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On the Mode of Oxygenation with the Ferric Perchlorate–Hydrogen Peroxide System[1]

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The reactions of three kinds of substrates with hydrogen peroxide catalyzed by ferric perchlorate in acetonitrile were investigated and compared with those occurring in the $Fe(acac)_3$/alkylhydroperoxide system, which are governed by a radical process. Allylic oxidation and epoxidation both proceeded in the reaction of cholesteryl acetate, and the α-stereoselectivity of the epoxidation was enhanced by the presence of a radical scavenger. In the reactions of *cis*- and *trans*-stilbenes, stereospecific epoxidation by a non-radical process occurred, as well as a non-stereospecific reaction. The third substrate, adamantane, was shown to undergo more extensive oxygenation at its secondary carbon atoms than it did in the autoxidation and the $Fe(acac)_3$/ROOH systems. Thus, it was concluded that the reaction in the $Fe(ClO_4)_3/H_2O_2/CH_3CN$ system involves both radical and non-radical processes.

Keywords——ferric perchlorate; hydrogen peroxide; cholesteryl acetate; stilbene; adamantane; α-epoxidation of cholesteryl acetate; stereospecific epoxidation of stilbene; oxygenation of adamantane; non-radical process; radical process

Oxygenation using peroxide and a metal complex or ion has been the subject of extensive investigation.[2a] There has also been much interest in the biological oxidations catalyzed by transition metals, among which iron is particularly important in activating oxygen moieties and propagating the oxidative reactions, as seen, for example, in the lipid peroxidation and the hydroperoxide dependent hydroxylation catalyzed by cytochrome P-450.[3,4] In a series of studies on the reactions of cholesteryl acetate(**1**) with various alkylhydroperoxides(ROOH) and tris(acetylacetonato)iron (III)($Fe(acac)_3$), we found that radical processes seemed to dominate in the reaction leading to allylic oxidation and epoxidation of **1**;[5a-d] the high stereoselectivity of the β-epoxidation is in accord with that observed in the biological reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent lipid peroxidation system.[6] We also reported that the hexacarbonylmolybdenum($Mo(CO)_6$)/*tert*-butylhydroperoxide-(^{t}BuOOH) system, which generates Mo-^{t}BuOOH complex as an attacking species,[2b] gave only the epoxide of **1** with a stereoselectivity $\beta/(\alpha+\beta)$ of 0.5.[5c]

The ferric perchlorate/hydrogen peroxide system is known to oxygenate several alicyclic compounds[7] and to produce the NIH-shift in hydroxylating aromatic substrates.[8] Previously, we studied the Fe^{3+}-catalyzed decomposition of hydrogen peroxide in a high concentration of acetonitrile[9] and discussed the oxidant produced in relation to the competition of the hydroxyl radical (·OH) and ferryl ion (Fe^{4+}–OH) paths.[10] In this paper, we report thet both radical and non-radical processes participate in the oxygenation of cholesteryl acetate(**1**), stilbenes (**6** and **7**), or adamantane(**8**) with a mixture of ferric perchlorate and hydrogen peroxide in acetonitrile.

Results and Discussion

Oxygenation of Cholesteryl Acetate(1)

The reaction of **1** with the $Fe(acac)_3$/ROOH(R=H, alkyl) system led to allylic oxidation, giving the C(7)-alcohol(**2**), -one(**3**), and -alkylperoxide(**4**), and to epoxide(**5**) formation with high β-stereoselectivity, by radical processes.[5c,d,11,12] The oxygenation of **1** with the $Mo(CO)_6$/^{t}BuOOH system was, in contrast, very solvent-dependent as radical and non-radical processes participated in ^{t}BuOH and benzene solutions, respectively, and both processes occurred in acetonitrile.[5c]

Both allylic oxidation and epoxidation also occurred in the title reaction of **1** in acetonitrile. The stereo-selectivity of epoxidation was rather similar to that in the reaction with the Mo system, which gave more α-epoxide than the β-isomer in acetonitrile.[5c] When ^{t}BuOH was used as a solvent in the title reaction of **1**, β-selectivity became predominant, as in the Mo system[5c] (summarized in Table I). These results seemed to indicate that both radical and non-radical processes are also involved in the title reaction of **1** in acetonitrile.

