Peroxidation of Polyunsaturated Fatty Acids, Initiated by the Direct Interaction between a Cobalt Porphyrin Complex and Polyunsaturated Fatty Acids

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It has been shown that a cobalt porphyrin, CoTPPCl (TPP = tetraphenylporphyrin), can initiate the autoxidative radical-chain peroxidation of polyunsaturated fatty acids and esters (LH: linoleic acid, methyl linoleate, and linolenic acid) in an oxygen-saturated MeCN solution at 333 K by the direct interaction between CoTPPCl and LH, *i.e.*, the one-electron reduction of CoTPPCl by LH, based on independent kinetic studies on the initiation step in deaerated MeCN and the overall $CoTPP^+$-catalysed peroxidation of LH by dioxygen. The $CoTPP^+$ complex can function not only as an initiator but also a catalyst, as demonstrated by independent kinetic studies on the catalyst regeneration step, the oxidation of CoTPP by dioxygen in the presence of LH. In addition, the cobalt(II) porphyrin complex, CoTPP, acts as a radical scavenger by the one-electron reduction of the chain carrier radicals, lipid peroxyl radicals.

There has recently been a renewed interest in the mechanisms of oxidation of polyunsaturated fatty acids and esters (LH) by dioxygen, particularly in biological systems, since lipid peroxidation in biological membranes has been implicated as a cause of 'oxidative stress' such as membrane damage, aging, heart disease and cancer.[1–5] It has well been established that both autoxidative and enzymatic lipid peroxidation occurs by a free-radical mechanism.[6–10] When alkyl radicals ($L^\bullet$) derived from unsaturated fatty acids and esters (LH) are produced, the addition of dioxygen to $L^\bullet$ to give lipid peroxyl radicals ($LOO^\bullet$) occurs efficiently with diffusion-limited rates [equation (1)], and

$$L^\bullet + O_2 \longrightarrow LOO^\bullet \quad (1)$$

the propagation step involves the abstraction of an active methylene hydrogen of LH by $LOO^\bullet$, accompanied by regeneration of $L^\bullet$ [equation (2)].[6–10] These radical species $L^\bullet$

$$LOO^\bullet + LH \longrightarrow LOOH + L^\bullet \quad (2)$$

and $LOO^\bullet$ have been well characterized by e.s.r. spectroscopy.[11,12] Without radical initiators, the initiation step of free-radical generation usually involves the decomposition of lipid hydroperoxides or hydrogen peroxide in the presence of transition-metal ions,[13,14] since free-radical generation by direct interaction between LH and dioxygen is spin-forbidden, and the thermal homolysis of hydroperoxides is known to be extremely slow in the absence of metal ions.[15] However, no initiation step involving a non-enzymatic reaction between LH and metal complexes has so far been studied directly, although such an initiation step between Co^{3+} and linoleic acid has long been implicated.[16] In the case of an enzymatic peroxidation, the reduction of the ferric species in a lipoxygenase by linoleic acid to produce the fatty acid free radicals has been well established.[17,18]

In this study, we report that the reduction of a cobalt porphyrin complex, CoTPPCl (TPP = tetraphenylporphyrin) by unsaturated fatty acids or esters (LH) can initiate the free-radical peroxidation of LH by dioxygen in MeCN by the direct interaction between CoTPPCl and LH. In contrast with ferrous porphyrins which are rapidly and irreversibly oxidized by dioxygen to yield the corresponding μ-oxo dimers,[19] cobalt(II) porphyrins such as CoTPP are stable to dioxygen in MeCN. In the presence of acids, however, CoTPP is known to be readily oxidized by dioxygen to regenerate the cobalt(III) porphyrin, $CoTPP^+$.[20,21] In addition, $CoTPP^+$ is known to be rather inert to hydrogen peroxide.[21] Thus, the $CoTPP^+$/CoTPP redox system may be the best choice among transition-metal complexes with which to study the initiation step, independent of the decomposition of hydroperoxides. Moreover, we can examine independently the initiation step for both the reduction of $CoTPP^+$ by LH and the oxidation of CoTPP by dioxygen in the presence of LH, as well as the overall $CoTPP^+$-catalysed peroxidation of LH, since $CoTPP^+$ (λ_{max} 434 nm) and CoTPP (λ_{max}412 nm) can be readily distinguished from each other by spectroscopic measurements.

