KINETICS AND EQUILIBRIA OF THE RING-OPENING REACTIONS OF EPOXIDES WITH HALIDE IONS

by

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ABSTRACT

KINETICS AND EQUILIBRIA OF THE

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A study was made of the reversible ring-opening reactions of epoxides with halide ions in methanol at 25°C. The reactions produce halohydrins and methoxide ion. The concentration of methoxide ion was determined by a spectrophotometric technique utilizing its reversible reaction with p-nitrophenol. The rate and equilibrium constants for the reactions of chloride, bromide and iodide ions with propylene oxide were evaluated. The equilibrium constants for the reactions of bromide ion with 1-oxaspiro[2,5] octane and with 1,2-epoxy-2,3-dimethylbutane were also evaluated. The results showed that alkyl and gem-dialkyl substitution stabilized the epoxide ring toward opening by halide ions. The extra ring stability obtained by substituting an isopropyl substituent for a hydrogen substituent amounted to at least 3.6 kcal. The results were discussed in terms of possible explanations for the stabilizing effect of alkyl groups.

ACKNOWLEDGEMENTS

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CHAPTER I

INTRODUCTION

A large amount of evidence in the literature shows that gem-dialkyl groups substituted on cyclic compounds tend to stabilize them against ring opening, and that gem-dialkyl groups substituted on open-chain compounds tend to make them more reactive toward ring closure.[1-3, 8, 10-16, 18-24] This has become known as the gem-dialkyl effect.[8] Two general explanations have been advanced to account for this effect. The first is the Thorpe-Ingold hypothesis,[1-3, 8] which says that alkyl groups push one another apart, thereby increasing the exocyclic c-c-c bond angle, and that the endocyclic c-c-c bond angle is decreased in compensation. The second explanation is that of Allinger[13] and Bruice,[20-24] which proposes that the effect of large alkyl groups in the open-chain compounds is to decrease the population of rotational conformers which are not unfavorable for ring closure. The original experimental basis of the Thorpe-Ingold hypothesis has been refuted[9] and most of the subsequent evidence on the gem-dialkyl effect has been concerned with five- and six-membered rings, and therefore it is of interest to study the ring-opening reactions of three-membered rings.

The present research work was undertaken to investigate the effect of alkyl groups on the reversible ring opening of epoxides with halide ions. For this purpose, a study was made of the rates and equilibria of the reactions of halide ions with propylene oxide. The reactions of bromide ion with 1-oxaspiro [2,5] octane and with 1,2-

epoxy-2,3-dimethylbutane were also studied.

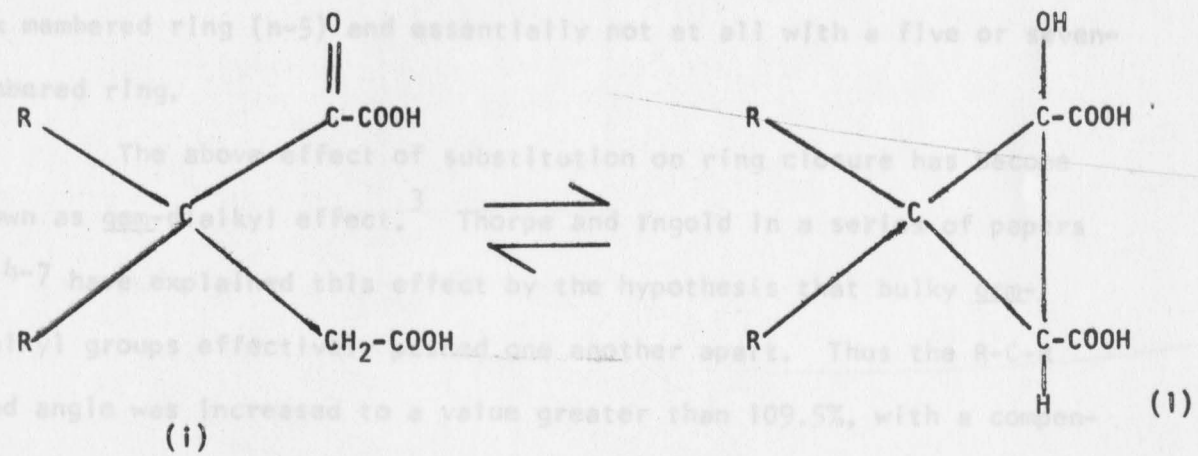
CHAPTER II

HISTORICAL

RING-OPENING REACTIONS

Many properties of cyclic compounds, such as the rates and equilibria of ring opening reactions, are affected by the size of the ring and the size and position of substituents.

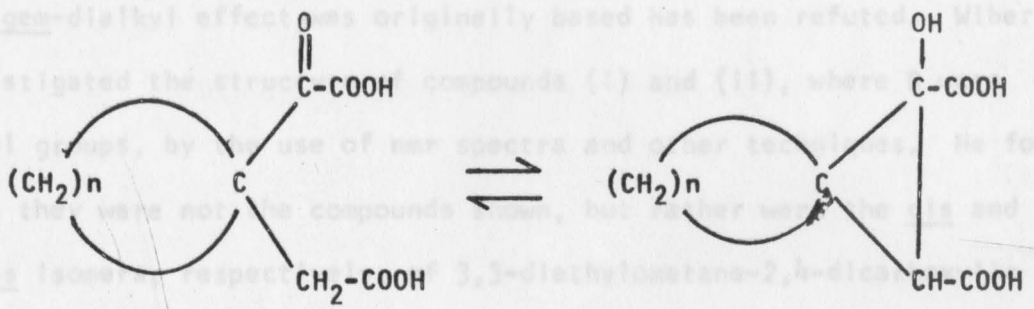
One of the earliest demonstrations of this effect was by Thorpe and Ingold.[1,2] They studied what they supposed to be the ring-chain tautomerism between 3,3-disubstituted α-ketoglutaric acids (i) and their cyclic tautomers (ii) as shown in equation (1).



(i) (ii) (1)

assuming that aldol condensation to be reversible.[3] It was reported that the equilibrium concentration of the cyclic tautomers (ii) was increased in the order: 0% when R was methyl, 62% when R was ethyl and 71% when R was n-propyl. They also studied the cyclic keto-dicarboxylic

acids (iii) and the supposed spiro tautomers (iv), as shown in equation (2).



(2)

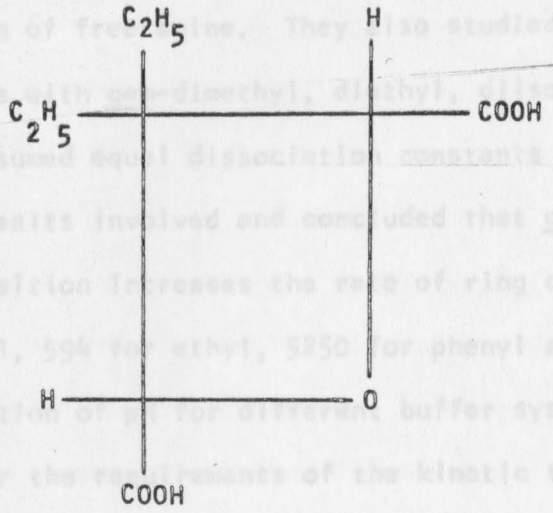
(iii) (iv)

The spiro tautomers were reported to be formed in 100% yields with a six membered ring (n=5) and essentially not at all with a five or seven-membered ring.

The above effect of substitution on ring closure has become known as gem-dialkyl effect.[3] Thorpe and Ingold in a series of papers [1, 4-7] have explained this effect by the hypothesis that bulky gem-dialkyl groups effectively pushed one another apart. Thus the R-C-R bond angle was increased to a value greater than 109.5%, with a compensating decrease in the bond angle to the other two groups, on the 3 carbon. With this angle smaller than normal, ring closure to the 3-membered ring would be more easily effected. The above hypothesis has become known as Thorpe-Ingold effect[8] or the Thorpe-Ingold hypothesis.[3] As applied to the closure of the spiro rings in equation (2), the Thorpe-Ingold hypothesis involved as an assumption that the cyclohexane ring

was flat with 120° bond angle,[1] which is now known to be incorrect.[3]

Unfortunately part of the experimental evidence on which the gem-dialkyl effect was originally based has been refuted. Wiberg[9] investigated the structure of compounds (i) and (ii), where R were ethyl groups, by the use of nmr spectra and other techniques. He found that they were not the compounds shown, but rather were the cis and trans isomers, respectively, of 3,3-diethyloxetane-2,4-dicarboxylic acid (v).

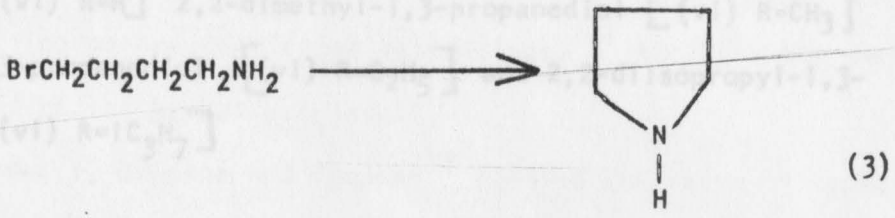


(v)

If the structures of compounds (i) and (ii) with other alkyl groups were also incorrect, along with compounds (iii) and (iv), then Thorpe and Ingold were actually investigating cis-trans isomerization rather than ring-chain tautomerism.

Although the original experimental basis for the gem-dialkyl effect is in doubt, a great deal of reliable evidence has accumulated to

show that it is a real effect.[3, 8, 10-16, 18-22] Brown and Van Gulick[10] studied the rate of cyclization of 4-bromobutylamine to pyrrolidine (Equation 3).

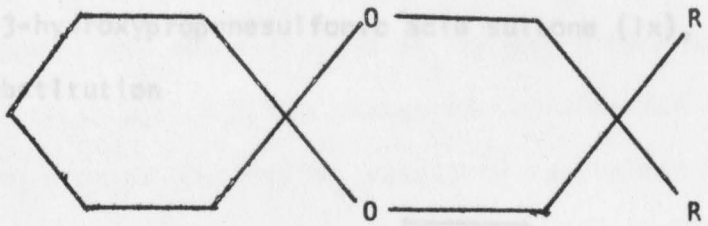


(3)

An acidic buffer was used to slow the rate of cyclization by limiting the concentration of free amine. They also studied the cyclization of 4-bromobutylamine with gem-dimethyl, diethyl, diisopropyl and diphenyl groups. They assumed equal dissociation constants for the various 4-bromobutylamine salts involved and concluded that gem-dialkyl substitution in the 2 position increases the rate of ring closure by a factor of 158 for methyl, 594 for ethyl, 5250 for phenyl and 9190 for isopropyl. Since the estimation of pH for different buffer systems was not sufficiently exact for the requirements of the kinetic treatment, the above numbers cannot be taken as exact but the general trend was adequately established.[10]

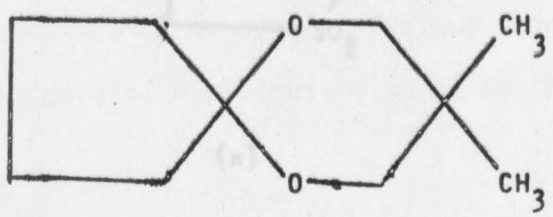
Newman and Harper[11] studied the rate of acid hydrolysis of a series of fifteen spiro-ketals of cyclohexanone, cyclopentanone and 2-methyl cyclopentanone, in which the alcohol portion of the ketal was ethylene glycol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol, and 2,2-diisopropyl-1,3-propanediol. The results,

in general, showed a trend supporting the gem-effect. For example, the rate constants for the hydrolysis of cyclohexanone ketals of 1,3-propanediol [(vi) R=H] 2,2-dimethyl-1,3-propanediol [(vi) R=CH_3] 2,2-diethyl-1,3-propanediol [(vi) R=C_2H_5] and 2,2-diisopropyl-1,3-propanediol [(vi) R=iC_3H_7]



(vi)

were in the ratio 30.6 : 2.1 : 0.888 : 0.335 respectively. This may show increased stability of the ring as the size of the R groups are increased. However, the relationship of rate constant to ring stability is not completely clear in this case, since the intermediate is an oxo-carbonium ion. The transition state must therefore involve a change from tetrahedral to trigonal carbon. Newman and Harper[11] also reported a preliminary estimate of the equilibrium constants for the ring opening of the 2,2-dimethyl-1,3-propanediol ketals of cyclohexanone [(vi) R=CH_3], cyclopentanone (vii) and 2-methylcyclohexanone (viii). These were



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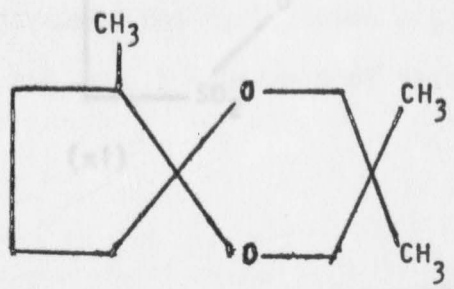
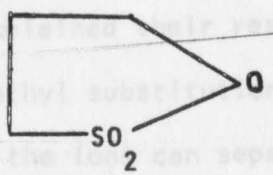


(viii)

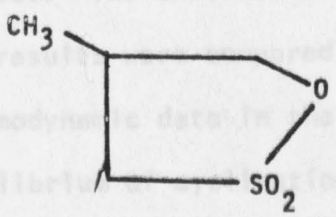
2, 0.2 and 0.04 respectively. These should indicate relative ring stability, since the change from tetrahedral to trigonal carbon is not involved. The relative ring stability shown does not follow the prediction of Thorpe and Ingold for spiro-rings,[1-7] but does not necessarily contradict the gem-effect itself.

Bordwell, Osborne and Chapman[12] studied the rates of hydrolytic ring opening of 3-hydroxypropanesulfonic acid sultone (ix), and of sultones with substitution

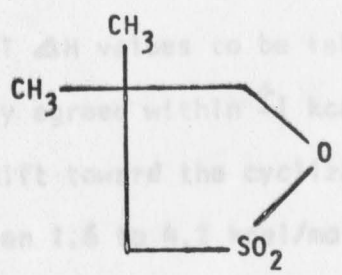


(ix)

in positions α, β and γ to the ring oxygen by methyl and gem-dimethyl groups. They found that β-methyl substitution decreased the rate of hydrolysis by more than would be expected in analogous open-chain p-toluenesulfonate esters. Thus the relative rates of hydrolysis for (ix), (x) and (xi) were in the order of 1 : 0.21 : 0.0035.



(x)



(xi)

This compares with the relative rates of hydrolysis of propyl, isobutyl and neopentyl p-toluenesulfonates which are in order 6.5 : 2.1 : 1. Methyl substitution in the α and γ position had analogous effects, showing the change in mechanism in proceeding from the sulfonates of a primary alcohol to that of a secondary and tertiary alcohol. Methyl substitution in any of the positions had the effect of decreasing the entropy of activation, which was contrary to experience with open-chain compounds. This work was an excellent demonstration of the gem-effect in stabilizing the five membered ring, although the change in coordination around the solvolyzing carbon atom as SN_p and SN_2 reactions take place must also be taken into account. Bordwell et al.[12] explained their results on the basis of restricted rotation caused by methyl substitution. In this solvolysis of open-chain sulfonic esters the ions can separate by translational motion, but in cyclic sulfonate esters the separation must occur by rotation around carbon-carbon bonds.

Allinger and Zalkow[13] calculated the change in enthalpy, entropy and free energy for the hypothetical cyclization of methyl, dimethyl and ethyl substituted cyclohexanes, using the unsubstituted hexane-cyclohexane reaction as the zero point. The calculation of ΔH was based on the formula involving the number of gauche interactions in the reactant and product. The calculation of ΔS was carried out by a statistical method. The results were compared with experimental ΔH values to be taken from thermodynamic data in the literature. They agreed within ± 1 kcal. The equilibrium of cyclization was found to shift toward the cyclization with increasing substitution by an amount between 1.6 to 4.2 kcal/mole of free

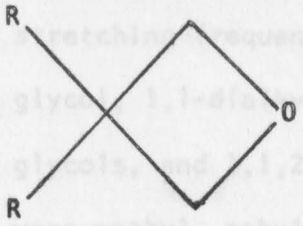
energy. Both enthalpy and entropy changes contributed to the shift. The enthalpy change could be explained by a reduced number of gauche interactions in the cyclic as opposed to the noncyclic hydrocarbon. The entropy changes could be explained on the basis of restriction by the substituent groups of rotation in the noncyclic hydrocarbon. Qualitatively, the experimental thermodynamic values for cyclopentane derivatives showed the same trend.

Wheeler and Almeida[14] studied the rates of hydrolysis of glutaric anhydrides substituted in the 2 and 3 positions with methyl and ethyl groups. They found that substitution decreased the rate of hydrolysis. The rates were in the order 100 : 70 : 11 : 4.5 for unsubstituted, 3-methyl, 3.3-dimethyl, 3-ethyl and 3.3-diethyl glutaric anhydrides respectively. Similar results were found for succinic anhydrides, except that the substitution of one methyl group gave a small increase in rate. The results were explained on the basis of steric inhibition to the approach of solvent in the formation of the carbonyl addition intermediates.

