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Supramolecular Catalysis

A double-cavity-containing porphyrin host as a highly stable epoxidation catalyst

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Abstract: We describe a manganese porphyrin catalyst containing two adjacent cavities, which can be used for the epoxidation of alkenes by sodium hypochlorite. A pyridine ligand bound in one of the cavities regulates the rate and selectivity of the epoxidation reaction that takes place in the adjoining cavity. Pyridine binding studies suggest that site-to-site communication exists between the two cavities. The alkene substrates are completely converted into epoxides by the manganese double-cavity catalyst, but the observed epoxidation rates are very low. These low rates are proposed to be a result of the energetically less favourable binding of the substrate into the cavity containing the active site due to an allosteric pinching effect. In the manganese double-cavity arrangement the catalytically active manganese complex is efficiently protected against decomposition, leading to a catalytic system with enhanced stability. The presented work may open a new route to the construction of highly stable catalysts of which the activity and selectivity may eventually be controlled by allosteric interactions.

Introduction

Enzymes continue to be a major source of inspiration for the design and synthesis of new abiotic catalysts that display high stabilities and selectivities.[1] Recent advances in supramolecular chemistry have made it possible to mimic the complexity and functionality of natural enzymes in simplified man-made catalysts. Such artificial enzyme-like systems have led to new concepts and interesting applications in the field of catalysis, for example cooperative,[1c] substrate selective,[2a] allosteric,[2b] and processive catalysis.[2c] In heme-containing enzymes such as cytochrome P-450 (CYP), the axial ligand plays an important role in directing the chemical and biochemical outcome of the catalytic reaction.[3,4] Hence, in a model system the effect of the ligand on catalysis should be optimized. Another important feature is the “cage effect”. In natural enzymes, the protein chain, in particular the superstructure present in the vicinity of the active site, controls the selection of the substrate molecules based on their shape, size, charge, and their conversion into product.[5] It is very challenging to design a synthetic enzyme that would demonstrate the key effects of the natural enzyme CYP, i.e. an axial ligand and a reaction center that is sterically protected allowing for an increased lifetime of the catalyst. In the present paper, we describe a highly stable epoxidation catalyst based on a double cage compound containing a porphyrin catalytic core whose structure and function are inspired by CYP. We demonstrate that this catalyst displays control over the selectivity of substrate molecules and the product that is formed. Furthermore, we show that the stability of the catalyst is increased manifold when compared to a normal porphyrin catalyst or a porphyrin catalyst containing a single cavity. The new catalyst can be recycled with little loss in activity, which is very uncommon for homogeneous porphyrin oxidation catalysis. During the catalytic cycle, one cavity of the double cage compound is involved in substrate binding and catalysis, whilst the other cavity is used to bind a “regulatory” axial ligand, such as pyridine. This new design for the active site of CYP opens possibilities for the construction of efficient and more stable oxidation catalysts.

Results and Discussion

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Design

In our previous studies on biomimetic catalytic systems we focused on the mono-cavity containing manganese(III) porphyrin catalyst **MnMC** (Figure 1a) for the epoxidation of low molecular weight and polymeric alkenes.[6] Although **MnMC** shows an excellent catalytic performance, the system has some disadvantages hindering its practical use as an epoxidation catalyst. It requires a large excess (ca. 500 equiv.) of axial ligand, such as a bulky pyridine derivative, to efficiently block the outer face of the catalyst, thus forcing the catalytic reaction to occur inside the cavity.[6a-e] (Figure 1c). Providing the porphyrin catalysts with a strap has made it possible to perform oxygenation reactions under steric control, whilst also inhibiting catalyst decomposition.[7-8] One of the effects of the strap is to increase the stability of the metal porphyrin during the oxygenation reaction by hindering the proposed catalyst-deactivation, *i.e.* the formation of a μ-oxo-bridged (metal-O-metal) dimer.[9] In order to obtain such a stable catalyst, we designed the double-cavity containing Mn(III) catalyst **MnDC** (Figure 1b). We here present the synthesis of **MnDC** and its application as a catalyst in the epoxidation of alkenes.

It was shown before[6] that the coordination of an electron-donating axial ligand increases the activity of **MnMC**, as expected for manganese porphyrin catalysts.[11] In the case of pyridine (**py**), which is small enough to fit inside the cavity of **MnMC**, the oxygenation reaction occurred on the outside of the porphyrin catalyst (approach **A** in Figure 1c). When 4-*tert*-butyl-pyridine (**tbpy**), which is too sterically demanding to fit inside the cavity was used, oxygenation occurred inside the cavity in a pseudo-rotaxane geometry (approach **B** in Figure 1c). The difference between the two approaches was evident from the measured rates of the epoxidation reactions and from the stabilities of the catalysts, with approach **B** showing a dramatic increase in catalyst stability compared to approach **A** and to an electronically related manganese porphyrin without a protecting cavity. Due to the weak binding of the ligand, 500 equivalents of **tbpy** were required to completely block the outside of the cavity. In contrast, as a result of a much stronger binding, in approach **A** only one equivalent of axial ligand was effective in significantly increasing the activity of the catalyst. Catalyst **MnDC** combines both approaches **A** and **B**, *i.e.* catalyst activation by the coordination of one equivalent of axial ligand, and an increased catalyst stability compared to non-protected porphyrins (Figure 1d).

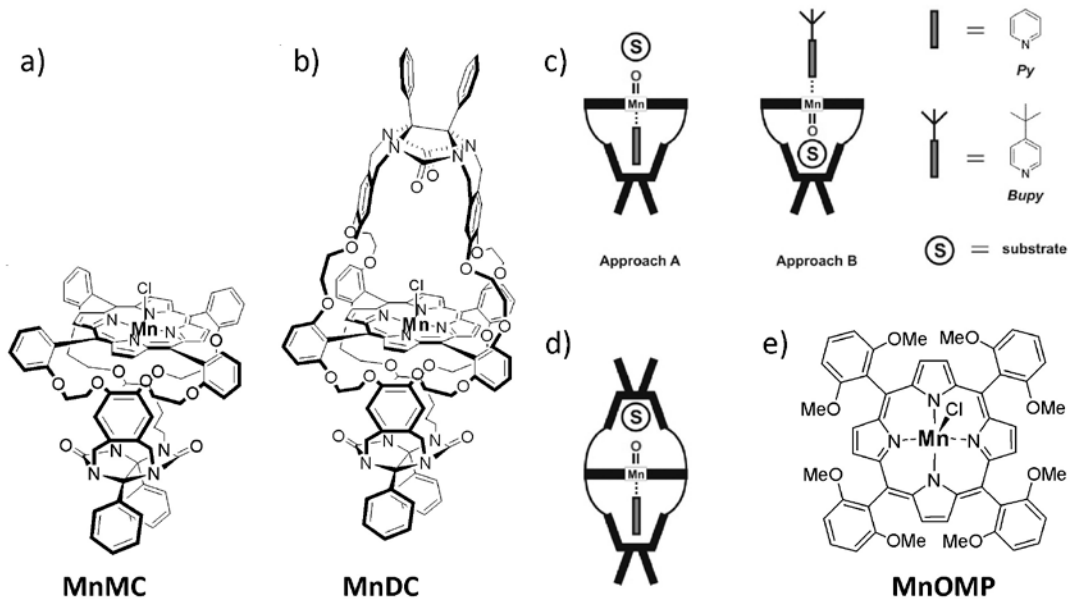


Figure 1. a) Structure of the mono-cavity-containing manganese(III) porphyrin **MnMC**. b) Structure of the double-cavity-containing manganese(III) porphyrin **MnDC**. c) Schematic representation of the two approaches in which **MnMC** is used as an epoxidation catalyst in combination with **py** or **tbpy** as the axial ligand. d) Schematic representation of the combination of approaches A and B in the manganese double-cavity-containing catalyst **MnDC**. e) Structure of the reference porphyrin catalyst **MnOMP**.

