The biomimetic oxidation of dieldrin using polyhalogenated metalloporphyrins

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Biomimetic oxidation of dieldrin produces the same metabolites as generated *in vivo*, which suggest a 'radical oxygen-rebound' mechanism.

Dieldrin **1**, like other insecticides, accumulates in the food chain and its use, as with other organochlorinated materials such as DDT, has been banned in many countries. Dieldrin accumulates principally in adipose tissue and is only slowly metabolized. Even though it has not been used in North America for more than two decades[1] it is, to this day, still found in the food chain. In the laboratory it was found that one year after injection of dieldrin only ~50% of the material had been metabolized and excreted, while half the dose was still retained by rabbits.[2] Some of the less interesting dieldrin metabolites arose from opening of the epoxide ring, but one particular metabolite, the intramolecularly bridged pentachloro ketone **6**, allowed for some very interesting speculation as to its mechanism of formation. McKinney *et al.* suggested[3] that the other principle mammalian metabolite, *syn*-9-hydroxydieldrin **3**, might be an intermediate in the formation of **6**, but they eventually considered this unlikely since feeding of **3** to a rat produced no pentachloro ketone in its liver, where it is known to accumulate. It was suggested, in 1975,[4] that a common intermediate, the species containing a radical at C-9 (**2**, Scheme 1), could account for the formation of both **3** and **6**; this suggestion is consistent with Groves' oxygen-rebound mechanism for the hydroxylation of alkanes by cytochrome P-450 which was formulated in 1976.[5,6]

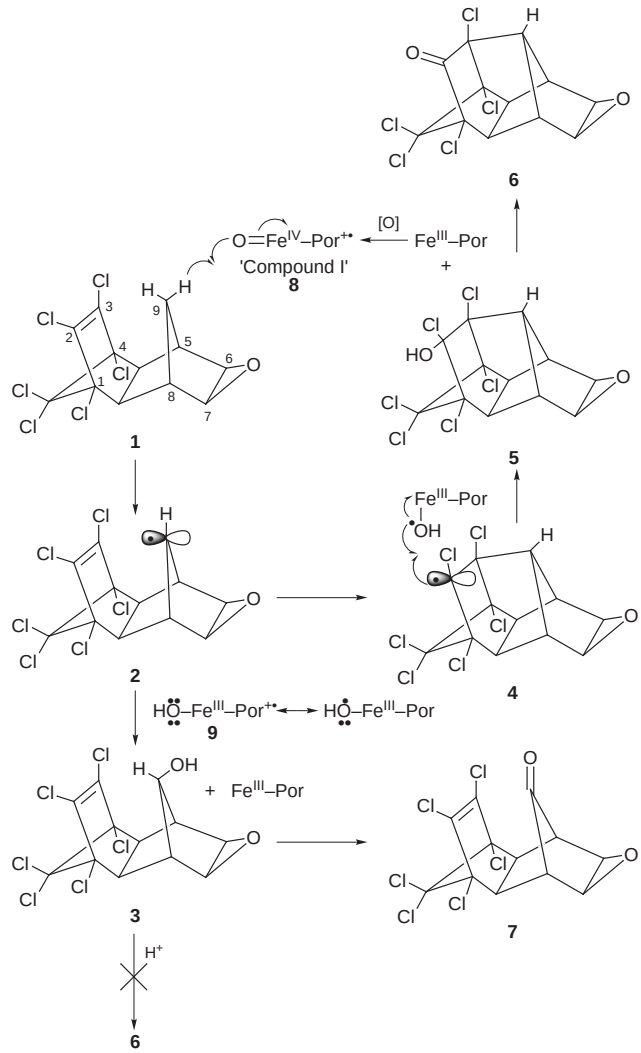
We have been unsuccessful in oxidizing dieldrin using isolated liver microsomes, due principally to its solubility properties and the destruction of microsomes under forcing conditions. We also failed in oxidizing dieldrin using metalloporphyrins derived from tetrakis(2,6-dichlorophenyl)porphyrin as biomimetic catalysts since dieldrin is quite recalcitrant towards oxidation and the porphyrin catalysts were destroyed before sufficient substrate oxidation could occur.

