April, 1976] BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(4), 1063—1071 (1976)

Solvent Effects on Stereo and Regioselectivities of Ring-opening Reaction of Epoxide with Aluminum Chloride

Masashi Inoue, Toshio Sugita,* Yoshiaki Kiso, and Katsuhiko Ichikawa

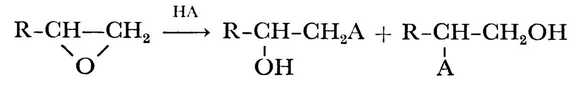
Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606

(Received May 31, 1975)

The ring-opening of 2,3-epoxybutane with aluminum chloride yielding 3-chloro-2-butanol was carried out in several different solvents. The reaction proceeds with 94% retention of configuration in a nitromethane solvent. The retentive ring-opening was observed to variable extents when nitro compounds, ethers, and aromatics were utilized as the solvents, but a complete inversion resulted in the other solvents. The regioselectivity was examined using 1,2-epoxypropane. The composition of the 1-chloro-2-propanol and 2-chloro-1-propanol thus produced was also strongly affected by the solvent. The latter was exclusively produced in nitromethane, though the former predominated in several other solvents. The structure of aluminum chloride in various solvents is discussed, and aluminum chloride–solvent 1 : 1 addition compounds in solution are concluded to be important for retentive and abnormal ring-opening.

Much has been written regarding the ring-opening reaction of epoxides. Nevertheless, the stereo and regioselectivities of the reaction are still somewhat confused subjects.¹⁾ Ring-openings of epoxides with a nucleophile are generally accompanied with inversion of configuration at the point of attack, and can be explained by S_N2 mechanism. Reactions which proceed with retention of configuration have been reported in some cases of phenyl and acyl substituted epoxides. A double inversion mechanism with neighboring groups and a four-centered mechanism with an ion-pair have been proposed for these reactions.²⁻⁵⁾ Parker and Isaacs proposed that the reactions which proceed with racemization take place not by S_N1, but by concurrent S_N2 and S_Ni mechanisms.¹ᵃ⁾

When unsymmetrically substituted epoxides are involved, ring-opening can occur in either of two different directions:



$$\text{R-CH—CH}_2\ (\text{O}) \xrightarrow{\text{HA}} \underset{\text{OH}}{\text{R-CH}}\text{-CH}_2\text{A} + \underset{\text{A}}{\text{R-CH}}\text{-CH}_2\text{OH}$$

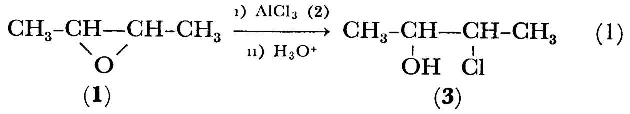
Normal product Abnormal product

In general, a reaction to cleave the bond between less substituted carbon and oxygen is termed "normal ring-opening," while the other direction is termed "abnormal." In the case of base-induced reactions of epoxides, normal ring-opening is predominant, but acid-catalyzed substitution reactions usually give considerable amounts of abnormal products.

Yielding chlorohydrins by the reaction of epoxides with aluminum chloride is well known not only as a side reaction of the Friedel-Crafts reaction, but also as a modification of catalyst in cationic polymerizations of epoxides. We reported in a previous paper that an alkyl-substituted epoxide, propylene oxide, afforded a chlorohydrin with a retained configuration in a reaction with aluminum chloride in a nitromethane solution.⁶⁾ In the present paper, we wish to report the solvent effect on the stereo and regioselectivities of the ring-opening reaction of epoxide with aluminum chloride.

Results and Discussion

Stereoselectivity. The ring-opening reaction of *cis*- and *trans*-2,3-epoxybutane (**1**) with aluminum chloride (**2**), yielding *erythro*- and *threo*-3-chloro-2-butanols (**3**), was examined in several different kinds of solvents. The stereochemical results are summarized in Table 1. It was also confirmed that the stereochemistry of the product was not affected in the course of hydrolysis of the produced aluminum alkoxide, since no ^{36}Cl was introduced into the product when the reaction mixture was hydrolyzed with aqueous $H^{36}Cl$.



$$\underset{(\mathbf{1})}{\text{CH}_3\text{-CH—CH-CH}_3\ (\text{O})} \xrightarrow[\text{ii) H}_3\text{O}^+]{\text{i) AlCl}_3\ (\mathbf{2})} \underset{(\mathbf{3})}{\text{CH}_3\text{-}\underset{\text{OH}}{\text{CH}}\text{—}\underset{\text{Cl}}{\text{CH}}\text{-CH}_3} \quad (1)$$

The solvents in which the reaction proceeds with retention of configuration are limited to aromatics, ethers, and nitro compounds. The product corresponding to the retention of configuration predominated only in the solvents of nitro compounds.

The ring-opening of **1** with **2** was carried out in carbon disulfide containing variable amounts of nitro-

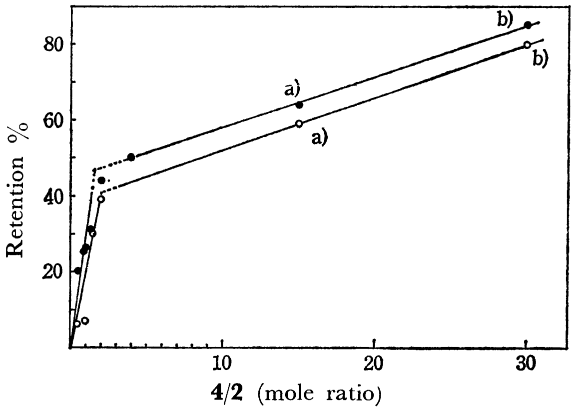


Fig. 1. Plot of $CH_3NO_2/AlCl_3$ *vs.* stereochemistry of ring-opening reaction of 2,3-epoxybutane: (●) *cis*-**1**, (○) *trans*-**1**.

