High Efficient Catalytic Oxidation of Steroidal Olefins by Metalloporphyrin-Reductant-Molecular Oxygen Biomimetic Systems

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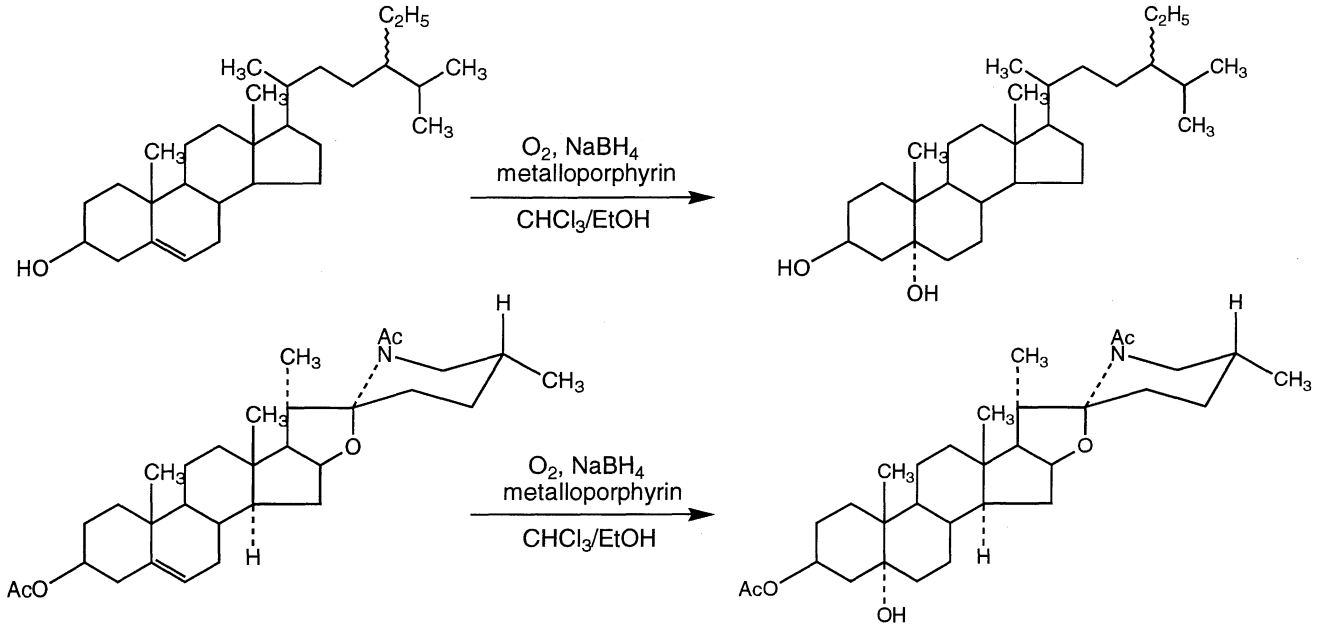
Catalytic oxidation of steroidal olefins by metalloporphyrin-reductant-molecular oxygen systems produces stereoselectively corresponding 5-α-hydroxy derivatives with high yields and the manganese complexes show higher efficiency in comparison with the iron complex due to the difference in metal-porphyrin orbital interactions.

So far a great variety of chemical model systems based on metalloporphyrin derivatives are successfully applied to mimic monooxygenase functional activity of cytochrome P-450 enzymes.[1] Of particular value are catalytic systems which are able to show high stereo- and regioselectivity in hydrocarbon oxidation reactions. These properties appear to be a quite important and promising for production and modification of fine organic compounds, biologically active substances, medical drugs. However, up to now only a limited number of natural substances has been used as substrates for these catalytic reactions.

In this communication we describe for the first time an efficient hydroxylation reaction of two steroidal compounds:[2] sitosterol and N,O-diacylsolisodine which are used as precursors for steroidal drugs by metalloporphyrin-reductant-molecular oxygen catalytic systems. All the metalloporphyrin catalysts (MnTPP, MnTMP, MnTPyP, MnTNP, MnTAP, FeTPP)[4] used were tetraphenylporphyrin derivatives and were distinguished by substituents in phenyl rings and by central metal ions. The syntheses of porphyrin free base and metal insertion have been carried out according to the reported methods.[5] Sodium borohydride has been used as reductant. Homogeneous hydroxylation[6] of steroidal substrates was performed under the standard conditions.[7] The reactions occurred stereoselectively to yield corresponding 5-α-hydroxy derivatives as the main (in many cases the only one) oxidized (Scheme 1) product which has been identified by comparison of its NMR spectrum and $[\alpha]_D$ value with those of the reference sample.[8]