Recently, however, new highly halogenated porphyrins containing eight halogen atoms on the porphyrin periphery have been reported and these third generation catalysts (**10**, **11**) are showing exciting potential as biomimetic and industrial catalysts.[7] The oxidizing power of these catalysts and the turnover numbers that they exhibit are extraordinary, and both the iron and manganese complexes **10** and **11** effectively oxidize dieldrin to give the same products (**3**, **6**) as those previously identified from mammalian metabolism studies.

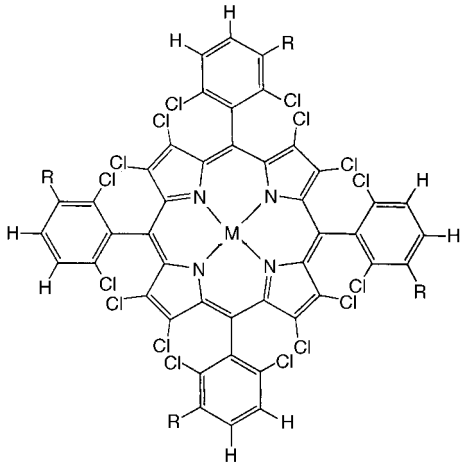
We have examined a number of cooxidants in addition to those shown in Table 1 and found that Oxone ($KHSO_5$) and H_2O_2 caused considerable destruction of catalyst and, at best, gave only a trace of oxidized dieldrin. On the other hand, surprisingly good yields of **3** and **6** were observed using hypochlorite, iodosylbenzene (PhIO) and alkyl hydroperoxides in mixed aqueous/organic solvents; small amounts of the ketone **7** were also seen when the reaction was carried out in only organic solvents. Ketone **7** arises from the over-oxidation of **3**; when **3** was treated with **10a** and PhIO, **7** was isolated from the reaction in 24% yield. Similar overoxidation of an initially formed alcohol regularly occurs with these P-450 mimics, but the extent of overoxidation can be often controlled by choice of catalyst, cooxidant and reaction conditions.[11]

The general concensus is that the majority of P-450 mediated hydroxylations proceed *via* radical rearrangements. Radical rearrangements have been well-documented in P-450 biochemistry[6] and 'radical clocks' have been used to measure the rate of the rebound process.[12] Thus bicyclo[2.1.0]pentane gave a 7:1 mixture of *endo*-2-hydroxybicyclo[2.1.0]pentane and cyclopent-3-en-1-ol when oxidized by rat liver microsomes.[13] The bicyclo[2.1.0]pentan-2-yl radical rearranges to the cyclopent-3-en-1-yl radical with a rate constant of 2.4×10^9 s^{-1}.[14]

In addition, Groves *et al.*[15] have shown that when a chiral iron porphyrin hydroxylated ethylbenzene, the differences observed between the *pro-R* and *pro-S* hydrogen atoms were best explained *via* radical intermediates. Nevertheless, Newcomb, Hollenberg and their colleagues[16] have recently concluded, from their studies on a hypersensitive cyclopropyl radical probe, that ring opening of a cyclopropylmethyl radical is unreasonable in their system and that a cationic species is



Scheme 1



10 R = H, M = Fe
11a R = SO_3H, M = Fe
11b R = SO_3H, M = Mn

Table 1 Oxidation of dieldrin (ref. 8)

Catalyst	Co-oxidant	Solvent[a]	Product (%)[b] 6	3	7	1	Ratio 6/(3 + 7)
10	NaOCl	C	3	7	2	65	0.33
10	NaOCl	D	12	5	trace	73	2.4
10	Bu^tOOH	C	16	25	4	47	0.64
10	Bu^tOOH	D	36	19	trace	30	1.9
11a	NaOCl	A	24	5	—	63	19
11a	NaOCl	B	31	3	—	51	10
11a	PhIO	B	6	trace	trace	70	
11a	Bu^tOOH	A	38	14	—	30	2.7
11a	Bu^tOOH	B	43	12	—	32	3.6
11b	NaOCl	A	12	3	—	77	4
11b	NaOCl	B	15	8	—	60	1.9
11b	PhIO	A	8	trace	—	81	
11b	PhIO	B	11	trace	—	80	
11b	Bu^tOOH	A	31	10	—	40	3.1
11b	Bu^tOOH	B	41	8	—	36	5.1
Fenton[c]	H_2O_2	MeCN	8	13	—	18	0.6

