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## Mechanism of Alkene Epoxidation by a Cytochrome P-450 Model. Effect of Additives

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Alcohols and styrene change the kinetics and the mechanism of alkene epoxidation by the mono-oxygenase model (tetra-*p*-tolylporphinato)manganese(III) acetate–sodium hypochlorite.
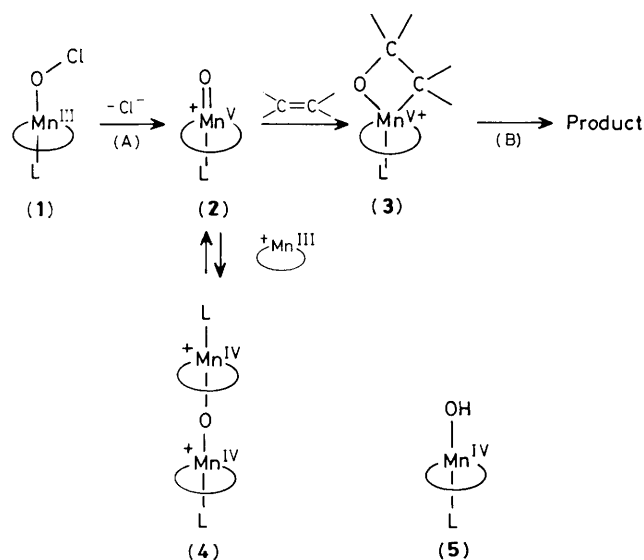
Elucidation of the mechanisms by which the cytochrome P-450 enzymes activate dioxygen and catalyse oxygen transfer to relatively unreactive substrates has been the goal of a number of research groups.[1] Considerable progress in attaining this goal has been achieved with model systems, *e.g.* porphyrin complexes of iron, manganese, and chromium as catalysts, and iodosylbenzene, amine oxides, and hypochlorite as oxygen sources.[2] We recently reported on the mechanism of cyclohexene epoxidation by *meso*-(tetraphenylporphinato)-manganese(III) acetate and sodium hypochlorite in a two phase water–dichloromethane system (Meunier system[2c]).[2h] Kinetic data suggest that the rate-determining step in the catalytic process is the conversion of the manganese(III) hypochlorite complex (**1**) into a high-valent oxo-manganese species. This step is catalysed by pyridine. We report here that alcohols and styrene change the kinetics and mechanism of alkene epoxidation by (**1**).

In the present experiments we used (tetra-*p*-tolyl-porphinato)manganese(III) acetate (Mn$^{III}$TTP) as catalyst and benzyltriethylammonium chloride as phase-transfer reagent.† Aliphatic alkenes are converted into epoxides with a selectivity of 90%. Styrene yields a mixture of styrene oxide (~75%) and phenylacetaldehyde (~20%). Rates were determined by measuring the formation of epoxide by g.l.c. In the absence of alcohols reactions are zero order in alkene up to 80% conversion. Remarkably however, different alkenes are epoxidized at different rates. The dependence of the rate on Mn$^{III}$TTP concentration is shown in Figure 1. Styrene displays a relatively high rate of epoxidation, which increases linearly

with increasing concentration of catalyst. Cyclohexene, 1-methylcyclohexene, and cyclo-octene are converted with lower rates. Their rates do not depend linearly on catalyst concentration but they go through a maximum. In the presence of methanol the reaction order in alkene changes from zero to first order. The initial reaction rate increases with increasing concentration of methanol up to a factor of 3 at an overall MeOH to CH$_2$Cl$_2$ volume ratio of 1:4 (in the organic phase MeOH to CH$_2$Cl$_2$ ratio ~1:10 v/v). Subsequently the rate decreases owing to precipitation of the catalyst. The product distribution is not affected by the presence of methanol. When ethanol, n-propanol, or n-butanol is substituted for methanol, similar features are observed.

