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OXIDATIVE DECARBOXYLATION OF CARBOXYLIC ACIDS BY IRON PORPHYRIN - IODOSYLBENZENE SYSTEM[1)]

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Abstract: An iodosylbenzene - iron tetraarylporphyrin catalyst system decarboxylated α-aryl carboxylic acids and α,α,α-trisubstituted acetic acids efficiently to give the corresponding alcohol and carbonyl derivatives.

Metalloporphyrins, especially Fe(III) and Mn(III) complexes, have been revealed to work well as catalysts for the oxidation of a wide variety of compounds which are typical substrates for cytochrome P-450[2)]. These complexes can therefore be used as the chemical models of P-450 enzymes for the investigation of drug metabolism[3)].

In this communication, we report that an iodosylbenzene - iron *meso*-tetraarylporphyrin catalyst system[4)] readily decarboxylates carboxylic acids oxidatively to afford mainly the alcohols and carbonyl compounds. As far as we know, this type of reaction is novel in oxidation systems catalyzed by metalloporphyrins. The oxidation of α-(*p*-isobutylphenyl)propionic acid (Ibuprofen) ($\mathbf{I_c}$) with the system provides a typical procedure of the reaction. To a solution of the carboxylic acid (206 mg) and *meso*-tetrakis(pentafluorophenyl)porphyrin iron chloride (Fe^{III}(TPFPP)Cl)[5)] (5 mg, 0.5 mol%) in 10 ml dichloromethane was added iodosylbenzene (PhIO) (440 mg, 2 equiv.) and the mixture was stirred for 20 h at r.t. under argon atmosphere. After completion of the reaction, the products were isolated by silica gel column chromatography to give 1-(*p*-isobutylphenyl)ethanol ($\mathbf{II_c}$)[6)] (91 mg, y. 51.3 %) and *p*-isobutylphenyl methyl ketone ($\mathbf{III_c}$)[6)] (36 mg, y. 20.3 %).

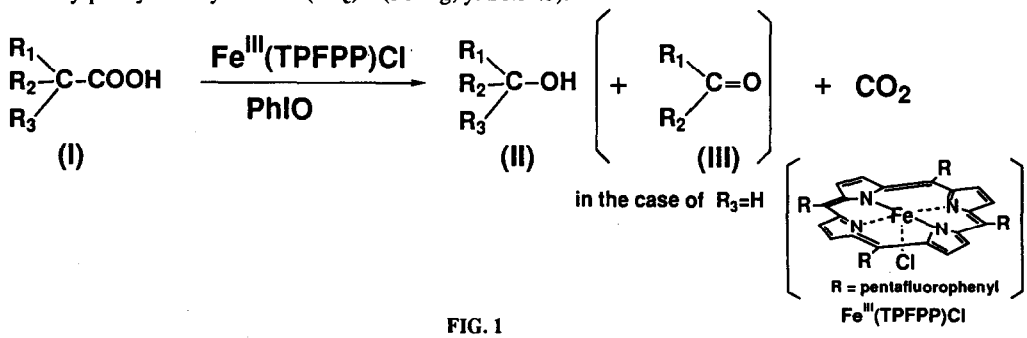
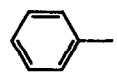
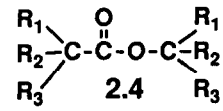
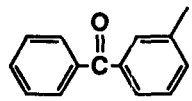
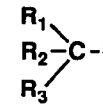
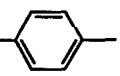
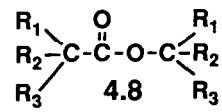
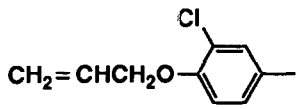
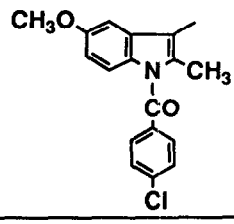
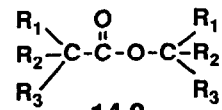
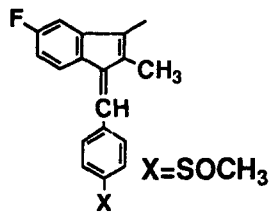
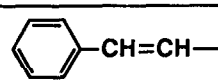
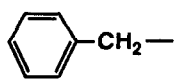
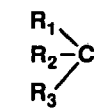
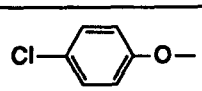
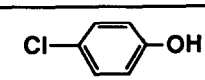


FIG. 1

Table 1. Oxidation products of carboxylic acids by Fe^{III}(TPFPP)Cl / PhIO System

				Isolated Yield (%)		
	R_1	R_2	R_3	(II)	(III)	Other
I_a		CH_3	H	45.6	3.4	 2.4
I_b		CH_3	H	48.2	25.7	 12.5
I_c	$(CH_3)_2CHCH_2$— 	CH_3	H	51.3	20.3	 4.8
I_d		H	H	51.9	24.3	R_1COOH 5.0
I_e		H	H	8.5	7.6	 14.2
I_f		H	H	30.4 (X=SO_2CH_3) 22.3 (X=$SOCH_3$)	6.3 5.2	R_1COOH 1.2
I_g		H	H	31.8		
I_h		CH_3	CH_3	9.2		 18.1
I_i		CH_3	CH_3			 29.5

Condition : [Substrate]=100 mM,[PhIO]=200 mM,[Fe^{III}(TPFPP)Cl]=0.5 mM in CH_2Cl_2
The mixture was stirred at r.t. for 20 h under Ar.

