Chem. Pharm. Bull.
28(6)1836—1841(1980)

The Reactions of Cholesteryl Acetate with Various Hydroperoxides in the Presence of Tris(acetylacetonato)iron (III) and Hexacarbonylmolybdenum[1]

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(Received January 5, 1980)

Epoxidation and allylic oxidation of cholesteryl acetate were studied using hydroperoxide (ROOH: R=H, ethyl, iso-propyl, *tert*-butyl, or cumyl) and a metal complex [Fe(acac)$_3$ or Mo(CO)$_6$] in benzene or acetonitrile. In the presence of the iron catalyst, formation of the epimeric C(5,6)-epoxides predominated in the reactions with H_2O_2, while allylic oxidation giving C(7)-ketone, epimeric C(7)-alcohols and C(7)-alkyl peroxides was favored in the reactions with alkyl hydroperoxide, regardless of the polarity of the solvent. The stereoselective β-epoxidation was independent of the structure of ROOH, but the ratio of allylic oxidation to epoxidation was dependent on it.

When the iron catalyst was replaced by the molybdenum catalyst, β-epoxidation decreased and solvent effects on the reaction were sufficiently marked to exclude allylic oxidation in the non-polar medium.

Keywords——alkyl hydroperoxide; allylic oxidation; cholesterol; epoxide; ferric acetylacetonate; hydrogen peroxide; molybdenum hexacarbonyl; solvent effects; stereoselective epoxidation

While extensive studies on the oxy-functionalization of olefins have been made with mixtures of hydroperoxides and metal complexes, the conditions leading to epoxidation or allylic oxidation are not fully understood. Little is known either about similar reactions of cholesterol, which is a natural, biologically essential olefin. In the previous paper of this series, we reported that the hydrogen peroxide/tris(acetylacetonato)iron (III) system gave a stereoselective β-epoxidation of cholesterol.[3] In contrast, allylic oxidation predominated in the reaction of cholesteryl acetate with *tert*-butyl hydroperoxide in the presence of the same metal complex, Fe (acac)$_3$.[4] In this paper, we descibe several differences in the allylic oxidation and in the epoxidation of cholesteryl acetate using various hydroperoxides and metal complexes in different solvents.

Results

Based on the observed predominance of epoxidation with hydrogen peroxide[3] and of allylic oxidation with *tert*-butyl hydroperoxide,[4] the use of these as well as ethyl, iso-propyl, and cumene hydroperoxides was examined to determine the nature of the reactions. Benzene and acetonitrile were selected as solvents of different polarities and were used at their boiling points. In addition to Fe (acac)$_3$, a molybdenum complex, Mo(CO)$_6$, was examined, since it is known to catalyze the epoxidation of olefins[5] including cholesteryl acetate (I) by alkyl

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[1] This paper constitutes Part XII of a series entitled "Metal Ion-catalyzed Oxidation of Steroids;" Part XI: M. Kimura, T. Yamamoto, K. Nagasawa, and M. Tohma, *Chem. Pharm. Bull.*, **27**, 2203 (1979).

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[3] M. Tohma, T. Tomita, and M. Kimura, *Tetrahedron Lett.*, **1973**, 4359.

[4] M. Kimura and T. Muto, *Chem. Pharm. Bull.* **27**, 109 (1979).

[5] *a*) M.N. Sheng and J.G. Zajacek, *J. Org. Chem.* **35**, 1839 (1970); *b*) G.R. Howe and R.R. Hiatt, *ibid.*, **36**, 2493 (1971); *c*) T.N. Baker, III, G.J. Mains, M.N. Sheng, and J.G. Zajacek, *ibid.*, **38**, 1145 (1973); *d*) A.O. Chong and K.B. Sharpless, *ibid.*, **42**, 1587 (1977).

hydroperoxides.[6] Each reaction of I was carried out under optimal conditions. The products, 3β-acetoxy-5,6-epoxycholestanes (II), 3β-acetoxycholest-5-en-7-one (III), 3β-acetoxycholest-5-en-7-ols (IV), and 3β-acetoxycholest-5-ene-7-alkyl peroxides (V), were quantitatively determined. The reaction system without a metallic catalyst gave no product.

Iron Catalyses

In the presence of Fe(acac)$_3$, epoxidation predominated in the hydrogen peroxide system and decreased in extent with increase in the size of the alkyl group attached to the α-carbon atom of the alkyl hydroperoxide (Table I). In contrast, a marked formation of the C(7)-ketone (III) which was assumed to be produced *via* the intermediary C(7)-alkyl peroxisde (V),[4] was observed in the reactions using alkyl hydroperoxides. The ratio of β-epimer to the total epoxides (II) was nearly constant (Table I) and thus stereoselective epoxidation[3] also proceeds in the Fe (acac)$_3$/alkyl hydroperoxide system.