Synthesis of double-cavity porphyrin compounds DC, ZnDC and MnDC:

In the previously reported synthesis of **DC** (Scheme 1) two separate routes to obtain this host molecule were described

(Figure 2a).[10] The first involved the addition of one equivalent of tetra-tosylate molecule **2** to the octa-hydroxy porphyrin **1** in acetonitrile to yield an intermediate tetra-hydroxy mono-cavity-appended porphyrin (isomer **I** in Figure 2b). This isomer could then be further reacted with an excess of **2** in DMF to yield **DC** (route **A** in Figure 2a). The second route was a one-step reaction in DMF between **1** and two equivalents of **2** (route **B** in Figure 2a). In both approaches two double-cavity porphyrin isomers were obtained in a 10:1 ratio: isomer **III** (**DC**) and isomer **IV**. The low yields obtained in the synthesis of **DC** as compared to **MC** suggest that the final cyclization is extremely difficult due to the presence of significantly more strain in the former molecule. The unequal product ratio of isomer **III** and isomer **IV** (10:1) typically has its origin in the C_2-symmetry of the cavity in isomer I, which results in the reaction with a second molecule of **2** being energetically more favorable for one orientation than for the other. We found that during the synthesis of **DC** in route B an additional double-cavity porphyrin isomer, which had an identical mass to that of **DC**, could also be isolated, as was demonstrated by MALDI-TOF and NMR spectrometry (isomer **V**; Figure 2c). In addition, an intermediate of this isomer, isomer II of the tetra-hydroxy mono-cavity porphyrin, was also found (Figure 2b). In these isomers (**II** and **V**) the porphyrin plane is not orthogonal to the cavity of the host molecule, but attached in a "sideway" geometry. This geometry is confirmed by the observation that the signals of the β-pyrrolic protons of these isomers positioned inside the cavity exhibit a significant upfield shift (≈ -0.8 ppm) when compared to those situated on the outside of the cavity (Supporting Information Figure S1b and e).

A ^{1}H-NMR spectrum containing a mixture of all the reaction products (with a mass equal that of **DC**), obtained *via* column chromatography, showed trace amounts of two other species, which we tentatively identified as isomers **VI** and **VII** (Figure 2c). These additional isomers could not be isolated from the mixture due to their extremely low yield. The formation of the different isomers appeared to be kinetically determined, since the ratios in which they were formed varied in every batch of double-cavity porphyrin molecules that was synthesized.

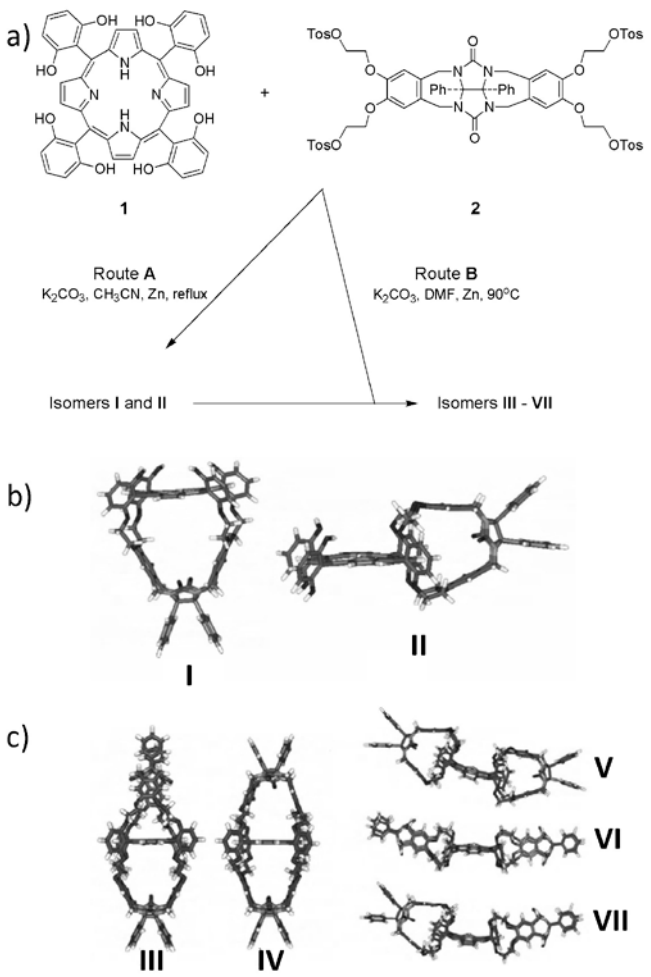
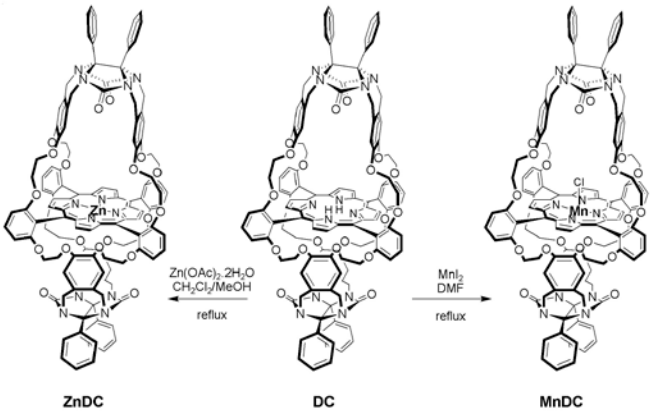


Figure 2. a) Synthesis of the mono- and double-cavity porphyrins. Route **A**, step 1: (1) K_2CO_3/Zn/CH_3CN/reflux, 16 h, ratio **1**:**2** = 1:1, (2) HCl; step 2: (1) K_2CO_3/Zn/DMF/90°C, 16 h, excess **2**, (2) HCl; route **B**: K_2CO_3/DMF/90°C, 16 h, ratio **1**:**2** = 1:2. b) The two tetra-hydroxy mono-cavity porphyrin isomers **I** and **II** formed from the reaction between one porphyrin molecule **1** and one molecule of **2**. c) The five different double-cavity porphyrin isomers **III**-**VII** formed from the reaction between one porphyrin molecule **1** and two molecules of **2** or from one tetra-hydroxy mono-cavity porphyrin (I) and one molecule of **2**.