Reactions were run in carbon disulfide (8 ml) at 0 °C. An equivalent amount (4 mmol) of **2** to **1** was used. a) Neat **4** (4 ml) was used as a solvent. b) Neat **4** (8 ml) was used as a solvent.

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* To whom all correspondence should be addressed.

TABLE 1. STEREOCHEMISTRY OF RING-OPENING REACTION OF 2,3-EPOXYBUTANE WITH $AlCl_3$[a]

Solvent	**1**	Reaction temperature[b] °C	**3** Yield %	Steric course Retention %
Carbon disulfide	*cis*	0	15.0	0
Chloroform	*cis*	0	42.3	0
Acetonitrile	*cis*	0	38.1	0
Acetone	*cis*	0	4.6	0
Ethanol	*trans*	0	76.1	0
Nitromethane (**4**)	*cis*	−10	24.1	94
Nitromethane	*cis*	0	12.7	85
Nitromethane	*cis*	18	13.2	36
Nitromethane	*cis*	27	10.6	25
Nitromethane	*trans*	−11	18.5	93
Nitromethane	*trans*	0	13.8	80
Nitromethane	*trans*	24	12.3	30
Nitromethane + Chloroform[c]	*trans*	0		65
1-Nitropropane	*trans*	0	24.1	59
2-Nitropropane	*trans*	0	30.3	49
Nitrobenzene	*trans*	0	14.4	48
Benzene	*trans*	7	5.9	trace
Toluene	*trans*	0	3.8	0.6
Mesitylene	*trans*	0	1.4	2.8—4.9
Ethyl ether	*trans*	0	16.5	52
Anisole	*trans*	0	4.2	2
Diphenyl ether	*trans*	28	8.3	0
DMSO	*trans*	0	4.6	0
DMF	*trans*	0	7.8	0
Sulfolane	*cis*	27	17.0	trace
Sulfolane + 1,2-Dichloroethane[d]	*cis*	0		0[g]
Dimethyl sulfone + 1,2-Dichloroethane[e]	*cis*	0		0
Pyridine-*N*-oxide + Chloroform[f]	*cis*	0		3
Triethylamine	*cis*	0	42.5	0

a) Reactions were run in 8 ml of the solvent unless specified otherwise on 4 mmol scale of **1** with 1.5 equiv. of **2** for 2 h. b) Cooling bath temperature. c) **1** (4.88 mmol), **2** (5.59 mmol), **4** (4 ml), $CHCl_3$ (4 ml). d) **1** (2.80 mmol), **2** (5.60 mmol), sulfolane (39.4 mmol), $(CH_2Cl)_2$ (4 ml). e) **1** (5.30 mmol), **2** (5.48 mmol), $(CH_3)_2SO_2$ (100 mmol), $(CH_2Cl)_2$ (20 ml). f) **1** (4.35 mmol), **2** (5.07 mmol), C_5H_5NO (17.0 mmol), $CHCl_3$ (10 ml). g) Nakajima reported that the ring-opening reaction of 1,2-epoxypropane with **2** proceeds with 12% retention of configuration in a mixed solvent of sulfolane and 1,2-dichloroethane.[7]

TABLE 2. STEREOCHEMISTRY OF RING-OPENING OF 2,3-EPOXYBUTANE WITH $AlCl_3$ IN THE PRESENCE OF NITROBENZENE DERIVATIVES (p-X-C_6H_4-NO_2)[a]

X	Stereochemistry Retention %	Hammett $\sigma_p-\sigma_m$
H[b]	60	—
CH_3[b]	61	−0.109
Cl[b]	65	−0.146
OCH_3[b]	75	−0.383
CN[c]	0	+0.100
NH_2[c]	1.3	−0.49
OH[c]	2.4	−0.82

a) Reactions were carried out using *cis*-**1** in 1,2-dichloroethane containing nitrobenzene derivatives (1.0 M) at 0 °C, **2**/**1** = 1.0−1.4, nitrobenzene derivatives/**2** = 8.6−8.9. b) Reaction is homogeneous. c) Reaction is heterogeneous.

methane (**4**). In Fig. 1, the percentages of retention are plotted against the amounts of **4** added. Nearly linear correlations between the amounts of **4** added and the percentage of retention are observed in the regions of **4**/**2**<0.5 and **4**/**2**>4. From the intersection to these two straight lines, values of **4**/**2**=1.4 and 1.8 are obtained for *cis*- and *trans*-**1** respectively. This fact seems to indicate that the ring-opening is connected with the 1 : 1 addition compound of **2** and **4**, although the possibility of the participation of the 1 : 1.5 or 1 : 2 addition compound cannot be completely excluded. On the other hand, it has been reported that nitroalkanes and many aromatic nitro compounds react with **2** to form crystalline solids, generally with the formula of $AlCl_3 \cdot RNO_2$, but also, in a few cases, that of $AlCl_3 \cdot 2RNO_2$.[8a)]

The substituent effects of *p*-substituted nitrobenzenes were investigated in order to account for the specificity of nitro compounds; the results are shown in Table 2. Within the nitro compounds which are soluble in 1,2-dichloroethane, a good correlation is obtained between the percentages of retention and the $\sigma_p-\sigma_m$ values of the substituents, which have been suggested as measures of the resonance effect of the given substituents. This fact indicates that the resonance between π-electrons of an aromatic ring and a nitro group is very significant in the retention process. On the other hand, the $\sigma_p-\sigma_m$ values should reflect the stabilities of the 1 : 1 addition compounds, of which structural information has been reported by Gagnaux.[9] Thus, the more stable 1 : 1 addition compounds, $AlCl_3 \cdot Sv$ (**5**, Sv=solvent), increases the retentive ring-opening reaction.

p-Cyano-, *p*-hydroxy- and *p*-amino-nitrobenzenes are insoluble in 1,2-dichloroethane, and the reaction systems are heterogeneous. A nonpolar solvent capable of undergoing a homogeneous reaction was searched for in vain. The reaction is accompanied with an almost complete steric inversion when these nitrobenzenes were added. In these cases, the group coordinating to aluminum may be not nitro, but cyano, hydroxyl or amino group, even if these compounds form complexes with **2**.