Molybdenum Catalyses

When Fe(acac)$_3$ was replaced with Mo(CO)$_6$, epoxidation occurred exclusively and no allylic oxidation occurred in the reactions of I with alkyl hydroperoxides in benzene (Table II). However, the predominance of steroselective β-epoxidation was largely lost in these systems. The heterogeneous reaction mixture of I with hydrogen peroxide in benzene gave the epoxide (II) in a poor yield of 6% with a negligible amount of unchanged substrate (I). A large amount of a new product (VI) was obtained instead, and this proved to have an aldehyde group at C(5) and a five-membered B ring.[7] Since the deformed steroid (VI) was exclusively formed when the freshly prepared epoxide (II) came into contact with the same reagent system, epoxide formation from I may be similarly exclusive in the Mo(CO)$_6$/H_2O_2/benzene system.

Solvent Effects

When the non-polar solvent (benzene) was replaced with a polar one (acetonitrile) in the reactions using iron catalyst (Table I), the conversion of I into II was greatly increased in the hydrogen peroxide system. However, the ratioo of β-epimer to the total epoxides (II) and that of allylic oxidation to epoxidation remained almost unchanged in a given alkyl hydroperoxide system. In the case of molybdenum catalyst, the formation of epoxide was no longer occurred exclusively, and allylic oxidation was observed to proceed in acetonitrile solutions; this was especially marked in the hydrogen peroxide system (Table II).

TABLE I. Reactions of Cholesteryl Acetate catalyzed by Tris(acetylacetonato)iron(III)[a]

Solvent	Hydroperoxide	Conversion (%)	Epoxide[b] (II)	Ketone (III)	Alcohol (IV)	Peroxide (V)	$\frac{\text{Allyl. Oxid.}}{\text{Epoxid.}}$
C_6H_6	HOOH	2	2(0.73)	0	0	0	0
C_6H_6	EtOOH	65	31(0.75)	28	6	trace	1.10
C_6H_6	iso-PrOOH	68	17(0.72)	47	4	trace	3.00
C_6H_6	*tert*-BuOOH	100	13(0.72)	74	3	10	6.77
C_6H_6	CuOOH[c]	74	4(0.82)	56	2	12	17.5
CH_3CN	HOOH	73	64(0.80)	4	5	0	0.14
CH_3CN	EtOOH	90	45(0.74)	40	5	0	1.00
CH_3CN	iso-PrOOH	70	16(0.71)	24	5	25	3.31
CH_3CN	*tert*-BuOOH	42	4(0.72)	8	trace	30	9.50
CH_3CN	CuOOH[c]	26	2(0.78)	4	4	16	12.0

a) Figures are the means of three runs.
b) Numbers in parentheses are ratios of β-epoxide to the total epimers formed.
c) Cumene hydroperoxide.

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6) G.A. Tolstikov, V.P. Yur'ev, I.A. Gailyunas, and U.M. Dzhemilev, *Zhurnal Obshchei Khimii*, **44**, 215 (1974).

7) M. Kimura and T. Muto, in preparation.

Table II. Reactions of Cholesteryl Acetate catalyzed by Molybdenum Hexacarbonyl[a)]

Solvent	Hydroperoxide	Conversion (%)	Epoxide[b)] (II)	Ketone (III)	Alcohol (IV)	Peroxide (V)	Allyl. Oxid./Epoxid.
C_6H_6	HOOH	100	6(0.33)	0	0	0	0
C_6H_6	EtOOH	80	80(0.25)	0	0	0	0
C_6H_6	iso-PrOOH	80	80(0.25)	0	0	0	0
C_6H_6	*tert*-BuOOH	97	97(0.50)	0	0	0	0
C_6H_6	CuOOH[c)]	26	26(0.30)	0	0	0	0
CH_3CN	HOOH	67	25(0.65)	25	5	12	1.68
CH_3CN	EtOOH	17	14(0.41)	1	1	1	0.21
CH_3CN	iso-PrOOH	43	32(0.41)	4	3	4	0.34
CH_3CN	*tert*-BuOOH	36	21(0.44)	8	4	3	0.42
CH_3CN	CuOOH[c)]	5	2(0.38)	1	0	2	1.5

a) Figures are the means of three runs.
b) Numbers in parentheses are ratios of β-epoxide to the total epimers formed.
c) Cumene hydroperoxide.