[a] A: H_2O–CH_2Cl_2–MeOH = 2 : 10 : 30. B: pH 2 buffer–CH_2Cl_2–MeOH = 2 : 10 : 30. C: CH_2Cl_2. D: CH_2Cl_2–MeOH = 1 : 1. [b] Ref. 9. [c] Ref. 10.

intermediate in the rearrangements. In order to best accommodate their observations they suggest that the active oxidant in P-450 hydroxylations might be an iron–H_2O_2 complex and that the first species formed in the hydroxylation reaction is a protonated alcohol formed by 'OH^+' insertion into a C–H bond and that any subsequent rearrangements occur *via* solvolysis.

The question then arises as to how the principal oxidation product **6** is generated. Metabolic studies suggest that **6** does not derive from **3** and we have found no acid catalyzed reactions of **3** which generated **6**. Moreover, carbonium ion intermediates on the highly chlorinated 'perchlorocyclopentadiene ring' seem unlikely. Radical intermediates, however, would be consistent with the oxygen-rebound mechanism proposed by Groves and a radical at C-2 would be stabilized by the chlorine atom. Indeed, the P-450 mediated oxidation of dieldrin and the parallel biomimetic studies described here add further support to the oxygen-rebound mechanism and the intermediacy of substrate radicals where, as shown in Scheme 1, an initial hydrogen atom abstraction from C-9 by 'Compound I' (the common intermediate in these oxidations, $O{=}Fe^{IV+\cdot}$ **8**) would generate the substrate radical **2** and a heme intermediate **9** which can be formulated as an hydroxyl radical coordinated to (and stabilized by) the ferric iron. Intermediate **2** can then react at C-9 to give the alcohol **3** (and the ferric porphyrin ready for another catalytic cycle) or rearrange to the more stable tertiary radical at C-2 (**4**) where transfer of an hydroxyl radical from iron followed by loss of HCl would generate **6**.

The fact that we have been unable to bring about the acid catalyzed conversion of **3** → **6** does not preclude cationic intermediates in the P-450 metalated hydroxylation of dieldrin. Nevertheless, we conclude that the present study favors radical intermediates in the biomimetic oxidation of dieldrin and by analogy in the enzymatic reaction as well. Perhaps we should not be too surprised in either this case or that of Newcomb and Hollenberg *et al*. that electronically stacking a particular substrate may impose different reaction pathways for P-450-mediated hydroxylations.

As shown previously[7] these highly chlorinated metalloporphyrins can accurately mimic the cytochromes P-450. Not only can the production of natural metabolites be mimicked (and presumably predicted) but milligram (and even larger if required) amounts of such metabolites can be produced at the bench.

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8 The cooxidant (0.66 mmol) was added with stirring, at room temperature, in ten equal portions every 30 min to a solution of the porphyrin catalyst (0.032 mmol) in 10 ml of solvent (A, B, or C). An hour after the last addition of cooxidant the mixture was poured onto water (50 ml) and CH_2Cl_2 (50 ml). After separation the aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to 1 ml which was applied to a thick layer silica TLC plate and developed with light petroleum–EtOAc (5 : 1).
9 The isolated products had identical NMR and IR spectra to authentic samples.
10 A solution of dieldrin (0.26 mmol) and $Fe(ClO_4)_2$ (0.1 mmol) in MeCN (5 ml) was flushed with argon, H_2O_2 (0.1 mmol) in MeCN (0.5 ml) was slowly added over 15 min and the solution was then allowed to stand at room temperature for 1 h. The mixture was then extracted with CH_2Cl_2 (2 × 20 ml) and the products separated by TLC.
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