Since the effective yield of **DC** (isomer **III**) was very low (<1%), several attempts were undertaken to optimize its synthesis. No significant improvement, however, could be made upon changes in (*i*) the reaction time (0.5-3 days), (*ii*) the solvent (acetonitrile or DMF) or (*iii*) the base (K_2CO_3 or Cs_2CO_3). When a 1:1 mixture of molecule **2** and porphyrin **1** was employed, both mono-cavity and double-cavity containing porphyrins were formed in both the solvents CH_3CN and DMF. In this case, the number of oligomeric side products was reduced when compared to an experiment in which a 2:1 mixture of **2** and **1** was used. The decrease in the amount of side products resulted in an increase in the overall yield of **DC** and also the yield of the mono-cavity containing isomer **I**. Isomer **I** could be reacted further with **2** to

form **DC** and isomer **IV**. The different isomers for both mono-cavity and double-cavity containing porphyrins were always formed, independent of the synthetic route that was followed. First refluxing an acetonitrile solution of clip molecule **2** and porphyrin **1** in a 1:1 molar ratio, with an excess of K_2CO_3, followed by heating of the separated isomers **I** and **II** with another equivalent of **2** in DMF, was found to be the most successful procedure for the synthesis of **DC**. The isolation of **DC** was also not trivial. The double-cavity containing porphyrin isomers were easily separable from their mono-cavity-containing analogues *via* column chromatography, but the R_f-values within each set of isomers (**I**-**II** and **III**-**V**) were very similar. Careful column chromatography using a gradient ranging from 1.2% to 1.6% methanol in chloroform, with incremental increases of 0.05%, was necessary to separate and isolate the different double-cavity porphyrins. This last purification step could only be performed successfully after the separation of the double-cavity porphyrin isomers from the other species. The latter separation was accomplished by column chromatography over silica and alumina (to remove traces of tetra-hydroxy functionalized mono-cavity containing porphyrins), followed by the insertion of a zinc ion into the porphyrin isomers and column chromatography over silica with 1% (v/v) pyridine present in the eluent (employing the different binding behaviour of cavity-appended and non-cavity-appended porphyrins towards this ligand). The penultimate step was treatment of the cavity molecules with hydrochloric acid to remove the zinc ions from the porphyrins. The unavoidable small loss of the desired product in each of the purification steps is also responsible for the low overall yield of **DC**. **ZnDC** was synthesized by refluxing **DC** with $Zn(OAc)_2.2H_2O$ in a mixture of chloroform and methanol (Scheme 1), and obtained in 92% yield after purification by column chromatography.

A manganese ion was inserted into **DC** by refluxing this compound under an argon atmosphere in DMF in the presence of an excess of MnI_2 (Scheme 1). Stirring the product for three days under air in a two-phase system of chloroform and brine exchanged the iodide for a chloride anion and oxidized the manganese(II) ion to manganese(III). **MnDC** was obtained in 83% yield after purification by column chromatography.



Scheme 1: Synthesis of **ZnDC** and **MnDC**.

Host-guest binding studies:

Before conducting catalytic studies with the newly synthesized **MnDC**, we decided to test the possible communication between the two cavities by studying the host-guest binding properties of **ZnDC**. From the binding properties exhibited by the related molecule **DC** it is known that the two cavities influence each other upon the binding of methyl viologen (*N*,*N*′-dimethyl-4,4′-bipyridinium dichloride dihexafluorophosphate) (**V**) in a negative allosteric fashion. For example, when two **V** guest molecules are bound, the first binding event expands one cavity, resulting in a concomitant pinching of the second cavity, as a result of which the binding constant for the second **V** molecule drops by a factor of 1400 compared to that of the first.[10]

In order to obtain more information regarding the allosteric binding of pyridine and guest molecules, the binding of pyridine in **ZnDC** with and without viologen present as a model substrate was determined (Figure 3). The latter molecule was selected because it is known to bind strongly in the cavity of porphyrin cages[16] while alkene substrates do not display a strong binding and hence cannot be studied. In the absence of viologen the association constant for the binding of **py** in **ZnDC** in $CHCl_3/CH_3CN$ 4:1 (v/v) was measured to be $K_a = 2.2 \times 10^4$ M^{-1}, which is only slightly lower than the association constant between **py** and **ZnMC** ($K_a = 7.5 \times 10^4$ M^{-1}). Remarkably, the association constant between **py** and **ZnDC** in the presence of one equivalent of viologen increased 5-fold to $K_a = 1.1 \times 10^5$ M^{-1} (Figure 3a and b), which indicates a significant positive heterotropic allosteric binding effect. We propose that as a result of the pinching of the second cavity by the binding of viologen in the first cavity, the pyridine molecule can bind more strongly because of a better fit between the aromatic rings of the cavity walls, which leads to better π–π stacking interactions between the ligand and the host. Hence, the observed positive allosteric effect in fact is a result of decreased space, which in the case of the binding of two viologen molecules leads to a negative allosteric effect.[10] It should be mentioned, however,

that the binding of a viologen molecule in **ZnDC** might also exert an electrostatic effect on the metal center, such that pyridine binds more strongly to the zinc ion.[14,15]

The increased binding strength of pyridine is accompanied by a slow exchange of this ligand, which results in signals for both bound and free pyridine. With the help of 2D-NMR all the proton resonances of the **ZnDC:V:Py** complex could be assigned (Supporting Information Figure S1 f-i).

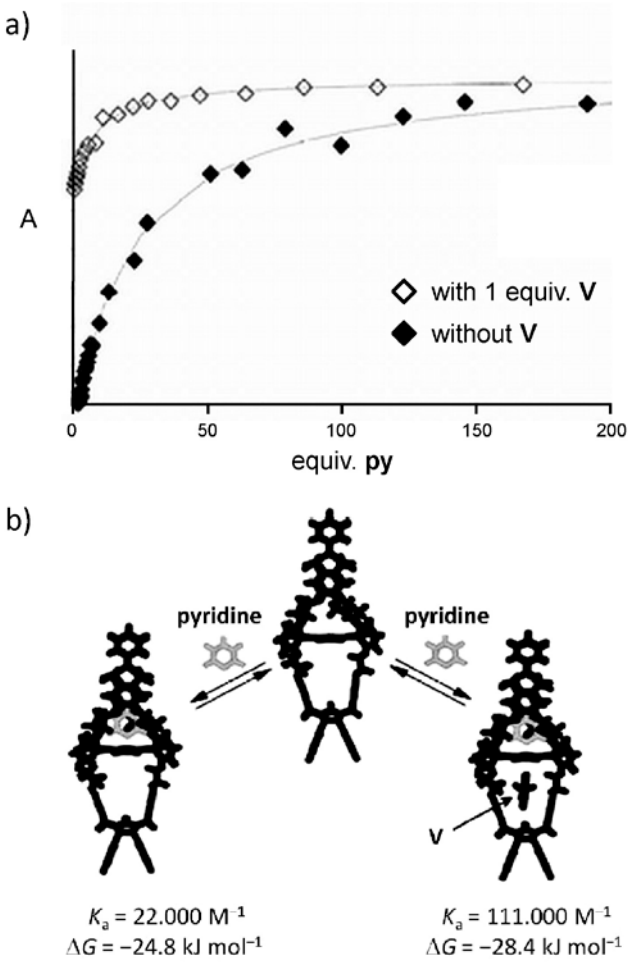
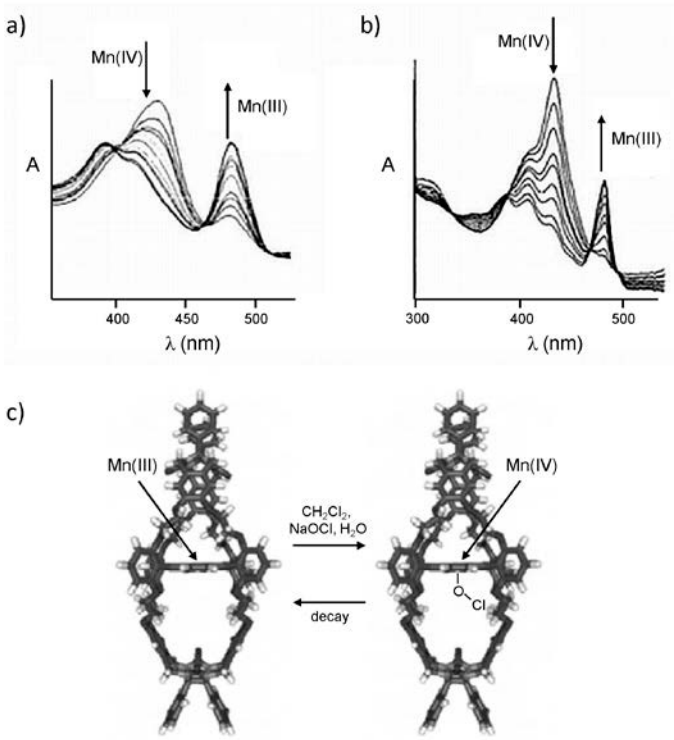


