Bioorganic Chemistry **29,** 321–331 (2001)
doi:10.1006/bioo.2001.1215, available online at http://www.idealibrary.com on IDEAL®

Regioselective Oxidation of Steroids by a Manganese Porphyrin Carrying Metal Coordinating Groups

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Received February 22, 2001

A manganese porphyrin having four 2,2′-bipyridyl groups on its meso positions was synthesized. In the presence of Cu^{2+} ions it catalyzes the regioselective oxidation of steroid substrates carrying auxiliary metal coordinating groups.

Key Words: steroid oxidation; metal coordination; cytochrome P450; enzyme mimics.

INTRODUCTION

Enzymes are remarkable catalysts. They are able to transiently bind substrates in their active site in a specific geometric arrangement and then perform reactions whose regio- and stereoselectivity are the result of geometric control rather than of the intrinsic substrate reactivity. Achieving the same level of control using a relatively small synthetic catalyst is still an open challenge for biomimetic chemistry (*1*). A key issue is the incorporation of appropriate recognition elements on substrate and catalyst (*2*). Over the years we have reported the use of covalent binding, ion pairing, metal coordination, and the hydrophobic effect as inducers of geometric control (*1a*, *3*). The possibility of mimicking the reactions catalyzed by cytochrome P-450, in particular the hydroxylation of unreactive C–H bonds, has been particularly studied (*4*). There are several examples from this and other groups about the use of porphyrin-based catalysts that can achieve geometric control via covalent binding (*5*) or hydrophobic binding within vesicles (*6*) or β-cyclodextrins (*7*).

Now we are focusing our attention on the possibility of using metal coordination as the recognition element. Previous work from this laboratory showed that an olefin carrying auxiliary metal ligands is oxidized preferentially over a nonbinding one by an iron porphyrin with appended metal ligand groups in the presence of Cu^{2+} ions (*8*). We decided to extend this approach to the selective hydroxylation of steroids by using a new manganese porphyrin carrying metal coordinating groups. In the designed

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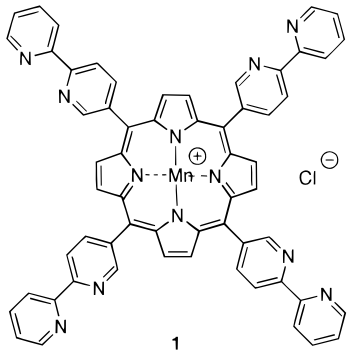
0045-2068/01 $35.00

catalytic cycle (Fig. 1), the substrate should coordinate via its auxiliary group to a metal ion on a porphyrin bipyridyl and undergo a geometrically controlled oxidation. Herein we report examples of metal coordination-directed oxidations.

RESULTS AND DISCUSSION

The manganese porphyrin **1** was synthesized by the standard Adler-Longo method (9) from 2,2′-bipyridyl-5-carboxyaldehyde.



1

Having obtained the catalyst, we started to evaluate possible metal coordinating groups to be attached to the steroid substrates. In an obvious extension of our previous work on epoxidation (*8*), we tried to oxidize steroid nicotinates. Unfortunately the

