Biomimetic Oxidation of Curcumin with Hydrogen Peroxide Catalyzed by 5,10,15,20-Tetraarylporphyrinato-iron(III) Chlorides in Dichloromethane

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The biomimetic oxidation of curcumin, a main turmeric pigment with hydrogen peroxide catalyzed by different 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides [TAPFe(III)Cl] in dichloromethane has been studied to give a C–C coupled curcumin dimer in 40—70% yield. The structure of the dimer has been elucidated by 1H-, 13C-NMR, IR and FAB-Mass spectroscopic data.

Key words biomimetic oxidation; curcumin; 5,10,15,20-tetraarylporphyrinatoiron(III) chloride; hydrogen peroxide; curcumin dimer

Curcumin [(E,E)-1,7-bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione] (1a) is the main phenolic pigment extracted from turmeric, the powdered rhizome of Curcuma longa along with demethoxy curcumin and bisdemethoxy curcumin.1 It has been shown to possess potent antioxidant,2 anti-inflammatory,3 anti-tumor,4 anti-carcinogenic5 and anti-HIV properties.6 It also inhibits lipid peroxidation and scavenges superoxide anion, singlet oxygen, nitric oxide and hydroxyl radicals.7 Curcumin mainly undergoes reductive biotransformations to give tetrahydrocurcumin, hexahydrocurcumin and their glucuronides whereas the in vivo oxidative transformations have not been reported.8 However degradation products such as vanillin, ferulic acid, feruloylmethane and trans-6-(4'-hydroxy-3'-methoxy-phenyl)-2,4-dioxo-5-hexenal have been reported under in vitro oxidative conditions.9 Cytochrome P450 related monooxygenases are responsible for the oxygenative and oxidative metabolites of different endogenous and exogenous organic compounds.10 The reaction of 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides with monooxygen donors form high-valent iron-oxo intermediates which mimic the various reactions of cytochrome P450 enzyme systems in the oxygenation and oxidation of various drugs and other biologically active compounds.11–14 Herein, we report the biomimetic oxidation of 1a with hydrogen peroxide catalyzed by different 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides [TAPFe(III)Cl] (5a—c) in dichloromethane to understand the mechanism of oxidative transformations of curcumin and related compounds and their role as antioxidant in biological systems.

1a has been isolated from the powdered rhizomes of Curcuma longa by extraction with dichloromethane and repetitive chromatography on silica gel and preparative TLC following the literature procedure.15 In a typical run hydrogen peroxide (30% v/v, 2.0 mmol) is added to a mixture of 1a (1.0 mmol) and 5,10,15,20-tetrakis(2'-6'-dichlorophenyl)porphyrinatoiron(III) chloride [Cl5(TPFP)Fe(III)Cl] (5b) (0.01 mmol) in dichloromethane (20.0 ml). The reaction mixture is stirred under nitrogen atmosphere at room temperature for 3 h. A yellow coloured compound separates out which is filtered off from the reaction mixture and is washed with dichloromethane (2x10 ml). The physical and spectroscopic data suggests that the solid compound is a C–C coupled curcumin dimer (2).16

The dimer (2) is insoluble in most of the common organic solvents, but is soluble in dimethyl sulfoxide (DMSO). The FAB-MS of compound 2 shows the molecular ion peak at 734 (M+) corresponding to the molecular formula C42O12H38 confirming it to be a curcumin dimer. The peak at 391 (monomer+Na+) shows that it is a symmetrical dimer formed from coupling of two units of curcumin C-radicals. The 1H-NMR spectrum of 2 shows two doublets at δ 7.39 and δ 7.12 (J=15 Hz), suggesting the presence of a CH=CH–C=O group. Further, two singlets are observed at δ 5.36 and 5.83 for two enol olefin protons indicating that the linkage is not through the methine carbons. The signals between 6.76—7.05 have been integrated for the remaining twelve aromatic protons. Two peaks at 91.00 and 101.84 have been assigned to two enolate carbon atoms of the two units of curcumin dimer in its 13C-NMR spectrum.

The HPLC analysis of the filtrate shows the presence of vanillin (3a) and ferulic acid (4a) in 2.8 and 1.9% yields, respectively, by comparison of their HPLC retention time with that of authentic samples.

The dimer formation of 1a with H2O2 in the absence of 5a—c has not been observed even after stirring for 24 h. The yield of 2 increases to 70% in the reaction of 1a with H2O2 catalyzed by 5b in the presence of acetylacetone (acac). This type of increase in the yield of the polymer in the presence of acetylacetone has been reported during the polymerization of acrylamide and vinyl monomer by HRP and hydrogen peroxide.16 Further, no oxidative product is observed in the presence of 2,4,6-tri-tert-butyl phenol (BPH) even after stirring the reaction mixture for 24 h, indicating that the oxidation of curcumin with H2O2 catalyzed by 5b in CH2Cl2 has been quenched. The reaction of dimethoxycurumin (1b) with 5b and H2O2 in dichloromethane gives degradation products, 3,4-dimethoxybenzaldehyde (3b) and 3,4-dimethoxycinnamic acid (4b) in 3.7 and 2.5%, yields, respectively and no dimer formation is observed (Table 1). These reactions suggest that the driving force for the dimer formation and progress of the reaction is the presence of phenolic hydrogen atom at the para position. The mechanism of the formation of dimer is believed to proceed by the abstraction of phenolic hydrogen atom by iron-oxo cation radical intermediate to give curcumin O-radical, which tautomerizes to give curcumin C-radicals having a quinone methide structure. The combination of curcumin C-radicals may give C–C coupled dimer (2). However, the reaction of 1a with AIBN has been reported to give dimers with dihydrofuran moiety along with degradative products such as vanillin and ferulic acid.17,18 Recently, it has also been shown that soyabean lipooxygenase L1 catalyzes the oxygenation of 1a to give an unusual dioxygen inserted product.19

