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Short Communication

Biomimetic oxidation of guggulsterone with hydrogen peroxide catalyzed by iron(III) porphyrins in ionic liquid

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ABSTRACT

The biomimetic oxidation of E- and Z-guggulsterones was studied with hydrogen peroxide catalyzed by different 5,10,15,20-tetraarylporphyrinatoiron(III)chlorides in dichloromethane as well as in an ionic liquid to understand the mechanism of oxidative transformation of guggulsterone in biological system.

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1. Introduction

Z-Guggulsterone (**1a**) and E-Guggulsterone (**1b**) [4,17(20)-cis-Pregnadiene-3,16-dione] are the most active compounds isolated from the gum resin "guggul" obtained from *Commiphora mukul* [1]. Guggulsterones possess a high degree of human bioactivity as they inhibit cholesterol biosynthesis [2], mobilize fat from tissues [3], reduce the stickiness of blood platelets [4], affect thyroid metabolism [5], control cystic acne and affect dermal (skin) functions [6]. They have been used as hypocholesterolemic agent as they lower total cholesterol (LDL-cholesterol), while elevating HDL-cholesterol levels [7,8]. Guggulsterone protects LDL against depletion of lipid constituents such as cholesterol, cholesterol esters, triglycerides and phospholipids as well as inhibits the conversion of cholesterol into oxygenated cholesterols [9]. It is also found to be efficacious in the treatment of rheumatoid arthritis [10], obesity [11], inflammatory bowel diseases [12] and allied disorders [13]. It has been shown that guggulsterone can act as an antagonist ligand for farnesoid X receptor (FXR), a nuclear hormone receptor that is activated by bile acids and this inhibition of FXR activation is the basis for the cholesterol-lowering activity of guggulsterones [14]. It also exhibits cytotoxic activity against head and neck cancer cells [15] and prostate cancer cells [16]. The protective action of guggulsterones may be due to their anti-oxidant and free radical scavenging property as they significantly inhibit the generation of hydroxyl radicals in a non-enzymic system [17]. Studies on the microbial transformation of guggulsterones by *Aspergillus niger* and *Cephalosporium aphidicola* resulted in the formation of hydroxylated steroidal derivatives [18].

Guggulsterone is a steroidal compound containing two α, β-unsaturated carbonyl groups in the same molecule. The epoxidation of electron-deficient C═C bond in such systems is rather difficult and has been best carried out by using alkaline H_2O_2 [19]. Metalloporphyrins as model catalysts of cytochrome P450 have been used to mimic various oxygenation and oxidation reactions of different drugs and biologically active compounds [20–24]. Metalloporphyrins have proven to be highly efficient catalysts for the epoxidation of electron-rich double bonds with various monooxoygen donors like hydrogen peroxide (H_2O_2), potassium monopersulfate ($KHSO_5$) and iodosylarenes (ArIO) [25,26]. However, the epoxidation of electron-deficient substrates with these oxidants catalyzed by metalloporphyrins gives only very poor yields. Further, studies have shown that the catalytic activity of cytochrome-c, hemin and microperoxidase-11 has been increased in ionic liquids compared to that in methanol or DMSO [27]. The anionic water-soluble porphyrins also showed enhanced stability in ionic liquids [20].

Ionic liquids (ILs) have been used as green solvents in various catalytic and non-catalytic chemical and biochemical transformations [28]. They have also been used as novel reaction media for metalloporphyrin catalyzed different types of reactions, studying non-covalent interactions and supramolecular chemistry [20]. Herein, we report the biomimetic oxidation of E- and Z-guggulsterones with hydrogen peroxide catalyzed by different 5,10,15,20-tetraarylporphyrinatoiron(III)chlorides in dichloromethane as well as in an ionic liquid to understand the mechanism of oxidative transformations of guggulsterones in biological system.

