Phase Transfer Agents. II. Stereospecific Hydroxylation of Oleyl and Elaidyl Alcohol and Periodic Acid Cleavage of Epoxides[1]

TOMOYUKI OKIMOTO and **DANIEL SWERN,** Fels Research Institute
and Department of Chemistry, Temple University, Philadelphia, PA 19122

ABSTRACT AND SUMMARY

Oleyl and elaidyl alcohol have been stereospecifically hydroxylated by cold, dilute alkaline potassium permanganate to *erythro-* and *threo*-9,10-dihydroxyoctadecanol, respectively, in 40-80% yields in a water-methylene chloride heterogeneous system. Phase transfer agents (PTA) were used to transport permanganate ion from the aqueous to the organic phase. In the absence of PTA, hydroxylation did not take place. Periodic acid cleavage of epoxides in a water-methylene chloride system was studied in the absence and presence of PTA. At slow stirring rates PTA exert a rate accelerating effect in cleaving certain epoxides to aldehydes but with vigorous stirring use of PTA has only a marginal advantage.

INTRODUCTION

In our previous paper (1) we reported on the comparative efficiency of quaternary ammonium and phosphonium halides as phase transfer agents (PTA) in transferring permanganate, periodate, and cyanate ions from aqueous to organic phases in heterogeneous systems. With that information we were now in a position to study the reaction of those water-soluble inorganic ions with lipids and other water-insoluble compounds in heterogeneous aqueous-organic solvent systems. In this paper we are reporting our results on the stereospecific dihydroxylation of oleyl and elaidyl alcohol with alkaline potassium permanganate and the carbon-carbon cleavage of water-insoluble epoxides by periodic acid—both reactions being conducted in the presence of selected PTA.

No problem exists in the stereospecific hydroxylation of oleic and elaidic acid with aqueous alkaline potassium permanganate to *erythro-* and *threo*-9,10-dihydroxystearic acid, respectively, as both unsaturated fatty acids form water-soluble soaps (2). In contrast, the insolubility of oleyl and elaidyl alcohol in aqueous base precludes a similar direct hydroxylation procedure. This problem was overcome by Collin and Hilditch (3) who prepared the base-soluble hydrogen phthalate esters of these alcohols and then hydroxylated the salts of the monoesters with cold, dilute aqueous alkaline potassium permanganate. This hydroxylation procedure is indirect and cumbersome as it first requires esterification of the alcohols and then hydrolysis of the resulting hydroxylated esters. We desired a direct, single step stereospecific oxidation of oleyl and elaidyl alcohol to *erythro-* and *threo*-9,10-dihydroxyoctadecanol, respectively, by potassium permanganate.

RESULTS AND DISCUSSION

Stereospecific Hydroxylation

Weber and Shepherd (4) were apparently the first to show that certain cyclic olefins—cyclohexene, *cis*-cyclooctene and *trans*-cyclododecene—can be oxidized stereospecifically to vicinal *cis*-diols by cold dilute alkaline potassium permanganate using catalytic quantities of benzyltriethylammonium chloride as the PTA in a water-methylene chloride system. Yields of 1,2-diols do not exceed 50% with the large ring cycloalkenes and are substantially lower (15%) with cyclohexene. We have confirmed Weber and Shepherd's results and have also shown that the low yields are a consequence of considerable overoxidation to ketols, diketones, and dibasic acids (Okimoto and Swern, unpublished observations). Overoxidation is more severe with cyclohexene as the resulting 1,2-diol has considerable solubility in the aqueous potassium permanganate phase. In the absence of PTA, oxidation is extremely slow and yields of diols are less than 10% even in the more favorable cases; after lengthy reaction times olefin is largely recovered.

Based on our work on the efficiency of transfer of MnO_4^- from water into organic solvents (1) and that of Herriott and Picker (5), we selected tetrabutylphosphonium chloride (TBPC) and tetrabutylammonium bromide (TBAB) as the preferred PTA for studying the alkaline potassium permanganate hydroxylation of oleyl and elaidyl alcohol in water-methylene chloride systems. Tables I and II summarize the results of numerous experiments on the hydroxylation of oleyl and elaidyl alcohol, respectively, at O C in the heterophasic system of aqueous alkaline potassium permanganate and methylene chloride containing PTA.

Experiment 1, Table I, demonstrates that hydroxylation of oleyl alcohol does not occur in the absence of PTA and the alcohol is largely unaltered (91-96%). For best results (Expts. 4-6) (a) an excess of potassium permanganate is needed (molar ratio 3:1); (b) the preferred concentration of base is 15-20%; (c) the volume of methylene chloride should be minimal; and (d) 6-10 hr reaction time are optimum. TBPC and TBAB give virtually identical results under the optimum conditions. Maximum yields of *erythro*-9,10-dihydroxyoctadecanol, mp 126 C (3), are 60-80%.