TABLE I. Oxygenation of Cholesteryl Acetate

Catalyst	ROOH	Solvent	Conversion (%)	Yield (%)			
				2	**3**	**4**	**5** $\beta/(\alpha+\beta)$[a]
$Fe(ClO_4)_3$	HOOH	CH_3CN	54	8	6	0	40(0.33)
		^{t}BuOH	7	1	0	0	6(0.77)
$Fe(acac)_3$	HOOH	CH_3CN	7	1	1	0	5(0.78)
		^{t}BuOH	6	0	1	0	5(0.77)
	^{t}BuOOH[b]	Benzene	100	3	74	11	13(0.72)
		CH_3CN	42	0	8	30	4(0.72)
		^{t}BuOH	96	3	61	25	7(0.75)
$Mo(CO)_6$	^{t}BuOOH[c]	Benzene	100	0	0	0	97(0.50)
		CH_3CN	36	4	8	3	21(0.44)
		^{t}BuOH	90	2	66	11	11(0.78)

a) Numbers in parentheses are ratios of β-epoxide to the total epimers formed.
b) See ref. 5*d*.
c) See ref. 5*c*.

It was previously shown that the radical scavenger, 2,6-bis-(1,1-dimethylethyl)-4-methylphenol(BHT), inhibited the reaction of **1** with the $Fe(acac)_3$/ROOH system, and thus neither allylic oxidation nor epoxidation occurred.[5d] BHT was also shown to block the allylic oxidation, though it only slightly reduced the epoxidation, in the reaction of **1** with the $Mo(CO)_6$/^{t}BuOOH/CH_3CN system.[5c] This may indicate that epoxidation by a non-radical process can still occur in the presence of BHT. As for the title reaction of **1**, the effect of BHT was similar to that on the Mo system; the allylic oxidation was greatly retarded and the α-selectivity of epoxidation was increased, as summarized in Table II. Thus, the title reaction of **1** in aceto-

TABLE II. Effect of BHT on the Oxygenation of Cholesteryl Acetate

Catalyst	ROOH	BHT	Conversion (%)	Yield (%)			
				2	**3**	**4**	**5** $\beta/(\alpha+\beta)$[a]
$Fe(ClO_4)_3$	HOOH	−	54	8	6	0	40(0.33)
		+	37	1	0	0	36(0.17)
$Fe(acac)_3$	HOOH	−	7	1	1	0	5(0.78)
		+	0				
	^{t}BuOOH[b]	−	42	0	8	30	4(0.72)
		+	0				
$Mo(CO)_6$	^{t}BuOOH[c]	−	36	4	8	3	21(0.44)
		+	14	0	0	0	14(0.41)

Solvent: CH_3CN.
a) Numbers in parentheses are ratios of β-epoxide to the total epimers formed.
b) See ref. 5*d*.
c) See ref. 5*c*.

nitrile may involve epoxidation by a non-radical process, as well as epoxidation and allylic oxidation by radical processes.

Epoxidation of Stilbenes(6 and 7)

The epoxidation of stilbene by a radical process is known to form an intermediate which can rotate around the attacked C–C bond to attain conformational equilibrium, and thus gives an epoxide mixture with similar isomeric ratio from both *cis*- and *trans*- stilbenes.[13,14] In the epoxidations of two stilbenes with the Fe(acac)$_3$/ROOH system, the ratios were the same, *i.e.*, *cis*: *trans*=4: 96.[5d] The title reactions of *cis*- and *trans*-stilbenes gave, in contrast, an epoxide mixture with a ratio of *cis*: *trans*=61 : 39 and a *trans*-epoxide alone, respectively. In the presence of a radical scavenger,[15a] the formation ratio of *cis*-epoxide from *cis*-stilbene increased with increasing scavenger concentration, though *trans*-stilbene still gave only a *trans*-epoxide, as summarized in Table III. Epoxidation of stilbenes(**6** and **7**) in the title reaction may, therefore, also occur by radical as well as non-radical processes.