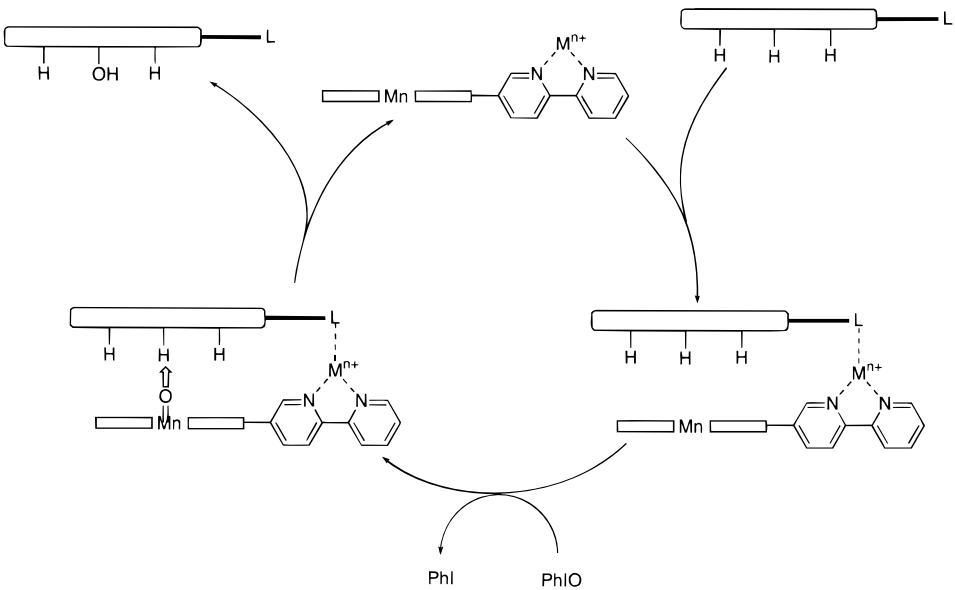
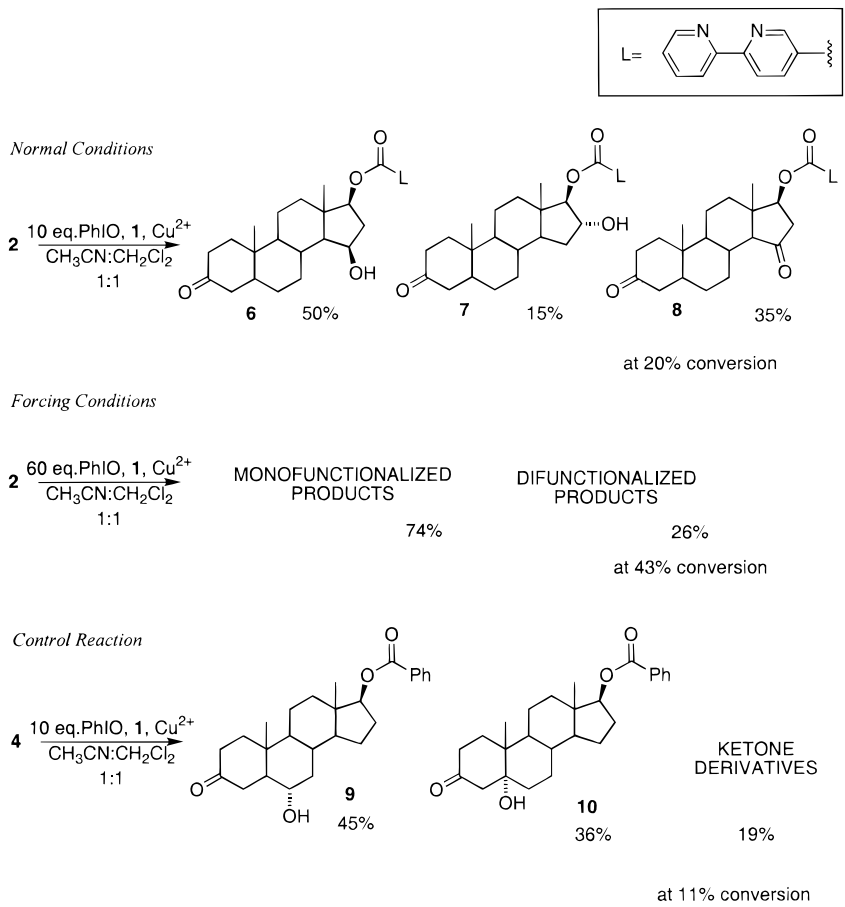


FIG. 1. Selective hydroxylation of a particular carbon on a substrate bound, by metal coordination, to an enzyme mimic with a manganese–porphyrin catalytic group.

