Organometallic Chemistry

Synthesis and catalytic properties of manganese complexes of substituted tetraphenylporphyrins in the stereoselective hydroxylation of cholesterol

R. P. Evstigneeva,[a] S. E. Gribkova,[a] V. N. Luzgina,[a] A. B. Solov'eva,[b] and E. A. Lukashova[b]*

[a]*M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 86 prosp. Vernadskogo, 117571 Moscow, Russian Federation. Fax: +7 (095) 430 7983*

[b]*N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117333 Moscow, Russian Federation. Fax: +7 (095) 137 8284*

Manganese(III) complexes of 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin, 2-(2-carboxyvinyl)-5,10,15,20-tetraphenylporphyrin, and their derivatives containing electron-donor and electron-acceptor substituents have been synthesized. Manganese(III) porphyrinates (PMn) are catalytically active in the stereoselective hydroxylation of cholesterol to form 3β,5α-cholestanediol. The influence of substitutents in the porphyrin ring on the ability of PMn to associate in solution, the hydroxylation rate constants, and the turnover number of the catalyst are discussed.

Key words: porphyrins, manganese(III) complexes; aminoacids, tyrosine, tryptophan; quinones.

It has been shown previously[1,2] that manganese(III) complexes of porphyrin (PMn) catalyze the selective hydroxylation of the C(5)=C(6) double bond of cholesterol in the presence of sodium borohydride. This hydroxylation occurs at room temperature in one stage at a high rate to form the 5α-hydroxy derivative, 3β,5α-cholestanediol, in a preparative yield.

In the present work, the effects of substituents in the porphyrin ring on the catalytic activity of manganese(III) porphyrinates in the hydroxylation of cholesterol have been analyzed.

Results and Discussion

We studied the catalytic properties of Mn^{III} complexes with tetraphenylporphyrin and its derivatives **(1—11)** containing both electron-donor (NH_2, see complexes **2** and **3**) and electron-acceptor (COOH, see **6** and **7**) groups and electron-donor (aminoacids, see **4**, **5**, **8**, and **9**) and electron-acceptor (quinones, see **10** and **11**) fragments.

Manganese complexes were prepared by boiling solutions of porphyrins with manganese(II) acetate hydrate

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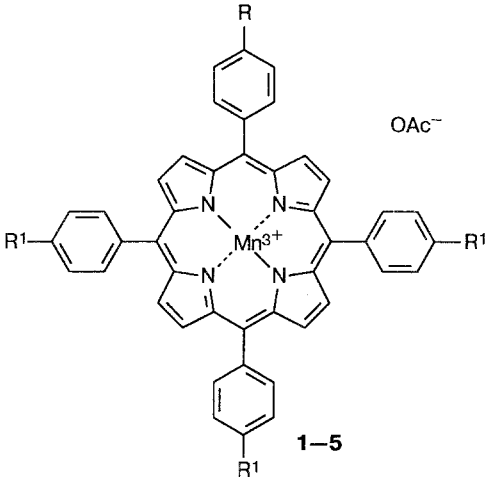
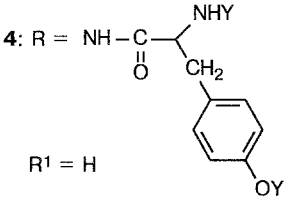
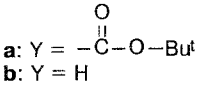
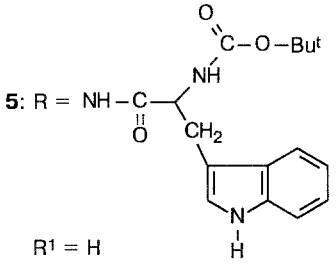


