Temperature Effects on the Stereochemistry of the Solvolysis of *trans*-2,3-Diphenyloxirane[†]

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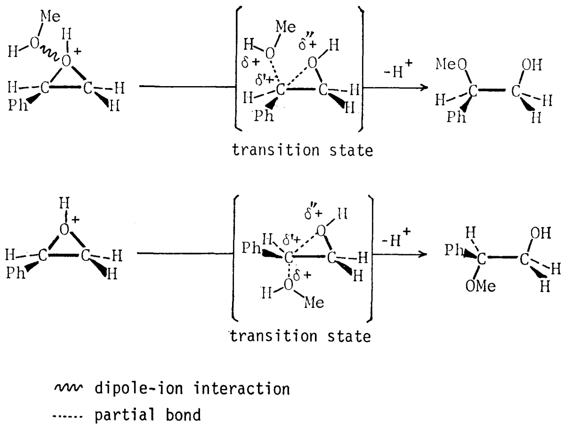
The temperature effects on the stereochemistry of the acid-catalyzed ethanolysis of *trans*-2,3-diphenyloxirane were examined. The stereochemistry of the reaction became more retentive as the reaction temperature was raised. The reaction mechanisms are discussed, and it is concluded that concurrent reactions take place in the ethanolysis, one of them giving an inverted product, and the other, a retained one, and that the former reaction is caused by a nucleophilic attack of ethanol on the carbon of the conjugate acid of the epoxide, while the latter proceeds *via* an intermediate which has a carbonium-ion character.

Nucleophlic ring-opening reactions of epoxide have been widely studied.[1)] It is now generally accepted that epoxides react by means of an S_N2 mechanism under basic conditions. The mechanism of the ring opening of epoxides in acidic media is, however, quite a complex matter. The initial protonation to the epoxide oxygen atom is recognized as a fast, reversible step.[2)] In the limiting form, two mechanisms are possible for the ring opening and the attack of the nucleophile, *i.e.*, *A*1 and *A*2 mechanisms. As the attacking nucleophile is the solvent in the solvolyses, though, both mechanisms lead to the same rate expression. Thus, alternative criteria have been used. They have been carefully discussed by Chapman and his coworkers.[3)] Long *et al.*,[4)] following a suggestion by Taft and his coworkers,[5)] proposed the use of $\Delta S^{\neq}$ as a criterion for the mechanism of a hydrolytic reaction. The entropies of activation for the acid-catalyzed hydrolysis of simple epoxides are between -6.1 and -3.9 cal mol^{-1} K^{-1},[6)] much lower than those of the reactions of the established *A*1 mechanism and yet greater than those of the established *A*2 mechanism; these values can be explained in terms of a borderline *A*2 mechanism.[1a,7)]

A nucleophilic attack by an *A*2 mechanism involves complete inversion of configuration, whereas an *A*1 mechanism involves racemization in the limiting form. It is generally recognized that simple aliphatic epoxides give inverted products in acid-catalyzed ring opening.[1a)] The only exception is the reaction of *cis*- and *trans*-2,3-dimethyloxirane with aluminum chloride in nitromethane, which yields more than 85% retained 3-chloro-2-butanol.[8)]

In aryl- or carbonyl-substituted epoxides, reactions are known in which epoxides ring-open with retention of configuration at the position attacked. In a few epoxides, ring openings give rise to both stereoisomeric products. Parker and Isaacs concluded that concurrent S_Ni and S_N2 mechanisms take place in reactions of this type.[1a)]

Recently Chapman and his coworkers have studied the acid-catalyzed ethanolysis of 2-phenyloxirane both kinetically and stereochemically.[3,9)] The reaction yielded a mixture of 89% inverted and 11% retained products at 23 °C. They explained their observation by only a borderline *A*2 mechanism involving the transition states depicted in Scheme 1. Obviously, the two transition states, which have different situations around the carbon atom attacked by ethanol, are different in energy. Therefore, the reaction parameters, activation enthalpy and activation entropy, are different for the two reactions, one of which yields a retained product, while the other gives an inverted one. As the two reactions have different activation parameters, it is ridiculous to discuss the two reactions in terms of a single pair of $\Delta H^{\neq}$ and $\Delta S^{\neq}$. The stereochemical outcome must also be altered by the variation in the reaction temperatures. They did not, however, explore the temperature effects on stereochemistry.



