Facile Formation of *trans*-Cyclohexanediols by the Aerobic Oxidation of Cyclohexenes with Sodium Disulfite

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Synopsis. Disulfite was found to be an excellent oxidizing reagent for a gentle and stereoselective reaction to produce *trans*-diols via corresponding epoxides from the cyclohexenes, such as 1-*p*-menthen-8-yl acetate, 1,8-*p*-menthadiene, and 2-pinene.

Disulfite has been frequently used as an antioxidant or reductant; e.g., sodium disulfite is one of the best antioxidants for the photostabilization of *N*-[(4-aminophenyl)sulfanyl]acetamide and sulfanilamide solutions[1] and it has a significant stabilizing effect on Vitamin C in bottled orange juice kept at room temperature.[2] However, although our attempt to use sodium disulfite as an antioxidant agent for the isolation of oxidases from plant cells was unsuccessful, it allowed us to discover that disulfite was concerned with an aerobic oxidation of olefins to epoxides and glycols. In this paper we describe the characterization of this oxidation and consider the mechanism of the reaction.

Results and Discussion

Monoterpenes, such as (*R*)-1-*p*-menthen-8-yl acetate (**1**), (*R*)-1,8-*p*-menthadiene (**2**), and (1*R*,5*S*)-2-pinene (**3**), were incubated at 37 °C for 12 h in an aqueous $Na_2S_2O_5$ solution under various conditions. It was found that (*R*)-1-*p*-menthen-8-yl acetate (**1**) was oxidized to (1*R*,2*S*,4*R*)-1,2-epoxy-8-*p*-methanyl acetate (**4**), (1*S*,2*R*,4*R*)-1,2-epoxy-8-*p*-menthanyl acetate (**5**), (1*S*,2*S*,4*R*)-1,2-dihydroxy-8-*p*-mentanyl acetate (**6**), and (1*R*,2*R*,4*R*)-1,2-dihydroxy-8-*p*-menthanyl acetate (**7**), as shown in Table 1 (Chart 1). Similar results were found regarding incubation with an Na_2SO_3 solution, though no product was obtained by the use of Na_2SO_4, $Na_2S_2O_3$, $Na_2S_2O_6$, and $Na_2S_2O_7$ solutions or a $Na_2S_2O_5$ solution containing 0.01% H_2O_2. Similarly, it was found that (*R*)-1,8-*p*-menthadiene (**2**) was oxidized to (1*R*,2*S*,4*R*)-1,2-epoxy-8-*p*-menthene (**8**) (13.4% yield), (1*S*,2*R*,4*R*)-1,2-epoxy-8-*p*-menthene (**9**) (9.1%), and (1*S*,2*S*,4*R*)-8-*p*-menthene-1,2-diol (**10**) (5.3%) with $Na_2S_2O_5$ in 50% aq acetone and (1*R*,5*S*)-2-pinene (**3**) was oxidized to (1*R*,2*R*,3*S*,5*R*)-2,3-epoxypinane (**11**) (trace) and (1*R*,2*S*,3*S*,5*R*)-2,3-pinanediol (**12**) (33.9%).

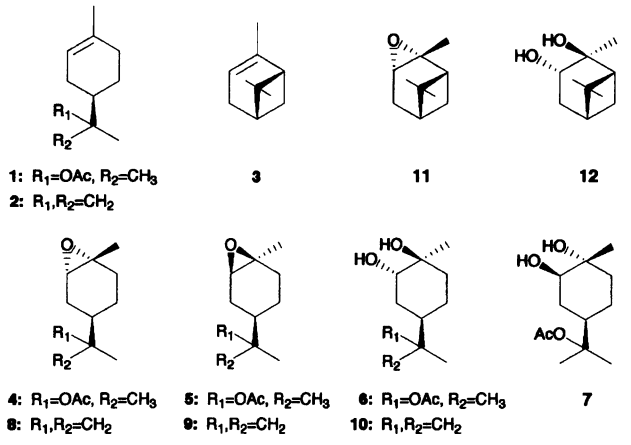

Chart 1.

The time-course for the oxidation of (*R*)-1-*p*-menthen-8-yl acetate (**1**) in the $Na_2S_2O_5$ solution was followed and the formation of 1,2-epoxy-8-*p*-methanyl acetates, **4** and **5**, was observed during the earlier period of incubation. However, the amounts of **4** and **5** gradually decreased with the lapse of incubation time, as shown in Fig. 1. Such a decrease in the amount of epoxides may have been due to a further conversion[3] to the corresponding *trans*-diols (**6** and **7**), which were the major products in the above reaction.

The effect of the pH on the oxidation of (*R*)-1-*p*-menthen-8-yl acetate (**1**) was examined. With the basic solutions, although no oxidation products were obtained, significant oxidation was observed at pH values lower than 7.

