DIHEDRAL ANGLE AND TRANSITION STATE GEOMETRY IN ELIMINATION REACTIONS

A STUDY OF THE RELATIONSHIP BETWEEN DIHEDRAL ANGLE AND TRANSITION STATE GEOMETRY IN BIMOLECULAR ELIMINATION REACTIONS

By

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SCOPE AND CONTENTS:

The nitrogen and hydrogen-deuterium isotope effects have been measured for the base-promoted elimination reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions and cis- and trans-2-phenylcyclohexyltrimethylammonium ions. The observations have been interpreted as indicative of a concerted E2 mechanism for both trans and cis elimination processes. In the cis eliminations, however, proton transfer to base is far advanced at the transition state resulting in a much higher degree of carbanionic character associated with the transition state than for the trans eliminations.

The kinetic isotope effect results for these cyclic systems establish that the two bond-rupture processes complement each other; the greater the extent of proton transfer to base at the transition state, the smaller is the extent of C-N bond weakening. These observations are interpreted in terms of the coupling of the motion which extends the lengths of the H-C and C-N bonds at the transition state and the approach to coplanarity of the bonds involved in the elimination process.

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General Introduction

Bimolecular elimination reactions have generally been considered to proceed most readily *via* a trans coplanar transition state in which the four atoms H-C-C-X involved in the reaction are in one plane with the departing groups trans to one another. This geometric requirement has been regarded as arising out of the necessity for the pair of electrons initially in the H-C_β bond to act on the α-carbon from one side while the leaving group departs from the other side. In acyclic systems, such an arrangement of atoms, with a dihedral angle of 180°, is usually possible because of the freedom of rotation around the C_α-C_β bond. Cyclic systems, however, do not always have the participating atoms arranged in a trans coplanar relationship and elimination often proceeds *via* a transition state in which the departing groups are cis to one another. These cis eliminations usually proceed less readily than trans eliminations.

In recent years, there has been considerable controversy over the mechanism of both trans and cis elimination reactions. As a result, a large number of studies have been made in order to determine the detailed pathway of these elimination processes. It is now generally accepted that trans eliminations, in which the departing groups are able to attain coplanarity at the transition state, proceed *via* an E2 mechanism. Furthermore, in these processes it is now evident that

C-H and C-X bond changes need not be fully synchronous and either C-H or C-X bond rupture may be advanced over the other depending upon the structure of the substrate and the conditions of the reaction. The mechanism of cis elimination, as well as of trans elimination in which the leaving groups do not have a coplanar relationship, is not clear. Some investigators have proposed that such reactions proceed by the E2 mechanism, while others have favoured the E1cb mechanism.

Cristol suggested that the slower rate for cis elimination and for non-coplanar trans elimination is a consequence of the inability of the reactant to assume a transition state configuration in which the electron pair initially associated with the C-H bond acts on the α-carbon from the backside to displace the leaving group. He proposed that a possible reaction pathway involves removal of the proton by base, leaving a high-energy carbanion which then ejects the leaving group to form an olefin (1,2,3,4,5).

Rapid bimolecular cis eliminations have been observed in systems where removal of the hydrogen by base is facilitated by the presence of an electron-withdrawing group on the β-carbon atom (6,7,8,9). Results from studies of elimination reactions in such cases clearly show that the presence of an electron-withdrawing group on the β-carbon atom is more effective in directing the course of elimination than is the geometrical relationship of H and X.

Bordwell found general base rather than specific base catalysis in both trans and cis eliminations from cyclic systems in which a sulphone group is attached to the β-carbon (8). This observation demonstrated that the reactions proceed either by a concerted pathway or by a rate-controlling proton transfer followed by a rapid reaction of the anion to give products. If a carbanion intermediate were to be formed in such systems, elimination from analogous open-chain systems should be non-stereoselective. He found (9), however, that elimination in the open-chain systems occur stereoselectively trans. Furthermore, the activation energy for cis elimination in the cyclic systems was smaller than that for the trans eliminations. This observation does not provide the basis for the assumption of an energetically unfavourable two-stage process in cis eliminations. On the basis of these results, Bordwell concluded that cis and trans eliminations in systems where removal of the hydrogen by base is facilitated by the presence of an electron-withdrawing group attached to the β-carbon proceed via an E2 mechanism.

In 1962, DePuy proposed that the essential feature of the geometry for an E2 process is not the trans relationship of the eliminated atoms or groups, but coplanarity of the four centre system. He suggested that a plot of the rate of elimination versus the dihedral angle between the hydrogen and the departing group would show maxima at both 0° and 180° and a minimum at 90°. This means that coplanar transition states, whether cis or trans, have a lower energy than non-coplanar transition states, and that elimination is more facile when the dihedral angle is 0° or 180°. Furthermore, he predicted that as the dihedral angle deviates from 0° or 180° and approaches 90°, the elimination would approach E1cb (10).

The objectives of the work reported in this thesis were to use the kinetic isotope effects associated with the leaving atoms, H and X, to elucidate the mechanism of cis elimination and also to determine the relationship between the dihedral angle and the extent of H-C and C-X bond weakening at the transition state.

The base-promoted elimination reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions and cis- and trans-2-phenylcyclohexyltrimethylammonium ions were investigated at 60°C. These compounds were chosen because one has some knowledge of the geometrical relationship of the participating groups in such cyclic systems and because the isotope effect associated with the departing atom, nitrogen, can be readily determined with a high degree of precision. In addition, the nitrogen isotope effect associated with the elimination reaction of 2-phenylethyltrimethylammonium ion was measured. Because of the freedom of rotation about the C_1-C_2 bond, this open-chain compound was considered to undergo E2 elimination via a trans coplanar transition state and might be thought of as a standard of reference for the trans E2 process.

In 1960, Cristol (11) reported the rates of reaction and Arrhenius activation parameters for the elimination reactions of cis- and trans-2-phenylcyclohexyltrimethylammonium ions. The corresponding values have now been determined for the cyclopentyl series and compared with the results for the cyclohexyl series.

When DePuy's rule is applied to these elimination reactions, one would predict that trans elimination in the cyclohexyl system and cis and trans eliminations in the cyclopentyl series will proceed *via* an E2 mechanism. The cis elimination in the cyclohexyl system, however, might be expected to proceed by the E1cb mechanism or by an E2 process in which, at the transition state, rupture of the H-C bond is well advanced over that of the C-X bond.

HISTORICAL INTRODUCTION

- - - -

A. β-Elimination Reactions

General

The most common elimination process, called 1,2- or β-elimination, involves the loss of two substituents from a pair of adjacent atoms resulting in the formation of a double bond, as represented in equation (1). In the majority of β-eliminations, hydrogen and some

$$X-M-N-Y \longrightarrow X^{+} + M{=}N + Y^{-} \qquad (1)$$

other atom or group are removed from adjacent carbon atoms to generate an olefin. Equation (2) illustrates this process in which B^{-} is a base

$$B^{-} + H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X \longrightarrow BH + {>}C{=}C{<} + X^{-} \qquad (2)$$

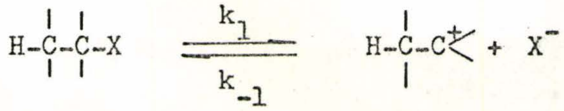
and the leaving group, X, is fluoride (12,13), chloride (14), bromide (15), iodide (16), dialkylsulphonium (17,18,19) trialkylammonium (20,21) or arylsulphonate (22,23).

Various mechanisms have been suggested to account for experimental observations and these mechanisms will be discussed in this section. In particular, the one-step E2 process and the two-step Elcb process will be considered in detail. Inasmuch as a portion of this thesis is concerned with the elucidation of the mechanism of cis elimination, for which both E2 and Elcb mechanisms have been suggested, a discussion is included on the various experimental criteria which have been used to clarify the nature of the transition state in bimolecular elimination reactions.

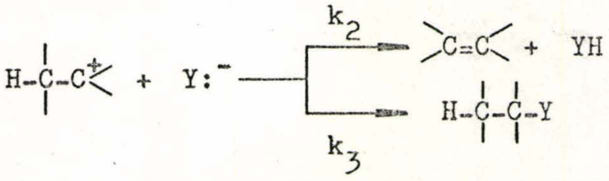
Several complete reviews (24-30) have been published in the past few years presenting the various mechanisms suggested for β-eliminations and detailed discussions have been given concerning factors which affect the reaction pathway. Consequently, only brief descriptions of the mechanisms will be given here.

The El Mechanism

Hughes (31), in 1935, was the first to propose the mechanism in which the slow step, involving the heterolysis of the C-X bond, gives an intermediate carbonium ion which subsequently loses a β-hydrogen to yield an olefin. This unimolecular mechanism is designated as El and is represented by equations (3) and (4). The carbonium ion intermediate may proceed by three pathways: (a) it may recapture X^- regenerating the substrate; (b) it may decompose with the loss of a beta hydrogen to give the elimination product; or (c) it may undergo substitution as the result



$$\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X} \quad \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}C^{+}\!\!<} + \mathrm{X}^{-} \qquad (3)$$



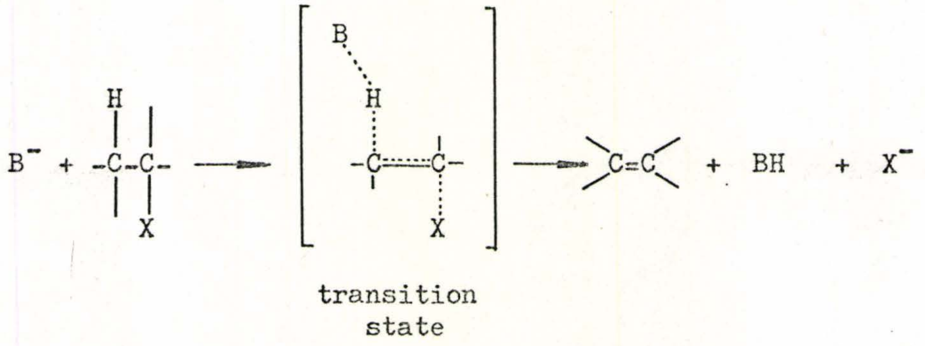
$$\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}C^{+}\!\!<} + \mathrm{Y{:}^{-}} \begin{cases} \xrightarrow{k_2} \mathrm{>C{=}C<} + \mathrm{YH} \\ \xrightarrow[k_3]{} \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}Y} \end{cases} \qquad (4)$$

of neutralisation by a solvent molecule or any other available nucleophile, Y^-. The partitioning of the carbonium ion is, therefore, controlled by the relative reaction rates of the three processes.

The E2 Mechanism

Hanhart and Ingold (20), in 1927, reported on a mechanistic study of elimination reactions in which they proposed a concerted bimolecular mechanism for the decomposition of quaternary ammonium salts. This mechanism for beta elimination has been extended to other types of substrates and now appears to be the normal pathway for base-promoted elimination reactions.

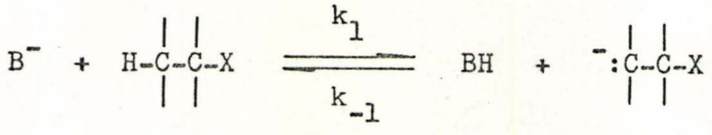
In the reaction, a base, B, which may be neutral or negatively charged, removes a proton from the beta-carbon atom of the substrate while the leaving group, X, splits off in a concerted process to generate the unsaturated product. The leaving group, X, is an electron-attracting group that may be neutral or positively charged. Equation (5) depicts the formulation for this E2 (bimolecular elimination) mechanism with a transition state in which concerted C-H and C-X bond rupture is accompanied by π-bond formation between the carbon atoms.



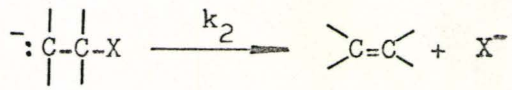
(5)

The Elcb Mechanism

In 1933, Ingold suggested another mechanism consistent with second order kinetics and designated it as Elcb, meaning unimolecular elimination involving the conjugate base of the substrate. In this process proton transfer to base, giving rise to an intermediate carbanion, is completed before any change has occurred at the C-X bond. Unimolecular ejection of X^- from the conjugate base of the substrate then generates an olefin. This is shown in equations (6) and (7).

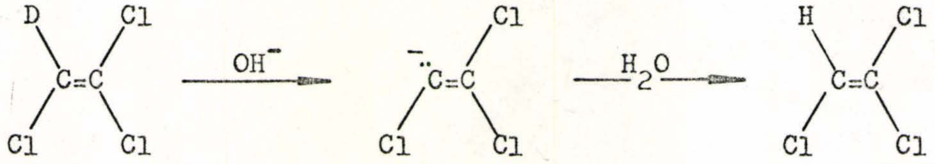


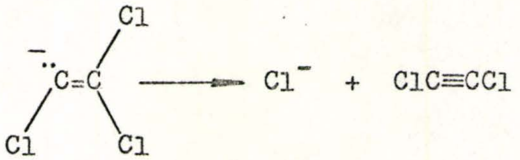
$$B^- + H{-}C{-}C{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + {}^-{:}C{-}C{-}X \qquad (6)$$



$$^-{:}C{-}C{-}X \xrightarrow{k_2} \rangle C{=}C\langle + X^- \qquad (7)$$

Miller (32), in 1959, was the first to demonstrate this reaction pathway when he reported that dihaloethylenes and trichlorethylene undergo base-catalysed deuterium exchange with solvent considerably more rapidly than dehydrohalogenation. Isotope exchange was interpreted

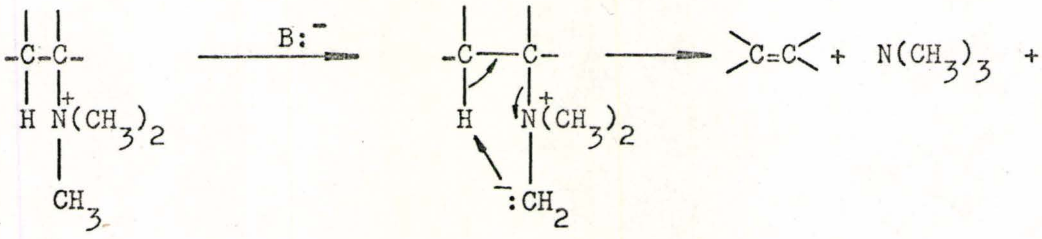

(8)


(9)

as indicating that the carbanion which is formed regenerates reactant by abstraction of a proton from the solvent. Miller further argues that the formation of the carbanion cannot be a side reaction for the energy required to eject the halide from the carbanion, in which there is a completely free electron pair, should be less than the energy required for an E2 reaction in which, at the transition state, the electron pair is only partially free. This test of isotopic exchange is now widely used as a criterion for the Elcb mechanism.

The α',β-Mechanism

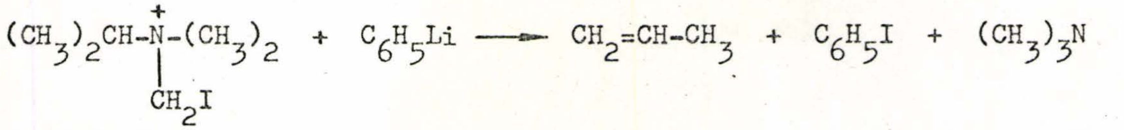
The α',β-mechanism of elimination, first suggested by Wittig in 1956, has been observed in the reaction of 'onium compounds with very strong bases such as phenyllithium. In this reaction, an alpha hydrogen is abstracted by the base to form a dipolar ylide, I, which then abstracts a beta hydrogen from another branch of the substrate by way of a cyclic transition state, equation (10).



I

(10)

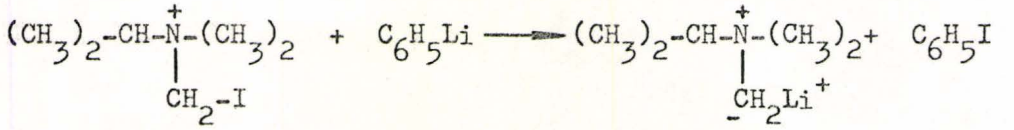
In Wittig's study of the reaction of dimethylisopropyl (iodomethyl)ammonium ion, II, with phenyllithium, (33), the reaction products were found to be propylene, iodobenzene and trimethylamine.



$$(CH_3)_2CH-\underset{\displaystyle CH_2I}{\overset{+}{N}}-(CH_3)_2 + C_6H_5Li \longrightarrow CH_2=CH-CH_3 + C_6H_5I + (CH_3)_3N \quad (11)$$

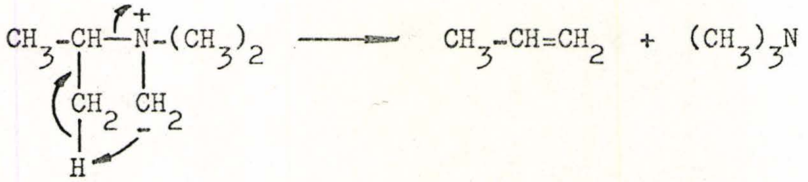
II

Clearly, a normal E2 reaction has not taken place for iodobenzene, rather than benzene, was formed. He interpreted the results in terms of the initial formation of alkyllithium, III, followed by an α',β-elimination to give the products.



$$(CH_3)_2\text{-}CH\text{-}\underset{\substack{|\\ CH_2\text{-}I}}{\overset{+}{N}}\text{-}(CH_3)_2 + C_6H_5Li \longrightarrow (CH_3)_2\text{-}CH\text{-}\underset{\substack{|\\ \underset{-}{C}H_2Li^+}}{\overset{+}{N}}\text{-}(CH_3)_2 + C_6H_5I \qquad (12)$$

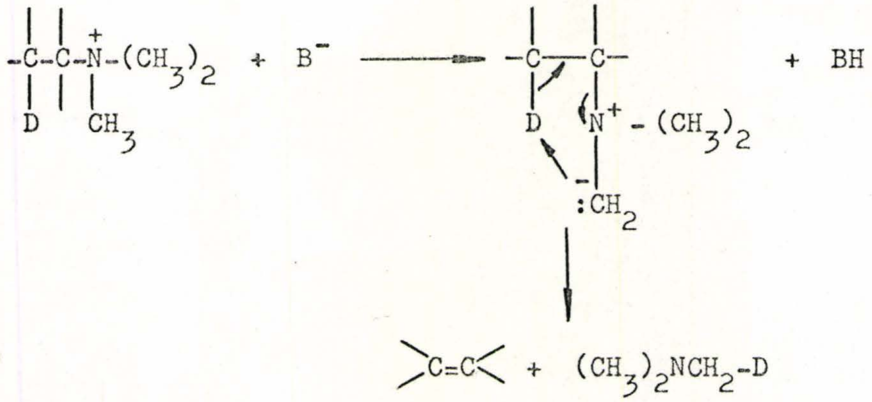
III



$$CH_3\text{-}\underset{\substack{|\\ CH_2\\ |\\ H}}{CH}\text{-}\underset{\substack{|\\ \underset{-}{C}H_2}}{\overset{+}{N}}\text{-}(CH_3)_2 \longrightarrow CH_3\text{-}CH{=}CH_2 + (CH_3)_3N \qquad (13)$$

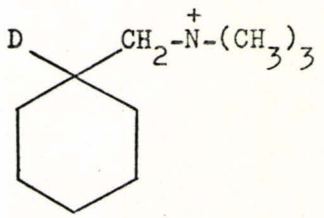
In studies on the stereochemical course of the reaction of cyclooctyltrimethylammonium ion with different bases, Wittig (34,35,36) observed that, with phenyllithium as the base, <u>cis</u>-cyclooctene is favoured 9:1. He found, however, that <u>trans</u>-cyclooctene is favoured when the base is hydroxide or amide. This was interpreted in terms of an ordinary E2 process when hydroxide is the base and an α',β-process when phenyllithium is the base. These conclusions are strongly supported by the results of the reaction of methyllithium on cyclooctyldimethyl (bromoethyl)ammonium ion which gives the same 9:1 ratio of <u>cis</u>- to <u>trans</u>-cyclooctene.

The best test for the α',β-mechanism involves the use of deuterium as a tracer. The hydrogens on the beta carbon are replaced by deuterium and the trimethylamine product is examined for the presence of this isotope. Equation (14) illustrates that if the α',β-mechanism is operative then one deuterium per molecule will be observed in the trimethylamine produced.



(14)

Cope (37) and Shiner (38) have applied this test in studies on the elimination reactions of the compounds IV and V, but were unable to detect deuterium in the trimethylamine. Ayrey (39) studied the cis

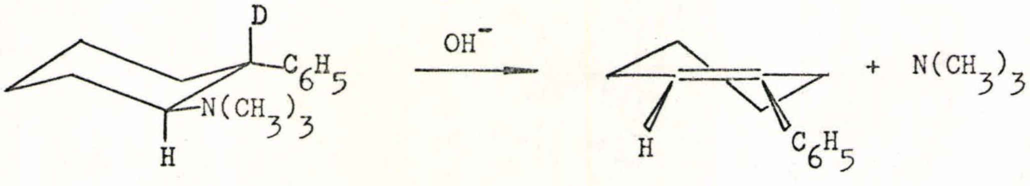


IV

$$CD_3CH_2\overset{+}{N}-(CH_3)_3\ OH^-$$

V

elimination of trans-2-phenylcyclohexyltrimethylammonium-2-d_1 ion, VI, with ethanolic potassium hydroxide, equation (15), and also found the

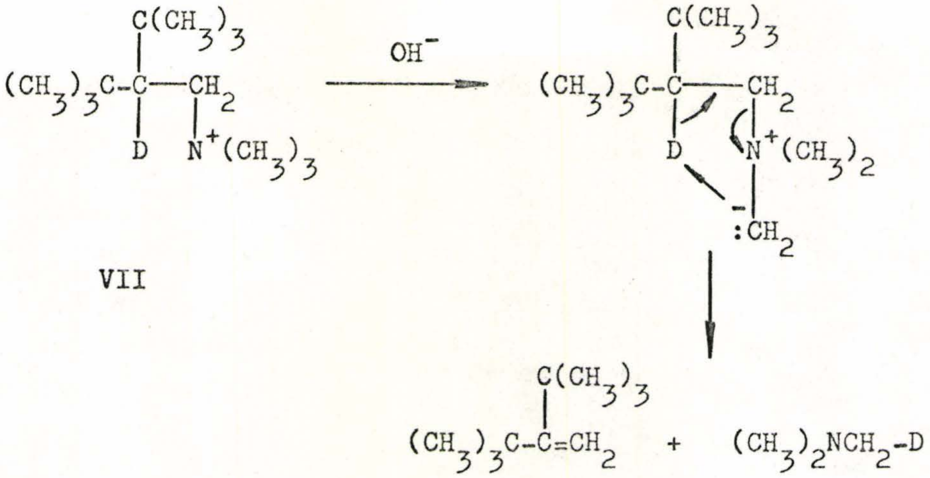


(15)

VI

resultant trimethylamine to be free of deuterium. Clearly, these results indicate that, under normal conditions, the Hofmann reaction does not proceed by way of an α',β-mechanism involving an ylide, even though in Ayrey's example (39) the E2 reaction is energetically unfavourable because the participating groups are unable to attain an anticoplanar relationship at the transition state. It has been suggested by Cope (40) that here the phenyl group on the alpha carbon promotes reaction by either an Elcb mechanism or an E2 mechanism in which C-H bond rupture is well in advance of C-N bond rupture and, therefore, that co-planarity considerations are of less importance than in a more synchronous E2 process.

Cope (40) did, however, establish the α',β-mechanism for the decomposition of 2-t-butyl-3,3-dimethylbutyltrimethylammonium-2-d hydroxide, VII. Steric interactions make it difficult for the

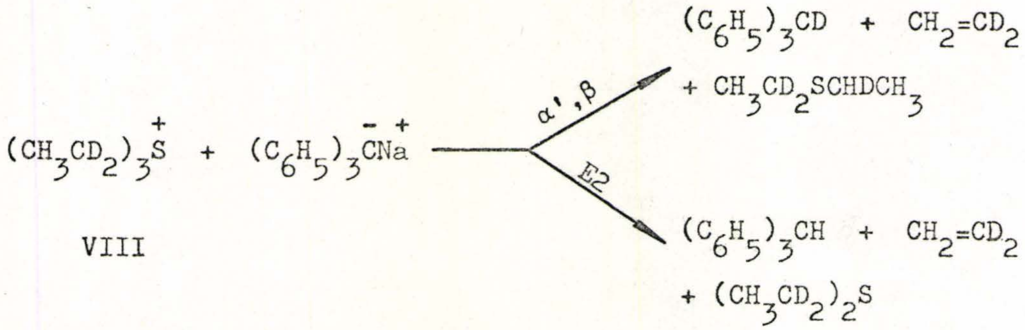


VII

(16)

eliminating groups to attain the anticoplanar transition state necessary for a facile E2 process. Instead, the alternative α',β-mechanism, in which the groups have a cis relationship, finds favour, equation (16).

Franzen (41), in an investigation of the reaction of tri(ethyl-1,1-$\underline{d}_2$)sulphonium ion, VIII, with trityl sodium,equation (17), found that only seventy five per cent of the triphenylmethane was deuterated, indicating that the reaction does not proceed exclusively by the $\alpha'\beta$-mechanism but that an E2 process contributes as well.



VIII

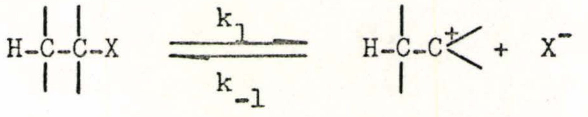
(17)

Kinetic Distinction Between the E1, E2 and E1cb Mechanisms

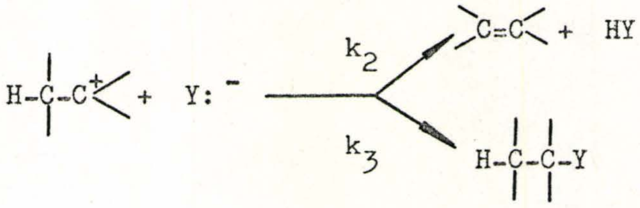
An important diagnostic tool in the mechanistic investigation of β-elimination reactions is the determination of the number of molecules involved in the transition states of the various reaction steps. The E1, E2 and E1cb mechanisms will be examined separately to see how a study of the kinetics of the reaction can contribute to the characterisation of the elimination process.

The E1 Mechanism

The unimolecular mechanism is represented by equations (18) and (19) and the kinetic expression for the formation of the olefinic product is shown in equation (20).



(18)



(19)

$$\text{Rate of elimination} = \frac{k_1k_2(\text{Substrate})(Y^-)}{k_{-1}(X^-) + (k_2 + k_3)(Y^-)} \qquad (20)$$

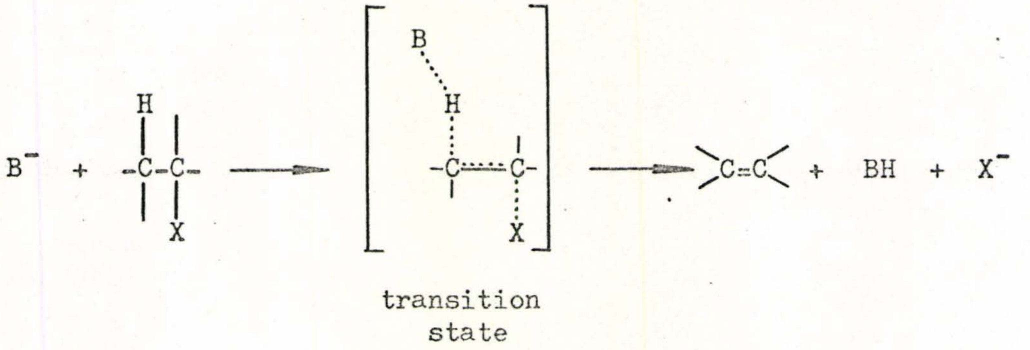
If the initial step is irreversible, in other words, if $k_{-1}(X^-)$ is very small with respect to $(k_2 + k_3)(Y^-)$, the rate of elimination assumes the familiar rate expression for first-order kinetics, equation (21). This expression then governs the rate of elimination when the

$$\text{Rate of elimination} = \frac{k_1 k_3(\text{Substrate})}{(k_2 + k_3)} \qquad (21)$$

initial heterolysis is rate determining and is the form usually observed in E1 reactions.

<u>The E2 Mechanism</u>

The important distinction between the E1 and E2 mechanisms is that the rate of the former is not affected by the addition of bases whereas E2 processes are accelerated by base and are exceedingly slow in the absence of added base. Referring to equation (22), formulating



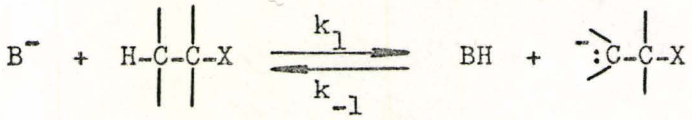
(22)

the E2 process, it is evident that eliminations of this type can be expected to exhibit second-order kinetics, first order in each of substrate and base, equation (23).

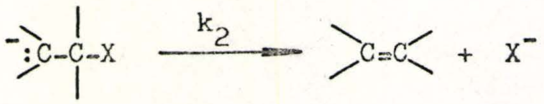
$$\text{Rate of elimination} = k_2(\text{Substrate})(\text{B}^-) \qquad (23)$$

The Elcb Mechanism

The Elcb mechanism is also consistent with the observation of second-order kinetics. In this process, the base removes the β-hydrogen to form a carbanion which subsequently loses the leaving group to give the olefin. From equations (24) and (25), it can be seen that the



(24)



(25)

rate of elimination is given by equation (26), and that when the base

$$\text{Rate of elimination} = \frac{k_1k_2(\text{Substrate})(\text{B}^-)}{k_2 + k_{-1}(\text{BH})} \qquad (26)$$

is the lyate ion of the solvent, as usually is the case, the reaction follows simple second-order kinetics.

There are two limits, however, that must be considered. First, the formation of the carbanion from the substrate could be an equilibrium process in which $k_{-1}(BH) \gg k_2$. The rate of elimination is then given by

$$\text{Rate of elimination} = \frac{k_1 k_2(\text{Substrate})(B^-)}{k_{-1}(BH)} \qquad (27)$$

equation (27) and, because it is proportional to $(B^-)/(BH)$, specific base catalysis will be observed. The other limit is when $k_{-1}(BH) \ll k_2$. Essentially, then, every carbanion formed is converted to elimination product. The rate expression reduces to equation (28) and the reaction

$$\text{Rate of elimination} = k_1(\text{Substrate})(B^-) \qquad (28)$$

proceeds by way of a rate-determining proton transfer followed by a rapid reaction of the anion to give products. The reaction rate will be dependent upon the sum of the reactions of all bases present and general base catalysis will be observed.

Criteria for Distinguishing between the E2 and Elcb Mechanisms

Because of the kinetic similarities in the E2 and Elcb processes, it is often not possible to differentiate between them from kinetic information alone. The usual approach to the problem of distinguishing between Elcb and E2 processes is to test for hydrogen-deuterium exchange between the reactant and the solvent which is the conjugate acid of the basic reagent. It can be seen from equations (29)

$$B^- + R_2CH\text{-}CH_2\text{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2\overset{-}{\ddot{C}}\text{-}CH_2\text{-}X + BH \tag{29}$$

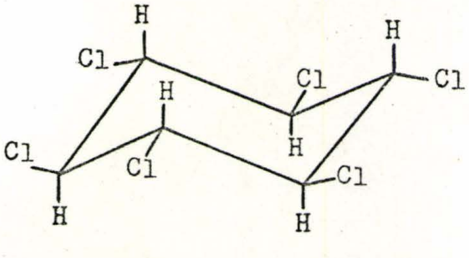
$$R_2\overset{-}{\ddot{C}}\text{-}CH_2\text{-}X \xrightarrow{k_2} R_2C{=}CH_2 + X^- \tag{30}$$

and (30) that if a carbanion is formed deuterium may be incorporated into the reactant by way of proton abstraction from deuterated solvent, BD. The observation of deuterium in recovered substrate is considered to be evidence for the formation of this reaction intermediate.

The absence of deuterium pick-up, however, does not necessarily exclude a carbanion intermediate since its decomposition to olefinic product may proceed at a much faster rate than its reaction with solvent to regenerate substrate. In this case, reaction will proceed via a rate-determining proton transfer followed by rapid decomposition to products. The limits of detection are such that deuterium enrichment will only be observed if the $k_2/k_{-1}(BH)$ ratio is less than about one hundred (38).

The first reported application of the deuterium exchange test for distinguishing between the Elcb and E2 mechanisms was reported in 1945 by Skell and Hauser (42) for the reaction of 2-phenylethyl bromide with ethoxide ion in deuterium ethoxide. No deuterium, however, was detected in the reactant. Hauser (43) later reported on the reaction of Et_2CDCH_2Br with sodamide in liquid ammonia in which the very strong basic conditions might have been expected to promote hydrogen abstraction. In this example as well, isotopic exchange was not observed. These results are consistent with either a one-step mechanism or a two-step process in which the carbanion decomposes rapidly to product.

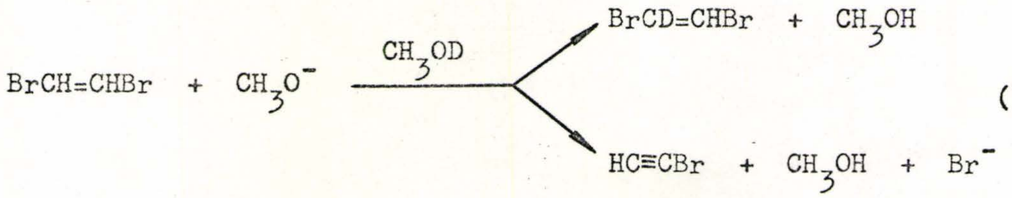
A deuterium exchange test was conducted by Cristol (44) on the dehydrohalogenation of beta hexachlorocyclohexane, IX, which, unlike all other isomers of hexachlorocyclohexane, is unable to undergo a facile E2 reaction since no pair of hydrogen and chlorine atoms on adjacent carbon atoms have a trans relationship to each other. When the reaction was carried out with sodium ethoxide in deuterated ethanol to fifty per cent completion, infrared analysis indicated no deuterium pickup.



IX

Mass spectrometric analysis, however, indicated that 0.079 excess atom per cent deuterium was present in unreacted substrate and this result was interpreted as indicative of the existence of a carbanion intermediate in which one carbanion reverted to initial reactant for every one hundred and fifty which passed on to products. Other workers, however, have questioned this interpretation (45) because of the very small amount of exchange that was observed and they have indicated preference for a forced concerted process, the transition state for which has an unfavourable geometry.

Fast deuterium exchange was found by Miller (46) in the reactions of cis- and trans-dihaloethylenes with methoxide ion in deuterated methanol. The rate of exchange was observed to be about twenty-five times faster than the rate of elimination and Miller interpreted this in terms of an Elcb mechanism, equation (31).



$$BrCH{=}CHBr + CH_3O^- \xrightarrow{CH_3OD} \begin{cases} BrCD{=}CHBr + CH_3OH \\ HC{\equiv}CBr + CH_3OH + Br^- \end{cases} \qquad (31)$$

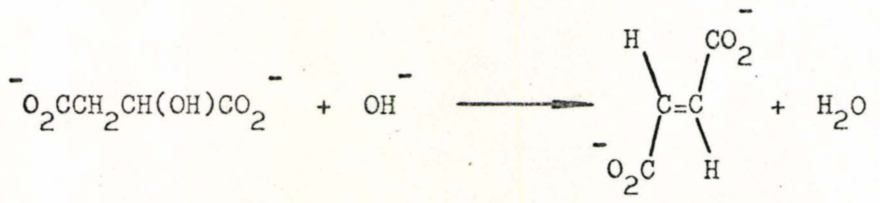
Hine (47) found in the elimination of DF from $CDCl_2CF_3$ that base-catalysed deuterium exchange with solvent occurred at a rate which is rapid compared to the consumption of alkali, equations (32) and (33). The undeuterated analogues, when treated with base in deuterium oxide,

$$CDCl_2CF_3 + B^- \rightleftharpoons {}^{-}\!:CCl_2CF_3 + BD \qquad (32)$$

$$ {}^{-}\!:CCl_2CF_3 \longrightarrow CCl_2{=}CF_2 + F^- \qquad (33)$$

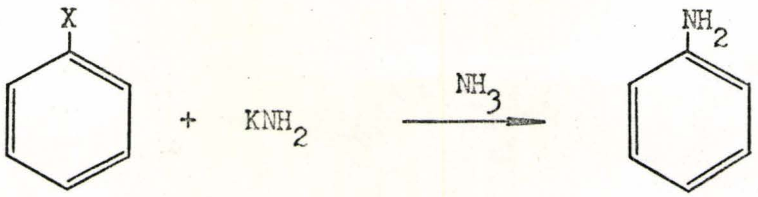
exhibited changes in their infrared spectra in a manner expected for a deuteration process. Hine interpreted these results as indicative of an Elcb mechanism in which the rate of return of carbanion to starting material is fast relative to the rate of conversion of carbanion to product.

Erickson (48) investigated the dehydration of malic acid to fumaric acid, equation (34), and observed rapid exchange of the methylene protons in malic acid for deuterons in deuterium oxide, indicating

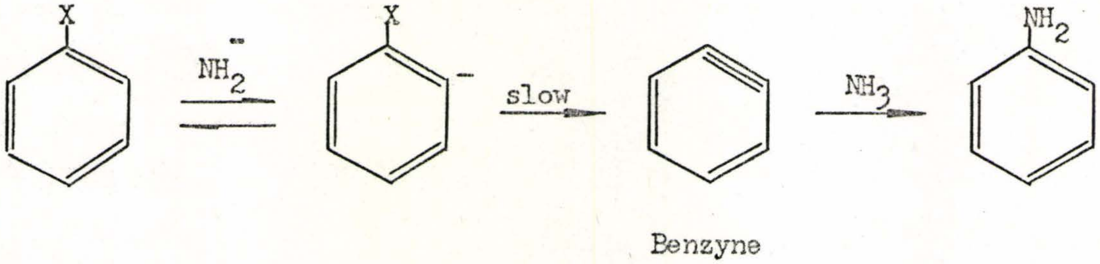


(34)

reaction by a carbanion mechanism. Roberts (49), in a study of the amination of halobenzenes, equation (35), found fast deuterium exchange for both fluorobenzene and chlorobenzene. He concluded that the reaction involves the initial formation of a carbanion which is then converted into product by way of a benzyne intermediate, equation (36).



(35)



(36)

In each example cited it has been assumed that hydrogen-deuterium exchange accompanying elimination is indicative of the Elcb mechanism. It is possible, however, that carbanion formation is an irrelevant reaction and that in systems in which the presence of this ionic species is demonstrated by hydrogen-deuterium exchange, the elimination reaction itself proceeds by the one-step process. Hine (50) has put forth the point of view that departure of the leaving group must certainly be easier from a carbanion with its completely free beta-electron pair than from an incipient carbanion in which the beta-electron pair is only partially freed. Therefore, he argues, if a carbanion is formed, as demonstrated by isotopic exchange, its decomposition to elimination product should outweigh reaction by the one-step process.

Breslow (51), on the other hand, argues that because the E2 transition state has less negative charge on carbon it can be expected to have a lower energy than the transition state leading from the carbanion to product. Therefore, he concludes, reaction by the E2 process will be more likely than reaction by way of a reversibly-formed carbanion, although isotopic exchange might still be observed if the energy of the transition state for anion formation is lower than that for either the E2 process or the Elcb process. His argument, however, does not include consideration of the relative energies of the partial C-X bond in the two systems, which could very well favour the transition state for the Elcb reaction.

Breslow also argues that electron-withdrawing groups on the phenyl ring of 2-phenylethyl derivatives would be expected to decrease the rate of conversion of a carbanion to product if the important factor is the ability of the beta-electron pair to "push" the leaving group off as formation of the double bond occurs. Such substituents, however, which decrease the charge density on the beta carbon, increase the rate of elimination. He attributes this to a lowering of the energy of the partially anionic transition state for reaction by the E2 process. He neglects to note, however, that the transition state in an Elcb process will also have high carbanionic character and therefore will be stabilised by electron-withdrawing groups giving rise to an increase in the rate of elimination. The shortcoming in Breslow's argument based on substituent effects is that he has concentrated his attention on the energy difference between the carbanion intermediate and the transition state leading from it to product, rather than the energy difference between the initial state and this transition state.

It is impossible to generalize with respect to the mechanism of elimination in a system showing hydrogen-deuterium exchange.

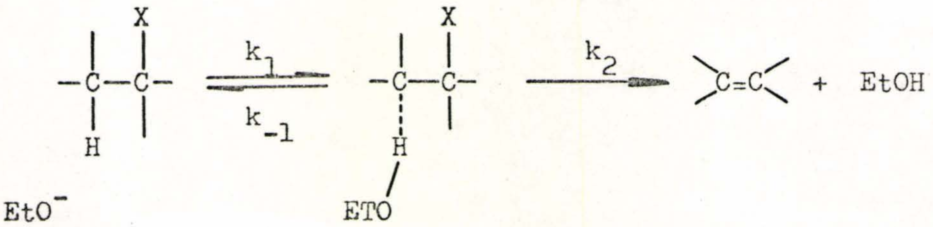
Demonstration of isotopic exchange can not necessarily be considered as evidence for a carbanion intermediate in β-elimination reactions and the absence of isotopic exchange does not establish the E2 mechanism. In a particular case, the elimination may be proceeding by way of the carbanion intermediate whose presence has been demonstrated by exchange or it may be proceeding by the entirely different E2 process. Clearly, other criteria are necessary to distinguish between these two processes.

The first attempt to distinguish between the E2 and E1cb mechanisms for a reaction which does not exhibit deuterium exchange was by Buncel and Bourns (52) who pointed out that this problem can be resolved by evaluating the kinetic isotope effect associated with the leaving group. In a concerted E2 process, the C-X bond will be broken in the rate-determining step and this should result in an isotope effect of considerable magnitude. In the carbanion mechanism in which $k_2 \gg k_{-1}$, the rate-determining step is the formation of the carbanion. The C-X bond is essentially intact at the transition state and no isotope effect, or an extremely small one, can be expected.

Buncel and Bourns found a very small amount of deuterium exchange in the carbonyl-elimination reaction of benzyl nitrate with

$$C_6H_5CH_2\text{-}O\text{-}NO_2 + CH_3CH_2O^- \xrightarrow{CH_3CH_2OH} C_6H_5CH{=}O + NO_2^- \qquad (37)$$

ethoxide ion in ethanol giving benzaldehyde, equation (37). It follows that if the reaction is proceeding by the Elcb mechanism, the formation of the carbanion intermediate must be rate determining. The nitrogen isotope effect, $(k^{14}/k^{15} - 1)100$, associated with the formation of the nitrite ion, was found to be 1.96 per cent at 30°C. This isotope effect, which is one of the largest observed for nitrogen in a rate process, unequivocally establishes that the O-N bond is undergoing rupture at the transition state. This result, coupled with the lack of significant isotopic exchange, eliminates reaction by way of a carbanion intermediate which is hydrogen bonded at the carbanionic centre with a molecule of solvent. Not excluded, however, is reaction by way of a carbanion which is specifically hydrogen bonded to the molecule of ethanol formed by abstraction of the β-hydrogen by base, equation (38).