Scheme 1.

Although a number of papers, including those of Chapman *et al.*, have discussed the temperature effects on reaction kinetics, *i.e.*, activation parameters, only a few papers have dealt with the effects on stereochemistry. Even so, two contrasting results have appeared in the literature. Fisher and Koch reported the acid-catalyzed hydrolysis of *trans*- and *cis*-2-methyl-3-phenyloxiranes in aqueous dioxane.[10)] The reaction afforded 67% inverted and 33% retained glycols from the trans epoxide and 76% inverted and 24% retained ones from the cis isomer, and the stereochemistry of the reaction did not change in the temperature range of 20—45 °C. From these results, one can expect that the reaction has only one transition state, yielding both retained and inverted products.

On the other hand, Macchia *et al.* reported that the acid-catalyzed solvolysis of 1-aryl-1,2-epoxycyclohexane afforded larger amounts of the retained product at higher reaction temperatures.[11)] From this observation,

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[†] Taken from Ph D. thesis of M. I.

one can expect that concurrent reactions take place, one of which leads to a inverted product, and the other, to a retained one.

A previous paper has described the co-solvent effects on the stereochemistry of the ethanolysis of *trans*-2,3-diphenyloxirane (**1**). In that paper, we reported that the steric course of the reaction can be controlled from 85% retention–15% inversion (nitromethane: ethanol= 20: 2 by volume) to 10% retention–90% inversion (HMPA: ethanol=10: 12) by the choice of co-solvent.[12] This paper will report the temperature effects on the stereochemistry of the ethanolysis of **1** and will discuss the mechanism of the reaction.

Results and Discussion

In the study of the stereochemistry of the acid-catalyzed ethanolysis of **1** in the temperature range below the boiling point of ethanol, the same experimental conditions as in the previous paper were chosen. The results are summarized in Table 1. The reaction products were *threo*-2-ethoxy-1,2-diphenylethanol (*threo*-**2**, the retained product), the erythro isomer (*erythro*-**2**, the inverted product), 1,1-diethoxy-2,2-diphenylethane (**3**), and benzophenone (**4**, an oxidized product of diphenylacetaldehyde (**5**) in the course of the work-up); the identification and an outline of the sequence of the formation of these products have already been presented in the previous paper. As is shown in Table 1, the proportion of the retained product *threo*-**2** increased as the reaction temperature was raised. Similar temperature effects were observed in the experiments in binary solvent systems.

To examine the stereochemistry of the reaction at temperatures higher than the boiling point of ethanol, experiments were carried out in an autoclave. Unexpectedly, sulfuric acid, which was used as a catalyst in the experiments listed in Table 1 and in those of the previous paper, has no catalytic activity in the temperature range higher than 130 °C; only the starting material, **1**, accompanied by traces of 1,2-diphenylethanol (**6**) and 2,2-diphenylethanol (**7**), 1,2-diphenyl-2-hydroxyethanone (**8**), and/or diphenylethanedione (**9**), was detected on GLC analysis when an ethanolic solution of **1** containing sulfuric acid was allowed to stand at 200 °C for 4 h. This observation may be attributed to the facts that sulfuric acid acts as an oxidizing agent and that the reduced material of sulfuric

TABLE 1. TEMPERATURE EFFECTS ON THE ETHANOLYSIS OF *trans*-2,3-DIPHENYLOXIRANE (**1**)[a]

Reaction temp (°C)	Solvent	Product distribution (%)				Retention[b] (%)
		3	**4**	*threo*-**2**	*erythro*-**2**	
30	EtOH	8	tr	18	74	20
50	EtOH	12	tr	23	65	26
70	EtOH	16	tr	26	58	31
50	EtOH–CH_3CN (46: 54, vol)	9	15	36	40	48
70	EtOH–CH_3CN (46: 54, vol)	18	12	37	33	53

a) The experimental conditions were described in a previous paper (Ref. 12).
b) The proportion of *threo*-**2** to the total **2**.