Discussion

In the reactions of olefins with organic peroxides such as *tert*-butyl and cumene hydroperoxides, the extents of allylic oxidation and epoxidation are known to depend on the metallic catalyst.[8c)] Allylic oxidation became predominant when the catalyst was a salt of a metal ion of lower valence such as Cu(I), Co(II), Mn(II), Ni(II), or Fe(II).[8b,c,e)] Epoxide formation was predominant in the same reactions when Ce (IV) salt or a complex of a metal ion such as Co, Cr, Cu, Mn, Mo,[5d)] V,[5d)] or W was used as a catalyst.[8a,c,d,e)] The results in this study clearly show that the ratio of allylic oxidation to epoxidation depends on the hydroperoxide employed when the reaction of I is catalyzed by Fe (acac)$_3$; to our knowledge, this is the first report of such a dependence. In addition to this ratio, that of β-epimer to the total epoxides (II) was clearly different in the systems catalyzed by iron from those catalyzed by molybdenum. The system catalyzed by Fe(acac)$_3$ gave almost constant ratios, of between 0.7 and 0.8 (Table I). We have recently shown that the Fe(acac)$_3$/H_2O_2 system in acetonitrile epoxidizes olefins by a two-step non-stereospecific process and that the ferryl (FeO^{3+}) ions[9)] may be involved in the epoxidation.[10)] The Fe(acac)$_3$/alkyl hydroperoxide system may also produce ferryl ions, as well as other oxidant(s) which may include a metal-hydroperoxide complex,[11)] a metal-bonded alkylperoxy radical,[12)] and/or oxidant(s) derived from these complexes.

It was also shown that the epoxidation occurs exclusively and is independent of the type of hydroperoxide when the iron catalyst is replaced by molybdenum complex in benzene. In the Mo(CO)$_6$-catalyzed epoxidation of olefins by alkyl hydroperoxide in non-polar solvent, it was postulated that the initial step is a rapid equilibrium formation of peroxo metal-hydroperoxide complex and that the second step is the rate-determining reaction of this complex with the olefin.[5c)]

The ratios of allylic oxidation to epoxidation and of β-epimer to the total epoxides (II) formation were hardly affected by the solvent, when the reactions were catalyzed by Fe(acac)$_3$

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8) *a*) N. Indictor and W.F. Brill, *J. Org. Chem.*, **30**, 2074 (1965); *b*) N. Indictor, T. Jochsberger, and D. Kurnit, *ibid.*, **34**, 2855 (1969); *c*) G. Sosnovsky and D.J. Rawlinson, "Organic Peroxides," Vol. II, ed. by D. Swern, John Wiley, and Sons, Inc., New York, 1971, pp. 195—211; *d*) R.A. Sheldon and J.A. Van Doorn, *J. Catal.*, **31**, 427 (1973); *e*) R.A. Sheldon and J.K. Kochi, *Adv. Catal.*, **25**, 272 (1976).

9) V. Ullich and Hj. Staudinger, "Biological and Chemical Aspects of Oxygenases," ed. by O. Hayaishi, Maruzen Company Ltd., Tokyo, 1965, p. 243; and see ref. 9 in 10).

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11) J.F. Black, *J. Am. Chem. Soc.*, **100**, 527 (1978).

12) F. Mares and R. Tang, *J. Org. Chem.*, **43**, 4631 (1978).

(Table I). Solvent effects were, in contrast, clearly observed in the reactions catalyzed by molybdenum complex and were particularly marked in epoxidation with the $Mo(CO)_6/H_2O_2$ system (Table II). In the epoxidation of allyl chloride and 1-octene with Mo $(CO)_6$/*tert*-butyl hydroperoxide system, the rates and selectivities were highest in polychlorinated hydrocarbons, slightly lower in hydrocarbon solvents, and very poor in coordinating solvents such as alcohols, ethers, *etc.*[13] Formation of a metal-alkyl hydroperoxide complex was proposed to be responsible for the epoxidation.[5c] Acetonitrile under reflux is known to displace three carbonyl ligands from $Mo(CO)_6$.[14] The polar solvent, acetonitrile, may thus interfere with the complexation of molybdenum with alkyl hydroperoxide, resulting in greatly decreased conversion of the substrate and the participation of allylic oxidation.

In this study, which was prompted by several investigations of oxy-functionalization using hydroperoxides and metal complexes of biological origin,[15] we observed two types of epoxide formation: the first is accompanied by allylic oxidation, where the product distribution and stereoselectivity do and do not depend on the hydroperoxide structure, respectively, and the second is low in the β-selectivity, with no allylic oxidation in a non-polar solvent (hydroperoxide merely acts as an oxygen donor).

