Stereoselectivity in the Epoxidation of βγ-Unsaturated Carboxylic Acids

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Epoxidation of the βγ-unsaturated acids (VII)—(IX) by peroxy-acids over a range of reaction conditions has been
investigated.   In non-basic solvents there is a significant tendency for preferential epoxidation cis to carboxy-group,
which is more marked for (IX) with pseudoaxial CO_2H.   This preference, which disappears in more basic solvents,
is explained in terms of H-bonding between CO_2H and peroxy-acid in the transition state (XVI).

THE influence of neighbouring functional groups on the
epoxidation of proximate double bonds by peroxy-
acids has been investigated extensively.[1]   However the
role of the carboxy-group in this respect seems to have
escaped systematic attention.   In a number of examples
from natural product chemistry of the epoxidation of un-
saturated carboxylic acids,[2] the influence of the carboxy-
group is obscured by the stereochemical complexity of

the system.   One particularly intriguing case is the
epoxidation of the dihydrophthalic acid (I) to the mono-
epoxide (II) and further to the diepoxide (III) in 84%
yield by *m*-chloroperbenzoic acid in ethyl acetate.[3]   In
contrast, the cycloheptadienedicarboxylic acid (IV) is
reported[4] to give the *cis*- (V) and the *trans*-epoxide (VI)
in the ratio 7 : 3 with *m*-chloroperbenzoic acid.   With
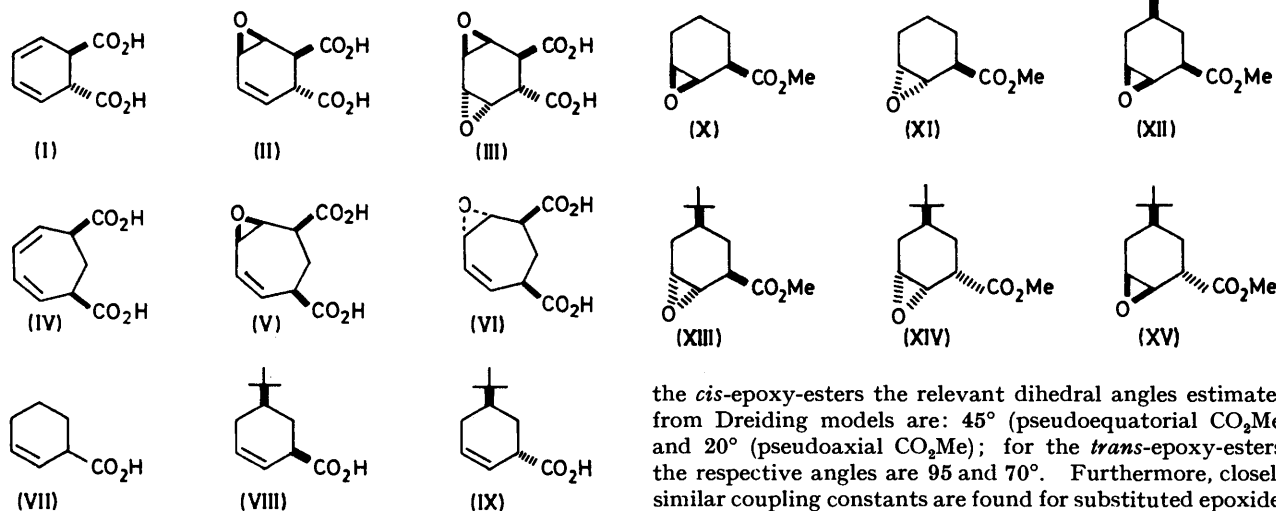these precedents in mind, we investigated the stereo-

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R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1; E. J. Corey, T. M.
Brennan, and R. L. Carney, *J. Amer. Chem. Soc.*, 1971, **93**, 7316.

[3] B. A. Chiasson and G. A. Berchtold, *J. Amer. Chem. Soc.*,
1974, **96**, 2898.
[4] S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard,
P. E. Georghiou, and G. S. Bates, *J. Amer. Chem. Soc.*, 1975, **97**,
3512.

chemistry of epoxidation of cyclohex-2-ene-1-carboxylic acid (VII) and the conformationally biassed analogues (VIII) and (IX), and their methyl esters.