TABLE 2. TYPICAL RESULTS OF ACID-CATALYZED ETHANOLYSIS OF *trans*-2,3-DIPHENYLOXIRANE AT HIGH TEMPERATURES

Temp (°C)	Time (h)	Acid[c] (μl)	Product distribution[a] (%)								Retention (%)
			1	**3**	**4**	*threo*-**2**	*erythro*-**2**	**11**	**10**	Others[b]	
90±2	4	100	37.3	0.4	1.1	18.5	41.7	0.6			29.6
103±1	4	100	29.2	1.3	1.0	22.9	45.1	0.5			33.7
120±3	3.5	100	22.1	3.2	2.3	27.1	43.8	0.6		0.1	38.9
130±2	3	100	17.9	5.0	1.1	30.7	44.7	0.6		tr	40.7
140±1	3	80	18.9	5.5	1.3	30.7	42.6	0.7			41.9
149±1	2	100	19.8	6.1	0.5	30.7	42.9	tr			41.3
165±1	2	100	5.7	16.1	0.8	30.9	39.5	1.1	5.9		43.9
190±4	2	75	22.0	4.3	3.6	30.3	36.2	3.2		0.4	45.6
206±3	2	20	57.6	0.2	4.9	13.9	14.8	5.7		2.6	48.4
220±3	2	50	28.5	3.0	3.2	28.3	29.4	3.9	1.2	2.1	49.1
130±2	3	200	0.4	10.6	0.5	28.0	50.9	0.4	9.2		35.5
130±2	3	150	0.7	15.3	0.4	28.6	48.3	0.4	6.3		37.2
130±2	3	80	25.5	2.7	1.7	28.1	41.0	0.8		0.2	40.7
130±2	3	50	49.3	0.3	1.4	19.7	28.6	0.7			40.8
130±2	3	30	68.9	0.1	0.8	12.2	17.7	0.6			41.3

a) Determined by the relative area ratio on GLC. b) The oxidation-reduction products, **6**, **7**, **8**, and **9**. c) Hydrochloric acid (*ca.* 0.005 mol/l) in ethanol was added to 1 ml of an ethanolic solution containing 10 mg of **1**.

acid has no catalytic activity toward the ethanolysis. Therefore, hydrochloric acid was used as the catalyst for the experiments at higher reaction temperatures. Some typical results are given in Table 2. As is shown in Table 2, larger proportions of the retained product were observed at higher temperatures, and almost equal amounts of retained and inverted products were formed at 200 °C. Although it is interesting whether or not the proportion of the retained product increases monotonously at more higher temperatures, no clear-cut results could be obtained because of the formation of undesired products, *i.e.* rearranged products (**3**, **5**, 1,2-diphenyl-1-ethoxyethylene (**10**), and benzyl phenyl ketone (**11**)) and oxidation-reduction products (**6**, **7**, **8**, and **9**). It must be noted that the yield of **11** increased suddenly at higher than 160 °C; **11** has previously been reported not to be formed in the rearrangement by acid.13)

Higher acid concentrations gave more inverted product; this forms a striking contrast to the results mentioned in the previous paper, in which we reported that the stereochemical outcome of the sulfuric acid-catalyzed ethanolysis of **1** at ordinary temperatures was not affected by the variation in the acid concentration. Four reasons for this can be considered: **a** the effects of a trace of water contaminating the acid solution; **b** the contamination of the non-acid-catalyzed reaction which yields the retained product; **c** the formation of chlorohydrin, or the subsequent ethanolysis of the chlorohydrin, and **d** the effects of the ion-pairing of the acid. To examine the effects of water, reactions were carried out with small amounts of water added. The results are shown in Fig. 1. As the proportion of the retained product increased with an increase in the amount of water added, the **a** reason can be excluded. The **b** reason can also be easily excluded because no reaction occurred without an acid catalyst. The **c** reason was recently proposed by Whalen *et al.* as the specific effects of chloride ion in the hydrolysis of phenanthrene 9,10-oxide;14) it cannot be completely excluded in the present case, though no chlorohydrin was detected in the reaction products and the chloride-ion concentrations are a hundred times smaller than those of **1**. The **d** reason was proposed by Wylde and his coworkers;15) it seems to be the most probable explanation in the present case. As the counter anion exists near the protonated oxygen in the ion pair of protonated epoxide and chloride, the probability of the existence of ethanol in the front side of the epoxide ring decreases as compared with that in free ion, and an inversion reaction is favored by the ion pair. As the dilution of the acid solution causes the ion pair to dissociate into free ions, the reaction becomes more retentive with a lowering in the acid concentration.