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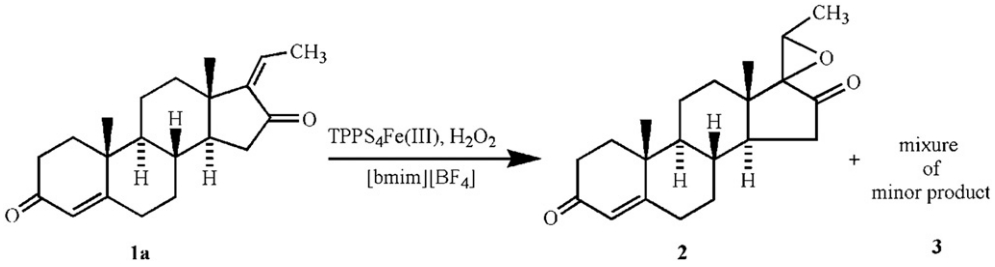

Scheme 1. Epoxidation of guggulsterone catalyzed by metalloporphyrin in ionic liquid.

2. Results and discussion

Guggulsterones were isolated from the gum resin of *Commiphora mukul* by extraction with ethyl acetate at room temperature and repetitive column chromatography on silica gel (60–120 mesh) column with petroleum ether: EtOAc (80:20) following the literature procedure [29]. The iron(III)5,10,15,20-tetrakis(2′,6′-dichloro-3′-sulfonatophenyl)porphyrin [$Cl_8TPPS_4Fe(III)$] was solubilized in ionic liquid, [bmim][BF_4]. The UV–visible spectrum of $Cl_8TPPS_4Fe(III)$ in [bmim][BF_4] is similar to that in aqueous solution with a slight broad Soret band at 420 nm and Q-bands at 583 and 634 nm. The broadening of Soret peak has been observed and has been attributed to the formation of ion-pair complexes as reported for the tetracationic porphyrins and tetrasulfonic calix[4]arenes. Further, the addition of N-methylimidazole (NMI) to the solution shifted the Soret band indicating the non-coordinating nature of BF_4^- with central metal. Addition of H_2O_2 to the solution shifted the Soret band at 431 nm with decreased intensity due to formation of anionic iron peroxo intermediate [30]. The ionic liquid containing water-soluble iron(III)porphyrin was extracted with ethyl acetate, diethyl ether and water and the extracts were screened with UV–visible spectroscopy. There was no peak in the 410–435 nm regions showing that the catalyst was completely immobilized in ionic liquid without any appreciable leaching.

In a typical run, hydrogen peroxide (30% v/v, 2.0 mmol) was added to a well stirred solution of **1a** (1.0 mmol) and [$Cl_8TPPS_4Fe(III)Cl$] (0.01 mmol) in [bmim][BF_4] (2.0 mL) in nitrogen atmosphere. The reaction mixture was stirred under nitrogen atmosphere at an ambient temperature. After completion of the reaction, the reaction mixture was extracted with mixture of petroleum ether: ethyl acetate (30: 70) and subjected to HPLC with the mobile phase acetonitrile: water (60: 40). The products 4-pregnanene-3, 16-di-one-17(20)-epoxide (**2**) and a hydroxylated product (**3**) appeared at retention times of 13 and 5 min and were formed in 33.5% and 12.3% yields respectively (Scheme 1). Purification was carried out by preparative TLC and the products were characterized by various spectroscopic data. Similar reaction of **1a** with hydrogen peroxide catalyzed by [$TPPS_4Fe(III)$] in [bmim][BF_4] gave 4-pregnanene-3, 16-di-one-17(20)-epoxide (**2**) as the major product in 24.8% yield (Table 1). Z-guggulsterone (**1a**) was found to be more reactive than E-guggulsterone (**1b**) as the epoxidation of **1a** predominantly took place when similar reaction was performed with a mixture of **1a** and **1b**. This might be due to presence of bulky methyl group in E-isomer which hinders the attack of peroxy anion intermediate at reactive site of substrate. In the Z-isomer, hydrogen atom present at the opposite side provides enough space to incoming peroxy anion intermediate to react sufficiently with the substrate resulting in formation of epoxide. The reaction of Z-guggulsterone (**1a**) with hydrogen peroxide in the absence of catalyst did not give any product (Table 1, entry 5) and the starting compound was recovered in 99% yield after 24 h showing the role of iron(III)porphyrin in the formation of reactive intermediate responsible for the formation of product.