Experimental

Materials.—Cobalt(II) tetraphenylporphyrin (CoTPP) was prepared as described in the literature.[22] The CoTPP was oxidized by dioxygen in the presence of HCl in methanol to obtain tetraphenylporphinatocobalt(III) chloride (CoTPPCl),[23] which was purified by recrystallization from ethanol. Pivalic acid, isobutyric acid, valeric acid, and oleic acid were obtained commercially. Linoleic acid, methyl linoleate, and linolenic acid were purchased from Nakarai Chem. Co., 99% grade, free from isomers. The concentrations of hydroperoxides in unsaturated fatty acids or ester before use were confirmed to be $< 1.0 \times 10^{-4}$ mol dm^{-3}. Perchloric acid (70%) and sodium iodide were obtained from Wako Pure Chemicals. Acetonitrile used as a solvent was purified and dried by the standard procedure,[24] and stored on calcium hydride under an atmospheric pressure of nitrogen.

Reaction Procedure.—Typically, a small amount of CoTPPCl (9.6×10^{-8} mol) was added to a square quartz cuvette that contained an oxygen-saturated MeCN solution (2.0 cm^3) of linoleic acid (0.10 mol dm^{-3}), and the cuvette was sealed with a septum under a stream of dioxygen. The cuvette was then immersed in a water bath which was thermostatted at 333 K. The concentration of $CoTPP^+$ during the peroxidation of LH was monitored by means of the absorption band due to $CoTPP^+$ (λ_{max} 434 nm). The electronic absorption spectra were recorded using a Union SM-401 spectrophotometer. The total amount of hydroperoxides formed in the CoTPPCl-catalysed peroxidation was determined by the standard method (titration by iodide ion);[25,26] the diluted MeCN solution (200–1 000 fold)

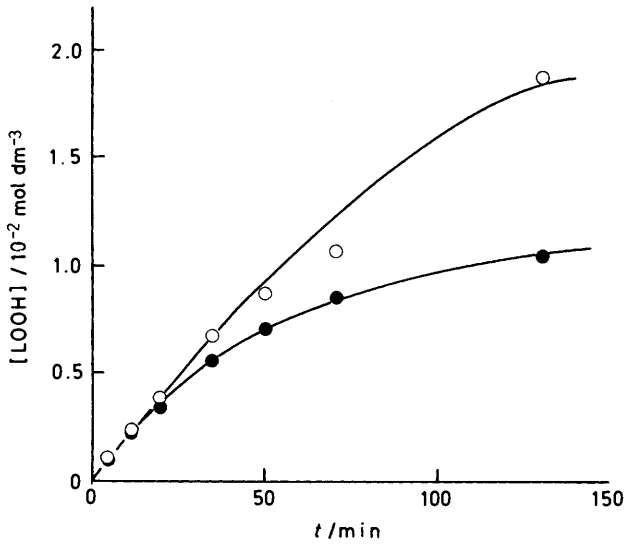


Figure 1. Time dependence of the formation of *total hydroperoxides, i.e.* the sum of conjugated and non-conjugated diene hydroperoxides (○) and conjugated diene hydroperoxides (●), measured by idometry and by the absorption at 233 nm for the peroxidation of linoleic acid (0.10 mol dm^{-3}) in an oxygen-saturated MeCN solution containing CoTPPCl (5.0×10^{-5} mol dm^{-3}) at 333 K, respectively.

Table 1. Rates of the formation of LOOH in the CoTPP$^+$-catalysed peroxidation of fatty acids and ester (LH: 0.10 mol dm^{-3}) in the presence of CoTPPCl (5.0×10^{-5} mol dm^{-3}) in an oxygen-saturated MeCN solution at 333 K.

LH	d[LOOH]/dt[a] /mol dm^{-3} s^{-1}
Isobutyric acid	*b*
Valeric acid	*b*
Pivalic acid	*b*
Crotonic acid	*b*
Oleic acid	*b*
Linoleic acid	2.9×10^{-6}
Methyl linoleate	2.7×10^{-6}
Linolenic acid	4.2×10^{-6}

[a] Determined by iodometry. The experimental errors are within ±5%. [b] $\ll 10^{-8}$ mol dm^{-3} s^{-1}.

of the product mixture was treated with excess amounts of NaI, and the amount of I_3^- formed was determined by the visible spectrum (λ_{max} 361 nm, ε 2.50×10^4 dm^3 mol^{-1} cm^{-1}). The concentration of conjugated diene hydroperoxides was determined from the absorption band at 233 nm. The extinction coefficient [ε = (2.6 ± 0.2) × 10^4 dm^3 mol^{-1} cm^{-1}][27] has been reported to be constant, irrespective of various conjugated diene isomers.