(38)

If this specifically-solvated carbanion* were in equilibrium with reactants, the second step involving O-N bond rupture would be rate determining and a normal isotope effect would be observed. The β-

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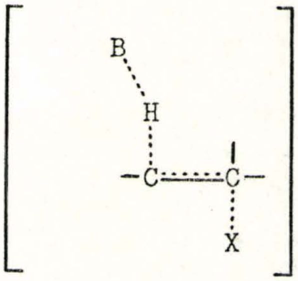
* Cram (53) has reported evidence for such intermediates in the base-catalysed hydrogen-deuterium exchange reaction of 2-octylphenylsulphone.

hydrogen-deuterium isotope effect associated with such a process, however, would be very small, or even less than unity, since it would arise from an equilibrium proton transfer between carbanion and ethoxide ion (54). The hydrogen-deuterium isotope effect, k^H/k^D, observed by Buncel and Bourns was 5.0 at 60°C., a value close to the maximum calculated (ca. 5.6) for complete loss of the carbon-hydrogen stretching frequency at the transition state (55), and certainly much larger than that expected for an equilibrium process. On the basis of these three observations, namely, negligible deuterium exchange, a normal nitrogen isotope effect and a large hydrogen-deuterium isotope effect, any mechanism involving a carbanion intermediate is excluded and the reaction would appear to be an E2 process.

In a similar study, Smith (54) reported on the mechanism of the carbonyl-elimination reaction of 9-fluorenyl nitrate with acetate ion in which no detectable deuterium exchange had been observed. The primary nitrogen isotope effect of 0.9 per cent excludes reaction by way of a freely-solvated carbanion intermediate and the observation of a hydrogen-deuterium isotope effect of 4.25 at 30°C. excludes any possibility of a pre-equilibrium formation of a specifically hydrogen-bonded carbanion. Clearly, these results also preclude any form of a two-step carbanion mechanism and are in accord with a concerted process.

Transition State Geometry in Bimolecular Elimination Reactions.

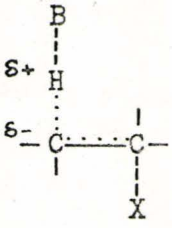
The transition state for a bimolecular elimination reaction involves partial breakage of the C-H and C-X bonds with simultaneous formation of a carbon-carbon double bond and a base-to-hydrogen bond, X. Until recently, these processes were apparently considered to be



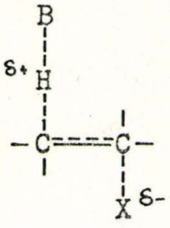
transition state
for an E2 reaction

X

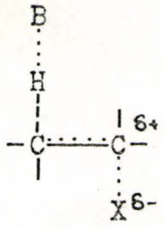
essentially synchronous with the C-H and C-X bonds breaking to about the same degree, XII. It is now evident, however, that either C-H or C-X bond rupture may be advanced over the other and that the relative



XI



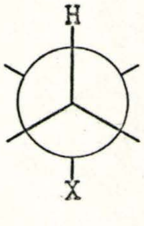
XII



XIII

extent of the two bond-rupture processes depends on the structure of the substrate and the conditions of the reaction. This means that there can be a range of possible transition states (29). In one extreme, the "nearly E1" transition state, XIII, extensive C-X bond rupture occurs while the C-H bond remains nearly intact. The alpha carbon carries considerable positive charge but there is only a slight development of the carbon-carbon double bond. In the other extreme, XI, C-H bond rupture is far advanced over C-X bond rupture and the transition state is "E1cb-like". A variety of factors will determine the quality of the transition state and a large portion of this thesis is concerned with the relationship between the stereochemical disposition of the eliminating groups and the nature of the transition state.

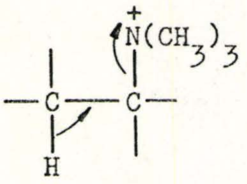
Concerted bimolecular elimination reactions have generally been considered to prefer transition states in which the four atoms H-C-C-X involved in the reaction are in one plane with the departing groups <u>trans</u> to one another, XIV, (26). This geometric requirement has



trans Elimination

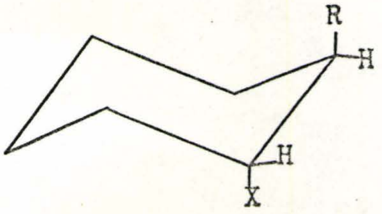
XIV

been regarding as arising out of the necessity for the pair of electrons initially in the C-H bond to act on the alpha carbon from one side while the leaving group departs from the other side, XV. In acyclic systems, such an arrangement of atoms, with a dihedral angle of 180°,



XV

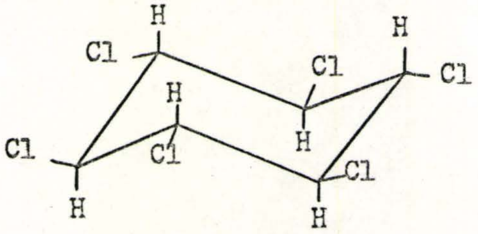
is usually possible because of the freedom of rotation around the C_α-C_β bond. Cyclic systems, however, do not always have the participating atoms arranged in a trans coplanar relationship and a much slower rate of elimination often results. For example, in the cyclohexyl system, coplanarity with a dihedral angle of 180° requires the departing groups to be axial and trans. When H and X have a cis relationship this preferred stereochemistry for synchronous rupture of the C-H and C-X bonds with simultaneous formation of the double bond is not possible and instead one bond ruptures in advance of the other.



XVI

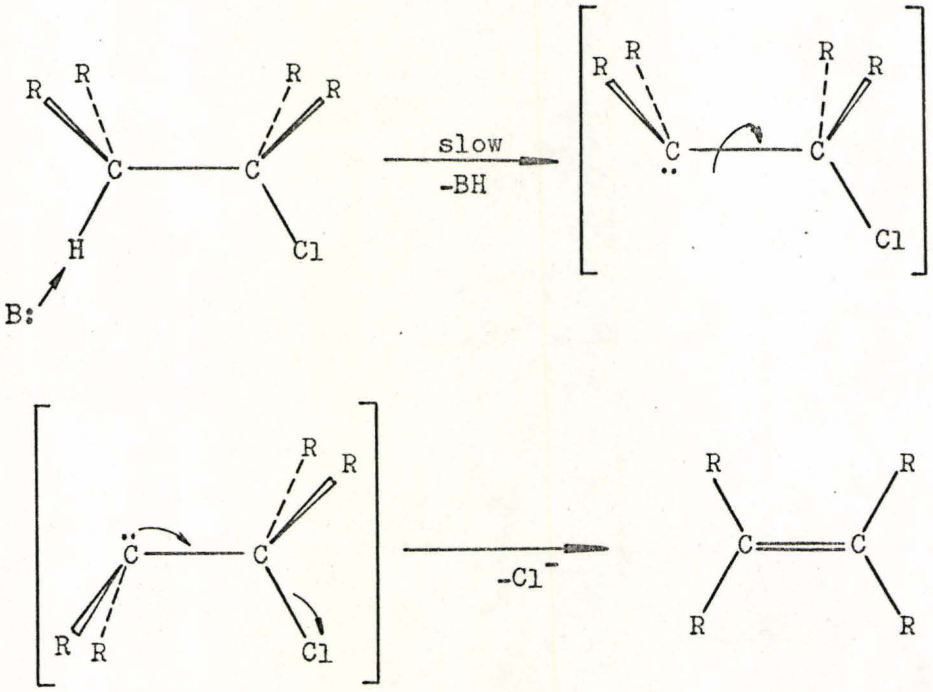
When strong electron-withdrawing groups, R, are attached to the beta carbon, XVI, it has been suggested that it is the C-H bond which is rupturing first, and, in the extreme where complete C-H bond rupture occurs prior to any stretching of the C-X bond, an intermediate carbanion is formed (29).

Cristol (1) , in 1947, showed that the beta isomer of hexachlorocyclohexane, XVII, in which there are no trans hydrogens and chlorines, undergoes bimolecular cis elimination at a rate 1/7000 to 1/24000 as fast as the other isomers. The activation energy (ca. 31 kcal. mole^{-1}) for this cis elimination is about 12 kcal. mole^{-1} greater than for trans elimination in the other isomers. Cristol (2) suggested that this is a consequence of the inability of the reactant to assume a transition state configuration in which the electron pair initially associated with the C-H bond acts on the alpha carbon from the backside



XVII

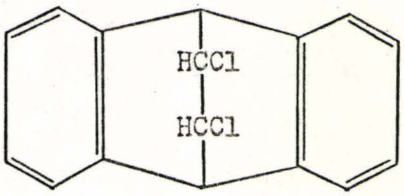
to displace chloride ion. He proposed that a possible reaction pathway involves removal of the proton by base leaving a high-energy carbanion which may racemise rapidly with inversion of the beta carbon followed by displacement of the chloride ion from the alpha carbon and formation of the double bond, equation (39).



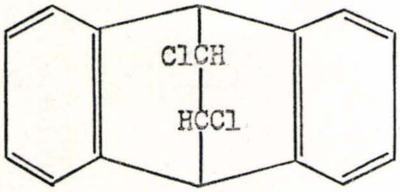
(39)

The standard technique for demonstrating the existence of an intermediate carbanion has been the deuterium exchange test. The reaction is carried out to about fifty per cent completion in deuterated solvent and the presence of deuterium in recovered reactant has been accepted as an indication that a carbanion mechanism is operating. As was discussed earlier in this thesis, Cristol performed such a test on the cis elimination of beta hexachlorocyclohexane (44) and recovered a very small amount of deuterated reactant. He interpreted this finding as a demonstration of the existence of a carbanion intermediate in this elimination reaction.

In a further investigation of the factors responsible for relative reactivities in *cis* and *trans* systems, Cristol studied elimination reactions in a number of bicyclic halides. He first reported on the dehydrohalogenation reactions of *cis*- and *trans*-11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene, XVIII and XIX (3).

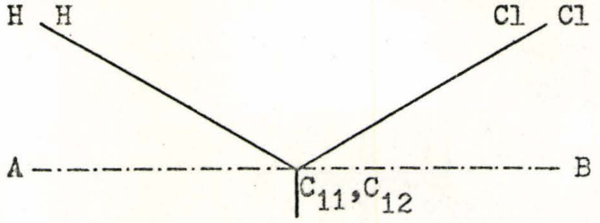


XVIII



XIX

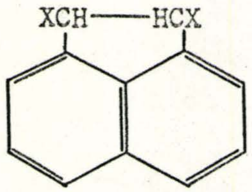
Both reactions were found to be very sluggish with cis elimination from the *trans*-compound being preferred by a factor of about eight over trans elimination from the *cis*-compound. This was the first time that cis elimination had been observed to be faster than trans elimination. Cristol points out that by looking down the axis through C_{11} and C_{12}, XX, it can be seen that the hydrogens and chlorines are each out of the hypothetical plane AB by about thirty five degrees and are unable to attain planarity owing to restriction of rotation. The substituents



XX

are positioned trans to each other but the requirement of coplanarity is not fulfilled. Trans elimination becomes very slow and, in fact, slower than cis elimination.

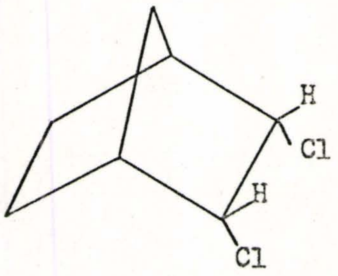
In 1956, Cristol (56) reported on the bimolecular dehydrohalogenation reactions of 1,2-dihaloacenaphthenes, XXI. Trans elimination is favoured over cis elimination by a factor of about 750 and Cristol



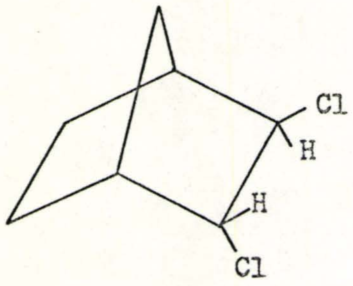
XXI

concluded from activation data that in this system there is sufficient freedom of rotation about the C_1-C_2 bond to allow the trans elimination to approach coplanarity at the transition state. He noted that the trans/cis ratio is not as great as in the hexachlorocyclohexanes (ca. 10^4) (1,2) and he ascribed this to an increase in rate of cis elimination resulting from stabilisation afforded the carbanion intermediate by the naphthalene ring system.

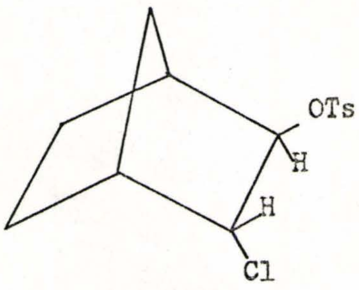
Cristol then turned his attention to the elimination reactions of a series of 2,3-norbornane derivatives, XXII, XXIII and XXIV, with sodium 1-pentoxide in 1-pentanol (4,5) and observed a preference for cis elimination over trans elimination by a factor of about 10^2. Cristol considered that in these cases the preference of cis elimination does not arise from factors increasing its rate but rather from factors markedly decreasing the rate of trans elimination. The geometry in the cis isomers is unfavourable for a trans coplanar transition state and trans elimination becomes very slow. He interpreted the activation data for both cis and trans eliminations on the basis of a process involving a carbanion intermediate.



XXII

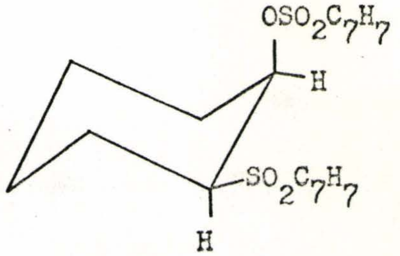


XXIII

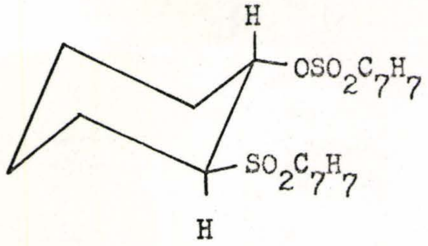


XXIV

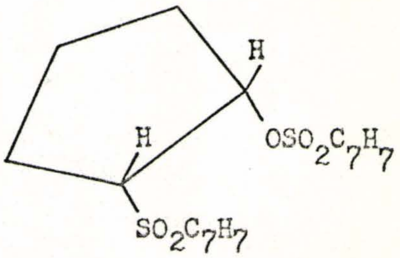
Bimolecular cis eliminations have also been observed in cases



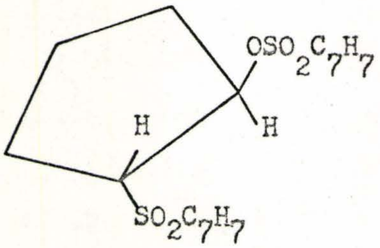
XXV



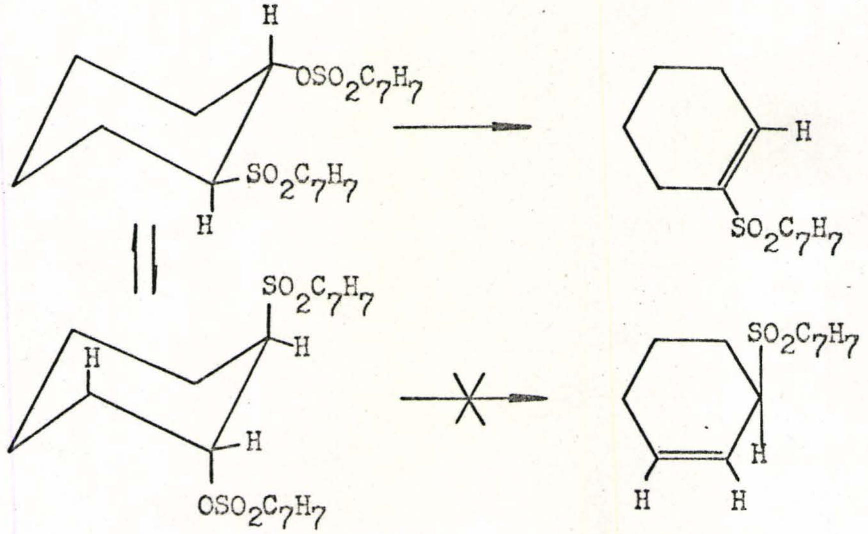
XXVI



XXVII



XXVIII



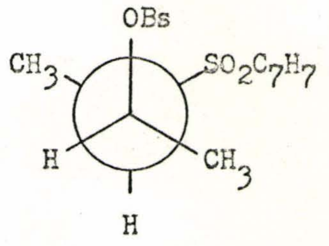
(40)

where removal of the hydrogen by base is facilitated by the presence of an electron-withdrawing group on the beta carbon. In 1956, Bordwell (6,7) reported on the base-catalysed E2 reactions of cis- and trans-2-(p-tolylsulphonyl)cyclohexyl p-toluenesulphonates, XXV and XXVI, and the corresponding cis- and trans-isomers in the cyclopentane system, XXVII and XXVIII. The trans-isomers each gave an α,β-unsaturated sulphone corresponding to elimination of a hydrogen cis to the tosylate group in preference to an unactivated hydrogen trans to the tosylate group, equation (40), the latter mode of elimination being the preferential one if a trans relationship of groups eliminated were the dominant factor. It is clear from this result that the presence of an electron-withdrawing group on the beta carbon is more effective in directing the course of elimination than is the geometrical relationship of H and X.

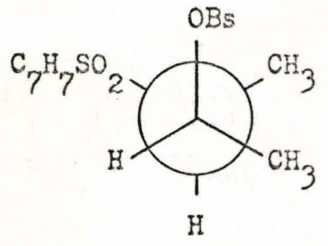
The ratio of trans elimination to cis elimination in the cyclohexane series is about 435 and in the cyclopentane series is about 20. It is interesting to note that trans elimination in the cyclopentane series is three times faster than trans elimination in the cyclohexane series even though a planar four-centred transition state can be achieved in the latter case. Bordwell attributes this to relief of steric strain in the cyclopentane series resulting from a reduction in the number of eclipsed hydrogens or other groups as the ring is converted to a cyclopentene system. He suggests that this factor is probably responsible for the rule that "it is easier to introduce a double bond into a five-membered ring than into a six-membered ring" (57,58). The rate ratios of 435 and 20 favouring trans over cis elimination are much smaller than the rate ratios of approximately 10^4 observed by Cristol in the elimination reactions of the isomeric hexachlorocyclohexanes. Bordwell concludes that the reason for this is that the four-centred transition state, with groups to be eliminated occupying trans positions, is not nearly as important a factor in these systems where the hydrogen being eliminated is activated by an electron-withdrawing group.

In a subsequent publication, Bordwell reported that both the cis and trans eliminations from isomeric 2-*p*-tolylsulphonylcyclohexyl and 2-*p*-tolylsulphonylcyclopentyl p-toluenesulphonates are general base rather than specific hydroxide ion catalysed (8). This observation demonstrated that the reactions proceed either by a concerted pathway or by a rate-controlling proton transfer followed by a rapid reaction of the anion to give products.

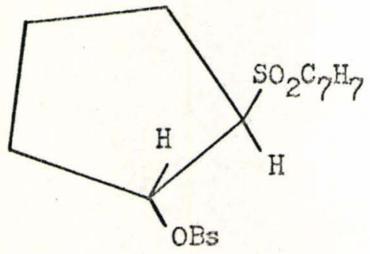
Bordwell then extended his studies to analogous open-chain systems in which formation of a carbanion intermediate should lead to a non-stereoselective elimination (9). He found, however, that the elimination reactions of dl-*threo*- and dl-*erythro*-3-*p*-tolylsulphonyl-2-butyl *p*-bromobenzenesulphonates, XXIX and XXX, occur selectively trans, thus ruling out the possibility of an intermediate carbanion. In addition, he determined that cis elimination of *trans*-2-*p*-tolylsulphonylcyclopentyl *p*-bromobenzenesulphonate, XXXI, under comparable conditions is seven times faster than trans elimination in the dl-*threo* case, XXIX, and



XXIX



XXX



XXXI

three times faster than trans elimination in the dl-erythro case, XXX. Furthermore, the activation energy for this cis elimination is of the same magnitude or smaller than that for the trans eliminations.

Cristol (1,2), on the basis of a much smaller rate and about 12 kcal. mole^{-1} higher activation energy for cis elimination compared to trans elimination in the hexachlorocyclohexane systems, suggested a two-step mechanism for cis elimination in beta hexachlorocyclohexane. Subsequently, he generalised this viewpoint to include other cis eliminations (4,5). Bordwell's data, however, does not provide the basis for the assumption of an energetically unfavourable two-stage process in cis eliminations. The observation of general base catalysis in cis elimination and the observation that comparable trans eliminations in open-chain systems are stereoselective show that formation of a carbanion intermediate is very unlikely in the elimination reactions of the sulphonyl sulphonates. Bordwell concludes that these results point to a concerted mechanism for cis as well as for trans eliminations in systems where removal of the hydrogen by base is facilitated by the presence of an electron-withdrawing group attached to the beta carbon.

Since the presence of the sulphonyl group on the beta carbon would be expected to strongly stabilise the carbanion, it would seem unlikely that a carbanion is formed in systems where such a stabilising influence is smaller or absent. On this basis, Bordwell was of the opinion that all the earlier cis eliminations reported by Cristol are probably E2 rather than Elcb reactions, bearing in mind, however, that the distinction between Elcb and E2 vanishes as the life-time of the carbanion intermediate becomes infinitessimally small.

Cristol (11), in 1960, reported on the elimination reactions of _cis_- and _trans_-2-phenylcyclohexyltrimethylammonium ions and _cis_- and _trans_-2-phenylcyclohexyldimethylsulphonium ions. He found that in the ammonium series trans elimination is 133 times faster than cis elimination and that in the sulphonium series the trans/cis rate ratio is 383. These results were interpreted by Cristol in terms of a concerted E2 process for trans elimination and a multi-stage process for cis elimination.

The trans/cis rate ratios are again smaller than that observed in the hexachlorocyclohexanes and Cristol explained this on the basis of conformational considerations. A chair conformer for a trans coplanar elimination must have the leaving groups, H and $\overset{+}{N}(CH_3)_3$ or $\overset{+}{S}(CH_3)_2$, in the axial positions where there will be extreme crowding. On the other hand, it is likely that in the ground state the 'onium groups will reside in an equatorial position with the phenyl group in the axial position. The slower rate of elimination could then be the result of the increase in energy to force the 'onium group into the axial position required for the formation of the anti-coplanar transition state.

In 1962, DePuy (10) reported on the base-promoted eliminations of cis- and trans-2-arylcyclopentyl tosylates in which k_{trans}/k_{cis} is only about 14. For the cis elimination of the trans-2-arylcyclopentyl tosylates, he determined a Hammett rho value of 2.34 ± 0.03. In previous work (23) on a series of 2-arylethyl tosylates, which can acquire a trans coplanar conformation, he found a rho value of 3.39 ± 0.29. This must mean that there is a smaller development of negative charge at the transition state for the cis elimination than in the trans elimination of the acyclic compound suggesting that the former is the more concerted process.

On the basis of these results and the results of the other cis elimination reaction studies previously cited, DePuy (10) proposed that the essential feature of the geometry for an E2 process is not the trans relationship of the eliminated atoms or groups, H and X, but coplanarity of the four-centre system. He suggested that a plot of the rate of elimination versus the dihedral angle between the hydrogen and the departing group would show maxima at both 0° and 180° and a minimum at 90°. This means that coplanar transition states, whether cis or trans, have a lower energy than non-coplanar transition states, and, consequently, elimination will be more facile when the dihedral angle is 0° or 180°. As a corollary to this, he predicted that as the dihedral angle approached 90° from either 0° or 180°, the elimination would approach E1cb.

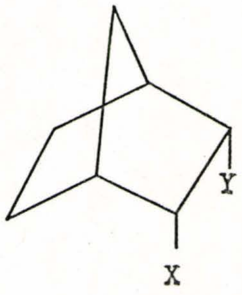
On the basis of these predictions, previous results reported in the literature are more readily understood. Cristol (4) had found that in the 2,3-dihalobicycloheptane series cis elimination is faster than trans elimination. Here, cis elimination can proceed by way of a coplanar transition state whereas trans elimination cannot. Furthermore, in the study of the elimination reaction of 11,12-dichloro-9,10-ethanoanthracene, Cristol (3) found k_{cis}/k_{trans} to be about eight. A cis coplanar transition state is attainable but coplanarity is not possible for trans elimination.

In 1965, DePuy (59) reported in detail on the elimination reactions of 2-arylcyclopentyl tosylates with t-butoxide ion in t-butyl-alcohol. First, he established conclusively that the reactions of trans-2-arylcyclopentyl tosylates are indeed cis eliminations. He then investigated in more detail than in his first paper (10) the steric and electronic characteristics of the transition state for these eliminations. He found a slightly larger rho value of 2.76 ± 0.04 for cis elimination, compared to 2.34 reported earlier (10). For trans elimination in the cis-2-arylcyclopentyl tosylates, a rho value of 1.5 was observed.

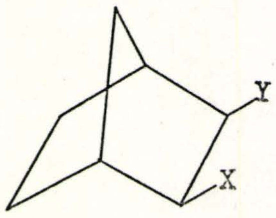
The transition state for the reaction of 2-phenylethyl tosylate is considered to be a good model for a concerted E2 reaction lying slightly to the carbanion side of the "central state" (29). A comparison of its rho value of 3.4 (47) with the rho values for the reactions of the 2-arylcyclopentyl tosylates shows that the transition state for both the cis elimination and the trans elimination in the cyclic systems have less carbanionic character than the transition state for trans elimination in the phenylethyl system.

Although the cis elimination reaction of trans-2-arylcyclopentyl tosylate may have some carbanion character, there is no indication that the reaction is in fact proceeding by way of a carbanion intermediate. First, the reaction conditions appear to be too mild to permit the formation of a benzyl carbanion. Secondly, a rho value of 2.8 seems too small for an Elcb mechanism. Thirdly, the hydrogen-deuterium isotope effect, k^H/k^D, for cis elimination of trans-2-phenylcyclopentyl p-toluenesulphonate is 5.6 at 50°C. If this reaction was proceeding by a carbanion mechanism, the extent of proton transfer to base at the transition state would be expected to be considerably greater than at the transition state for a concerted process. According to present theory, page 67 of this thesis, this would result in a lower isotope effect. The k^H/k^D value for 2-phenylethyl p-toluenesulphonate at 30°C. is 5.7 (61) (estimated 5.2 at 50°C.). The similarity in isotope effects for cis elimination in the 2-phenylcyclopentyl system and trans elimination of the 2-phenylethyl system would indicate that the two processes proceed by the same mechanism. Clearly, these results establish rather conclusively that cis elimination from trans-2-phenylcyclopentyl p-toluenesulphonate is indeed a concerted process.

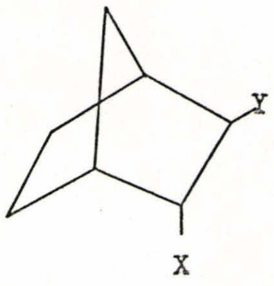
LeBel (60,62), in 1963, reported on a particularly thorough study of the E2 reactions of a number of 2,3-dihalonorbornanes with sodium 1-pentoxide in 1-pentanol. The results of dehydrohalogenation clearly confirmed the noted preference for cis elimination that Cristol (4) had observed in his earlier work on bicyclic systems. At 110°C., the cis/trans rate ratios were found to be 31, 29 and 67 for dibromides, chlorobromides and dichlorides, respectively. The enthalpies and entropies of activation vary in the same direction and by approximately



XXXII X=Y=Br
XXXIII X=Br, Y=Cl
XXXIV X=Y=Cl



XXXV X=Y=Br



XXXVI X=Y=Br
XXXVII X=Cl, Y=Br
XXXVIII X=Y=Cl

the same magnitude in the series dibromide : chlorobromide : dichloride, regardless whether a cis or trans elimination course is followed. LeBel interpreted this trend as indicating that both cis and trans eliminations proceed by similar mechanistic courses.

This similarity of mechanism for these cis and trans eliminations had been advanced by Cristol (4,5). He proposed that a multi-stage mechanism occurs for systems in which the bonds are rigidly held in eclipsed positions and for which a trans coplanar transition state is geometrically improbable. It was LeBel's contention, however, that his data permits a choice between an Elcb and an E2 mechanism and that the evidence best fits concerted dehydrohalogenations.

If the elimination reactions proceed by way of a carbanion mechanism, the rate-determining step will depend on the ease with which the beta-hydrogen can be abstracted by base. In the 2,3-dihalonorbornanes, the *trans*-isomers would present more hindrance to base attack than would the *endo*-*cis*-isomers and cis eliminations might be expected to proceed more slowly. The opposite is consistently observed, however, in keeping with a one-step mechanism.

Additional support for the concerted mechanism is derived from isotopic studies. When the dideuterated analogues of XXXII and XXXVI were partially reacted no deuterium exchange was found in the recovered substrates. This criterion does not establish the concerted nature of the reaction; however, it is a necessary criterion.

The hydrogen-deuterium isotope effect is better evidence.

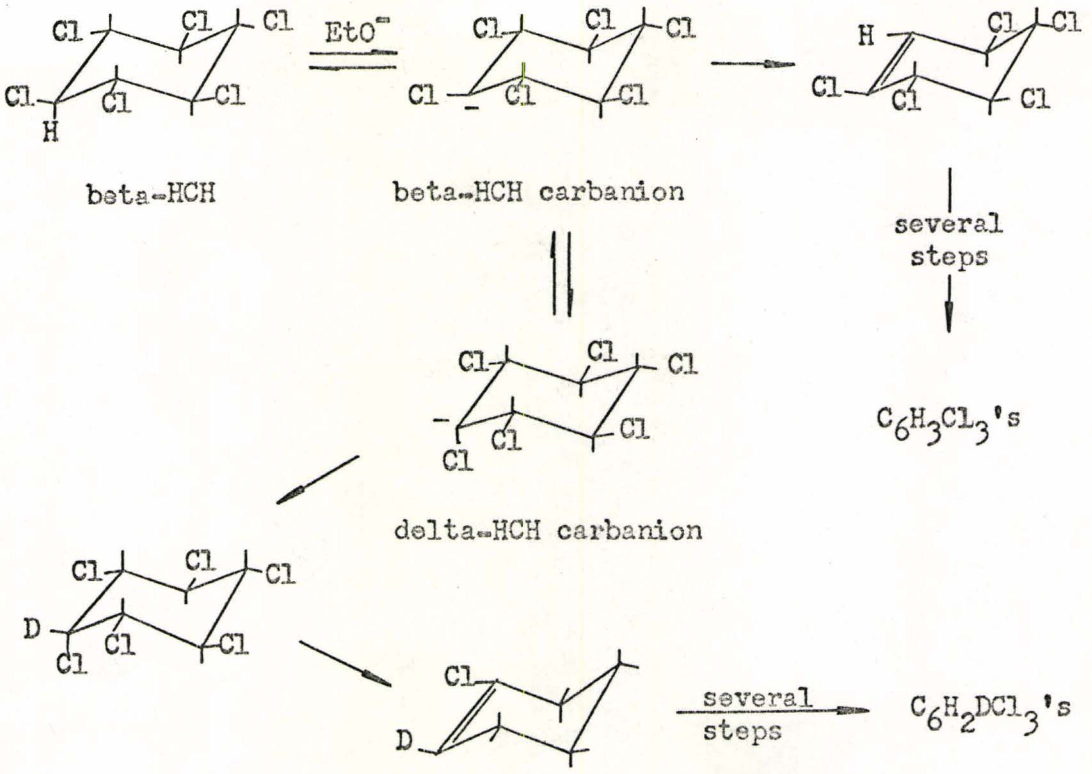
The k^H/k^D value for trans elimination of XXXII is 3.4 at 126.7°C. and for cis elimination of XXXVI is 3.6 at 96.3°C. For comparison, the beta-phenylethyl system is generally considered a good model for the concerted E2 reaction. Extrapolation of Saunders' value of k^H/k^D for the dehydrobromination of 2-phenylethyl bromide with sodium ethoxide in ethanol (61) leads to an estimate of 3.6 at 127°C. On the basis of present theory, as mentioned earlier, the similarity in isotope effects found in the reactions of the 2,3-dihalonorbornanes and the E2 reaction of the 2-phenylethyl bromide would indicate that the two processes proceed by the same mechanism.

Additional evidence in favour of a one-step mechanism for the dehydrohalogenations of the 2,3-norbornanes is obtained from consideration of the products of elimination for the bromochlorides, XXXIII and XXXVII. Both cis- and trans-isomers give predominantly 2-chloro-2-norbornene. If compounds XXXIII and XXXVII underwent elimination by an Elcb mechanism, one would predict predominant carbanion formation at the carbon atom bearing the bromine substituent (63), with subsequent rapid elimination of the chloride ion. The fact that dehydrobromination predominates in both cis and trans elimination indicates, therefore, that bromide, the better leaving group, is involved in the rate-determining step. This is compelling evidence that the reactions are indeed E2 processes.

LeBel's observations support the premise that the reactions of 1,2-dihalides follow a concerted pathway with varying degrees of C-H and C-X bond rupture depending upon the dihedral angle and the structures of the substrate and the olefinic product. LeBel concludes, therefore, that geometrical features preventing H and X from becoming trans and coplanar do not necessarily lead to reaction by the carbanion mechanism.

Hine, in his investigations on the carbanion mechanism for β-elimination reactions, became interested in Cristol's work on the dehydrochlorination of beta hexachlorocyclohexane (1,2). It will be recalled that, on the basis of 0.08 per cent excess deuterium found in unreacted beta hexachlorocyclohexane after the reaction had proceeded about fifty per cent to completion, Cristol (44) proposed an Elcb mechanism for the elimination process. He pointed out that in a deuterated solvent the intermediate carbanion suggested for the reaction could either be deuterated with retention of configuration to yield labelled starting material, be deuterated with inversion of configuration to yield labelled delta hexachlorocyclohexane, or lose a chloride ion to give a pentachlorocyclohexene. Either the delta isomer or the pentachlorocyclohexene would then be rapidly dehydrochlorinated to a mixture of trichlorobenzenes, equation (41). Reaction (64) in the deuterated solvent will therefore lead to deuteriopentachlorocyclohexene. Subsequent dehydrochlorination of the pentachlorocyclohexene, which would be a cis elimination but activated by the double bond(s) already present in the molecule, would not be likely to remove the deuterium. Therefore, the trichlorobenzene formed would be expected to be partly deuterated.

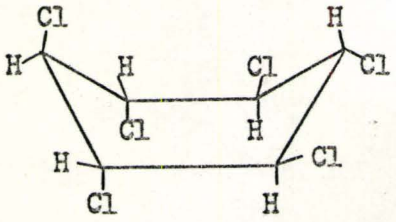
Hine (65) studied the dehydrochlorination of beta hexachlorocyclohexane with sodium methoxide in methanol-O-d and observed 0.02 to 0.05 deuterium atom per molecule in the 1,2,4-trichlorobenzene product



(41)

after seventy per cent reaction. It was found, however, that 1,2,4-trichlorobenzene undergoes deuterium exchange to a significant extent under the reaction conditions and that the amount of deuterium found is no more than would have been expected from deuterium exchange of the trichlorobenzene after its formation. Hine concluded that if the dehydrochlorination of beta hexachlorocyclohexane proceeds to any major extent by carbanion formation, the intermediate carbanions must almost always lose chloride ions and are only very rarely reprotonated to give either the beta isomer or, after isomerisation, the delta isomer. On the other hand, one cannot rule out the possibility that the carbanion formation suggested by Cristol's observation of deuterium exchange occurs for only a very small portion of the reaction.

Dehydrochlorination of the beta hexachlorocyclohexane may proceed by a concerted cis elimination from a boat conformer. Reaction via such a boat conformer would require perhaps 5 kcal. mole^{-1} additional activation energy (66). Possibly part of the higher activation energy for the beta isomer is due to this. Certainly, cis elimination via a boat form would permit a small dihedral angle between the reacting C-H and C-Cl bonds near 0°, XXXIX. As was postulated by DePuy (10), such eliminations with a dihedral angle of 0° appear to be favoured relative to those in which the dihedral angle is of an intermediate size.

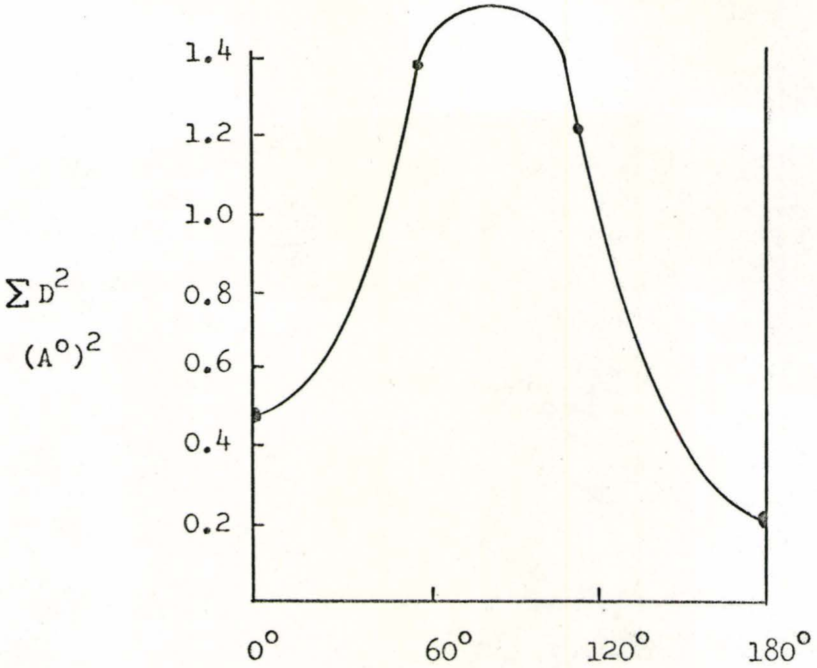


XXXIX

In a subsequent publication Hine (67) discussed the basis for the relationship between dihedral angle and rates of elimination in terms of his principle of least motion (68,69). According to this principle, those elementary reactions will be favoured that involve the least change in atomic positions and electronic configuration. A reaction should therefore occur in such a manner as to require the least expenditure of energy in changing the relative positions of atoms. Since the energy required to stretch or bend a bond is proportional to the square of the distance that the bond is bent or stretched, it is assumed that the reaction takes place so as to minimise the sums of the squares of the atomic displacements.

Hine applied the principle of least motion to the case of the E2 transformation of ethyl chloride to ethylene and calculated the distances the two carbon and four hydrogen atoms must move during the reaction. The geometry of the reactant, that minimises the sums of the squares of the distances the six atoms must move in assuming the transition state was calculated for the elimination reaction with dihedral angles of 0°, 60°, 120° and 180°. A plot of the minimum sums of squares for atomic displacements against dihedral angle is shown in Figure (1). From the four values calculated it is clear that there should be a tendency for pure trans eliminations (dihedral angle of 180°) to be faster than pure cis elimination (dihedral angle of 0°) which in turn should be faster than eliminations in which the dihedral angle is in the range 60° to 120°.

The principle of least motion, therefore, seems to provide a simple and plausible explanation for the stereochemistry of elimination reactions. It provides an explanation for the greater facility for



Plot of the sums of the squares of the distances that the atoms must move in an elimination reaction versus the dihedral angle.

Figure (1)

trans eliminations in which the dihedral angle is 180° and for cis eliminations in which the dihedral angle is 0° and substantiates DePuy's hypothesis (10).

B. Isotope Effects

In this section, there will be presented a review of the general theory of isotope effects in unidirectional processes. Emphasis will be placed on Bigeleisen's (70) contribution in his paper on the relative reaction velocities of isotopic molecules in which he uses the absolute rate theory to develop a theory of chemical isotope effects. A discussion will also be given on hydrogen-deuterium isotope effects in hydrogen-transfer processes with particular emphasis being placed on recent contributions by Westheimer (71), Long (72,73) and Thornton (74,75).

Classical statistical mechanics, in which kinetic energy obeys the equipartition law and the Boltzman's equation describes the distribution of the energies of molecules with temperature, predicts a very small isotope effect in unidirectional reactions of an order greater than one and no isotope effect in equilibrium processes. In both rate and equilibrium processes, however, chemical isotope effects of considerable magnitude have been observed and quantum phenomena are considered to be responsible.

The kinetic energy, E, of a molecule is considered to be the sum of the translational energy, E_t, and the internal energy, E_i, the latter being made up of the electronic energy, E_e, the rotational energy, E_r, and the vibrational energy, E_v, equation (42). Each of these

$$E = E_t + E_e + E_r + E_v \tag{42}$$

energy terms is quantised. The translational energy levels are very closely spaced and are considered to be continuous and classical. In most reactions, the electrons are in their respective ground states and because electronic ground states are nearly identical for isotopic molecules, differences in electronic energy are not considered to contribute to an isotope effect. Furthermore, except for the hydrogen molecule and at very low temperatures, one can consider the rotational energy levels to be classical. The vibrational energy levels, however, which are relatively far apart, are affected by quantum considerations and are considered to be the source of chemical isotope effects.

If it is accepted that a diatomic molecule behaves as a harmonic oscillator, then quantum mechanics states that the vibrational energy is equal to $(n + \frac{1}{2})h\nu$, where n is the quantum number which may be zero or any integer, h is Plank's constant, and ν is the fundamental vibration frequency of the molecule in the ground state. The frequency of a harmonic oscillator is given by equation (43), where f is the force

$$\nu = \frac{1}{2\pi}\left(\frac{f}{\mu}\right)^{\frac{1}{2}} \tag{43}$$

constant between the two atoms and μ is the reduced mass, $(\frac{1}{m_1} + \frac{1}{m_2})^{-1}$. The calculation of the vibrational energy is more complicated for polyatomic molecules, but the energy levels of each normal mode of vibration can be calculated in an analogous manner.

It is therefore seen that the vibrational energy of a molecule is a function of the masses of the atoms which constitute the molecule. For isotopic diatomic molecules in their lowest vibrational energy state in which the quantum number, n, is zero, the energy difference, referred to as the zero-point energy difference, will be given by $\frac{1}{2}h(\nu_1 - \nu_2)$, where ν_1 and ν_2 are the vibrational frequencies of the light and heavy isotopic species, respectively. In a reaction in which the bond of the diatomic molecule is being broken, the motion of the two atoms with respect to one another is no longer a vibration at the transition state but a translational motion in which the two atoms are moving apart. Consequently, the difference in zero-point energies for the two isotopic transition states will be zero. It follows that the energy required for the lighter isotopic molecule to reach the transition state will be less than for the heavier isotopic molecule and the ratio of the rate constants will be larger than unity. This, then, is the origin of an isotope effect in a reaction involving rupture of a bond to the isotopic atom in the rate-determining process.

Bigeleisen (76) has applied the theory of absolute reaction rates to derive equations for the calculation of the ratio of the rate constants for the reaction of isotopic molecules from vibrational frequency data. His approach is summarised in the following paragraphs.

In reactions between $A_1,B,C,\ldots.$ to give P_1, and $A_2,B,C,\ldots.$ to give P_2, where A_1 and A_2 are isotopic molecules, the rate constants can be expressed as follows:

$$k_1 = K_1 \frac{C_1^*}{C_{A_1}C_B\ldots} \left(\frac{kT}{2\pi m_1^*}\right)^{\frac{1}{2}} \frac{1}{d_1} \qquad (44)$$

$$k_2 = K_2 \frac{C_2^*}{C_{A_2}C_B\ldots} \left(\frac{kT}{2\pi m_2^*}\right)^{\frac{1}{2}} \frac{1}{d_2} \qquad (45)$$

where K_1 and K_2 are the transmission coefficients, C^* is the concentration of the activated complex, m^* is the effective mass of the activated complex along the coordinate of decomposition, and d is the length of the top of the potential energy barrier along the reaction coordinate. Transmission coeeficients represent the fraction of transition states which cross the energy barrier to form products and, as a first approximation, they can be considered to be independent of isotopic mass. Also, since the structure of the electron cloud surrounding a nucleus is nearly independent of the atomic mass of a nucleus in isotopic molecules, the potential energy surfaces for isotopic molecules are essentially indentical and d_1 is equal to d_2. Therefore,

$$\frac{k_1}{k_2} = \frac{C_{A_2} \times C_1^*}{C_{A_1} \times C_2^*}\left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \qquad (46)$$

The ratios of the concentrations of the individual molecules can then be replaced by the corresponding ratios of the complete partition functions to give equation (47).

$$\frac{k_1}{k_2} = \frac{Q_{A_2} \times Q_1^*}{Q_{A_1} \times Q_2^*}\left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \qquad (47)$$

Bigeleisen and Mayer (77) have shown that the ratio of the partition functions for isotopic molecules can be expressed as a simple function of the vibrational frequencies of these molecules and the masses of the isotopic atoms as follows:

$$\frac{Q_{A_2}}{Q_{A_1}} = \frac{s_1}{s_2} \prod_j \frac{m_{j(2)}}{m_{j(1)}} \prod_i^{3n-6} \frac{u_i}{u_i + \Delta u_i} \cdot e^{\Delta u_i/2} \cdot \frac{1 - e^{-(u_i + \Delta u_i)}}{(1 - e^{-u_i})} \qquad (48)$$

where $m_{j(1)}$ and $m_{j(2)}$ are the masses of the isotopic atoms in the isotopic molecules, the s terms are symmetry numbers which indicate the number of indistinguishable positions for the isotopic molecules in question, $u_i = h\nu_i/kT$ and refers to the heavier isotopic molecule, and $u_i + \Delta u_i$ is the corresponding term for the lighter molecule. A similar expression may be written for Q_2^*/Q_1^*, the partition function ratio for the isotopic transition states. Combining these in equation (47) and cancelling like terms gives equation (49). This is the fundamental equation expressing the ratio of the rate constants for the reaction of isotopic molecules in terms of initial state and transition state vibrational frequencies.

