MECHANISMS OF EPOXIDE REACTIONS

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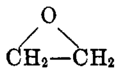
CONTENTS

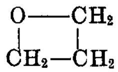
I. INTRODUCTION

This review is concerned only with the three-membered-ring α- or 1,2-epoxides, all of which can be regarded as derivatives of ethylene oxide (I). It is not concerned with derivatives of trimethylene oxide (II) or tetrahydrofuran (III), which are sometimes called 1,3- and 1,4-epoxides, respectively. The last review of the chemistry of α-epoxides was published by Winstein and Henderson in 1950 (285). Eliel (68) has also reviewed some aspects of their reactions.



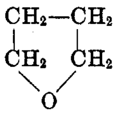
I

Ethylene oxide



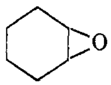
II

Trimethylene oxide



III

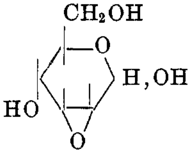
Tetrahydrofuran



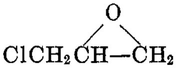
IV

Cyclohexene oxide

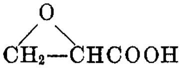
The nomenclature of α-epoxides is somewhat confusing. Thus ethylene oxide (I) is also called "epoxyethane" or "oxirane," cyclohexene oxide (IV) is also called "1,2-epoxycyclohexane," "1,2-oxidocyclohexane," or "7-oxabicyclo[4.1.0]heptane," and, when epoxides are regarded as derivatives of α-glycols, the prefix "anhydro-" is used. The latter term is used particularly for sugar epoxides, e.g., V is 2,3-anhydro-D-allose. In addition, several simple epoxides have trivial names, e.g., epichlorohydrin (VI) and glycidic acid (VII).



V



VI
Epichlorohydrin



VII
Glycidic acid

Since this review is concerned only with mechanisms of epoxide reactions, and not with the reactions as such, reference is made only to those investigations which appear to throw light on the mechanisms involved. This has necessitated a somewhat arbitrary choice in many cases, but the authors have tried to present all the important evidence. In addition to work of the above kind, a section on structure is included, since it is desirable to have this clearly in mind when considering mechanisms.

II. STRUCTURE OF EPOXIDES

The bond lengths and angles in ethylene oxide as determined by earlier electron-diffraction studies (285) have been corrected by microwave spectroscopy measurements (57, 58, 268), and the new values have now been confirmed by electron diffraction (124). They are shown in figure 1. Each CH_2 group is in a plane at right angles to the plane of the ring and the angle between each CH_2 plane and the carbon–carbon bond is 159°25′.

The dipole moment of ethylene oxide is 1.82 D in benzene solution and 1.91 D in the gas phase (88). Measurements of the heat of mixing with chloroform, the frequency shift of the OD band in the infrared spectrum of CH_3OD solutions (235, 236), and the chemical shifts in proton magnetic resonance (98) combine to show that the electron density on the oxygen atom is unusually low compared to that in acyclic and larger-ring cyclic ethers. The strain energy, taken as the difference between the experimental and the calculated heats of formation, has been found to be 13 kcal./mole for ethylene oxide (188). An important aspect of

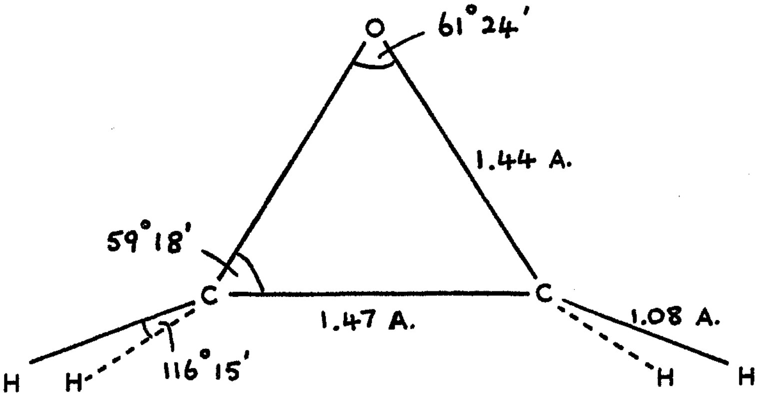
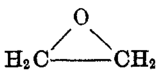
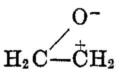


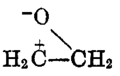
FIG. 1. Bond lengths and angles in ethylene oxide

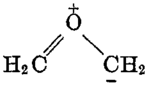
the structure of the epoxide ring, from our point of view, is its undoubted ability to conjugate with an attached unsaturated group. This has been demonstrated by ultraviolet spectroscopy (36, 222). It has also been shown that such conjugation does not occur if the π orbitals of the unsaturated groups cannot orient themselves with their axes parallel to the plane of the epoxide ring (55). It follows, therefore, that the orbitals in the epoxide ring which are responsible for the conjugation must lie in the plane of the ring (and not above and below it, as in benzene).

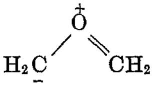
Various structures have been put forward for ethylene oxide. Zimakov (290) favors a resonance hybrid of VIII, IX, and X. This is supported by McDowell (169) but criticized by Searles, Tamres, and Lippincott (236), who prefer a hybrid of VIII, XI, and XII. Walsh (277) put forward structure XIII and, although it has been criticized on various grounds by Karrer (130), McDowell (169), and Robinson (221), it is supported by the force constants of the CH bonds (144) and by the anomalously high magnetic susceptibility of ethylene oxide (136). Of all the structures so far mentioned it is the only one which comes near to satisfying the above experimental facts (most of which were unknown at the time that these structures were put forward). Walsh has elaborated his structure in later papers (278, 279) and in this form (XIV) it is probably the best representation available. The carbon atoms are trigonally (sp^2) hybridized and one such orbital from each carbon atom overlaps with an atomic orbital of oxygen

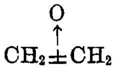

VIII

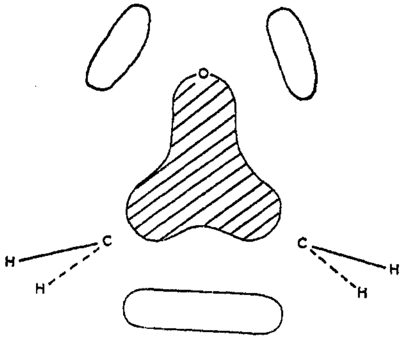

IX


X

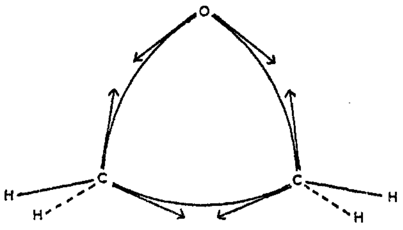

XI


XII


$$CH_2 \overset{\overset{O}{\uparrow}}{\pm} CH_2$$
XIII



XIV[1]



XV

to form the molecular orbital represented by the shaded area in the center of the ring. Two electrons go into this orbital and the remaining four electrons go into delocalized molecular orbitals in the plane of the ring, represented by the unshaded areas. These latter orbitals are formed by sideways overlap of atomic *p* orbitals in the plane of the ring, and their presence accounts for the conjugating

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[1] Reproduced in a modified form by permission of the Faraday Society.

ability of the epoxide ring. The only reasonable alternative to this would seem to be a "bent-bond" structure (XV), similar to that put forward by Coulson and Moffitt (50, 51) for cyclopropane. In such a structure the ring atoms do not lie along the lines of greatest electron density of the atomic orbitals from the neighboring atoms (shown by arrows in XV), but the smaller amount of overlapping which this involves is more than offset by a decrease in the strain energy. For the similar compound, cyclopropane, the orbitals of the carbon atoms in the plane of the ring are calculated to be at an angle of 106° to each other (51). There is probably no fundamental difference between structures XIV and XV (*cf.* discussion on analogous structures for cyclopropane (51)) and they both account for the conjugating power of the epoxide ring, the shortening of the carbon–carbon bond, and for most of the other experimental facts (although not, apparently, for the low electron density on the oxygen atom). Sugden (258) has also considered the structure from a molecular-orbital standpoint and his conclusions appear to be similar to structures XIV and XV.

Propylene oxide and epichlorohydrin have been investigated by electron diffraction (125), and in each case the bond joining the exocyclic carbon atom to the ring is 1.52 ± 0.03 A. in length. A partial structure determination of propylene oxide by microwave spectroscopy (260) gives the length of this bond as 1.51 ± 0.02 A.

An electron-diffraction study of 1,2-epoxycyclohexane (193) has given the dimensions shown in figure 2. The four carbon atoms nearest to the oxygen are coplanar and the angles C_1—C_2—C_3 and C_2—C_1—C_6 are 118.5°, the angles C_2—C_3—C_4 and C_1—C_6—C_5 are 116°, and the angles C_6—C_5—C_4 and C_5—C_4—C_3 are 109.5°. It is obviously important to bear this structure in mind when considering the reactions of steroid epoxides and six-membered-ring sugar epoxides.

A microwave spectroscopic investigation of 1,2-epoxycyclopentane (72) has shown that the oxygen atom is out of the approximate plane of the carbon ring. The carbon–carbon distance (in the epoxide ring) is 1.52 A. and the carbon–oxygen distance 1.47 A., and the angle between the carbon ring and the epoxide ring is 98.1°.

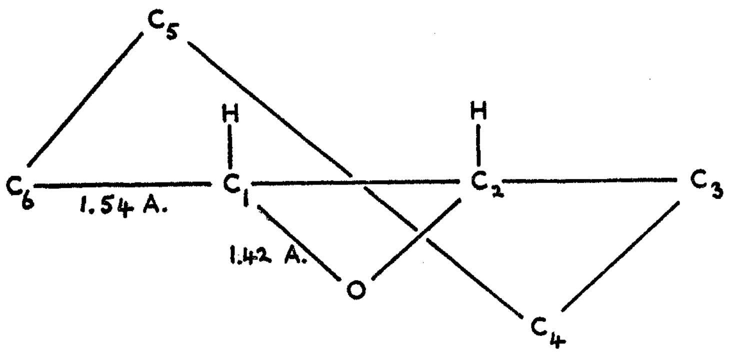
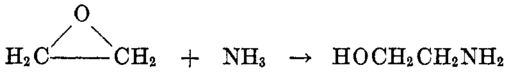


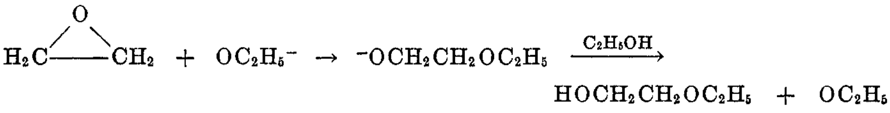
FIG. 2. Dimensions of 1,2-epoxycyclohexane

III. TYPES OF REACTION

The vast majority of epoxide reactions have been studied in solution; only these reactions will be considered and not thermal decompositions or other reactions in the gas phase. Almost all the reactions in solution involve the opening of the epoxide ring and the addition of a molecule of reagent, e.g.,



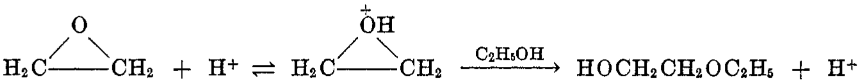
If the reagent is an anion, the reaction is completed by the solvent, e.g.,



In this case, since ethoxide ion is not consumed, the reaction is referred to as a base-catalyzed addition of ethanol. A somewhat similar case is the addition of thiosulfate in water, where hydroxide ion is produced:

In spite of the formal differences, it is obvious that the above three reactions, and indeed all ring-opening reactions under basic or neutral conditions, are essentially similar, involving, as they do, the attack of a nucleophile on one of the epoxide carbon atoms.

A real difference does, however, exist when the reactions are carried out under acidic conditions. The addition of most nucleophiles is considerably accelerated by acids and this is due to the reversible formation of the more reactive conjugate acid of the epoxide:

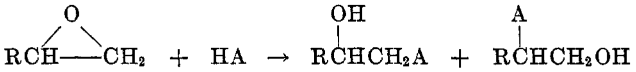


Zimakov (291) has found that the solvation of ethylene oxide increases in acidified solutions; he attributes this to the presence of the oxonium form in solution.

There is very little doubt that the ring-opening reactions of epoxides take place by ionic mechanisms. The bond which is broken is the highly polar carbon–oxygen bond, which would be expected to break ionically, and the reactions are generally carried out in polar solvents. The reaction between ethylene oxide and diethylamine in methanol has been shown not to occur in the absence of solvent (114). Possible exceptions to the rule of ionic mechanisms are the reactions with hydrogen and a catalyst, which may take place by a free-radical mechanism. The evidence available for arriving at the mechanisms will be considered under three headings: (*a*) orientation of ring opening, (*b*) stereochemistry of ring opening, and (*c*) kinetics of ring opening. The reactions involving rearrangement are discussed next and then the reactions with Grignard reagents. Finally attention is given to the reactions of steroid epoxides and of sugar epoxides, since these represent fairly self-contained groups.

IV. ORIENTATION OF RING OPENING

In the general case of reaction with an unsymmetrically substituted epoxide two products are possible:



XVI XVII

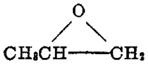
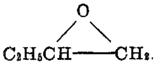
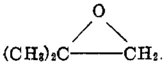
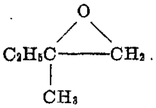
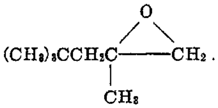
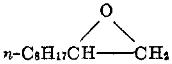
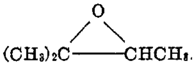
Krassusky (132, 133) summarized the early work with ammonia in a rule which stated that "when ammonia adds to unsymmetrical olefin oxides, the amino group attaches itself to the carbon atom bearing the greater number of free hydrogen atoms." In accordance with general practice, products (with other reagents as well as ammonia) resulting from compliance with this rule will be termed "normal," while those from additions violating it will be termed "abnormal." Thus, in the above equation XVI is the normal product and XVII is the abnormal product. In much of the early work on orientation only the major product of the reaction was isolated, often in not very high yield, and deductions from results of this kind must be made with caution. Even in more recent investigations, where quantitative product analyses have been carried out, the methods used frequently leave much to be desired. For work of this kind to be reliable, it is necessary to have a sensitive and accurate method of analyzing mixtures of the two possible isomers. Such methods are not easy to find, but one of the best to date involves a comparison of the infrared spectrum of the product with that of each pure isomer synthesized unambiguously (80, 197, 237, 257).

In order to obtain information about mechanisms from the data on orientation it is necessary to relate orientation to the effect of substituent groups in the epoxide ring. For this purpose it is advisable to bear in mind the three main effects of substituent groups: steric, polar (i.e., inductive), and conjugative. If one assumes for the present that opening of the epoxide ring involves a bimolecular reaction with a nucleophile, then it will be obvious that steric effects of substituent groups (being unidirectional and always tending to inhibit the approach of a reagent to the adjacent carbon atom) will always promote normal addition, whereas polar and conjugative effects of substituent groups may act in either direction. The direction of ring opening in alkyl- and cycloalkyl-substituted epoxides, for which most data are available, probably comes nearest to being governed entirely by steric factors. Some results of orientational studies on these types of compounds are assembled in table 1 (see also table in reference 68), which is divided into reactions carried out under basic or neutral conditions and reactions carried out under acidic conditions. An examination of this table shows that, under basic or neutral conditions, the normal isomer (corresponding to attack on the least substituted carbon atom) is nearly always the major or only isolated product. This provides strong evidence for an S_N2 attack of a reagent molecule or ion on the epoxide ring carbon atom, involving a transition state of the type

TABLE 1

Orientational results with alkyl- and cycloalkyl-substituted epoxides

A. Reactions under basic or neutral conditions

Epoxide	Reagent	Normal Product*	Abnormal Product	References
		per cent	*per cent*	
	$Na^+[CH_3COCHCOOC_2H_5]^-$	Only	None	(1)
	$C_2H_5OH + NaOH$	Only	None	(39)
	C_6H_5ONa	Only	None	(170, 237)
	C_6H_5SNa	Only	None	(233)
	2-Thienylsodium	Only	None	(272)
	$ArH + AlCl_3$	Only	None	(143)
	C_6H_5Li	Only	None	(53)
	Na + liquid NH_3	Only	None	(17)
	NaN_3	Only	Trace?	(270)
	C_2H_5OH	55.9	16.2	(39)
	$LiBH_4$	100	0	(83)
	NaN_3	Only	Trace?	(270)
	$Ba(SH)_2$	Only	None	(162)
	Ethylenimine	Only	None	(84)
	RONa, ArONa, NH_3, RNH_2, R_2NH, NaSR, $NaHSO_3$	Only	None	(91)
	H_2 + Raney nickel	None	Only	(91)
	$LiAlH_4$	100	0	(189)
	Na/Hg	88	12	(189)
	H_2 + Raney nickel	<10	90	(189)
	H_2 + Raney nickel + NaOH	89	8	(189)
	CH_3ONa	Mainly	Trace?	(205, 286)

B. Reactions under acidic conditions

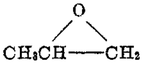
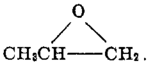
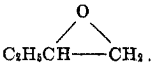
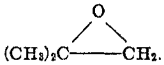
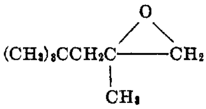
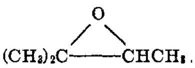
Epoxide	Reagent	Normal Product*	Abnormal Product	Reference
		per cent	*per cent*	
	$C_6H_5OH + C_6H_5SO_3H$	49	51	(237)
	$C_6H_5SH + C_6H_5SO_3H$	Some	Some	(233)
	C_2H_5OH + 0.82% H_2SO_4	41	24	(39)
	C_2H_5OH + 1.3% H_2SO_4	25	31	(39)
	$HCl/(C_2H_5)_2O$ (−55°C.)	89	11	(257)
	$HCl/(C_2H_5)_2O$ (+35°C.)	74	26	(257)
	HCl/H_2O (+15°C.)	62	38	(257)
	HCl/H_2O (+83°C.)	56	44	(257)
	$HBr/(C_2H_5)_2O$ (−45°C.)	92	8	(257)

TABLE 1—*Concluded*

Epoxide	Reagent	Normal Product*	Abnormal Product	Reference
		per cent	*per cent*	
 $\overset{O}{CH_3CH-CH_2}$	$HBr/(C_2H_5)_2O$ (+15°C.)	85	15	(257)
	HBr/H_2O (+15°C.)	76	24	(257)
	HBr/H_2O (+75°C.)	71	29	(257)
	HI/H_2O (−10°C.)	88	12	(257)
	HI/H_2O (+65°C.)	82	18	(257)
 $\overset{O}{C_2H_5CH-CH_2}$	HCl	80	20	(242)
 $\overset{O}{(CH_3)_2C-CH_2}$	HCl	45	55	(242)
 $(CH_3)_3CCH_2\underset{CH_3}{\overset{O}{C-CH_2}}$	$HCl/(C_2H_5)_2O$	Only	None	(91)
	$ROH + H_2SO_4$	None	Only	(91)
 $\overset{O}{(CH_3)_2C-CHCH_3}$	$ROH + BF_3$	None	Only	(205)
	$CH_3OH + H_2SO_4$	Trace?	Only	(286)

* That is, attack at the least substituted position.

shown in figure 3. Such reactions are well known to be sensitive to steric hindrance (primary steric effect) and, provided the group R has no very marked polar or conjugative effect, it is to be expected that the normal isomer will be formed for steric reasons. The only exceptions in the table are two cases involving hydrogenation in the presence of Raney nickel. These reactions, however, take place on a metal surface and may very well involve a quite different mechanism. It is not surprising, therefore, that they are exceptional. Other exceptions appear in the work of Mousseron (175, 176, 177, 178, 179, 181, 182, 183, 184, 185) on epoxides of the cyclohexane and cyclopentane series, but aspects of this work have been disputed by three groups of later investigators (238, 254; 68, footnote on p. 110) and it cannot, therefore, be said to be well substantiated.