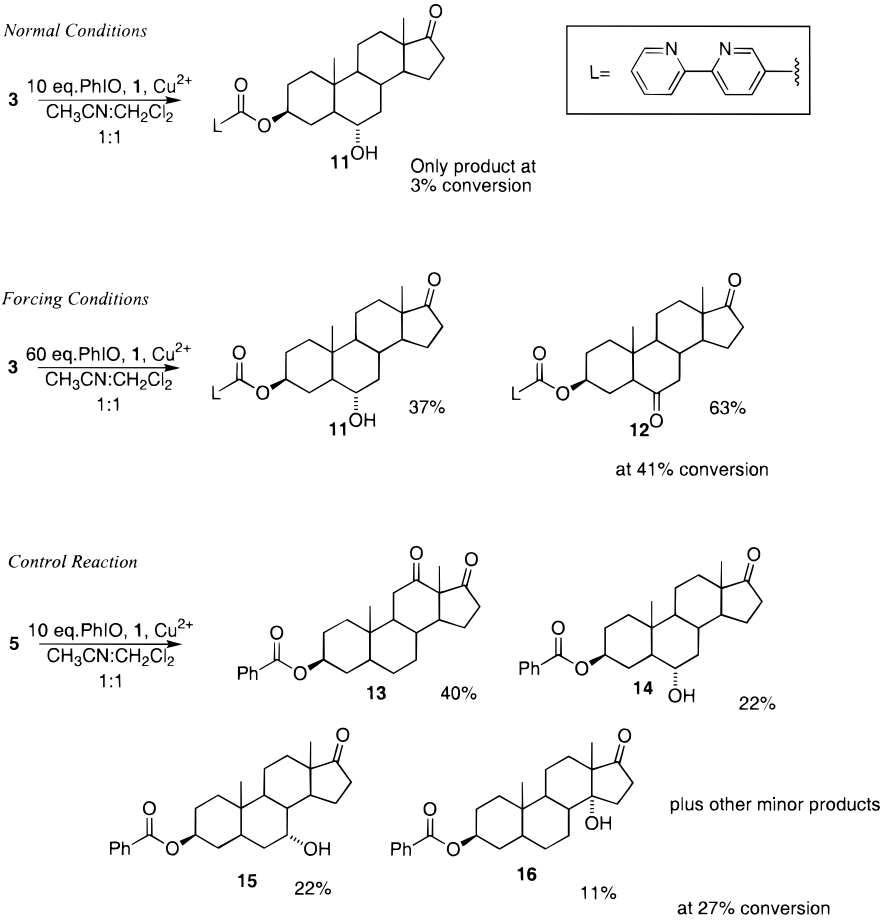
auxiliary group was oxidized to the corresponding N-oxide under the conditions required for C–H activation. Other metal coordinating groups such as picolinate, 2-pyridylhydrazone, and 8-hydroxyquinoline-7-carboxylate were also tested but they all proved to be oxidatively unstable.

We finally settled on the use of 2,2′-bipyridyl-5-carboxylate. The metal chosen for coordination was Cu^{2+}. A bipyridyl group from the substrate and one from the porphyrin should be coordinated around a copper ion in a distorted square planar geometry (*10*). The mutual orientation of steroid and porphyrin within the complex should then determine the regioselectivity of the oxidation.

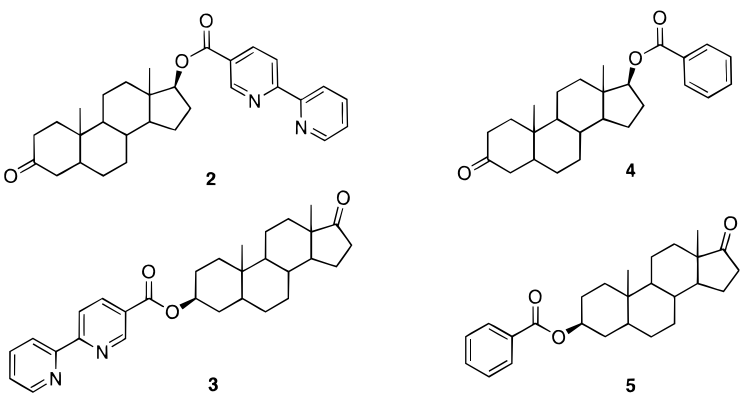
The two androstane derivatives **2** and **3** were prepared and subjected to oxidation by iodosylbenzene (PhIO) catalyzed by **1**. To determine the intrinsic reactivity of these steroid structures in the absence of metal coordination, the corresponding benzoates **4** and **5** were prepared and oxidized in control reactions. The results are reported in Schemes 1 and 2.