Methanol stabilizes the oxygen-transferring species as can be concluded from the u.v.–visible spectra of the reaction mixtures. In the presence of methanol the u.v.–visible spectrum shows a Soret band at 422 nm. This band is indicative

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† In a typical experiment the following components were mixed: alkene (0.480 mol), toluene (internal standard, 0.105 mmol), MnTTP (1.72 × 10$^{-3}$ mmol), 4-methylpyridine (0.670 mmol), and benzyltriethylammonium chloride (2.8 × 10$^{-3}$ mmol) in CH$_2$Cl$_2$ (0.5 ml). To this solution an aqueous solution of NaOCl (0.35 mol dm$^{-3}$; pH ~13) was added. The mixture was stirred magnetically at a constant rate. From time to time samples (1 μl) were taken which were analysed for epoxide by g.l.c. (Carbowax 20 M on Chromosorb W-HP). The u.v.–visible measurements were performed in reaction mixtures which had the same concentration of reagents as used in the g.l.c. experiments. After rapid stirring for 2 min and separation of the layers the increase in absorption at 476 nm (Soret band of Mn$^{III}$TTP) was measured as a function of time. Reaction temperature 25.0 °C.
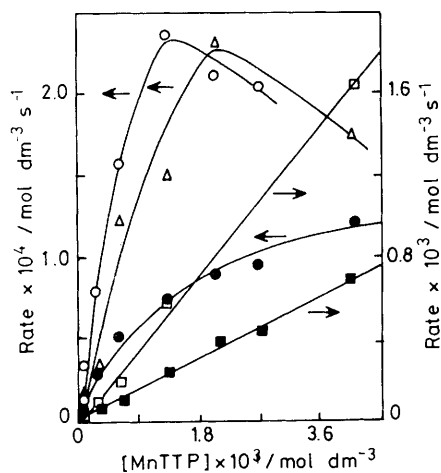


**Scheme 1.** L = pyridine or MeO$^-$.

**Figure 1.** Rate of epoxidation as a function of $Mn^{III}TTP$ concentration in the absence of methanol; 1-methylcyclohexene ($\circ$), cyclo-octene ($\triangle$), styrene ($\square$), cyclohexene ($\bullet$, non-competitive experiment), cyclohexene ($\blacksquare$, competitive experiment with styrene).
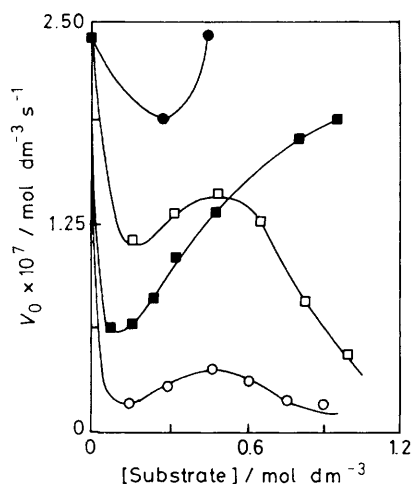


**Figure 2.** Initial rate of oxygen transfer to styrene ($\bullet$), methyl-cyclohexene ($\square$), cyclohexene ($\blacksquare$), and cyclo-octene ($\circ$) as a function of substrate concentration, in the presence of methanol.

of a high-valent manganese complex,[2c] probably (**2**).‡ Without addition of methanol we observed a strong band at 476 nm (Soret band of $Mn^{III}TTP$) and a much weaker band at 422 nm which soon disappeared. This suggests that under these conditions the oxygen-transferring species rapidly reacts with the substrate to form the product.

The rate of oxygen transfer from (**2**) to various alkene substrates in the presence of methanol was measured by following the increase in absorption at 476 nm. G.l.c. was used to verify the formation of epoxides under the conditions employed. The rates of oxygen transfer are first order in (**2**) up to 90% conversion. Pyridine and substituted pyridines appreciably enhance the decomposition rate of (**2**). Experiments were performed using a concentration of cyclohexene of 0.99 mol dm$^{-3}$, an initial concentration of (**2**) of 3.4 × 10$^{-4}$ mol dm$^{-3}$, and the MeOH to CH$_2$Cl$_2$ volume ratio mentioned above. These experiments showed a linear dependence on 4-methylpyridine concentration with $k_{py} = (2.79 \pm 0.04) \times 10^{-4}$ mol dm$^{-3}$ s$^{-1}$ in the equation $v = k_{py}$ [py][(**2**)]. The dependence of the rate of oxygen transfer on substrate concentration in the presence of 4-methylpyridine for various alkenes is given in Figure 2. We analyse the curves in this figure as follows: Without substrate the high-valent manganese species is rapidly decomposed to $Mn^{III}TTP$. Addition of an alkene substrate stabilizes the high-valent species. With increasing substrate concentration the rate of this decomposition is therefore decreased, whereas at the same time the rate of oxygen transfer to the substrate, in which the epoxide and $Mn^{III}TTP$ are formed, increases.