Elaidyl alcohol does not give as high yields of triol as oleyl alcohol does. As shown in Table II, maximum yields of *threo*-9,10-dihydroxyoctadecanol, mp 82 C (3), are only 40-50%. A smaller excess of potassium permanganate can be used but more methylene chloride is required because of the lower solubility of elaidyl alcohol at 0 C. With elaidyl alcohol, considerable overoxidation occurs.

Material unaccounted for in Tables I and II consists largely of oily overoxidation products; they were recovered from filtrates in workup procedures. No work was done on the byproduct mixture from oleyl alcohol as its conversion to triol was reasonably high but the byproducts from elaidyl alcohol oxidations were reduced with sodium borohydride (6). The major gas liquid chromatography (GLC) peak had the same retention time as that of authentic triol but no further work was done on the complex byproduct mixture.

Periodic Acid Cleavage of Epoxides

Cleavage of the carbon-carbon bond of epoxides by periodic acid is well known. The reaction has been con-

---

[1] Presented at the AOCS meeting, New York, May 1977.

TABLE I

Alkaline Potassium Permanganate Oxidation of Oleyl Alcohol to *erythro*-9,10-Dihydroxyoctadecanol[a]

Expt. No.	CH_2Cl_2, ml	$KMnO_4$, mol	NaOH Solution		PTA[b], mol	Time, hr	Triol, %	Oleyl Alcohol, %
			Conc, %	Volume, ml				
1	100	0.02	40	100	0	16	0-Tr[c]	91-96[c]
2	100	0.02	40	100	TBPC 0.005	16	35[c]	35[c]
3	80	0.04	15	200	TBPC 0.002	10	50[c]	13[c]
4	80	0.06	15	200	TBPC 0.004	6	70[c]	5[c]
5	80	0.06	20	200	TBAB 0.004	9	62[d]	Not determined
6	20	0.06	20	200	TBAB 0.004	8	80[e]	Not determined

[a] Oleyl alcohol (5.37 g, 0.02 mol) and PTA dissolved in CH_2Cl_2. $KMnO_4$ dissolved in aqueous NaOH solution. The two phase system was stirred vigorously at 0 C for the times indicated. For workup see Experimental Procedures.

[b] TBPC = tetrabutylphosphonium chloride; TBAB = tetrabutylammonium bromide.

[c] Determined by gas liquid chromatography using authentic *erythro*-triol and oleyl alcohol for calibration purposes (see Experimental Procedures).

[d] The triol was isolated by washing the reaction mixture successively with aqueous $NaHSO_3$ and 6 *N* HCl and either filtering it off or extracting it with ether. The crude triol was usually about 95% pure, mp 126 C. Recrystallization from ethyl acetate yielded analytically pure *erythro*-triol.

[e] The triol was isolated by filtration as described in footnote d but owing to the high concentration of the solution, the product was >90% pure, mp 126 C (to turbid liquid).

TABLE II

Alkaline Potassium Permanganate Oxidation of Elaidyl Alcohol to *threo*-9,10-Dihydroxyoctadecanol[a]

Expt. No.	CH_2Cl_2, ml	$KMnO_4$, mol	NaOH Solution		TBPC, mol	Time, hr	Triol, %	Elaidyl Alcohol, %
			Conc, %	Volume, ml				
1	80	0.02	40	100	0.002	10	40[b]	40[b]
2	80	0.04	15	200	0.004	6	50[b]	3[b]
3	120	0.06	15	200	0.004	6	40-45[b]	2[b]
4	120	0.06	30	200	0.004	6	45-50[b]	9[b]

[a] Elaidyl alcohol (5.37 g, 0.02 mol) and TBPC dissolved in CH_2Cl_2. $KMnO_4$ dissolved in aqueous NaOH solution. The two-phase system was stirred vigorously at 0 C for the times indicated. For workup see Experimental Procedures.

[b] Determined by gas liquid chromatography using authentic *threo*-triol and elaidyl alcohol for calibration purposes (see Experimental Procedures).

ducted in aqueous dioxane solution (7), in aqueous dispersion (8), and in other solvent systems (9,10). We became interested in determining the effect, if any, of PTA on the rate of carbon-carbon cleavage of some model water-insoluble epoxides in a two-phase system (methylene chloride-water). Epoxides studied were prepared from cyclohexene, cyclooctene, styrene, *trans*-β-methylstyrene, norbornene, α-pinene and *trans*-stilbene. Two PTA were selected, namely, tetrabutylphosphonium chloride (TBPC) and trioctyl-*n*-propylammonium bromide (TOPAB), as we know from our earlier work (1) that they were the most efficient PTA we had examined for transferring IO_4^- from water to methylene chloride.

