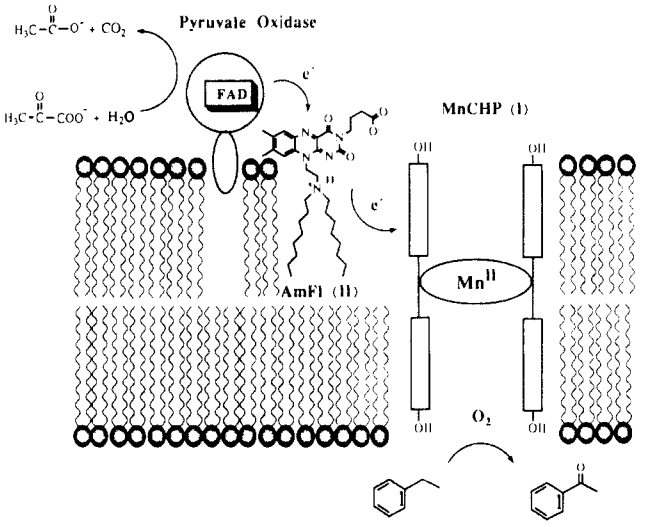

Figure 2. Schematic representation of biocompatible catalysis in a synthetic multicomponent redox membrane containing pyruvate, pyruvate oxidase (PO), amphiphilic flavin (II), Mn^{III}ChPCl (I), ethylbenzene, and DPPC.

The membrane-spanning tetrakis[*o*-(3-hydroxy-5-cholenoylamino)phenyl]porphyrin (H_2ChP) and its manganese(III) derivative (MnChPCl, I) were prepared as we have previously described.[4] The amphiphilic flavin (AmFl, II) was synthesized from 6,7-dimethyl-9-formylisoalloxazine[5a] by reductive amination with *N,N*-dioctylamine, subsequent N-alkylation with ethyl 4-bromobutyrate, and acid hydrolysis of the ethyl ester.

The reduction of Mn^{III}ChPCl to Mn(II) (I) in dipalmitoylphosphocholine (DPPC) vesicles[4] was followed by changes in the visible absorption spectrum following the injection of oxygen-free sodium pyruvate (Figure 1). Under these conditions the time course of the reduction of Mn(III) to Mn(II) was found to be triphasic (Figure 1 inset). No reduction of Mn(III) was observed in the absence of the enzyme, and only traces of Mn(II) were observed over a 24-h period if the amphiflavin (II) was omitted or was replaced by flavin adenine dinucleotide (FAD). Furthermore, in a separate experiment, we found that the pyruvate oxidase/pyruvate system reduced the amphiphilic flavin (II) rapidly in vesicles lacking Mn(ChP)Cl. Thus, we conclude that the rate-determining step in this reduction is electron transfer from AmFl (II) to Mn^{III}ChPCl.

Next we investigated the enzymic reduction of I in the presence of molecular oxygen and ethyl benzene. Vesicles containing 40 μmol of DPPC, 10 μmol of ethylbenzene, 0.1 μmol of Mn(ChP)Cl, 0.2 μmol of amphiflavin (II), and 4 μmol of *N*-methylimidazole were prepared by sonication in 4 mL of buffer solution. Following the addition of 2 nmol of pyruvate oxidase, the reaction mixture was allowed to stand at 30 °C for 15 h. Products were isolated as we have previously described and analyzed by GC and GC-MS vs authentic samples. Acetophenone was obtained in 20% conversion, representing 20 turnovers of the Mn(III) catalyst. In separate experiments we found that no oxygenation took place when any of the components was omitted.

