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Hydroxylation of steroids with an artificial P-450 catalyst bearing synthetic cyclophanes as binding groups

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Abstract—A novel catalyst has been synthesized in which a manganese–porphyrin unit is linked to four hydrophobic cyclophane binding groups. Relative to a previous catalyst in which the binding groups were cyclodextrins, the new catalyst shows somewhat higher catalytic turnovers before it is destroyed, but less selective product formation. © 2002 Elsevier Science Ltd. All rights reserved.

We have described hydroxylations of steroids in water solution by mimics of the enzyme class cytochrome P-450, in which we used manganese porphyrins **1** and **2** carrying cyclodextrins to bind hydrophobic substrates.[1–6] When a steroid—as a water soluble ester **3** carrying hydrophobic *t*-butylphenyl binding groups—was doubly bound to the catalyst, hydroxylation by iodosobenzene was directed selectively to the 6α position of the steroid.[1–3] Furthermore, the resulting alcohol **4′**, subsequently hydrolyzed to **4**, was not oxidized to the ketone, apparently because the 6β hydrogen is inaccessible to the Mn=O species of the catalyst intermediate in the catalyst/substrate complex. When the catalyst carried an *o*-nitrophenyl group, as many as 3000 turnovers accompanied the C-6 hydroxylation before the catalyst was destroyed.[5,6] We have also seen that triple binding to the P-450 mimic of a steroid **5** esterified at positions 3β, 6α, and 17β led to selective hydroxylation at the steroid C-9 position.[4,5]

The porphyrin system in the catalyst can be destroyed by oxidation, and some of our work was aimed at protecting it with electron-withdrawing groups.[2,6] However, at some point it seemed that we were losing the cyclodextrin binding groups by oxidation. Thus we have now examined catalysts related to **2** in which the cyclodextrins have been replaced by synthetic cyclophanes that are also able to bind hydrophobic groups in water. We have previously made a related comparison. We had synthesized compounds in which a pyridoxamine was covalently attached to β-cyclodextrin, which gave the pyridoxamine significant selectivity to perform transamination with ketoacids that could bind into the cyclodextrin cavity.[7,8] We then examined[9] a related compound in which the cyclodextrin was replaced by a synthetic macrocycle related to the Koga cyclophane.[10] We saw that this pyridoxamine derivative with a synthetic macrocycle was fundamentally equivalent to the corresponding cyclodextrin analog in selectively accelerating the transamination of phenylpyruvic acid relative to pyruvic acid. Controls showed that this reflected the hydrophobic binding of the phenylpyruvic acid into the non-polar cavity in the cyclophane group. Since macrocycles of this type (see below) are more oxidatively stable than is cyclodextrin (the benzylic positions of the macrocycle are not activated because a benzylic radical or cation would be geometrically orthogonal to the phenyl rings), we believed that a new cytochrome P-450 mimic such as **6** would be likely to show better catalytic turnover in substrate oxidation.

Catalyst **6** was synthesized as shown in Scheme 1. The bis-tosylamide **7** was selectively linked with pentamethylene dibromide to form **8**[11] in 30–40% yield after chromatography. Then this was cyclized to **9**[12] with 3-chloro-2-chloromethyl-1-propene and NaOH under phase transfer conditions in benzene/water at high dilution using a syringe pump, in 26% yield after chromatography. Compound **9** was then converted to **10**[13] in 50% yield by hydroboration, then to mesylate **11** which was converted to thioacetate **12**.[14] This was then treated under argon with NaOMe in MeOH to generate the thiolate, which was coupled to 5,10,15,20-tetrakis(pentafluorophenyl-21-H,23-H porphine to produce **13**[15] in 65% yield. The tosyl groups were then removed with H_2SO_4 in $AcOH/CH_2Cl_2$. to produce **14**[16] in 95% yield. This was acylated with chloracetyl chloride, then treated with $HNMe_2$ to afford **15**[17] in 80% yield, which

