A dynamic supramolecular system exhibiting substrate selectivity in the catalytic epoxidation of olefins†

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Received (in Cambridge, UK) 4th August 2004, Accepted 25th October 2004
First published as an Advance Article on the web 2nd December 2004
DOI: 10.1039/b411978a

A dynamic supramolecular system involving hydrogen bonding between a Mn(III) salen catalyst and a Zn(II) porphyrin receptor exhibits selectivity for pyridine appended *cis*-β-substituted styrene derivatives over phenyl appended derivatives in a catalytic epoxidation reaction.

Enzymes are very powerful catalysts, capable of carrying out reactions on specific substrates with high turnover numbers and frequencies. It has been of a great interest in the last decades to mimic such processes[1] and supramolecular catalysis is one approach.[1b,1e] Most supramolecular catalysts to date rely on rigid, preorganized systems, and few are able to compete with their natural counterparts. Sanders has pointed out that more flexible systems, based on weaker, non-covalent interactions, might be the way to solve some of the inherent problems.[1e] However, this point has not been tested so far, mainly due to the difficult design and the synthetic effort required. In recent examples of catalysts assembled by hydrogen bonding,[2] as well as metal–ligand coordination,[3,4e] the non-covalent interactions are kinetically stable or show slow exchange kinetics,[3c] and thus do not contribute to the overall flexibility of the cavity.

Following the discussion above, we herein present a self-assembled macrocyclic epoxidation catalyst (**1**, Fig. 1),† in which all recognition motifs, both between catalyst subunits, and between substrate and catalyst, are kinetically labile.[4]‡

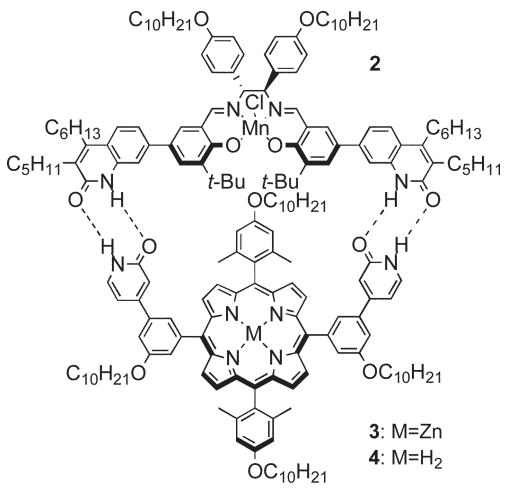
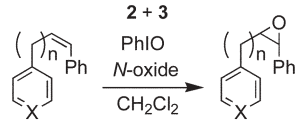


Fig. 1 The supramolecular catalyst **1** (**2** + **3**).

The catalytic subunit **2** is a derivative of the successful Jacobsen–Katsuki epoxidation catalysts;[5] a Mn(III)Cl–salen complex with 2-quinolone groups appended to the ligand framework. The receptor subunit **3** is a Zn(II) tetraarylporphyrin with peripheral 2-pyridone units. The hydrogen-bonding moieties are positioned in space to favor the formation of the heterodimer **1**, from **2** and **3**, disfavoring discrete homoassemblies. The complementary 2-pyridone-2-quinolone framework[6] in **1** provides kinetically labile and relatively weak association between **2** and **3**, allowing the system to be dynamic in its operation.‡ The receptor subunit takes advantage of the frequently employed pyridine-Zn(II) porphyrin association for substrate recognition.[7]

There are potential advantages with such an approach compared to a covalent or a kinetically stable one. Briefly: (a) facilitated synthesis of the macrocyclic cavity. (b) The cavity is flexible enough to accommodate all the different intermediates and transitions states of the catalytic cycle. (c) The processes of substrate binding and assembly/disassembly of the cavity should not severely slow down the catalytic process or result in product inhibition.