TABLE III. Epoxidation of Stilbenes in the Fe^{III}/ROOH System

Catalyst	ROOH	Stilbene	[GA]mM	*cis* : *trans*
Fe(ClO$_4$)$_3$	HOOH	*cis*	0	61 : 39
			11.0	76 : 24
			22.2	85 : 15
		trans	0	0 : 100
			22.4	0 : 100
Fe(acac)$_3$	ROOH[a]	*cis*	0	4 : 96
		trans	0	4 : 96

Solvent: CH$_3$CN; GA: gallic acid.
a) See ref. 5*d*.

Oxygenation of Adamantane(8)

Hydroxylation predominantly occurred at the tertiary carbons in the autoxidation (radical process) of **8**, and high regioselectivity (secondary selectivity) was observed when it was catalyzed by an iron chelate(non-radical process).[16] Oxygenation of **8** with the Fe(acac)$_3$/ROOH system and autoxidation using a radical initiator, 2,2′-azobisisobutyronitrile(AIBN), showed secondary regioselectivity with ratios S/(S+T)[15b] ranging from 0.11 to 0.18. The title reaction of the same substrate, on the other hand, gave a ratio of 0.37, as summarized in Table IV. Thus, a non-radical process is also likely to participate in this reaction. The radical scavenger, gallic acid, lowered the conversion of **8** to about 24% with increasing scavenger concentration and greatly retarded the oxygenation at the tertiary carbons(**9**), as expected. In contrast, the secondary regioselectivity forming the C(2)-alcohol(**10**) or -one(**11**) was not appreciably reduced, as shown in Fig. 1.

From the results described above, we concluded that both radical and non-radical processes participate in the title reaction. Thus, an alicylic substrate, adamantane(**8**), was more oxygen-

TABLE IV. Oxygenation of Adamantane

Catalyst	ROOH	Conversion %	Yield (%)			
			9	**10**	**11**	S/(S+T)
Fe(ClO$_4$)$_3$	HOOH	33.9	18.2	11.0	4.7	0.37
Fe(acac)$_3$	HOOH	22.0	17.4	1.1	3.5	0.15
	EtOOH	6.7	5.5	0.5	0.6	0.12
	^{i}PrOOH	2.4	1.8	0.1	0.5	0.18
	^{t}BuOOH	3.7	3.1	0.3	0.3	0.11
AIBN	O$_2$	13.0	11.0	1.3	0.7	0.11

Solvent : CH$_3$CN.