Results are summarized in Table 1. The high yields of oxidized olefins were observed in all the reactions catalyzed by manganese porphyrins. The values of product yields, reaction rate constants (k_1) and turnover numbers (n) were about the same for manganese tetraphenylporphyrins (with somewhat smaller yields and k_1 for MnTPP) regardless of the porphyrin structure that indicates lack of the substitution effect of the phenyl rings and thus of the effect of the porphyrin ligand redox properties on catalytic efficiency of these systems. The sole exception for manganese complexes is MnTPyP that shows increased yield (in the case of sitosterol substrate) and enhanced k_1 values compared to those of other tetraphenylporphyrin derivatives. Pyridyl substituents of one MnTPyP molecule are likely to be external ligands for manganese central ion of another MnTPyP molecule forming intermolecular coordination complex that possesses



Scheme 1. Catalytic oxidation of sitosterol and N,O-diacylsolisodine by metalloporphyrin-$NaBH_4$-molecular oxygen system.

Table 1. Catalytic oxidation of steroidal olefins by metalloporphyrin-$NaBH_4$-molecular oxygen system[a]

Substrate	Metallo-porphyrin	Yield/ %[b]	Reaction rate constant, k_1/ l mol^{-1}·s^{-1}[c]	Turnover number, n[d]
Sitosterol	MnTPP	70	8	160
	MnTMP	80	10	160
	MnTPyP	95	25	140
	MnTNP	80	10	160
	MnTAP	80	10	190
	FeTPP	40	2	90
N,O-diacyl-solisodine	MnTPP	95	15	170
	MnTMP	100	20	180
	MnTPyP	100	40	150
	MnTNP	100	20	180
	MnTAP	100	20	200
	FeTPP	50	5	80

[a]Reaction conditions: substrate ($2.6\cdot10^{-2}$ mol l^{-1}), metalloporphyrin (10^{-4} mol l^{-1}), $NaBH_4$ (10^{-2} mol l^{-1}), ethanol:chloroform (4:1), r.t. [b]Yields based on used substrate. [c]$k_1=k_{obs}/c_{sub}\cdot c_{cat}$, where k_{obs} is the rate constant of product formation at the beginning of the reaction, c_{sub} is the substrate concentration, c_{cat} is the metalloporphyrin concentration. [d]Moles of product formed per mole of consumed metalloporphyrin.

enhanced efficiency compared to that of manganese porphyrin without external ligand. It has been reported previously that pyridine served as external ligand considerably increases metalloporphyrin catalytic performance in oxidation reactions.[9] This is probably due to the fact that such ligation reduces a displacement of the manganese central ion from the porphyrin plane resulting in prevention of an electron loss from the macrocycle.

The catalytic efficiency of FeTPP drastically reduced in comparison with that of MnTPP. This is in general agreement with the differences between metal-porphyrin orbital structures of high-spin Fe(IV)TPP and of Mn(IV)TPP states. Thus, the similar energies of the manganese e_g (d_{xz},d_{yz}) orbitals and the porphyrin e_g (π^*) LUMO virtual orbitals may lead to a significant interaction and mixing of the manganese e_g and the porphyrin e_g orbitals also preventing an electron loss from the porphyrin a_{2u} orbital. In contrast to the manganese porphyrins, the iron e_g (d_{xz},d_{yz}) orbitals are located below the porphyrin e_g (π^*) orbitals hindering the orbital interaction.

In conclusion, high efficient stereoselective catalytic oxidation of steroidal olefins has been demonstrated by manganese porphyrin-reductant-molecular oxygen systems. These results open promising perspectives for the application of metalloporphyrin based catalytic systems for modification of steroidal olefins and production of valuable hormone drugs. Further experiments are being carried out to increase rate constant values and stability of catalysts by selection of porphyrin ligands and by incorporation of metalloporphyrins into structurally organized matrixes.

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References and Notes

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2 Sitosterol was isolated from softwood sulfate soap and N,O-diacylsolisodine was obtained by acetylation of solisodine with acetic anhydride.[3]

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4 Abbreviations: MnTPP, manganese *meso*-tetraphenylporphyrin; MnTMP, manganese *meso*-tetra(4-methoxyphenyl)porphyrin; MnTPyP, manganese *meso*-tetra(4-pyridyl)porphyrin; MnTNP, manganese *meso*-tetra(4-nitrophenyl)porphyrin; MnTAP, manganese *meso*-tetra(4-aminophenyl)porphyrin; FeTPP iron *meso*-tetraphenylporphyrin.

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6 The mechanism of these catalytic oxidation reactions we believe is similar to that described previously in details[1] and includes the followed general steps: the reduction of manganese (III) porphyrins by a reductant to manganese (II) species, the coordination of molecular oxygen, the formation of a high-valent manganese (IV/V) porphyrin-oxo-complex which acts as an active specie in substrate oxidation.

7 To the vigorously stirred chloroform-ethanol solution of corresponding metalloporphyrin and substrate at 20 °C the solution of sodium borohydride in ethanol was added and the reaction time was counted instantly. The reaction kinetics was monitored by oxygen absorption.

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