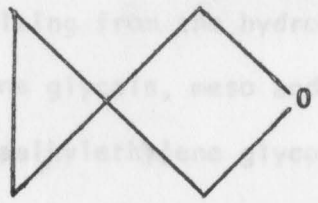
Wheeler and Rodriguez[15] studied the rates and equilibria of the acid catalyzed hydrolysis of γ-butyrolactones and δ-valerolactones substituted with methyl groups and gem-dimethyl groups in the β-positions (and in some cases in the α, δ and γ positions). The equilibrium constants for butyrolactone, β-methylbutyrolactone and β,β-dimethylbutyrolactone were 34.7×10^{-2}, 4.81×10^{-2} and $< 1 \times 10^{-2}$, respectively. The equilibrium constants for valerolactone, β-methylvalerolactone and β,β-dimethylvalerolactone were 16.3, 0.92 and 0.09 respectively. Methyl substitution in the α, γ and δ positions

similarly increased the ring stability. In those cases where the equilibrium constant was sufficiently large for the measurement of rates of hydrolysis, the rates were decreased by methyl and gem-dimethyl substitution, and the valerolactone hydrolyzed about 100 times faster than the butyrolactone. The authors explained their results by reference to the conclusion of Allinger and Zalkow.[13]

The gem-effect given in the example above can be interpreted by arguments similar to those of Allinger and Zalkow.[13] They cannot be interpreted by Thorpe-Ingold hypothesis, since there should be very little compression of bond angles in five- and six-membered rings. In order to seek confirmation of the Thorpe-Ingold hypothesis it is necessary to work with three- and four-membered rings. Searles, Lutz and Tamer[8] pointed out bond angle measurements in the literature which show, for example, that cyclopropane has an endocyclic c-c-c bond angle of 60° and an exocyclic H-C-H bond angle of 118°-120°, while cyclobutane has an endocyclic c-c-c bond angle of 90° and an exocyclic H-C-H bond angle $114 \pm 8^{\circ}$. In an effort to demonstrate the Thorpe-Ingold hypothesis, they investigated the relative electron donor ability of a series of oxetanes toward hydrogen bonding, as measured by the shift of the O-D stretching bond for CH_3OD in the infrared. The oxetanes studied were oxetane [(xii) R=H], 3,3-diethyloxetane [(xii) R=C_2H_5], 2-oxaspiro [3,2] hexane (xiii), 2-oxaspiro [3,3] heptane (xiv), 2-oxaspiro [3,4] octane (xv) and 2-oxaspiro [3,5] nonane (xvi).



(xii)



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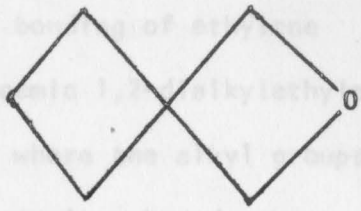

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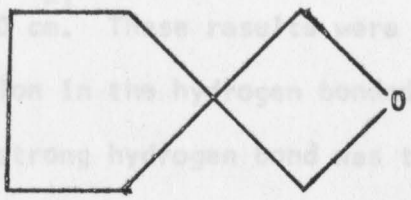
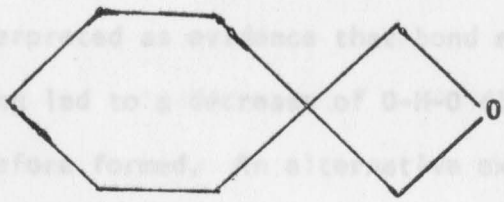


(xv)



(xvi)

The O-D shift for oxetane was 120 cm^{-1} while that for 3,3-dimethyl oxetane was 115 cm^{-1}, and the corresponding values for the spiro-oxetanes were 122 for (xiii), 128 for (xiv), 135 for (xv), 120 for (xvi). Although the results did not show consistent shifts, the authors were able to rationalize them by assuming that a decrease in the c-o-c bond angle decreased the oxygen electron density, the cyclopropane ring withdrew electrons inductively, and axial 3-hydrogen interactions in (xvi) compressed the oxetane ring.

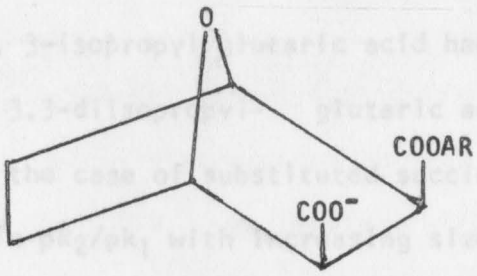
A series of papers on internal hydrogen bonding in diols[3, 16-18] gives evidence of possible bond angle deformation related to the Thorpe-

Ingold hypothesis. Kuhn[16,17] studied the infrared shift in the O-H stretching frequency resulting from the hydrogen bonding of ethylene glycol, 1,1-dialkylethylene glycols, meso and racemic 1,2-dialkylethylene glycols, and 1,1,2,2-tetraalkylethylene glycols, where the alkyl groups were methyl, ethyl, isopropyl and t-butyl. The results showed an increase in the frequency with increasing size of the alkyl group, from 51 cm^{-1} for 1,1-dimethylene glycol to 97 cm^{-1} for 1,1-di-t-butylethylene glycol. 1,1,2,2-tetra-t-butylethylene glycol had a frequency shift of 170 cm^{-1}. These results were interpreted as evidence that bond angle deformation in the hydrogen bonded ring led to a decrease of O-H-O distance. A strong hydrogen bond was therefore formed. An alternative explanation which was cited was bending of the c-c bond.

Schleyer[3] carried out the same type of study using 2,2-dialkylpropane-1,3 diols. In these cases all the OH groups were primary and bent bonds were not likely. As the size of the alkyl groups increased, the frequency shift increased, when the alkyl groups were primary and decreased as the alkyl groups become secondary or tertiary. The results were explained by the Thorpe-Ingold hypothesis, with the provision that conformation changes occured which increased the O-H-O distance when the alkyl groups become very large. Kuhn, Schleyer, Battinger and Eberson[18] studied the infrared frequency shifts in internally hydrogen-bonded 1,4-diols, and found that conformational effects were important. The O-H-O bond angle was shown to be important, along with bond distance, in determining the strength of hydrogen bonds.

Eberson and Forsen[19] studied the nmr chemical shift of the acidic proton in the monopotassium salt of dialkyl and tetraalkylsuccinic acids. The high ratio of $k1/k_2$ for the dissociation of these acids was taken as evidence for strong internal hydrogen bonding in the racemic salts.

Bruice and Pandit[20] studied the hydrolysis of the sodium salts of the monoaryl esters of substituted succinic and glutaric acids. They found that the reaction occured in two stages. The first stage was ring closure to an anhydride with the loss of a phenolate anion, and the second was the basic hydrolysis of the anhydride ring. A kinetic study of the two steps showed that gem-dialkyl substitution in the acid portion of ester had a large positive effect on the rate of anhydride ring closure, and a small negative effect on the rate of anhydride hydrolysis. Also the succinic ester ring closure to a five membered anhydride ring was much faster than the glutaric ester ring closure to a six-membered anhydride ring, but the basic hydrolysis of the glutaric anhydride ring was only slightly faster than the basic hydrolysis of the succinic anhydride ring. It was proposed that the gem-dialkyl effect on ring closure was caused by steric inhibition of the alkyl groups to rotation in the esters leading to rotational conformers which were unprofitable for ting closure. The lesser gem-dialkyl effect in anhydride hydrolysis was assigned to a steric inhibition of hydroxide ion to the ring. This was further shown by the hydrolysis of the aryl ester salt of 3,6-endoxo-Δ^4-tetrahydrophthalic acid (xvii)



(xvii)

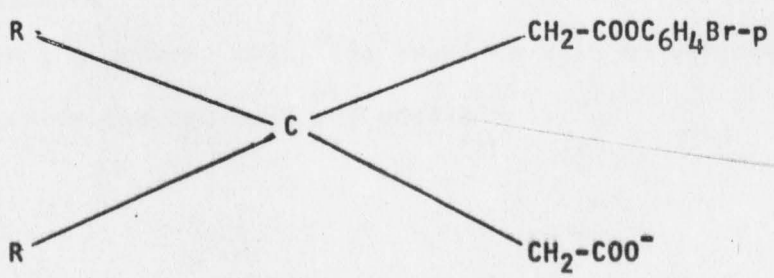
in which the carboxyl groups are prevented by the regid ring system from moving to give rotational conformers which are unprofitable for ring closure. The rate of anhydride formation from this ester was the largest of the compounds studied and was 53,000 times that of unsubstituted glutaric ester.

Bruice and Bradbury[21] further studied the rate of basic hydrolysis of 3-substituted and 3,3-disubstituted glutaric anhydrides. By an application of the Taft δ-Es relationship, they estimated the equilibrium constant for axial equatorial conformation for the large groups in unsymmetrically substituted glutaric anhjaude rings. They concluded that there was not a pronounced preference for equatorial conformation, and thus that the anhydride ring must exist in the half-chair form.

Bruice and Bradbury[23] investigated the first and second ionization constants of 3-monoalkyl and 3,3-dialkyl glutaric acids. Increasing the size of the alkyl groups had a small positive effect on the first ionization constant, and a large negative effect on the second ionization constant. Gem-dialkyl substitution had a much greater effect than monosubstitution. For example, unsubstituted glutaric acid had a pk_1 of

4.42 and pk_2 of 5.44, 3-isopropyl glutaric acid had a pk_1 of 4.28 and pk_2 of 5.51, and 3,3-diisopropyl- glutaric acid had a pk_1 of 3.63 and pk_2 of 7.68. In the case of substituted succinic[20] and malonic[25] acids, the increase in pk_2/pk_1 with increasing size of alkyl substituted was greater than in the glutaric acid case, and was explained by increasing stability of the internal hydrogen bond.[20,25] In the case of substituted glutaric acids, Bruice and Bradbury assumed that intramolecular hydrogen bonding would be negligible in comparison to intermolecular hydrogen bonding in water solution, and that the gem-dialkyl effect on pk_1 and pk_2 could be ascribed to an electrostatic effect. The magnitude of the electrostatic effect depends on the product of the distance between carboxyl groups and the dielectric constant separating them. The electrostatic effect normally passes through the hydrocarbon portion of the molecule, a medium of low dielectric constant. When substitution by gem-dialkyl groups decreases the average distance between the carboxyl groups, by inhibiting the formation of rotational conformers in which the carboxyl groups are widely separated, the authors proposed that the electrostatic effect on k_1 and k_2 could occur through the solvent, a medium of high dielectric constant.

Bruice and Bradbury[24] studied the solvolysis of the p-bromophenyl 3-alkyl and 3,3-dialkylglutarate monoester (xviii),



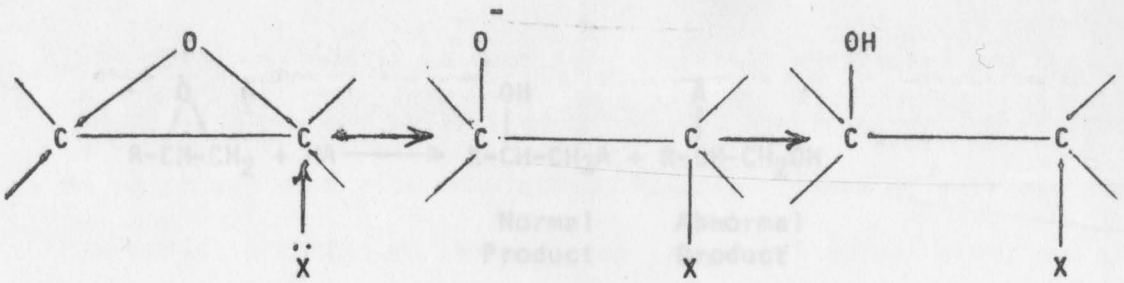
(xviii)

R,R^1=H, methyl, ethyl, isopropyl, phenyl) at different temperatures. The solvolysis was shown previously to proceed through the cyclic anhydride. The enthalpy of activation, $\Delta H^{\neq}$ was constant within experimental error regardless of the size of the alkyl group. The entropy term $T\Delta S^{\neq}$ was found to increase with increasing size of the alkyl groups. The increase was about 3 kcal per mole when R and R^1 were changed from hydrogen to isopropyl. The authors suggested that this provide evidence for the inhibition of rotation in the open-chain isomer by gem-dialkyl groups. However, they pointed out $T\Delta S^{\neq}$ is dependent upon electronic effects and solvation as well as upon steric effects, and therefore that interpretations posed on activation entropy are open to some question.

Epoxide Ring-Opening Reactions

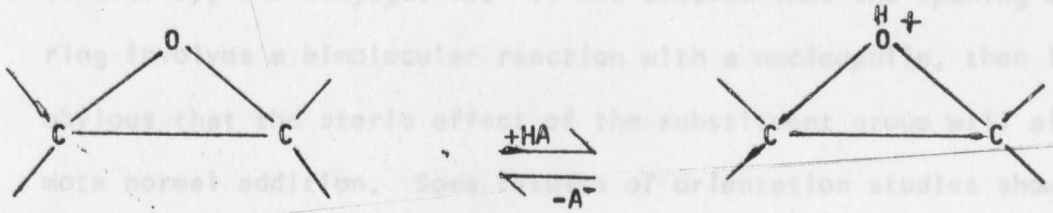
The formation and hydrolysis of spoxide rings has been the subject of several reviews.[26-28] The formation of halohydrins from epoxides is reversible and may take place with either hydrogen halide or halide ion addition.

In the opening of oxide rings there is a nucleophilic displacement on carbon, the displaced group being the ring oxygen atom. If the displacement is on the oxide itself, (xix) the intermediate (xx) is produced. Similarly, (xix) gives the open-chain product (xxi) by gaining a proton.



(xix) (xx) (xxi)

If the displacement is on the conjugate acid of oxide (xviii), it reacts faster than the oxide itself to give product (xxii)



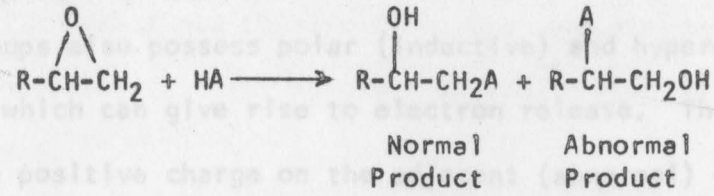
(xix) (xxii)

Bronsted[29] studied the hydration of 3-chloropropylene oxide and the conjugate acid of 3-chloropropylene oxide, and observed that the conjugate acid of the oxide reacts 400 times faster than oxide itself.

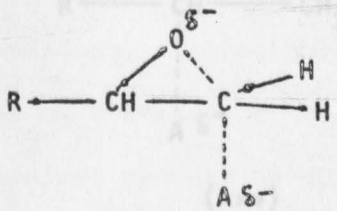
The ring opening reaction may take place either by a carbonium ion[30-31] or a direct displacement mechanism. The evidence available for arriving at the mechanism will be considered under three parts: (a) Orientation, (b) Stereochemistry, (c) kinetics of ring-opening.

(a) Orientation:[27]

In the general case, the reaction with an unsymmetrically substituted epoxide two products are possible.



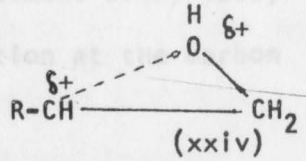
In order to obtain information about the mechanism from data on orientation, it is necessary to relate orientation to the effect of the substituted group in the epoxide. For this purpose it is advisable to bear in mind the three main effects of substituent groups: Steric, polar (i.e. inductive), and conjugative. If one assumes that the opening of epoxide ring involves a bimolecular reaction with a nucleophile, then it will be obvious that the steric effect of the substituent group will always promote normal addition. Some results of orientation studies show 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 type (xxiii).



(xxiii)

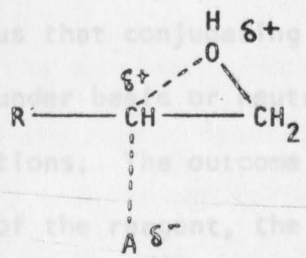
Many epoxides which give entirely the normal product under basic conditions produce a mixture of normal and abnormal product under acidic conditions. It is impossible to rationalize this phenomenon on steric

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 the positive charge on the adjacent (abnormal) carbon atom, and there are two mechanisms in which the transition state (xxiv) for a rate-determining step carries a partial positive charge on the carbon atom. The first mechanism is essentially SN_1 in which the secondary carbonium ion is partially solvated by the -hydroxyl group as shown in (xxiv).



(xxiv)

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 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 partial positive charge as shown in (xxv).



(xxv)

Such a mechanism is known as "borderline S_N2" or as one in which bond breaking is more important than bond making. Support for this mechanism is provided by the reaction of propylene oxide with halogen halides in water. At comparable temperatures the proportion of abnormal product

obtained are in the order HCl > HBr > HI. This could be caused by steric effect due to size of halide ions and also by the fact that the transition state for abnormal attack is more polar than that for normal attack.