These results can be explained as follows. Pyruvate oxidase catalyzes the oxidative decarboxylation of pyruvate to acetate and carbon dioxide and the concomitant reduction of the tightly bound FAD cofactor to $FADH_2$.[6,7] Thiamine pyrophosphate and Mg^{2+} are known to be cofactors of this reaction. The enzyme has been shown to bind to phospholipid vesicles when the cofactors and the substrate are simultaneously present.[8] It has been suggested that a change in the conformation of the protein exposes a membrane-binding hydrophobic peptide segment.[9] It is expected that the amphilic flavin (II) will bind to the vesicle wall such that one edge of the isoalloxazine ring penetrates into the bilayer interior while the other edge is near the lipid-water interface to accommodate the two alkyl groups and the amino acid ion pair. This component thus serves not only as the initial electron acceptor for the reduced enzyme but also as the reductant for the membrane-spanning Mn^{III}(ChP)Cl located at the center of the bilayer.[4] Figure 2 depicts the sequence of chemical events that take place upon introduction of pyruvic acid to the multicomponent catalytic system: (1) binding of the enzyme to the vesicles, (2) oxidative decarboxylation of pyruvic acid with the concomitant reduction of enzyme-bound FAD to $FADH_2$, (3) electron transfer from $FADH_2$ to AmFl (II), (4) reduction of Mn^{III}ChPCl (I) to Mn(II) by reduced AmFl, and (5) binding and reductive activation of molecular oxygen to produce a high-valent manganese oxo species responsible for hydrocarbon oxidation.[10]

Thus we have shown that a properly arranged catalytic bilayer assembly can productively harvest electrons from a membrane-bound redox enzyme. This approach can also be used to probe the relative position of membrane components and the pathways for trans-membrane electron transfer.

Acknowledgment. Support of this research by the National Institutes of Health (GM-36928) is gratefully acknowledged.

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Competing Reaction Pathways in Protonation Reactions of a Low-Valent Tungsten Alkylidyne Isocyanide Complex: Formation of Nitrilium and Aminoalkyne Ligands

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Protonation reactions of low-valent alkylidyne, or Fischer-type carbyne, complexes have been observed to lead to alkylidyne hydride metal complexes or alkylidene complexes or to result in further transformations of the alkylidyne ligands.[1,2] The outcome of these reactions depends strongly on the nature of the ancillary ligands.[3] For example, we obtained the complexes [W(CPh)Br_2(H)(PMe_3)$_3$] (**1**), [W(CHPh)Cl_2(CO)(PMe_3)$_2$] (**2**), and [W(CHPh)Cl_2(PhC_2Ph)(PMe_3)$_2$] (**3**) from protonation reactions of alkylidyne metal complexes.[4] These complexes differ overall only in a single ligand (PMe_3, CO, and PhC_2Ph, respectively, neglecting the difference in the halides, yet **1** is an alkylidyne hydride metal

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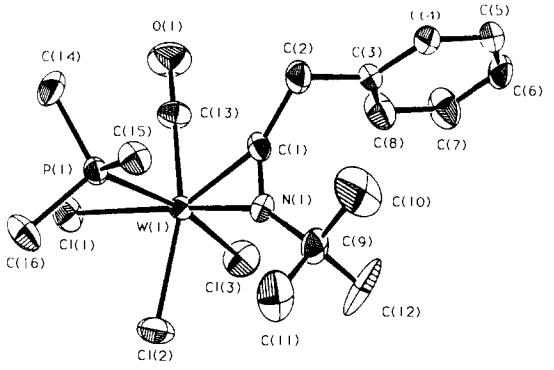
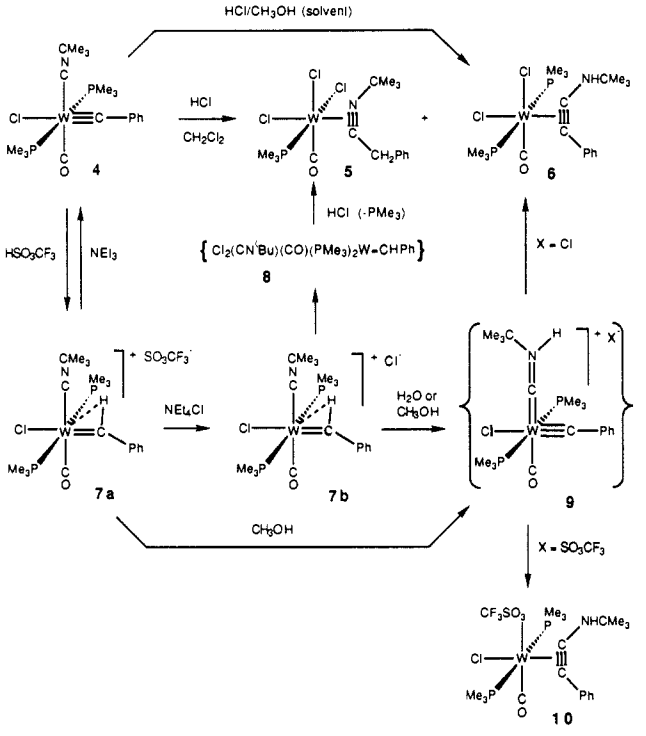