In the case of reaction under acidic conditions there is a marked tendency towards the formation of abnormal products. Many epoxides which give entirely normal products under basic conditions produce a mixture of normal and abnormal products under acidic conditions. It is impossible to rationalize this phenomenon on steric grounds alone, and it is necessary to recall that alkyl and cycloalkyl groups also possess polar (inductive) and hyperconjugative effects, both of which can give rise to electron release. These effects can stabilize a positive charge on the adjacent (abnormal) carbon atom, and there are two mechanisms which involve the production of such a charge. The first of these is the

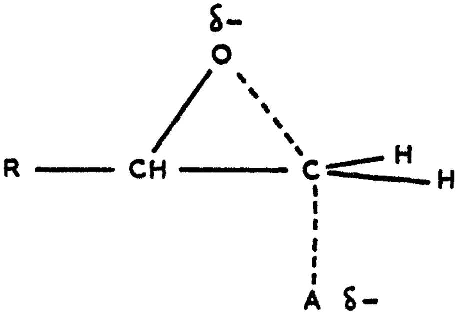
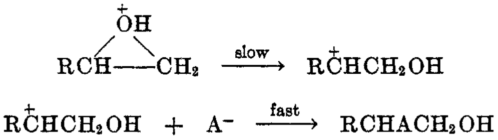


FIG. 3 S_N2 transition state for attack of an anion at the normal position of an epoxide

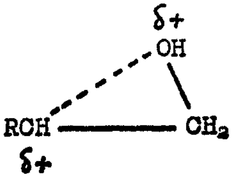
S_N1 mechanism:



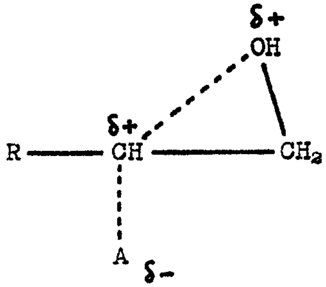
$$\overset{\overset{+}{\mathrm{O}}\mathrm{H}}{\mathrm{RCH{-}CH_2}} \xrightarrow{\text{slow}} \mathrm{R\overset{+}{C}HCH_2OH}$$

$$\mathrm{R\overset{+}{C}HCH_2OH} + \mathrm{A^-} \xrightarrow{\text{fast}} \mathrm{RCHACH_2OH}$$

In this mechanism the transition state for the rate-determining step carries a partial positive charge on the carbon atom:



Such a charge will be stabilized by electron release (both inductive and hyperconjugative) from R only if it is on the abnormal carbon atom (i.e., the one adjacent to R). The second mechanism is an S_N2 type in which the reagent is further away than usual from the seat of attack, and the driving force of the reaction is provided more by transfer of electrons from carbon to oxygen than from reagent to carbon. Under these conditions, when both partial bonds of the transition state are longer than usual, it is reasonable to suppose that the central carbon atom carries a fractional positive charge:



Such a mechanism is sometimes referred to as "borderline S_N2," or as one in which bond breaking is more important (i.e., more nearly complete in the transition state) than bond making. The positive charge can clearly be stabilized by electron release from R in the same way as for the S_N1 mechanism. This mechanism, unlike the S_N1 case, will be subject to steric hindrance from R, although to a smaller extent than an ordinary S_N2 mechanism, since the reagent is not so close in the transition state. Support for this mechanism is provided by the results in table 1 for the reactions of propylene oxide with the halogen hydracids in water. At comparable temperatures the proportions of abnormal products obtained are in the order HCl > HBr > HI. This could be caused by a steric effect, due to the size of the halide ions. Also, the greater proportion of abnormal product in water than in ether for these reactions must mean that the transition state for abnormal attack is more polar than that for normal attack. This supports the modified S_N2 mechanism for abnormal attack, with its longer partial bonds and consequent greater charge separation in the transition state. On the basis of the same mechanism the greater proportion of abnormal isomer produced from 1,1-dimethylethylene oxide than from ethylethylene oxide by reaction with hydrochloric acid would be ascribed to the greater hyperconjugative effect of two methyl groups than of one ethyl group, this effect outweighing the greater steric effect of the two methyl groups. It should be pointed out, however, that arguments of this kind are based on the assumption that a greater proportion of abnormal product is due to a greater rate of reaction at the abnormal position. This, of course, is not necessarily a valid assumption. A greater proportion of abnormal product could equally be due to a decreased rate of attack at the normal position. This difficulty can only be resolved by kinetic measurements coupled with accurate product analyses. Unfortunately such experiments have rarely been carried out. In view of this, the above arguments in favor of the modified S_N2 mechanism are inconclusive. However, as will appear later, the stereochemical evidence is fairly definitely in favor of this mechanism.

Table 2 summarizes the results of orientational studies on epoxides with polar substituents. Only substituents with no conjugative effect, or in which the conjugative effect is unlikely to obscure the polar inductive effect, are included. These substituents also possess steric effects, but it is clear from an examination of the table that the polar effects are the dominant ones. Most of the substituents are electron-withdrawing and, in almost every case, the presence of such a substituent inhibits reaction at the carbon atom to which it is attached. This effect is shown by $C—NR_2$, C—OH, C—OR, $C—OC_6H_5$, C—Cl, C—Br, CF_3, $COOC_2H_5$, and $CONH_2$. It can be seen that CF_3 is more powerfully inhibiting than $COOC_2H_5$. A remarkable feature of these reactions is the fact that reagents apparently still prefer to avoid attacking a carbon atom carrying an electron-withdrawing group even when attack at the alternative carbon atom must be subject to very considerable steric hindrance. This emerges clearly from the work of Martynov (60, 152, 153, 154, 155, 156, 157, 158, 159, 163, 164, 165), for example, in the reaction between dicyclohexylamine and β,β-dimethylglycidamide. Since, in a bimolecular reaction, the presence of an electron-withdrawing sub-

TABLE 2

Orientational results with epoxides containing polar substituents

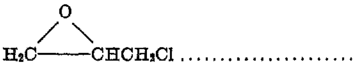
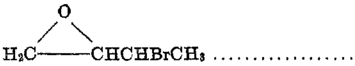
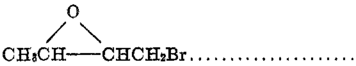
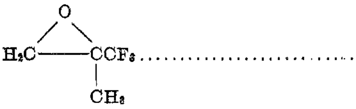
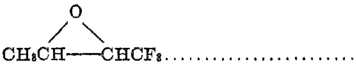
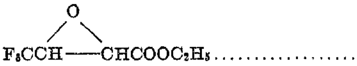
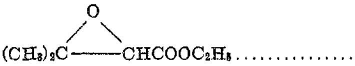
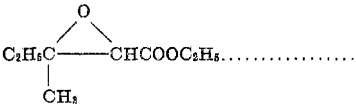
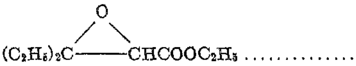
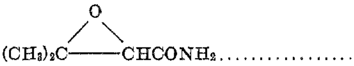
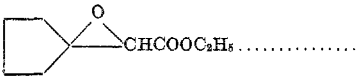
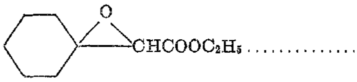
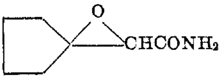
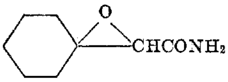
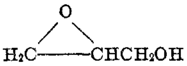
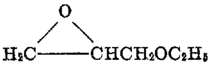
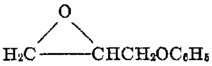
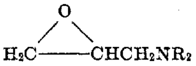
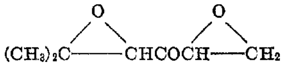
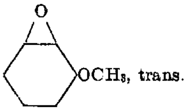
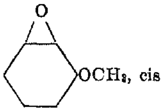
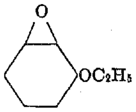
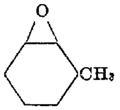
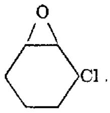
Epoxide	Reagent	Position of Attack*	References
 $H_2C-CHCH_2Cl$	$(C_2H_5)_2NH$	A	(225)
	$NaCN \cdot KCN$	A	(56)
	2-Thienylsodium	A	(272)
	NaN_3	A	(270)
	HCl	A	(242)
 $H_2C-CHCHBrCH_3$	$LiAlH_4$, RONa	A	(281)
	C_6H_5ONa	A	(227)
 $CH_3CH-CHCH_2Br$	C_6H_5ONa	A	(227)
 $H_2C-CHCF_3$	$LiAlH_4$, $(C_2H_5)_2NH$, C_2H_5ONa, NH_3, HBr, $C_2H_5OH + H_2SO_4$	A	(166)
 H_2C-CCF_3 with CH_3	C_2H_5ONa, $C_2H_5OH + H_2SO_4$	A	(167)
 $CH_3CH-CHCF_3$	C_2H_5ONa, $C_2H_5OH + H_2SO_4$	A	(167)
 $F_3CCH-CHCOOC_2H_5$	$LiAlH_4$, NH_3	B	(274)
 $(CH_3)_2C-CHCOOC_2H_5$	NH_3	A	(60)
	$ArNH_2$	A	(152)
	$Ba(SH)_2$	B	(163)
 $C_2H_5C-CHCOOC_2H_5$ with CH_3	NH_3	A	(165)
	$ArNH_2$	A	(152, 159)
 $(C_2H_5)_2C-CHCOOC_2H_5$	$C_6H_5NH_2$	A	(152)
 $(CH_3)_2C-CHCONH_2$	Cyclohexylamine, dicyclohexylamine, C_6H_5-CH_2NH_2	A	(155)
 $CHCOOC_2H_5$	$ArNH_2$	A	(157)
 $CHCOOC_2H_5$	$C_6H_5NH_2$	A	(156)

TABLE 2—*Concluded*

Epoxide	Reagent	Position of Attack*	References
	Cyclohexylamine, $C_6H_5CH_2NH_2$	A	(164)
	$C_6H_5CH_2NH_2$	A	(164)
 $H_2C\overset{O}{—}CHCH_2OH$	$C_6H_5NH_2$, $C_6H_5NHCH_3$, $C_6H_5NHC_2H_5$ HCl, HNO_3, C_2H_5OH, $C_2H_5OH + H_2SO_4$	A A	(151) (126, 242)
 $H_2C\overset{O}{—}CHCH_2OC_2H_5$	$Na^+[CH(COOC_2H_5)_2]^-$	A	(273)
 $H_2C\overset{O}{—}CHCH_2OC_6H_5$	$Na^+[CH(COOC_2H_5)_2]^-$	A	(273)
 $H_2C\overset{O}{—}CHCH_2NR_2$	$Na^+[CH(COOC_2H_5)_2]^-$	A	(226)
 $(CH_3)_2C\overset{O}{—}CHCOCH\overset{O}{—}CH_2$	CH_3OH, piperidine	$(CH_3)_2C$	(187)
	$LiAlH_4$, CH_3ONa	A	(140)
	CH_3ONa	A	(140)
	NH_3 $LiAlH_4$	A A	(168) (179)
	NH_3 HCl	B A and B	(181) (181)
	$LiAlH_4$	A	(179)

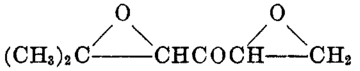
* A = attack at left-hand carbon atom (in formula as written).
B = attack at right-hand carbon atom.

stituent facilitates the approach of a nucleophilic reagent but inhibits bond breaking, it seems likely that we are dealing here with S_N2 reactions in which bond breaking is more important than bond making, i.e., with what the authors have called the modified S_N2 mechanism. An S_N1 mechanism should also be inhibited by the presence of an electron-withdrawing group, but it is very unlikely that the reactions under consideration here are S_N1, particularly the ones in which a strongly nucleophilic reagent attacks a primary carbon atom.

The only case in the table where an electron-withdrawing group does not inhibit reaction at the adjacent carbon atom is the reaction between ethyl β,β-dimethylglycidate and the sulfhydryl ion. It is difficult to see why this should be exceptional and it would probably repay further investigation, particularly as the yield of isolated product was very low (about 20 per cent).

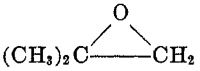
There is only one case in table 2 of an epoxide carrying an electron-repelling group and that is 2,3-epoxy-1-methylcyclohexane. Ammonia attacks this epoxide at the carbon atom nearest to the methyl group and this is in accordance with the modified S_N2 mechanism. However, hydrochloric acid attacks both positions to give a mixture of products.

In the diepoxide XVIII the carbonyl group would be expected to inhibit attack at either of the secondary carbon atoms adjacent to it and, of the two remaining epoxide carbon atoms, attack at the primary should be favored over attack at the tertiary for steric reasons. However, as can be seen in table 2, both methanol and piperidine initially attack the tertiary carbon atom. This is very surprising, particularly in the case of piperidine, since 1,1-dimethylethylene oxide (XIX) is invariably attacked at the primary carbon atom by basic reagents.



XVIII

2,3:5,6-Diepoxy-2-methyl-4-hexanone



XIX

1,1-Dimethylethylene oxide

The third type of substituents comprises those groups which can conjugate and, in particular, those groups which can stabilize a positive charge by conjugative electron release from a π orbital or an atomic p orbital. Four such groups have been studied. These are a carbon–carbon double bond, a carbon–carbon triple bond, a benzene ring, and an alkoxy group. For conjugation to be possible the groups must be directly attached to one of the carbon atoms of the epoxide ring. A selection of results with epoxides containing substituents of this type is collected in table 3. It is immediately obvious from an examination of this table that conjugating groups favor attack on the adjacent carbon atom, both under basic or neutral conditions and, even more so, under acidic conditions. In reactions of styrene oxide and of 3,4-epoxy-1-butene (sections A and B of table 3) there is clearly a balance between the conjugative effect of the substituent, directing attack to the abnormal position, and its steric effect, directing attack to the normal position. The outcome of these two opposing effects depends on the size of the reagent, the smaller the reagent the greater the proportion of abnormal product being formed. This is particularly evident in the reaction of 3,4-epoxy-1-

TABLE 3

Orientational results with epoxides containing conjugative substituents

A. Styrene oxide

Reagent	Normal Product*	Abnormal Product†	Reference
	per cent	*per cent*	
$Na^+[CH(COOC_2H_5)_2]^-$	Only	None	(229)
$Na^+[CH_3COCHCOOC_2H_5]^-$	Only	None	(1)
$Na^+[NCCHCOOC_2H_5]^-$	Only	None	(292)
2-Thienylsodium	Only	None	(272)
C_6H_5Li	Only	None	(53)
Ethylenimine	Only	None	(84)
$LiAlH_4$	Only	None	(267)
$LiBH_4$	74	26	(83)
C_6H_5ONa	24	76	(96)
C_6H_5OH (no catalyst)	12	88	(93)
$C_6H_5OH + ArSO_3H$	6	94	(97)
Piperidine/C_2H_5OH (60°C.)	96	4	(38)
$C_6H_5CH_2NH_2/C_2H_5OH$ (20°C.)	83	17	(128)
$C_6H_5CH_2NH_2/C_2H_5OH$ (40°C.)	78	22	(128)
$C_6H_5CH_2NH_2/C_2H_5OH$ (60°C.)	73	27	(128)
$C_6H_5CH_2NH_2$ (no solvent)	94	6	(29)
$C_6H_5CH_2NH_2 + H^+$ (no solvent)	86	14	(29)
$C_6H_5CH_2NH_2 + H^+/CH_3OH$	35	65	(29)
NH_3	53	15	(37)
NaN_3	None	Only	(270)
CH_3ONa	66–75	34–25	(217)
$CH_3OH + H_2SO_4$	10	90	(217)
H_2 + Raney nickel	None	Only	(189)
$H_2 + PtO_2/C_2H_5OH$	0	100	(197)

B. 3,4-Epoxy-1-butene

Reagent	Normal Product*	Abnormal Product†	References
	per cent	*per cent*	
$Na^+[CH(COOC_2H_5)_2]^-$	Only	None	(229)
$Na^+[CH_3COCHCOOC_2H_5]^-$	ca. 50	ca. 50	(1)
$Na^+[NCCHCOOC_2H_5]^-$	Only	None	(292)
$LiAlH_4$	Only	None	(267)
$LiAlH_4$ (2.1 moles)	70	30	(82)
$LiAlH_4$ (0.68 mole)	78	22	(82)
$LiAlH_4$ (0.26 mole)	83	17	(82)
RNH_2, R_2NH	Only	None	(19, 204)
NH_3	45	7	(73)
NaN_3	None	Only	(270)
CH_3ONa	Mainly	Some	(13)
CH_3OH + acid	None	Only	(13)

* Normal product: attack at primary carbon atom.

† Abnormal product: attack at secondary carbon atom.