The oxidation of Z-guggulsterone (**1a**) with hydrogen peroxide catalyzed by [$Cl_8TPPFe(III)Cl$] in dichloromethane gave 4-pregnanene-3,16-di-one-17(20)-epoxide (**2**) in 16.1% yield. The same reaction of **1a** with hydrogen peroxide catalyzed by [$TPPFe(III)Cl$] in CH_2Cl_2 gave the epoxide (**2**) in 10.2% yield (Table 2). The high yield of epoxide in the reactions of water soluble iron (III) porphyrins in ionic liquids may be attributed to weakly coordinating nature of ionic liquid, which may accelerate the reaction by stabilizing the highly charged iron-peroxo or oxo intermediates (compound 1 of cytochrome P450) generated during the reaction [30–32]. This stabilization is due to formation of hydrogen bond between anionic species and C-2 hydrogen of imidazolium cation of [bmim][BF_4] [28]. Similar type of effect for the stabilization of metal-oxo intermediate by ionic liquid has been reported for the epoxidation and hydroxylation of olefins by $PhI(OAc)_2$ catalyzed by meso-tetrakis(pentafluorophenyl) porphyrinatomanganese(III)chloride [33].

The oxidized product has been identified by ^1H NMR and MS data. The ^1H NMR spectrum of compound **2** showed a singlet at δ 5.75 ppm for the olefinic proton on C-4. The quartet at δ 6.54 ppm due to presence of other olefinic proton in guggulsterone disappeared and instead another quartet appeared at δ 3.41 ppm for one proton which could be attributed to the C-20 proton and indicated the formation of C (19–20) epoxide. The presence of molecular ion peak (M^+) at 328 in mass spectrum further confirmed the structure of epoxidized product.

The reaction of hydrogen peroxide with iron(III)porphyrin in protic solvent produces high valent iron-oxo radical cation by protonation followed by O – O bond heterolysis whereas in the neutral aprotic solvent such as [bmim][BF_4] or dichloromethane, generation of ferric peroxo anion intermediate followed by O – O bond homolysis

Table 1
Biomimetic oxidation of Z-guggulsterone (**1a**) with monooxygen donors catalyzed by iron(III)porphyrins in an ionic liquid, [bmim][BF_4] under nitrogen atmosphere.[a].

S. No.	System	Time (h)	% Yield[b]		Selectivity
			2	Mixture	
1.	**1a**/$TPPS_4Fe(III)/H_2O_2$/IL	5	24.8	8.6	2.88
2.	**1a**/$Cl_8TPPS_4Fe(III)/H_2O_2$/IL	3	33.5	12.3	2.72
3.	**1a**/$Cl_8TPPS_4Fe(III)/H_2O_2$/NMI/IL	3	40.2	13.9	2.89
4.	**1a**/$Cl_8TPPS_4Fe(III)/KO_2$/IL	3	35.7	14.3	2.49
5.	**1a** + **1b**/$Cl_8TPPS_4Fe(III)/H_2O_2$/IL	3	23.5	8.2	2.86

[a] The reaction mixture contained 2.0 mmol of hydrogen peroxide, 0.01 mmol of iron(III)porphyrin and 1.0 mmol of substrate in ionic liquid (2 mL).
[b] Based on HPLC analysis.

Table 2
Biomimetic oxidation of Z-guggulsterone (**1a**) with monooxygen donors catalyzed by iron(III)porphyrins in organic medium under nitrogen atmosphere.[a].

S. No.	System	Time (h)	% Yield[b]		Selectivity
			2	Mixture	
1.	**1**/H_2O_2/DCM	24	–	–	–
2.	**1**/$TPPFe(III)Cl/H_2O_2$/DCM	5	10.2	5.0	2.04
3.	**1**/$Cl_8TPPFe(III)Cl/H_2O_2$/DCM	3	16.1	7.3	2.20
4.	**1**/$Cl_8Cl_8TPPFe(III)Cl/H_2O_2$/DCM	3	25.5	8.1	3.14
5.	**1**/$Cl_8Cl_8TPPFe(III)Cl/H_2O_2$/NMI/DCM	3	28.7	9.0	3.18

[a] The reaction mixture contained 2.0 mmol of hydrogen peroxide, 0.01 mmol of iron(III)porphyrin and 1.0 mmol of substrate in DCM (15 mL).
[b] Based on HPLC analysis.

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