The formation of curcumin radicals and quinone methide type intermediate in the dimer formation is further supported by the UV-visible studies. The addition of hydrogen peroxide to the mixture of porphyrin 5b and 1a in dichloromethane in

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a UV-cuvette results in decrease in the absorption at 419 nm and increase in the absorption at 504 nm with respect to time. Similar spectral changes have been observed with ceric ammonium nitrate and 1a. This type of hydrogen abstraction from phenolic compounds and subsequent quinone methide intermediate formation with ceric ammonium nitrate has also been reported.20 It is noteworthy to mention that the phenolic hydrogen atom is necessary for the dimerization and no dimer formation is observed when phenolic hydrogen is absent.

In conclusion, the oxidation of 1a with hydrogen peroxide catalyzed by 5,10,15,20-Tetraarylporphyrinatoiron(III) chlorides ([TAPFe(III)Cl] (5a—c) under N2 Atmosphere gives C–C coupled dimer and degradation products. Thus these model systems may be useful to understand the mechanism of oxidative biotransformation of curcumin and C–C bond formation in synthetic organic chemistry.

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References and Notes
6) Li C. J., Zhang L. J., Dezube, B. J., Crumpacker C. S., Pardee A. B.,

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Table 1. Biomimetic Oxidation of 1a—b with H2O2 Catalyzed by 5,10,15,20-Tetraarylporphyrinatoiron(III) Chlorides [TAPFe(III)Cl] (5a—c) under N2 Atmosphere

<table>
<thead>
<tr>
<th>Run</th>
<th>System</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a/H2O2</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>1a/TPPFe(III)Cl/H2O2</td>
<td>4</td>
<td>40.0</td>
</tr>
<tr>
<td>3</td>
<td>1a/Cl8TPPFe(III)Cl/H2O2</td>
<td>3</td>
<td>54.0</td>
</tr>
<tr>
<td>4</td>
<td>1a/Cl8TPPFe(III)Cl/H2O2</td>
<td>3</td>
<td>61.0</td>
</tr>
<tr>
<td>5</td>
<td>1a/Cl8TPPFe(III)Cl/acac/H2O2</td>
<td>2.5</td>
<td>70.0</td>
</tr>
<tr>
<td>6</td>
<td>1a/Cl8TPPFe(III)Cl/BPH/H2O2</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
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<td>1b/H2O2</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>1b/TPPFe(III)Cl/H2O2</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>1b/Cl8TPPFe(III)Cl/H2O2</td>
<td>24</td>
<td>—</td>
</tr>
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a) Substrate : oxidant : catalyst = 100 : 200 : 1. b) Based on substrate and isolated yields. c) acac : Cl8TPPFe(III)Cl = 10 : 1. d) BPH : Cl8TPPFe(III)Cl = 0.5 : 1.0.
9) Physical and spectroscopic data of C–C coupled curcumin dimer (2): 1H-NMR (300 MHz, DMSO-d6/TMS): δ 3.69 (s, 2OCH3), 3.84 (s, 2OCH3), 5.36 (s, 4H), 6.76 (d, *J* = 15 Hz, 1 and 1H), 7.39 (d, *J* = 15 Hz, 1 and 1H), 7.42 (s, 7H), 7.59 (s, 7H), 9.08 (s, 2H, D2O exchangeable), 9.37 (s, 2H, D2O exchangeable); 13C-NMR (300 MHz, DMSO-d6/TMS): δ 187.06 (C-3, 3), 168.71 (C-5, 5), 150.04 (C-4’, 4’, 4”, 4”), 148.82 (C-3’, 3”), 148.36 (C-3”, 3”), 141.83 (C-1, 1”, 7”), 129.74 (C-1’, 1’”), 127.31 (C-1”, 1””, C-6, 6”), 125.01 (C-6’, 6”), 123.88 (C-6’, 6”), 120.14 (C-2, 2”), 116.49 (C-2’, 2”), 111.52 (C-2”, 2”), 111.32 (C-5’, 5’, 5”, 5”), 101.84 (C-4”), 91.00 (C-4), 56.70 (C-3” and 3””), 56.42 (C-3’ and 3’” OCH3); IR (KBr, cm−1): 3476, 1618, 1594, 1517, 1429, 1270; FAB-MS (m/z): 734 (M+), 391 (M+ − 368 + Na+), 220, 191, 178, 149.