STUDIES ON THE ELIMINATION REACTION OF 2-ARYLETHYLAMMONIUM SALTS

ISOTOPE EXCHANGE AND KINETIC ISOTOPE EFFECT STUDIES ON THE ELIMINATION REACTION OF 2-ARYLETHYLAMMONIUM SALTS

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SCOPE AND CONTENTS:

The mechanism of the elimination reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol has been examined using tracer and kinetic isotope effect methods. The absence of exchange of the β-hydrogen with solvent and the observation of a nitrogen-15 isotope effect of 1.4 per cent have eliminated a two-step process involving a carbanion intermediate. Tracer studies using α- and β-deuterium labelled compounds have also excluded the less probable reaction pathways involving ylide and carbene intermediates. It is concluded, therefore, that the reaction is a concerted E2 process.

Information concerning the extent of C-H and C-N bond weakening at the transition state has been obtained by determining the influence of base strength on the nitrogen isotope effect in the reaction of ethyltrimethylammonium ion and the influence of _para_-substitution on both hydrogen and nitrogen isotope effects in the reaction of a series of 2-arylethyltrimethylammonium salts. The results have been interpreted in terms of a hypothesis 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.

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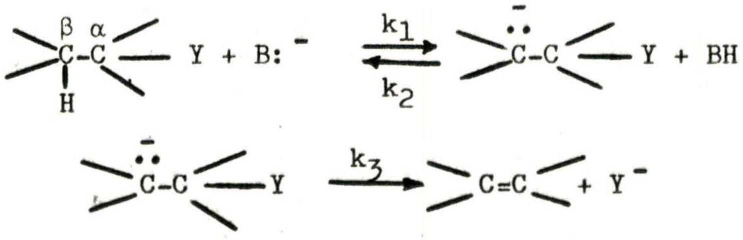
GENERAL INTRODUCTION

In a β-elimination process two atoms or groups are lost from adjacent atoms and an unsaturated product is formed. The most common example of this reaction is where hydrogen is lost from a β-carbon atom and some other atom or group, Y, is displaced from an α-carbon atom to form an olefin. Common "leaving groups" are trialkylammonium, dialkylsulfonium, and the halogens. In recent years there has been considerable interest in the mechanism of this important class of reactions which have theoretical as well as synthetic importance. A large number of studies have been directed to the question of elucidating the detailed pathway of the elimination process as well as to the question of the extent to which bond changes have taken place at the transition state.

Two different reaction pathways have been proposed:

Mechanism I One-Step Process

Mechanism II Two-Step Process



Here, B is the abstracting base which removes the hydrogen from the β-carbon in a step which may or may not be rate-determining and Y is the "leaving group". In the one-step process, the removal of hydrogen by base, B, occurs at the same time as the formation of the carbon-carbon double bond and separation of the leaving group, Y. The alternative possibility is a two-step process in which the base first removes the hydrogen to form a carbanion intermediate which subsequently eliminates the leaving group, Y, with formation of the double bond.

The classical means used for the detection of a carbanion intermediate is the deuterium exchange test. This involves conducting the reaction part way to completion in deuterated solvent, which is the conjugate acid of the basic reagent, and analyzing for the presence of deuterium in the recovered reactant.

The observation of appreciable deuterium pick-up is good evidence for the formation of a free carbanionic intermediate which, by interaction with solvent, regenerates reactant labelled in the β-position. The absence of deuterium exchange, however, does not necessarily exclude the intervention of a carbanion intermediate, since the rate at which the carbanion decomposes to product could be so much greater than its rate of return to reactant by combination with solvent (i.e., $k_3 \gg k_2$) as to preclude the observation of deuterium in the substrate by the available experimental methods.

This ambiguity, which arises from the observation of little or no deuterium pick-up, can be resolved by the evaluation of the kinetic isotope effect associated with that atom of the leaving group, Y, which is bonded to the α-carbon. In the concerted process, the C-Y bond is broken in the rate-determining step and this should result in an isotope effect of considerable magnitude. In the two-step mechanism where $k_3 \gg k_2$, which is the only possibility for a carbanion mechanism permitted by the observation of negligible deuterium pick-up, the rate-determining step is the formation of the carbanion in which the bond associated with the leaving group, Y, is still intact. In this case, there should be no isotope effect associated with the leaving group, or at the most a secondary isotope effect of a few-tenths of a per cent.

This criterion of mechanism has been used only once to establish the mechanism of an elimination process. The deuterium exchange test, in combination with the leaving group isotope effect, has led to the unequivocal conclusion that benzyl nitrate reacts with base to give benzaldehyde through a concerted E2 mechanism rather than through a two-step mechanism involving a carbanion intermediate (1).

The establishment of the concerted mechanism for an elimination reaction leads to the question of whether or not the C-H and C-Y bond weakening processes are synchronous; i.e., whether or not both bonds are broken to the same extent at the transition state. It is now generally accepted that the C-H and C-Y bond changes need not be synchronous and, indeed, much experimental evidence, such as eclipsing effects and secondary k^{DO^-}/k^{HO^-} effects, has been interpreted in terms of a spectrum of transition states for an elimination process. These range all the way from an E1-like transition state in which there is a large degree of C-Y and very little C-H bond rupture to an Elcb-like transition state in which the relationship of the two bond rupture processes is the reverse.

It is an unsettled question whether a structural change in the substrate or base, which brings about an increase in C-H bond weakening in the transition state, increases or decreases the amount of C-Y bond rupture. This problem results chiefly from the difficulty in interpreting the magnitude of the hydrogen-deuterium isotope effect in terms of the amount of C-H bond rupture. Application of a theoretical treatment of hydrogen isotope effects by Westheimer (2), which is based on the assumption that the magnitude of the effect is determined mainly by stretching frequencies in the transition state, leads to exactly opposite conclusions depending upon whether one considers that the proton is more or less than half transferred to base at the transition state. A consideration of the E2 reaction of some quaternary ammonium ions in the light of this hypothesis has led several groups of workers to conclude that the C-H and C-Y bond rupture processes in the transition state are complementary; that is, the more one is weakened the less the other will be weakened.

The first part of the work reported in this thesis is concerned with the elucidation of the mechanism of the elimination reaction of 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol. Conflicting data in the literature (3,4) concerned with the differentiation between the carbanion and concerted mechanisms for this reaction has prompted the author to measure the nitrogen isotope effect associated with the reaction as well as to examine possible exchange of the β-hydrogen with solvent. This latter test was performed by carrying out the reaction of the β-dideuterated ion in undeuterated solvent, rather than of unlabelled ion in deuterated solvent so that the position, as well as the extent, of exchange could be determined.

A deuterium exchange experiment with α-dideuterated substrate, as well as other tracer studies using both the α-dideuterated and β-dideuterated compounds, have been used to test for carbene and ylide mechanisms as possible reaction pathways.

The second and major part of the work reported in this thesis is concerned with the nature of the transition state in the E2 reaction of some quaternary ammonium ions. Nitrogen isotope effects for reaction of ethyltrimethylammonium ion with two bases of different strength and both nitrogen and hydrogen isotope effects for the reaction of a series of para-substituted 2-arylethyltrimethylammonium ions with ethoxide ion have been measured. The results are discussed in terms of a hypothesis 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 or, in other words, that the extent of C-H and C-Y bond rupture at the transition state parallel each other.

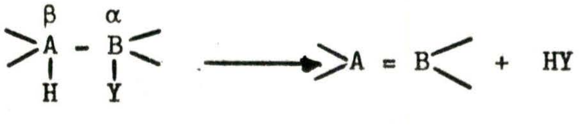
HISTORICAL INTRODUCTION

A. β-Elimination Reactions

General

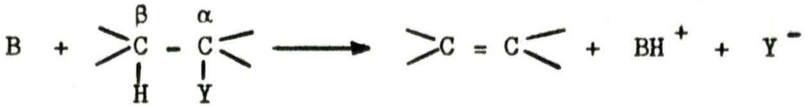
This section of the thesis will be concerned with β-elimination reactions. A short general discussion of the various mechanisms which have been suggested to account for experimental observations will first be presented. Following this, there will be presented a more detailed account of two of the mechanisms, the concerted or one-step process (E2) and the carbanion or two-step process (E1cb), since a major concern of the work reported in this thesis has been to distinguish between these reaction pathways for an olefin-forming elimination reaction. The section concludes with a discussion of the different experimental criteria which have been used to shed light on the nature of the transition state in the concerted E2 process.

Nearly all elimination reactions of theoretical or synthetic importance are β-elimination processes. These reactions lead to an unsaturated product since two atoms or groups are lost from adjacent atoms, equation 1. The most common example of this reaction is the case where



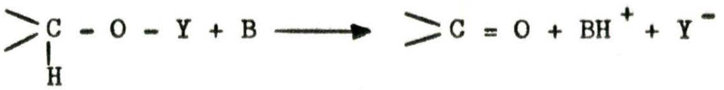
$$>\underset{H}{\overset{\beta}{A}}-\underset{Y}{\overset{\alpha}{B}}< \longrightarrow >A=B< + HY \qquad (1)$$

H and some other atom or group Y are removed from vicinal saturated carbon atoms (A and B) to form an olefin. This is shown in equation 2,



$$\mathrm{B} + >\!\underset{\mathrm{H}}{\overset{\beta}{\mathrm{C}}} - \underset{\mathrm{Y}}{\overset{\alpha}{\mathrm{C}}}\!< \longrightarrow\ >\!\mathrm{C} = \mathrm{C}\!< + \mathrm{BH}^{+} + \mathrm{Y}^{-} \tag{2}$$

where B is a base and the "leaving group" Y may be trialkylammonium (5.6), dialkylsulfonium (7), bromide (8), chloride (9), iodide (10), fluoride (11,12) arylsulfonate (13,14). A less common but related β-elimination is the so-called carbonyl elimination reaction shown in equation 3. In this reaction the α-carbon of the substrate in



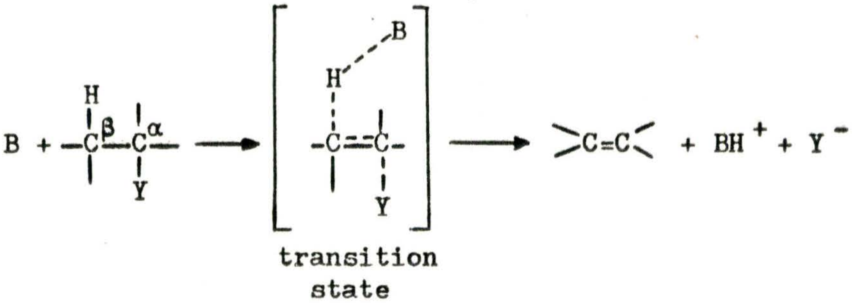
$$>\!\underset{\mathrm{H}}{\mathrm{C}} - \mathrm{O} - \mathrm{Y} + \mathrm{B} \longrightarrow\ >\!\mathrm{C} = \mathrm{O} + \mathrm{BH}^{+} + \mathrm{Y}^{-} \tag{3}$$

equation 2 has been replaced by oxygen and a ketone or aldehyde is formed instead of an olefin. The leaving group, Y, in this reaction can be, for example, arylsulfinate (15,16) or nitrite (17,18,19).

During the past few years a number of excellent reviews (20-25) have appeared which present the experimental evidence for the different β-elimination mechanisms and discuss the way in which reaction conditions and the structure of reactant can determine the reaction pathway. For this reason, only a brief description of each mechanism and the main lines of evidence supporting it will be presented in this thesis.

The E2 Mechanism

A concerted bimolecular mechanism for β-elimination was first proposed by Hanhart and Ingold (5) to account for the second-order kinetics observed (6) in the decomposition of quaternary ammonium hydroxides. Since this pioneering work many other examples of this so-called E2 mechanism have been observed and it would appear to be the normal reaction pathway for elimination reactions promoted by strong base. A general formulation for reaction by this mechanism is given in equation 4, where the base B can be neutral or negatively

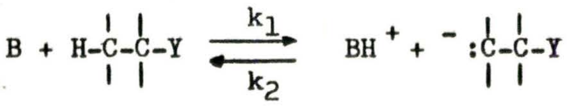


$$B + H\text{-}\overset{}{C}_{\beta}\text{-}C_{\alpha}\text{-}Y \longrightarrow \left[\,B\cdots H\cdots C\overset{\cdots}{=}C\cdots Y\,\right] \longrightarrow {>}C{=}C{<} + BH^{+} + Y^{-} \qquad (4)$$

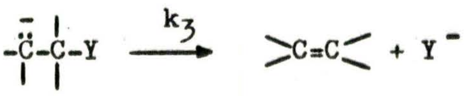
charged and the leaving group Y may be neutral or positively charged. In the transition state for the reaction the C-H and C-Y bonds are partially broken and a π bond between the carbon atoms is partially formed.

The E1cb Mechanism

The relative extent to which the two bond rupture processes have developed at the transition state of an E2 process may vary widely from reaction to reaction. If C-H bond rupture is advanced over C-Y rupture, negative charge will develop at the β-carbon. In the extreme, proton transfer to base may be complete before any change has taken place at the C-Y bond, with the result that a true intermediate, a carbanion, now intervenes between reactants and products. This is shown in equations 5 and 6. This mechanism was suggested by

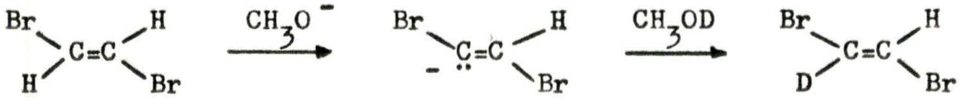


$$B + H\text{-}C\text{-}C\text{-}Y \underset{k_2}{\overset{k_1}{\rightleftharpoons}} BH^{+} + {}^{-}{:}C\text{-}C\text{-}Y \qquad (5)$$



$$\text{-}\overset{-}{\ddot{C}}\text{-}C\text{-}Y \xrightarrow{k_3} {>}C{=}C{<} + Y^{-} \qquad (6)$$

Ingold in 1933 as a possible reaction pathway and was designated by him as E1cb, meaning unimolecular decomposition of the conjugate base of the reactant. The first demonstration of a reaction following this mechanism did not come for another twenty-five years, although it had several times been suggested as the pathway for second-order elimination reactions of compounds in which the eliminated elements have a *cis* relationship to one another. In 1959, Miller (26) observed that trichloroethylene and a number of dihaloethylenes undergo base-catalyzed deuterium exchange with solvent considerably more rapidly than they undergo dehydrohalogenation. Isotopic exchange shows that a



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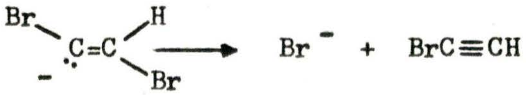
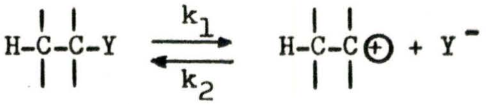


(8)

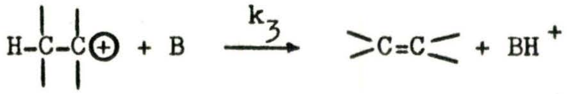
carbanion is formed which can regenerate the reactant by abstraction of a proton (or deuteron) from the solvent. Although the formation of a carbanion could be an irrelevant side reaction, it was argued (26) that the energy required for the ejection of a halide ion from this species in which there is 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. Isotopic exchange has also been shown to accompany the dehydrofluorination of various 2,2-dihalo-1,1,1-trifluoroethanes. The validity of the isotopic-exchange criterion of mechanism and further examples of elimination reactions in which a carbanion intermediate has been suggested will be discussed more fully in a subsequent section.

The E1 Mechanism

The other extreme to a carbanion mechanism is where the heterolysis of the C-Y linkage occurs first, with the formation of a carbonium ion intermediate which then can lose a β-hydrogen to give an olefin, equations 9 and 10. This mechanism was first proposed by

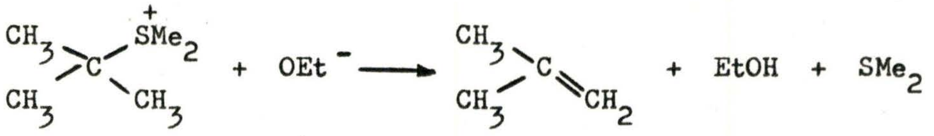


$$\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}Y} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\oplus} + \mathrm{Y}^- \tag{9}$$



$$\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\oplus} + \mathrm{B} \xrightarrow{k_3} \mathrm{>C{=}C<} + \mathrm{BH}^+ \tag{10}$$

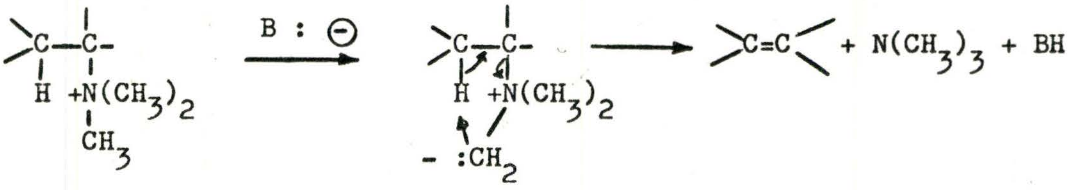
Hughes (27) and has been well authenticated, along with the E2 mechanism, by many workers. It is seen that the above reaction sequence can lead to first-order or to second-order kinetics depending upon the relative values of $k_2\left[Y^-\right]$ and k_3. If k_3 is large relative to $k_2\left[Y^-\right]$, then the formation of the carbonium ion will be rate-determining and the reaction will follow first-order kinetics. If, however, $k_2\left[Y^-\right]$ is large relative to k_3, a rate-determining attack of base on the carbonium ion will follow an initial pre-equilibrium step and the overall reaction will be second-order. Reactions can be expected to follow the E1 mechanism in cases where the substrate yields a relatively stable carbonium ion; that is, when the α-carbon is secondary or tertiary, and especially when an α-phenyl or α-vinyl group is present. Furthermore, it is possible for the reaction of a given compound to proceed either by the E1 or the E2 mechanism depending on conditions. For example, it has been found (28) that the reaction of t-butyldimethylsulfonium ion (I) with ethoxide ion in 97% ethanol, equation 11, exhibits second-order kinetics when the base concentration is high while the reaction follows first-order kinetics when the concentration of base falls below 0.01 molar.


(11)

I

The Ylide (α',β)-Mechanism

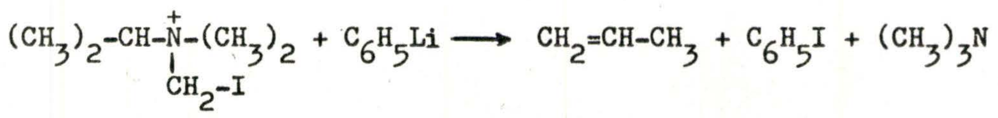
Reaction of onium salts in the presence of a very strong base, such as phenyllithium, has been shown to proceed by way of an intermediate, called an ylide (II), which is formed by the abstraction of a proton from an α-carbon of the salt


(12)

II

This has been called the α',β-mechanism of elimination.

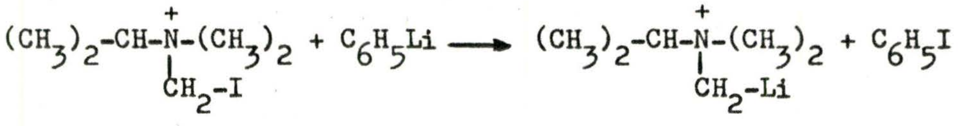
The first evidence that an ylide can be an intermediate in a β-elimination process was provided by Wittig (29), who observed that the reaction of dimethylisopropyl(iodomethyl)ammonium ion (III) with phenyllithium furnishes propylene, iodobenzene and trimethylamine. The formation of iodobenzene, rather than benzene, excludes a normal E2


(13)

$$(CH_3)_2\text{-}CH\text{-}\overset{+}{\underset{CH_2\text{-}I}{N}}\text{-}(CH_3)_2 + C_6H_5Li \longrightarrow CH_2{=}CH\text{-}CH_3 + C_6H_5I + (CH_3)_3N \qquad (13)$$

III

mode of elimination and is most readily understood in terms of the initial formation of an alkyllithium, IV, followed by an α',β-elimination of this ylide intermediate as shown in the second step of



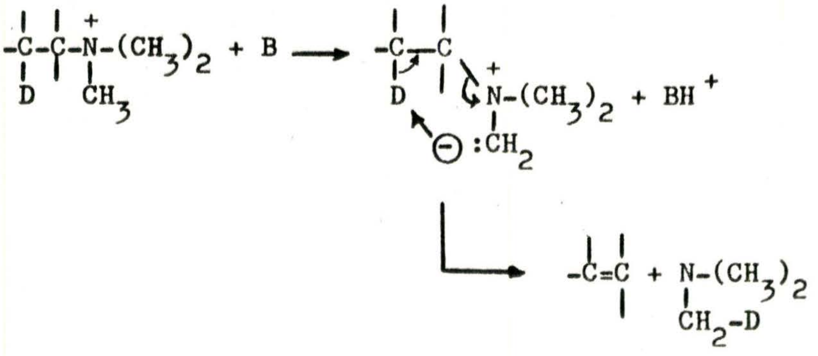
$$(CH_3)_2\text{-}CH\text{-}\overset{+}{N}(CH_3)_2(CH_2\text{-}I) + C_6H_5Li \longrightarrow (CH_3)_2\text{-}CH\text{-}\overset{+}{N}(CH_3)_2(CH_2\text{-}Li) + C_6H_5I \qquad (14)$$

IV

equation 12.

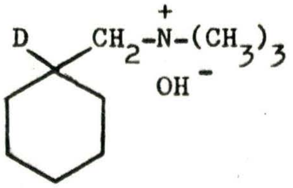
Evidence for the α',β-mechanism of elimination for ordinary quaternary salts, as distinct from their α-halo derivatives, is found in the work of Wittig (30,31,32) on the stereochemical course of the reaction of cyclooctyltrimethylammonium ion with different bases. It was observed that the reaction of cyclooctyltrimethylammonium ion with either hydroxide or amide ion gives more trans- than cis-cyclooctene, but that cis-cyclooctene is favoured 9 : 1 when phenyllithium is the base. This suggests that there is a change from the ordinary E2 mechanism when hydroxide is the base to some other mechanism when phenyllithium is used. That this is the ylide mechanism is strongly indicated by the fact that the reaction of methyl lithium on cyclooctyldimethyl(bromomethyl)ammonium ion gives the same 9 : 1 ratio of cis- to trans-octene.

The most direct test for the α',β-mechanism is to be found in tracer studies in which the hydrogens on the β-carbon of the reactant are replaced by deuterium and the eliminated trimethylamine is examined for the presence of this isotope. If the α',β-mechanism is operative then the trimethylamine should contain one deuterium per molecule, as shown in equation 15. This test has been applied to the thermal



(15)

decomposition of the two compounds, V and VI, (33,34) and in both cases the recovered trimethylamine was found to have no deuterium

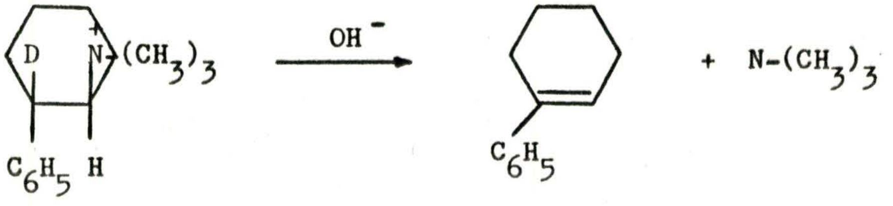


V

$$CD_3CH_2\overset{+}{N}\text{-}(CH_3)_3OH^-$$

VI

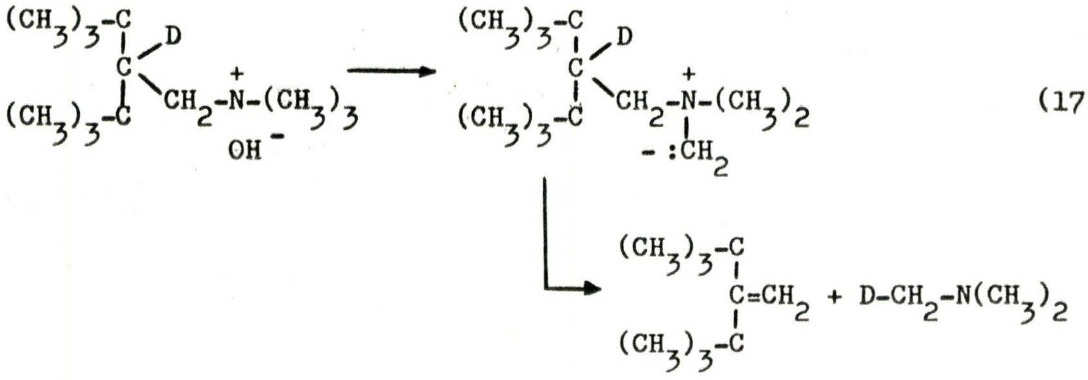
enrichment. This shows that the Hofmann reaction under ordinary conditions does not proceed by way of the ylide mechanism and this conclusion is consistent with the results from the stereochemical studies. Even in the case where reaction by the E2 mechanism is energetically unfavourable because of the inability of the system to form a transition state with an anti-coplanar relationship of carbon-hydrogen and carbon-nitrogen bonds, the ylide mechanism is not always followed. For example, Ayrey and Bourns (35) have shown the cis-elimination of trans-2d-2-phenylcyclohexyltrimethylammonium ion (VII) with ethanolic potassium hydroxide forms trimethylamine which is deuterium free, equation 16.



VII

(16)

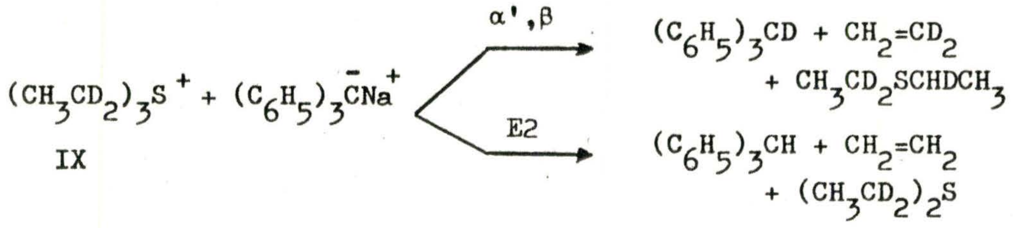
On the other hand, Cope and Mehta (36) have demonstrated the ylide mechanism for the decomposition of the quaternary base N,N,N-trimethyl-2-*t*-butyl-3,3-dimethylbutylammonium hydroxide-2-*d* (VIII), equation 17.



(17)

The anti-coplanar relationship of the C-H and C-N bonds required in the transition state for reaction proceeding via the E2 mechanism is difficult for steric reasons and the alternative α',β-mechanism involving a transition state in which the β-H and the nitrogen have a *cis* relationship competes successfully. Cope and Mehta suggest that the reason that the *cis*-elimination of *trans*-2-phenylcyclohexyltrimethylammonium ion does not follow the ylide mechanism is because the presence of the phenyl group on the β-carbon promotes either an Elcb mechanism or an E2 mechanism in which carbon-hydrogen bond rupture is well advanced over carbon-nitrogen bond rupture. In either case, the coplanarity requirement would be of much less importance than in a more synchronous E2 process.

Sulfonium salts, like the ammonium compounds, appear to react by way of an ylide intermediate in the presence of a very strong base. Franzen (37) investigated the reaction of tri(ethyl-1,1-d_2)sulfonium ion (IX) with trityl sodium using the tracer technique, equations 18 and 19, and found that only seventy-five per cent of the triphenylmethane was deuterated. Although the reaction proceeds mainly by the ylide mechanism, it does not do so exclusively, as indicated by the presence of the undeuterated triphenylmethane, which is probably formed by a reaction proceeding via the E2 mechanism, equation 19.



$$\underset{\text{IX}}{(CH_3CD_2)_3S^+} + (C_6H_5)_3\bar{C}Na^+ \xrightarrow{\alpha',\beta} (C_6H_5)_3CD + CH_2{=}CD_2 + CH_3CD_2SCHDCH_3 \qquad (18)$$

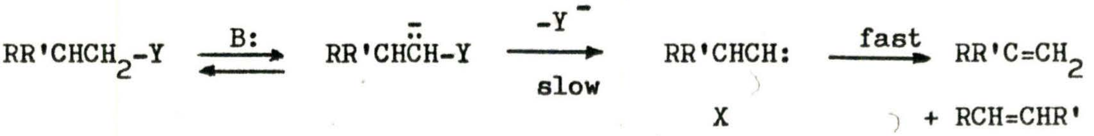
$$\underset{\text{IX}}{(CH_3CD_2)_3S^+} + (C_6H_5)_3\bar{C}Na^+ \xrightarrow{E2} (C_6H_5)_3CH + CH_2{=}CH_2 + (CH_3CD_2)_2S \qquad (19)$$

Carbene Mechanism

A possible mechanism for overall β-elimination involves the initial loss of α-hydrogen followed by migration of a hydrogen or another group from the β-position either before, concurrent with, or after the loss of the other α-fragment, which can be, for example, halogen (38) or dimethylsulfonium (39). Migration prior to loss of Y, equation 20, seems unlikely since this would involve migration to a negative centre, a process which has never been observed, at least not in protic solvents. Reaction in which a carbene (X), an electron-

$$\mathrm{RR'CHCH_2\text{-}Y} \overset{\mathrm{B:}}{\rightleftharpoons} \mathrm{RR'CH\overset{-}{\ddot{C}}H\text{-}Y} \longrightarrow \mathrm{RR'C{=}CH_2} + \mathrm{RCH{=}CHR'} \qquad (20)$$

deficient intermediate, is formed, equation 21, is more probable, however, since chloroform is known to decompose in this way, and carbenes have been established as intermediates in other reactions (40,41). In this carbene-forming process the base, B, first removes an α-hydrogen to form a carbanion intermediate which subsequently

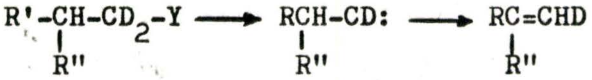


$$\mathrm{RR'CHCH_2\text{-}Y} \overset{\mathrm{B:}}{\rightleftharpoons} \mathrm{RR'CH\overset{-}{\ddot{C}}H\text{-}Y} \underset{\text{slow}}{\xrightarrow{-\mathrm{Y}^-}} \underset{\mathrm{X}}{\mathrm{RR'CHCH:}} \xrightarrow{\text{fast}} \mathrm{RR'C{=}CH_2} + \mathrm{RCH{=}CHR'} \qquad (21)$$

expels the leaving group, Y, in a slow step as a negatively charged species to form the carbene. The carbene then rearranges in a fast step, most commonly by means of hydrogen migration, to form an olefin.

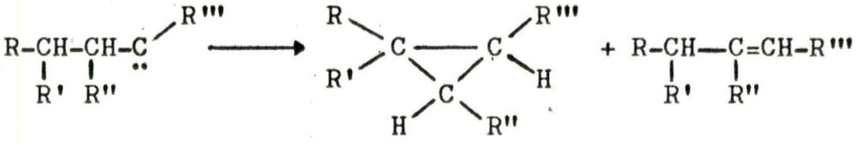
Deuterium tracer studies provide a means of detecting reaction by this mechanism. If the deuterium is on the β-carbon of the reactant, elimination by way of a carbene intermediate will give olefin in which the label appears on the α-carbon, equation 22. Labelling the α-hydrogens of reactant will give a product in which there is one less deuterium atom per molecule than in the starting material, equation 23. Additional evidence for the intermediacy of a

$$\mathrm{R\text{-}\underset{R''}{\overset{D}{C}}_{\beta}\!\!-\!\!\underset{\alpha}{\overset{H}{C}}:} \longrightarrow \mathrm{R\text{-}\underset{R''}{\overset{\beta}{C}}{=}\overset{\alpha}{C}HD} \qquad (22)$$



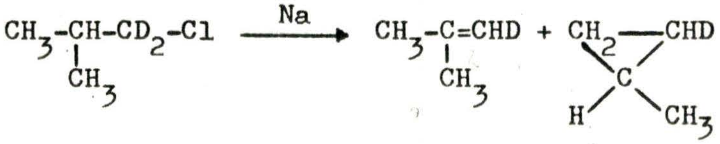
$$\mathrm{R'\text{-}\underset{R''}{CH}\text{-}CD_2\text{-}Y} \longrightarrow \mathrm{R\underset{R''}{CH}\text{-}CD:} \longrightarrow \mathrm{R\underset{R''}{C}{=}CHD} \qquad (23)$$

carbene is found in the formation of a cyclopropane derivative in addition to the olefin product. Such a result can be best understood in terms of a mechanism in which a carbene undergoes intramolecular insertion either between a γ-carbon-hydrogen bond to give the cyclopropane or between a β-carbon-hydrogen bond to form the olefin, equation 24.



(24)

Several studies have been reported in which these criteria of mechanism have been applied with positive results. Kirmse and Doering (38) found that the reaction of sodium or potassium on α-d_2 isobutyl chloride gives mainly monodeuterated methylcyclopropane and monodeuterated isobutylene, equation 25. Similarly, α-d_2 n-butyl chloride



(25)

was found to give 94 per cent monodeuterated products, 1-butene and methylcyclopropane when phenyl sodium is used as base, but only 10 per cent when the reagent is sodium methoxide (42). These results show that the α-elimination process competes successfully with β-elimination only when a very powerful base is used. Under the usual conditions for carrying out dehydrohalogenation the reaction proceeds by the normal bimolecular β-elimination mechanism. Others have obtained similar results (34,43). Finally, the observation by Franzen (44) of methylcyclopropane and isobutylene among the reaction products in the reaction of isobutyldiphenylsulfonium fluoroborate with trityl sodium suggests that reaction by the carbene mechanism can occur with sulfonium salts as well as with halogen compounds.

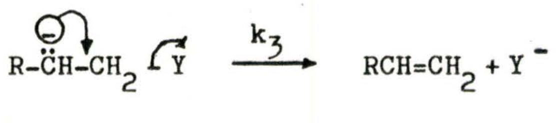
Means for Distinguishing between the E2 and Elcb Mechanisms

The conventional means of detecting a carbanion intermediate in a reaction is to test for hydrogen-deuterium exchange between the reactant and a solvent which is the conjugate acid of the basic reagent. If a true carbanion intermediate is present then the reverse of the first stage will result in deuterium pickup by the substrate. This method for distinguishing between the one- and two-step mechanisms for β-elimination reactions showing second order kinetics was first applied by Skell and Hauser (45). They demonstrated that when the reaction of β-phenylethyl bromide with ethoxide is carried part way to completion in C_2H_5OD, the recovered reactant shows no deuterium enrichment, within the limits of measurement. From this result, they concluded that the reaction proceeds via the concerted or one-step mechanism rather than through the carbanion or two-step mechanism.

The observation of an appreciable pickup of deuterium by the substrate is evidence that a carbanion is present in the reaction system. It is important to realize, however, that the absence of deuterium pickup does not necessarily exclude this species as a reaction intermediate. If the carbanion intermediate decomposes to

Elcb Mechanism

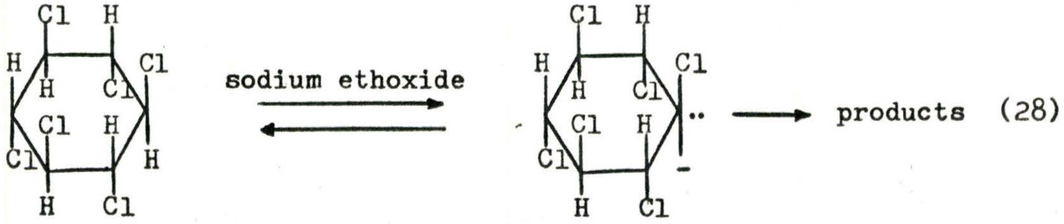
$$RCH_2\text{-}CH_2 - Y + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} R\overset{-}{\ddot{C}}H\text{-}CH_2 - Y + BH \qquad (26)$$



$$R\text{-}\overset{\ominus}{\ddot{C}}H\text{-}CH_2\,Y \xrightarrow{k_3} RCH{=}CH_2 + Y^- \qquad (27)$$

product at a rate much greater than its reaction with solvent to form starting material ($k_2\,[BH] \ll k_3$ in equations 26 and 27) then there will be no observable exchange. Only if $k_2\left[BH\right]$ is at least one one-hundredth of k_3 will deuterium enrichment be experimentally observable (34).

Other attempts have been made to use the deuterium exchange test for the detection of a carbanion intermediate in β-elimination reactions. Cristol (46) studied the reaction of β-benzene hexachloride, which cannot easily undergo normal E2 reactions because of stereochemical restrictions, with sodium ethoxide in deuterated ethanol, equation 28. He found that the recovered starting material after



(28)

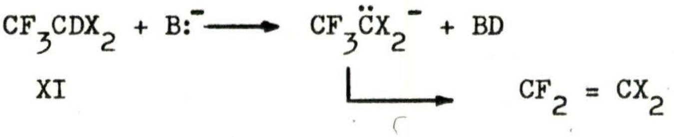
50 per cent reaction contained an amount of deuterium which was too small for detection by infrared analysis. Mass spectrometric analysis, however, indicated that the recovered substrate contained about 0.079 excess atom per cent deuterium and this result was interpreted to mean that the reaction was in fact proceeding via a carbanion intermediate. This interpretation has been questioned, however, because of the very small amount of exchange which was observed (47).

Miller and Lee (26) investigated the reaction of <u>cis</u>- and <u>trans</u>-dihaloethenes with base. They found that the rate of exchange, equation 29, was approximately twenty-five times greater than the rate of elimination, equation 30, and they therefore concluded that the

$$cis\text{-}C_2H_2Br_2 + CH_3OD \xrightarrow{CH_3O^-} cis\text{-}C_2DHBr_2 + CH_3OH \qquad (29)$$

$$C_2H_2Br_2 + CH_3O^- \longrightarrow HC\equiv CBr + CH_3OH + Br^- \qquad (30)$$

reaction was following the Elcb mechanism. Similarly, Hine (48) studied the reaction of 2-deuterio-2,2-dihalo-1,1,1-trifluoroethane (XI) with sodium methoxide in methanol, equation 31, where X can be Cl, Br or I. He found that these compounds undergo base-catalyzed



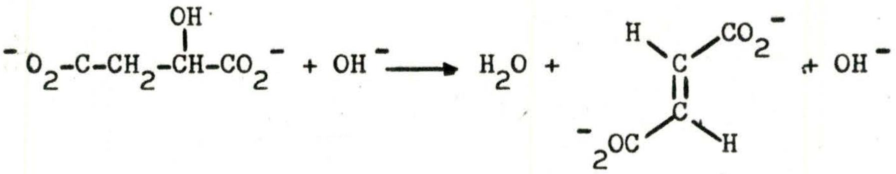
$$CF_3CDX_2 + B:^- \longrightarrow CF_3\ddot{C}X_2^- + BD, \quad CF_3\ddot{C}X_2^- \longrightarrow CF_2 = CX_2$$

XI

(31)

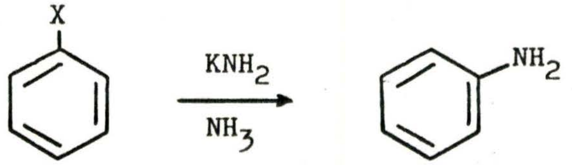
deuterium exchange with solvent at a rate which is rapid compared to the rate of alkali consumption. Also, when the undeuterated analogues of these compounds (XI) are treated with base in heavy water their infrared spectra are found to change in the manner expected for a deuteriation process. These experimental results led Hine to conclude that compound XI reacts by the 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.

The mechanism of the dehydration of malic acid to fumaric acid has been investigated by Erickson and Alberty (49), equation 32. They



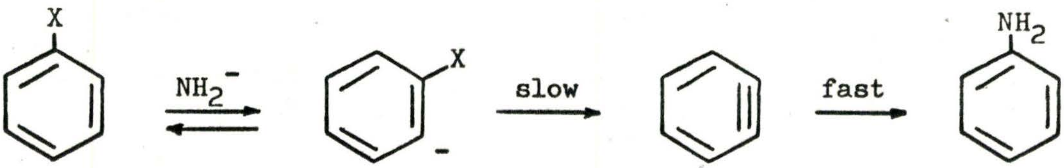
(32)

found that the methylene protons of malate exchange with deuterons in D_2O more rapidly than the overall reaction occurs and this result was considered to provide strong evidence for the carbanion mechanism. Similarly, Roberts et al. (50) have studied the amination of halobenzenes, equation 33, and have found that for both chloro- and fluorobenzene deuterium exchange is faster than the rate of formation of the amination products. They concluded that a carbanion intermediate



(33)

is involved in the elimination process forming a benzyne intermediate (XII), which then rapidly adds ammonia to form product, equation 34.



(34)

XII

In all of these studies it has been assumed that the demonstration of reversible carbanion formation under elimination reaction conditions is tantamount to demonstrating a carbanion elimination mechanism. It has, of course, always been recognized that the formation of a carbanion could be entirely unrelated to the elimination reaction, which could proceed by the one-step E2 process. Hine (51), however, has argued that this is unlikely. He maintains that if partial freeing of a β-electron pair at the transition state of the E2 process is sufficient to cause the ejection of the leaving group, then the complete freeing of this pair in the carbanion should be even more effective. Therefore, in a reaction in which a carbanion is formed, as shown by isotopic exchange, its conversion to elimination product should swamp out any reaction by the one-step process. Breslow, however, has recently (52) taken the stand that not only is reaction by the E2 process possible in a system showing isotopic exchange but it is even more likely than is elimination by way of a reversibly formed carbanion.

One argument used by Breslow to support his position is that the lesser negative charge on the E2 transition state, $B^{\delta-}$----H---C===C---$X^{\delta-}$, should result in its being more stable than the transition state, $C^{\delta-}$===C---X, leading from the carbanion to product. This approach fails to take into account the relative energies of the partial C-X bond in the two systems, which could very well favour the transition state of an Elcb reaction.