Figure 1. Molecular structure of complex **5**. Selected bond distances (Å) and angles (deg): C(1)–N(1), 1.27 (1); W(1)–Cl(1), 2.417 (2); W(1)–Cl(2), 2.446 (2); W(1)–Cl(3), 2.392 (2); W(1)–C(1), 2.014 (7); W(1)–C(13), 1.966 (9); W(1)–N(1), 1.982 (6); W(1)–P(1), 2.508 (2); Cl(1)–W(1)–Cl(2), 84.70 (9); Cl(1)–W(1)–Cl(3), 91.01 (9); Cl(1)–W(1)–P(1), 78.67 (8); Cl(1)–W(1)–C(13), 76.5 (3); Cl(2)–W(1)–N(1), 89.3 (2); C(1)–W(1)–C(13), 72.8 (3); C(1)–W(1)–N(1), 36.9 (3); C(1)–N(1)–C(9), 134.4 (7); N(1)–C(1)–C(2), 138.7 (8).

Scheme I



complex, in **2** the C–H bond of the alkylidene ligand is interacting with the metal center, and **3** exhibits characteristics of an electronically saturated alkylidene metal complex. To test the potential influence of isocyanide ligands in this series of complexes, we investigated protonation reactions of the complex $[W(CPh)Cl(CNCMe_3)(CO)(PMe_3)_2]$ (**4**). This study shows that the primary site of protonation of complex **4** is the alkylidyne carbon and demonstrates the occurrence of competing secondary reactions leading to products derived from protonation at the alkylidyne carbon or at the isocyanide nitrogen atom.

The reaction of complex **4** in CH_2Cl_2 with 3 equiv of dry gaseous HCl affords two products (Scheme I). $[WCl_3(\eta^2\text{-}PhCH_2CNCMe_3)(CO)(PMe_3)]$ (**5**) is the major product.[5] After recrystallization from CH_2Cl_2/hexane, **5** is obtained as light green crystals in 53% yield. The molecular structure[6] of **5** is shown in Figure 1. It reveals the presence of a tightly bound η^2-nitrilium ligand, which is derived from combination of a doubly protonated alkylidyne (benzyl) ligand with the isocyanide ligand. $[WCl_2(PhCCNHCMe_3)(CO)(PMe_3)_2]$ (**6**) is the minor product (<10% by IR).[7] The molecular structure[6] of complex **6** is shown in Figure 2. It features an aminoalkyne ligand, which is derived from combination of the akylidyne ligand with a protonated isocyanide ligand. The structure and bonding of complexes **5** and **6** are related to those of well-established alkyne complexes of the type $[WX_2(alkyne)(CO)L_2]$, in which the alkyne is acting as a four electron donor ligand.[8]

