A host–guest epoxidation catalyst with enhanced activity and stability

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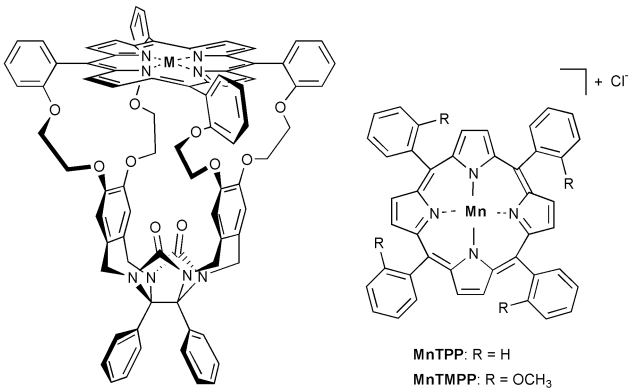
A porphyrin-capped molecular clip epoxidises olefins, depending on the axial ligand used, with enhanced activity or stability

The mono-oxygenase cytochrome P450 selectively binds substrates in the direct proximity of an Fe(III) protoporphyrin IX, which catalyses the activation of molecular oxygen and the subsequent incorporation of one of the oxygen atoms into the bound substrate and reduction of the other one to water.[1] Much research has been devoted to the elucidation of the complex working mechanisms of the enzyme, and several simplified synthetic models have been constructed which make use of molecular oxygen or a single oxygen donor (*e.g.* sodium hypochlorite) as the oxidant. Many of these model systems utilize Mn(III) porphyrins functionalised with straps or caps to establish an environment in which the oxygen transfer from the metal to the substrate is under steric control.[2] Regio- and stereoselective oxidation has been achieved,[3] in which for example *cis*-stilbene has been oxidised with a major preference for the production of the *cis*-epoxide.[4] Other approaches involve the coupling of a metalloporphyrin to known cavity molecules, such as cyclodextrins[5] and cyclophanes,[6] which can bind substrates and oxidise them with enhanced rates or selectivities. Here we describe initial catalytic studies using the new cavity-containing manganese porphyrin **Mn1** as a catalyst. The molecule consists of a molecular clip[7] equipped with a porphyrin roof situated symmetrically above the receptor, thus creating a rigid and relatively closed cavity with a diameter of approximately 9 Å.[8] Whilst the free base host **$H_2$1** has been applied in the construction of rotaxanes, it was also our intention to utilize its Mn(III) derivative as an olefin epoxidation catalyst. In this paper, the catalytic properties of **Mn1** in the



epoxidation of α-pinene and *cis*- and *trans*-stilbene, applying the biphasic dichloromethane–aqueous NaOCl system previously used by us[9] and by other groups,[10] are compared to those of the reference porphyrins **MnTPP** and **MnTMPP**. Particular emphasis is directed toward the relative activity and stability of these catalysts. It will be shown that by a strong host–guest binding of the axial ligand in the cavity of **Mn1** the rate of epoxidation is enhanced, while by shielding the outside of the cavity of **Mn1** the catalyst's stability is increased. Although the Fe(III) porphyrin in cytochrome P450 features axial coordination by a cysteine thiolate, most of its synthetic mimics utilize more stable pyridine, imidazole or phenolate derivatives to enhance the activity and stereoselectivity of the catalytic center. In previous studies in which **MnTPP** was used as the catalyst, it was found that the strength of axial ligand binding was related to the enhancement of the activity of the catalyst, since the electron donating properties of the ligand facilitate the formation of the proposed Mn(V)–oxo species.[9] For optimal results 500 equivalents of pyridine (Py) were, however, required in the reaction, because of its relatively weak binding to the porphyrin metal ($K_a \approx 1000\ M^{-1}$). Since NMR studies had revealed that in host **Zn1** Py is bound within the cavity with a very high association constant ($K_a = 1.1 \times 10^5\ M^{-1}$) due to stabilising cavity effects,[8] it was calculated that under the applied epoxidation reaction conditions† **Mn1** would require only *one* equiv. of Py to achieve a >99% binding to the porphyrin metal (Fig. 1, approach A). Indeed, the effect of this supramolecular activation of **Mn1** by Py, compared to **MnTPP** under the same reaction conditions (*one* equiv. of Py), resulted in a 5–10 fold initial rate enhancement in the epoxidation of olefins (Table 1, Fig. 2). As a result of this, it requires more than 10 h for the reaction to be completed in the case when **MnTPP** is used as the catalyst, while when using **Mn1** it is complete within 2 h. The rate enhancement exhibited by the **Mn1**–Py system is not caused by electronic or steric effects of the alkoxy groups, as control experiments using **MnTMPP** showed that this catalyst exhibited even lower epoxidation rates than **MnTPP** (Table 1). The rate enhancing effect is further illustrated when one equiv. of the even stronger binding axial ligand imidazole (K_a with **Zn1** $= 3.2 \times 10^5\ M^{-1}$) is used as the axial ligand in **Mn1**: α-pinene is epoxidised by **Mn1** within approximately 1 h with an initial rate $k_0 = 17 \times 10^5$/mol dm^{-3} s^{-1}. In addition to rate enhancement, Py-activated epoxidation of *cis*-stilbene by **Mn1** preferentially produced *cis*-stilbene oxide over the *trans*-isomer (Table 1), which is a commonly observed phenomenon for Py–Mn(III) porphyrin catalyst systems.[9,10]