C. Miscellaneous epoxides

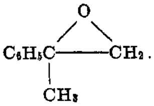
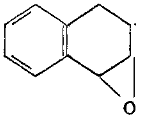
Epoxide	Reagent	Position of Attack*	References
 $C_6H_5C(CH_3)(O)CH_2$	$Ba(SH)_2$	B	(162)
	$Na^+[CR(COOC_2H_5)_2]^-$	A	(271)

TABLE 3—*Continued*

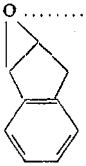
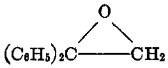
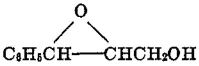
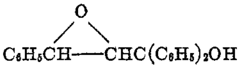
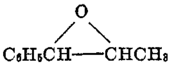
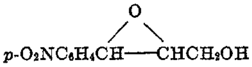
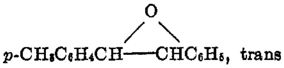
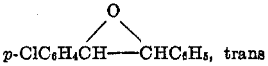
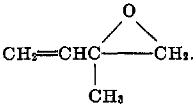
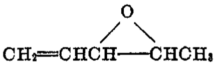
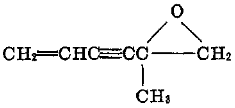
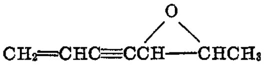
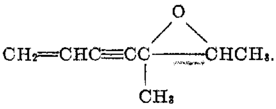
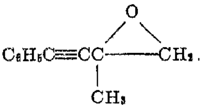
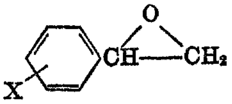
Epoxide	Reagent	Position of Attack*	References
	H_2 + Raney nickel, Na + moist $(C_2H_5)_2O$	B	(121)
 $(C_6H_5)_2C\overset{O}{—}CH_2$	C_6H_5Li	B	(53)
 $C_6H_5CH\overset{O}{—}CHCH_2OH$	RNH_2 NH_3, CH_3NH_2	A B	(86) (20)
 $C_6H_5CH\overset{O}{—}CHC(C_6H_5)_2OH$	Piperidine, morpholine, $C_6H_5CH_2NH_2$, $(CH_3)_2NH$ $(C_2H_5)_2NH$	A No reaction	(11) (11)
 $C_6H_5CH\overset{O}{—}CHCH_3$	Ethylenimine CH_3NH_2	A 65% A, 17% B	(84) (20)
 $p\text{-}O_2NC_6H_4CH\overset{O}{—}CHCH_2OH$	NH_3	A	(86)
 $p\text{-}CH_3C_6H_4CH\overset{O}{—}CHC_6H_5$, trans	$LiAlH_4$	60% A, 40% B	(74)
 $p\text{-}ClC_6H_4CH\overset{O}{—}CHC_6H_5$, trans	$LiAlH_4$	40% A, 60% B	(74)
 $CH_2{=}CH\underset{CH_3}{C}\overset{O}{—}CH_2$	RNH_2, R_2NH RONa ROH + BF_3	B Mainly B A	(2) (216) (216)
 $CH_2{=}CHCH\overset{O}{—}CHCH_3$	$(C_2H_5)_2NH$ $CH_3OH + BF_3$	A A	(208) (208)
 $CH_2{=}CHC{\equiv}C\underset{CH_3}{C}\overset{O}{—}CH_2$	NH_3, $C_2H_5NH_2$, $(C_2H_5)_2NH$ CH_3ONa $CH_3OH + H_2SO_4$	B B A	(201, 203) (201) (201)
 $CH_2{=}CHC{\equiv}CCH\overset{O}{—}CHCH_3$	CH_3NH_2	B	(199)

TABLE 3—*Continued*

Epoxide	Reagent	Position of Attack*	References
 $CH_2{=}CHC{\equiv}C\underset{CH_3}{C}\overset{O}{\text{——}}CHCH_3$	NH_3, $C_2H_5NH_2$, $(C_2H_5)_2NH$	B	(203)
	CH_3ONa	B	(201)
	$CH_3OH + H_2SO_4$	A	(201)
 $C_6H_5C{\equiv}C\underset{CH_3}{C}\overset{O}{\text{——}}CH_2$	NH_3, $C_2H_5NH_2$, $(C_2H_5)_2NH$	B	(203)

* A = attack at left-hand carbon atom (in formula as written).
B = attack at right-hand carbon atom.

D. Styrene oxides substituted in the benzene ring

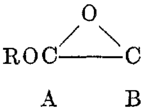


X	Reagent	Normal Product*	Abnormal Product†	References
		per cent	*per cent*	
p-NO_2	$Na^+[CH(COOC_2H_5)_2]^-$	Only	None	(54)
p-CH_3O	$LiBH_4$	5	95	(80, 83)
p-CH_3	$LiBH_4$	33	67	(80, 196)
	$LiBH_4 + MgBr_2$	11	89	(196)
H	$LiBH_4$	74	26	(83)
m-CH_3O	$LiBH_4$	77	23	(80)
p-Br	$LiBH_4$	84	16	(83)
3,4-Dichloro	$LiBH_4$	95	5	(80)
p-NO_2	$LiBH_4$	38	62	(83)
	$LiBH_4 + MgBr_2$	88	12	(196)
p-CH_3O	$C_6H_5OH + C_6H_5ONa/H_2O$	None	Only	(95)
H	$C_6H_5OH + C_6H_5ONa/H_2O$	24	76	(94)
p-NO_2	$C_6H_5OH + C_6H_5ONa/H_2O$	64	36	(94)
m-NO_2	$C_6H_5OH + C_6H_5ONa/H_2O$	67	33	(94)
o-NO_2	$C_6H_5OH + C_6H_5ONa/H_2O$	72	28	(94)
p-CH_3	$H_2 + PtO_2/C_2H_5OH$	0	100	(197)
H	$H_2 + PtO_2/C_2H_5OH$	0	100	(197)
m-CH_3O	$H_2 + PtO_2/C_2H_5OH$	12	88	(197)
p-Br	$H_2 + PtO_2/C_2H_5OH$	18	82	(197)
3,4-Dichloro	$H_2 + PtO_2/C_2H_5OH$	65	35	(197)

* Normal product: attack at primary carbon atom.
† Abnormal product: attack at secondary carbon atom.

TABLE 3—*Continued*

E. Epoxy ethers



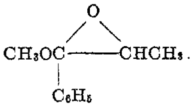
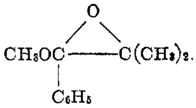
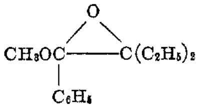
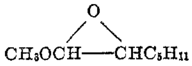
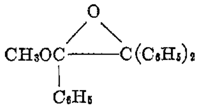
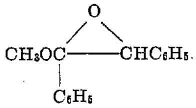
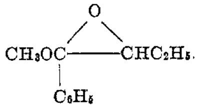
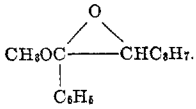
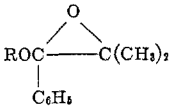
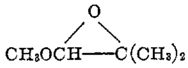
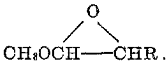
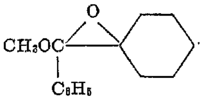
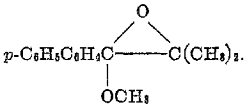
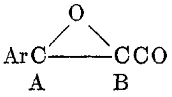
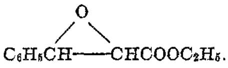
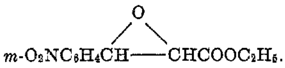
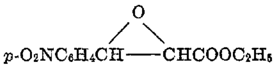
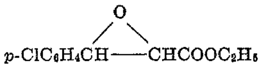
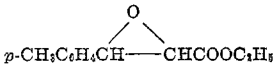
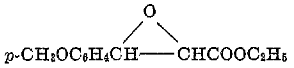
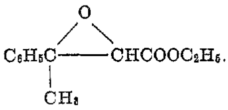
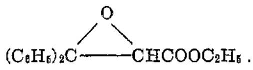
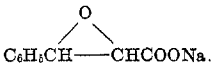
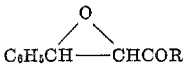
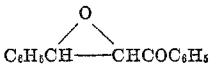
Epoxide	Reagent	Position of Attack	Reference
	CH_3ONa $LiAlH_4$	A A	(265) (245)
	C_6H_5OH/C_6H_6 $LiAlH_4$	A A	(269) (245)
	$LiAlH_4$	A	(245)
	$LiAlH_4$	A	(245)
	$LiAlH_4$ (as above) CH_3OH alone $CH_3OH + CH_3ONa$ $CH_3OH + H_2SO_4$	No reaction No reaction No reaction A	(245) (246) (246) (246)
	CH_3ONa	A	(255)
	C_6H_5OH/C_6H_6	A	(269)
	C_6H_5OH/C_6H_6	A	(269)
	$ROH + H^+$	A	(253)
	$RCOOH/(C_2H_5)_2O$, $CH_3OH + HCl$	A	(251)

TABLE 3—*Concluded*

Epoxide	Reagent	Position of Attack	References
 $CH_3OCH—CHR$	RCOOH, $CH_3OH + H_2SO_4$	A	(250)
 $CH_3OC(C_6H_5)$—cyclohexylidene	CH_3OH	A	(249)
 $p\text{-}C_6H_5C_6H_4C(OCH_3)—C(CH_3)_2$	3,5-Dinitrobenzoic acid	A	(247)

F. α-Aryl-β-carbonyl epoxides



Epoxide	Reagent	Position of Attack	Reference
 $C_6H_5CH—CHCOOC_2H_5$	NH_3, RNH_2	B	(160)
	NH_3, RNH_2	A	(78)
	$ArNH_2$	B	(78)
 $m\text{-}O_2NC_6H_4CH—CHCOOC_2H_5$	$C_6H_5NH_2$	B	(161)
 $p\text{-}O_2NC_6H_4CH—CHCOOC_2H_5$	$C_6H_5NH_2$	B	(161)
 $p\text{-}ClC_6H_4CH—CHCOOC_2H_5$	NH_3, $C_6H_5NH_2$	B	(161)
 $p\text{-}CH_3C_6H_4CH—CHCOOC_2H_5$	NH_3, $C_6H_5NH_2$	B	(160)
 $p\text{-}CH_3OC_6H_4CH—CHCOOC_2H_5$	$ArNH_2$	B	(160)
 $C_6H_5C(CH_3)—CHCOOC_2H_5$	NH_3	A	(165)
 $(C_6H_5)_2C—CHCOOC_2H_5$	NH_3	A	(165)
 $C_6H_5CH—CHCOONa$	$C_6H_5NH_2$	B	(160)
 $C_6H_5CH—CHCOR$	$H_2 + Pd/Ni$	A	(264)
 $C_6H_5CH—CHCOC_6H_5$	$H_2 + PtO_2$, $H_2 + Pd$, $H_2 +$ Raney nickel	A	(110)
	Piperidine, morpholine, tetrahydroisoquinoline	A	(11)
	$(CH_3)_2NH$, $(C_2H_5)_2NH$, $C_6H_5CH_2NHCH_3$	No reaction	(11)

butene with lithium aluminum hydride, studied by Fuchs and VanderWerf (82). The attacking reagent is initially the AlH_4^- ion, but as the reaction proceeds this is replaced by the bulkier $AlH_3(OR)^-$, $AlH_2(OR)_2^-$, etc. The greater the excess of lithium aluminum hydride used, the more is the reaction confined to attack by AlH_4^- and hence the greater is the proportion of abnormal product formed. This balance between the steric and conjugative effects of substituents is largely borne out by the results in section C of table 3. If each epoxide carbon atom carries a substituent of similar size, then the conjugative effect is decisive, as in the reactions of 3,4-epoxy-1-pentene. This is still true even when the reagent is the bulky secondary amine, diethylamine. A similar explanation probably accounts for the direction of attack of sodiomalonic esters on 1,2-epoxytetralin. One obvious anomaly in section C is the reaction of β-phenylglycidol with aliphatic primary amines, where contradictory results have been obtained by different investigators.

Reactions of nuclear-substituted styrene oxides are collected in section D of table 3. In so far as the substituents are in the meta or para positions of the benzene ring, these reactions represent a series where the steric effect of the aryl group is constant. In nearly every case an electron-withdrawing substituent decreases, and an electron-repelling substituent increases, the proportion of abnormal isomer. This must mean that the aryl group is exerting a specific conjugative electron-release effect, thereby promoting attack on the adjacent carbon atom (or, what is much less likely, inhibiting attack on the further carbon atom). As before, the two mechanisms which involve an increase of positive charge at the point of attack in the formation of the transition state, and which therefore fit the above experimental facts, are the S_N1 and modified ("borderline") S_N2 mechanisms.

Section E of table 3 lists some reactions of epoxy ethers in which an alkoxy group is directly attached to one of the epoxide carbon atoms. These reactions, without exception, involve attack at the carbon atom carrying the alkoxy group. In the light of the above considerations, there is little doubt that this is due to conjugative electron release from the alkoxy oxygen stabilizing an incipient positive charge on the carbon atom being attacked.

Reactions of epoxides containing an aryl group attached to one carbon atom and a carbonyl group attached to the other are summarized in section F of table 3. Since it has already been seen that a carbonyl group inhibits attack on an adjacent carbon atom, while an aryl group facilitates such attack, it would be expected that these epoxides would invariably undergo attack at the carbon atom adjacent to the aryl group. An examination of the table shows, however, that reaction can take place at either carbon atom, depending on the exact nature of the reagent and of the epoxide. The reactivity of the two positions appears to be fairly evenly balanced, aromatic amines tending to attack the carbon atom adjacent to the carbonyl group and catalytic hydrogenation reactions giving products of attack at the carbon atom adjacent to the aryl group. Ammonia and aliphatic amines can apparently attack either position, depending on the epoxide, and, in the case of the reaction between ethyl β-phenylglycidate and ammonia or aliphatic primary amines, there is a direct contradiction between the results of different investigators.

Attack at the carbon atom adjacent to the carbonyl group is very difficult to understand. It can hardly be due to prevention of reaction at the other carbon atom by steric hindrance, because of cases such as the reaction between β,β-dimethylglycidamide and dicyclohexylamine (table 2), where reaction does take place at the β-carbon atom. It is probable that the aryl group and the carbonyl group will be conjugated together through the epoxide ring in these compounds, and it is possible (though not very likely) that, because of this, the positive charge on the carbonyl carbon atom will be transferred to the aryl group, thereby removing the inhibiting effect of the carbonyl group on attack at the position adjacent to it. However, it should be pointed out that the position of attack in all the reactions of this section has been determined only by isolation of one reaction product, sometimes in very low yield. Further work is very necessary before any definite conclusions can be reached.

Before leaving considerations of the effect of conjugative substituents it is worth noting that there is some evidence that the reagent itself may be able to conjugate with a developing positive charge. Thus, sodium cyanide is reported to give the abnormal product with propylene oxide (61), and sodium acetylide in liquid ammonia reacts similarly with a series of monosubstituted epoxides (266). Both these reagents (the cyanide ion and the acetylide ion) have a triple bond attached to the atom which does the attacking, and it is conceivable that the π-electron parts of these bonds can conjugate with, and thereby stabilize, a developing positive charge on the epoxide carbon atom being attacked. There would thus be not only a partial σ bond between the reagent and the epoxide in the transition state, but also a partial π bond. The transition state would be approximately as depicted in figure 4, where the broken lines represent partial σ bonds and the dotted line a partial π bond. (It should be noted that participation of the π orbitals of the reagent in a transition state in this way is possible only when the two partial σ bonds are nonlinear. Under these conditions the orbital used for the partial σ bonds can have a component at right angles to the breaking bond, and this can be used to overlap with the π orbital of the reagent.) The positive charge in such a transition state would also be stabilized by inductive and hyperconjugative electron release from the methyl group, and this would explain the preference for attack at the abnormal position. The formation of only abnormal product from styrene oxide and azide ion (section A of table 3) may be capable of a similar explanation, since other small reagents, such as methoxide ion, still give mainly normal product with styrene oxide. It should be emphasized that this suggestion of participation by the π bond of a reagent is put forward only very tentatively. Very little evidence is available and accurate product analyses for reactions of epoxides with this type of reagent would be extremely valuable.

In the reaction between 3,4-epoxy-1-butene and azide ion two products are formed (270). One of these is the abnormal isomer and the other results from an

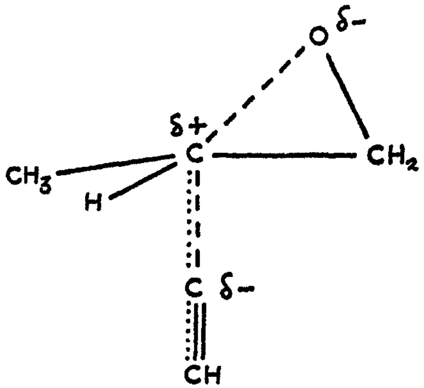
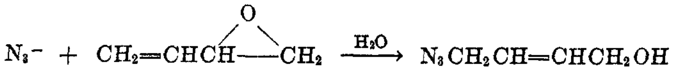


FIG. 4. Participation by a π bond of the reagent in the transition state for abnorma attack.

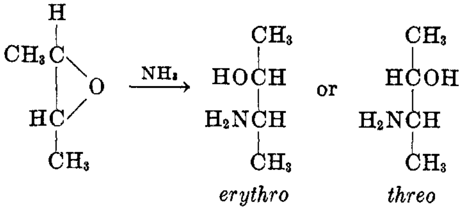
S_N2 mechanism:



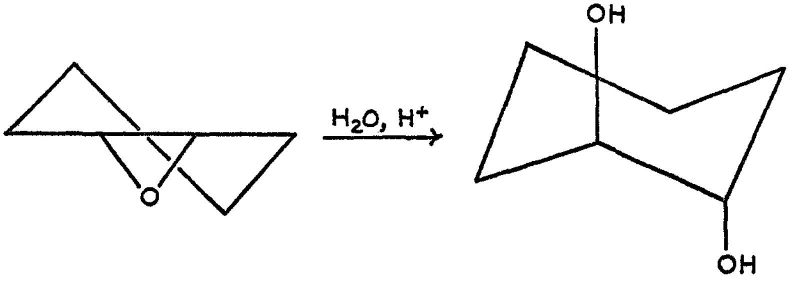
$$N_3^- + CH_2{=}CHCH\overset{O}{\frown}CH_2 \xrightarrow{H_2O} N_3CH_2CH{=}CHCH_2OH$$

V. STEREOCHEMISTRY OF RING OPENING

With certain epoxides the products of ring opening can exist in two stereoisomeric forms. Thus the reaction of ammonia with *trans*-2,3-epoxybutane might give either *erythro*- or *threo*-3-amino-2-butanol:

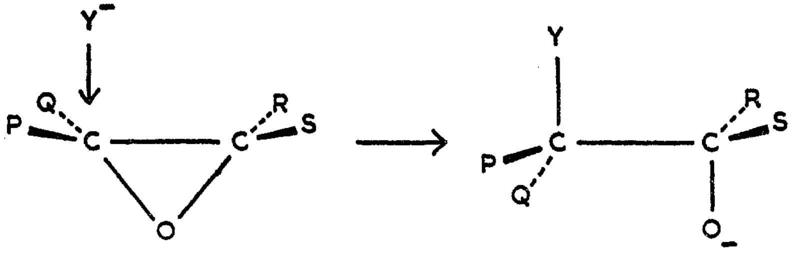


In fact, only the *erythro* isomer is produced (62), corresponding to inversion of configuration at the point of attack. Similarly, the acid-catalyzed hydration of cyclohexene oxide gives only *trans*-cyclohexane-1,2-diol, none of the cis isomer being formed (21, 52).

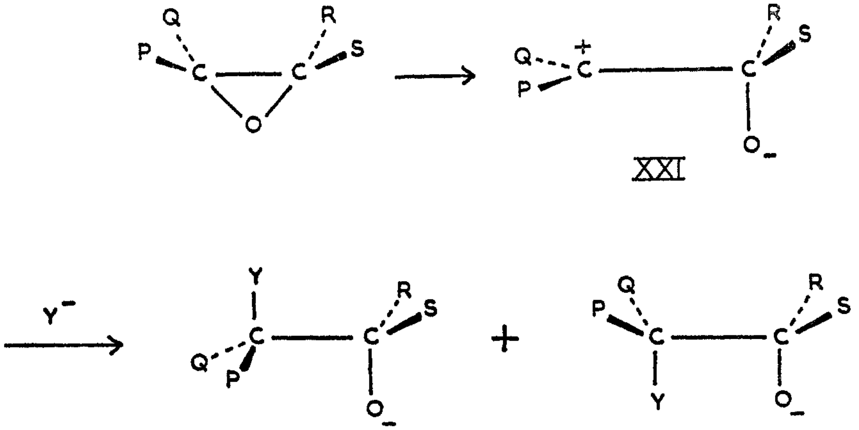


Here again inversion of configuration has taken place at the carbon atom attacked, and there can be no doubt that this is the general rule for all ring-opening reactions of epoxides. Reactions in which inversion of configuration has been established are collected in section A of table 4, and it can be seen that they include the reactions under basic, neutral, and acidic conditions of a considerable variety of epoxides.