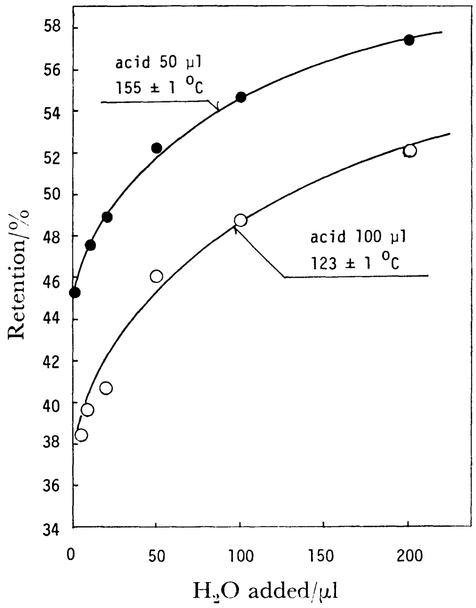


Fig. 1. Effects of water on ethanolysis of *trans*-2,3-diphenyloxirane.

As the stereochemistry of the ethanolysis is affected by the reaction temperatures, two reaction are expected to take place in the ethanolysis. If Parker-Isaacs' conclusion is true, the overall kinetical expression is as follows:

$$k_{\mathrm{obsd}} = k'K[\mathrm{H}^+] = (k_{\mathrm{ret}}+k_{\mathrm{inv}})K[\mathrm{H}^+]$$

in which k_{ret} is a second-order rate constant for the reaction which gives the retained product, while k_{inv} is that for the inversion reaction. The pre-equilibrium constant between **1** and the oxonium ion is presented as K. Then, the reaction parameters for each of the reactions can be defined as16)

$$k_{\mathrm{ret}} = \gamma \exp\left(\frac{-\Delta G^{\ddagger}_{\mathrm{ret}}}{RT}\right) = \exp\left(\frac{T\Delta S^{\ddagger}_{\mathrm{ret}}-\Delta H^{\ddagger}_{\mathrm{ret}}}{RT}\right)$$

$$k_{\mathrm{inv}} = \gamma' \exp\left(\frac{-\Delta G^{\ddagger}_{\mathrm{inv}}}{RT}\right) = \exp\left(\frac{T\Delta S^{\ddagger}_{\mathrm{inv}}-\Delta H^{\ddagger}_{\mathrm{inv}}}{RT}\right).$$

Therefore,

$$\frac{k_{\mathrm{ret}}}{k_{\mathrm{inv}}} = \frac{\gamma}{\gamma'} \exp\left(\frac{\Delta S^{\ddagger}_{\mathrm{ret}}-\Delta S^{\ddagger}_{\mathrm{inv}}}{R}\right) \exp\left(-\frac{\Delta H^{\ddagger}_{\mathrm{ret}}-\Delta H^{\ddagger}_{\mathrm{inv}}}{RT}\right)$$

Assuming that the activation parameters are constant in the temperature range of the experiments, the following equation can be deduced:

$$\ln\left(\frac{k_{\mathrm{ret}}}{k_{\mathrm{inv}}}\right) = -\frac{\Delta H^{\ddagger}_{\mathrm{ret}}-\Delta H^{\ddagger}_{\mathrm{inv}}}{RT} + \mathrm{Const.}$$

If two reactions have the same reaction order, which was proved to be the case by the constancy of the stereochemical outcomes with the variation in the reaction times, the ratio of the two rate constants, $k_{\mathrm{ret}}/k_{\mathrm{inv}}$, can be substituted for the ratio of the two reaction products, *threo*-**2**/*erythro*-**2**. Therefore, a straight line should be obtained if ln(*threo*-**2**/*erythro*-**2**) is plotted *vs.* $1/T$; the results are shown in Fig. 2. From the results, $\Delta H^{\ddagger}{}_{\mathrm{ret}} > \Delta H^{\ddagger}{}_{\mathrm{inv}}$ and $\Delta S^{\ddagger}{}_{\mathrm{ret}} > \Delta S^{\ddagger}{}_{\mathrm{inv}}$ are obtained. The enthalpic factor favors the formation of the inverted product, whereas the entropic factor favors the retention reaction.