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*}\left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{\prod_i^{3n-6} \frac{u_i}{u_i + \Delta u_i} \cdot e^{\Delta u_i/2} \quad \frac{1 - e^{-(u_i + \Delta u_i)}}{1 - e^{-u_i}}}{\prod_i^{3n'-6} \frac{u_i^*}{u_i^* + \Delta u_i^*} \cdot e^{\Delta u_i^*/2} \cdot \frac{1 - e^{-(u_i^* + \Delta u_i^*)}}{1 - e^{-u_i^*}}} \qquad (49)$$

Heavy Atom Approximation

For all isotopes other than those of hydrogen, Δu_i is very much smaller that u_i. Resolution into series of each of the three quantities appearing in the product terms of equation (49), and neglecting in these series terms of second and higher order, leads to the following approximations:

$$\frac{u_i}{u_i + \Delta u_i} \approx 1 - \frac{\Delta u_i}{u_i} \;; \qquad e^{\Delta u_i/2} \approx 1 + \frac{\Delta u_i}{2}$$

and $$\frac{1 - e^{-(u_i + \Delta u_i)}}{1 - e^{-\Delta u_i}} \approx 1 + \frac{\Delta u_i}{e^{u_i} - 1}$$

Substituting these into equation (49), multiplying and neglecting second- and third-order terms gives

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*} \left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{\prod_i^{3n-6} \left[1 + \left(\frac{1}{2} - \frac{1}{u_i} + \frac{1}{e^{u_i} - 1}\right) \Delta u_i\right]}{\prod_i^{3n'-6} \left[1 + \left(\frac{1}{2} - \frac{1}{u_i^*} + \frac{1}{e^{u_i^*} - 1}\right) \Delta u_i^*\right]} \tag{50}$$

Defining a function $G(u_i) = \frac{1}{2} - \frac{1}{u_i} + \frac{1}{e^{u_i} - 1}$ and substituting into equation (50) gives equation (51).

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*} \left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{\prod_i^{3n-6} \left[1 + G(u_i) \Delta u_i\right]}{\prod_i^{3n'-6} \left[1 + G(u_i^*) \Delta u_i^*\right]} \tag{51}$$

The product term in equation (51) can be written as a sum by i fold multiplication and the rejection of terms of second and higher powers. Equation (51) thus becomes

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*}\left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{\left[1 + \sum_{i}^{3n-6} G(u_i)\Delta u_i\right]}{\left[1 + \sum_{i}^{3n'-6} G(u_i)\Delta u_i^*\right]} \qquad (52)$$

which as a first approximation can be written as

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*}\left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \left[1 + \sum_{i}^{3n-6} G(u_i)\Delta u_u - \sum_{i}^{3n'-6} G(u_i^*)\Delta u_i^*\right] \qquad (53)$$

This is the basic equation, known as the Bigeleisen equation, for the calculation of isotope effects associated with heavier atoms.

The quantity in the square brackets of equation (53) gives a quantitative measure of the energy differences in the initial and transition states and is sometimes referred to as the free energy term. Assuming that all molecules are in their ground states, the first summation in this term refers to the zero-point energy difference for the two isotopic molecules in their initial states and the second to the corresponding differences at the transition state. The quantity $(m_2^*/m_1^*)^{\frac{1}{2}}$ is known as the effective mass term and arises from the effect of isotopic mass upon the rate with which a reacting molecule passes over the energy barrier.

In the derivation of equation (53), the crossing of the barrier has been treated as a translation and the partition function corresponding to this motion has been treated as a vibration. An alternative approach, and a theoretically sounder one, is to treat both motion over the barrier and its associated partition function as a translation. When this is done, the expression corresponding to equation (49) has the form

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*} \; \frac{\nu_1^*}{\nu_2^*} \; \frac{\prod_i^{3n-6} \frac{u_i}{u_i + \Delta u_i} \cdot e^{\Delta u_i/2} \cdot \frac{1 - e^{-(u_i + \Delta u_i)}}{1 - e^{-u_i}}}{\prod_i^{3n'-7} \frac{u_i^*}{u_i^* + \Delta u_i^*} \cdot e^{\Delta u_i^*/2} \cdot \frac{1 - e^{-(u_i^* + \Delta u_i^*)}}{1 - e^{-u_i^*}}} \qquad (54)$$

where ν_1^* and ν_2^* are imaginary frequencies corresponding to motion along the decomposition coordinate. The degree of freedom corresponding to this motion is therefore missing from the product term in the denominator which now corresponds to $3n' - 7$ rather than $3n' - 6$ vibrational frequencies. Using the same approximations employed in deriving equation (53), equation (54) may be written in terms of $G(u_i)$ functions as follows:

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*} \frac{\nu_1^*}{\nu_2^*} \left[1 + \sum_i^{3n-6} G(u_i)\Delta u_i - \sum_i^{3n'-7} G(u_i^*)\Delta u_i^* \right] \qquad (55)$$

where ν_1^* and ν_2^* have replaced m_1^* and m_2^*, respectively, and the summation for the transition state is for $3n' - 7$ vibrational modes.

In the foregoing derivations, the ratio of the transmission coefficients for isotopic molecules has been taken as unity. Model potential energy surfaces, however, show that transmission coefficients may depend strongly on the mass of the activated complex and its energy. In a later treatment (70), Bigeleisen has taken this into account and also has expressed vibrational frequency differences for isotopic molecules in terms of isotopic masses and force constants using the so-called "sum rule" formulated by equation (56)

$$4\pi^2 \sum_i^{3n-6} (\nu_{1_i}^2 - \nu_{2_i}^2) = \sum_j^{3n} \left(\frac{1}{m_{1_j}} - \frac{1}{m_{2_j}}\right) a_{ii} \qquad (56)$$

where a_{ii} is the diagonal force constant, and m_j is the mass of the jth. atom. This leads to a particularly powerful equation in which the ratio of rate constants is expressed in terms of the change in the force constants associated with the isotopic molecules as they are converted from the initial to the transition state.

$$\frac{k_1}{k_2} = \frac{s_1 s_2^*}{s_2 s_1^*} \frac{\nu_1^*}{\nu_2^*} \left[1 + \frac{G(u_i)}{2\,u_i}\left(\frac{hc}{kT}\right)^2 \sum_{j}^{3n}\left(\frac{1}{m_{1_j}} - \frac{1}{m_{2_j}}\right)(a_{ii} - a_{ii}^*) \right] \tag{57}$$

It is readily seen from this equation that the greater is the decrease in the force constants associated with the isotopic atom at the transition state the larger will be the isotope effect for the reaction in question. It follows then that one can interpret the relative magnitude of the isotope effects observed in a reaction series in terms of the relative extent to which the bond associated with the isotopic atom is "weakened" at the transition state.

Light Atom Approximation

Applying the basic equation (49), page 58, to compounds of hydrogen and deuterium, u_{Di} may be substituted for u_i and $u_{Hi}-u_{Di}$ for Δu_i to give equation (58). It can be assumed that all fundamental

$$\frac{k_H}{k_D} = \left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}} \left(\frac{s_H/s_H^*}{s_D/s_D^*}\right) \frac{\prod_{i}^{3n-6} \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \cdot \frac{1-e^{-u_{Hi}}}{1-e^{-u_{Di}}}}{\prod_{i}^{3n'-6} \frac{u_{Di}^*}{u_{Hi}^*} \cdot e^{\frac{u_{Hi}^*-u_{Di}^*}{2}} \cdot \frac{1-e^{-u_{Hi}^*}}{1-e^{-u_{Di}^*}}} \tag{58}$$

vibrational modes which do not involve important motion of the isotopically substituted hydrogen are the same in the initial and transition states and hence cancel out in the quotient involving the frequency terms. There are left three vibrations in the initial state (one stretching and two bending modes) and two bending modes in the transition state. The vibrational fequency of most bonds to hydrogen is greater than 1000 cm^{-1}, therefore, e^{-u_i} terms are very much less than one at ordinary temperatures and may be neglected. In addition, if there is no change in the bending frequencies in going from the initial to the transition state, the terms for these frequencies cancel. Equation (58) then reduces to

$$\frac{k_H}{k_D} = \left(\frac{s_H/s_H^*}{s_D/s_D^*}\right)\left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}} \cdot \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \qquad (59)$$

where u_i refers only to the stretching frequency which is lost in proceeding from the initial to the transition state. Since, in almost any molecule H-R, $m_H \ll m_R$, it follows that $u_{Di} / u_{Hi} \approx (m_H^*/m_D^*)^{\frac{1}{2}}$ and, therefore, equation (59) becomes

$$\frac{k^H}{k^D} = \left(\frac{s_H / s_H^*}{s_D / s_D^*}\right) e^{\frac{u_{Hi} - u_{Di}}{2}} \qquad (60)$$

If, however, the bending frequencies of the carbon-hydrogen bond approach zero at the transition state a different simplification can be made.

$$\text{Firstly} \quad \lim_{u_i^* \to 0} \frac{1 - e^{-u_{Hi}^*}}{1 - e^{-u_{Di}^*}} = \frac{u_{Hi}^*}{u_{Di}^*}$$

$$\text{Secondly,} \quad \lim_{u_i^* \to 0} e^{\frac{u_{Hi}^* - u_{Di}^*}{2}} = 1$$

Equation (58) now becomes

$$\frac{k^H}{k^D} = \left(\frac{s_H / s_H}{s_D / s_D^*}\right)\left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}} \prod_i^3 \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi} - u_{Di}}{2}} \qquad (61)$$

The product $\prod_i^3 \frac{u_{Di}}{u_{Hi}}$ is made up of three terms. One of these, namely that corresponding to a stretching motion, cancels $\left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}}$, while the two bending frequency ratios together give m_H/m_D. Also, it can be shown by resolution into series that the product

$$\prod_{i}^{3} e^{\frac{u_{Hi} - u_{Di}}{2}}$$

can be written as a sum

$$\sum_{i}^{3} e^{\frac{u_{Hi} - u_{Di}}{2}}$$

Hence, equation (61) becomes

$$\frac{k^H}{k^D} = \left(\frac{s_H / s_D}{s_D / s_D^{*}}\right) \frac{m_H}{m_D} \sum_{i}^{3} e^{\frac{u_{Hi} - u_{Di}}{2}} \tag{62}$$

In equations (60) and (62), the frequencies of the deuterated compound, if unknown, can be calculated from the corresponding frequencies in the lighter molecule making use of the relationship

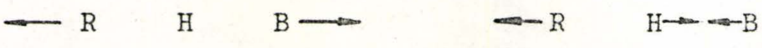
$$\frac{u_{Hi}}{u_{Di}} = \frac{\nu_H}{\nu_D} = \left(\frac{m_D}{m_H}\right)^{\frac{1}{2}} \tag{63}$$

Equation (60) predicts $k^H/k^D \sim 7$ at room temperature for C-H bond rupture and many hydrogen-deuterium isotope effects are close to this value (78). Equation (61) predicts k^H/k^D values greater than 7 and higher values are indeed observed in some reactions. In many cases, however, primary hydrogen-deuterium isotope effects are considerably less than the maximum value predicted by the foregoing considerations and it is clear that this simplified approach to the problem of calculating hydrogen isotope effects from vibrational frequency data is inadequate.

In 1961, it was independently pointed out by Westheimer (71) and Melander (79) that most reactions involving the rupture of a bond to hydrogen are three-centre displacement processes of the type

$$RH + B \rightleftharpoons [R{-}{-}{-}{-}H{-}{-}{-}{-}B] \longrightarrow R + HB \qquad (64)$$

where $[R{-}{-}{-}{-}H{-}{-}{-}{-}B]$ is a linear transition state restricted to the x-axis. If R----H----B were a linear molecule rather than a transition state, it would have two stretching vibrations, a symmetrical and an anti-symmetrical one.



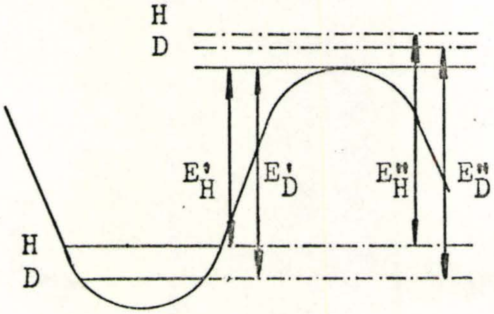
Symmetric   Antisymmetric

Neither of these vibrations corresponds to the stretching vibration of R-H or H-B. Since [R----H----B] is a transition state, one of these vibrations, namely the antisymmetrical one, is not a real vibration since it is motion which leads to reaction and, therefore, it makes no zero-point energy contribution. The symmetrical vibration, however, is a real vibration and its contribution to the zero-point energy difference between the two isotopic transition states will depend upon the relative magnitude of the force constants for the two partial bonds. If the force constants between RH and BH are the same, the hydrogen remains motionless and the frequency of the symmetrical vibration is, therefore, independent of the isotopic mass of the atom. The formation of the transition state should give rise to a large isotope effect because the full zero-point energy difference between the ground state vibrational modes of the C-H and C-D bonds will contribute to the difference in activation energy for reaction of the isotopic molecules.* When the strengths of the partial bonds R--H and H--B are not equal, the "symmetrical" vibration will no longer consist merely of the motion of R and B; the proton will also move and the vibration frequency will depend to some extent on the mass of the central atom. The zero-point energy will be different for the two isotopic transition states and this difference will decrease the contribution of the ground state zero-point energy difference to the isotope effect. Consequently, the

---

* It is assumed in this treatment that the contribution to the isotope effect by changes in the frequencies of bending modes involving hydrogen is small relative to the contribution from stretching modes. For a different point of view on the matter see Reference (80).

isotope effect will be smaller than in the previous case. This is shown in Figure (2) where the activation energy difference, $E_D'' - E_H''$, for the reaction in which the strengths of the partial bonds R--H and H--B are not equal, is less than $E_D' - E_H'$, the activation energy difference for the reaction in which the force constants between RH and HB are the same.



Zero point energies and hydrogen-deuterium isotope effect for a proton transfer reaction.

Figure (2)

From these considerations it is seen that the maximum hydrogen-deuterium isotope effect should be observed when the proton is half transferred from R to B at the transition state and this is depicted in Figure (3).

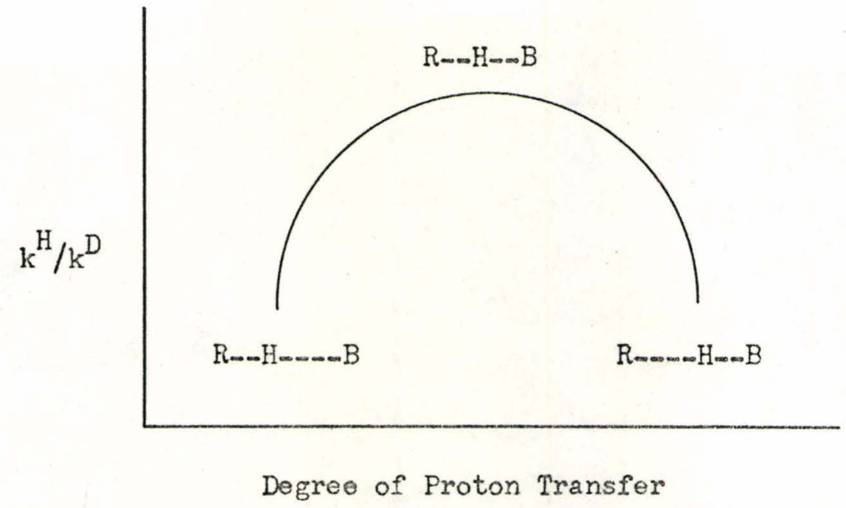


Figure (3)

In 1967, Long (72,73) furnished experimental evidence which supports Westheimer's theoretical prediction of a maximum hydrogen isotope effect in the region where the transition state is symmetrical. He reported on a study of the acid-catalysed rate of exchange of hydrogen atoms attached to various substituted azulenes. He had noted that experimental data available on the hydrogen isotope rate ratios pertaining to the protonation of carbon bases (81,82,83) strongly suggested the possibility of a maximum in the k^H/k^D ratio in the region where the acidities of the protonated substrate and of the catalysing acid are similar. Unsubstituted azulene was known to be a relatively strong base and it is unique in that the acidity of its conjugate acid is nearly identical with that of the hydronium ion. He predicted, therefore, a hydrogen isotope effect close to maximum for the acid-catalysed proton exchange of this substrate.

The acid-catalysed exchange of hydrogen atoms attached to an aromatic nucleus has been shown to proceed by the exchange mechanism A-SE2 (72), equation (65). Long studied the rates of proton transfer for azulene and some substituted azulenes with several catalysts and determined the hydrogen isotope effects associated with these reactions. The results are shown in Table I together with the acidity difference between the protonated substrate and the acid catalyst (Δ pK = pK protonated substrate - pK catalyst). The k^H/k^D data are represented as a function of ΔpK in Figure (4).

Table I

Correlation of Δ pK and Kinetic Isotope Effect for Hydrogen Removal from Azulinium and Substituted Azulinium Ions

Protonated Substrate	Catalyst	(k^H/k^D)calc'd	Δ pK
1. Guaiazulene	H_2O	6.0	3.3
2. Trimethylazulene	H_2O	9.6	2.3
3. Guaiazulene-2-sulphonate	H_2O	7.4	1.1
4. Azulene	H_2O	9.2	0
5. 1,3,5-Trimethyoxybenzene	H_2O	6.7	-3.5
6. Azulene	Formate Ion	6.3	-5.5
7. Azulene	Acetate Ion	6.1	-6.5

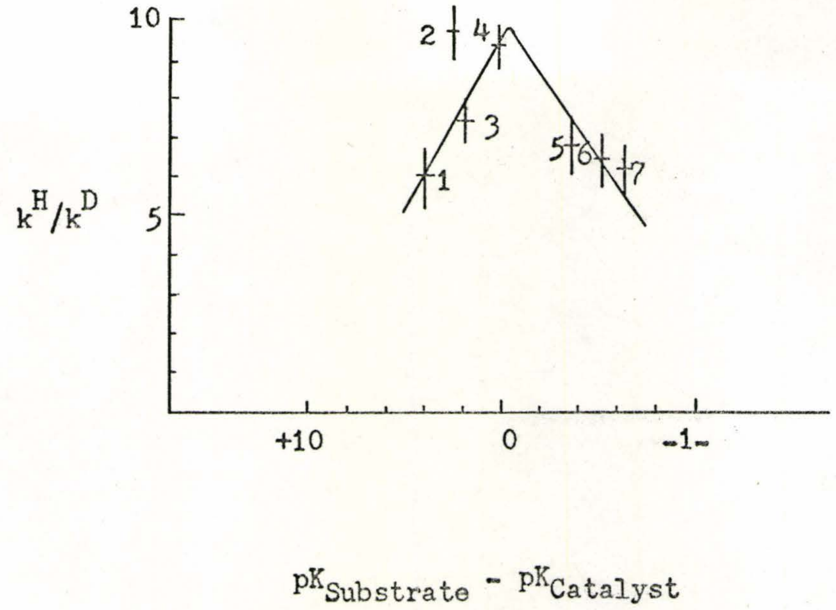
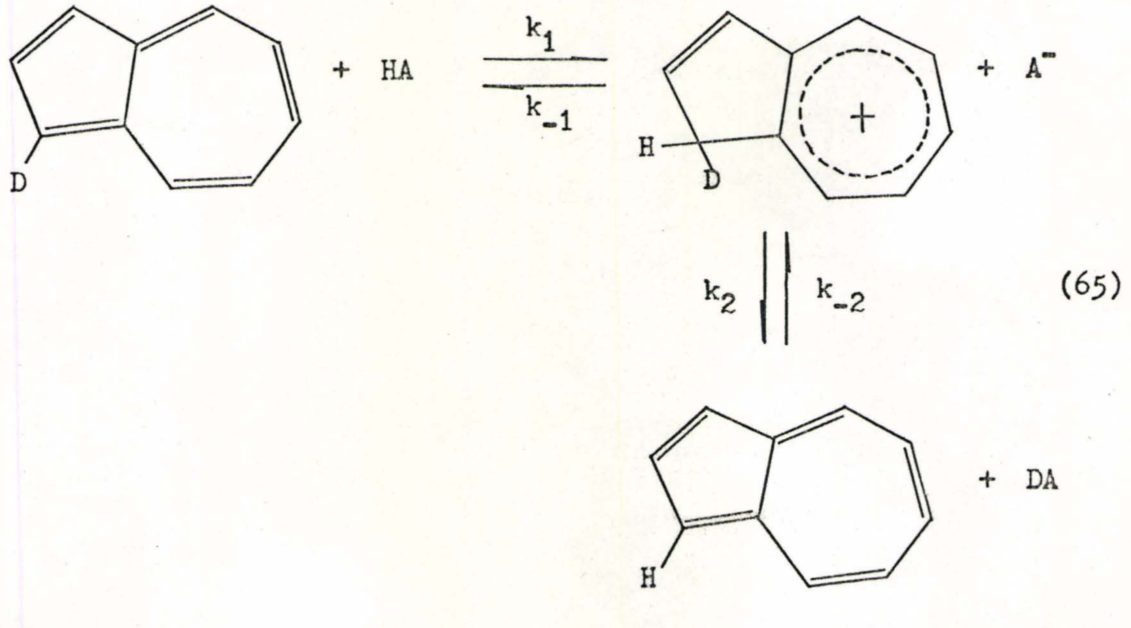

10
5
k^H/k^D
1
2
3
4
5
6
7
+10
0
-1-
$pK_{Substrate} - pK_{Catalyst}$

Figure (4)


D
+ HA
k_1
k_{-1}
H
D
+
+ A^-
k_2
k_{-2}
H
+ DA

(65)

It is evident that the isotope ratios for the aromatic carbon acids pass through a definite maximum. The exact position of the maximum, however, is somewhat in doubt owing to the limits of error in the measurement, but it is in the region close to $\Delta pK = 0$. In two cases, the k^H/k^D value was determined to be in excess of the maximum value (~7) predicted on the basis of simple zero-point energy differences in the C-H and C-D bonds for the reactant species only. This prediction, however, does not include the effect of bending modes in the initial and transition states, or the possibility of tunneling. It appears that one or both of these effects may be coming into play in this reaction.

On the basis of this data, the existence of a maximum in the hydrogen isotope effect for carbon acids seems fairly well established. Also, the results are in accord with the prediction that a maximum hydrogen isotope effect will occur in the region where hydrogen is half transferred from one base to another at the transition state.

Examination, now, of Figure (3) reveals that it is possible for two reactions to give rise to the same hydrogen-deuterium isotope effect while having quite different extents of C-H bond weakening at the transition state. The transition state may be reached before the proton is half transferred to base giving rise to an isotope effect which is smaller than the maximum. On the other hand, the same isotope effect may be observed if, at the transition state, the proton is more than half transferred to base. Other criteria are therefore necessary in order to determine the particular side of the symmetrical situation on which the transition state lies.

Isotope Effects Arising from the Difference in Basicity between DO^- in D_2O and HO^- in H_2O.

A further approach to the problem of determining the extent of proton transfer to base at the transition state has recently been advanced by Thornton (74,75). This involves a comparison of the relative reaction rates with base DO^- in D_2O and HO^- in H_2O.

The relative basicity of the hydroxide ion and deuteroxide ion is determined by the equilibrium

$$2DO^- + H_2O \overset{K_B}{\rightleftharpoons} 2HO^- + D_2O \qquad (66)$$

where K_B can be determined from self-ionisation constants of H_2O and D_2O, equations (67) and (68), and from L, equation (69).

$$2H_2O \overset{K_H}{\rightleftharpoons} HO^- + H_3O^+ \qquad (67)$$

$$2D_2O \overset{K_D}{\rightleftharpoons} DO^- + D_3O^+ \qquad (68)$$

$$2D_3O^+ + 3H_2O \overset{L}{\rightleftharpoons} 2H_3O^+ + 3D_2O \tag{69}$$

The ratio K_H/K_D determines the equilibrium constants, K_{eq}., for the exchange reaction

$$2H_2O + DO^- + D_3O \overset{K_{eq}}{\rightleftharpoons} 2D_2O + HO^- + H_3O^+ \tag{70}$$

where $K_H/K_D = K_{eq}$. From these considerations it can be seen that

$$K_B = \frac{K_{eq}^2}{L} \tag{71}$$

and that the isotope effect for the conversion of <u>one</u> DO^- bond in the solvated deuteroxide ion to one DO bond in heavy water is

$$\frac{K_D}{K_H} = K_B^{\frac{1}{2}} \tag{72}$$

The maximum isotope effect, K^D/K^H, will occur when the proton is completely transferred from H_2O to DO^-, equation (66). This value is the square root of the equilibrium constant K_B and it can be calculated using values of $L = 9.6$, $K_H = 1 \times 10^{-14}$ and $K_D = 1.56 \times 10^{-15}$ (75). For reaction at 25°C., $K_B^{\frac{1}{2}} = 2.07$. At 80°C., this value is expected to be 1.88 for complete proton transfer at the transition state. For a transition state in which the proton is half transferred between the substrate and base, the isotope effect should be $(1.88)^{\frac{1}{2}} = 1.37$.

C. The Nature of the Transition State in Bimolecular Elimination Reactions.

Insight into the effect of structural and environmental factors on the extents of bond weakening at the transition state for bimolecular elimination reactions can be gained from the kinetic isotope effects associated with the rupture of the C-X bond and with the transfer of hydrogen to base. In the previous section, which has covered the theoretical background for an understanding and interpretation of kinetic isotope effects, the magnitude of the leaving group isotope effect was shown to be proportional to the decrease in the composite force constant associated with the bond between the alpha carbon and the leaving group at the transition state. Interpretation of the hydrogen-deuterium isotope effect, however, is not as straight forward. The relationship between the change in the hydrogen-deuterium isotope effect and the extent of hydrogen transfer to base in two reactions depends upon whether the proton is more or less than half transferred at the transition state. If the proton is less than half transferred from substrate to base, then that reaction with the larger k^H/k^D value will have a transition state in which the extent of hydrogen transfer is greater. On the other hand, if the proton is more than half transferred at the transition state, a smaller hydrogen-deuterium isotope effect will be indicative of greater proton transfer to base. Clearly, then, in order to interpret the relationship of hydrogen-deuterium isotope effects in a reaction series the extent of proton transfer at the transition state must be known.

A good deal of work using kinetic isotope effects to elucidate the nature of the transition state in elimination reactions has been done with ammonium and sulphonium salts because their leaving groups lend themselves to isotope effect measurements. This section will concentrate on work reported for such compounds since the writer's research involves analogous cyclic quaternary ammonium salts.

Recently, Thornton (75) has clarified the question of the extent of proton transfer to base in elimination reactions of such systems. Theory predicts that the larger the secondary isotope effect, k^{DO^-}/k^{HO^-}, the greater will be the extent of proton transfer to base at the transition state. It was shown in the previous section that a maximum value of 1.88 would be expected for a reaction in which the proton is completely transferred to base at the transition state and a

Table II

Isotope Effects for Reaction of 2-Phenylethyl Derivatives with Hydroxide Ion in Water.

Substrate	k^{DO^-}/k^{HO^-} [b] at 80°C.	k^H/k^D at 50°C.
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	1.79	3.02[a]
p-$ClC_6H_4CH_2CH_2\overset{+}{N}(CH_3)_3$	1.73	3.48[a]
$C_6H_5CH_2CH_2\overset{+}{S}(CH_3)_2$	1.57	5.05

[a] Saunders (105). Measured in 50% ethanol-water.
[b] Thornton (74).

value of 1.37 for a transition state in which the proton is half transferred. The secondary isotope effects at 80°C. for the E2 reactions of 2-phenylethyltrimethylammonium bromide, p-chloro-2-phenylethyltrimethyl-bromide and 2-phenylethyldimethylsulphonium bromide are shown in Table II. Thornton considered that these values, in relation to the theoretical value for complete proton transfer, indicated a high degree of bond formation between the proton and base at the transition state; that is, the transition states are product-like with the proton being much more than half transferred. Even more convincing evidence for a transition state in which the proton is more than half transferred to base is provided by a comparison of the change in the primary and secondary (base strength) isotope effects for the three salts. The trend in the k^{DO^-}/k^{HO^-} ratios show that the extent of proton transfer to base decreases in the order $C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$, p-$ClC_6H_4CH_2CH_2\overset{+}{N}(CH_3)_3$ and $C_6H_5CH_2CH_2\overset{+}{S}(CH_3)_2$. This is the order, however, of increasing primary hydrogen isotope effects. The only way in which a decrease in the extent of proton transfer to base at the transition state can result in an increased primary hydrogen isotope effect is for the extent of proton transfer for the two ammonium salts, and probably for the sulphonium salt as well, to correspond to positions on the right hand side of the maximum of Figure (3).

Saunders was the first to use primary hydrogen isotope effect studies to obtain information concerning the nature of the transition state in elimination processes. He measured the variation of the magnitude of the hydrogen-deuterium isotope effect with respect to the nature of the leaving group for the reaction of some 2-phenylethyl derivatives with sodium ethoxide in ethanol (61), equation (73). The results are shown in Table III.

$$C_6H_5CD_2CH_2X + EtO^- \xrightarrow{EtOH} C_6H_5CD{=}CH_2 + EtOD + X^- \qquad (73)$$

Table III

Kinetic Isotope Effects and Hammett Reaction Constants for the Reaction of 2-Phenylethyl Derivatives with Sodium Ethoxide in Ethanol at 30°C.

Leaving Group	k^H/k^D	$(k^L/k^H-1)100$ at 60°C.	rho (ref)
Br	7.1	-	2.14 (16)
OTs	5.7	-	2.27 (23)
$\overset{+}{S}(CH_3)_2$	5.1	0.64	2.64 (100)
$\overset{+}{N}(CH_3)_3$	3.5[a]	0.94	3.77 (87)

[a] Estimated from a value of 3.0 at 50°C.

It is seen that the value of k^H/k^D increases in the order

$\overset{+}{N}(CH_3)_3 < \overset{+}{S}(CH_3)_2 <$ OTs $<$ Br. At that time, it was considered that the larger the hydrogen isotope effect associated with a reaction the greater the extent of C-H bond weakening at the transition state. On the basis of the argument based on Thornton's DO^- vs HO^- studies, however, it is now clear that for the ammonium salt, at least, the β-hydrogen is more than half transferred to base at the transition state. The larger isotope effects in the other systems must, therefore, mean that the extent of C-H bond weakening is actually decreasing in the series $\overset{+}{N}(CH_3)_3$ to Br. Indeed, the isotope effect, k^H/k^D, of 7.1 for the bromide is about what would be expected if there was approximately half proton transfer at the transition state for this reaction. In other words, the transition state for the bromide compound would appear to correspond to a position at about the maximum of the curve of Figure (3) with the transition states for the others falling to the right in the order OTs, $\overset{+}{S}(CH_3)_2$ and $\overset{+}{N}(CH_3)_3$.

This interpretation of Saunders' isotope effect results is consistent with the relative magnitudes of the Hammett rho constants for the 2-phenylethyl derivatives (see Table III). The larger extent of proton transfer to base for the ammonium salt might be expected to result in a larger development of negative charge on the β-carbon and, therefore, a greater sensitivity of reaction rates to substituent effects. This is what is observed; the rho value for the ammonium salt elimination is 3.77 compared to 2.14 for the bromide system.

The first leaving group isotope effect work in elimination reactions was also performed on the phenylethyl system. Saunders obtained the very low sulphur isotope effect of 0.15 per cent for the reaction of 2-phenylethyldimethylsuphonium ion with hydroxide ion in water (18). Shortly thereafter, Ayrey and Bourns (85) reported a nitrogen isotope effect of 0.94 per cent for the reaction of the corresponding ammonium ion with ethoxide ion in ethanol. It would appear then that C-N bond rupture is much more advanced at the transition state for the ammonium salt reaction than C-S bond rupture for the sulphonium salt. Saunders, however, has recently reinvestigated the sulphonium salt reaction and has come to the conclusion that the sulphur isotope effect is actually 0.64 per cent (19). Both effects, therefore, are about one third the theoretical maximum for complete loss of the C-X composite force constant and, apparently, there is little difference in the extent of C-X bond rupture in the two systems.

Smith (86), in these laboratories, undertook a study of the kinetic isotope effects associated with the E2 reactions of ethyltrimethylammonium ion and 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol in order to test the prediction of Bunnett (29) on the effect of a β-aryl group on the relative timing of the two bond-rupture processes. Bunnett maintained that the introduction of a β-aryl substituent should stabilise a β-carbanion-like transition state and therefore cause a shift towards the "nearly Elcb" extreme. Furthermore, one might intuitively expect that any structural change in an E2 reaction which facilitates the departure of one atom (H or X) will cause the bond to that atom to be weakened more and the bond to the other atom to be weakened less at the transition state.

The results shown in Table IV indicate that there is less C-N bond weakening at the transition state for the reaction of 2-phenylethyltrimethylammonium ion than for ethyltrimethylammonium ion. Furthermore, since the hydrogen isotope effect is larger for the former compound, one must conclude on the basis of Westheimer's hypothesis (71) and Thornton's DO^- versus HO^- studies (74,75) that the introduction of a phenyl group on the β-carbon results in a transition state in which there is less transfer of hydrogen to base than in the reaction of the unsubstituted

Table IV

Isotope Effects in the E2 Reaction of Quaternary Ammonium Ions at 60°C.

Ion	Reaction Condition	$(k^{14}/k^{15}-1)100$	k^H/k^T
$CH_3CH_2\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.86^a	
	basic hydrate (vacuum)		3.0^c
	hydroxide in triethylene glycol		2.8^d
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.42^b	
	methoxide in methanol		4.2^c

[a] Solvent - 95% ethanol.
[b] Solvent - absolute ethanol at 40°C.
[c] Simon (88).
[d] Calculated by Simon (88) from an experimental value of 1.23 at 130°C.

salt. It would appear then that, contrary to expectations, the less advanced the rupture of one bond at the transition state the less advanced is the rupture of the other bond.

Smith then carried out a much more thorough investigation of the effect of the β-aryl group on the transition state of β-elimination reactions by making a systematic study of the effect of substituents on the benzene ring of 2-arylethyltrimethylammonium ion on the magnitude of the nitrogen and hydrogen-deuterium isotope effects (86). His results are summarised in Table V.

Table V

Isotope Effects for the E2 Reaction
of 2-Arylethyltrimethylammonium Ion
with Sodium Ethoxide in Ethanol at 40°C.

para-Substituent in $ArCH_2CH_2\overset{+}{N}(CH_3)_3$	$(k^{14}/k^{15}-1)100$	k^H/k^D
OMe	1.37	2.64
H	1.42	3.23
Cl	1.14	3.48
CF_3	0.88	4.15

It is seen that the nitrogen isotope effect decreases and the hydrogen isotope effect increases as the substituent in the para-position becomes more electron withdrawing. Since it now appears to be well established that the proton is more than half transferred to base at the transition state for the elimination reactions of quaternary ammonium salts, it follows that the presence of the electron-withdrawing groups decreases the extent of C-H bond rupture as well as of C-N bond rupture at the transition state in this reaction series. These results, as well as the relative magnitude of the isotope effects found in the ethyl- and 2-phenylethyltrimethylammonium ion reactions, led Smith to postulate that any structural change which causes one bond to be weakened more at the transition state will have a corresponding effect on the other bond. In other words, the extent of C-H and C-X bond rupture at the transition state for E2 reactions parallel each other.

A test for this hypothesis has been provided by investigations made by Smith (86) and Saunders (87) into the effect that a change in base has on the goemetry of the transition state. Smith determined the nitrogen isotope effects associated with the reactions of ethyltrimethylammonium with ethoxide ion in ethanol and with t-butoxide ion in t-butyl alcohol, while Saunders determined the hydrogen-deuterium isotope effects and Hammett rho constants for the reactions of 2-phenylethyltrimethylammonium ion with the same two bases. The results are shown in Table VI.

The nitrogen isotope effect for the ethoxide-promoted reaction

Table VI

Hammett Correlations and Isotope Effects in the Reactions
of Ethyltrimethylammonium Ion and
2-Phenylethyltrimethylammonium Ion
with Ethoxide Ion and *t*-Butoxide Ion.

Substrate	Base/Solvent	$(k^{14}/k^{15}-1)100^{c}$	k^{H}/k^{D}	rho[a]
$CH_3CH_2\overset{+}{N}(CH_3)_3$	EtO^-/95% EtOH	1.86 ± 0.04		
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	EtO^-/EtOH		2.98^{b}	3.86
$CH_3CH_2\overset{+}{N}(CH_3)_3$	*t*-BuO^-/*t*-BuOH	1.41 ± 0.03		
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	*t*-BuO^-/*t*-BuOH		6.97^{a}	3.04

[a] Saunders (87) at 30°C.
[b] Saunders (87) at 50°C.
[c] Smith (86) at 60°C.

of ethyltrimethylammonium ion is significantly greater than for the *t*-butoxide-promoted reaction showing that there is more carbon-nitrogen bond rupture at the transition state in the former than in the latter. Moreover, the lower hydrogen-deuterium isotope effect for reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol indicates a more complete proton transfer to base at the transition state than for reaction with t-butoxide ion in t-butyl alcohol. The higher rho value for the ethoxide-promoted reaction shows that the transition state in this reaction has a more highly developed negative charge on the β-carbon than has the transition state for reaction with the stronger base. These results are therefore consistent with Smith's hypothesis that the two bond-rupture processes parallel each other in E2 reactions.

It is interesting to note that the conclusions which have been drawn from the isotope effect studies are consistent with the predictions of the so-called Hammond hypothesis. This hypothesis, which relates transition state geometry to the relative energy contents of reactants and products (or intermediates), predicts that the more exothermic is a particular reaction step the more the transition state for that step resembles the initial state. Conversely, the more endothermic is the reaction the more product-like will be the transition state. It follows that increasing the electron affinity of the leaving group, increasing the electron-withdrawing capacity of substituents on the β-carbon, or increasing the strength of the base should all tend to lower the energy of products relative to reactants and hence make the transition state more reactant-like. For each of these changes, the isotope effect results indicate that there has been a decrease in the extent of proton transfer to base and C-X bond rupture at the transition state in accordance with prediction.

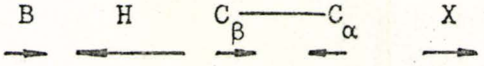
A short-coming of the Hammond hypothesis is that it involves a comparison of the transition state with reactants, products or intermediates, all of which may differ in energy by relatively large amounts from the transition state. Indeed, there is a distinct possibility of "crossover" effects in the potential energy curves for differently-substituted systems so that predictions concerning the transition state based on substituent effects on reactants and/or products may lead to completely erroneous results.

Recently, Thornton (74,75) has published a simple theory for predicting the effects of structural change on the transition state directly without reference to the reactants or products of the reaction. In this theory, account has been taken of the substituent effects, not only on motion along the reaction coordinate (parallel motion), but also on the normal modes of vibration of the transition state (motion perpendicular to the reaction coordinate).

Thornton's approach has been to describe the effect of a substituent on a bond by the addition of a linear perturbation to the parabolic potential energy function for that bond. For motion along the reaction coordinate, the potential energy as a function of distance can be approximated as an inverted parabola in the region of the potential energy maximum. Because of this, it turns out that the effect of a substituent on bond length which results from its effect on the motion along the reaction coordinate is exactly the opposite to its effect on the normal vibrational modes of the transition state. Whereas a substituent change which makes an increase in the coordinate X of a transition state more difficult leads to a perturbed equilibrium geometry in which X is decreased if the force constant for the X motion is positive (perpendicular motion), it leads to an equilibrium geometry in which X is increased if the force constant is negative (parallel motion).

Although the effect of structural change on both perpendicular and parallel motion must be considered for a complete description of the change in transition state geometry, in most cases consideration of the latter is sufficient. This is because the magnitude of the change in coordinate X is inversely proportional to the force constant, or curvature of the potential energy surface in the region of energy maximum. Since in most systems this curvature is considerably smaller for parallel than for perpendicular motion, the geometrical change will be determined largely by the substituent effect on the former.

For an E2 elimination process, the reaction coordinate motion can be described as follows:



Electron release at C_β will be expected to strengthen the H-C_β bond and hence make the motion which extends this bond more difficult. On the other hand, it will make compression of the C_β-C_α bond easier. The effect of the substituent on the H-C_β bond can be expected to control the parallel motion, however, since the presence of the C_β-C_α σ bond will prevent a large change in the carbon-carbon bond length. Since, for parallel motion, a structural feature which makes extension of a bond more difficult will result in a transition state in which that bond is longer than in the absence of this feature, it follows that electron releasing substituents on C_β will lengthen the H-C_β bond while electron withdrawing substituents will shorten it. Extension of the H-C_β bond in the parallel motion is accompanied by shortening of the B-H bond and lengthening of the C_α-X bond. Accordingly, electron releasing substituents on C_β, in addition to lengthening the H-C_β bond, will shorten the B-H bond and extend the C_α-X bond. In other words, the transition state becomes more product-like. The primary hydrogen and nitrogen isotope effects observed by Smith (86) and the k^{DO^-}/k^{HO^-} effects observed by Thornton (74,75) are all completely in accord with these predictions.

The theory predicts that increasing the base strength of B will make compression of the B-H bond easier. If it is assumed that this effect controls the motion, as seems reasonable since the B-H bond is closest to the centre of structural change, then the stronger base, in addition to increasing the B-H bond length at the transition state, will shorten both H-C_β and C_α-X. The transition state, therefore, becomes more reactant like. This prediction is in accord with the observations of Smith (86) and Saunders (87) relating to the effect on nitrogen and hydrogen isotope effects, respectively, in changing base from EtO^- in EtOH to t-BuO^- in t-BuOH.

Finally, it is predicted that for leaving groups which are more basic extension of the C_α-X bond will become more difficult and, therefore, the transition state will become more product like. The trend in the primary hydrogen isotope effects shown in Table III for leaving groups Br, OTs, $\overset{+}{S}(CH_3)_2$ and $\overset{+}{N}(CH_3)_3$ is in accord with these predictions as is also the larger secondary isotope effects for the E2 reaction of $C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$, $k^{DO^-}/k^{HO^-} = 1.79$, compared to $C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_2C_6H_5$, $k^{DO^-}/k^{HO^-} = 1.62$, recently reported by Thornton (74).