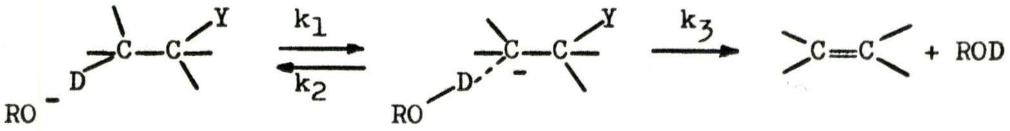
A second argument used by Breslow is that electron-withdrawing substituents on the benzene ring of β-phenylethyl compounds, by lowering the concentration of negative charge on carbon, would be expected to decrease the rate of conversion of a carbanion to product by reducing the "push" for departure of X. That such substituents actually increase rather than decrease rate of olefin formation (53) is considered by him to militate against the Elcb mechanism. There is, however, a flaw in this argument. Electron-withdrawing groups most certainly will increase the energy required to transform the carbanion to the transition state leading to product. The rate of elimination for an Elcb process in which a carbanion is in equilibrium with reactant, however, depends not upon this energy but on the energy difference between *reactant* and the *transition state*. This transition state, since it will have high carbanion character (24), will be stabilized by electron-withdrawing groups in the same way as is the carbanion itself and the elimination rate will be increased, as is observed.

Although Breslow's arguments are not convincing, it is nevertheless still conceivable that reaction by the E1cb and the E2 mechanisms might be proceeding concurrently and that in any particular system most or essentially all of the reaction could proceed by the latter mechanism, even though carbanions are present in the system. As Breslow has pointed out such criteria as general vs. specific base catalysis and kinetic hydrogen isotope effect measurements might be used to settle this question.

Whether or not detection of deuterium exchange can be considered as evidence for a carbanion intermediate in β-elimination there is no question but that the absence of deuterium exchange cannot be considered to establish the E2 mechanism. Herein lies the difficulty; the observation of no deuterium exchange can be equally well interpreted in terms of a one-step E2 mechanism or a two-step carbanion mechanism where the rate of conversion of the carbanion to product is very much greater than the rate of its return to reactants by abstraction of a hydrogen from solvent; i.e., $k_2 \left[\text{solvent}\right] \ll k_3$ in equations 26 and 27.

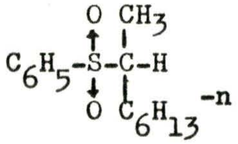
The first successful attempt to distinguish between the two possibilities for a bimolecular elimination reaction showing no deuterium exchange was made by Buncel and Bourns (1). These workers found that the carbonyl-elimination reaction of benzyl nitrate with ethoxide ion in ethanol giving benzaldehyde shows no deuterium exchange and gives a normal nitrogen isotope effect $(k^{14}/k^{15} - 1)\ 100$, of

2.0 per cent, the latter showing that C-N bond rupture is taking place in the rate-determining step. These results eliminate reaction by way of a carbanion intermediate which is hydrogen-bonded with solvent, since the absence of exchange would require that the rate-determining step for such a mechanism must be the formation of this intermediate in which the C-N bond is still intact. Not excluded by these observations, however, is reaction by way of a carbanion intermediate which is specifically hydrogen-bonded to the molecule of EtOH formed by abstraction of the β-hydrogen by base, equation 35. Cram (54) has recently obtained



(35)

evidence for such intermediates in the base-catalyzed hydrogen-deuterium exchange reaction of 2-octylphenylsulfone (XIII). If this specifically



$$C_6H_5\text{-}\overset{O\uparrow}{\underset{O\downarrow}{S}}\text{-}\overset{CH_3}{\underset{C_6H_{13}\text{-}n}{C}}\text{-}H$$

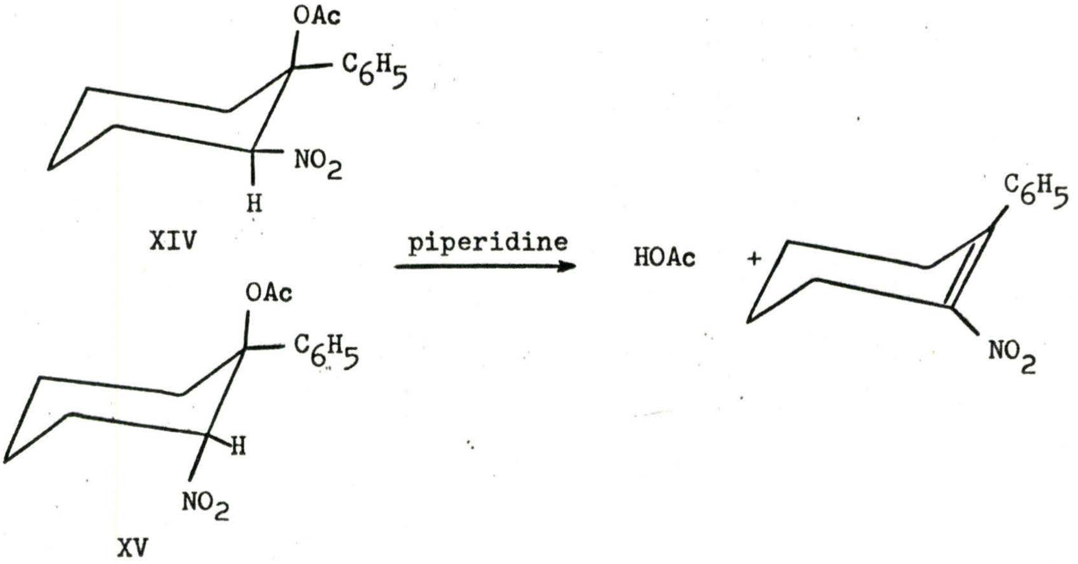
XIII

solvated carbanion were in equilibrium with reactants, the second step involving C-N bond rupture would be rate-determining and a normal nitrogen isotope effect would result, as is observed. The β-deuterium isotope effect (k^H/k^D) associated with such a process, however, would be very small, or even less than unity, since it would be that resulting from an equilibrium proton transfer between carbanion and alkoxide ion (54). The observation by Buncel and Bourns of a normal effect for

k^H/k^D of 5.0 at 60° excludes this possibility and requires that proton transfer take place in a rate rather than in an equilibrium process. On the basis of their three observations, namely, no deuterium exchange, a normal nitrogen effect and a normal H/D effect, any mechanism involving a carbanion intermediate is excluded and the reaction would appear to be a simple one-step E2 process.

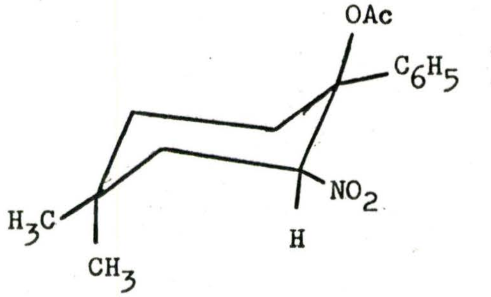
There is ample evidence that the usual stereochemical course of the E2 elimination reaction is trans. Cis eliminations following second-order kinetics are known, but these usually require a higher energy of activation. For example, the elimination reaction of β-benzene hexachloride, the only isomer in which all hydrogens and chlorines on adjacent carbons have a cis relationship, has an energy of activation of 32 k cal/mole compared to approximately 20 k cal/mole for all of its isomers (47). There has been considerable controversy concerning the mechanism of this reaction. Cristol and Fix (46), as noted earlier in this section, carried out a deuterium exchange experiment in 70% EtOD - 30% EtOH with ethoxide as base and obtained a very small incorporation of the label, namely 0.08 atom % excess deuterium. From this result, they concluded that β-benzene hexachloride undergoes elimination through a carbanion intermediate whose rate of return to reactant is about 1/150th that of its transformation to product. Ingold (47) has questioned this interpretation, and has preferred a forced one-step or E2 mechanism with the extra 12 k cal/mole of activation energy required to force the relevant portion of the molecule more nearly into the anti-coplanar configuration of the normal trans elimination.

Another system has recently come under study where the relative rates of elimination from cis- and trans-isomers of substituted cyclohexanes have been determined. Bordwell (55) investigated cis- and trans-elimination from the stereoisomeric 1-acetoxy-2-nitro-1-phenylcyclohexanes (XIV and XV), as brought about by piperidine in chloroform-ethanol solution, equation 36. It was

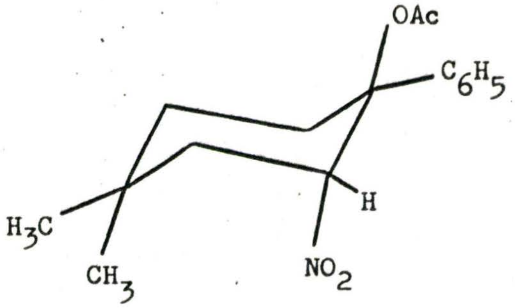


(36)

found that cis-elimination was somewhat faster than trans-elimination, contrary to the results of Ingold (47) and Cristol (56,57) on the elimination reaction of the stereoisomers of benzene hexachloride. The effect of changing ionic strength was the same for each isomer and, most significantly, Hammett plots of the rate of reaction of the isomeric m- and p-substituted compounds gave an identical ρ-value of +1.45. These results led the authors to conclude that both isomers were reacting through a carbanion intermediate and they suggested that the cis-elimination proceeds faster than the trans-elimination because of steric hindrance to carbanion formation. This latter view receives support in the observation that the cis/trans rate ratio is increased sharply (from 3.5 to 78) by the introduction of an axial methyl group (compounds XVI and XVII).



XVI



XVII

The fundamental question in the problem of differentiating between the E2 and Elcb mechanisms for reactions showing no isotopic exchange is whether or not the bond to the leaving group or atom is partially broken in the highest energy state through which the system passes in going from reactants to products. This information can be obtained through isotope effect measurements on the atom of the leaving group whose bond to carbon is broken in the overall reaction. Ayrey and Bourns (58) examined this problem by comparing the nitrogen isotope effects in the reactions with ethoxide ion of cis- and trans-2-phenylcyclohexyltrimethylammonium ion (XVIII and XIX), giving 1-phenylcyclohexene. The reaction of the former is the ordinary trans-elimination process and its nitrogen isotope effect was found to be 1.2 per cent*

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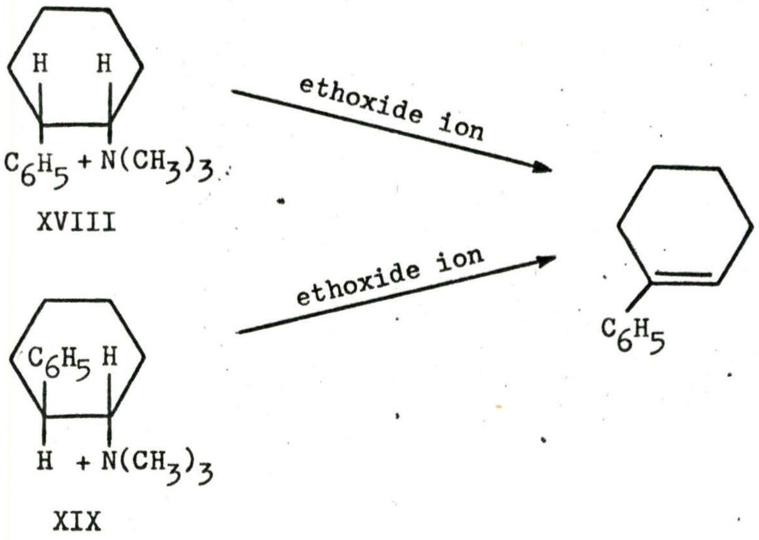
* This effect may be compared with an effect of 0.9 per cent at 60° found by Ayrey and Bourns (3) for the reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol.



(37)

at 60°, which is about one-third the maximum effect possible in a reaction involving carbon-nitrogen bond rupture.

A number of mechanisms must be considered for the reaction of the trans-cyclohexyl salt. A reasonable possibility is a prior trans-elimination to give 3-phenylcyclohexene followed by a tautomeric shift of a hydrogen. It has been shown, however, that 3-phenylcyclohexene does not undergo rearrangement under the conditions of the elimination reaction (59) and, furthermore, a Hofmann elimination of the trans salt labelled with deuterium on the β-methylene group gives 1-phenylcyclohexene without loss of label (60). This mechanism, therefore, must be discarded. Tracer studies have also eliminated the ylide mechanism (35) as well as a sequence involving epimerization at the α-carbon (61). From these results, it would appear that reaction of the trans compound is an ordinary cis β-elimination process. Application of the deuterium exchange test for the detection of a carbanion intermediate furnished a negative result. It follows then that the reaction is either an E2 process or proceeds by way of a carbanion whose rate of conversion to product is very rapid compared to its rate of reversion to reactant by abstraction of a proton from solvent. The nitrogen isotope effect for the reaction was found by Ayrey and Bourns to have the very small value of 0.2 per cent, compared to 1.2 per cent for the trans-elimination of the cis-isomer. The most reasonable explanation for this result is that a carbanion intermediate is formed in a rate-determining step, although a one-step mechanism in which the composite force constant is almost the same in the initial and transition states is not entirely excluded. In either case, however, the transition state for the reaction must have large carbanionic character.

In all of the nitrogen isotope effect work of Ayrey and Bourns, 2-phenylethyltrimethylammonium ion was used as the standard for comparison since it was assumed that the β-elimination of this compound would be a trans E2 process. Although an isotopic exchange test was not made on this particular compound, Hodnett and Flynn (62) had previously obtained a negative result for p-nitrophenyltrimethylammonium ion, as had Ayrey and Bourns in their study of the cis-elimination of trans-2-phenylcyclohexyltrimethylammonium ion. If the assumption that the β-phenylethyl system would show no deuterium exchange is correct, then the observation of a significant nitrogen effect of 0.9 per cent at 60° is entirely compatible with the concerted mechanism.

After this work of Ayrey and Bourns had been completed, Banthorpe and Ridd (4), in the course of an investigation of the properties of strongly basic solutions, made the surprising observation that 2-phenylethyltrimethylammonium ion apparently does undergo isotopic exchange with solvent under elimination reaction conditions. When the reaction was carried to about 25-30 per cent completion in deuterated methanol or ethanol and the unchanged reactant was recovered as its tetraphenylborate, the observed extent of deuterium uptake was that shown in Table I, where the exchange is expressed as a percentage of that for complete exchange at one C-H position. The amount of exchange was found to decrease with increasing concentration of sodium methoxide and this was accounted for on the basis of a decrease in the activity of the methanol solvent from which a carbanion must abstract a proton or deuteron to regenerate starting material. The amount of exchange is small in all cases and this was interpreted to mean that the formation of the intermediate carbanion is almost but not completely rate-determining. This would be expected to give rise to a much smaller nitrogen effect than was reported by Ayrey and Bourns. Banthorpe and Ridd attempted to rationalize these conflicting results by suggesting

Table I

Results of Deuterium-Exchange Study

on 2-Phenylethyltrimethylammonium Ion

Solvent	MeOD			EtOD
$[OR^-]$ M	0.137	0.98	3.83	0.16
Temp.	60°	45°	45°	45°
Exchange %	7.9	2.3	0.8	12.0

that the transition state for proton loss to give the carbanion derives some stabilization from a partial breaking of the carbon-nitrogen bond which results in some double-bond character to the $\overset{\alpha}{C}-\overset{\beta}{C}$ bond. It is the view of the present author that, if this were so, the transformation of carbanion to product should be so rapid that no deuterium exchange would be observed. Furthermore, it is difficult to visualize a carbanion intermediate with a sufficiently weakened C-N bond that a nitrogen isotope effect of one per cent would result.

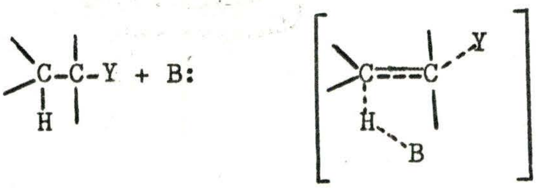
At about the same time as Banthorpe's and Ridd's results were reported, Asperger (63) completed measurements on the nitrogen effect for 2-phenylethyltrimethylammonium ion using water as solvent. He obtained the extremely small value $(k^{14}/k^{15} - 1)$ 100 of 0.14 per cent at 97°. This is entirely consistent with the formation of a carbanion intermediate in a step which is almost but not completely rate-determining, as was indicated by Banthorpe's and Ridd's exchange studies. It is most surprising, however, that the magnitude of the nitrogen isotope effect should be so solvent dependent - 0.14 per cent at 97° in H_2O compared with 0.9 per cent at 60° in ethanol.

Asperger found support for his conclusion that the reaction of β-phenylethyltrimethylammonium ion with hydroxide ion in water proceeds by the Elcb mechanism in the observed magnitude of the secondary α-deuterium isotope effect (63). The rate ratio, k^H/k^D, for the reaction of undeuterated and α-dideuterated 2-phenylethyltrimethylammonium ion with hydroxide ion in water was found to be only 1.024, compared to 1.18 for the reaction with ethoxide ion in ethanol of the corresponding phenylethyl bromide (64). Asperger interpreted this much smaller effect in the onium salt elimination to mean that there is very little development of double-bond character between the α- and β-carbon atoms in the transition state of the reaction. This would be the case if the elimination involved the rate-determining formation of a carbanion intermediate.

From the conflicting experimental data concerning the mechanism of the reaction of 2-phenylethyltrimethylammonium ion with base it is apparent that clarification is required. Not only is this mechanism in doubt but also conclusions based on it, for example, the interpretation of the results obtained from the cis- and trans-isomers of the 2-phenylcyclohexyl system is open to question. A major part of the work of this thesis is concerned with clarification of this matter.

Nature of the Transition State for E2 Reactions

In the transition state of a reaction proceeding by the E2 mechanism, the C-Y and C-H bonds are partially broken while the double bond and the base-hydrogen bond are partially formed, equation 38.

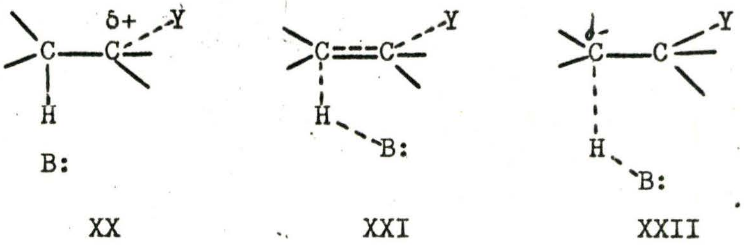


(38)

Transition State

Until recently, these processes were generally thought to be synchronous; i.e., the C-H and C-Y bonds are broken to the same degree at the transition state, although Hanhart and Ingold (5) did suggest very early that this is not necessarily so. The present consensus is that while this synchroneity may exist in some cases, represented by transition state XXI, more commonly either C-Y or C-H bond rupture will have taken precedence over the other. In other words, there can be a spectrum of possible transition states, ranging from one approaching that of the E1 mechanism (XX) all the way to one approaching that of the Elcb mechanism (XXII). A transition state like XX will have carbonium-ion character at the α-carbon, and one like XXII will have carbanion character at the β-carbon. Obviously, the stereochemical and electronic character of the transition state will, in this picture, be subject to considerable variation.

Transition States for an E2 Process



It is generally accepted that a trans-elimination of H and Y is favoured over cis-elimination (22), and that the best geometry for the E2 transition state is anti-coplanar (the H-C, C-C and C-Y bonds all in one plane, and arranged as shown in transition state XXI).*

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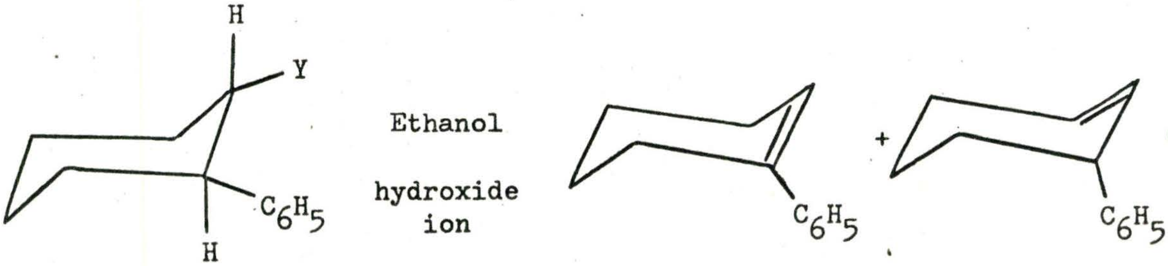
* Recently, DePuy and co-workers (65) have suggested that there is a conformational preference involved for cis-eliminations as well as for trans. They found that a cis- E2 elimination is almost as favourable as a trans- E2 reaction for the 2-phenylcyclopentyl tosylates in direct contrast to the results obtained for the corresponding cyclohexyl compounds where the trans-elimination proceeds by a factor of at least 10^4 faster than the cis-elimination. They reasoned that a coplanar transition state is preferable to a non-coplanar transition state as far as a concerted elimination reaction is concerned. Thus a cis-elimination from the cyclopentyl compound should be much more favourable than a cis-elimination from the cyclohexyl compound because it is easier to form a coplanar transition state for the cyclopentyl compound.

Presumably, this geometry is favourable for a synchronous electron shift, whereby the electrons released from the C-H bond can enter the octet of the α-carbon on the back side with respect to the departing group Y (66). If this is so, the "requirement" for an anti-coplanar conformation should be less stringent, the less synchronous the mechanism. Transition states on the nearly E1 and nearly E1cb extremes might, therefore, be encountered in systems where the attainment of anti-coplanar geometry is difficult (cis-eliminations from cyclohexane derivatives), or impossible (cis-elimination from a rigid system). Since eliminations of this latter type are known then the stereoelectronic preference for trans-elimination must not be absolutely essential.

The elimination reactions of trans-2-phenylcyclohexyl derivatives with potassium hydroxide in ethanol, equation 39, illustrates how different leaving groups can influence the nature of the transition state for an elimination process in a cyclic system. The reaction of trans-2-phenylcyclohexyltrimethylammonium ion with

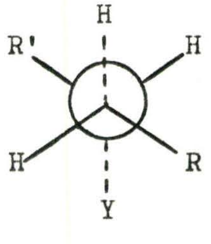


(39)

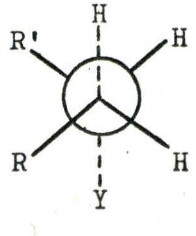
Y = $-\overset{+}{N}(CH_3)_3$	64%	2%
Y = -OTs	20%	53%

KOH in ethanol, which has already been discussed, gives predominantly 1-phenylcyclohexene, a product of cis-elimination (59,60,61,67). This is reasonable since Ayrey and Bourns (58) have shown from their very low value of the nitrogen isotope effect that this substrate reacts via a transition state at the very "nearly carbanion" extreme. A transition state of this kind can be expected to lower the stereoelectronic preference for trans-elimination and, in fact, cis-elimination is observed. A change to a different leaving group, i.e., tosylate, however, causes a greater predominance of 3-phenylcyclohexene, a product of trans-elimination. This presumably is the result of a more or less "central" transition state, where the C-Y bond is broken more than in the ammonium case, since p-toluenesulfonate anion is generally considered to be a much better leaving group than is trimethylamine.

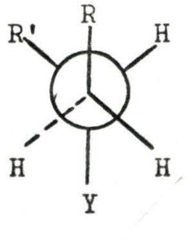
Recently, Sicher (68) has demonstrated preferred formation of a cis-olefin in bimolecular elimination from a non-cyclic substrate. He found that the reaction of 5-nonyltrimethylammonium ion with methoxide ion in methanol yielded 94 per cent of the cis-olefin in the cis-trans mixture. A fully coupled E2 reaction should give preferentially the trans-olefin because of the lesser eclipsing of the R groups in transition state XXIII than in XXIV. Sicher prefers an Elcb-like transition state, XXV, where the non-bonded interactions are smaller than in XXIII and XXIV since the bulky onium group is now flanked by



XXIII



XXIV

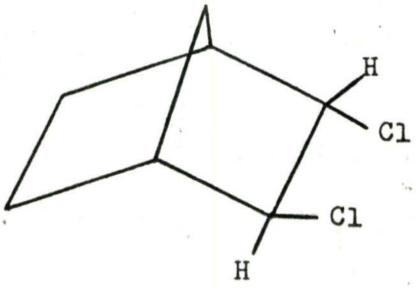


XXV

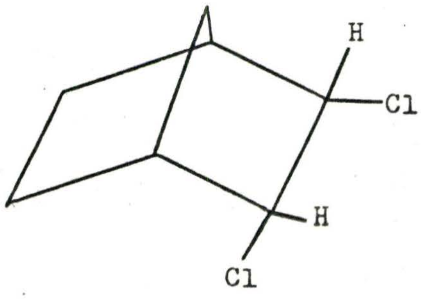
$Y = -\overset{+}{N}(CH_3)_3$

hydrogen atoms. Thus, the choice of this transition state, XXV, allows Sicher to conclude that the substrate sacrifices the advantages of antiperiplanarity for a sterically less encumbered transition state.

Similarly, studies on the cis- and trans-isomers of 2,3-dihalonorbornanes, which have a rigid conformation, have shown that in this system cis-elimination is also more favourable than trans-elimination. Cristol (56,69,70,71) found that trans-2,3-dichloronorbornane (XXVI) loses HCl under the influence of sodium 1-pentoxide faster than does its isomer, endo-cis-2,3-dichloronorbornane (XXVII) and he suggested that perhaps the carbanion mechanism was operative for these and related reactions. Recently, however, LeBel (72) has obtained evidence that both the cis- and trans-eliminations of bicyclic compounds proceed by a concerted pathway. He found that the entropies and enthalpies of activation vary in the same direction for the series where the halogen substitution is 1,2-dibromo, 1-bromo-2-chloro, 1,2-dichloro, regardless of whether a cis- or a trans-elimination course is followed. This trend indicates that both isomers are reacting via the same mechanism and LeBel concludes, after making



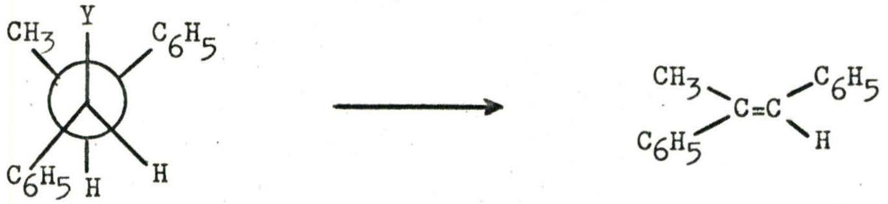
XXVI



XXVII

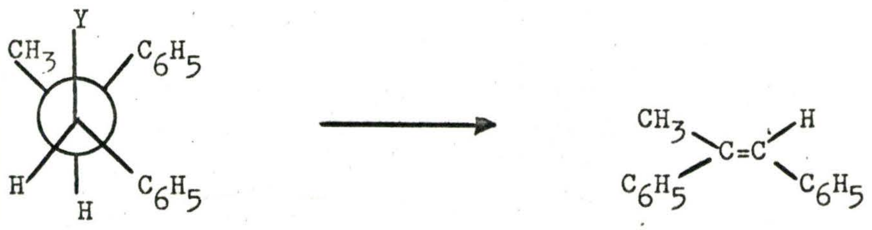
comparisons with kinetic data obtained with simple 1,2-dihalides which undergo elimination by concerted processes, that both isomers react by an E2 rather than an E1cb mechanism.

Studies of eclipsing effects (73) have provided more evidence that the degree of bond-breaking and bond-forming can be variable at the transition state. Normal *trans*-elimination from *threo*- and *erythro*-isomers of 1,2-diphenyl-1-propyl derivatives leads to *trans*- and *cis*-α-methylstilbene, respectively (equations 40 and 41). Since the stereoisomeric reactants should differ little in stability, while the *trans*-olefin is considerably more stable than is the *cis*, Cram *et al*. suggested that a reaction in which the transition state resembles product should proceed much faster with the *threo*-isomer than with the *erythro*. On the other hand, there should be little



(40)

threo



(41)

erythro

difference in rate between the diastereomers for reactions in which there is very little double bond formation at the transition state, i.e., transition states XX and XXII, page 33. Both the bromide and the chloride with ethoxide ion in ethanol show $k^{threo}/k^{erythro}$ ratios near unity, and it was concluded that the transition state has a high degree of carbonium ion character since halogen is generally regarded as a good leaving group. Changing to the trimethylammonium ion, a poor leaving group, on the other hand, raises the ratio to fifty-seven, which was interpreted to be a result of eclipsing in a transition state having a considerable degree of double bond character.

A study of the electronic effect of substituents on reaction rate has been used to shed light on the nature of the transition state. This criterion is illustrated by rate studies on the 2-phenylethyl system, where electronic effects can be varied without steric complications by placing <u>meta</u>- and <u>para</u>-substituents on the phenyl ring.

The reactions of <u>m</u>- and <u>p</u>-substituted benzene derivatives can often be correlated by the Hammett equation (74,75), equation 42,

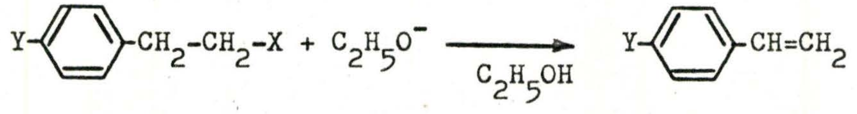
$$\log k/k_o = \rho\sigma \qquad (42)$$

where k is the rate or equilibrium constant for the substituted, and k_o the rate or equilibrium constant for the unsubstituted compound. The parameter, σ, is characteristic only of the substituent and represents the ability of the group to attract or repel electrons. It is defined as

$$\sigma = \log\left(\frac{k\ x\text{-}C_6H_4\text{-}COOH}{k\ C_6H_5COOH}\right) \qquad (43)$$

where $k\ x\text{-}C_6H_4\text{-}COOH$ and $k\ C_6H_5COOH$ are the ionization constants for the substituted and unsubstituted benzoic acids, respectively. The second parameter, ρ, is characteristic of the reaction series in question and is a measure of the sensitivity of the reaction to ring substitution. It follows from equation 42 that ρ is unity for the ionization of benzoic acids. Since σ is positive for electron-withdrawing and negative for electron-repelling substituents, ρ will be positive if the reaction is favoured by electron withdrawal. Further, electron-withdrawing substituents should favour reactions in which there is an increase in electron density at the reaction site in the transition state, and hinder reactions for which the converse is true. In the 2-phenylethyl system, the sign and magnitude of ρ, therefore, provide a measure of the electron density at the β-carbon in the transition state relative to the ground state.

Values of ρ for reaction of ring-substituted β-phenylethyl derivatives with ethoxide ion, equation 44, have been determined for different leaving groups X and are given in Table II. It can be seen



(44)

Table II

Hammett Reaction Constants for the Reaction of 2-Arylethyl Derivatives with Sodium Ethoxide in Ethanol at 30°

Leaving group, X	ρ	Reference
I	+2.07	76
Br	+2.14	76
OTs	+2.27	14
Cl	+2.61	11
SMe_2	+2.64	77
F	+3.13	11
NMe_3	+3.77	53

that the magnitude of ρ increases as the leaving tendency of the group-X becomes progressively poorer, indicating that this structural change results in an increasing release of electron charge at the β-carbon at the transition state. An interpretation of this result is that as the leaving group becomes poorer, the pathway of lowest energy is that in which the C-X bond is ruptured less and the C-H bond more at the transition state.

The conclusions arrived at from a study of the Hammett equation and of orientation effects shed light on the overall quality of the transition state. A study of kinetic isotope effects, however, can allow one to focus attention on one particular bond in the transition state. The C-H bond can be examined by using deuterium or tritium substitution while the C-X bond can be studied using heavy element isotope effects, for example, nitrogen (3), sulfur (78) or carbon (79) isotope effects. Qualitative interpretation of the magnitude of the leaving group isotope effect appears to be quite straightforward. The size of this effect depends on the extent to which the composite force constant of the C-X bond is decreased in going from the initial to the transition state (80). In other words, the X-isotope effect can be expected to increase regularly in a reaction series with the extent of bond weakening in the transition state.

The magnitude of the hydrogen-deuterium isotope effect, however, is not quite as easy to interpret. If one treats the E2 reaction as a simple proton transfer, equation 45, then it has been

$$B + HA \longrightarrow \left[B\text{---}H\text{---}A\right] \longrightarrow BH + A \qquad (45)$$

shown by Westheimer (2), if certain assumptions are made, that the magnitude of the hydrogen-deuterium isotope effect is at a maximum when the proton is one-half transferred from A to B at the transition state. He considered that low values for the isotope effect will result when H is more tightly bonded to A than to B or *vice versa.* This is shown in Fig. 1 where the degree of proton transfer is plotted against the magnitude of the hydrogen-deuterium isotope effect. Very recently,

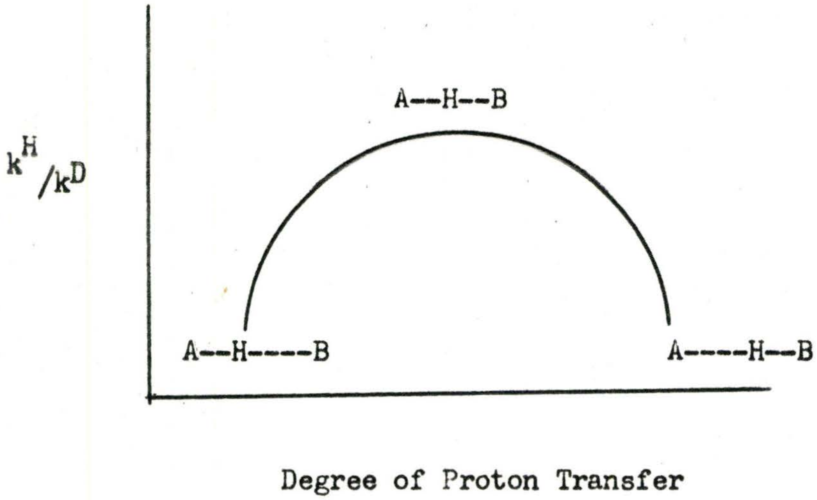


Fig. 1.

other interpretations have been given to the variation in hydrogen isotope effects in reaction series and these will be discussed in the next section of this thesis, along with a more detailed discussion of Westheimer's work.

The variation in the magnitude of the hydrogen deuterium isotope effect (k^H/k^D) with respect to the leaving group has been studied by Saunders and Edison (81) for the reaction of 2-phenylethyl derivatives with sodium ethoxide in ethanol, equation 46. The results are shown in Table III. It is seen that the value for k^H/k^D increases

$$C_6H_5\text{-}CD_2\text{-}CH_2\text{-}X + EtO^- \xrightarrow{EtOH} C_6H_5\text{-}CD{=}CH_2 + X^- + EtOD \qquad (46)$$

Table III

Isotope Effects in the Elimination Reaction of

2-Phenylethyl Derivatives in Ethanol at 30° (81)

Leaving Group	k^H/k^D
Br	7.1
OTs	5.7
SMe_2	5.1
NMe_3	3.5*

* Estimated from a value of 3.0 at 50°.

from 3.5 when trimethylamine is the leaving group to 7.1 when the departing species is bromide ion. This trend shows that the better leaving groups have associated with them larger values for the hydrogen-deuterium isotope effect. These results have been satisfactorily rationalized in terms of the Westheimer hypothesis by assuming that proton transfer at the transition state for the entire series is past the half-way point and most nearly complete for the poorest leaving group, $-\overset{+}{N}(CH_3)_3$. This interpretation of the variation in H/D effects with leaving group is in agreement with the conclusion reached on the basis of the ρ values shown in Table II.

There have been only two studies on the leaving group isotope effects on the β-phenylethyl system, one by Saunders and Asperger (78) for the sulfonium ion and one by Ayrey and Bourns (3) for the ammonium system. The results are given in Table IV. The values of 0.9 per cent for the N^{14}:N^{15} effect for the ammonium compound and 0.15 per cent for the S^{32}:S^{34} effect for the sulfonium compound led Ayrey and Bourns to conclude that $C-\overset{+}{N}$ bond rupture is more fully advanced in the transition state of the 2-phenylethyltrimethylammonium ion reaction than is $C-\overset{+}{S}$ bond rupture for the corresponding sulfonium salt.

Table IV

Comparison of Isotope Effects found in the E2 Reactions of Ammonium and Sulfonium Salts

Substrate	$(k^L/k^H-1)100$* at 60°	k^H/k^D	ρ
$PhCH_2CH_2\overset{+}{N}(CH_3)_3$	0.94	2.98[‡]	3.77[§]
$PhCH_2CH_2\overset{+}{S}(CH_3)_2$	0.15[†]	5.07[¶]	2.64[††]

* $k^L/k^H = k^{14}/k^{15}$ for the ammonium compound and k^{32}/k^{34} for the sulfonium compound.

[†] Hydroxide ion in water. Reference 78.

[‡] Ethoxide in ethanol at 50°. Reference 81.

[¶] Ethoxide ion in ethanol at 30°. Reference 81.

[§] Saunders and Bushman, reported in Reference 24.

[††] Ethoxide ion in ethanol at 30°. Reference 82.

The results of the leaving group isotope effect study for the ammonium and sulfonium salts, when considered with the relative magnitude of the H/D isotope effects and the Hammett ρ values in the two systems, have allowed Ayrey and Bourns to draw certain conclusions with respect to the extent of proton transfer to base in the transition state of these reactions (see Table IV). Since both the leaving group isotope effects and the Hammett ρ values are greater for the reaction of the ammonium salt more electron charge must be released from the C-H bond at the transition state in this salt than in the sulfonium salt. In other words, proton transfer to base must be more complete in the former. On the basis of the Westheimer hypothesis, a greater extent of proton transfer at the transition state will result in an increase in the H/D effect if for the two reactions the proton is less than half-transferred in the transition state (left-hand side of curve of Fig. 1), a decrease in the H/D effect if the proton is more than half-transferred (right-hand side of curve of Fig. 1). Since the hydrogen-deuterium isotope effect is considerably smaller for the ammonium salt elimination, 3.0 compared to 5.1, Ayrey and Bourns concluded that for the ammonium salt reaction, and very likely for the sulfonium salt as well, the proton is more than half-transferred at the transition state. This conclusion agrees with the results of Thornton (83) who found that the isotope effect for DO^- in D_2O vs. HO^- in H_2O as attacking bases gave a value of k^D/k^H at 80° of 1.79 for the 2-phenylethyltrimethylammonium ion. Thornton considered that this large effect was indicative of a transition state which is product-like, in other words, a transition state which has a larger H-O than C-H stretching force constant.

Ayrey and Bourns (3) went on to compare the relative magnitudes of the isotope effects in the reactions of 2-phenylethyltrimethylammonium ion and of ethyltrimethylammonium ion with base. They obtained a value of 1.7 per cent at 60° for the nitrogen isotope effect with the ethyl compound and a value of 0.9 per cent at 60° for the β-phenylethyl salt. These effects indicate that $C-\overset{+}{N}$ bond rupture has progressed to a greater degree at the transition state for the ethyl compound.

The hydrogen-deuterium isotope effect for these two substrates have been measured by other workers - 3.0 has been found for the β-phenylethyl compound with EtO^- in EtOH (81) and 3.9 for the reaction of the ethyl compound with OH^- in diethylene glycol at 137° (34). The latter value would correspond to an effect of 5-6 at 60°. Although a direct comparison between these two results is not possible because different bases and solvents were used, it would seem justifiable to conclude that the hydrogen-deuterium effect is significantly larger for the ethyl compound. On the basis of the conclusion that the proton is more than one-half transferred to base at the transition state for an ammonium salt elimination reaction, it follows that the reactant which gives the lower isotope effect, the β-phenylethyl compound has its proton transferred more to base at the transition state. Ayrey and Bourns concluded, therefore, that their results provide evidence for the hypothesis that, for reactants of the same type, any structural factor 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 in the transition state than would be the case in the absence of this factor.

The conclusions of Ayrey and Bourns with respect to the two ammonium salts depend to a large extent on the magnitude of the hydrogen-deuterium isotope effect obtained for the ethyltrimethylammonium ion. There is, however, considerable uncertainty with respect to this value. Recently, Simon (84) has measured both the intra- and intermolecular tritium isotope effects for the reaction of this ion with ethoxide in ethanol at 60°C and has obtained values which were very much less than would be expected on the basis of the deuterium results in diethylene glycol at 137°C. Furthermore, converting Simon's results to a deuterium effect which can be directly compared to the deuterium effect of 3.0 at 50° found for the reaction of the β-phenylethyltrimethylammonium salt (see Table IV), one obtains a value of k^H/k^D for ethyltrimethylammonium ion of 2.1. In other words, Simon's results indicate that the presence of the phenyl group on the β-carbon causes an increase rather than a decrease in the hydrogen isotope effect. If this is so, then the conclusions of Ayrey and Bourns have no validity. Clearly, therefore, additional experimental work is required to resolve this difficulty. Furthermore, it should be emphasized that the reasoning of these authors depends to a large extent on Westheimer's hypotheses concerning the interpretation of the magnitude of the hydrogen-deuterium isotope effect. As mentioned previously in this section other treatments of the problem of hydrogen isotope effects in hydrogen transfer reactions have appeared recently and have an important bearing on this problem. These will be discussed in some detail in the following section.

Simon and Mullhofer (79) have also determined the C^{14} isotope effect (k_c^{12}/k_c^{14}) associated with the C^{14}-N^+ bond rupture for ethyltrimethylammonium ion and 2-(p-nitrophenyl)ethyltrimethylammonium ion. They obtained a value of $k_c^{12}/k_c^{14} = 1.06$ at 40° for the ethyltrimethylammonium ion and a value of $k_c^{12}/k_c^{12} = 1.026$ at 100°, which corresponds to a value of 1.03 at 40°, for the 2-(p-nitrophenyl)ethyltrimethylammonium ion. These results are compatible with the nitrogen-15 isotope effect results of Ayrey and Bourns for the ethyl and β-phenylethyl substrates and show that $C-N^+$ bond rupture is more advanced at the transition state for the alkyl compound than for the β-aryl compounds.

B. Isotope Effects

In this section of the thesis, the general theory of isotope effects in unidirectional processes will be discussed with particular emphasis being placed on Bigeleisen's contribution (85) to the development of this theory. The section will conclude with a discussion of hydrogen-deuterium isotope effects in hydrogen transfer processes as presented in the recent publications of Westheimer (2 .), Bader (86), Willi (87) and Bell (88).

