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BIOMIMETIC OXIDATION OF 21-HYDROXY, 21-FORMYL AND 21-CARBOXYLIC PREGN-4-EN-3,20-DIONE WITH CHEMICAL CYTOCHROME P450 MODEL SYSTEMS

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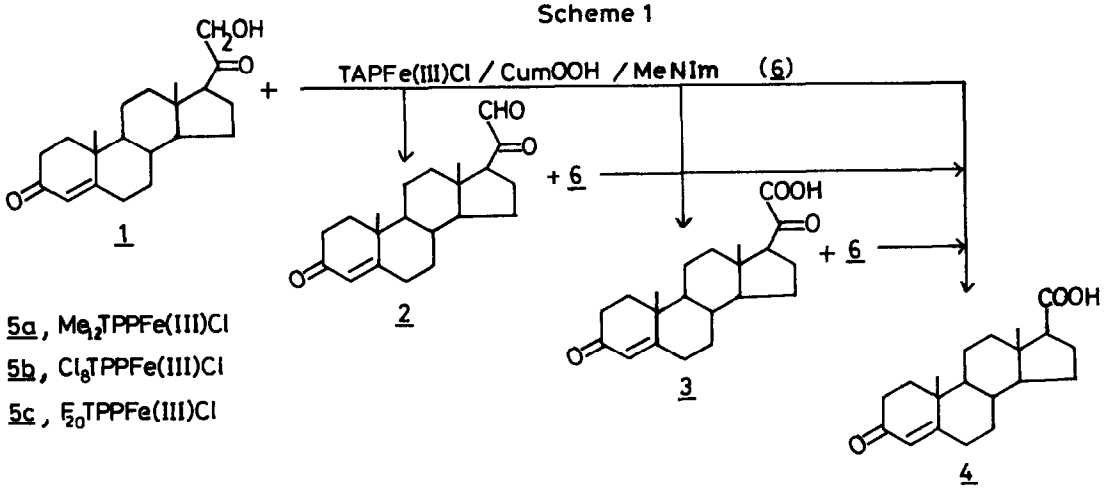
Abstract: The electron withdrawing 5,10,15,20-tetra(2',6'-dichlorophenyl)porphyrin iron(III)chloride [Cl_8TPPFe(III)Cl] and 5,10,15,20-tetra(2',3',4',5',6'-pentafluorophenyl)porphyrin iron(III)chloride [F_{20}TPPFe(III)Cl] are more efficient catalysts than sterically hindered 5,10,15,20-tetra(2',4',6'-trimethylphenyl)porphyrin iron(III)chloride during the biomimetic oxidation of 21-hydroxypregn-4-en-3,20-dione with CumOOH in the presence of N-methylimidazole.

Cytochrome P450 model systems are currently used in selective hydroxylation and epoxidation in organic synthesis and oxidative metabolism of drugs and pesticides[1-5]. Cytochrome P450 model systems consisting of iron(III) 5,10,15,20-tetraarylporphyrins [TAPFe(III)Cl] and monooxygen donors form high valent iron(IV) oxoporphyrin radical cations[6,7] which are responsible for the hydroxylation[1,2], epoxidation[4], C-C bond cleavage[5] and other oxidation reactions[8]. The 21-hydroxypregn-4-en-3,20-dione (1) is hydroxylated at 11 and 18 positions by 11β-hydroxylase and 18-hydroxylase respectively during its conversion to aldosterone in mitochondrial membrane[9], whereas 1 is oxidized to 3-oxoandrost-4-en-17β-carboxylic acid (4), pregn-4-en-3,20-dioxo-21-oic acid (3), 20-hydroxypregn-4-en-3-oxo-21-oic acid and other various non acidic products by human liver enzyme[10-13]. The biomimetic oxidation with cumene hydroperoxide (CumOOH) catalyzed by sterically hindered and electron withdrawing 5,10,15,20-tetraarylporphyrin iron(III) chlorides in the presence of N-methylimidazole (MeNIm) is reported to understand the ring hydroxylation and side chain oxidation of 21-hydroxypregn-4-en-3,20-dione (1).

The oxidation of 21-hydroxypregn-4-en-3,20-dione (1) with CumOOH catalyzed by sterically hindered 5,10,15,20-tetra(2',4',6'-trimethylphenyl) porphyrin iron(III)chloride [Me_{12}TPPFe(III)Cl, (5a)] in dichloromethane at room temperature for 12 h gave pregn-4-en-3,20-dioxo-21-al (2), pregn-4-en-3,20-dioxo-21-oic acid (3) and 3-oxoandrost-4-en-17β-carboxylic acid (4) in 2.0, 7.9 and 60.0% yields respectively (Table 1). The oxidation of 1 with CumOOH/Cl_8TPPFe(III)Cl/MeNIm gave 2, 3 and 4 in 0.5, 1.4 and 79.4% yield respectively. The oxidation products of 1 with other model systems are given in Scheme 1 and Table 1.