There has been a considerable body of evidence suggesting that the more product-like transition states have relatively more carbanionic character. This is particularly evident from the trend in rho values shown in Table III which show a very much higher electron density on the β-carbon in the 2-phenylethyltrimethylammonium ion reaction than in the reactions of the compounds having less basic leaving groups. The reaction coordinate motion depicted earlier accounts for this. By making H move more relative to C_α and C_β move more relative to X, it follows that making the transition state more product like produces relatively more carbanion character at C_β than carbonium character at C_α. In other words, the transition state becomes more Elcb like.

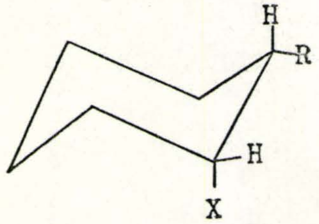
Although the theory of Thornton in general leads to the same conclusions as the Hammond postulate, it is on a much sounder basis theoretically since it focuses attention directly on the coordinate motion of the transition state. Furthermore, by taking into account the normal vibrational motion of the transition state as well as motion along the reaction coordinate, it has been able to account for a number of observations which are in contradiction to the Hammond postulate.

RESULTS

In the Historical Introduction it was pointed out that concerted bimolecular elimination reactions have been considered to proceed most readily when the leaving groups occupy trans coplanar positions. It has recently been found, however, that in certain cases rapid cis elimination can also take place. The mechanism of cis eliminations, as well as of trans eliminations in which the leaving groups do not have a coplanar relationship, is not clear. Some investigators have proposed that such reactions proceed by the Elcb mechanism while others have favoured the one-step E2 process.

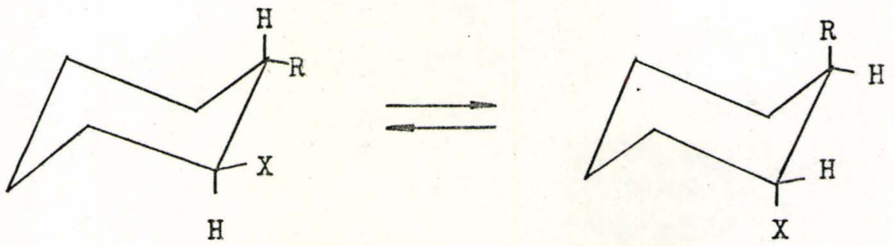
Recently, DePuy has presented evidence suggesting that the essential condition for rapid concerted elimination is coplanarity of the participating groups, a relationship which is found when the dihedral angle between such groups is either 0° or 180°. A large deviation from this angle, he suggests, will greatly increase the energy of activation for a concerted process and, as a consequence, the mechanism of the process may change so that one bond-rupture process is complete before the other has begun.

The purpose of the study reported in this thesis is to use the isotope effects associated with the leaving atoms, H and X, to determine the relationship between dihedral angle and the extent of C-H and C-X bond weakening at the transition state using cyclic systems in which one has some knowledge of the geometrical relationship of the participating groups. Hydrogen-deuterium and nitrogen isotope effects have been determined for the cis and trans elimination reactions of 2-phenylcyclohexyltrimethylammonium ions and 2-phenylcyclopentyltrimethylammonium ions. For the <u>cis</u>-cyclohexyl compound, trans coplanar elimination giving 1-phenylcyclohexene can occur if the departing groups are in the axial positions, XL. On the other hand, cis elimination

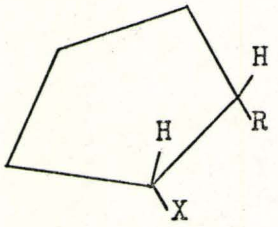


XL

from the <u>trans</u>-cyclohexyl compound involves a dihedral angle of approximately 60° between the participating orbitals, XLI , whether or not X departs from an axial or an equatorial position. The situation in the cyclopentyl system is quite different and rather unique. In the ground state, the ring is slightly puckered with one ring carbon above the plane of the other four by 0.5 Å, XLII . A relatively small twist in one direction will result in a dihedral angle of 180° for trans bonds while a small twist in the other direction will result in a dihedral angle of 0° for cis bonds.



XLI



XLII

When DePuy's rule is applied to these elimination reactions, one would predict a concerted E2 process for the trans elimination in the cyclohexyl system and for both cis and trans elimination in the cyclopentyl system. Cis elimination in the cyclohexyl system, on the other hand, might be expected to proceed by the Elcb mechanism or by an E2 process in which, at the transition state, rupture of the C-H bond is well advanced over that of the C-X bond.

Ayrey (89), in these laboratories, has measured the hydrogen-deuterium isotope effects and nitrogen isotope effects for the reactions of <u>cis</u>- and <u>trans</u>-2-phenylcyclohexyltrimethylammonium ions with sodium ethoxide in ethanol. The hydrogen-deuterium isotope effect results, however, were not considered reliable because the labelled compounds were not isotopically pure. These effects were therefore remeasured by the writer. In addition, since the study required a comparison of nitrogen isotope effects which differ by quite small amounts, it seemed desirable to repeat Ayrey's nitrogen isotope effect work on the cyclohexyl compounds as well. The reason for this is that small discrepancies in the isotope effect measurements of different investigators can lead to erroneous conclusions when the variation in isotope effects in a reaction series is being considered. The small systematic errors in the isotope effect measurements of an individual investigator are more likely to cancel and thus the conclusions based on the results will be more reliable.

The nitrogen isotope effect associated with the elimination reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion was also measured. In the phenylethyl system, freedom of rotation about the C_1-C_2 bond permits a trans coplanar transition state. This reaction, therefore, might be thought of as a standard of reference for the trans E2 process. Ayrey has also measured the nitrogen isotope effect for this compound, but it was redetermined in the present study so that the best comparison might be made.

Cristol (11), in 1960, measured the rates of reaction and determined the Arrhenius activation parameters for the elimination reactions of the isomeric 2-phenylcyclohexyltrimethylammonium ions. It was decided, therefore, to determine the corresponding parameters for the cyclopentyl series and make comparisons with the results for the cyclohexyl series.

Product Analyses for the Reactions of *cis*- and *trans*-2-Phenylcyclopentyltrimethylammonium Ions and *cis*- and *trans*-2-Phenylcyclohexyltrimethylammonium Ions with Sodium Ethoxide in Ethanol at 60°C.

The *cis*- and *trans*-2-phenylcyclopentyltrimethylammonium ions reacted readily with sodium ethoxide to give 1-phenylcyclopentene as the sole product as determined by ultraviolet spectrophotometric analysis and vapour phase chromatography. In these reactions, the possibility existed that some or all of the 1-phenylcyclopentene might have resulted from isomerisation of 3-phenylcyclopentene formed by trans elimination. This was shown, however, not to be the case. A mixture of the two olefins, when treated with sodium ethoxide under the reaction conditions for a long period of time, was shown by ultraviolet analysis and vapour phase chromatography to have undergone no change in composition.

The reaction of *cis*-2-phenylcyclohexyltrimethylammonium ion with sodium ethoxide was found to give 1-phenylcyclohexene as the sole product using the same analytical techniques that were used for the cyclopentyl system. Vapour phase chromatography of the reaction product from trans-2-phenylcyclohexyltrimethylammonium ion, however, indicated that 3-phenylcyclohexene and trans-N,N-dimethyl-2-phenylcyclohexylamine had been formed in addition to the product of cis elimination, 1-phenylcyclohexene. The tertiary amine resulted from an S_N2 substitution at an N-methyl carbon.

The compositions of the products from the reactions of unlabelled and 2-deutero-labelled trans-2-phenylcyclohexyltrimethylammonium ions were determined in order to evaluate the hydrogen-deuterium isotope effect for this system. The results are shown in Table VII. Four experiments were conducted for both the unlabelled and deuterated compounds and the products from each run were analysed twice by vapour phase chromatography.

Table VII

The Relative Amounts of the Elimination and
Substitution Products from Reactions of
trans-2-Phenylcyclohexyltrimethylammonium Ion and
trans-2-Phenylcyclohexyltrimethylammonium-2-d_1 Ion with
Sodium Ethoxide at 60°C.

Compound	1-Phenylcyclohexene	3-Phenylcyclohexene	Substitution Product
trans	61 ± 1	1	38 ± 1
trans-2-d_1	37 ± 1	1	62 ± 1

It was decided to perform all the kinetic isotope effect measurements at 60°C. since this was the most suitable temperature for obtaining measurable reaction rates for most of the compounds and also for controlling the extent of reaction in the nitrogen isotope effect studies. At this temperature, however, the reaction of <u>trans</u>-2-phenylcyclohexyltrimethylammonium ion with sodium ethoxide is very slow. It was not possible, therefore, to carry out the reaction to completion in order to obtain absolute yields for the products. Ayrey (89), working at the much higher temperature of 110°C. and using an internal standard in the vapour phase chromatographic analysis, found that the three products accounted for 94 per cent and 101 per cent of the total reaction of the unlabelled and labelled compounds, respectively. It would appear, therefore, that within the limits of error in the analysis, the total yield of the products of elimination and substitution is close to quantitative. At 60°C., there should be an even smaller tendency for the formation of other products and, therefore, it can be safely assumed that the data of Table VII correspond to absolute as well as relative yields.

It has previously been shown by Cristol that 1-phenylcyclohexene is formed directly by a cis elimination from <u>trans</u>-2-phenylcyclohexyltrimethylammonium ion and not by isomerisation of 3-phenylcyclohexene, the product of trans elimination (11).

Determination of Reaction Rates and Arrhenius Activation Parameters for the Reactions of cis- and trans-2-Phenylcyclopentyltrimethylammonium Ions with Sodium Ethoxide in Ethanol.

The reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions with sodium ethoxide to give 1-phenylcyclopentene were clearly second order. For the determination of the activation parameters, the rate studies were carried out under pseudo first-order reaction conditions. The first-order rate constants were determined by a least squares analysis of the data and the second-order rate constants were calculated by dividing the first-order rate constants by the concentration of sodium ethoxide.

Rates of reaction for the trans elimination were determined at five different temperatures, with duplicate experiments being conducted at each temperature. For the cis elimination, reaction rates were determined at three temperatures, again with duplicate runs at each temperature. Each kinetic experiment was carried out to at least 70 per cent reaction and good linear plots were obtained for both compounds. The rate constants are shown in Tables VIII and IX and details of representative runs at each temperature are given in Appendix A.

The Arrhenius energies of activation for these compounds were calculated from the kinetic data by a least squares method and the entropies of activation were determined from the corresponding enthalpies of activation. This data is shown in Table X, and the plots of the kinetic data for the determination of the energies of activation are shown in Figures (5) and (6).

Table VIII

Kinetic Results for the E2 Reaction of *trans*-2-Phenylcyclopentyltrimethylammonium Iodide With Sodium Ethoxide in Ethanol.

Temperature °C.	Initial Concentrations m./l. Ethoxide	Salt x 10^3.	k_1 X 10^{6*} sec^{-1}	k_2 X 10^{5*} 1/mole/sec
59.9	0.203	10.3	6.45 ± 0.11	3.17 ± 0.05
	0.203	7.00	6.47 ± 0.07	3.19 ± 0.03
			mean	3.18
68.1	0.201	7.62	20.4 ± 0.1	10.2 ± 0.05
	0.197	10.6	19.4 ± 0.1	9.83 ± 0.07
			mean	10.0
76.1	0.209	10.3	57.5 ± 0.4	27.5 ± 0.2
	0.209	10.3	57.4 ± 0.4	27.5 ± 0.2
			mean	27.5

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[*] The limits shown are standard deviations.

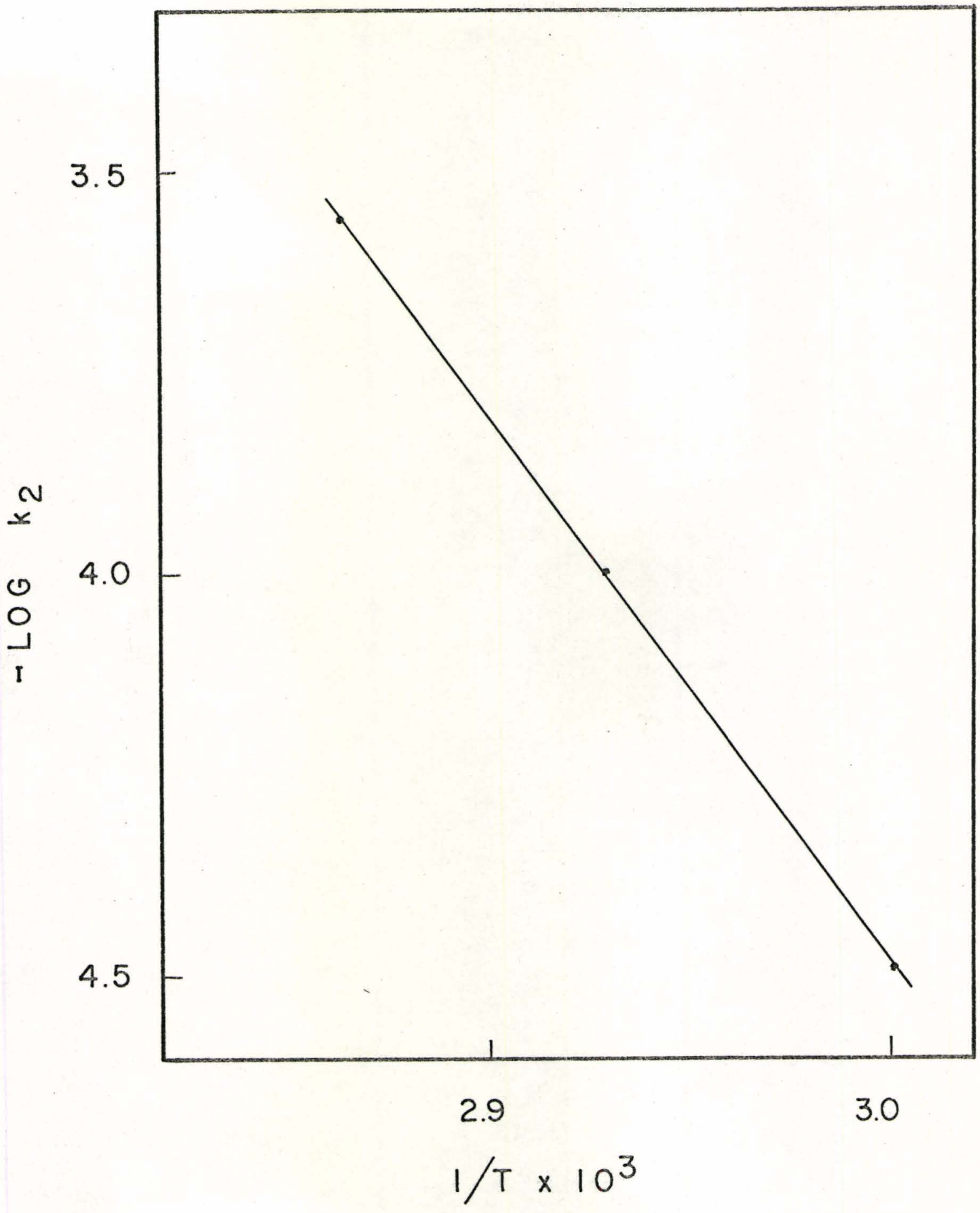

Figure 5. Plot of -log k_2 versus 1/T for the reaction of trans-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in ethanol.

Table IX

Kinetic Results for the E2 Reaction of

cis-2-Phenylcyclopentyltrimethylammonium Iodide

with Sodium Ethoxide in Ethanol.

Temperature °C.	Initial Concentrations m./l. Ethoxide	Salt x 10^3.	$k_1 \times 10^5$* sec^{-1}	$k_2 \times 10^5$* 1/mole/sec
29.7	0.198	4.53	2.25 ± 0.02	11.4 ± 0.1
	0.198	4.57	2.25 ± 0.02	11.4 ± 0.1
			mean	11.4
34.9	0.199	4.82	4.62 ± 0.04	23.2 ± 0.2
	0.199	4.77	4.58 ± 0.04	23.0 ± 0.2
			mean	23.1
39.9	0.204	4.75	9.00 ± 0.1	44.1 ± 0.3
	0.204	4.91	9.17 ± 0.1	45.1 ± 0.3
			mean	44.6
44.9	0.196	4.69	18.0 ± 0.2	91.7 ± 0.8
	0.196	4.71	18.0 ± 0.1	92.5 ± 0.7
			mean	92.1
50.0	0.204	4.96	35.0 ± 0.3	172 ± 1.4
	0.204	4.91	35.2 ± 0.3	173 ± 1.6
			mean	172.5

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* The limits shown are standard deviations.

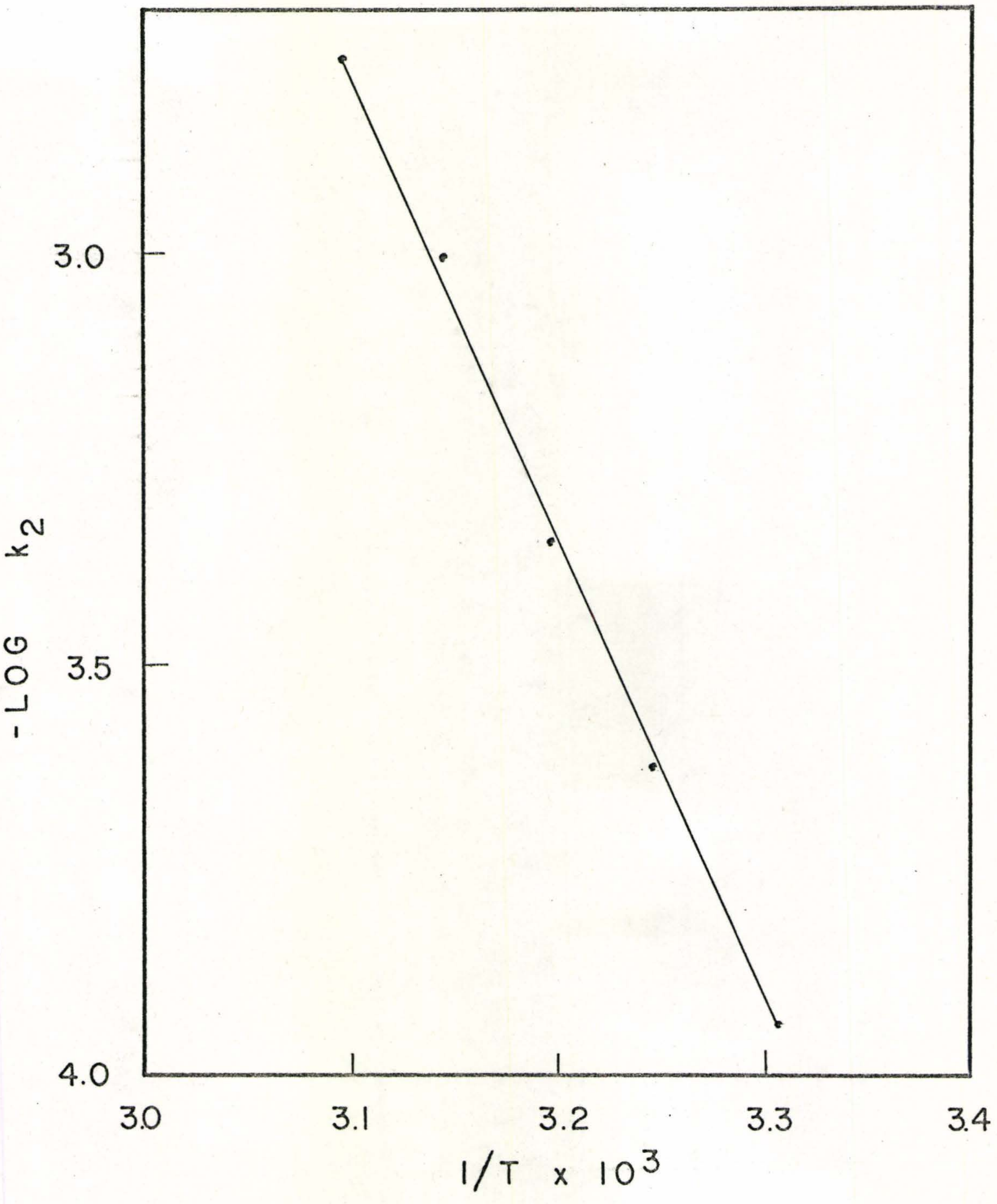

Figure 6. Plot of -log k_2 versus 1/T for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in ethanol.

Table X

Arrhenius Activation Parameters for Elimination of *cis*- and *trans*-2-Phenylcyclopentyltrimethylammonium Ions with Sodium Ethoxide in Ethanol.

Compound	Mode of Elimination	E_{act} kcal/mole	$\Delta S^{\ddagger}$ cal./deg
cis	trans	26.2	7.8
trans	cis	30.6	10.5

In this study, a lack of reproducibility of rate constants by as much as six per cent was observed for different batches of sodium ethoxide. DePuy (59) had experienced a similar difficulty with potassium *t*-butoxide and found that the problem arose from trace impurities in the metal. In order to achieve the best accuracy possible in this kinetic study, the rate constants for each compound were determined using the same batch of sodium ethoxide.

Determination of Hydrogen-Deuterium Isotope Effects for the Reactions of *cis*- and *trans*-2-Phenylcyclopentyltrimethylammonium Ions and *cis*- and *trans*-2-Phenylcyclohexyltrimethylammonium Ions with Sodium Ethoxide at 60°C.

Hydrogen-deuterium isotope effects were determined for the reactions of *cis*- and *trans*-2-phenylcyclopentyltrimethylammonium ions and cis- and trans-2-phenylcyclohexyltrimethylammonium ions with sodium ethoxide in ethanol at 60°C. The rate studies were conducted under pseudo first-order reaction conditions and the rate constants were determined by the method used in the kinetic studies for the determination of the activation parameters for the reactions of the isomeric cyclopentyl compounds.

The reaction rates for each pair of compounds in the determination of the hydrogen-deuterium isotope effects were measured simultaneously using the same batch of sodium ethoxide. This was done in order to minimise any small discrepancies which might occur between runs conducted at different times. The results of these studies are given in Tables XI, XII, XIII, XIV and XV.

The reaction of cis-2-phenylcyclopentyltrimethylammonium ion with sodium ethoxide was found to be too fast to follow at 60°C. The hydrogen-deuterium isotope effect for this reaction at 60°C. was therefore calculated by extrapolation from the hydrogen-deuterium isotope effects measured at 30°C. and 45°C.

The reaction of trans-2-phenylcyclohexyltrimethylammonium ion was found to be very slow at 60°C., therefore a much higher concentration of base was used in order to obtain a reasonable rate of reaction. This increase in base strength resulted in a five-fold increase in ionic strength. Smith (86), in his study of the hydrogen-deuterium isotope effect for the reaction of 2-(p-fluoromethylphenyl)ethyltrimethylammonium bromide at 40°C., found that a ten-fold increase in ionic strength did not alter the hydrogen-deuterium isotope effect to a

Table XI

Second Order Rate Constants and Hydrogen-Deuterium Isotope Effects for the Reaction of trans-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C.

	Initial Concentrations m./l.			$k_2 \times 10^{5*}$
Compound	Ethoxide	Salt x 10^3.		l/mole/sec
trans	0.191	4.42		3.55 ± 0.02
	0.191	4.38		3.53 ± 0.02
			mean	3.54
trans-2-d_1	0.191	4.37		1.15 ± 0.01
	0.191	4.51		1.15 ± 0.01
			mean	1.15
			k^H/k^D =	3.08

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[*] The limits shown are standard deviations.

Table XII

Second Order Rate Constants and Hydrogen-Deuterium Isotope Effects for the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 30°C.

Compound	Initial Concentrations m./l. Ethoxide	Salt x 10^3.	$k_2 \times 10^{5*}$ l/mole/sec
cis	0.1988	4.86	12.1 ± 0.1
	0.1988	4.86	12.3 ± 0.1
	0.1947	4.34	12.1 ± 0.1
		mean	12.1
cis-2-d_1	0.1988	4.03	2.44 ± 0.02
	0.1988	4.11	2.44 ± 0.02
	0.1947	3.99	2.45 ± 0.02
		mean	2.44

$k^H/k^D = 5.00$

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[*] The limits shown are standard deviations.

Table XIII

Second Order Rate Constants and Hydrogen-Deuterium Isotope Effects for the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 45°C.

	Initial Concentrations m./l.			$k_2 \times 10^5$*
Compound	Ethoxide	Salt x 10^3.		l/mole/sec
cis	0.1984	4.77		86.7 ± 0.7
	0.1984	5.32		86.7 ± 0.8
	0.1939	4.45		86.6 ± 0.7
			mean	86.7
cis-2-d_1	0.1984	4.03		18.4 ± 0.2
	0.1984	4.36		18.1 ± 0.2
	0.1939	4.31		18.8 ± 0.2
			mean	18.4

$k^H/k^D = 4.71$

---

*The limits shown are standard deviations

Table XIV

Second Order Rate Constants and
Hydrogen-Deuterium Isotope Effects for the Reactions of
cis-2-Phenylcyclohexyltrimethylammonium Iodide with
Sodium Ethoxide in Ethanol at 60°C.

Compound	Initial Concentrations m./l. Ethoxide	Salt x 10^3.		$k_2 \times 10^{5*}$ l/mole/sec
cis	0.207	7.32		14.2 ± 0.1
	0.207	7.19		14.3 ± 0.1
			mean	14.3
cis-2-*d*$_1$	0.207	7.64		2.68 ± 0.02
	0.207	7.32		2.62 ± 0.02
			mean	2.65

$k^H/k^D = 5.40$

[*] The limits shown are standard deviations.

Table XV

Second Order Rate Constants and Hydrogen-Deuterium Isotope Effects for the Elimination and Substitution Reactions from trans-2-Phenylcyclohexyltrimethylammonium Iodide with 0.949 M. Sodium Ethoxide in Ethanol at 60°C.

	Init. Conc.	$k_2 \times 10^7$, l/mole/sec		
Compound	m./l. Salt x 10^2.	Overall*	Elimination*	Substitution*
trans	2.10	9.15 ± 0.08	5.58 ± 0.06	3.48 ± 0.03
	2.11	8.99 ± 0.09	5.48 ± 0.06	3.41 ± 0.03
		mean	5.53	3.45
trans-2-d_1	2.36	5.68 ± 0.05	2.10 ± 0.02	3.52 ± 0.03
	2.38	5.67 ± 0.06	2.10 ± 0.02	3.52 ± 0.03
		mean	2.10	3.52
			$(k^H/k^D)_{elim}$	(k^H/k^D) subst
			= 2.63	= 0.98

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[*] The limits shown are standard deviations.

measurable extent. The writer feels, therefore, that the hydrogen-deuterium isotope effect determined in this study for the cis elimination of trans-2-phenylcyclohexyltrimethylammonium ion is the same as the isotope effect that would have been found if conditions of lower ionic strength had been used.

In the reaction of trans-2-phenylcyclohexyltrimethylammonium ion, in contrast to that of the other compounds, the 1-phenylcycloalkene is but one of three reaction products. The rate constants for the cis elimination, therefore, were obtained by multiplying the overall rate constant, measured spectrophotometrically, by the fraction of the total reaction which proceeds by this pathway (see Table XV). Similarly, the rate constants for substitution were obtained by multiplying the overall rate constant by the fraction of the total reaction producing trans-N,N-dimethyl-2-phenylcyclohexylamine.

The hydrogen-deuterium isotope effect of 5.40 found for the trans elimination of cis-2-phenylcyclohexyltrimethylammonium iodide is in good agreement with the value of 5.60 determined by Ayrey (89). On the other hand, the 2.63 hydrogen-deuterium isotope effect for cis elimination from trans-2-phenylcyclohexyltrimethylammonium iodide does not agree well with Ayrey's value of approximately 3.2 calculated from his value of 3.01 at 110°C. The writer believes that the value found in the present study is the more reliable result. It was pointed out earlier that the isotopic purity of Ayrey's deuterated material was in doubt. In addition, the lack of reproducibility in his rate constants to the extent of ± 8 per cent casts doubt on the reliability of the isotope effect calculated from his data. Also, the ratio of the rate constants found in the present work for the substitution reaction is a much more reasonable one than that observed by Ayrey. The isotope effect for this reaction would be expected to be very close to unity since the site of substitution is not close to the proton attached to the β-carbon and secondary isotope effects, therefore, should be extremely small. In the present study, a value of 0.98 was obtained for (k^H/k^D) subst., compared with 0.89 calculated from Ayrey's data.

The Determination of the Nitrogen Isotope Effects for the Reactions of *cis*- and *trans*-2-Phenylcyclopentyltrimethylammonium Ions, *cis*- and *trans*-2-Phenylcyclohexyltrimethylammonium Ions and 2-Phenylethyltrimethylammonium ion with Sodium Ethoxide at 60°C.

Nitrogen isotope effects were determined for the reactions of *cis*- and *trans*-2-phenylcyclopentyltrimethylammonium ions, cis- and *trans*-2-phenylcyclohexyltrimethylammonium ions and 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol at 60°C and the results are shown in Tables XVI, XVII, XVIII, XIX, XX, XXI, XXII and XXIII. For each compound, the reaction was carried out under the same conditions as were used for the determinations of the corresponding hydrogen-deuterium isotope effects. The nitrogen isotope effects were then evaluated from equation (74) by comparing the nitrogen isotopic abundance in the starting material with the nitrogen isotopic abundance

Table XVI

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-Phenylethyltrimethylammonium Bromide with Sodium Ethoxide in Ethanol at 60°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	75	100[d]	272.27	-
2	75	100[d]	272.28	-
3	75	100[d]	272.35	-
4	75	100[d]	272.28	-
5	75	100[d]	272.26	-
6	60	10.0[e]	274.96	1.0103
7	60	10.4	274.86	1.0100
8	60	20.2	274.68	1.0099
9	60	21.2	274.61	1.0096
10	60	25.5	274.60	1.0099
11	60	28.5	274.53	1.0098
12	60	39.7	274.49	1.0105
13	60	40.0	274.25	1.0094
			mean	1.0099 ± 0.0004[c]

[a] Based on the yield of trimethylamine.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.

[c] The limit shown is the standard deviation.

[d] Isotopic ratio is based on $(CH_3)_3N$ formed after 100 per cent reaction.

[e] Base strength was 5×10^{-3} Molar (deficient base-see page 180).

Table XVII

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of *trans*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	75	100[d]	268.42	-
2	75	100[d]	268.17	-
3	75	100[d]	268.18	-
4	75	100[d]	268.02	-
5	75	100[d]	267.39	-
6	75	100[d]	268.12	-
7	75	100[d]	268.15	-
8	60	9.2[e]	269.59	1.0060
9	60	14.7	269.79	1.0070
10	60	14.7	269.65	1.0064
11	60	20.0	269.46	1.0058
12	60	24.9	269.71	1.0071
13	60	25.0	269.43	1.0059
			mean	1.0064 ± 0.0006[c]

[a] Based on the yield of trimethylamine.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.

[c] The limit shown is the standard deviation.

[d] Isotopic ratio is based on $(CH_3)_3N$ formed after 100 per cent reaction.

[e] Base strength was 0.2 Molar.

Table XVIII

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 30°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	60	100[d]	274.13	-
2	60	100[d]	274.17	-
3	60	100[d]	273.81	-
4	60	100[d]	274.17	-
5	60	100[d]	274.16	-
6	60	100[d]	274.25	-
7	30	7.8[e]	277.27	1.0120
8	30	8.8	277.40	1.0125
9	30	14.3	277.17	1.0120
10	30	18.5	277.28	1.0128
11	30	18.8	277.16	1.0123
12	30	44.5	276.78	1.0132
13	30	52.2	276.60	1.0134
			mean	1.0126 ± 0.0006[c]

[a] Based on the yield of trimethylamine.
[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.
[c] The limit shown is the standard deviation.
[d] Isotopic ratio is based on $(CH_3)_3N$ formed after 100 per cent reaction.
[e] Base strength was 0.2 Molar.

Table XIX

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 45°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	60	100[d]	274.13	-
2	60	100[d]	274.17	-
3	60	100[d]	273.81	-
4	60	100[d]	274.17	-
5	60	100[d]	274.16	-
6	60	100[d]	274.25	-
14	45	17.4[e]	277.06	1.0118
15	45	23.7	276.76	1.0111
16	45	25.8	276.89	1.0118
17	45	28.0	276.83	1.0117
18	45	45.4	276.54	1.0121
			mean	1.0117 ± 0.0004[c]

[a] Based on the yield of trimethylamine.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.

[c] The limit shown is the standard deviation.

[d] Isotopic ratio is based on $(CH_3)_3N$ formed after 100 per cent reaction.

[e] Base strength was 0.2 Molar.

Table XX

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of cis-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	60	100[d]	274.13	-
2	60	100[d]	274.17	-
3	60	100[d]	273.81	-
4	60	100[d]	274.17	-
5	60	100[d]	274.16	-
6	60	100[d]	274.25	-
19	60	17.1[e]	276.75	1.0106
20	60	17.4[e]	276.79	1.0107
21	60	24.0[e]	276.62	1.0105
22	60	24.4[e]	276.72	1.0109
23	60	38.7[e]	276.46	1.0110
24	60	39.4[e]	276.45	1.0110
			mean	1.0108 ± 0.0002[c]

[a] Based on the yield of trimethylamine.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.

[c] The limit shown is the standard deviation.

[d] Isotopic ratio was based on $(CH_3)_3N$ formed after 100 per cent reaction.

[e] The amount of base corresponding to the desired extent of reaction was used. Base strength was 5.6×10^{-3} Molar.

Table XXI

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of cis-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C.

Expt. No.	Reaction Temp. °C.	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$
1	75	100[d]	274.83	-
2	75	100[d]	274.24	-
3	75	100[d]	274.28	-
4	75	100[d]	274.14	-
5	75	100[d]	274.31	-
6	60	14.7[e]	277.39	1.0120
7	60	15.0	277.40	1.0120
8	60	15.4	277.44	1.0122
9	60	23.7	277.55	1.0134
10	60	24.1	277.42	1.0128
11	60	29.6	277.00	1.0115
12	60	33.6	276.84	1.0112
13	60	38.8	276.88	1.0119
14	60	40.0	276.98	1.0125
15	60	47.8	276.76	1.0123
16	60	48.8	276.86	1.0130
			mean	1.0123 ± 0.0007[c]

[a] Based on the yield of trimethylamine.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50

[c] The limit shown is the standard deviation.

[d] Isotopic ratio is based on $(CH_3)_3N$ formed after 100 per cent reaction

[e] Base strength was 0.2 Molar.

Table XXII

N^{14}/N^{15} Ratios and Uncorrected Kinetic Isotope Effects in the E2 Reaction of trans-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C.

Expt. No.	Reaction Temp. °C.	Overall Extent of Reaction %	f[a]	N^{14}/N^{15} Ratios[b]	k^{14}/k^{15}[c] Uncorrected
1	120	100[d]		278.39	-
2	120	100[d]		278.15	-
3	120	100[d]		278.33	-
4	120	100[d]		278.47	-
5	60	13.5[f]	8.5	279.15	1.0031
6	60	13.5	8.5	278.87	1.0020
7	60	28	19.0	279.20	1.0035
8	60	28	19.0	279.16	1.0033
9	60	40	28.6	278.96	1.0027
10	60	40	28.6	279.09	1.0033
11	60	50	37.5	278.90	1.0026
12	60	50	37.5	278.99	1.0030
				mean	1.0029 ± 0.0005[e]

[a] Calculated using equation (76), page 125.

[b] The ratios are relative to a standard nitrogen source whose $N^{14}N^{14}/N^{14}N^{15}$ ratio was arbitrarily chosen as 136.50.

[c] Calculated on the assumption of no isotope effect associated with the substitution reaction.

[d] The trimethylamine and the tertiary amine were collected after 100 per cent reaction.

[e] The limit shown is the standard deviation.

[f] Base strength was 1.2 Molar.

Table XXIII

Kinetic Isotope Effects in the Elimination Reaction of trans-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide in Ethanol at 60°C. with a Correction for the Substitution Isotope Effect.

Expt. No.	f^a	Corrected Isotope Effect, k^{14}/k^{15}, Based on the Indicated Values for the Substitution Isotope Effect.			
		1.0%	1.5%	2.0%	2.5%
5	8.5	1.0033	1.0035	1.0036	1.0037
6	8.5	1.0023	1.0024	1.0025	1.0026
7	19.0	1.0040	1.0043	1.0046	1.0048
8	19.0	1.0038	1.0042	1.0045	1.0047
9	28.6	1.0036	1.0041	1.0045	1.0050
10	28.6	1.0042	1.0047	1.0051	1.0055
11	37.5	1.0040	1.0047	1.0052	1.0059
12	37.5	1.0044	1.0051	1.0057	1.0064
	means	1.0037	1.0041	1.0045	1.0048

[a] Calculated using equation (76), page 125.

in the product after the reaction had proceeded to some known extent of completion. In equation (74), $r = (N^{14}/N^{15})\text{reactant}/(N^{14}/N^{15})\text{product}$ and f is the mole fraction of the reactant which has undergone reaction.

$$k^{14}/k^{15} = \frac{\ln (1-f)}{\ln (1-rf)} \tag{74}$$

The isotopic ratio for the starting material was determined from the elimination product, trimethylamine, after the reaction had proceeded to completion. The reaction was carried out for ten half-lives and the trimethylamine was collected. Kjeldahl digestion of the trimethylamine converted it to ammonia which was then oxidised by sodium hypobromite to nitrogen gas. The nitrogen gas was purified and its isotopic abundance was determined by mass spectrometric analysis. In the reaction of trans-2-phenylcyclohexyltrimethylammonium ion with sodium ethoxide, two nitrogen-containing compounds are formed. In this case, the substitution product, trans-N,N-dimethyl-2-phenylcyclohexylamine, was isolated and combined with the trimethylamine and the two were then converted to nitrogen gas for analysis. For each compound, at least five values for the isotopic ratio of the starting material were obtained. The average value in each case was then used for the calculation of the nitrogen isotope effects by equation (74).

The nitrogen isotopic abundance of the product, trimethylamine, formed in reactions which had proceeded to some known extent of completion, was determined in the same manner. In previous work in these laboratories, it had been observed that isotope effect measurements determined from isotopic ratios for the product formed during the first few per cent reaction were not always reliable. The partial reactions, therefore, were carried out to extents of reaction ranging from five to fifty per cent, and the isotope effect was determined from an average of the isotope effects found over this range. Except for the cis elimination of trans-2-phenylcyclohexyltrimethylammonium ion, no trends in the isotope effects obtained in the present studies were noted over the range of extent of reaction used.

The nitrogen isotope effect results for the 2-phenylethyltrimethylammonium ion are given in Table XVI. The value of 0.99 ± 0.04 per cent agrees well with the value of 0.94 ± 0.04 per cent reported by Ayrey and Bourns (85).

For the cyclopentyl series, a nitrogen isotope effect of 0.64 ± 0.06 per cent was found for cis elimination of the trans-salt at 60°C. Although the nitrogen isotope effect for the trans elimination of the cis-salt was also measured at 60°C., there was some concern about its reliability since the reaction rate at this temperature was too fast to permit good control of reaction conditions. Accordingly, the nitrogen isotope effect for this reaction was determined at 30°C. and 45°C. and an extrapolated value was calculated for 60°C. from this data. This value turned out to be identical with the experiment result obtained at 60°C. At 30°C., an isotope effect of 1.26 per cent was found while at 45°C. the value was 1.17 per cent. The isotope effect at 60°C. was found to be 1.08 per cent.

The nitrogen isotope effect of 1.23 ± 0.07 per cent reported in Table XXI for the trans elimination of cis-2-phenylcyclohexyltrimethylammonium ion at 60°C. agrees well with the value of 1.21 ± 0.08 per cent reported by Ayrey (89).

The determination of the nitrogen isotope effect associated with cis elimination from trans-2-phenylcyclohexyltrimethylammonium ion is not as straight forward as in the previous cases because there are also nitrogen isotope effects associated with the two competing reactions. The trans elimination reaction, giving 3-phenylcyclohexene in one per cent yield, constitutes such a small portion of the overall reaction that its contribution to the isotope effect associated with trimethylamine formation is very small, of the order of 0.02 per cent, and it therefore can be neglected. The substitution reaction, however, presents a serious complicating factor. The isotopic ratio of reactant will be enriched in N^{15} as the substitution reaction proceeds and this will in turn influence the isotopic ratio of the trimethylamine product from cis elimination. In addition, an estimate of f is made difficult for cis elimination for now it cannot simply be taken as the mole fraction of the reactant which has been consumed.

A somewhat similar problem was encountered in these laboratories by Baliga in a study carried out of the isotope effects in aromatic bromodesulphonation reactions (90). Although the competing reaction in that case was not isotopically dependent, it is possible to adapt the method of calculation employed by Baliga to the present problem.

An approximation of the quantity f in equation (74), page 122 for the elimination reaction may be made by considering that an amount of the reactant, corresponding to that part of the reaction undergoing substitution is actually withdrawn before the elimination reaction gets going. If a is the initial amount of quaternary salt in moles, x is the amount of total reaction, and p is the fraction which undergoes substitution, then xp is the amount of reactant considered to have been consumed prior to the elimination reaction and (a-xp) is the amount of reactant remaining after taking into account the material removed by substitution. An estimate of f is then given by the following expression

$$f \approx \frac{x(1-p)}{a - xp} \qquad (75)$$

where (1-p) is the fraction of the reaction which is elimination. This may be rewritten as

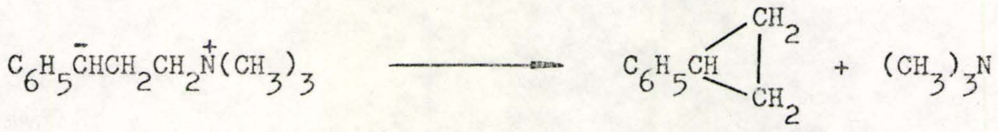
$$f = \frac{f'(1-p)}{1-f'p} \qquad (76)$$

where f' = x/a, the mole fraction of the reactant consumed by both reactions.

The use of f, as defined in equation (76), for the calculation of an isotope effect from equation (74) results in the values given in Table XXII. This approximation, however, has involved the invalid assumption that the substitution reaction proceeds without isotopic fractionation. Because of experimental difficulties, the isotope effect was not determined for the substitution reaction. It is possible, however, to make a reasonable assumption of its magnitude. Furthermore, as will become evident later, the correction for the substitution reaction is not particularly sensitive to the value of the isotope effect used.

A number of studies have been reported of leaving-group isotope effects in substitution reactions. Swain and Thornton (91) found a 0.9 per cent S^{32}/S^{34} isotope effect in the reaction of benzyldimethylsulphonium p-toluenesulphonate with hydroxide ion at 60°C., while Hill and Fry (92) have reported a Cl^{35}/Cl^{37} isotope effect of approximately 0.6 per cent for the reaction of a number of nucleophiles with benzyl chloride at 30°C. Since an isotope effect associated with nitrogen would be expected to be about twice that of sulphur and chlorine for the same decrease in force constants at the transition state, these results would suggest a substitution isotope effect of 1-2 per cent in the present system.

Even more direct evidence for a substitution isotope effect of this magnitude is found in recent studies from this laboratory. Smith (86) reported that in the reaction of ethyltrimethylammonium ion with ethoxide ion the nitrogen isotopic ratio of the total amine product, trimethylamine from elimination and dimethylethylamine from substitution, is almost identical to that in the elimination product only. In other words, the nitrogen isotope effect for substitution is very close to the 1.86 per cent found for elimination at 60°C. Finally, Westaway (93) has found a 2.2 per cent nitrogen isotope effect in the γ-elimination reaction of 3-phenylpropyltrimethylammonium ion with amide ion at -55°C., a reaction which would appear to involve a rate-determining attack of a γ-carbanionic centre at the α-carbon. This result would correspond to



(77)

an isotope effect of approximately 1.5 per cent at 60°C.