From the results of orientation studies in relation to the polar effect it is clear that 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 the reaction at the carbon atom to which it is attached.

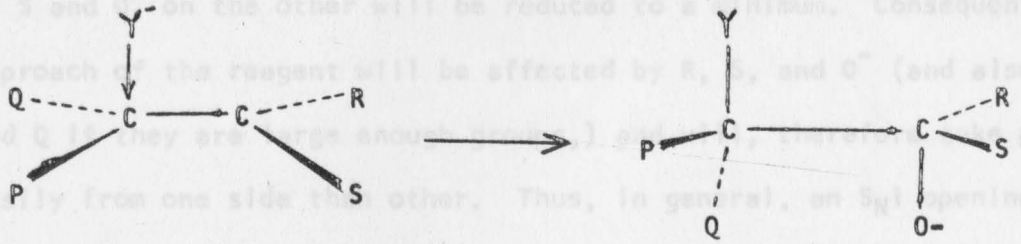
The third type of substituent comprises those groups which can conjugate and, in particular, those groups which can stabilize a positive charge by conjugative electron release from a π orbital or an atomic p orbital. Four such groups have been studied. These are a carbon-carbon double bond, a carbon-carbon 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. From the result it is obvious that conjugating groups favor attack on the adjacent carbon atom, both under basic or neutral conditions, and even more so, under acidic conditions. The outcome of conjugative and steric effect depends on the size of the reagent, the smaller the reagent, the greater proportion the abnormal product being formed. It is also important to note that there is some evidence[32,33] that the reagent itself may be able to conjugate with the developing charge.

Reeve and Sadle[34] studied the reaction of propylene oxide with methanol and found that 1-methoxypropanol-2- was the only isomer detected

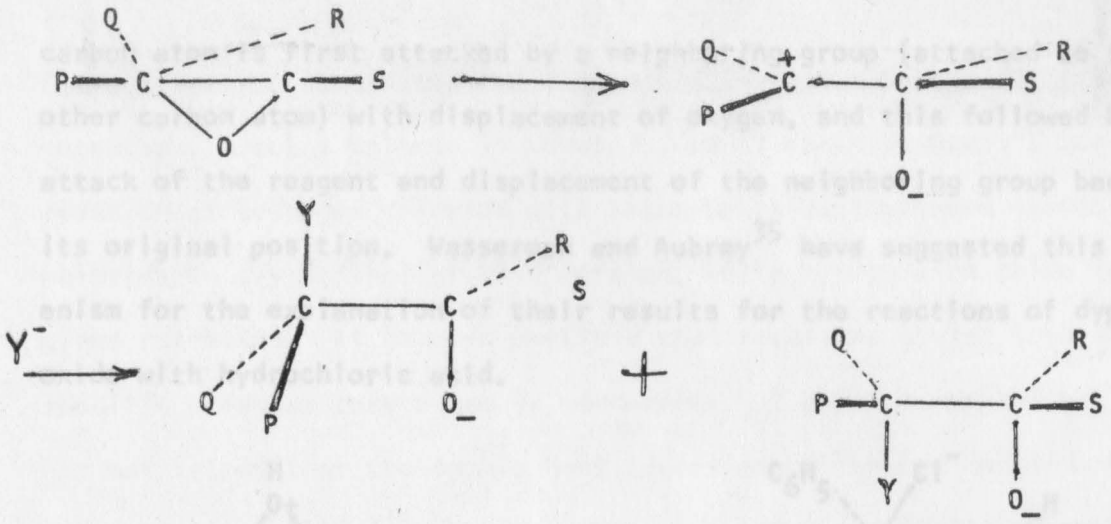
in the sodium methoxide catalyzed reaction while the mixture of both the isomers were obtained under acid catalyzed condensation.

(b) Stereochemistry:[28]

Since ring-opening reactions are nucleophilic displacements on carbon, inversion of configuration is usually observed as the steric result of oxide opening. In other words, the opening is trans. 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 but is incomplete with an S_N1 mechanism. In S_N2 reactions inversion occurs because of the approach of reagent on the side remote from the oxygen.



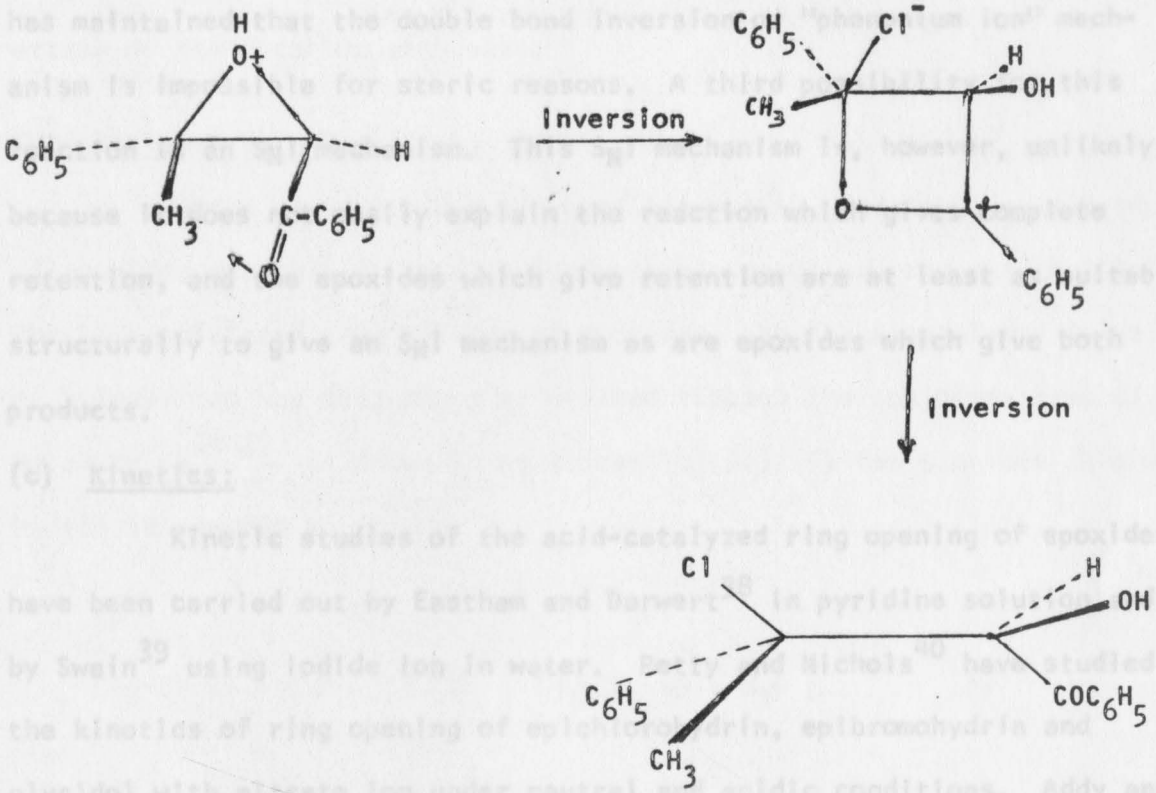
In acid catalyzed reactions the epoxide oxygen is initially protonated but the process is otherwise the same. Reactions following an S_N1 mechanism, on the other hand, involve the formation of an intermediate carbonium ion and, since the three bonds attached to the central carbon atom of a carbonium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



The intermediate carbonium ion is likely to take a preferred conformation in which the nonbonded interactions between P and Q on the one hand and 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 they are large enough groups,) and will, therefore take place more easily from one side than other. Thus, in general, an S_N1 opening would not be expected to give the two stereoisomeric products in equal amount. 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 should be noted that the ring-opening reactions of steriod epoxides and sugar epoxides also invariably involve the inversion of configuration.

In some studies ring-opening reactions give retention of configuration. Neither an S_N1 nor an S_N2 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 atom is first attacked by a neighboring group (attached to the other carbon atom) with displacement of oxygen, and this followed by attack of the reagent and displacement of the neighboring group back to its original position. Wasserman and Aubrey[35] have suggested this mechanism for the explanation of their results for the reactions of dypnone oxide with hydrochloric acid.



An alternative explanation of the above reaction was also suggested by Wasserman and Aubrey.[35] 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.[2]

Finally, a few epoxide ring-opening reactions give rise to both stereospecific products. In these cases there is a delicate balance between

the S_N2, giving inversion, and the double inversion mechanism, giving retention. Such a balance is possible, as is shown by House[36] for the reaction of hydrogen chloride with trans-benzalacetophenone oxide. Hydrogen chloride in dry ethanol gives inversion, while hydrogen chloride in ether gives retention. It is also possible that reactions giving both stereospecific products take place by concurrent S_N2 and S_N1 mechanism. Brewster[37] has maintained that the double bond inversion or "phenonium ion" mechanism is impossible for steric reasons. A third possibility for this reaction is an S_N1 mechanism. This S_N1 mechanism is, however, unlikely, because it does not easily explain the reaction which gives complete retention, and the epoxides which give retention are at least as suitable structurally to give an S_N1 mechanism as are epoxides which give both products.

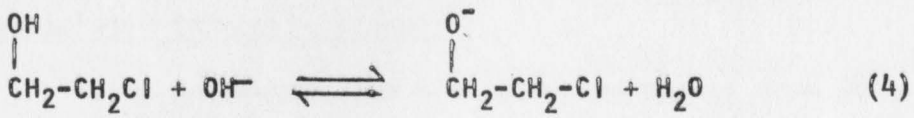
(c) Kinetics:

Kinetic studies of the acid-catalyzed ring opening of epoxides have been carried out by Eastham and Darwert[38] in pyridine solution and by Swain[39] using iodide ion in water. Petty and Nichols[40] have studied the kinetics of ring opening of epichlorohydrin, epibromohydrin and glycidol with nitrate ion under neutral and acidic conditions. Addy and Parker[41] studied the rate of the ring opening reaction between propylene oxide and chloride ion in water as a function of temperature and pH. They followed the rate by a continuous titration to constant pH with perchloric acid, making allowance for the simultaneous formation of glycol, which was measured by periodate titration. Both normal and abnormal

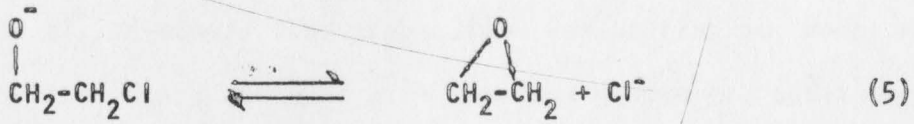
products were observed. The percentage of abnormal products increased with increasing temperature and decreasing pH, from 9% at 20°C and pH 7.0 to 36% at 40°C and pH 3.6. Second-order rate constants, activation energies and activation entropies were reported for the uncatalyzed reaction and the acid-catalyzed reaction. The results showed that almost all of the uncatalyzed reaction occured by chloride ion attack on the 1-carbon of propylene oxide, but that there was a very small amount of attack on the 2-carbon atom also.

Epoxide-Halohydrin Equilibria

Under neutral and basic conditions, the ring opening reactions of epoxides with halide ions is a reversible reaction, the reversal being the base-catalyzed ring closure of epoxides. The base-catalyzed solvolysis of halohydrins has been shown to proceed through the conjugate base of the halohydrins[26-28] as shown in equations (4) and (5) for ethylene chlorohydrin in aqueous solution:

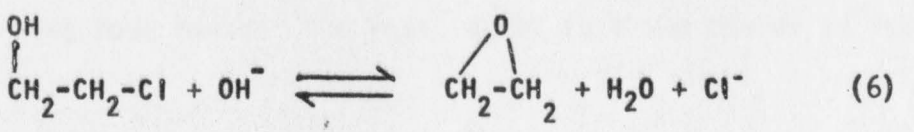


(4)



(5)

The overall equilibrium reaction is obtained by adding equation (4) and (5) and is shown in equation (6).



(6)

The hydrolysis of the halohydrins to yield ethylene glycol can proceed further with attack on the epoxide ring by hydroxide ion or water. The equilibrium constant for reaction (6) has been measured, and the forward and the reverse rate constants have also been measured.[42]

A number of kinetic studies of the base catalyzed ring closure of halohydrins have been made.[26-28] Of particular interest is a study of the relative rates of hydroxide-ion-catalyzed ring closure reactions of halohydrins.[43,44] The rate of ring closure was shown to increase when methyl groups were added to the oxirane ring. For example the relative rates of ring closure were: ethylene chlorohydrin, 1; 1-chloro-2-propanol, 21; 1-chloro-2-methyl-2-propanol, 252; and 2,3-dimethyl-3-chloro-2-butanol, 11,600. Also of interest is a study of the effect of solvent on the ring closure of ethylene chlorohydrin.[45] It was found that alcohols, particularly methanol, had a strong retarding effect on the rate of reaction.

CHAPTER III

EXPERIMENTAL

Materials:

All materials were of reagent grade. 2-Bromopropane and chloroacetone were obtained from Eastman Kodak Company and were redistilled. Methanol was obtained from Matheson Coleman and Bell Company.

P-Nitrophenol was obtained from Research Plus Laboratories. Sodium chloride, sodium bromide and sodium iodide were obtained from Baker Chemicals Company.

Propylene oxide was obtained from the Aldrich Chemical Company.

1-Oxaspiro (2,5) octane was prepared by Mr. Bipinchandra T. Desai.[46]

1,2-Epoxy-2,3-dimethylbutane was prepared from 2,3-dimethyl-4-chloro-3-butanol by a modification of the method of Malinvoskii and Yudasiana.[47]

2,3-Dimethyl-4-Chloro-3-butanol:

Isopropylmagnessium bromide was prepared from 58 g. (2.4 mol.) magnessium in 85 ml. and 152.5 ml. (208 g., 1.7 mol) of isopropyl bromide in 400 ml. of ether. The preparation was carried out under nitrogen in a two-liter flask equipped with a reflux condenser, addition funnel, mechanical stirrer, thermometer and drying tube. The reaction began after 15 ml. of the isopropyl bromide solution had been added. The remainder of the isopropyl bromide was added at a rate sufficient to maintain reflux, requiring four hours. The reaction mixture was heated at reflux with

stirring for one hour, and then cooled to -5°C. A solution of 113 ml. (130 g., 1.4 mol) of freshly distilled chloroacetone, b.p. 119°C, was slowly added to the Grignard solution with stirring under nitrogen. The addition required three hours at -5°C, during which time the reaction mixture solidified to a pasty mass. The Grignard salt was decomposed with about 2 kg. of cracked ice in a three-liter beaker, after which the magnesium salts were dissolved by the slow addition of 300 ml. of cold 15% sulfuric acid. The excess magnesium was separated by decantation. The ether layer was separated and the aqueous layer was extracted with four 150 ml. portions of ether. The ether layers were combined, washed with 700 ml. of 5% sodium carbonate. The ether was removed by distillation on a steam bath and the residue was subjected to steam distillation. The steam distillation was used at this point because it had been observed that the crude product contained a high-boiling residue. Attempts to distill the product directly before prior steam distillation resulted in overheating, with the formation of hydrogen chloride and degradation of the product. The steam distillate (51 g.) was separated from water, dried with anhydrous sodium carbonate and distilled under vacuum. A total yield of 30 g. (15.7%) of product was obtained in two fractions: 10.6 g., b.p. 57-61° C (12 mm.), and 19.4 g., b.p. 61-66° C (12 mm). Lit:[47] 45-46°C (3-5 mm.). The infrared spectra of the two fractions were identical, and showed the hydrogen-bonded O-H strech at 3500 cm!

1,2-Epoxy-2,3-dimethylbutane

Pulverized potassium hydroxide (200 g.) was placed in a 500 ml.

flask equipped with a nitrogen inlet, mechanical stirrer, addition funnel, reflux condenser and drying tube. A solution of 30 g. (0.22 mol) of 2,3-dimethyl-4-chloro-3-butanol in 90 ml. of ether was added slowly over a period of one hour with stirring, and the salts were removed by filtration. The ether was removed by distillation through a short column and the crude product (9.5 g.) was distilled under vacuum, b.p. 30-42°C (65-70 mm). This product was redistilled at atmospheric pressure. After a forerum b.p. 80-96°C, 4.0 g. (18%) of the epoxide was obtained. b.p. 96-99°C. Lit:[47] 50-52°C. (70 mm.). The nmr spectrum gave the following peaks: $\delta^{CCl_4}_{TMS}$ 2.47 (d, 1Hm1-CH_2), 2.36 (d, 1H, 1-CH_2), 1.34 (m, 1H, 3-CH), 1.18 (S, 3H, 2-CH_3), 0.97 (d, 3H, 3-CH_3), 0.91 (d, 3H, 3-CH_3).

Preparation of Solutions

Standard solutions of sodium halides and of epoxides were prepared by weighing the solute on an analytical balance and diluting in a volumetric flask. Aliquots were further diluted by the use of volumetric pipettes and volumetric flasks.