To study the selectivity of system (**2** + **3** ⇌ **1**) as an epoxidation catalyst, we designed and synthesized three substrates, **5**–**7** (Scheme 1).† All three are *cis*-β-substituted styrene derivatives appended by phenyl or 4-pyridyl groups and should have similar reactivities at the double bond. Selectivity should arise from the different abilities of the substrates to bind to **3** and the distance between their binding and reacting functionalities. All three possible pairs of substrates were subjected to competitive epoxidation by system (**2** + **3** ⇌ **1**) (**2** : **3** = 1 : 1) in CH_2Cl_2 using PhIO as the oxidant.[8] The relative selectivity was determined after 20% conversion.† All reactions were run in the presence of a rigid long pyridine *N*-oxide derivative (4-(4-*tert*-butylphenyl)-pyridine *N*-oxide, **11**), in order to compensate for potential activation of the Mn(III) salen catalyst by pyridine substrates[9] and in an attempt to block the outside of **1** from participating in non-selective catalysis. The results are summarized in Table 1.



5: X=CH, n=2
6: X=N, n=2
7: X=N, n=3
8: X=CH, n=2
9: X=N, n=2
10: X=N, n=3

Scheme 1

† Electronic supplementary information (ESI) available: analytical and selected synthetic data for compounds **2**–**7** and **11**; experimental data for the epoxidations, selectivity and estimation of association constant; derivation of eqn. 1. See http://www.rsc.org/suppdata/cc/b4/b411978a/

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Table 1 The selectivity of the catalytic system (**2** + **3** ⇌ **1**) for different substrate pairs

Entry[a,b]	Description	Selectivity[c] GC	NMR
1	**6** *vs.* **5**	1.55 ± 0.16	1.44 ± 0.12
2	**6** *vs.* **7**	—	1.18 ± 0.08
3	**7** *vs.* **5**	1.28 ± 0.05	1.34 ± 0.09

[a] General procedure: **2** (3 μmol), **3** (3 μmol), 2 substrates, **5**, **6** or **7** (30 μmol each), PhIO (12 μmol), **11** (12 μmol), DCM (0.60 ml), rt. [b] Approx. 70% of **2** bound as **1**. [c] Relative selectivity.[8]

While the selectivities[8] observed for **1** are modest, they deviate clearly and consistently from those of **2**. The system (**2** + **3** ⇌ **1**) favors the pyridine containing substrates **6** and **7** over the non-coordinating substrate **5**. However, **5** still shows substantial reactivity. To investigate the limiting behavior and to get an insight into the mechanism of selectivity, we subjected the substrate pair showing the highest selectivity, **6** and **5**, to a variety of reaction conditions (see Table 2). Comparing the results from entries 1–3 in Table 2, we can conclude that under standard conditions (entry 1), the system is already close to the selectivity limit; increasing the concentration of **3** three times, resulting in a higher amount of catalyst part **2** bound as **1**, gives only a minor change in selectivity (entry 2), whereas dilution, dissociating **1** to free **2** + **3** to a larger extent, results in lower selectivity (entry 3). Moreover, replacing **3** with the metal free porphyrin **4** or Zn(II)TPP resulted only in insignificant selectivity, ruling out non-coordinative involvement of the co-factor **3** (entries 4 and 5). 4-Ethylpyridine was identified as a competitive inhibitor of **1** since the selectivity dropped in the presence of this compound (entry 6), proving that the pyridyl appended substrates **6** and **7** are epoxidized while bound to the Zn-moiety of **1**. Replacing **11** with the smaller pyridine *N*-oxide did not result in a significant change in selectivity (entry 7).

Variation of the concentration of **3** allows for the estimation of the inherent selectivity of **1**, which cannot be directly observed. Non-linear curve fitting of entries 1 and 2 (Table 2) to an expression for the observed selectivity (eqn. 1),† gave an estimate of the upper limit for the selectivity of **6** *vs.* **5** (*sel*(**1**)) as 1.66. Further, the mole fractions of **1** and **2** (%**1**, %**2**) are derived from the equilibrium K_{assoc} = [**1**]/[**2**][**3**], and so a rough estimate of $K_{assoc} = 2{\cdot}10^3\ M^{-1}$ could also be obtained.[10] Based on that value, 70% of **2** is bound as **1** under standard conditions. The term k_{52}/k_{51}, representing the ratio of epoxidation rates of non-coordinating substrate **5** by catalysts **2** and **1** respectively, was found to be very close to 1, implying that the observed selectivity is a result of an increase in the reactivity of catalyst **1** towards substrate **6** rather than a decrease in reactivity towards **5** compared to catalyst **2**.