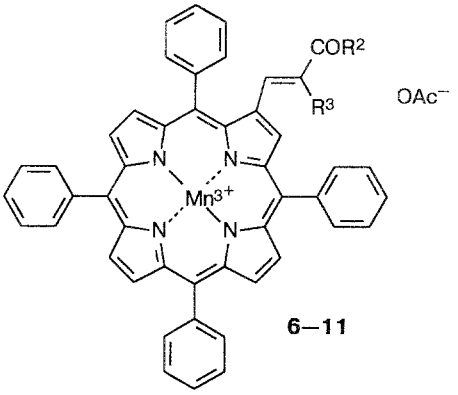
1–5

1: R = R¹ = H
2: R = NH_2; R¹ = H
3: R = R¹ = OMe



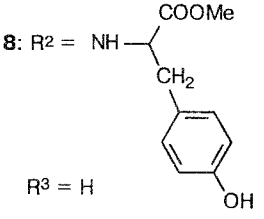


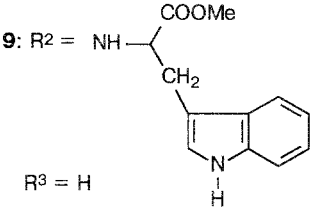


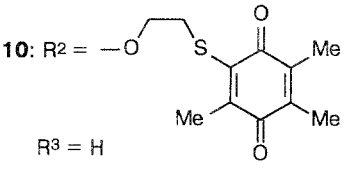


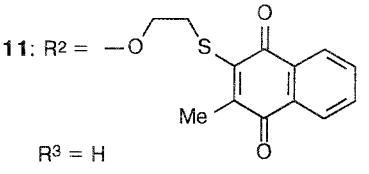
6–11

6: R² = OH; R³ = H
7: R² = OH; R³ = COOH









in a chloroform—methanol (2.5 : 1) mixture. Purity of the compounds synthesized was monitored by TLC; their structures were confirmed by UV and mass spectra, in which the signal of the $[M-OAc]^+$ ion was observed. The UV spectra correspond to complexes with Mn^{III}, *i.e.*, Mn^{II} is oxidized to Mn^{III} during the preparation.

The catalytic activity of the complexes synthesized was studied in the dark hydroxylation of cholesterol. The kinetics of the process was monitored by following the absorption of oxygen by the reaction system. It was shown by TLC (Silufol, detection with a 5 % ethanolic solution of phosphomolybdic acid) that 3β,5α-cholestanediol, whose formation occurred *via* an intermediate 5α-hydroperoxycholestan-3β-ol,[3] is the single product of the oxidation of cholesterol in the presence of all of the studied metallocomplexes.

The efficiency of the catalysts used was estimated by the following parameters: K_{eff}/L mol^{-1} s^{-1} is a "specific" (referred to one mole of substrate and one mole of catalyst) effective rate constant of hydroxylation and μ is the turnover number of a catalyst equal to the molar amount of the product formed in the presence of one mole of a catalyst before its complete degradation.[3] The values of K_{eff} and μ for the PMn synthesized are listed in Table 1; previously obtained data[1,2] relating to hydroxy-

Table 1. Kinetic parameters of the homogeneous hydroxylation of cholesterol at different MP concentrations at 20 °C in an ethanol—chloroform (1 : 1) mixture ([Cholesterol] = $2 \cdot 10^{-2}$ mol L^{-1}, [$NaBH_4$] = 10^{-2} mol L^{-1})

MP	K_{eff}/L mol^{-1} s^{-1}					μ*
	$C = 0.3 \cdot 10^{-4}$	$C = 0.6 \cdot 10^{-4}$	$C = 1.2 \cdot 10^{-4}$	$C = 2.5 \cdot 10^{-4}$	$C = 5 \cdot 10^{-4}$	
1	—	200	100	50	32	330
2	333	138	62	35	31	400
3	—	221	110	66	35	330
4a	148	82	55	30	25	330
4b	221	88	58	40	25	330
5	—	92	63	35	20	200
6	—	57	44	26	25	250
7	67	47	40	30	25	350
8	120	93	50	30	15	300
9	—	131	70	30	25	300
10	—	166	90	40	30	430
11	166	138	80	35	25	430

Note. $K_{eff} = K_{obs}/([Substrate] \times [Catalyst])$, where K_{obs} is the observed rate constant determined from the slopes of the kinetic curves of oxygen absorption and product formation at the initial moments (the catalytic process occurred without an induction period); C/mol L^{-1} is the concentration of MP. * The values of μ were determined at $C = 0.6 \cdot 10^{-4}$ mol L^{-1}.

lation of cholesterol in the presence of complexes **1** and **3** are also presented for comparison.

It has been shown previously in studies of the catalytic activity of *meso*-tetraphenyl-substituted PMn in mixtures of polar and nonpolar solvents (ethanol—benzene and ethanol—chloroform) at catalyst concentrations (C) equal to 10^{-5}—10^{-3} mol L^{-1} that in the $C < C'$ range ($C' = 10^{-4}$ mol L^{-1}) the value of K_{eff} depends on the catalyst concentration and at $C = (3—6) \cdot 10^{-5}$ mol L^{-1} K_{eff} is 10—12 times higher than the corresponding value of K_{eff} obtained at $C > 5 \cdot 10^{-3}$ mol L^{-1}. The observed features were related to the formation of associates of metalloporphyrin (MP) molecules in the reaction medium at $C > C'$.[4] It has been assumed that at $C > C'$ the process involves associates (dimers) of MP, which dissociate as the solution is diluted, so that monomeric MP's participate in the catalytic reaction at $C < C'$.[4]

The dependences of K_{eff} of the hydroxylation of cholesterol in the presence of synthesized MP on catalyst concentration in an ethanol—chloroform (1 : 1) solvent mixture are presented in Fig. 1. It is seen that an increase in K_{eff} as the concentration decreases (characteristic of complexes **1** and **3**) is observed for all of the MP obtained, *i.e.*, it is evident that the presence of bulky substituents at the *meso*-positions of the porphyrin ring does not prevent the association of MP.