All glassware used in the preparation and reaction of solutions was cleaned by concentrated sulfuric acid, then with concentrated ammonium hydroxide, then with water, then with distilled water, methanol and finally rinsed with the reaction solutions.

Standard solutions of sodium methoxide in methanol were prepared by dissolving about 0.07 gm. of sodium methoxide in methanol and diluting to 250 ml with methanol in a volumetric flask. The concentration

was determined by titration against 0.0107 N aqueous HCl with a bromophenol blue indicator. The stock solution of 1.2×10^{-2} mole/liter concentration was used for further dilutions.

Measurements of Concentration:

Measurements of optical density in the 300-500 nm region were carried out with a carey 14 spectrophotometer using matched 1 cm. quartz cells maintained at $25 \pm 0.1^{\circ}C$ by means of a Haake circulating bath. The concentration of methoxide ion produced in the ring-opening reaction was measured indirectly by means of its equilibrium with p-nitrophenol to produce p-nitrophenoxide ion (Equ. 7.)

$$p\text{-}NO_2\text{-}C_6H_4\text{-}OH + CH_3O^- \rightleftharpoons p\text{-}NO_2\text{-}C_6H_4\text{-}O^- + CH_3OH \qquad (7)$$

p-Nitrophenol in water is reported to have a single absorption band in the 300-500 nm region with λmax 317.5 and εmax 10,000.[48] The p-nitrophenoxide ion in 1N aqueous sodium hydroxide is reported to have an absorption band at λmax 402.5 nm with εmax 19,200. In the present work, p-nitrophenol in methanol was found to have a single absorption band with λmax 320 nm and εmax 10,800 (Fig. 1). Mixtures of sodium methoxide and p-nitrophenol in methanol gave p-nitrophenol peak at 320 nm and a p-nitrophenoxide ion peak at 390 nm. In a solution of 1×10^{-4} M p-nitrophenol and 0.9×10^{-4} M sodium methoxide the 320 and 390 nm peaks showed absorbance of 0.845 and 0.586, respectively. In a solution of 1×10^{-4} M p-nitrophenol

alone, the single 320 nm peak showed an absorbance of 1.095.

No attempt was made to evaluate to the equilibrium constant of reaction (7) or the extinction coefficient of the p-nitrophenoxide band at 390 nm. However, it was found that the absorbance at 390 nm was linearly related to the concentration of methoxide ion added initially, within the range of 0 to 9×10^{-5} M methoxide ion (Fig. 2). The linear plot had a slope of 6100 (least squares) and an intercept of 0.025 absorbance units, owing to the residual absorbance of p-nitrophenol at 390 nm.

In unknown solutions the concentration of methoxide ion was calculated by equation (8),

$$[CH_3O^-] = \frac{A-0.025}{6100} \qquad (8)$$

where A is absorbance. The value of 0.025 for the absorbance of p-nitrophenol at 390 nm. was found to remain constant within experimental error over the concentration range represented by absorbance between 0.845 and 1.095 at 320 nm. The sum of p-nitrophenol and p-nitrophenoxide concentration in all known and unknown solutions was 1.00×10^{-4} M.

Kinetics and Equilibrium Measurements:

The reactions of epoxides and sodium halides were carried out in stoppered test tubes or unfilled 10 ml. volumetric flasks in a water bath thermostatted at 25 $\pm$ 0.1 °C. Standard solutions of the epoxide in methanol and standard solutions of sodium halide in methanol were added to the reaction tube from 10 ml. burettes. It was established independently through the use of volumetric flasks that there was no measurable volume

change caused by mixing the two solutions. The solutions were mixed and left for the requisite time. The reaction mixture was then washed into a volumetric flask containing sufficient 1×10^{-3} M p-nitrophenol in methanol to give a final concentration of 1×10^{-4} M (or the p-nitrophenol solution was added to the volumetric flask already containing the reaction mixture), and the solution was diluted to the mark with methanol. The absorbance was then read at 390 nm on the final solution.

The final dilution with methanol and p-nitrophenol, and the measurement of absorbance, were carried out rapidly. The elapsed time between the removal of the reaction mixture and the measurement of absorbance was never more than three minutes. It was shown that the presence of p-nitrophenol disturbs the epoxide-halohydrin equilibrium and permits the ring-opening reaction to go further. However, this further reaction was very slow in diluted solution. There was no measurable change in absorbance over a period of at least fifteen minutes in the presence of p-nitrophenol, whether the reaction mixture used was taken before or after the establishment of equilibrium.

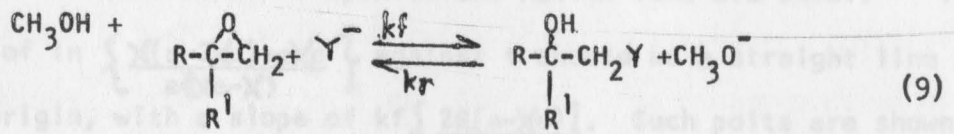
The concentration of methoxide ion in the diluted solution was calculated from equation (8), and the concentration of methoxide ion in the original reaction mixture was calculated from the dilution factor.

In a typical case, 5.00 ml. of 1.00×10^{-2} M sodium bromide and 5.00 ml of 1.00×10^{-2} M propylene oxide were mixed to give 10.00 ml of a solution 5.00×10^{-3} M in each. After 152 hours at $25 \pm 0.1^{\circ}$C., to establish equilibrium, 2.5 ml of 1×10^{-3} M p-nitrophenol were added and the solution was diluted to 25 ml. The absorbance was 0.405 and the concen-

tration of methoxide ion in the original reaction mixture was calculated to be 1.56×10^{-4} M, indicating that the reaction had gone to 3.12% completion at equilibrium. Higher initial concentrations were used for the other epoxides because of the smaller value of the equilibrium constant.

Calculations:

For an epoxide ring-opening reaction:



(9)

Where Y^- is halide ion, let a be the initial concentration of epoxide, b be the initial concentration of halide ion, and x the concentration of methoxide ion (equal to the concentration of halohydrin) at any arbitary time . The concentration of methoxide ion at equilibrium will be designated X_e. The equilibrium constant may be calculated by equation (10). If the initial concentration

$$K = \frac{X_e^2}{(a-Xe)(b-Xe)} \qquad (10)$$

of epoxide and halide ion are equal, the equilibrium constant may be calculated by equation (11).

$$K = \frac{X_e^2}{(a-Xe)^2} \qquad (11)$$

The second-order rate of the forward reaction in equation (9) may be calculated from equation (12),

$$\ln \left\{ \frac{X(a-2Xe)+aXe}{a(Xe-X)} \right\} = kf \left\{ \frac{2a(a-Xe)}{Xe} \right\} t \qquad (12)$$

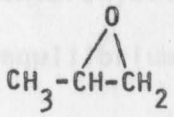
which is applicable for second order reversible reaction providing the initial concentration of epoxide and halide ions are equal.[49] Thus a plot of $\ln \left\{ \frac{X(a-2Xe)+aXe}{a(Xe-X)} \right\}$ against t should be a straight line through the origin, with a slope of $kf\left\{ \frac{2a(a-Xe)}{Xe} \right\}$. Such polts are shown in figure [5,6,8,11,12] for propylene oxide.

CHAPTER IV

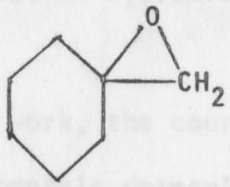
RESULTS AND DISCUSSION

A number of workers in the past have sought quantitative information on the stabilization of cyclic compounds by gem-dialkyl groups. (See Historical section). With a few exceptions, past studies have been concerned primarily with the rates of ring-opening or ring-closing reactions, rather than with equilibrium. The interpretation of results, then, has rested on assumptions concerning the nature of the transition state. Also, most studies in the past have been concerned with five- and six-membered rings, with the exception of the work of Searles[8] on the hydrogen bonding of oxetanes, which required assumptions concerning the relationship of base strength to the c-o-c bond angle. Rotational explanations of the gem-dialkyl effect, Similar to those described by Allinger[13] are important for both intermediate and large rings, but the bond angle contractions proposed in Thorpe-Ingold hypothesis[1-7] should be much more important to the stabilization of small rings than to the stabilization of larger rings.

In the present work, we have sought to obtain quantitative information on the equilibrium between three-membered rings and open chain compounds. The reaction chosen for this purpose was the bimolecular ring opening of terminal epoxides by halide ions in methanol solution. The three epoxides studied were propylene oxide (I), 1-oxaspiro-[2,5] octane (II) and 1,2-epoxy-2,3-dimethylbutane (III).



(I)



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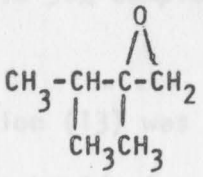
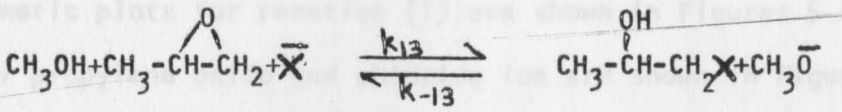


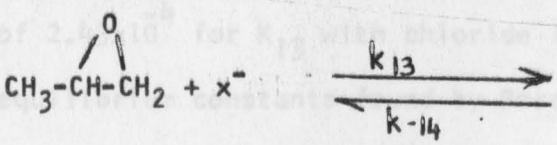
(III)

Propylene oxide reacts with halide ions according to reaction (13). It is assumed that

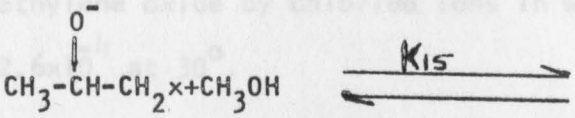


(13)

where x=Cl, Br or I, the "normal" product shown is formed almost exclusively, as would be expected from the result of Porret[42] with propylene oxide in water. Reaction (13) is relatively slow in methanol and consists of a slow bimolecular ring opening reaction (14) followed by a rapid proton transfer from the solvent (reaction (15).[26]



(14)



(15)

Reaction (13) is a reversible reaction but the equilibrium lies well to the left at a concentration of 0.005 M propylene oxide and 0.005 M sodium bromide in methanol. In the present work, reaction (13) proceeded to about 3.2% completion at equilibrium and 25°C. This is in substantial agreement with the report of Porret[49] that the ring closure of ethylene

chlorohydrin in aqueous sodium hydroxide proceeds to 98% completion at equilibrium and 20°C.

In the present work, the course of reaction (13) was followed at 25°C by a spectrophotometric determination of methoxide ion as described in the experimental section. For propylene oxide and bromide ion, the results are shown in Figures 3 and 4. The concentration of methoxide ion increased with increasing time at 25°, and reached equilibrium at 152 hours. Kinetic plots for reaction (13)are shown in Figures 5 and 6. The results for propylene oxide and chloride ion are shown in Figures 7 and 8 and the results for propylene oxide and iodide ion are shown in Figures 9-12.

The equilibrium constant, K_{13} for reaction 13 is shown in Table I for X=Cl, Br and I. The equilibrium constants did not change greatly with different halide ions. They were in the approximate ratio of 1:4:8 for chloride, bromide and iodide ions respectively. The value of 2.43×10^{-4} for K_{13} with chloride ion at 25°C may be compared with the equilibrium constants found by Porret[49] for the ring opening reaction of ethylene oxide by chloride ions in water. These were 3.3×10^{-4} at 20° and 2.6×10^{-4} at 30°.

The rate constants k_{13}, for the forward reaction (13) are also shown in Table I. They were in the approximate ratio of 1:10:100 for chloride, bromide and iodide ions respectively. This order of rate constants is as expected for the relative nucleophilicity of halide ions.

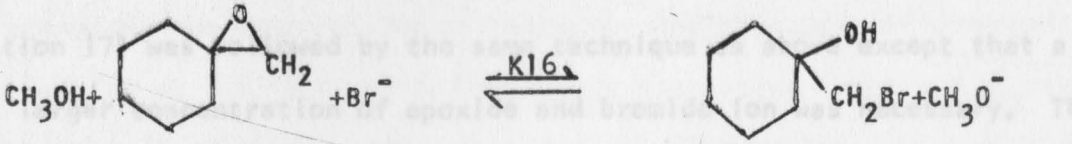
TABLE I

Reaction of Propylene Oxide (I) with Sodium Halide in Methanol. Kinetic and Equilibrium data.

Halide	Conc. of Halide $mol.\ liter^{-1}$	Conc. of Epoxide $mol.\ liter^{-1}$	Equilibrium constant K_{13}	ΔG° kcal/mole	k_{13} $mol.^{-1}\ liter.\ sec.^{-1}$	k_{-13} $mol.^{-1}\ liter.\ sec.^{-1}$
NaCl	1.6×10^{-2}	1.6×10^{-2}	2.43×10^{-4}	4.93	2.28×10^{-6}	9.38×10^{-3}
NaBr	5×10^{-3}	5×10^{-3}	$1.00\pm0.08\times10^{-3}$	4.09	2.49×10^{-5}	2.49×10^{-2}
	5×10^{-3}	5×10^{-3}			2.17×10^{-5}	2.17×10^{-2}
NaI	5×10^{-3}	5×10^{-3}	2.752×10^{-3}	3.50	2.53×10^{-5}	9.19×10^{-2}
	5×10^{-3}	5×10^{-3}	1.660×10^{-3}	3.79	1.95×10^{-4}	11.74×10^{-2}

The rate constants, k-13, for the reverse reaction (13) are also shown in Table 1. They were not measured directly, but were calculated from the relation $K_{13}=k13/k\text{-}13$. The value of k-13 for chloride ion at 25°, 9.38×10^{-3}, represents the second-order rate constant for the ring closure of propylenechlorohydrin by methoxide ion in methanol. This may be compared with the value of 3.75×10^{-4} found by Stevens, McCabe and Warner[45] for the ring closure of ethylene chlorohydrin by methoxide ion at 30° in methanol.

The reaction of 1-oxaspiro [2,5] octane (II) with bromide ion (Reaction 16) was followed by the same spectrophotometric technique used to follow reaction (13).



(II) (IV) (16)

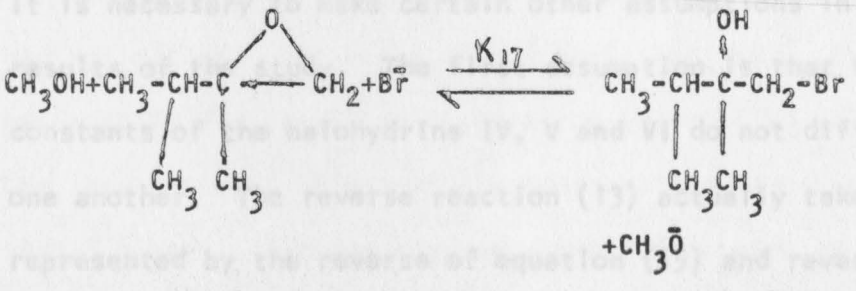
It is assumed that the "normal" product, 1-(bromoethyl) cyclohexanol (IV) was formed exclusively since a direct bimolecular displacement should be very slow at a tertiary carbon atom. The results are shown in Figures 13 and 14. The equilibrium constant was much smaller for reaction (16) than for reaction 13, and therefore it was necessary to start with much larger concentrations of epoxide and bromide ion. For this reason, the rate of appearance of methoxide ion was too large to measure conveniently, and no attempt was made to evaluate the rate for reaction (16). The equilibrium constant for reaction (16) is given in Table II.

TABLE II

Reaction of 1-oxaspiro [2,5] octane with sodium bromide in methanol. Equilibrium data.

Conc. of NaBr $mol.\ liter^{-1}$	Conc. of epoxide $mol.\ liter^{-1}$	Equilibrium constant K	ΔG° kcal/mole
2.5×10^{-1}	2.5×10^{-1}	3.79×10^{-5}	6.03
4.75×10^{-1}	2.5×10^{-1}	3.23×10^{-5}	6.12

The reaction of 1,2-epoxy-2,3-dimethylbutane (III) with bromide ion (Reaction 17) was followed by the same technique as above except that a still larger concentration of epoxide and bromide ion was necessary. The product 1-bromo-2,3-dimethyl-2-butanol was assumed to be formed exclusively, because direct bimolecular displacement at a tertiary carbon atom should be very slow.



(17)

(III) (VI)

The results are given in figures 15 and 16, and the equilibrium constant is given in Table III.

TABLE III

Reaction of 1,2-Epoxy-2,3-dimethylbutane with sodium bromide in methanol. Equilibrium data.

Conc. of NaBr mol. liter^{-1}	Conc. of epoxide mol. liter^{-1}	Equilibrium constant K	ΔG° kcal/mole
9×10^{-1}	9×10^{-1}	2.09×10^{-6}	7.74
5×10^{-1}	$4\times75\times10^{-5}$	2.39×10^{-6}	7.66

The results of this study provide further conformation of the gem-dialkyl effect on the stability of ring compounds. Tables I, II and III show standard free energies for the ring opening reactions of compounds I, II and III as 7.1, 6.1 and 7.7 kcal., respectively. Thus $\Delta\Delta G^{\circ}$, the change in the free energy of ring opening associated with a change of substituent on the epoxide ring from hydrogen is isopropyl, is about 3.6 kcal.