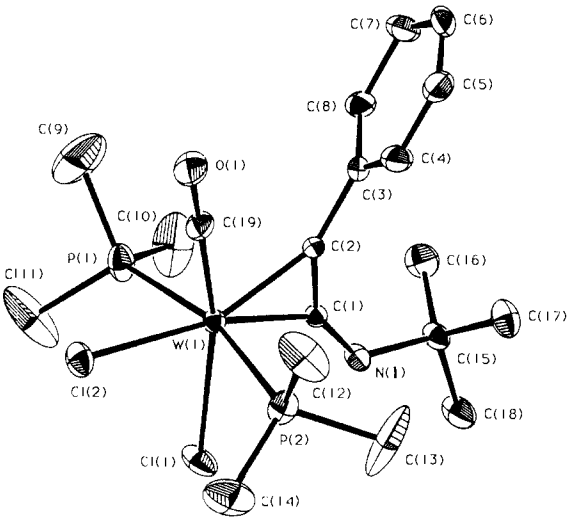


Figure 2. Molecular structure of complex **6**. Selected bond distances (Å) and angles (deg) (values are for one of two molecules in asymmetric unit cell): C(1)–C(2), 1.34 (1); C(1)–N(1), 1.32 (1); C(2)–C(3), 1.48 (1); W(1)–Cl(1), 2.523 (3); W(1)–Cl(2), 2.473 (3); W(1)–C(1), 1.995 (9); W(1)–C(2), 2.014 (9); W(1)–C(19), 1.96 (1); W(1)–P(1), 2.513 (4); W(1)–P(2), 2.501 (4); C(1)–C(2)–C(3), 142.8 (9); C(2)–C(1)–N(1), 146.8 (9); C(2)–W(1)–C(19), 75.3 (4); C(1)–W(1)–Cl(1), 81.0 (3); Cl(1)–W(1)–Cl(2), 84.4 (1); Cl(2)–W(1)–C(19), 80.2 (3); P(1)–W(1)–P(2), 166.9 (1); C(1)–W(1)–C(2), 39.2 (3).

To learn more about the pathways of formation of **5** and **6**, additional experiments were carried out. Protonation of **4** with 1.1 equiv of CF_3SO_3H in CH_2Cl_2 affords $[W(CHPh)Cl(CO)(CNCMe_3)(PMe_3)_2][CF_3SO_3]$ (**7a**).[9] The benzylidene ligand in complex **7a** contains an agostic C–H bond as evidenced by the proton resonance at δ −3.0 and a C–H coupling constant of 67 Hz.[1a] Addition of 1 equiv of NEt_4Cl to **7a** causes only a slight shift of spectroscopic parameters, indicating the exchange of Cl^- for $CF_3SO_3^-$ in (presumably ion-paired) **7a** to form $[W(CHPh)Cl(CO)(CNCMe_3)_2][Cl]$ (**7b**).[9] The alkylidene complex **7** is easily deprotonated with NEt_3 to give back **4**. With only a

(5) **5**: mp 129–131 °C; IR (cm^{-1}, CH_2Cl_2) ν_{CO} 1993; ^1H NMR (ppm, $CDCl_3$) 7.4–7.2 (m, 5 H, Ph), 5.80 (d, 1 H) and 5.60 (d, J = 14.4 Hz, 1 H, CH_2Ph), 1.77 (s, 9 H, $(CH_3)_3NC$), 1.50 (d, 9 H, PMe_3); ^{13}C NMR (ppm, CH_2Cl_2) 241.2 (CCH_2), 216.8 (CO), 39.5 (CH_2); ^{31}P NMR (ppm, $CDCl_3$) −20.7 (J_{CW} = 278 Hz, $P(CH_3)_3$). Anal. Calcd for $C_{16}H_{25}Cl_3PONW$ (sample recrystallized twice): C, 33.80; H, 4.43; Cl, 18.71. Found: C, 34.92; H, 4.50; Cl, 17.45.

(6) Crystal data for **5** and **6**. **5**: $WCl_3PNOC_{16}H_{25}$, FW = 568.56, orthorhombic, *Pbca*, a = 14.38 (1) Å, b = 15.227 (2) Å, c = 19.458 (3) Å, V = 4261 (4) Å^3, Z = 8, ρ_{calcd} = 1.77 g cm^{-1}, μ(Mo Kα) = 61.9 cm^{-1}, 1980 unique observed data, $3° < 2\theta < 50°$, R = 0.027, R_w = 0.034. **6**: $W_2Cl_4P_4C_{38}O_2N_2H_{66}$, FW = 1216.36, monoclinic, $C2/C$ (No. 15), a = 34.487 (7) Å, b = 11.381 (7), c = 32.084 (6) Å, β = 124.76 (2)°, V = 10 345 Å^3, Z = 8, ρ_{calcd} = 1.562 g cm^{-1}, μ(Mo Kα) = 49.0 cm^{-1}, 4895 unique observed data, $3° < 2\theta < 50°$, R = 0.035, R_w = 0.039. All intensity measurements were made at room temperature, using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å), and a variable-rate, ω–2θ scan technique. Empirical absorption corrections were applied. The structures were solved by conventional heavy-atom methods and refined by full-matrix least squares. All calculations were performed by using the TEXRAY programs.

