Catalytic Epoxidation of Methyl Linoleate

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ABSTRACT: The epoxidation of methyl linoleate was examined using transition metal complexes as catalysts. With a catalytic amount of methyltrioxorhenium (4 mol%) and pyridine, methyl linoleate was completely epoxidized by aqueous H_2O_2 within 4 h. Longer reaction times (6 h) were needed with 1 mol% catalyst loading. Manganese tetraphenylporphyrin chloride was found to catalyze the partial epoxidation of methyl linoleate. A mono-epoxidized species was obtained as the major product (63%) after 20 h.

Paper no. J10722 in *JAOCS 81*, 477–480 (April 2004).

KEY WORDS: Catalytic epoxidation, epoxidized fatty acid methyl esters, iron porphyrin, manganese porphyrin, methyl linoleate, methyltrioxorhenium.

Biorenewable materials such as FA derivatives and carbohydrates have recently received increasing attention as a means of addressing environmental and economical concerns. Introduction of functional groups into these substances provides new materials that can replace petroleum-derived compounds, serve as valuable intermediates, or be utilized directly. For example, epoxidized FA are used as plasticizers and stabilizers for halogen-containing polymers such as polyvinyl chloride (1).

Traditionally, FA and their derivatives are epoxidized by peracids that are generated *in situ* or preformed by the reaction of formic or acetic acid with hydrogen peroxide (2). However, these processes suffer from acid-catalyzed epoxy ring-opening reactions. By using *in situ*-generated peracids at low concentrations, unwanted epoxide ring opening can be minimized. Efforts to develop milder and more effective epoxidation of FA and related derivatives are continuing. More recently, procedures using enzymatic peroxygenase to epoxidize FA have appeared (3,4).

A number of efficient transition metal-based catalysts have been developed to effect the epoxidation of olefins, some with excellent regio-, stereo-, and enantioselectivities. For example, the Sharpless epoxidation catalysts based on titanium(IV) alkoxide complexes are highly effective at converting allylic alcohols to allylic epoxides (5). With the simple addition of tartrates, high enantioselectivity can be achieved.

Metalloporphyrins have been widely investigated owing to their relevance to biological oxidation reactions. In particular, manganese and iron porphyrins have shown great activity as olefin epoxidation catalysts, utilizing a variety of oxygen sources such as iodosylbenzene, alkyl hydroperoxide, aqueous sodium hypochlorite (NaOCl), persulfate, and O_2 with a reducing cofactor (6). Use of inexpensive NaOCl is especially attractive. Chiral salen-based manganese complexes have given remarkable results in the asymmetric epoxidation of olefins (7).

Methyltrioxorhenium (MTO) is another effective catalyst for the epoxidation of olefins (8,9). Further elaboration of this system revealed that addition of a large excess of nitrogenous bases, particularly pyridine under biphasic conditions, is beneficial for both product selectivity and catalyst lifetime (10). This system has been utilized successfully in the epoxidation of fish oils (11) and soybean oils (12).

Linoleic acid, bearing two nonconjugated C=C double bonds, is one of the major components in soybean oils. In this study, methyl linoleate was chosen as a model compound for FAME and oils. We examined the utility of metalloporphyrins and MTO in the catalytic epoxidation of methyl linoleate using the readily available oxidants NaOCl and H_2O_2.

EXPERIMENTAL PROCEDURES

Reagents. Methyl linoleate (containing 6.5% methyl oleate) was prepared by urea fractionation of safflower oil (13). *Cis*- and *trans*-9,10-epoxystearic acids were obtained from Sigma (St. Louis, MO) and esterified with diazomethane according to a literature method (14). MTO, *meso*-tetraphenylporphyrin manganese(III) chloride [Mn(TPP)Cl], *meso*-tetraphenylporphyrin iron(III) chloride [Fe(TPP)Cl], *m*-chloroperoxybenzoic acid (*m*CPBA), and tetra-*n*-butylammonium bromide (n-Bu_4NBr) were obtained from Aldrich (Milwaukee, WI). Hydrogen peroxide (30%) and pyridine were obtained from Fisher Scientific (Fair Lawn, NJ). Aqueous NaOCl (6.0% by wt) was obtained from Clorox Co. (Oakland, CA). Chemicals obtained from commercial vendors were used as received.

