Fe(TPP)]_2O$ and $[Fe(TPP)]_2N$ complexes (18). Accordingly its IR spectrum exhibits two bands at 940 (very strong) and 883 cm^{-1}, which do not exist in the IR spectra of Fe(TPP)(Cl) , $Fe(TPP)(Py)_2$ and $Fe(TPP)(CCl_2)$ and which are the counterparts of the IR bands observed for $[Fe(TPP)]_2O$ (885 , 870 cm^{-1}) and $[Fe(TPP)]_2N$ (910 , 885 cm^{-1}). These bands should correspond to the asymmetric stretch of the Fe-Y-Fe systems (Y = O , N or C) (18).
Furthermore, complex 3 is formed with more than 80% yield by reaction of CI_4 with Fe^{II}(TPP) in the molar proportions 1/2, in the presence of sodium dithionite in excess :

$$2\ Fe(TPP) + CI_4 + 4\ e^- \ (S_2O_4^{2-}) \xrightarrow{-\ 4\ I^-} \underset{\updownarrow\ 3}{\begin{matrix}[(TPP)Fe^{IV}=C=Fe^{IV}(TPP)] \\ [(TPP)Fe^{II}\leftarrow C\rightarrow Fe^{II}(TPP)]\end{matrix}} \qquad \text{(eq. 3)}$$

This stoichiometry is in agreement with the proposed structure of complex 3. Two results indicate that complex 3 is formed via the intermediate Fe(TPP)(CI_2) complex, the C-I bons of which are sufficiently reactive to be reductolyzed by Fe^{II}(TPP) in excess :

(i) - When the reactions between two iron-porphyrins are prevented by using "basket-handle" porphyrins (19), the stable Fe(basket-handle porphyrin)(CI_2) complex is easily isolated from reaction of the corresponding Fe^{II}(porphyrin) with CI_4(37). This complex exhibits spectral characteristics and chemical properties very similar to those of the Fe(TPP)(CCl_2) or Fe(TPP)(CBr_2) complexes (16).

(ii) - Fe(TPP)(CBr_2) reacts slowly with Fe^{II}(TPP) in the presence of a reducing agent in excess to give complex 3 (16).

II. C. PREPARATION OF Fe(TPP) COMPLEXES OF CARBENES BEARING AN ELECTRON-WITHDRAWING SUBSTITUENT

By the general reaction indicated before (eq. 2), it is also possible to obtain Fe(TPP) complexes of the carbenes CClCN, CClCOOEt (20) and $CClCF_3$ (21), which are sufficiently stable to be isolated in the crystalline state. They are however considerably more reactive towards dioxygen and nucleophiles than Fe(TPP)(CCl_2) (20). Their isolation is remarkable since, among the very few examples of transition metal carbene complexes bearing an electron-withdrawing substituent (22), they are the first ones not to have any substituent, such as phenyl, NR_2 or OR, able to efficiently stabilize the carbene electron deficiency. The relative stability of the Fe(TPP)(CClA), A = CN, COOEt or CF_3, complexes may be due to the stabilizing effect of the electron rich porphyrin ligand.

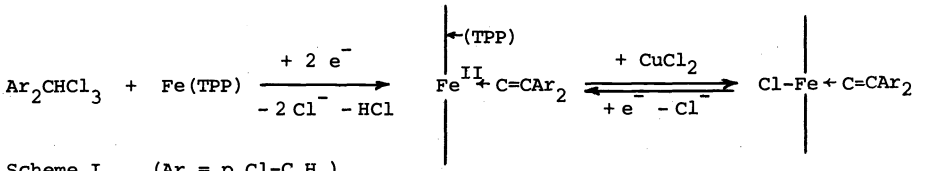
II. D. REACTION OF IRON-PORPHYRINS WITH ALKYL-CCl_3 COMPOUNDS ; THE PARTICULAR CASE OF DDT

When applied to polyhalogenated compounds of the $RCCl_3$ type with R = $-CH_3$ or CH_3CHOH-, reaction of eq. 2 (with P = TPP), leads to the expected Fe(TPP)(CClR) complexes (23). With the widely used insecticide DDT (R = $CH(p.Cl-C_6H_4)_2$), the reaction does not stop at the CClR complex ; a further elimination of HCl affords the vinylidene carbene complex Fe[TPP][$C=C(p.ClC_6H_4)_2$] 4 (scheme 1) (24). Compared to the previously described Fe(TPP)(carbene) complexes, complex 4 exhibits the following distinctive properties :

- It is sufficiently stable to be purified by column or thin-layer chromatography without decomposition.

- It is indefinitely stable to dioxygen even in solution.