SCHEME 1.


Normal Conditions
3
10 eq.PhIO, 1, Cu2+
CH3CN:CH2Cl2
1:1
11
Only product at
3% conversion
L=
Forcing Conditions
3
60 eq.PhIO, 1, Cu2+
CH3CN:CH2Cl2
1:1
11
37%
12
63%
at 41% conversion
Control Reaction
5
10 eq.PhIO, 1, Cu2+
CH3CN:CH2Cl2
1:1
13
40%
14
22%
15
22%
16
11%
plus other minor products
at 27% conversion

SCHEME 2.


2
4
3
5

The androstanolone derivative **2** was first oxidized in a relatively dilute solution (1 mM) in the presence of 0.5 mM (0.5 eq.) catalyst **1** and 2 mM $Cu(OTf)_2$ using 10 eq. of PhIO. The products **6–8**, all derived from oxidation on the D ring of the steroid, were obtained in 50, 15, and 35% yield, respectively, with 20% total conversion.

In a control reaction performed on the corresponding benzoate (**5**), a mixture of products hydroxylated on C5 and C6 was observed together with minor quantities of ketones. It should be noted that in this control reaction higher concentrations were needed for both the substrate and catalyst (5 mM and 1 mM (0.2 eq.), respectively, with 5 mM $Cu(OTf)_2$) in order to obtain detectable amounts of products. Trying to improve the conversion to products, the oxidation of **2** was also attempted at higher substrate and catalyst concentration and adding a larger excess of oxidant (up to 60 eq.) until the reaction did not proceed any further and extensive porphyrin bleaching was observed. Under these forcing conditions 43% conversion to products was obtained, yielding a complex mixture of mono (74%) and difunctionalized (26%) steroids. Although the 15-oxo derivative **6** remained the major product, species derived from the attack on uncomplexed substrate, such as the 5- and 6-hyroxy derivatives, could be detected.

The epiandrosterone derivative **3** appeared to be slightly less reactive than **2**: it was necessary to react a 5 mM solution with 10 eq. of PhIO in the presence of 1 mM (0.2 eq.) catalyst and 5 mM $Cu(OTf)_2$. Under these conditions, it was selectively oxidized to the 6α hydroxy derivative **11** with very low conversion (3%). In the control reaction, run under the same conditions, products of oxidation on C7, C12, and C14 were also observed. In this case we also tried to obtain higher conversion by adding a larger excess of oxidant until no further change was observed. Indeed, higher amounts of products were obtained; at 41% conversion the regioselectivity of oxidation was maintained, and a mixture of 6α hydroxy (37%) and 6-keto (63%) derivatives was obtained.

The results can be rationalized in the context of a slightly distorted square planar Cu^{2+} complex in which both substrate and catalyst contribute a bipyridyl ligand (Fig. 2). The use of CPK models confirms that the observed products are consistent with the proposed model. The orientation effect by metal coordination can be seen at its best in the case of 17-substituted androstanes **2** and **4**. Two completely different sets of products are obtained in the presence or absence of a metal ligand on the substrate.

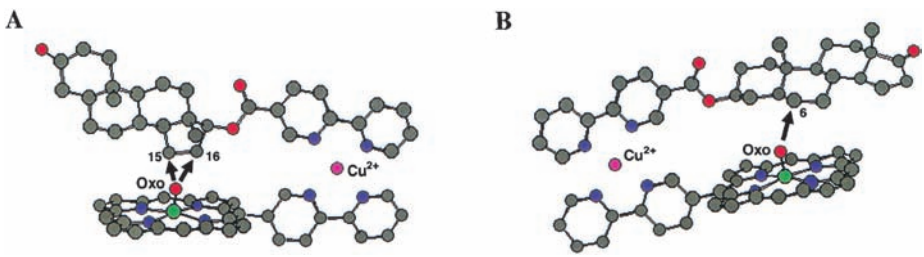


FIG. 2. Molecular models with square planar complexing of catalyst to substrate correctly predict the observed selective hydroxylation products.