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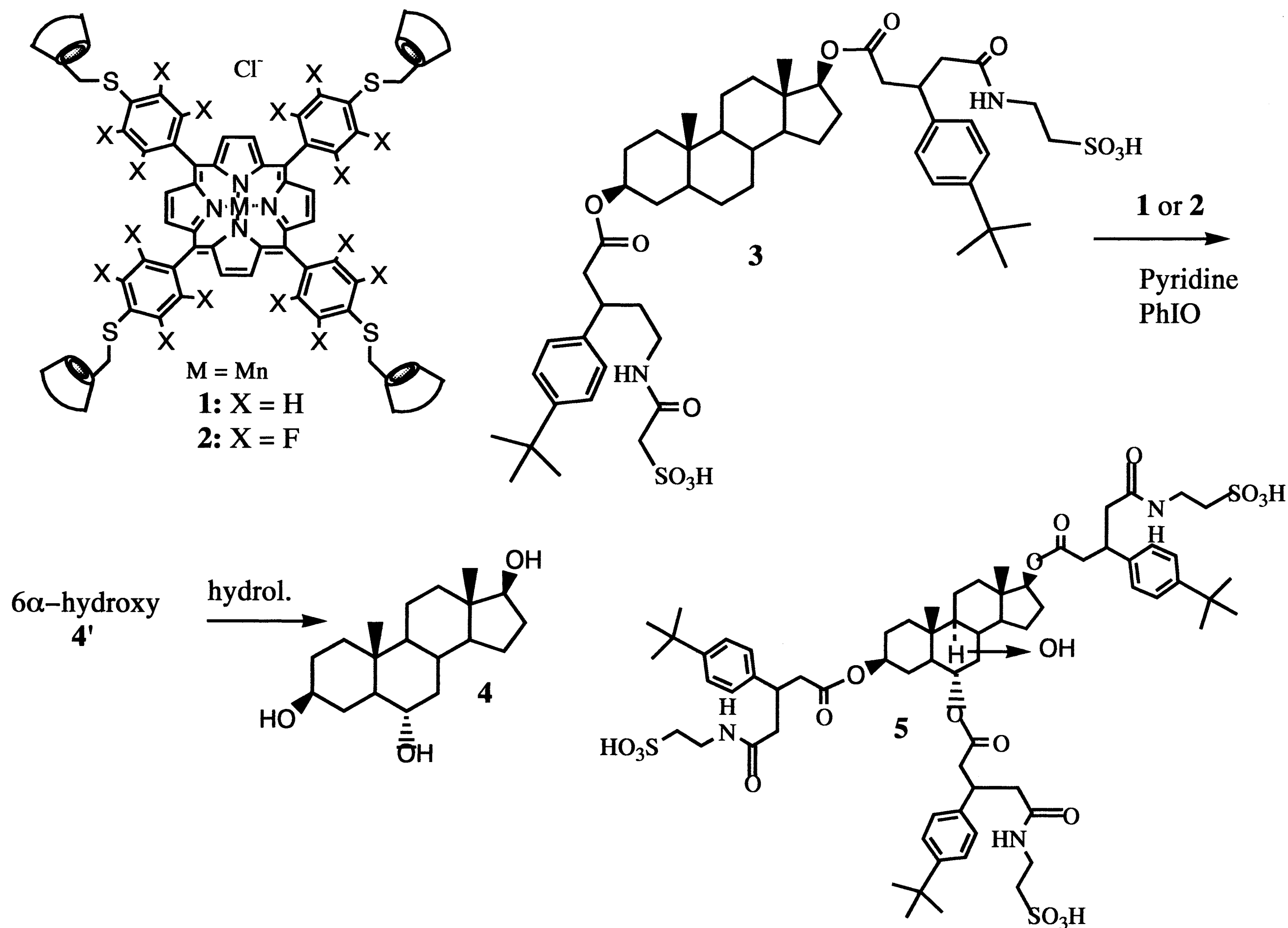


with $MnCl_2$ afforded 16[18] in 95% yield. Quaternization with methyl triflate converted this to 17[19] in 95% yield, which was quantitatively converted to 6[20] by an anion exchange column in the chloride form.

We examined **6** as a catalyst for the hydroxylation of substrate **3**, which we have described previously. For the hydroxylation, 0.06 mmol of substrate **3** was dissolved in 60 ml water and the pH was adjusted to 5.5. Then catalyst **6** was added (various numbers of equivalents) and 5 equiv. of iodosylbenzene in 3.0 ml methanol was added over 3 h. After an additional 3 h, 0.5 g sodium thiosulfate was added, followed by 2.0 g solid NaOH. After overnight standing the solution was neutralized with ammonium chloride (3 g) and extracted with four 30 ml portions of ethyl acetate. After solution drying and evaporation the products were isolated by chromatography.

With 0.1% of catalyst **6** relative to substrate (either the chloride **6** or the triflate salt **17**) we observed a 30% conversion of the substrate **3** to the 6α hydroxylated product **4**, identical with that produced earlier using the cyclodextrin-based catalysts **1** or **2**. However, in the present case we also obtained a 10% conversion of substrate to the 15α hydroxylated product **18**, which had not been formed with the cyclodextrin-based catalysts **1** or **2**. There were thus 400 turnovers with **6**, while catalyst **2** had performed 187 turnovers.

In the cyclodextrin case, we had also examined the hydroxylation of triester substrate **5**, and had seen the selective hydroxylation at C-9 with about 70 turnovers. With our new catalyst **6** and triester substrate **5** we also see about 70 turnovers, but now only 60% of the hydroxylation occurs at C-9 while 40% occurs at various other positions. Again the cyclophane catalyst is not as selective as was the cyclodextrin analog. Thus we see that when we substitute this cyclophane for the cyclodextrins in catalyst **2** we do indeed see somewhat similar hydroxylation patterns, and in one case with some improvement in catalyst stability. However, the poorer selectivity with the cyclophane-based catalyst means that it is not preferred to our original catalyst in the biomimetic selective hydroxylation of these steroid substrates.