On the basis of classical statistical mechanics, where kinetic energy follows the equipartition law and the distribution of the energies of molecules with temperature is given by the Boltzmann equation, there should be no chemical isotope effects in equilibrium processes. Classical theory, however, would allow a very small isotope effect in unidirectional reactions of higher order than one because the collision numbers of molecules are a function of their masses. Since chemical isotope effects of considerable magnitude do occur in both rate and equilibrium processes, these effects then must be a result of quantum phenomena.

The energy, E, of a molecule may be considered to be the sum of two independent terms, the translational energy, E_t, and the internal energy, E_i. The latter term may be expanded further as a sum of electronic energy, E_e, rotational energy, E_r, and vibrational energy, E_v. Thus,

$$E = E_t + E_i = E_t + E_e + E_r + E_v$$

According to quantum mechanics, all of these are quantized. The translational energy levels are very closely spaced and are considered to be continuous and hence classical. The electronic ground states for isotopic molecules are almost identical and in most chemical reactions the electrons are in their respective ground states. Electronic energy differences, therefore, cannot be considered as a source of isotope effects. Similarly, except for the hydrogen molecule and at very low temperatures, one can consider the rotational energy level distribution to be classical since the product 'kT' is large. The vibrational energy levels, however, are relatively far apart. The vibrational energy is normally, therefore, the only type of internal energy to be affected by quantum considerations and generally is the source of chemical isotope effects.

According to quantum mechanics the vibrational energy of a diatomic molecule, assuming that it behaves as a harmonic oscillator, which is very nearly true, is equal to $(n + \frac{1}{2})h\gamma$. In this expression, n is the quantum number and may be zero or any integer, h is Planck's constant, and γ is the fundamental vibration frequency of the molecule in the ground state. The frequency of such a harmonic oscillator is a function of the masses, m_1 and m_2, of the two atoms and is given by the equation:

$$\nu = \frac{1}{2\pi} \sqrt{f/\mu} , \qquad (47)$$

where f is the force constant between the atoms and μ is the reduced mass, defined as $\frac{1}{\mu} = \frac{1}{m_1} + \frac{1}{m_2}$. 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 a similar way.

The vibrational energy of a molecule, being dependent on frequency, is therefore a function of the masses of the atoms which constitute the molecule. In the lowest energy level, where the quantum number is zero, there will be an internal energy difference between two isotopic diatomic molecules of $\frac{1}{2} h(\nu_1 - \nu_2)$, where ν_1 and ν_2 are the vibrational frequencies for the light and heavy molecules, respectively. This energy difference is known as the zero-point energy difference. The situation for polyatomic molecules, though more complex, is essentially the same.

A theory of chemical isotope effects in unidirectional processes has been developed by Bigeleisen (85) using the hypothesis of the absolute rate theory. According to this theory, for reactions in which A_1, B, C, --- react to give P_1, and A_2, B, C, --- give P_2, where A_1 and A_2 are isotopic molecules, one can express the rate constants as follows:

$$k_1 = K_1 \frac{C_1^{\ddagger}}{C_{A_1} C_B ---} \left(\frac{kT}{2\pi m_1^*}\right)^{\frac{1}{2}} \frac{1}{\delta_1} \qquad (48)$$

$$k_2 = K_2 \frac{C_2^{\ddagger}}{C_{A_2} C_B} \text{ --- } \left(\frac{kT}{2\pi m_2^*}\right)^{\frac{1}{2}} \frac{1}{\delta_2} \qquad (49)$$

where K_1 and K_2 are transmission coefficients, $\ddagger$ indicates the activated complex, m* is the effective mass of the activated complex moving along the reaction co-ordinate, and δ is the length of the top of the potential energy barrier along the reaction co-ordinate. The transmission coefficients simply represent the fraction of transition states passing the energy barrier in the forward direction which will lead to completed reaction. There are theoretical reasons for believing that the transmission coefficients should 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 surface, interatomic distances and vibrational force constants are assumed to be unchanged by isotopic substitution. It therefore appears valid to make the assumption that $\frac{\delta_2}{\delta_1} = 1$ and hence,

$$\frac{k_1}{k_2} = \frac{C_{A_2}}{C_{A_1}} \quad \frac{C_1^{\ddagger}}{C_2^{\ddagger}} \left(\frac{m^*_2}{m^*_1}\right)^{\frac{1}{2}} \qquad (50)$$

The concentrations of the various molecular species in equation 50 may be replaced by the complete partition functions, Q_{A_1} and Q_{A_2}, equation 51.

$$\frac{k_1}{k_2} = \frac{Q_{A_2}}{Q_{A_1}} \quad \frac{Q_1^{\ddagger}}{Q_2^{\ddagger}} \left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \qquad (51)$$

Bigeleisen and Mayer (89) have expressed the ratio of the partition functions for isotopic molecules in terms of a function f, which is defined as

$$f = \frac{Q_2}{Q_1} \prod_i \left(\frac{m_{1j}}{m_{2j}}\right)^{3/2} , \tag{52}$$

where the m_j's refer to the masses of the isotopic atoms in the isotopic molecules. Using this new "partition function" one can now express the ratio of the rate constants for isotopic molecules by equation 53,

$$\frac{k_1}{k_2} = \left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{f}{f^{\ddagger}} , \tag{53}$$

the terms involving the isotopic atomic masses having cancelled. It has been shown (89) that the quantity f is a function of molecular vibrations only and takes the form

$$f = \frac{S_1}{S_2} \prod_i^{3n-6} \frac{u_i}{u_i+\Delta u_i} \cdot e^{\Delta u_i/2} \cdot \frac{1-e^{-(u_i+\Delta u_i)}}{1-e^{-u_i}} \tag{54}$$

where u_i equals $\frac{h\nu_i}{kT}$ and refers to the heavier isotopic molecule, $u_i + \Delta u_i$ is the corresponding quantity for the lighter molecule, and the s terms are symmetry numbers which indicate the number of indistinguishable positions for the isotopic molecules in question. The product in equation (54) is taken over all the 3n-6 fundamental vibrational frequencies of the molecule. A similar expression may be written for $f^{\ddagger}$, only in this case one of the vibrational modes is now imaginary and corresponds to motion along the co-ordinate of decomposition. Substituting for f and $f^{\ddagger}$ in equation 53 leads to

$$\frac{k_1}{k_2} = \frac{S_1}{S_2} \cdot \frac{S_2^{\ddagger}}{S_1^{\ddagger}} \left(\frac{m_2^*}{m_1^*}\right)^{\frac{1}{2}} \frac{\prod\limits_{i}^{3n-6} \frac{u_i}{u_i+\Delta u_i} \cdot e^{\Delta u_i/2}\, \frac{1-e^{-(u_i+\Delta u_i)}}{1-e^{-u_i}}}{\prod\limits_{i}^{3n'-6} \frac{u_i}{u_i + \Delta u_i} \cdot e^{\frac{\Delta u_i^{\ddagger}}{2}} \cdot \frac{1-e^{-(u_i^{\ddagger}+\Delta u_i^{\ddagger})}}{1-e^{-u_i^{\ddagger}}}} \qquad (55)$$

For compounds of hydrogen and deuterium, u_{Di} may be substituted for u_i and $u_{Hi}-u_{Di}$ for Δu_i to give equation 56. If it is assumed that

$$\frac{k^H}{k^D} = \left(\frac{m^*_D}{m^*_H}\right)^{\frac{1}{2}} \left(\frac{S_H/S_H^{\ddagger}}{S_D/S_D^{\ddagger}}\right) \frac{\prod\limits_{i}^{3n-6} \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \cdot \frac{1-e^{-u_{Hi}}}{1-e^{-u_{Di}}}}{\prod\limits_{i}^{3n-6} \frac{u_{Di}^{\ddagger}}{u_{Hi}^{\ddagger}} \cdot e^{\frac{u_{Hi}^{\ddagger}-u_{Di}^{\ddagger}}{2}} \cdot \frac{1-e^{-u_{Hi}^{\ddagger}}}{1-e^{-u_{Di}^{\ddagger}}}} \qquad (56)$$

the isotopic reactant serves as a model for the transition state, as in a unimolecular decomposition, and also that vibrations which do not involve important motion of isotopic hydrogen are unchanged during reaction, then only three vibrations (one stretching and two bending) for the initial state and two bending modes for the transition state must be taken into account in calculating the isotope effect. Furthermore, since the vibrational frequency of most bonds to hydrogen are >1000 cm^{-1}, the e^{-u_i} terms in equation 56 for the initial state are very small relative to unity at ordinary temperatures and may be neglected. Also, if there is no change in the two bending frequencies in going from the initial state to the transition state, the terms for these frequencies in the transition state cancel the corresponding terms in the initial state. Equation 56 then becomes

$$\frac{k^H}{k^D} = \left(\frac{S_H/S^{\ddagger}_H}{S_D/S^{\ddagger}_D}\right)\left(\frac{m^*_D}{m^*_H}\right)^{\frac{1}{2}} \cdot \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \tag{57}$$

In equation 57, u_i refers only to the stretching frequency which is lost in going from the initial to the transition state. Since in almost any molecule H-X, $m_H \ll m_X$ it follows that

$$\frac{u_{Di}}{u_{Hi}} \approx \left(\frac{m^*_H}{m^*_D}\right)^{\frac{1}{2}}$$

Therefore, equation 57 reduces to

$$\frac{k^H}{k^D} = \left(\frac{S_H/S^{\ddagger}_H}{S_D/S^{\ddagger}_D}\right) \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \tag{58}$$

If, on the other hand, the bending frequencies of the bond being broken were to approach zero in the transition state, a different simplification can be made.

Firstly, $$\lim_{u^{\ddagger}_i \to 0} \frac{1-e^{-u^{\ddagger}_{Hi}}}{1-e^{-u^{\ddagger}_{Di}}} = \frac{u^{\ddagger}_{Hi}}{u^{\ddagger}_{Di}}$$

Secondly, $$\lim_{u^{\ddagger}_i \to 0} e^{\frac{u_{Hi}-u_{Di}}{2}} = 1$$

Equation 56, now becomes,

$$\frac{k^H}{k^D} = \left(\frac{S_H/S^{\ddagger}_H}{S_D/S^{\ddagger}_D}\right)\left(\frac{m^*_D}{m^*_H}\right)^{\frac{1}{2}} \prod_{i}^{3} \frac{u_{Di}}{u_{Hi}} \cdot e^{\frac{u_{Hi}-u_{Di}}{2}} \tag{59}$$

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 $(\frac{m^*_D}{m_H^*})^{\frac{1}{2}}$, 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 59 becomes

$$\frac{k^H}{k^D} = (\frac{S_H/S_H^{\ddagger}}{S_D/S_D^{\ddagger}}) \cdot \frac{m_H}{m_D} \cdot \sum_{i}^{3} e^{\frac{u_{Hi}-u_{Di}}{2}} \qquad (60)$$

In equations 58 and 60 the frequencies of the deuterated compound, if unknown, can be calculated from the corresponding frequencies in the lighter molecule making use of the relationship,

$$\frac{u_{Hi}}{u_{Di}} = \frac{\nu_H}{\nu_D} = (\frac{m_D}{m_H})^{\frac{1}{2}} \qquad (61)$$

Equation 58 predicts $k^H/k^D \sim 7$ at room temperature for C-H bond rupture and many hydrogen isotope effects are close to this figure (90). Equation 59 predicts k^H/k^D values greater than 7 and higher values are indeed observed in some reactions.

In a number of reactions, the observed deuterium isotope effect has been found to be less than that calculated using the preceding assumptions. Westheimer (2), in a recent review article, has suggested a theoretical justification for such results based on the fact that most reactions involving hydrogen are three-centre displacement processes of the type

$$\mathrm{AH} + \mathrm{B} \rightleftharpoons \left[\mathrm{A}\text{---}\mathrm{H}\text{---}\mathrm{B}\right] \longrightarrow \mathrm{A} + \mathrm{HB} \qquad (62)$$

where $\left[\mathrm{A}\text{--}\mathrm{H}\text{--}\mathrm{B}\right]$ is a linear transition state. He points out that if A--H--B were a linear molecule rather than a transition state, it would have two stretching vibrations, a symmetrical and an antisymmetrical one. Neither of these corresponds to the stretching vibration

$$\leftarrow \mathrm{A} \quad \mathrm{H} \quad \mathrm{B} \rightarrow \qquad\qquad \leftarrow \mathrm{A} \quad \mathrm{H} \rightarrow \;\; \leftarrow \mathrm{B}$$

symmetric   antisymmetric

of A-H or B-H. Because the species is a transition state the antisymmetrical stretching mode is a translational mode leading to product formation. Consequently, there is no zero-point energy contribution associated with this mode. This is, however, not the case for the symmetrical mode which is a real vibration. Now if this vibration is truly symmetrical, there is no motion of the hydrogen atom and the frequency will be unaffected by isotopic substitution. Consequently, this vibrational, as well as the antisymmetrical mode, will make no contribution to a zero-point energy difference in the transition state. This is a case which should give rise to a large isotope effect because the full zero-point energy difference of the ground state vibrational stretching mode of the C-H and C-D bonds will contribute to the activation energy difference for the reaction of the isotopic molecules ($E_D'-E_H'$ in Fig. 2). When the strengths of the partial bonds of H to A and to B are not equal, however, the so-called "symmetrical" vibration will no longer consist merely of the motion of A and B; the hydrogen atom will move as well. Therefore, the vibration frequency will depend to some extent on the mass of the central atom, i.e., on whether it is hydrogen or deuterium. The "symmetric" vibration will have a zero-point energy for hydrogen different from that for deuterium, and this difference will decrease the contribution of the ground state zero-point energy difference to the isotope effect. Consequently, the isotope effect will be smaller than in the previous case. This is shown in Fig. 2 where the activation energy difference E_D-E_H is less than $E_D'-E_H'$.

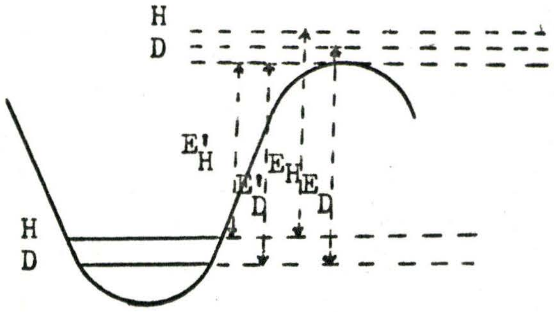
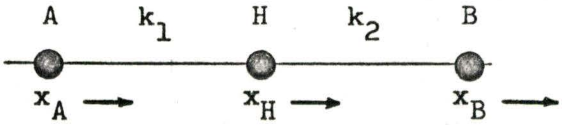


Fig. 2 - Zero-point energies and hydrogen-isotope effect for a proton transfer reaction

According to this treatment the maximum H/D isotope effect should be found when the proton is one-half transferred from substrate (A) to base (B) at the transition state. This conclusion has already been shown diagramatically in Fig. 1 on page 42 of the thesis.

Westheimer has also developed his ideas on a quantitative basis using the following linear molecule for the transition state



where the groups A, H and B are in one-dimensional space and x_A, x_H and x_B are the displacement of these atoms from their equilibrium positions in the molecule. If the force constants for the stretching of the bonds between A and H and B and H are called k_1 and k_2, respectively, and β is the coupling constant between the stretching of these two bonds, it then can be shown that

$$m_A m_H m_B \lambda^3 - (m_A m_H k_2 + m_A m_B k_1 + m_A m_B k_2 + m_H m_B k_1 - 2m_A m_B \beta)\lambda^2 + (m_A + m_H + m_B)(k_1 k_2 - \beta^2)\lambda = 0 \qquad (63)$$

where m_A, m_H, m_B are the masses of the groups or atoms and $\lambda = 4\pi^2\gamma^2$.

Since A-H-B represents an activated complex rather than a molecule, absolute rate theory demands that a frequency be either zero or imaginary, i.e., one of the vibrations must become a translation. A zero frequency corresponds to a zero curvature of the potential energy surface at the top of the barrier and, for the sake of simplicity, Westheimer has made this assumption in his treatment. This condition, namely $\lambda = 0$, is met when the last term, $k_1k_2 - \beta^2$, of equation (63) is equal to zero, which requires that the coupling constant in the transition state be equal to the square root of the product of the two other force constants. With this assumption equation (63) becomes

$$\lambda = 4\pi^2 \nu^{\ddagger 2} = \frac{k_1}{m_A} + \frac{k_2}{m_B} + \frac{k_1 + k_2 - 2\sqrt{k_1 k_2}}{m_H} \qquad (64)$$

This equation shows the influence of isotopic mass upon the frequency (and hence upon the zero-point energy) of the symmetric vibration in the transition state.

When $k_1 = k_2 = k$, equation 64 becomes

$$\lambda = 4\pi^2 \nu^{\ddagger 2} = k\left(\frac{1}{m_A} + \frac{1}{m_B}\right) \qquad (65)$$

Since the mass of the hydrogen atom does not enter this expression, the frequency is unchanged on isotopic substitution and therefore, the zero-point energy for the two isotopic activated complexes will be the same. As stated earlier, this will result in a maximum isotope effect since the difference in activation energy for the two isotopic molecules will correspond to the full difference in the zero-point energies of their ground states.

If the force constants k_1 and k_2 are not equal, for example, $k_1 >\!>\!> k_2$, equation 64 reduces to equation 66:

$$\lambda = 4\pi^2 \nu_H^{\ddagger 2} = k_1\left(\frac{1}{m_A} + \frac{1}{m_H}\right) \qquad (66)$$

The mass of the hydrogen or deuterium atom now enters into the expression for the frequency of the "symmetrical" vibration. Furthermore, since m_A and m_B are usually large compared to the mass of either a hydrogen or deuterium atom, the frequencies $\nu_H^{\ddagger}$ and $\nu_D^{\ddagger}$ will be almost in inverse ratio to the square root of the masses of the isotopes.

The situation is similar if $k_2 >> k_1$. If the magnitude of $\nu^{\ddagger}_{H}$ is large, the difference between the zero-point energies of A-H-B and A-D-B may be as large as that between A-H and A-D, and the contribution of zero-point energy differences to the isotope effect may vanish.

Two assumptions are inherent in the Westheimer treatment. One is the assumption that the curvature of the potential energy surface is zero at the top of the barrier, which merely means curvature is negligible over a small distance at the top of the energy barrier. The second is that bending frequencies can be neglected as making a significant contribution to the isotope effect. Each of these assumptions have been examined by recent workers.

Willi and Wolfsberg (87) have pointed out that in slow organic reactions, where potential energy barriers are large, curvature will not be negligible and they have calculated the transition state force fields leading to the imaginary frequencies $\nu^{\ddagger}_{i}$ corresponding to negative curvature. The system for which these calculations were made was the proton or deuteron transfer from a group A of mass 18 (corresponding to H_2O) to a carbon atom of a group of mass 100. The initial state force constant, F_{AH}, for the OH stretch in H_3O^+ is 6.00 millidynes/A° and the force constant, F_{BH}, for the C-H bond in the product is 4.80 md/A° (91). It was then assumed that the force constants for the partial O-H and H-C bonds in the transition state, k_1 and k_2, respectively, can be expressed as a function of x, the relative amount of bond-making or bond-breaking as follows:

$$k_1 = 6.00\ (1 - x) + a \qquad \text{millidynes/A}^{\circ}$$

$$k_2 = 4.80\ (x) + b \qquad \text{millidynes/A}^{\circ}$$

where a and b are constants. A curvature parameter, d, was defined as equal to $k_1k_2 + \beta^2$. (Recall that Westheimer's treatment shows that this quantity is zero when zero curvature is assumed.) It was then postulated that the coupling constants β is zero when x is either zero (corresponding to no bond formation) or unity (corresponding to complete bond formation), from which it follows that $d = k_1k_2 = 4.80a = 6.00b$. Isotope effects were then calculated as a function of x and a. It was found, in agreement with Westheimer, that for zero curvature (a = 0), that k^H/k^D rises to a sharp maximum at $x \approx 0.55$, as shown in curve A in Fig. 3. When, however, the curvature is negative, the region of maximum k^H/k^D as a function of x becomes wider. This is shown in Fig. 3 for two values of a, namely, -1 and -4. It clearly follows from the results of this more refined treatment that one cannot make any definite conclusion concerning the

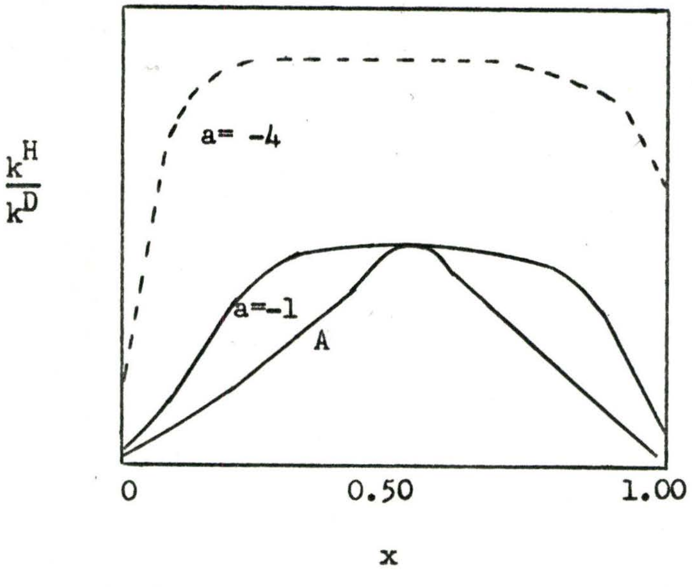


Fig. 3. k^H/k^D at 25°C vs. x (relative amount of bond making or bond breaking) as a function of the curvature parameter a ($d = 4.80a$).

relative amount of bond-making and bond-breaking at the transition state from a k^H/k^D value at a single temperature. Even for a very unsymmetrical transition state, a high value of k^H/k^D can result. It would also appear that the large variations which are experimentally observed in k^H/k^D in a reaction series cannot be a result of a change in the frequency of the symmetrical stretching vibration since no significant change in the frequency takes place over a broad spectrum of transition states differing in the relative extents of bond rupture and bond formation.

Bell (88) has reached similar conclusions from a calculation of the symmetrical stretching frequencies ν_1^H and ν_1^D for different relative values of k_1k_2 and β; that is for different negative curvatures at the potential energy barrier. He chose as his model a very unsymmetrical transition state such that $k_1 = 10\ k_2$. The results of these calculations are shown in Table V. It is seen that

Table V

Longitudinal Motions of the Transition State

$\lambda_1 = 4\pi^2\nu_1^2,\ k_1 = 10\ k_2,\ m_A = 12,\ m_B = 16$

$\beta/(k_1k_2)^{\frac{1}{2}}$	$m\ \lambda_1^H/k_1$	ν_1^H/ν_1^D
1	0.558	1.32
1.27	0.415	1.28
1.74	0.233	1.14
3.16	0.138	1.08

an increase in β results in a decrease in γ_1 and γ_1^H/γ_1^D, which means a decrease in the zero-point energy difference in the transition state and an increase in the isotope effect. Although it is difficult to predict a value of β corresponding to any real case, Bell suggests that the ratio $\beta/(k_1k_2)^{\frac{1}{2}}$ may be as large as the last value given in Table IV. If this is the case, then even for a very unsymmetrical transition state, the symmetrical vibration cannot account for the low values of k^H/k^D often observed and for the variation in a reaction series.

The theoretical calculations on the hydrogen-deuterium isotope effect for a proton-transfer reaction, which have just been discussed, do not include a consideration of bending frequencies. Bader (86), however, has argued that the bending frequencies in the transition state for a hydrogen-transfer reaction are more important in determining the difference in zero-point energies for isotopic species than are the symmetrical stretching frequencies. He justifies his conclusions with data from ground-state hydrogen bonded systems, which are used by him as models for the transition state.

The fundamental equation used by Bader in his treatment is that of Poisson (92)

$$k_{\parallel} + 2k_{\perp} = 4\pi\rho(H) = 4\pi(\rho_A(H) + \rho_B(H)) \qquad (67)$$

where $k_{\parallel}$ is the force constant for assymetric motion of the three-atom system A-H---B, $k_{\perp}$ is the force constant corresponding to each of the degenerate modes involving displacement of the proton perpendicular to the bond, and $\rho_A(H)$ and $\rho_B(H)$ are the electron densities at the position of the proton due to A and B, respectively. For a transition state, the asymmetric mode corresponds to motion along the reaction co-ordinate. Bader then makes the assumption of zero curvature of the potential surface at the region of the transition state, which is equivalent to assuming that $k_\parallel$ equals zero (vide supra). Equation 67 then reduces to equation 68

$$2k_\perp = 4\pi\rho(H) = 4\pi\left[\rho_A(H) + \rho_B(H)\right] \tag{68}$$

from which it is seen that the higher the electron density in the vicinity of the hydrogen atom, the greater the bending force constants, $k_\perp$, and hence the greater the contribution of this vibrational mode to the difference in zero-point energies for isotopic species in the transition state.

Bader has considered three cases for proton transfer, the simplest of which is that where a spherical charge density on both the acid and basic species is assumed. The degenerate frequencies, $\nu_\perp$, corresponding to the bending vibrations, as well as the distances r_a

$$\sim\text{O-H} + \text{O}^{\delta-} \longrightarrow \left[\text{O}\overset{r_a}{---}\text{H}\overset{r_b}{---}\text{O}\right]^{\delta-}$$

and r_b between the proton and each of the two oxygens were calculated for varying amounts of negative charge, δ^-. When $\delta = 1$, $\rho_A = \rho_B$ and the transition state is symmetrical. As the base strength is decreased by virtue of a smaller value of δ^-, r_b decreases and r_a increases, as does also the sum $r_a + r_b$, as shown in Table VI. The transition state becomes looser as a result of the lower electron density and, as a consequence, $\nu_\perp$ decreases. This is seen from the data in the last column of Table VI.

Table VI

Transition State Data for O-H + $O^{\delta -}$

ρ	r_a	r_b	$r_a + r_b$	$4\pi \rho_A(H)$	$4\pi \rho_B(H)$	$\nu_\perp$
1.0	2.32	2.32	4.64	0.1206	0.1206	1790
0.9	2.80	2.21	5.01	0.0233	0.1710	1600
0.8	3.10	2.25	5.35	0.0081	0.1468	1440

The second case is like the first except that the base density is polarized, i.e., the charge is not spherically symmetrical. This causes the base to be stronger than the base with spherical density,

$$\dot{O}H + O^{\delta -} \longrightarrow \left[O\text{--}H\text{--}O\right]^{\delta -}$$

(polarized) (polarized)

even though the total charge is the same. The results of these calculations are shown in Table VII. It is seen that the quantity $r_a + r_b$ at first decreases with a resulting increase in $\nu_\perp$ when ρ is made smaller. A further decrease in ρ causes an increase in $r_a + r_b$ with a resulting decrease in $\nu_\perp$.

The consequence with respect to the magnitude of the hydrogen-deuterium isotope effect for each of these two cases is readily seen from the values of $\nu_\perp$ in the two Tables. It is evident that for all the unsymmetrical transition states $\nu_\perp$ is large, resulting in small isotope effects for these reactions. This conclusion is in agreement with that of Westheimer who also predicts low values for the isotope effects when the transition state is unsymmetrical, but for a different

Table VII

Transition State Data for O-H + $O^{\delta -}$ (polarized)

δ	r_a	r_b	$r_a + r_b$	$4\pi\rho_A(H)$	$4\pi\rho_B(H)$	$\nu_{\perp}$
1.0	2.16	2.79	4.95	0.2068	0.0277	1762
0.54	2.22	2.24	4.46	0.1680	0.1217	1960
0.50	2.57	2.05	4.62	0.0515	0.2438	1980
0.44	2.80	2.05	4.85	0.0233	0.2438	1870
0.36	3.00	2.07	5.05	0.0116	0.2260	1780

reason.

In both of the previous cases, it has been assumed that the density distribution in the acid (O-H) remains fixed at the transition state, regardless of the strength of the base $O^{\delta -}$. But in most real situations more than "one bond" is changing at a time and the charge density is transferred to some other part of the molecule, for example, to form the π bond as in an elimination reaction. Bader argues that this will tend to equalize the charge density between hydrogen and each of the two bases with the result that $r_a \simeq r_b$. In other words, the transition state remains close to the symmetrical, regardless of the strength of the base $O^{\delta -}$. In Table VIII are given data for such symmetrical transition states for the spherical O^- model with varying total charge (δ). It is seen that the values of $\nu_{\perp}$ range from 2000 cm^{-1} to ∼700 cm^{-1}, which should lead to a whole range of isotope effects. In other words, the present model predicts that the magnitude of isotope effects should depend not so much upon the symmetry of the transition state but upon the tightness or looseness of the hydrogen-

Table VIII

Date for Symmetrical Transition States With Varying Total Charge

δ	r	$r_a + r_b$	$4\pi\rho(H)$	$\nu\perp$
1.0	2.32	4.64	0.2411	1790
0.5	2.58	5.16	0.0925	1100
0.4	2.67	5.34	0.0668	940
0.3	2.78	5.56	0.0449	770

bonding in the transition state, which in turn depends upon electron density.

Bader points out that a maximum isotope effect, as predicted by the previous theories, corresponding to a symmetrical transition state, has never been observed in a system in which the acid or base strength is varied. Bader's model, however, predicts for the symmetrical transition states where the electron density can be readily delocalized, isotope effects which simply decrease as the base is made stronger and the proton becomes more tightly bound in the transition state. This receives experimental support from a study of the decomposition of substituted β-keto acids (93), where substituents which increase the basicity of the keto oxygen cause the isotope effect to undergo a regular decrease.

A basic assumption inherent in the treatments which have so far been presented in this review is that the reacting system in passing over the energy barrier behaves classically; in other words, that there is no contribution to the isotope effect from what has come to be known as the tunnel effect. A short discussion of the origin of this effect and the means which have been used to detect it will now be given. The approach will follow closely that of Bell (94), who has given a detailed treatment of the subject.

The path followed by a particle moving along the reaction co-ordinate in the vicinity of the transition state goes through a maximum, which is referred to as an energy barrier. If the particle behaves according to classical mechanics, there is a minimum amount of energy (the energy of activation) which this particle must have in order to pass over this barrier. This situation is illustrated in Fig. 4 where a particle of mass m and energy w is moving toward an energy barrier of height E (energy of activation).

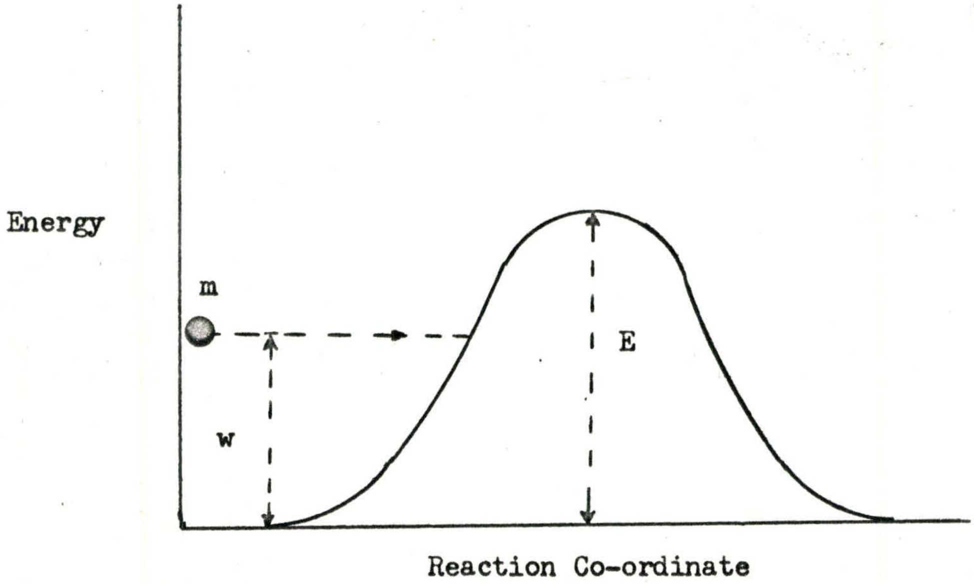


Fig. 4. Path of Particle Along the Reaction Co-ordinate

If $w < E$, the probability that the particle will reach the other side of the barrier is zero; if $w > E$, the probability is one. Quantum theory, on the other hand, states that the probability is a continuous function of w. The dotted and full lines in Fig. 5 shown the dependence of the probability, G, on w in the classical and quantum cases, respectively. Not only does quantum theory predict a finite probability for $w < E$, but there is also a probability that a particle of $w > E$ will be reflected back.

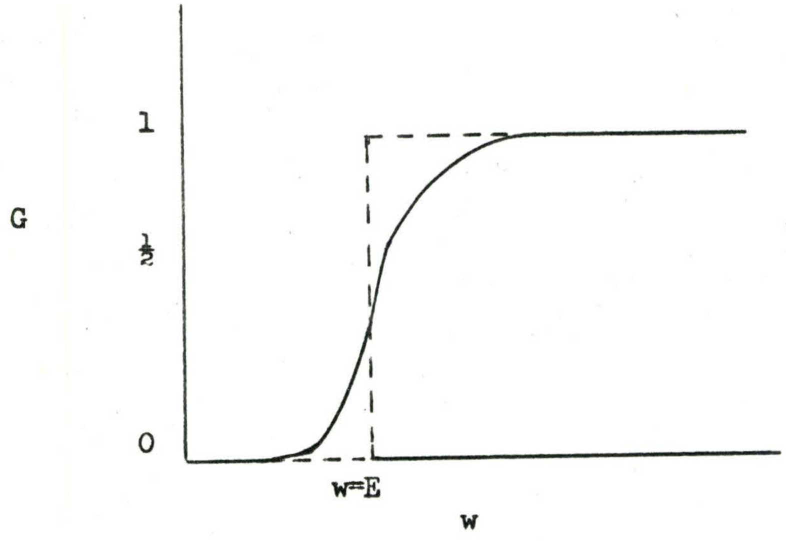


Fig. 5. Probability of Tunneling in Classical and Quantum Cases

The De Broglie equation assigns a wavelength $\lambda = h/mv$ to a particle of mass m and velocity v, and it is therefore to be expected that the largest deviations from classical behaviour will occur for particles of low mass. Indeed, tunneling has been observed in cases involving electrons and high energy α-particles (95,96). In most types of chemical reaction, where the motion of nuclei is involved as well as the motion of electrons, it is clear that appreciable deviations from classical behaviour can only be expected for light nuclei, notably protons. The deuterium nucleus is twice as heavy as that of protium and therefore would be expected to exhibit nearly classical behaviour. If protons tunnel to a greater extent than do deuterons, then the rate of reaction of a hydrogen compound should be increased by this effect more than is the rate of the corresponding deuterium compound and, as a consequence, k^H/k^D should be larger than that predicted on the basis of zero-point energy considerations alone.

There are other experimental consequences of tunneling besides rate and isotope effects. If tunneling is occurring in a reaction, the energy of activation for that reaction will be lower than that calculated from classical theory. Also E_D-E_H will be larger than the classical prediction because tunneling is more prominent in the protium case. (A classical limit of $\Delta E = 1.15$ k cal/mole has been calculated by considering only the stretching frequencies of the C-H and C-D bonds (2).)

An Arrhenius plot of log k vs. 1/T for both the quantum and classical cases, i.e., with and without the tunnel correction, is shown in Fig. 6. The true intercept of either plot at $T = \infty$ is

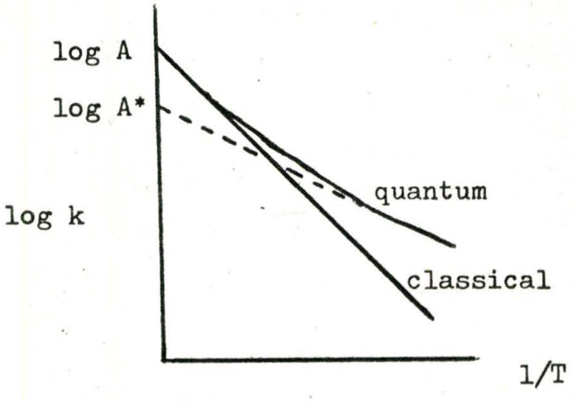


Fig. 6. Temperature Variation of Reaction Velocity in Classical and Quantum Cases

log A. It is seen, however, that when this extrapolation is made from experimental measurements taken over a finite temperature range, it can lead to a lower value of A, say A*, because of the curvature of the plot for a system showing quantum mechanical tunneling. Bell has predicted limits, neglecting tunneling, for A^{*H}/A^{*D} of 0.5 to 1, and therefore, a value of A^{*H}/A^{*D} which is appreciably below this range will provide strong evidence for tunneling.

Several groups of workers have obtained experimental results which strongly indicate the presence of tunneling in their systems. Bell, Fendley and Hulett (97) have measured Arrhenius parameters for the isotope effect in the base-catalyzed bromination of 2-carboethoxy-cyclopentanone-2-d. The results are given in Table IX. The experimental values of A^{*H}/A^{*D} and E_D-E_H, obtained when D_2O and $CH_2ClCO_2^-$ are the catalysts, appear to be normal. It is seen, however, that when fluoride ion is the catalyst the quantity A^{*H}/A^{*D} is smaller by a factor of ten than the value expected from the simple picture. Also, the value of

Table IX

Observed Arrhenius Parameters in the Bromination of 2-Carboethoxy-cyclopentanone

Catalyst	D_2O	$CH_2ClCO_2^-$	F^-
k^H/k^D	3.24	3.91	2.66
A^{*H}/A^{*D}	0.44 ± 0.05	0.35 ± 0.05	0.042 ± 0.003
E_D-E_H (k cal/mole)	1.21 ± 0.08	1.45 ± 0.08	2.44 ± 0.10

$E_D - E_H = 2.44$, obtained when fluoride ion is the catalyst, is significantly greater than the value corresponding to the difference in zero-point energies for the stretching vibrations of a C-H and C-D bond. The results obtained for the fluoride ion catalyzed reaction strongly indicate the presence of tunneling.

A relation between steric hindrance to reaction and tunneling has been demonstrated by Funderburk and Lewis (98) for the base-catalyzed iodination of 2-nitropropane. Their results are shown in Table X. The abnormally large isotope effects in the reactions catalyzed by 2,6-lutidine and 2,4,6-collidine, and the large differences in the energies of activation and the A factors in the reaction catalyzed by 2,4,6-collidine, were considered by the authors to provide strong evidence for tunneling. They suggest that for reactions in which the base has a high steric requirement the potential energy barrier is high and therefore readily penetrated.

Table X

Date of Lewis and Funderburk for the Pyridine Base-Catalyzed Iodination of 2-Nitropropane in Aqueous t-Butyl Alcohol at 24.88°C

Base	k^H/k^D	E_D-E_H (k cal/mole)	A^{*H}/A^{*D}
pyridine	9.84	-	-
2-picoline	10.6	-	-
2,6-lutidine	24.1	-	-
2,4,6-collidine	24.2	3.03	0.146

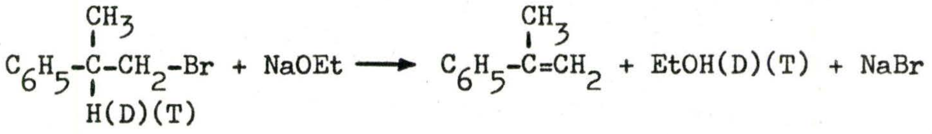
Perhaps the most definitive test for tunneling in any reaction is provided by a comparison of the deuterium and tritium isotope effects.

Swain (99) has shown that on the basis of zero-point energy considerations alone the following relationship should hold between the two effects

$$k^H/k^T = (k^H/k^D)^{1.442} \qquad (69)$$

Funderburk (100) has found that the isotope effects, $k^H/k^D = 8.39$ and $k^H/k^T = 10.6$, for the acid-catalyzed bromination of α-methyldesoxybenzoin deviate considerably from this relationship. Indeed, if one assumes that tunneling is negligible in the reactions of the deuterated and tritiated compounds because of the mass of the heavier isotopic atoms, then in order to fit the two experimental isotope effects to this equation it would be necessary for the reaction of the protium compound to be five times faster than is classically expected. It was therefore concluded that tunneling is important in the reaction of the protium compound.

Even stronger evidence for tunneling has been provided by Shiner and Martin (101) who determined the Arrhenius parameters for the reaction of 1-bromo-2-phenylpropane and its 2-deutero- and 2-tritio-analogues with ethoxide ion in dry ethanol, equation 70.



$$C_6H_5-\underset{H(D)(T)}{\overset{CH_3}{C}}-CH_2-Br + NaOEt \longrightarrow C_6H_5-\overset{CH_3}{C}=CH_2 + EtOH(D)(T) + NaBr \qquad (70)$$

The results are shown in Table XI. It is seen that whereas the ratio A^{*D}/A^{*T} is very close to unity, as is expected for reaction in which tunneling is negligible, the corresponding ratio A^{*H}/A^{*D} is considerably smaller than one. This result, as well as the larger value of

Table XI

Arrhenius Parameters for the Reaction of 1-Bromo-2-phenylpropane with Ethoxide in Ethanol

$E_D{}^* - E_H{}^* = 1766 \pm 115$ cal/mole

$E_T{}^* - E_D{}^* = 679.5 \pm 25$ cal/mole

$A^{*H}/A^{*D} = .395$

$A^{*D}/A^{*T} = .840$

$E_D{}^* - E_H{}^*$ compared with $E_T{}^* - E_H{}^*$ led the authors to conclude that tunneling is important for the reaction of the protium compound but not for either of the heavier isotopic molecules.

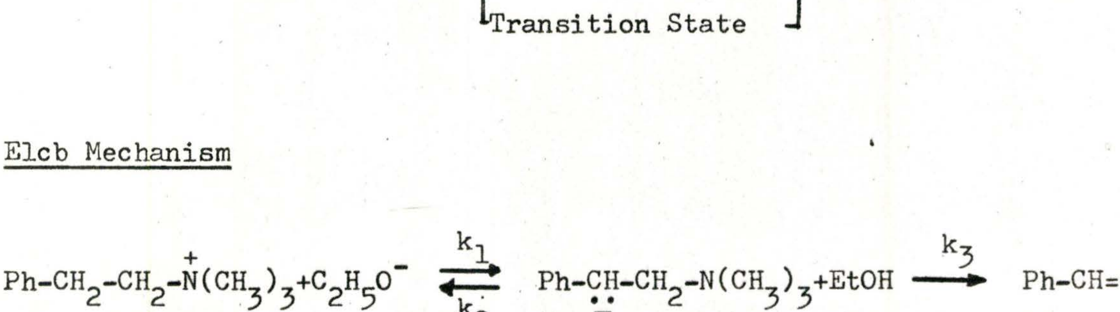
DISCUSSION AND RESULTS

E2 Versus Elcb Mechanism for the Reaction of 2-Arylethyltrimethylammonium Ions with Sodium Ethoxide in Ethanol

In the Historical Introduction it was pointed out that there has been considerable controversy concerning the mechanism of the reaction of 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol. It was partly as a result of the uncertainty regarding the mechanism of this reaction that the present study was undertaken.