- It reacts with one equivalent of $FeCl_3$ or $CuCl_2$ without irreversible rupture of the Fe-carbene bond, leading to a new very stable complex which is, at least formally, a Fe^{III}[TPP][$C=C(p.ClC_6H_4)_2$][Cl] complex (2e). It is noteworthy that the iron-vinylidene-carbene bond of complex 4 remains stable even after the one-electron oxidation of the iron-porphyrin.



Scheme I (Ar = $p.Cl-C_6H_4$)

II. E. REACTION OF IRON-PORPHYRINS WITH $RSCCl_3$ OR $RSeCCl_3$ COMPOUNDS : OBTENTION OF Fe(P)(CS) and Fe(P)(CSe) COMPLEXES

Various compounds of the $RSCCl_3$ type are used as fungicides or insecticides, their biological action having been related to the presence of the CCl_3 group (25). When applied to $C_6H_5CH_2SCCl_3$, reaction of eq. 2 (P = TPP) leads to the expected carbene complex, Fe(TPP)($CClSCH_2C_6H_5$), when sodium dithionite is used as reducing agent. However it leads to the thiocarbonyl complex 5, Fe(TPP)(CS), when iron powder is used as reducing agent (26). Complex 5 is also obtained by reduction of thiophosgene $CSCl_2$ by Fe^{II}(TPP) in the presence

of iron powder in excess (27). When treated by a catalytic amount of a Lewis acid such as $FeCl_2$, at room temperature, the Fe(TPP)($CClSCH_2C_6H_5$) complex is quantitatively transformed into Fe(TPP)(CS), 5, and $C_6H_5CH_2Cl$ (26). This allows to explain the direct formation of complex 5 in the reaction of $C_6H_5CH_2SCCl_3$ with Fe(TPP) in the presence of iron powder in excess, since $FeCl_2$ is formed in the course of the reaction (scheme 2).

$$C_6H_5CH_2SCCl_3 + Fe(TPP) \xrightarrow[-\,2\,Cl^-]{+\,S_2O_4^{2-}} Fe{\leftarrow}C(Cl)SCH_2C_6H_5 \xrightarrow{+\,FeCl_2} Fe{\leftarrow}C{=}S + C_6H_5CH_2Cl$$

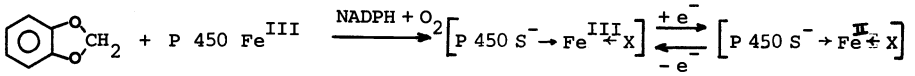
5

Scheme 2

The reactivity of the Fe(TPP)($CClSCH_2C_6H_5$) complex towards dioxygen is comparable to that of complex 1, while complex 5 is stable to dioxygen at least for months. It involves a Fe-CS bond which is considerably stronger than the Fe-CO bond of the previously described porphyrin-Fe^{II}-CO complexes (27). Like complex 4, it can be purified by thin-layer chromatography without decomposition (27).
Similar reactions with $C_6H_5CH_2SeCCl_3$ afford the Fe(TPP)($CClSeCH_2C_6H_5$) and Fe(TPP)(CSe) complexes (28). The latter complex is as stable as Fe(TPP)(CS), which is certainly related to the known good π-accepting ability of CS and CSe ligands (29). The formation of these selenium containing complexes from a readily available and easy to handle precursor, $C_6H_5CH_2SeCCl_3$, is a new method of preparation of selenocarbonyl and selenocarbene complexes of transition metals which are so far very few in the literature (30).

III. FORMATION OF A CYTOCHROME P 450-Fe-CRR' CARBENE COMPLEX BY OXIDATION IN SITU OF CH_2RR' (31)

The 1,3-benzodioxole derivatives are oxidatively metabolized by cytochrome P 450-dependent monooxygenases with formation of very stable complexes of this cytochrome in the ferrous state characterized by a Soret peak at 455 nm (32). The iron in these complexes can be reversibly oxidized to the Fe^{III} state (33). It has been proposed that the exogenous ligand X present in these complexes is the 1,3-benzodioxol-2-carbene (34), formed by oxidation of the methylene group of 1,3-benzodioxole (scheme 3) :