Figure 3. a) UV-vis titration curves of the binding of **ZnDC** with **py** in the absence and in the presence of one equivalent of **V** in $CHCl_3/CH_3CN$ 4:1 (v/v). b) Computer-modeled representation of the positive heterotropic allosteric binding behaviour of **ZnDC**.

Catalytic properties

We first investigated the oxidation of the manganese porphyrin catalyst **MnDC** with an oxygen donor in the absence of substrate. When a dichloromethane solution of **MnDC** was thoroughly mixed with a 0.6 M aqueous NaOCl solution, the UV-Vis spectrum showed a shift of the porphyrin Soret band from 479 to 425 nm. Based on similar experiments reported in the literature, the structure (P)Mn(IV)OCl is proposed for the formed species.[12] Apparently, despite the steric restraints, the



manganese ion can be readily oxidized by hypochlorite. The mixture was allowed to stand at room temperature and UV-Vis spectra showed that the intensity of the band at 425 nm gradually decreased, accompanied by an increase in intensity of the band at 479 nm, which corresponds to the **Mn(III)DC** species (Figure 4a). The decay process of the Mn(IV) species back to Mn(III) took approximately 20 minutes for **MnDC**, while the complete decay for **MnMC** was observed to require approximately 15 minutes (see Figure 4b). For a standard manganese(III)tetra-phenyl porphyrin (**MnTPP**), the same decay occurs within only 2 minutes. These experiments suggest that the oxidized species of **MnDC** is slightly more stable than that of **MnMC**, whereas they are both considerably more stable than the oxidized species of **MnTPP**. In spite of the long lifetime of the hypochlorite complex, no decomposition was observed for **MnDC**.

Figure 4. a) UV-Vis spectra of **MnDC** in CH_2Cl_2 after treatment with an aqueous NaOCl-solution. b) Idem, of **MnMC**. c) Computer-modeled representation of the formation and decay of **Mn(IV)DC**-OCl.

In a second series of experiments the epoxidation of alkenes was investigated employing the standard two-phase hypochlorite-dichloromethane reaction conditions already reported for **MnMC** (Table 1).[6a,6c] First, the epoxidation of *cis*-stilbene using **MnDC** as the catalyst was investigated. Upon the binding of one equivalent of **py** in the cavity of **MnDC**, the rate of the epoxidation reaction increased, in a similar fashion to that observed for **MnMC**. The addition of more equivalents of **py** to **MnDC** resulted in a subsequent decrease in reaction rate, indicating that both cavities of the catalyst become occupied by axial ligands, which block the approach of substrates to the catalytic metal center. The binding of two pyridine ligands to a manganese(III) porphyrin has been reported before, and is known to exhibit strong negative cooperative coordination behavior.[13] The measured reaction rates for **MnDC** were significantly lower than the rates observed when the electronically analogous reference catalyst *o*-octa-methoxy-porphyrin **MnOMP** (Figure 1e) was used. In contrast to **MnDC**, this porphyrin catalyst exhibited an increased activation upon an increase in the amount of added axial ligand (Table 1). The observed reduced rate for **MnDC** is proposed to be the result of the reaction occurring within a sterically demanding cavity and competitive binding of a second axial ligand to the manganese center.

When **MnOMP** was used as the catalyst in the epoxidation of *cis*-stilbene, almost exclusively the *cis*-epoxide was formed. This is in contrast to the situation for **MnDC**, where, depending on the amount of axial ligand present, also a significant amount of *trans*-epoxide was found. Similar behaviour was observed when **MnMC** was used as the catalyst in combination with **tbpy** as the axial ligand.[6a,6c] The above results indicate that the pseudo-rotaxane geometry of the catalyst-substrate complex imposes steric constraints on the bulky reaction intermediate in the transition state, causing its partial isomerization.

Table 1. Epoxidation of alkenes by **MnDC** and the reference catalysts **MnMC** and **MnOMP** under standard epoxidation reaction conditions (see experimental section for details).

Substrate	Axial ligand	Equiv. axial ligand	Rate MnDC[a]	Rate MnMC[a]	Rate MnOMP[a]	MnDC f.c.[b]	MnDC c:t[d]	MnOMP c:t[d]
cis-Stilbene[d]		0	0.5	n.d.[e]	0.08	>99%	46:54	99:1
cis-Stilbene[d]	**py**	1	0.7	20	2.6	>99%	39:61	97:3
cis-Stilbene[d]	**py**	10	0.5	n.d.	45	>99%	55:45	96:4
cis-Stilbene[d]	**py**	500	0.4	n.d.	91	n.d.	67:33	99:1
cis-Stilbene[d]	**tbpy**	500	n.d.	15.5[f]	n.d.	n.d.	n.d.	n.d.
trans-Stilbene[d]		0	1.6	n.d.	0.03	n.d.	-[g]	-[g]
trans-Stilbene[d]	**py**	1	2	19	0.2	n.d.	-[g]	-[g]
trans-Stilbene[d]	**py**	10	0.5	n.d.	0.3	>99%	-[g]	-[g]
trans-Stilbene[d]	**py**	500	0.3	n.d.	1.3	n.d.	-[g]	-[g]
trans-Stilbene[d]	**tbpy**	500	n.d.	24	n.d.	n.d.	n.d.	n.d.