The kinetic results can be explained by Scheme 1.[2i] Without alcohol, the rate-determining step is the formation of the high-valent oxomanganese(v) complex (**2**), in which L probably is a pyridine ligand (step A). As is well known, species (**2**) can be in equilibrium with the manganese(iv) dimer (**4**).[2d,h] The stationary-state concentration of (**2**) will be lower, when the alkene is more reactive. Accordingly, less manganese is present in the (**2**) ⇌ (**4**) equilibrium and consequently the concentration of (**1**) is higher. This mechanism explains the

different rates for the various alkenes, although they do not directly participate in the rate-determining step. Support for this interpretation is provided by our observation that on anchoring the catalyst, which decreases dimer formation, the rate is considerably enhanced.[2h] In the presence of alcohol the conversion of uncharged (**1**) to charged (**2**) is facilitated because of the higher polarity of the medium. Now, step (A) is so much faster that the rate-determining step of the reaction changes to (B). An additional feature in the mechanism may be the trapping of intermediate (**2**) as its L = MeO$^-$ derivative. This derivative has a less electrophilic oxygen atom and, therefore, may be less able to form an intermediate complex with an alkene. Only after exchange of MeO$^-$ for pyridine is oxygen transfer possible.

In a second series of experiments we mixed various alkenes in a 1:1 ratio and measured their rates of epoxidation under competitive conditions by g.l.c. Mixtures of two aliphatic alkenes display a reaction order in catalyst between 1 and ~0. However, when an aliphatic alkene is mixed with styrene, the rate of epoxidation of the former compound increases and the order in catalyst changes to 1 (Figure 1). For styrene the reaction order in catalyst remains 1, while $k_{cat}$ decreases from 0.41 ± 0.01 to 0.16 ± 0.005 s$^{-1}$. The pronounced effect of styrene is also evident from u.v.–visible measurements. Species (**2**) was generated by rapidly stirring a dichloro-methane–methanol solution (10:1 v/v) of $Mn^{III}TTP$ and alkene, having the same concentration of reagents as used in the g.l.c. experiments, with an aqueous solution of sodium hypochlorite. After rapid separation of the layers the increase in absorption at 476 nm was measured as a function of time. Mixtures of aliphatic alkenes and styrene show curves in which the decomposition of (**2**) is sigmoidal in time, suggesting that after an induction period styrene becomes involved in the process of oxygen transfer to the aliphatic alkene.

In order to trace the nature of this synergistic effect of styrene, we tested the effect of other aromatic additives on the epoxidation of aliphatic alkenes. Benzene, toluene, methoxy-benzene, and nitrobenzene had, within experimental error, no effect on the rate of the epoxidation reaction. Benzaldehyde, however, showed a similar rate-enhancing effect as styrene. In the presence of 0.35 mol dm$^{-3}$ of this additive the rate of cyclohexene epoxidation increased by a factor of 1.75. Benzaldehyde itself was only slowly oxidized under the reaction conditions employed. Naphthol and 2-nitrosonaph-

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‡ The manganese complex $Mn^{IV}TTP(OMe)_2$ has a u.v.–visible spectrum very similar to that of (**2**).[2d] Its involvement in the catalytic process, however, is unlikely. We prepared this complex separately and found that under our conditions it does not catalyse the epoxidation of alkenes.

thol completely blocked the epoxidation. The latter compounds probably give rise to the formation of diaryloxymanganese(IV) porphyrin complexes, which are known to have low oxidising properties.[2d]

The induction period observed indicates that the rate-accelerating species is not styrene itself but one of its reaction products. These products are styrene oxide and phenylacetaldehyde. We propose that this aldehyde, just as benzaldehyde, transfers a hydrogen atom to the oxygen atom of the oxo-manganese species (2) to give species (5). Thus, in the presence of aldehyde the epoxidation of alkenes would proceed *via* (5). Consequently, the stationary-state concentration of (2) is lower than in the absence of aldehyde. The dimerization equilibrium (2) $\rightleftharpoons$ (4) will shift to the left and the order in [$Mn^{III}TTP$] changes to 1.

Our experiments indicate that care should be taken in drawing mechanistic conclusions from competitive experiments with aromatic and alkene substrates, as has been done recently.[2f] A reinterpretation of data in the literature[2f] may be required.

## References

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