Two mechanisms were under consideration, the concerted or E2 mechanism and the carbanion or Elcb mechanism.

E2 Mechanism



(71)

Elcb Mechanism

$$Ph\text{-}CH_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 + C_2H_5O^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ph\text{-}\underset{\overset{\bullet\bullet}{-}}{CH}\text{-}CH_2\text{-}N(CH_3)_3 + EtOH \xrightarrow{k_3} Ph\text{-}CH{=}CH_2 + N(CH_3)_3 \qquad (72)$$

In the concerted mechanism the removal of hydrogen by base occurs at the same time as the formation of the carbon-carbon double bond and separation of trimethylamine. The Elcb mechanism is a two-step process in which the base first removes the hydrogen to form a carbanion intermediate, which subsequently eliminates trimethylamine with the formation of styrene.

Banthorpe and Ridd (4), in the course of a study of reactions in strongly basic media, found that when the reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol-O-d was carried out to 25-30 per cent completion and the unreacted substrate was recovered as its tetraphenylborate, there was a small but significant amount of deuterium in this salt. This result led the authors to infer that some exchange accompanies elimination and, therefore, that the elimination reaction is proceeding via the Elcb mechanism with the formation of the carbanion mainly rate-determining; that is, $k_3 > k_2 [\mathrm{EtOH}]$.

In conflict with this conclusion was the earlier work of Ayrey and Bourns who observed a significant nitrogen isotope effect in the reaction. The value of $(k^{14}/k^{15}-1)100$ of 1.2 at 40° is approximately one-third the theoretical maximum for a reaction in which $\mathrm{C}-\overset{+}{\mathrm{N}}$ bond rupture is completely rate-determining and this would require, for the Elcb mechanism, that the rate of return of the intermediate to reactants must be at least as large as its rate of conversion to products, $k_3 \leq k_2 [\mathrm{EtOH}]$. This relationship of rates, however, should lead to a greater extent of isotopic exchange than had been reported.

There were, however, two serious shortcomings in the experimental procedure as carried out by Banthorpe and Ridd. In the first place, their method involved the measurement of the amount of label picked up by reactant from deuterated solvent, which does not allow one to draw any conclusions concerning the actual position of exchange. They could not, therefore, distinguish between exchange at an α- rather than a β-carbon. In the second place, they isolated the unreacted quaternary ammonium ion as the very insoluable tetraphenylborate, a salt which cannot be readily purified.

In the present investigation, the exchange between ethanol of normal isotopic abundance and the quaternary salt specifically labelled with deuterium on the β-position was examined. Any depletion of the heavy isotope in the recovered reactant would of necessity be the result of exchange at the β-carbon. Also, in this work the unreacted ion was recovered as the original bromide, since not only can this salt be readily purified by recrystallization but deuterium analysis on initial and recovered ion would involve the same salt.

2-Phenylethyltrimethylammonium-2,2-$\underline{d}_2$ bromide, analyzing for 1.88 atoms D per molecule*, was treated with 0.11 M sodium ethoxide in anhydrous ethanol at 40° and the reaction was allowed to proceed half-way to completion. The unreacted salt was isolated and purified by successive recrystallizations and was found, within the limits of the analysis (± 2%), to have exactly the same deuterium content as the initial material. From this result, it can be concluded that there is no significant exchange of the hydrogens at the β-position and, hence,

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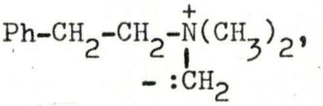
* Except where stated, all analyses were performed by Mr. J. Nemeth, 303 W. Washington St., Urbana, Illinois, who combusted the samples and analyzed the water so-obtained for deuterium by the falling-drop method.

that a two-step mechanism, involving a solvated zwitterionic intermediate $Ar-\underset{-}{\underset{\cdot\cdot}{C}}H-CH_2-\overset{+}{N}(CH_3)_3$ in partial or complete equilibrium with reactant, is excluded. Since the nitrogen isotope effect results require that $C-\overset{+}{N}$ bond rupture occurs in a slow step, a two-step mechanism in which this zwitterion is formed in the rate-determining step is also eliminated.

A possible explanation for the presence of deuterium in the salt isolated in Banthorpe and Ridd's experiments is that the exchange is taking place at the α-methylene carbon. The intermediate zwitterion for such a process could be an intermediate in an α-elimination process or might have no relevance to the styrene-forming reaction at all. To determine whether exchange does take place at the α-position, the exchange experiment was repeated using 2-phenylethyltrimethylammonium-1,1-$\underline{d}_2$ bromide. The initial reactant analyzed for 1.94 atoms D per molecule and the material recovered from a reaction which had been allowed to proceed to half completion analyzed for 1.92 atoms D per molecule. These two values are the same within the error of measurement and it therefore must be concluded that α-exchange cannot account for the results of the English workers.

The only other possible hydrogens which might undergo exchange are those of the N-methyl groups. If such were to occur, then the resulting zwitterion,  $Ph-CH_2-CH_2-\underset{-:CH_2}{\underset{|}{\overset{+}{N}}}(CH_3)_2$, called an ylide, could be an intermediate leading to styrene formation by the α',β-mechanism (see page 11). Before a test for methyl hydrogen exchange could be carried out, Banthorpe and Ridd, in a Private Communication (102), informed us that they had established that the deuterium found in the quaternary ammonium tetraphenylborate recovered from partial reactions does not have its origin in an exchange process. They suggested that the presence of the label in the recovered salt is a result of a slight co-precipitation of trimethylammonium tetraphenylborate. This contaminant would contain deuterium since the trimethylammonium ion would be formed from trimethylamine and the solvent C_2H_5OD. They had evidence that this co-precipitated salt is not easily removed from the precipitated 2-phenylethyltrimethylammonium tetraphenylborate. An erratum on their report on the exchange has now been published (103).

Although the exchange test on the α-dideutero compound shows that the zwitterion $C_6H_5CH_2\text{-}\overset{-}{\ddot{C}}H\text{-}\overset{+}{N}(CH_3)_3$, if formed, does not abstract a proton from the solvent under elimination reaction conditions, its intermediacy in an α-elimination process, equation 21, page 16, is still a possibility, provided that it were to be formed in the rate-determining step of the reaction. Tests for this α-elimination mechanism were carried out by determining the position of the deuterium label in the styrene formed from 2-phenylethyltrimethylammonium-2,2-$\underline{d}_2$ and 2-phenylethyltrimethylammonium-1,1-$\underline{d}_2$ bromides.

The basis of this test using the former compound is seen from the following equations:

$$Ar\text{-}CD_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 + OEt^- \longrightarrow Ar\text{-}CD_2\text{-}\overset{-}{\ddot{C}}H\text{-}N(CH_3)_3 + EtOH \qquad (73)$$

$$Ar\text{-}CD_2\text{-}\overset{-}{\ddot{C}}H\text{-}\overset{+}{N}(CH_3)_3 \longrightarrow Ar\text{-}CD_2\text{-}\ddot{C}H + (CH_3)_3\text{-}N \qquad (74)$$

$$Ar\text{-}CD_2\text{-}\ddot{C}H \longrightarrow Ar\text{-}CD{=}CHD \qquad (75)$$

Loss of trimethylamine from the zwitterion formed in the first step would give rise to a carbene, Ar-CD$_2$-$\ddot{\text{C}}$H, which could undergo a 1,2-deuterium shift to produce styrene containing a single hydrogen atom which is located on the terminal carbon. A β-elimination process, on the other hand, would give a product in which two hydrogen atoms are attached to this carbon, equation 76,

$$\text{Ar-CD}_2\text{-CH}_2\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3 + \text{EtO}^- \longrightarrow \text{C}_6\text{H}_5\text{-CD=CH}_2 + \text{EtOD} + (\text{CH}_3)_3\text{N} \tag{76}$$

Equations 77, 78, 79 show the application of this test for the α-elimination mechanism using quaternary salt labelled in the α-position.

$$\text{Ar-CH}_2\text{-CD}_2\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3 + \text{EtO}^- \text{———} \text{Ar-CH}_2\text{-}\overset{-}{\ddot{\text{C}}}\text{D-}\overset{+}{\text{N}}(\text{CH}_3)_3 + \text{EtOD} \tag{77}$$

$$\text{Ar-CH}_2\text{-}\overset{-}{\ddot{\text{C}}}\text{D-}\overset{+}{\text{N}}(\text{CH}_3)_3 \longrightarrow \text{Ar-CH}_2\text{-}\ddot{\text{C}}\text{D} + (\text{CH}_3)_3\text{N} \tag{78}$$

$$\text{Ar-CH}_2\text{-}\ddot{\text{C}}\text{D} \longrightarrow \text{Ar-CH=CHD} \tag{79}$$

The styrene formed in such a process would carry hydrogen atoms on each ethylenic carbon, whereas a β-elimination would produce a product containing a simple hydrogen which is located on the carbon adjacent to the ring (α-carbon), equation 80.

$$\text{Ar-CH}_2\text{-CD}_2\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3 + \text{EtO}^- \longrightarrow \text{Ar-CH=CD}_2 + \text{EtOH} + \text{N}(\text{CH}_3)_3 \tag{80}$$

Determination of the number and location of the hydrogen atoms in the styrene formed in each experiment was determined by N.M.R. analysis on styrene dibromide. Figure 7 shows the spectrum for unlabelled styrene dibromide, from which it can be seen that the peaks corresponding to the phenyl-, α- and β-hydrogens are well

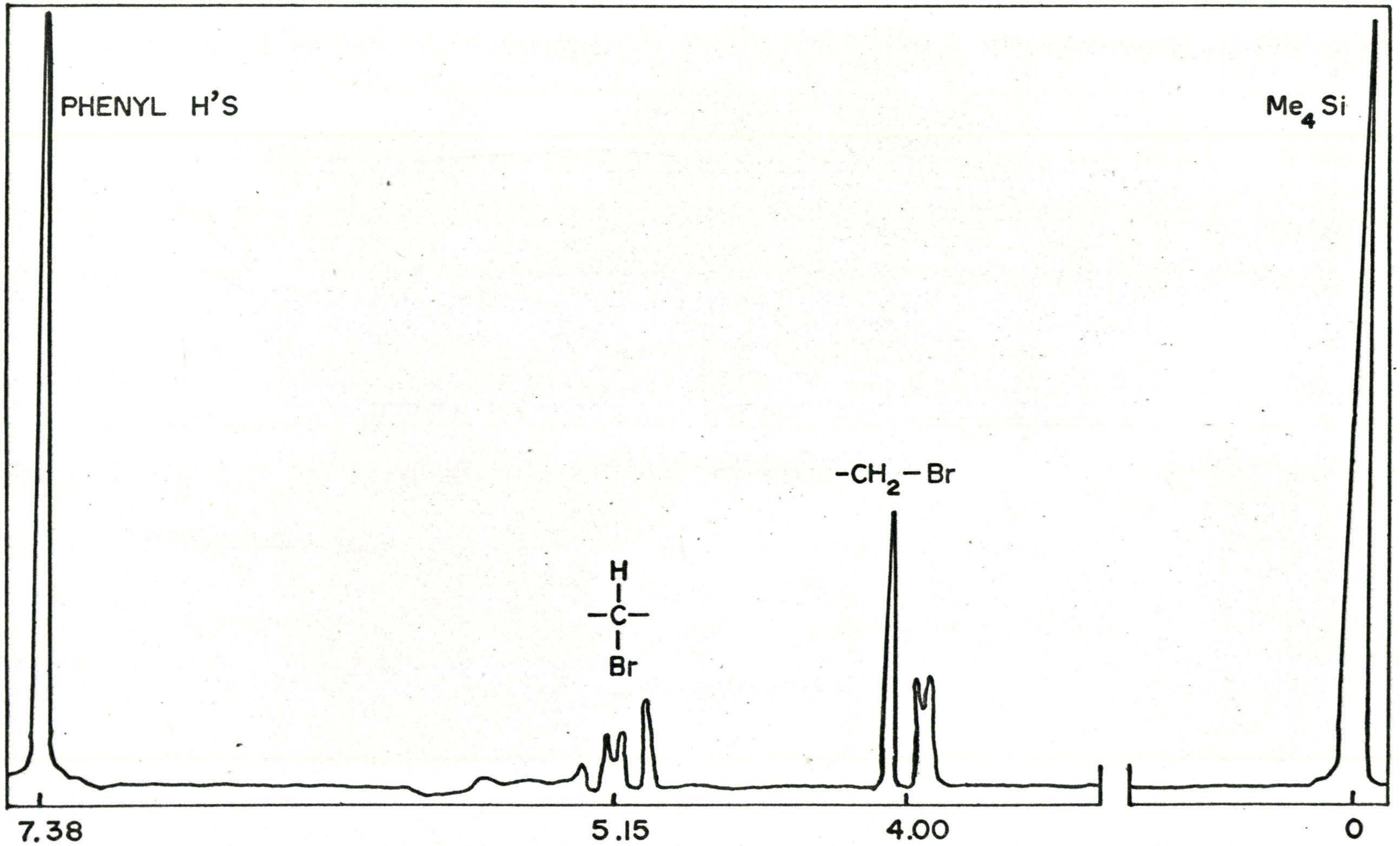


Fig. 7 . THE N.M.R. SPECTRUM OF 1,2-DIBROMO-1-PHENYLETHANE, $C_6H_5CHBrCH_2Br$.

separated at 7.38 p.p.m., 5.15 p.p.m., and 4.00 p.p.m. and in the ratio of 5:1:2, respectively. Figure 8 shows the spectrum for the product formed in the reaction of the β-deuterated compound having signals at 7.38 p.p.m. and 2.62 p.p.m. in the ratio of 5.00 : 2.04, and no detectable signal at 5.15 p.p.m. corresponding to the resonance of a hydrogen on the carbon adjacent to the benzene ring. The product formed in the reaction of the α-deuterated compound was also examined. The N.M.R. spectrum (Fig. 9) showed peaks at 7.38 p.p.m. and 5.15 p.p.m. in the ratio of 5.0 : 0.93 but no detectable peak at 4.00 p.p.m., corresponding to the resonance of the hydrogens on the β-position of the styrene dibromide. (This position corresponds to the α-carbon of the quaternary salt.)

A comparison of the number of hydrogen atoms found at the β-carbon of the styrene dibromide formed from each labelled salt with the number predicted for each of the two mechanisms is shown in Table XII. It is seen that the results clearly eliminate an α-elimination mechanism and are in complete accord with a β-elimination process. This conclusion finds further support from the results of a total deuterium analysis (falling drop method) of 2-phenylethyltrimethylammonium-2,2-d_2-bromide and the styrene dibromide formed from it. As can be seen from equation 76, a β-elimination mechanism requires the loss of one of the two atoms present in the reactant, while the α-elimination would retain both deuteriums in the styrene product. It was found that a 2-phenylethyltrimethylammonium-2,2-d_2 analyzing for 1.88 atoms D per molecule gave styrene dibromide containing 0.94 atoms D per molecule. Finally, the fact that in all of these tracer studies

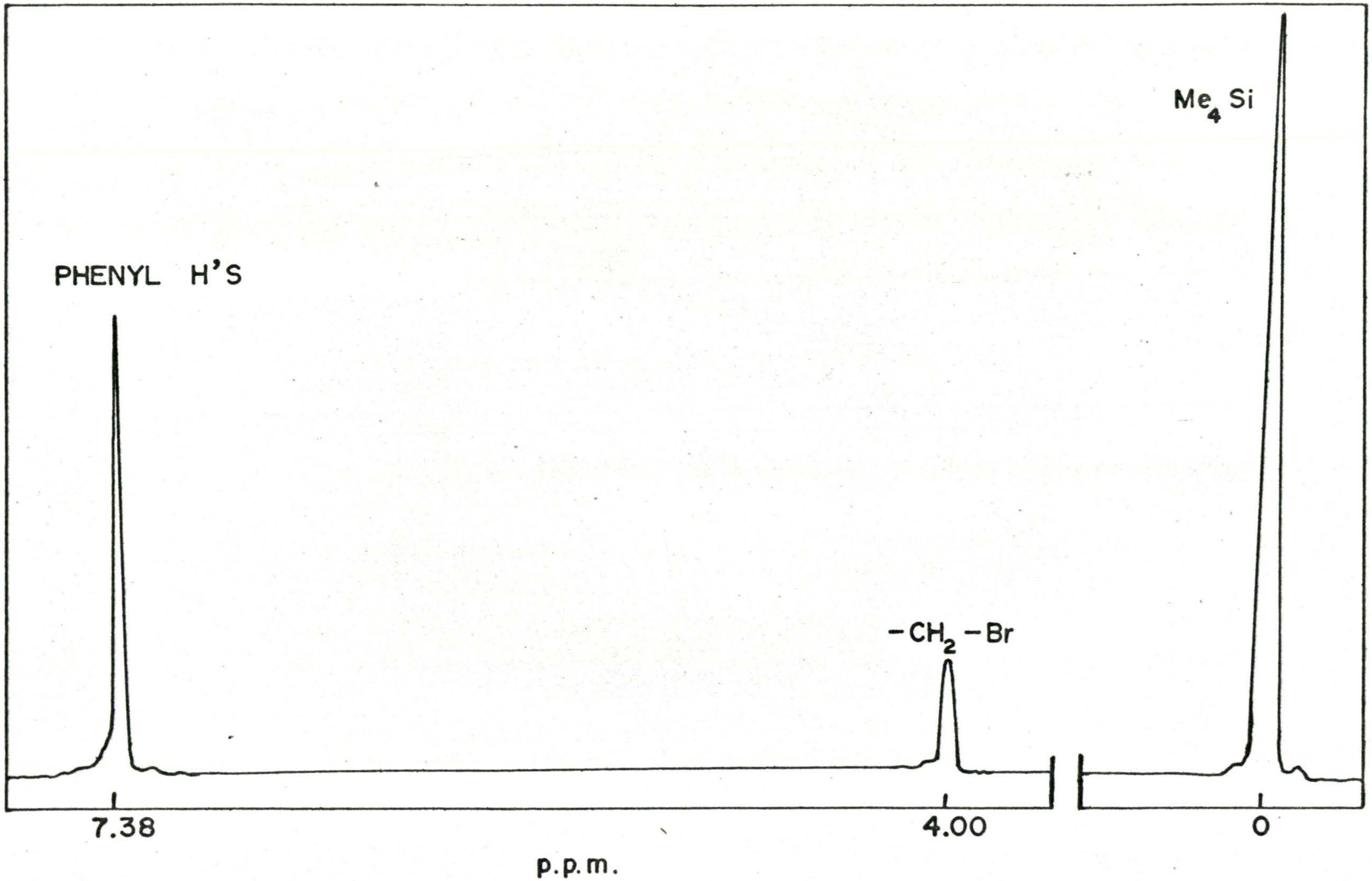


Fig. 8 . THE N.M.R. SPECTRUM OF 1,2-DIBROMO-1-PHENYLETHANE FORMED FROM 2-PHENYLETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE.

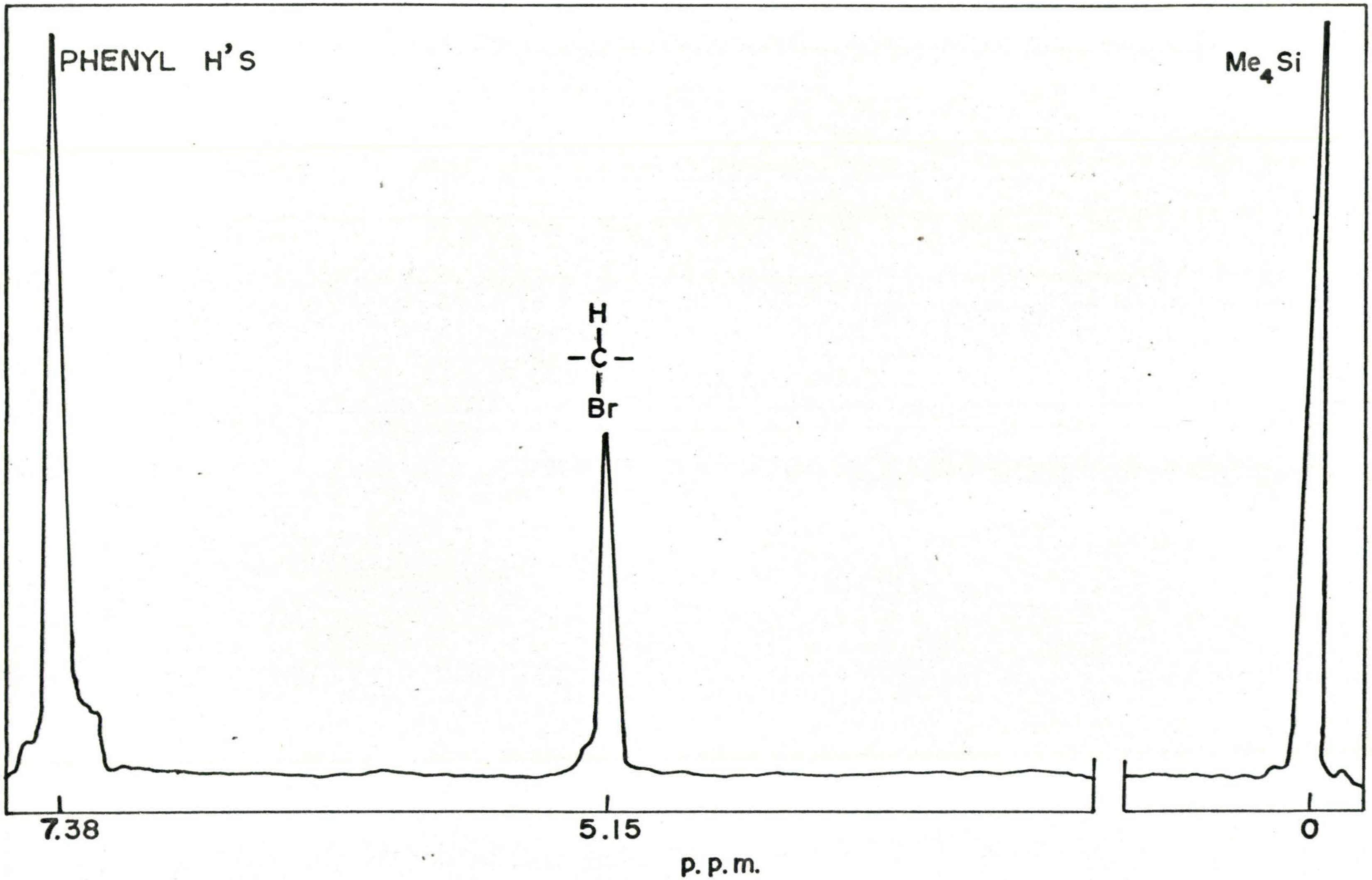


Fig. 9 . THE N.M.R. SPECTRUM OF 1,2-DIBROMO-PHENYLETHANE FORMED FROM 2-PHENYLETHYLTRIMETHYLAMMONIUM-1,1-d_2 BROMIDE.

Table XII

A Comparison of the Number of Hydrogen Atoms Found by N.M.R. Analysis on the Terminal Carbon of Styrene Dibromide with the Number Predicted for the β- and α-Elimination Mechanisms

Compound	Atoms of hydrogen per molecule on the terminal carbon		
	Found	Predicted for Mechanisms	
		β-elim.	α-elim.
$Ph\text{-}CD_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3$	2.04	2	1
$Ph\text{-}CH_2\text{-}CD_2\text{-}\overset{+}{N}(CH_3)_3$	0.0	0	1
$\underline{p}\text{-}CF_3\text{-}Ph\text{-}CD_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3$	1.99	2	1

the amount of deuterium present in the styrene dibromide product is exactly that predicted for a β-elimination process is added evidence that no isotopic exchange accompanies the elimination process.

Although the results of these experiments have shown conclusively that the reaction of 2-phenylethyltrimethylammonium ion does not proceed either by an α-elimination mechanism or by an Elcb process involving a freely-solvated zwitterionic intermediate, these conclusions do not necessarily apply to other 2-arylethyl salts. In particular, strong electron-withdrawing groups on the benzene ring might be expected to so facilitate the loss of a proton from the β-carbon, that a change from a concerted to an Elcb mechanism might occur.

Hodnett and Flynn (62) have already shown that there is no isotopic exchange in the conversion of $p\text{-}O_2N\text{-}C_6H_4\text{-}CHT\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3$ to p-nitrostyrene at pH 7, from which it can be concluded that a zwitterionic intermediate, if formed, must be transformed to product more rapidly than it abstracts a proton from solvent. Unfortunately, the reaction of this compound is too rapid to permit a nitrogen effect study to determine whether or not the $C\text{-}\overset{+}{N}$ bond is broken in a rate-determining step. Accordingly, we turned to the $\underline{p}\text{-}CF_3$ compound, which has present a rather powerful electron-withdrawing group yet still reacts slowly enough to permit nitrogen isotope effect measurements.

The test for exchange with this compound was carried out by an N.M.R. analysis of p-trifluoromethylstyrene dibromide formed by reaction of $\underline{p}\text{-}CF_3C_6H_4CD_2CH_2\overset{+}{N}(CH_3)_3$ with ethoxide ion in ethanol. The N.M.R. spectrum (Fig. 10) showed peaks at 7.30 p.p.m. and 4.10 p.p.m. which, upon integration, had areas of 4 : 1.99, respectively. There

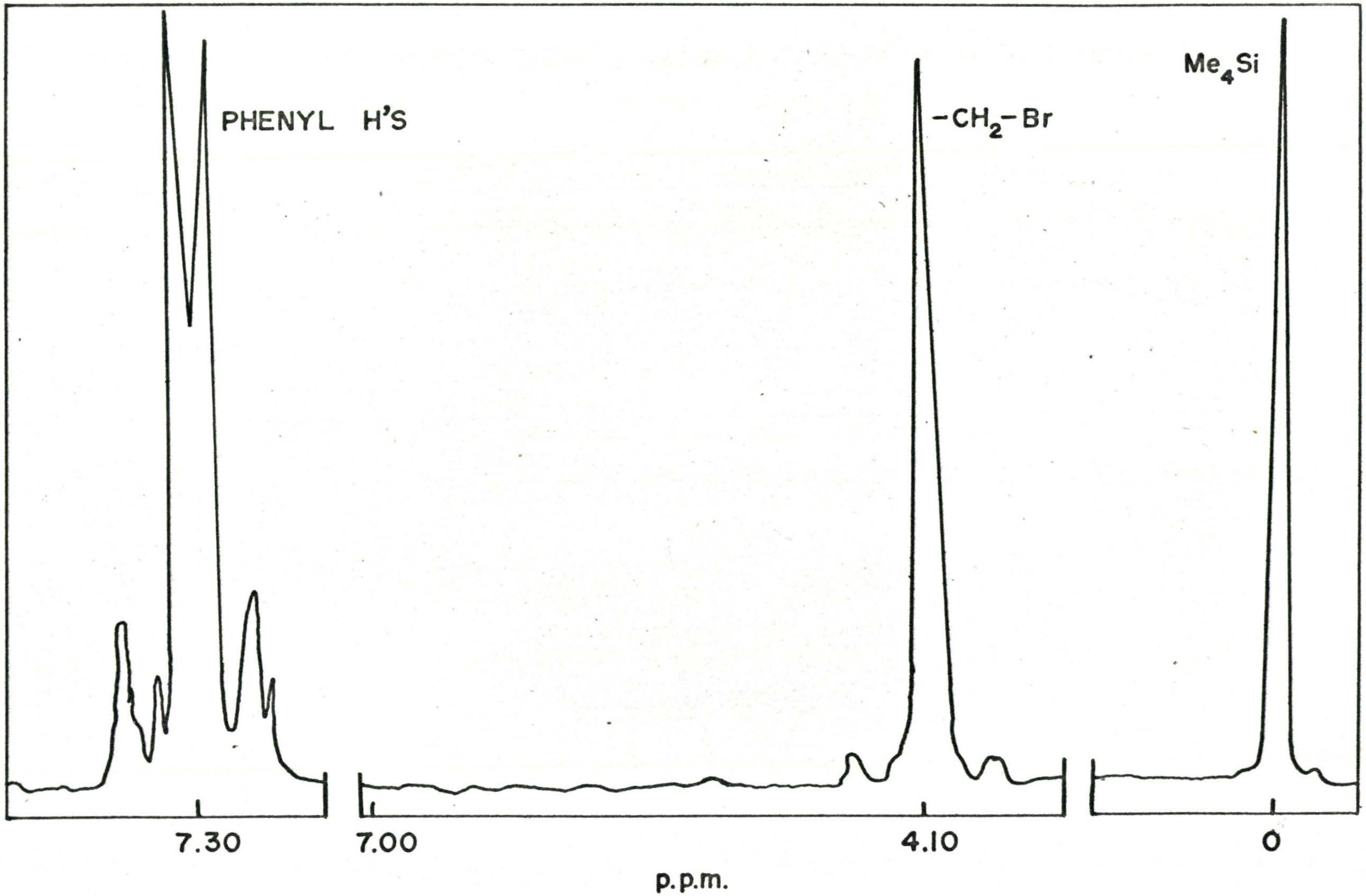


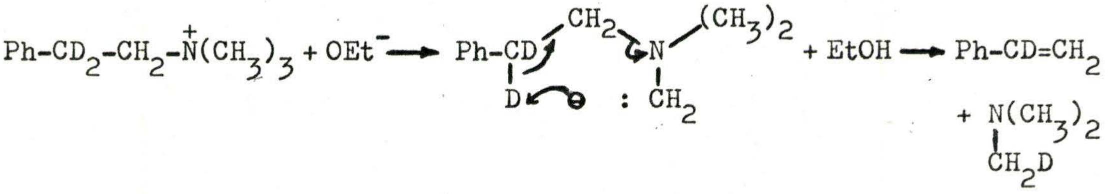
Fig. 10. THE N.M.R. SPECTRUM OF 1,2-DIBROMO-(*p*-TRIFLUOROMETHYLPHENYL)ETHANE FORMED FROM 2-(*p*-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE.

was no detectable peak between 4.2 p.p.m. and 7.0 p.p.m., which would result from the resonance of the hydrogen on the position adjacent to the ring of the dibromostyrene.

The absence of hydrogen on the carbon adjacent to the ring shows that isotopic exchange at this position is negligible. As in the case of the unsubstituted compound, it follows that if the reaction is proceeding in two steps by way of a solvated zwitterionic intermediate, the formation of this species must be rate-determining and the rupture of the $C-\overset{+}{N}$ bond must follow in a rapid subsequent step. It was found, however, that the 2-(p-trifluoromethylphenyl)ethyltrimethylammonium compound, like the unsubstituted compound, gives rise to an appreciable nitrogen effect. The value for $(k^{14}/k^{15}-1)100$ of 0.9 per cent, although smaller than the 1.4 per cent obtained for the 2-phenylethyltrimethylammonium salt, nevertheless establishes that $C-\overset{+}{N}$ bond rupture is taking place in the rate-determining step. It therefore must be concluded that a two-step mechanism involving a solvated zwitterion is excluded for the p-trifluoromethyl-substituted salt as well as for the parent compound.

Finally, the observation that two hydrogen atoms are present on the terminal carbon of p-trifluoromethylstyrene dibromide (see Fig. 10) excludes any contribution from an α-elimination process as well. This is shown in Table XII.

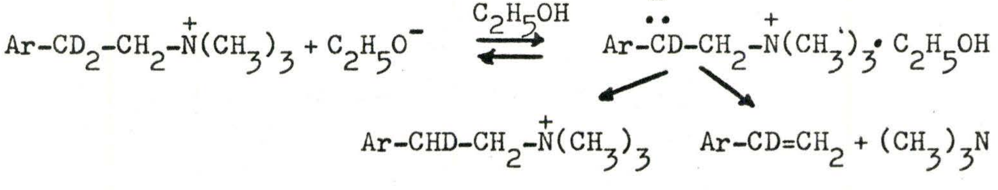
An elimination pathway which is not excluded by any of the foregoing results is the α',β-mechanism, which was discussed in some detail in the Historical Introduction. In view of the work of Ayrey, Buncel and Bourns (35), which excluded this mechanism for the cis-elimination of trans-2-phenylcyclohexyltrimethylammonium ion, it is a most improbable pathway for the much more facile elimination of 2-arylethylammonium compounds. Nevertheless, the availability of 2-phenylethylammonium-2,2-$\underline{d}_2$ ion made it possible to readily test for this mechanism by the conventional method of examining the trimethylamine product for the presence of the tracer, equation 81. The



$$Ph{-}CD_2{-}CH_2{-}\overset{+}{N}(CH_3)_3 + OEt^- \longrightarrow Ph{-}\underset{D}{CD}{-}CH_2{-}\underset{:CH_2^{\ominus}}{\overset{+}{N}}(CH_3)_2 + EtOH \longrightarrow Ph{-}CD{=}CH_2 + \underset{CH_2D}{N}(CH_3)_2 \quad (81)$$

reaction of 2-phenylethyltrimethylammonium-2,2-$\underline{d}_2$ bromide with sodium ethoxide in ethanol at 40° was allowed to proceed to completion and the eliminated trimethylamine was collected as the hydrochloride. No deuterium enrichment was found in this product, thus eliminating the α',β-mechanism as a possible reaction pathway.

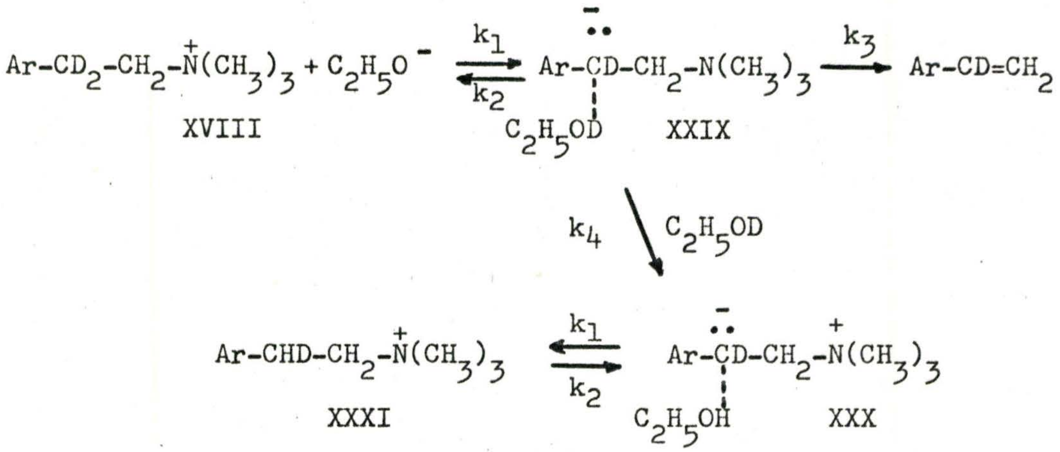
Although the absence of isotopic exchange at the β-carbon, coupled with a normal nitrogen isotope effect, has clearly eliminated an Elcb mechanism involving a freely-solvated zwitterionic intermediate, equation 82, there is one further two-step mechanism which must be considered. This is a process in which there is formed a zwitterionic



$$Ar{-}CD_2{-}CH_2{-}\overset{+}{N}(CH_3)_3 + C_2H_5O^- \underset{}{\overset{C_2H_5OH}{\rightleftarrows}} Ar{-}\overset{\overset{-}{\cdot\cdot}}{C}D{-}CH_2{-}\overset{+}{N}(CH_3)_3 \cdot C_2H_5OH \quad (82)$$

$$\longrightarrow Ar{-}CHD{-}CH_2{-}\overset{+}{N}(CH_3)_3 \qquad \longrightarrow Ar{-}CD{=}CH_2 + (CH_3)_3N$$

species which is specifically hydrogen-bonded to the molecule of ethanol formed by removal of a β-hydrogen by ethoxide ion, equation 83.



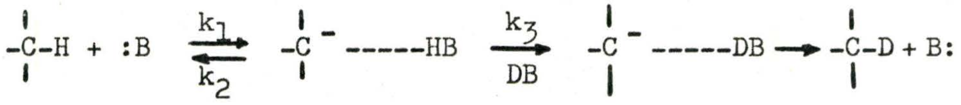
$$\underset{\text{XVIII}}{\mathrm{Ar{-}CD_2{-}CH_2{-}\overset{+}{N}(CH_3)_3}} + \mathrm{C_2H_5O^-} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{\text{XXIX}}{\mathrm{Ar{-}\underset{\underset{C_2H_5OD}{\vdots}}{\overset{\bar{\cdot\cdot}}{C}}D{-}CH_2{-}N(CH_3)_3}} \xrightarrow{k_3} \mathrm{Ar{-}CD{=}CH_2} \quad (83)$$

$$\Big\downarrow k_4 \; \mathrm{C_2H_5OD} \quad (83)$$

$$\underset{\text{XXXI}}{\mathrm{Ar{-}CHD{-}CH_2{-}\overset{+}{N}(CH_3)_3}} \underset{k_2}{\overset{k_1}{\leftrightharpoons}} \underset{\text{XXX}}{\mathrm{Ar{-}\underset{\underset{C_2H_5OH}{\vdots}}{\overset{\bar{\cdot\cdot}}{C}}D{-}CH_2{-}\overset{+}{N}(CH_3)_3}}$$

If $k_3 \gg k_4$, then there would be no hydrogen exchange with solvent, and if $k_3 \leq k_2$, there would be a nitrogen isotope effect since the step involving $\mathrm{C{-}\overset{+}{N}}$ bond rupture would be partially or entirely rate-determining.

Such a specifically hydrogen-bonded species has been invoked by Cram (54) to account for very low or reverse hydrogen-deuterium isotope effects in certain isotopic exchange processes. Application



$$\mathrm{{-}\overset{|}{\underset{|}{C}}{-}H} + \mathrm{:B} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{{-}\overset{|}{\underset{|}{C}}^{-}\text{-----}HB} \xrightarrow[\mathrm{DB}]{k_3} \mathrm{{-}\overset{|}{\underset{|}{C}}^{-}\text{-----}DB} \longrightarrow \mathrm{{-}\overset{|}{\underset{|}{C}}{-}D} + \mathrm{B:} \quad (84)$$

of the steady state approximation to equation (84) gives $k_{\text{obs.}} = \dfrac{k_1k_3}{k_2+k_3}$ and the deuterium isotope effect $\left(\dfrac{k^H}{k^D}\right)_{\text{obs.}} = \dfrac{k_1^H\ k_3^H}{k_1^D \cdot k_3^D} \cdot \dfrac{k_2^D + k_3^D}{k_2^H + k_3^H}$

When $k_3 \gg k_2$, this reduces to $(k^H/k^D)_{\text{obs.}} = k_1^H/k_1^D$ and a normal isotope effect favouring abstraction of hydrogen will result. This was found, for example, in the H/D exchange of toluene and $C_6H_5CD_3$ using lithium cyclohexylamide in cyclohexylamine (104,105). On the other hand, if $k_2 \gg k_3$, the equation for the ratio of isotopic rate constants becomes

$$(k^H/k^D)_{obs.} = \frac{k_1^H \cdot k_2^D \cdot k_3^H}{k_1^D \cdot k_2^H \cdot k_3^D} = \frac{K^H}{K^D} \cdot \frac{k_3^H}{k_3^D}$$

The hydrogen isotope effect for the second step will be small since it involves only hydrogen bonds. The equilibrium isotope effect will also be small, and even may favour the deuterated reactant, since the vibrational stretching frequency of the H-B bond, where B is N or O, will be greater than that of the original C-H bond. The overall isotope effect then will be small or less than unity. A suggested example of this situation ($k_2 >> k_3$) is the hydrogen-deuterium exchange reaction of toluene in dimethyl sulfoxide-potassium tert-butoxide, where $k^H/k^D \sim 0.6$ was obtained (106).

In the 2-phenylethyl system, the hydrogen-deuterium isotope effect has been measured by Saunders (81), who found $k^H/k^D = 3.0$ at 50°. This is a relatively low effect compared to values of 6 or more that are frequently observed for reactions in which a C-H bond is broken in a slow step. It is, however, much larger than would be expected if the zwitterion XXIX of equation 83 were to be in equilibrium with reactant ($k_2 >> k_3$). The rupture of the C-H bond must therefore be at least partially rate-determining, if this is the mechanism. Furthermore, the nitrogen isotope effect of 1.4 per cent, although also relatively small in comparison with the theoretical maximum of about 3 per cent, also requires that the bond to the isotopic atom be broken in a step which is at least partially rate-determining.

The only way in which the two isotope effect results could be accommodated by the mechanism of equation 83 would be for the two steps, namely the formation and the decomposition of the carbanion XXIX, to be comparable in rate ($k_3 \approx k_2$); that is, for each to be partially rate-determining. Although this equality in rates might occur for a particular reactant, under a specific reaction condition, it should not be maintained as the structure of the reactant or the nature of the solvent is varied. Return of XXIX to reactant involves the conversion of a zwitterion to a positively charged species, while its decomposition to product results in the formation of neutral molecules. The effect of a change in reaction conditions or in the structure of the reactant upon the rates of these two processes therefore should be quite different. Consequently, if these rates were to be about equal for the reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol they should differ considerably for the reaction of this reactant with hydroxide ion in water or for the reaction of p-substituted 2-phenylethyl salts. This difference would be reflected in a large change in the magnitude of the hydrogen and nitrogen effects.

As pointed out in the Historical Introduction, Asperger examined the nitrogen isotope effect for the reaction of 2-phenylethyltrimethylammonium ion with hydroxide ion in water and obtained the very small value for $(k^{14}/k^{15}-1)100$ of 0.14 per cent at 97°, compared to 1.4 per cent observed in the present study for reaction with ethoxide ion in ethanol at 40°. If Asperger's result is correct, then the large change in isotope effect predicted by the mechanism of equation 83 is realized.