(I)   (II)   (III)

(IV)   (V)   (VI)

(VII)   (VIII)   (IX)

(X)   (XI)   (XII)

(XIII)   (XIV)   (XV)

0 Hz. This is in line with expectations from the usual vicinal coupling constant–dihedral angle relationship.[6] For the cis-epoxy-esters the relevant dihedral angles estimated from Dreiding models are: 45° (pseudoequatorial CO_2Me) and 20° (pseudoaxial CO_2Me); for the trans-epoxy-esters, the respective angles are 95 and 70°. Furthermore, closely similar coupling constants are found for substituted epoxides of authentic stereochemistry in steroidal[7] and t-butylcyclohexyl[8] systems.

^{13}C N.m.r. chemical shift data for the six epoxy-esters are given in Table 1.

RESULTS

The preparation of the βγ-unsaturated acids (VII)—(IX) and their methyl esters is described elsewhere.[5]

TABLE 1

^{13}C Chemical shift data for epoxy-esters

Compound	C-1	C-2	C-3	C-4	C-5	C-6	CO_2	OMe	CMe_3	Me_3C
(X)	40.8	52.1 ^{a}	52.0 ^{a}	23.2 ^{b}	18.8	21.2 ^{b}	173.3	51.8		
(XI)	40.3	51.9	51.9	23.6 ^{a}	16.5	23.4 ^{a}	173.7	51.5		
(XII)	43.4	52.1 ^{a}	51.9 ^{a}	24.4 ^{b}	43.0	22.1 ^{b}	173.7	52.3	27.3	27.0
(XIII)	42.2	54.2 ^{a}	52.5 ^{a}	27.1 ^{b}	38.3	26.1 ^{b}	174.4	52.0	32.0	27.1
(XIV)	39.2	54.7 ^{a}	51.6 ^{a}	26.2 ^{b}	36.1	24.2 ^{b}	173.0	51.9	31.8	27.0
(XV)	41.1	52.6 ^{a}	52.1 ^{a}	24.8 ^{b}	38.9	22.2 ^{b}	173.6	51.8	32.0	26.8

^{a,b} Assignments interchangeable.

TABLE 2

Amount (%) of cis-epoxide for βγ-unsaturated carboxylic acids and esters

Method *	Solvent	(VII) Me ester	(VII)	(IX) Me ester	(IX)	(VIII) Me ester	(VIII)
(a)	$CHCl_3$	36	54	35	78	34	59
	CH_2Cl_2	37	55	36	79	32	59
	C_6H_6	36	55	38	78	31	57
	Et_2O	38	37	36	44	34	32
	EtOAc	36	38		53		31
(b)	CH_2Cl_2–AcOH	40	38	43	44	41	38
(c)	CH_2Cl_2	36	54	36	79	33	56
	Et_2O	35	37		34		32
(d)	$[CH_2]_4O$		36		37		34
	$CHCl_3$		55		77		60
(e)	$CHCl_3$–AcOH		38				

* See Experimental section; (a), (b), (e) with peroxyacetic acid, (c) with m-chloroperoxybenzoic acid, and (d) with polymeric peroxy-acid.

For assignment of stereochemistry to the respective epoxides, the methyl esters of the acids (VII)—(IX) were epoxidised with peracetic acid in methylene chloride, and the mixtures of epoxides formed were separated by chromatography. The cis-epoxy esters showed $J_{1,2}$ 4—5 Hz in the n.m.r. spectra, whereas the trans-epoxy-esters had $J_{1,2}$ ca.

Having assigned stereochemistry to the epoxy-esters, we could analyse the corresponding epoxy-acids by esterification with diazomethane followed by g.l.c. The results obtained for the stereochemistry of epoxidations of the carboxylic acids and esters under a range of conditions are summarised in Table 2.

[5] S. G. Davies and G. H. Whitham, *J.C.S. Perkin I*, 1976, 2279.

[6] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 281.

[7] D. K. Fukushima, M. Smuiowitz, J. S. Liang, and G. Lukacs, *J. Org. Chem.*, 1969, **34**, 2702; G. Lukacs and D. K. Fukushima, *ibid.*, p. 2707.

[8] P. Chamberlain, unpublished results; cf. ref. 9.

[9] P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc. (B)*, 1970, 1374.