According to the previously obtained results,[1,2] the rate constant of the hydroxylation of cholesterol in the presence of PMn is the highest for *meso*-substituted PMn. The value of K_{eff} depends slightly on the nature of the *meso*-substituents (see Table 1). The turnover number of the catalyst, μ, which determines the stability of the active form of PMn^{2+}, is higher for the derivatives with electron-acceptor quinoid fragments. As has been shown previously,[3] MP's with the strongest electron-donor substituents at the *meso*-positions degrade more rapidly. In fact, the data in Table 1 attest to the absence of a correlation between the values of K_{eff} and μ.

Of the new MP complexes, manganese porphyrinates containing, in addition to *meso*-substituents, derivatives of acrylic acid with naphtho- and benzoquinones (**10**, **11**) are the most active in terms of turnover. They are also promising catalysts for the photooxidation of unsaturated hydrocarbons.

Experimental

Electronic spectra were recorded on DU-6 and Hitachi UV-240 spectrophotometers. IR spectra were recorded on a

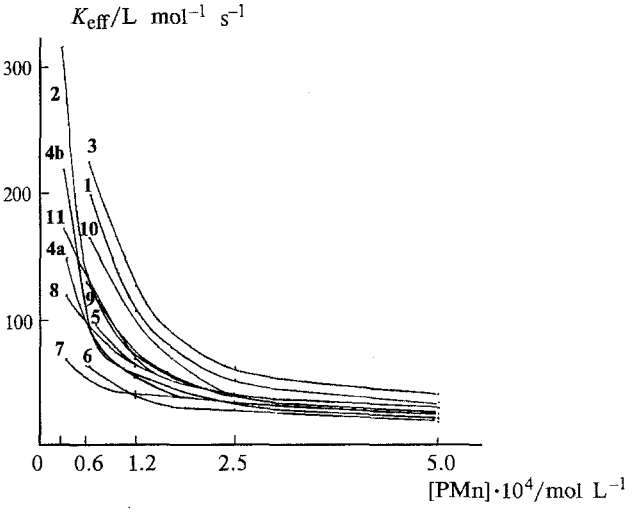


Fig. 1. Dependence of K_{eff} for the hydroxylation of cholesterol with the molecular O_2—PMn^{II}—$NaBH_4$ system on the concentration of PMn^{III} ([$NaBH_4$] = 10^{-2} mol L^{-1}, [Cholesterol] = $2.5 \cdot 10^{-2}$ mol L^{-1}). Numeration of curves corresponds to the numbers of compounds.

Shimadzu IR-435 spectrometer. Mass spectra were obtained on a BC MS spectrometer (Selmy, Ukraine) by the method of time-of-flight mass-spectroscopy.

The purity of the compounds synthesized and the course of the chemical reactions were monitored by TLC on Silufol UV-254 plates (Kavalier) in the chloroform—methanol, 10 : 0.5 (*A*), ether (*B*), and chloroform—methanol, 4 : 1 (*C*) systems. Substances were purified by column chromatography on Silica gel L 100/160. Additional purification was performed by TLC on Kiesel gel G-60 plates (Merck) (20×20 cm). Manganese complexes of compounds **1** and **3** were prepared by the known procedure.[5] Amino acid derivatives of porphyrins were synthesized by the previously described method.[6] Quinoid derivatives of porphyrins were prepared according to the previously published work;[7] the procedure for the synthesis of the initial porphyrin for the preparation of complexes **6—11** has been presented previously.[8]

Cholesterol was hydroxylated in air in a chloroform—ethanol (1 : 1) mixture in a temperature-controlled reactor at 20 °C in the presence of PMn and an activator (reducing agent), sodium borohydride. A solution of cholesterol and metalloporphyrin in the chloroform—ethanol mixture was introduced into the reactor, vigorously stirred until their complete dissolution, then an ethanolic solution of sodium borohydride was added, and reading of the reaction time was begun.