The requirement of molecular oxygen for the oxidation with disulfite was examined. The total yield of oxidation products for the reaction performed under a nitrogen atmosphere was only half that formed for the reaction under an oxygen atmosphere during a 12-h reaction at 37 °C. Furthermore, the relative yield de-

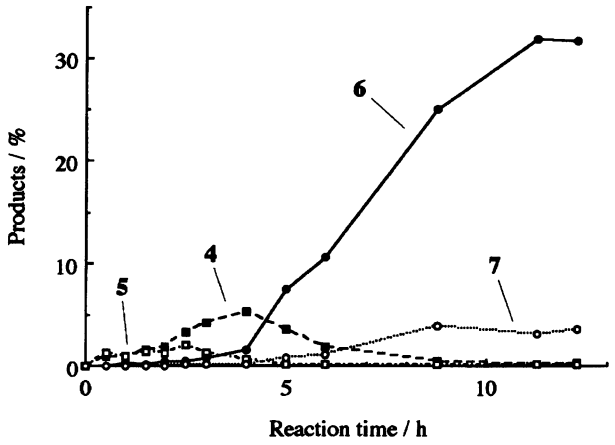

Fig. 1. Time-course for the formation of epoxides (**4** and **5**) and the glycols (**6** and **7**) during the aerobic oxidation of (*R*)-1-*p*-menthen-8-yl acetate (**1**) with $Na_2S_2O_5$.

Table 1. Oxidation of (*R*)-1-*p*-menthen-8-yl Acetate (**1**) Employing Various Conditions

Reagents	Solvent	pH	Yield of products/%			
			4	**5**	**6**	**7**
$Na_2S_2O_5$	H_2O	6.5	0.3	0.2	31.8	2.7
	H_2O+0.01%H_2O_2	6.5	Tr.	Tr.	0	0
	50%EtOH	6.5	0.5	Tr.	17.3	Tr.
	50%Acetone	6.5	7.1	11.9	4.5	Tr.
	50%Acetone	3.7	Tr.	Tr.	65.7	2.7
	50%Acetone	8.0	0.2	Tr.	0	0
Na_2SO_3	50%Acetone	6.5	3.3	Tr.	22.6	Tr.
Na_2SO_4	50%Acetone	6.5	0	0	0	0
$Na_2S_2O_3$	50%Acetone	6.5	0	0	0	0
$Na_2S_2O_6$	50%Acetone	6.5	0	0	0	0
$Na_2S_2O_7$	50%Acetone	6.5	0	0	0	0

creased to 11% in the condition of low dissolved oxygen by adding glucose oxidase and glucose to the reaction mixture under a nitrogen atmosphere. This indicates that the oxidation of (*R*)-1-*p*-menthen-8-yl acetate (**1**) with sodium disulfite requires molecular oxygen.

These observations are supportive of the pathway for the epoxidation of the carbon-carbon double bond, as shown in Fig. 2. It has been reported that the disulfite ion, $S_2O_5^{2-}$, in aqueous solution exists in equilibrium with the hydrogensulfite ion, HSO_3^-.[4,5] Hydrogensulfite is a weak acid which dissociates according to the following equilibrium: $HSO_3^- + H_2O \rightleftarrows H_3O^+ + SO_3^{2-}$. Therefore, there is an equilibrium between $S_2O_5^{2-}$ and SO_3^{2-}.[6] The key step is probably the addition of molecular oxygen to SO_3^{2-} to give the peroxomonosulfate ion, SO_5^{2-}. The observation that no products were obtained in a reaction with the $Na_2S_2O_5$ solution containing 0.01% H_2O_2 supports the direct action of the SO_3^{2-} ion as an acceptor of molecular oxygen, because SO_3^{2-} is easily oxidized by H_2O_2 to a stable sulfate ion, SO_4^{2-}. The resultant peroxomonosulfate ion, SO_5^{2-}, may abstract a proton under acidic conditions to yield the peroxomonosulfate ion, $^-O_3SOOH$, which can directly transfer oxygen to a carbon–carbon double bond, as is the case with various organic peroxy acids.[7—9]

Thus, the disulfite ion is found to be an efficient agent

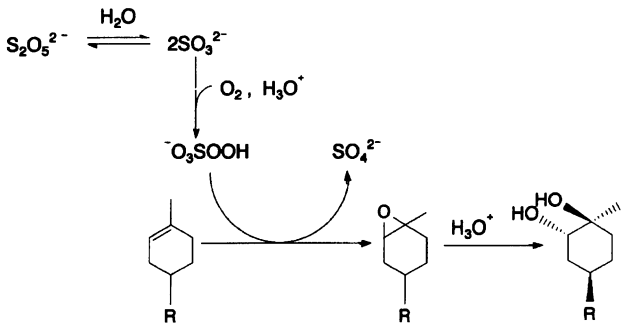

Fig. 2. Possible mechanism for the formation of epoxides and glycols by the aerobic oxidation of olefins with $Na_2S_2O_5$.

for introducing of molecular oxygen into the carbon–carbon double bond of olefins under mild and aqueous conditions.