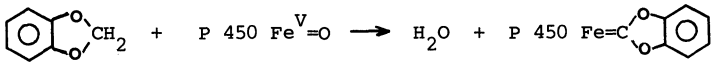
Scheme 3

We have prepared a model of this cytochrome P 450 Fe^{II} complex in two steps : first, the preparation, according to eq. 2, of the Fe(TPP)(1,3-benzodioxol-2-carbene) complex, 6, from reduction of 2,2-dichloro-1,3-benzodioxole by Fe(TPP), and, then, the addition of n-butylthiolate in excess to this complex (scheme 4). The expected Fe(TPP)(1,3-benzodioxol-2-carbene)($nBuS^-$) complex 7, which is characterized by a Soret peak at 459 nm, is formed immediately after the addition of $nBuS^-$ to complex 6, but then disappears within a few minutes because of an irreversible reaction between the carbene ligand and thiolate in excess.
The visible difference spectrum of complex 7 versus Fe(TPP)(Cl) in the presence of $nBuS^-$ in excess, is very similar to the difference spectrum of the benzodioxole metabolite-cytochrome P 450 Fe^{II} complex versus cytochrome P 450-Fe^{II} (31). This similarity indicates that complex 7 is a model for the cytochrome P 450-Fe^{II} ← X complex (scheme 3), strongly supporting the 1,3-benzodioxol-2-carbene nature of the X metabolite.

$$Fe(TPP) + R_2CCl_2 \xrightarrow[-\,2\,Cl^-]{+\,2\,e^-} \underset{6}{Fe(TPP)(CR_2)} \xrightarrow{+\,nBuS^-} \underset{7}{nBuS^- \rightarrow Fe^{II} \leftarrow CR_2}$$

Scheme 4 (R_2 = )

The formation of the cytochrome P 450-1,3-benzodioxol-2-carbene complex is the first example leading to a transition metal-CRR' carbene complex after direct in situ oxidation of a methylene precursor $RR'CH_2$. If one admits the proposition that the active oxygenating cytochrome P 450 complex involves a highly reactive oxo ligand (2) (Fig. 1), the formation of the carbene complex derived from 1,3-benzodioxole oxidation, corresponds formally to the replacement of this oxo ligand by the 1,3-benzodioxol-2-carbene (scheme 5).



Scheme 5

CONCLUSION

The above mentioned reactions of ferroporphyrins strongly support the involvement of iron-carbon bonds during the metabolism of substrates by cytochrome P 450. Cytochrome P 450-carbene complexes are thus formed either by in situ reduction of some substrates by cytochrome P 450-Fe^{II}, or by in situ oxidation of others by the active-oxygen cytochrome P 450 complex (Fig. 1).

These results underline the importance of the exchange of ideas between the fields of metalloenzyme biochemistry and organometallic chemistry. On one side, the hypothesis of formation of cytochrome P 450-carbene complexes from biochemical data (7,8) has led to the discovery of a very general preparation method of iron-carbene complexes differing only by the nature of the carbene carbon substituents. This could be of interest for the comparison of the properties of various carbenes bound to the same entity. This method has allowed the preparation of iron complexes with carbenes never stabilized on a transition metal such as the dihalogenocarbenes, and the obtention of new structures in coordination chemistry such as Fe=C=Fe. Moreover, presumably because of the stabilizing effect of the porphyrin ligand, iron carbene complexes, either with electron-withdrawing substituents on the carbene carbon (Fe(TPP)(CClCN) for instance) or with the metal in an unusual formal oxidation state (Fe(TPP)($C=CAr_2$)(Cl)), have been isolated.

On the other hand, the study of the properties of the above described iron-porphyrin-carbene complexes, should allow to understand, or even to predict, the formation and the properties of the corresponding cytochrome P 450-carbene complexes. Depending upon the stability and possible evolutions of the latter complexes, their involvement may imply different biological consequences (Fig. 3). One can distinguish two cases :