Preparation of manganese complexes (general procedure). A porphyrin derivative (0.03 mmol) in a solution of 10 mL of chloroform and 4 mL of methanol was added to 0.06 mmol of manganese(II) hydrate acetate, and the reaction mixture was boiled for 2 h. After cooling, the reaction mixture was washed with water (2×30 mL). The chloroform extract was dried with sodium sulfate, passed through a layer of silica gel (5 cm), and the solvent was removed *in vacuo*. The residue was stirred with pentane and dried *in vacuo* over paraffin and P_2O_5.

[5-(*p*-Aminophenyl)-10,15,20-triphenylporphyrinato]manganese(III) acetate (2). Yield 0.020 mg (85 %). R_f 0.57 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619.5 (4.98), 584.5 (3.71), 486.5 (30.22), 378 (20.26). MS, *m/z*: 682.7 $[M-OAc]^+$.

[5-{*p*-*N*-(*O*,*N*-Di-*tert*-butoxycarbonyl-L-tyrosyl)aminophenyl}-10,15,20-triphenylporphyrinato]manganese(III) acetate (4a). Yield 0.036 g (87 %). R_f 0.58 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619.5 (3.74), 584.5 (3.23), 481.2 (23.49), 413.0 (15.23), 378.0 (17.04). MS, *m/z*: 1046.0 $[M-OAc]^+$.

[5-{*p*-*N*-(L-Tyrosyl)aminophenyl}-10,15,20-triphenylporphyrinato]manganese(III) acetate (4b). Yield 0.032 g (45.7 %). R_f 0.62 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619.5 (16.66), 584.5 (14.81), 483.0 (122.18), 406.0 (54.81), 381.5 (64.79). MS, *m/z*: 845.4 $[M-OAc]^+$.

[5-{*p*-*N*-(*N*$^{\alpha}$-*tert*-Butoxycarbonyl-L-tryptophyl)aminophenyl}-10,15,20-triphenylporphyrinato]manganese(III) acetate (5). Yield 0.023 g (67.12 %). R_f 0.56 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619.5 (5.97), 582.7 (5.33), 481.2 (38.80), 404.2 (24.73), 379.7 (27.5). MS, *m/z*: 969.4 $[M-OAc]^+$.

[2-(2-Carboxyvinyl)-5,10,15,20-tetraphenylporphyrinato]manganese(III) acetate (6). Yield 0.028 g (67.5 %). R_f 0.43 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 623.0 (4.71), 588 (5.88), 486.5 (55.31), 409.5 (30.59), 388.5 (32.95). MS, *m/z*: 737.4 $[M-OAc]^+$.

[2-(2,2-Dicarboxyvinyl)-5,10,15,20-tetraphenylporphyrinato]manganese(III) acetate (7). Yield 0.019 mg (82.3 %). R_f 0.62 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 608 (2.66), 574 (3.36), 478 (22.70), 420 (18.50), 386 (19.06). MS, *m/z*: 781.7 $[M-OAc]^+$.

***N*-(2-{[2-(5,10,15,20-Tetraphenylporphyrinato)]manganese(III) acetate}acryloyl)-L-tyrosine methyl ester (8).** Yield 0.028 g (83.2 %). R_f 0.19 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 623.0 (3.36), 588.0 (3.97), 486.5 (29.17), 410 (18.94), 388.5 (20.17). MS, *m/z*: 913.88 $[M-OAc]^+$.

***N*-(2-{[2-(5,10,15,20-Tetraphenylporphyrinato)]manganese(III) acetate}acryloyl)-L-tryptophan methyl ester (9).** Yield 0.023 g (80.6 %). R_f 0.23 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 623.0 (4.89), 588.5 (5.71), 486.5 (35.51), 409.5 (27.14), 390.2 (28.57). MS, *m/z*: 936.5 $[M-OAc]^+$.

[2-{2-[2-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)thioethoxycarbonyl]vinyl}-5,10,15,20-tetraphenylporphyrinato]manganese(III) acetate (10). Yield 0.018 g (80 %). R_f 0.7 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 626.0 (3.71), 594.0 (4.77), 482.0 (46.94), 410.0 (24.40), 384.0 (13.26). MS, *m/z*: 948.2 $[M-OAc]^+$.

[2-{2-[2-(3-Methyl-1,4-naphthoquinon-2-yl)thioethoxycarbonyl]vinyl}-5,10,15,20-tetraphenylporphyrinato]manganese(III) acetate (11). Yield 0.019 g (80 %). R_f 0.79 (*B*). Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 626.0 (2.12), 594.0 (2.64), 486.0 (28.03), 410.0 (14.81), 384.0 (16.92). MS, *m/z*: 968.9 $[M-OAc]^+$.

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