For the most part, results were disappointing. When stirring was *vigorous*, rates of reaction of epoxides (0.01-0.02 mol) in methylene chloride at 30-55 C with a slight excess (10-20%) of aqueous periodic acid were almost identical in the absence or presence of PTA (5 mole % based on epoxide), with the exception of *trans*-stilbene epoxide, cyclooctene epoxide, and norbornene epoxide.

Stilbene epoxide underwent only 5-10% cleavage after 6-10 hr at 55 C in the absence of PTA but in their presence cleavage to benzaldehyde [nuclear magnetic resonance (NMR) identification] was dramatically increased to 40 (TBPC)-70%(TOPAB). Cyclooctene epoxide was not cleaved either with or without PTA; the epoxide was virtually unchanged after 15 hr (NMR identification). Norbornene epoxide was consumed but no aldehyde proton signal was observed in the NMR in the absence or presence of PTA, although complex changes occurred in the NMR spectrum. We assume that norbornene epoxide undergoes extremely rapid periodic acid-catalyzed Wagner-Meerwein rearrangement so that cleavage cannot occur. With the remaining epoxides cleavage amounted to 35-95% based on NMR monitoring.

With *slow*-stirring, on the other hand, PTA had a significant rate-enhancing effect on the carbon-carbon bond cleavage of styrene oxide (85% cleavage, PTA present, 6 hr; 40% cleavage, PTA absent, 6 hr) and of *trans*-β-methylstyrene epoxide (45% cleavage vs. 12%). We did not study the cleavage of the other epoxides at a slow stirring rate.

In view of these results, there is little advantage in using PTA to accelerate epoxide cleavage by periodic acid. Vigorous stirring accomplishes the desired result in most of the cases we studied and dissolution of both the epoxide and periodic acid in an aqueous organic solvent permits rapid cleavage with other (cleavable epoxides.

EXPERIMENTAL PROCEDURES

Starting Materials

PTA were purchased from various chemical supply houses (1) and were used as received. Periodic acid was purchased from the G.F. Smith So., (Columbus, OH). Potassium permanganate was analytical reagent grade. Oleyl alcohol (99%), bp 207 C/13 mm, was purchased from Applied Science Laboratories (State College, PA). Elaidyl alcohol, mp 37.5-38 C, was prepared from oleyl alcohol by isomerization with selenium and multiple recrystallizations (11). Methylene chloride was the best commercial grade; it was dried and fractionally distilled before use (12). Cyclohexene oxide and styrene oxide were commercial samples that were fractionally distilled under vacuum before use. Cyclooctene epoxide, mp 58-60 C, [lit 56-57 C (13)]; *trans*-stilbene epoxide, mp 68-69 C [lit 68-69 C (14)]; *trans*-β-methylstyrene epoxide, bp 60-63 C/0.8-0.9 mm; α-pinene epoxide, bp 32-33 C /0.8 mm; and norbornene epoxide, mp 126 C [lit 126 C (15)] were prepared by conventional epoxidation of the corresponding olefins with commercial 40% peroxyacetic acid that had been buffered with excess sodium acetate to neutralize sulfuric acid (16).

Hydroxylation Studies. Oleyl Alcohol (Table I)

A solution of oleyl alcohol (5.37 g, 0.02 mol) and PTA (TBAB or TBPC, 0.002-0.004 mol) in methylene chloride (20-80 ml) was sitrred vigorously for 6-10 hr at 0 C with a solution of potassium permanganate (0.06 mol preferred) in sodium hydroxide (20% by weight, 200 ml) that had been added dropwise. To the stirred reaction mixture, excess aqueous sodium bisulfite was then added slowly below 10 C followed by careful acidification with 6 *N* hydrochloric acid to pH 1-2. Triol was isolated by filtration (Expts. 5 and 6) as it is only slightly soluble in methylene chloride. The crude triol was usually of good quality (95-98%); it was recrystallized from ethyl acetate to obtain analytically pure specimens of *erythro*-9,10-dihydroxyoctadecanol, mp 126 C.

In material balance studies, the sodium bisulfite-hydrochloric acid decolorized reaction mixture was continuously extracted with ether in a liquid-liquid extractor. GLC was used to determine conversion of oleyl alcohol to *erythro* triol.

GLC was conducted with a Varian Aerograph 2100 using 15% SE-30 on Gas Chrom P. Oleyl alcohol and authentic triol were used for quantitation. To avoid tailing of GLC peaks, the Gas Chrom P was first washed with concentrated hydrochloric acid, treated with hexamethyldisilazane and then coated with SE-30. GLC conditions: injection port, 250 C; column temperature, 210 C; carrier gas nitrogen 25 ml/min. Retention time of oleyl (or elaidyl alcohol) was about 3 min and that of the triol about 15 min.

