NIH Shift in Haemin–Iodosylbenzene-mediated Hydroxylations

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Summary Iron(III) and manganese(III) porphyrins catalyse the oxygen transfer from iodosylbenzene to aromatic substrates to yield phenolic products; the resultant *p*-methoxyphenol or *p*-cresol exhibits a marked NIH shift.

THERE has been considerable interest in understanding the nature of mono-oxygenase-catalysed reactions.[1,2] The principal roles of these enzymes are hydroxylation of unactivated alkanes, epoxidation of olefins, and formation of arene oxides which lead to phenols with concomitant migration and retention of aromatic ring substituents (NIH shift).[3] Recent model studies have demonstrated that facile alkane hydroxylation and olefin epoxidation can be achieved using iron(III) and manganese(III) porphyrins as an oxygen transfer catalyst.[4–7] When iodosylbenzene is used as the oxygen source, the reaction characteristics of the chemical model are very similar to those of cytochrome P-450. To evaluate further these porphyrin model systems, it is necessary to test whether they are capable of bringing about the NIH shift during aromatic hydroxylations. We now report that this last mode of reactivity is also exhibited by the model systems, making them the first haem based catalyst to mimic P-450 in all important aspects.

Although the reaction of iron(III)tetraphenylporphyrin (TPP) chloride with iodosylbenzene can give a good yield of aliphatic alcohols and epoxides,[4–7] the yield of phenolic products from aromatic substrates is extremely poor. We have noted previously that the low efficiency of the system in most cases is the result of irreversible oxidations of the porphyrin ring which destroy the catalyst.[4] We have discovered that the stability of the catalyst can be greatly enhanced if fluorinated porphyrins such as iron(III)tetra-(pentafluorophenyl)porphyrin (TFPP) chloride† are used.

TABLE. Comparison of yields for haemin-catalysed oxidations.

Reactant	Product	Fe^{III}(TTP)Cl [c]	Fe^{III}(TFPP)Cl [c]
Cyclohexane [a]	Cyclohexanol	5	71
Cyclohexene [a]	Cyclohexene oxide	49	95
	Cyclohex-2-enol	16	5
Anisole [b]	*o*-Methoxyphenol [d]	0·2	3
	p-Methoxyphenol [d]	1·0	8
	Phenol [d]	0·8	0·4

[a] In CH_2Cl_2. [b] Neat. [c] % Yields based on iodosylbenzene initially added. [d] Phenols reacted further to give polyhydroxylated products.

This compound also has greater reactivity towards substrates since the electron-deficient porphyrin presumably would generate a more electrophilic oxene complex. The Table provides a quantitative comparison between TPP and the fluorinated complexes. The reactions were carried out under nitrogen at 22 °C with an initial concentration of iodosylbenzene of 2×10^{-2} mol/l and of haemin of 2×10^{-3} mol/l. The reaction mixtures were stirred for 2—3 h, then washed with dilute aqueous sodium hydrogen sulphite solution, and analysed by g.l.c.–mass spectrometry. Mn^{III}(TFPP)Cl† was effective in these reactions with yields comparable to those with Fe^{III}(TFPP)Cl. It should be noted that in the many aromatic hydroxylations we have examined, only the *ortho*- and *para*-substituted phenols were observed. The absence of the *meta*-product is expected from the oxene addition–rearrangement mechanism.[3]

When [*p*-^{2}H]anisole (deuterium content 98%) was hydroxylated, mass spectra of the isolated (*via* the phenolate) *p*-methoxyphenol showed 72% deuterium retention using Fe^{III}(TFPP)Cl as catalyst. Similarly, with [*p*-^{2}H]toluene (deuterium content 90%), 70% deuterium retention in *p*-cresol was observed. The extent of these NIH shifts is comparable with those for microsomal systems and is generally much higher than those obtained from hydroxylations with trifluoroperacetic acid.[8] However, the amount of deuterium retention varied with different porphyrin catalysts. For example, while Fe(TPP)Cl and Mn(TFPP)Cl exhibited 60% deuterium retention for *p*-methoxyphenol, Mn(TPP)Cl showed only 26%. This may be understandable since the main products of the Mn(TPP)Cl-catalysed anisole oxidation are phenol (12%), $PhOCH_2CH_2OPh$ (4%), and other coupling products derived from radical processes, with the yield of *p*-methoxyphenol being only 0·1%. The radical nature of the Mn(TPP)–iodosylbenzene system has been noted earlier in the hydroxylation of cyclohexane to produce halogenated cyclohexanes and bicyclohexyl[6] as well as in the ring opening of norcarane.[5] It is conceivable that, with this catalyst, oxygen may be introduced to the benzene ring by hydrogen abstraction or other mechanisms alternative to the arene oxide pathway.

The marked NIH shift exhibited by the haemin–iodosylbenzene hydroxylating systems therefore confirms the utility of the porphyrin complex as a functional model for cytochrome P-450. The high efficiency of the fluorinated compounds further demonstrates the feasibility of developing a catalyst for synthetic oxidation reactions.

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† The new fluorinated porphyrins have been adequately characterized by spectroscopic and elemental analyses.

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