Experimental

General Methods——Melting points were taken on a micro hot-stage apparatus and are uncorrected. NMR spectra were measured with a Hitachi R-24A spectrometer at 60 Mc using tetramethylsilane as an internal standard. TLC was carried out on silica gel (Wako-gel B5F) plates developed with PhH/AcOEt (19: 1; system 1; for II, III, and IV) or *n*-hexane/PhH (4: 6; system 2; triple development; for V) and stained with 10% H_2SO_4, with heating at about 130° for 5 min.

Materials——EtOOH (92%) and iso-PrOOH (94%) were prepared by the method of Williams and Mosher.[16] H_2O_2 (28%, Mitsubishi Gas Chem. Co.), *tert*-BuOOH (92%, Nakarai Chem. Co.) and cumene hydroperoxide (94%, Nakarai Chem. Co.) were obtained commercially and their concentrations were determined by iodometry. $Fe(acac)_3$ and $Mo(CO)_6$ were obtained from Dozin Yakkagaku Lab. and Strem Chem. Inc., respectively and used without purification. Authentic specimens of 3β-acetoxycholest-5-ene (I, mp 115.5—116°, lit.[17a] 116°), 3β-acetoxycholest-5-en-7-one (III, mp 159.5—161.5°, lit.[17b] 159—160°), 3β-acetoxycholest-5-en-7α-ol (IVa, mp 136.5—139°, lit.[17c] 139°), and 3β-acetoxycholest-5-en-7β-ol (IVb, mp 109—110°, lit.[17d] 110—111°) were prepared by the cited methods. 5ξ,6ξ-Epoxycholestan-3β-ol acetate (II, an equimolar epimeric mixture, as determined by NMR) was obtained by the reaction of I with the $Mo(CO)_6$/*tert*-BuOOH system.

General Procedure for the Title Reaction——A mixture of the substrate (I), metal complex, hydroperoxide, and solvent was refluxed for 24 hr under an Ar atmosphere and then saturated aqueous NaCl was added to the reaction mixture after treatment with aq. Na_2SO_3. The aqueous layer was extracted with ether and the ether solution was combined with the organic layer. The mixed solution was washed with saturated aq. NaCl, dried over anhydrous Na_2SO_4, filtered, and finally the solvent was evaporated off *in vacuo* to give an oily residue which was subjected to TLC for determination of the product distribution or for separation of the products on a preparative scale.

Determination of Product Distribution——The peak areas in TLC of the oily residue obtained from the reaction mixture as described above were determined by using a hydrogen-flame-ionization detector on an Iatron TFG-10 Thichrograph. The apparent yields of steroidal products were calculated from the ratio of the peak areas thus obtained, tentatively taking the relative sensitivity of each steroid to the substrate (I) as unity.

The fraction of β-epoxide in the total epimers (II) was obtained from the ratio of peak intensities in NMR spectra due to C(6)–H of II, after separation by preparative TLC (*Rf* 0.25) using solvent system 1.

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13) R.A. Sheldon, J.A. Van Doorn, C.W.A. Schram, and A.J. De Jong, *J. Catal.*, **31**, 438 (1973).

14) J.P. Cardlin, K.A. Taylor, and D.T. Thompson, "Reactions of Transition-Metal Complexes," Elsevier Publishing Co., Amsterdam, 1968, pp. 358.

15) H. Danielson and K. Wikvall, *FEBS Lett.*, **66**, 299 (1976); E.G. Hrycay, J.-Å. Gustafsson, M. Ingelman-Sundberg, and L. Ernster, *Eur. J. Biochem.*, **61**, 43 (1976); A. Ishimaru and I. Yamazaki, *J. Biol. Chem.*, **252**, 6118 (1977).

16) H.R. Williams and H.S. Mosher, *J. Am. Chem. Soc.*, **76**, 2984 (1954).

17) *a*) W. Buser, *Helv. Chim. Acta*, **30**, 1379 (1947); *b*) B.W. Finucane and J.B. Thomson, *J. Chem. Soc.* (*D*), **1969**, 1220; *c*) H.B. Henbest and E.R.H. Jones, *ibid.*, **1948**, 1792; *d*) *Idem*, *ibid.*, **1948**, 1798.