From the point of view of mechanism the stereochemical evidence is very revealing. Inversion of configuration is the expected result of an S_N2 mechanism (borderline or otherwise), but is incompatible with an S_N1 mechanism. In S_N2 reactions inversion occurs because of the approach of the reagent on the side remote from the displaced group (in this case, the oxygen atom):



(In acid-catalyzed reactions the epoxide oxygen is initially protonated, but the process is otherwise the same.) Reactions following an S_N1 mechanism, on the other hand, involve the formation of an intermediate carbonium ion and, since the three bonds attached to the central carbon atom of a carbonium ion are coplanar, the reagent can attack from either side to give a mixture of products:


XXI

The intermediate carbonium ion (XX) is likely to take up a preferred conformation, in which the nonbonded interactions between P and Q on the one hand and

TABLE 4

Stereochemical results of ring-opening reactions

A. Reactions giving inversion of configuration

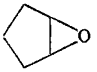
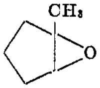
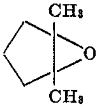
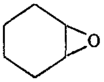
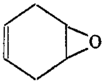
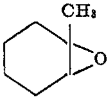
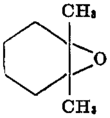
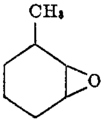
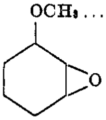
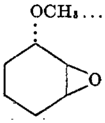
Epoxide	Reagent	References
	NH_3, RNH_2 NaN_3 $Na^+[CH(COOC_2H_5)_2]^-$ $H_2O + H^+$	(176) (270) (92) (21)
	$H_2O + H^+$	(21)
	$LiAlH_4$	(267)
	NH_3, RNH_2, R_2NH Piperidine $Na^+[RCHCN]^-$ NaN_3 $COCl_2$ Pyridine, 3-picoline, and isoquinoline salts HCl, $ZnCl_2/(C_2H_5)_2O$ $H_2O + H^+$ $CH_3OH + H^+$	(176) (180) (173, 174) (270) (129) (105) (12) (21, 52) (284)
	$H_2O + H^+$, $p\text{-}CH_3C_6H_4SO_3H$	(3)
	$H_2O + H^+$	(21)
	$LiAlH_4$	(267)
	H_2O	(181)
	CH_3ONa, $NaOH$	(140)
	CH_3ONa, $NaOH$	(140)

TABLE 4—*Continued*

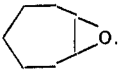
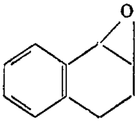
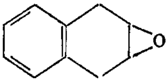
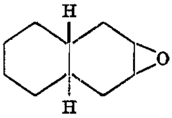
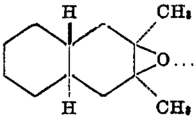
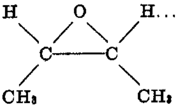
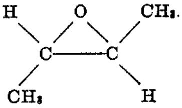
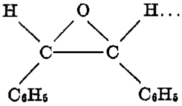
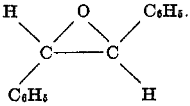
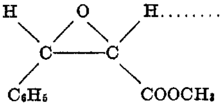
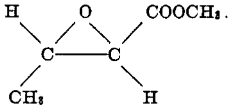
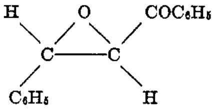
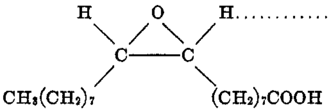
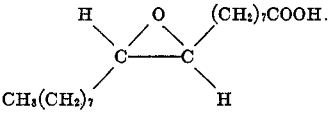
Epoxide	Reagent	References
	HCl, HBr, HI, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3COOH NH_3, CH_3NH_2	(195) (176)
	$Na^+[CR(COOC_2H_5)_2]^-$	(271)
	$H_2O + H^+$ CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3COOH	(3, 21) (3)
	$H_2O + H^+$ (→ 90% diaxial)	(4, 107)
	$H_2O + H^+$ (→ 71% diaxial, 23% diequatorial)	(107)
	NH_3 HCl HBr HI	(62) (150) (287) (149)
	NH_3 $C_2H_5NH_2$ $COCl_2$ $CH_3OH + H^+$, $C_2H_5OH + H^+$ HCl HBr HI CH_3COOH	(21) (89) (129) (106) (150) (287) (149) (288)
	Piperidine Piperidine + piperidine hydrochloride	(29) (29)
	Piperidine Piperidine + piperidine hydrochloride	(29) (29)
	p-$CH_3C_6H_4SO_3H$	(145)

TABLE 4—*Continued*

Epoxide	Reagent	References
	CH_3OH $p\text{-}CH_3C_6H_4SO_3H$	(63) (145)
	HCl/C_2H_5OH (addition of HCl)	(116)
	NaOH, $H_2O + H^+$	(261)
	NaOH, $H_2O + H^+$	(261)

B. Reactions giving retention of configuration

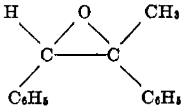
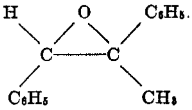
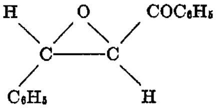
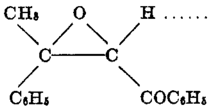
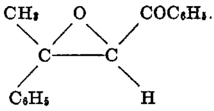
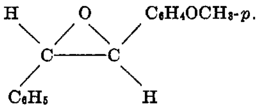
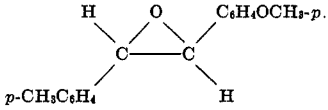
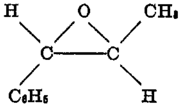
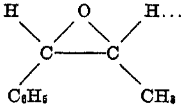
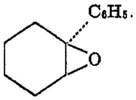
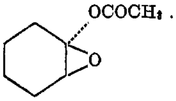
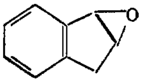
Epoxide	Reagent	References
	$H_2O + H^+$, RCOOH	(228)
	$H_2O + H^+$ ArCOOH	(27, 228) (228)
	$HCl/(C_2H_5)_2O$ $BF_3/(C_2H_5)_2O$ (addition of HF)	(116) (116)
	HCl	(280)
	HCl	(280)
	C_6H_5COOH	(59)
	C_6H_5COOH	(59)

TABLE 4—*Concluded*

C. Reactions giving both stereoisomeric products

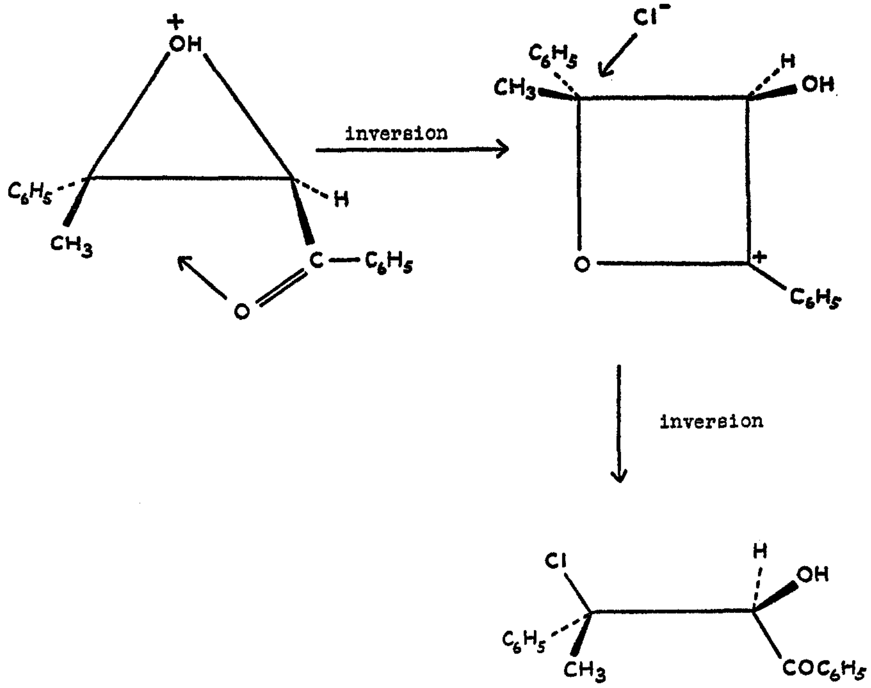
Epoxide	Reagent	Reference
	$H_2O + H^+$ (63% inversion, 37% retention)	(230)
	$H_2O + H^+$ (80% inversion, 20% retention)	(230)
	$H_2O + H^+$ (ca. 50% inversion, 50% retention)	(21)
	$LiAlH_4$ (ca. 50% inversion, 50% retention)	(238)
	H_2O, $H_2O + H^+$, very dilute $Ba(OH)_2$	(21)

R, S, and O^- on the other will be reduced to a minimum. Consequently the approach of the reagent will be affected by R, S, and O^- (and also by P and Q if these are large enough groups) and will, therefore, take place more easily from one side than the other. Thus, in general, an S_N1 opening would not be expected to give the two stereoisomeric products in equal amounts. It is conceivable that, in some cases, this inequality might be so great that virtually only one product is formed and this could be the isomer corresponding to inversion. It is extremely unlikely, however, that all the results in section A of table 4 can be explained in this way and they must be regarded as strong evidence for the S_N2 mechanism. It should be noted that the ring-opening reactions of steroid epoxides and of sugar epoxides (both of which are discussed later) also almost invariably involve inversion of configuration.

A further point worthy of note in these reactions with inversion is the case of 2,3-epoxy-*trans*-decalin. The hydration of this epoxide can give rise to two *trans*-diols, a *trans*-diaxial and a *trans*-diequatorial, both resulting from inversion of configuration (as well as a *cis*-diol resulting from retention of configuration). In fact, acid-catalyzed hydration gives a 90 per cent yield of the *trans*-diaxial-diol as the only isolated product (107). In the similar case of 2,3-dimethyl-2,3-epoxy-*trans*-decalin acid-catalyzed hydration gives 71 per cent of the *trans*-

diaxial-diol and 23 per cent of the *trans*-diequatorial-diol (107). It will be seen later that ring-opening to give *trans*-diaxial products is a general rule in the steroid epoxides.[2]

There are a few examples of ring-opening reactions giving retention of configuration. These are collected in section B of table 4. Neither an S_N2 nor an S_N1 mechanism would be expected to give rise to retention of configuration, and an explanation of these reactions must be sought in terms of a different mechanism. The most likely mechanism seems to be a two-stage one involving a double inversion. One of the epoxide carbon atoms is first attacked by a neighboring group (attached to the other epoxide carbon atom) with displacement of oxygen, and this is followed by attack of the reagent and displacement of the neighboring group back to its original position. Wasserman and Aubrey (280) have suggested this mechanism as a possible explanation of their results for the reactions of the dypnone oxides with hydrochloric acid:



A similar mechanism can be put forward for epoxides containing aryl groups but no acyl groups, e.g., for the reaction of *trans*-*p*-methoxystilbene oxide with ben-

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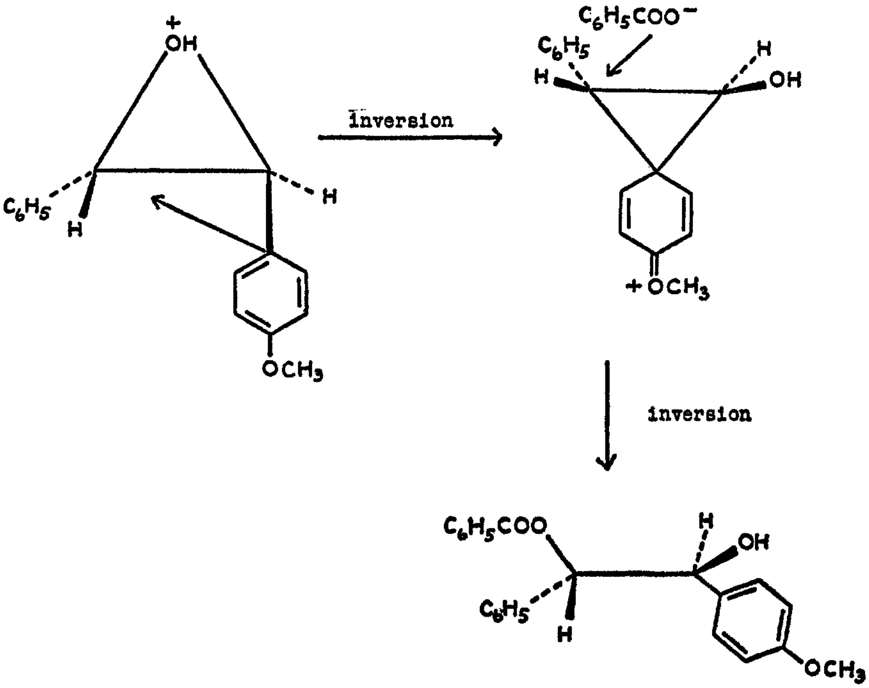
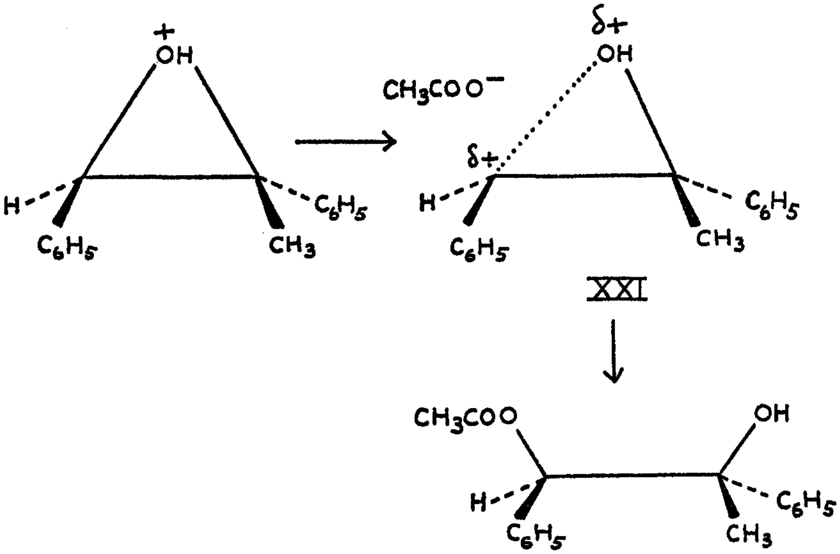
[2] Since an epoxide ring and a cyclohexane ring can only be fused cis, the formation of trans products on epoxide ring opening signifies inversion. The same is true of cyclopentene and cycloheptene oxides, but not of cycloöctene oxide, which can be either cis or trans.

zoic acid (59):



Some of these reactions have received an alternative explanation. Thus Brewster (27) has suggested that, in the reaction of *trans*-α-methylstilbene oxide with acetic acid, most of the driving force of the reaction is provided by the bond stretching (assisted by the protonation of the oxygen, the conjugation of the phenyl group with the partial positive charge on the carbon atom, and the release of ring strain). Consequently very little help is required from the nucleophilic reagent (acetate ion) and the stereochemical result of the reaction will depend on the position of the most accessible nucleophile. If this is kept close to the epoxide oxygen as part of an ion-pair in a "cage" of solvent molecules, then retention of configuration will result:

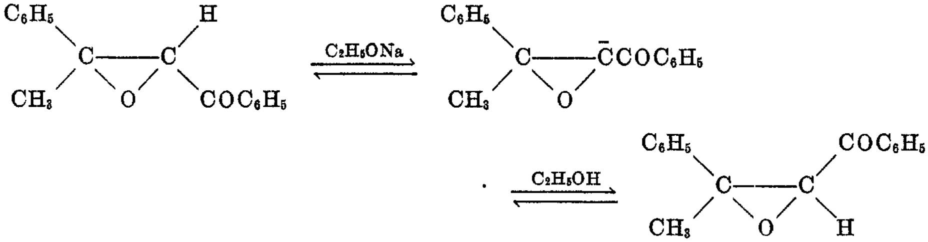


XXI

The transition state XXI, shown here in the way depicted by Brewster, should really contain a partial bond between the acetate ion and the positive carbon atom if any help at all is received from the reagent. This is then similar to the "modified" S_N2 mechanism of the authors, with the added proviso that the reagent is held close to the (protonated) epoxide oxygen by electrostatic forces and therefore attacks from the same side as the oxygen, thus giving retention. A similar mechanism has been put forward by Wasserman and Aubrey as one possible explanation of their results in the reactions of the dypnone oxides with hydrogen chloride. If the reagent is assumed to be actually attached by hydrogen bonding to the protonated epoxide oxygen, then this mechanism becomes the internal displacement mechanism, S_Ni, of Ingold (127). It is difficult to see, however, why a mechanism of this kind should be restricted to a few aryl-substituted epoxides. On the other hand, the postulated intermediate in the double-inversion mechanism receives support from the rearrangement reactions of epoxides (see below), in which aryl groups have a greater tendency to migrate than other groups. The rearrangement reactions involving migration of aryl groups must presumably go through a transition state very similar to the above postulated intermediate.

Finally, a few epoxide ring-opening reactions give rise to both stereoisomeric products. These are summarized in section C of table 4. Once again the epoxides concerned all have a conjugative substituent (benzene ring or alkoxy group) directly attached to the epoxide ring and it is, therefore, possible to write a mechanism of the above double-inversion type for all of them. It is probable that in these cases there is a delicate balance between the S_N2 mechanism (giving inversion) and the double-inversion mechanism (giving retention), both routes being followed in any one case. That such a balance is possible is shown by the reaction of hydrogen chloride with *trans*-benzalacetophenone oxide (116). Hydrogen chloride in dry ethanol gives inversion, while hydrogen chloride in ether gives retention (sections A and B of table 4). A similar example is the hydration of indene oxide, where the proportion of *cis*- to *trans*-diol formed is very sensitive to pH and to temperature (21), although Brewster (27) has maintained that the double-inversion or "phenonium-ion" mechanism is impossible in this case for steric reasons. It is also possible that reactions giving both stereoisomeric products take place by concurrent S_N2 and S_Ni (or "ion-pair") mechanisms, and a third possibility for these reactions is an S_N1 mechanism. The latter is, however, unlikely. An S_N1 mechanism could not easily explain the reactions which give complete retention, and the epoxides which give retention are at least as suitable structurally to give an S_N1 mechanism as are the epoxides which give both products.

Before leaving considerations of stereochemistry it should be noted that House and Ro (119) have shown that one epoxide at least can be stereochemically isomerized by alkali. Studies with deuterium have shown that the mechanism is as follows:



Stereochemical results of ring-opening reactions with bases on epoxides carrying a benzoyl or other electron-withdrawing substituent must, therefore, be treated with caution. It is unlikely, however, that any of the results in table 4 could be complicated by the incursion of such isomerization.