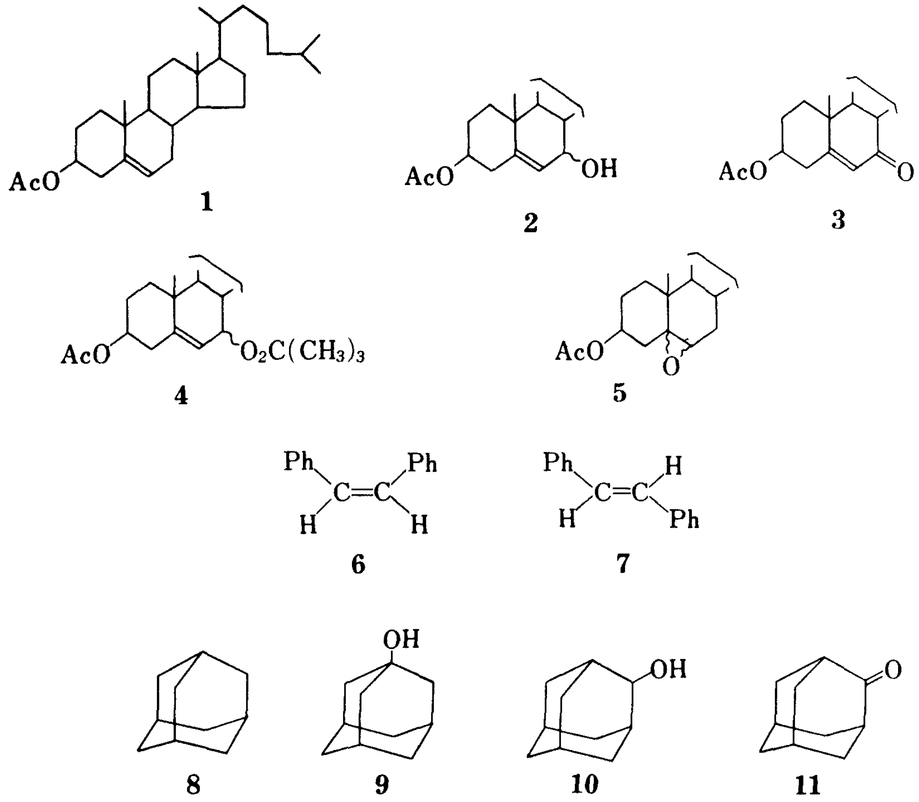

Chart 1

ated at the secondary carbon atoms than was the case in the Fe(acac)$_3$/ROOH system, which is governed by a radical process alone. The non-radical process in the title reaction also affected the stereoselective epoxidation of the olefinic substrates, cholesteryl acetate (**1**) and stilbenes(**6** and **7**); the highly stereoselective α-epoxidation of **1** was quite similar to that catalyzed by cytochrome P-450.[17] Castle and Smith[8] observed the NIH-shift in the hydroxylation of aromatic substrates with the Fe(ClO$_4$)$_3$/H$_2$O$_2$/CH$_3$CN system. The title reaction system may, therefore, be regarded as a model for the hydroperoxide-dependent hydroxylation catalyzed by this ferric enzyme.[4] A useful general approach for examining the mode of oxygenation in a given system may thus be to use a set of characteristic substrates as cholesteryl acetate, stilbenes, and adamantane, together with appropriate radical scavengers.

Experimental

General Methods——Determination of the product distribution and the epimeric ratio of the epoxide in the reaction mixture were carried out by the reported methods[5a,b] using an Iatron TFG-10 Thin-chrograph (TLC–FID) and a proton magnetic resonance (PMR) spectrometer, respectively. PMR spectra were measured with a JEOL JNM-FX 100FT spectrometer at 100 MHz with tetramethylsilane as an internal standard in CDCl$_3$. Gas chromatographic (GLC) data were obtained with a Shimadzu GC-4CM gas chromatograph equipped with a hydrogen flame ionization detector and a glass column (2 m × 3 mm i.d.) packed with 10% SE-30.

Materials and Authentic Specimens——Cholesteryl acetate (**1**), cholest-5-ene-3β,7-diol 3-monoacetate (**2**), 3β-acetoxycholest-5-en-7-one (**3**), 7-*tert*-butylperoxycholest-5-en-3β-ol acetate (**4**), 5,6-epoxycholestan-3β-ol acetate (**5**) and ethyl and isopropyl hydroperoxides were prepared as reported.[5a,b] Other reagents and authentic specimens of 1-hydroxy-, 2-hydroxy-, and 2-keto-adamantanes (**9**, **10**, and **11**) were obtained commercially and used without purification.

Reaction of Cholesteryl Acetate (1) with Iron(III) Catalyst and Hydrogen Peroxide (Table I)——A mixture of **1** (50 mg, 0.12 mmol), Fe catalyst (1.48×10^{-3} mmol), 30% H$_2$O$_2$ (0.05 ml, 0.49 mmol), and organic solvent (5 ml) was refluxed for 4 h under an Ar atmosphere and then diluted with ether (80 ml). The organic layer was washed with sat.aq.Na$_2$SO$_3$ and sat.aq.NaCl successively, dried over anhydrous Na$_2$SO$_4$, and filtered.

The filtrate was evaporated to dryness *in vacuo* and subjected to TLC-FID. The consumption of **1**, product distribution, and the epimeric ratio of the epoxides were determined as reported.[5b)]

Effect of Radical Scavenger on the Reaction of Cholesteryl Acetate (1) (Table II)——An acetonitrile solution of **1**, Fe catalyst, and H_2O_2 in the same amounts as described above was refluxed for 4 h under an Ar atmosphere in the presence of BHT (56.0 mg, 0.26 mmol). After work-up as described above, the consumption of **1**, product distribution, and the epimeric ratio of the epoxides were determined according to the general methods.