In contrast to III and IV, C(7)-alkylperoxides (V) ran with I on TLC using solvent system 1, but system 2 was reasonably effective, giving the following *Rf* values (as blue spots on Merck Kieselguhr 60F254 on staining with H_2SO_4): ethyl-(0.20), iso-propyl-(7α: 0.25; 7β: 0.40), *tert*-butyl-(7α: 0.50; 7β: 0.60), and cumyl-(7α: 0.50; 7β: 0.60)-peroxides [*c.f.* I (0.75)]. The distribution ratios of the individual C(7)-peroxides could thus be calculated by using I as a parameter. C(5)-Alkylperoxides (solvent system 2; iso-propyl: 0.50, *tert*-butyl: 0.70, and cumyl: 0.70) were similarly detected in the early stages of the reaction but none of them was detectable in the final products.

Reactions in the Presence of Fe(acac)$_3$ (Table I)——Using the general procedure, reactions were carried out with the following materials, and gave the results cited below:

Peroxide	Substrate (I)	Metal complex	Solvent	Oily residue	Epoxide (II)
A. In benzene solution					
1. H_2O_2					
5.5 ml	100 mg	936 mg	100 ml	620 mg	1.7 mg
(5.4×10^{-1} M)	(2.2×10^{-3} M)	(2.5×10^{-2} M)			
2. EtOOH					
2.0	97.2	9.2	4	89.7	20
(3.3)	(3.8×10^{-2})	(4.3×10^{-3})			
3. iso-PrOOH					
3.0	317.4	26.6	15	308.1	54.1
(2.0)	(4.1×10^{-2})	(4.2×10^{-3})			
4. *tert*-BuOOH					
4.7	101.8	929.1	100	105	10
(4.7×10^{-1})	(2.4×10^{-3})	(2.6×10^{-2})			
5. Cum.OOH					
1.0	509.4	46.9	30	723	51.8
(2.2×10^{-1})	(3.8×10^{-2})	(4.2×10^{-3})			
B. In acetonitrile solution					
1. H_2O_2					
5.5	102	942.8	100	98	56
(5.4×10^{-1})	(2.4×10^{-3})	(2.7×10^{-2})			
2. EtOOH					
1.0	50	4.7	2	60	20
(3.3)	(3.9×10^{-2})	(4.4×10^{-3})			
3. iso-PrOOH					
0.5	50	4.7	2.5	60	9
(2.0)	(3.9×10^{-2})	(4.4×10^{-3})			
4. *tert*-BuOOH					
4.7	98	933.7	100	91	3
(4.7×10^{-1})	(2.3×10^{-3})	(2.6×10^{-2})			
5. Cum.OOH					
0.1	50	4.7	3	170	1
(2.3×10^{-1})	(3.9×10^{-2})	(4.4×10^{-3})			

Reactions in the Presence of Mo(CO)$_6$ (Table II)——Using the general procedure, reactions were carried out with the following materials and gave the results cited below:

Peroxide	Substrate (I)	Metal complex	Solvent	Oily residue	Epoxide (II)
A. In benzene solution					
1. H_2O_2					
0.5 ml	499.8 mg	1.9 mg	30 ml	513 mg	52 mg
(1.6×10^{-1} M)	(3.8×10^{-2} M)	(2.4×10^{-4} M)			
2. EtOOH					
0.1	108.7	0.38	6	95.7	66.6
(1.7×10^{-1})	(4.2×10^{-2})	(2.3×10^{-4})			
3. iso-PrOOH					
0.08	108.7	0.38	6	96.3	57.5
(1.6×10^{-1})	(4.2×10^{-2})	(2.3×10^{-4})			
4. *tert*-BuOOH					
0.05	50	0.19	3	48	a)
(1.7×10^{-1})	(4.2×10^{-2})	(2.3×10^{-4})			

Peroxide	Substrate (I)	Metal complex	Solvent	Oily residue	Epoxide (II)
5. Cum.OOH					
0.07	206.6	0.78	14	281.8	61.2
(4.1×10^{-2})	(4.0×10^{-2})	(2.3×10^{-4})			
B. In acetonitrile solution					
1. H_2O_2					
0.1	100	0.39	5	113	48
(1.6×10^{-1})	(3.9×10^{-2})	(2.5×10^{-4})			
2. EtOOH					
0.1	100	0.4	5	108	15
(1.7×10^{-1})	(3.8×10^{-2})	(2.5×10^{-4})			
3. iso-PrOOH					
0.08	100	0.4	5	117	34
(1.6×10^{-1})	(3.8×10^{-2})	(2.5×10^{-4})			
4. *tert*-BuOOH					
0.05	52.3	0.19	3	69	11.1
(1.7×10^{-1})	(4.2×10^{-2})	(2.3×10^{-4})			
5. Cum.OOH					
0.035	100	0.4	5	143	3
(4.1×10^{-2})	(3.8×10^{-2})	(2.5×10^{-4})			

a) not weighed.

Acknowledgement A part of this work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, for which we are grateful.