Biomimetic Oxidation of Curcumin with Hydrogen Peroxide Catalyzed by 5,10,15,20-Tetraarylporphyrinatoiron(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 ^{1}H-, ^{13}C-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-carcinogenic[5)] and anti-HIV properties.[6)] It also inhibits lipid peroxidation and scavenges superoxide anion, singlet oxygen, nitric oxide and hydroxyl radicals.[7,8)] Curcumin mainly undergoes reductive biotransformations to give tetrahydrocurcumin, hexahydrocurcumin and their glucuronides whereas the *in vivo* oxidative transformations have not been reported.[9)] However degradation products such as vanillin, ferulic acid, feruloylmethane and *trans*-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal have been reported under *in vitro* oxidative conditions.[10)] Cytochrome P450 related monooxygenases are responsible for the oxygenative and oxidative metabolites of different endogenous and exogenous organic compounds.[11)] 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.[12—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.[1)] 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 [Cl_8TPPFe(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 (2×10 ml). The physical and spectroscopic data suggests that the solid compound is a C–C coupled curcumin dimer (**2**).[15)]

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 $C_{42}O_{12}H_{38}$ 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 ^{1}H-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 ^{13}C-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 H_2O_2 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 H_2O_2 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 H_2O_2-**5b** in CH_2Cl_2 has been quenched. The reaction of dimethoxy curcumin (**1b**) with **5b** and H_2O_2 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 lipoxygenase 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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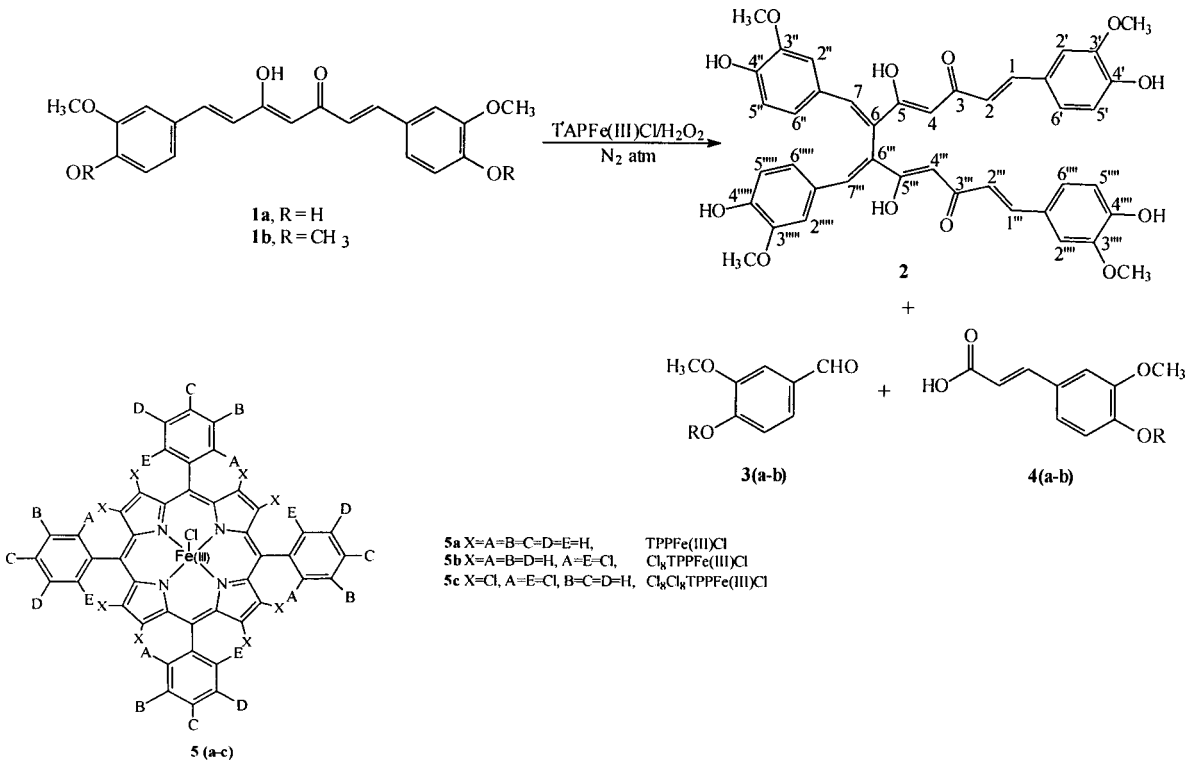

Chart 1

Table 1. Biomimetic Oxidation of **1a**—**b** with H_2O_2 Catalyzed by 5,10,15,20-Tetraarylporphyrinatoiron(III) Chlorides [TAPFe(III)Cl] (**5a**—**c**) under N_2 Atmosphere[a)]

Run	System	Time (h)	Yield (%)		
			2[b)]	**3(a—b)**	**4(a—b)**
1	**1a**/H_2O_2	24	—	—	—
2	**1a**/TPPFe(III)Cl/H_2O_2	4	40.0	1.9	1.2
3	**1a**/Cl_8TPPFe(III)Cl/H_2O_2	3	54.0	2.8	1.9
4	**1a**/Cl_8Cl_8TPPFe(III)Cl/H_2O_2	3	61.0	2.9	1.7
5	**1a**/Cl_8TPPFe(III)Cl/acac/H_2O_2[c)]	2.5	70.0	3.3	2.1
6	**1a**/Cl_8TPPFe(III)Cl/BPH/H_2O_2[d)]	24	—	—	—
7	**1b**/H_2O_2	24	—	—	—
8	**1b**/TPPFe(III)Cl/H_2O_2	24	—	3.2	2.3
9	**1b**/Cl_8TPPFe(III)Cl/H_2O_2	24	—	3.7	2.5

a) Substrate : oxidant : catalyst = 100 : 200 : 1. *b*) Based on substrate and isolated yields. *c*) acac : Cl_8TPPFe(III)Cl = 10 : 1. *d*) BPH : Cl_8TPPFe(III)Cl = 0.5 : 1.0.

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 (**5a**—**c**) as cytochrome P450 model systems under nitrogen 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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15) Physical and spectroscopic data of C–C coupled curcumin dimer (**2**): ^{1}H-NMR (300 MHz, DMSO-d_6/TMS): δ 3.69 (s, 2×OCH_3), 3.84 (s, 2×OCH_3), 5.36 (s, 4‴H), 5.83 (s, 4H), 6.76 (d, J=8 Hz, 5′, 5″, 5‴, 5⁗), 7.03 (s, 2′, 2″, 2‴, 2⁗), 7.05 (d, J=8 Hz, 6′, 6″, 6‴, 6⁗), 7.12 (d, J=15 Hz, 2 and 2‴H), 7.39 (d, J=15 Hz, 1 and 1‴H), 7.42 (s, 7H), 7.59 (s, 7‴H), 9.08 (s, 2H, D_2O exchangeable), 9.37 (s, 2H, D_2O exchangeable); ^{13}C-NMR (300 MHz, DMSO-d_6/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‴,7,7‴), 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⁗ OCH_3) and 56.42 (C-3′ and 3‴ OCH_3); IR (KBr, cm^{-1}): 3476, 1618, 1594, 1517, 1429, 1270; FAB-MS (m/z): 734 (M^+), 391 ($M^+-368+Na^+$), 220, 191, 178, 149.
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