Characterization methods. All ^1H NMR and proton-decoupled ^{13}C NMR spectra were acquired on a 400 MHz Bruker DRX (Karlsruhe, Germany) or a 300 MHz Varian VXR (Palo Alto, CA) spectrometer using $CDCl_3$ as a solvent. Chemical shifts were referenced to proton solvent impurities (δ 7.24 for ^1H, 77.5 for ^{13}C). GC–MS analyses were performed on a Varian gas chromatograph (DB-5MS capillary column; oven program: 110°C for 3 min, 15°C/min to 280°C and held for 10 min) coupled to a Finnigan Magnum ITD ion-trap detector (Bremen, Germany). GC analyses were performed on a Hewlett-Packard (Wilmington, DE) HP 5890II gas chromatograph

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equipped with an FID and a DB-5 capillary column (30 m × 0.32 mm i.d; oven program: 110°C for 2 min, 15°C/min to 250°C, and held for 10 min). TLC was performed using 500-µm silica gel GF plates (Alltech Associates Inc., Deerfield, IL) and hexane/diethyl ether 3:1 (vol/vol) as eluent.

Purification of methyl vernoleate. *Vernonia galamensis* seed lipids were extracted by hexane and converted into their methyl esters according to Hammond (15). Methyl vernoleate (*cis*-12,13-epoxy-9-octadecenoate) was then obtained by TLC purification of the methyl esters using hexane/diethyl ether 3:1 (vol/vol) as the eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.55–5.35 (*m*, 2H, vinyl-H), 3.64 (*s*, 3H, $COOCH_3$), 2.90 (*m*, 2H, epoxy-C*H*), 2.40–2.10 (*m*, 2H, 11-CH_2), 2.27 (*t*, *J* = 7.2 Hz, 2H, 2-CH_2), 2.01 (*m*, 2H, $CH{=}CHCH_2CH_2$), 1.63–1.20 (*m*, aliphatic CH_2), 0.87 ppm (*m*, 3H, 18-CH_3). The ^{1}H NMR data agreed with those in the literature (16).

Epoxidation of methyl linoleate with m*CPBA*. To a stirred solution of methyl linoleate (87.6 mg, 0.297 mmol) in CH_2Cl_2 (5 mL), a solution of *m*CPBA (166 mg, 0.963 mmol) in CH_2Cl_2 (5 mL) was added portionwise. The mixture was stirred for 6 h at room temperature, washed with 5% $NaHCO_3$ (2 × 10 mL), then with water (3 × 10 mL), and dried over anhydrous Na_2SO_4. Removal of solvent under vacuum afforded a yellowish oil, 69.2 mg (72%). ^{1}H NMR spectroscopy showed it was a diepoxide. ^{1}H NMR data were experimentally identical to those listed below.

Catalytic epoxidation of methyl linoleate using MTO/H_2O_2/pyridine. A round-bottomed flask was charged with MTO (3.8 mg, 0.015 mmol) in CH_2Cl_2 (1.5 mL). A solution of pyridine (22.4 mg, 0.283 mmol) and methyl linoleate (109 mg, 0.371 mmol) in CH_2Cl_2 (1.5 mL) was added. The reaction was started by addition of 30% H_2O_2 (0.25 mL, 2.5 mmol). The mixture turned yellow immediately and remained yellow throughout the reaction. After completion of the reaction (4 h), as detected by the disappearance of methyl linoleate by GC, the mixture was washed with water (2 × 10 mL) and aqueous $Na_2S_2O_3$ (10%, 5 mL), dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation under vacuum. This provided a yellowish oil. Yield: 106 mg (88%). TLC separation of the reaction mixture afforded methyl 9,10-12,13-diepoxystearate (81% yield) and ~7% methyl *cis*-9,10-epoxystearate, resulting from epoxidation of methyl oleate, which was present (6.5%) in the starting material. Methyl 9,10-12,13-diepoxystearate: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.64 (*s*, 3H, $COOCH_3$), 3.08 (*m*, 2H, 10, 12-C*H*), 2.95 (*m*, 2H, 9, 13-C*H*), 2.28 (*t*, *J* = 7.4 Hz, 2H, 2-CH_2), 1.72 (*m*, 2H, 11-CH_2), 1.59 (*m*, 2H, 3-CH_2), 1.48 (*m*, 8H), 1.30 (*m*, 10H), 0.87 ppm (*t*, *J* = 7.0 Hz, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 174.53 ($COOCH_3$), 57.33, 57.29, 57.05, 57.00, 54.68, 54.67, 54.52 (OCH), 51.76 ($COOCH_3$), 34.37, 32.01, 29.62, 29.49, 29.35, 28.23, 28.16, 27.55, 27.27, 26.87, 26.76, 26.59, 26.48, 25.22, 22.91, 14.32 ppm (CH_3CH_2). EI–MS: *m/z* 327 ($[M + 1]^+$), 309 ($[M + 1]^+ - 18$), 277, 253, 187, 165, 155 (base peak), 147, 137, 109, 95, 81. Methyl *cis*-9,10-epoxystearate: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.65 (s, 3H, $COOCH_3$), 2.88 (*m*, 2H, epoxy-C*H*), 2.29 (*t*, *J* = 7.6 Hz, 2H, 2-CH_2), 1.60 (*t*, *J* = 7.2 Hz, 2H), 1.47 (*m*, 4H), 1.45–1.20 (*m*, 20H), 0.86 ppm (*t*, *J* = 6.8 Hz, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 174.77 ($COOCH_3$), 57.79, 57.74 (OCH), 51.92, 34.45, 32.33, 30.03, 30.01, 29.79, 29.70, 29.64, 29.42, 28.28, 28.24, 27.07, 27.03, 25.10, 23.14, 14.58. EI–MS: *m/z* 313 ($[M + 1]^+$), 295 ($[M + 1]^+ - 18$), 281 ($M^+ - OCH_3$), 263 ($M^+ - OCH_3 - 18$), 245, 199, 171, 155, 109. These data agreed with that of an authentic methyl *cis*-9,10-epoxystearate sample. The epoxy protons at 2.88 ppm are characteristic of a *cis* epoxy group. The ^{1}H NMR data for an authentic *trans*-9,10-epoxystearic acid sample showed that the *trans* epoxy protons resonated at 2.63 ppm: ($CDCl_3$, 400 MHz) δ 2.63 (*m*, 2H, epoxy-C*H*), 2.32 (*t*, *J* = 7.6 Hz, 2H, 2-CH_2), 1.60 (*m*, 2H), 1.47 (*m*, 4H), 1.20–1.45 (*m*, 20H), 0.85 ppm (*t*, *J* = 6.8 Hz, 3H, 18-CH_3).