Since equilibrium rather than kinetic data were used, no assumptions regarding the nature of the transition state are necessary. However, it is necessary to make certain other assumptions in order to interpret the results of the study. The first assumption is that the acid dissociant constants of the halohydrins IV, V and VI do not differ appreciably from one another. The reverse reaction (13) actually takes place in two steps, represented by the reverse of equation (15) and reverse of equation (14). Therefore

$$k_{-13} = \frac{k_{-14}}{K_{15}} \qquad (18)$$

and

$$K_{13} = \frac{k_{13}}{k_{-13}} = \frac{k_{13}K_{15}}{k_{-14}} \qquad (19)$$

The equilibrium constant for reaction (15), of course, is inversely related to the acidity constant of the halohydrin (IV) in methanol by the relation:

$$K_{15} = Km/Kh \qquad (20)$$

Where Km is the self-dissociation constant of methanol and Kh is the acid dissociation constant of IV.

Similar arguments can be made for the halohydrins V and VI, and therefore it is necessary to assume that the acid dissociation constants of halohydrins are equal. This assumption may not be strictly correct, especially when comparing the secondary alcohol IV with the tertiary alcohol V and VI. It is generally accepted[50] that tertiary alcohols are weaker acids than secondary alcohols, and that secondary alcohols are weaker acids than primary alcohols. However, if the acid dissociation constant of the halohydrins V and VI were smaller than that of IV, then the equilibrium constants K_{16} and K_{17} should be greater than K_{15} (see equation (20), other factors being equal. Thus the effect of acid dissociation constants works in a direction opposite to the gem-dialkyl effect. The value of 3.6 kcal. for $\Delta\Delta G^{\circ}$ obtained by replacing hydrogen by isopropyl would represent the minimum value to be expected. The actual steric effect of the isopropyl group may be somewhat larger than 3.6 kcal. Similar arguments could be presented for reaction (13) with chloride, bromide and iodide ions, based on increasing acidity of the halohydrins with increasing electronegativity of the halogen atom. This

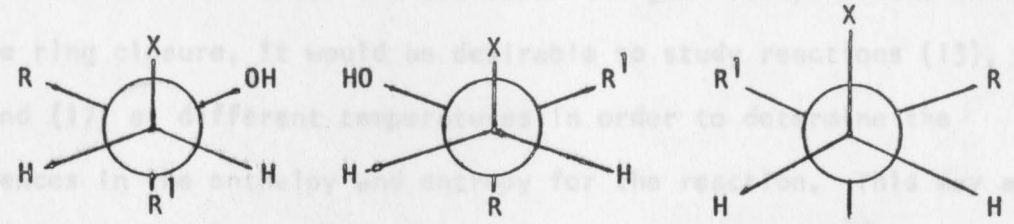
effect would also work in a direction opposite to that shown in Table I.

The second assumption which must be made in order to interpret the results of the study is that solvation of the reactants and products does not appreciably affect the relative equilibrium constants for the compound studied. This assumption is open to question. It cannot be stated positively how much of the differences between K_{13}, K_{16} and K_{17} could be caused by steric and polar effects on solvation. It is not clear in which direction this would affect the equilibrium constants. The effect be certainly important in reaction (13) with chloride, bromide and iodide ions, where the energy of solvation decreases with increasing ionic radius.[51] This would operate in the same direction as that shown in Table I.

There is a large change in c-c-o bond angle associated with closing the epoxide ring. Therefore, the gem-dialkyl effect in the present case may possibly arise from two causes. The first of these can be described as by the rotational argument developed by Allinger[13] and by Bruice.[20-24] The second of these is the original Thorpe-Ingold hypothesis[1-8] in which the steric effect of the alkyl substituents on the halohydrins would decrease the c-c-o bond angle.

It is clear that gem-dialkyl groups in open-chain compounds may decrease the population of conformers unprofitable for ring closure to five and six-membered rings. In the case of ring-closure to three-membered epoxide rings, this argument loses force. In this case, only the rotation around the 1 and 2 carbons has significance for ring closure. The three

staggered conformers for this rotation are shown in Newman projections VII, VIII and IX. Of these, only



VII VIII IX

the trans conformer IX can lead to ring closure. However, this is precisely the conformer which is most sterically hindered when the alkyl groups R and R^1 become larger, especially if the halogen atom is large. Consequently, the rotational argument would predict that gem-dialkyl groups would destabilize the epoxide ring with respect to ring opening by halide ions. This is contrary to experience with the gem-dialkyl effect (See Historical Section) and it is also contrary to the present results.

Although the present results disprove the rotational argument [13, 20-24] as applied to epoxide ring closure, they cannot be said to prove the Thorpe-Ingold hypothesis. Alternative explanations such as a steric inhibition to solvation of hydroxide group, may be put forward. The steric inhibition of the β-alkyl groups to the approach of a solvated halide ion must also be taken into account. Streitwieser[52] has tabulated the average reactivities of primary halides to direct displacement reactions. The relative reactivities were in the order ethyl, 1.0. n-propyl, 0.4., isobutyl, 0.03., and neopentyl, 10^{-5}. In order to determine how this affects

the equilibrium constants in Tables II and III, it would be necessary to measure the rates of ring opening.

In order to trace the course of the gem-dialkyl effect on epoxide ring closure, it would be desirable to study reactions (13), (16) and (17) at different temperatures in order to determine the differences in the enthalpy and entropy for the reaction. This may allow a decision concerning solvent effects. It would also be desirable to study other epoxides, particularly spiro-epoxides in which both rings are small. If the Thorpe-Ingold hypothesis is valid, then the epoxide ring should be destabilized by decreasing the size of the spiro ring, as was originally pointed out by Searles.[8] The techniques developed in this work for following the course of epoxide ring opening should make the above studies relatively easy.

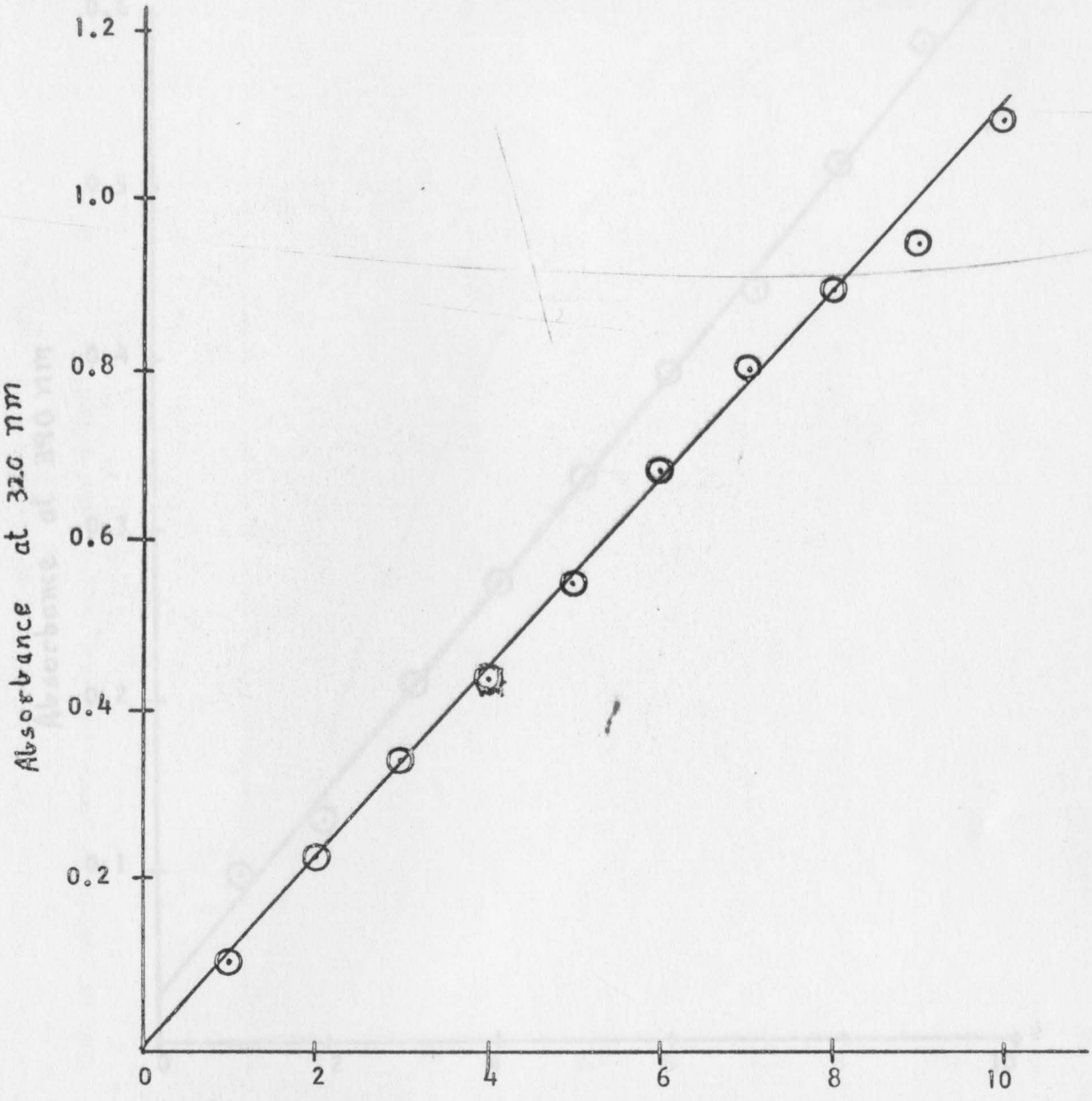


Fig. 1. Absorbance at 320 nm vs. concentration of p-nitrophenol in methanol.

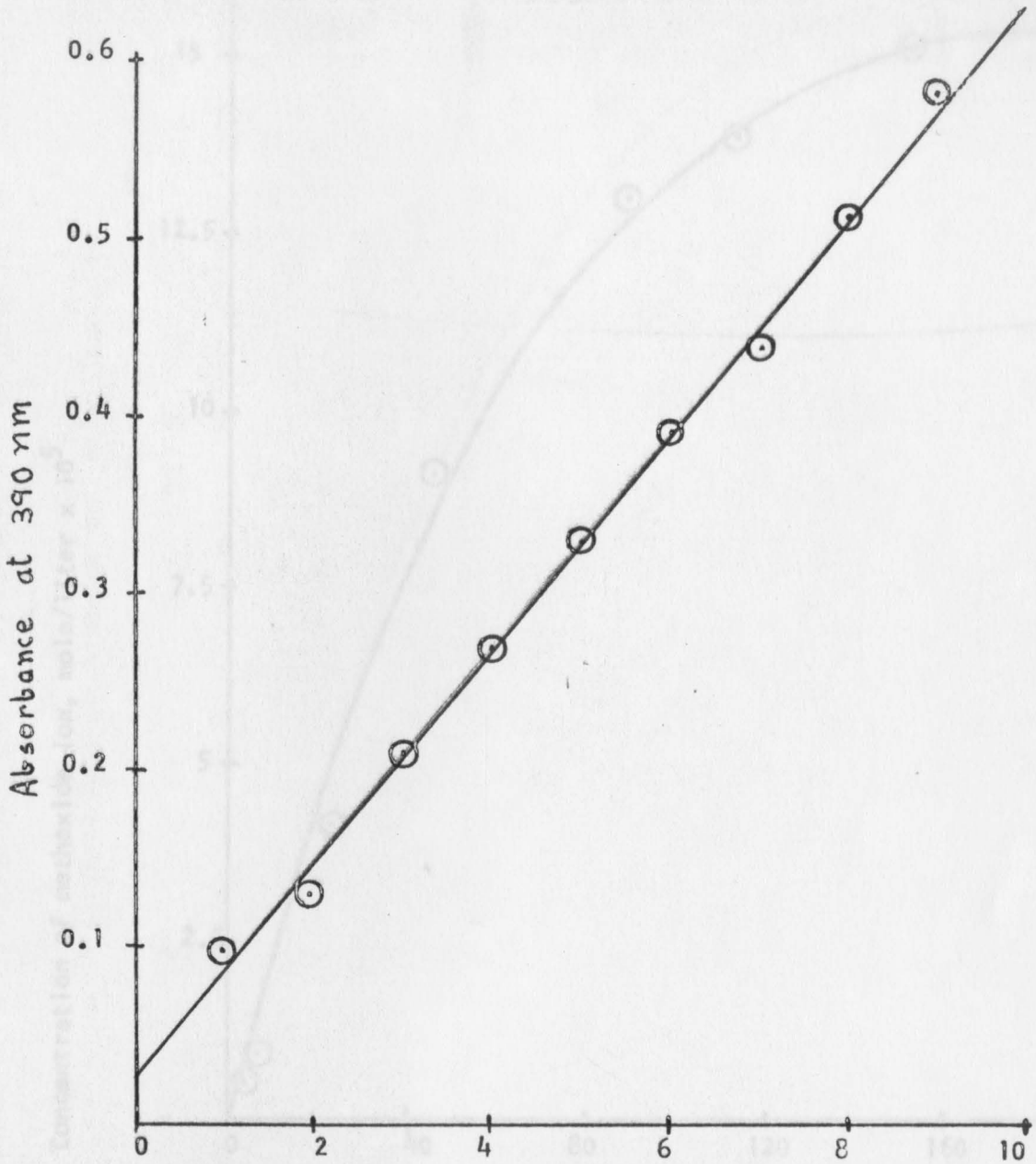


Fig. 2. Absorbance at 390 nm *vs.* concentration of sodium methoxide in methanol.

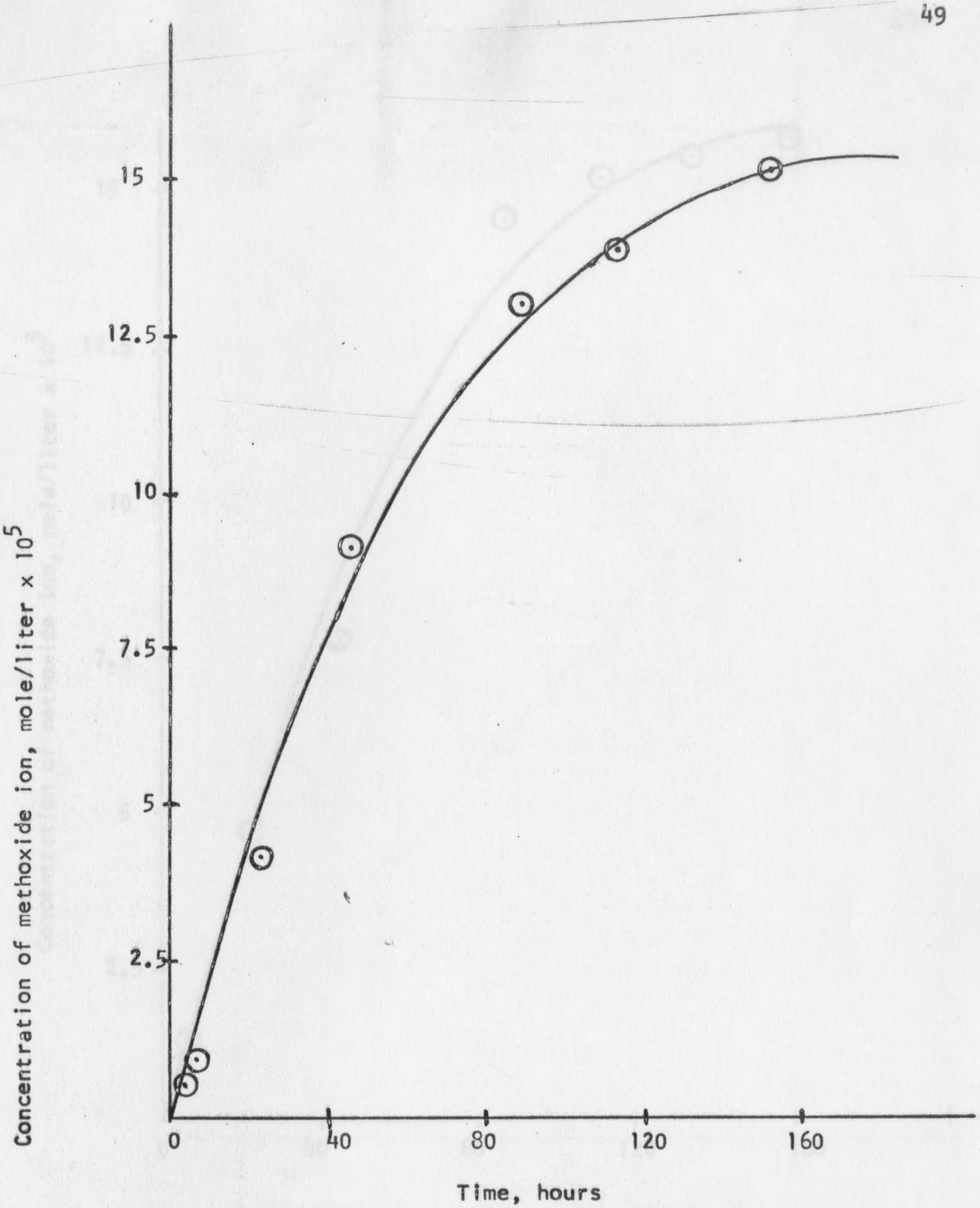


Fig. 3. Reaction of propylene oxide with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time.