Epoxidation of Stilbenes (Table III)——An acetonitrile solution (50 ml) of *cis*- or *trans*-stilbene (200 mg, 1.11 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (0.782 mg, 1.69×10^{-3} mmol), and 30% H_2O_2 (1.5 ml, 14.7 mmol) was refluxed for 18 h under an Ar atmosphere. After usual work-up, the epimeric ratio of the epoxides was determined by the PMR method previously reported.[5c)]

Effect of Radical Scavenger on the Epoxidation of Stilbenes (6 and 7)——An acetonitrile solution (80 ml) of **6** or **7** (320 mg, 1.78 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (1.25 mg, 2.70×10^{-3} mmol), and 30% H_2O_2 (2.4 ml, 23.5 mmol) was refluxed for 18 h under an Ar atmosphere in the presence of gallic acid·H_2O (337 mg, 1.79 mmol for *trans*-stilbene; 166 mg, 0.88 mmol, or 333 mg, 1.77 mmol for *cis*-stilbene). The reaction mixture was diluted with ether (400 ml). The organic layer was washed with sat.aq.Na_2SO_3, 2 N aq.KOH, and sat.aq.NaCl successively, dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness *in vacuo*. The epimeric ratio of the epoxides was determined as reported.[5d)]

Reaction of Adamantane (8) with Ferric Perchlorate and Hydrogen Peroxide (Table IV)——An acetonitrile solution (10 ml) of **8** (50 mg, 0.40 mmol), Fe catalyst (1.076 mg, 2.33×10^{-3} mmol), and 30% H_2O_2 (0.1 ml, 0.98 mmol) was heated at 90°C in a sealed tube for 4 h under an Ar atmosphere. The reaction mixture (0.2 ml) was added to acetone (0.1 ml) containing *trans*-decalin as an internal standard and subjected to GLC (column temp. 100°C) for the determination of the substrate consumption and the yield of the oxygenated products.

Effect of Radical Scavenger on the Reaction of Adamantane (Fig. 1)——An acetonitrile solution of **8**, Fe salt, and H_2O_2 in the same amounts as cited above was similarly treated in the presence of gallic acid·H_2O (0.0552 mg, 2.94×10^{-4} mmol; 0.138 mg, 7.34×10^{-4} mmol; 0.276 mg, 1.47×10^{-3} mmol; 0.552 mg, 2.94×10^{-3} mmol; 1.104 mg, 5.87×10^{-3} mmol). The consumption of **8** and the yield of the oxygenated products were determined as described above.

Reaction of Adamantane (8) with Tris(acetylacetonato)Iron(III) and Hydroperoxide (ROOH)——An acetonitrile solution (10 ml) of **8** (50 mg, 0.40 mmol), Fe chelate (9.614 mg, 2.72×10^{-2} mmol for H_2O_2, EtOOH, or iso-PrOOH; 24.035 mg, 6.80×10^{-2} mmol for *tert*-BuOOH), and ROOH (H_2O_2 0.2 ml, 1.96 mmol; EtOOH 0.2 ml, 1.80 mmol; iso-PrOOH 0.5 ml, 2.50 mmol; *tert*-BuOOH 0.5 ml, 4.90 mmol) was heated at 90°C in a sealed tube for 4 h under an Ar atmosphere. A portion (0.2 ml) of the reaction mixture was treated as described above for determining the substrate consumption and the yield of the oxygenated products.

Autoxidation of Adamantane with Radical Initiator (AIBN)——An acetonitrile solution (10 ml) of **8** (50 mg, 0.40 mmol) and AIBN (8.15 mg, 4.97×10^{-2} mmol) was heated at 90°C in a sealed tube for [illegible] h under an O_2 atmosphere. The consumption of **8** and the yield of the oxygenated products were determined as described above.

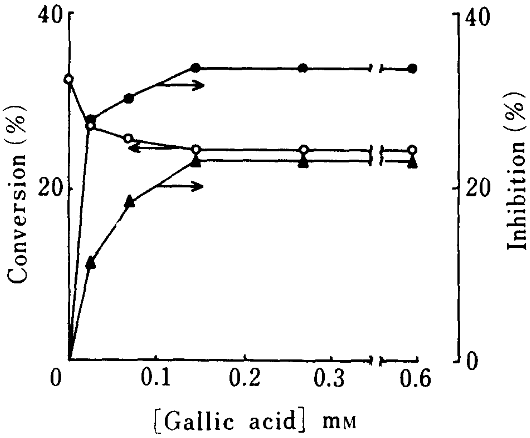

Fig. 1. Effect of Gallic Acid on the Oxygenation of Adamantane

—○—, conversion; —●—, **9**; —▲—, **10+11**.

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