A drawback of the **MnTPP** and **MnTMPP** catalysts is their instability. During the course of the epoxidation reaction the brown organic layer gradually decolourises, especially when the

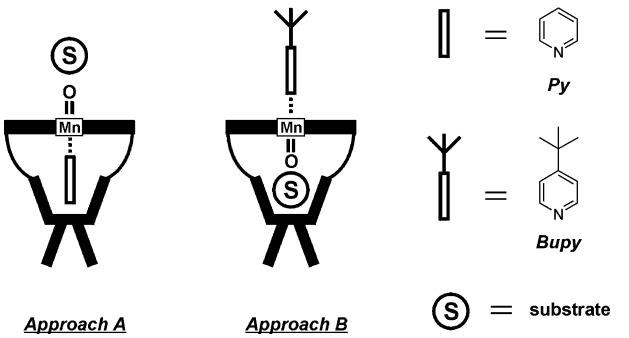


Fig. 1 Two approaches in which **Mn1** is used as an epoxidation catalyst in combination with Py or Bupy as the axial ligand.

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Table 1 Epoxidation of olefins by **Mn1** and the reference catalysts **MnTPP** and **MnTMPP**

		Mn1[a]			**MnTPP**[a]			**MnTMPP**[a]		
Substrate	Axial ligand	Yield[b]	Rate[c]	*c*:*t*[d]	Yield[b]	Rate[c]	*c*:*t*[d]	Yield[b]	Rate[c]	*c*:*t*[d]
α-pinene	Py[e]	81	12.0	—	10	1.2	—	—[f]	—[f]	—[f]
cis-stilbene	Py[e]	57	19.9[g]	96:4	39	3.7[g]	65:35	33	2.9	63:37
trans-stilbene	Py[e]	72	18.9	[h]	9	3.8	[h]	8	< 1.0	[h]
α-pinene	Bupy[i]	82	10.9	—	80	12.9	—	—[f]	—[f]	—[f]
cis-stilbene	Bupy[i]	57	15.5[g]	90:10	70	57.0[g]	90:10	52	39.3	92:8
trans-stilbene	Bupy[i]	72	24.1	[h]	63	21.2	[h]	65	20.0	[h]

[a] Standard reaction conditions.† [b] Yield (%) after 3 h. [c] Initial rate × 10^5 mol dm^{-3} s^{-1}. [d] Ratio *cis*–*trans* epoxide product after 3 h. [e] 1 equiv. per Mn(III)-catalyst. [f] Not determined. [g] Rate of formation of the *cis*-epoxide. [h] No *cis*-epoxide was detected. [i] 500 equiv. per Mn-catalyst.

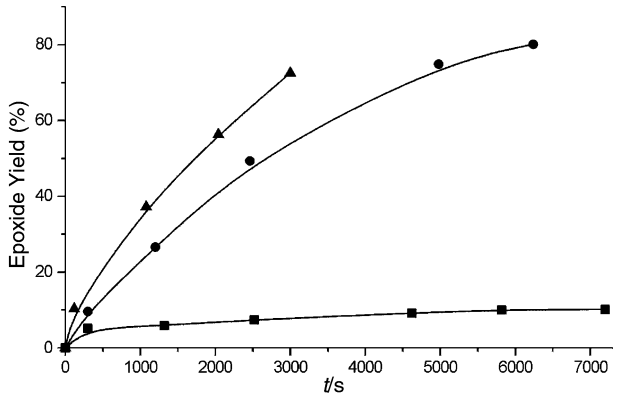

Fig. 2 Epoxidation of α-pinene using 1 equivalent of an axial ligand. **MnTPP**–Py (■), **Mn1**–Py (●), **Mn1**–Im (▲).