DISCUSSION

With regard to the epoxidations of the βγ-unsaturated esters, Table 2 shows that the stereochemical outcome is insensitive to the conditions of epoxidation and to the precise orientation of the methoxycarbonyl group, i.e. whether pseudoaxial or pseudoequatorial. We consider that these observations are best interpreted in terms of the steric and polar influence of CO_2Me leading to predominant trans-epoxidation.[10]

The results for epoxidation of the βγ-unsaturated carboxylic acids can be divided into two groups: (a) those involving H-bond acceptor solvents (Et_2O, tetrahydrofuran, EtOAc, and AcOH) where the stereochemical outcome is closely similar to that for the corresponding esters, and (b) those involving a non-acceptor solvent ($CHCl_3$, CH_2Cl_2, or C_6H_6) where a cis-directing effect for CO_2H is apparent.

For the H-bond acceptor solvents it is considered that H-bonding between carboxy-group and solvent effectively disfavours interaction of CO_2H with peroxy-acid in the transition state. In support, it is known that carboxylic acids exist as monomers in such acceptor solvents.[11]

When non-H-bonding solvents are used it is apparent that interaction between $-CO_2H$ and the incoming peroxyacid can occur, thus favouring cis-epoxidation [cf. (XVI)]. In contrast to the situation in cyclic allylic


(XVI)
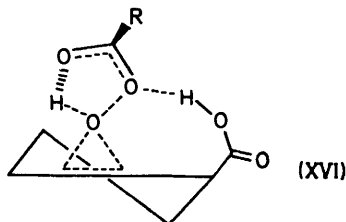
alcohols where a pseudoequatorial hydroxy-group is the more effective,[9] it is the pseudoaxial carboxy-group which is more efficient for these unsaturated acids. Owing to uncertainty about the precise positioning of peroxy-acid with respect to double bond in the epoxidation transition state [9] it is not however possible to provide a clear explanation for this.

The polymeric peroxy-acid of Hodge et al.[12] gave results for epoxidation of (VII) identical with those obtained with conventional peroxy-acids.

In the light of the maximum value of 79% cis-epoxidation found for epoxidation of the pseudoaxial acid (IX) in methylene chloride, the very efficient conversion of (I) to (II) in ethyl acetate is surprising. It may be that a number of factors conspire to give an anomalous result for (I); thus some indication that special steric effects could be present in the trans-5,6-disubstituted cyclohexa-1,3-dienyl system is given by the observation [13] that the

[10] G. Bellucci, F. Marioni, and A. Marsili, Tetrahedron, 1972, 28, 3393.
[11] R. P. Bell, O. M. Lidwell, and M. W. Vaughan-Jackson, J. Chem. Soc., 1936, 1798.

diacetate (XVII) is converted by perbenzoic acid in chloroform into the isomeric epoxides (XVIII) and (XIX) in the ratio 2 : 1. Another consideration is that the stronger dicarboxylic acid could be more effective in

(XVII)   (XVIII)   (XIX)

(XX)   (XXI)
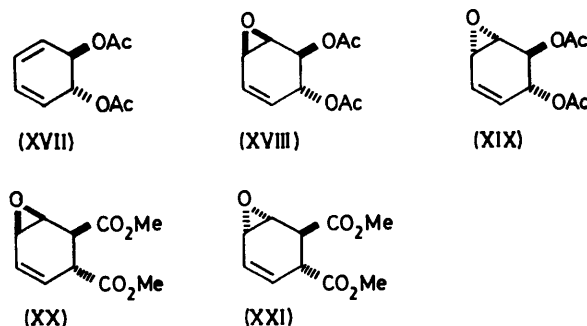
favouring a transition state akin to (XVI), though our results (Table 2) show that ethyl acetate would not be expected to be a favourable solvent in this respect.

In a recent paper [14] the epoxidation of the dimethyl ester of (I) with m-chloroperbenzoic acid in chloroform was described. The epoxides (XX) and (XXI) were formed in the ratio 90 : 10. This result was used to argue that the CO_2Me group can have a cis-directing effect on epoxidation of a βγ-double bond. Our results on the epoxidation of the esters of the acids (VII)—(IX) do not substantiate this suggestion, and, as explained earlier, we believe that it is unwise to generalise from results in the trans-5,6-disubstituted cyclohexa-1,3-dienyl system.