(7) **6**: mp 185–188 °C dec; IR (cm^{-1}, CH_2Cl_2) ν_{CO} 1937, ν_{CN} 1677; ^1H NMR (ppm, $CDCl_3$) 7.50 (br, 1 H, NH), 7.45–6.8 (m, 5 H, Ph), 1.42 (t, 18 H, PMe_3), 1.18 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR (ppm, $CDCl_3$) 230 ($CNHCMe_3$), 208 (CPh), 202 (J_{PC} = 17 Hz, CO); ^{31}P NMR (ppm, $CDCl_3$) −20.5 (J_{CP} = 278 Hz, $P(CH_3)_3$). Anal. Calcd for $C_{19}H_{33}Cl_2P_2NOW$: C, 37.52; H, 5.47. Found: C, 37.63; H, 5.41.

(8) Templeton, J. L. *Adv. Organomet. Chem.* **1989**, *29*, 1.

(9) **7a**: IR (cm^{-1}, CH_2Cl_2) ν_{CO} 1993; ^1H NMR (ppm, $CDCl_3$, −40 °C) −3.0 (CHPh); ^{13}C NMR (ppm, CD_2Cl_2, −40 °C) 231 (J_{CH} = 67 Hz, CHPh), 218 (CO). **7b**: IR (cm^{-1}, CH_2Cl_2) 1996; ^1H NMR (ppm, $CDCl_3$) −2.5 (CHPh); ^{13}C NMR (ppm, CD_2Cl_2, −40 °C) 243 (J_{CH} = 67 Hz, CHPh).

slight excess of $NEt_4Cl(\cdot xH_2O)$[10] (1.2 equiv) **7** transforms at 20 °C within 15 min to **6** without a detectable amount of **5**. However, formation of the nitrilium complex **5** is favored by an increase in chloride concentration. For example, upon addition of a 10-fold excess of $NEt_4Cl(\cdot xH_2O)$ to **7** at room temperature, a 1:2 mixture of **5** and **6** (estimated by IR) forms within 15 min.[10] The transformation of **7b** to **6** can also be induced by addition of CH_3OH.[11a] When CH_3OH is used as the solvent, the reaction of **4** with HCl (gas or concentrated aqueous HCl) affords only **6**. From the latter reaction, complex **6** may be isolated in 83% yield after chromatography on silica (CH_2Cl_2/hexane, 1:1; -40 °C) and recrystallization from THF/hexane.

These experiments show that the preferred site of protonation of **4** is the alkylidyne carbon (MC π bond). The resulting alkylidene ligand is easily deprotonated, but it does not rearrange into an alkylidyne hydride system, nor does it undergo coupling with either the carbonyl or isocyanide ligand. Formation of the nitrilium complex **5** is proposed to involve addition of Cl^- to **7** to give the seven-coordinate alkylidene complex $[W(CHPh)Cl_2(CNCMe_3)(CO)(PMe_3)_2]$ (**8**). The postulation of **8** as an intermediate is based on the observation that an increase of the chloride ion concentration favors formation of **5**. A second protonation of the former alkylidyne carbon in **8**, followed by migration of the generated benzyl ligand to the isocyanide ligand,[12] would generate the nitrilium ligand. Final substitution of trimethylphosphine by choride would then give **5**. An analogous reaction of $[W(CC_6H_4\text{-}4\text{-}CH_3)(\eta^5\text{-}C_5H_5)(CO)_2]$ with HCl, resulting in formation of the η^2-acyl complex $[WCl_2(\eta^2\text{-}OCCH_2C_6H_4\text{-}4\text{-}CH_3)(\eta^5\text{-}C_5H_5)(CO)]$, was reported by Kreissl.[2a] The formation of the aminoalkyne complex **6** is facilitated by the presence of H_2O or CH_3OH. These reagents are believed to play a dual role: to reduce the nucleophilicity of the chloride ions, thus inhibiting formation of **8**, and to act as weak bases for the transfer of the proton from the alkylidyne carbon atom to the isocyanide nitrogen atom, thereby generating the alkylidyne aminocarbyne metal complex $[W(CPh)(CNHCMe_3)Cl(CO)(PMe_3)_2]^+$ (**9**). Whether the actual ligand-coupling step to give the aminoalkyne occurs spontaneously after proton transfer or the chloride ion is actively assisting this step is under current investigation.[11b] The proton-induced coupling of alkylidyne and isocyanide ligands[13] was recently demonstrated by Filippou.[14] Proton and electrophile-induced coupling reactions of carbyne ligands with isocyanide and carbonyl ligands were previously postulated and recently demonstrated by Lippard to be involved as key steps in coupling reactions of isocyanide and carbon monoxide ligands.[15]