The nitrogen isotope effect for cis elimination of trans-2-phenylcyclohexyltrimethylammonium ion was recalculated using values for the isotope effect associated with substitution of 1.0, 1.5, 2.0 and 2.5 per cent. For each value of the substitution isotope effect, the change in the isotopic composition of the starting material attributable to substitution alone was calculated using equation (78), where f is the fraction of reaction undergoing substitutuion, R_f is the N^{14}/N^{15} ratio in the unreacted substrate after the fraction f has reacted, and R_o is the N^{14}/N^{15} ratic in the starting material. It was then assumed

$$k^{14}/k^{15} = 1 + \frac{\log R_f/R_o}{\log (1-f)\,\frac{1+R_o}{1+R_f}} \qquad (78)$$

that the isotopic ratio of the reactant for elimination is the average of R_o and R_f. These average values were then used as the (N^{14}/N^{15})reactant in equation (74) and the nitrogen isotope effect was recalculated for the elimination reaction, again using the value for f as derived from Baliga's relationship.

It is seen from Table XXIII that when a 2.5 per cent isotope effect is assumed for the substitution reaction there is a definite upward trend in the calculated isotope effect for elimination with increasing extent of reaction. This is the result to be expected if the assumed substitution isotope effect is too high. On the other hand, it is unlikely that the substitution isotope effect is less than one per cent. It therefore is concluded that the isotope effect for the cis elimination of trans-2-phenylcyclohexyltrimethylammonium ion is 0.4 per cent with an uncertainty of less than ± 0.1 per cent.

Examination of the results shown in Table XXII reveals that the isotope effect values obtained in experiments for which f=8.5 appear to be significantly lower than the values obtained at higher extents of reaction. Ayrey's experiments at 60°C. were all in the range of f=6 to f=7 and his average isotope effect of 0.28 per cent (based on an assumed substitution effect of 1.5 per cent) corresponds precisely to the average of the results of Expts. Nos. 5 and 6 in the present study. These results would suggest that the trimethylamine formed in the early extent of reaction may not be completely representative of the elimination reaction, a complication to which Collins has drawn attention (94) and which has been previously observed in these laboratories.

DISCUSSION

Relative Rates and Activation Parameters.

TableXXIV presents the relative rates of elimination, based on rate constants extrapolated to 25°C. from values at higher temperatures, and the activation parameters for the reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions, cis- and trans-2-phenylcyclohexyltrimethylammonium ions and 2-phenylethyltrimethylammonium ion. The values shown for the acyclic and cyclohexyl compounds are those reported by Cristol (11).

The results show that trans eliminations are more facile than cis eliminations with trans/cis rate ratios of 133 and 310 being observed for the cyclohexyl and cyclopentyl series, respectively. A point worthy of note is that the trans elimination from the cis-cyclopentyl salt is more rapid than the trans elimination from the cis-cyclohexyl salt by 214 fold. At first, this seemed somewhat surprising because the dihedral angle between the participating orbitals in the cyclopentyl system is not quite 180°, whereas a trans coplanar transition state is attainable for the cyclohexyl system.

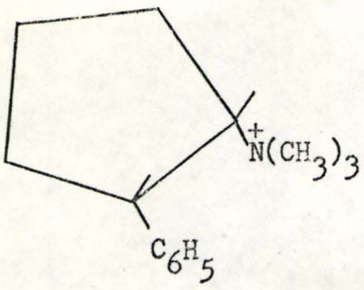
Two factors would appear to be responsible for this. First, the cis-cyclopentyl isomer in its ground state will have the bulky phenyl and trimethylammonium groups in positions such that considerable non-bonded interaction will exist between them, XLIII. Steric acceleration, therefore, will result from a decrease in this non-bonded repulsion at the transition state as the C-N bond becomes stretched and the phenyl group starts to become coplanar with the developing cyclopentene ring. Second, in the ground state of the *cis*-cyclohexyl compound, the

Table XXIV

Relative Rates of Elimination and Arrhenius Activation Parameters for the *cis*- and *trans*-Isomers of 2-Phenylcyclohexyltrimethylammonium Iodides, 2-Phenylcyclopentyltrimethylammonium Iodides, and for 2-Phenylethyltrimethylammonium Bromide.

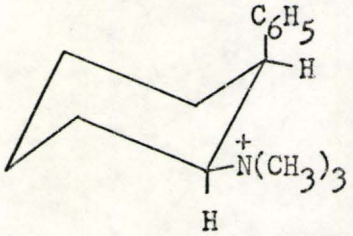
Compound	cis elimination			trans elimination		
	Rel. Rates	E_{act} kcal/mole	$\Delta S^{\ddagger}$ cal/deg	Rel. Rates	E_{act} kcal/mole	$\Delta S^{\ddagger}$ cal/deg
Cyclohexyl QAS[a]	1	33.4	11.9	133	30.3	11.2
Cyclopentyl QAS	92	30.6	10.5	28600	26.2	7.8
Phenylethyl QAS[a]				10700	25.5	3.7

[a] Determined by Cristol (11) using potassium hydroxide in 92.6 per cent ethanol.



XLIII

trimethylammonium group will reside in the equatorial position, XLIV. For trans coplanar elimination to occur, this leaving group must be forced into a crowded axial position at the transition state, resulting

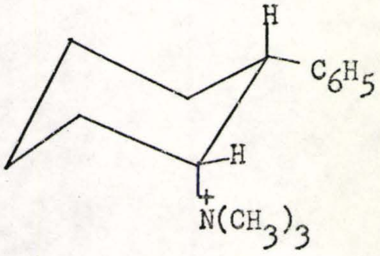


XLIV

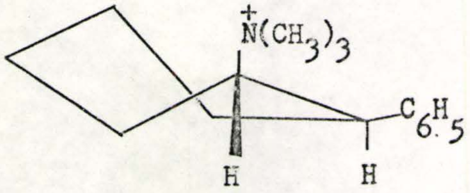
in steric retardation.

This steric retardation of trans elimination in the cis-cyclohexyl salt and steric acceleration in the cis-cyclopentyl salt is also considered to be responsible for the lower trans/cis rate ratio in the cyclohexyl series. As was pointed out in the Historical Introduction, normally this ratio is very much higher with cyclohexyl isomers than with the corresponding cyclopentyl compounds because the dihedral angle for cis elimination from the latter is close to that required for coplanarity of the reacting bonds at the transition state.

The nature of the reacting conformer for trans elimination in the cyclohexyl series is difficult to identify. There are two possible conformations in which the trimethylammonium group is in an axial position and from which the formation of a coplanar transition state is possible: the chair conformation, XLV, and the twist-boat conformation, XLVI. Models would suggest that the twisted boat conformation would have the less crowding and it, therefore, is probably the reacting conformer.



XLV



XLVI

The faster rate of trans elimination of the cis-cyclopentyl compound compared to the reaction of 2-phenylethyltrimethylammonium salt was unexpected since the latter has always been considered to be a trans process as well, and since coplanarity of the reacting bonds is difficult to achieve in the five-membered ring system. The result, however, is consistent with steric acceleration resulting from a decrease in the non-bonded interactions between eclipsed phenyl and trimethylammonium groups in the cyclic compound. (Later in this thesis, the possibility will be raised that elimination from the open-chain compound might be a cis- rather than a trans-process.)

The cis elimination in the cyclopentyl series is found to proceed as readily as trans elimination in the cyclohexyl series and is considerably more facile than cis elimination in the cyclohexyl series. This result is certainly in accord with DePuy's rule (10). It is seen, however, that in the cyclopentyl series cis elimination, with a dihedral angle of approximately 0°, is not as facile as trans elimination in the same series in which the dihedral angle is near 180°.

Finally, it can be seen that, with one exception, the rate differences can be attributed mainly to differences in the energy of activation. The relatively low entropy of activation for the reaction of 2-phenylethyltrimethylammonium ion is to be expected since this compound will have a greater freedom for rotation in the ground state than its cyclic analogues.

Kinetic Isotope Effects.

The hydrogen-deuterium and nitrogen isotope effects for the elimination reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions, cis- and trans-2-phenylcyclohexyltrimethylammonium ions and 2-phenylethyltrimethylammonium ion with sodium ethoxide at 60°C. are summarised in Table XXV.

Table XXV

Isotope Effects Found for the E2 Reactions of
cis- and trans-2-Phenylcyclopentyltrimethylammonium Ions,
cis- and trans-2-Phenylcyclohexyltrimethylammonium Ions, and
2-Phenylethyltrimethylammonium Ion
with Sodium Ethoxide in Ethanol at 60°C.

Compound	Mode of Elimination	$(k^{14}/k^{15}-1)100$	k^{H}/k^{D}
cis-Phenylcyclohexyl	trans	1.23 ± 0.07	5.40
cis-Phenylcyclopentyl	trans	1.08 ± 0.02	4.44
trans-Phenylcyclopentyl	cis	0.64 ± 0.06	3.08
trans-Phenylcyclohexyl	cis	0.40 ± 0.10	2.63
Phenylethyl	?	0.99 ± 0.04	2.80[a]

[a] Saunders (105). Estimated from 2.98 at 50°C.

It was shown earlier on the basis of the secondary isotope effect, k^{DO^-}/k^{HO^-}, and the primary isotope effect, k^H/k^D, that in the elimination from 2-phenylethyltrimethylammonium ion, the proton is considerably more than half transferred to base at the transition state. It is highly probable, therefore, that at the transition state for elimination from the cyclic analogues, the proton is also more than half transferred to base. It follows that the smaller the hydrogen-deuterium isotope effect, the greater is the extent of proton transfer. Furthermore, it may be concluded on the basis of the Bigeleisen treatment of heavy-atom isotope effects that the larger the nitrogen isotope effect in the quaternary ammonium salt eliminations the greater is the decrease in the force constants associated with this atom at the transition state.

The nitrogen isotope effect of 1.23 per cent for trans elimination from the cis-cyclohexyl compound is a little more than one-third the theoretical maximum effect of 3.2 per cent calculated by the method of Bigeleisen and Wolfsberg (see page 63) using for the diagonal force constant for the C-N bond a value of 5.50×10^5 dynes cm^{-1} (95) and 955 cm^{-1} for the stretching frequency (96). Clearly, there is a significant decrease in the composite force constant of the C-N bond in going from the initial state to the transition state. In addition, the hydrogen-deuterium isotope effect of 5.4 indicates that at the transition state for this reaction, the proton is slightly more than half transferred to base.

It is clear from these results that there is a high degree of concertedness in the bond-rupture processes in this trans elimination reaction. Since this requires effective overlap of the participating orbitals, it follows that the reaction must be proceeding via a coplanar transition state in which the bulky trimethylammonium group occupies an axial position. Whether the reacting conformer which provides this relationship is the chair or a twisted boat is, however, not clear (see page 133).

The smaller nitrogen and hydrogen isotope effects, $(k^{14}/k^{15}-1)100 = 1.08$ and $k^{H}/k^{D} = 4.44$, respectively, in the trans elimination of the cis-cyclopentyl salt show that there is a somewhat smaller extent of C-N bond weakening and a somewhat greater extent of hydrogen transfer to base at the transition state in this reaction than in the trans elimination in the cyclohexyl series. In other words, there is a greater carbanionic character associated with the transition state for the cyclopentyl compound.

An interesting result is found for cis elimination in the cyclopentyl series. The nitrogen isotope effect of 0.64 per cent is considerably smaller than the nitrogen isotope effects for the trans eliminations in the cyclic systems, although its magnitude leaves no doubt that the C-N bond is undergoing rupture as the reacting system proceeds to the transition state. The hydrogen-deuterium isotope effect of 3.08 shows that the proton transfer to base is far advanced at the transition state. Clearly, the reaction does not involve the formation of an intermediate carbanion* but proceeds by an E2 mechanism in which

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*No test was carried out for H/D exchange with solvent in this system. However, it has been demonstrated by Ayrey (89) that no exchange accompanies the cis elimination of trans-2-phenylcyclohexyltrimethylammonium ion for which much more rigorous conditions are required than for the reaction of the trans-cyclopentyl compound.

there is a much higher degree of carbanionic character associated with the transition state than for the trans eliminations.

The nitrogen isotope effect for cis elimination in the cyclohexyl system is approximately 0.4 per cent, a small yet significant value, while the hydrogen-deuterium isotope effect is only 2.63. Two mechanisms need to be considered in relation to these isotope effect results, the two-step **E1cb** mechanism and a one-step E2 mechanism in which the transition state is Elcb - like*.

Ayrey (89) attempted to demonstrate a carbanion intermediate in this reaction by carrying out the reaction part way to completion in deuterated solvent. He failed, however, to detect any deuterium enrichment in recovered starting material. This rules out the possibility of a reversibly formed carbanion intermediate, but it does not exclude a rate-determining formation of this intermediate.

The decision as to which mechanism is operating rests with the interpretation of the nitrogen isotope effect. If the reaction proceeds by way of an Elcb mechanism, then the 0.4 per cent isotope effect must be a secondary isotope effect arising from rather large changes in the bending frequencies of the C-N bond in going from the initial to the transition state. It seems, however, that the bending frequencies would be more likely to increase rather than to decrease and, if anything, a reverse isotope effect would result. The basis for this conclusion is that as a proton is being removed to form the carbanion, conjugation

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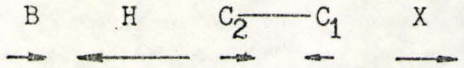
*Ayrey (89) has shown that the α'β- or ylide mechanism is not the reaction pathway for this elimination.

will develop between the phenyl group and the carbon atom carrying the negative charge. The phenyl group will, therefore, move closer to the trimethylammonium group causing the bending frequencies associated with the nitrogen atom to increase. Whether such changes would make a significant contribution to an isotope effect is difficult to predict, but it certainly would not be expected to favour reaction of the lighter isotopic species.

The conclusion that must be drawn from this is that the 0.4 per cent nitrogen isotope effect arises from a weakening of the stretching force constant associated with the C-N bond at the transition state, and, therefore, that the reaction proceeds by an E2 mechanism with a transition state that has very high carbanionic character. The hydrogen-deuterium isotope effect substantiates this conclusion since an even smaller isotope effect would probably have been observed if the reaction was proceeding by an Elcb mechanism. Recently, isotope effects associated with the dehydrofluorination of CF_3CHCl_2 and $CF_3CHBrCl$, reactions which proceed by way of an intermediate carbanion, were found to be 1.26 and 1.42, respectively (47). The hydrogen-deuterium isotope effect of 2.63 seems too large with respect to these values for an Elcb mechanism to be operating for the cis elimination in the cyclohexyl system.

The kinetic isotope effect results for the cyclic systems clearly establish that the two bond-rupture processes complement each other; the greater the extent to which the proton is transferred to base at the transition state, the smaller is the extent of C-N bond weakening. These observations are entirely the opposite to those of Smith in these laboratories (86) who has demonstrated rather convincingly that changes in substituents at the β-carbon or changes in the strength of the proton-abstracting base which cause one bond to be weakened more at the transition state has a corresponding effect on the other bond. It is necessary, therefore, to explore the origin of these two apparently contradictory observations.

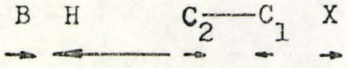
It will be recalled that Thornton (74), in his recent paper on transition state geometry in elimination reactions, proposed that the effect of a change in electron density on bond distance at the transition state is determined mainly by its influence on the reaction coordinate motion XLVII. Substituents which make this motion more difficult will increase the length of both the H-C and C-X bonds at the transition state.



XLVII

The extent of coupling of the motion which extends the lengths of the H-C and C-X bonds at the transition state can be expected to depend upon the degree of overlap of the participating orbitals which in turn will depend upon the approach to coplanarity of the bonds involved in the elimination process. When orbital overlap is effective, as in the case of the trans elimination of the cis-cyclohexyl salt, the reaction coordinate motion may be represented as XLVII and the reaction can be described as a highly concerted E2 process. When, for geometrical reasons, coplanarity is more difficult to achieve at the transition state, the degree of coupling of the two bond-rupture processes will be less and one bond change will be considerably more advanced over the other. Clearly, the energy required to achieve the transition state for such a process will be greater than in a concerted process. Furthermore, to reach this higher energy, there must be a greater degree of electron redistribution in the bond whose rupture is the more advanced. In other words, a decrease in the extent of coupling of the motions associated with the two bond-rupture processes will result in a transition state in which one bond has been extended more and the other bond extended less than in a more concerted process.

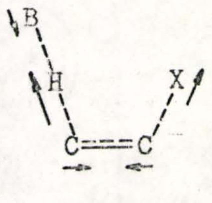
In the present series of compounds in which X is a very poor leaving group and the β-carbon bears the acidifying phenyl group, it would be reasonable to predict that it will be the C-H bond, rather than the C-N bond, which can most readily achieve the electron redistribution necessary to attain the highly energetic transition state for a poorly coupled process. In other words, the transition state can be expected to move toward the Elcb rather than the El end of the spectrum of possible transition state (29) as coupling becomes more difficult. Consequently, one would predict that for the cis elimination of the trans-cyclohexyl salt, which provides a dihedral angle of approximately 60°, C-N bond weakening should be less and proton transfer to base should be greater at the transition state than for any other compound in the series. The reaction coordinate motion for this compound, therefore, can be represented as in XLVIII. The isotope effect results clearly are in accord with this prediction.



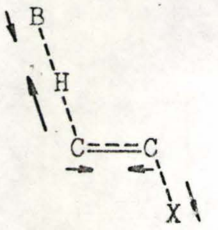
XLVIII

The greater carbanionic character of the transition state for trans elimination in the cyclopentyl series compared to that for the cyclohexyl series suggests that the former has more difficulty in attaining a dihedral angle of 180° at the transition state. This would have been difficult to predict *a priori* since it is impossible to assess what is likely to be the best compromise between eclipsing effects, ring strain and orbital overlap in the transition states for the trans elimination.

Of particular interest is the considerably greater carbanionic character of the transition state for cis elimination in the cyclopentyl



XLIX



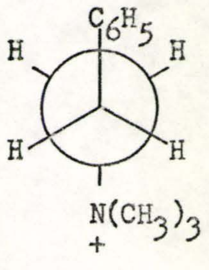
L

series compared to that of the transition states for the two trans elimination processes. It is difficult to assess the extent to which this can be attributed to an inherently smaller degree of coupling of the two bond-rupture processes in a cis coplanar transition state, XLIX compared to that in the trans coplanar transition state L , and the extent to which this arises from a deviation from the 0° dihedral angle because of the puckering of the cyclopentane ring. It is interesting to note, however, that a recent quantum mechanical treatment of orbital energies for the two transition states would suggest that coupling is indeed likely to be smaller in the cis case (97). In this connection, study of the isotope effects associated with cis elimination in a bicyclic system in which the rigidity of the molecule would maintain the 0° dihedral angle at the transition state would be extremely informative.

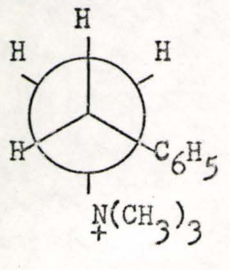
The isotope effects associated with the elimination reaction of 2-phenylethyltrimethylammonium ion would suggest a considerably greater extent of carbanionic character for its transition state than for the trans elimination reactions in the cyclic series. Not only is the nitrogen isotope effect smaller but the hydrogen-deuterium isotope effect would indicate that the extent of proton transfer to base is as great as in a cis elimination process. This raises the interesting possibility that this elimination reaction is not a trans process, as has always been assumed, but instead involves a departure of cis elements. Indeed, there are good reasons that this might be the case.

In the ground state, the preferred conformation for 2-phenylethyltrimethylammonium ion is undoubtedly LI which places the bulky groups in a trans relationship with one another. In order to achieve a transition state in which the departing groups are trans and coplanar, the bulky groups must move into staggered positions, conformation LII, resulting in considerable steric retardation. As a result, a normally less favoured transition state geometry which avoids this strong **repulsive** interaction between the two large groups might be favoured.

Strong support for this suggestion comes from recent work by Sicher who has found that similar systems do indeed react preferentially by a cis elimination (98,99). Reaction of 5-nonyltrimethylammonium ion with methoxide ion in methanol, for example, resulted in the preferential formation of the cis-olefin by a factor of four. Reaction by a trans coplanar E2 mechanism should have resulted in the preferential formation of the trans-olefin because of the lesser eclipsing of the alkyl groups in LIII than in LIV. Sicher suggests that the transition state leading to the cis-product is the Elcb-like conformer, LV , where non-bonded interaction between the bulky trimethylammonium group and groups on the

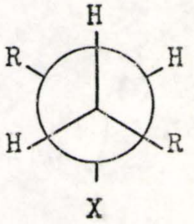


LI

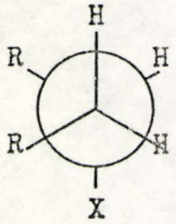


LII

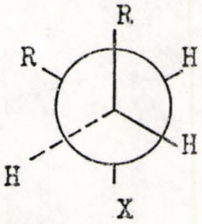
adjacent carbon are minimised. This choice of transition state allows Sicher to conclude that the molecule sacrifices the advantages of trans coplanarity for the sterically less encumbered transition state, LV.



LIII



LIV



LV

EXPERIMENTAL

The Synthesis of Unlabelled
2-Phenylethyltrimethylammonium Bromide, *cis*- and *trans*-2-Phenylcyclopentyltrimethylammonium Iodides and *cis*- and *trans*-2-Phenylcyclohexyltrimethylammonium Iodides.

General

2-Phenylethyltrimethylammonium bromide was prepared by displacing the tosylate group from 2-phenylethyl tosylate with dimethylamine then quaternising the resultant dimethyl 2-phenylethylamine with methyl bromide.

The *cis*-2-phenylcyclopentyltrimethylammonium iodide was prepared by Brown's (101) method of hydroboration on 1-phenylcyclopentene to give first *trans*-2-phenylcyclopentanol. Nucleophilic displacement by azide ion in dimethylsulphoxide on the corresponding tosylate gave *cis*-2-phenylcyclopentylazide which was then reduced with lithium aluminum hydride to *cis*-2-phenylcyclopentylamine. An Eschweiler-Clarke (102) dimethylation followed by quaternisation with methyl iodide gave the desired product.

The *trans*-2-phenylcyclopentyltrimethylammonium iodide was also prepared from 1-phenylcyclopentene. The olefin was reacted with formic acid and hydrogen peroxide to give 2-phenyl-2-hydroxylcyclopentyl formate which was then hydrolysed to 2-phenyl-1,2-cyclopentanediol. A pinacol-type rearrangement of the 1,2-diol gave 2-phenylcyclopentanone which was then converted to the oxime and catalytically reduced to trans-2-phenylcyclopentylamine. Eschweiler-Clarke (102) dimethylation followed by reaction with methyl iodide gave the quaternary ammonium salt.

The cis-2-phenylcyclohexyltrimethylammonium iodide was prepared from 1-phenylcyclohexene by the same method as was used for the preparation of cis-2-phenylcyclopentyltrimethylammonium iodide. The tosylate derivative of trans-2-phenylcyclohexanol underwent displacement by azide ion followed by reduction to give cis-2-phenylcyclohexylamine. Dimethylation followed by quaternisation with methyl iodide yielded cis-2-phenylcyclohexyltrimethylammonium iodide.

The trans-2-phenylcyclohexyltrimethylammonium iodide was prepared by Brown's (103) method of boroamination on 1-phenylcyclohexene to give first trans-2-phenylcyclohexylamine which was converted to the tertiary amine by the Eschweiler-Clarke procedure. Quaternisation of the tertiary amine with methyl iodide gave the desired product.

All melting points in the following procedures have been corrected.

2-Phenylethyltrimethylammonium Bromide

Preparation of 2-Phenylethyl p-Toluenesulphonate

This compound was prepared by the method of Tipson (104).

2-Phenylethyl alcohol (Fisher Certified Reagent), distilled before use, b.p. 100-101°C./7 mm., 12.7 g. (0.104 mole), was dissolved in 150 ml. of dry pyridine (Fisher Certified Reagent) which had been purified by refluxing for 14 hours over barium oxide and then distilling. The solution was cooled to 0°C. in an ice-salt bath and freshly recrystallised p-toluenesulphonyl chloride*, 21.5g. (0.113 mole), was added with swirling. The reaction mixture was kept at 0°C. for two hours after which time water was added in two 10 ml. portions. The reaction mixture was then diluted with 150 ml. of water and was extracted thrice with 75 ml. portions of chloroform. The combined chloroform extracts were washed thrice with 50 ml. aliquots of ice-cold 10% sulphuric acid followed by three washings with 10% sodium bicarbonate and finally with three 50 ml. portions of water. The chloroform layer was dried over anhydrous sodium sulphate and then taken to dryness under reduced pressure to yield 22.5 g. (78%) of 2-phenylethyl p-toluenesulphonate, m.p. 37-38.5°C, (Saunders (105), m.p. 37.4-38°C.).

Preparation of Dimethyl 2-Phenylethylamine

A solution of 2-phenylethyl p-toluenesulphonate, 27.6 g. (0.10 mole), and anhydrous dimethylamine (Eastman), 9.0 g. (0.20 mole), in 200 ml. of anhydrous ether was permitted to stand for two days with a

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* The p-toluenesulphonyl chloride was purified immediately before use. Thirty-five grams of p-toluenesulphonyl chloride was dissolved in 70 ml. of chloroform and the solution diluted to 400 ml. with 30-60° petroleum ether. The resulting solution was treated with Norit A Decolourising Carbon and filtered. The volume of the filtrate was reduced to 65 ml. on a rotary evaporator and the p-toluenesulphonyl chloride was allowed to crystallise from the concentrated solution.

little absolute ethanol being added occasionally to keep the mixture homogeneous. The reaction mixture was concentrated to 60 ml. under reduced pressure and was then poured into 150 ml. of water. The aqueous solution was extracted with five 20 ml. portions of ether and the ether extracts were in turn extracted with five 20 ml. portions of 10% hydrochloric acid. The acid solution was made basic by the addition of 10% sodium hydroxide and the resultant solution was extracted with three 40 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulphate and the ether removed under reduced pressure. Distillation of the resultant oil gave 9.2 g. (61%) of dimethyl 2-phenylethylamine, b.p. 104°C./20 mm. (Saunders (105), b.p. 111°C./20 mm.).

Preparation of 2-Phenylethyltrimethylammonium Bromide

Dimethyl 2-phenylethylamine, 9.2 g. (0.061 mole), in nitromethane (150 ml.) was treated with methyl bromide (Eastman), 12.6 g. (0.13 mole), and the reaction mixture was allowed to stand at room temperature for one day. The precipitated salt was collected by filtration and recrystallised three times from ethanol-ether to give 24 g. (79%) of 2-phenylethyltrimethylammonium bromide, m.p. 237.5-238°C. (Saunders (105), m.p. 238-239°C.). Anal. Calcd. for $C_{11}H_{18}NBr$: C, 54.10; H, 7.43; N, 5.74. Found: C, 54.10; H, 7.42; N, 5.73.

cis-2-Phenylcyclopentyltrimethylammonium Iodide

Preparation of 1-Phenylcyclopentene

This compound was prepared by the method of Baddeley (106). Magnesium turnings, 24.3 g. (1 mole) (Fisher Reagent), were placed in a one-litre, three-neck round-bottom flask fitted with a condenser, mercury-seal stirrer and dropping funnel. The apparatus was swept with a low flame and allowed to cool to room temperature. Bromobenzene, 3 g. (0.02 mole) (Fisher), dissolved in sodium-dried ether (50 ml.) was added and the reaction initiated with vigorous stirring. Bromobenzene, 154 g. (0.98 mole), in anhydrous ether (200 ml.) was added dropwise at sufficient rate to maintain reflux and the solution was stirred until almost all of the magnesium had reacted. Cyclopentanone 84 g. (1 mole) (Eastman), in anhydrous ether (100 ml.) was then added dropwise at such a rate as to maintain gentle reflux; the solution was then cooled to room temperature. Ammonium chloride, 53.5 g. (1 mole), in 100 ml of water was then added dropwise to decompose the complex. The ether layer was separated from the resulting mixture which was then washed further with three 50 ml. portions of ether. The ether extracts were washed with 25 ml. of water and then dried over anhydrous sodium sulphate. The ether was removed under reduced pressure to yield 127.5 g. (78.5%) of crude 1-phenylcyclopentanol. A 90% solution of formic acid (400 ml.) was added to the alcohol and the resulting solution was stirred at room temperature for 2 hours. The olefin that was formed remained as an upper layer and was separated and washed with two 15 ml. portions of water and then distilled under reduced pressure to give 99 g. (69%) of 1-phenylcyclopentene, b.p. 104-105°C./9 mm. (Baddeley (106), b.p.

107-108°C./12 mm.).

Preparation of trans-2-Phenylcyclopentanol

This compound was prepared by the method of Brown (101). Sodium borohydride, 3 g. (0.08 mole) (Merck, Sharpe & Dohme), and 1-phenylcyclopentene, 30.3 g. (0.21 mole), were dissolved in 200 ml. of bis(2-methoxy)ethyl ether (diglyme) which had been dried and distilled over lithium aluminum hydride. The solution was placed in a dry one-litre, three-neck round-bottom flask equipped with a nitrogen inlet, a mercury-seal stirrer and a pressure-equilibrated dropping funnel fitted with a nitrogen outlet. The solution was cooled to 2°C. with an ice-water bath and flushed with dry nitrogen. Freshly distilled borontrifluoride etherate, 15.4 g. (0.108 mole), in 50 ml of diglyme was added dropwise over one half hour and the resulting solution was stirred for one hour at 2°C. and one hour at room temperature. The nitrogen inlet was replaced with a reflux condenser and the solution was hydrolysed with the addition of 30 ml. of water. When hydrogen was no longer evolved, 25 ml. of 3N sodium hydroxide was added and oxidation was carried out with the addition of 30 ml. of 30% hydrogen peroxide at such a rate as to maintain reflux. The reaction mixture was cooled to room temperature and treated with ice-water (50 ml.). The product separated as an upper layer and was taken up in ether (50 ml.). The ether layer was dried over anhydrous sodium sulphate and distilled to yield 27.1 g. (80%) of trans-2-phenylcyclopentanol, b.p. 128-130°C./ 8 mm.

Preparation of trans-2-Phenylcyclopentyl p-Toluenesulphonate

This compound was prepared by the procedure described for 2-phenylethyl p-toluenesulphonate. trans-2-Phenylcyclopentanol, 58.8 g. (0.362 mole) was treated with p-toluenesulphonyl chloride, 76 g. (0.397 mole) in 300 ml. of dry pyridine. The product was recrystallised out of ether-petroleum ether to give 76 g. (66%) of trans-2-phenylcyclopentyl p-toluenesulphonate, m.p. 70-71°C. (DePuy (60), m.p. 68-69°C.).

Preparation of cis-2-Phenylcyclopentylazide

trans-2-Phenylcyclopentyl p-toluenesulphonate, 76 g. (0.24 mole), and sodium azide, 78 g. (1.20 mole) (Fisher Purified), were mixed in 350 ml. of freshly distilled dimethylsulphoxide and heated at 60°C. for 30 hours with occasional swirling. The mixture was poured into 200 ml. of ice-water and extracted with four 30 ml. portions of ether. The ether layers were dried over anhydrous sodium sulphate, then evaporated under reduced pressure to give 44.7 g. (100%) of crude cis-2-phenylcyclopentylazide.

Preparation of cis-2-Phenylcyclopentylamine

cis-2-Phenylcyclopentylazide, crude, 44.7 g. (0.24 mole), was dissolved in anhydrous ether (250 ml.) and added dropwise to a slurry of lithium aluminum hydride, 10 g. (0.264 mole), in 200 ml. of anhydrous ether in a one-litre round-bottom flask equipped with a condenser, dropping funnel and magnetic stirrer. The mixture was stirred at room temperature for 6 hours and then hydrolysed by the dropwise addition of water (50 ml.). The ether layer was separated and the aqueous layer was washed with three 15 ml. portions of ether. The combined ether layers was dried over anhydrous sodium sulphate and evaporated to give 32.8 g. (85%) of crude cis-2-phenylcyclopentylamine.

Preparation of cis-N,N-Dimethyl-2-phenylcyclopentylamine

cis-2-Phenylcyclopentylamine, crude, 32.8 g. (0.204 mole), was added dropwise to a solution of 37% formaldehyde, 49.6 g. (0.612 mole), and 90% formic acid, 75 g. (1.47 mole), and the resulting solution was refluxed for seven hours. Concentrated hydrochloric acid (15 ml.) was added to the cooled solution and the excess formic acid was removed under reduced pressure. The residue was poured into 50 ml. of water and the solution was then made basic with the addition of 30% sodium hydroxide. The mixture was extracted with three 15 ml. portions of ether and the combined ether extracts were dried over anhydrous sodium sulphate. The ether was removed under reduced pressure and the product was distilled to yield 18.5 g. (48%) of cis-N,N-dimethyl-2-phenylcyclopentylamine, b.p. 80-81°C./0.5 mm.

Preparation of cis-2-Phenylcyclopentyltrimethylammonium Iodide

cis-N,N-Dimethyl-2-phenylcyclopentylamine, 18.5 g. (0.098 mole), in sodium-dried ether (200 ml.) was treated with methyl iodide, 28 g. (0.198 mole) (Fisher Reagent), dissolved in 50 ml. of anhydrous ether. The reaction mixture was allowed to stand for 36 hours at room temperature in the dark and the crude salt was then collected by filtration. Three recrystallisations from ethanol-ether yielded 29 g. (58%) of cis-2-phenylcyclopentyltrimethylammonium iodide, m.p. 179-180°C. Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 50.65; H, 6.70; N, 4.05.

trans-2-Phenylcyclopentyltrimethylammonium Iodide

Preparation of 2-Phenylcyclopentanone

This compound was prepared according to the procedure of Goldschmidt and Veer (107). A mixture of 1-phenylcyclopentene, 62.4 g. (0.433 mole), and 90% formic acid, 350 g. (6.85 mole), was placed in a one-litre three-neck round-bottom flask equipped with a dropping funnel and a mercury-seal stirrer. A 30% solution of hydrogen peroxide, 56.3 g. (0.496 mole), was added dropwise with stirring over one-half hour with the temperature being maintained at 60°C. The solution was stirred for two hours at 40°C. and then refluxed for three hours. The excess formic acid was 200 ml. of removed under reduced pressure, the residue poured into 200 ml. of water and the aqueous solution extracted with four 30 ml. portions of ether. The combined ether layers were washed with 10% sodium hydroxide until the washes remained alkaline and then dried over anhydrous sodium sulphate. The ether was evaporated under reduced pressure and distillation of the residual oil yielded 36.3 g. (52.5%) of 2-phenylcyclopentanone, b.p. 134-136°C./8mm. (Arnold (108), 135-140°C./9 mm.).

Preparation of 2-Phenylcyclopentanone Oxime

Hydrated sodium acetate, 71 g. (0.522 mole), and 2-phenylcyclopentanone, 36.3 g. (0.227 mole), were added to a solution of hydroxylamine hydrochloride, 36.3 g. (0.522 mole), in 100 ml. of water with enough ethanol to cause complete solution when hot. The solution was allowed to stand for 15 minutes on the steam bath and then cooled slowly. The precipitate was filtered and recrystallised from ethanol to yield 34 g. (86%) of 2-phenylcyclopentanone oxime, m.p. 145-146°C. Anal. Calcd. for $C_{11}H_{12}O$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.40; H, 7.58; N, 7.80.

Preparation of trans-2-Phenylcyclopentylamine Hydrochloride

Sodium, 4.0 g. (1.74 mole), cut into small pieces, was added rapidly to a refluxing solution of 2-phenylcyclopentanone oxime, 31.5 g. (0.18 mole), in dry absolute ethanol (300 ml.) and the reaction mixture was refluxed until all of the sodium had dissolved (1.5 hours). The solution was made acidic with concentrated hydrochloric acid and the ethanol evaporated under reduced pressure. The residue was dissolved in 150 ml. of water and extracted with three 25 ml. portions of ether to remove unreacted oxime. The aqueous layer was made basic with 30% sodium hydroxide and extracted with four 30 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulphate, treated with Norit A Decolourising Carbon and filtered. Dry hydrogen chloride gas was bubbled through the etheral solution to precipitate trans-2-phenylcyclopentylamine hydrochloride which was then collected by filtration. Three recrystallisations from ethanol-ether yielded 17.5 g. (49.5%), m.p. 147.5-148.5°C.

Preparation of trans-N,N-Dimethyl-2-phenylcyclopentylamine

This compound was prepared by the procedure described for cis-N,N-dimethyl-2-phenylcyclopentylamine. trans-2-Phenylcyclopentylamine hydrochloride, 13.2 g. (0.067 mole), was dissolved in 50 ml. of water and the solution was made basic with 30% sodium hydroxide. The aqueous mixture was extracted with three 20 ml. portions of ether, the combined ether layers then being evaporated under reduced pressure to yield 10.7 g. (100%) of trans-2-phenylcyclopentylamine. This compound, 10.7 g. (0.067 mole). was reacted with a solution of 37% formaldehyde, 11 g. (0.136 mole), and formic acid, 50 g. (0.98 mole), to give 10.7 g. (84%) of colourless crude trans-N,N-dimethyl-2-phenylcyclopentylamine. A vapour phase chromatographic analysis was performed on this product using a 3/8" by 5' aluminum column packed with the detergent Tide and mounted in an Aerograph A-700 chromatograph. The detergent packing was prepared beforehand by heating it in a beaker at 180°C. for 48 hours to expel volatile materials. At a column temperature of 175°C. and with a helium flow rate of approximately 200 ml./min., cis-N,N-dimethyl-2-phenylcyclopentylamine and trans-N,N-dimethyl-2-phenylcyclopentylamine had retention times of 17 and 26 minutes, respectively. Analysis indicated that the product contained greater than 99 per cent of the trans-isomer and less than one per cent of the cis-isomer.

Preparation of trans-2-Phenylcyclopentyltrimethylammonium Iodide

This compound was prepared by the procedure described for cis-2-phenylcyclopentyltrimethylammonium iodide. The tertiary amine, 10.7 g. (0.056 mole), was treated with methyl iodide, 18 g. (0.127 mole), in 150 ml. of anhydrous ether to give 11.3 g. (61%) of trans-2-phenylcyclopentyltrimethylammonium iodide, m.p. 228-228.5°C. Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 51.30; H, 6.75; N, 4.29.

cis-2-Phenylcyclohexyltrimethylammonium Iodide

Preparation of 1-Phenylcyclohexene

This compound was prepared by the procedure described for 1-phenylcyclopentene. One molar amounts of reactants yielded 89 g. (62%) of 1-phenylcyclohexene, b.p. 90°C./2 mm.

Preparation of trans-2-Phenylcyclohexanol

This compound was prepared by the procedure described for the preparation of trans-2-phenylcyclopentanol. Sodium borohydride, 5.4 g. (0.142 mole), and 1-phenylcyclohexene, 33.4 g. (0.211 mole) in 200 ml. of diglyme were treated with borontrifluoride etherate, 27 g. (0.19 mole), in 60 ml. of diglyme to yield 23 g. (62%) of trans-2-phenylcyclohexanol after recrystallisation from n-hexane, m.p. 52-53°C. (Cook (109), m.p. 56-57°C.).

Preparation of trans-2-Phenylcyclohexyl p-Toluenesulphonate

trans-2-Phenylcyclohexanol, 37.2 g. (0.211 mole), was dissolved in dry pyridine (250 ml.) and p-toluenesulphonyl chloride, 44.2 g. (0.23 mole), was added to the solution with shaking. The reaction mixture was kept at room temperature for 36 hours and then poured into 100 ml. of water. The resulting precipitate was filtered, washed with water and recrystallised from ethanol to yield 49.2 g. (70.5%) of *trans*-2-phenylcyclohexyl *p*-toluenesulphonate, m.p. 130-131.5°C. (Cristol (59), m.p. 130-131°C.).

Preparation of cis-2-Phenylcyclohexylazide

trans-2-Phenylcyclohexyl p-toluenesulphonate, 49.2 g. (0.149 mole), and sodium azide, 49.2 g. (0.756 mole), were added to freshly distilled dimethylsulphoxide (300 ml.) and the reaction mixture was heated at 85°C. for 23 hours with occasional swirling. The mixture was poured into ice-water (150 ml.) and extracted with four 30 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulphate and then evaporated to give 30 g. (100%) of crude cis-2-phenylcyclohexylazide.

Preparation of cis-2-Phenylcyclohexylamine

This compound was prepared by the procedure described earlier for *cis*-2-phenylcyclopentylamine. *cis*-2-Phenylcyclohexylazide, 30 g. (0.149 mole), in anhydrous ether (150 ml.) was reacted with lithium aluminum hydride, 11.3 g. (0.298 mole), in 150 ml. of anhydrous ether to yield 23.5 g. (90%) of crude cis-2-phenylcyclohexylamine.

Preparation of cis-N,N-Dimethyl-2-phenylcyclohexylamine

This compound was prepared by the procedure for cis-N,N-dimethyl-2-phenylcyclopentylamine. cis-2-Phenylcyclohexylamine, 23.5 g. (0.134 mole), was reacted with 37% formaldehyde, 32.5 g. (0.4 mole), and 90% formic acid, 100 g. (1.95 mole), to give 14.2 g. (52.4%) of cis-N,N-dimethyl-2-phenylcyclohexylamine, b.p. 100°C./0.7 mm.

Preparation of cis-2-Phenylcyclohexyltrimethylammonium Iodide

This compound was prepared by the procedure previously described for the preparation of cis-2-phenylcyclopentyltrimethylammonium iodide. cis-N,N-Dimethyl-2-phenylcyclohexylamine, 14.2 g. (0.07 mole), was treated with methyl iodide, 20 g. (0.14 mole) in 150 ml. of anhydrous ether to give 14.2 g. (41%) of cis-2-phenylcyclohexyltrimethylammonium iodide, m.p. 216-217°C. (Cristol (57), m.p. 215-216°C.). Anal. Calcd. for $C_{15}H_{24}NI$: C, 52.18; H, 7.01; N, 4.06. Found: C, 52.36; H, 7.06; N, 4.12.

trans-2-Phenylcyclohexyltrimethylammonium Iodide

Preparation of trans-2-Phenylcyclohexylamine

This compound was prepared by Brown's method (103) of boroamination. Sodium borohydride, 7.8 g. (0.206 mole) (Merck, Sharpe &

Dohme), and 1-phenylcyclohexene, 79 g. (0.5 mole), were dissolved in 200 ml. of bis-(2-methoxy) ethyl ether (diglyme) in a one-litre three-neck round-bottom flask equipped with a nitrogen inlet, a mercury-seal stirrer and a pressure-equilibrated dropping funnel fitted with a nitrogen inlet. The solution was cooled to 2°C. with an ice-water bath and flushed with dry nitrogen. Freshly distilled borontrifluoride etherate, 40 g. (0.282 mole) in 60 ml. of diglyme was added dropwise and the resulting solution was stirred at 2°C. for 15 minutes and at room temperature for three hours. The nitrogen inlet was replaced with a reflux condenser and hydroxylamine-O-sulphonic acid, 62 g. (0.55 mole) (Allied Chemical), was added. The mixture was heated at 95°C. for four hours and then cooled. Concentrated hydrochloric acid (50 ml.) was added and the reaction mixture was poured into 200 ml. of water. The resulting mixture was extracted with three 30 ml. portions of ether and the aqueous layer was then made basic with the addition of 30% sodium hydroxide. The aqueous mixture was extracted with four 30 ml. portions of ether and the combined ether extracts were dried over anhydrous sodium sulphate. Ether was removed under reduced pressure and the residue was distilled to yield 12.5 g. (14.6%) of trans-2-phenylcyclohexylamine, b.p. 105-106°C./1.7 mm.

Preparation of trans-N,N-Dimethyl-2-phenylcyclohexylamine

This compound was prepared by the procedure previously described for cis-N,N-dimethyl-2-phenylcyclopentylamine. trans-2-Phenylcyclohexylamine, 24.7 g. (0.141 mole), was reacted with a solution of 37% formaldehyde, 35 g. (0.433 mole) and 90% formic acid, 120 g. (2.35 mole) to give 18.3 g. (64%) of trans-N,N-dimethyl-2-phenylcyclohexylamine, b.p. 86°C./0.3 mm.