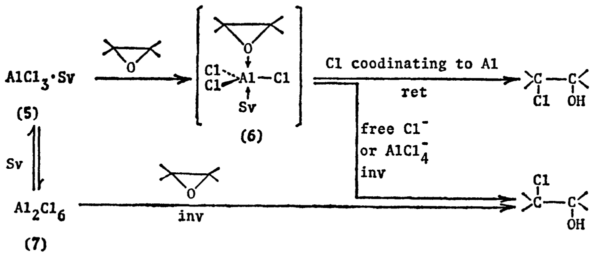
The proportions of the retention slightly increase in the order of: benzene<toluene<mesitylene, although the Friedel-Crafts reactions occur predominantly in these solvents. It is still less certain that **2** interacts with aromatic hydrocarbon, but these has been evidence of weak complex formation from solubility measurements.[8b)] Roberts[10] reported that the susceptibility toward a **2**-induced rearrangement of *n*-propyl side chains decreased in the series of *n*-propylbenzene, *n*-propyltoluene, and *n*-propylxylene. He attributed

this to the postulate that the catalyst is progressively less active due to complex formation with aromatics with increasing Lewis basicities. In the present case, the percentage of retention is also proportional to the stability order of the aluminum chloride complexes to be formed.

The same conclusion can also be drawn from a series of aliphatic nitro compounds. It is well-known that the steric effects have an important influence on the stability of the 1 : 1 complexes of Lewis acids and bases.[11] Brown[12] reported that the stabilities of the 1 : 1 complexes of boron trifluoride and ethers decreased in the order of: $Me_2O \cdot BF_3 > Et_2O \cdot BF_3 > i\text{-}Pr_2O \cdot BF_3$. The stabilities of the complexes of **2** and nitro compounds are expected as: $MeNO_2 \cdot AlCl_3 > n\text{-}PrNO_2 \cdot AlCl_3 > i\text{-}PrNO_2 \cdot AlCl_3$. The sequence is actually consistent with the observed order of the percentages of retention.

In the earlier reports on the ring-opening reactions of epoxides which proceeded with retention of configuration, the mechanism was discussed in the following terms: 1) a double inversion with the participation of neighboring groups, and 2) a four-centered or an ion-pair mechanism. Although the mechanism 1 was proposed for the case of phenyl- and carbonyl-substituted epoxides,[2,3,5] it is improbable for an alkyl-substituted epoxide in the present case. The mechanism 2 was proposed by Wasserman and Aubrey[5] as a possible explanation of the results of the reaction of dypnone oxide with hydrogen chloride. Brewster[4] also supposed an ion-pair in a solvent cage to explain the *cis* ring-opening of *trans*-α-methylstilbene oxide with acetic acid. An analogous mechanism, shown in Scheme 1, seems to be applicable to the present case.

Solvates of different compositions are known for **2** containing from one to six donor molecules per molecule of **2**. Solvents of a weak coordinating affinity give 1 : 1 addition compounds, and those of better coordinating properties give 1 : 1, 1 : 1.5, and 1 : 2 compounds, while 1 : 4 and 1 : 6 compounds are limited only to some powerful coordinating solvents. A solvate of the $AlCl_3 \cdot Sv$ type was regarded as an acceptor solvate,[13] since it is capable of accepting further solvent or other donor molecules.



Scheme 1.

On the addition of epoxide, the solvated aluminum chloride (**5**) may accept lone-pair electrons of epoxide and is transformed into the complex **6**. The collapse of **6** gives chlorohydrin of a retained configuration whose chlorine comes from the coordinating site to aluminum. On the contrary, the inverted product can be derived by the attack of the free chloride ion in the solution on the solvated complex **6**. An analogous mechanism involving a common intermediate leading to both *cis* and *trans* oxymercurials was recently proposed by Bach and Richter.[14] Furthermore, in the present case, the solvated complex **5** may be equilibrated with the aluminum chloride dimer (**7**). **2** is well-known to exist as a dimer in carbon disulfide or in chloroform. Since a chlorohydrin with an inverted configuration is obtained in these solvents, the reaction of epoxide and **7** is considered to proceed with inversion. In the system involving a stable addition compounds, the equilibrium should lie towards the complex **5** rather than **7**; that is, the more stable addition compounds afford an increased amount of the chlorohydrin with a retained configuration.

If the ring-opening of epoxide with **2** is assumed to follow Scheme 1, free ion species and also **7** should not exist in the system which produces a chlorohydrin with a retained configuration. However, an inconsistency inheres in this condition. To satisfy the condition, the solvent must be moderately basic; free chloride ion may be formed by the cleavage of Al–Cl bonds if the solvent basicity is too strong.

TABLE 3. STEREOCHEMISTRY OF RING-OPENING OF 2,3-EPOXYBUTANE WITH $AlCl_3$ IN NITROMETHANE. EFFECTS OF THE ADDITIONAL LITHIUM HALIDE

Lewis acid (mole ratio)	Stereochemistry Retention %
2	85
2+LiCl (1 : 1)	6
2+HCl (1 : 1)	3
2+HCl (1 : 0.03)	72
2+LiBr (1 : 1)	2[a]
$AlBr_3$+LiCl (1 : 1)	1[a]
(LiCl)	No reaction
(LiBr)	No reaction

a) The product is 3-bromo-2-butanol containing trace of **3**.