[a]Initial rate of olefin conversion × 10^{-5} mol dm^{-3} s^{-1}. Estimated error: 15%. [b]f.c.= Final conversion. [c]Ratio cis-trans epoxide product after 4 h. [d]The blank epoxidation rate with all the components present except **MnDC** in the same ratios and amounts as in a typical epoxidation experiment was 0.0 mol dm^{-3} s^{-1} within experimental error. [e]Not determined. [f]Ratio cis-trans epoxide product after 3 h. = 90:10. [g]No cis-epoxide was detected.

In order to compare the influence of the cavity of **MnDC** with that of **MnMC**, a situation had to be established in which both the manganese porphyrins experienced a similar activation by an axial ligand, which can only be achieved when **MnDC** is used in combination with one equivalent of **py** and **MnMC** with 500 equivalents of **tbpy**. Taking the related association constants of the ligand with **ZnDC** into account, it can be expected that in both cases >99% of the hosts bind an axial ligand, whereas at the same time the cavities remain available for catalysis. Compared to **MnDC**, it was found that **MnMC** epoxidized *cis*-stilbene 22 times faster and *trans*-stilbene 12 times, which suggests that the cavity of **MnDC** is more sterically

hindered. It had been previously shown that binding of a ligand in one cavity influences the geometry of the second cavity. The lack of activity of **MnDC** compared to **MnMC** is in agreement with this observation. Another observation that supports this hypothesis is that the use of the more sterically demanding oxygen donor iodosylbenzene in combination with **MnDC** did not result in the epoxidation of any substrate, neither did the addition of this oxygen donor to a dichloromethane solution of **MnDC** result in changes in the UV-vis spectrum. In contrast, the formation of the catalytically active manganese species and the epoxidation of styrene, *cis*- and *trans*-stilbene and polybutadiene have been reported for **MnMC** in combination with iodosylbenzene.[6]

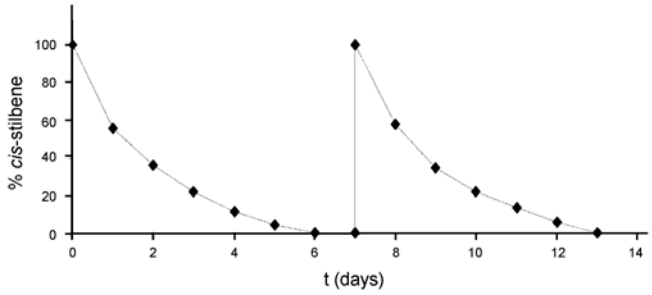


Figure 5. Epoxidation of twice 250 equivalents of *cis*-stilbene by **MnDC** in the presence of one equivalent of **py**. Epoxidation of a second batch of reveals an identical rate (within 15%) of epoxidation, highlighting the stability of the catalyst.

The stability of the **MnDC** catalyst was found to be remarkably high. Although the rates of epoxidation for both *cis*- and *trans*-stilbene were very low, the reaction went to completion in all cases (Table 1). In the presence of one equivalent of **py** it took 6 days to complete the epoxidation of *cis*-stilbene without any catalyst decomposition. The addition of a second batch of substrate again resulted in a complete conversion into the epoxide, with no apparent loss of activity of the catalyst (Figure 5). After 13 days, the main products were *cis*- and *trans*-stilbene oxide, with only a trace of benzaldehyde. During the reaction time, the brown colour of the dichloromethane phase did not alter, which is an indication that the catalyst was not decomposed. In contrast, under the same reaction conditions **MnOMP** decomposed within 24 hours. This remarkable difference in catalyst stability can be attributed to the shielding of the manganese porphyrin by the two diphenylglycoluril-based cavity molecules in **MnDC**, which prevents μ-oxo dimer formation to occur, an effect that is absent in **MnOMP**, and the inability of the active catalyst to oxidize itself. This latter effect clearly demonstrates that the epoxidation in the presence of **py** does probably not occur *via* a radical mechanism. *trans*-Stilbene and *trans*-stilbene oxide fit better in the cavities of **MnDC** than their more sterically demanding *cis*-isomers, which is reflected in the initial reaction rates, which for the epoxidation of *trans*-stilbene in the presence of one equivalent of pyridine (**py**) are higher than that for *cis*-stilbene under the same conditions.

Conclusions

Porphyrin epoxidation catalyst **MnDC** combines supramolecular activation induced by the binding of only one equivalent of axial ligand in its cavity with a huge increase in catalyst stability. Although the observed epoxidation reaction rates are very low, the catalyst remains stable for at least two weeks without showing any signs of decomposition, which is attributed to the inability of the catalyst to form μ-oxo dimeric species, which has been proposed to be the first step in the decomposition reaction. Investigations on the use of this double-cavity-containing catalyst for processive catalysis,[2d] using polymeric substrates and allosterically controlled enantioselective catalysis by binding a chiral guest in one of the cavities of **MnDC**, are in progress.

Experimental Section

Materials and methods: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DMX-300, Varian Unity Inova 400 and Bruker FDRX-500 instruments at 298 K. NMR signals are reported in ppm downfield from the internal standard TMS (0.00 ppm) and abbreviations used are: s = singlet, d = doublet, t = triplet, and m = multiplet. UV-Vis spectra were recorded on a Varian Cary 50 UV-Vis spectrophotometer, GC-spectra were recorded on a Varian GC3800 instrument and IR spectra were recorded on a ATI Mattson Genesis FT-IR spectrometer, equipped with a Harrick Split Pea ATR apparatus. Melting points were recorded on a Jeneval polarization microscope THMS 600 hot stage and MALDI-TOF MS spectra were recorded on a Bruker Biflex III spectrometer using dithranol as a matrix. FAB mass spectra were recorded on a Finnigan MAT 900 S with *m*-nitrobenzyl alcohol as the matrix. All solvents were distilled under nitrogen prior to use. Dichloromethane was distilled from CaH_2. DMF was predried over BaO for one week and then distilled under reduced pressure, discarding the first and last 25% of the distillate. 5,10,15,20-Tetrakis(2,6-dihydroxyphenyl)porphyrin **1**[10] and compound **2**[6f] were synthesized according to literature procedures. Association constants were determined using a literature procedure.[10] All other solvents and chemicals were commercial materials and used without purification. Acros Aluminium Oxide 90 (activity III) and Merck Silica Gel 60 and 60H were used for column chromatography.

Synthesis of double-cavity containing porphyrin DC and its isomers III - V: **Step 1**: To a mixture of porphyrin **1** (180 mg, 0.24 mmol), compound **2** (327 mg, 0.24 mmol), K_2CO_3 (332 mg, 2.40 mmol) and finely grounded zinc powder (5 mg, 0.08 mmol), under an argon atmosphere, was added freshly distilled CH_3CN (150 mL) that had previously been purged with argon. The mixture was refluxed for 16

h under an argon atmosphere. After cooling, aqueous HCl (1 M) was added until the solution turned green and then a few drops of saturated aqueous $NaHCO_3$ were added until a brown coloured solution was obtained (pH 8-9). The mixture was filtered and the residue washed with $CHCl_3$ and CH_3CN until the filtrate remained colourless. The combined filtrates were evaporated to dryness and the residue was subjected to column chromatography (Merck 60, $CHCl_3/CH_3OH$, 97:3 (v/v)) to yield both a mixture of mono-cavity containing porphyrin isomers **I** and **II** and a mixture of double-cavity containing porphyrin isomers **III**-**VII**.