Table 2 The selectivity of **6** *vs.* **5** under various conditions

Entry	System[g]	Selectivity of **6** *vs.* **5**[a] GC	NMR
1[b]	**2** (3 μmol) + **3** (3 μmol)	1.55 ± 0.16	1.44 ± 0.12
2[c]	**2** (3 μmol) + **3** (9 μmol)	1.57 ± 0.09	1.68 ± 0.21
3[d]	**2** (3 μmol) + **3** (3 μmol)	1.30 ± 0.11	1.32 ± 0.13
4	**2** (3 μmol) + **4** (3 μmol)	1.14 ± 0.07	1.06 ± 0.08
5	**2** (3 μmol) + Zn(II)TTP (3 μmol)	—	0.97 ± 0.14
6[b,e]	**2** (3 μmol) + **3** (3 μmol)	1.32 ± 0.18	1.29 ± 0.14
7[b,f]	**2** (3 μmol) + **3** (3 μmol)	1.56 ± 0.25	1.49 ± 0.09

[a] Relative selectivity.[8] [b] Approx. 70% of **2** bound as **1**. [c] Approx. 95% of **2** bound as **1**. [d] DCM (6.0 ml): approx. 40% of **2** bound as **1**. [e] 4-Ethylpyridine (90 μmol). [f] Pyridine *N*-oxide (12 μmol) instead of **11**. [g] The general procedure was followed unless otherwise noted: **5** (30 μmol), **6** (30 μmol), PhIO (12 μmol), **11** (12 μmol), DCM (0.60 ml), rt.

$$sel(\text{obs}) = (\%\mathbf{1}\cdot sel(\mathbf{1}) + \%\mathbf{2}\cdot k_{52}/k_{51})/(\%\mathbf{1} + \%\mathbf{2}\cdot k_{52}/k_{51}) \quad (1)$$

To validate the model represented by eqn. 1, the above obtained values of *sel*(**1**), k_{52}/k_{51} and K_{assoc} can be used to predict the observed selectivity of entry 3 (Table 2). The predicted selectivity of 1.25 proves quite close to the experimental one, thus supporting the model.

The results from the epoxidation studies clearly indicate that **1** is the major catalytic species under the reaction conditions. The remaining reactivity of **5** can be attributed either to a reaction on the outer face of the catalyst, or by the ability of **5** to enter the cavity without being coordinated to Zn.

To our knowledge, this is the first example where substrate selectivity is imposed on a nonselective catalyst by formation of a dynamic hydrogen bonded supramolecular assembly around the catalytic center. Although the observed selectivities are not high, they are a clear testament that the concept is working, and that weak, kinetically labile interactions can in fact be successfully applied to the design of supramolecular catalysts.

Encouraged by the initial results, further studies will be conducted to increase the selectivity of the system by more efficiently blocking the outer face of the assembly **1**, to elucidate the kinetics of the processes involved in the catalysis and finally to address the potential advantages given earlier ((a)–(c)). Given the versatility of metal-salen complexes as catalysts, other types of reactions could also be adopted.[11]

We are grateful to Dr Karl-Erik Bergquist for his expert assistance on quantitative NMR analysis. We thank the Swedish Research Council as well as the Crafoord Foundation, the Lars-Johan Hierta Foundation, the Magn. Bergvall Foundation, and the Royal Physiographic Society for generous grants.

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Notes and references

‡ All interactions are fast on the NMR timescale; signals represent averages of bound and unbound species, thus the term: "kinetically labile".

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