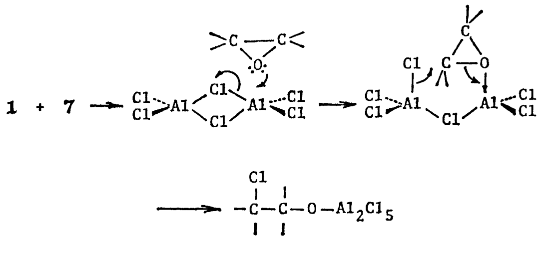
In order to discuss the effect of a free ion, the ring-opening reaction of **1** was pursued in **4** by the addition of lithium salts as a source of free ions. The results are tabulated in Table 3. The reaction process alters from retention to inversion by the addition of an equivalent amount of lithium chloride. In the experiments using $Li^{36}Cl$, the produced **3** contained 22.6% of the activity. This result indicates that all the chlorines of lithium chloride and **2** are equivalent within the limits of experimental error. The addition of lithium chloride creates an equilibrium:

$$AlCl_3 \cdot Sv + LiX \overset{Sv}{\rightleftharpoons} LiSv_n^+ + AlCl_3X^- \qquad (2)$$

The anion, $AlCl_4^-$, formed in this equilibrium attacks epoxide, and the reaction proceeds with inversion of configuration.

A mechanism involving the back-side shielding by a solvent may be expected, but it is inadequate for the present system by the facts that a high retention of configuration is observed only in nitro compound solvents, and that the reaction proceeds with complete inversion in acetonitrile, which exhibits a good back-side shielding effect in solvolysis.[15] The substitution reaction of epoxides under acidic conditions was claimed not to proceed by the $A1$ mechanism, but by the borderline $A2$ mechanism even in a system stabilizing the carbonium ion such as styrene oxide.[16] It was also reported that the rearrangement of oxirane to carbonyl compounds does not occur through a planar carbonium ion, but occurs in a more concerted manner.[17] The temperature effect on the stereoselectivity shown in Table 1 seems to constitute evidence for the arguments on the intermediacy of the fully developed carbonium ion. If the ring-opening in **4** proceeds by means of the carbonium ion–back-side shielding mechanism, the ratio of racemization would increase at higher temperatures. At 27 °C, the result is 25% retention and 75% inversion, which means 50% inversion and 50% racemization. As inversion and racemization at 18 °C are 28 and 72% respectively, an inversion process prevails at higher temperatures. The observed temperature effects cannot be explained by assuming the formation of a carbonium ion. These results suggest a larger activation entropy and enthalpy for the reaction accompanied with steric inversion than for the reaction with retention. Taking the cyclic transition state, the S_Ni reaction can be expected to have a smaller activation enthalpy and a larger negative value of activation entropy than the S_N2 reaction. The observed temperature effect is explainable by assuming the S_N2 mechanism for the ring-opening reaction with inversion and the S_Ni mechanism for the reaction with retention. However, the differences in the relative rates due to the reaction temperature are too large to be accounted for by only the competition of S_N2 and S_Ni reactions. These differences may also be due to an equilibrium between **5** and **7**, as is indicated in Scheme 1.

The ring-opening reaction proceeds with inversion of configuration in nonpolar solvents, such as carbon disulfide and chloroform, in which **2** is dimeric. In these solvents, however, it is difficult to assume a free ionic species which attacks the coordinated epoxide from the back-side. Therefore, it seems to be difficult to explain an inversion mechanism by a model for the transition state at a single metal atom center. A mechanism which involves two separate metal sites has been proposed by Price for the triethylaluminum–water catalyzed epoxide polymerization, which proceeds with inversion of configuration at the carbon atom undergoing ring-opening attack.[18] We propose, on these bases, a most plausible mechanism for the ring-opening of epoxide with **7** in a nonpolar solvent (Scheme 2), although we expected a mechanism including two molecules of **2** for the reaction in a previous paper.[6]



Scheme 2.

Many studies have been made concerning the structure of **2** in solutions; among them, the investigation by means of NMR appears to be most reliable. The solution structures of **2** can be classified into the following four groups on the basis of the experimental results obtained by NMR techniques:

Type 1. Solutions in which **2** is completely dissociated into ions.

Solutions of **2** in protic and aprotic polar solvents belong to this group. In dimethyl sulfoxide (DMSO)[19] and ethanol,[20] the Al–Cl bonds are completely dissociated into ions, and the aluminum cation is coordinated by six molecules of the solvents.

$$AlCl_3 + 6Sv \longrightarrow AlSv_6^{3+} + 3Cl^- \qquad (3)$$

Type 2. Solutions in which disproportionation occurs.

The apparent solvation number of **2** in acetonitrile is 1.5,[21] and the Al–Cl bonds dissociate partially into ions.[20,22]

$$4AlCl_3 + 6Sv \longrightarrow AlSv_6^{3+} + 3AlCl_4^- \qquad (4)$$

Type 3. Solutions in which **2** forms 1 : 1 addition compounds with the solvents.

$$AlCl_3 + Sv \longrightarrow AlCl_3 \cdot Sv \qquad (5)$$

Although many compounds are reported to form 1 : 1 addition compounds in the crystalline state with **2**, the existence of the 1 : 1 compounds in solution has been confirmed in a few cases. Nitro compounds are considered to form the 1 : 1 adduct in solution.[23] Ether and benzene may also form 1 : 1 adducts in the equilibrium state.[20,24] The 1 : 1 adducts are acceptor solvates, as has been mentioned before.

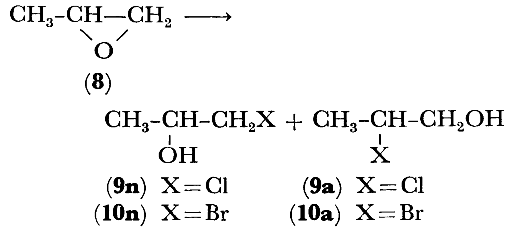
Type 4. Solutions in which **2** exists as a dimer.

2 exists as a dimeric form (**7**) in nonpolar solvents, such as carbon disulfide and chloroform.[25] Ether and benzene are considered to contain **7** under equilibrium with the 1 : 1 adducts.[20,24]

The ring-opening of epoxide with **2** proceeds with retention of configuration only in the solvents of Type 3. In mixed solvents, the one with the stronger ability to coordinate to aluminum determines the nature of the solution; *e.g.*, the solution structures of the mixed solvents of Types 1 and 2, and of Types 2 and 3 are dominated by the solvent natures of Types 1 and 2 respectively. When an equivalent amount of **4** to **2** is added to an acetonitrile solvent, the structure of the solution is Type 2, and the epoxide is ring-opened with 100% inversion. This result is in good contrast with that of the reaction carried out in a carbon disulfide solution containing **4**.