Step 2: Under an argon atmosphere was added freshly distilled DMF (15 mL), that had previously been purged with argon, to a mixture of compound **2** (27 mg, 0.020 mmol), dried K_2CO_3 (40 mg, 0.30 mmol), finely grounded zinc powder (5 mg, 0.08 mmol) and the mixture of mono-cavity porphyrin isomers **I** and **II** (23 mg, 0.016 mmol) from Step 1, The mixture was stirred at 90-100 °C for 16 h under an argon atmosphere. After cooling, aqueous HCl (1 M) was added until the solution turned green and then a few drops of saturated aqueous $NaHCO_3$ were added to until a brown-coloured solution was obtained (pH 8-9). The mixture was filtered and the residue washed with $CHCl_3$ and CH_3CN until the filtrate remained colourless, and the combined filtrates were evaporated to dryness. At this point the previously obtained mixture of double-cavity porphyrin isomers **III**-**VII** was added. Column chromatography over silica (Merck 60H, $CHCl_3/CH_3OH$, 98:2 (v/v)) was followed by column chromatography over alumina ($CHCl_3/CH_3OH$, 99.5:0.5 (v/v)). Zinc(II) was inserted in the porphyrin mixture by refluxing the compounds in the presence of 10 eq of $Zn(OAc)_2.2H_2O$ in $CHCl_3/CH_3OH$ 3:1 (v/v) for 3 h. After cooling the solvent was removed under reduced pressure. Column chromatography over silica (Merck 60, $CHCl_3/CH_3OH$/Pyridine, 97:2:1 (v/v)) afforded a mixture of the different double-cavity porphyrin isomers **III**-**V** (10 mg) with high purity (>99%). Demetallation using aqueous HCl (6 M) in CH_2Cl_2 and, after neutralization, further chromatography over silica (Merck 60, $CHCl_3/CH_3OH$, 98.8:1.2 → 98.4:1.6 (v/v)) yielded the separate isomers **III**-**V**. Yield isomer III: 0.5%, traces of isomer **IV** and **V**.

Isomer I: m.p. > 300°C; IR (KBr-pellet) ν: 3945, 3692, 3055, 2987, 2686, 2522, 2411, 2306, 2155, 2126, 2055, 1706, 1674, 1604, 1550, 1422, 1264, 1177, 896, 738 and 716 cm^{-1}; UV-Vis (CH_2Cl_2) λ/nm: 420, 515, 543, 588, 650; ^{1}H-NMR ($CDCl_3$, 300 MHz, see SI for proton numbering): δ = 8.90 (s, 4H, *H12*), 8.79 (s, 4H, *H13*), 7.65 (t, 4H, ^3J= 8.2 Hz, *H9*), 7.07 (d, 8H, ^3J= 8.3 Hz, *H8,10*), 7.08-6.91 (m, 6H, *H1,2*), 6.80-6.76 (m, 4H, *H3*), 6.16 (s, 4H, *H5*), 4.88 (bs, 4H, O*H*), 4.30-4.20 (m, 4H, *H7*), 4.21 (d, 4H, ^2J= 15.9 Hz, *H4*), 4.13-4.08 (m, 4H, *H7*), 3.72 (d, 4H, ^2J= 16.2 Hz, *H4*), 3.54-3.48 (m, 4H, *H6*), 3.40-3.32 (m, 4H, *H6*), -2.74 (bs, 2H, N*H*) ppm; FAB-MS *m/z*: 1409 $(M+H)^+$.

Isomer II: ^{1}H NMR (DMSO-d_6, 400.15 MHz, see SI for proton numbering): δ = 9.50 (s, 4H, O*H*), 8.78 (s, 2H, *H11*), 8.70 (d, 4H, ^3J = 4.7 Hz, *H12b*), 8.52 (d, 4H, ^3J = 4.7 Hz, *H12a*), 7.88 (t, 2H, ^3J = 8.4 Hz, H9a), 7.81 (s, 2H, H13), 7.39 (t, 2H, ^{3}J = 8.2 Hz, H9b), 7.31 (d, 4H, ^{3}J = 8.4 Hz, H8a), 7.25-7.18 (m, 4H, *H2*), 7.18-7.10 (m, 6H, *H1,3*), 6.79 (d, 4H, ^3J = 8.2 Hz, *H8b*), 6.73 (s, 4H, *H5*), 4.57 (d, 4H, ^2J = 15.7 Hz, *H4*), 4.46-4.37 (m, 4H, *H7*), 4.37-4.28 (m, 4H, *H7*), 4.04 (d, 4H, ^2J = 15.7 Hz, *H4*), 3.68-3.56 (m, 8H, *H6*), -2.85 (br, 2H, N*H*) ppm; MS (MALDI-TOF) *m/z*: 1409 $(M+H)^+$.

DC (isomer III): m.p. > 300°C; IR ($CHCl_3$) ν: 2956, 2923, 2856, 1702, 1589, 1511, 1461, 1425, 1307, 1272, 1247, 1216, 1141, 1112, 1016, 964, 943, 794, 765, 721 and 696 cm^{-1}; UV-Vis ($CHCl_3/CH_3CN$ 4:1 (v/v)) λ/nm ($\log(\varepsilon/M^{-1}cm^{-1})$): 276 (4.36), 405sh (4.68), 423 (5.43), 517 (4.06), 549 (3.49), 591 (3.56), 571 (3.68), 651 (3.00) nm; ^{1}H-NMR ($CDCl_3$, 300 MHz, see SI for proton numbering): δ = 8.65 (s, 8H, *H12*), 7.70 (t, 4H, ^3J= 8.4 Hz, *H9*), 7.04 (d, 8H, ^3J= 8.4 Hz, *H8*), 6.97-6.92 (m, 12H, *H1,2*), 6.82-6.78 (m, 8H, *H3*), 6.21 (s, 8H, *H5*), 4.25 (d, 8H, ^2J= 15.7 Hz, *H4*), 4.28-4.17 (m, 8H, *H7*), 4.04-3.97 (m, 8H, *H7*), 3.74 (d, 8H, ^2J= 15.7 Hz, *H4*), 3.49-3.43 (m, 8H, *H6*), 3.35-3.27 (m, 8H, *H6*), -2.58 (s, 2H, N*H*) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 159.88, 156.93, 146.80, 133.69, 129.94, 129.67, 128.41, 128.10, 122.06, 115.71, 09.87, 105.94, 84.71, 67.72, 67.18, 44.36 ppm; MS (HR-MALDI-TOF) m/z: 2074.697 $[(M)^+$, calcd for $C_{124}H_{98}N_{12}O_{20}$: 2074.702].