Preparation of trans-2-Phenylcyclohexyltrimethylammonium Iodide

This compound was prepared by the procedure previously described for cis-2-phenylcyclopentyltrimethylammonium iodide. trans-N,N-Dimethyl-2-phenylcyclohexylamine, 16 g. (0.079 mole), was treated with methyl iodide, 22.4 g. (0.158 mole), in 150 ml. of anhydrous ether to yield 11.6 g. (42.6%) of trans-2-phenylcyclohexyltrimethylammonium iodide, m.p. 235-236°C. (Cristol (57), m.p. 232-234°C.; Ayrey (89), m.p. 234-235°C.). Anal. Calcd. for $C_{15}H_{24}NI$: C, 52.18; H, 7.01; N, 4.06. Found: C, 52.31; H, 7.11; N, 4.15.

The Synthesis of Deuterated cis- and trans-2-Phenylcyclopentyltrimethylammonium Iodides and cis- and trans-2-Phenylcyclohexyltrimethylammonium Iodides

General

The cis-2-phenylcyclopentyltrimethylammonium-2-d_1 iodide and cis-2-phenylcyclohexyltrimethylammonium-2-d_1 iodide were prepared by Brown's (101) method of hydroboration employing sodium borodeuteride to provide the deuterium atom for attachment to the 2-position. The synthetic sequences were identical with those for the unlabelled compounds and product yields were comparable.

The *trans*-2-phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ iodide and *trans*-2-phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ iodide were prepared by Brown's (103) method of boroamination again using sodium borodeuteride. Dimethylation of the resultant primary amines followed by methyl iodide quaternisation gave the two products.

The deuterium content of the quaternary ammonium salts was determined by Nemeth of the University of Illinois using the falling drop method.

cis 2-Phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ Iodide

Preparation of *trans* 2-Phenylcyclopentanol-2-$\underline{d}_1$

This compound was prepared by the procedure described for the synthesis of the undeuterated compound. Sodium borodeuteride, 2.2 g. (0.053 mole) (Merck, Sharpe & Dohme), and 1-phenylcyclopentene, 20.2 g. (0.14 mole), in 50 ml. of diglyme was treated with boron-trifluoride etherate, 11 g. (0.077 mole), in 15 ml. of diglyme to yield 17.6 g. (78%) of trans-2-phenylcyclopentanol-2-$\underline{d}_1$, b.p. 120-122°C./ 5.5 mm. (Undeuterated compound, b.p. 128-130°C./8 mm.).

Preparation of *trans*-2-Phenylcyclopentyl-2-$\underline{d}_1$ *p*-Toluenesulphonate

This compound was prepared by treatment of *trans*-2-phenylcyclopentanol-2-$\underline{d}_1$, 17.6 g. (0.108 mole), with p-toluenesulphonyl chloride, 23.6 g. (0.124 mole), in dry pyridine (75 ml.) as described previously for the preparation of the undeuterated compound. The resulting *trans*-2-phenylcyclopentyl-2-$\underline{d}_1$ *p*-toluenesulphonate was recrystallised thrice from ether-petroleum ether to yield 23 g. (67%), m.p. 69-70°C. (Undeuterated compound, m.p. 70-71°C.).

Preparation of *cis*-2-Phenylcyclopentylazide-2-$\underline{d}_1$

This compound was prepared by the method previously described for the undeuterated-*cis*-2-phenylcyclopentylazide. *trans*-2-Phenyl pentyl-2-$\underline{d}_1$ *p*-toluenesulphonate, 23 g. (0.073 mole), was reacted with sodium azide, 22 g. (0.338 mole), in 200 ml. of dimethylsulphoxide at 60°C. to yield 12.9 g. (94%) of *cis*-2-phenylcyclopentylazide-2-$\underline{d}_1$.

Preparation of *cis*-2-Phenylcyclopentylamine-2-$\underline{d}_1$

This compound was prepared by the reduction of *cis*-2-phenylcyclopentylazide-2-$\underline{d}_1$, 12.9 g. (0.069 mole), with lithium aluminum hydride, 5.2 g. (0.118 mole), as was previously described for the undeuterated material, to give 7.8 g. (70%) of crude *cis*-2-phenylcyclopentylamine-2-$\underline{d}_1$.

Preparation of *cis*-N,N-Dimethyl-2-phenylcyclopentylamine-2-$\underline{d}_1$

This compound was prepared by the Eschweiler-Clarke procedure as described for the synthesis of the undeuterated compound. *cis*-2-Phenylcyclopentylamine-2-$\underline{d}_1$, 7.8 g. (0.048 mole), was reacted with a solution of 37% formaldehyde, 11.7 g. (0.105 mole), and 90%

formic acid, 50 g. (0.98 mole), to give 2.25 g. (24.6%) of cis-N,N-dimethyl-2-phenylcyclopentylamine-2-$\underline{d}_1$, b.p. 72-73°C./0.3 mm. (Undeuterated compound, b.p. 80-81°C./0.5 mm.).

Preparation of cis-2-Phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ Iodide

cis-N,N-Dimethyl-2-phenylcyclopentylamine-2-$\underline{d}_1$, 2.25 g. (0.012 mole), was treated with methyl iodide, 4 g. (0.028 mole), in sodium-dried ether (80 ml) as was described for the undeuterated compound, to yield cis-2-phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ iodide, 1.5 g. (38%), m.p. 178.5-179.5°C. (Undeuterated compound, m.p. 179-180°C.). Deuterium analysis indicated that this compound had 1.01 atoms of deuterium per molecule. Anal. Calcd. for $C_{14}H_{21}DNI$: C, 50.61; H+D, 6.98; N, 4.22. Found: C, 50.57; H+D, 6.91; N, 4.31.

trans-2-Phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ Iodide

Preparation of trans-2-Phenylcyclopentylamine-2-$\underline{d}_1$

This compound was prepared by the procedure used for the preparation of trans-2-phenylcyclohexylamine. Sodium borodeuteride, 4 g. (0.096 mole), and 1-phenylcyclopentene, 40 g. (0.278 mole), in 200 ml. of diglyme was treated with borontrifluoride etherate, 21 g. (0.141 mole) in 50 ml. of diglyme. The resulting solution was reacted with hydroxylamine-O-sulphonic acid, 34.6 g. (0.306 mole), at 95°C. to yield 12.8 g. (28.5%) of trans-2-phenylcyclopentylamine-2-$\underline{d}_1$, b.p. 84°C./1 mm.

Preparation of trans-N,N-Dimethyl-2-phenylcyclopentylamine-2-d_1

This compound was prepared by the procedure previously described for the undeuterated compound. trans-2-Phenylcyclopentylamine-2-d_1, 12.8 g. (0.079 mole), was reacted with a solution of 37% formaldehyde, 15 g. (0.185 mole), and 90% formic acid, 50 g. (0.98 mole), to give 9.4 g. (62.5%) of trans-N,N-dimethyl-2-phenylcyclopentylamine-2-d_1, b.p. 80°C./0.6 mm.

Preparation of trans-2-Phenylcyclopentyltrimethylammonium-2-d_1 Iodide

This compound was prepared from trans-N,N-dimethyl-2-phenylcyclopentylamine-2-d_1, 9.4 g. (0.049 mole), by treatment with methyl iodide, 10 g. (0.071 mole), in anhydrous ether (150 ml.) as was described for the undeuterated compound. The product was recrystallised three times from ethanol to yield trans-2-phenylcyclopentyltrimethylammonium-2-d_1 iodide, m.p. 227-227.5°C. (Undeuterated compound, m.p. 228-228.5°C.). Deuterium analysis indicated that this compound had 0.99 atoms of deuterium per molecule. Anal. Calcd. for $C_{14}H_{21}DNI$: C, 50.61; H+D, 6.98; N, 4.22. Found: C, 50.50; H+D, 7.11; N, 4.25.

cis-2-Phenylcyclohexyltrimethylammonium-2-d_1 Iodide

Preparation of trans-2-Phenylcyclohexanol-2-d_1

This compound was prepared by the procedure previously described for the synthesis of the undeuterated compound. Sodium borodeuteride, 2.2 g. (0.053 mole), and 1-phenylcyclohexene, 22.2 g. (0.14 mole), were treated with borontrifluoride etherate, 11 g. (0.077 mole), in 100 ml. of diglyme to yield 13.5 g. (54.5%) of trans-2-phenylcyclohexanol-2-d_1, m.p. 52-53.5°C. (Undeuterated compound, m.p. 52-53.5°C.).

Preparation of trans-2-Phenylcyclohexyl-2-d_1 p-Toluenesulphonate

This compound was prepared by reacting trans-2-phenylcyclohexanol-2-d_1, 13.5 g. (0.076 mole), with p-toluenesulphonyl chloride, 15.9 g. (0.083 mole) in dry pyridine (90 ml.) as was described for the preparation of the undeuterated compound. The product was recrystallised from ethanol to yield 13.9 g. (61%) of trans-2-phenylcyclohexyl-2-d_1 p-toluenesulphonate, m.p. 136-137°C. (Undeuterated compound, m.p. 130-131°C.).

Preparation of cis-2-Phenylcyclohexylazide-2-d_1

trans-2-Phenylcyclohexyl-2-d_1 p-toluenesulphonate, 13.9 g. (0.042 mole), and sodium azide, 13.9 g. (0.214 mole), were added to dimethylsulphoxide (140 ml.) and the reaction mixture was maintained at 85°C. for 24 hours, as was described in the preparation of the undeuterated compound. The yield of the product was 8.5 g. (100%) of cis-2-phenylcyclohexylazide-2-d_1.

Preparation of cis-2-Phenylcyclohexylamine-2-d_1

This compound was prepared by the procedure previously described for cis-2-phenylcyclohexylamine. cis-2-Phenylcyclohexylazide-2-d_1, 8.5 g. (0.042 mole), was reduced with lithium aluminum hydride, 3.2 g. (0.084 mole), in anhydrous ether (150 ml.) to give 6.4 g. (86%) of crude cis-2-phenylcyclohexylamine-2-$\underline{d}_1$.

Preparation of cis-N,N-Dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$

cis-2-Phenylcyclohexylamine-2-$\underline{d}_1$, 6.4 g. (0.036 mole), was reacted with a solution of 37% formaldehyde, 12 g. (0.148 mole), and 90% formic acid, 40 g. (0.87 mole), as was described for the undeuterated compound, to yield cis-N,N-dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$, 4 g. (54%), b.p. 104-106°C./0.9 mm. (Undeuterated compound, b.p. 100°C./0.7 mm.).

Preparation of cis-2-Phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ Iodide

This compound was prepared by the procedure previously described for the undeuterated compound. cis-N,N-Dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$ 4 g. (0.0196 mole), was treated with methyl iodide, 6.1 g. (0.043 mole), in 125 ml. of anhydrous ether to give 3.85 g. (57%) of cis-2-phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ iodide, m.p. 220-221°C. (Undeuterated compound, m.p. 216-217°C. Mixed m.p. 218-219°C.). Deuterium analysis indicated that this compound has 0.99 atoms of deuterium per molecule. Anal. Calcd. for $C_{15}H_{23}DNI$: C, 52.02; H+D, 7.27; N, 4.05. Found: C, 51.90; H+D, 7.18; N, 4.13.

trans-2-Phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ Iodide

Preparation of trans-2-Phenylcyclohexylamine-2-$\underline{d}_1$

This compound was prepared by the procedure previously described for the preparation of the undeuterated compound. Sodium borodeuteride, 4 g. (0.096 mole), and 1-phenylcyclohexene, 39.5 g. (0.25 mole), were treated with borontrifluoride etherate, 19.5 g. (0.137 mole), in 140 ml. of diglyme. The resulting solution was reacted with hydroxylamine-O-sulphonic acid, 31 g. (0.274 mole), to yield 8.83 g. (20%) of *trans*-2-phenylcyclohexylamine-2-$\underline{d}_1$, b.p. 94°C./0.6 mm., m.p. 51-53°C. (Undeuterated compound, b.p. 105-106°C./1.7 mm.).

Preparation of trans-N,N-Dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$

This compound was prepared from *trans*-2-phenylcyclohexylamine-2-$\underline{d}_1$, 8.83 g. (0.05 mole), by reaction with a solution of 37% formaldehyde, 12.1 g. (0.149 mole), and 90% formic acid, 40 g. (0.78 mole), as was described for the undeuterated compound, to yield 7.72 g. (76%) of *trans*-N,N-dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$, b.p. 101-102°C./ 1.1 mm. (Undeuterated compound, b.p. 86°C./0.3 mm.).

Preparation of trans-2-Phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ Iodide

trans-N,N-Dimethyl-2-phenylcyclohexylamine-2-$\underline{d}_1$, 7.72 g. (0.038 mole), was treated with methyl iodide, 11.8 g. (0.083 mole), in anhydrous ether (150 ml.), as was described for the undeuterated compound, to give 4.14 g. (31.5%) of trans-2-phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ iodide, m.p. 233-234°C. (Undeuterated compound, m.p. 235-236°C. Mixed m.p. 234-235°C.). Deuterium analysis indicated that this compound had 0.97 atoms of deuterium per molecule. Anal. Calcd. for $C_{15}H_{23}DNI$: C, 52.02; H+D, 7.27; N, 4.05. Found: C, 52.02; H+D, 7.15; N, 4.21.

Test for the Isomerisation of
3-Phenylcyclopentene to 1-Phenylcyclopentene

Preparation of 3-Phenylcyclopentene and 1-Phenylcyclopentene

These compounds were prepared according to the procedure described by Talent (110). trans-2-Phenylcyclopentanol, 17.3 g. (0.107 mole), was placed in a two-neck 100 ml. round-bottom flask equipped with a condenser and a dropping funnel. Phosphoric acid (20 ml. of a 85% solution) was added dropwise and the solution stirred with a magnetic stirrer for four hours at 90°C. Ice-water (30 ml.) was then added and the mixture was extracted with three 20 ml. portions of benzene. The combined benzene extracts were dried over anhydrous sodium sulphate and then the benzene was removed under reduced pressure. The residual oil was fractionated through a 24-inch by one-quarter inch column fitted with a spiral of nichrome wire to give 4 g. (26%) of 3-phenylcyclopentene, b.p. 83-84°C./12 mm., and 6.8 g. (44%) of 1-phenylcyclopentene, b.p. 109-110°C./12 mm. Vapour phase chromatography analysis indicated that both fractions were pure.

Isomerisation Test

3-Phenylcyclopentene, 0.078 g. (0.541 mole), and 1-phenylcyclopentene, 0.077 g. (0.535 mole), was dissolved in 0.2N sodium ethoxide (50 ml.) and the solution was maintained at 60°C. for 40 hours. A one-millilitre aliquot was withdrawn at the beginning of the heating period, diluted with 95% ethanol and its ultraviolet spectrum was determined. Four similar aliquots were then withdrawn, one each at 10 hours, 20 hours, 30 hours and 40 hours, diluted with ethanol, and their ultraviolet spectra were also determined. It was found that the optical density at 256 millimicrons was the same for all five samples.

The composition of the five samples was also determined by vapour phase chromatography using a 3/8" by 20' aluminum column packed with SE 30 (30%) on 45/60 mesh Chromasorb P mounted in an Aerograph A-700 Chromatograph. At a column temperature of 170°C. and a helium flow rate of 190 ml.min., 3-phenylcyclopentene and 1-phenylcyclopentene had retention times of 28 and 42 minutes, respectively. The relative peak areas for the two compounds was the same for all five samples.

A similar study has been carried out by Cristol (57) for the phenylcyclohexenes in which it was also found that 3-phenylcyclohexene does not isomerise to 1-phenylcyclohexene under the conditions used.

Vapour Phase Chromatographic Analysis of the Products of the Reaction of trans-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide at 60°C.

The products of the reactions of unlabelled and deuterated trans-2-phenylcyclohexyltrimethylammonium iodides with sodium ethoxide were analysed on an Aerograph A-700 Chromatograph using a 3/8" by 5' aluminum column packed with the detergent Tide. With a column temperature of 170°C. and helium flow of approximately 180 ml./min., it was found that three products were formed in the reactions: 1-phenylcyclohexene from a cis elimination, 3-phenylcyclohexene from a trans elimination, and trans-N,N-dimethyl-2-phenylcyclohexylamine from S_N2 attack of ethoxide ion on the N-methyl group. Analysis of synthetic mixtures of these three compounds showed that the thermal conductivities of all three compounds were identical within the limits of detection. An internal standard, therefore, was not used in the determination of the relative amounts of the three products formed in the two reactions.

Kinetic Studies

General

Briefly, the kinetic procedure was as follows. The desired compound was accurately weighed into a 50 ml. volumetric flask and dissolved in anhydrous ethanol. After equilibration at the reaction temperature, standardised sodium ethoxide solution was transferred to the reaction flask and ethanol added to the calibration mark. The flask was then briefly shaken to obtain homogeneity. One millilitre aliquots were withdrawn at regular time intervals and the reaction quenched by dilution with 95% ethanol. Each sample was diluted to a standard volume and the optical density determined at the appropriate wavelength for the particular olefin formed. All reactions were conducted under pseudo first-order conditions with ethoxide ion in large excess.

The cis- and trans-2-phenylcyclopentyltrimethylammonium ions reacted readily with ethoxide ion in ethanol to give 1-phenylcyclopentene as the sole product as determined by ultraviolet spectrophotometric analysis and vapour phase chromatography. The reactions were followed spectrophotometrically and the kinetics determined by observing the increase in absorption at 256 millimicrons. They were clearly second order and yields of 1-phenylcyclopentene were quantitative.

The possibility existed that some or all of the 1-phenylcyclopentene formed from reaction of trans-2-phenylcyclopentyltrimethylammonium ion might have resulted from isomerisation of 3-phenylcyclopentene formed by a trans elimination. That this was not the case, however, was shown by the fact that there was no change in the relative quantities of the two olefins when a mixture of the two was treated under the reaction conditions for a long period of time, (see page 170)

The cis-2-phenylcyclohexyltrimethylammonium ion reacted with ethoxide ion in ethanol to give 1-phenylcyclohexene as the sole product. The kinetics of this reaction were determined spectrophotometrically by observing the increase in absorption at 247 millimicrons.

Three products were formed in the reaction of trans 2-phenylcyclohexyltrimethylammonium ion with sodium ethoxide. The expected cis elimination gave the major product, 1-phenylcyclohexene. In addition, a trans elimination gave a very small amount of 3-phenylcyclohexene, while substitution at the N-methyl carbon produced trans-N,N-dimethyl-2-phenylcyclohexylamine in a significant amount. The kinetics were followed spectrophotometrically by observing the increase in absorption at 247 millimicrons and the rate constant for the cis elimination was then calculated by taking into account the amount of 1-phenylcyclohexene formed via this pathway from the quaternary ammonium salt. Cristol (11) has shown that isomerisation of 3-phenylcyclohexene to 1-phenylcyclohexene does not occur under the reaction conditions by performing an experiment similar to that for the cyclopentyl series.

Procedures

Molar Extinction Coefficients

Molar extinction coefficients were determined in 95% ethanol and are listed in Table XXVI :

Table XXVI

Compound	λ max mμ	Molar Extinction Coefficient
1-Phenylcyclopentene	256	14,600[a]
3-Phenylcyclopentene	263	435[b]
1-Phenylcyclohexene	247	12,600[c]

[a] DePuy (59), 256.5 mμ, 14,700
[b] DePuy (59), 263 mμ, 432
[c] Cristol (11), 247 mμ, 12,940

Preparation of Sodium Ethoxide Solutions for Kinetic Measurements

Anhydrous ethanol (250 ml.), purified by the method of Lund and Bjerrum (111), was placed in the vessel shown in Figure 7 and cooled to 2°C. in an ice-water bath. Purified nitrogen gas (112) was bubbled through the vessel for one hour. Sodium metal, 6.9 g. (0.3 mole), was then added in small portions and the mixture was allowed to stand at 2°C. until all of the sodium had dissolved (8 hours). The resultant

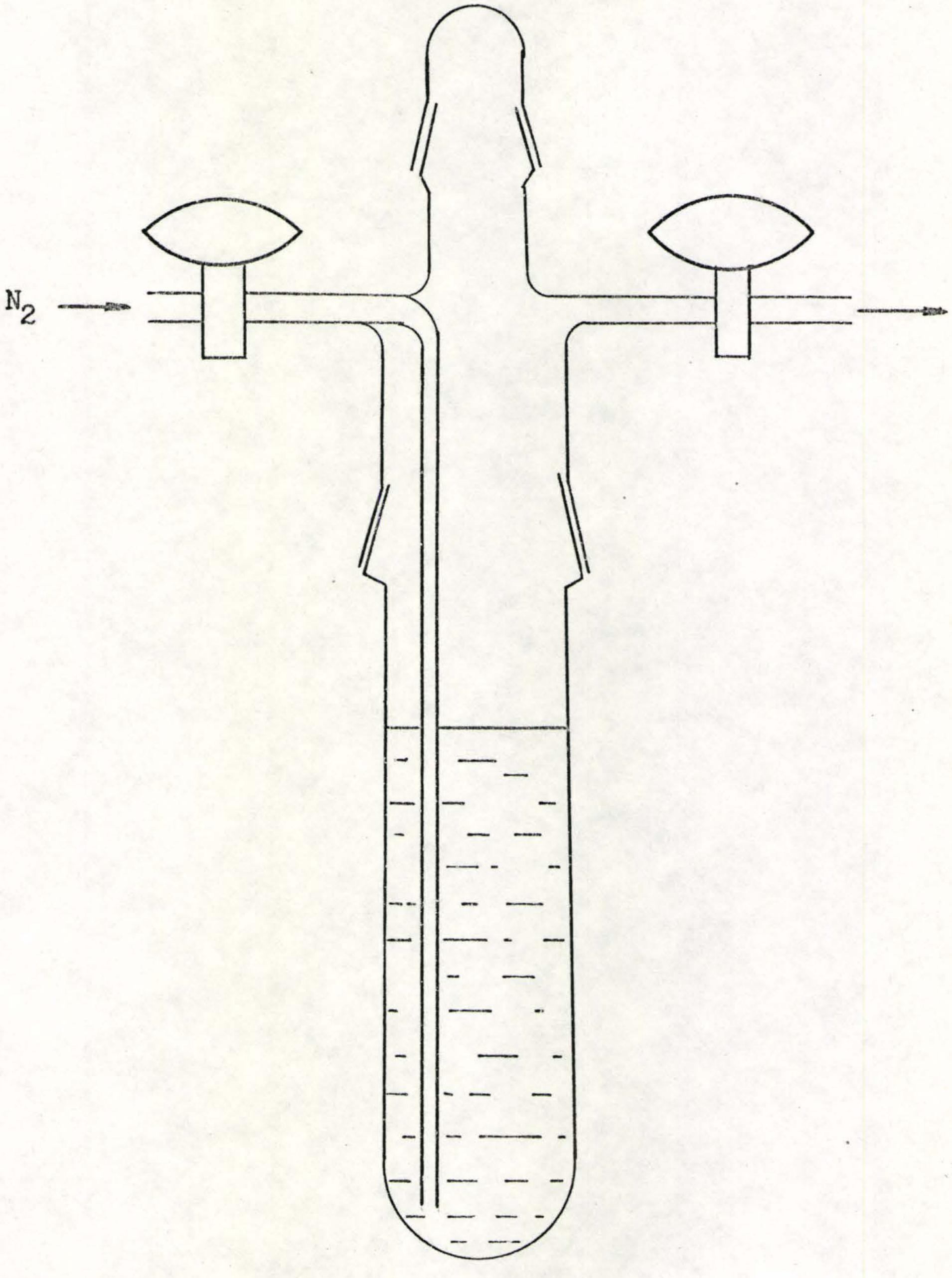


Figure. 7 Apparatus for the preparation and storage of stock sodium ethoxide solutions.

stock solution (1.2 N) was stored in the refrigerator and aliquots were used to prepare solutions for kinetic measurements.

Kinetic Measurements

An accurately weighed amount (ca. 0.2 mmole) of the desired quaternary ammonium salt was placed into the reaction vessel consisting of a 50 ml. volumetric flask to which was attached, above the calibration mark, a side arm bearing a 10 ml. bulb, Figure 8.

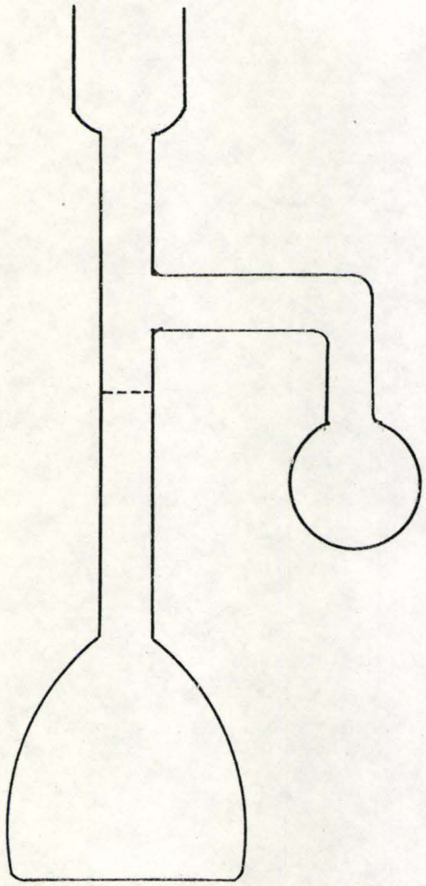


Figure 8. Reaction flask used for kinetics.

Anhydrous ethanol (24 ml.) was added to dissolve the quaternary ammonium salt and the reaction vessel was sealed with a rubber syrum stopper.

A standard sodium ethoxide solution was prepared by taking an aliquot of the stock sodium ethoxide solution and diluting it with anhydrous ethanol. This standard solution and the reaction vessel were then placed in the constant-temperature bath maintained at the desired temperature. After one hour, the sodium ethoxide solution was standardised by removing one millilitre aliquots and titrating with standard acid using methylene blue - neutral red as indicator. Twenty-five millilitres of the standardised sodium ethoxide solution was then transferred to the reaction vessel, anhydrous ethanol was added to the calibration mark and the solution was shaken to obtain homogeneity. These operations were carried out as rapidly as possible and normally required less than one minute. When one half of the sodium ethoxide solution had been added the stopwatch was started.

At regular intervals, a calibrated one millilitre hypodermic syringe with a six inch needle was inserted through the rubber stopper and a sample was withdrawn. Each sample was quenched by dilution with 95% ethanol and then further diluted to a standard volume. The solution was mixed thoroughly and the optical desnity determined using a Perkin-Elmer Hitachi Spectrophotometer set at the appropriate wavelength for the particular olefin formed.

In all reactions it was found that the rate of reaction was inversely dependent upon the ionic strength. In order to minimise these ionic strength effects each kinetic run was conducted under conditions of almost identical ionic strength.

For all kinetic runs pseudo first-order reaction conditions, with ethoxide ion in fifty-fold excess, were employed. The pseudo first-order reaction rate constant, k_1, is given by the expression

$$k_1 t = 2.303 \log \frac{O.D._\infty - O.D._o}{O.D._\infty - O.D._t} \qquad (79)$$

where $O.D._\infty$ is the optical density of the solution at $t = \infty$, $O.D._o$ is the initial optical density of the solution and $O.D._t$ is the optical density of the solution at time t. The rate constant, k_1, was determined by plotting $\ln(O.D._\infty - O.D._t)$ against time with a best fit of the line to thepoints being achieved by a least squares treatment of the data. The second-order reaction rate constant, k_2, was calculated from the pseudo first-order rate constant by dividing k_1 by the concentration of sodium ethoxide.

Data for a representative kinetic experiment for each compound and the appropriate plot of this data are given in the Appendix.

Hydrogen-Deuterium Isotope Effect Measurements

The hydrogen-deuterium isotope effects associated with the elimination reactions of cis- and trans-2-phenylcyclopentyltrimethylammonium ions and cis- and trans-2-phenylcyclohexyltrimethylammonium ions were determined by conducting kinetic runs for the unlabelled and deuterated compounds simultaneously. Four kinetic runs were carried out simultaneously for each of the isomers, two for the unlabelled species and two for the deuterated species, with particular care being taken to use identical base for all four runs.

Nitrogen Isotope Effect Measurements

General

The ratio of the rate constants for reaction of two isotopic compounds may be obtained by dividing the isotopic ratio for the atom under consideration in the reactant by the corresponding ratio for the product formed during an infinitesimally small extent of reaction. In practice, however, the reaction is allowed to proceed to some known extent, two to fifty per cent, and the isotope effect is calculated from an expression relating the ratio of the isotopic rate constants to the extent of reaction and to the isotopic ratios in the product and in the original reactant.

The isotopic ratio in the product, trimethylamine, was obtained by converting it to ammonia by Kjeldahl digestion and thence by hypobromite oxidation to nitrogen gas for mass spectrometric analysis. For the reactant, reaction was carried out to completion and the trimethylamine produced was collected and converted to ammonia and thence to nitrogen gas by the method just described.

Two methods were used to obtain the desired extent of reaction. For compounds of relatively low reactivity, the reaction was stopped by cooling the reaction flask rapidly in liquid air and then removing the trimethylamine under reduced pressure at ice-water temperature. This method of quenching, however, is unsatisfactory for reactive compounds such as *cis*-2-phenylcyclopentyltrimethylammonium ion and 2-phenylethyltrimethylammonium ion. In such cases, the desired extent of reaction was achieved by adding the amount of base corresponding to the extent of reaction required and allowing the reaction to proceed for twenty half lives.

Collins (94) has pointed out that in isotope effect measurements involving a comparison of isotopic ratios in reactant and the product from the first few per cent reaction, the presence in this reactant of material formed from trace quantities of highly reactive impurity can lead to error. To obviate such a complication in the present work, the reaction of each compound was carried out to extents of reaction ranging from five to fifty per cent.

In all the reactions studied but one, trimethylamine was the only nitrogen containing product of the reactions and elimination was shown to be 100 per cent of the total reaction. In the reaction of *trans*-2-phenylcyclohexyltrimethylammonium iodide with sodium ethoxide, however, it was shown by Ayrey (89) that cis elimination giving 1-phenylcyclohexene is accompanied by a very small amount of *trans*-

elimination forming 3-phenylcyclohexene. In addition, approximately 38% of the product is formed by S_N2 substitution at a N-methyl carbon to give the tertiary amine, trans-N,N-dimethyl-2-phenylcyclohexylamine. The elimination product, trimethylamine, is, however, readily separated from the much less volatile substitution product by low-pressure distillation.

Procedures

Solvents and Bases

Ethanol and sodium ethoxide were prepared and stored as described in the section dealing with kinetics.

Partial Reaction and Collection of Trimethylamine

Quaternary ammonium salt (ca. 2 mmole) was weighed into flask K, Figure 9 . The required amount of base was added and the flask was quickly attached to a vacuum manifold and cooled in liquid nitrogen. After thrice degassing, which involved alternative freezing and thawing of the reaction solution and pumping on the frozen liquid, the vessel was sealed at the constriction and place in a thermostatted bath for the period of time required to achieve the desired extent of reaction based on the previously determined rate constant for the compound in question. The flask was then removed from the bath, cooled in liquid nitrogen, opened, and the trimethylamine distilled over a period of 25 minutes into a liquid nitrogen trap, L, at a pressure of 0.1 mm.

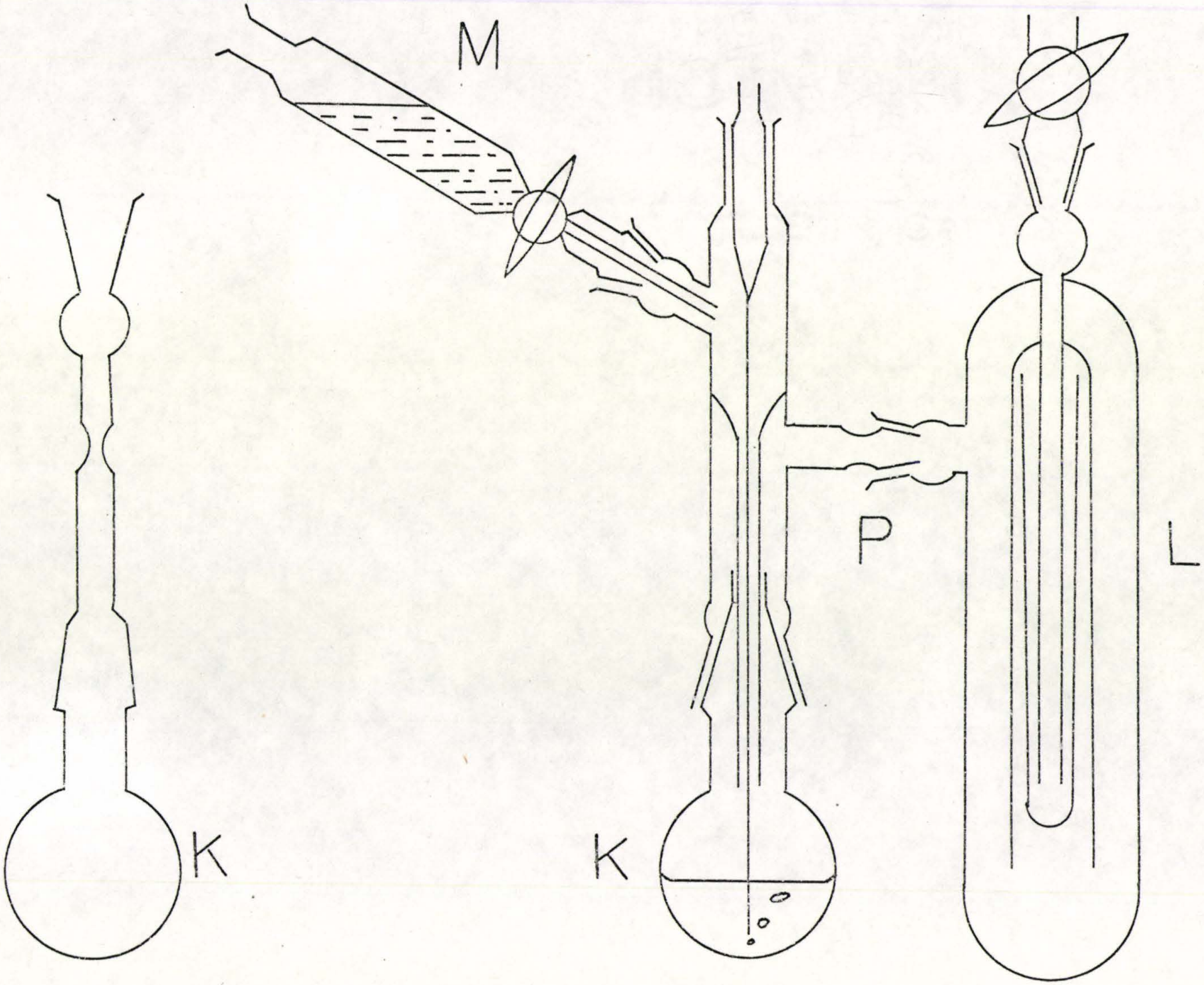


Figure 9. Apparatus used for the collection of trimethylamine.

and a temperature below $0^{o}C$. From time to time solvent was added from the dropping funnel, M, to avoid undue concentration of reactants. This distillation procedure was rigorously tested and it was shown that removal of trimethylamine was quantitative and that there was not significant further reaction during the time required.

Trap L, was then disconnected, stoppered at P and the trimethylamine and solvent were distilled in vacuo into excess standard sulphuric acid. The acid was back titrated with standard alkali and this was followed by the immediate addition of 10 ml. of 0.01 N sulphuric acid to prevent loss of amine. In all cases, the trimethylamine recovered was better than 99 per cent for the complete reaction and the extent of reaction calculated from the trimethylamine recovered for the partial reaction was always within one per cent of that calculated from the kinetic data. The trimethylammonium sulphate solution was evaporated to a volume of about one millilitre and transferred to a Kjeldahl flask for digestion.

In the cis elimination of trans-2-phenylcyclohexyltrimethyl ammonium ion, the trimethylamine recovered from a partial reaction was within one per cent of that calculated from the kinetic data. For complete reaction, the trimethylamine was collected in the same manner as was described for the other compounds. The reaction mixture was then extracted with ether to remove trans-N,N-dimethyl-2-phenylcyclohexylamine. The combined extracts were added to the trimethylammonium sulphate solution and the resulting solution was evaporated under reduced pressure to a volume of about one millilitre.

Kjeldahl Digestion of Trimethylammonium Sulphate Samples

One millilitre of sulphuric acid was added to the trimethylammonium sulphate solution in the Kjeldahl flask and the flask was heated with a micro-burner until all the water had been removed and fuming and charring had begun. After the contents of the flask had cooled to room temperature, 1.5 g. of potassium sulphate (B.D.H. Analar), 0.1 g. of mercuric oxide (Fisher Reagent), and 2 ml. of sulphuric acid were added and the mixture was strongly heated for four hours.

The ammonia from the Kjeldahl digestions was liberated by the addition of 15 ml. of 40% sodium hydroxide and was distilled, using a standard Kjeldahl apparatus, into standard sulphuric acid. The Kjeldahl digestion always gave better than 98 per cent recovery as determined by titration of the excess sulphuric acid using standard alkali. After titration, 10 ml. of 0.01 N sulphuric acid was added to the solution to prevent loss of ammonia. The ammonium sulphate solution was concentrated to about three millilitres in preparation for its conversion to nitrogen.

Preparation of Sodium Hypobromite

Sodium hypobromite was prepared by the method of Rittenburg (114). Analytical reagent bromine (50 ml.) was added dropwise with vigorous stirring to 150 ml. of a 40% solution of sodium hydroxide at 2°C. An additional 150 ml. of 40% sodium hydroxide was then added and the solution was placed in the refrigerator for storage. After two days, the precipitated sodium bromide was removed by filtration and potassium iodide (0.4 g.)

was added to the filtrate to stabilise it.

Preparation of Samples for Mass Spectrometric Analysis

The high-vacuum system used for the preparation and purification of nitrogen samples is shown in Figure 10 . The ammonium sulphate solution (3 ml.) from the Kjeldahl distillation was placed in flask A and 5 ml. of sodium hypobromite in flask B. The flasks were partially evacuated through the direct connection to the pumping system, then surrounded by liquid nitrogen and the evacuation completed. The two flasks were isolated from the pumping system and their contents thawed. This procedure of alternate freezing, pumping and thawing was performed three times to ensure that the solutions were completely degassed.

The two flasks were isolated from the vacuum system and the hypobromite solution was added to the ammonium sulphate solution by inverting flask B. This caused liberation of nitrogen gas. Flask A and trap E were surrounded by liquid nitrogen and the stopcock opened to admit the nitrogen to the purification system. The gas was quantitatively transferred to this part of the line by means of an automatic Urry Toeppler (113), F, over a period of 45 minutes and was then circulated for one hour through the furnances C and D containing copper wire and copper oxide, respectively, and maintained at 750°C. Carbon dioxide, water, and other contaminants were condensed in trap E.

After purification, the gas was transferred by means of a manual Toeppler pump, H, to a standard volume, G, where the yield was

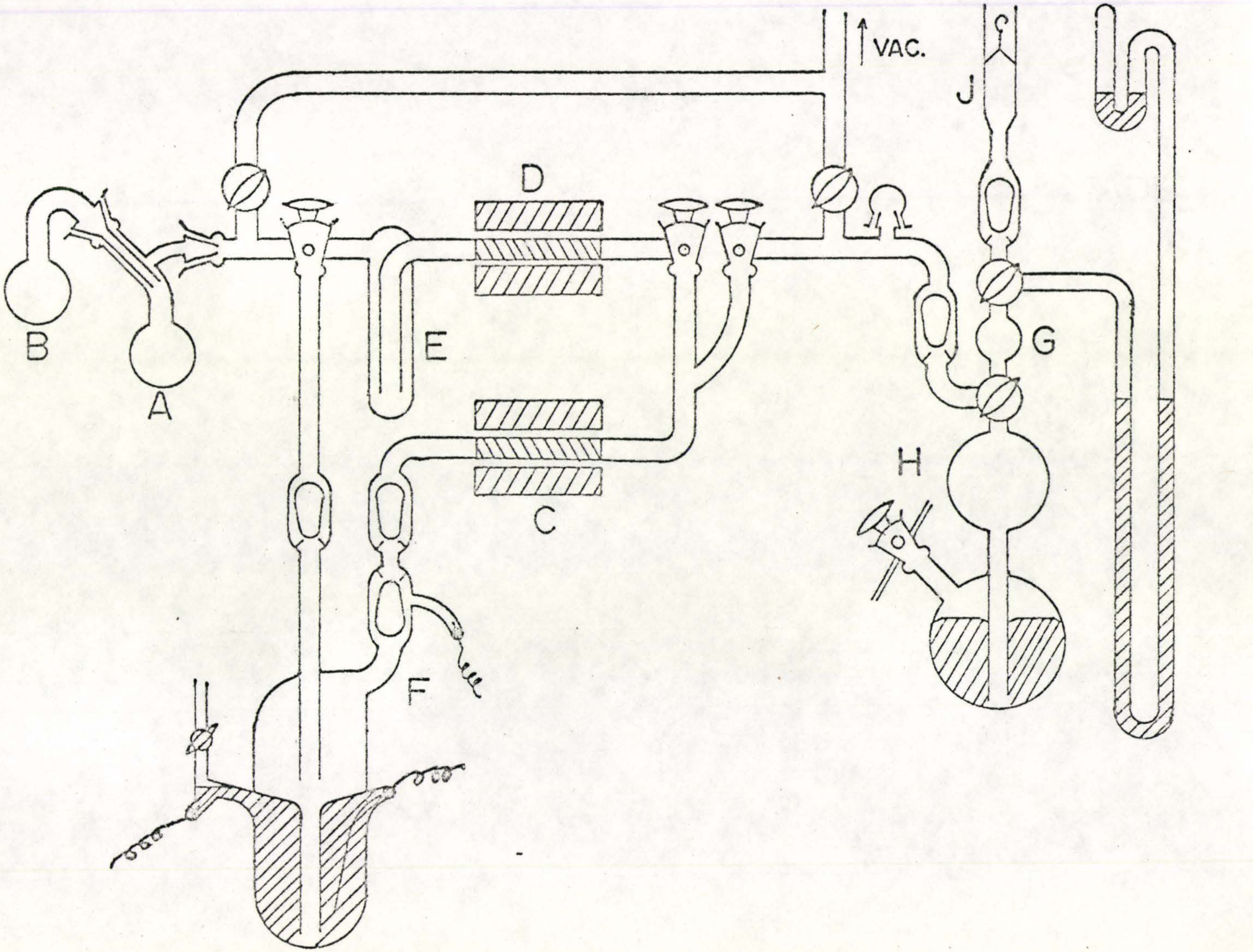


Fig. 10 APPARATUS USED FOR THE PREPARATION AND PURIFICATION OF NITROGEN SAMPLES.

determined. Finally, the nitrogen gas was pumped into the break-seal tube, J, which was then sealed. The necessity of using this procedure for the purification of nitrogen for precise mass spectrometry has been stressed by Hoering (115,116), and it has been confirmed by work in these laboratories that, in addition to the obvious interference by carbon monoxide at mass 28, the presence of oxygen has detrimental effects upon the stability of the mass spectrometer.