Rates of the reduction of CoTPP$^+$ by LH in deaerated MeCN at 333 K were determined by monitoring the disappearance and rise of the absorption bands at λ_{max} 434 and 412 nm due to the decay of CoTPP$^+$ and the formation of CoTPP, respectively. Rates of oxidation of CoTPP by dioxygen in the presence of LH were also followed by the decay of CoTPP or the formation of CoTPP$^+$. The kinetic measurements were carried out under pseudo-first order conditions, in which the concentrations of LH were maintained at ≫tenfold excess of the CoTPP$^+$ concentration. Pseudo-first order rate constants were determined by a least-squares curve fit, using a microcomputer. The pseudo-first order plots were linear for three or more half-lives with the correlation coefficient ρ >0.999. Second-order rate constants were obtained from the slopes of the pseudo-first order rate constants *vs.* the LH concentrations by least-squares analysis.

Results and Discussion

CoTPP$^+$-*Catalysed Peroxidation of Polyunsaturated Fatty Acids.*—No appreciable peroxidation of peroxide-free linoleic acid (LH: 0.10 mol dm^{-3}) in an oxygen-saturated MeCN solution has been observed after 2 h at 333 K in the dark. The addition of a catalytic amount of CoTPPCl (4.8×10^{-5} mol dm^{-3}) to the LH–O_2 system results in the efficient peroxidation of LH to yield the hydroperoxides (LOOH). Figure 1 shows the formation of total hydroperoxides and conjugated diene hydroperoxides determined by iodometry and the absorption band at 233 nm, respectively (see Experimental). At the initial stage of the reaction, the concentrations of total hydroperoxides, are about the same as those of conjugated diene hydroperoxides, indicating that the conjugated diene hydroperoxides are mainly formed as reported for normal autoxidation of linoleic acid initiated by free radical initiators.[28–32] The various isomers of the conjugated diene hydroperoxides formed by the autoxidation have been characterized extensively.[28–32] After a prolonged reaction time, however, the concentrations of non-conjugated diene hydroperoxides become smaller than those of the total hydroperoxides (Figure 1), probably because of secondary oxidation of the conjugated diene hydroperoxides, some of which are known to result in the loss of conjugation.[32] During the peroxidation of LH, the CoTPP$^+$ concentration remained the same as the initial CoTPP$^+$ concentration and thus no appreciable degradation of the catalyst was being observed. When CoTPPCl was replaced by CoTPP, the peroxidation of LH at 333 K was also initiated by the addition of CoTPP (λ_{max} 412 nm), which was immediately converted to CoTPP$^+$ (λ_{max} 434 nm). Thus, the CoTPP$^+$/CoTPP redox system acts as an efficient catalyst for the peroxidation of LH to yield conjugated diene hydroperoxides (LOOH), equation (3).

$$LH + O_2 \xrightarrow{CoTPP^+/CoTPP} LOOH \qquad (3)$$

Initial rates (d[LOOH]/dt) of the peroxidation of various fatty acids and esters in the presence of CoTPPCl (5.0×10^{-5} mol dm^{-3}) in an oxygen-saturated MeCN solution were determined by iodometry, and the values are listed in Table 1. While no appreciable hydroperoxides are produced from fatty acids containing no double bonds (isobutyric acid, valeric acid, and pivalic acid) or one double bond (crotonic acid and oleic acid), the CoTPP$^+$-catalysed peroxidation occurs for polyunsaturated fatty acids and ester containing a 1,4-diene unit, *i.e.*, linoleic acid, methyl linoleate, and linolenic acid (Table 1). Thus, the presence of double allylic hydrogen atoms is required for the reaction [equation (3)] to occur. Such a drastic difference in the reactivity between the double allylic hydrogens (linoleic acid, methyl linoleate, and linolenic acid) and the simple allylic hydrogens (oleic acid) is rather unusual since oleic acid is known to undergo normal autoxidation at reasonable rates when initiated by free-radical initiators at elevated temperatures.[33] The order of the reactivity in Table 1 is, however, the same as that observed in the normal radical chain autoxidation.[34]