Haraguchi reported the order of coordination affinity against aluminum as $H_2O > EtOH \gg I > Br > Cl > PhCN > CH_3CN$.[20,24] If lithium halide is added to the solutions of Types 2 and 3, aluminum in the solution will mostly be in the state of $AlCl_3X^-$, since the halogen has a stronger affinity than the solvent does. In these systems, the reaction proceeds with inversion.

Regioselectivity. The reaction was carried out in a way similar to that mentioned in the stereochemical section, using 1,2-epoxypropane (**8**) instead of **1**. The isomer distributions of the produced chloropropanols (**9**) are summarized in Table 4.



$$CH_3\text{-}CH\text{—}CH_2 \longrightarrow \quad (\textbf{8}: \text{epoxide, O bridging CH and } CH_2)$$

$$CH_3\text{-}\underset{OH}{CH}\text{-}CH_2X + CH_3\text{-}\underset{X}{CH}\text{-}CH_2OH \qquad (6)$$

(**9n**) X=Cl (**9a**) X=Cl
(**10n**) X=Br (**10a**) X=Br

Table 4. Ring-opening reaction of 1,2-epoxypropane with $AlCl_3$ in various solvents[a)]

Solvent	Yield **9** (%)	Product ratio (%) **9n**	Product ratio (%) **9a**
CS_2	54.0	47	53
$ClCH_2CH_2Cl$	71.0	17	83[b)]
Et_2O	26.3	57	43
CH_3NO_2	51.6	2	98
CH_3CN	97.5	87	13
EtOH	96.4	91	9
DMSO	18.7	81	19

a) Experimental conditions are **8** : **2** : solvent=1 : 1 : 50. b) The proportion of **9a** depends upon the rate of addition of **8**, and it decreases until a minimum 18% when **8** is added rapidly.

In contrast with the fact that normal ring-opening is predominant in acetonitrile, ethanol, and DMSO, the proportion of the abnormal ring-opening product (**9a**) is increased in ether, carbon disulfide, and 1,2-dichloroethane. Furthermore, an extensive abnormal ring-opening as much as 98% is observed in nitromethane. A few reactions are known which proceed with more than 90% abnormal ring-opening. In these cases, nucleophiles preferably attack the hindered carbon atom.

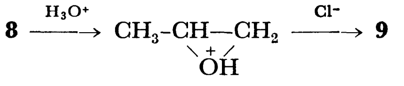
Although several different mechanisms have been called into play to explain the divergent results of ring-opening reactions of epoxides, a consistent explanation can be given in terms of a "push-pull" mechanism.[26)] Because of the strain in the three-membered ring of epoxide, the cleavage of the C–O bond will be important, especially in acid-catalyzed reactions, in which proton or Lewis acid coordinates to the epoxide oxygen. The coordination of these acids provides a strong pull in the displacement. As a result, steric factors are less influential than usual.

The ring-opening of aliphatic epoxide with **2** in **4** cannot be considered to involve a fully developed carbonium ion, but the 1 : 1 adduct of **2** and **4** is an acceptor solvate and can coordinate on the epoxide oxygen. Thus, favorable bond-breaking may occur between secondary carbon and oxygen giving the abnormal product (**9a**).

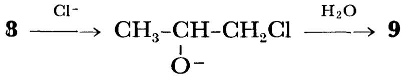
Such mode of reaction is often observed in the substitution reactions of heterocyclic compounds.[27)] For example, the Friedel-Crafts reaction of **8** proceeds with inversion of configuration, accompanied with a complete abnormal ring-opening.[6)] The ring cleavage of cyclic sulfate has been considered to proceed by S_N1 mechanism under acidic conditions, because the reaction of unsymmetrical cyclic sulfate from 1,3-butanediol with hydrochloric acid takes place on the secondary carbon.[28)] However, the ring-opening of the cyclic sulfate of 2,4-pentanediol with hydrochloric acid proceeds with complete inversion of configuration, yielding 4-chloro-2-pentanol.[29)]

As has been postulated in the foregoing stereochemical section, $AlCl_3\cdot Sv$ (**5**) is the reacting species in **4** and ether solutions, and the chlorine atom of the products comes from the coordination sphere of aluminum. In DMSO, ethanol, and acetonitrile, on the contrary, chloride and $AlCl_4^-$ ions play an important role in the nucleophilic substitution of epoxide. The dissociated aluminum cation is completely solvated, fulfilling its coordination number, and it seems no longer to provide a strong pull by the coordination of the epoxide oxygen.

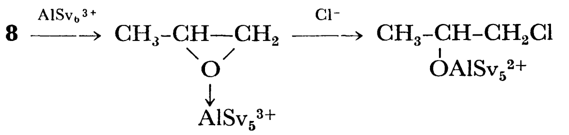
It has also been reported that the ring-opening reaction of **8** with hydrochloric acid proceeds concurrently by the two paths shown in Eqs. 7 and 8.[16)] Analogous courses can be considered for the reaction of **8** with **2** in polar solvents (Eqs. 9 and 10):



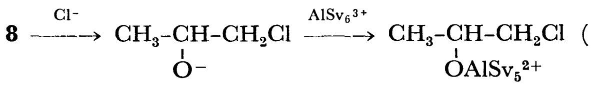
$$\textbf{8} \xrightarrow{H_3O^+} CH_3\text{-}CH\text{—}CH_2\ (\text{ring } \overset{+}{O}H) \xrightarrow{Cl^-} \textbf{9} \qquad (7)$$



$$\textbf{8} \xrightarrow{Cl^-} CH_3\text{-}\underset{O^-}{CH}\text{-}CH_2Cl \xrightarrow{H_2O} \textbf{9} \qquad (8)$$



$$\textbf{8} \xrightarrow{AlSv_6{}^{3+}} CH_3\text{-}CH\text{—}CH_2\ (\text{ring O} \rightarrow AlSv_5{}^{3+}) \xrightarrow{Cl^-} CH_3\text{-}\underset{OAlSv_5{}^{2+}}{CH}\text{-}CH_2Cl \qquad (9)$$



$$\textbf{8} \xrightarrow{Cl^-} CH_3\text{-}\underset{O^-}{CH}\text{-}CH_2Cl \xrightarrow{AlSv_6{}^{3+}} CH_3\text{-}\underset{OAlSv_5{}^{2+}}{CH}\text{-}CH_2Cl \qquad (10)$$