VI. KINETICS OF RING OPENING

A considerable number of ring-opening reactions of epoxides have been studied kinetically. As far as reactions in basic or neutral solution are concerned, kinetic studies covering a range of epoxides (more than three) have been carried out for the reactions with ammonia and various amines (6, 7), thiocyanate ion (192), nitrate ion (206), thiosulfate ion in aqueous acetone (224), and thiosulfate ion in aqueous ethanol (81). Less extensive studies, covering not more than three epoxides, have been made for the reactions with water (28, 67, 142, 214, 241), ammonia (16, 75, 100, 211, 240), various amines (11, 65, 100, 101, 102, 240, 241), a series of phenols (25), chloride ion (10, 28, 67, 206, 209, 210), bromide ion (10, 28, 67, 206), iodide ion (10, 28, 67, 259), thiocyanate ion (28), various carboxylate ions (28), hydroxide ion (67, 142, 215), and sulfite ion (232). The acid-catalyzed reaction with water has been studied for a series of epoxides (212), and less extensive studies (not more than three epoxides) have been carried out for the acid-catalyzed reactions with water (28, 67, 206, 243, 289), chloride ion (28, 67), bromide ion (28, 67), iodide ion (67, 259), nitrate ion (206), and pyridine (also used as solvent) (64, 66). Unless otherwise stated all the reactions were studied in aqueous solution.

For rate studies on unsymmetrical epoxides to be significant they must be coupled with product analyses, in order that the separate rates of normal and of abnormal reaction can be calculated. Only if this is done is it possible to derive any understanding of mechanism from the effect of substituents in the epoxide molecule on rates. Unfortunately, product analyses have hardly ever been carried out in the investigations mentioned above and, where this has not been done, it is very difficult to attach any precise significance to the kinetic results for unsymmetrical epoxides. Bartlett and Ross (13) have shown that, for the reaction of 3,4-epoxy-1-butene with sodium methoxide, the order of reaction is the same for both normal and abnormal attack. If it can be assumed that this is true for all epoxide ring-opening reactions under basis or neutral conditions, it follows that:

$$k_{\text{obs}} = k_N + k_A$$

where k_{obs} is the observed rate constant, k_N is the rate constant for normal attack, and k_A that for abnormal attack. Furthermore, the ratio of k_N to k_A will be equal to the ratio of normal to abnormal product, provided that the product ratio is determined at the same temperature and in the same solvent as for the rate studies. As far as can be judged from the evidence available, it seems likely that the normal and abnormal reactions under basic or neutral conditions are of the same kinetic order and that they are, in fact, invariably both second order, indicating S_N2 mechanisms. This is what would have been expected on the basis of the almost invariable stereochemical inversion accompanying reactions under basic or neutral conditions. Further evidence for the S_N2 mechanism can be gained from table 5, which summarizes some of the more extensive kinetic investigations on monosubstituted ethylene oxides. For the reactions with ammonia, thiocyanate ion, nitrate ion, and thiosulfate ion, it is clear that electron-withdrawing substituents (e.g., the chloromethyl group or the *p*-nitrophenyl group) increase the rate. Insofar as it can be assumed that the reactions are unidirectional (i.e., corresponding to exclusively normal attack) this substituent effect is consistent with an S_N2 mechanism for normal attack, in which bond forming is dominant. It is certainly incompatible with an S_N1 mechanism. The substituent effect can be put into a quantitative form by making use of the Taft linear free-energy relationship. Taft (262, 263) wrote the following equation:

$$\log k - \log k_0 = \rho^*\sigma^* + E_s$$

where k_0 is the rate constant for the reaction of a given compound, k is the rate constant for the same reaction of one of its substituted derivatives, σ^* is the polar substituent constant characteristic of the substituent, E_s is the steric substituent constant, and ρ^* is the reaction constant, measuring the susceptibility of the reaction to the polar effect of substituents. Taft first developed this equation for ester hydrolysis and, to adapt it to other reactions, it is desirable to introduce a second reaction constant, ρ_s, as a measure of the susceptibility of the reaction to the steric effects of substituents. If the polar reaction constant is renamed ρ_p, to distinguish it from ρ_s, the equation becomes:

$$\log k - \log k_0 = \rho_p\sigma^* + \rho_s E_s$$

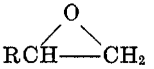
Dividing by σ^* gives a more convenient form for plotting:

$$\frac{\log k - \log k_0}{\sigma^*} = \rho_p + \rho_s \frac{E_s}{\sigma^*}$$

In figure 5 $(\log k - \log k_0)/\sigma^*$ is plotted against E_s/σ^* for the reactions of a series of epoxides with ammonia in aqueous solution at 20°C. (see table 5). The best straight line has been found by the least-squares method and, from its intercept and slope, ρ_p and ρ_s are found to be +0.77 and +0.36, respectively (compared to 2.48 and 1 for the substituent effect of R in the alkaline hydrolysis of the esters $RCOOC_2H_5$ (263)). The fit of the points to the straight line is by no means good, but this is not surprising in view of the considerable doubt as to whether all the reactions give exclusively normal attack. The fit is certainly much better than

TABLE 5

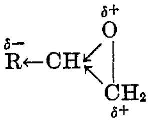
Rate constants for ring-opening reactions of monosubstituted ethylene oxides



	R	NH_3	CNS^-	NO_3^-	$S_2O_3^-$	Aqueous $HClO_4$
		10^5k_2 20°C. (7)	10^3k_2 25°C. (192)	10^8k_2 25°C. (206)	10^3k_2 25°C. (81)	10^5k_1 0°C. ($H_0 = 0$) (212)
		l. mole^{-1} sec.$^{-1}$	*l. mole^{-1} sec.$^{-1}$*	*l. mole^{-1} sec.$^{-1}$*	*l. mole^{-1} sec.$^{-1}$*	*sec.$^{-1}$*
A	H	6.87	1.88			63
	CH_3	7.25	2.13			350
F	CH_3CH_2	5.45				
I	$CH_3CH_2CH_2$	4.32				
K	$(CH_3)_2CH$	2.28				
H	$CH_3CH_2CH_2CH_2$	4.47				
L	$(CH_3)_2CHCH_2$	2.80				
	$CH_3CH_2CH(CH_3)$	1.27				
J	$(CH_3)_3C$	1.28				
G	Cyclo-C_5H_9	4.15				
N	Cyclo-C_6H_{11}	1.98				
B	CH_3OCH_2	7.33				
C	$C_6H_5CH_2$	8.05				
D	C_6H_5	7.8			2.04	
	$HOCH_2$	6.98	1.93	6.7		26.6
E	$ClCH_2$	30	8.95	26		4.8
	$BrCH_2$		7.73	25		3.8
	ICH_2		6.13			
	$(CH_3)_2CHOCH_2$		2.12			
	$CH_2{=}CHCH_2OCH_2$		1.85	13		
	O_2NOCH_2		6.48	22		
	p-Tolyl				2.40	
	p-Bromophenyl				3.07	
	3,4-Dichlorophenyl				4.19	
	p-Nitrophenyl				5.94	

All the reactions were studied in aqueous solution except for the reactions with thiosulfate ion, which were studied in aqueous ethanol.

that obtained by plotting log k against σ^*, according to the simplified form of the Taft equation which ignores steric effects. The fact that ρ_p is positive indicates that electron-withdrawing substituents increase the rate and is usually interpreted as meaning that the reactions are S_N2, with bond making more important than bond breaking. There is a reason why this interpretation may not be correct in the case of epoxide reactions, however. In most S_N2 reactions (e.g., the reactions of alkyl halides with hydroxide ion) the effect of an electron-withdrawing substituent is to put a positive charge on the carbon atom being attacked, and this facilitates bond making but inhibits bond breaking. In epoxides, however, an electron-withdrawing group puts a positive charge on the oxygen as well as on the carbon atom:



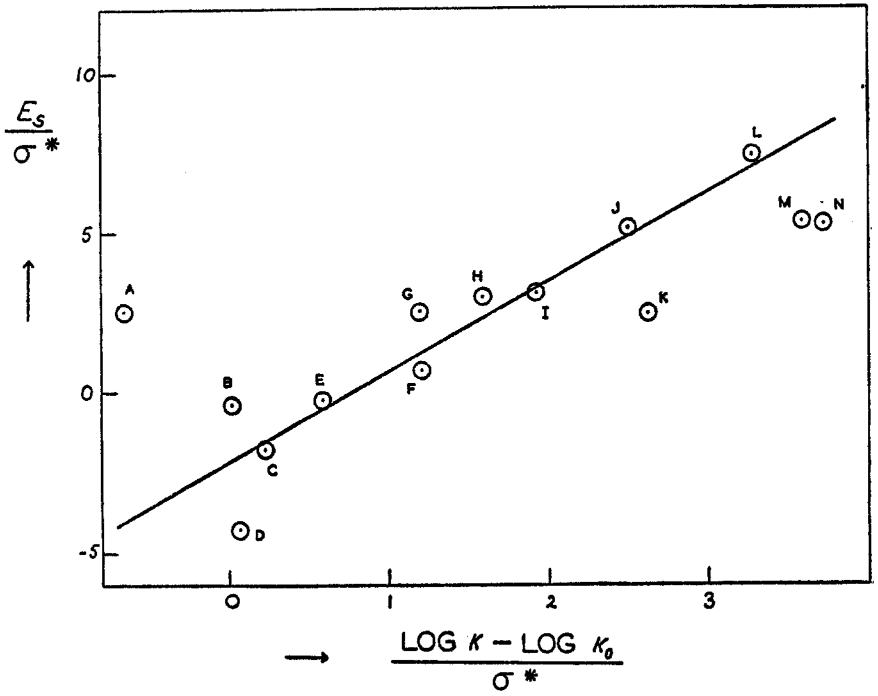
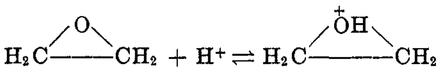


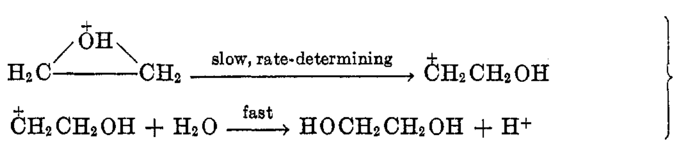
FIG. 5. Plot of $(\log k - \log k_0)/\sigma^*$ against E_s/σ^* for the reactions of fourteen monosubstituted ethylene oxides with ammonia in aqueous solution at 20°C. (7). The parent compound (with rate constant k_0) is propylene oxide, for which σ^* and E_s are both zero. The substituent groups of the monosubstituted ethylene oxides are as follows: A, H; B, CH_3OCH_2; C, $C_6H_5CH_2$; D, C_6H_5; E, $ClCH_2$; F, C_2H_5; G, cyclopentyl; H, n-C_4H_9; I, n-C_3H_7; J, *tert*-C_4H_9; K, iso-C_3H_7; L, iso-C_4H_9; M, *sec*-C_4H_9; N, cyclohexyl.

Thus both ends of the carbon–oxygen bond are affected, to a more or less equal extent, and the effect of the group R on the bond breaking is, therefore, likely to be small. Its effect on bond making is consequently dominant, *even though bond breaking may be a more important factor than bond making in the formation of the transition state.* It should be noted that this applies only to attack at the normal position and not to attack at the abnormal position. It has already been seen that in abnormal attack the effect of substituents on bond breaking appears to be dominant.

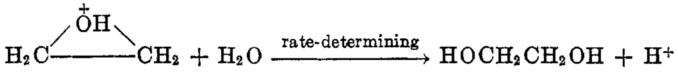
In acid-catalyzed reactions the kinetic evidence is even less decisive than in basic and neutral reactions. Catalysis by acids has been demonstrated for the reactions with water (67), chloride ion (67), bromide ion (67), iodide ion (67), nitrate ion (206), thiosulfate ion (234), and amines (29), and there can be little doubt that this is due to an initial equilibrium to give the conjugate acid of the epoxide, which is then more reactive than the epoxide itself:



It is the nature of the further reaction of the conjugate acid, however, which is in doubt. The only investigation of an acid-catalyzed reaction covering a range of epoxides is for the reaction with water (212). Since this is a solvolytic reaction it is necessarily first order, irrespective of whether the conjugate acid breaks up unimolecularly or whether it undergoes a bimolecular reaction with a water molecule. These two mechanisms are referred to as A1 and A2, respectively (147):



(A1)



(A2)

It has often been claimed (146, 147, 212) that mechanisms of these types can be distinguished by the application of the Hammett acidity function, H_0. For A1 mechanisms in general, where the rate-determining step does not involve a water molecule, log k is expected to be directly proportional to $-H_0$, with a slope of unity. For A2 mechanisms, log k should be proportional to log c_{H^+}. Since $-H_0$ and log c_{H^+} do not differ at acid concentrations below about 1 M, it is necessary to carry out kinetic studies at acid concentrations higher than this. Pritchard and Long (212) have investigated the kinetics of the reactions of ten epoxides in aqueous perchloric acid, seven of them at concentrations of acid greater than 1 M. They find that log k is proportional to $-H_0$ in every case, with slopes varying from 0.86 to 1.06, and they interpret these results as indicating the A1 mechanism. They have also utilized the simplified form of the Taft equation:

$$\log k - \log k_0 = \rho^*\sigma^*$$

A plot of log k against σ^* for the reactions of the ten epoxides gives points which (with one exception) fit well on a straight line, the slope of which gives a ρ^* value of -1.95. The high negative value of ρ^* is also interpreted by Pritchard and Long as indicating the A1 mechanism. This is not necessarily correct, however. A negative value of ρ^* means that the reaction is facilitated by electron-releasing substituents. Such substituents, by increasing the electron density on the oxygen atom of the epoxide, will increase the amount of epoxide conjugate acid produced in the initial equilibrium and will therefore increase the overall rates for both the A1 and the A2 mechanisms (since these rates are both directly proportional to the concentration of conjugate acid). Even if this were not so, a negative value for ρ^* would be accommodated by a bimolecular reaction with predominant bond breaking, as well as by a unimolecular mechanism. Furthermore, the reactions studied by Pritchard and Long are almost certainly not unidirectional, some of the reactions probably giving mainly normal product and others mainly abnormal product, and this must detract from the significance of their results. The only definite evidence for the A1 mechanism, therefore, is the proportionality between log k and $-H_0$ for the reaction of ethylene oxide itself and for those other reactions which are known to be unidirectional. As against this, the stereochemical evidence is almost overwhelmingly in favor of a bimolecular mechanism to account for inversion. Whereas the A2 mechanism is consistent with inversion, the A1 mechanism should lead to a mixture of stereoisomers, since it involves an intermediate carbonium ion which must be planar and hence susceptible to attack by a water molecule from either side. An explanation of this apparent contradiction between the stereochemical evidence and the evidence of the acidity function has been given by Bunton and Llewellyn (33, 34) and also by Pritchard and Long (148, 215). They suggest that, in the A1 mechanism, the attack of a water molecule takes place before the carbon–oxygen bond has completely broken, or before the carbonium ion has had time to become planar. It seems to the authors that this is the same as assuming an A2 mechanism with a rate-determining step in which bond breaking is more important than bond making (i.e., a rate-determining step which takes place by the modified S_N2 mechanism (see page 746)). This interpretation would account for the stereochemical evidence, but would involve acceptance of the possibility of an A2 mechanism giving rise to dependence of log k on $-H_0$. There seems to be no reason why this should not happen when the rate-determining step involves mainly bond breaking; Long himself has pointed out (146) that the real basis of the log $k/-H_0$ correlation is an empirical one and that there is a distinct possibility that contradictory results may be discovered. A "modified" A2 mechanism, with the partial bonds of the transition state for the rate-determining step both longer than usual, would also account for the small importance of steric effects in these reactions. That steric effects are of little importance is shown by the success of the simplified Taft equation (which ignores steric effects) as applied to the results of Pritchard and Long. Further evidence for a "modified" A2 mechanism is provided by the kinetic studies of Long, Pritchard, and Stafford (148) on the acid-catalyzed reactions of three epoxides with water. The values of the entropy of activation, $\Delta S^\ddagger$, obtained (-6.1 to -4) are intermediate between those for acid-catalyzed hydrolyses of established A1 mechanism ($+5.8$ to $+9$) and those for acid-catalyzed hydrolyses of established A2 mechanism (-24.6 to -20.9).

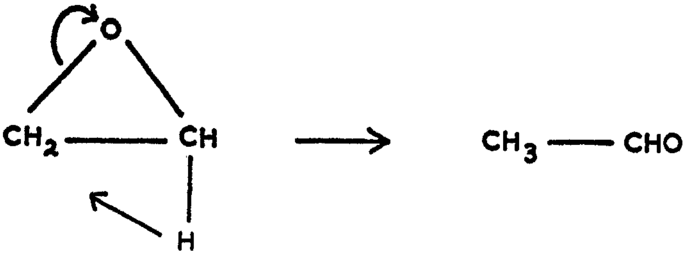
Pritchard and Long (213) have measured the rates of the acid-catalyzed hydration of three epoxides in both water and deuterium oxide and find that the ratio k_{D_2O}/k_{H_2O} varies from 1.9 to 2.2. They interpret their results as supporting the A1 mechanism, but they can equally be interpreted in favor of the A2 mechanism. Acid-catalyzed reactions are faster in deuterium oxide than in water because of the smaller dissociation of acids in deuterium oxide. Consequently, in deuterium oxide a greater concentration of conjugate acid is formed in the initial equilibrium. Since the overall rates for both the A1 and the A2 mechanisms are directly proportional to the concentration of conjugate acid, both mechanisms would be expected to show an increase of rate in deuterium oxide.

It is interesting to compare the reactivities of ethylene oxide and trimethylene oxide. Towards hydroxide ion (215), thiosulfate ion (234), and water (215), ethylene oxide is considerably more reactive than trimethylene oxide and this is no doubt due to the much greater strain energy of the three-membered ring. Under conditions of acid catalysis, however, the reactivities become much more nearly equal (148, 234). The reason for this greater susceptibility of trimethylene oxide to acid catalysis is not apparent.

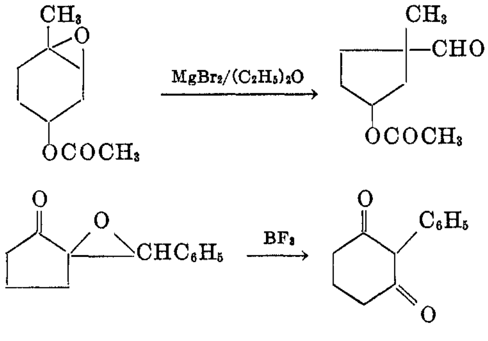
Before leaving the consideration of kinetic studies, it should be mentioned that there is a very great need for accurate kinetic data *coupled with product analyses* for reactions under both basic and acidic conditions. It would then be possible to analyze the effect of substituents on reactivity at each epoxide position separately. Such data would be very valuable for elucidating mechanisms, particularly if they were obtained under conditions where it was possible to distinguish between first-order and second-order reactions.