Experimental

GLC analyses were performed on a Shimadzu GC-6A gas chromatograph equipped with FID and a glass column (3 mm×2 m) packed with 2% OV-17 on Chromosorb W (AW-DMCS; 80—100 mesh) by programming the column temperature at 90—250 °C at a rate of 2 °C min^{-1}. GLC-MS were recorded on a Shimadzu QP-1000 mass spectrometer equipped with an EI ion source operating at 70 eV and installed with a gas chromatograph equipped with an OV-17 column operating at 80—200 °C at a rate of 3 °C min^{-1}.

Materials. (+)-(*R*)-1-*p*-Menthen-8-yl acetate (**1**) [>99.5% pure on GLC; $[\alpha]_D^{25}$ +69.1 (*c* 1.02, EtOH); IR ν_{max} (film) 1750 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ=1.2—2.1 (5H, m, $-CH_2-$×3 and >CH–), 1.41 and 1.44 (s, >C(CH_3)$_2$), 1.64 (3H, s, 7-Me), 1.96 (3H, s, OAc), and 5.36 (1H, bs, >C=CH–); MS *m/z* (rel intensity) 136 (M^+ − AcOH, 80%), 121 (90), and 93 (100)] was prepared from (+)-(*R*)-1-*p*-menthen-8-ol by acetylation with acetic anhydride. (+)-(*R*)-1,8-*p*-Menthadiene (**2**) [>99.4% pure on GLC; $[\alpha]_D^{25}$ +107.8 (*c* 2.06, EtOH) (lit,[10] $[\alpha]_D^{20}$ +126.1)] was donated from Ogawa Perfumery Co., Ltd and (+)-(1*R*,5*S*)-2-pinene (**3**) [>99.1% pure on GLC; $[\alpha]_D^{25}$ +49.0 (*c* 10.2, EtOH) (lit,[10] $[\alpha]_D^{20}$ +51.1)] was commercial material of Aldrich Chem. Company.

General Procedures. To a reaction vessel containing a solution (1 cm^3, pH 6.5) of 20 mol m^{-3} $Na_2S_2O_5$, 1 mg of a material, such as (+)-(*R*)-1-*p*-menthen-8-yl acetate (**1**) in ethanol (0.02 cm^3), was added. Solutions of pH 6.5 were prepared by adding small amounts of 1 M sodium hydroxide solution (1 M=1 mol dm^{-3}). The mixture was bubbled for 1 min with oxygen, and incubated at 37 °C for 12 h with continuous shaking. The presence of dissolved molecular oxygen in the solutions was determined by an oxygen electrode method; the concentration of the dissolved oxygen in the solution was about 1.5 mol m^{-3}.

To study the oxygen dependence in the reaction, the $Na_2S_2O_5$ solution was bubbled for 30 min with nitrogen prior to initiation of the reaction, and the reaction was carried out under a nitrogen atmosphere (0.49 mol m^{-3} dissolved oxygen in the solution). One of the samples was treated with the addition of 1.2 U glucose oxidase

and 8 mol m^{-3} glucose to remove molecular oxygen (<0.15 mol m^{-3} dissolved oxygen).[11]

The incubation mixture was extracted with ether after a regular time interval. Each extract was concentrated by distillation and then subjected to GLC. The products were identified by a comparison of GLC and GLC-MS with authentic samples.[3] The yields of the products were determined on the basis of the peak areas on GLC, and are expressed as a relative percent for the total amount of the entire reaction product extracted.