Catalytic epoxidation of methyl linoleate using Mn(TPP)-Cl/NaOCl/pyridine/Bu_4NBr. A round-bottomed flask was charged with Mn(TPP)Cl (4.5 mg, 0.0064 mmol), pyridine (29.9 mg, 0.378 mmol), *n*-Bu_4NBr (37.1 mg, 0.115 mmol), methyl linoleate (101 mg, 0.341 mmol), and CH_2Cl_2 (8 mL). Aqueous NaOCl (1.0 mL, 0.80 mmol) was added to the solution with stirring, and after 8 h another 1 mL of NaOCl was added. After an additional 12 h of reaction time, GC analysis showed the total consumption of methyl linoleate. The reaction mixture was washed with water (4 × 10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under vacuum afforded a yellow oil, 86.2 mg. ^{1}H NMR spectroscopy revealed that the major species was the monoepoxidation product. ^{1}H NMR of the monoepoxide ($CDCl_3$, 400 MHz): δ 5.55–5.35 (*m*, 2H, vinyl-H), 3.64 (*s*, 3H, $COOCH_3$), 2.90 (*m*, 2H, epoxy-C*H*), 2.40–2.10 (*m*, 2H, 11-CH_2), 2.28 (*t*, *J* = 7.5 Hz, 2H, 2-CH_2), 2.01 (*m*, 2H, $CH{=}CHCH_2CH_2$), 1.63–1.20 (*m*, CH_2), 0.87 ppm (*m*, 3H, 18-CH_3). EI–MS: *m/z* 311 ($[M + 1]^+$, base peak), 293 ($[M + 1]^+ - 18$), 279 ($M^+ - 31$), 261, 243. The presence of diepoxide was observed with a monoepoxide/diepoxide ratio of 3.5:1. Minor peaks for allylic hydroxylation products (<5%) were also observed at 3.4 and 4.1 ppm.

RESULTS AND DISCUSSION

We examined the utility of metalloporphyrins for catalyzing the epoxidation of methyl linoleate. Mn(TPP)Cl (2 mol%) was used as a catalyst, with NaOCl (2.4 equiv per linoleate) as the oxidant in the presence of a phase-transfer agent, *n*-Bu_4NBr. Pyridine was added to reduce the oxidative degradation of the catalyst. A second portion of NaOCl (2.4 equiv) was added after 8 h. The reaction proceeded relatively slowly, taking ~20 h to consume all the starting methyl linoleate. After workup, the ^{1}H NMR spectrum showed that monoepoxide was the major product. Vinylic (5.55–5.35 ppm) and epoxy (2.90 ppm) proton signals were both observed as 2H multiplets. ^{1}H NMR data for the monoepoxide agreed with that of an authentic sample of methyl vernoleate. However, the reactivity of the two C=C bonds toward epoxidation was very similar and it was difficult to differentiate between the resulting monoepoxidized methyl 12,13-epoxy-9-octadecenoate (16) and methyl 9,10-epoxy-12-octadecenoate (17) by ^{1}H NMR spectroscopy alone. Indeed, it appeared that both of them were present in the

TABLE 1
Epoxidation of Methyl Linoleate Catalyzed by Methyltrioxorhenium (MTO)[a]