The radical chain character of the CoTPP$^+$-catalysed peroxidation of LH is confirmed by the inhibitory effect of isopentyl nitrite, which is known to be a strong radical scavenger,[35,36] as shown in Figure 2, where the induction period is observed in the presence of 1.4×10^{-3} mol dm^{-3} isopentyl nitrite. When all the radical scavenger is exhausted, the peroxidation starts again (Figure 2). In the presence of a larger amount of isopentyl nitrite (2.2×10^{-2} mol dm^{-3}), the

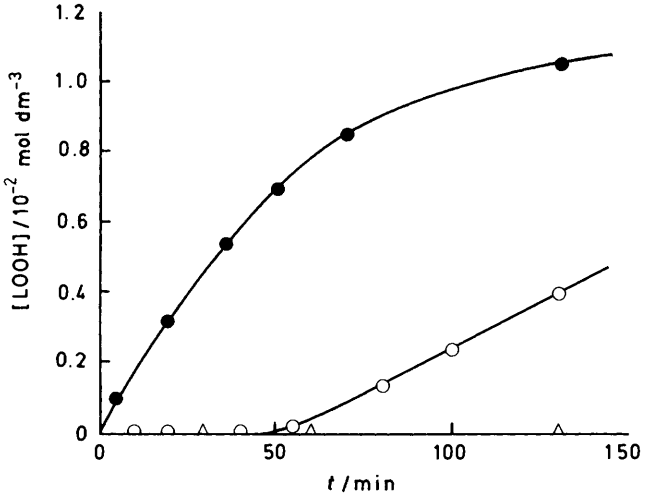


Figure 2. Effect of a radical scavenger, isopentyl nitrite, on the peroxidation of linoleic acid (0.10 mol dm^{-3}) in an oxygen-saturated MeCN solution containing CoTPPCl (5.0 × 10^{-5} mol dm^{-3}) at 333 K; no inhibitor (●), isopentyl nitrite 1.4 × 10^{-3} (○) and 2.2 × 10^{-2} (△) mol dm^{-3}.

Table 2. Second-order rate constants by k_i for the reduction of CoTPP$^+$ by fatty acids and ester (LH) in deaerated MeCN at 333 K.

LH	k_i[a]/dm^3 mol^{-1} s^{-1}
Isobutyric acid	[b]
Valeric acid	[b]
Pivalic acid	[b]
Crotonic acid	[b]
Oleic acid	[b]
Linoleic acid	3.7 × 10^{-2}
Methyl linoleate	3.8 × 10^{-2}
Linolenic acid	3.1 × 10^{-2}

[a] The experimental errors are within +10%. [b] ≪ 10^{-4} dm^3 mol^{-1} s^{-1}.

peroxidation is inhibited completely (Figure 2). The initiation rate (R_i) of free-radical generation in the CoTPP$^+$-catalysed peroxidation of linoleic acid (0.10 mol dm^{-3}) in the presence of CoTPPCl (5.0 × 10^{-5} mol dm^{-3}) in an oxygen-saturated MeCN solution is found to be 4.2 × 10^{-7} mol dm^{-3} s^{-1} at 333 K. A similar value (4.7 × 10^{-7} dm^3 mol^{-1} s^{-1}) was obtained when linoleic acid was replaced by methyl linoleate.

CoTPP$^+$-*Catalysed Initiation Step.*—If the CoTPP$^+$/CoTPP-catalysed decomposition of hydroperoxides to generate free radicals is the main initiation step, as reported for most transition-metal ion-catalysed peroxidations of unsaturated fatty acids,[13,14] the peroxidation should proceed in a autocatalytic fashion. However, no induction or autocatalytic behaviour is observed in the CoTPP$^+$-catalysed peroxidation of peroxide-free linoleic acid, as shown in Figure 1. Thus, the initiation step may involve the direct reaction between CoTPP$^+$and linoleic acid, independent of the hydroperoxide decomposition, as implicated for the Co^{3+}-catalysed peroxidation of linoleic acid.[16] Thus, the one-electron reduction of CoTPP$^+$ by unsaturated fatty acids and esters (LH) may produce the lipid alkyl radicals (L$^\cdot$) as shown in equation (4). In fact, such a reaction occurs in deaerated MeCN at the same

$$\text{CoTPP}^+ + \text{LH} \xrightarrow{k_i} \text{CoTPP} + \text{L}^\cdot + \text{H}^+ \qquad (4)$$