Elaidyl Alcohol (Table II).

Hydroxylation was conducted as described for oleyl alcohol but considerably more methylene chloride was required to maintain a solution of elaidyl alcohol at 0 C. Yields given in Table II were determined by GLC. Yields of isolated *threo*-9,10-dihydroxyoctadecanol, mp 82 C, were about 60% of the GLC values.

Periodic Acid Cleavage of Epoxides. Typical Procedure

The epoxide (0.02 mol) was dissolved in methylene chloride (14-15 ml) containing a PTA (TBPC or TOPAB, 0.001 mol) and benzene (1 ml), in the cases of epoxides that did not contain aromatic protons. A solution of periodic acid (0.022 mol) in water 5-10 ml) was added and the mixture was stirred vigorously (V) or slowly (S) at 30-55 C. Cleavage to aldehyde, if any, was determined by integration of the NMR signal of the aldehyde proton and comparison with the signal of aromatic protons initially present in the molecule or with the benzene added as internal standard. A control experiment under identical conditions without PTA was always run.

Styrene Epoxide

(V) PTA absent: 80% cleavage to benzaldehyde, 2 hr, 35 C. PTA present: 93% cleavage. (S) PTA absent: 9% cleavage. PTA present: 69% cleavage. Slow stirring for 6 hr gave 40% and 85% cleavage with PTA absent and present, respectively.

trans-β-Methylstyrene Epoxide

(V) PTA absent: 75% cleavage to benzaldehyde, 5 hr, 35 C. PTA present: 77% cleavage. (S) PTA absent: 12% cleavage. PTA present: 45% cleavage.

Cyclohexene Epoxide

(V) PTA absent: 66% cleavage, 4 hr, 30 C. PTA present: 64% cleavage.

α-Pinene Epoxide

(V) PTA absent: 35% cleavage, 4 hr, 35 C. PTA present: 45% cleavage.

trans-Stilbene Epoxide

(V) PTA absent: 5-10% cleavage, 6-10 hr, 55 C. PTA present: 40% (TBPC)-70%(TOPAB) cleavage.

Norbornene and cyclooctene epoxides showed no aldehyde proton signals in the NMR in the absence or presence of PTA after 6 hr at 35 C. The NMR spectrum of norbornene epoxide underwent dramatic and complex changes attributable to Wagner-Meerwein rearrangements. Cyclooctene epoxide was unchanged.

ACKNOWLEDGMENT

Partial support for this work came from the Samuel S. Fels Fund and the National Cancer Institute, DHEW (Grants Number CA-07803 and CA-12227).

REFERENCES

1. Okimoto, T., and D. Swern, JAOCS 54:862A (1977).
2. Swern, D., in "Fatty Acids," Second Ed., Part 2, Edited by K.S. Markley, Interscience Publishers, 1976, pp. 1316-1322.
3. Collin, G., and T.P. Hilditch, J. Chem. Soc. 246 (1933).
4. Weber, W.P., and J.P. Shepherd, Tetrahedron Lett. 4907 (1972).
5. Herriott, A.W., and D. Picker, Tetrahedron Lett. 1511 (1974).
6. Carison, D.G., and W.H. Tallent, J. Gas Chrom. Sci. 8:276 (1970).
7. Maerker, G., and E.T. Haeberer, U.S. Patent 3,405,149 (1968).
8. Nagarkatti, J.P., and K.R. Ashley, Tetrahedron Lett. 4599 (1973).
9. Fieser, L., and S. Rajagopalan, J. Am. Chem. Soc., 72:3938 (1949).
10. Felkin, H., Bull. Soc. Chim. Fr. 915 (1951).
11. Swern, D., E.F. Jordan, Jr., and H.B. Knight, J. Am. Chem. Soc., 68:1673 (1946).
12. Riddick, J.A., and W.B. Burger, "Organic Solvents. Physical Properties and Methods of Purification," Wiley-Interscience Publishers, New York, NY, 1970, p. 770.
13. Cope, A.C., S.W. Fenton, and C.F. Spencer, J. Am. Chem. Soc. 74:5884 (1952).
14. Reif, D.J., and H.O. House, Org. Syn. 38:83 (1958).
15. Soloway, S.B., and S.J. Cristol, J. Org. Chem., 25:327 (1960).
16. D. Swern, in "Organic Peroxides," Vol. 2, Chapt. V, Wiley-Interscience Publishers, New York, NY, (1971) pp. 418-424, edited by D. Swern.

[Received October 27, 1976]