Formation of 6-Formyl-7-hydroxy-8-methoxycoumarin and 5,8-Dioxopsoralen by Reaction of 8-Methoxypsoralen with H_2O_2 and Potassium Superoxide (KO_2) Catalyzed by Halogenated or Perhalogenated 5,10,15,20-Tetraarylporphyrinatoiron(III) Chlorides

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The oxidation of 8-methoxypsoralen (2) with hydrogen peroxide and potassium superoxide catalyzed by 5,10,15,20-(2,4,6-trimethylphenyl)porphyrinatoiron(III) chlorides [Me_{12}-TPPFe(III)Cl] (1a) and 5,10,15,20-(2,6-dichlorophenyl)porphyrinatoiron(III) chlorides [Cl_8TPPFe(III)Cl] (1b) in dichloromethane gives 6-formyl-7-hydroxy-8-methoxycoumarin (3) in moderate yields, whereas the oxidation of (2) with H_2O_2 catalyzed by 5,10,15,20-(2,6-dichlorophenyl)-β-octahaloporphyrinatoiron(III) chlorides [$Cl_8\beta X_8$TPPFe(III)Cl] (X=Cl, Br) (1c, 1d) gives specifically 5,8-dioxopsoralen (4) in moderate yields.

Key words 8-methoxypsoralen; H_2O_2 and KO_2; halogenated and perhalogenated iron(III)porphyrins; 5,8-dioxopsoralen; 6-formyl-7-hydroxy-8-methoxycoumarin

The 8-methoxypsoralen (**2**) is an important photodynamic agent, used in the treatment of vitiligo, psorisis and other deseases.[1] The 8-methoxypsoralen are metabolized by different isoforms of cytochrome P450 in man,[2] dog,[3] rat[4] and insects.[5] Formation of different metabolic products in man indicate that specific product has formed by specific isoform of cytochrome P450 enzyme systems. The selected drugs have been oxidized with different monooxygen donors catalyzed by metalloporphyrins in different conditions.[6—10] Aqueous hydrogen peroxide is an ideal oxidant and it has been used in the environment-consious chemical process.[11,12] The reaction of hydrogen peroxide and potasium superoxide with 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides form, high valent oxo-iron(IV)porphyrin radical cation and related species which mimic the different reaction of cytochrome P450 enzyme system.[13] We report the biomimetic oxidation of 8-methoxypsoralen (**2**) with hydrogen peroxide (H_2O_2) and potassium superoxide (KO_2) catalyzed by different halogenated and perhalogenated iron(III) porphyrins to understand the molecular mechanism of different isoforms of cytochrome P450 in different reaction conditions.

The reaction of hydrogen peroxide (0.05 mmol) with 8-methoxypsoralen (**2**) catalyzed by 5,10,15,20-(2,4,6-trimethylphenyl)porphyrinatoiron(III) chlorides [Me_{12}TPPFe-(III)Cl] (**1a**) (0.005 mmol) in dichloromethane (10 ml) gave 6-formyl-7-hydroxy-8-methoxycoumarin (**3**) in 25.5% yield (Chart 1) and confirmed by different spectroscopic data.[14] Similarly the reaction of H_2O_2 with **2** in presence of 5,10,15,20-(2,6-dichlorophenyl)porphyrinatoiron(III) chlorides [Cl_8TPPFe(III)Cl] (**1b**) gave **3** in 29.5% yield. Further the reaction of KO_2 with **2** in presence of **1a** gave **3** in 21% yield. Moreover **3** can be obtained by the photooxidation of **2** with $^1O_2$ in 1.4% yield.[15] Therefore H_2O_2/TAPFe(III)Cl is the better system for the preparation of **3** from **2**.

The reaction of H_2O_2 with **2** in presence of 5,10,15,20-(2,6-dichlorophenyl)-β-octahaloporphyrinatoiron(III) chlorides [$Cl_8\beta X_8$TPPFe(III)Cl] (X=Cl, Br) (**1c**, **1d**) gave 5,8-dioxopsoralen (**4**) in 8.0% and 9.5% yield respectively (Chart 1). Similarly the reaction of **2** with KO_2/MeOH catalyzed by **1c** gave **4** in 2.0% yield. The formation of psoraleneqiunone (**4**) is confirmed by IR, ^{1}H-NMR, EI-MS and other spectroscopic data.[16]

The reaction of iron(III)porphyrins (**1a**, **1b**) and H_2O_2 forms hydroperoxoiron(III)porphyrin species initially and iron(IV)porphyrin oxo radical cation species subsequently which may epoxidise the electron rich 4′,5′ double bond of **2**. The electrocyclic ring opening of **2** and subsquent decomposition in presence of water is responsible for the formation of **3**.[17] The formation of hydroperoxoiron(III) and iron(IV)-porphyrin-oxo complexes by the reaction of H_2O_2 or KO_2 and synthetic iron(III)porphyrins and their application in the oxidation of different organic substrates have been reported.[18,19] Although the oxidation of different methoxybenzenes to quinones have been reported by the reaction with monooxygen donors and metalloporphyrins,[20] but the reaction with **2** with H_2O_2 or KO_2 in presence of **1a** and **1b** does not give the quinone **4**.

