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Biomimetic oxidation of metribuzin with hydrogen peroxide catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides☆

Shive M. S. Chauhan* and Pratibha Kumari

Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi, India

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Abstract—The biomimetic oxidation of metribuzin, a pre- and post-emergence herbicide with hydrogen peroxide catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides [TAPFe(III)Cl], has been studied yielding 6-*t*-butyl-3-methylthio-1,2,4-triazine-5(4*H*)-one, 4-amino-6-*t*-butyl-3,5(2*H*,4*H*)-dione and 6-*t*-butyl-1,2,4-triazin-3,5(2*H*,4*H*)-dione under various reaction conditions.

Metribuzin, 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4*H*)-one (**1**), is a potent pre- and post-emergence herbicide widely used to remove a variety of broadleaf and grass weeds from potato, soyabean, tomato, sugar cane and other tolerant crops.[1] In herbicide-resistant plants,[1,2] soil[3] and animals,[4,5] metribuzin mainly undergoes oxidative biotransformation to give 6-*t*-butyl-3-methylthio-1,2,4-triazine-5(4*H*)-one (**2**), 4-amino-6-*t*-butyl-1,2,4-triazin-3,5(2*H*,4*H*)-dione (**3**), 6-*t*-butyl-1,2,4-triazin-3,5(2*H*,4*H*)-dione (**4**) and the sulfoxide of 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4*H*)-one (**5**) (Scheme 1). However, little is known about its in vitro oxidative degradation.[6,7]

Cytochrome P450 monooxygenases are haemoproteins present in microorganisms, plants and animals which metabolize many drugs, pollutants, chemical carcinogens and other xenobiotics.[8,9] Many synthetic chemical models of cytochrome P450 have been developed by the reaction of different iron(III) or manganese(III) porphyrins with various monooxygen donors to investigate the mechanism of metabolism as well as to isolate the metabolites and reactive intermediates in sufficient amounts for further biological studies.[10–13] In particular, the reactions of metalloporphyrins with hydrogen peroxide have attracted much attention as hydrogen peroxide is a biologically important and environmentally clean oxidant, leading to the formation of only water as the side product. Although biomimetic oxidative transformations of many drugs have been examined using chemical models of cytochrome P450 enzymes,[14,15] similar studies of agrochemicals with monooxygen donors catalyzed by iron(III)porphyrins are limited.[16–18] Herein, we report the biomimetic oxidation of **1** with hydrogen peroxide catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides [TAPFe(III)Cl], in dichloromethane, under various reaction conditions to mimic the reactions of natural cytochrome P450 enzymes.

The oxidation of **1** with hydrogen peroxide in the absence of 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides (**6a**–**d**) (Fig. 1) did not give any product even after stirring the reaction mixture for 24 h at room temperature under a nitrogen atmosphere. The oxidation of **1** (1 mmol) with H_2O_2 (2 mmol, 30%) catalyzed by **6a** (0.01 mmol) in dichloromethane gave three main products, **2**, **3** and **4** in 3%, 11% and 2% yields (Scheme 1, Table 1, entry 2), respectively. The yields of the oxidative products were improved substantially using iron(III)

Keywords: Metribuzin; Biomimetic oxidation; Metalloporphyrin; Hydrogen peroxide; Herbicide.

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* Corresponding author. Tel./fax: +91 11 27666845; e-mail: smschauhan@chemistry.du.ac.in

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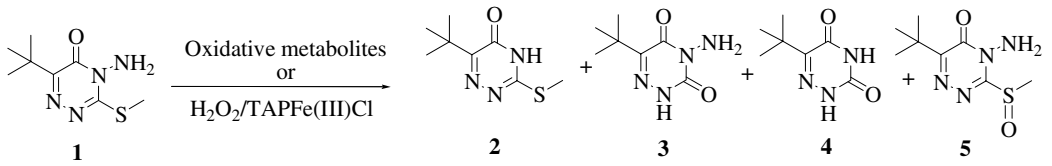


Scheme 1.