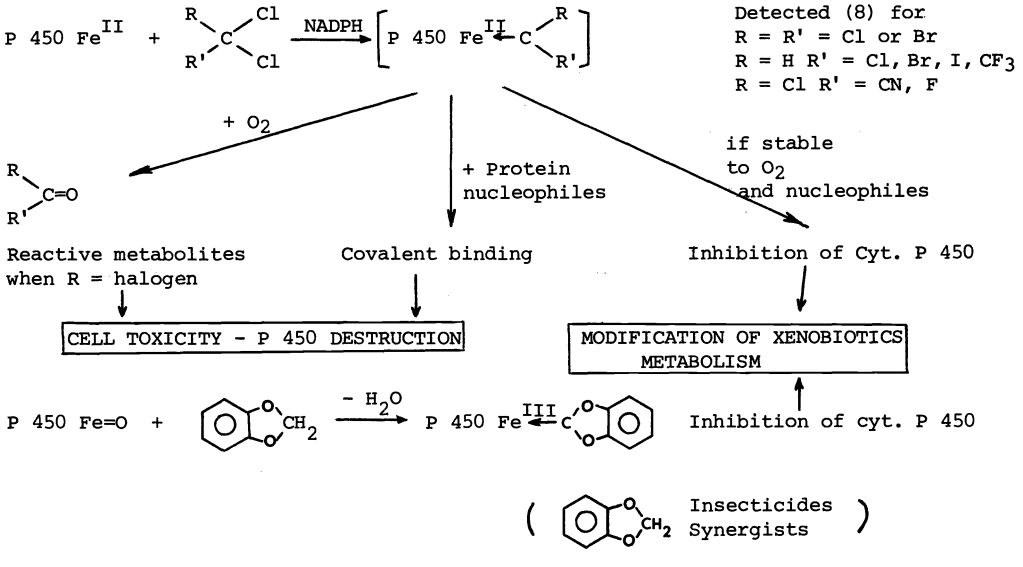


Fig. 3 Possible biological implications of the involvement of cytochrome P 450 - carbene complexes.

- In the first case, the iron-carbene bond is very stable towards dioxygen and nucleophiles possibly present in the active site of cytochrome P 450 ; therefore, the sixth coordination position of the iron is blocked, preventing dioxygen fixation and the hydroxylating function of the cytochrome (Fig. 1). This seems to be the case for the insecticide synergists of the 1,3-benzodioxole series. The stability of the cytochrome P 450-1,3-benzodioxol-2-carbene complex formed during their oxidative metabolism should be at the origin of the severe inhibition of cytochrome P 450-dependent monooxygenases by the benzodioxole derivatives in vivo and in vitro (32). This may explain the synergistic effects of these compounds when they are associated with insecticides, since they cause an important inhibition of the detoxifying system of the insects. Since we have noted a great stability of the iron-porphyrin complexes derived from the insecticide DDT or the fungicides of the $RSCCl_3$ type, it seems likely that the formation of the corresponding cytochrome P 450 complexes, if it occurs, would lead to a similar inhibition.

- In the second case, the iron-carbene bond is reactive towards nucleophiles possibly present in the active site of cytochrome P 450 or towards dioxygen normally present in the cell. The first reaction could lead to an irreversible binding of the carbene moiety to the protein. The reaction of dioxygen could lead to reactive metabolites dangerous for the cell. Evidence has been presented (Fig. 2) in favor of phosgene formation during oxidation of the $Fe(TPP)(CCl_2)$ complex by dioxygen (chapter I) (15). Similarly, the metabolism of CCl_4 by liver cytochrome P 450 could lead to phosgene formation by oxidation of the cytochrome P 450-Fe^{II} CCl_2 complex (even produced in low steady-state concentration (35)), by dioxygen (Fig. 4). The formation of phosgene, a very electrophilic metabolite, could account for some of the hepatotoxic effects of CCl_4, another metabolite, the radical $^{\cdot}CCl_3$, which induces lipid peroxidation, being mainly responsible for CCl_4 hepatotoxicity (36). Moreover, hydrolysis of phosgene may explain the formation of CO_2, an important metabolite of CCl_4 in vivo. More generally, one could expect that the reaction of the cytochrome P 450-Fe^{II} CXR (X = halogen) carbene complexes with dioxygen would lead to the electrophilic acylhalide derivatives RCOX, able to bind covalently to cell macromolecules leading to cytotoxic effects.

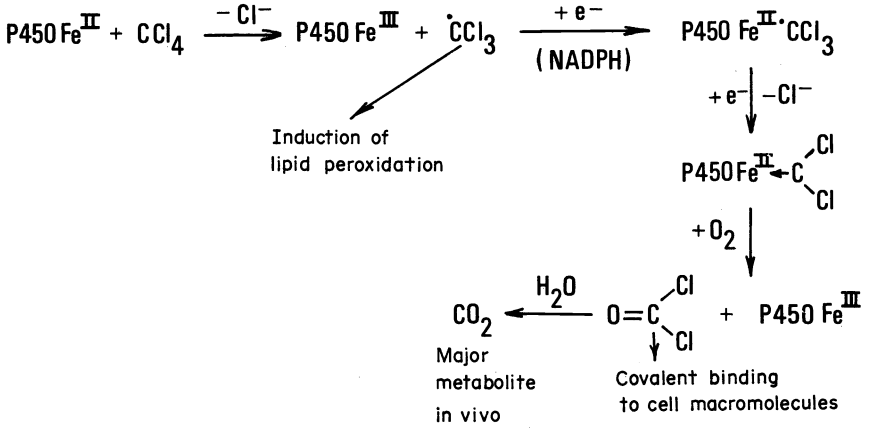


Fig. 4 Possible mechanisms for the metabolism and hepatotoxicity of CCl_4 (see also (36b))

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