Isomer IV: m.p. > 300°C; ^{1}H-NMR ($CDCl_3$, 500.14 MHz, see SI for proton numbering): δ = 8.76 (s, 4H, *H12*), 8.60 (s, 4H, *H13*), 7.67 (t, 4H, ^3J= 8.1 Hz, *H9*), 7.05 (d, 8H, ^3J= 8.2 Hz, *H8*), 6.95-6.93 (m, 12H, *H1,2*), 6.83-6.81 (m, 8H, *H3*), 6.15 (s, 8H, *H5*), 4.22 (d, 8H, ^2J= 15.9 Hz, *H4*), 4.06-4.05 (m, 8H, *H7*), 4.02-4.00 (m, 8H, *H7*), 3.72 (d, 8H, ^2J= 15.9 Hz, *H4*), 3.57-3.54 (m, 8H, *H6*), 3.26-3.25 (m, 8H, *H6*), -2.51 (s, 2H, N*H*) ppm; MS (HR-MALDI-TOF) *m/z*: 2074.697 $[(M)^+$, calcd for $C_{124}H_{98}N_{12}O_{20}$: 2074.702].

Isomer V: m.p. > 300°C; IR ν: 3745, 3459, 2923, 2850, 1696, 1592, 1519, 1458, 1419, 1286, 1221, 1095, 940, 879, 793, 767, 724, 693, 581 cm^{-1}; UV-Vis ($CHCl_3$) λ/nm: 418, 556, 588; ^{1}H-NMR ($CDCl_3$, 400.15 MHz, see SI for proton numbering): δ = 8.78 (s, 4H, *H12*), 7.94 (s, 4H, *H13*), 7.85 (t, 4H, ^3J= 8.3 Hz, *H9*), 7.19-7.13 (m, 28H, *H1,2,3,8*), 6.77 (s, 8H, *H5*), 4.68 (d, 8H, ^2J= 15.9 Hz, *H4*), 4.23-4.16 (m, 16H, *H7*), 4.12 (d, 8H, ^2J= 15.6 Hz, *H4*), 3.67-3.62 (m, 8H, *H6*), 3.58-3.53 (m, 8H, *H6*), -2.55 (s, 2H, N*H*) ppm; MS (MALDI-TOF) *m/z*: 2075 $(M)^+$.

Synthesis of ZnDC: To a solution of isomer **III** (**DC**) (4.7 mg, 0.0026 mmol) in $CHCl_3$ (15 mL) was added $Zn(OAc)_2{\cdot}2H_2O$ (4 mg, 0.018 mmol) in CH_3OH (8 mL). The reaction mixture was refluxed for 4 h under a nitrogen atmosphere in the absence of light. After cooling, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (Merck 60, $CHCl_3$/MeOH 98.2:1.8 (v/v)). Yield: 92%. M.p. > 300°C; IR (KBr-pellet) ν: 2956, 2892, 2846, 1702, 1625, 1581, 1509, 1457, 1421, 1307, 1261, 1118, 1099, 1016, 995, 941, 806, 765, 746, 719, 694, 669 cm^{-1}; UV-Vis ($CHCl_3/CH_3CN$ 4:1 (v/v)) λ/nm ($\log(\varepsilon/M^{-1}cm^{-1})$): 282 (4.16), 431 (5.35), 561 (3.97), 601 (3.24); ^{1}H-NMR ($CDCl_3$500.14 MHz, see SI for proton numbering): δ = 8.75 (s, 8H, *H12*), 7.69 (t, 4H, ^3J= 8.0 Hz, *H9*), 7.07 (d, 8H, ^3J= 7.4 Hz, *H8*), 6.97-6.91 (m, 6H, *H1,2*), 6.83-6.78 (m, 4H, *H3*), 6.18 (s, 4H, *H5*), 4.24 (d, 8H, ^2J= 15.8 Hz, *H4*), 4.25-4.20 (m, 8H, *H7*), 4.00-3.80 (m, 8H, *H7*), 3.74 (d, 8H, ^2J= 15.8 Hz, *H4*), 3.43-3.28 (m, 8H, *H6*), 3.25-3.10 (m, 8H, *H6*) ppm; ^{13}C-NMR (100 MHz, CDCl3): δ = 159.20, 148.04, 134.10, 129.68, 129.19, 128.58, 128.26, 117.21, 85.96, 69.02, 45.50 ppm; MS (HR-MALDI-TOF) *m/z*: 2136.631 $[(M)^+$, calcd for $C_{124}H_{96}N_{12}O_{20}$ Zn: 2136.615].

Synthesis of MnDC: isomer **III** (**DC**) (3.5 mg, 1.7 μmol) was dissolved in dry DMF (2 mL) and to this solution was added MnI_2 (75 mg, 0.25 mmol) and NaOAc (1.1 mg 0.013 mmol). The reaction mixture was stirred overnight under an argon atmosphere in the absence of light at 160°C. After cooling, the solvent was removed under reduced pressure. $CHCl_3$ (20 mL) and brine (20 mL) were added and the two-phase system was stirred vigorously for three days. The organic layer was washed with water three times and evaporated

to dryness. The crude product was purified by column chromatography (Merck 60, $CHCl_3$/MeOH 98.5:1.5 → 95:5 (v/v)). Yield: 83% (green solid). M.p. > 300°C; IR (KBr-pellet) ν: 2962, 2915, 2879, 2855, 1712, 1695, 1590, 1515,1468, 1454, 1425, 1303, 1251, 1106, 1076, 1012, 944, 796, 767, 721, 696 cm^{-1}. UV-Vis (CH_2Cl_2, λ/nm ($\log(\varepsilon/M^{-1}cm^{-1})$): 279 (4.25), 342 (4.23), 392 (4.46), 415 (4.33), 479 (4.58), 493 (4.29), 571 (3.68), 651 (3.00); MS (HR-MALDI-TOF) *m/z*: 2127.621 [$(M-Cl)^+$, calcd for $C_{124}H_{96}N_{12}O_{20}Mn$: 2127.624].

Standard epoxidation 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, and an internal standard (1,3,5-tri-*tert*-butylbenzene; 0.17 M) in a Schlenck tube was added an aqueous NaOCl solution (2 mL, 0.6 M). The mixture was stirred vigorously at a constant rate under nitrogen and during the course of the reaction samples were taken from the organic layer for ^{1}H-NMR and/or GC-analysis. All experiments were performed in triplicate.

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[1] a) D. Ringe, G. A. Petsko, *Science,* **2009**, *320*, 1428-1429. b) M. J. Wiester, P. A. Ulmann, C. A. Mirkin, *Angew. Chem. Int. Ed.,* **2011**, *50*, 114-137. c) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766-771.

[2] a) E. Lindbäck, S. Dawaigher, K. Wärnmark, *Chem. Eur. J.,* **2014**, *20*, 13432-13481. b) H. J. Yoon, J. Kuwabara, J. H. Kim, C. A. Mirkin, Science, **2010**, *330*, 66-69. c) S. F. van Dongen, J. A. A. W. Elemans, A. E. Rowan, R. J. M. Nolte. *Angew. Chem. Int. Ed.,* **2014**, *53*, 11420-11428.

[3] B. Meunier, M. E. De Carvalho, O. Bortolini, M. Momenteau, *Inorg. Chem.*, **1988**, *27*, 16-164.

[4] L. A. Freiburger, O. M. Baettig, T. Sprules, A. M. Berghuis, K. Auclair, A. K. Mittermaier, *Nat. Struct. Mol. Biol.*, **2011**, *18*, 288-294.

