Tosylamidation of Cyclohexane by a Cytochrome P-450 Model

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Reaction of cyclohexane with (tosyliminoiodo)benzene and manganese(III)- or iron(III)-tetraphenylporphyrin chloride affords *N*-cyclohexyltoluene-*p*-sulphonamide.

Numerous model systems have been explored which imitate the chemistry of catalysis by cytochrome P-450 and related enzymes.[1-3] Of these, the closest model is the system reported by Groves[1] which uses iron tetraphenylporphyrin (TPP) to catalyse the insertion of oxygen from iodosylbenzene into such hydrocarbons as cyclohexane. The enzyme itself can also transfer the oxygen of iodosylbenzene.[4] There is evidence[5] that the model reaction proceeds by oxygen atom transfer to form an oxo-metal compound, which is able to remove aliphatic hydrogen and capture the resulting carbon radical with the other product, a metal-bound hydroxy-group. Manganese porphyrins have also been shown to catalyse oxygen insertions.[6,7]

Metal oxide chemistry can often be imitated by compounds in which the oxygen is replaced by a tosylimide group.[8] Furthermore, we have shown[9] that a cyclohexenyl radical, generated electrochemically, can be tosylamidated by a vanadium tosylimide species. Although it was not at all clear that the entire insertion reaction sequence could be duplicated in the nitrogen series, we have now found that a metal-porphyrin can catalyse the tosylamidation of cyclohexane (reaction 1), in direct analogy to the known hydroxylation.

$$\mathrm{PhI{=}NSO_2C_6H_4Me\text{-}}p + \text{Mn(TPP) or Fe(TPP)} + \text{cyclohexane} \rightarrow \mathrm{C_6H_{11}NHSO_2C_6H_4Me\text{-}}p \quad (1)$$

In a typical experiment, a solution of Mn^{III}(TPP) chloride in CH_2Cl_2 was added to a suspension of (tosyliminoiodo)-benzene[10] in cyclohexane under argon to give a solution 2.5 mM in porphyrin and 50 mM in suspended iodo-compound in 1 : 1 (v/v) CH_2Cl_2–cyclohexane at room temperature. The solution went from deep green[6] to red-brown on mixing. After 3 h stirring the solid had dissolved, and the solution was again deep green. Work-up with aqueous Na_2SO_3 and g.l.c. assay indicated that *N*-cyclohexyltoluene-*p*-sulphonamide was formed in 136% yield based on the porphyrin catalyst, 6.8% yield based on oxidant. (An 8% yield of cyclohexanol based on iodosylbenzene was observed by Groves,[1] although higher yields have been obtained subsequently.[3]) The identity of our product sulphonamide was confirmed by n.m.r. and g.l.c. comparison with an authentic sample.

With Fe^{III}(TPP) chloride under the same conditions we obtained *N*-cyclohexyltoluene-*p*-sulphonamide in 62% yield based on catalyst, 3.1% based on iodo-compound. With both catalysts, replacing CH_2Cl_2 by benzene as co-solvent led to lower yields. A reaction with Mn^{III}(TPP) chloride in CH_2Cl_2 for 4.5 h under the same conditions but with 125 mM of iodo-compound gave a 310% yield based on catalyst, 6.5% based on iodo-compound. *N*-Cyclohexyltoluene-*p*-sulphonamide was also formed in a reaction catalysed by Mn(TPP) acetate in cyclohexane–benzene, so a pathway involving chlorination is excluded.

It remains to be seen whether cytochrome P-450 itself can be induced to perform amidations in place of its normal oxygenations. In any case, the model amidations are of considerable interest. Amides and amines are useful compounds, especially if produced selectively. The additional valence of nitrogen, relative to oxygen, permits variations in structure and makes it particularly clear how intramolecular functionalizations could be performed. The reactive intermediate in the amidation process could be oriented next to a substrate atom, to produce biomimetic selective functionalization[11] related to remote oxidation reactions. Thus the synthetic potential of metal–porphyrin catalysed nitrogen insertions seems at least as great as that of the well studied oxygenation systems.

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