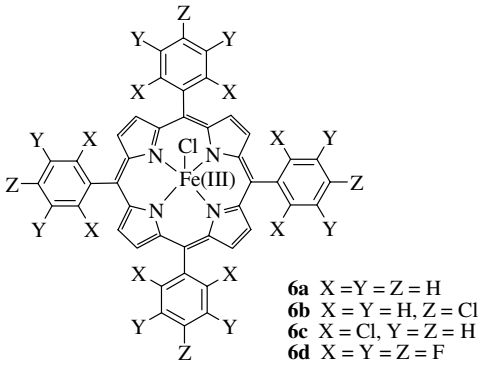


Figure 1.

porphyrins bearing electron-withdrawing groups on the phenyl ring (**6b–d**) as catalysts, implying their reduced oxidative degradations by hydrogen peroxide.[19,20] The oxidation of **1** with H_2O_2 catalyzed by **6d** gave triazines **2**, **3** and **4** in 9%, 24% and 4% yields, respectively, after 3 h whereas intermediate **5** was isolated in 30% yield after 25 min (Table 1, entries 5 and 6). The structures of the products were identified from spectroscopic data. A strong band at 1050 cm^{-1} in the IR spectrum of **5** was assigned to S=O stretching. The appearance of $[M+H]^+$ and $[M+Na]^+$ peaks at *m/z* 231 and 253 further indicated the formation of **5** as an intermediate in the above reaction. The partial decomposition of **5** to **3** was observed within 24 h either neat or in dichloromethane.

The oxidation of **1** with 1 equiv of H_2O_2 catalyzed by **6d** gave deaminated product **2** in 10% yield after 10 min but **5** was the major product (22% yield) in the reaction within 25 min (Table 1, entries 7 and 8). On prolonging the reaction for 4 h, the yield of **3** increased to 20% at the expense of **5**, no trace of **5** was detected by HPLC and TLC analysis of the reaction mixture (Table 1, entry 9). Similar results were obtained using other iron(III) porphyrins (**6a–c**) in oxidation reactions of **1** under similar conditions. Further, the presence of a strongly coordinating axial ligand such as *N*-methylimidazole (NMI) in the reaction of **1** with H_2O_2 catalyzed by **6d** enhanced the yield of the oxidative products (Table 1, entry 10). An increase in the amount of H_2O_2 from 1 equiv to 3 equiv reduced the reaction time and increased the yield of oxidative products; in particular, **5** was rapidly converted to **3**, which was the major final product. More-

Table 1. Biomimetic oxidation of **1** with H_2O_2 catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides (**6a–d**) under different conditions

Entry	System[a]	Time	Conversion[b] (%)	% Yields[b]			
				2 (4.3)[c]	**3** (3.4)[c]	**4** (2.3)[c]	**5**[d]
1	**1**/H_2O_2	24 h	0	0	0	0	0
2	**1**/**6a**/H_2O_2	5 h	19	3	11	2	0
3	**1**/**6b**/H_2O_2	4 h	25	5	15	2	0
4	**1**/**6c**/H_2O_2	3 h	34	7	20	4	0
5	**1**/**6d**/H_2O_2	3 h	47	11 (9)[d]	26 (24)[d]	6 (4)[d]	0
6	**1**/**6d**/H_2O_2	25 min	45	12	3	0	30
7	**1**/**6d**/H_2O_2[e]	10 min	13	10	0	0	Trace
8	**1**/**6d**/H_2O_2[e]	25 min	34	10	Trace	0	22
9	**1**/**6d**/H_2O_2[e]	4 h	32	9	20	Trace	0
10	**1**/**6d**/H_2O_2/NMI[e,f]	3 h	40	12	25	Trace	0
11	**2**/**6d**/H_2O_2[e,g]	3 h	32	68	—	10	—
12	**3**/**6d**/H_2O_2[e,h]	3 h	12	—	88	8	—
13	**1**/**6d**/H_2O_2[i]	2 h	56	14	30	10	0
14	**1**/**6d**/H_2O_2[e,j]	5 min	58	12	10	0	35
15	**1**/**6d**/H_2O_2[e,j]	1 h	62	14	24	22	0
16	**1**/**6d**/H_2O_2[e,k]	3 h	34	10	22	Trace	0

[a] Substrate/H_2O_2/catalyst = 100:200:1.
[b] Based on HPLC analysis.
[c] HPLC retention time of products.
[d] Isolated yields.
[e] Substrate/H_2O_2/catalyst = 100:100:1.
[f] Substrate/H_2O_2/catalyst/NMI = 100:200:1:10.
[g] The sulfoxide of **2** was observed as the major product (16% yield) along with one minor unidentified product.
[h] One minor unidentified product was also observed.
[i] Substrate/H_2O_2/catalyst = 100:300:1.
[j] Reaction was performed in dry methanol.
[k] Reaction was performed in acetonitrile.