Because of the importance of this result in relation to the mechanism of the reaction it was decided to carefully redetermine the isotope effect for the reaction of the 2-phenylethyl compound with both ethoxide ion in ethanol and hydroxide ion in water. The results are shown in Table XIII. Although it was necessary to use different temperatures in the determination of the effects under the two reaction conditions, it is possible to calculate the approximate change in effect with temperature. Using the Bigeleisen equation (page 53) and a $C-\overset{+}{N}$ stretching frequency of 955 cm^{-1} (107), it can be shown that the nitrogen effect would be increased by an amount somewhere in the range of 0.25-0.50 per cent for a change in temperature from 97^{o} to 40^{o}. This would make the nitrogen isotope effect in water at 40^{o} approximately 1.0-1.3 per cent, compared to the value of 1.4 per cent for reaction with ethoxide ion in ethanol. Our value for the reaction in water differs markedly from the small value of 0.14 per cent at 97^{o} obtained by Asperger. We place confidence in our result partly because good agreement was obtained using widely differing extents of reaction and partly because of the general internal consistency of all the isotope effects measured in this investigation. In a Private Communication (63) Asperger has expressed a similar point of view with respect to this discrepancy.

Although the value for reaction with hydroxide ion in water appears to be significantly lower than for ethoxide ion in ethanol the difference is no greater than might be expected for reaction by the concerted E2 process. A much larger change than this would be

Table XIII

Nitrogen Isotope Effects in the E2 Reaction of 2-Phenylethyltrimethylammonium Bromide

Expt. No.	Temp.	Extent of Reaction	$(k^{14}/k^{15}-1)100$
A. Reagent: ethoxide ion in ethanol			
1	40	7.4	1.43
2	40	14.3	1.39
3	40	14.6	1.48
4	40	23.8	1.38
5	40	23.8	1.43
		Mean	1.42 ± 0.04*
B. Reagent: hydroxide ion in water			
1	97	8.1	0.63
2	97	9.8	0.90
3	97	31.6	1.02
4	97	29.0	0.72
5	97	13.5	0.74
6	97	13.1	0.73
7	97	13.1	0.78
		Mean	0.78 ± 0.13*

*The error limits are given as the standard deviation.

anticipated for the two-step mechanism if, as required by the isotope effect data, the rate of return of the zwitterionic intermediate to product and the rate of its conversion to styrene are about equal for the reaction in ethanol. The results of this study, therefore, appear to support the E2 process.

Further support for this mechanism is found in the study of the influence of para-substituents on the magnitude of both the β-hydrogen/deuterium and the nitrogen isotope effects in the reaction of 2-arylethyltrimethylammonium salts with ethoxide in ethanol*. These results are given in Table XIV where it is seen that there is a small but regular variation in the magnitude of both effects. Thus in going from the 2-phenylethyltrimethylammonium ion to the 2-(p-trifluoromethylphenyl)-ethyltrimethylammonium ion, k^H/k^D varies from 3.23 to 4.15 and $(k^{14}/k^{15}-1)100$ from 1.4 to 0.9 per cent. Both the small magnitude of the change and its regularity would seem to exclude the carbanion mechanism but find ready interpretation in terms of an E2 process. In conclusion, it is considered that all of the results provide strong evidence that the Hofman elimination in the 2-arylethyl system proceeds by a concerted E2 mechanism.

Before concluding this section attention should be drawn to the fact that the 1.42 ± 0.04 per cent effect obtained in the present study

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* Experimental data and graphs for representation kinetic runs for the deuterated and undeuterated compounds can be found in Appendix A. Mass spectrometric data used for the calculation of the nitrogen isotope effects can be found in Appendix B.

Table XIV

Comparison of Isotope Effects Found in the E2 Reaction of 2-Arylethyltrimethylammonium Ions with Sodium Ethoxide in Ethanol at 40°

p-Substituent in $Ar-CH_2-CH_2-N(CH_3)_3$	Temp.	k^{14}/k^{15} +	k^H/k^D ‡
H	40°	1.0142	3.23 ± 0.04
OMe	40°	1.0137	2.64 ± 0.04
Cl	40°	1.0114	3.48 ± 0.06
CF_3	40°	1.0088	4.15 ± 0.07

+ Standard deviation ± 0.001.

‡ Ratio of rates of elimination; deviation = $\pm(k^H/k^D)\left[(r_H/k_H)^2 + (r_D/k_D)^2\right]^{\frac{1}{2}}$, where r is the standard deviation in k.

for the reaction of 2-phenylethyltrimethylammonium ion appears to differ significantly from the value of 1.17 ± 0.04 per cent obtained some years ago in these laboratories by Ayrey (3). There is no obvious explanation for this discrepancy. It should be noted, however, that in Ayrey's experiments in anhydrous ethanol at 40° all reactions were carried out to about the same extent of completion (11-12 per cent). Collins has recently pointed out (108) that isotope effect results based on isotopic ratios found for the product of the first few per cent reaction can often be in serious error because the product formed in the early stages of reaction may contain a proportionally large amount of material formed from trace impurities in the reactant. In the present study, the individual experiments covered a range of 7-24 per cent reaction and good agreement was obtained throughout. It is the view of the author that the effect obtained in the present study is the more reliable.

A Discussion of the Nature of the Transition State for E2 Reaction of Some Quaternary Ions

The basic premise, as described by Bunnett (24), that bimolecular β-eliminations may differ in the relative extents of C-Y and C-H bond rupture at the transition state, appears to be well established. For example, considerable data has been obtained (Historical Introduction) which indicates that in the E2 reaction of 2-phenylethyl derivatives the transition state can be of a highly variable nature. The Hammett ρ constants, Table XV, suggest a varying degree of carbanion character at the β-carbon in the transition state throughout the reaction series*. Similarly, the wide range of primary hydrogen-deuterium isotope effects shown in Table XV for the 2-phenylethyl compounds also suggests quite different degrees of proton transfer from the substrate to the base at the transition state, although the actual extent of proton transfer is a matter of considerable controversy. Kinetic isotope effect data obtained for the E2 reaction of some quaternary salts will now be presented and will be discussed in the light of the proposal of a variable transition state. Furthermore, this isotope effect data, together with other results (i.e., Hammett ρ constants, secondary k^{DO^-}/k^{HO^-} values), will be used to support a hypothesis that in the transition state of an E2 process the lengthening of one bond (C-H) will cause a corresponding increase in the length of the other bond (C-Y); that is, the lengthening of the C-H and C-Y bonds parallel one another.

The results obtained in the present work from an investigation of the nitrogen isotope effect associated with the reaction of ethyltrimethylammonium ion with ethoxide ion in ethanol and with t-butoxide ion in t-butyl alcohol provides one test for the hypothesis that C-H and C-Y bond lengthening parallel one another in the transition state for a concerted E2 process. The nitrogen isotope effects for the two reactions are shown in Table XVI, where it is seen that the effect is

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* It must be recognized that an uncertainty exists as to the significance of ρ, since it could conceivably be a measure of double-bond character in the transition state rather than a measure of the amount of negative charge at the β-carbon.

Table XV

Dependence of Kinetic Effects on the Leaving Group in the Elimination Reaction of 2-Phenylethyl Derivatives, $C_6H_5CH_2CH_2Y$, with Ethoxide Ion in Ethanol

Leaving Group, Y	Hammett ρ	k^H/k^D at 30°
I	+2.07	
Br	+2.14	7.1
OTs	+2.27	5.7
Cl	+2.61	
SMe_2^+	+2.75	5.1
F	+3.12	
NMe_3^+	+3.77	3.0[+]

[+] At 50°

significantly greater when the base is ethoxide* than when it is t-butoxide ion; i.e., $(k^{14}/k^{15} - 1)100$ is 1.86 per cent compared with 1.41 per cent. Since the magnitude of the C-Y isotope effect depends on the extent to which the composite force constant of the C-Y bond is

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[*] A common medium for E2 reactions is ethanol containing a few per cent of water, either present at the outset or produced by dissolving KOH in absolute ethanol. A study by Caldin and Long (109) suggests that the base present in such solutions is mainly ethoxide ion.

decreased in going from the initial to the transition state (80), the Y-isotope effect can be expected to increase regularly in a reaction series with the extent of bond weakening in the transition state. The larger nitrogen isotope effect associated with the reaction of ethyltrimethylammonium ion with ethoxide than with t-butoxide, therefore, shows that there is more $C-\overset{+}{N}$ bond rupture in the transition state for the ethoxide-promoted reaction.

Table XVI

Nitrogen Isotope Effects Associated with Reaction of Ethyltrimethylammonium Ion

Substrate	Base	Solvent	$(k^{14}/k^{15} - 1)100$
$CH_3\cdot CH_2\cdot\overset{+}{N}(CH_3)_3I^-$	EtO^-	95% EtOH	1.86 ± 0.04
$CH_3\cdot CH_2\cdot\overset{+}{N}(CH_3)_3NO_3^-$ [+]	$t\text{-}BuO^-$	t-BuOH	1.41 ± 0.03

[+] The nitrate salt was necessary to achieve the desired solubility in t-butyl alcohol.

Conclusions concerning the extent of C-H bond rupture in the transition state for the reaction of ethyltrimethylammonium ion with ethoxide ion in ethanol and t-butoxide ion in t-butyl alcohol are more difficult to make, since the β-hydrogen is involved in a three-centre displacement. Although no hydrogen-deuterium effect studies have been carried out for the reaction of the ethyl quaternary salt with the two different bases, theoretical considerations can give some insight into the relative extent of proton transfer to base in the two cases.

If one considers only the C---H---B system, then a rule, which was recently formulated by Swain and Thornton (110), predicts that stronger the base the longer will be its bond to hydrogen at the transition state and the shorter will be the bond of the hydrogen to carbon. If it is assumed that in comparing the reactions with ethoxide ion in ethanol and t-butoxide ion in t-butyl alcohol solvent effects are less important in determining the extent of hydrogen transfer than base strength effects, then the rule predicts that C-H bond is shorter in the reaction with t-butoxide since it is the stronger base.

Although the rule of Swain and Thornton will be discussed in some detail in a later part of this section, it should be noted that the statement of the rule appears to be conceptually sound. It seems reasonable that the formation of a potentially stronger bond, i.e., the H----O^--t-Bu bond, should require less bond-formation before the free energy maximum that is the transition state is reached; i.e., supplying electrons to a bond being formed should increase the length of that bond in the transition state. Similarly, it is intuitively reasonable that a stronger bond should require more stretching before the transition state can be reached, and therefore supplying electrons to a bond being broken should increase the length of that bond in the transition state.

A postulate suggested by Hammond in 1955 (111) also allows one to make certain predictions concerning the relative weakening of the C-H bond in the transition state for an E2 reaction in which the strength of the abstracting base is varied. The postulate which relates the energy contents of reactants, intermediates, and products to the expected geometry of the transition states roughly states that the more exothermic is a particular reaction step the more the transition state for that step will resemble the initial state. Conversely, the less exothermic or more endothermic the reaction the more the transition state will resemble products. Comparing the E2 reactions of ethyltrimethylammonium ion, the reaction with the stronger base, t-butoxide ion in t-butyl alcohol, is energetically more favourable. Consequently, the transition state for the removal of the hydrogen should come earlier along the reaction co-ordinate. In agreement then with the conclusions drawn from the application of the Swain-Thornton rule to a proton-transfer reaction, the Hammond postulate allows one to conclude that the C-H bond is stretched less in the transition state for the reaction of ethyltrimethylammonium ion with t-butoxide ion than with ethoxide ion; i.e., the stronger abstracting base causes less C-H bond weakening in the transition state.

Finally, recent theoretical calculations of Bader (86) (see page 63) allow one to arrive at the same conclusions concerning the degree of C-H bond weakening in the transition state of an E2 reaction when the strength of the abstracting base is varied. The results of these calculations, using the model O-H + $O^{\delta-}$, where the density distribution in the acid species remains fixed regardless of the strength of the base, and where the base has varying amounts of negative charge, are shown in Table XVII. It is seen that when $\delta = 1$, $r_a = r_b$ and the transition state therefore is symmetrical. As the base strength decreases, that is, as δ becomes less than one, r_a increases and r_b decreases indicating that the proton is becoming

Table XVII

Transition State Data for $O_a - H + O_b^{\delta-}$

δ	r_a	r_b
1.0	2.32	2.32
0.9	2.80	2.21
0.8	3.10	2.25

closer to O_b as the base strength of O_b decreases. These results, therefore, allow one to conclude that, for the E2 reaction of ethyl quaternary ion with two different bases, the proton will be less removed from carbon at the transition state for the reaction where the abstracting base is stronger. In other words, C-H bond weakening will be less (r_a) and B-H bond rupture will be greater (r_b) as δ (strength of abstracting base) increases.*

The conclusion drawn from the theoretical considerations just discussed is that the C-H bond is weakened to a lesser extent in the transition state for the reaction of the ethyl quaternary salt with t-butoxide rather than with ethoxide ion as the abstracting base. Since the nitrogen isotope effect results have shown that the C-N bond is also weakened less in the ethoxide reaction, it follows that the change in

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* This conclusion is reached using Bader's assumption that the density distribution in the acid species remains fixed. In fact, this will not be strictly the case in the E2 reaction of ethyltrimethylammonium ion with base where there is more than one bond changing at a time.

the extent of rupture of the two bonds with change in base strength parallel each other. This is in agreement with the hypothesis stated at the beginning of this section.

The 2-phenylethyl system is suitable for an examination of the effect of changing the leaving group on the relative amounts of weakening of the C-H and C-Y bonds in an E2 reaction. This discussion will be concerned with the E2 reactions of 2-phenylethyltrimethylammonium ion and 2-phenylethyldimethylsulfonium ion with base. In contrast to the very low sulfur isotope effect (0.15 per cent at 60°) found by Saunders (78) for the reaction of the sulfonium salt with hydroxide ion in water, an effect of 0.79 per cent was found for the reaction of the corresponding ammonium salt with the same base in the same solvent at 97°, Table XVIII.

Table XVIII

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

Substrate	$(k^L/k^H-1)100$ at 60°[†]	k^H/k^D at 50°
$PhCH_2CH_2\overset{+}{N}(CH_3)_3$	0.79[‡]	3.02[*]
$PhCH_2CH_2\overset{+}{S}(CH_3)_2$	0.15	5.05

[†] k^L/k^H is k^{14}/k^{15} for the ammonium compound and k^{32}/k^{34} for the sulfonium compound.

[‡] Measured at 97°. The effect at 60° would be about 1.0 per cent.

[*] Measured in 50% ethanol-water.

Even after taking into account that, for the same relative decrease in the C-Y^+ force constant at the transition state, a sulfur isotope effect can be expected to be little more than half a nitrogen isotope effect, it is clear that C-N^+ bond rupture must be more fully advanced in the transition state of the 2-phenylethyltrimethylammonium ion reaction than is C-S^+ bond rupture for the corresponding sulfonium salt.

The conclusions just reached concerning the relative weakening of the C-Y^+ bond in the transition state for the E2 reactions of 2-phenylethylammonium and sulfonium salts is consistent with the Hammond postulate which predicts that a better leaving group (SMe_2) should enable the transition state to be reached sooner along the reaction co-ordinate, giving rise to a more reactant-like transition state.

The relative extent of rupture of the C-Y^+ bonds in the transition states for the two quaternary salt reactions under discussion is also predicted by the Swain-Thornton rule discussed earlier. This rule predicts that electron release at a bond being formed or ruptured will lengthen the partial bond at the transition state. With trimethylamine as the leaving group there should be more electron density in the C-N^+ bond than in the C-S^+ bond of the corresponding sulfonium ion because the valence electrons are more densely distributed about the nitrogen than about the sulfur nucleus (trimethylamine is more basic than dimethylsulfide).* The greater

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* Swain and Thornton have emphasized in the statement of their rule that basicity rather than nucleophilicity is to be taken as a measure of electron release.

electron density in the $C-N^+$ bond provides for increased electron supply and, therefore, the $C-N^+$ bond should be longer than the $C-S^+$ bond in their respective transition states.

The extent of carbon-hydrogen bond rupture in the transition state for the reaction of 2-phenylethyltrimethylammonium ion and 2-phenylethyldimethylsulfonium ion with base has been indicated by two different lines of experimental evidence. The first of these is the secondary isotope effects k^D/k^H for attack of DO^- in D_2O vs. HO^- in H_2O arising from the difference in the basicity of the two bases.

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

$$2DO^- + H_2O \underset{}{\overset{K_B}{\rightleftharpoons}} 2HO^- + D_2O \qquad (85)$$

K_B can be determined from the self-ionization constants of H_2O and D_2O (equations 86 and 87) and from L (equation 88).

$$2H_2O \overset{K_H}{\rightleftharpoons} HO^- + H_3O^+ \qquad (86)$$

$$2D_2O \overset{K_D}{\rightleftharpoons} DO^- + D_3O^+ \qquad (87)$$

$$2D_3O^+ + 3H_2O \overset{L}{\rightleftharpoons} 2H_3O^+ + 3D_2O \qquad (88)$$

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

$$2H_2O + DO^- + D_3O^+ \overset{K_{eq.}}{\rightleftharpoons} 2D_2O + HO^- + H_3O^+ \qquad (89)$$

where $K_{eq.} = K_H/K_D$. It can readily be shown that $K_B = K_{eq.}^2/L$ and that the isotope effect for the conversion of one OD^- bond in the solvated deuteroxide ion to one OD bond in heavy water is $k_D/k_H = K_B^{\frac{1}{2}}$.

Steffa (112), using values of $L = 9.6$, $K_H = 1.00 \times 10^{-14}$ and $K_D = 1.38 \times 10^{-15}$ to 1.56×10^{-15}, calculated the maximum isotope effect for the conversion of a DO^- bond to a DO (neutral) bond and for the corresponding conversion of HO^- to HO to be 2.1 - 2.3 at 25°. For reaction at 80°, this isotope effect for complete hydrogen transfer would be approximately 2.0.

Steffa and Thornton (113) have measured the isotope effects for DO^- in D_2O vs. HO^- in H_2O as attacking bases in the E2 elimination reaction of the two 2-phenylethyl derivatives at 80° and have found $k_D/k_H = 1.79$ and 1.57 for the ammonium and sulphonium salts, respectively. They considered that these large effects provide strong evidence that in the transition states for the two reactions the proton positions are product-like; that is, they have a larger H-O than C-H stretching force constant since the effects are very close to the expected maximum values for complete transfer. Furthermore, the relative values of these secondary isotope effects show that the proton is more tightly attached to the oxygen atom in the ammonium transition state than in the sulfonium transition state. In other words, there is greater C-H bond rupture in the transition state for the ammonium compound than for the corresponding sulfonium salt. This conclusion, taken with the interpretation of the leaving group isotope effects for the two compounds, establishes that both C-H and C-Y bond rupture are greater in the ammonium than in the sulfonium compound. This again is in agreement with the original hypothesis outlined at the beginning of this section.

The second line of evidence which can be used as an indication of the relative degree of C-H bond rupture in the transition state for the two 2-phenylethyl salts involves a consideration of the Hammett _rho_ constants for the two reactions in relation to the leaving group isotope effects. In a concerted E2 process, the negative charge released by the partial transfer of the hydrogen to the base at the transition state will reside in part on the β-carbon and its attached aryl group and in part on the leaving group Y. A measure of the former is provided by the Hammett _rho_ value for the reaction; the larger the _rho_ the more charge is accommodated on the β-aryl group. A measure of the latter is provided by the magnitude of the isotope effect associated with Y. Now it has already been shown from a comparison of nitrogen and sulfur isotope effects that $C-N^+$ bond weakening is more fully advanced in the transition state of the ammonium salt reaction than $C-S^+$ bond weakening for the sulfonium salt. Furthermore, the Hammett _rho_ is considerably greater in the ammonium salt reaction (Table XV). It, therefore, must be concluded that more electron charge is accommodated _both_ on the β-aryl group _and_ on the leaving group atom Y in the reaction of the ammonium ion. This is only possible if there is more electron charge to be accommodated; that is, if C_β-H bond weakening is considerably more advanced in the transition state of the E2 reaction of the ammonium salt than in that of the sulfonium salt. This conclusion is the same as that reached from a consideration of the secondary k_D/k_H effects, with DO^- in D_2O

and HO^- in H_2O as the abstracting bases, and it reinforces the conclusion that in the 2-phenylethyl system, where the leaving group is either trimethylamine or dimethylsulfide, the bond rupture processes parallel one another.

The primary hydrogen-deuterium isotope effects have been measured for both the 2-phenylethyltrimethylammonium and 2-phenylethyldimethylsulfonium systems, but because of the ambiguity with respect to the factors determining such effects an interpretation is not entirely clear. The results given in Table XV show that this effect is significantly greater for the reaction of the sulfonium than for the ammonium compound; i.e., 5.05 compared with 3.02. An interpretation of these results depends upon which factor - a change in stretching or in bending frequencies in going from the initial to the transition state - is considered to be the more important in determining the magnitude of the effect. On the assumption that it is the former, one can conclude that since the larger isotope effect is associated with the reaction of the sulphonium salt in which there is less C-H stretching at the transition state, the proton is more than half transferred to base at the transition state of these reactions. This agrees completely with Thornton's conclusions based on the large DO^-/HO^- effects.

The relative magnitudes of the hydrogen-deuterium effects for the two 2-phenylethyl substrates also can be rationalized in terms of the hypothesis proposed by Bader (86). Recall that Bader has argued that the bending frequencies in the transition state for a hydrogen-transfer reaction are more important in determining the difference in zero-point energies for isotopic species than are the symmetrical stretching frequencies which are deemed to be important in Westheimer's treatment. Bader arrives at the conclusion that the lower primary hydrogen-deuterium isotope effect should result from the situation where there is more electron density at the β-carbon and consequently a higher interaction force constant at the transition state.

From a consideration of the Hammett <u>rho</u> values, Table XV, it would appear that there is considerably more electron density at the β-carbon in the transition state for the ammonium salt reaction than for the sulfonium salt reaction. This conclusion, therefore, using the Bader hypothesis, would allow one to predict a lower hydrogen-deuterium effect for the ammonium compound and this, in fact, is what is observed (Table XV).

A further test for the hypothesis that the more advanced is the rupture of one bond at the transition state the more advanced is the rupture of the other is obtained from a comparison of the isotope effects in the E2 reaction of ethyltrimethylammonium and 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol. The nitrogen isotope effects shown in Table XIX were obtained in the present study, while the hydrogen effects have been reported by previous workers.

The discrepancy which exists between the nitrogen effect given in the Table for the 2-phenylethyl compound and that of Ayrey (3) has already been discussed in the section concerned with the elucidation of the mechanism of the reaction of 2-phenylethyltrimethylammonium ion with base. There is also a small difference in the nitrogen isotope effect of 1.86 per cent obtained in this study for the reaction of

Table XIX

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

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[†]	
	basic hydrate (vacuum)		3.0[ε]
	hydroxide in triethylene glycol		2.8[**]
$C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.42[‡]	
	methoxide in methanol		4.2[ε]

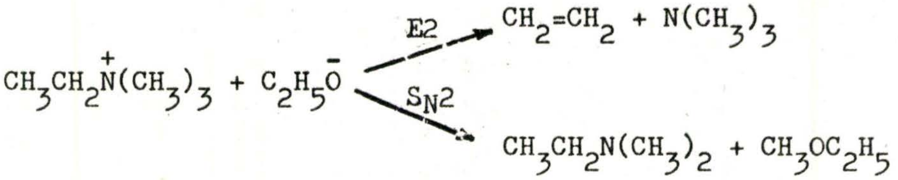
[†] Present work; solvent 95% ethanol

[‡] Present work; solvent absolute ethanol, at 40°

[ε] Simon (84)

[**] Calculated by Simon (84) from an experimental value of 1.23 at 130°

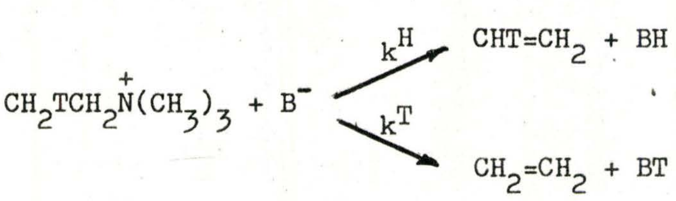
ethyltrimethylammonium ion and the effect of 1.73 per cent reported previously by Ayrey. This difference, if experimentally significant, is probably a consequence of the fact that Ayrey in his work had erroneously assumed that the total reaction is one of elimination. That this is not the case, however, was shown by Banthorpe (114) who found that ethyltrimethylammonium ion reacts with ethoxide ion in ethanol at 104° to yield 70.1 per cent olefin and trimethylamine in the E2 process and also 29.9 per cent dimethylethylamine formed in an S_N2 reaction, equation 90. Since the two amines have similar volatilities, Ayrey, would have collected both amines and his nitrogen isotope effect, therefore, would be a composite effect embracing both reactions, substitution and elimination. It was for this reason that



$$\begin{aligned} CH_3CH_2\overset{+}{N}(CH_3)_3 + C_2H_5\overset{-}{O} &\xrightarrow{E2} CH_2{=}CH_2 + N(CH_3)_3 \\ &\xrightarrow{S_N2} CH_3CH_2N(CH_3)_2 + CH_3OC_2H_5 \end{aligned} \qquad (90)$$

the nitrogen isotope effect for the ethyltrimethylammonium ion reaction was redetermined in the present work. The trimethylamine, resulting from the E2 reaction, was separated by vapour-phase chromatography from the dimethylethylamine formed in the substitution reaction and was then converted to nitrogen for mass spectrometric analysis. This permitted the determination of isotopic fractionation in the elimination reaction alone. It is the view of this author that the nitrogen results obtained in this work for both compounds, and shown in Table XIX, are more reliable than those previously reported.

The hydrogen-tritium effects shown in Table XIX are the so-called intramolecular isotope effects which, for the reaction of ethyltrimethylammonium ion, are defined by the ratio of the rate constants for the following equations:



$$\begin{aligned} CH_2TCH_2\overset{+}{N}(CH_3)_3 + B^- &\xrightarrow{k^H} CHT{=}CH_2 + BH \\ &\xrightarrow{k^T} CH_2{=}CH_2 + BT \end{aligned} \qquad (91)$$

Hydrogen-deuterium effects have also been measured for the two quaternary ammonium salts, but differ from the hydrogen-tritium effects in that they give a ratio of rate constants for two isotopically different compounds

$$\begin{aligned} CH_3CH_2\overset{+}{N}(CH_3)_3 + B^- &\xrightarrow{k^H} CH_2{=}CH_2 + BH \\ CD_3CH_2\overset{+}{N}(CH_3)_3 + B^- &\xrightarrow{k^D} CD_2{=}CH_2 + BD \end{aligned} \qquad (92)$$

Although hydrogen-tritium effects can be converted into hydrogen-deuterium effects using an equation suggested by Swain (115), $k^H/k^D = (k^H/k^T)^{\frac{1}{1.44}}$, the values so obtained in this case are not strictly comparable to the experimentally-measured deuterium effects because of the secondary isotope effects associated with the hydrogen atoms remaining on the β-carbon of the product. Nevertheless, for the 2-phenylethyltrimethylammonium ion, the deuterium isotope effect calculated from Simon's tritium result agrees rather well with the experimental deuterium value; $k^H/k^D = 4.2^{\frac{1}{1.44}} = 2.7$ for reaction with methoxide in methanol at 60° compared to an experimental k^H/k^D of 3.23 obtained in the present work for reaction with ethoxide ion in ethanol at 40° and 2.98 obtained by Saunders (81) for the same reaction at 50°.

In contrast to the agreement obtained for 2-phenylethyltrimethylammonium ion, there is a marked disagreement between Simon's result for ethyltrimethylammonium ion and that obtained some years ago by Shiner who measured the deuterium effect at 137° for reaction in basic diethylene glycol. Expressing all results as k^H/k^D at 60°, Shiner's isotope effect is approximately 6 compared with a value of 2 calculated from the tritium results obtained by Simon. This difference, of course, cannot be accounted for on the basis of secondary isotope effects.

There are several reasons for believing that Simon's results are the more reliable. First, the isotope effects found for the reaction of the ethyltrimethylammonium ion under two different reaction conditions are in good agreement (see Table XIX). Secondly, Simon's data for a number of compounds form a consistent pattern: k^H/k^T of 3.0, 2.8, 4.2 and 8.0 for reaction at 60° of ethyl-, propyl-, 2-phenylethyl- and 2-(p-nitrophenyl)ethyltrimethylammonium ions, respectively. Finally, as stated previously, the value obtained by Simon for the 2-phenylethyl ion is in accord with values obtained by two different workers for the deuterium effect for this reactant. The interpretation of hydrogen isotope effects which is presented in the following paragraphs, therefore, will be based on Simon's results.

The significantly larger nitrogen isotope effect for reaction of ethyltrimethylammonium ion compared to that found for 2-phenylethyltrimethylammonium reactant clearly establishes that there is greater $C-N^+$ bond weakening in the transition state for the former compound.* If one assumes the validity of the Westheimer hypothesis that the magnitude of the hydrogen effect is determined mainly by

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* A similar conclusion has been reached recently by Simon who has observed α-carbon isotope effects, $(k^{12}/k^{14} - 1)100$, of 6 and 3 per cent for ethyl- and 2-(p-nitrophenyl)ethyltrimethylammonium ions, respectively.

the symmetrical stretching frequency of the three-centre system at the transition state, then it must be concluded that the C-H bond is weaker in the transition state of the ethyltrimethylammonium ion as well. This is because it has already been concluded on the basis of Westheimer's hypothesis that in the reaction of ammonium salts the β-proton is more than half-transferred to base at the transition state, from which it follows that the reaction giving rise to the smaller hydrogen isotope effect will have this transfer to base more complete at the state of energy maximum. The tritium isotope effect reported by Simon for the ethyl compound is 2.8 - 3.0, compared to 4.2 for the 2-phenylethyl reactant. Hence, proton transfer to base has proceeded further at the transition state for the former compound.

The same conclusion is reached if one assumes, with Bader (86), that the important factor determining the size of a hydrogen isotope effect is the magnitude of bending frequencies in the transition state. The smaller isotope effect for the reaction of the ethyl compound implies a higher electron density in the three-centre system for proton transfer at the transition state and this in turn implies greater electron release by the carbon base. The Swain-Thornton rule then predicts that the stronger a base the longer will be the bond of this base to hydrogen at the transition state. Again, then we find that the reactant in which the bond to leaving group is weakened most at the transition state is the one in which there has been the greater extent of proton transfer to base.

Application of the Hammond hypothesis supports this conclusion. The elimination reaction proceeds much less readily with the ethyltrimethylammonium ion than with the 2-phenylethyltrimethylammonium substrate. The transition state for the former then should be further along the reaction co-ordinate and both C-N and C-H bonds should be longer than in the reaction of the more reactive 2-phenylethyl species.

Although the hypothesis that C-H and C-Y bond weakening parallel each other in the transition state for an E2 process has received support from the foregoing, objection can be raised against certain of the arguments presented. First, with respect to the argument based on the different base strengths of ethoxide ion in ethyl alcohol and t-butoxide ion in t-butyl alcohol, any influence of solvent on the nature of the transition state has been ignored. Secondly, with respect to the data for the reaction of the 2-phenylethyltrimethylammonium and sulphonium ions, it may be argued that the reactants are too dissimilar to allow a valid comparison, particularly with respect to the leaving group isotope effect. It was for this reason that a systematic study has been made of the effect of substituents on the benzene ring of 2-arylethyltrimethylammonium ion on the magnitude of the nitrogen and β-hydrogen isotope effects. This investigation represents a major part of the work of this thesis.

The nitrogen isotope effect results for the reaction of 2-phenylethyltrimethylammonium ion and of three different p-substituted compounds with ethoxide ion in anhydrous ethanol at 40° are shown in Table XX. Each individual isotope effect value is based on the isotopic ratio for the product formed in a reaction taken to the extent of completion indicated. Details of the experimental procedures are

Table XX

Nitrogen Isotope Effect Results for the Reactions of 2-Arylethyltrimethylammonium Bromides with Sodium Ethoxide in Ethanol at 40°

Para Subst.	Extent of Reaction	$(k^{14}/k^{15} - 1)^{*}100$
H	7.4	1.43
H	14.3	1.39
H	14.6	1.48
H	23.8	1.38
H	23.8	1.43
		mean = 1.42 ± 0.04
OCH_3	4.9	1.25
OCH_3	4.9	1.35
OCH_3	8.1	1.41
OCH_3	12.6	1.37
OCH_3	23.2	1.33
OCH_3	23.5	1.53
		mean = 1.37 ± 0.09
Cl	17.1	1.13
Cl	14.6	1.18
Cl	16.3	0.98
Cl	29.0	1.18
Cl	29.0	1.22
		mean = 1.14 ± 0.09

Table XX cont.

Para Subst.	Extent of Reaction	$(k^{14}/k^{15} - 1)100^{*}$
CF_3	23	0.84
CF_3	17.3	0.88
CF_3	46.2	0.92
CF_3	43.6	0.93
CF_3	73	0.93
CF_3	60	0.78
		mean = 0.88 ± 0.06

* The limits shown are the standard deviation.

given in the Experimental Section of this thesis and individual isotopic ratios for reactants and products are given in Appendix B.

The kinetic experiments for the undeuterated and 2-arylethyltrimethylammonium-2,2-$\underline{d}_2$ ions were carried out using ethoxide ion as base in ethanol at 40°. The same concentration of base was used in all of the experiments except for the $\underline{p}$-CF_3 substrate where the reaction was too fast at 40° to enable kinetic measurement. For this compound, the kinetics were determined at 25° and 15° with the same concentration of base as was used for the other compounds and the resultant hydrogen-deuterium effects were used to determine an extrapolated value at 40°. In this way, it was possible to compare isotope effects for all compounds under the same conditions of ionic strength. The extrapolated value for the CF_3 compound agrees very well with the hydrogen-deuterium effect determined at 40° for this compound using a lower concentration of base.

The results of the kinetic runs for all of the ammonium salts are shown in Tables XXI and XXII. The hydrogen-deuterium effects calculated from the rate data and a summary of the nitrogen effects are given in Table XXIII. A sample kinetic run for each compound with a plot of the data can be found in Appendix A.

Hammett plots of log k/k_o $\underline{vs}$. σ^- are shown in Fig. 11 and 12 for the undeuterated and deuterated series, respectively. The slope, rho, for the former is +3.66, with a correlation coefficient r of 0.998. This value of rho agrees quite well with the value of +3.58 reported by Bushman for reaction under the same conditions. The slope of the plot for the deuterated series is +3.47, with a correlation

Table XXI

Rate Constants for the Reaction of 2-Arylethyltrimethylammonium Ions with Sodium Ethoxide in Ethanol

Para Subst.	Temp. ± 0.03°	Initial Concentrations m./l.		Rate Constant $k \times 10^4$
		Ethoxide	Quaternary Salt	l. mole^{-1} sec.$^{-1}$
H	40.00	.1137	.03712	4.38
		.1137	.04005	4.29
		.1240	.03648	4.32
Cl	40.00	.1111	.03986	29.3
		.1111	.03739	30.5
		.1586	.02610	30.0
MeO	40.00	.1268	.05139	0.418
		.1268	.04581	0.424
		.1268	.05306	0.418
CF_3	40.00	.01735	.01735	1950
		.01735	.01735	1940
		.01735	.01735	1940
	25.00	.1154	.000574	196
		.1154	.000574	200
	15.00	.1154	.000574	47.1
		.1154	.000574	46.7

Table XXII

Rate Constants for the Reactions of the 2-Arylethyltrimethylammonium-2,2-$\underline{d}_2$ Ions with Sodium Ethoxide in Ethanol

Para Subst.	Temp. ± 0.03°	Initial Concentrations m./l. Ethoxide	Initial Concentrations m./l. Quaternary Salt	Rate Constant $k \times 10^4$ $l.\ mole^{-1}\ sec.^{-1}$
H	40.00	.1267	.04138	1.33
		.1267	.03671	1.36
		.1267	.04048	1.33
Cl	40.00	.1253	.04210	8.53
		.1253	.03898	8.65
		.1586	.04298	8.62
MeO	40.00	.1304	.05468	0.157
		.1304	.04534	0.162
		.1304	.05069	0.157
CF_3	40.00	.01714	.01714	476
		.01714	.01714	460
		.01714	.01714	465
	25.00	.1154	.000472	46.8
		.1154	.000472	46.4
	15.00	.1154	.000453	11.2
		.1154	.000453	10.7

Table XXIII

Isotope Effects Found for the E2 Reaction of 2-Arylethyltrimethylammonium Ions with Sodium Ethoxide in Ethanol

Para-Substituent in $ArCH_2CH_2\overset{+}{N}(CH_3)_3$	Temp.	$(k^{14}/k^{15}-1)100$[†]	(k^H/k^D)[‡]
OMe	40°	1.37	2.64 ± 0.04
H	40°	1.42	3.23 ± 0.04
Cl	40°	1.14	3.48 ± 0.06
CF_3	40°	0.88	4.15 ± 0.05
	25°	-	4.25 ± 0.05
	15°	-	4.28 ± 0.12

[†] Standard deviation ± 0.01

[‡] Ratios of rates of elimination; deviation = $\pm (k^H/k^D) \left[(r^H/k^H)^2 + (r^D/k^D)^2\right]^{\frac{1}{2}}$, where r is the standard deviation in k.

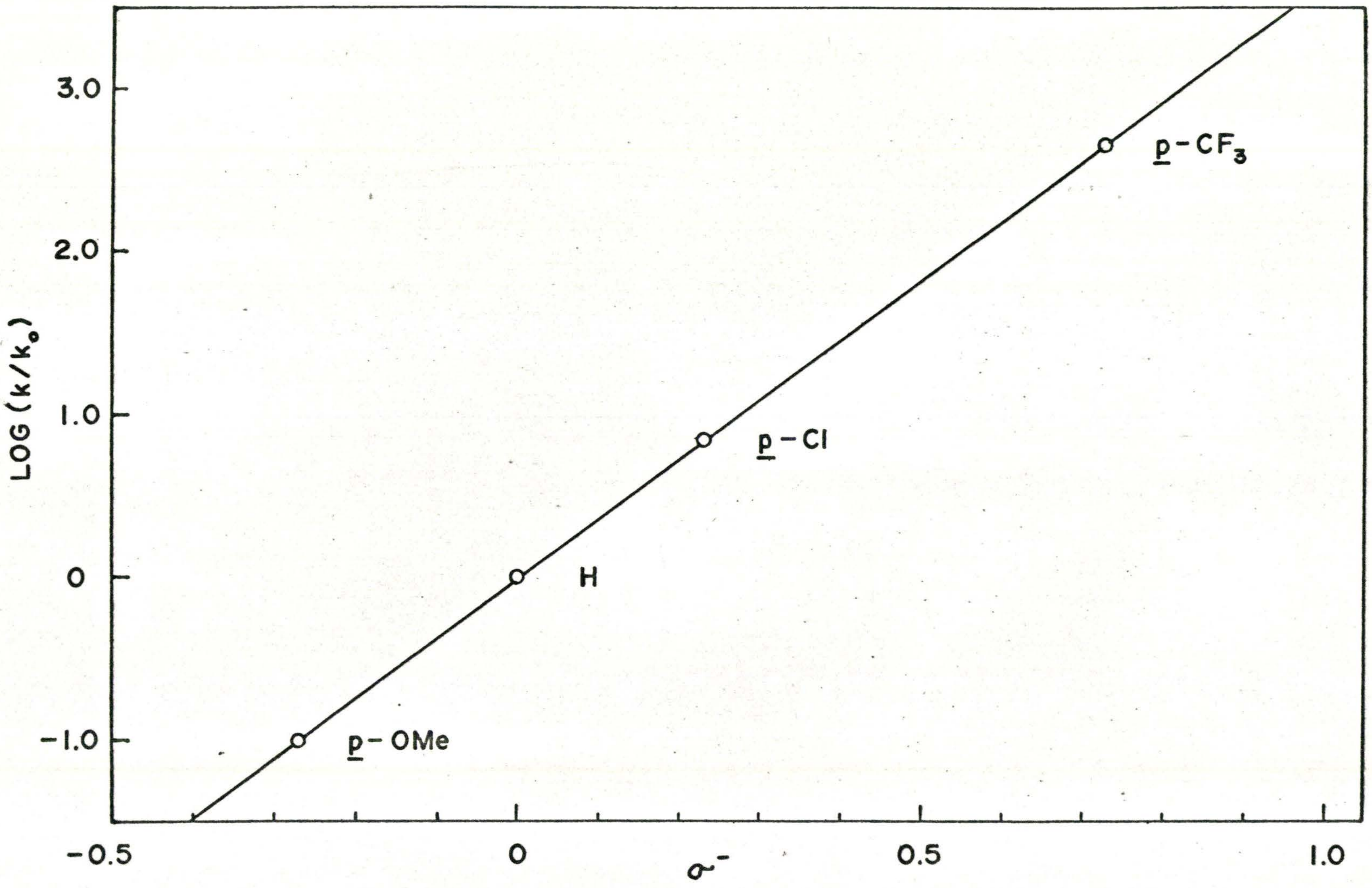


Fig. 11. PLOT OF LOG (k/k$_o$) versus σ^- FOR THE REACTION OF 2-ARYLETHYLTRIMETHYLAMMONIUM IONS WITH SODIUM ETHOXIDE IN ETHANOL AT 40°C.