Time (h)	Methyl linoleate%	Monoepoxide%	Diepoxide%	Epoxidation%[b]
0.5	46.0	51.9	2.1	28.5
1.0	30.9	59.7	9.3	41.7
2.0	11.8	65.4	22.8	53.3
3.0	6.7	65.1	28.2	62.8
4.5	1.4	58.5	40.1	72.0
6.0	0	51.8	48.2	76.8

[a] Reaction conditions: 1 mol% MTO, 24 mol% pyridine, 3.6 equiv H_2O_2.
[b] Epoxidation (%) of all C=C bonds. This was determined by the disappearance of vinyl proton signals by ^{1}H NMR spectroscopy. Within NMR error, epoxidation% = 1/2 monoepoxide% + diepoxide%.

monoepoxide sample above, as four peaks of roughly equal intensity (133.08, 132.93, 124.30, and 124.16 ppm) were observed in the alkenic carbon region in the ^{13}C NMR spectrum. In contrast, only two peaks were observed in this region for the authentic methyl vernoleate (16). The presence of diepoxide was also observed with a monoepoxide/diepoxide ratio of ~3.5 to 1. The level of overall epoxidation was about 61%, as determined by the disappearance of vinylic protons and the appearance of epoxy protons (3.1–2.8 ppm). Notably, very small peaks around 3.4 and 4.1 ppm were also observed, indicating the presence of hydroxy groups, probably resulting from epoxide ring opening reactions or allylic oxidation (<5%).

Fe(TPP)Cl (2 mol%) was examined under similar conditions, using NaOCl (3.8 equiv per linoleate) as the oxidant in the presence of a phase-transfer agent. However, the epoxidation reaction was significantly slower than the Mn(TPP)Cl-catalyzed process. Methyl linoleate was still present after 5 d of reaction, even with a higher catalyst loading (~4 mol%) and a larger amount of oxidant (6.3 equiv per linoleate). The degradation of the Fe(TPP)Cl catalyst was quite fast, as the characteristic dark-brown color of the iron(III) porphyrin faded within 1 h.

MTO was found to be a highly effective catalyst for the epoxidation of methyl linoleate. With 4 mol% of MTO and 6.6 equiv of H_2O_2, methyl linoleate was oxidized within 4 h to the diepoxide in 81% isolated yield. The yellow color of the initial solution was maintained throughout the reaction and is characteristic of the catalytically active species responsible for epoxidation. This indicated that the catalyst system is robust (18). The product obtained by this procedure has an NMR spectrum experimentally identical to that obtained from *m*CPBA epoxidation of methyl linoleate. The presence of hydroxy groups was not detected by ^{1}H NMR spectroscopy in either case. The complete disappearance of vinylic protons at 5.35 ppm and the appearance of epoxide protons at 3.07 and 2.95 ppm in the ^{1}H NMR spectrum indicated the total conversion of double bonds to epoxides. In accord with this, alkenic carbons were not observed in the ^{13}C NMR spectrum. Instead, seven peaks of roughly equal intensity around 54–58 ppm were attributed to epoxide carbons. This also suggested that the product diepoxide was actually a mixture of diastereomers with an *anti/syn* ratio of approximately 1:1 (19). GC–MS data supported this analysis with two closely spaced GC peaks of similar integrated areas and measured masses of 327 amu for the $[M + 1]^+$ ion.

An analysis of the geometric form of the diepoxide was based on the ^{1}H NMR data for *cis* and *trans* monoepoxides. The epoxy protons in *cis*-9,10-epoxystearate appeared at 2.88 ppm (20). In an authentic sample of *trans*-9,10-epoxystearate, the epoxy protons appeared at 2.63 ppm. Moreover, the presence of a homoallylic vinyl group had little effect on the position of *cis* epoxy protons (2.90 ppm) in methyl vernoleate. On these grounds, it seemed reasonable to assume that the diepoxide obtained here was exclusively of the *cis-cis* configuration, since no epoxy proton signals near 2.6 ppm were observed. This is consistent with the general aspect of MTO-catalyzed epoxidations in which the stereochemistry about double bonds is retained in the product (8).

The reaction course of the MTO-catalyzed epoxidation of methyl linoleate was further followed in $CDCl_3$ *via* NMR spectroscopy, using 1 mol% catalyst (Table 1). It is clear that the activity of this catalytic system decreased over time, as the consumption of methyl linoleate became slower with time and the accumulation of pyridine oxide was evident from ^{1}H NMR spectroscopy (18). Unlike the enzyme-catalyzed system (4), the formation of diepoxide occurred in the early stages of the reaction and well before the total consumption of methyl linoleate.

ACKNOWLEDGMENTS

This work was supported in part by a research grant from the U.S. Department of Energy Renewable Resources, New Catalysts and Processes Program, administered by the Institute for Physical Research and Technology.

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[Received August 21, 2003; accepted March 4, 2004]