The reaction of 1 with CumOOH catalyzed by Cl_8TPPFe(III)Cl in dichloromethane gave 2 which was isolated by preparative TLC and characterized by different spectroscopic techniques[14]. Further, the formation of 2 was confirmed by preparation of the derivative 2-(3-oxo-pregn-4-en-17β-yl) quinoxaline by reaction of 2 with ortho-phenylenediamine[15].

Scheme 1



5a, Me_{12}TPPFe(III)Cl
5b, Cl_8TPPFe(III)Cl
5c, F_{20}TPPFe(III)Cl

TABLE-1

OXIDATION PRODUCTS OF 1 WITH DIFFERENT TAPFe(III)Cl/CumOOH/MeNIm SYSTEMS

Experiment No.	Catalyst*	Substance	% Yield+		
			2	3	4
1.	Me_{12}TPPFe(III)Cl	1	2.0	7.9	60.0
2.	Cl_8TPPFe(III)Cl	1	0.5	1.4	79.2
3.	F_{20}TPPFe(III)Cl	1	1.8	0.4	82.3
4.	Cl_8TPPFe(III)Cl	2	-	6.1	29.1
5.	F_{20}TPPFe(III)Cl	2	-	1.5	76.0
6.	Cl_8TPPFe(III)Cl	3	-	-	83.0
7.	F_{20}TPPFe(III)Cl	3	-	-	84.0

*Reaction conditions: Substrate (30 mmol): porphyrins : CumOOH : MeNIm in the ratio 100:1:25:10 and the reactions were carried out in dry dichloromethane (5.0 ml) at 25°C for 12 h.

+Relative yields estimated by HPLC (with respect to oxidant used): HPLC conditions: Zorbax ODS column (reverse phase, 15 cm x 4 mm i.d.); acetonitrile solvent (0.4 ml/min.); UV detector (245 nm); retention times in min. : 1, 11.2; 2, 9.4; 3, 16.8 and 4, 12.7.

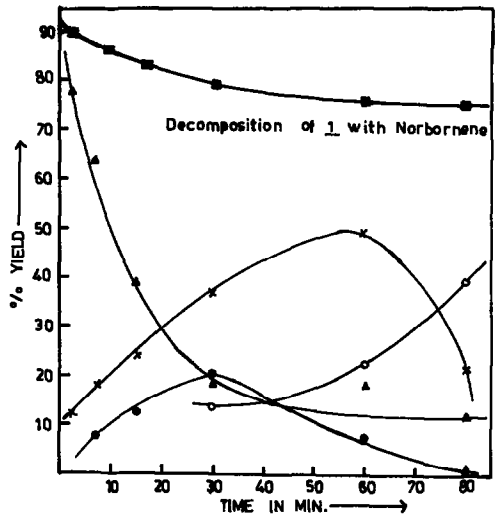


Fig. 1. Time dependent decomposition of 1(- ▲ -) and formation of products 2(-X-), 3(-●-), 4(-o-) by using Cl_8TPPFe(III)Cl/CumOOH/MeNIm in dichloromethane.

The reaction of 1 with CumOOH catalyzed by 5a gave 3 in 7.9% which was confirmed by comparing the HPLC retention time with that of authentic sample prepared from pregn-4-en-3,20-dioxo-21-al (2) and their reaction with KCN followed by hydrolysis[16]. The formation of 4 was confirmed by comparing R_f values and HPLC retention time with those of authentic sample[17] prepared by HIO_4 oxidation of 1 or oxidation of 3 with HIO_4[18].

The time dependent oxidation of 1 with Cl_8TPPFe(III)Cl/CumOOH/MeNIm or F_{20}TPPFe(III)Cl/CumOOH/MeNIm (1:25:10) is given in Fig. 1 and Fig. 2