Macchia *et al.* proposed the mechanism shown in Scheme 2 for the acid-catalyzed solvolysis of 1-aryl-1,2-epoxycyclohexanes.11) However, we cannot agree with their mechanism in view of the following considerations: (1) the entropy of the transition state, **12**, is expected to be equal to, or smaller than, that of **13**, because **12** involves a molecule of ethanol and (2) the enthalpy of

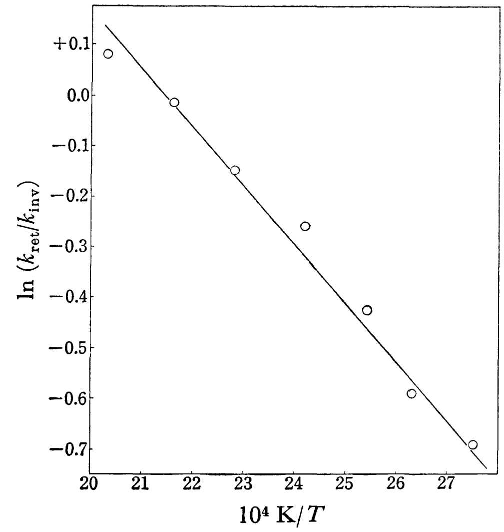
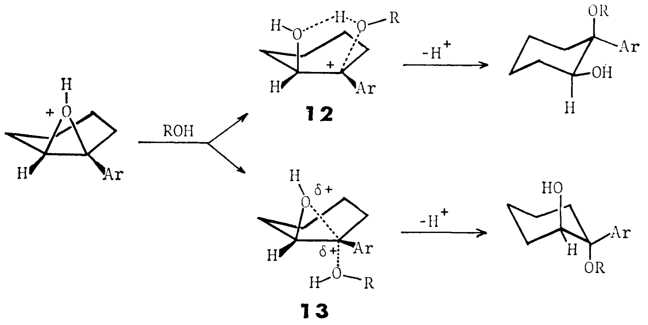


Fig. 2. Plot of ln(k_{ret}/k_{inv}) *vs.* 1/T for the ethanolysis of *trans*-2,3-diphenyloxirane.

12 is expected to be smaller than that of **13**, because hydrogen bonding from the ethanol involved in the transition state to the oxygen of the epoxide supplies an additional stabilization energy to **12**. Both suppositions are contrary to the observations.

Bruice *et al.* examined the temperature effects on the product distribution of the hydrolysis of phenanthrene 9,10-oxide[18] and reported those relative activation parameters: $\Delta H^{\neq}_{ret}-\Delta H^{\neq}_{inv}=2.05$ kcal mol^{-1} and $\Delta S^{\neq}_{ret}-\Delta S^{\neq}_{inv}=5.0$ cal deg^{-1} mol^{-1}. They explained their observations in terms of an S_N1 mechanism. The energy difference, 2.05 kcal mol^{-1}, however, seems to be rather large for the fast reaction step after the rate-determining formation of a carbonium ion.