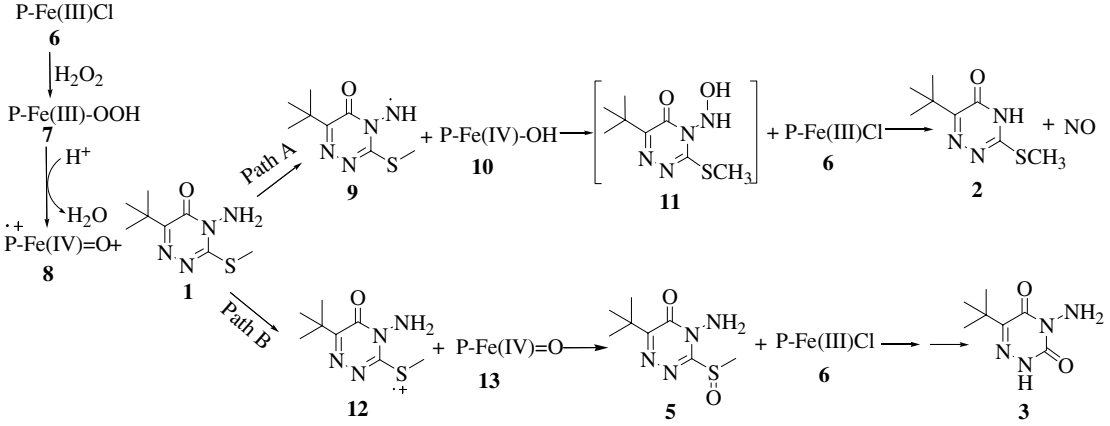
over, the yield of **4** was also greatly affected by the amount of H_2O_2 in the reaction. Further, the oxidative transformation of **1** was faster in methanol than in dichloromethane and acetonitrile under similar reaction conditions (Table 1, entries 14 and 15).

Products **2** and **3** were also synthesized by chemical methods[5] and oxidized with H_2O_2 using **6d** as catalyst in dichloromethane to give **4** in 10% and 8% yields, respectively (Table 1, entries 11 and 12). It was observed that the sulfoxide of **2**, identified by comparing the retention time with an authentic sample prepared using the literature method,[5] was formed in 25% yield in the oxidation reaction of **2** after 30 min, which on further oxidation gave **4** in a minor amount and the sulfoxide of **2** (16%) remained in the reaction after 3 h (Table 1, entry 11). This implied the relative stability of the sulfoxide of **2** under the reaction conditions but its oxidative transformation to **4** became more prevalent on increasing the amount of H_2O_2 from 1 equiv to 2 equiv (results not shown). However, the formation of the sulfoxide of **2** was not detected as a product in the oxidation of **1** with H_2O_2 catalyzed by iron(III) porphyrins (**6a**–**d**) as insufficient **2** was formed and its subsequent oxidation was slow. It is noteworthy that the N-deamination reaction of **3** as well as the oxidative demethylthiolation of **2** with H_2O_2 catalyzed by iron(III) porphyrins (**6a**–**d**) resulted in lower yields of product in longer reaction times compared to similar reactions of **1**.

In metalloporphyrin catalyzed oxidation reactions, similar to cytochrome P450 catalyzed metabolic reactions in biological systems,[21,22] various electrophilic and nucleophilic catalytic intermediate species such as ferric peroxy anions (Fe^{III}–OO^-), a ferric hydroperoxy complex (Fe^{III}–OOH) and oxoferrylporphyrin π-cation radicals (Fe^{IV}=$O^{\cdot+}$) have been postulated.[23–28] The UV–vis spectrum of **6d**, on addition of hydrogen peroxide, showed a decrease in the absorption at 412 nm (Soret band), indicating the formation of high valent oxoiron(IV) radical cations (**8**) (like compound **I** of cytochrome P450) (Scheme 2) during the reaction.[24] The presence of NMI in the solution of **6d** caused a large decrease in the Soret band intensity on addition of H_2O_2, which supports the formation of products in good yields and short reaction times due to favouring conditions for formation of complex **8**.[24] The high yields of products with catalysts bearing electron-withdrawing groups (**6b**–**d**) could be attributed to the generation of the more electrophilic and reactive intermediate **8** in the reaction, which showed greater selectivity towards sulfur than the nitrogen and carbon in **1**.