temperature as that employed in the CoTPP$^+$-catalysed peroxidation of LH. The rate can be readily followed by the disappearance and rise of the absorption due to CoTPP$^+$ (λ_{max} 434 nm) and CoTPP (λ_{max} 412 nm), respectively (see Experimental). The rate expression is given by equation (5). The

$$\text{d[CoTPP]}/\text{d}t = k_i[\text{CoTPP}^+][\text{LH}] \qquad (5)$$

second-order rate constants k_i for various fatty acids and esters in MeCN at 333 K are listed in Table 2. The presence of double allylic hydrogen atoms is also required for the reaction [equation (4)] to occur, as is the case with the overall peroxidation reaction [equation (3)]. This may be the reason for the drastic difference in reactivity between the double allylic hydrogens and the simple allylic hydrogens, since the difference in the reactivity in the initiation step [equation (4)] is multiplied by that in the propagation step [equation (2)],[34,37] for the overall peroxidation reaction [equation (3)].

On the other hand, the cobalt(II) porphyrin complex, CoTPP, is readily oxidized by dioxygen to CoTPP$^+$ in the presence of linoleic acid even at 298 K, equation (6). The rate of formation

$$\text{CoTPP} + \text{O}_2 + \text{H}^+ \longrightarrow \text{CoTPP}^+ + \text{HO}_2^\cdot \qquad (6)$$

of CoTPP$^+$ obeyed pseudo-first order kinetics in the presence of a large excess of linoleic acid (LH) in an oxygen-saturated MeCN solution. The pseudo-first order rate constant was proportional to the concentration of LH—which may act as an acid in reaction (6)—as given by equation (7). The k'_1 values

$$\text{d[CoTPP}^+]/\text{d}t = k'_i[\text{CoTPP}][\text{LH}] \qquad (7)$$

for linoleic acid in air-saturated and oxygen-saturated MeCN solutions at 298 K were found to be 7.0 and 13 dm^3 mol^{-1} s^{-1}, respectively.

It has been reported that the $HO_2^\cdot$ radical formed in the reaction [equation (6)] can abstract the double allylic hydrogen atom of linoleic acid, with a rate constant 1.2 × 10^3 dm^3 mol^{-1} s^{-1} in aqueous ethanolic solution at 296 K,[38] equation (8). Thus

$$\text{HO}_2^\cdot + \text{LH} \longrightarrow \text{H}_2\text{O}_2 + \text{L}^\cdot \qquad (8)$$

the slow initiation to produce L$^\cdot$ [equation (4)] may be followed by the facile oxidation of CoTPP by dioxygen in the presence of LH [equation (6)] to give $HO_2^\cdot$ which is readily converted to L$^\cdot$ in the reaction [equation (8)]. In such a case, the reduction of CoTPP$^+$ by LH [equation (4)] becomes the rate-determining step, when the rate of formation of L$^\cdot$, *i.e.*, the initiation rate R_i, is given by equation (9). Then, the R_i values at [CoTPP$^+$] =

$$R_i = 2k_i[\text{CoTPP}^+][\text{LH}] \qquad (9)$$

5.0 × 10^{-5} mol dm^{-3} and [LH] = 0.10 mol dm^{-3} are obtained from the rate constants k_i in Table 2 using equation (9), and are found to be 3.7 × 10^{-7} (linoleic acid) and 3.8 × 10^{-7} (methyl linoleate) dm^3 mol^{-1} s^{-1}, respectively. These values show reasonable agreement with those obtained by independent experiments, *i.e.*, the inhibition by a radical scavenger described above (4.2 × 10^{-7} and 4.7 × 10^{-7} dm^3 mol^{-1} s^{-1} for linoleic acid and methyl linoleate, respectively). Thus, it may be concluded that the reduction of CoTPP$^+$ by LH is the rate-determining initiation step for the generation of lipid alkyl radicals L$^\cdot$.