[5] a) M. L. Merlau, M. P. Mejia, S. T. Nguyen, J. T. Hupp, *Angew. Chem. Int. Ed.*, **2001**, *40*, 4239-4242. b) J. P. Collman, X. Zhang, R. T. Hembre, J. I. Brauman, *J. Am. Chem. Soc.,* **1990**, *112*, 5356-5357. c) B. Y. Wang, T. Žujović, D. A. Turner, C. M. Hadad, J. D. Badjić**,** *J. Org. Chem.*, **2012**, *77*, 2675-2688.

[6] a) J. A. A.W. Elemans, E. J. A. Bijsterveld, A. E. Rowan, R. J. M. Nolte, *Chem. Commun.*, **2000**, 2443-2444. b) P. Thordarson, E. J. A. Bijsterveld, A. E. Rowan, R. J. M. Nolte, *Nature*, **2003**, *424,* 915-918. c) J. A. A. W. Elemans, E. J. A. Bijsterveld, A. E. Rowan, R. J. M. Nolte, *Eur. J. Org. Chem.*, **2007**, 751-757. d) A. E. Rowan, J. A. A. W. Elemans, R. J. M. Nolte, *Acc. Chem. Res.*, **1999**, *32*, 995-1006. e) C. Monnereau, P. Hidalgo Ramos, A. B. C. Deutman, J. A. A. W. Elemans, R. J. M. Nolte, A. E. Rowan, *J. Am. Chem. Soc.*, **2010**, *132*, 1529-1531. f) J. A. A. W. Elemans, M. B. Claase, P. P. M. Aarts, A. E. Rowan, A. P. H. J. Schenning, R. J. M. Nolte, *J. Org. Chem.* **1999**, *64*, 7009-7016.

[7] a) F. G. Doro, J. R. L. Smith, A. G. Ferreira, M. D. Assis, *J. Mol. Catal. A: Chem.*, **2000**, *164*, 97-109. b) E. Brulé, K. K. Hii, Y. R. de Miguel, *Org. Biomol. Chem.*, **2005**, *3*, 1971-1976. c) I. O. Benítez, B. Bujoli, L. J. Camus, C. M. Lee, F. Odobel, D. R. Talham, *J. Am. Chem. Soc.*, **2002**, *124*, 4363-4370. d) I. D. Cunningham, T. N. Danks, J. N. Hay, I. Hamerton, S. Gunathilagan, C. Janczak, *J. Mol. Catal. A: Chem.*, **2002**, *185*, 25-31. e) M. V. Avdeev, E. I. Bagrii, G. B. Maravin, Y. M. Korolev, *Kinet. Catal.*, **2002**, *43*, 38- 44. f) R. Naik, P. Joshi, S. Umbarkar, R. K. Deshpande, *Catal. Commun.*, **2005**, *6*, 125-129. g) L. Kovbasyuk, R. Krämer, *Chem. Rev.*, **2004**, *104*, 3161-3187.

[8] a) J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, S. E. Hayes, K. S. Suslick, *J. Am. Chem. Soc.*, **1978**, *100*, 2761-2766. b) J. P. Collman, R. R. Gagne, T. R. Halbert, J. C. Manchon, C. A. Reed, *J. Am. Chem. Soc.*, **1973**, *95*, 7868-7870. c) D. H. Burns, K. Calderon-Kawasaki, S. Kularatne, *J. Org. Chem.*, **2005**, *70*, 2803-2807. d) J. Goodwin, T. Kurtikyan, J. Standard, R. Walsh, B. Zheng, D. Parmley, J. Howard, S. Green, A. Mardyukov, D. E. Przybyla, *Inorg. Chem.*, **2005**, *44*, 2215-2223. e) B. Meunier, *Chem. Rev.*, **1992**, *92*, 1411-1456. f) J. P. Collman, L. Fu, *Acc. Chem. Res.*, **1999**, *32*, 455-463. g) J. P. Collman, X. Zhang, V. J. Lee, E. S. Uffelman, J. I. Brauman, *Science*, **1993**, *261*, 1404-1411.

[9] A. W. van der Made, R. J. M. Nolte, W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **1990**, *109*, 537-551.

[10] P. Thordarson, E. J. A. Bijsterveld, J. A. A. W. Elemans, P. Kasák, R. J. M. Nolte, A. E. Rowan, *J. Am. Chem. Soc.*, **2003**, *125*, 1186-1187.

[11] a) A. W. Van der Made, R. J. M. Nolte, *J. Mol. Catal.*, **1984**, *26*, 333-335. b) E. Guilmet, B. Meunier, *Nouv. J. Chim.*, **1982**, *6*, 511-513.

[12] a) J. T. Groves, M. K. Stern, *J. Am. Chem. Soc.*, **1988**, *110*, 6828-6838. b) J. T. Groves, J. Lee, S. S. Marla, *J. Am. Chem. Soc.*, **1997**, *119*, 6269-6273. c) R. D. Arasasingham, G. X. He, T. C. Bruice, *J. Am. Chem. Soc.*, **1993**, *115*, 7985-7991.

[13] a) E. M. Davoras, R. Diaper, A. Devissi, M. J. Tornaritis, A. G. Coutsolelos, *J. Porphyrins Phthalocyanines*, **1998**, *2*, 53-60. b) A. N. de Sousa, M. E. Moreira Dai de Carvalho, Y. M. Idemori, *J. Mol. Catal. A Chem.*, **2001**, *169*, 1-10.

[14] P. Thordarson, R. G. E. Coumans, J. A. A. W. Elemans, P. J. Thomassen, J. Visser, A. E. Rowan, R. J. M. Nolte, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4755-4759.

[15] A. B. C. Deutman, C. Monnereau, M. Moalin, R. G. E. Coumans, N. Veling, M. Coenen, J. M. M. Smits, R. de Gelder, J. A. A. W. Elemans, G. Ercolani, R. J. M. Nolte, A. E. Rowan, *Proc. Natl. Acad. Sci. USA*, **2009**, *106*, 10471-10476.

[16] a) A. E. Rowan, P. P. M. Aarts, K. W. M. Koutstaal, *Chem. Commun*.**1998**, 611-612. b) A. B. C. Deutman, S. Varghese, M. Moalin, J. A. A. W. Elemans, A. E. Rowan, R. J. M. Nolte, *Chem. Eur. J.,* **2015**, *21*, 360-370.

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A highly stable double-cavity-containing catalytic porphyrin host has been developed. A pyridine ligand bound in one of the cavities regulates the rate and selectivity of an epoxidation reaction that takes place in the other cavity. Binding studies suggest that site-to-site communication exists between the two cavities.

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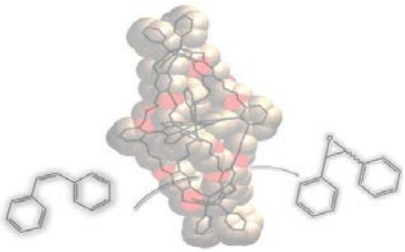

Supramolecular Catalysis

Paul J. Thomassen, Shaji Varghese, Edward J. A. Bijsterveld, Johannes A. A. W. Elemans, Alan E. Rowan,* and Roeland J. M. Nolte**

■■ – ■■

A double-cavity containing porphyrin host as a highly stable epoxidation catalyst