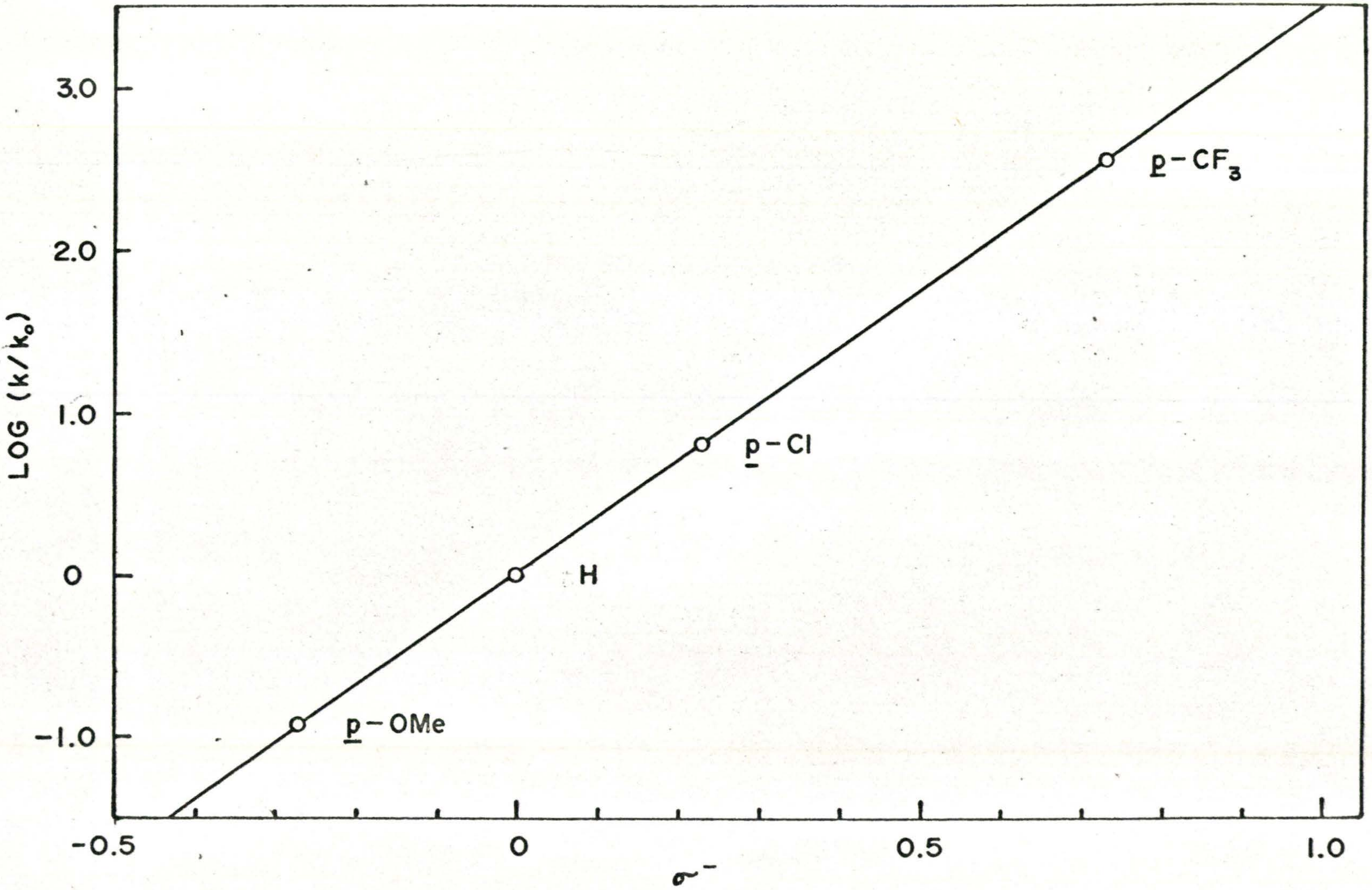


Fig. 12 . PLOT OF LOG (k/k_0) versus σ^- FOR THE REACTION OF 2-ARYLETHYLTRIMETHYLAMMONIUM-2,2-d_2 IONS WITH SODIUM ETHOXIDE IN ETHANOL AT 40°C.

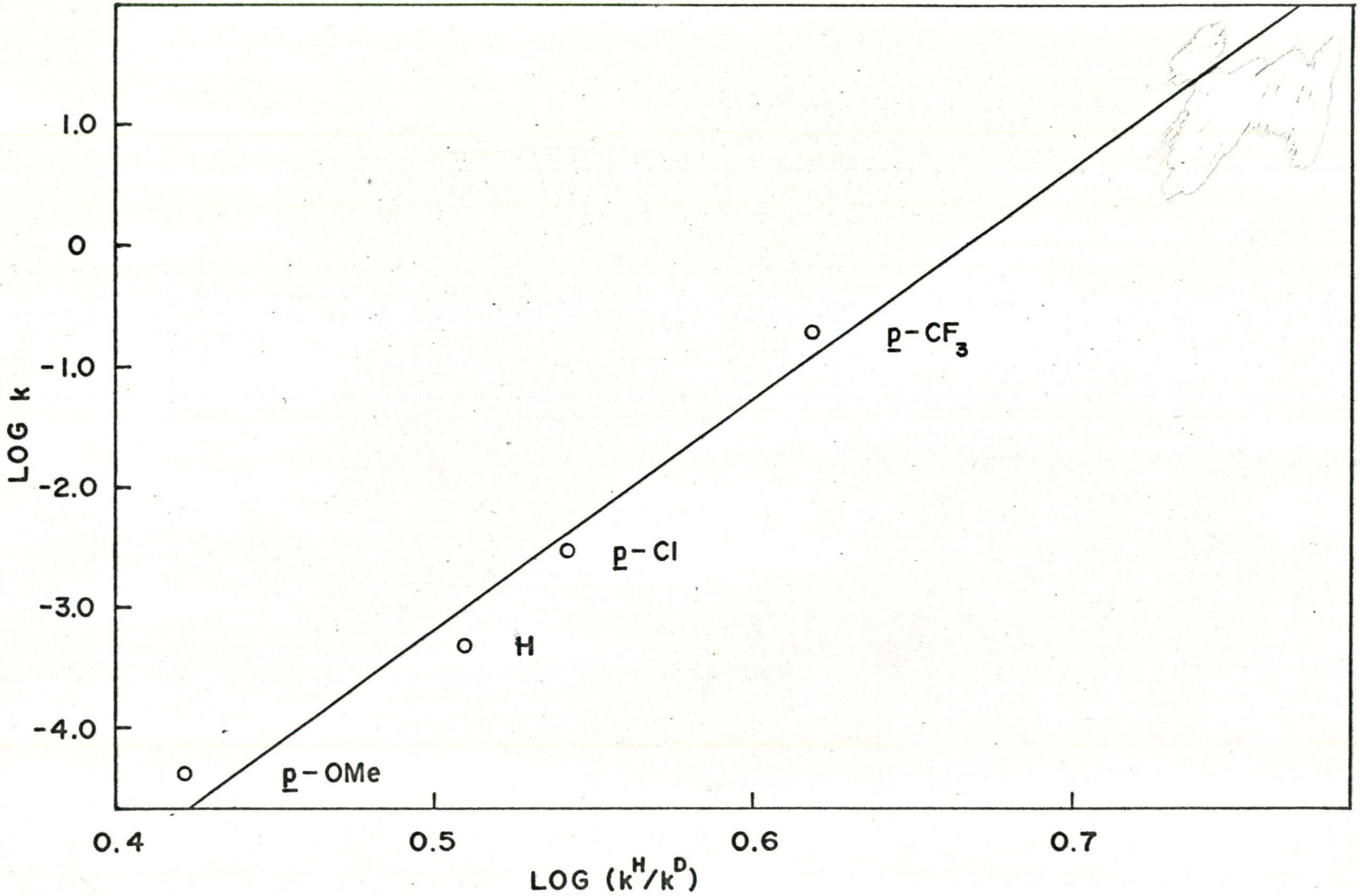


Fig. 13. PLOT OF LOG k versus LOG (k^H/k^D) FOR THE REACTION OF 2-ARYLETHYLTRIMETHYLAMMONIUM IONS WITH SODIUM ETHOXIDE IN ETHANOL AT 40° C.

coefficient of 0.999. Finally, in Fig.13 is shown a plot of log k^H/k^D against σ^-.

The results of the nitrogen isotope effect study on the reactions of the 2-arylethyltrimethylammonium ions with sodium ethoxide in ethanol at 40°, Table XXIII, show a relationship between the magnitude of the effect and the electron-withdrawing or donating ability of the para-substituent. Although the effects for the para-H and para-OCH_3 compounds are the same within experimental error there is a significant decrease in the magnitude of the effect when electron-withdrawing substituents are placed on the benzene ring; i.e., $(k^{14}/k^{15} - 1)100$ is 1.42 for the para-unsubstituted compound and 0.88 for the para-CF_3 substrate. The position of the para-methoxy compound is difficult to explain. The error limits in the results would allow the isotope effect for this compound to be slightly higher than for the unsubstituted compound, but certainly not as high as might have been expected on the basis of the influence of other substituents on the observed effects. A possible explanation is that there is an abnormally small electron release by the CH_3O group in the transition state because of the high negative charge carried on the β-carbon. This is not a very satisfactory explanation, however, since the rate effects are normal. In any case, the general trend of the nitrogen isotope effects with para-substitution is clear.

The interpretation of the nitrogen effect results is straightforward. They clearly indicate that carbon-nitrogen bond rupture is decreased in the transition state when the para-substituents become more electron-withdrawing. In other words, the degree of $C-N^+$ bond rupture at the transition state reflects the electron-donating or withdrawing nature of the para-substituent. This will be discussed in more detail at the end of this section when the Swain-Thornton rule and the Hammond hypothesis are discussed.

A clear trend is also shown in the magnitude of the hydrogen-deuterium isotope effects recorded in Table XXIII, where it is seen that the effect increases with the increased electron-withdrawing ability of the para-substituent. In fact, there is an approximate linear relationship between the effect of substituents upon the free energy of activation for the elimination reaction and their effect on the free energy of activation difference between undeuterated and deuterated compounds. This is apparent in the rather good straight line obtained in a plot of log k versus log k^H/k^D, as shown in Fig. 13.

Of particular interest is the positive slope of this plot, which means that the lower the free energy of activation of the reaction the higher the isotope effect. This is contrary to a suggestion made by Wiberg (116) some years ago that the more readily a reaction proceeds the smaller will be the hydrogen-deuterium isotope effect associated with it.

An interpretation of these hydrogen-deuterium effects in terms of the relative extent of C-H bond rupture at the transition state will be considered first on the basis of the Westheimer hypothesis. It has already been established previously in this discussion that the proton is more than one-half transferred from carbon to base at the transition state for the reaction of 2-phenylethyltrimethylammonium ion with sodium ethoxide in ethanol. If it is assumed, as seems reasonable, that in the transition state for the reaction of the substituted 2-arylethyltrimethylammonium ions the proton is also more than one-half transferred, then the lower hydrogen-deuterium effects indicate increased C-H bond weakening. Thus, C-H bond rupture is greater for the reaction of the p-MeO-compound than for the p-CF_3 compound at the transition state since k^H/k^D = 2.64 and 4.15, respectively. Therefore, in this reaction series as well, it can be concluded that greater C-H bond weakening in the transition state is accompanied by greater $C-N^+$ bond rupture, in agreement with the hypothesis stated at the beginning of this section.

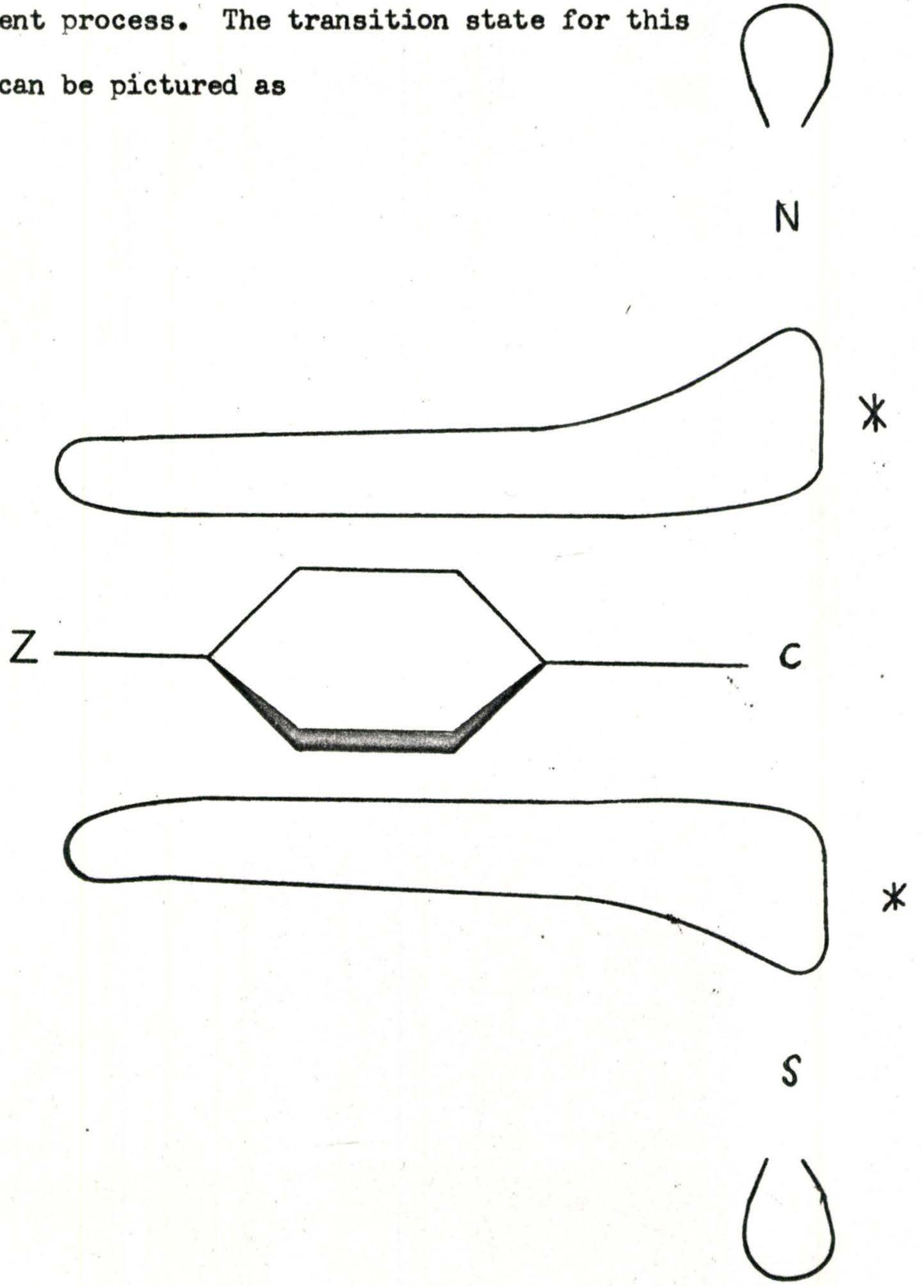
A similar conclusion is reached if one considers that it is the bending frequencies which play the major role in the determination of the magnitude of the hydrogen-deuterium isotope effect. As pointed out earlier in this section, Bader considers that a decrease in electron density at the β-carbon, by decreasing the magnitude of the bending frequencies in the transition state, results in an increase in the magnitude of the hydrogen-deuterium effect. The higher isotope effects observed for the ammonium salts containing the more powerful electron-withdrawing groups therefore would be considered by him to reflect the lower electron density at the β-carbon. Application of the Swain-Thornton rule, that the weaker a base the smaller will be the extent to which a proton is transferred from it to a second base at the transition state, allows one again to conclude that the C-H bond weakening is less in the transition states in which there is the smallest weakening of the $C-N^+$ bond.

A further development of the Swain-Thornton hypothesis relating to the effect of electron density on the magnitude of bond changes at the transition state is appropriate at this point. So far in this discussion it has been applied only with respect to the isolated three-atom system, C---H---B, without reference to the rest of the molecule. Its application to the total reacting system in an E2 process will now be explored.

Expressed formally, the Swain-Thornton rule states that electron-supplying substituents lengthen reacting bonds, which are bonds that are present in the transition state but entirely absent in either the reactants (for bonds being made) or in the products (for bonds being broken). Electron-withdrawing substituents, on the other hand, shorten such bonds. In addition, an alternating effect is predicted, such that if one bond is lengthened in the transition state then adjacent reacting bonds are shortened.

In conjugated systems, where the π system present can be conjugated with the transition state bonds, bond-lengthening and bond-shortening effects are considered to be associated with a reacting orbital and not with a single bond. A reacting orbital is defined as an electron cloud bounded by nuclei but containing no nuclei, which includes one reacting bond. The rule can be simply applied if, after identifying the reacting orbitals (each composed of the atomic orbital portions of a reacting bond plus all other atomic orbital portions which overlap with them at the transition state), one starts at the point of structure change and stars (*) the nearest reacting orbital(s) and alternate more remote reacting orbitals. The other reacting orbitals are denoted by wavemarks (~). The rule states that the bond utilizing starred orbitals are lengthened at the transition state by electron-supplying substituents and shortened by electron-withdrawing substituents; the opposite is true for bonds utilizing waved orbitals.

This rule can be illustrated using as an example an S_N2 displacement process. The transition state for this reaction can be pictured as



Here there are two reacting orbitals, one above the plane of the ring, one below. If one considers the substituent Z as the point of structure change, then both reacting orbitals must be starred since the substituent is symmetrically placed between them. Predictions based on the rule are borne out by experimental evidence when Z is made electron-withdrawing or electron-donating (110).

This rule has wide application in many reactions (110), although with E2 eliminations certain problems arise. One difficulty appears to reside in the definition of the rule. In the E2 transition state there are four reacting bonds: the B-H, C -H, C-Y, and the C_{α}-C_{β} bond. The rule states that a reacting orbital includes one reacting bond, but it does not specify whether more than one reacting bond can be present. The statement of the rule might suggest picturing the E2 reacting orbitals as in Fig. 14, where the lobes represent the orbitals. As illustrated, there are three orbitals

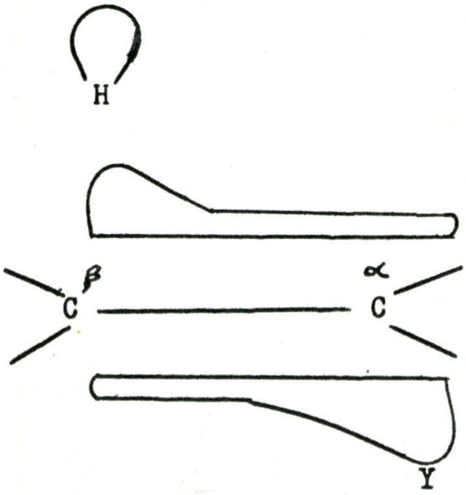


Fig. 14. Reacting Orbital Model For E2 Transition State

containing four reacting bonds, and the C_α-C_β bond is a part of two separate orbitals. Applying the rule to this model, electron-withdrawal at the β-carbon should shorten both the C-H and C-Y bonds in the transition state, since the substituent is symmetrically located between both reacting orbitals.

In the 2-arylethyltrimethylammonium ion reaction substituents on the <u>para</u>-position should have the same effect on C-H and C-N^+ bonds at the transition state. Electron-releasing substituents would be expected to lengthen these bonds, electron-withdrawing substituents should shorten them. This application of the Swain-Thornton rule therefore would appear to provide theoretical justification for the hypothesis that C-H and C-Y bond rupture parallel one another in the transition state of E2 reactions.

Further support for the hypothesis comes from the application of the "Hammond postulate" to the 2-arylethyltrimethylammonium series. Since, for an E2 reaction, the rupture of the C-H bond is involved in the rate-determining step, then electron-withdrawing substituents should help stabilize the developing negative charge and make the removal of the β-hydrogen energetically easier. That this is the case, is shown in Table XXI, where it is seen that the reaction of the <u>p</u>-CF_3 compound (where the CF_3 group is strongly electron-withdrawing) proceeds a great deal faster than the unsubstituted compound, k = 1950 and 4.38 l. mole^{-1} sec.$^{-1}$, respectively. The transition state for the CF_3 reaction, therefore, should occur earlier along the reaction co-ordinate than the transition state for the <u>p</u>-OMe compound and have less C-H and C-Y bond rupture.

Conclusions which are completely contrary to those of this thesis have been drawn by Simon (84) on the basis of his carbon and tritium isotope effect measurements, to which reference has been made earlier in this thesis. It will be recalled that the α-C^{14} effect was found to decrease with increased electron-withdrawal from the β-carbon, in agreement with the N^{15} results of the present study, and the β-tritium isotope effects were found to increase with this structural change. Thus, k^H/k^T was found to be 3.0 for $CH_3CH_2\overset{+}{N}(CH_3)_3$, 4.2 for $C_6H_5CH_2CH_2\overset{+}{N}(CH_3)_3$, and 8.0 for p-$NO_2C_6H_4CH_2CH_2\overset{+}{N}(CH_3)_3$. These results also agree with the work of this thesis. Simon then starts with the assumption that the sum of the "bond cleavages" in the transition state with the different compounds should be about the same. Since electron-withdrawing groups decrease C-N^+ bond rupture they must increase C-H rupture if this equality of total bond changes is to be retained. Interpretation of the hydrogen effects in terms of Westheimer's treatment then forces Simon to the conclusion that in the E2 reactions of the ammonium salts the β-hydrogen must be less than half transferred to base at the transition state. It is the view of the present author that the arguments presented in this thesis, based on both theoretical and experimental considerations, show that Simon's conclusion concerning the position of the proton in the three centre system, C---H---B, is not valid.

Finally, before concluding this discussion, reference should be made to some very recent work of Hodnett and Sparapany (117) on the magnitude of the nitrogen isotope effect in the E2 reaction of 2-(p-nitrophenyl)ethyltrimethylammonium ion. They found the very large effect of $(k^{14}/k^{15} - 1)100 = 2.4$ per cent for the reaction at 98° carried out in an aqueous solution buffered at a pH of 6.0. This value does not agree at all with the k^{14}/k^{15} effects for the reaction of 2-arylethyltrimethylammonium ions with sodium ethoxide in ethanol as shown in Table XXIII, where the observed trend with para-substitution would suggest a value of less than 0.8 per cent for the reaction of the p-nitro compound at 40°. The discrepancy might possibly be caused by differences between the solvents and bases used in the two studies. It is the view of the author that it is uncertain which species, water or hydroxide ion, is the active base for the reaction of the p-nitro compound in water in a buffered solution at pH = 6.0. If the base is water, then according to the hypothesis developed in this thesis, both the C-H and $C-N^+$ bonds should be ruptured a great deal more than when the base is ethoxide ion, and a larger nitrogen isotope effect would result. If the abstracting base is hydroxide ion, however, it becomes very difficult to rationalize the large effect found for the p-nitro compound in terms of the base strength of the abstracting base. One must then conclude that the solvent is playing an important role in determining the degree of bond rupture of the $C-N^+$ bond at the transition state or, alternatively, that either Hodnett and Sparapany's results or our own are in error. In this connection, it should be pointed out that in Hodnett and Sparapany's work isotopic analyses were performed on nitrogen gas originating from both the quaternary nitrogen and the nitro group and, furthermore, they did not appear to make any great effort to obtain pure nitrogen samples.

Theoretical Considerations Relating to the Interpretation of Hydrogen-Deuterium Effects

It is clear from the discussion in the preceeding section that, at the present time, there is no agreement concerning the relative importance of the different factors which can determine the magnitude of isotope effects in hydrogen transfer processes. Whereas Westheimer has assumed that stretching frequencies are of prime importance and has ignored bending frequencies, Bader has taken the completely opposite point of view. There is no question but that an exact treatment requires a consideration of both stretching and bending frequency changes.

At the present time, this author favours the Bader approximation. Willi and Wolfsberg (87) and Bell (88) have recently presented theoretical arguments suggesting that a consideration of stretching frequencies cannot account for the wide range of hydrogen-deuterium effects found. Furthermore, Bader's treatment, which states that the greater the electron density the lower the hydrogen-deuterium effect, receives some support from the isotope effect data presented in this thesis. It is seen, Fig. 13, that an approximately linear relationship exists between the rates of elimination, which depend to a large extent upon the acidity of a β-hydrogen, and the observed isotope effects.

Bader's hypothesis also receives support from a comparison of the results of the present study on the elimination reaction of 2-arylethyltrimethylammonium salts with those of Stewart (118) for the chromic acid oxidation of aryltrifluoromethylcarbinols. Whereas these two reaction systems show an entirely different relationship for the effect of substituents on rate (ρ = +3.66 for the 2-arylethyl system and -1.01 for the oxidation reaction) they exhibit exactly the same behaviour with respect to the effect of substituents on the hydrogen-deuterium isotope effect. This suggests that the magnitude of the hydrogen-deuterium effect is determined by a common factor in both cases. This could be the bending frequencies in the transition state as determined by the electron density.

EXPERIMENTAL

The Synthesis of a Series of Unlabelled 2-Arylethyltrimethylammonium Salts

General

Two methods were used for the preparation of the unlabelled 2-arylethyltrimethylammonium salts. One method, which was applied to the synthesis of the phenyl compound as well as to the p-methoxy- and p-chloro-substituted compounds, consisted of the displacement of tosylate ion from the 2-arylethyl tosylate by dimethylamine and quaternization of the resultant dimethyl 2-arylethylamine by reaction with methyl bromide. The second method, which was used for the p-trifluoromethyl-substituted compound, involved reduction of the substituted benzyl cyanide to primary amine which was then converted to the tertiary amine by the Eschweiler-Clarke reaction (119). The tertiary amine was then quaternized with methyl bromide.

2-Phenylethyltrimethylammonium Bromide

Preparation of 2-Phenylethyl p-Toluenesulfonate

This compound was prepared by the method of Tipson (120), 2-Phenylethyl alcohol (Fisher Certified Reagent), distilled before use, b.p. 110.5-111° (14 mm.), 25.3 g. (0.207 mole), was dissolved in 250 ml. of dry pyridine (Fisher Certified Reagent) which had been purified by refluxing for 8 hours over barium oxide and then distilling. The solution was cooled to -5° in an ice-salt bath and p-toluenesulfonyl chloride*, 43 g. (0.226 mole), was added with shaking to effect solution. After two hours, water was added in portions (3 x 4 ml., 8 ml. and 20 ml.) at 5 min. intervals with swirling while the temperature was kept below 5°. The reaction mixture was then diluted with 250 ml. of water and was extracted thrice with 250 ml. portions of chloroform. The combined chloroform extracts were washed five times with 200 ml. aliquots of ice-cold 10% sulfuric acid followed by three washings with 10% sodium bicarbonate and finally with three 250 ml. portions of water. The chloroform layer was dried over anhydrous sodium sulfate and then taken to dryness under reduced pressure to yield 46.5 g. (82%) of 2-phenylethyl p-toluenesulfonate, m.p. 37-38.5° (Saunders (81), m.p. 37.4-38.0).

Preparation of Dimethyl 2-Phenylethylamine

A solution of 55.2 g. of 2-phenylethyl p-toluenesulfonate (0.20 mole) and 18.0 g. of anhydrous dimethylamine (Eastman) (0.40 mole)

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* The p-toluenesulfonyl chloride was purified immediately before use. Thirty-five grams of p-toluenesulfonyl 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 Decolorizing Carbon and filtered. The volume of the filtrate was reduced to 65 ml. on a rotary evaporator and the p-toluenesulfonyl chloride was allowed to crystallize from the concentrated solution.

in 400 ml. of anhydrous ether was allowed to stand for two days with a little absolute ethanol being added occasionally to keep the mixture homogeneous. The reaction mixture was concentrated to 100 ml. under reduced pressure and was then poured into 300 ml. of water. This solution was extracted with five 50 ml. portions of ether and the ether extracts in turn were extracted with five 50 ml. portions of 10% hydrochloric acid. This acid solution was made basic by the addition of 10% sodium hydroxide and the resultant solution was extracted with three 100 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether was removed by distillation under reduced pressure to yield 19 g. (64%) of dimethyl 2-phenylethylamine, b.p. 99-100°/23 mm. (Saunders (81), b.p. 111°/20 mm.).

Preparation of 2-Phenylethyltrimethylammonium Bromide

Dimethyl 2-phenylethylamine, 19 g. (0.127 mole), in nitromethane (250 ml.) was treated with 24.2 g. (0.25 mole) of methyl bromide (Eastman). After standing for one day at room temperature, the crude salt was collected by filtration and after four recrystallizations from ethanol-ether it weighed 27 g. (87%), m.p. 237-238° (Saunders (81), m.p. 238-239°).

2-(p-Anisyl)ethyltrimethylammonium Bromide

The starting compound for the synthesis of 2-(p-anisyl)ethyltrimethylammonium bromide was p-methoxyacetophenone. This compound was converted to 2-(p-anisyl)acetic acid by means of the Willgerodt reaction (121). Reduction of the ethyl ester of this acid using lithium aluminum hydride converted it into 2-(p-anisyl)ethyl alcohol which was converted to the tosylate and thence to the quaternary salt in the usual way.

Preparation of 2-(p-Anisyl)acetic Acid

A mixture of 84 g. (0.56 mole) of p-methoxyacetophenone (Eastman), 27 g. of sulfur, and 60 ml. of morpholine was refluxed for 13 hr. under mechanical stirring in a fume-hood. The reaction mixture was then poured into 500 ml. of cold water to give an orange solid which was filtered, washed with water and then allowed to dry. This solid, 140 g., was added to 1100 ml. of 10% alcoholic sodium hydroxide solution and the resulting solution was refluxed for 10 hr. After removal of most of the alcohol by distillation, 400 ml. of water was added and the solution was acidified with 10% hydrochloric acid. This solution was extracted thrice with 200 ml. portions of ether and the combined extracts were dried overnight over anhydrous sodium sulfate. Removal of the solvent under reduced pressure produced a yellow crystalline product, 87 g. (92%) which was recrystallized three times from water to furnish a white solid, m.p. 87-90° (Dombrovskii (122), m.p. 86°).

Preparation of Ethyl 2-(p-Anisyl)acetate

A solution of 2-(p-anisyl)acetic acid, 32.0 g. (0.193 mole), in 100 ml. of absolute ethanol containing 4 ml. of conc. sulfuric acid was refluxed for 7 hr. The ester, 33 g. (88%), b.p. 158-158.5°/20 mm. (Livshits (123) b.p. 136-137°/10 mm.) was isolated in the usual way.

Preparation of 2-(p-Anisyl)ethanol

Ethyl 2-(p-anisyl)acetate was reduced with lithium aluminum hydride in ether to 2-(p-anisyl)ethanol by the method of Amundsen and Nelson (124). To an ice-cold solution of 6.84 g. (0.18 mole) of lithium aluminum hydride (Metal Hydrides, Inc.) in 300 ml. of anhydrous ether was slowly added with stirring 33.0 g. (0.17 mole) of ethyl 2-(p-anisyl)acetate dissolved in 50 ml. of anhydrous ether. After the addition, the reaction mixture was warmed with a water bath so as to maintain a gentle reflux for one hour. The reaction mixture was allowed to cool and water was then slowly added to decompose the excess hydride. The precipitated salts were removed by filtration and the filtrate was dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was distilled to give 22.1 g. (86%) of 2-(p-anisyl)ethanol, b.p. 154.5-155° /21 mm. (DePuy (10), b.p. 110-113°/1 mm.).

Preparation of 2-(p-Anisyl)ethyl p-Toluenesulfonate

p-Toluenesulfonyl chloride, purified by the procedure described on Page 138 of this thesis, 30.6 g. (0.16 mole), was added in three portions to an ice-cold solution of 22 g. (0.145 mole) of 2-(p-anisyl)-ethanol in 72 g. of purified anhydrous pyridine. The solution was swirled occasionally and kept at 0° for two days. The reaction mixture was then added slowly to 225 ml. of ice-cold 15% sulfuric acid and then 100 ml. of chloroform was added to achieve solution of the white solid present. The organic layer was separated and the aqueous layer extracted with five 90 ml. portions of chloroform. The organic layer and the extracts were combined and washed successively with 15% sulfuric acid, saturated sodium chloride, 10% sodium bicarbonate, and finally with saturated sodium chloride solution. The chloroform solution was then dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give 36.2 g. (83%) of 2-(p-anisyl)-ethyl p-toluenesulfonate, m.p. 58.5-59.5° (Winstein (125), 57-58°).

Preparation of Dimethyl 2-(p-Anisyl)ethylamine

Cold anhydrous dimethylamine, 13.0 g. (0.238 mole), was added to a cold solution of 36.0 g. (0.118 mole) of 2-(p-anisyl)ethyl p-toluenesulfonate in 240 ml. of anhydrous ether. The reaction was allowed to proceed for 9 days with small portions of absolute ethanol being added from time to time to maintain solution. The reaction mixture was then refluxed for 4 hours followed by concentration to 50 ml. under reduced pressure. The product was obtained from this solution by the same method as was described for the preparation of dimethyl 2-phenylethylamine. There was obtained 19.3 g. (91%) of product, b.p. 71-72°/0.05 mm. (Bushman (53), 100°/2 mm.).

Preparation of 2-(p-Anisyl)ethyltrimethylammonium Bromide

A two-fold excess of methyl bromide, 21 g. (0.22 mole), cooled to -30° in an acetone-dry ice bath was added to a similarly cooled solution of 19.3 g. (0.11 mole) of dimethyl 2-(p-anisyl)ethylamine in 125 ml. of nitromethane. The solution was allowed to stand for one day at room temperature and the solid product was filtered and recrystallized four times from ethanol-ether to give 27.3 g. (92%) of white crystals, m.p. 216.9-217.7 (Bushman (53), m.p. 217.7-218.2°).

2-(p-Chlorophenyl)ethyltrimethylammonium Bromide

This compound was made by a reaction sequence starting with p-chlorobenzyl cyanide. This compound was converted to ethyl 2-(p-chlorophenyl)acetate by ethanolysis, and the ester was reduced with lithium aluminum hydride to give 2-(p-chlorophenyl)ethanol. This alcohol was then converted to the tosylate and thence to the quaternary salt in the usual way.

Preparation of Ethyl 2-(p-Chlorophenyl)acetate

A solution of 76 g. (0.5 mole) of p-chlorobenzyl cyanide, 120 ml. of 95% ethanol and 53 ml. of conc. sulfuric acid was refluxed for 8 hours. At the end of this period the solution was cooled and then poured into 50 ml. of water. The upper layer was separated and was washed with 10% sodium carbonate, sodium chloride being added to facilitate the separation of the layers. The product was collected at 96-98°/1 mm. and weighed 90 g. (90%).

Preparation of 2-(p-Chlorophenyl)ethanol

This compound was prepared by the method of Amundsen and Nelson (124)by the reduction of 2-(p-chlorophenyl)ethyl acetate with lithium aluminum hydride as described in the synthesis of 2-(p-anisyl)-ethanol. Ethyl 2-(p-chlorophenyl)acetate, 90 g. (0.45 mole), was reduced with 17.2 g. (0.45 mole) of lithium aluminum hydride to produce 64.5 g. (91%) of 2-(p-chlorophenyl)ethanol, b.p. 86-87°/0.04 mm.

(DePuy (10), b.p. 98-100°/1 mm.).

Preparation of 2-(p-Chlorophenyl)ethyl p-Toluenesulfonate

This compound was prepared by the same method as was used for 2-(p-anisyl)ethyl p-toluenesulfonate. 2-(p-Chlorophenyl)ethanol, 64.5 g. (0.41 mole) was treated with 86.2 g. (0.45 mole) of p-toluenesulfonyl chloride to produce 109.4 g. (86%) of 2-(p-chlorophenyl)ethyl p-toluenesulfonate which was recrystallized twice from n-hexane - 30-60° petroleum ether - chloroform, m.p. 79.5-86.0° (Bushman (53), 79.5-80.1°).

Preparation of Dimethyl 2-(p-Chlorophenyl)ethylamine

This compound was prepared by the procedure described for dimethyl 2-(p-anisyl)ethylamine. 2-(p-Chlorophenyl)ethyl p-toluenesulfonate, 109.5 g. (0.35 mole), was treated with 38.4 g. (0.85 mole) of anhydrous dimethylamine to produce 55.2 g. (86%) of dimethyl 2-(p-chlorophenyl)ethylamine, b.p. 63-65°/0.2 mm. (Bushman (53), 104-106°/1.2 mm.).

Preparation of 2-(p-Chlorophenyl)ethyltrimethylammonium Bromide

This compound was prepared by the procedure described for 2-(p-anisyl)ethyltrimethylammonium bromide. A two-fold excess of methyl bromide, 63 g. (0.66 mole) was added to 55 g. of dimethyl 2-(p-chlorophenyl)ethylamine to produce 77.5 g. (92%) of crude 2-(p-chlorophenyl)ethyltrimethylammonium bromide, which was recrystallized five times from ethanol-ether to produce white crystals, m.p. 239.2-239.5° (Bushman (53), 242.3-242.6).

2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide

This compound was made by a reaction sequence starting with p-trifluoromethylbenzoic acid. This acid was converted to p-trifluoromethylbenzoyl chloride which was treated with ethanol to produce ethyl p-trifluoromethylbenzoate. The ester was converted to the alcohol by reduction with lithium aluminum hydride. The alcohol was then converted to the bromide by treatment with hydrobromic acid and this bromide was converted to the nitrile by a cyanide displacement. Reduction of the nitrile with lithium aluminum hydride and aluminum chloride produced the primary amine which was converted to dimethyl 2-(p-trifluoromethylphenyl)ethylamine by the Eschweiler-Clarke reaction (119). Quaternization of the tertiary amine produced 2-(p-trifluoromethylphenyl)ethyltrimethylammonium bromide.

Preparation of p-Trifluoromethylbenzoyl Chloride

To 88 g. (0.46 mole) of p-trifluoromethylbenzoic acid (Pierce Chemical Co.) was added 110 ml. of thionyl chloride, purified by the method described in Fieser and Fieser (126), and the mixture was refluxed on the steam bath for 24 hours. After removal of the excess thionyl chloride by distillation under reduced pressure, p-trifluoromethylbenzoyl chloride was distilled as a colourless liquid, 91.4 g. (95%), b.p. 84-85°/20 mm. (Jones (127), b.p. 199-200°/750 mm.).

Preparation of Ethyl p-Trifluoromethylbenzoate

Absolute (super-dry) ethanol, 72 g. (1.57 mole), was added dropwise to a solution of 98.5 g. (0.47 mole) of p-trifluoromethylbenzoyl chloride and 37.4 g. (0.47 mole) of pyridine at 10°. The reaction mixture was refluxed for three hours and, after cooling, was poured into 200 ml. of water which was then extracted thrice with 100 ml. portions of benzene. The combined benzene extracts were washed successively with 10% sulfuric acid, 10% sodium bicarbonate, and water. After removal of the solvent under reduced pressure, ethyl p-trifluoromethylbenzoate was distilled to give 90.6 g. (88%) of product, b.p. 106-107°/24 mm. (Haas (128), b.p. 80.0-80.5°/5.5 mm.).

Preparation of p-Trifluoromethylbenzyl Alcohol

Ethyl p-trifluoromethylbenzoate, 44 g. (0.20 mole), in 200 ml. of dry ether was added dropwise over a period of three hours to a mixture of 5.7 g. (0.15 mole) of lithium aluminum hydride in 100 ml. of dry ether. This mixture was refluxed for two hours and, after cooling water was added dropwise to destroy the excess lithium aluminum hydride. This was followed by the slow addition of 200 ml. of 10% sulfuric acid. The ether layer was separated and was washed successively with 10% sodium bicarbonate and water and was then dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, p-trifluoromethylbenzyl alcohol was distilled to give 34.3 g. (97%) of product, b.p. 116-117°/27 mm. (Haas (128), b.p. 78.5-80°/4 mm.).

Preparation of p-Trifluoromethylbenzyl Bromide

p-Trifluoromethylbenzyl alcohol, 35 g. (0.20 mole), was added to 105 g. (0.65 mole) of 48% hydrobromic acid and the resulting solution was refluxed for three hours. The reaction mixture separated into two layers on cooling. The aqueous layer was extracted with three 100 ml. portions of ether, the extracts were combined with the organic layer and washed successively with water, 10% sodium bicarbonate, and water. The ether solution was dried over anhydrous sodium sulfate and, following removal of the solvent by distillation, the product was distilled to give 35.7 g. (73%) of p-trifluoromethylbenzyl bromide, b.p. 93.5-94°/20 mm. (Haas (128), b.p. 65-66°/5 mm.).

Preparation of p-Trifluoromethylbenzyl Cyanide

This compound was prepared by cyanide displacement on p-trifluoromethylbenzyl bromide by the method described in Vogel (129). Sodium cyanide, 8.8 g., and 9 ml. of water were placed in a 100 ml. flask which was fitted with a reflux condensor. The mixture was warmed on the steam bath to dissolve the cyanide and then a solution of 33 g. (0.138 mole) of p-trifluoromethylbenzyl bromide in 40 ml. of 95% ethanol was added dropwise over a period of thirty minutes. The mixture was heated on the steam bath for four hours, then cooled and the precipitated sodium bromide removed by suction filtration. The filtrate was concentrated by distillation at reduced pressure and, after the addition of 100 ml. of water, the solution was extracted with three 100 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether was removed by distillation under reduced pressure. The product was distilled to give 18.6 g. (73%) of p-trifluoromethylbenzyl cyanide, b.p. 131-132°/20 mm. Analysis*: Calc. for $C_9H_6NF_3$; C, 58.40%; H, 3.26%; N, 7.56%. Found: C, 58.62%; H, 3.42%; N, 7.28%.

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* Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Preparation of 2-(p-Trifluoromethylphenyl)ethylamine

This compound was prepared by the method described by Nystrom (130). A solution of 0.1 mole of lithium aluminum hydride in 100 ml. of anhydrous ether was placed in a three-necked flask fitted with a dropping funnel, reflux condenser, and a mercury-sealed stirrer. A solution of 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 100 ml. of anhydrous ether was added rapidly with vigorous stirring and after five minutes, a solution of 0.1 mole of p-trifluoromethylbenzyl cyanide in 150 ml. of dry ether was added dropwise over one hour. Water was added to decompose the excess hydride and the aluminum salts were brought into solution by the addition of 160 ml. of 6 N sulfuric acid followed by 100 ml. of water. The clear solution was placed in a separatory funnel and the ether layer was separated and discarded. The aqueous layer was washed with four 100 ml. portions of ether, then cooled in ice and treated with 10% sodium hydroxide until a pH of 11 was reached. The basic solution was diluted to 500 ml. with water and then extracted with four 100 ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure gave the product which was distilled to give 15.1 g. (80%) of 2-(p-trifluoromethylphenyl)ethylamine, b.p. 105.5-106°/22 mm. Analysis: Calc. for $C_9H_{10}NF_3$; C, 57.20%; H, 5.34%; N, 7.40%. Found: C, 55.59%; H, 5.20%; N, 7.18%.