The nucleophiles produced in DMSO and ethanol are free and solvated chloride ions respectively, but $AlCl_4^-$ ion is the nucleophile in acetonitrile.[19,20,22)] Equation 9 may be considered as a usual acid-catalyzed reaction *via* an onium ion, and Eq. 10, as a reaction with a base. It is well known that the base-induced reaction of epoxide exclusively results in the normal ring-opening. As the normal product (**9n**) is favored in DMSO, ethanol, and acetonitrile, the respectable part of the ring-opening in these solvents is expected to proceed by means of Eq. 10.

The regioselectivity of the ring-opening reaction appears to depend upon the counterbalance of the pull by Lewis acids and the push by nucleophiles. The result that the normal product predominates in the polar solvents may reflect the weak pull by the $AlSv_6{}^{3+}$ cation and the strong push by the chloride and $AlCl_4^-$ ions. This is in good contrast with the results of the Friedel-Crafts reaction, in which a bulky and weak nucleophile, benzene, provides only a weak push, while **2** pulls very strongly; thus, the result is a complete abnormal ring-opening, as has been mentioned before.

Table 5. Ring-opening reaction of 1,2-epoxypropane in the presence of salts[a]

Solvent	Addendum	Yield **9**+**10** (%)	Product ratio (%)			
			9n	**9a**	**10n**	**10a**
CH_3NO_2	none	48.3	4	96		
CH_3NO_2	LiCl	72.6	62	38		
CH_3NO_2	NaCl	53.3	58	42		
CH_3NO_2	KCl	58.4	73	27		
CH_3NO_2	LiBr	81.5	14	4	69	13
CH_3NO_2	KBr	65.4	15	4	73	8
Et_2O	none	34.8	57	43		
Et_2O	LiBr	37.8	4	1	89	6
Et_2O	NaBr	29.0	61	39	0	0
Et_2O	KBr	33.0	57	43	0	0

a) Experimental condition; **8** : **2** : addendum : solvent= 1 : 1 : 1 : 50.

Table 6. Solvent effect on the ring-opening of 1,2-epoxypropane in the presence of lithium bromide[a]

Solvent	Yield **9**+**10** (%)	Product ratio (%)			
		9n	**9a**	**10n**	**10a**
CS_2	36.3	61	34	5	trace
$ClCH_2CH_2Cl$	37.9	44	40	9	3
Et_2O	34.8	21	3	70	6
CH_3NO_2	84.9	11	3	75	11
CH_3COCH_3	92.7	12	1	83	4
CH_3CN	96.1	8	1	86	5
DMF	22.1	63	7	29	1
DMSO	13.8	69	13	17	1
EtOH	80.4	69	8	21	2
EtOH	100	49	6	43	2

a) Experimental condition; **8** : **2** : LiBr : solvent= 1 : 1 : 1 : 20.

To confirm these considerations we examined the effect of added alkali metal halide on the regioselectivity of the ring-opening of **8** with **2**. Quite a different regioselectivity was observed when the salts are added to **4** and ether solvents.

The results shown in Table 5 can be summarized as follows: 1) the normal ring-opening becomes predominant when the salts are added, and bromides are more effective than chlorides; 2) the bromopropanols (**10**) predominate when bromides are added, except in the cases of sodium and potassium bromides in ether; 3) the difference of cation has little influence on the product compositions.

As is shown in Table 6, the product distribution in acetonitrile is similar to those obtained in **4** and ether; in these solvents $AlCl_3Br^-$ is a reacting species, but it distinctly differs from those in DMSO and ethanol, in which the added salts completely dissociate into ions. This fact indicates that the regioselectivity is related intimately to the anionic species. It has been reported that AlX_4^- has nucleophilicity to some extent, though it is a weaker nucleophile than halide ion.[30]

If the equilibrium 2 is taken into account, lithium cation should be the acid providing the pull in Eq. (9) when the solvents of the second and third types are used. Although it has been reported that lithium salts have catalytic activities in the ring-opening and rearrangement reactions of epoxides,[31] only a weak participation of lithium cation may be displayed by the electrostatic interaction in the present case, since not only lithium but potassium salt is effective and the reaction is not so much affected by the change of cations. As the pull provided by the lithium cation may be much weaker compared with that by **5**, the more normal ring-opening results when the lithium halides are added to **4**. When sodium and potassium bromides are added, the equilibrium 2 stays far to the left in ether, because these salts are insoluble in this solvent. Thus, these salts seem to have no influence on the regioselectivity in an ether solvent.

As affinity of bromide ion to aluminum is stronger than that of chloride,[24] the formation of AlX_4^- species in the equilibrium is more satisfactory when lithium bromide instead of chloride is added. As a result, the more normal ring-opening product is obtained by the addition of lithium bromide.

The results shown in Table 6 can be explained appropriately by taking the before-mentioned types of the solution structure into account. The first class of solvent, consisting of polar solvents such as DMSO, DMF, and ethanol, can completely dissociate **2** and lithium salts into ions. In these solvents, metal cations are strongly coordinated by the solvent molecules. The distribution of the halohydrins produced depends upon the nucleophilicities of the halide ions. In aprotic polar solvents, halide ions are not solvated and their nucleophilicities depend upon their basicities, $Cl^- > Br^-$.[32] On the contrary, halide ions are solvated in protic solvents, their nucleophilicities do not depend upon the basicities, and the order of nucleophilicities has been well established as $Br^- > Cl^-$.[33] Accordingly, the predominant product is **9** in aprotic polar solvents, and the extended proportion of **10** results in protic solvents.