The eight chlorine atoms bonded to the ortho phenyl groups change the redox potential of the Fe(III)/Fe(II) couple of Cl_8TPPFe(III)Cl (**1b**) ($E_{1/2}=-0.34$) by only 50 mV compared to TPPFe(III)Cl ($E_{1/2}=-0.39$), the additional eight chlorine on the porphyrin ring in $Cl_8\beta Cl_8$TPPFe(III)Cl (**1b**) ($E_{1/2}=+0.10$) move the potential by more than 600 mV compared to TPPFe(III)Cl. Therefore the electron deficient iron–oxo porphyrin complexes having high positive redox potentials are much better electron acceptors than the corresponding species derived from simple TPPFe(III) complexes and they are more efficient oxidants for hydroxylation for aromatic and aliphatic hydrocarbons. Therefore **1c** and H_2O_2 system preferentially hydroxylates the position 5 of **2** which

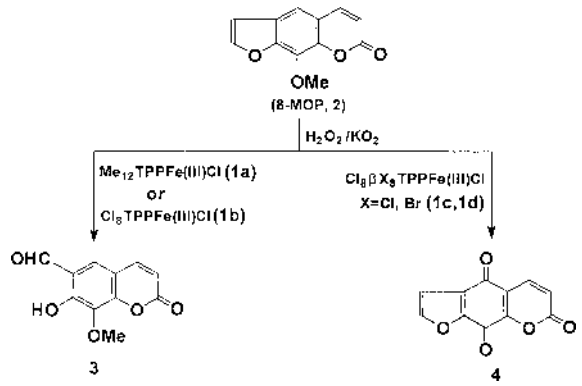

Chart 1. Oxidation of 8-Methoxypsoralen (**2**) with Hydrogen Peroxide (H_2O_2) Catalyzed by Me_{12}TPPFe(III)Cl (**1a**), Cl_8TPPFe(III)Cl (**1b**) and $Cl_8\beta$-X_8TPPFe(III)Cl (X=Cl, Br) (**1c**, **1d**) in Dichloromethane

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on ipso substitution[20] at position 8 of **2** and subsequent elimination of methanol leading to formation of **4**. The high selectivity of reactive intermediates formed by reaction of hydrogen peroxide with iron(III)porphyrins (**1a**, **1b**) for epoxidation of olefins and perhalogenated iron(III)porphyrins (**1c**, **1d**) for hydroxylation of hydrocarbons may be used in the selective oxidation of organic substrates in different reaction conditions.

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14) 6-Formyl-7-hydroxy-8-methoxycoumarin (**3**), mp 193 °C (lit.[17] mp 194—195 °C); UV ($CHCl_3$, λ_{max}, rel. abs.): 277 (1.5), 310 (sh, 0.8), 361 (0.75) and 421 (0.6) nm; IR (KBr) ν_{max}: 1727, 1659, 1622 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 11.30 (s, 1H, 7-OH), 9.89 (s, 1H, 6-CHO), 7.64 (d, 1H, H-3), 7.45 (s, 1H, H-5), 6.32 (d, 1H, H-4), 4.30 (s, 3H, $-OCH_3$); ^{13}C-NMR ($CDCl_3$) δ ppm: 195 (CHO), 159.3 (C-2), 157.5 (C-7), 152.7 (C-6), 143.2 (C-4), 135.7 (C-8), 128.3 (C-4), 118.8 (C-4a), 114.9 (C-3), 113.3 (C-5), 61.8 (OCH_3); EI-MS *m*/*z*: 220 (M^+), 205 (M^+-CH_3), 192 (M^+-CO), 177 (205−CO), 164 (192−CO), 149 (177−CO).
15) 5,8-Dioxopsoralen (**4**), mp 254 °C (lit.[22,23] mp 255 °C); UV-visible (EtOH) λ_{max}: 275 and 312 nm; IR (KBr) ν_{max}: 1740, 1710, 1680, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, δ ppm) 7.92 (d, 1H, *J*=10 Hz), 7.76 (d, 1H, *J*=2.5 Hz), 6.90 (d, 1H, *J*=2.5 Hz), 6.57 (d, 1H, *J*=10 Hz); EI-MS *m*/*z* (%): 216 (M^+, 42), 188 (65), 160 (100), 130 (38),104 (70).
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