Kinetics and Mechanism.—The dependence of the initial rate for the peroxidation of linoleic acid (LH), d[LOOH]/dt, on the LH concentration is shown in Figure 3. Although the rate seems to exhibit a more than first-order dependence on [LH] at low LH concentrations (< 5.0 × 10^{-3} mol dm^{-3}), the rate increases linearly with an increase in the LH concentration(> 5.0 × 10^{-2}

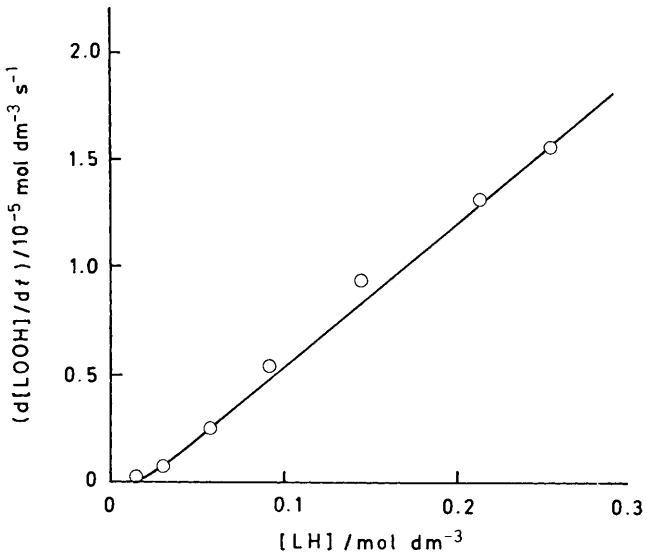


Figure 3. Plot of the initial peroxidation rate d[LOOH]/dt of linoleic acid in an oxygen-saturated MeCN solution containing CoTPPCl (5.0×10^{-5} mol dm^{-3}) at 333 K *vs.* the concentration of linoleic acid [LH].

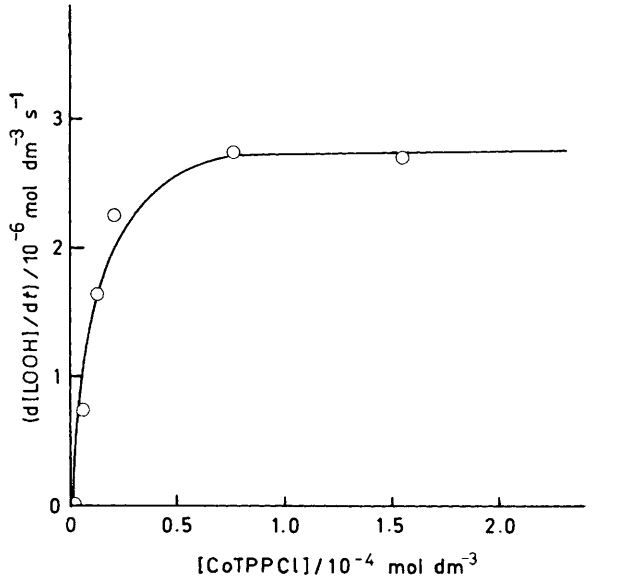


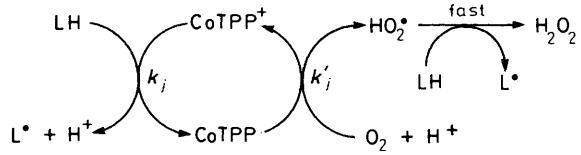
Figure 4. Plot of the initial peroxidation rate d[LOOH]/dt of linoleic acid (0.10 mol dm^{-3}) in an oxygen-saturated MeCN solution containing CoTPPCl at 333 K *vs.* the concentration of CoTPPCl.

mol dm^{-3}). The dependence of the rate on the catalyst concentration [CoTPPCl] is shown in Figure 4. The rate increases with an increase in the CoTPPCl concentration, but reached a constant value at high concentrations ($> 3 \times 10^{-5}$ mol dm^{-3}), at which the cobalt–porphyrin complex may act not only as a catalyst for the free-radical generation but also as a free radical scavenger. Such a radical-scavenging behaviour of lower transition-metal ions such as Co^{2+} has been well established.[39] Thus, in the present case, the chain carrier radicals LOO$^{\bullet}$ may be reduced by CoTPP, equation (10), in which H^+ may be

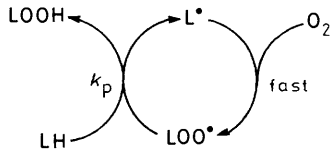
$$LOO^{\bullet} + CoTPP + H^+ \longrightarrow LOOH + CoTPP^+ \quad (10)$$

provided by LH, constituting another termination step in addition to the normal bimolecular decay of LOO$^{\bullet}$.

Initiation



Propagation



Termination

$$2LOO^{\bullet} \xrightarrow{k_t} \text{decay}$$

$$LOO^{\bullet} + CoTPP + H^+ \xrightarrow{k'_t} LOOH + CoTPP^+$$

Scheme.