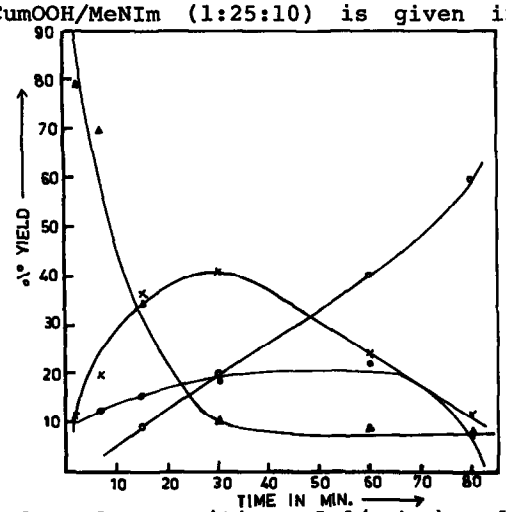
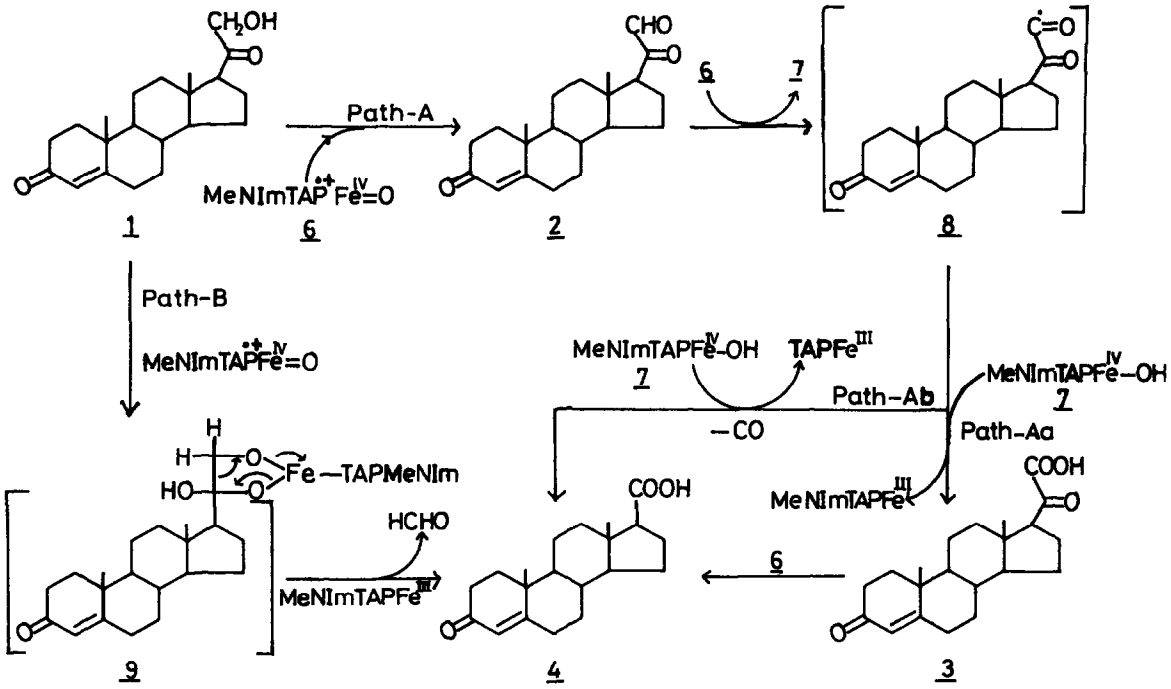


Fig. 2. Time dependent decomposition of 1(- ▲ -) and formation of products 2(-X-), 3(-●-) and 4(-o-) by using F_{20}TPPFe(III)Cl/CumOOH/MeNIm in dichloromethane.

respectively. The rate of decomposition of 1 is faster with F_{20}TPPFe(III)Cl than with Cl_8TPPFe(III)Cl at room temperature due to high electron withdrawing nature of F_{20}TPPFe(III)Cl. When norbornene was added to the above model systems the decomposition of 1 was suppressed and the formation of different oxidation products of 1 was reduced (Fig. 1).

Scheme 2



The reaction of TAPFe(III)Cl with CumOOH in the presence of N-methylimidazole produces high-valent oxo iron intermediates [(MeNImTAP)$^{\bullet+}$Fe^{IV}=o] (6)[19-22] which react with norbornene to form the corresponding epoxides[19-21]. The initial oxidation of 1 with 6 forms the ketoaldehyde (2). The reaction of 2 with 6 gave 3 and 4 in 6.1 and 29.1% yield respectively. The hydrogen abstraction from 2 by 6 forms the radical species 8, which on recombination with 7 (MeNImTAPFe^{IV}-OH) leads to keto carboxylic acid 3 (Path Aa, Scheme 2). Similar hydrogen abstraction and recombination mechanism has been proposed during the oxidation of aldehydes of carboxylic acids by meta-chloroperbenzoic acid catalyzed by TAPFe(III)Cl[23]. The initial decarbonylation of 8 followed by recombination with 7 gave 4 (Path Ab, Scheme 2). The formation of 4 in high yield by 5c as compared to 5b indicates that path Ab is more favoured with

highly electron withdrawing F_{20}TPPFe(III)Cl (5c) than Cl_8TPPFe(III)Cl (5b). The oxidation of 3 with CumOOH catalyzed by 5b gave 4 in 83% yield (experiment No.6, Table 1). The reaction of 1 with CumOOH catalyzed by 5b gave 4 in 79.2% (experiment No. 2 Table 1) whereas 4 is formed from 2 in 29.1% (experiment No. 4, Table 1) in similar conditions. This may be explained by formation of cyclic intermediate 9 by reaction of 1 with 6, followed by its spontaneous decomposition to form formaldehyde and 4 (Scheme 2, Path B).

Thus, the side chain oxidation of 1 occurs in high yields with CumOOH catalyzed by electron withdrawing 5,10,15,20-tetraarylporphyriniron(III) chlorides in dichloromethane in presence of N-methylimidazole than ring hydroxylation.

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