In the moderately basic solvents of the second type (acetonitrile, acetone, *etc.*), and in **4** and ether of the third type, a larger amount of **10** was yielded than was to be expected from the nucleophilicities of halide ions in aprotic solvents. The reaction without the addendum in **4** and ether proceeds *via* the complex **6**, where no ionic species are present. An $AlCl_3Br^-$ ion is formed according to Eq. 2 when the lithium bromide is added to solvents of the second and the third classes. It is most reliable that the ring-opening is caused by the attack of $AlCl_3Br^-$ instead of free chloride or bromide ions in these systems. However, insufficient evidence is available to us at this time to interpret the predominant formation of **10** with the use of $AlCl_3Br^-$. One of the most reasonable elucidations for this subject may be offered by Pearson's HSAB principle. Bromine is a softer base within four halogens in $AlCl_3Br^-$, and the carbon atom of epoxide is a soft acid. As a soft acid is favorable to react with a soft base, **10** should be the predominant product of the reaction with $AlCl_3Br^-$.

If the reaction conditions of $LiBr/\mathbf{8} \geqq 1$ are satisfied

TABLE 7. EFFECTS OF MOLE RATIO OF THE REAGENTS ON THE RING-OPENING REACTION[a)]

Mole ratio			Product ratio (%)			
8	**2**	LiBr	**9n**	**9a**	**10n**	**10a**
1	1	1	7	1	85	7
1	1	0.5	37	9	50	4
1	1	2	2	trace	89	9
1	0.5	1	4	1	87	8
1	2	1	4	2	86	8
0.5	1	1	5	1	84	10
2	1	1	36	8	51	5

a) Solvent: Et_2O (100 mol eq.)

as is shown in Table 7, **10** is the principal product and no difference is observed in the product distributions. The exhaustive formation of **10** in the system of **8** : **2** : LiBr = 1 : 2 : 1 may be indicative that the reaction rate of $AlCl_3Br^-$ and **8** is faster than that of **5** and **8**, for the same amount of **5** as $AlCl_3Br^-$ should exist in the system even if Eq. 2 is completely shifted to the right under these conditions.

In the nonpolar solvents which are classified as the fourth type (carbon disulfide, dichloroethane, *etc.*), the abnormal ring-opening product indicates a tendency to predominate over the normal product. The addition of lithium bromide shows little effects, as is shown in Tables 4 and 6. The composition of the normal ring-opening product, **9n**, was increased in the order of 17, 27 and 37% with an increase in the mole ratio of **8**/**2**=1.0, 2.0, and 3.0 in 1,2-dichloroethane. These results indicate that the alkoxyaluminum chloride, which is given by the reaction of **8** and **2**, reacts with additional **8** to give more **9n** than in the reaction of **2**. The proportion of normal ring-opening seems to increase in the order of **2**<$AlCl_2OR$<$AlCl(OR)_2$; these reacting species may be present as dimers in such solvents. As the Lewis acidities generally increase with an increase in the electronegativities of X in metal salts, MX_n, the Lewis acidities decrease in the order of **2**>$AlCl_2OR$>$AlCl(OR)_2$. Thus, the abnormal ring-opening should be favored in the cases of stronger Lewis acids. The product distribution was strongly affected by the rate of addition of **8** to **2**, and the proportion of **9n** was varied from 17 to 82% by rapid addition. As **2** is less soluble in these solvents, the reaction was initially heterogeneous, but **2** was completely dissolved when an equivalent amount of **8** had been carefully added. When **8** is added rapidly, the ring-opening reaction with $AlCl_2OR$ and $AlCl(OR)_2$ may not be neglected. The reactions in these nonpolar solvents are insufficiently reproducible. Since the dissolving rate of **2** should be significantly influenced by the nature of the crystal of **2** and with the mechanical stirring efficiency, the insufficiency of reproducibility appears to be due to these facts.

The results of the present paper are summarized in Table 8.

Experimental

Materials. *cis*-2,3-Epoxybutane (*cis*-**1**) and *trans*-2,3-epoxybutane (*trans*-**1**) were prepared by the method of Pasto and Cumbo.[34)] VPC analysis (a 45 m polypropylene glycol Ucon oil LB-550X capillary column was employed) indicated the *trans*-**1** to be free of any *cis*-isomer, whereas *cis*-**1** was accompanied with 1.4% of the *trans*-isomer. Commercial 1,2-epoxypropane (**8**, special grade) was distilled before use. Commercial special grade aluminum chloride (**2**) was purified by sublimation three times under a reduced pressure before each use. Lithium chloride and bromide were dried over P_2O_5 at 140 °C in vacuum. All the solvents were dried by the most efficient ways appeared in the literature[35)] and were distilled before use.

A Typical Procedure of Ring-opening Reaction. Into a solution of **2** (0.877 g, 6.58 mmol) in 4 ml of acetonitrile,[36)] **1** (0.318 g, 4.69 mmol) in 4 ml of acetonitrile was slowly added under well-stirring in an ice bath. It took 2 h for the addition at a constant temperature, and stirring was continued for an additional 30 min. After the duration, the reaction mixture was poured into a mixture of 10 ml of concd HCl and 50 g of ice. The organic layer was separat-

TABLE 8. SOLUTION STRUCTURE OF $AlCl_3$ AND THE RING-OPENING REACTION OF EPOXIDES

Type	Solution structure[a)]	Solvation number	Typical solvent	Selectivity	
				Stereo	Regio
1	$AlSv_6^{3+}+3\mathit{Cl}^-$	6	DMSO, DMF	inv	nor
1′	$AlSv_6^{3+}+3\mathit{ClSv_n}^-$	6	EtOH	inv	nor
2	$AlSv_6^{3+}+3\mathit{AlCl_4}^-$	1.5	CH_3CN	inv	nor
3	$\mathit{AlCl_3\cdot Sv}$	1	CH_3NO_2	ret	abnor
4	$\mathit{Al_2Cl_6}$	—	CS_2, $CHCl_3$	inv	mixture