The reaction of hydrogen peroxide with TAPFe(III)Cl (**6**) gave intermediate **8**, which reacted with **1** to form N-deaminated product **2**, whereas the reactions of alkyl or arylalkylhydrazines are known to yield carbon hydroxylated products.[29,30] The mechanism of N-deamination is believed to proceed by abstraction of hydrogen from the $-NH_2$ group by **8** to give amino N-radical (**9**) (Scheme 2, Path A). The resulting radical **9** is trapped by activated oxygen (from iron-hydroxo complex **10**) and subsequent decomposition of the resulting N-hydroxylated product (**11**) gives **2**. A similar oxidative N–N cleavage has been proposed for the oxidation of **1** with *tert*-butylhydroperoxide catalyzed by cobalt(II) salen in dichloromethane.[6] The formation of **3** may be explained by the transfer of oxygen from **8** to **1**, leading to the formation of **5** which on *ipso* substitution followed by elimination of $-S(O)CH_3$ gives **3** in high yield (Scheme 2, Path B). This is in accordance with the reported sulfoxidation of sulfur compounds[31,32] and *ipso* substitution followed by elimination in some organic species with iron-oxo intermediate **8**.[11] Similarly, N-deamination of **3** and oxidative demethylthiolation of **2** via overoxidation of the sulfoxide of **2** by intermediate **8** gave the terminal oxidized product **4**.

In conclusion, the oxidation of **1** with H_2O_2 catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides (**6a**–**d**) provides a suitable chemical model of natural cytochrome P450 enzymes and gives products very similar to its in vivo metabolites. Metalloporphyrins bearing electron-withdrawing substituents on the phenyl ring give good yields of oxidized products and help in the identification of metabolically susceptible functional groups in **1**. Therefore, the chemical model system consisting of iron(III) porphyrin and H_2O_2 may be useful to understand the molecular mechanisms of cytochrome P450 catalyzed metabolic reactions of **1** and to isolate



Scheme 2. Proposed mechanism for the oxidation of **1** using H_2O_2 and **6a**–**d**.

any unstable metabolites for further biological evaluation under mild and environmentally benign conditions.

Oxidation of metribuzin (**1**) *with hydrogen peroxide catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides* (**6a–d**) *in dichloromethane*: Metribuzin (**1**) (1 mmol) and a catalytic amount of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrinatoiron(III) chloride (**6d**) (0.01 mmol) in dichloromethane (15 mL) was stirred under a nitrogen atmosphere. To this, hydrogen peroxide solution (2 mmol, 30%) was added. The progress of the reaction was monitored by TLC and HPLC analyses. After the reaction, the solvent was removed under reduced pressure and the oxidative products were separated by column chromatography over neutral alumina. Elution of the column with chloroform/methanol (99:1, v/v) gave triazines **2**, **3** and **4**. Intermediate **5** was isolated by preparative TLC (solvent system: chloroform/ethyl acetate 1:1, v/v) after 25 min of reaction.

Data for **2**: mp 199–200 °C; UV–vis: λ_{max} (CH_2Cl_2)/nm 236 (1.47); IR (KBR): ν_{max}/cm^{-1} 3450, 2970, 2929, 2766, 1615, 1583, 1517, 1449, 1384, 1357, 1193, 590; ^1H NMR: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.35 (s, 9H, $-C(CH_3)_3$), 2.55 (s, 3H, $-SCH_3$); EI-MS: *m*/*z* 199 (M^+), 198, 181, 171, 144, 116, 85, 71, 57, 43.

Data for **3**: mp 167–168 °C; UV–vis: λ_{max} (CH_2Cl_2)/nm 258 (0.95); IR (KBR): ν_{max}/cm^{-1} 3326, 3232, 2957, 2927, 1721, 1661, 1550, 1453, 1248, 1144, 909, 736, 669; ^1H NMR: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.33 (s, 9H, $-C(CH_3)_3$), 5.25 (s, 3H, $-SCH_3$); EI-MS: *m*/*z* 184 (M^+), 183, 167, 152, 141, 114, 83, 69, 57, 41.

Data for **4**: sublimed 260–264 °C; IR (KBR): ν_{max}/cm^{-1} 3325, 2922, 1721, 1664, 1551, 1452, 909; ^1H NMR: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.34 (s, 9H, $-C(CH_3)_3$); EI-MS: *m*/*z* 169 (M^+), 168, 153, 141, 85, 71, 57, 43.

Data for **5**: UV–vis: λ_{max} (CH_2Cl_2)/nm 231 (1.74), 274 (1.73); IR (film): ν_{max}/cm^{-1} 3301, 3242, 3182, 1672, 1558, 1541, 1461, 1363, 1247, 1187, 1050, 967, 720; ^1H NMR: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49 (s, 9H, $-C(CH_3)_3$), 3.25 (s, 3H, $-S(O)CH_3$), 5.91 (s, 2H, NH_2); ESI-MS: *m*/*z* 231 $[M+H]^+$, 253 $[M+Na]^+$.

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