(Run 1)

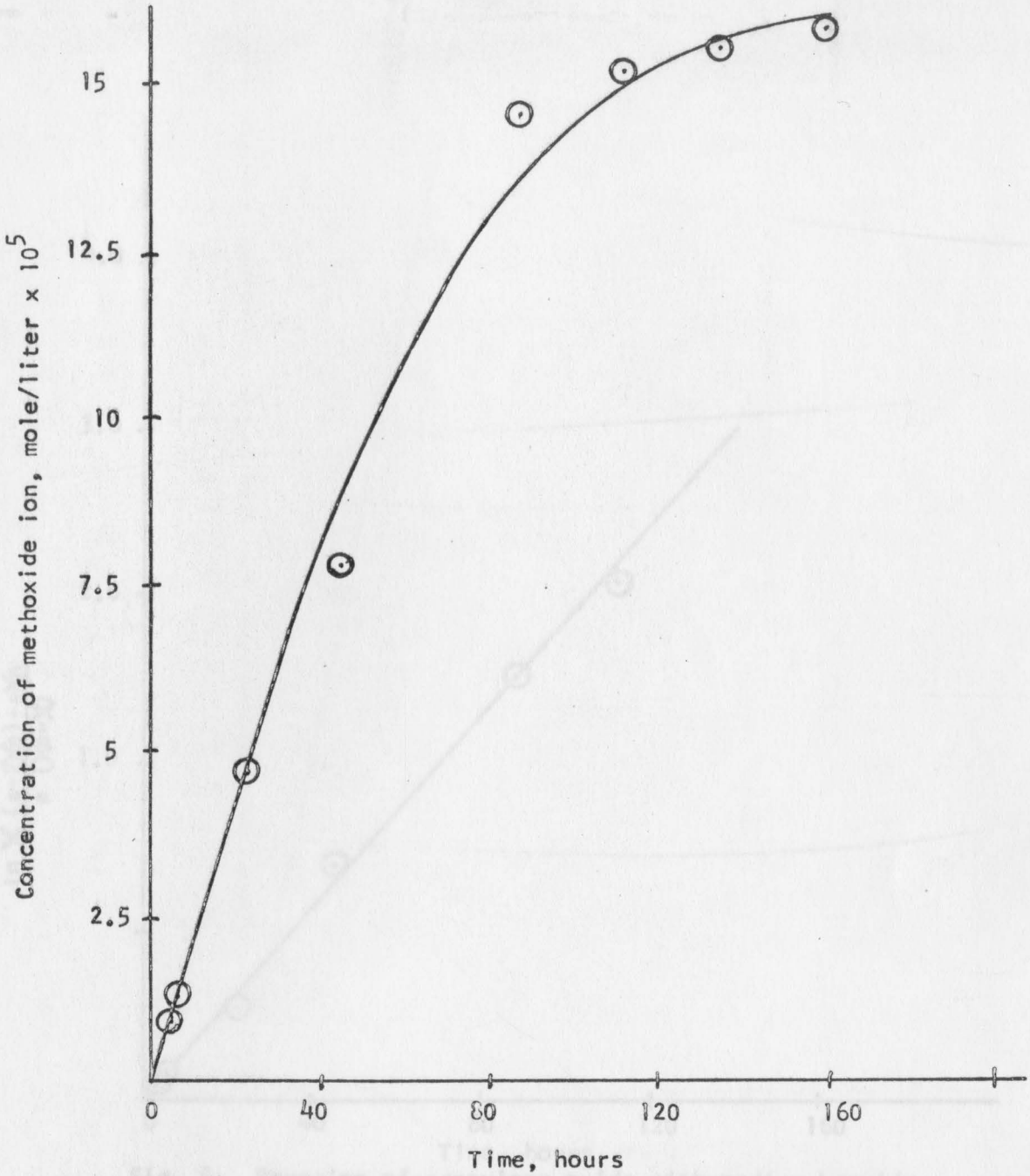


Fig. 4. Reaction of propylene oxide with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 2)

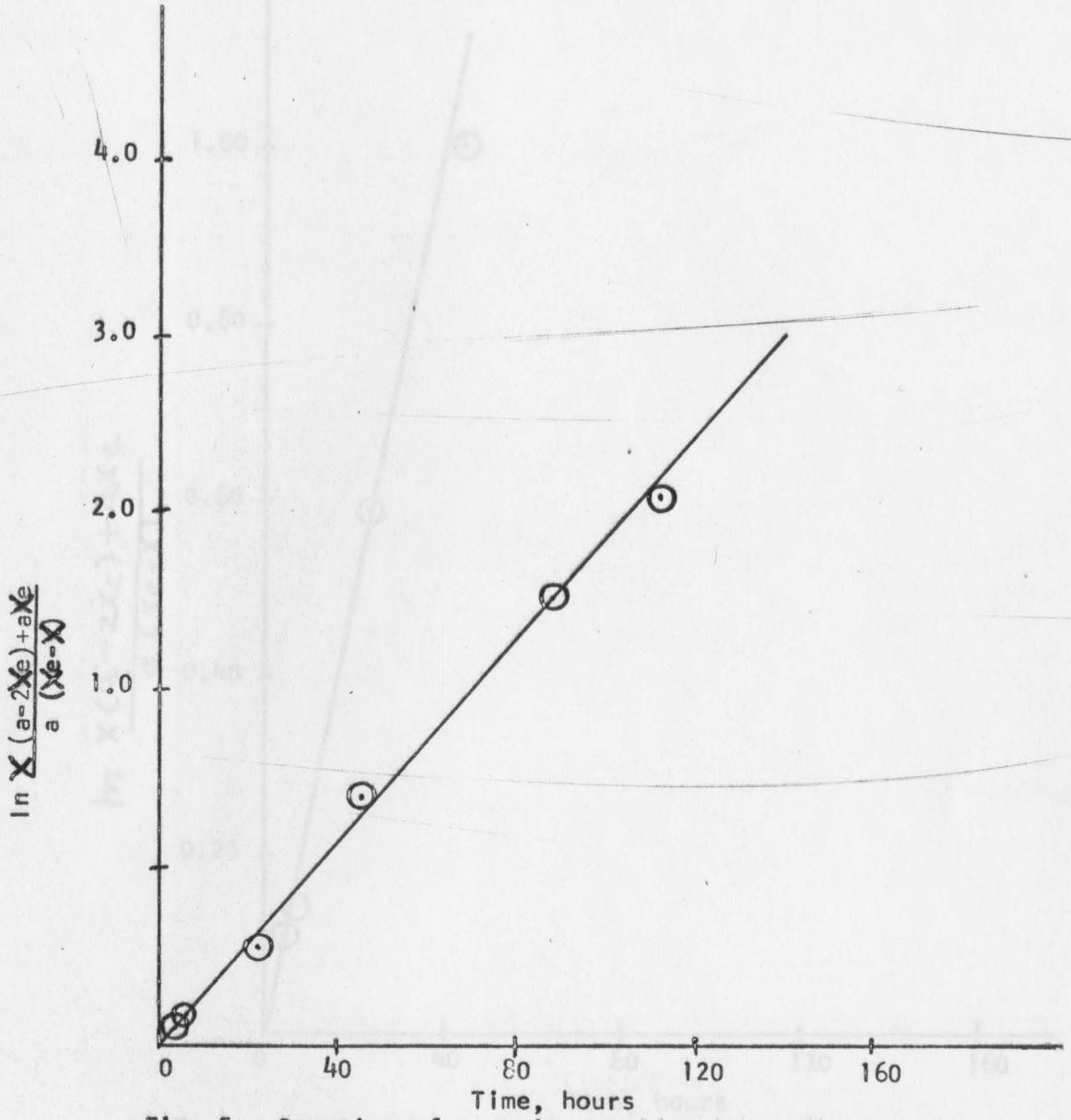


Fig. 5. Reaction of propylene oxide with sodium bromide in methanol at 25°C. Kinetic plot for second-order reversible reaction. (Run 1)

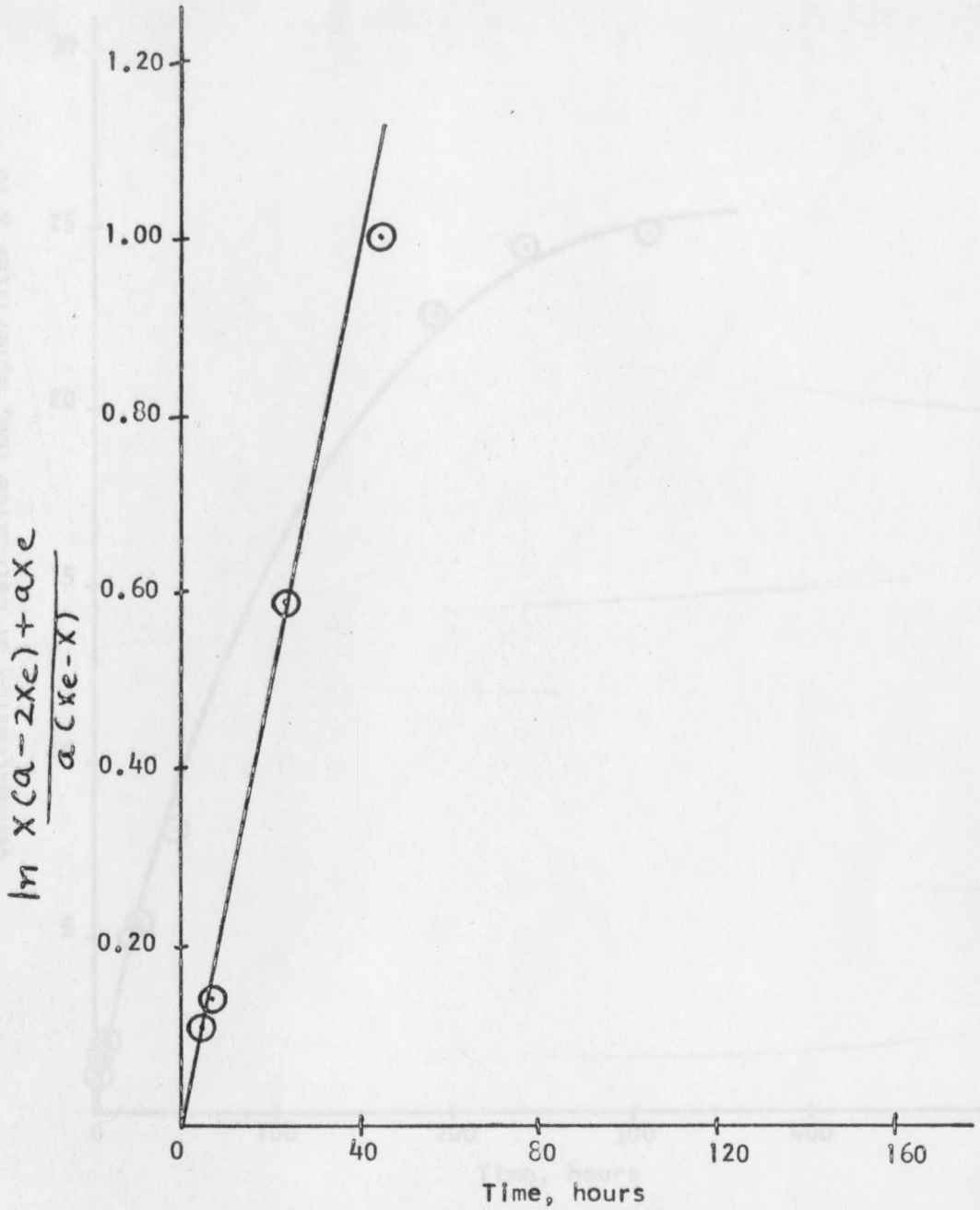


Fig. 6. Reaction of propylene oxide with sodium bromide in methanol at 25°C. Kinetic plot for second-order reversible reaction (Run 2).

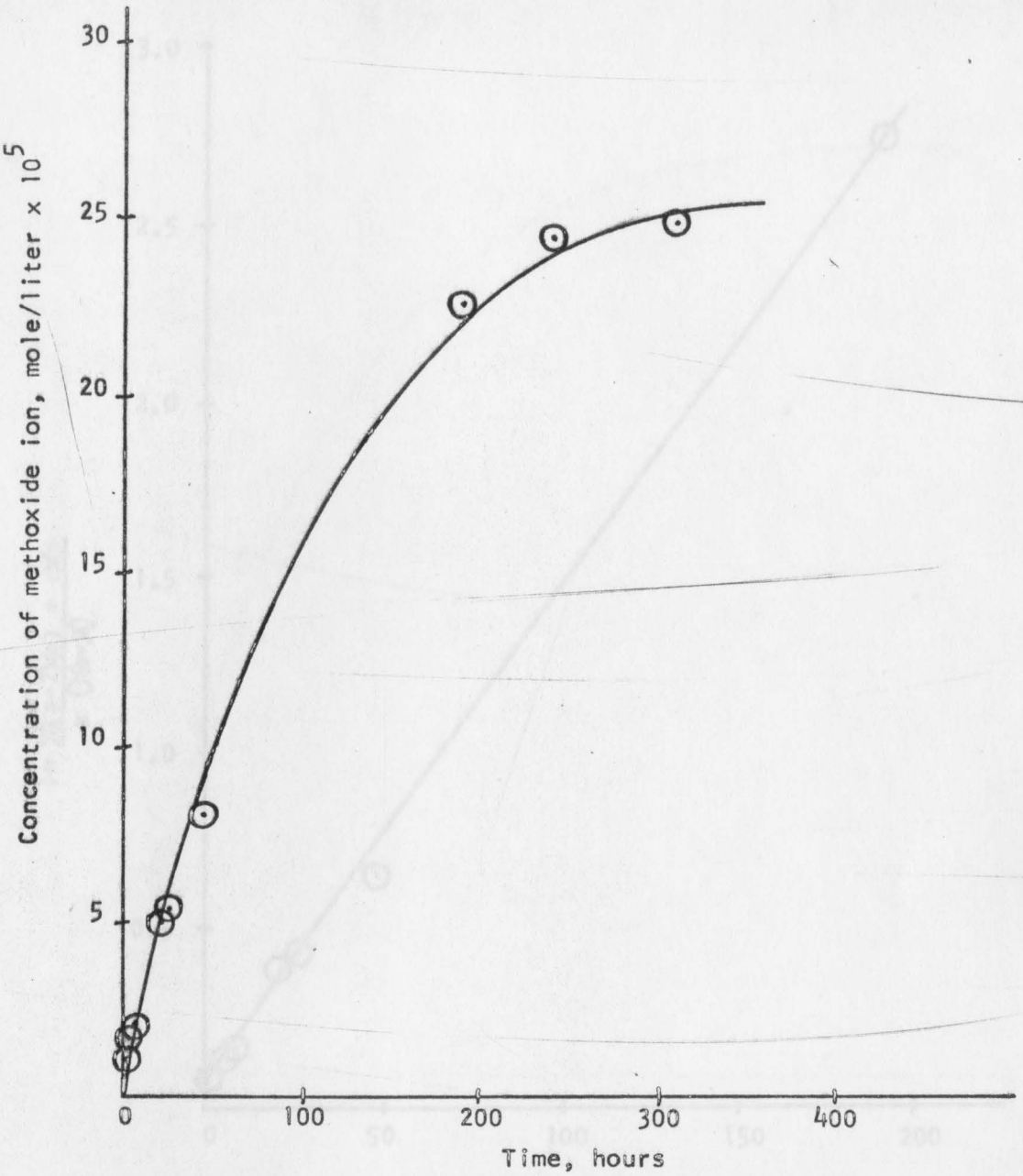


Fig. 7. Reaction of propylene oxide with sodium chloride in methanol at 25°C. Concentration of methoxide ion produce vs. time.