VII. REARRANGEMENT REACTIONS

The reactions so far considered have involved attack on an epoxide carbon atom by an external nucleophilic reagent. If such a reagent is not available its place may be taken by a substituent group in the epoxide molecule. The group migrates from one epoxide carbon atom to the other, with production of an aldehyde or ketone. Thus ethylene oxide rearranges to acetaldehyde:



In some cases ring contraction or ring expansion may accompany the rearrangement, as shown by the following two examples (26, 120):



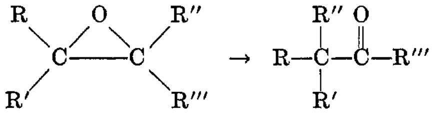
Rearrangement reactions of this kind are usually catalyzed by Lewis acids (e.g., magnesium bromide/ether, boron trifluoride/ether) but they may also be brought about by the action of heat alone. The subject was reviewed by Winstein and Henderson in 1950 (285), and some results of investigations that have been made since that time are summarized in table 6. As pointed out by Winstein and Henderson, the course of the rearrangement process is governed by two main factors:

the direction of ring opening and the relative migratory aptitude of the different substituent groups. There is no doubt that the direction of ring opening is determined by the ease of breaking of the carbon–oxygen bond, as shown by the effect of electron-releasing groups, which always facilitate breaking of the bond between oxygen and the carbon atom to which they are attached. Thus, if the reaction is written in the following way, R and R′ together will be more powerfully electron-releasing than R″ and R‴. Alkoxy and aryl groups are particularly effective electron-releasing agents, as can be seen in table 6, and Stevens (246, 248, 253, 255) has shown that epoxy ethers always rearrange in such a way that the bond which breaks is the one between oxygen and the alkoxy-bearing carbon


(1)

TABLE 6

Rearrangement reactions



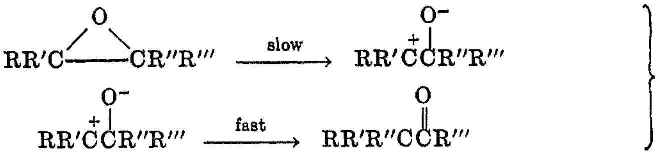
R	R′	R″	R‴	Reagent	Reference
p-$C_6H_5C_6H_4$	CH_3O	CH_3	CH_3	$MgBr_2/(C_2H_5)_2O$	(248)
C_6H_5	CH_3O	$(CH_2)_5$	$(CH_2)_5$	$MgBr_2/(C_2H_5)_2O$	(248)
C_6H_5	CH_3O	C_6H_5	C_6H_5	$MgBr_2/(C_2H_5)_2O$	(248)
C_6H_5	CH_3O	H	C_6H_5	$MgBr_2/(C_2H_5)_2O$	(248)
C_6H_5	CH_3O	H	CH_3	$MgBr_2/(C_2H_5)_2O$	(248)
p-$C_6H_5C_6H_4$	CH_3O	C_2H_5	CH_3	$MgBr_2/(C_2H_5)_2O$	(248)
H	CH_3O	H	*n*-C_5H_{11}	$MgBr_2/(C_2H_5)_2O$	(248)
$C_6H_5C{\equiv}C$	CH_3	H	CH_3	$ZnCl_2/(C_2H_5)_2O$	(200)
$CH_2{=}CHC{\equiv}C$	CH_3	H	CH_3	$H_2SO_4/(CH_3CO)_2O$	(200)
$(CH_2)_4$	H	$(CH_2)_4$	H	$MgBr_2$ (60°C.)	(186)
$(CH_2)_4$	CH_3	$(CH_2)_4$	H	$MgBr_2$ (0°C.)	(186)
$(CH_2)_4$	CH_3	H	$(CH_2)_4$	$MgBr_2$ (60°C.)	(186)
$(CH_2)_4$	H	$(CH_2)_4$	CH_3		
$(CH_2)_4$	C_2H_5	$(CH_2)_4$	H	$MgBr_2$ (0°C.)	(186)
$(CH_2)_4$	C_2H_5	H	$(CH_2)_4$	$MgBr_2$ (60°C.)	(186)
C_6H_5	H	C_6H_5CO	C_2H_5	BF_3/C_6H_6	(118)
C_6H_5	H	C_6H_5CO	H	$BF_3/(C_2H_5)_2O$	(115)
C_6H_5	CH_3	C_6H_5CO	H	$BF_3/(C_2H_5)_2O$	(115)
C_6H_5	C_6H_5	C_6H_5CO	H	$BF_3/(C_2H_5)_2O$	(115)
C_6H_5	H	C_6H_5	C_6H_5CO	$BF_3/(C_2H_5)_2O$	(115)
$(CH_3)_3CCH_2$	$(CH_3)_3CCH_2$	H	H	Dilute acids	(112)
CH_3	CH_3	$(CH_3)_3C$	H	Dilute H_2SO_4	(111)
CH_3	H	H	H	$AlCl_3$	(69)
CH_3	CH_3	H	H	$AlCl_3$	(69)
CH_3	CH_3	H	CH_3	$AlCl_3$	(69)
C_6H_5	H	H	H	$AlCl_3$	(69)
C_6H_5	C_6H_5	H	H	$AlCl_3$	(69)
C_6H_5	C_6H_5	H	C_6H_5	$AlCl_3$	(69)
C_6H_5	H	C_6H_5	H	$BF_3/(C_2H_5)_2O$	(49)
C_6H_5	C_6H_5	H	H	$BF_3/(C_2H_5)_2O$	(49)
C_6H_5	C_6H_5	C_6H_5	H	$BF_3/(C_2H_5)_2O$	(49)
C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$	H	$BF_3/(C_2H_5)_2O$	(49)
C_6H_5	H	H	Cyclo-C_6H_{11}	H_2SO_4	(24)

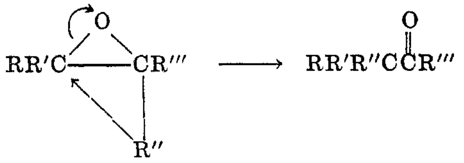
---

* The symbol $(CH_2)_n$ repeated in two columns means that one or both of the epoxide carbon atoms form part of a ring. Thus the tenth entry in the table is cyclohexene oxide.

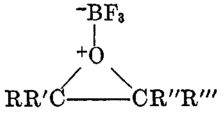
atom. One consequence of the high electron-releasing power of aryl groups is that monoaryl-substituted ethylene oxides invariably rearrange to give products in which the carbonyl group and the benzene ring are not conjugated. Thus styrene oxide gives phenylacetaldehyde rather than acetophenone.

This substituent effect of electron-releasing groups (groups which stabilize an adjacent positive charge) must mean that the reaction is either a two-stage process involving a rate-determining unimolecular break of the oxide ring, followed by a fast migration step (2), or a one-stage concerted process (but still unimolecular) in which carbon–oxygen bond breaking is more important than bond making (3):


(2)

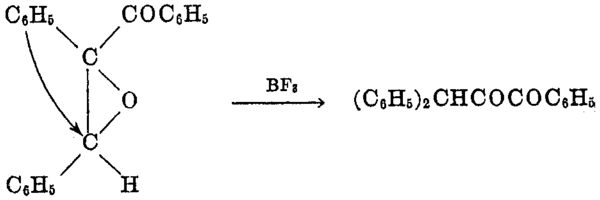

(3)

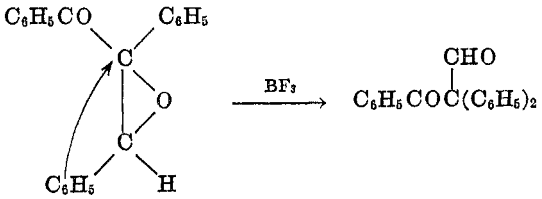
Since the reactions are normally catalyzed by a Lewis acid, the entity which rearranges is not the epoxide itself, but its complex with the acid, e.g.,



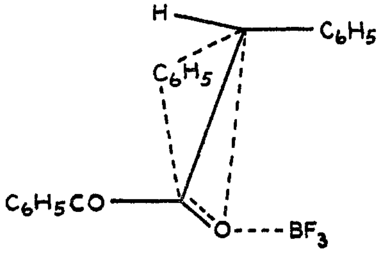
The acid has been omitted from the above equations for the sake of simplicity.

From the evidence available at present it is not generally possible to distinguish between the above two mechanisms, but in one case there is definite evidence for the concerted mechanism. Thus House and Reif (117) showed that a pair of geometrical isomers rearrange to give different products:

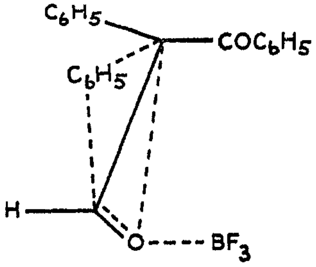

(4)


(5)

If the two-stage mechanism were operating it would be difficult to see why the two epoxides should not give the same intermediate carbonium ion (or, to be precise, a pair of enantiomorphous carbonium ions) and hence the same product. In the concerted process, however, steric effects become important. Neither of the transition states for the concerted process for the above reactions involves unfavorable cis-orientation of bulky groups, as can be seen from the following diagrams:



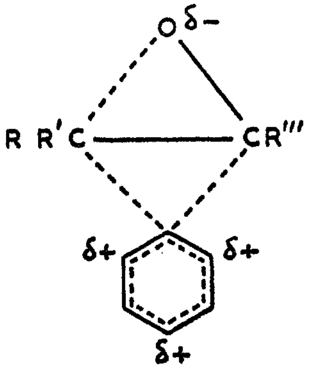
Concerted transition
state for reaction 4



Concerted transition
state for reaction 5

Such unfavorable cis-orientation (for example, of a phenyl and a benzoyl group) would necessarily occur in one case if both oxides rearranged to the same product.

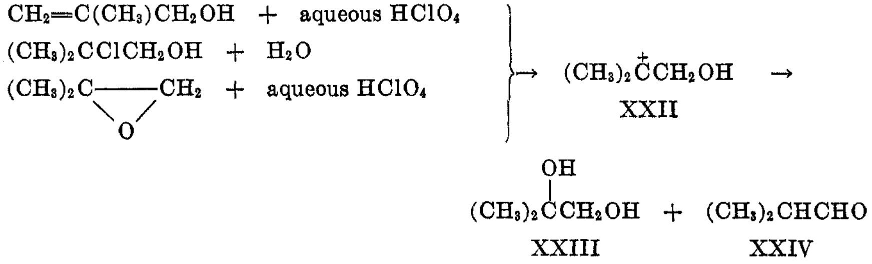
Once the direction of ring opening has been decided, as in equation 1, by the circumstance that R and R′ are together more electron-releasing than R″ and R‴, there remains a choice between migration of R″ or migration of R‴. This will be decided by the relative migratory aptitudes of the groups, and it appears that in general the order is aryl > acyl > H > ethyl > methyl (*cf.* table 6). The ease of migration of aryl groups may be due to the possibility of a "phenonium-ion" type of transition state for the concerted process:



A similar structure could be written for the second stage of the two-stage process, but this could not then account for the high migratory aptitude of aryl groups, since the second stage of the two-stage process would not be rate-determining. Further evidence of the ease of migration of phenyl groups has been produced by Stevens and Dykstra (248), who found that reactions involving migration of the phenyl group required considerably milder conditions than reactions involving migration of other groups.

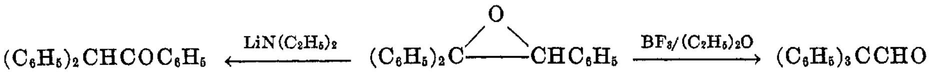
There are exceptions to the above order of migratory aptitudes. Thus hydrogen sometimes migrates in preference to phenyl (see table 6), but this is probably due to a steric effect, in particular to the avoidance of an unfavorable cis-orientation of bulky groups in the transition state. Steric effects of this sort could arise in either mechanism.

Before leaving the consideration of acid-catalyzed rearrangement reactions it is interesting to consider some work by Ley and Vernon (141), who showed that the following three reactions all give the same products, XXIII and XXIV, and postulated the existence of a common intermediate carbonium ion (XXII). If such an ion is a common intermediate, then the ratio of the substitution product XXIII to the rearrangement product XXIV should be the same in all three cases.

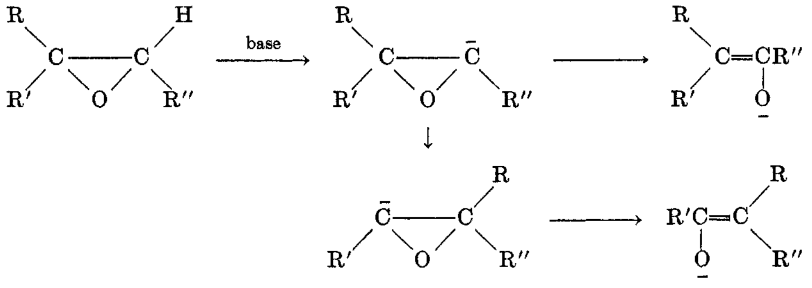


In fact, the first two reactions each give about 76 per cent XXIII and 22 per cent XXIV, while the epoxide reaction gives 92.5 per cent XXIII and 4.9 per cent XXIV. Ley and Vernon explain this discrepancy by assuming that the carbonium ion, when formed from the epoxide, undergoes substitution by a water molecule before reaching its equilibrium conformation, whereas it will not be likely to rearrange until it reaches this equilibrium conformation. It seems to the authors, however, that this explanation is equivalent to assuming that the substitution process is a bimolecular reaction between the conjugate acid of the epoxide and a water molecule, in which bond breaking is more important than bond making, i.e., what they have called a modified A2 mechanism. Ley and Vernon's results seem, in fact, to afford definite evidence that the substitution reaction is bimolecular (or, at least, of a higher order in water than the rearrangement reaction).

Rearrangements of certain epoxides to carbonyl compounds may also be brought about by basic catalysts, and the products may be different from those obtained under acidic conditions. Thus Cope, Trumbull, and Trumbull (49) showed that triphenylethylene oxide rearranges to benzhydryl phenyl ketone under basic conditions and to triphenylacetaldehyde under acidic conditions.

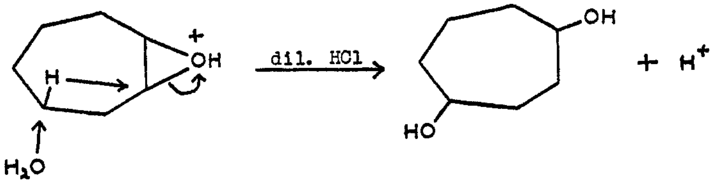


From this and other evidence they put forward the following two related mechanisms, either of which may be followed in a particular case. The products shown are the anions of the carbonyl compounds.



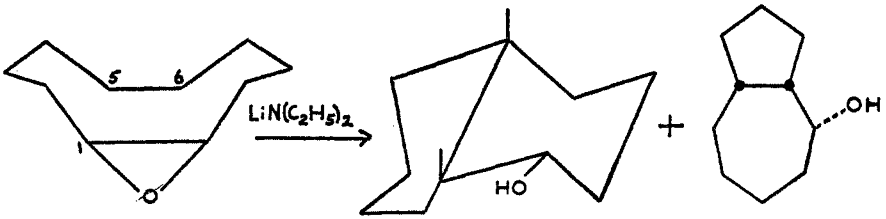
Other epoxides which have been shown to rearrange under conditions of basic catalysis include 1,1-diphenyl-2-(*p*-tolyl)ethylene oxide, *cis*- and *trans*-stilbene oxides (49), cycloöctatetraene oxide (48), and *trans*-cycloöctene oxide (46).

A different type of rearrangement reaction occurs in epoxides derived from large-ring olefins or from bicyclic olefins. Thus Cope, Liss, and Wood (47) have shown that cycloheptene oxide with aqueous acid gives, in addition to the expected *trans*-1,2-cycloheptanediol, some *cis*-1,4-cycloheptanediol. They explain the formation of the 1,4-diol by assuming a transannular hydride shift:

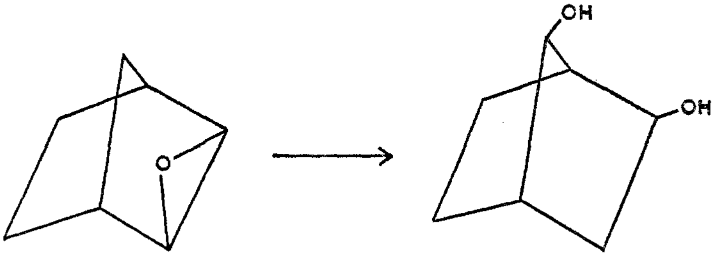


There is no evidence to show whether the hydride shift takes place before the attack of the water molecule, or whether the whole process is a concerted one. Similar transannular hydride shifts occur in the production of *trans*-1,4-cyclooctanediol from *trans*-cycloöctene oxide (43, 44) and of *cis*-1,4-cycloöctanediol from *cis*-cycloöctene oxide (45).

Transannular attack by carbon can also occur. Cope, Brown, and Lee (42) have shown that *cis*-cyclodecene oxide reacts under conditions of basic catalysis as follows:

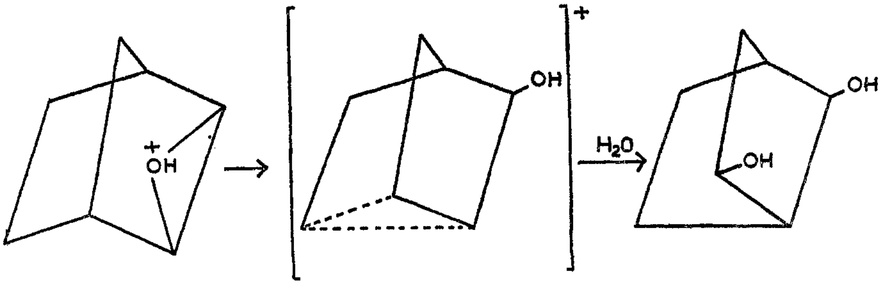


These products are assumed to arise by abstraction of a proton from position 5 or 6, followed by attack of the resulting anion on carbon atom 1. Similar reactions occur with *trans*-cyclodecene oxide (42) and with *cis*- and *trans*-cyclooctene oxides (46). A slightly different kind of transannular attack by carbon takes place in the bicyclo[2.2.1]heptane series. Thus Walborsky and Loncrini (275) showed that bicyclo[2.2.1]heptene-2 oxide gives a rearranged diol on acid-catalyzed hydration:



XXV

They postulated the following mechanism, but a concerted mechanism is equally possible. Other bicyclo[2.2.1]heptane epoxides have been shown to react in a similar way, under both acidic (134, 276) and basic conditions (171).