amount of unreacted olefin decreases. This phenomenon has been attributed to the formation of μ-oxo-bridged Mn(IV) porphyrin dimeric structures, which are unreactive in further catalysis and rapidly decompose.[9] This rapid decomposition was also found to occur in the case of the **Mn1**–Py system used in approach A. To prevent this, the bulky axial ligand 4-*tert*-butylpyridine (Bupy) was used to coordinate to **Mn1** on the outside of the cavity (Fig. 1, approach B). It was expected that coordination of this ligand, which does not fit within the cavity,‡ would efficiently prevent μ-oxo dimer formation since the other face of the porphyrin is protected by the receptor cavity. When the epoxidation reactions using **Mn1** were carried out in the presence of 500 equiv. of Bupy, catalyst destruction was indeed prevented, as was concluded from the fact that the organic layer retained its brown colour, and, more importantly, that newly added amounts of substrate were epoxidised. The epoxidation experiment was repeated sequentially several times. The observed initial rate was found in all cases to be almost identical, indicating that no decomposition of the catalyst occurred. This gave turnover numbers of > 1000 per catalyst.§ When **MnTPP** or **MnTMPP** were used as the catalyst in combination with Bupy, this stabilization did not occur and the catalysts decomposed.

Assuming complete shielding of the outside of **Mn1** by Bupy implies that the oxygen transfer to the substrate has to occur within the cavity. From molecular modelling studies it became clear that the substrates cannot react *via* the side of the cavity, *i.e.* they need to enter the cavity completely to reach the manganese–oxo species. The epoxidation results of *cis*- and *trans*-stilbene using the **Mn1**–Bupy system are summarised in Table 1 and compared to those when **MnTPP** or **MnTMPP** are used as the catalyst. Whilst for the epoxidation of *trans*-stilbene not much difference is observed between the catalysts with regard to initial rate and epoxide yield, the epoxidation rate of *cis*-stilbene clearly decreases going from **MnTPP** to **MnTMPP** to **Mn1**. This decrease in rate coincides with a simultaneous increase in steric hindrance by the substituents of the *meso*-phenyl rings. Apparently, these groups have more steric influence on a *cis*-stilbene substrate than on a *trans*-stilbene substrate. Remarkably, the rate of epoxidation of *cis*-stilbene catalysed by the **Mn1**–Bupy system (epoxidation within the cavity) is similar to that catalysed by the **Mn1**–Py system (epoxidation outside the cavity) (Table 1). This implies that additional factors play a role in the epoxidation reaction. Further studies are currently under investigation.

In summary, we have shown that by means of a unique supramolecular activation of **Mn1** only one equiv. of the axial ligands pyridine or imidazole are required to activate the catalyst for the epoxidation of olefins. Coordination of a bulky axial ligand on the outside of the cavity of **Mn1** strongly enhances the stability of the catalyst, which in this approach is protected from further oxidative decomposition. Current research is focused on the functionalisation of Mn(III) porphyrins with molecular clip receptors on both faces, so that both approaches of supramolecular activation and catalyst protection are combined.

Notes and references

† *Reaction conditions*: to a CH_2Cl_2 solution (0.65 ml) of the substrate (0.626 M), the manganese catalyst (2.5 mM), the phase transfer catalyst tetrabutylammonium chloride (5 mM), the axial ligand pyridine (2.5 mM) or 4-*tert*-butyl pyridine (1.25 M), and an internal standard (1,3,5-tri-*tert*-butylbenzene (0.17 M) in a Schlenk tube was added an aqueous NaOCl solution (2 ml, 0.6 M). The mixture was stirred at a constant rate under nitrogen for 3 h, and during the course of the reaction samples were taken from the organic layer which were analysed by GLC and ^{1}H NMR.

‡ This was concluded from ^{1}H NMR experiments on mixtures of **Zn1** and Bupy in $CDCl_3$, which indicated no binding within the cavity of the host even when 500 equiv. of the axial ligand were added.

§ More than 4 portions of substrate could be oxidised without any decomposition of the catalyst. Due to phase separation between the solvent and the epoxidation products it then became more difficult to measure a reliable rate of conversion when the number of portions were increased beyond 4.

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