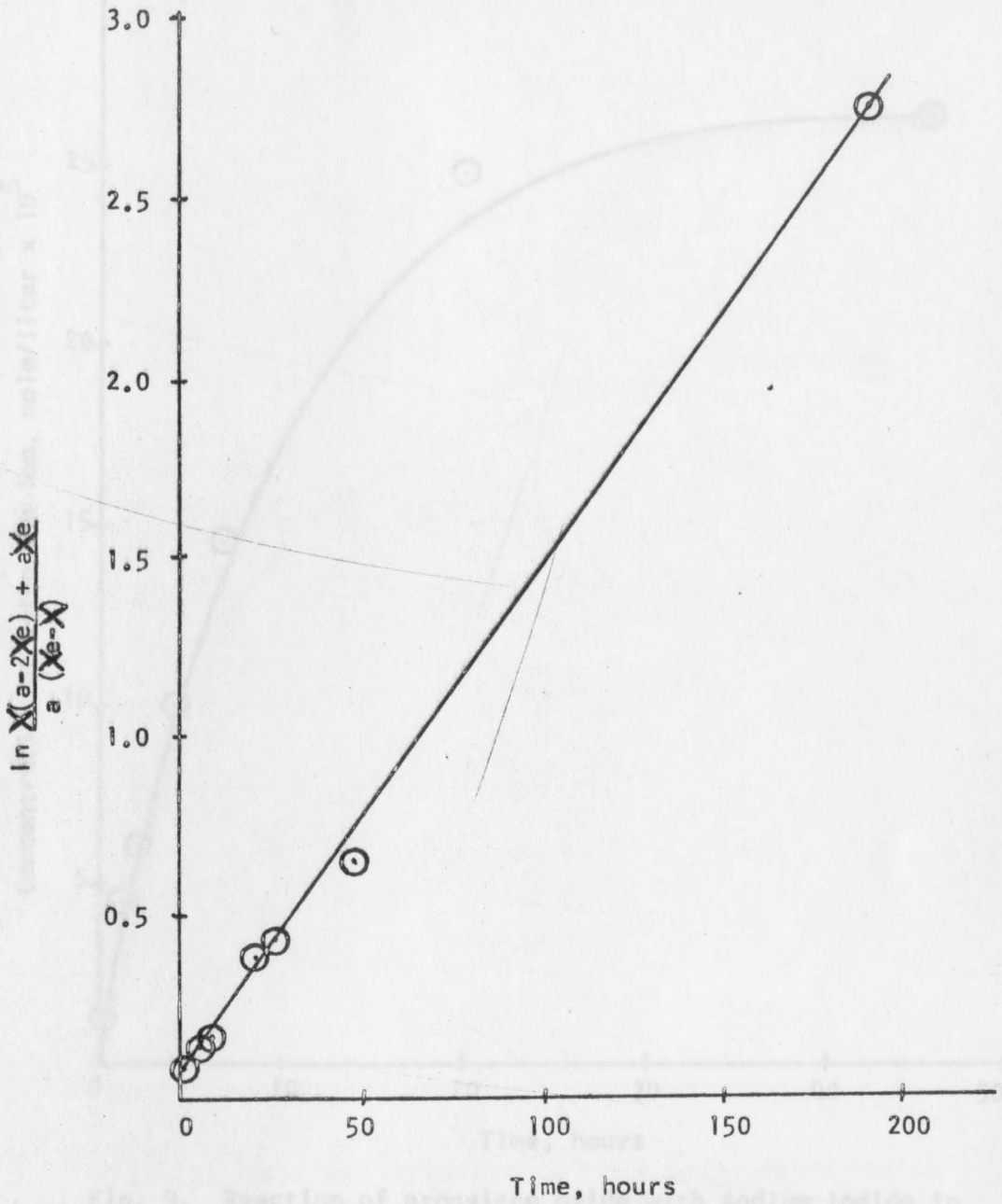


Fig. 8. Reaction of propylene oxide with sodium chloride in methanol at 25°C. Kinetic plot for second-order reversible reaction.

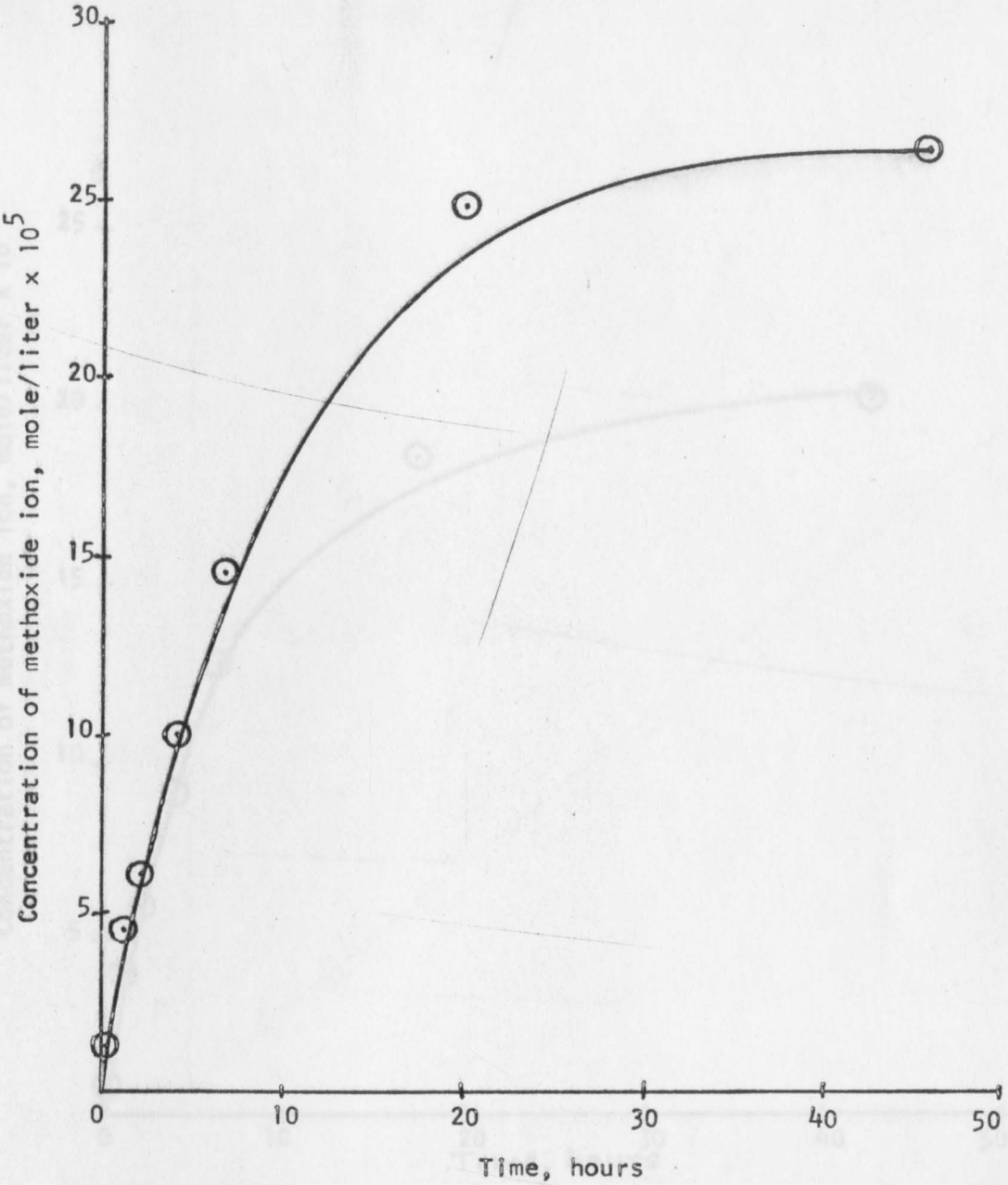


Fig. 9. Reaction of propylene oxide with sodium iodide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 1)

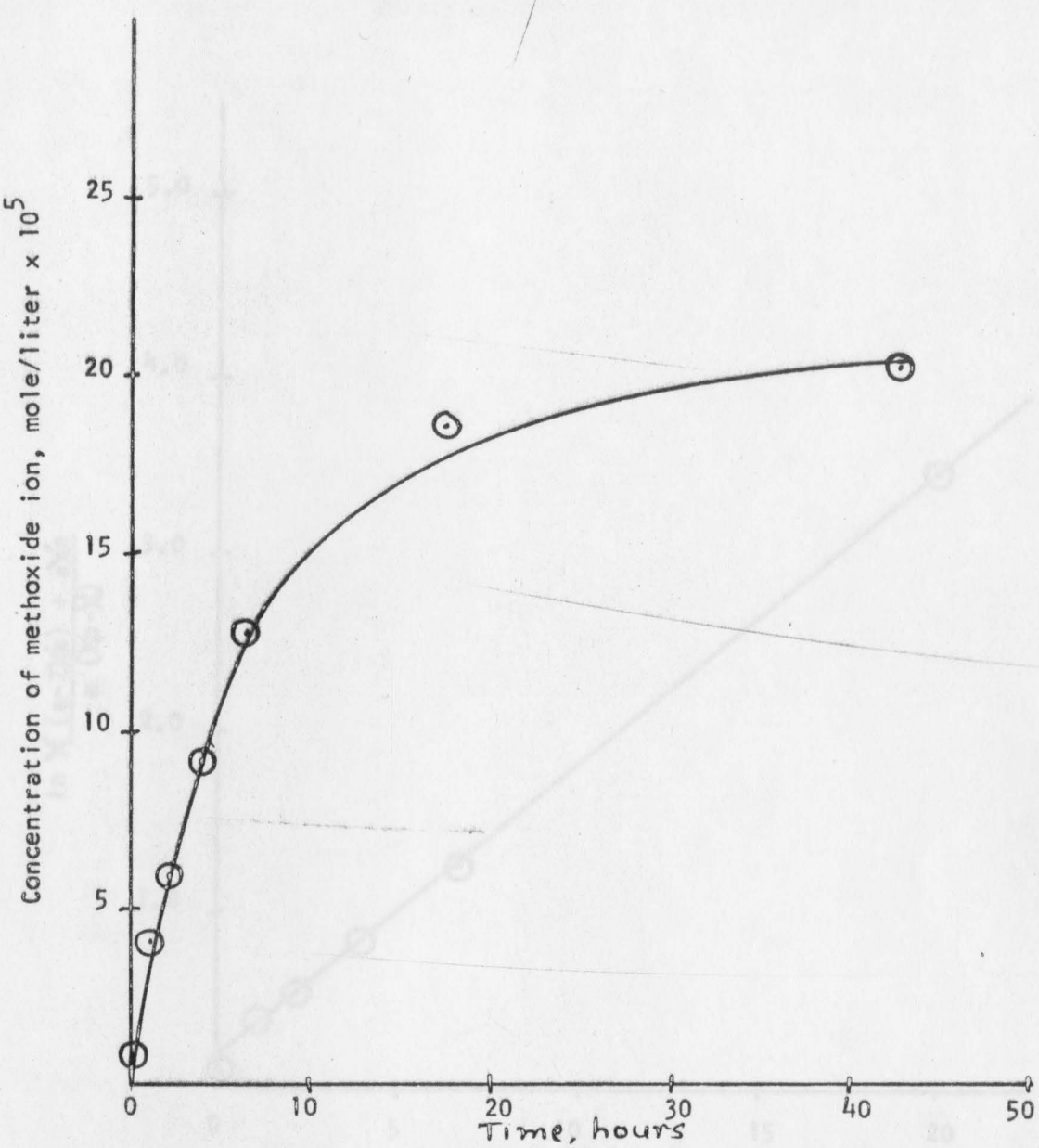


Fig. 10. Reaction of propylene oxide with sodium iodide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 2)

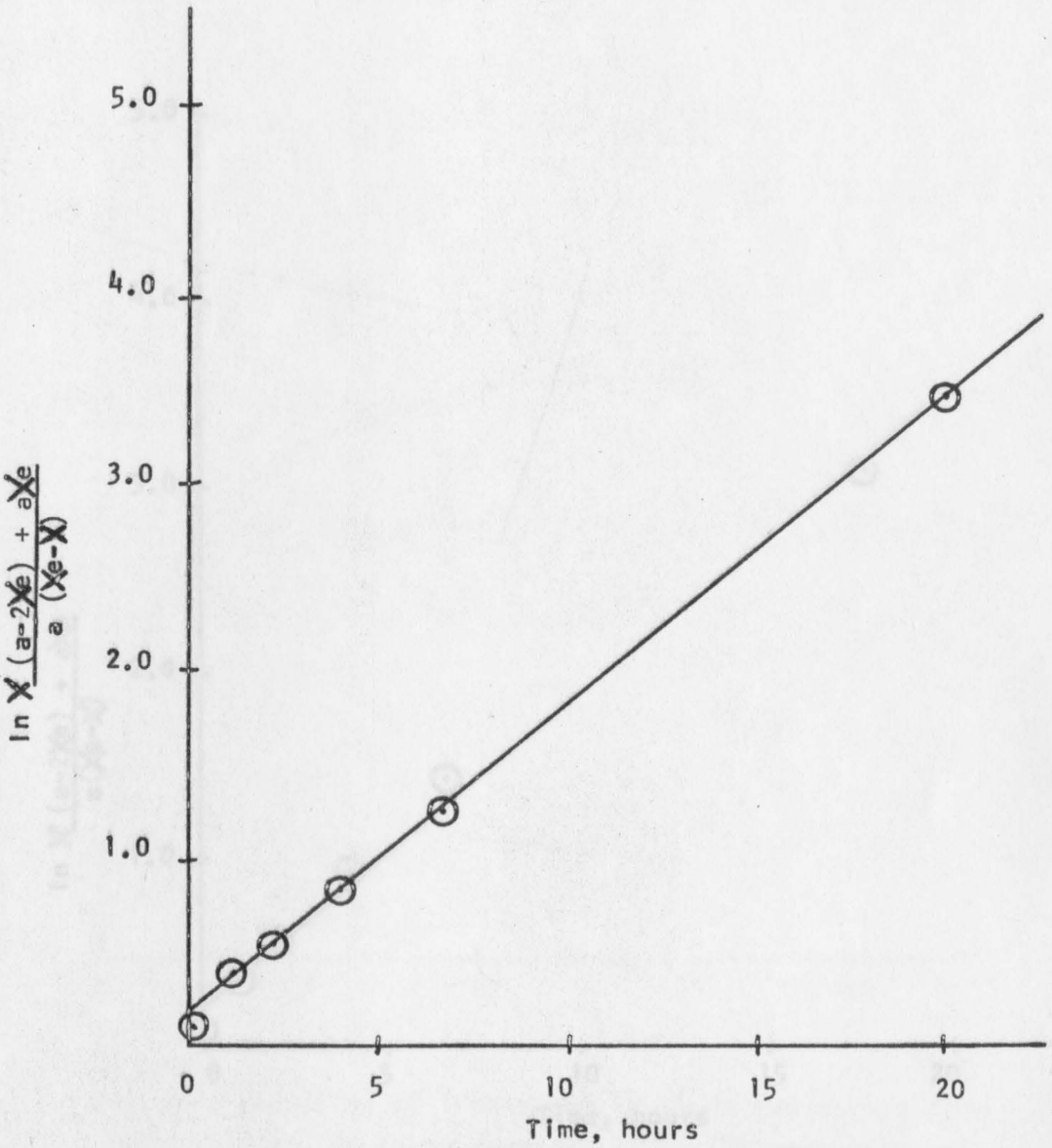


Fig. 11. Reaction of propylene oxide with sodium iodide in methanol at 25°C. Kinetic plot for second-order reversible reaction. (Run 1).

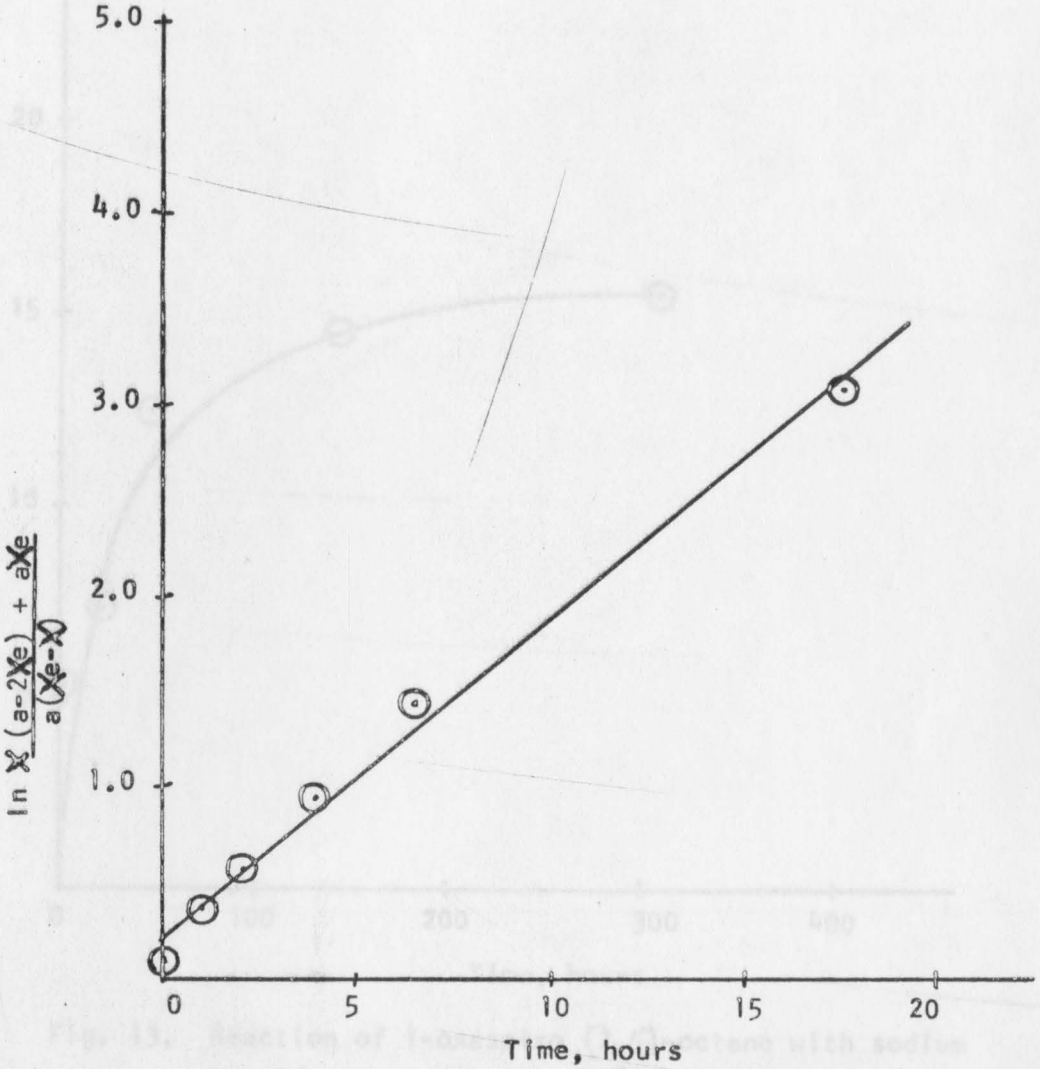


Fig. 12. Reaction of propylene oxide with sodium iodide in methanol at 25°C. Kinetic plot for second-order reversible reaction. (Run 2).