According to molecular orbital calculations on low-valent alkylidyne complexes, the HOMO in various systems may be a filled metal d orbital, the MC π bond(s), or a ligand-centered orbital.[16] However, the alkylidyne carbon is consistently calculated to carry a net negative charge, thus favoring charge-controlled attack at this atom. This work shows that the preferred site of protonation in the alkylidyne isocyanide complex **4** is the alkylidyne carbon. Protonation at the isocyanide ligand is thermodynamically much less favorable, but given the proper reaction conditions, it can become a step along the major reaction pathway.

Acknowledgment. We thank John D. Franolic and Prof. Stephen A. Koch for the X-ray crystallographic studies. This work was supported by the National Science Foundation (CHE 8896185 and CHE 8921564).

Supplementary Material Available: Tables of crystallographic parameters, atomic coordinates, thermal parameters, and bond distances and angles for **5** and **6** (22 pages); tables of observed and calculated structure factors for **5** and **6** (48 pages). Ordering information is given on any current masthead page.

(10) $NEt_4Cl\cdot xH_2O$ was dried in vacuo at 80 °C for 1 h. This material still contains residual H_2O. If NEt_4Cl is dried at 80 °C (10^{-2} Torr) for 6 h, complex **5** is obtained as the main product. However, in this case formation of **6** as the only product is achieved by addition of one drop of water prior to the addition of NEt_4Cl. Reactions were reproducible for given batches of NEt_4Cl.

(11) (a) Methanol was also found to assist formation of an aminoalkyne ligand in the triflate salt **7a**. Addition of a small amount of methanol to a solution of **7a** in CH_2Cl_2 affords $[WCl(CF_3SO_3)(CO)(PhCCNHCMe_3)(CO)(PMe_3)_2]$, **10**: 108-110 °C dec; IR (cm^{-1}, ether) ν_{CO} = 1957, ν_{CN} = 1651; ^1H NMR (ppm, $CDCl_3$) 8.18, (br, 1 H, NH), 6.7-7.4 (m, 5 H, C_6H_5), 1.41 (t, 18 H, $P(CH_3)_3$), 1.12 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (ppm, $CDCl_3$) 230.6 ($CNHCMe_3$), 209.1, 206.8 (CPh and CO), 119.1 (q, CF_3SO_3). (b) This result shows that a strongly nucleophilic anion does not need to be involved in the proton-induced alkylidyne-isocyanide coupling step.

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Remote Oxidation of Unactivated C-H Bonds in Steroids via Oxometalloporphinates

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Received May 7, 1990

Nature's ability to catalyze the monooxygenation of unactivated C-H bonds in steroids employing enzymatic systems (e.g., cytochrome P-450) has long been recognized.[1] In contrast, chemist's attempts to mimic nature by replacing a hydrogen atom attached to an unactivated carbon of a steroid with a hydroxyl group, while maintaining the integrity of the carbon atom, constitute a formidable challenge.[2] Despite the fact that the use of covalently attached templates to catalyze the remote functionalization of steroids was introduced by Breslow[3] over 20 years ago, the direct remote hydroxylation of steroids with high predictability and specificity has yet to be accomplished.

We report that synthetic metalloporphyrins attached to steroidal substrates catalyze the hydroxylation of unactivated carbons with iodosylbenzene as the source of oxygen (cf. **1** → **3**).[4,5] By manipulation of the length of the tether linking the steroid to the template, the intermediate oxometalloporphinate can be directed to abstract a hydrogen atom at either the C(12), C(14), or C(17) position, thereby leading to hydroxyl incorporation at these sites.

In a preliminary study, the manganese(III) (*m*-((androstanyloxy)carbonyl)phenyl)triphenylporphyrin **1** (R = OMe)[6] was

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(5) The selective C(25) hydroxylation of cholesterol has been achieved in ca. 2.0% yield (based on cholesterol) by employing a catalytic membrane-spanning manganese(III) porphyrin (Groves, J. T.; Neumann, R. *J. Org. Chem.* **1988**, *53*, 3891).

0002-7863/90/1512-7799$02.50/0