In summary we have shown that a suitably placed carboxy-group can provide a moderate facilitation of cis-epoxidation by a peroxy-acid provided that the reaction is not carried out in an H-bond acceptor solvent.

EXPERIMENT

[1]H N.m.r. were recorded with Perkin-Elmer R32 and R14 instruments operating at 90 and 100 MHz, respectively (Me4Si as internal standard). Pulse Fourier transform [13]C n.m.r. spectra were recorded with a Bruker WH 90 instrument operating at 22.63 MHz for 20% solutions in $CDCl_3$. Chemical shifts are quoted in p.p.m. downfield of internal Me4Si. Analytical g.l.c. was carried out on a 15% Carbowax column.

Methyl cis- and trans-2,3-Epoxycyclohexanecarboxylates.— Methyl cyclohex-2-ene-1-carboxylate (950 mg, 6.8 mmol), anhydrous sodium acetate (1 g), chloroform (25 ml), and peroxyacetic acid (20%; 5 ml, 2 equiv.) were stirred together at 20 °C for 14 h. The solution was washed successively with brine and aqueous sodium carbonate, and dried (MgSO4). Evaporation gave a mixture of epoxy-esters (930 mg). G.l.c. (135°) gave the ratio of trans to cis as 70 : 30, with relative retention times 1 : 1.5, respectively. Column chromatography [silica gel M60 (150 g); light petroleum–ether (2 : 1) as eluant] gave the two epoxy-esters as single compounds (g.l.c.).

[12] C. R. Harrison and P. Hodge, J.C.S. Chem. Comm., 1974, 1009; J.C.S. Perkin I, 1976, 605.
[13] M. Nakajima, A. Hasegawa, and N. Kurihara, Chem. Ber., 1962, 95, 2708.
[14] S. A. Cerefice and E. K. Fields, J. Org. Chem., 1976, 41, 355.

Methyl trans-2,3-*epoxycyclohexanecarboxylate* was further purified by distillation [b.p. 110° (bath) at 12 mmHg] (Found: C, 61.3; H, 7.9. $C_8H_{12}O_3$ requires C, 61.5; H, 7.75%), τ (CCl_4) 6.30 (3 H, s, Me), 6.76 (1 H, d, $J_{2,3}$ 4 Hz, C-2 H), 6.81 (1 H, m, C-3 H), 7.18 (1 H, dd, J 5 and 8 Hz, C-1 H), and 8.0—8.8 (6 H), m/e 156 $(M)^+$.

Methyl cis-2,3-*epoxycyclohexanecarboxylate* was further purified by distillation [b.p. 110° (bath) at 12 mmHg] (Found: C, 61.5; H, 7.7%) τ (CCl_4) 6.26 (3 H, s, Me), 6.70 (1 H, t, $J_{1,2} = J_{2,3} = 4$ Hz, C-2 H), 6.81 (1 H, m, C-3 H), 7.25 (1 H, m, C-1 H), and 8.0—8.9 (6 H), m/e 156 (M^+).

Epoxides from Methyl trans-5-t-*Butylcyclohex-2-enecarboxylate*.—The *trans*-methyl ester (500 mg), methylene chloride (15 ml), anhydrous sodium acetate (2 g), and per-oxyacetic acid (40%; 3.5 ml) were stirred at 20 °C for 14 h. Work-up as before gave a mixture of epoxy-esters (510 mg). Preparative t.l.c. [double elution with light petroleum–ether (4 : 1)] gave *methyl* trans-2,3-*epoxy*-trans-5-t-*butyl-cyclohexanecarboxylate* (200 mg), R_F 0.45 (Found: C, 68.15; H, 9.6. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%), τ (CCl_4) 6.29 (3 H, s, OMe), 6.75 (1 H, m, C-3 H), 6.85 (1 H, d, $J_{2,3}$ 3.5 Hz, C-2 H), 6.90 (1 H, m, J 5 and 8.5 Hz, C-1 H), 8.1—9.0 (5 H), and 9.16 (9 H, s, Bu^t), m/e 212 (M^+); and *methyl* cis-2,3-*epoxy*-trans-5-t-*butylcyclohexanecarboxylate* (150 mg), R_F 0.33 (Found: C, 67.9; H, 9.4%), τ (CCl_4) 6.26 (3 H, s, OMe), 6.70 (1 H, dd, $J_{2,3}$ 4, $J_{1,2}$ 5 Hz, C-2 H), 6.82 (1 H, t further split, $J_{2,3} = J_{3,4} = 4$ Hz, C-3 H), 7.05 (1 H, t further split, $J_{1,2} = J_{1,6} = 5$ Hz, C-1 H), 7.7—8.1 (2 H), 8.5—9.0 (3 H), and 9.12 (9 H, s, Bu^t), m/e 212 (M^+).