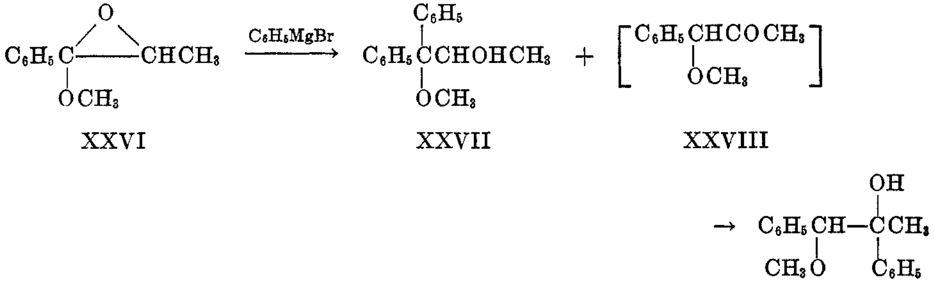
XXV

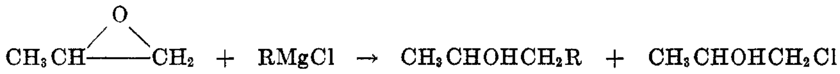
VIII. REACTIONS WITH GRIGNARD REAGENTS

These reactions, which were extensively reviewed by Gaylord and Becker in 1951 (87), are complicated by the inhomogeneity of solutions of Grignard reagents. An ethereal solution of ethylmagnesium bromide, for example, also contains diethylmagnesium and magnesium bromide, owing to the existence of the following equilibrium:

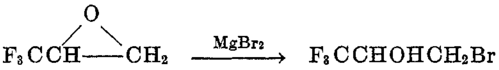
$$2C_2H_5MgBr \rightleftharpoons (C_2H_5)_2Mg + MgBr_2$$

The presence of magnesium bromide in such solutions frequently causes rearrangement of an epoxide to a carbonyl compound, in the same way as for the rearrangements considered in the last section. It is not surprising, therefore, that the products obtained from the reaction of an epoxide with a Grignard reagent often correspond to addition both to the epoxide itself and to its rearrangement product. Thus Stevens, Weiner, and Lenk (256) isolated two products from the action of phenylmagnesium bromide on the epoxy ether XXVI. Product XXVII arises by direct attack of a phenyl anion (or possibly of a diphenylmagnesium molecule) on the abnormal carbon atom of the epoxide, while product XXIX must arise by rearrangement of the epoxide to the ketone XXVIII, followed by further reaction of this ketone with Grignard reagent. It was shown that the ketone XXVIII could be isolated in 80 per cent yield by treatment of the epoxide with a solution of magnesium bromide in ether. Furthermore, addition of a solution of diphenylmagnesium to the epoxide gave XXVII as the only product. This latter result is a quite general one, and rearrangements can always be avoided by the use of dialkyl- or diarylmagnesiums or aryllithiums. These reagents add directly to one of the epoxide carbon atoms, the position of attack being determined by the nature of the epoxide and the size of the reagent, in the usual way. A further complication sometimes arises from the attack of a halide ion on one of the epoxide carbon atoms, giving rise to a halohydrin. Thus the action of alkylmagnesium chlorides on propylene oxide has been shown to give the chlorohydrin as well as the products of attack of an alkyl anion at the normal position (123):

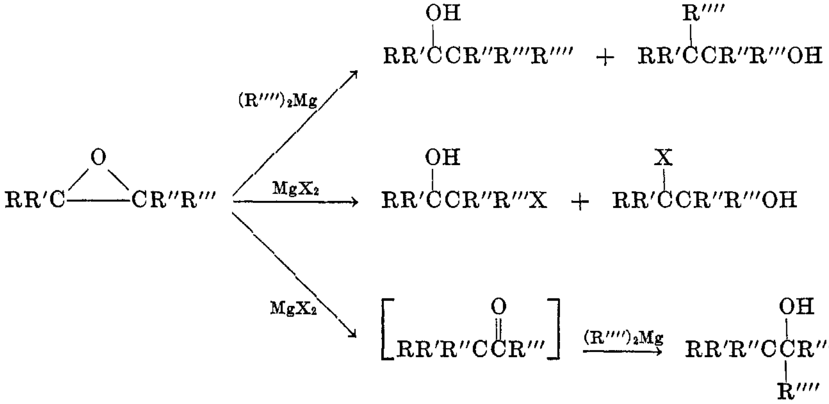

XXVI XXVII XXVIII XXIX



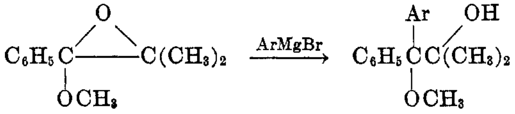
Ethylene oxide reacts with alkylmagnesium iodides in a similar way (122). The halide ions involved in these reactions presumably arise from the magnesium halides present in the Grignard solutions. Trifluoromethylethylene oxide reacts in this way with magnesium bromide alone (166):



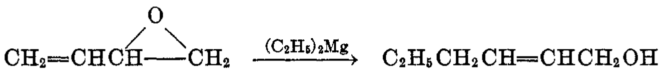
There are thus five possible products in the reaction of a Grignard reagent with an epoxide. They result from attack of an alkyl (or aryl) anion at either the normal or abnormal position of the epoxide ring, attack of a halide ion at either of these positions, and rearrangement of the epoxide to a carbonyl compound, followed by further reaction of this with Grignard reagent. The possibilities are summarized in the following reaction scheme:



Although all Grignard solutions presumably contain magnesium halide, they do not always cause rearrangement. Recent examples of reactions in which rearrangement does not occur include the action of 2-thienylmagnesium bromide on styrene oxide, propylene oxide, and epichlorohydrin (272), methylmagnesium bromide on trifluoromethylethylene oxide (166), alkylmagnesium bromides on two acetylenic epoxides (202), and arylmagnesium bromides on two epoxy ethers (252). In the case of the following epoxy ether reaction, Stevens and Holland (252) point out that rearrangement, if it did take place, would involve the migration of a methyl group, and migrations of alkyl groups are known to be more difficult than migrations of aryl groups or hydrogen. It is reasonable, therefore, that addition of an aryl anion should be easier than rearrangement.



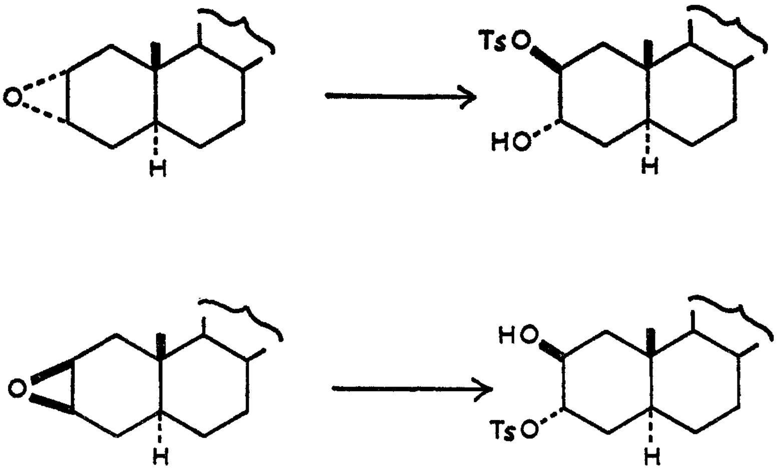
In reactions of 3,4-epoxy-1-butene with Grignard reagents and dialkylmagnesiums, several examples are known where attack takes place at the 1-position. Thus diethylmagnesium reacts with 3,4-epoxy-1-butene to give 2-hexen-1-ol as one of the products (79):



This is presumably an S_N2' reaction; similar products are formed with ethylmagnesium bromide (79, 113), methylmagnesium bromide and isopropylmagnesium bromide (113), and 2-thienylmagnesium bromide (90).

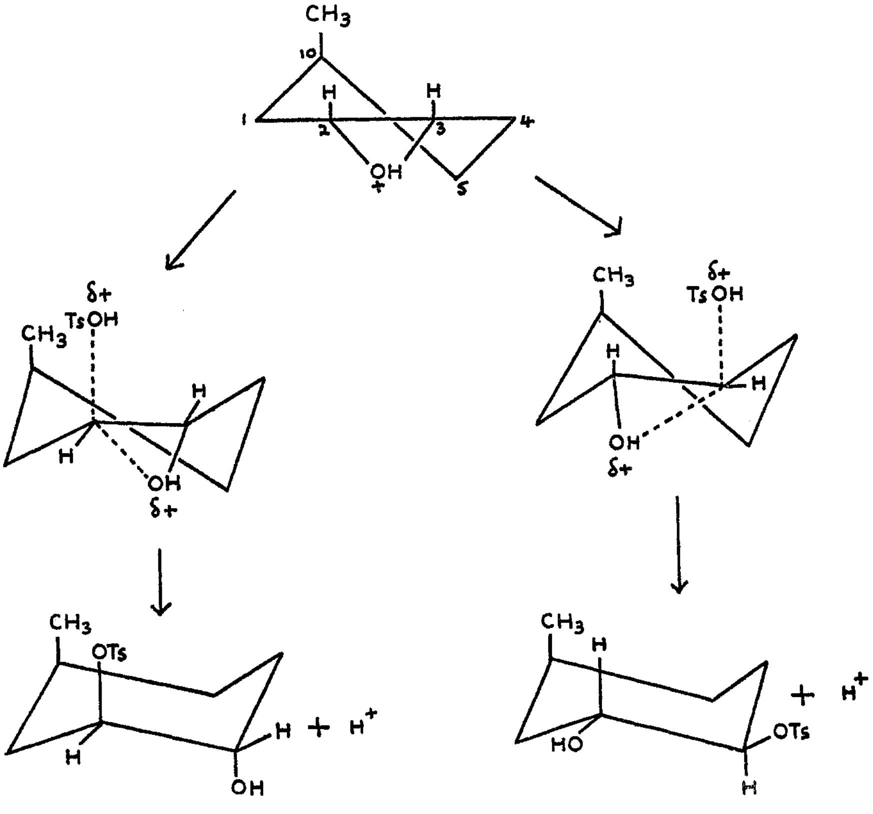
IX. STEROID EPOXIDES

Most of the steroid epoxides that have been studied contain no groups capable of exerting any marked polar or conjugative effects, at least in the vicinity of the epoxide ring. The direction of their ring-opening reactions is consequently decided by steric factors. Moreover, since steroids are conformationally homogeneous (14), the stereochemical results of the reactions of their epoxides are readily discernible. The outstanding fact which has emerged from the study of these epoxides is that they invariably open to give diaxial products, and this has been stated as a general rule by Fürst and Plattner (85). The rule still applies when the reactions are acid-catalyzed and very few exceptions to it are known. The reactions of the 2,3-epoxycholestanes with *p*-toluenesulfonic acid in ether are typical (239). The 2α,3α-oxide gives the 3α-hydroxy-2β-tosyloxy compound, while the 2β,3β-oxide gives the 2β-hydroxy-3α-tosyloxy product:



Ts = *p*-toluenesulfonyl.

It is not immediately obvious why these reactions give diaxial rather than diequatorial products. Either method of opening would involve inversion of configuration at the point of attack. The fact that such inversion occurs almost certainly means that the reactions are S_N2. Bearing this in mind and assuming that the structure of cyclohexene oxide (see page 740) is unaltered when it becomes part of a steroid epoxide, one can write the following schemes for the reaction of 2α,3α-epoxycholestane with *p*-toluenesulfonic acid to give either a diaxial or a diequatorial product (only ring A is shown). It has been assumed



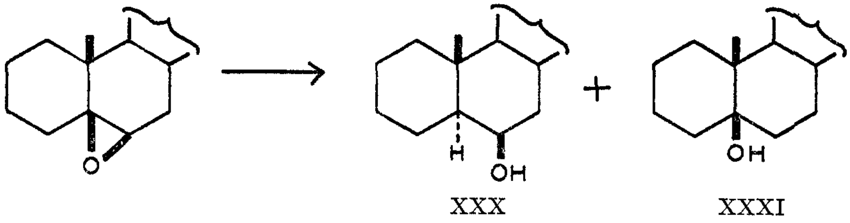
diaxial diequatorial

that the stable chair conformation of the cyclohexane ring is partly reëstablished in the transition states. The fact that only the diaxial product is obtained (see above) must mean that the diaxial transition state is more stable than the diequatorial one. That this is so can probably be attributed to the more nearly linear nature of the partial bonds in the diaxial transition state, and also to the fact that the reagent is in the same plane as the epoxide ring in the diaxial transition state, whereas this is probably not true for the diequatorial transition state (since partial reëstablishment of the chair conformation of the six-membered ring must mean that the partial bonds of this transition state have achieved some equatorial character).

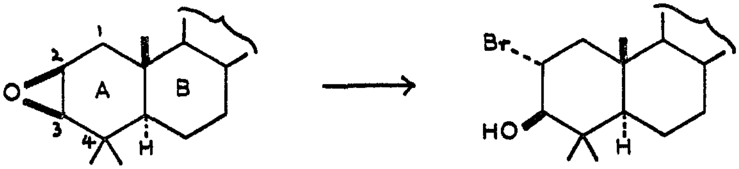
Other recent examples of diaxial opening of steroid epoxides include the reactions of $2\alpha,3\alpha$-epoxides with lithium aluminum hydride (40), lithium and ethylamine (99), and sulfuric acid in aqueous acetone (239), of $2\beta,3\beta$-epoxides with sulfuric acid in aqueous acetone (239), of $4\alpha,5\alpha$- and $4\beta,5\beta$-epoxides with lithium aluminum hydride (35), of $5\alpha,6\alpha$-epoxides with methylmagnesium iodide (41), lithium and ethylamine (99), and lithium aluminum hydride (207), of $5\beta,6\beta$-epoxides with lithium and ethylamine (99) and lithium aluminum hydride (207), of $7\alpha,8\alpha$- and $9\alpha,11\alpha$-epoxides with lithium and ethylamine (99), of

9β,11β-epoxides with hydrogen fluoride (70) and hydrochloric acid (283), and of 16α,17α-epoxides with hydrochloric acid (71) and hydrobromic acid (223).

Occasionally diequatorial products are formed, but these cases can usually be explained by the presence of factors causing destabilization of the diaxial transition state. Thus Hallsworth and Henbest (99) found that the reaction of 5β,6β-epoxycoprostane with lithium and ethylamine (postulated to involve attack of a solvated electron) gave a little of the diequatorial product (XXXI) in addition to the main diaxial product (XXX):

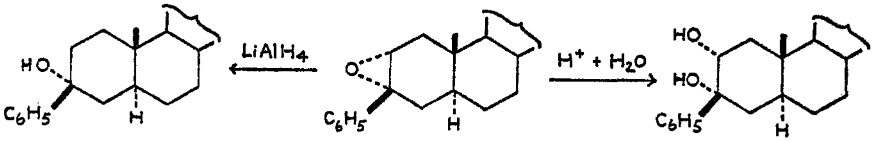


In this case attack at C_5 to give the diaxial product must be subject to considerably more steric hindrance than attack at C_6, and this may raise the energy of the diaxial transition state to a point where it is comparable with that of the diequatorial transition state. A similar explanation may account for the production of diequatorial 2α-bromo-3β-hydroxy compounds from the reaction of hydrobromic acid with 2β,3β-epoxides in the lanostane series (15). Attack at C_3 to give diaxial products would be subject to steric hindrance by the 4-methyl groups, and this may raise the energy of the diaxial transition state above that of the diequatorial transition state. Barton, Lewis, and McGhie (15) explained



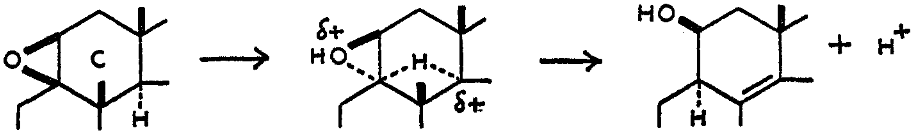
these results by assuming a "distorted-boat" form for ring A in the epoxides, but it is doubtful whether there is any difference between a "distorted-boat" and a "distorted-chair" form for this ring. If carbon atoms 1, 2, 3, and 4 are coplanar, as they are in cyclohexene oxide, then it is possible to write only one conformation for ring A in the above epoxides.

Ring opening with retention of configuration has been observed by Cookson and Hudec (40) in the acid-catalyzed hydration of 2α,3α-epoxy-3β-phenylcholestane with perchloric acid in aqueous acetone, although the same oxide gives a diaxial product with lithium aluminum hydride:



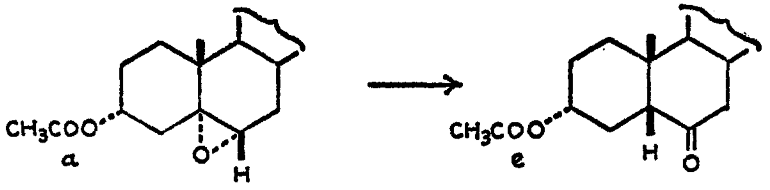
These authors suggest that the hydration reaction involves either unimolecular opening of the protonated oxide, followed by attack of water from the less hindered α-side (i.e., an A1 mechanism), or an unspecified S_Ni mechanism. It could equally well be explained, however, by a double-inversion mechanism, involving a phenonium-ion intermediate (*cf.* page 763).

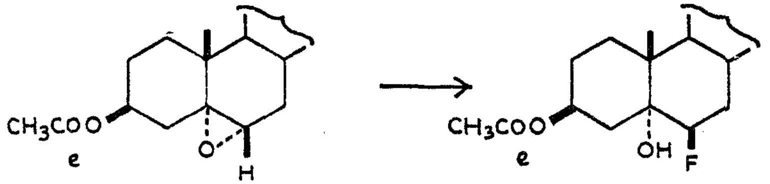
An example of transannular hydrogen transfer has been found in the reaction of a 9β,11β-epoxide with aqueous perchloric acid (282, 283). The mechanism suggested involves migration of H^- from $C_{14}\alpha$ to $C_9\alpha$, with subsequent loss of a proton from C_8:



Transannular hydrogen transfers have also been demonstrated (131) in the reactions of sodium methoxide and sodium thiophenoxide with two tricyclic ketone epoxides related to steroids.

Rearrangement reactions occur with steroid epoxides as with other epoxides (40, 108, 138). Interesting results have been obtained by Henbest and Wrigley (109), who studied a group of 5,6-epoxides and found that the presence of a substituent in the 3-position had a profound influence on the course of their reactions. Thus a 5α,6α-epoxide with a 3α-acetoxy substituent rearranges to a ketone when treated with boron trifluoride in ether, whereas the same epoxide with a 3β-acetoxy group forms a fluorohydrin when treated in the same way:



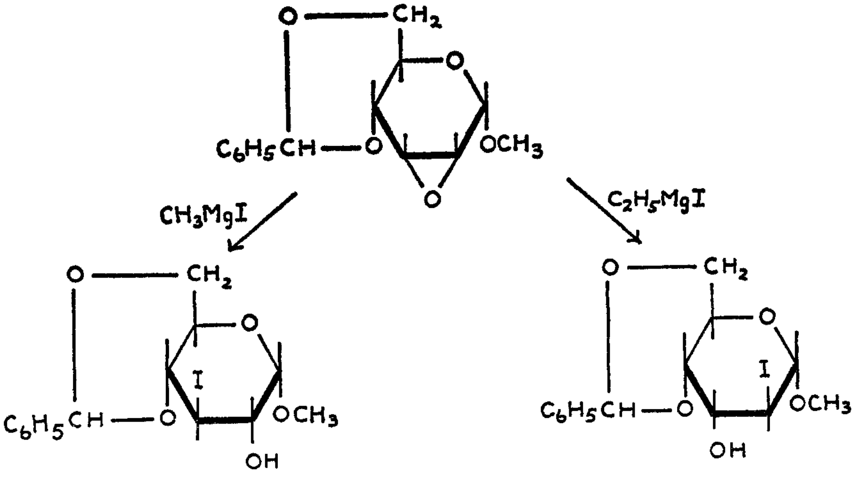


In each case the product contains an equatorial acetoxy group, whereas, if the first epoxide gave a fluorohydrin or if the second epoxide underwent rearrangement to a ketone, each product would contain the 3-acetoxy group in the less stable axial conformation. Evidently this difference (which would be partially developed in the transition states) is sufficient to swing the balance from addition to rearrangement, or *vice versa.*

X. SUGAR EPOXIDES

Ring-opening reactions of sugar epoxides have been reviewed by Newth in 1959 (190), by Sowden in 1957 (244), and by Overend and Vaughan in 1955 (194). None of these reviews, however, was specifically concerned with considerations of mechanism.