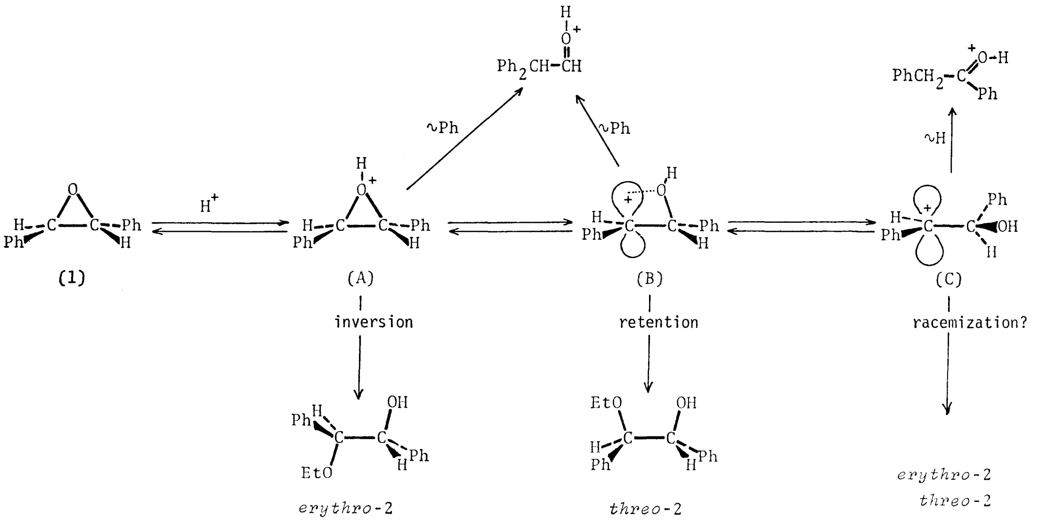
Scheme 2.

A possible mechanism for the reaction is shown in Scheme 3, in which (A) is the conjugate acid of the epoxide and (C) is a completely developed carbonium ion. The intermediate (B) is considered to be in a circumstance in which *p*-obital of the carbon is solvated by the intramolecular hydroxyl group. As the broken C–O bond provides more freedom to the system, the reaction which yields the retained product should have a lower activation entropy than the reaction yielding the inverted product.

Finally, we shall discuss briefly the rearrangement of **1**. Blum *et al.* reported that $Rh_2(CO)_4Cl_2$ catalyzed rearrangement of **1** gave 8% of **11**, 25% of **5**, 11% of diphenylmethane, 12% of 1,2-diphenylethylene, and 18% of *cis*-2,3-diphenyloxirane after 2 h at 210 °C, while the same catalyst gave 25% of **5**, 5% of 1,2-diphenylethylene, and 65% of unchanged **1** without **11** after 5 h in boiling benzene.[18] These results, together with the results shown in Table 2, indicate that the predominant factor affecting the rearranged-product distribution is the reaction temperature, and that high reaction temperatures favor the formation of **11**. These observations may be explained by Pearson's HSAB principle.[19] At low temperatures C–O bond breaking is assisted by the more polarizable (softer than hydride) phenyl group, resulting in phenyl migration to give **5**. On the other hand, the fully developed carbonium ion formed at a high temperature is attacked by the more electronegative (harder) hydride ion, since the positive charge of the cation is easily neutralized by the electron density of the hydride ion.

Experimental

The materials and analytical methods have been described in a previous paper.[12]



Scheme 3.

*Ethanolysis of **1** in an Autoclave.* To a 1-ml portion of an ethanolic solution containing 10 mg of **1**, a definite volume of hydrochloric acid in ethanol (*ca.* 0.005 mol/l) was added. The reaction mixture was then shaken vigorously, set in an autoclave, and heated to the desired temperature. Ten minutes usually (and thirty minutes at the longest) were required to arrive at the reaction temperature. After an appropriate time interval at that temperature, the mixture was cooled and poured into sampling tube containing a small amount of potassium carbonate. The quenched sample was then kept at room temperature for a day and analyzed by GLC.

Isolation of the Product. To a mixture of 206.4 mg of **1** and 20 ml of ethanol, 0.5 ml of ethanolic hydrochloric acid (*ca.* 0.005 mol/l) was added. The reaction mixture was then shaken vigorously, set in an autoclave, and heated to 240 °C. Thirteen minutes were required to arrive at that temperature; the autoclave was then held at that temperature (237—260 °C) for 3 h. To the cooled reaction mixture, a portion of potassium carbonate was added. The filtered mixture was washed with water, and the aqueous layers were extracted with ether. After the removal of the solvent, the dried product was chromatographed on an $8\phi \times 720$ mmH silica-gel column under a 1-m head of elutant (hexane, hexane–benzene and benzene–diethyl ether successively, with concentration gradients). The products (in the order of elution) and the yields were as follows: **10** (0.4%), recovered **1** (4%), **5** (9%), **4** (8%), **9** (0.5%), **3** (2%), **8** (0.3%), **6** (3%), **2** (50%), and **7** (3%).

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