Both isomers gave single peaks on g.l.c. (180 °C), with relative retention times 1 : 1.5, respectively.

Epoxides from Methyl cis-5-t-*Butylcyclohex-2-enecarboxyl-ate*.—Epoxidation of the *cis*-methyl ester in an analogous manner to the *trans*-ester gave a mixture of epoxy-esters (500 mg). Preparative t.l.c. under the same conditions as before gave *methyl* trans-2,3-*epoxy*-cis-5-t-*butylcyclohexane-carboxylate* (240 mg), R_F 0.45 (Found: C, 67.7; H, 9.6. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%), τ (CCl_4) 6.30 (3 H, s, CO_2Me), 6.75 (1 H, d, $J_{2,3}$ 4 Hz, C-2 H), 6.85 (1 H, d further split, $J_{2,3}$ 4 Hz, C-3 H), 7.32 (1 H, dd, $J_{1,6}$ 6 and 12 Hz), 8.4—9.0 (3 H), and 9.12 (9 H, s, Bu^t), m/e 212 (M^+); and *methyl* cis-2,3-*epoxy*-cis-5-t-*butylcyclohexanecarboxylate* (140 mg), R_F 0.33 (Found: C, 68.0; H, 9.6%), τ (CCl_4) 6.29 (3 H, s, CO_2Me), 6.72 (1 H, d further split, $J_{2,3}$ 4 Hz, C-3 H), 6.95

(1 H, dd, $J_{1,2}$ 5, $J_{2,3}$ 4 Hz, C-2 H), 7.39 (1 H, m, C-1 H), 8.0—9.1 (5 H), and 9.14 (9 H, s, Bu^t), m/e 212 (M^+).

Both isomers gave single peaks on g.l.c. (180 °C), with relative retention times 1.25 : 1.8, respectively, on the same scale as before.

Epoxidations of the βγ-*Unsaturated Acids and Esters*.— The results are summarised in Table 2. The ester epoxid-ations were worked up by adding ether (20 ml) and washing successively with brine (2 × 30 ml) and aqueous sodium carbonate. The organic solutions were dried ($MgSO_4$) and concentrated. The acid epoxidations were worked up by adding ether (10 ml), washing with brine (2 × 30 ml), and treating with an excess of diazomethane. The excess of diazomethane was destroyed with acetic acid and the result-ing solution worked up as for the esters.

The product mixtures were analysed by g.l.c. (15% Carbowax; 160 °C). Each value quoted in Table 2 is the average of three independent experiments (values within ±1%). The methods were as follows. (a) The acid or ester (0.4 mmol), solvent (10 ml), anhydrous sodium acetate (500 mg), and peroxyacetic acid (40%; 0.35 ml) were mixed and set aside at 20 °C for 90 min before work-up. (b) The acid or ester (0.4 mmol), solvent (1.25 ml), and peroxyacetic acid (40%; 0.35 ml) were mixed and set aside at 20 °C for 90 min. (c) The acid or ester (0.4 mmol), solvent (10 ml), and *m*-chloroperoxybenzoic acid (3 equiv.) were thoroughly mixed and set aside at 20 °C for 90 min. (d) The acid (0.4 mmol), polymeric peroxy-acid (100 mg, 2 equiv.), and solvent (10 ml) were stirred at 40 °C for 90 min. The mixture was filtered and worked-up as before. (e) The method was analogous to (a), but acetic acid (3.85 ml) was added to the reaction mixture.

The addition or omission of sodium acetate in method (a), (b), or (c) had no effect on the product ratio. If the reaction mixtures were left for a long time (16 h) before work-up, some decomposition of the *cis*-epoxy-acids oc-curred. The decomposition products were easily detect-able by g.l.c. after work-up.