While the poorer selectivity than with the cyclodextrin-based catalyst does make catalyst **6** less useful, our results add importantly to the general picture of these reactions. Apparently the geometry established by substrate binding of **3** or of **5** into catalyst **6** is too flexible, permitting a wobble in the complexes that brings more than one C–H into reach of the oxidizing Mn=O species. We had seen something similar when we oxidized substrate **19** with catalyst **2**.[6] The double binding of **19** into **2** did indeed steer hydroxylation to C-9, as models suggested, but we observed an almost equal amount of hydroxylation at C-15, as above in product **18**. We then were able to

$Br(CH_2)_5Br$
K_2CO_3, DMF

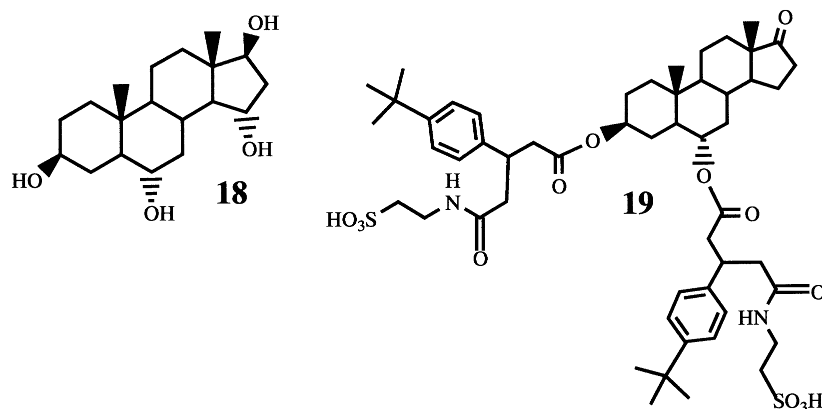
Bu$_4$NI
Benzene, 5%NaOH

7 **8** **9**

10: X = OH
11: X = OMs
12: X = SAc

13: X = Ts, M = H_2
14: X = H, M = H_2
15: X = CO-CH_2-NMe_2, M = H_2
16: X = CO-CH_2-NMe_2, M = Mn
17: X = CO-CH_2-NMe_3+, OTf-, M = Mn
6: X = CO-CH_2-NMe_3+, Cl-, M = Mn

Scheme 1.



readjust the geometry of the catalyst by attaching the cyclodextrin *meta*, rather than *para*, on the phenyl rings, whereupon the exclusive process was hydroxylation at C-9.[6] It is likely that something similar would be possible with catalyst **6**.

These results all together indicate that simple binding of substrate to catalyst is not in itself enough to achieve selective hydroxylation. As with enzymes, selectivity also requires relatively rigid binding into a unique geometry, It is in a sense fortunate that in the earliest

work with catalyst **2** such unique geometry of binding was apparently achieved.

Acknowledgements

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References

1. Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535–4536.
2. Breslow, R.; Huang, Y.; Zhang, X.; Yang, J. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11156–11158.
3. Breslow, R.; Gabriele, B.; Yang, J. *Tetrahedron Lett.* **1998**, *39*, 2887–2890.
4. Yang, J.; Breslow, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2692–2694.
5. Breslow, R.; Yang, J.; Yan, J. *Tetrahedron* **2002**, *58*, 653–659.
6. Breslow, R.; Yan, J.; Belvedere, S. *Tetrahedron Lett.* **2002**, *43*, 363–365.
7. Breslow, R.; Hammond, M.; Lauer, M. *J. Am. Chem. Soc.* **1980**, *102*, 421–422.
8. Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212–5219.
9. Winkler, J.; Coutouli-Argyropoulou, E.; Leppkes, R.; Breslow, R. *J. Am. Chem. Soc.* **1983**, *105*, 7198–7199.
10. (a) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504; (b) See also: Stetter, H.; Roos, E.-E. *Chem. Ber.* **1955**, *88*, 1390.
11. ^{1}H NMR as expected; FAB-MS: 1081 $[M+H]^{+}$.
12. ^{1}H NMR as expected; FAB-MS: 1157 $[M+Na]^{+}$.
13. ^{1}H NMR as expected; FAB-MS: 1151 $[M+H]^{+}$.
14. ^{1}H NMR as expected; FAB-MS: 1209 $[M+H]^{+}$.
15. ^{1}H NMR as expected; ^{19}F NMR: −131.8 (d, $J=15.0$ Hz), −135.8 (d, $J=15.0$ Hz); MALDI-MS: 5593 $[M+K]^{+}$.
16. ^{1}H NMR as expected; ^{19}F NMR: −132.9 (d, $J=15.0$ Hz), −135.7 (d, $J=15.0$ Hz); MALDI-MS: 3011 $[M+H]^{+}$.
17. ^{1}H NMR as expected; ^{19}F NMR: −132.1 (d, $J=15.0$ Hz), −136.2 (d, $J=15.0$ Hz); MALDI-MS: 4462 $[M+H]^{+}$, UV–vis: 414 (Soret), 506, 578 nm.
18. UV–vis: 458 (Soret), 556 nm.
19. UV–vis: 454 (Soret), 550 nm.
20. UV–vis: 458 (Soret), 556 nm.