Mass Spectrometric Analysis

The relative abundances of the nitrogen isotopes were measured using a six inch 90 degree, simultaneous collection mass spectrometer similar to that described by Wanless and Thode (117). This was a high precision instrument capable of measuring changes of isotopic ratios with a precision of 0.02 per cent. The conventional collector of a single beam instrument had been modified to permit simultaneous collection and the measurement by means of a null method of the ion currents resulting from ions of mass 28 and 29. The collection system was so constructed that only ion currents of these two masses strike the collector electrodes. A magnetic valve system permits rapid switching from a standard nitrogen gas to the unknown nitrogen sample thereby reducing the time required for analysis and making the rapid comparison of sample possible. The standard nitrogen gas was used for all analyses so that the ratios of all of the unknown samples can be determined relative to this arbitrary standard thus eliminating errors in the isotopic ratios caused by day to day fluctuations in the mass spectrometer

The procedure for comparing the isotope ratio of the unknown gas with that of the standard is as follows. The ion current produced by the mass-28 beam was amplified and applied to a put-and-take potentiometer. Some fraction of the current from the put-and-take potentiometer was balanced against the separately amplified current from the mass-29 beam and the balance point was recorded on a Minneapolis Honeywell Brown Electronik Recorder. Since the position of the balance varies on the ratios of the isotopes present in the sample, a shift of the balance point is a measure of the 28/29 ratio relative to the standard sample. The ion current from the mass-28 was used as a reference voltage and was adjusted to the same value for both the standard and the sample by changing the gas pressure of the sample until the peak height of mass-28, measured on a single collection, was identical with that of the standard. The standard was switched to simultaneous collection operation, the put-and-take potentiometer was adjusted to give balance near the centre of the recorder chart and the displacement of the null point of the sample from that of the standard was measured. The average of six displacements was used to calculate the per cent change in the isotope ratio of the sample relative to the standard.

An arbitrary value for the 28/29 ratio of 136.50 was assigned to the standard and the values of the 28/29 ratios of the unknown samples were normalised with respect to this standard value. The

N^{14}/N^{15} ratios of the unknown samples were simply two times the N^{28}/N^{29} ratios for these samples.

The following expression desrived by Stevens and Attree (118), was used for the calculation of the kinetic isotope effects.

$$k^{14}/k^{15} = \frac{\ln (1-f)}{\ln (1-rf)} \qquad (80)$$

In this expression, $r = (N^{14}/N^{15})$reactant/(N^{14}/N^{15})product, and f is the mole fraction of the reactant which has undergone reaction. This expression can be used for the calculation of kinetic isotope effects when the reaction under investigation does not have the complication of competing processes. In calculating the k^{14}/k^{15} values, the average $N^{14}N^{14}/N^{14}N^{15}$ ratio found for the nitrogen gas formed from the trimethylamine from six or more separate reactions carried to completion was combined in the above equation with the individual $N^{14}N^{14}/N^{14}N^{15}$ ratios for the nitrogen gas produced from the trimethylamine formed in each partial reaction of the salt.

Strictly speaking, f is the mole fraction of N^{14} which has undergone reaction. Because of the relative insensitivity of k^{14}/k^{15} to small variations in f, it is satisfactory to consider f the mole fraction of the total reactant (N^{14} + N^{15} species) which has reacted. This is the quantity which is actually measured in determining the amount of reactant consumed or product formed.

In the determination of the nitrogen isotope effect associated with the E2 reaction of <u>trans</u>-2-phenylcyclohexyltrimethylammonium iodide with sodium ethoxide in ethanol an estimate of f cannot be taken as the mole fraction of the reactant which has undergone elimination only, since part of the reactant is bein simultaneously removed by the substitution reaction. This complication is discussed in the presentation of the results.

APPENDIX A

Table XXVII

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 29.65°C.

(Initial concs.: Q.A.S. = 0.004536 m./l.; NaOEt = 0.1977 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
2.0	0.109	0.569	-0.5639
4.0	0.186	0.492	-0.7093
6.0	0.257	0.421	-0.8651
8.0	0.321	0.357	-1.0300
10.0	0.375	0.303	-1.1940
12.0	0.419	0.259	-1.3509
	0.678		

Calculation of rate constant:

k_1 = slope (least squares) = $(2.25 \pm 0.02) \times 10^{-5}$ sec^{-1}.

$k_2 = (11.4 \pm 0.1) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

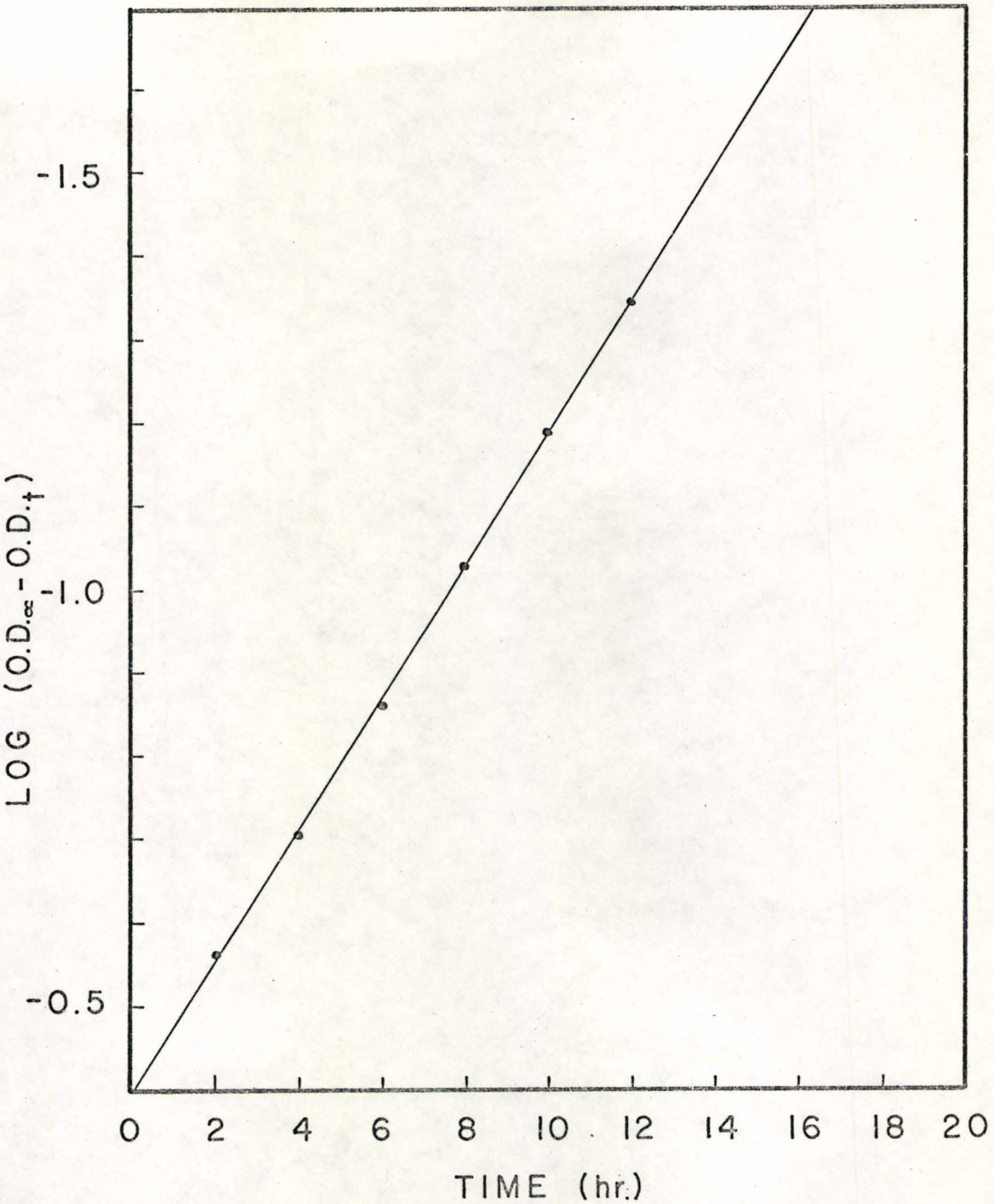


Figure 11. Plot of the kinetic data given in Table XXVII for a typical kinetic experiment for the reaction of cis-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 29.65°C.

Table XXVIII

Data for a Typical Kinetic Experiment in the Reaction
of cis-2-Phenylcyclopentyltrimethylammonium Iodide
with Sodium Ethoxide in Anhydrous Ethanol at 34.85°C.
(Initial concs.: Q.A.S. = 0.004818 m./l.; NaOEt = 0.1987 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
1	0.121	0.610	-0.4943
2	0.210	0.521	-0.6520
3	0.289	0.442	-0.8165
4	0.370	0.361	-1.0189
5	0.421	0.310	-1.1712
6	0.463	0.268	-1.3168
7	0.505	0.226	-1.4872
	0.731		

Calculation of rate constant:

$$k_1 = \text{slope (least squares)} = (4.62 \pm 0.04) \times 10^{-5}\ \text{sec}^{-1}.$$

$$k_2 = (23.2 \pm 0.2) \times 10^{-5}\ \text{l. mole}^{-1}\ \text{sec}^{-1}.$$

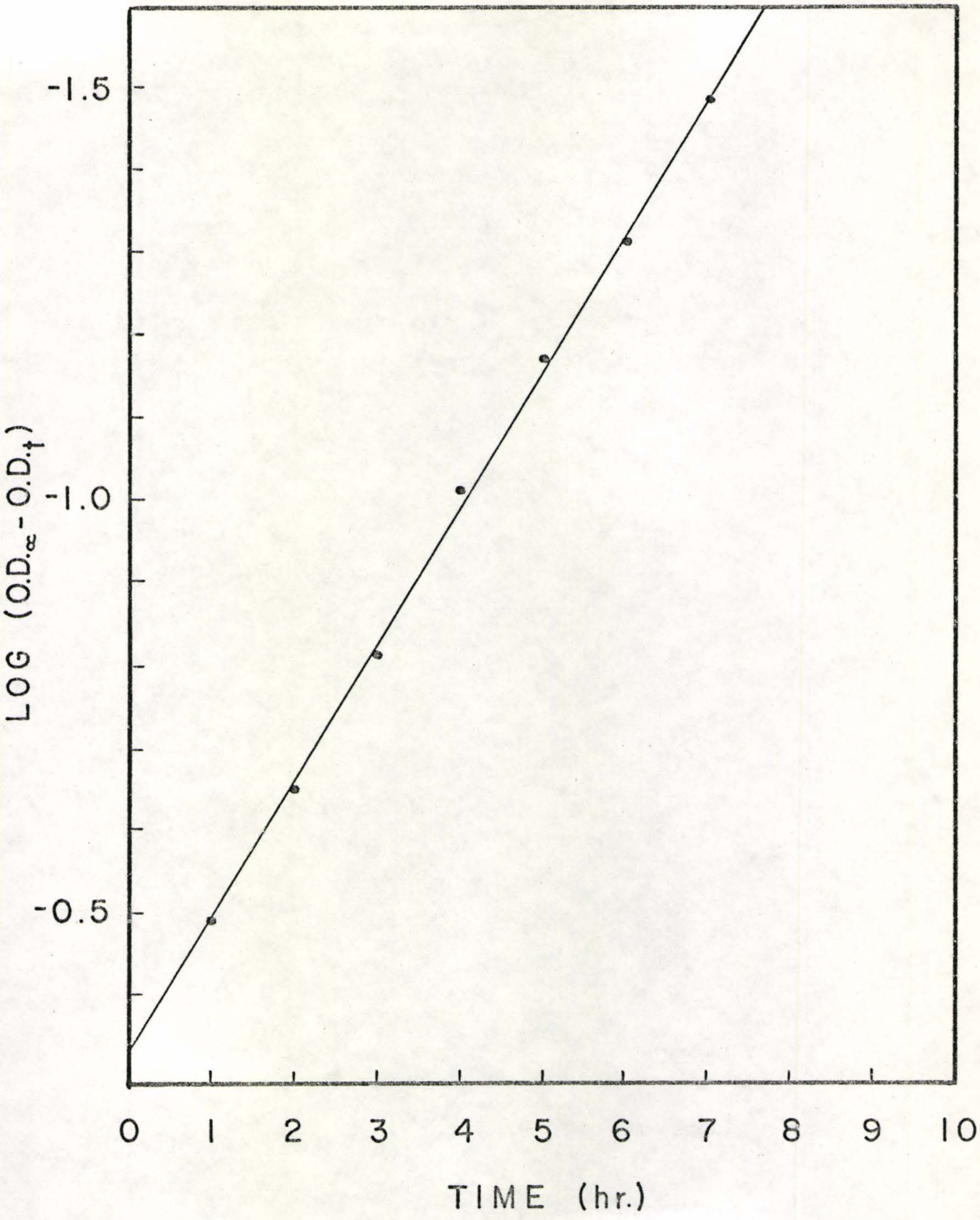


Figure 12. Plot of the kinetic data given in Table XXVIII for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 34.85°C.

Table XXIX

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 39.90°C.

(Initial concs.: Q.A.S. = 0.004745 m./l.; NaOEt = 0.2038 m./l.)

Time min.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
30	0.114	0.599	-0.5125
60	0.202	0.511	-0.6714
90	0.277	0.436	-0.8302
120	0.344	0.369	-0.9970
150	0.402	0.311	-1.1680
180	0.446	0.267	-1.3205
210	0.485	0.228	-1.4784
225	0.502	0.211	-1.5559
240	0.517	0.196	-1.6296
	0.713		

Calculation of rate constant:

k_1 = slope (least squares) = $(9.00 \pm 0.1) \times 10^{-5}\ \text{sec}^{-1}$.

$k_2 = (44.1 \pm 0.3) \times 10^{-5}\ \text{l. mole}^{-1}\ \text{sec}^{-1}$.

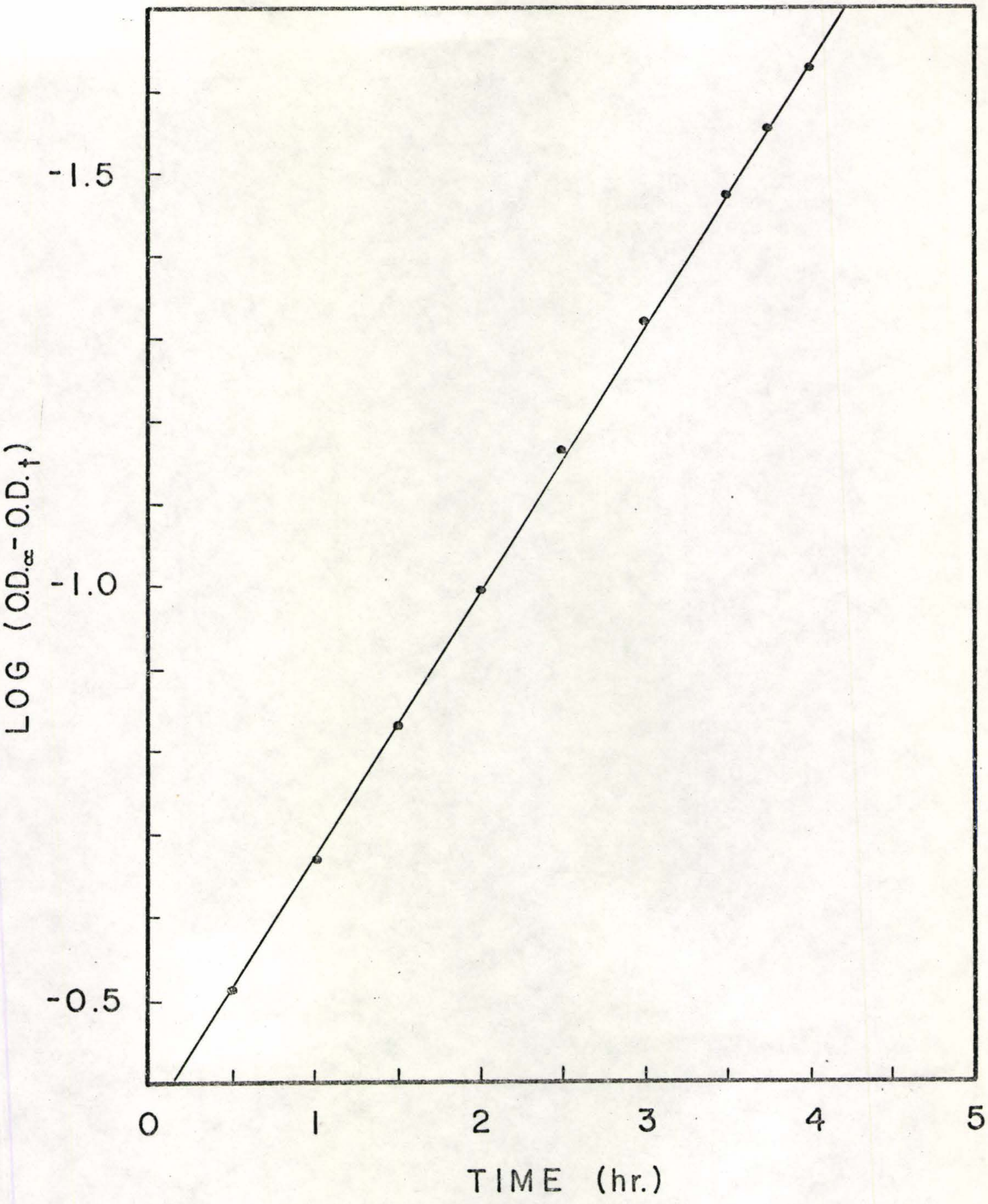


Figure 13. Plot of the kinetic data given in Table XXIX for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 39.90°C.

Table XXX

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 44.90°C.

(Initial concs.: Q.A.S. = 0.004692 m./l.; NaOEt = 0.1961 m./l.)

Time Min.	Optical Density	$OD_\alpha - OD_t$	$\ln(OD_\alpha - OD_t)$
20	0.139	0.582	-0.5413
40	0.248	0.473	-0.7487
60	0.350	0.371	-0.9915
80	0.422	0.299	-1.2073
100	0.476	0.245	-1.4065
120	0.522	0.199	-1.6145
	0.721		

Calculation of rate constant:

k_1 = slope (least squares) = $(18.0 \pm 0.2) \times 10^{-5}\ \mathrm{sec}^{-1}$.

$k_2 = (91.7 \pm 0.8) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

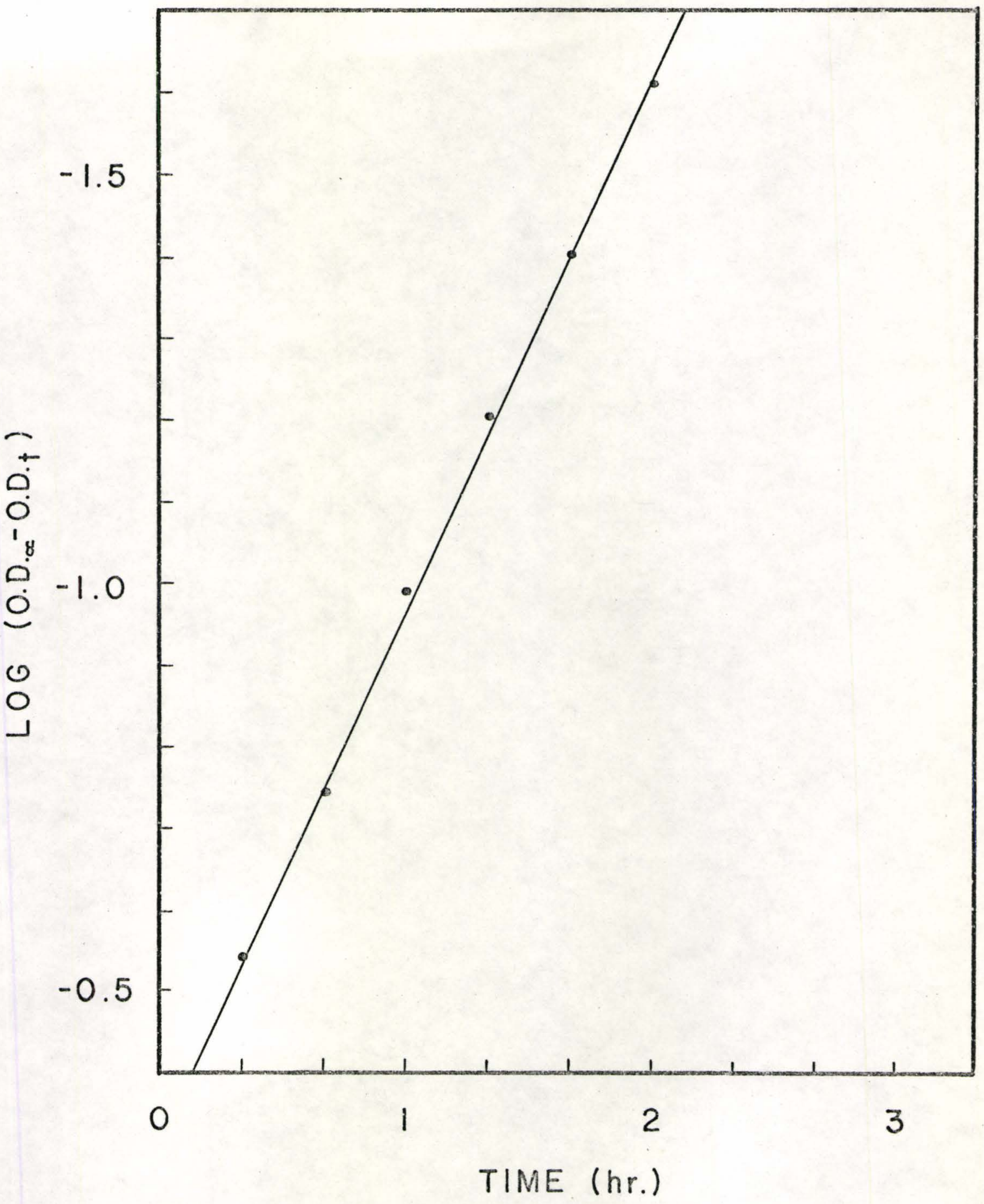


Figure 14. Plot of the kinetic data given in Table XXX for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 44.90°C.

Table XXXI

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 49.95°C.

(Initial concs.: Q.A.S. = 0.004906 m./l.; NaOEt = 0.2036 m./l.)

Time min.	Optical Density	$OD_{\alpha} - OD_{t}$	$\ln (OD_{\alpha} - OD_{t})$
10	0.126	0.605	-0.5025
20	0.241	0.490	-0.7134
30	0.328	0.403	-0.9088
40	0.411	0.320	-1.1394
50	0.469	0.262	-1.3394
60	0.519	0.212	-1.5512
	0.731		

Calculation of rate constant:

k_1 = slope (least squares) = $(35.0 \pm 0.3) \times 10^{-5}$ sec^{-1}.

$k_2 = (172 \pm 1.4) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

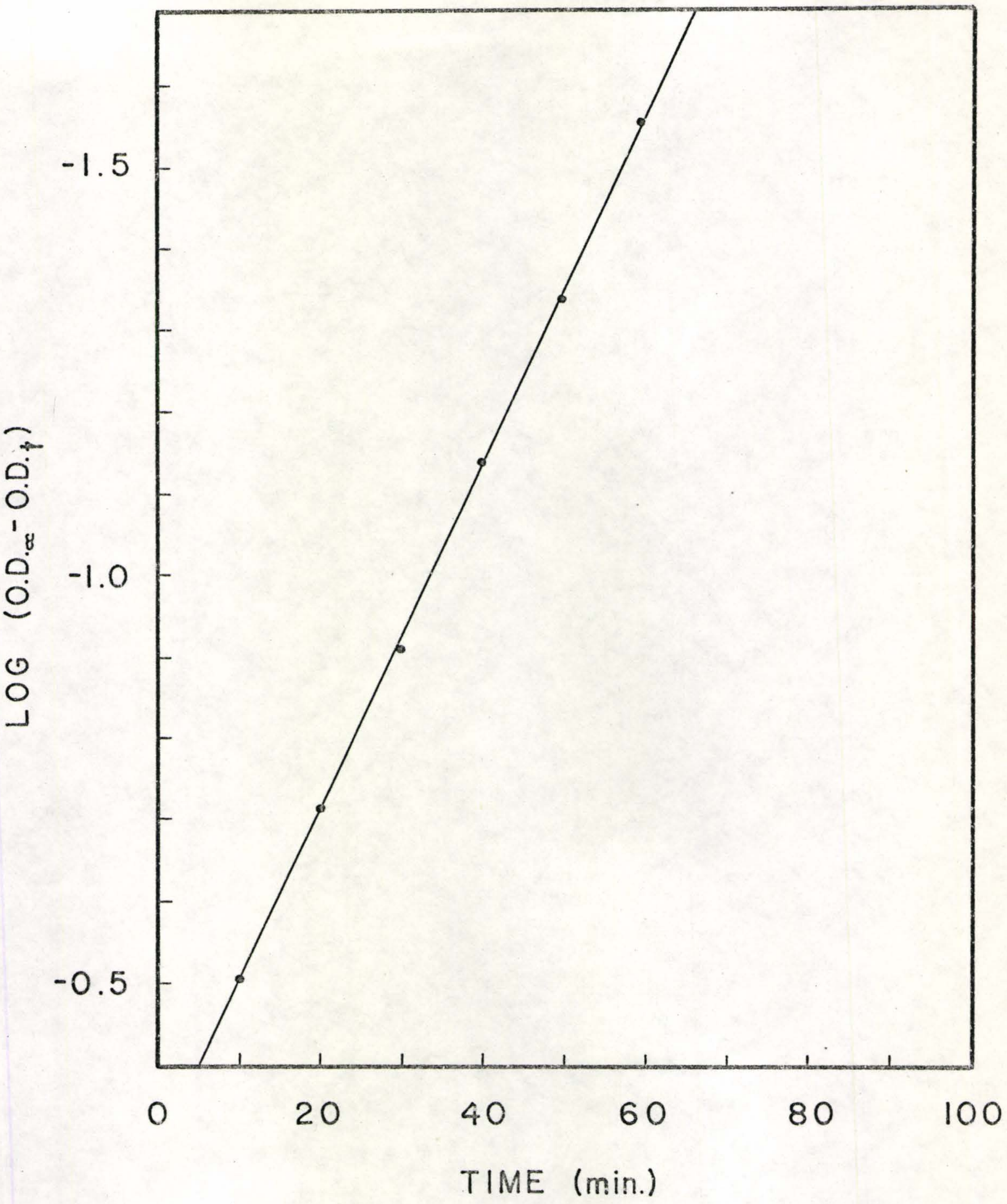


Figure 15. Plot of the kinetic data given in Table XXXI for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 49.95°C.

Table XXXII

Data for a Typical Kinetic Experiment in the Reaction of *trans*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 59.90°C.

(Initial concs.: Q.A.S. = 0.01027 m./l.; NaOEt = 0.2033 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln(OD_\alpha - OD_t)$
3.0	0.048	0.568	-0.5656
4.5	0.066	0.550	-0.5978
6.0	0.084	0.532	-0.6311
7.5	0.103	0.513	-0.6675
14.0	0.177	0.439	-0.8233
24.0	0.266	0.350	-1.0498
33.0	0.333	0.283	-1.2623
37.5	0.361	0.255	-1.3665
52.5	0.423	0.193	-1.6451
	0.616		

Calculation of rate constant:

k_1 = slope (least squares) = $(6.45 \pm 0.11) \times 10^{-6}$ sec^{-1}.

$k_2 = (3.17 \pm 0.05) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

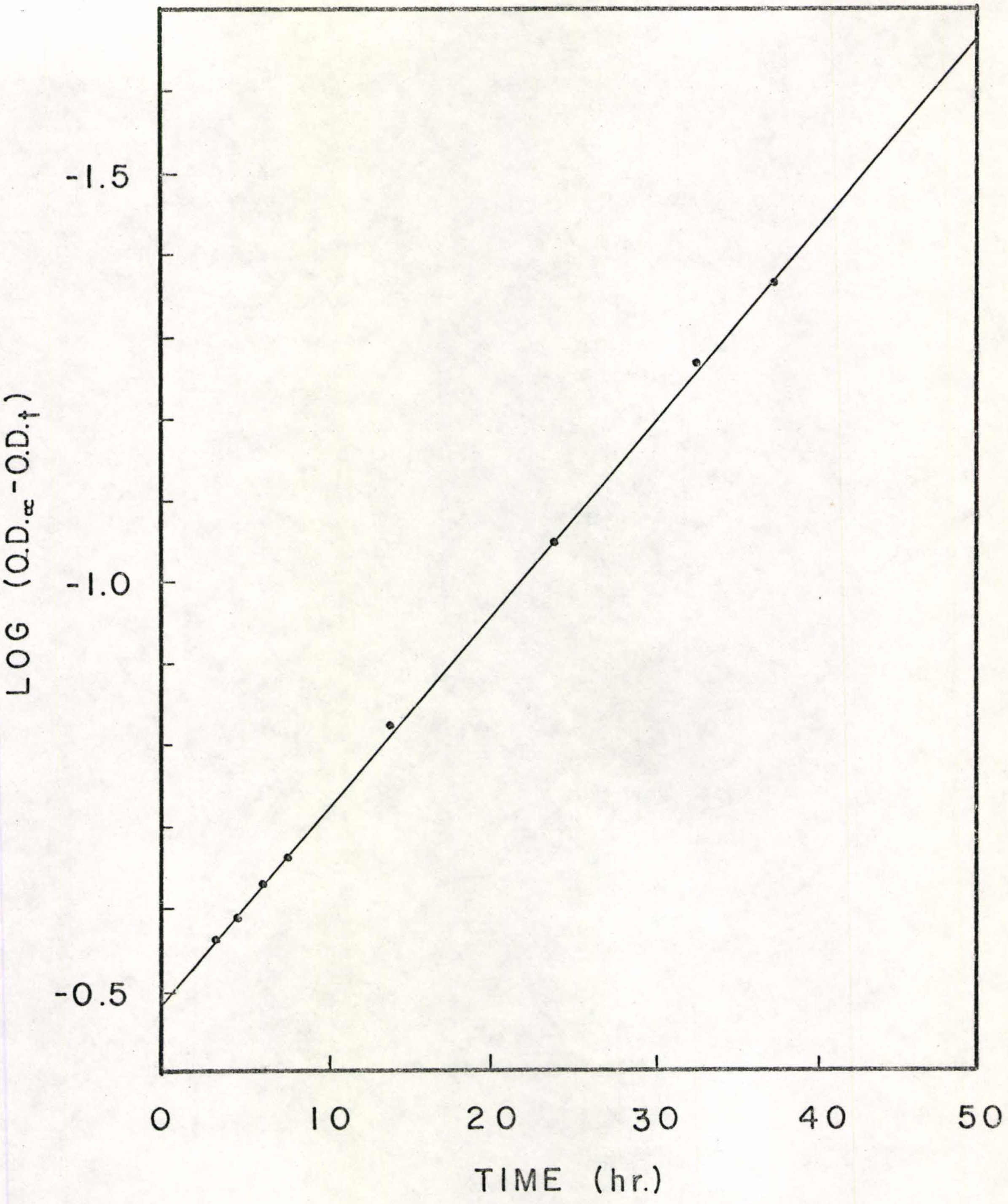


Figure 16. Plot of the kinetic data given in Table XXXII for a typical kinetic experiment for the reaction of trans-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 59.90°C.

Table XXXIII

Data for a Typical Kinetic Experiment in the Reaction of trans-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 68.10°C.

(Initial concs.: Q.A.S. = 0.00762 m./l.; NaOEt = 0.2006 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
2.0	0.067	0.395	-0.9289
4.0	0.120	0.342	-1.0730
6.0	0.171	0.291	-1.2344
6.5	0.180	0.282	-1.2659
8.0	0.210	0.252	-1.3783
11.0	0.258	0.204	-1.5896
13.0	0.286	0.176	-1.7373
	0.462		

Calculation of rate constant:

k_1 = slope (least squares) = $(20.4 \pm 0.1) \times 10^{-6}$ sec^{-1}.

$k_2 = (10.2 \pm 0.05) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

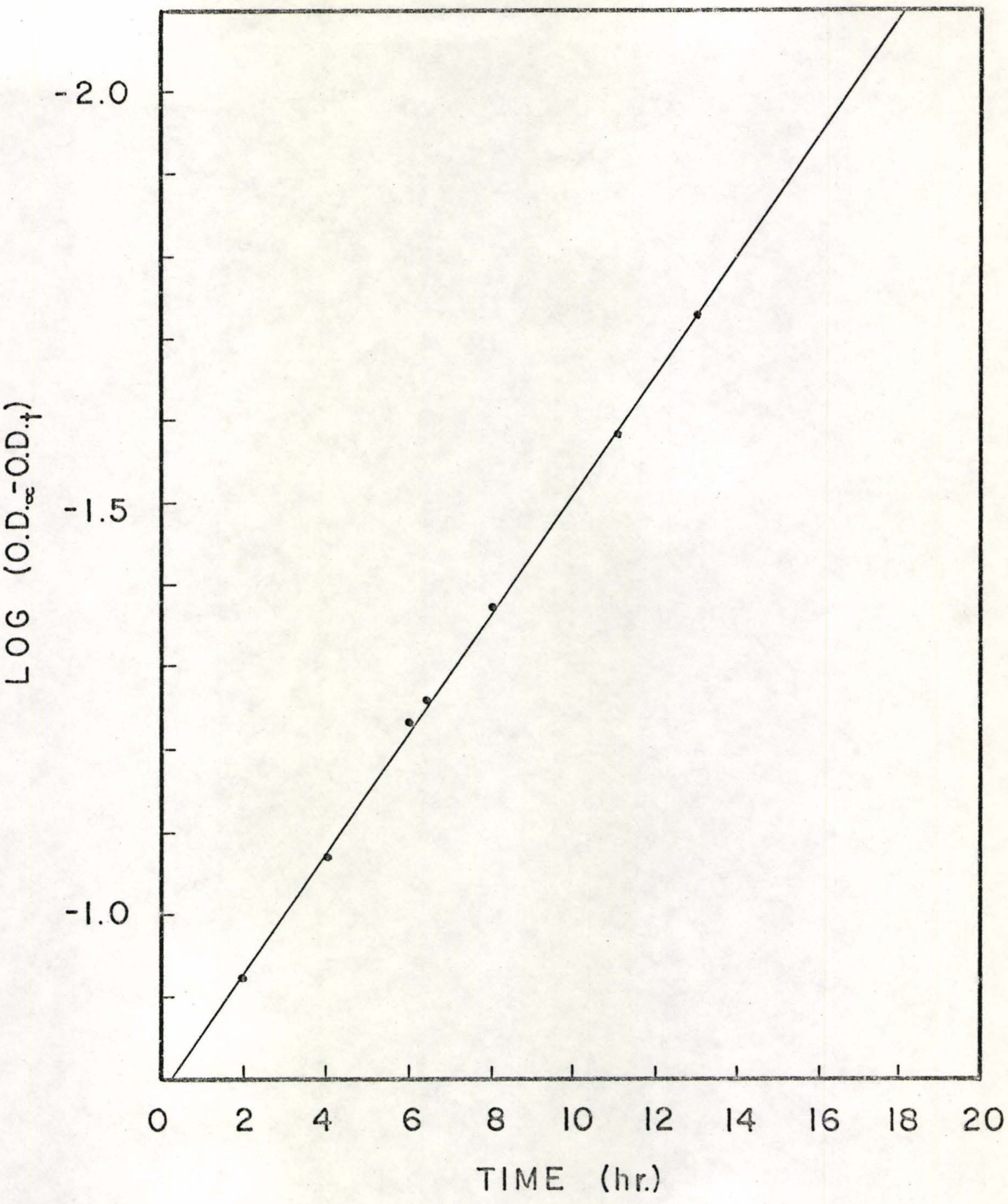


Figure 17. Plot of the kinetic data given in Table XXXIII for a typical kinetic experiment for the reaction of trans-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 68.10°C.

Table XXXIV

Data for a Typical Kinetic Experiment in the Reaction of *trans*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 76.10°C.

(Initial concs.: Q.A.S. = 0.01031 m./l.; NaOEt = 0.2090 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
0.50	0.057	0.573	-0.5569
1.00	0.116	0.514	-0.6655
1.50	0.160	0.470	-0.7550
2.00	0.212	0.418	-0.8723
2.53	0.252	0.378	-0.9729
3.00	0.285	0.345	-1.0642
3.75	0.340	0.290	-1.2379
6.50	0.464	0.166	-1.7968
	0.630		

Calculation of rate constant:

k_1 = slope (least squares) = $(57.5 \pm 0.4) \times 10^{-6}$ sec^{-1}.

$k_2 = (27.5 \pm 0.2) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

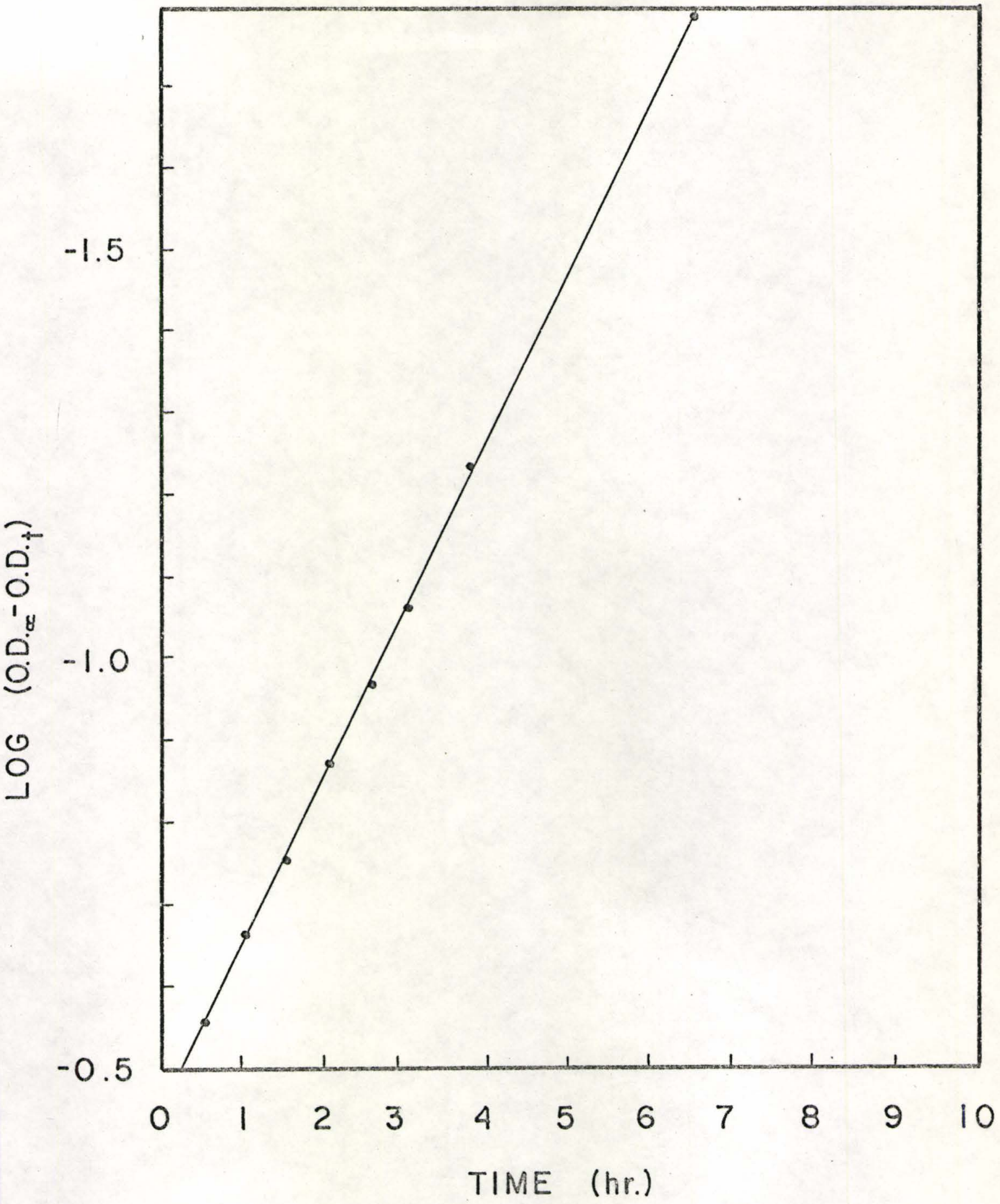


Figure 18. Plot of the kinetic data given in Table XXXIV for a typical kinetic experiment for the reaction of trans-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 76.10°C.

APPENDIX B

Table XXXV

Data for a Typical Kinetic Experiment in the Reaction of trans-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.

(Initial concs.: Q.A.S. = 0.004415 m./l.; NaOEt = 0.1907 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln(OD_\alpha - OD_t)$
4	0.066	0.592	-0.5244
8	0.118	0.540	-0.6163
12	0.170	0.488	-0.7176
21	0.265	0.393	-0.9341
29	0.338	0.320	-1.1398
37	0.391	0.267	-1.3208
	0.658		

Calculation of rate constant:

k_1 = slope (least squares) = $(6.76 \pm 0.09) \times 10^{-6}$ sec^{-1}.

$k_2 = (3.55 \pm 0.02) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

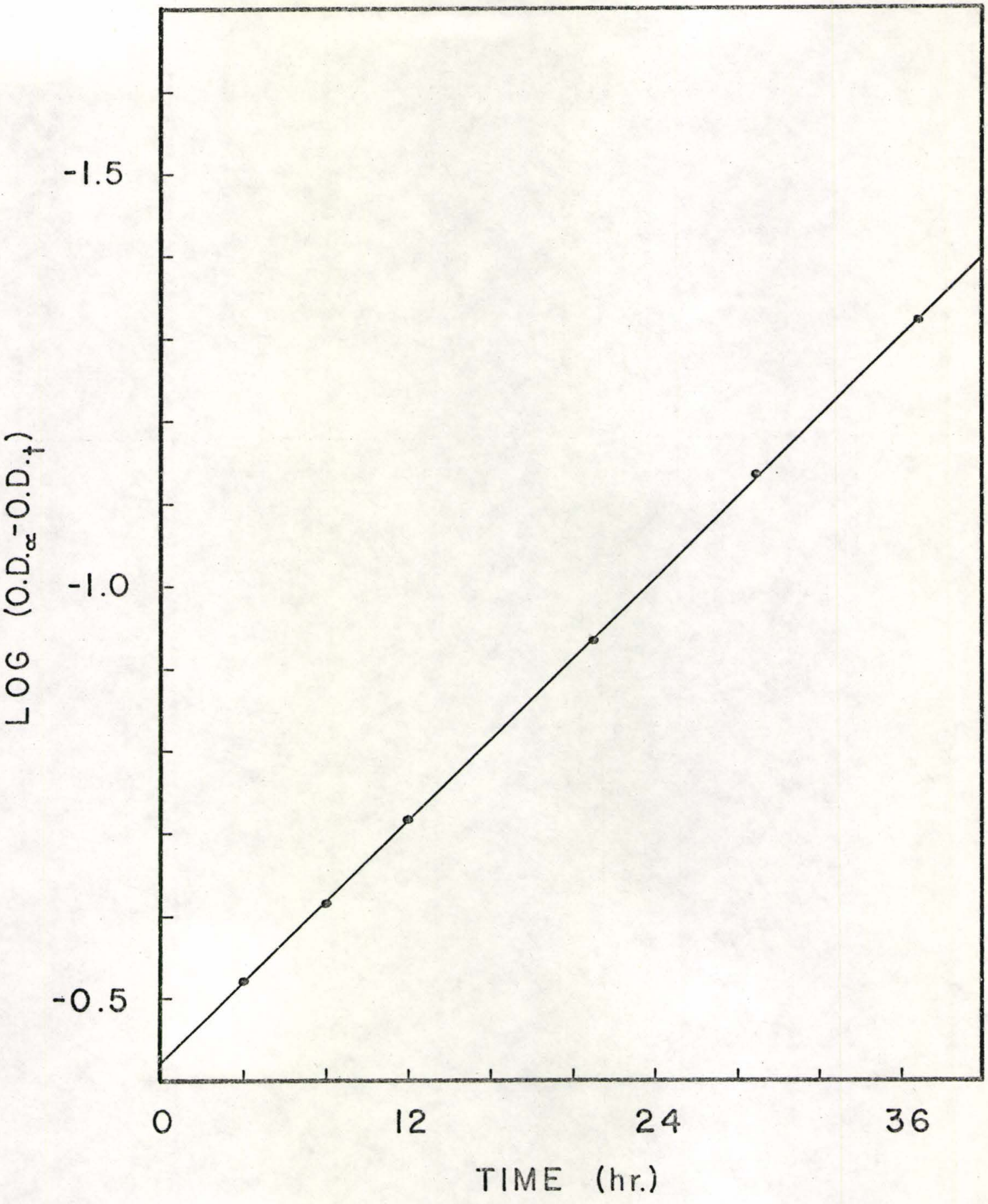


Figure 19. Plot of the kinetic data given in Table XXXV for a typical kinetic experiment for the reaction of trans-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

Table XXXVI

Data for a Typical Kinetic Experiment in the Reaction of trans-2-Phenylcyclopentyltrimethylammonium-2-d_1 Iodide with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.