Based on the above discussion, the reaction mechanism of the CoTPP$^+$/CoTPP-catalysed peroxidation of LH may be summarized as shown in the Scheme. According to this scheme, the rates of formation of CoTPP and LOO$^{\bullet}$ are given by equations (11) and (12), respectively. By applying the steady-state approximation to CoTPP in equation (11), the

$$d[CoTPP]/dt = k_i[CoTPP^+][LH] - k'_i[CoTPP][LH] - k'_t[LOO^{\bullet}][CoTPP][LH] \quad (11)$$

$$d[LOO\cdot]/dt = k_i[CoTPP^+][LH] + k'_i[CoTPP][LH] - 2k_t[LOO^{\bullet}]^2 - k'_t[LOO^{\bullet}][CoTPP][LH] \quad (12)$$

steady-state concentration of CoTPP may be given by equation (13), where reaction (6) is assumed to be much faster than

$$[CoTPP] = (k_i/k'_i)[CoTPP^+] \quad (13)$$

reaction (10). Similarly, from equations (11)–(13) is obtained equation (14) for the steady-state concentration of LOO$^{\bullet}$. Under

$$[LOO^{\bullet}] = -(k'_t k_i/k'_i)[CoTPP^+][LH]/2k_t + \{(k'_t k_i/k'_i)^2[CoTPP^+]^2[LH]^2 + 4k_i k_t[CoTPP^+][LH]\}^{\frac{1}{2}}/(2k_t) \quad (14)$$

conditions such that $A[CoTPP^+][LH] \ll 1$; $A = (k'_t k_i/k'_i)^2/(4k_i k_t)$, when the $(k'_t k_i/k'_i)[CoTPP^+][LH]$ term can be neglected by comparison with that of $(4k_i k_t)[CoTPP^+][LH]$,[‡] and equation (14) is reduced to equation (15). Alternatively, under conditions such that $A[CoTPP^+][LH] \gg 1$, equation

$$[LOO^{\bullet}] = (k_i/k_t)^{\frac{1}{2}}[CoTPP^+]^{\frac{1}{2}}[LH]^{\frac{1}{2}} \quad (15)$$

(14) can be rewritten by equation (16), which reduces to

$$[LOO^{\bullet}] = -(k'_t k_i/k'_i)[CoTPP^+][LH]/(2k_t) + (k'_t k_i/k'_i)[CoTPP^+][LH]\{1 + 4k_i k_t(k'_t k_i/k'_i)^{-2}[CoTPP^+]^{-1}[LH]^{-1}\}^{\frac{1}{2}}/(2k_t) \quad (16)$$

equation (17), since $(1 + x)^n \approx 1 + nx$ when $x \ll 1$. The rates of

$$[\mathrm{LOO}^{\bullet}] = k'_i/k'_t \quad (17)$$

the peroxidation, d[LOOH]/dt, under conditions such that $A[\mathrm{CoTPP}^+][\mathrm{LH}] \ll 1$ and $\gg 1$ are then given by equations (18) and (19), respectively.

$$\mathrm{d[LOOH]}/\mathrm{d}t = k_p(k_i/k_t)^{\frac{1}{2}}[\mathrm{CoTPP}^+]^{\frac{1}{2}}[\mathrm{LH}]^{\frac{3}{2}} \quad (18)$$

$$\mathrm{d[LOOH]}/\mathrm{d}t = k_p(k'_i/k'_t)[\mathrm{LH}] \quad (19)$$

Equations (18) and (19) explain well the experimental observations in Figures 3 and 4. The rate dependence on the LH concentration at a fixed CoTPP^+ concentration obeys equation (18), *i.e.*, proportional to $[\mathrm{LH}]^{\frac{3}{2}}$ at low LH concentrations, but the dependence may shift from equation (18) to equation (19) with an increase in the LH concentration, and thus the rate becomes proportional to [LH], as shown in Figure 3. Similarly, the rate dependence on the CoTPP^+ concentration may shift from equation (18) to equation (19), which is independent of the CoTPP^+ concentration at high concentrations (Figure 4). Thus, it can be concluded that the CoTPP^+/CoTPP redox system can act not only as a radical initiator by the direct reaction with LH [equation (4)] but also a catalyst by the oxidation of CoTPP by dioxygen [equation (6)] as well as a radical scavenger [equation (10)] as summarized in Scheme 1.

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