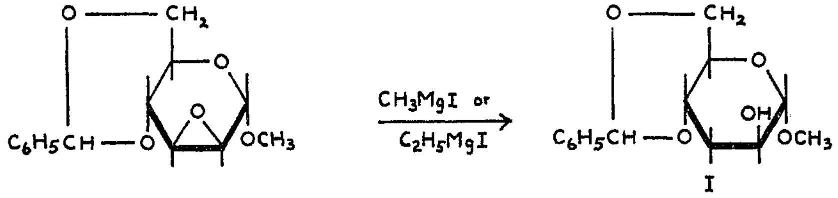
The epoxide rings of sugar epoxides invariably open with inversion to give trans products and, in most cases, to give diaxial products. Mills (172) has suggested that Fürst and Plattner's rule of diaxial opening of steroid epoxides (85) may also be applied to those sugar epoxides which have their conformations stabilized by a 1,6-anhydro ring or a 4,6-*O*-benzylidene group. Cases of this sort, in which the conformation is fixed, are similar to the steroid epoxides and, assuming that anhydropyranoses have a structure similar to that of cyclohexene oxide (page 740), diaxial opening is to be expected for the reasons discussed above. That this expectation is borne out in practice can be seen from an examination of the tables in Overend and Vaughan's review. Of forty reactions of conformationally stabilized sugar epoxides listed, thirty-five give diaxial products. The five exceptions (which give diequatorial products) include two heterogeneous hydrogenations, which may well take place by a quite different mechanism, and two acid-catalyzed reactions in which the conformation-stabilizing group is removed during the reaction (possibly before the opening of the epoxide ring). The fifth exception concerns methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside, which gives a diequatorial iodohydrin with methylmagnesium iodide (191) and diaxial halohydrins with ethylmagnesium iodide, ethylmagnesium bromide, and phenylmagnesium bromide (220):



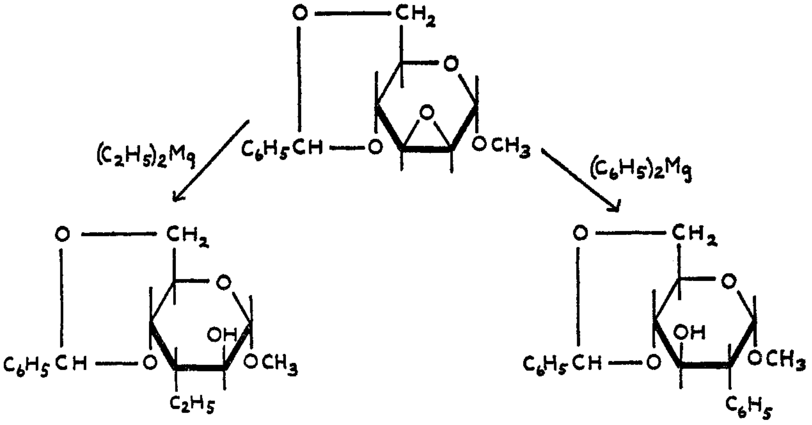
Diequatorial iodohydrin

Diaxial iodohydrin

It is very difficult to see why methylmagnesium iodide and ethylmagnesium iodide should give different iodohydrins in this case, especially as the two reagents give the same diaxial iodohydrin with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannoside (218):



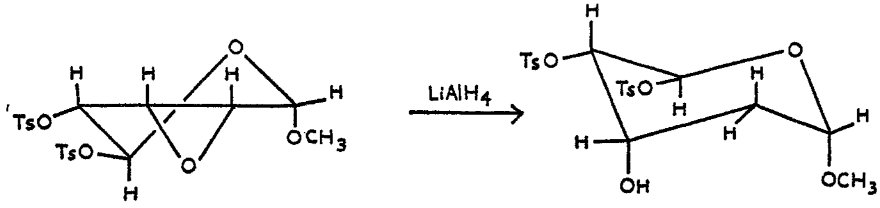
A somewhat similar but more readily understandable case of change from diaxial to diequatorial product occurs in the reactions of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannoside with organomagnesiums. Diethylmagnesium gives a diaxial product (77), whereas diphenylmagnesium gives a diequatorial product (219):



Diaxial product Diequatorial product

This is probably a simple steric effect. The formation of a diaxial product necessitates attack at C_3 and, in the case of diphenylmagnesium, such attack (presumably by the bulky phenyl anion) may well be subject to steric hindrance by the adjacent bulky benzylidene group. The energy of the diaxial transition state could then be raised above that of the diequatorial transition state.

Certain sugar epoxides may be conformationally stable, even though they contain no 4,6-*O*-benzylidene group or 1,6-anhydro ring. Thus methyl 2,3-anhydro-4,6-ditosyl-α-D-alloside probably exists almost entirely in that conformation in which the bulky tosyloxy groups are equatorial and, if this is so, the attack of lithium aluminum hydride at C_2 (22, 23) is another example of diaxial opening:



Anhydrides of monocyclic pyranoses, whose conformations are not stabilized, will normally exist as an equilibrium mixture of two conformations, corresponding to the two half-chair conformations of a six-membered ring. Hence, even if ring opening is always diaxial, two products are possible, as shown in figure 6 for 2,3-anhydrides, and each of these products can exist in either or both of two conformations. Although the case of a 2,3-anhydride is set out in figure 6, the same considerations apply to other anhydrides whose conformation is not stabilized, including anhydrofuranoses. For the case depicted in figure 6 the product ratio will be given by the expression:

$$\frac{P_C}{P_D} = \frac{k_A N_A}{k_B N_B}$$

where P_C and P_D are the concentrations of the products C and D, respectively; N_A and N_B are the mole fractions of conformations A and B, respectively; and k_A and k_B are the individual rate constants for the reactions of A and B, respec-

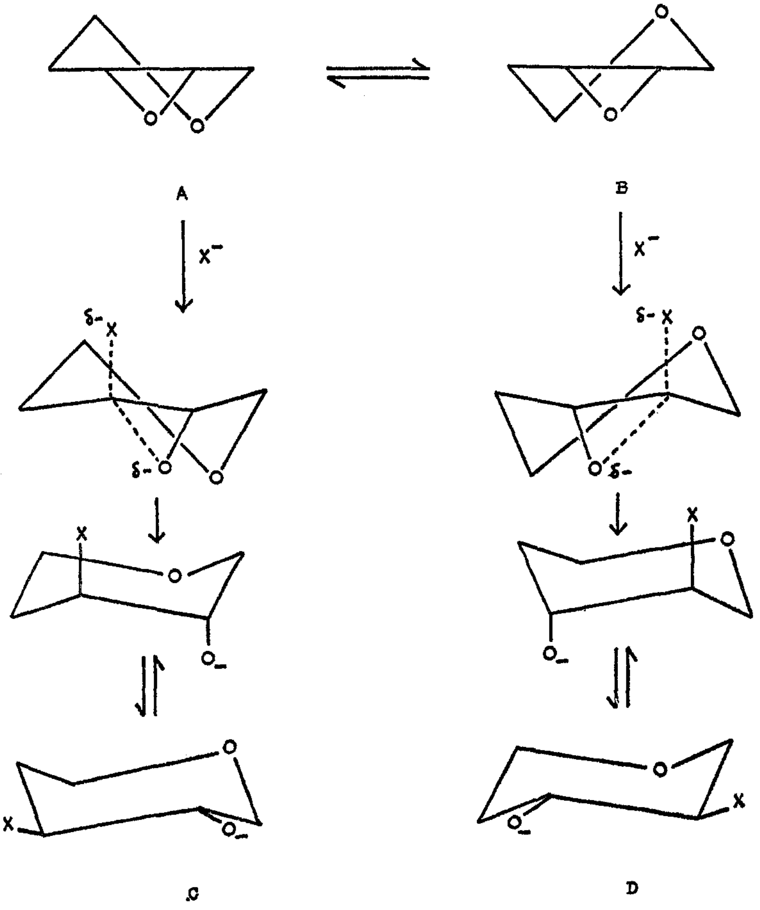
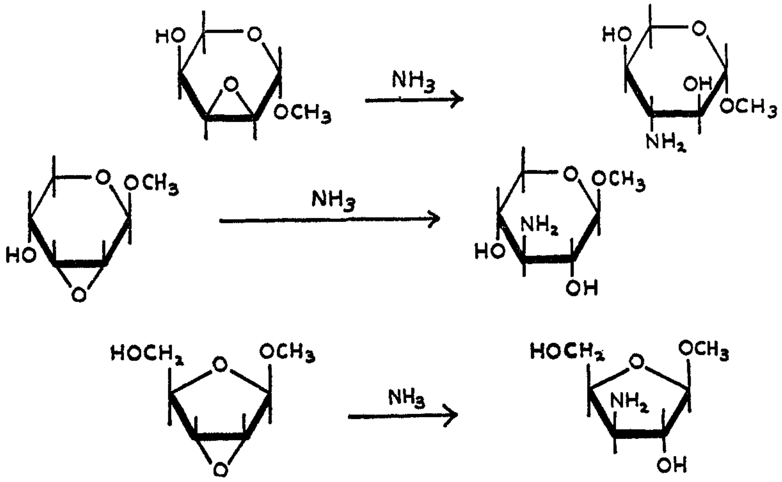


FIG. 6. Products from reaction of a 2,3-anhydride of a monocyclic pyranose

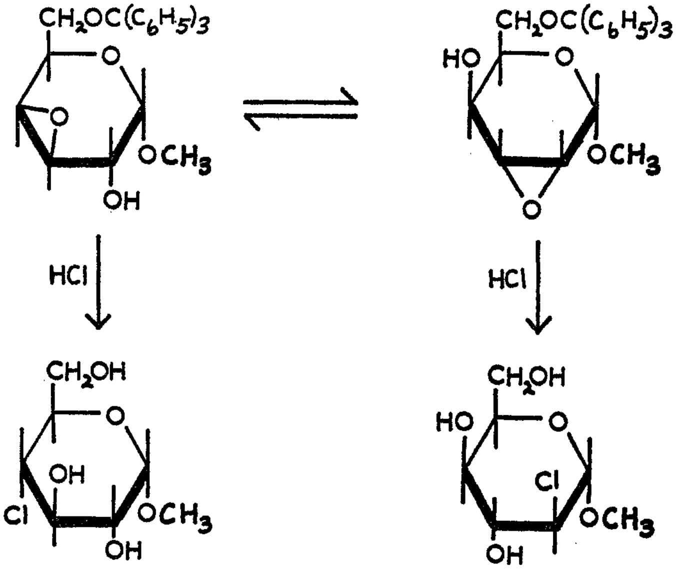
tively. In this expression the term N_A/N_B measures the proportions of the two conformations present in the initial epoxide, while the term k_A/k_B measures the relative reactivities of the two conformations towards the given reagent. In cases where there is no marked preference for one conformation or the other (and N_A/N_B is consequently near to unity), the product ratio will depend mainly on the ratio k_A/k_B, and this will be determined by simple steric and electronic factors (and also by the size and nature of the reagent). The following three epoxide reactions, all of which involve attack by ammonia at C_3 (5, 9, 231), may well be cases of this kind and the orientation is probably determined mainly by electronic factors.



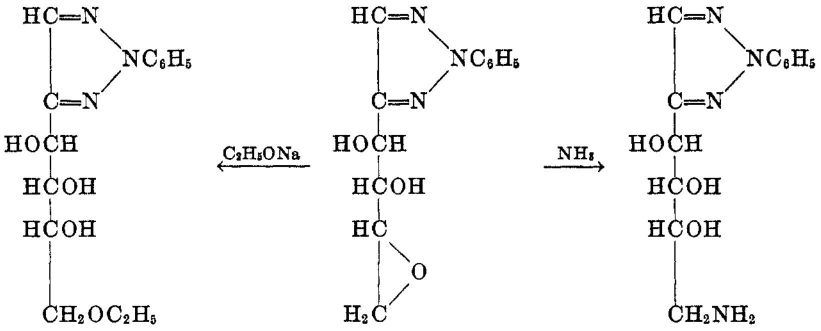
In each case C_1 (with its two attached oxygen atoms) is more electron-attracting than C_4 and consequently, since the steric environments of C_2 and C_3 are similar, attack is expected to take place at C_3 (see page 746).

Reactions of 1,2-anhydrides always involve attack at C_1 (103, 139, 198) and this is almost certainly a conjugative effect of the oxygen atom of the sugar ring, promoting attack at the epoxide carbon atom adjacent to it. These compounds are, in fact, epoxy ethers and they open in the same way as other epoxy ethers (*cf.* section E of table 3). Lemieux and Huber (139) have found that Brigl's anhydride (1,2-anhydro-α-D-glucopyranose triacetate) opens with retention of configuration when treated with certain bulky alcohols, and they have explained this on the basis of a double-inversion mechanism.

The reactions of certain epoxides are complicated by the possibility of "epoxide migration." This can occur when a hydroxyl group on an adjacent carbon atom is trans to an epoxy group, and it has been demonstrated by Angyal and Gilham (8) in a series of anhydroinositols and by Buchanan (30, 31, 32) in 3,4-anhydrogalactose derivatives. Buchanan (31) has shown that the conclusions of Labaton and Newth (135) regarding the reaction of methyl 3,4-anhydro-6-*O*-trityl-α-D-galactoside with hydrochloric acid are incorrect, and that the products actually formed arise as follows:



Terminal epoxides of sugars and related compounds always undergo attack at the least substituted carbon atom, giving normal products. Thus 5,6-anhydro-D-fructose phenylosotriazole reacts in this way with sodium ethoxide and with ammonia (104):



Other epoxides of this sort react in the same way with a variety of reagents (18, 76, 137), and the direction of ring opening in these cases is no doubt due to a simple steric effect, as with other monosubstituted ethylene oxides (*cf.* table 1).

XI. SUMMARY

Ring-opening reactions of epoxides in solution involve attack of a nucleophile on one of the epoxide carbon atoms with displacement of the epoxide oxygen atom. They are, therefore, nucleophilic substitution reactions and can be represented by the following generalized equation:

$$Y^- + R—X \rightarrow Y—R + X^-$$

For such reactions a continuous range of mechanisms is available, the transition states for which are shown in figure 7. In transition state XXXII bond forming has progressed to a considerable extent, while bond breaking has progressed very little (i.e., both partial bonds are short). As the transition states change from left to right in figure 7, the extent to which bond forming has progressed decreases and the extent to which bond breaking has progressed increases (i.e., both partial bonds become longer). In the extreme case of transition state XXXVIII no bond forming has taken place and the reagent does not participate in the rate-determining step. This is the S_N1 mechanism and will correspond to first-order kinetics and partial or complete racemization at the point of attack. All the other mechanisms are S_N2 and will correspond to second-order kinetics and inversion of configuration at the point of attack. It is possible, however, to distinguish between the different types of S_N2 mechanism. Those transition states towards the left-hand side of figure 7 will have a small negative charge on the central carbon atom and the reactions will therefore be facilitated by the presence of electron-withdrawing substituents in R, whereas the transition states towards the right-hand side of figure 7 will have a small positive charge on the central carbon atom and the reactions will be facilitated by the presence of electron-releasing substituents in R (as will the S_N1 reaction). The charges on the central carbon atoms of the transition states are not necessarily absolute charges, but are relative to any charges present on these atoms in the initial states.

Most of the evidence summarized in the present reivew, particularly the stereochemical evidence, indicates that epoxide reactions take place by a bimolecular mechanism (although there may be a few extreme cases which go by S_N1 mechanisms). In view of the strain inherent in the three-membered-ring structure, it is likely that bond breaking will have progressed to a considerable extent in the

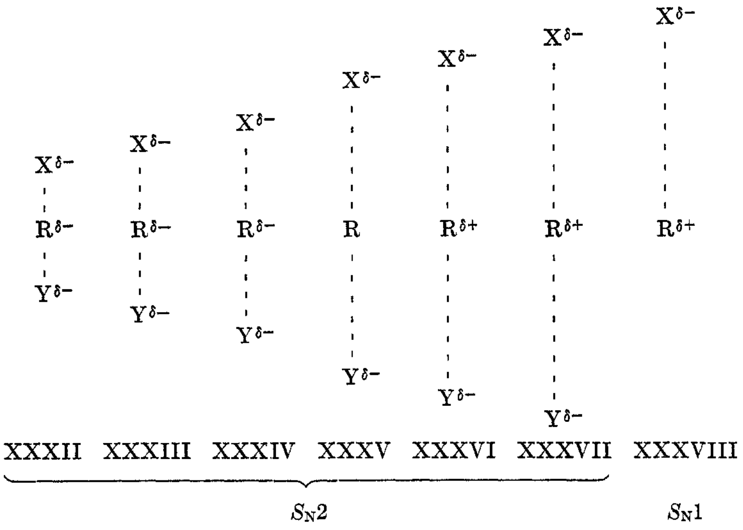


FIG. 7. Transition states for nucleophilic substitution reactions

transition state. This leads to a transition state towards the right-hand side of figure 7. Under conditions of acid catalysis the initial protonation of the epoxide oxygen atom is likely to produce a transition state for ring opening, in which bond breaking has progressed to an even greater extent. Thus the transition states for ring opening under basic or neutral conditions may be represented by XXXVI and those for acid-catalyzed ring opening by XXXVII. If this interpretation is correct, the reactions should be facilitated by the presence of electron-releasing substituents. What evidence there is supports this conclusion for attack at the abnormal position of a monosubstituted ethylene oxide. Attack at the normal position, however, is facilitated by the presence of electron-withdrawing substituents and there is a special reason why this should be so. (This has been discussed on page 768.)

The orientation of ring opening in monosubstituted ethylene oxides appears to be governed by a balance between the primary steric effect of the substituent group, inhibiting attack at the abnormal position, and the electron-releasing effect of the substituent group, promoting attack at the abnormal position. Acid catalysis usually increases the proportion of abnormal isomer, and this must be because the greater positive charge on the central carbon atom of transition state XXXVII than on that of XXXVI leads to a greater stabilization by an electron-releasing substituent. It follows that, in a monosubstituted ethylene oxide with an electron-withdrawing substituent, acid catalysis should decrease the proportion of abnormal isomer.

In cases where an epoxide ring is fused to another ring (e.g., in steroid epoxides or sugar epoxides), attack at one epoxide carbon atom will give diaxial opening (the hydroxyl group and the introduced group in axial positions), while attack at the other epoxide carbon atom will give diequatorial opening (the hydroxyl group and the introduced group in equatorial positions). In these situations diaxial opening is nearly always preferred, for reasons which have been discussed on page 782, and the orientation of ring opening in such cases is consequently determined by conformational effects, rather than by electronic or primary steric effects. It is probable, however, that in certain circumstances the presence of appreciable electronic or primary steric effects can increase the energy of the diaxial transition state until it is greater than that of the diequatorial transition state, and diequatorial opening then results.

Rearrangement reactions can be considered as a special case of ring-opening reactions where, in the absence of an external nucleophile, one of the epoxide carbon atoms is attacked by a neighboring group in the same molecule. These reactions are usually catalyzed by Lewis acids.

XII. REFERENCES

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