Table 1 shows the some results for the oxidative decarboxylation. The carboxylic acids of which α-carbon atoms are attached to aryl or alkenyl groups ($\mathbf{I_{a\sim g}}$) or α,α,α-trisubstituted acetic acids ($\mathbf{I_h}$ and $\mathbf{I_i}$) exhibited good reactivity in the system. However, α-mono or α,α-di-substituted acetic acid with no aryl group at its α position was inert under the reaction conditions (*e.g.*: lauric acid or 3-heptanoic acid). Methyl ester of Ketoprofen ($\mathbf{I_b}$) was also stable in this system though $\mathbf{I_b}$ itself was labile. Therefore, a free carboxyl group is necessary for progress of the reaction. The iron porphyrin / PhIO combination has been well known as an efficient epoxidation system[7]. Nevertheless, the alkenyl group of the acid ($\mathbf{I_d}$) was unaffected with the system while decarboxylation proceeded completely. The alcohols **II** were oxidized to afford the carbonyl products **III** by PhIO without iron porphyrin. The compounds **III** are, therefore, supposed to form partly by direct oxidation of **II** with PhIO. Formation of alkyl chlorides was observed in the case of $\mathbf{I_b}$ and $\mathbf{I_h}$. The products other than **II**, **III**, or alkyl chloride were the esters which can be made by condensation of the starting materials and products **II**. In the case of $\mathbf{I_i}$, the only detectable product was *p*-chlorophenol. The phenol was probably afforded by rapid decomposition of an unstable hemiacetal which was directly formed by the oxidative decarboxylation of $\mathbf{I_i}$. (-)-α-Phenylpropionic acid was converted into α-phenethyl alcohol which was almost completely racemic. Almost no reaction occurred when the iron porphyrin complex was omitted in this system. The oxidation of ketoprofen ($\mathbf{I_b}$) afforded a mixture of the alcohol, ketone and chloro adduct in yields of 1.5, 0.9 and 0.6 %, respectively, when *m*-chloroperoxybenzoic acid was used as oxidant. The formation of carbon dioxide in the oxidation of $\mathbf{I_b}$ with the Fe^{III}(TPFPP)Cl / PhIO system was confirmed by using FT-IR spectroscopy. The spectrum of the reaction mixture displayed a strong absorption at 2337 cm^{-1} due to carbon dioxide[8].

In this study, details of the reaction mechanism have not been clarified. However, the formation of alkyl chlorides is thought to support the generation of the corresponding alkyl radicals as the intermediates because their chlorine atoms must be derived from dichloromethane *via* a radical pathway. Moreover, the result that no alkyl chloride was formed with the oxidation system under O_2, provides evidence for the alkyl radical intermediates which are highly reactive toward O_2. A plausible mechanism can be described as follows. A highly electrophilic intermediate generated by PhIO - Fe porphyrin couple[9] oxidizes the carboxyl group of carboxylic acid to form the carboxyl radical. The radical is so unstable that it is very rapidly decarboxylated to give the carbon radical, and the radical recombines with an OH radical equivalent (HO-Fe^{IV}Por) or abstracts chlorine atom from dichloromethane to afford the products.

Most non-steroidal anti-inflammatory drugs have an α-arylacetic acid or α-arylpropionic acid structure. For example, all of the compounds $\mathbf{I_{b\sim f}}$ are the drugs actually used for anti-inflammation. It is possible that carboxylic acids are metabolized partly *via* an oxidative decarboxylation pathway although such a mode of drug metabolism has not been known yet. Study on this mode of metabolism *in vitro* and *in vivo*[10], and also further investigation into the mechanistic details is now in progress in our laboratory.

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6. Analytical data of $\mathbf{II_e}$: 400MHz ^{1}H-NMR; δ 0.90 (6H, d, J = 6.3 Hz, $(C\underline{H}_3)_2CH$), 1.48 (3H, d, J = 4.85 (1H, q, J = 6.4 Hz, $C\underline{H}(OH)CH_3$), 7.12 (2H, d, J = 8.3 Hz, H_{arom}), 7.26 (2H, d, J = 8.3 Hz, H_{arom}). IR spectra (neat, cm^{-1}); 3440 (OH), 2950, 2920, 2860 (CH); High Resolution Mass spectra (HRMS); Calcd. for $C_{12}H_{18}O$; 178.1357, Found; 178.1362. Analytical data of $\mathbf{III_e}$: 400MHz ^{1}H-NMR; δ 0.91 (6H, d, J = 6.4 Hz, $CH(C\underline{H}_3)_2$), 1.90 (1H, m, $C\underline{H}(CH_3)_2$), 2.54 (2H, d, J = 7.3 Hz, CH_2), 2.59 (3H, s, $CO\text{-}CH_3$), 7.23 (2H, d, J = 8.3 Hz, H_{arom}), 7.88 (2H, d, J = 8.3 Hz, H_{arom}); IR spectra; Mass (neat, cm^{-1}); 2960, 2920, 2870 (CH), 1680 (C=O); HRMS; Calcd. for $C_{12}H_{16}O$; 176.1200, Found; 176.1203. All of the other products, *i.e.*, **II**, **III**, chloro adducts and esters were also characterized by ^{1}H-NMR, IR and HRMS and/or elemental analysis.
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8. This value is in fair agreement with the value of dissolved carbon dioxide in dichloromethane.
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10. Our preliminary study on the metabolism of indomethacin ($\mathbf{I_e}$) indicated that its oxidatively decarboxylated compound (N-(4-chlorobenzoyl)-3-hydroxymethyl-5-methoxyindole) exists in the metabolites obtained by rat liver microsomal system. Details of this new type of metabolism of carboxylic acids will be reported in another paper.

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