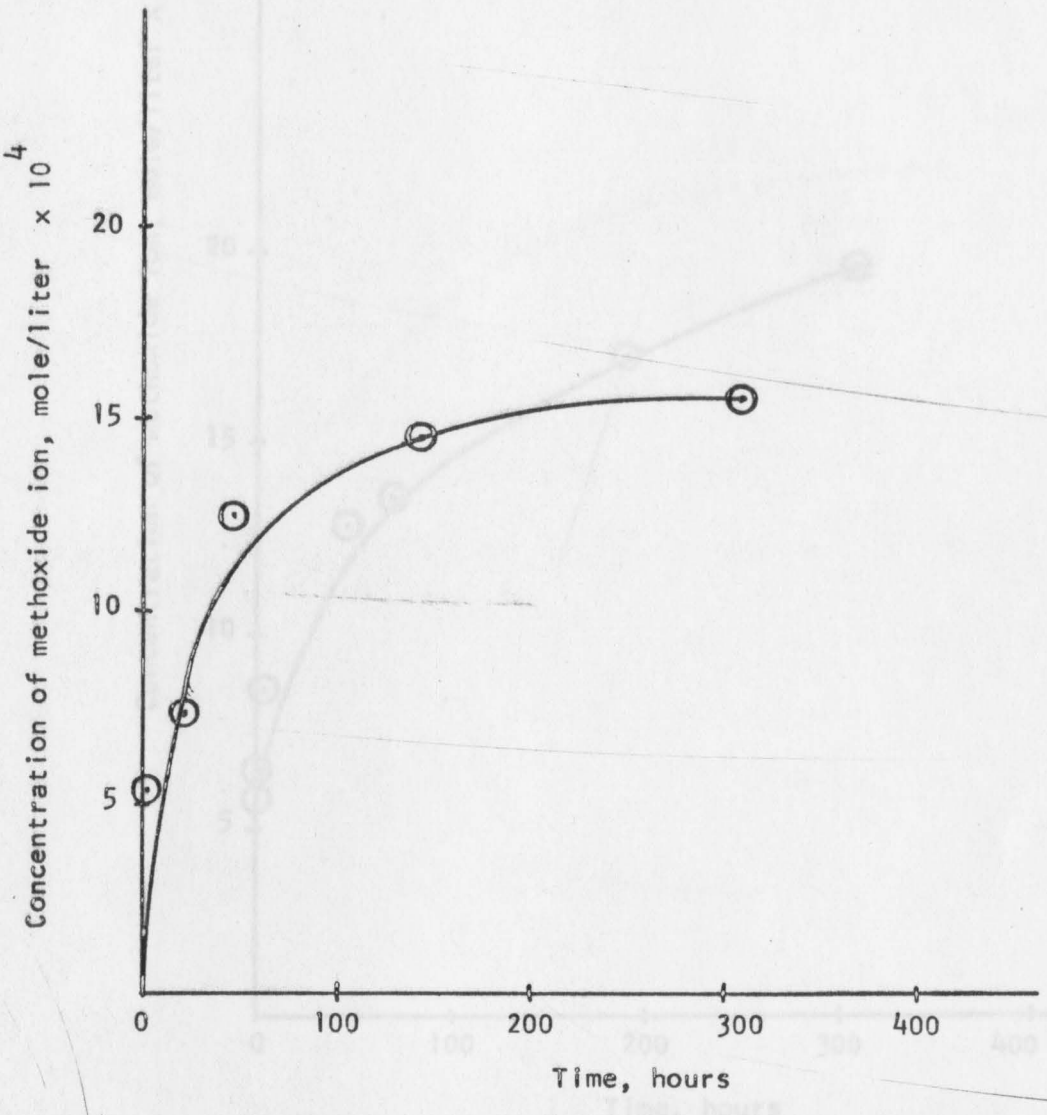


Fig. 13. Reaction of 1-oxaspiro [2,5]-octane with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 1.)

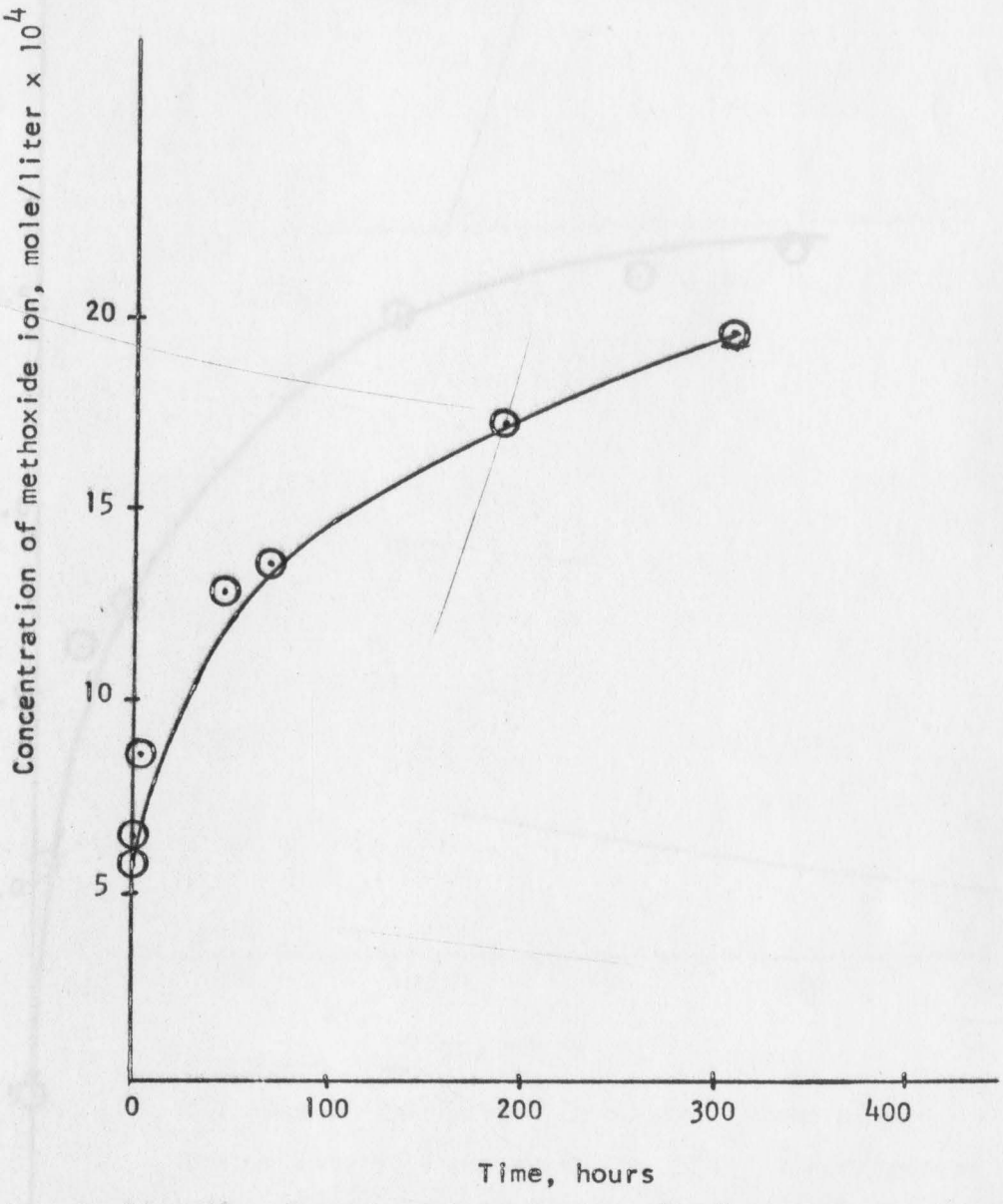


Fig. 14. Reaction of 1-oxaspiro [2,5]-octane with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 2).

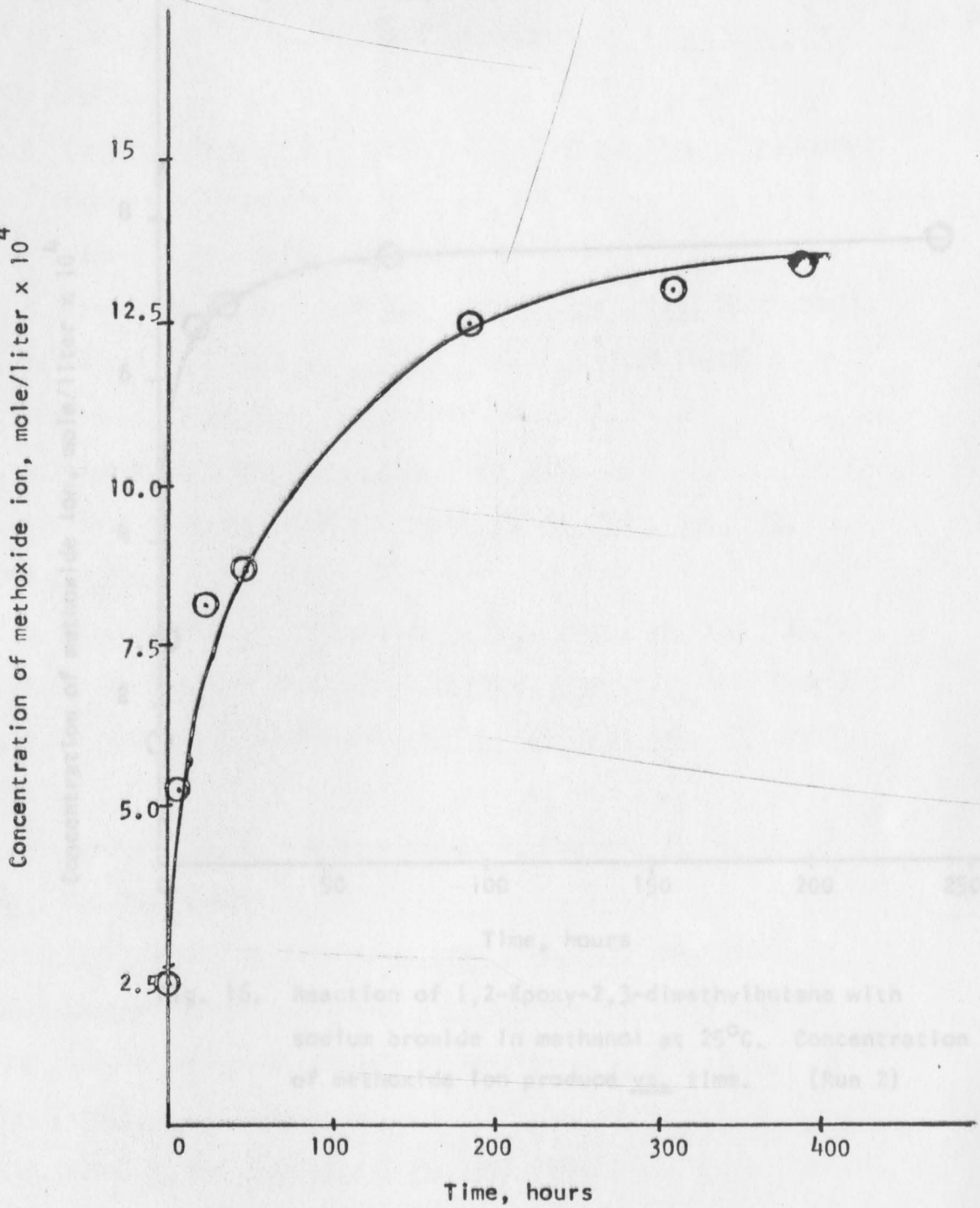


Fig. 15. Reaction of 1,2-Epoxy-2,3-dimethylbutane with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 1).

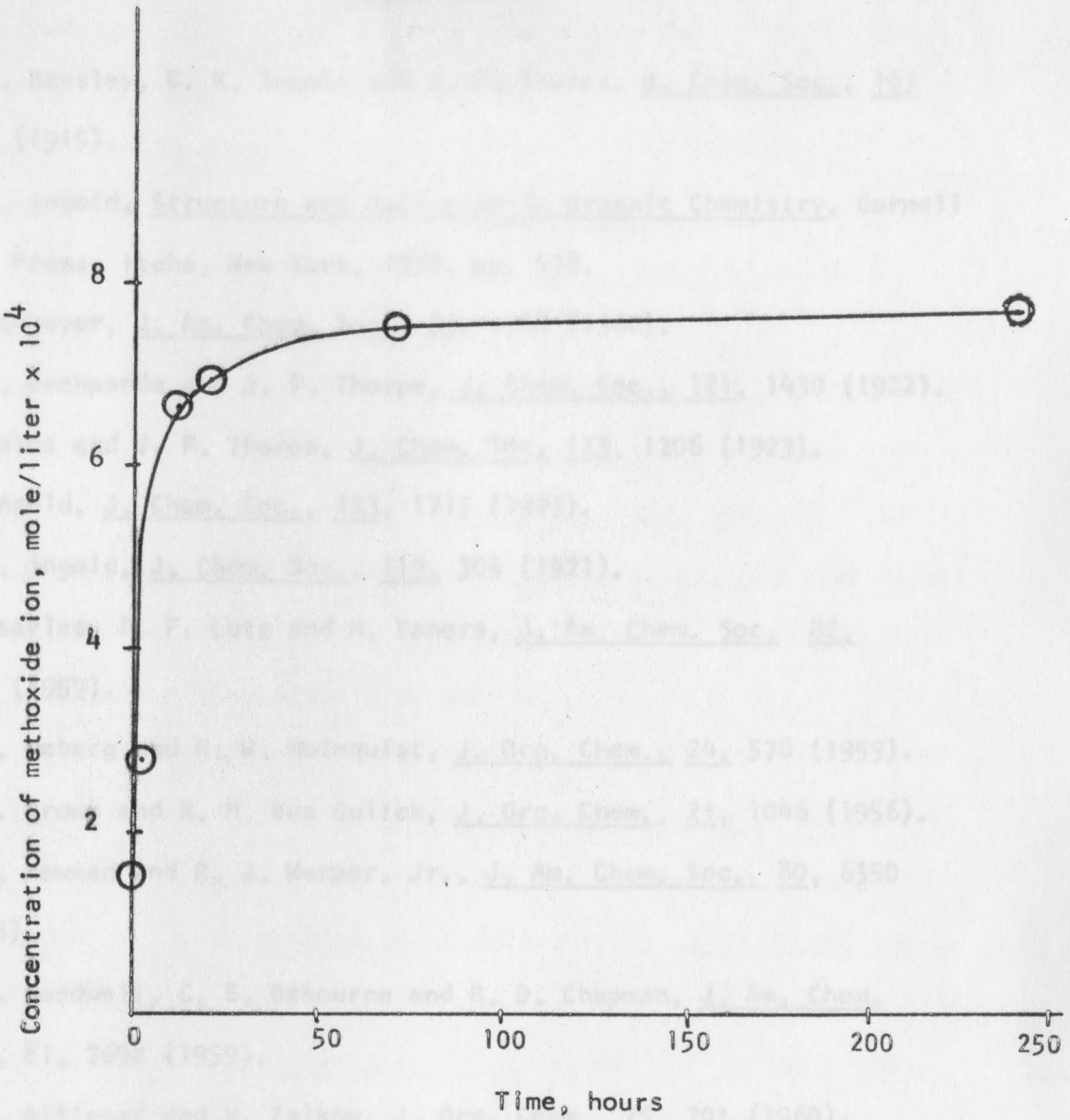


Fig. 16. Reaction of 1,2-Epoxy-2,3-dimethylbutane with sodium bromide in methanol at 25°C. Concentration of methoxide ion produce vs. time. (Run 2)

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