Preparation of Dimethyl 2-(p-Trifluoromethylphenyl)ethylamine

This compound was prepared from 2-(p-trifluoromethylphenyl)-ethylamine by the method described in Organic Syntheses (119). To 20.5 g. (0.4 mole) of ice-cooled 90% formic acid was added 15.1 g.

(0.08 mole) of 2-(p-trifluoromethylphenyl)ethylamine followed by 20.2 ml. (0.24 mole) of 37% formalin. The flask was fitted with a reflux condenser and heated in an oil bath at 95°C. Within five minutes a vigorous evolution of carbon dioxide was observed and the flask was then removed from the oil bath. After waiting fifteen minutes for the reaction to subside, the flask was returned to the oil bath for a further eight hours. The solution was cooled and 45 ml. of 4 N hydrochloric acid was added. The resulting solution was taken to dryness under reduced pressure, the resultant pale yellow solid was dissolved in 30 ml. of water and the organic base was liberated by the slow addition of 10% sodium hydroxide. The organic layer was separated and the aqueous layer was extracted thrice with 30 ml. portions of benzene. The base, together with the benzene extracts, was dried over five g. of anhydrous potassium carbonate and, after removal of the solvent by distillation under reduced pressure, the product was distilled to give 14.5 g. (84%) of dimethyl 2-(p-trifluoromethylphenyl)ethylamine, b.p. 108-108.5°/23 mm. Analysis: Calc. for $C_{11}H_{14}NF_3$; C, 60.81%; H, 6.50%; N, 6.45%. Found: C, 60.85%; H, 6.67%; N, 6.37%.

Preparation of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide

An ice-cooled solution of dimethyl 2-(p-trifluoromethylphenyl)-ethylamine, 14.5 g. (0.067 mole), in 120 ml. of nitromethane was treated with 12.8 g. (0.13 mole) of methyl bromide to yield 18.8 g. (89%) of 2-(p-trifluoromethylphenyl)ethyltrimethylammonium bromide which was recrystallized five times from ethanol-ether to give a product melting at 227.5-228°. Analysis: Calc. for $C_{12}H_{17}NBrF_3$; C, 46.18%; H, 5.49%; N, 4.49%. Found: C, 46.18%; H, 5.56%; N, 4.56%.

The Synthesis of Deuterated 2-Arylethyltrimethylammonium Salts

General

2-Phenylethyltrimethylammonium-2,2-$\underline{d}_2$ bromide has been synthesized previously by Saunders and Edison (81). Their method began with the preparation of ethyl phenylacetate-α,α-$\underline{d}_2$ by the treatment of the sodium salt of diethyl phenylmalonate with deuterium oxide. The ethyl phenylacetate-α,α-$\underline{d}_2$ was then converted to the quaternary ammonium salt by the following steps: reduction of the ester to the corresponding alcohol; preparation of the tosylate of the alcohol; displacement with dimethylamine on the tosylate to form the tertiary amine; and finally quaternization to form the quaternary ammonium salt.

It was found that the p-methoxy-derivative as well as the parent compound could be made successfully by this method. With the p-chloro- and p-trifluoromethyl-compounds, however, the products were found to be only approximately 70 per cent deuterated and it was necessary to use an alternative method of synthesis which is outlined in the following equations.

$$\text{Ar}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-OEt} \xrightarrow{\text{LiAlD}_4} \text{Ar-CD}_2\text{-OH} \qquad (93)$$

$$\text{Ar-CD}_2\text{-OH} \xrightarrow{\text{HBr}} \text{Ar-CD}_2\text{-Br} \qquad (94)$$

$$\text{Ar-CD}_2\text{-Br} \xrightarrow[\text{EtOD}]{\text{CN}^-} \text{Ar-CD}_2\text{-CN} \qquad (95)$$

$$\text{Ar-CD}_2\text{-CN} \xrightarrow[\text{AlCl}_3]{\text{LiAlH}_4} \text{Ar-CD}_2\text{-CH}_2\text{-NH}_2 \qquad (96)$$

$$\text{Ar-CD}_2\text{-CH}_2\text{-NH}_2 \xrightarrow[\text{HCOOH}]{\text{HCHO}} \text{Ar-CD}_2\text{-CH}_2\text{-N(CH}_3)_2 \qquad (97)$$

$$\text{Ar-CD}_2\text{-CH}_2\text{-N(CH}_3)_2 \xrightarrow{\text{CH}_3\text{Br}} \text{Ar-CD}_2\text{-CH}_2\text{-}\overset{+}{\text{N}}\text{(CH}_3)_3\text{Br}^- \qquad (98)$$

The appropriate *p*-substituted ethyl benzoate was first reduced with lithium aluminum deuteride to give the *p*-substituted benzyl-α,α-d_2 alcohol which was converted to the corresponding bromide by treatment with hydrobromic acid. Because the next step, which involves the displacement of bromide ion with cyanide ion, was found to give the nitrile with a significant loss of deuterium when carried out in hydroxylic solvents having natural isotopic abundance, this reaction was carried out in a mixture of EtOD and D_2O. The *p*-substituted benzyl-α,α-d_2 cyanide so obtained was better than 99 per cent deuterated. The nitrile was converted by reduction with lithium aluminum hydride/aluminum chloride to the primary amine, which was converted to the tertiary amine using the Eschweiler-Clarke reaction (119). Quaternization gave the *p*-substituted 2-phenylethyltrimethylammonium-2,2-d_2 bromide.

2-Phenylethyltrimethylammonium ion, labelled with deuterium in the α-position, was prepared by reducing ethyl phenylacetate with lithium aluminum deuteride to give 2-phenylethanol-1,1-$\underline{d}_2$, which was then converted to the quaternary salt through the p-toluenesulfonate and the tertiary amine in the usual way.

The deuterium content of each intermediate in every reaction sequence was determined by a nuclear magnetic resonance analysis using a Varian A-60 spectrometer. In all cases the deuterium content was found to be better than 99 per cent. Because of the complexity of the spectrum, N.M.R. analysis was not suitable for the quaternary salts. These were analyzed for their deuterium content by Nemeth of the University of Illinois using the falling-drop method. From the results, shown in Table XXIV, it would appear that the compounds were only 94 to 98 per cent deuterated in the 2-position. It is the view of the author, however, that Nemeth's values are low because of inter-

Table XXIV

Results of Deuterium Analyses* on the

2-Arylethyltrimethylammonium Bromides

Quaternary Ammonium Ion	Atoms D/ molecule
2-Phenylethyltrimethylammonium-2,2-$\underline{d}_2$ bromide	1.88
2-(p-Anisyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide	1.92
2-(p-Chlorophenyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide	1.92
2-(p-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide	1.96
2-Phenylethyltrimethylammonium-1,1-$\underline{d}_2$ bromide	1.94

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* Deuterium analyses on the quaternary ammonium salts were performed by Mr. J. Nemeth, 303 W. Washington St., Urbana, Ill.

ference of nitrogen and bromine in the compounds being analyzed. These elements are known to cause difficulties. This view is supported by the fact that N.M.R. analysis of all intermediates showed better than 99 per cent deuteration at the 2-position and, also, by the value of 2.00 atoms D/molecule obtained by Nemeth for 2-phenylethanol-1,1-$\underline{d}_2$, the precursor of 2-phenylethyltrimethylammonium-1,1-$\underline{d}_2$ bromide. Loss of deuterium in the quaternization step seems most unlikely.

2-Phenylethyltrimethylammonium-2,2-$\underline{d}_2$ Bromide

Preparation of Ethyl Phenylacetate-α,α-$\underline{d}_2$

A solution of 83 g. (0.35 mole) of diethyl phenylmalonate (Eastman) in 350 ml. of sodium-dried petroleum ether (30-60°) was filtered through a column of adsorption alumina and was then added over six hours to a well-stirred mixture of 150 ml. of petroleum ether and 16.6 g. of a 50% dispersion of sodium hydride in mineral oil (Metal Hydrides Inc.). The resulting white solid was removed by filtration after two hours of stirring and was repeatedly washed with petroleum ether. The solvent was removed from the solid by pumping overnight in a vacuum desiccator. The dried sodium salt, 74 g., was added to 60 g. of deuterium oxide and the mixture was refluxed for eight hours under purified nitrogen. The organic layer was separated and the aqueous layer was extracted thrice with 50 ml. portions of ether. The ether extracts, together with the organic layer, were dried over anhydrous magnesium sulfate and, after removal of the solvent by distillation under reduced pressure, the product was distilled through a short Vigreux column to give 15.1 g. (27%) of ethyl phenylacetate-α,α-$\underline{d}_2$, b.p. 101.5-102°/11 mm. (Saunders (53), b.p. 73-74°/0.5 mm.). N.M.R. analysis indicated 1.98 atoms D/molecule.

Preparation of 2-Phenylethanol-2,2-$\underline{d}_2$

This compound was prepared by a lithium aluminum hydride reduction of ethyl phenylacetate-α,α-$\underline{d}_2$ using the procedure previously described for the synthesis of 2-($\underline{p}$-anisyl)ethanol. Ethyl phenylacetate-α,α-$\underline{d}_2$, 15.1 g. (0.092 mole) was reduced with 0.082 mole of lithium aluminum hydride to yield 9.6 g. (86%) of 2-phenylethanol-2,2-$\underline{d}_2$, b.p. 105-106°/13 mm. (Saunders (53), b.p. 110°/20 mm.).

Preparation of 2-Phenylethyl-2,2-$\underline{d}_2$ $\underline{p}$-Toluenesulfonate

This compound was prepared from 2-phenylethanol-2,2-$\underline{d}_2$ by the procedure described for the synthesis of the undeuterated compound. 2-Phenylethanol-2,2-$\underline{d}_2$, 9.6 g., was treated with 16.3 g. of $\underline{p}$-toluenesulfonyl chloride in 95 ml. of dry pyridine to produce 19.2 g. (89%) of 2-phenylethyl-2,2-$\underline{d}_2$ $\underline{p}$-toluenesulfonate, m.p. 37.0-38.0° (Saunders (53), m.p. 37.4-38°).

Preparation of Dimethyl 2-Phenylethylamine-2,2-$\underline{d}_2$

This compound was prepared from 2-phenylethyl-2,2-$\underline{d}_2$ $\underline{p}$-toluenesulfonate by the procedure described for the synthesis of the undeuterated compound. 2-Phenylethyl-2,2-$\underline{d}_2$ $\underline{p}$-toluenesulfonate, 19.2 g., was treated with 6.3 g. of anhydrous dimethylamine in 110 ml. of anhydrous ether to produce 7.4 g. (57%) of dimethyl 2-phenylethylamine-2,2-$\underline{d}_2$, b.p. 99.5-100°/23 mm. (Saunders (53), b.p. 111°/20 mm.).

Preparation of 2-Phenylethyltrimethylammonium-2,2-$\underline{d}_2$ Bromide

This compound was prepared from dimethyl 2-phenylethylamine-2,2-$\underline{d}_2$ by treatment with methyl bromide as was described for the synthesis of the corresponding undeuterated compound. Dimethyl 2-phenylethylamine-2,2-$\underline{d}_2$, 7.4 g., in 60 ml. of nitromethane cooled to 0° was treated with 9.5 g. of methyl bromide. The resulting 2-phenylethyltrimethylammonium-2,2-$\underline{d}_2$ bromide, 10.2 g. (84%), was recrystallized four times from ethanol-ether, m.p. 237.3-238° (Saunders (53), m.p. 238-239°). Deuterium analysis by Nemeth indicated 1.88 atoms D/molecule.

2-(p-Anisyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ Bromide

Preparation of Diethyl p-Anisylmalonate

This compound was prepared by condensing ethyl oxalate with ethyl 2-(p-anisyl)acetate in the presence of base by the method described in Organic Syntheses (131). In a 500 ml. three-necked flask, fitted with a mercury sealed stirrer, reflux condenser and dropping funnel, was placed 93 ml. of absolute ethanol and 4.27 g. of cleanly-cut sodium was added in small portions. The mixture was warmed until the sodium had completely dissolved. After cooling the solution to 60°, 27 g. (0.185 mole) of ethyl oxalate was added in a rapid stream with vigorous stirring. The ethyl oxalate was washed down with a small amount of absolute ethanol which was followed immediately by the addition of 38 g. (0.185 mole) of ethyl 2-(p-anisyl)acetate. The stirring was continued for one-half hour at 60° and the solution then was allowed to stand at room temperature for twelve hours during which the product separated as a nearly solid paste. Following the addition of 150 ml. of dry ether, the solid was filtered and repeatedly washed with dry ether. After drying this salt in a vacuum desiccator for twelve hours, it was treated with dilute sulfuric acid (6 ml. of conc. sulfuric acid in 100 ml. of water) in order to liberate the p-anisyloxaloacetic ester. The almost colourless oil which separated was combined with three 20 ml. ether extracts of the aqueous phase and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residual oil was placed in a modified Claisen flask with a fractionating side-arm and then was heated under the pressure of approximately 10 mm. in a bath of Wood's metal. The temperature of the bath was brought gradually to 160° and kept there until the evolution of carbon monoxide was complete. The product distilling at 171-172°/3 mm. weighed 31 g. (63%). Analysis: Calc. for $C_{14}H_{18}O_5$; C, 63.10%; H, 6.81%. Found: C, 62.98%; H, 6.88%.

Preparation of Ethyl 2-(p-Anisyl)acetate-α,α-d_2

This compound was prepared from diethyl p-anisylmalonate by the procedure described for the preparation of ethyl phenylacetate-α,α-d_2 from diethyl phenylmalonate.

A solution of 61 g. of diethyl p-anisylmalonate was treated with 10.8 g. of a 50% dispersion of sodium hydride in mineral oil to produce 61.5 g. of the sodium salt which was heated with 50 ml. of deuterium oxide to form ethyl 2-(p-anisyl)acetate-α,α-d_2, 24 g. (54%), b.p. 162-164°/ 23 mm. (Livshits (123), b.p. 136-137°/10 mm.). N.M.R. analysis indicated that this compound was deuterated to better than 99 per cent at the benzyl carbon.

Preparation of 2-(p-Anisyl)ethanol-2,2-d_2

This compound was prepared by the lithium aluminum hydride reduction of ethyl 2-(p-anisyl)acetate-α,α-d_2 using the procedure described for the corresponding undeuterated compound. Ethyl 2-(p-anisyl)acetate-α,α-d_2, 9.3 g. (0.048 mole), was treated with 1.78 g. (0.047 mole) of lithium aluminum hydride to produce 7.1 g. (97%) of 2-(p-anisyl)ethanol-2,2-d_2, b.p. 159-160.5°/23 mm. (DePuy (10), b.p. 110-113°/1 mm.).

Preparation of 2-(p-Anisyl)ethyl-2,2-d_2 p-Toluenesulfonate

This compound was prepared from the corresponding alcohol by the same procedure used for the synthesis of the undeuterated compound. p-Toluenesulfonyl chloride, 7.5 g., was added to 5.4 g. of 2-(p-anisyl)-ethanol-2,2-d_2 to produce 7.0 g. (64%) of the deuterated tosylate, m.p. 58.2-59° (Winstein (125), m.p. 57-58°).

Preparation of Dimethyl 2-(p-Anisyl)ethylamine-2,2-d_2

This compound was prepared from the tosylate using the procedure described for the preparation of the corresponding undeuterated compound. 2-(p-Anisyl)ethyl-2,2-d_2 p-toluenesulfonate, 7.0 g., was treated with 2.5 g. of dimethylamine to produce dimethyl 2-(p-anisyl)ethylamine-2,2-d_2, b.p. 140-142°/22 mm. (Bushman (53), b.p. 100°/2 mm.) which weighed 4.2 g. (100%).

Preparation of 2-(p-Anisyl)ethyltrimethylammonium-2,2-d_2 Bromide

This compound was prepared by the same procedure as the corresponding undeuterated compound. Dimethyl 2-(p-anisyl)ethylamine-2,2-d_2, 4.2 g., was treated with 6.0 g. of methyl bromide to produce 6.0 g. (94%) of 2-(p-anisyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide which was recrystallized four times from ethanol-ether, m.p. 217.2-217.8° (Bushman (53), m.p. 217.7-218.2°). A deuterium analysis by Nemeth indicated that this compound had 1.92 atoms D/molecule.

2-(p-Chlorophenyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ Bromide

Preparation of p-Chlorobenzyl-α,α-$\underline{d}_2$ Alcohol

This compound was prepared by the lithium aluminum deuteride reduction of ethyl p-chlorobenzoate using the procedure described for the reduction of unlabelled ethyl p-trifluoromethylbenzoate. Ethyl p-chlorobenzoate, 16.1 g., was reduced with lithium aluminum deuteride (Metal Hydrides Inc.), 2.0 g., to produce 10.4 g. (83%) of p-chlorobenzyl-α,α-$\underline{d}_2$ alcohol, which was recrystallized from ethanol, m.p. 72-73° (Carothers (132), m.p. 73°). N.M.R. analysis indicated better than 99 per cent deuteration at the benzyl carbon.

Preparation of p-Chlorobenzyl-α,α-$\underline{d}_2$ Bromide

This compound was prepared by the procedure described for p-trifluoromethylbenzyl bromide. p-Chlorobenzyl-α,α-$\underline{d}_2$ alcohol, 10.4 g., was refluxed for three hours with 31 g. of 48% hydrobromic acid to give 14.0 g. (94%) of p-chlorobenzyl-α,α-$\underline{d}_2$ bromide, which was recrystallized twice from ethanol, m.p. 50.5-51.0° (Slater (133), m.p. 51°). N.M.R. analysis indicated better than 99 per cent deuteration at the benzyl carbon.

Preparation of p-Chlorobenzyl-α,α-$\underline{d}_2$ Cyanide

This compound was prepared by the same procedure as was p-trifluoromethylbenzyl cyanide. p-Chlorobenzyl-α,α-d_2 bromide, 13 g., in 19 ml. of ethanol-O-d, was treated with 3.0 g. of anhydrous sodium cyanide dissolved in 5.2 ml. of deuterium oxide to give 9.1 g. (95%) of p-chlorobenzyl-α,α-$\underline{d}_2$ cyanide, which was recrystallized from ethanol, m.p. 28-30° (Straus (134), m.p. 30°). An N.M.R. analysis of this compound indicated that it was better than 99 per cent deuterated at the benzyl carbon.

The ethanol-O-d was recovered from the reaction mixture by distillation under reduced pressure. Five milliliters of D_2O were added to the distillate, in order to decrease the solubility of organic material in the ethanol, and the resulting solution was extracted thrice with 10 ml. portions of ether. The product, approximately 60 per cent ethanol-O-d - 40 per cent D_2O, after fractional distillation, was shown to be free of organic materials by nuclear magnetic resonance and infrared analyses and contained less than one per cent ethanol-O-h.

Preparation of 2-(p-Chlorophenyl)ethylamine-2,2-$\underline{d}_2$

This compound was prepared by the method described for 2-(p-trifluoromethylphenyl)ethylamine. p-Chlorobenzyl-α,α-$\underline{d}_2$ cyanide, 9.1 g. (0.059 mole), was treated with 2.25 g. of lithium aluminum hydride and 7.8 g. of anhydrous aluminum chloride to give 7.7 g. (83%) of 2-(p-chlorophenyl)ethylamine-2,2-$\underline{d}_2$, b.p. 118-120°/15 mm. (McCoubrey (135), b.p. 120°/15 mm.). This compound was shown by N.M.R. analysis to be better than 99 per cent deuterated at the benzyl carbon.

Preparation of Dimethyl 2-(p-Chlorophenyl)ethylamine-2,2-d_2

This compound was prepared by the same procedure as was dimethyl 2-(p-trifluoromethylphenyl)ethylamine. 2-(p-Chlorophenyl)-ethylamine-2,2-d_2, 7.7 g. (0.049 mole), was treated with 12.6 g. of 90% formic acid and 12.3 ml. of a 37% solution of formaldehyde to give 8.0 g. (88%) of dimethyl 2-(p-chlorophenyl)ethylamine-2,2-d_2, b.p. 81-82°/0.8 mm. (Bushman (53), b.p. 104-106°/1.2 mm.).

Preparation of 2-(p-Chlorophenyl)ethyltrimethylammonium-2,2-d_2 Bromide

This compound was prepared by the procedure described for the corresponding undeuterated compound. Dimethyl 2-(p-chlorophenyl)ethylamine-2,2-d_2, 8.0 g., was treated with 9.2 g. of methyl bromide to give 11.0 g. (91%) of 2-(p-chlorophenyl)ethyltrimethylammonium-2,2-d_2 bromide, which was recrystallized four times from ethanol-ether, m.p. 240-240.5° (Bushman (53), m.p. 242.3-242.6°). A deuterium analysis by Nemeth indicated that this compound had 1.92 atoms D/molecule.

2-(p-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-d_2 Bromide

Preparation of p-Trifluoromethylbenzyl-α,α-d_2 Alcohol

This compound was prepared by the same method as the corresponding undeuterated compound. Ethyl p-trifluoromethylbenzoate, 15.3 g. (0.068 mole), was added to 2.0 g. of lithium aluminum deuteride to give 10.5 g. (87%) of p-trifluoromethylbenzyl-α,α-d_2 alcohol, b.p. 116-117°/27 mm. (Haas (128), b.p. 78.5-80°/4 mm.). An N.M.R. analysis of this compound showed that it was better than 99 per cent deuterated at the benzyl carbon.

Preparation of *p*-Trifluoromethylbenzyl-α,α-d_2 Bromide

This compound was prepared by the same procedure as was the corresponding undeuterated compound. *p*-Trifluoromethylbenzyl-α,α-d_2 alcohol, 5.0 g. (0.029 mole), was added to 48% hydrobromic acid, 15.0 g. (.093 mole), to give 5.1 g. (73%) of *p*-trifluoromethylbenzyl-α,α-d_2 bromide, b.p. 93.4-93.8°/20 mm. (Haas 128), b.p. 65-66°/5 mm.). This compound was shown by N.M.R. analysis to be better than 99 per cent deuterated at the benzyl carbon.

Preparation of *p*-Trifluoromethylbenzyl-α,α-d_2 Cyanide

This compound was prepared from *p*-trifluoromethylbenzyl-α,α-d_2 bromide by the method described for the corresponding undeuterated compound only using deuterated solvent in the cyanide displacement reaction. *p*-Trifluoromethylbenzyl-α,α-d_2 bromide, 12.4 g. in 15 ml. of 95% ethanol-O-*d*, was treated with 3.3 g. of anhydrous sodium cyanide dissolved in 3.4 ml. of deuterium oxide to give 9.3 g. (97%) of *p*-trifluoromethylbenzyl-α,α-d_2 cyanide, b.p. 130.5-131.5°/20 mm. This compound was shown by N.M.R. analysis to be better than 99 per cent deuterated at the benzyl carbon.

Preparation of 2-(*p*-Trifluoromethylphenyl)ethylamine-2,2-d_2

This compound was prepared from the *p*-substituted benzyl cyanide by the method described for the corresponding undeuterated compound. *p*-Trifluoromethylbenzyl-α,α-d_2 cyanide, 9.3 g., was treated with 1.9 g. of lithium aluminum hydride and 6.7 g. of anhydrous aluminum chloride in ether to give 7.2 g. (76%) of 2-(*p*-trifluoromethylphenyl)ethylamine-2,2-d_2, b.p. 58-59°/1 mm. An N.M.R. of this compound indicated that it was deuterated to better than 99 per cent at the benzyl carbon.

Preparation of Dimethyl 2-(p-Trifluoromethylphenyl)ethylamine-2,2-$\underline{d}_2$

This compound was prepared from the primary amine by the procedure described for the undeuterated compound. 2-(p-Trifluoromethylphenyl)ethylamine-2,2-$\underline{d}_2$, 7.2 g., was added to 9.8 g. of 90% formic acid and 9.6 g. of 37% formaldehyde solution and the solution was refluxed for 8 hours to produce 6.0 g. (73%) of dimethyl 2-(p-trifluoromethylphenyl)ethylamine-2,2-$\underline{d}_2$, b.p. 58-59°/0.8 mm.

Preparation of 2-(p-Trifluoromethylphenyl)trimethylammonium-2,2-$\underline{d}_2$ Bromide

This compound was prepared by the quaternization of the tertiary amine with methyl bromide. Dimethyl 2-(p-trifluoromethylphenyl)ethylamine-2,2-$\underline{d}_2$, 6.0 g., was treated with 5.3 g. of methyl bromide in nitromethane to yield 7.2 g. (84%) of 2-(p-trifluoromethylphenyl)ethyltrimethylammonium-2,2-$\underline{d}_2$ bromide, m.p. 228-228.5°. A deuterium analysis by Nemeth indicated that this compound had 1.96 atoms D/molecule.

2-Phenylethyltrimethylammonium-1,1-$\underline{d}_2$ Bromide

Preparation of 2-Phenylethanol-1,1-$\underline{d}_2$

This compound was prepared by the lithium aluminum deuteride reduction of ethyl phenylacetate as previously described. Ethyl phenylacetate, 15.0 g. (0.082 mole), was treated with 3.44 g. (0.082 mole) of lithium aluminum deuteride (Metal Hydrides Inc.) to yield 8.8 g. (86%) of 2-phenylethanol-1,1-$\underline{d}_2$, b.p. 115-115.5°/19 mm. (Mousseron (136), b.p. 120°/15 mm.). Deuterium analysis by Nemeth showed 2.00 atoms D/molecule.

Preparation of 2-Phenylethyl-1,1-d_2 p-Toluenesulfonate

This compound was prepared by the procedure described for the corresponding undeuterated compound. 2-Phenylethanol-1,1-d_2, 8.8 g., was treated with 15 g. of p-toluenesulfonyl chloride in 95 ml. of dry pyridine to give 17.0 g. (71%) of 2-phenylethyl-1,1-d_2 p-toluenesulfonate, m.p. 37-38° (Saunders (81), m.p. 37.4-38.0).

Preparation of Dimethyl 2-Phenylethylamine-1,1-d_2

This compound was prepared by the procedure described for the corresponding undeuterated compound. 2-Phenylethyl-1,1-d_2 p-toluenesulfonate, 17.0 g., was treated with 6.2 g. of anhydrous dimethylamine in 110 ml. of anhydrous ether to give 5.0 g. (55%) of dimethyl 2-phenylethylamine-1,1-d_2, b.p. 97-98°/20 mm. (Saunders (81), 111°/20 mm.).

Preparation of 2-Phenylethyltrimethylammonium-1,1-d_2 Bromide

This compound was prepared by the procedure described for the preparation of the corresponding undeuterated compound. Dimethyl 2-phenylethylamine-1,1-d_2, 5.0 g., was treated with 6.4 g. of methyl bromide in 50 ml. of nitromethane at 0°C to give 7.0 g. (86%) of 2-phenylethyltrimethylammonium-1,1-d_2 bromide, which was recrystallized four times from ethanol-ether, m.p. 237.5-238° (Saunders (81), m.p. 238-239°). A deuterium analysis by Nemeth indicated that this compound had 1.94 atoms D/molecule.

Kinetic Studies

General

A spectroscopic method described by Saunders and Williams (77) for product analysis at 100 per cent reaction, was used to follow the rates of reaction of the deuterated and undeuterated β-arylethyltrimethylammonium ions with sodium ethoxide in ethanol. The products, *para*-substituted styrenes, exhibit strong absorption in the ultra-violet, while the absorption of the other components of the reaction mixture at this wave length is negligible.

Briefly, the method was as follows. A small sample of the reaction mixture was withdrawn at regular time intervals and added to 95% ethanol. (The ethanol was distilled before use.) Each sample was diluted to a standard volume with additional 95% ethanol and the optical density was determined at the appropriate wave length for the particular styrene formed. The concentration of these solutions was calculated in the usual way from the extinction coefficient of the *para*-substituted styrene under investigation.

Both λ_{max} and the molar extinction coefficient at λ_{max} for styrene, *p*-methoxystyrene and *p*-chlorostyrene had previously been reported by Bushman (53) and his values for these quantities were used in the work of this thesis. *p*-Trifluoromethylstyrene had not been previously reported. A pure sample was therefore synthesized* by a

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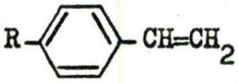
* The sample of *p*-trifluoromethylstyrene for extinction coefficient measurements was prepared as follows. 2-(*p*-Trifluoromethylphenyl)-ethyltrimethylammonium bromide, 5.0 g., was dissolved in 20 ml. of water, and 10 ml. of 10% sodium hydroxide was added. The mixture was gently refluxed by warming on the steam-bath until cessation of the trimethylamine evolution (2 hours). The contents of the reaction flask were poured into a separatory funnel and the styrene was separated and dried over drierite. It was distilled from 0.1 g. of pyrocatechol through a two-foot tantalum-wire volume under reduced pressure to give 2.5 g. (91%) of *p*-trifluoromethylstyrene, b.p. 71.5- 71.6°/43 m.m.; n_D^{25} = 1.4650 (Kraus (139), b.p. 65.8°/40 m.m.; n_D^{25} = 1.4648).

Hofmann elimination reaction on the quaternary salt and its ultraviolet spectrum determined. The optical properties of all four styrenes are given in Table XXV.

Table XXV

U.V. Absorption of p-Substituted Styrenes in 95% Ethanol



Compound R	λ_{max} mμ	Molar Extinction Coefficient x 10-4
H	248	1.38
OCH_3	258	1.92
Cl	253	1.97
CF_3	250	1.62

Procedures

Preparation of Sodium Ethoxide Solutions for Kinetic Measurements

One-hundred milliliters of anhydrous ethanol, purified by the method of Lund and Bjerrum (137), was placed in a storage vessel shown in Fig. 15 and cooled to 0°. Nitrogen gas, purified by the procedure outlined in Vogel (138), was allowed to bubble through the vessel for one hour. Sodium metal, 2.3g., was added in small portions giving in about five hours a clear, colourless solution of approximately one molar sodium ethoxide. This stock solution was stored in the refrigerator and used to prepare dilute solutions for kinetic measurements when required.

Kinetic Measurements

A standard solution of sodium ethoxide was prepared and placed in the constant-temperature bath maintained at the required temperature to ± 0.02°C. A known weight of the quaternary salt was weighed into the reaction flask (Fig. 16), which was a 50-ml. volumetric flask to which

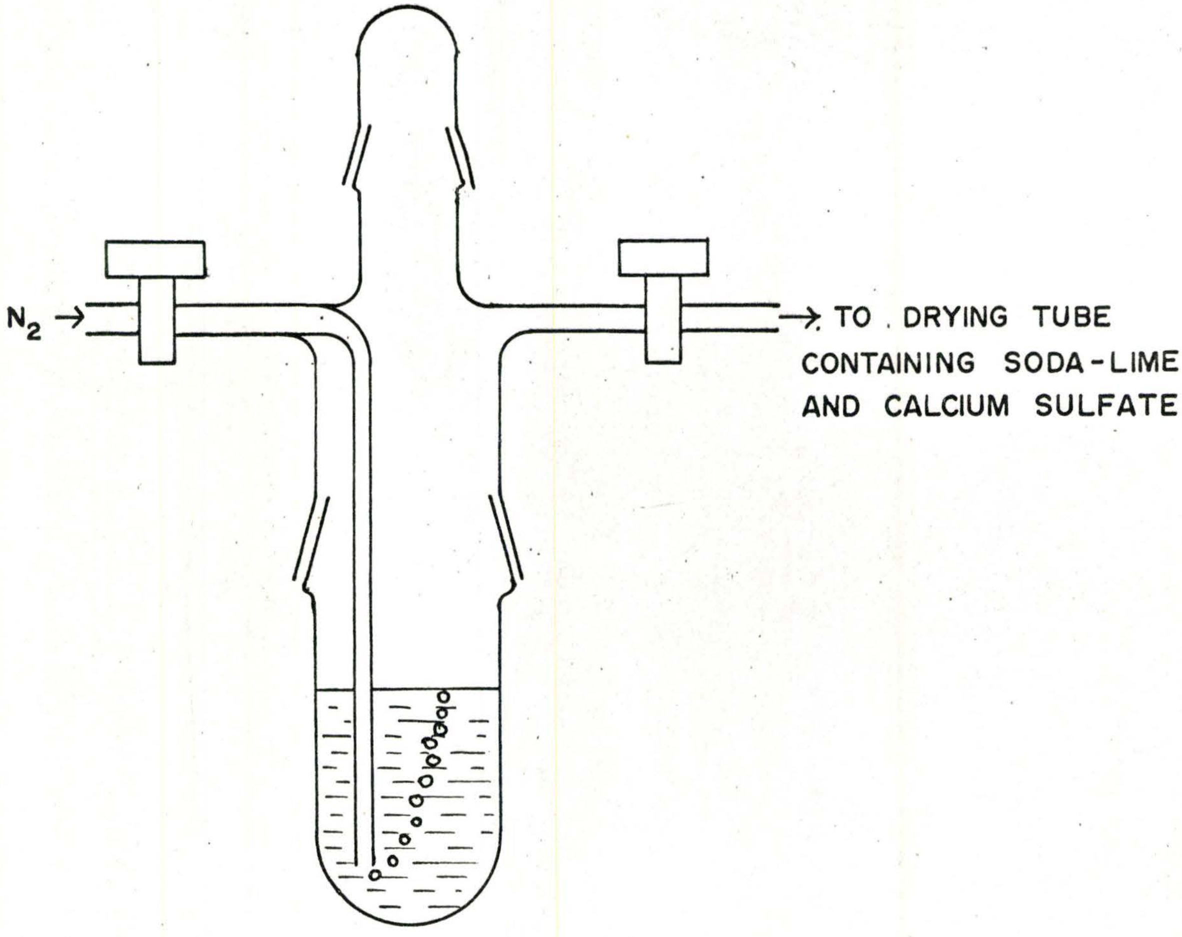


Fig. 15. APPARATUS FOR THE PREPARATION AND STORAGE OF STOCK SODIUM ETHOXIDE SOLUTIONS.

was attached, above the calibration mark, a side-arm bearing a 10-ml. bulb. To the reactor was added approximately 23 ml. of anhydrous

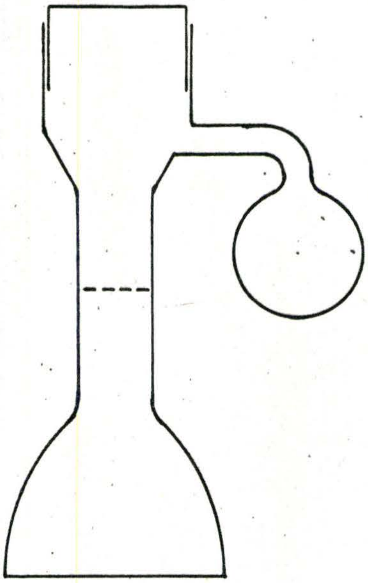


Fig. 16. REACTION FLASK USED FOR KINETICS.

ethanol and the flask was sealed with a rubber ampoule stopper. The reactor was also placed in the constant temperature bath. After one hour, 1.0 ml. samples of the sodium ethoxide solution were withdrawn and titrated with standard acid using methylene blue-neutral red as indicator. Twenty-five ml. of the standardized sodium ethoxide solution was then transferred to the reactor, anhydrous ethanol was added to the mark and the solution was shaken vigorously. These operations were carried out as rapidly as possible and normally required less than one minute. The stopwatch was started when one-half of the sodium ethoxide solution had been added.

At regular intervals, a sample was withdrawn from the reaction vessel by inserting a calibrated one **milliliter hypodermic syringe,** fitted with a 5-inch needle, through the rubber septum. This was added to approximately 22 ml. of 95% ethanol contained in a 25 ml. volumetric flask. The volume of the solution was carefully adjusted to the mark with redistilled 95% ethanol. The solution was mixed thoroughly and a 1.0 ml. sample was removed by means of a pipette and was introduced into another 25 ml. volumetric flask containing approximately 22 ml. of 95% ethanol. After again adjusting the volume to the mark with ethanol, the optical density of this solution* was measured immediately using a Perkin-Elmer Hitachi Spectrophotometer set at the appropriate wave length.

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* Separate experiments indicated that even for the diluted reaction mixture containing the fastest reacting compound, 2-(p-trifluoromethylphenyl)ethyltrimethylammonium bromide, no measureable increase in optical density occurred over a period of one hour, indicating that at the high dilutions further reaction was negligible during the time required for optical measurement.

The rate constants for all of the deuterated and undeuterated 2-arylethyltrimethylammonium salts, except the p-trifluoromethyl compound, were determined using second-order conditions in which the ethoxide component was in approximately three-fold excess. The reactions were found to follow a second-order rate law, viz.;

$$k = \frac{2.303}{t(a-b)} \log \frac{b}{a}\frac{(a-x)}{(b-x)} \qquad (99)$$

where a and b are the **initial** concentrations of ethoxide and quaternary salt respectively, and x is the concentration of the styrene at time t. The second-order rate constant, k, was evaluated from the slope of the line obtained by plotting log $\frac{a-x}{b-x}$ against time, the best fit to the data being obtained by the least squares treatment using an I.B.M. 7040 computer. Each kinetic experiment was carried out to at least 70 per cent reaction and good linear plots were obtained for all compounds.

The reaction of the 2-(p-trifluoromethylphenyl)ethyltrimethylammonium ion and its deuterated analogue at 40° was too rapid to permit the measurement of rate constants under second-order conditions using the same concentrations for substrate and base as were used for the kinetics of the other para-substituted quaternary ammonium ions. These rate constants, therefore, were evaluated using second-order conditions with equal concentrations of the two reactants. The rate constant, k, was calculated by plotting $^{x}/a-x$ versus time in the equation;

$$k = \frac{1}{ta}\frac{x}{(a-x)} \qquad (100)$$

where a is the concentration of both the substrate and the base and x is the amount of p-trifluoromethylstyrene present at time t. The best fit of the line to the points was obtained also by a least squares treatment of the data using the I.B.M. 7040 computer. The second-order rate constant was calculated by dividing the value obtained for the slope of the plot by the concentration, a, of the reactants.

Since the ionic strength for the reaction of 2-(p-trifluoromethylphenyl)ethyltrimethylammonium bromide at 40° under the conditions outlined in the previous paragraph was considerably less than with the other compounds it was uncertain whether its deuterium isotope effect would be strictly comparable, particularly since small differences in the magnitude of the hydrogen-deuterium isotope effects were anticipated. For this reason, measurements were also made at 15° and 25° at an ionic strength similar to that used for the other salts and the resulting k^H/k^D values extrapolated to 40°. For these latter runs pseudo first-order reaction conditions, with ethoxide ion in two hundred-fold excess, were employed. At regular intervals, 5 ml. samples of the reacting solution were removed and the reaction quenched by adding the samples to 4.8 ml. of 0.12 N acetic acid and immediately diluting to 50 ml. with 95% ethanol. The pseudo first-order rate constant, k', is given by the expression;

$$k't = 2.303 \log \frac{O.D._\infty - O.D._o}{O.D._\infty - O.D._t} \qquad (101)$$

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

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* Optical density at $t = \infty$ corresponded very close to 100 per cent reaction.

optical density of the solution at time t. The constant k' was calculated by plotting log $O.D._\infty - O.D._t$ against time. The best fit of the line to the points was obtained by a least squares treatment of the data using the I.B.M. 7040 computer. The second-order rate constant, k, was calculated from the pseudo first-order constant by dividing k' 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.

Deuterium Exchange Test

Exchange Tests Based on Deuterium Content of Recovered Reactant

2-Phenylethyltrimethylammonium-2,2-d_2 Bromide

The reaction of 2.1 g. (0.17 mole) of quaternary salt with 0.23 M sodium ethoxide in 100 ml. of ethanol at 40°C was allowed to proceed for about one half-life and the exact extent of reaction was determined spectrophotometrically. The solution was then cooled in an ice-bath and the reaction quenched by the addition of a dilute solution of hydrobromic acid to the bromocresol green end-point. This solution was then extracted three times with 30 ml. portions of benzene. The aqueous layer was taken to dryness under reduced pressure and the pale yellow residue was extracted four times with 50 ml. amounts of hot acetone (Analar). The combined acetone extracts were taken to dryness under reduced pressure and the residue was recrystallized three times from ethanol-ether. The recovered salt, m.p. 237.5-238°, was analyzed for deuterium.

2-Phenylethyltrimethylammonium-1,1-$\underline{\underline{d}}_2$ Bromide

The procedure described in the previous paragraph was applied to the α-dideuterated salt. The recovered reactant, after four recrystallizations from ethanol-ether, melted at 238.8-239.4°C.

Tracer Studies Based on Deuterium Content of Product Styrene

2-Phenylethyltrimethylammonium-2,2-$\underline{\underline{d}}_2$ Bromide

The reaction of 0.92 g. (0.074 mole) of 2-phenylethyltrimethylammonium-2,2-$\underline{\underline{d}}_2$ bromide in 45 ml. of 0.25 M sodium ethoxide in ethanol was allowed to proceed for a time corresponding to ten half-lives. The reaction was quenched by cooling and then 20 ml. of water were added and the solution extracted three times with 30 ml. amounts of benzene. The combined benzene extracts were washed with water and then the benzene was removed by distillation under reduced pressure leaving a pale yellow liquid. To this residue was added 2 ml. of dry chloroform followed by the dropwise addition of a solution of bromine in chloroform until the bromine colour persisted. This solution was taken to dryness under reduced pressure leaving a white solid which was recrystallized three times from aqueous ethanol to give 1,2-dibromo-1-phenylethane, m.p. 77.0-77.4° (Bailey (140), m.p. 73-74°). A deuterium analysis was carried out on this compound using N.M.R.

2-Phenylethyltrimethylammonium-1,1-$\underline{\underline{d}}_2$ Bromide

The procedure used was that described in the previous paragraph. The isolated styrene dibromide, m.p. 77.5-78°C, was analyzed for deuterium using N.M.R.

2-(*p*-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-*d*$_2$ Bromide

A solution of sodium ethoxide in ethanol was added to the quaternary salt so that the concentration of each reactant was 0.0174 M. The reaction was allowed to proceed to completion (twenty half-lives) at 40°C and the product, *p*-trifluoromethylstyrene, was converted to its dibromide by the method described for the parent compound. The white solid, 1,2-dibromo-1-*p*-trifluoromethylphenylethane, was recrystallized from ethanol-water to give white needles, m.p. 49-50°C. Analysis: Calc. for $C_9H_7Br_2F_3$; C, 32.53%; H, 2.13%; F, 17.17%. Found: C, 32.41%; H, 2.08%; F, 17.16%. A deuterium analysis was carried out on this compound using N.M.R.