Oxidation of (*R*)-1,8-*p*-Menthadiene (2) with $Na_2S_2O_5$. According to the above procedure, 50 mg of **2** in acetone (25 cm^3) was added to a 100 cm^3-conical flask containing an aqueous solution (25 cm^3, pH 6.5) of 20 mol m^{-3} $Na_2S_2O_5$. The mixture was bubbled for 1 min with oxygen and incubated at 37 °C for 24 h with continuous shaking. After the usual work-up, the reaction mixture (45 mg) was subjected to column chromatography on silica-gel with ethyl acetate–pentane (1 : 99) to give (1*R*,2*S*,4*R*)-1,2-epoxy-8-*p*-menthene (**8**) (5 mg) [^{1}H NMR ($CDCl_3$) δ=1.31 (3H, s, 10-Me), 1.70 (3H, s, 7-Me), 1.5—2.2 (5H, m, $-CH_2-\times2$ and $>CH-$), 3.05 (1H, bs, 2-H), and 4.70 and 4.73 (2H, s, $>C=CH_2$); MS *m/z* (rel intensity) 152 (M^+, 5%), 137 (15), 109 (23), 95 (27), 93 (32), 81 (30), 67 (100), and 53 (80)], (1*S*,2*R*,4*R*)-1,2-epoxy-8-*p*-menthene (**9**) (3 mg) [^{1}H NMR ($CDCl_3$) δ=1.32 (3H, s, 10-Me), 1.67 (3H, s, 7-Me), 1.5—2.2 (5H, m, $-CH_2-\times2$ and $>CH-$), 2.99 (1H, d, *J*=5.5 Hz, 2-H), and 4.67 (2H, bs, $>C=CH_2$); MS *m/z* (rel intensity) 152 (M^+, 2%), 137 (3), 109 (10), 95 (25), 93 (15), 81 (41), 67 (100), and 53 (75)], and (1*S*,2*S*,4*R*)-8-*p*-menthene-1,2-diol (**10**) (5 mg) [^{1}H NMR ($CDCl_3$) δ=1.28 (3H, s, 7-Me), 1.5—1.8 (4H, m, $-CH_2-\times2$), 1.68 (1H, td, *J*=3.0 and 14.0 Hz, 3-Ha), 1.74 (3H, s, 10-Me), 1.93 (1H, dt, *J*=3.0 and 11.5 Hz, 3-Hb), 2.28 (1H, bm, 4-H), 3.65 (1H, bs, 2-H), and 4.74 (2H, s, $>C=CH_2$); MS *m/z* (rel intensity) 152 (M^+-H_2O, 10%), 137 (19), 119 (13), 109 (13), 95 (32), 81 (30), 67 (100), and 55 (54)].

Preparation of Authentic Samples. Following the procedure described in the reference,[3] (1*R*,2*S*,4*R*)-1,2-epoxy-8-*p*-menthanyl acetate (**4**) and (1*S*,2*R*,4*R*)-1,2-epoxy-8-*p*-menthanyl acetate (**5**) were prepard from (+)-(*R*)-1-*p*-menthen-8-yl acetate (**1**) by epoxidation with *m*-chloroperbenzoic acid. After working-up as usual, the reaction products were isolated and purified by chromatography on a silica-gel column with chloroform–benzene (95 : 5, v/v). (1*R*,2*S*,4*R*)-1,2-Epoxy-8-*p*-menthene (**8**), (1*S*,2*R*,4*R*)-1,2-epoxy-8-*p*-menthene (**9**), and (1*R*,2*R*,3*S*,5*R*)-2,3-epoxypinane (**11**) were prepared from the corresponding compounds in the same manner as described above. (1*S*,2*S*,4*R*)-1,2-Dihydroxy-8-*p*-menthanyl acetate (**6**), (1*R*,2*R*,4*R*)-1,2-dihydroxy-8-*p*-menthanyl acetate (**7**), (1*S*,2*S*,4*R*)-8-*p*-menthene-1,2-diol (**10**), and (1*R*,2*S*,3*S*,5*R*)-2,3-pinanediol (**12**) were prepared from the corresponding epoxides by hydrolysis with hydrochloric acid (pH 4.0).

References

1) T. Ahmad and I. Ahmad, *Pol. J. Pharmacol. Pharm.*, **35**, 69 (1983).
2) E. E. Maeda and D. M. D. N. Mussa, *Food Chem.*, **22**, 51 (1986).
3) T. Hirata, S. Izumi, T. Ekida, and T. Suga, *Bull. Chem. Soc. Jpn.*, **60**, 289 (1987).
4) E. Hayon, A. Treinen, and J. Wilf, *J. Am. Chem. Soc.*, **94**, 47 (1972).
5) D. Littlejohn, S. A. Walton, and S. Chang, *Appl. Spectrosc.*, **46**, 848 (1992).
6) C. Mottley, R. P. Mason, C. F. Chignell, K. Sivarajah, and T. E. Eling, *J. Biol. Chem.*, **257**, 5050 (1982).
7) H. Yagi, O. Hernandez, and D. M. Jerina, *J. Am. Chem. Soc.*, **97**, 6881 (1975).
8) D. J. McCaustland and J. F. Engel, *Tetrahedron Lett.*, **30**, 2549 (1975).
9) H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda, and D. M. Jerina, *J. Am. Chem. Soc.*, **99**, 1604 (1977).
10) E. Guenther, "The Essential Oils," Van Nostrand Inc., New York (1949), Vol. 2.
11) M. Hagmann, W. Heller, and H. Grisebach, *Eur. J. Biochem.*, **142**, 127 (1984).