In the presence of lithium bromide

Type	Solution structure[a)]	Selectivity		Product
		Stereo	Regio	
1	$AlSv_6^{3+}+LiSv_m^{+}+3\mathit{Cl}^-+\mathit{Br}^-$	inv	nor	**9**>**10**
1′	$AlSv_6^{3+}+LiSv_m^{+}+3\mathit{ClSv_p}^-+\mathit{BrSv_q}^-$	inv	nor	**9**≧**10**
2	$\mathit{AlCl_3Br}^-+LiSv_m^{+}$	inv	nor	**10**
3	$\mathit{AlCl_3Br}^-+LiSv_m^{+}$	inv	nor	**10**
4	$\mathit{Al_2Cl_6}$	inv	mixture	**9**

a) Those indicated in italics are the active species of each reaction.

ed and washed with 20 ml of water. The combined aqueous layer was saturated with NaCl and extracted twice with 30 ml and then with 20 ml of ether. The combined organic layer was dried over Na_2SO_4 after the addition of mesitylene as an internal standard. The solvent was evaporated off, and the residual product was submitted to VPC analysis. *erythro*-3-Chloro-2-butanol (**3**) was obtained in 38% yield based on **1**, and neither *threo*-**3** nor the unreacted **1** was detected. The product was identified by a comparison of the VPC retention time with those of the authentic samples.37) The product was converted into *trans*-**1** with dil. NaOH.

When 1,2-epoxypropane (**8**) was treated with **2** in ether, 1-ethoxy-2-propanol (yield 8.1%) was obtained, accompanied with chloropropanols (**9**, yield 26.3%). The former was identified after the product mixture had been treated with dil. NaOH, converting **9** to **8**, by comparisons of the VPC retention time and the NMR spectrum with those of an authentic sample prepared from **8** and sodium ethoxide.

A Typical Reaction Procedure in the Presence of Lithium Bromide. In a cold nitromethane (30.5 g, 500 mmol), 1.4 g (10 mmol) of **2** was dissolved, then 0.87 g (10 mmol) of lithium bromide was added, the mixture turned to a brown homogeneous solution. To the well-stirred solution, 0.61 g (10.5 mmol) of **8** was added dropwise during a period of 20 min in an ice bath. After a duration of 40 min, the reaction mixture was worked up as mentioned above. The yields of **9** and **10** were 8.6 and 37.8% respectively by VPC analysis, the product ratio was 14.0 (**9n**), 4.5 (**9a**), 68.6 (**10n**), and 12.9% (**10a**).

It was confirmed that the products compositions did not change after they were treated again under the reaction conditions.

Vapor-phase Chromatographic (VPC) Analyses. The VPC analyses were carried out on Hitachi K-53 and Shimadzu 3AH gas chromatographs. The retention times of *threo*- and *erythro*-**3**, *threo*- and *erythro*-3-bromo-2-butanols, and mesitylene were 7.4, 8.9, 13.7, 15.7, and 10.4 min respectively on a 2 m column packed with 25% tricresyl phosphate and 1.5% H_3PO_3 on Chamelite CK at a column temperature of 100 °C. The retention times of **9n**, **9a**, **10n**, **10a**, and tetraline (an internal standard) were 3.2, 3.9, 4.8, 6.1, and 9.1 min respectively on a 3 m column of 10% PEG-20M on Celite 545 at 120 °C.

TABLE 9. RESULTS OF ^{36}Cl TRACER EXPERIMENTS OF RING-OPENING REACTION OF 2,3-EPOXYBUTANE WITH $AlCl_3$ IN NITROMETHANE SOLVENTS

Entry	Sample (mmol)	Automatic external standard ratio	dpm	dpm/mmol
1	Blank	0.8777	47.0	
2	**3** (0.292)a)	0.8817	63.9	
3	$H^{36}Cl$ (1.94×10^{-3})	0.6604	2839.9	1473.7×10^3
4	**3** (0.0534)b)	0.8965	43.1	807.1
5	$Li^{36}Cl$ (0.0292)	0.6959	14465.8	495404
6	**3** (0.183)c)	0.8718	20481.3	111920

a) An authentic non-active sample. b) The product obtained by hydrolyzing the non-active reaction mixture with $H^{36}Cl$ specified in entry 3. **2**: 15.58 mmol, $H^{36}Cl$: 4.85 mmol, ^{36}Cl/total Cl: 9.40%. c) The product obtained by the reaction with **2** (15.25 mmol) and $Li^{36}Cl$ (entry 6; 15.29 mmol), ^{36}Cl/total Cl: 25.2%, ^{36}Cl taken into **3**/total Cl: 22.6% (111920/495404).

^{36}Cl Tracer Experiments. The radioactivity measurements were performed by means of a Packard Tri-Carb liquid scintillation spectrometer model 3380. VPC preparation was made on an Aerograph Auto-prep A-700 chromatograph. Radioactive lithium chloride was prepared from lithium carbonate and 1 N $H^{36}Cl$; it was dried at 140 °C in vacuum until the weight was constant.

The crude **3** obtained by the reaction was purified by means of preparative VPC (Carbowax-20 M 20%, 20 ft column) and then submitted to measurements of the radioactivity. A solution of PPO (4 g) and dimethyl-POPOP (0.1 g) diluted with toluene to 1.0 l was used as the scintillator. The radioactivities of $H^{36}Cl$ and $Li^{36}Cl$ were measured in homogeneous solutions prepared by the addition of small amounts of ethanol or ethanol and water. Quenching corrections were carried out with the use of an external standard channel ratio method. The results of the experiments are summarized in Table 9.

We wish to express our thanks to Professors S. Suga and T. Nakajima, Kanazawa University, for their many helpful discussions. We are especially indebted to Drs. M. Hamada and R. Kiritani, Radiation Center of Osaka Prefecture, where the radioactive tracer experiments were carried out. This work was supported in part by a Scientific Research Grant from the Ministry of Education, Japan (No, 911511).

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