(Initial concs.: Q.A.S. = 0.00437 m./l.; NaOEt = 0.1907 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
4	0.023	0.627	-0.4668
8	0.042	0.608	-0.4977
12	0.062	0.588	-0.5311
21	0.105	0.545	-0.6071
37	0.167	0.483	-0.7280
45	0.198	0.452	-0.7943
49	0.217	0.443	-0.8143
61	0.259	0.391	-0.9392
85	0.317	0.333	-1.0999
	0.650		

Calculation of rate constant:

k_1 = slope (least square) = $(2.20 \pm 0.02) \times 10^{-6}$ sec^{-1}.

$k_2 = (1.15 \pm 0.01) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

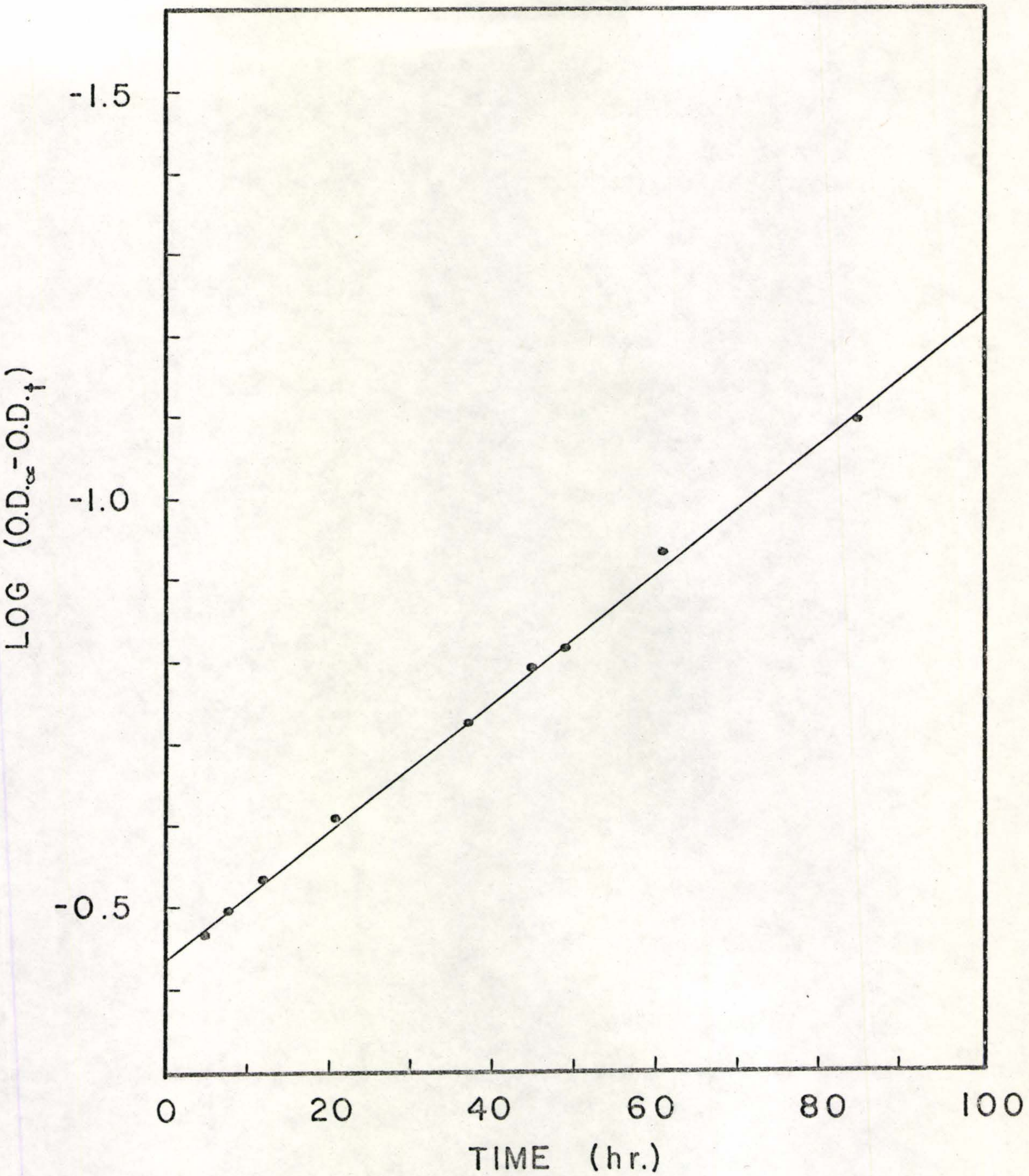


Figure 20. Plot of the kinetic data given in Table XXXVI for a typical kinetic experiment for the reaction of *trans*-2-phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

Table XXXVII

Data for a Typical Kinetic Experiment in the Reaction
of cis-2-Phenylcyclopentyltrimethylammonium Iodide
with Sodium Ethoxide in Anhydrous Ethanol at 30.00°C.
(Initial concs.: Q.A.S. = 0.00486 m./l.; NaOEt = 0.1988 m./l.)

Time hr.	Optical Density	$OD_{\alpha} - OD_{t}$	$\ln (OD_{\alpha} - OD_{t})$
2	0.109	0.574	-0.5552
4	0.196	0.487	-0.7196
6	0.284	0.399	-0.9190
8	0.341	0.342	-1.0731
10	0.396	0.287	-1.2485
12	0.441	0.242	-1.4191
	0.683		

Calculation of rate constant:

k_1 = slope (least squares) = $(24.1 \pm 0.02) \times 10^{-6}$ sec^{-1}.

$k_2 = (12.1 \pm 0.1) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

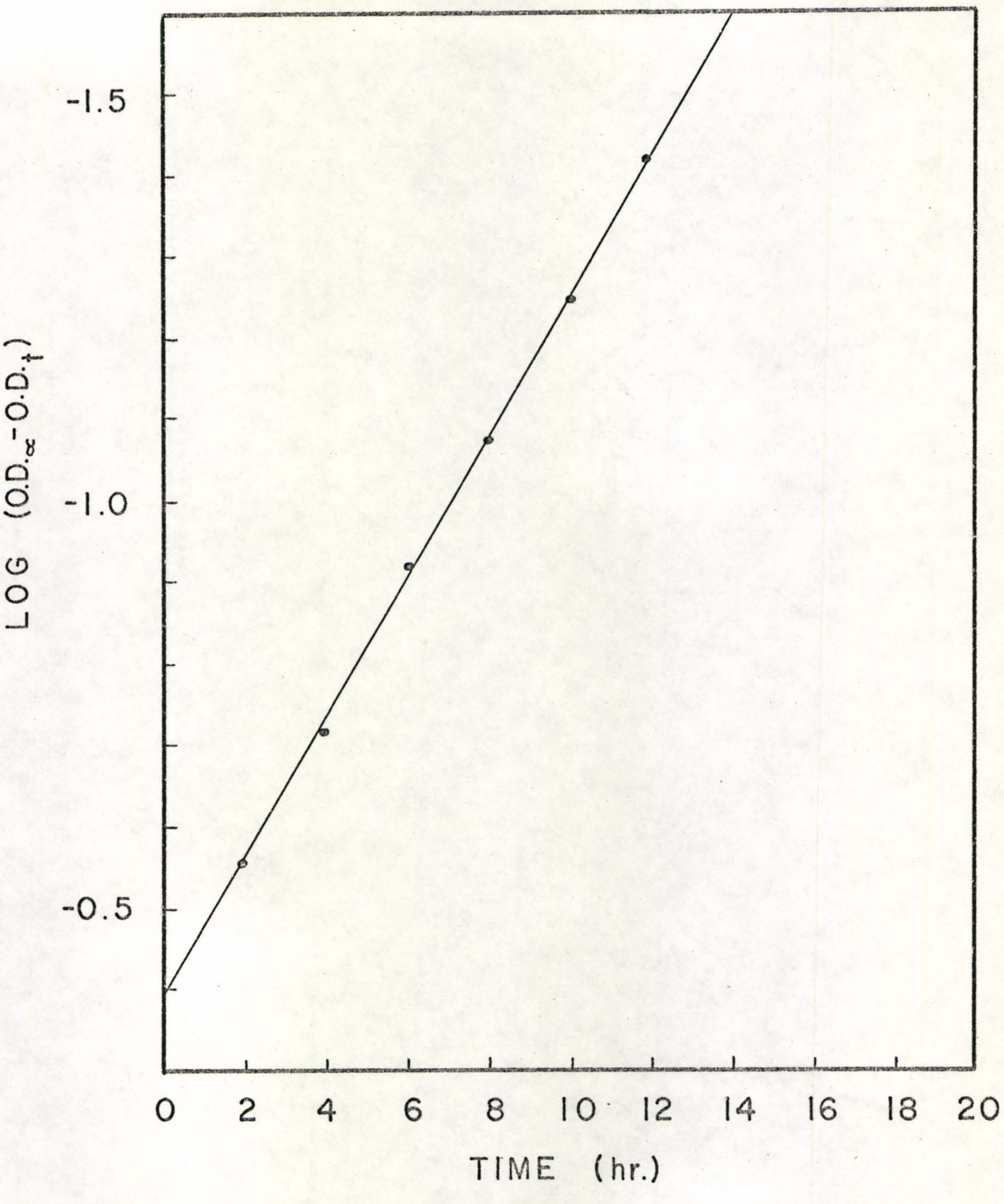


Figure 21. Plot of the kinetic data given in Table XXXVII for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 30.00°C.

Table XXXVIII

Data for a Typical Kinetic Experiment in the Reaction of cis-2-Phenylcyclopentyltrimethylammonium-2-d_1 Iodide with Sodium Ethoxide in Anhydrous Ethanol at 30.00°C.

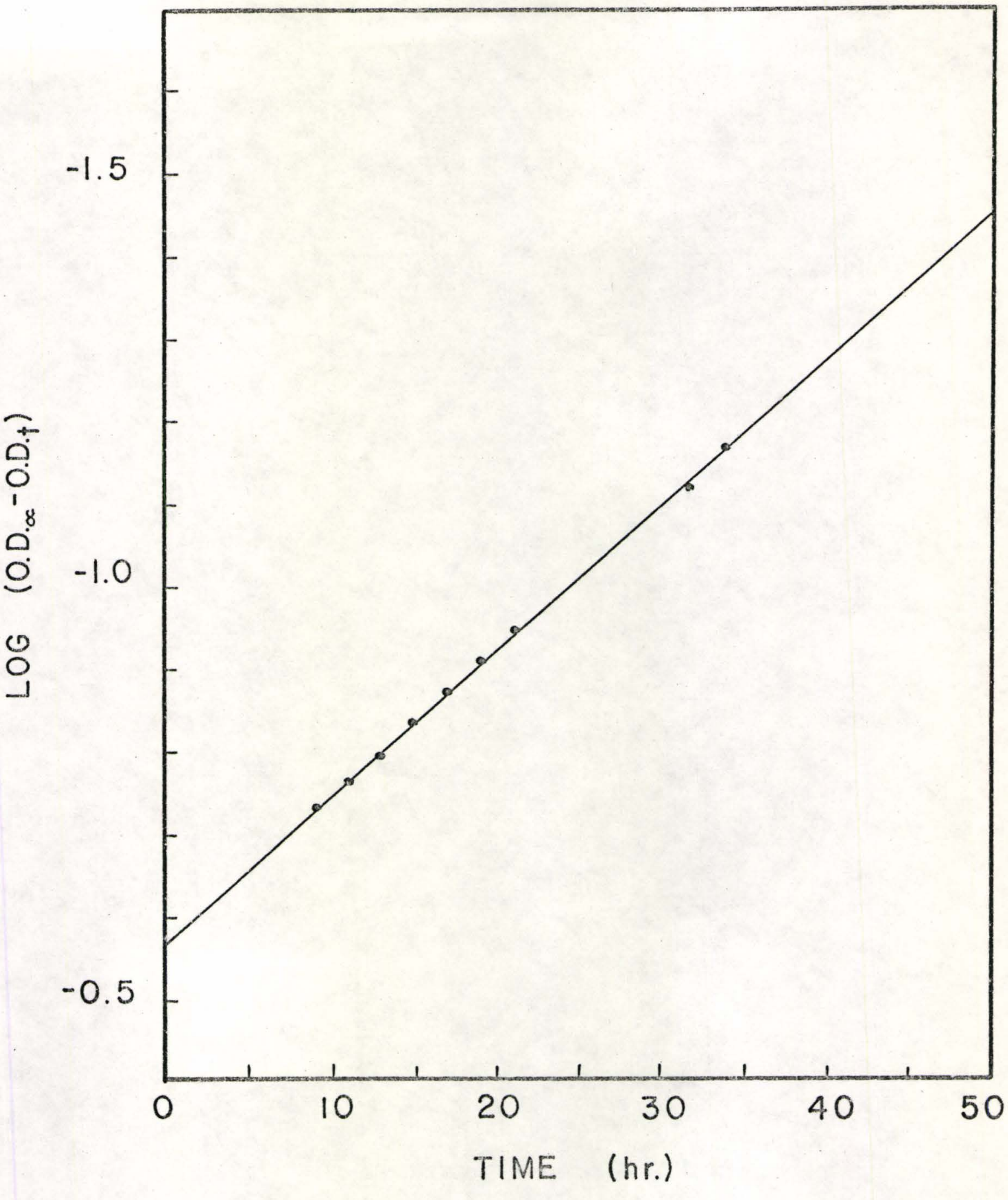
(Initial concs.: Q.A.S. = 0.00403 m./l.; NaOEt = 0.1988 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
9	0.103	0.485	-0.7238
11	0.118	0.470	-0.7552
13	0.134	0.454	-0.7897
15	0.152	0.436	-0.8302
17	0.166	0.422	-0.8629
19	0.182	0.406	-0.9016
21	0.198	0.390	-0.9417
32	0.261	0.327	-1.1181
34	0.275	0.313	-1.1619
	0.588		

Calculation of rate constant:

k_1 = slope (least squares) = $(4.85 \pm 0.04) \times 10^{-6}$ sec^{-1}.

$k_2 = (2.44 \pm 0.02) \times 10^{-5}$ l. mole^{-1} sec^{-1}.



<u>Figure 22.</u> Plot of the kinetic data given in Table XXXVIII for a typical kinetic experiment for the reaction of <u>cis</u>-2-phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ iodide with sodium ethoxide in anhydrous ethanol at 30.00°C.

Table XXXIX

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 45.00°C.

(Initial concs.: Q.A.S. = 0.004767 m./l.; NaOEt = 0.1984 m./l.)

Time min.	Optical Density	$OD_\alpha - OD_t$	$\ln(OD_\alpha - OD_t)$
20	0.102	0.569	-0.5640
40	0.214	0.457	-0.7832
60	0.304	0.367	-1.0025
80	0.363	0.308	-1.1779
100	0.424	0.247	-1.3986
120	0.470	0.201	-1.6047
	0.671		

Calculation of rate constant:

k_1 = slope (least square) = $(17.2 \pm 0.1) \times 10^{-5}$ sec^{-1}.

$k_2 = (86.7 \pm 0.7) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

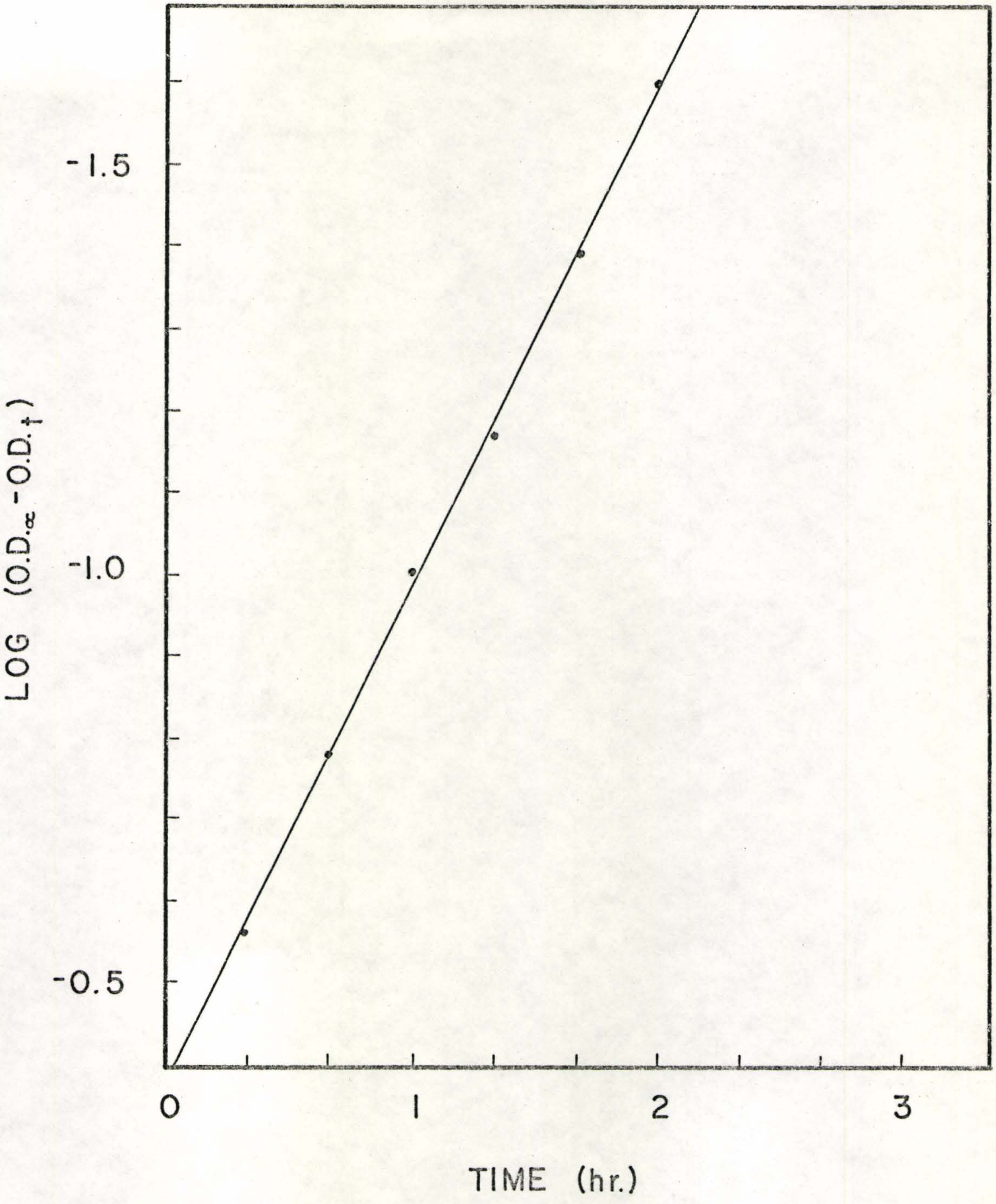


Figure 23. Plot of the kinetic data given in Table XXXIX for a typical kinetic experiment for the reaction of cis-2-phenylcyclopentyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 45.00°C.

Table XL

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclopentyltrimethylammonium-2-$\underline{d}_1$ Iodide with Sodium Ethoxide in Anhydrous Ethanol at 45.00°C.

(Initial concs.: Q.A.S. = 0.004032 m./l.; NaOEt = 0.1984 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
1	0.073	0.495	-0.7033
2	0.141	0.427	-0.8511
3	0.193	0.375	-0.9810
4	0.240	0.328	-1.1149
5	0.279	0.289	-1.2416
6	0.312	0.256	-1.3628
	0.568		

Calculation of rate constant:

k_1 = slope (least squares) = $(36.5 \pm 0.4) \times 10^{-6}$ sec^{-1}.

$k_2 = (18.4 \pm 0.2) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

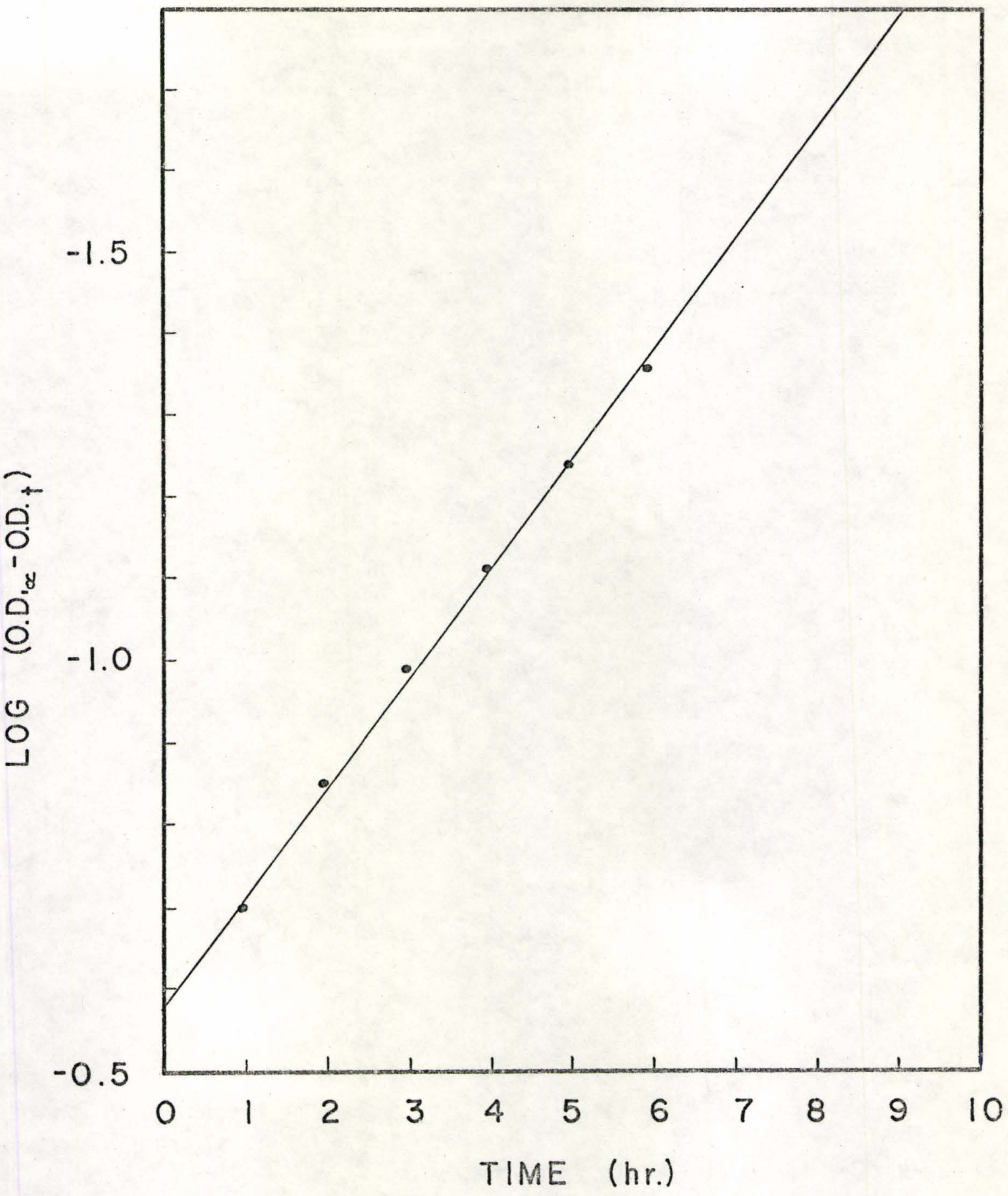


Figure 24. Plot of the kinetic data given in Table XL for a typical kinetic experiment for the reaction of *cis*-2-phenylcyclopentyltrimethylammonium-2-d_1 iodide with sodium ethoxide in anhydrous ethanol at 45.00°C.

Table XLI

Data for a Typical Kinetic Experiment in the Reaction of *cis*-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.

(Initial concs.: Q.A.S. = 0.00744 m./l.; NaOEt = 0.2068 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
1	0.044	0.334	-1.0969
2	0.075	0.303	-1.1943
3	0.105	0.273	-1.2984
4	0.131	0.247	-1.3986
5	0.152	0.226	-1.4875
6	0.174	0.204	-1.5900
7	0.194	0.184	-1.6932
8	0.211	0.167	-1.7901
	0.378		

Calculation of rate constant:

k_1 = slope (least squares) $(27.6 \pm 0.2) \times 10^{-6}$ sec^{-1}.

$k_2 = (13.5 \pm 0.1) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

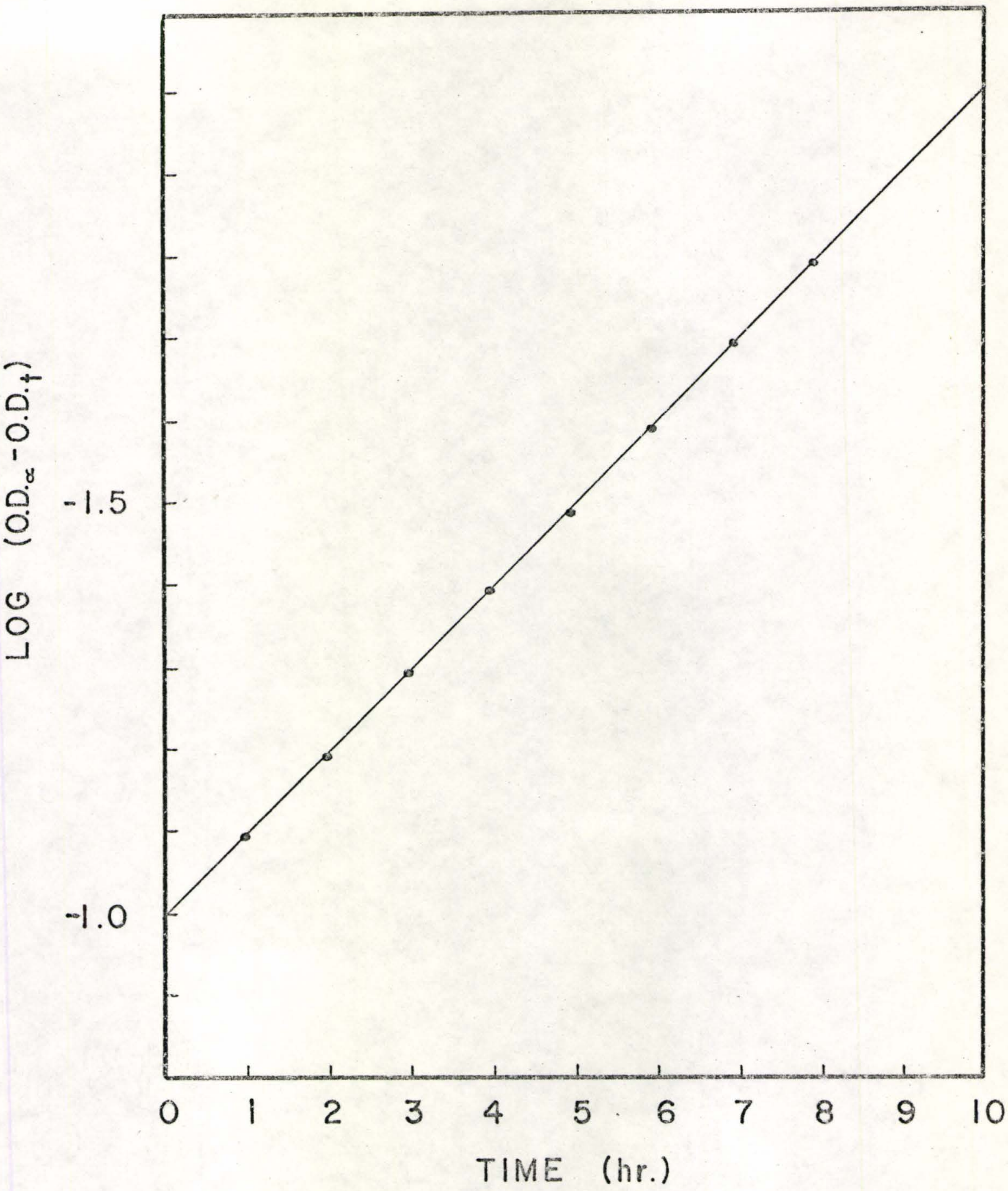


Figure 25. Plot of the kinetic data given in Table XLI for a typical kinetic experiment for the reaction of cis-2-phenylcyclohexyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

Table XLII

Data for a Typical Kinetic Experiment in the Reaction of

cis-2-Phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ Iodide

with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.

(Initial concs.: Q.A.S. = 0.00764 m./l.; NaOEt = 0.2068 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln (OD_\alpha - OD_t)$
4	0.041	0.339	-1.0820
6	0.056	0.324	-1.1273
8	0.069	0.311	-1.1681
10	0.080	0.300	-1.2042
12	0.090	0.290	-1.2381
16	0.114	0.266	-1.3245
24	0.155	0.225	-1.4919
30	0.180	0.200	-1.6098
36	0.200	0.180	-1.7150
	0.380		

Calculation of rate constant:

k_1 = slope (least squares) = $(55.4 \pm 0.4) \times 10^{-7}$ sec^{-1}.

$k_2 = (2.68 \pm 0.02) \times 10^{-5}$ l. mole^{-1} sec^{-1}.

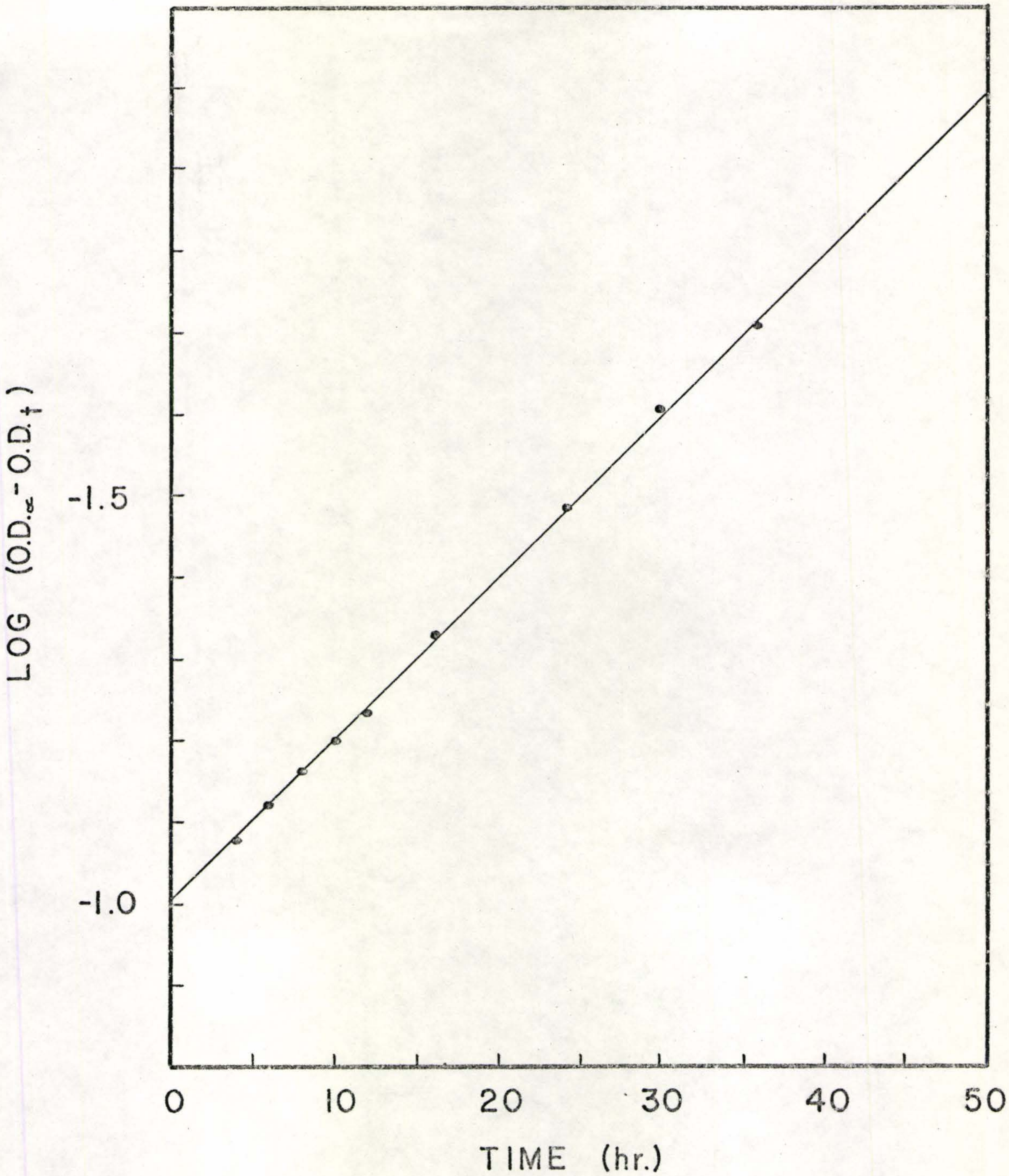


Figure 26. Plot of the kinetic data given in Table XLII for a typical kinetic experiment for the reaction of cis-2-phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

Table XLIII

Data for a Typical Kinetic Experiment in the Reaction of *trans*-2-Phenylcyclohexyltrimethylammonium Iodide with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.

(Initial concs.: Q.A.S. = 0.02111 m./l.; NaOEt = 0.949 m./l.)

Time hr.	Optical Density	$OD_{\alpha} - OD_{t}$	$\ln (OD_{\alpha} - OD_{t})$
22	0.067	0.567	-0.5675
26	0.073	0.561	-0.5781
32	0.082	0.552	-0.5944
52	0.116	0.518	-0.6580
72	0.148	0.486	-0.7218
81	0.161	0.473	-0.7487
96	0.182	0.452	-0.7943
105	0.193	0.441	-0.8190
120	0.214	0.420	-0.8678
	0.634		

Calculation of rate constant:

k_1 = slope (least squares) = $(85.3 \pm 0.9) \times 10^{-8}$ sec^{-1}.

$k_2 = (8.99 \pm 0.09) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

$k_{elim} = (5.48 \pm 0.06) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

$k_{subst.} = (3.41 \pm 0.03) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

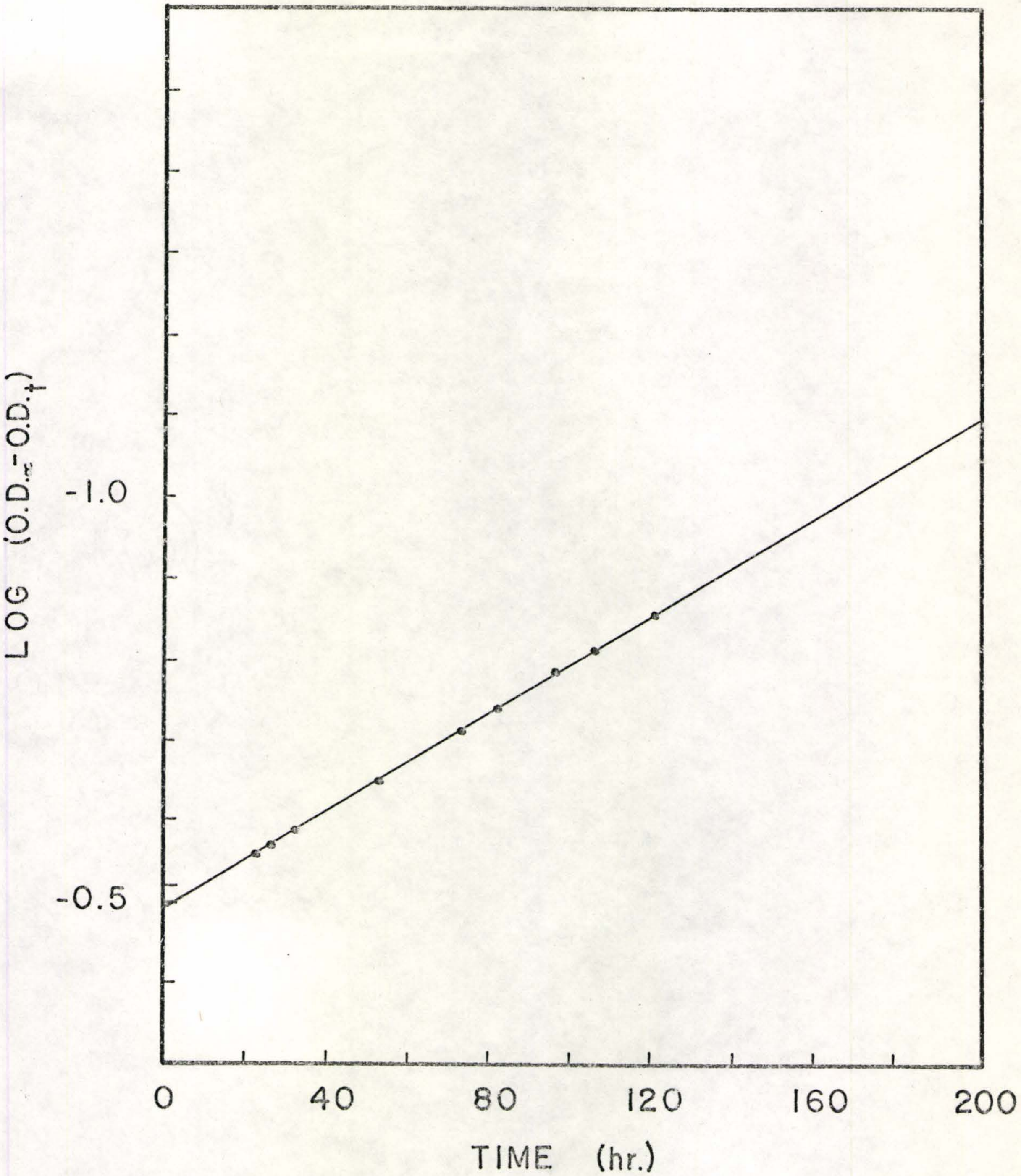


Figure 27. Plot of the kinetic data given in Table XLIII for a typical kinetic experiment for the reaction of trans-2-phenylcyclohexyltrimethylammonium iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

Table XLIV

Data for a Typical Kinetic Experiment in the Reaction of
trans-2-Phenylcyclohexyltrimethylammonium-2-$\underline{d}_1$ Iodide
with Sodium Ethoxide in Anhydrous Ethanol at 60.00°C.
(Initial concs.: Q.A.S. = 0.02361 m./l.; NaOEt = 0.949 m./l.)

Time hr.	Optical Density	$OD_\alpha - OD_t$	$\ln(OD_\alpha - OD_t)$
26	0.048	0.392	-0.9371
32	0.051	0.389	-0.9445
52	0.068	0.372	-0.9891
72	0.082	0.358	-1.0274
81	0.087	0.353	-1.0414
96	0.099	0.341	-1.0760
105	0.104	0.336	-1.0909
120	0.112	0.328	-1.1149
	0.440		

Calculation of rate constant:

k_1 = slope (least squares) = $(53.8 \pm 0.6) \times 10^{-8}$ sec^{-1}.

$k_2 = (5.67 \pm 0.06) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

$k_{elim} = (2.10 \pm 0.02) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

$k_{subst.} = (3.52 \pm 0.03) \times 10^{-7}$ l. mole^{-1} sec^{-1}.

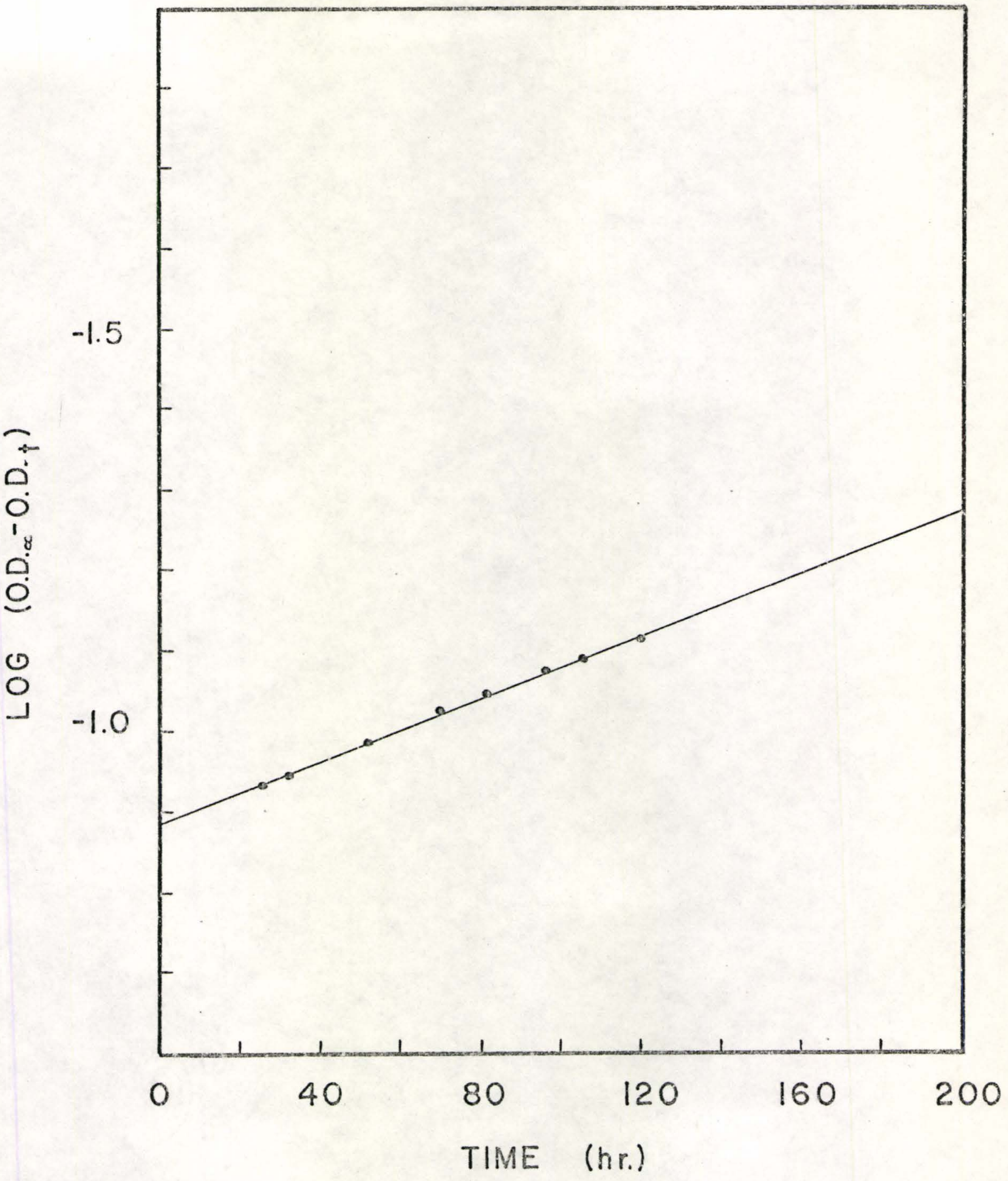


Figure 28. Plot of the kinetic data given in Table XLIV for a typical kinetic experiment for the reaction of trans-2-phenylcyclohexyltrimethylammonium-2-d_1 iodide with sodium ethoxide in anhydrous ethanol at 60.00°C.

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