Test for the Ylide Mechanism Based on the Deuterium Content of Trimethylamine from the Reaction of 2-Phenylethyltrimethylammonium-2,2-*d*$_2$ Bromide

Quaternary salt, 1.07 g. (0.087 mole), was treated with 50 ml. of 0.113 M sodium ethoxide in ethanol at 40°C in a sealed tube for one week. The trimethylamine was collected in 10 ml. of 2 N hydrochloric acid by a procedure which will be discussed in the next section dealing with the determination of nitrogen isotope effects. The hydrochloric acid solution was taken to dryness under reduced pressure to give a white, hydroscopic solid. The trimethylamine hydrochloride was recrystallized three times from anhydrous ethanol, m.p. 276-277° dec. (lit. (141), m.p. 277-278 dec.). This compound was analyzed for deuterium.

Nitrogen Isotope Effect Measurements

General

The ratio of the rate constants for reaction of two isotopic compounds is given directly 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. Two procedures were used for the reactant. The simplest involved direct Kjeldahl digestion of the quaternary salt to ammonia which was converted to nitrogen in the usual way. The second involved carrying out the reaction to completion and isolation of the trimethylamine which was converted to ammonia and thence to nitrogen gas by the method just described. The second procedure, although longer, might be expected to be more reliable since the nitrogen obtained from the complete and the partial reactions is obtained in exactly the same way and therefore any isotopic fractionation caused by the analytical procedures would be cancelled out. The isotopic ratios obtained by both procedures, as shown in the Tables in the Appendix, were essentially identical.

Depending upon the reactivity of the compound under investigation, either of two methods were used to obtain the desired extent of reaction. For salts of relatively low reactivity, the reaction was stopped by rapid cooling in liquid air and the trimethylamine was then removed by distillation under reduced pressure at ice-bath temperature. For reactive compounds, however, this method of quenching was unsatisfactory and the desired extent of reaction was achieved by adding the appropriate amount of base, corresponding to the extent of reaction required, and allowing the reaction to proceed for twenty half-lives. In these cases, the concentrations of the reactants were sufficiently low so that no more than one per cent reaction occurred during the mixing of the reacting solutions.

An important possible source of error in isotope effect measurements involving a comparison of isotopic ratios in reactant and the product from the first few per cent reaction, is the presence in this product of material formed from trace quantities of highly reactive impurity. Collins (108) has recently pointed out that many isotope effect results based on isotopic ratios found for the product of 2-10 per cent reaction are highly suspect. To obviate any such complication in the present work, the reaction of each compound was carried out to extents ranging from 5 to 60 per cent. The isotope effects so obtained were found to be independent of the extent of reaction, showing that at even very low extents of reaction the product contained no significant impurity.

In all of the reactions studied but one, trimethylamine was the only nitrogen containing product of the reactions and elimination was shown to be more than 99 per cent of the total reaction. In the reaction of ethyltrimethylammonium iodide with sodium ethoxide, however, it had been shown by Banthorpe (114) that substitution producing dimethylethylamine makes a significant contribution to the total reaction. For this reactant, therefore, it was necessary to separate the two amines by gas-phase chromatography so that only the isotopic ratio of the trimethylamine, the product of elimination, would be determined.

Procedures

Solvents and Bases

Ethanol and sodium ethoxide were prepared and stored as described in the experimental section dealing with kinetics. Tertiary butanol was dried by refluxing over and distilling from sodium metal. This process was repeated twice and the tertiary butanol was stored in the same way as the anhydrous ethanol. Potassium tertiary butoxide was prepared and stored using the procedure as outlined for the preparation of the sodium ethoxide solutions.

Partial Reaction and Collection of Trimethylamine

Quaternary ammonium salt (c a. 2 mmole) was weighed into flask K which was restricted as shown in Fig. 17. The required amount of base in the appropriate solvent was added and the flask was quickly attached to a vacuum manifold and cooled in liquid nitrogen. After thrice degassing, which involved alternate freezing and thawing of the reaction solution and pumping on the frozen liquid, the vessel was

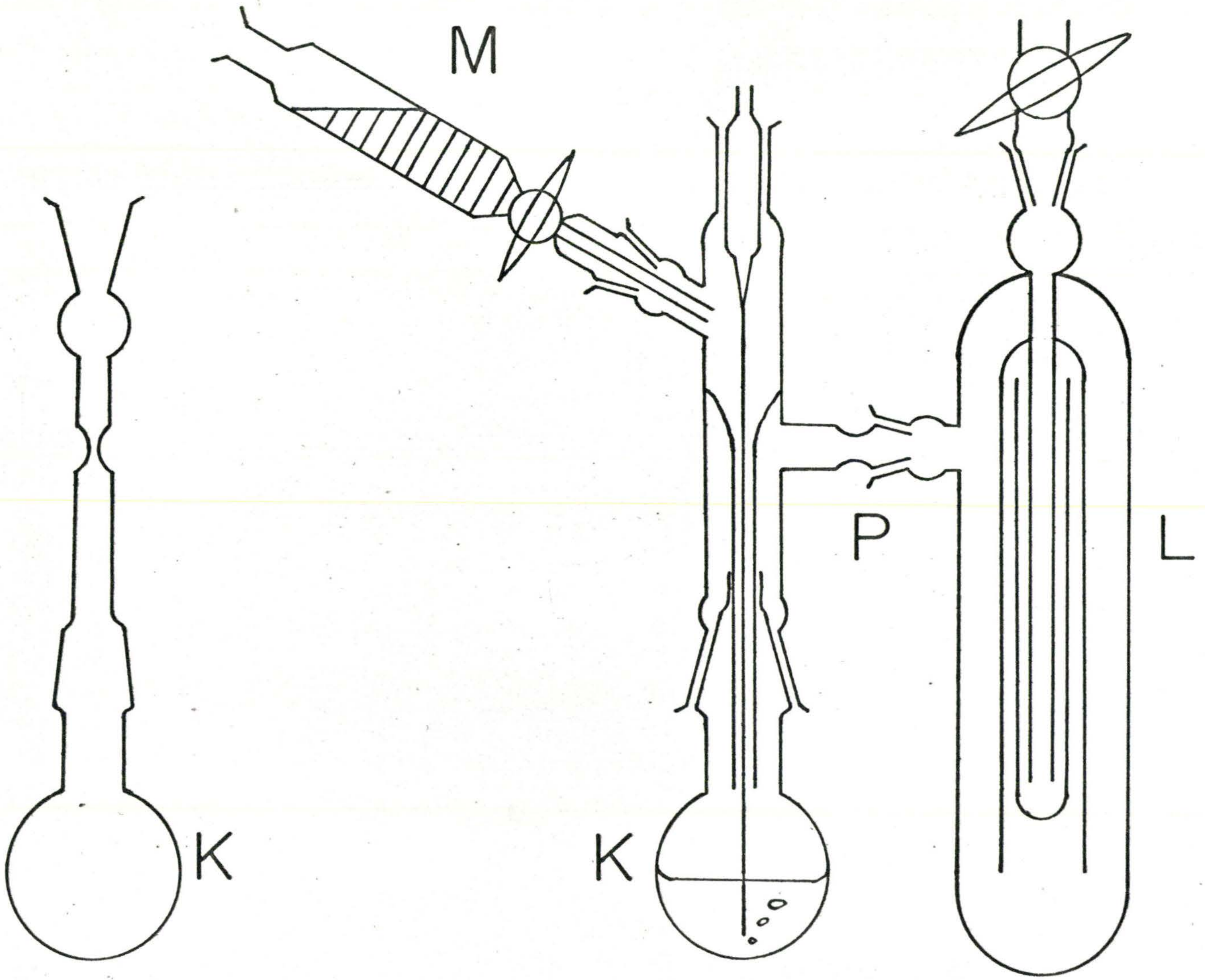

Fig. 17 . APPARATUS USED FOR THE COLLECTION OF TRIMETHYLAMINE.

sealed and placed in a thermostatted bath for a pre-determined time as calculated from the kinetic data reported earlier in this thesis. The flask was then removed from the bath, cooled in liquid air, opened, and the trimethylamine distilled over a period of 10-15 min. into a liquid nitrogen trap, L, at a pressure of 0.1 mm. and a temperature below 0°C. From time to time solvent was added from the 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 no significant further reaction occurred during the time required.

Trap L was then disconnected, stoppered at P and the trimethylamine and solvent were distilled in vacuo into excess standard sulfuric acid. The acid was back titrated with standard alkali and this was followed by the immediate addition of 3 ml. of 0.01 N sulfuric acid to prevent loss of amine. In all cases, the trimethylamine recovered was better than 99 per cent for complete reaction and the extent of reaction calculated from trimethylamine recovery for partial reaction was always within one per cent of that calculated from the kinetic data. The trimethylammonium sulfate solution was treated with 1.0 ml. of sulfuric acid and evaporated to a volume of about one ml. and transferred to a Kjeldahl flask for digestion.

Kjeldahl Digestion of Trimethylammonium Sulfate Samples

One milliliter of sulfuric acid was added to the trimethylammonium sulfate solution in the Kjeldahl flask and the flask was heated with a micro burner until all the water had distilled off and fuming and charring had begun. After the contents of the flask had cooled to room temperature, 1.5 g. of potassium sulfate (B. D. H. Analar), 0.1 g. of mercuric oxide (Fisher Reagent), and 2 ml. of sulfuric acid were added and the mixture was strongly heated for 8 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 sulfuric acid. The Kjeldahl digestion always gave better than 98 per cent recovery as determined by a titration of the excess sulfuric acid using standard alkali. After all titrations, 5 ml. of 0.01 N sulfuric acid was added to the solution to prevent loss of ammonia. The ammonium sulfate solution was concentrated to about 3 ml. in preparation for its conversion to nitrogen.

Kjeldahl Digestion of Quaternary Salts

To obtain quantitative recovery of nitrogen from the quaternary salts it was necessary to remove the halogen before the Kjeldahl digestion. This was accomplished by oxidizing the halide ion to the free halogen using hydrogen peroxide and boiling the solution to expel the halogen.

The quaternary ammonium salt (c.a. 0.2 mmole) was weighed into a 25 ml. Kjeldahl flask, water (1.0 ml.), 30% hydrogen peroxide (0.5 ml.), and sulfuric acid (0.5 ml.) were added, and the mixture was boiled to expel the liberated halogen. After removing most of the water by distillation, potassium sulfate (1.5 g.), mercuric oxide (0.1 g.) and sulfuric acid (2.5 ml.) were added and the mixture was heated strongly for 9 hours. Ammonia was liberated from these solutions and distilled into standard acid by the procedure described in the section on the Kjeldahl digestion of trimethylammonium sulfate samples.

Separation of Trimethylamine and Dimethylethylamine Formed in the Reaction of Ethyltrimethylammonium Ion

Ethyltrimethylammonium iodide, 1.0 g., was weighed into flask K (Fig. 17 , page 177) which was then restricted. The necessary amount of base was added and the flask was attached to a vacuum manifold. After thrice degassing the solution, the flask was sealed and then was placed in a constant temperature bath for a pre-determined time. The flask was then removed from the bath, cooled in liquid air, opened, and the amine products were distilled into the liquid nitrogen trap, L. The amines, together with some solvent which had distilled into trap, L, were then distilled into a 50 ml. round-bottomed flask which was tightly stoppered.

One-half milliliter amounts of this amine solution were injected directly on to a 10' x 3/8" Amines 220 column (KOH treated $^{60}/80$ Chrom. W) in an Aerograph Model A-700 gas chromatograph. Using an injector temperature of 122°C, a detector temperature of 155°C, a column temperature of 47°C, and a helium flow rate of 160 ml./min., a satisfactory separation of trimethylamine from dimethylethylamine was accomplished. The retention time was six minutes for the trimethylamine and eight minutes for the dimethylethylamine with a well-resolved peak obtained for each amine. The entire peak corresponding to the trimethylamine was collected in dilute sulfuric acid and this solution was prepared for Kjeldahl digestion. The results of the gas-phase chromatography analyses indicated that trimethylamine was produced in the reaction mixture to an extent of 88.5 per cent and that the remaining 11.5 per cent of the amine product was dimethylethylamine.

Preparation of Samples for Mass Spectrometric Analysis

The high-vacuum system used for the preparation and purification of nitrogen samples is shown in Fig.18 . The ammonium sulfate solution (3 ml.) from the Kjeldahl distillation was placed in flask A and 5 ml. of sodium hypobromite* in B. The two flasks were partially evacuated through the direct connection to the pumping system, then surrounded by liquid air and the evacuation completed. The two flasks were isolated from the pumping system and their contents thawed. This procedure of alternative 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 sulfate solution by inverting B. This caused liberation of nitrogen gas. Flask A and trap E were surrounded by liquid air 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 (142), F, and was then circulated through furnaces C and D containing copper wire and copper oxide, respectively, and maintained at 750°. Carbon dioxide, water and other contaminants were condensed

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* The sodium hypobromite solution was prepared by the method described by Nier and Rittenburg (143).

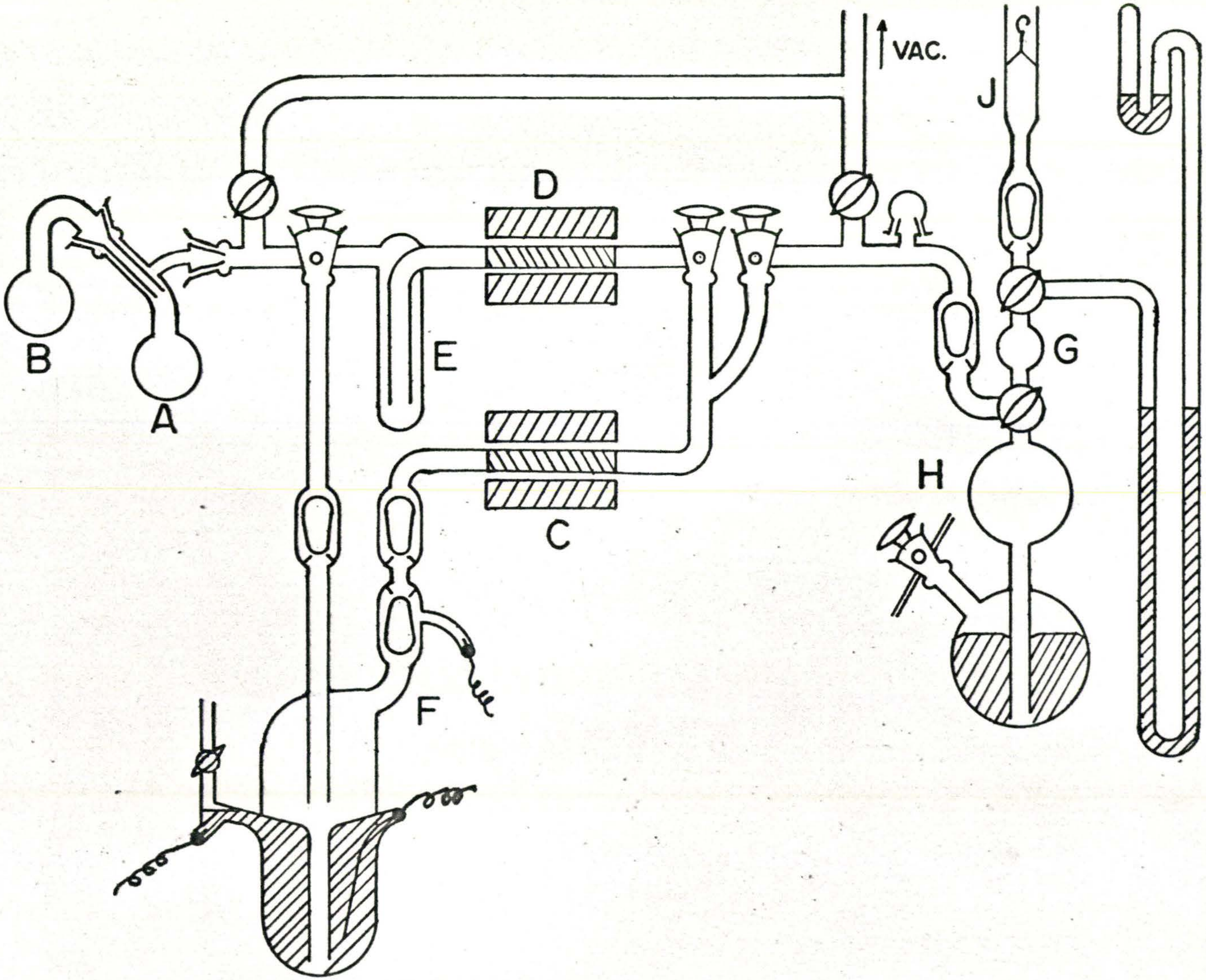

Fig. 18 APPARATUS USED FOR THE PREPARATION AND PURIFICATION OF NITROGEN SAMPLES.

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 (> 94%) was determined. Finally, the nitrogen 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 (144), 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 a deleterious effect upon the stability of the mass spectrometer.

Mass Spectrometric Analyses

The relative abundance of the nitrogen isotopes were measured using a 6-inch 90-degree, simultaneous collection mass spectrometer similar to that described by Wanless and Thode (145). 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 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 samples 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 gas 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 balance varies depending 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 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 single collection, was identical with that of the standard. The instrument was switched to simultaneous collection operation, the put-and-take potentiometer was adjusted to give a 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, 136.50, was assigned to the standard and the values of the $^{28}/29$ ratios of the unknown samples were normalized 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 derived by Stevens and Attree (146), was used for the calculation of the kinetic isotope effects. This expression can be used for the calculation of kinetic isotope effects when the reaction under investigation has no complication of competing processes:

$$k^{14}/k^{15} = \frac{\ln(1-f)}{\ln(1-rf)} \qquad (102)$$

where $r = (N^{14}/N^{15})$reactant/(N^{14}/N^{15})product, and f is the mole fraction of the reactant which has undergone reaction. In calculating the k^{14}/k^{15} values, the $N^{14}N^{14}/N^{14}N^{15}$ ratios, found for the nitrogen gas formed from a quaternary salt as well as from trimethylamine from complete reaction, were averaged and the resulting value 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 that salt.

In the determination of the nitrogen isotope effect associated with the E2 reaction of ethyltrimethylammonium ion with sodium ethoxide in ethanol an estimate of f is made difficult because of the competing reaction of substitution. It cannot be taken simply as the mole fraction of reactant which has been consumed since the isotope effect associated with substitution component of the total reaction is not known. Nor is a suitable value of f given by the mole fraction of the reactant which has undergone elimination only since part of the reactant is being simultaneously removed by the substitution process. A satisfactory approximation of f, however, may be made by considering that the substitution reaction gives rise to an isotope effect similar to that for the elimination reaction. Therefore, f can simply be taken as the mole fraction of the reactant which has undergone reaction. For the small conversions of ethyltrimethylammonium ion used in the present investigation ($\sim$8 per cent) the error introduced by using this approximation is negligible.

APPENDIX A

Table XXVI

Data for a Typical Kinetic Experiment in the Reaction of 2-Phenylethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.04005 m./l.; NaOEt = 0.1137 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.45317
45	.114	595	.00492	.49089
75	.174	595	.00750	.51255
105	.234	595	.01009	.53925
140	.295	595	.01272	.56752
165	.335	595	.01444	.58836
225	.415	595	.01789	.63587
285	.493	595	.02138	.68600
405	.605	595	.02818	.78704

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.000822357 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.000822357}{60 \times .07365}$$

$$= 4.29 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXVII

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Chlorophenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.03986 m./l.; NaOEt = 0.1111 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.44515
10	.213	595	.00643	.49573
18	.369	595	.01115	.54176
27	.510	595	.01540	.59246
37	.638	595	.01927	.64933
48	.373	1190	.02253	.70847
62	.426	1190	.02573	.78118
74	.463	1190	.02797	.84455

Calculation of rate constant:

Slope (least squares) = 0.00543778 min^{-1}

$$k = \frac{2.303 \times 0.00543778}{60 \times 0.07124}$$

$$= 29.3 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXVIII

Data for a Typical Experiment in the Reaction of 2-(p-Anisyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.05139 m./l.; NaOEt = 0.1268 m./l.)

Time hr.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.39221
4	.157	595	.00487	.41325
9	.265	595	.00821	.43878
14	.373	595	.01157	.46145
19	.460	595	.01426	.48758
25	.562	595	.01742	.51785
33	.678	595	.02101	.55704
45	.438	1190	.02715	.61395

Calculation of rate constant:

Slope (least squares) = 0.00493138 hr^{-1}

$$k = \frac{2.303 \times 0.00493138}{60 \times 60 \times 0.07541}$$

$$= 0.418 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXIX

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.01735 m./l.; NaOEt = 0.01735 m./l.)

Time min.	Optical Density	(x) m./l.	(a-x) m./l.	$\frac{x}{a-x}$
0	-	-	-	0
2	.137	.00503	.01232	.4083
4	.207	.00760	.00975	.7795
6	.258	.00948	.00787	1.2046
9	.305	.01120	.00615	1.8212
13	.347	.01275	.00460	2.5717
21	.385	.01414	.00321	4.2275
25	.403	.01480	.00255	5.0520

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.201774 \text{ min}^{-1}$$

$$k = \frac{0.201774}{60 \times 0.01735}$$

$$= 0.194 \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXX

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 25°C

(Initial concs.: Q.A.S. = 0.000574 m./l.; NaOEt = 0.1154 m./l.)

Time min.	Optical Density	$OD_\infty - OD_t$	$\log OD_\infty - OD_t$
2.5	.349	.591	-.22841
3.5	.500	.440	-.32655
5.5	.572	.368	-.43415
7.5	.650	.290	-.53760
12	.740	.102	-.82013
16	.852	.088	-1.05520
	.940	-	-

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.0588483 \text{ min}^{-1}$$

$$k' = \frac{2.303 \times 0.0588483}{60}$$

$$k = \frac{2.303 \times 0.0588483}{60 \times 0.1154}$$

$$= 0.0196 \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXI

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Anhydrous Ethanol at 15°C

(Initial concs.: Q.A.S. = 0.000574 m./l.; NaOEt = 0.1154 m./l.)

Time min.	Optical Density	$OD_{\infty} - OD_t$	$\log OD_{\infty} - OD_t$
4	.197	.743	-.12901
9	.308	.632	-.19928
14	.405	.535	-.27165
19	.480	.460	-.33724
25	.564	.376	-.42481
29	.610	.330	-.48149
34	.661	.297	-.55440
	.940	-	-

Calculation of rate constant:

Slope (least squares) = 0.0141393 min^{-1}

$$k' = \frac{2.303 \times 0.0141393}{60}$$

$$k = \frac{2.303 \times 0.0141393}{60 \times 0.1154}$$

$$= 0.00471 \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXII

Date for a Typical Kinetic Experiment in the Reaction of 2-Phenylethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.03671 m./l.; NaOEt = 0.1267 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.53796
75	.070	595	.00302	.56302
135	.118	595	.00510	.58241
210	.173	595	.00749	.60723
300	.224	595	.00966	.63619
405	.279	595	.01203	.66713
585	.366	595	.01578	.72485
720	.423	595	.01824	.76879

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.000318629 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.000318629}{60 \times 0.08999}$$

$$= 1.36 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXIII

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Chlorophenyl)ethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.03898 m./l.; NaOEt = 0.1253 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.50708
20	.160	595	.00483	.54747
35	.261	595	.00788	.57698
55	.380	595	.01148	.61692
75	.480	595	.01450	.65567
110	.622	595	.01879	.72227
150	.376	1190	.02271	.79972
200	.438	1190	.02646	.89735

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.00194462 \text{ min}^{-1}$$

$$k = \frac{2.303 \times 0.00194462}{60 \times 0.08632}$$

$$= 8.65 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXIV

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Anisyl)ethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.04534 m./l.; NaOEt = 0.1304 m./l.)

Time hr.	Optical Density	Dilution Factor	(x) m./l.	$\log \frac{a-x}{b-x}$
0	-	-	-	.45860
10	.126	595	.00390	.48148
20	.207	595	.00641	.50305
30	.285	595	.00883	.52286
40	.358	595	.01110	.54558
50	.435	595	.01348	.56405
77	.660	595	.02022	.62612

Calculation rate constant:

$$\text{Slope (least squares)} = 0.00215266 \text{ hr}^{-1}$$

$$k = \frac{2.303 \times 0.00215266}{60 \times 60 \times 0.08501}$$

$$= 0.162 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXV

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 40°C

(Initial concs.: Q.A.S. = 0.01714 m./l.; NaOEt = 0.01714 m./l.)

Time min.	Optical Density	Dilution Factor	(x) m./l.	(a-x) m./l.	$\frac{x}{a-x}$
0	-	-	-	-	0
4	.093	477	.00274	.01440	.1903
8	.167	477	.00492	.01222	.4026
13.5	.232	477	.00683	.01031	.6625
17	.268	477	.00789	.00925	.8530
21	.296	477	.00872	.00842	1.0356
25.5	.323	477	.00951	.00763	1.2464
31.5	.353	477	.01039	.00675	1.5395

Calculation of rate constant:

$$\text{Slope (least squares)} = 0.0489591 \text{ min}^{-1}$$

$$k = \frac{0.0489591}{60 \times 0.01714}$$

$$= 476 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXVI

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 25°C

(Initial concs.: Q.A.S. = 0.000472 m./l.; NaOEt = 0.1154 m./l.)

Time min.	Optical Density	$OD_\infty - OD_t$	$\log OD_\infty - OD_t$
5	.148	.617	-.20971
10	.247	.518	-.28567
15	.323	.442	-.35458
20	.387	.378	-.42251
25.25	.447	.318	-.49757
30	.492	.273	-.56384
35	.533	.232	-.63451
	.765	-	-

Calculation of rate constant:

Slope (least squares) = 0.0140677 min^{-1}

$$k' = \frac{2.303 \times 0.0140677}{60}$$

$$k = \frac{2.303 \times 0.0140677}{60 \times 0.1154}$$

$$= 0.00468 \text{ l. mole}^{-1} \text{ sec}^{-1}$$

Table XXXVII

Data for a Typical Kinetic Experiment in the Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium-2,2-d_2 Bromide with Sodium Ethoxide in Anhydrous Ethanol at 15°C

(Initial concs.: Q.A.S. = 0.000453 m./l.; NaOEt = 0.1154 m./l.)

Time min.	Optical Density	$OD_\infty - OD_t$	$\log OD_\infty - OD_t$
5	.061	.673	-.17198
12	.097	.637	-.19586
20	.134	.600	-.22185
32	.187	.547	-.26201
47	.247	.487	-.31207
65	.313	.421	-.37572
90	.384	.350	-.45592
	.734	-	-

Calculation of rate constant:

Slope (least squares) = 0.00335424 min^{-1}

$$k' = \frac{2.303 \times 0.00335424}{60}$$

$$k = \frac{2.303 \times 0.00335424}{60 \times 0.1154}$$

$$= 0.00112 \text{ l. mole}^{-1} \text{ sec}^{-1}$$

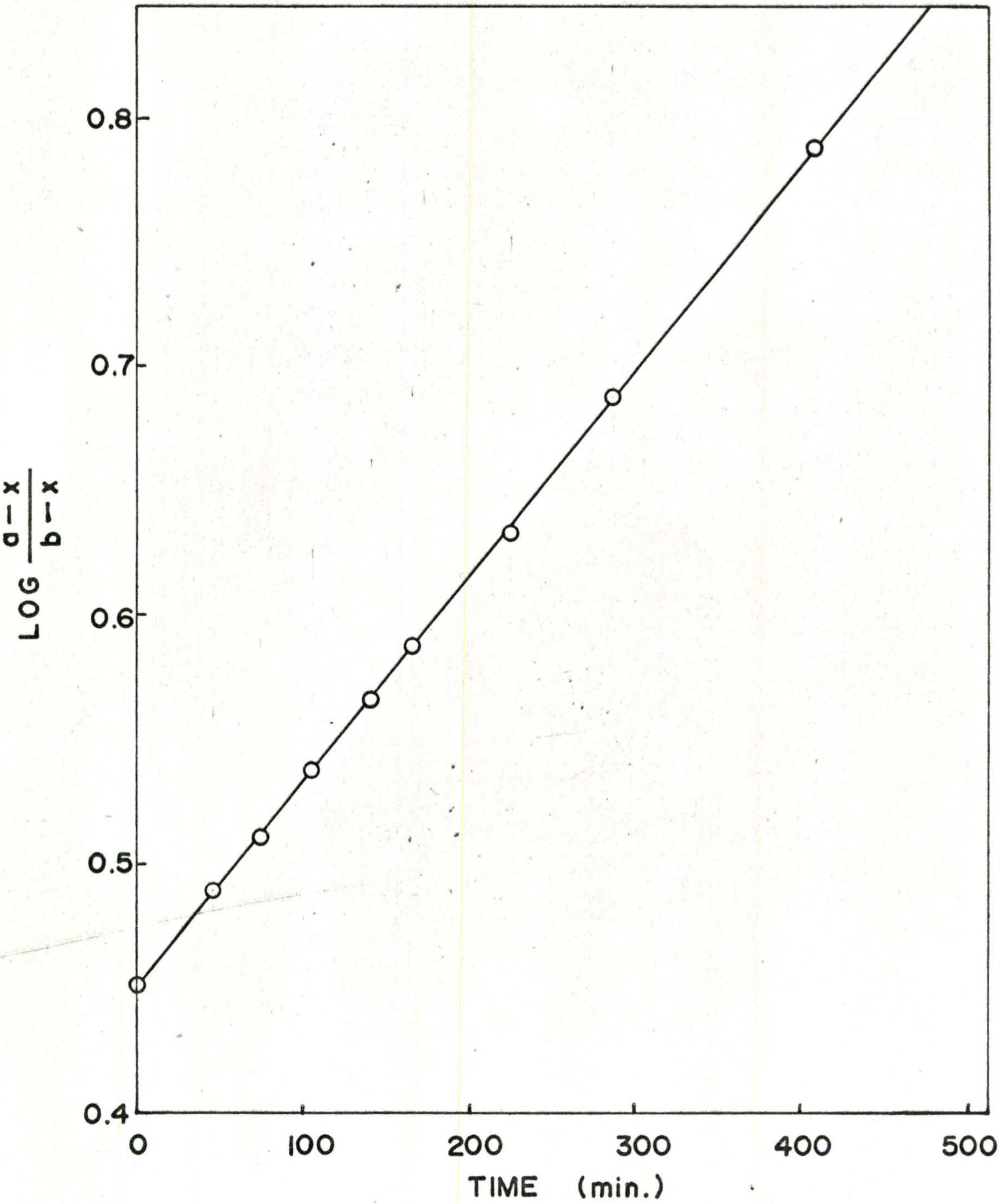

Fig. 19 PLOT OF THE KINETIC DATA GIVEN IN TABLE XXVI FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-PHENYLETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

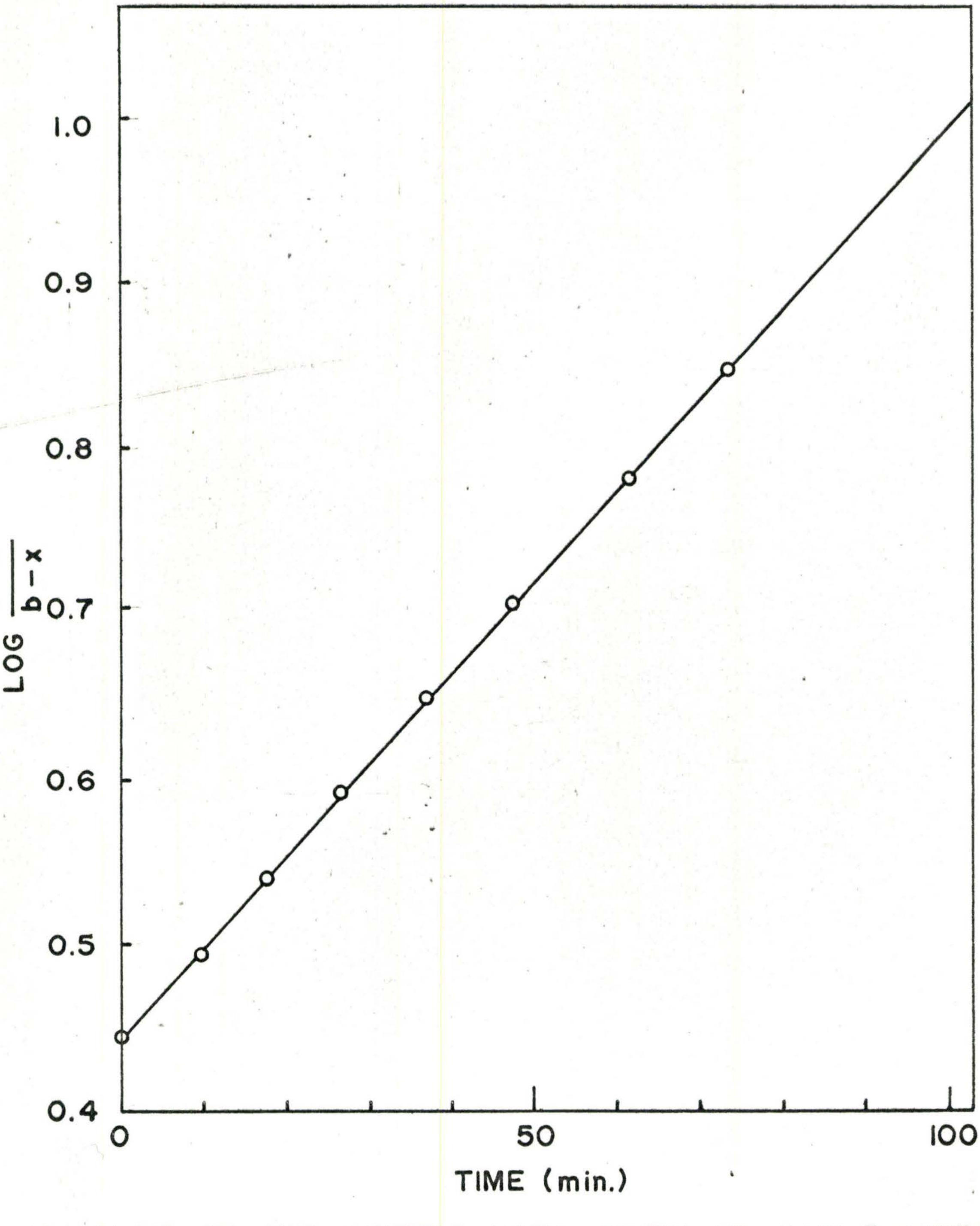

Fig.20 . PLOT OF THE KINETIC DATA GIVEN IN TABLE XXVII FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-CHLOROPHENYL)ETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

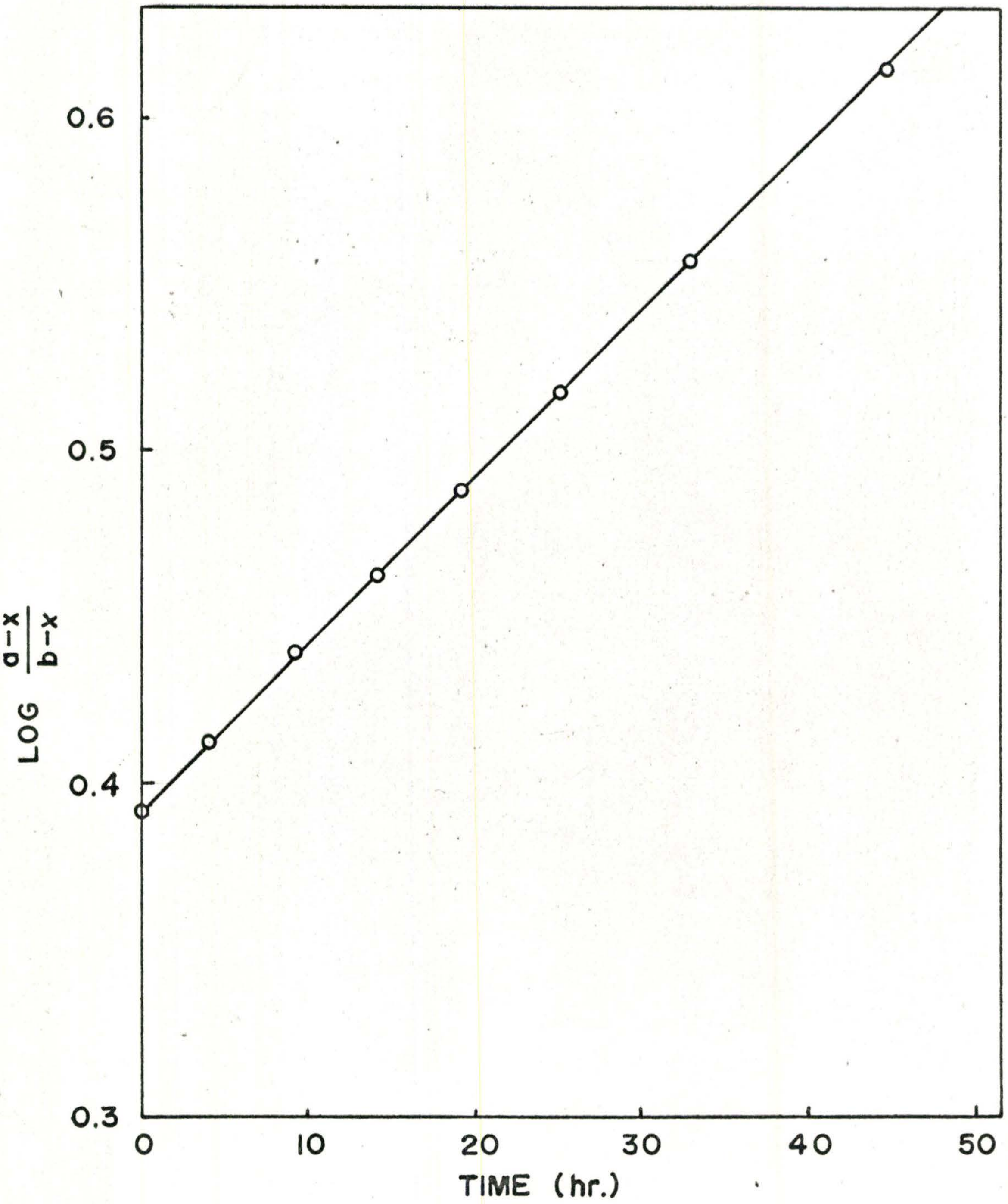

Fig. 21. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXVIII FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-ANISYL)ETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

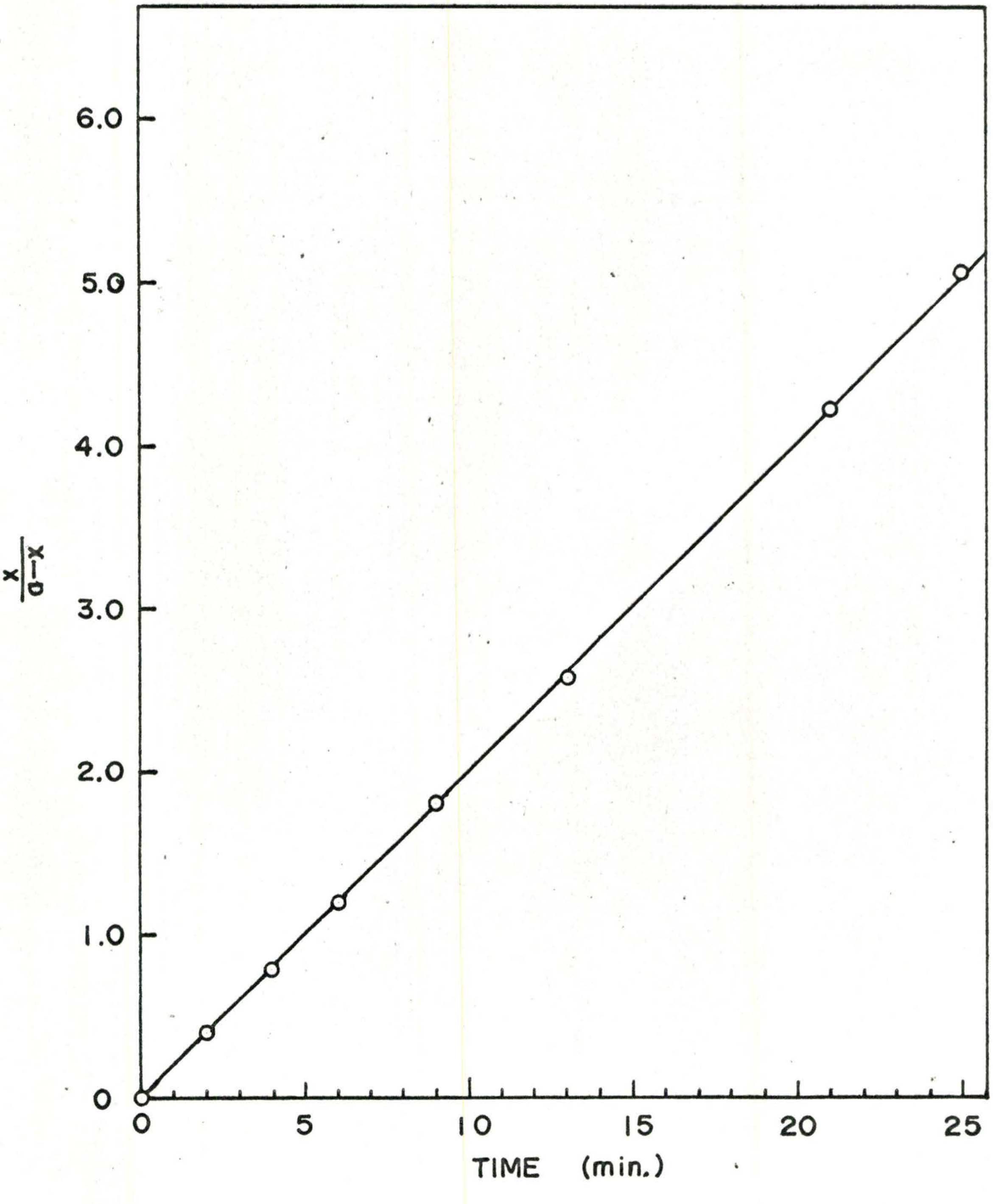

Fig. 22 . PLOT OF THE KINETIC DATA GIVEN IN TABLE XXIX FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

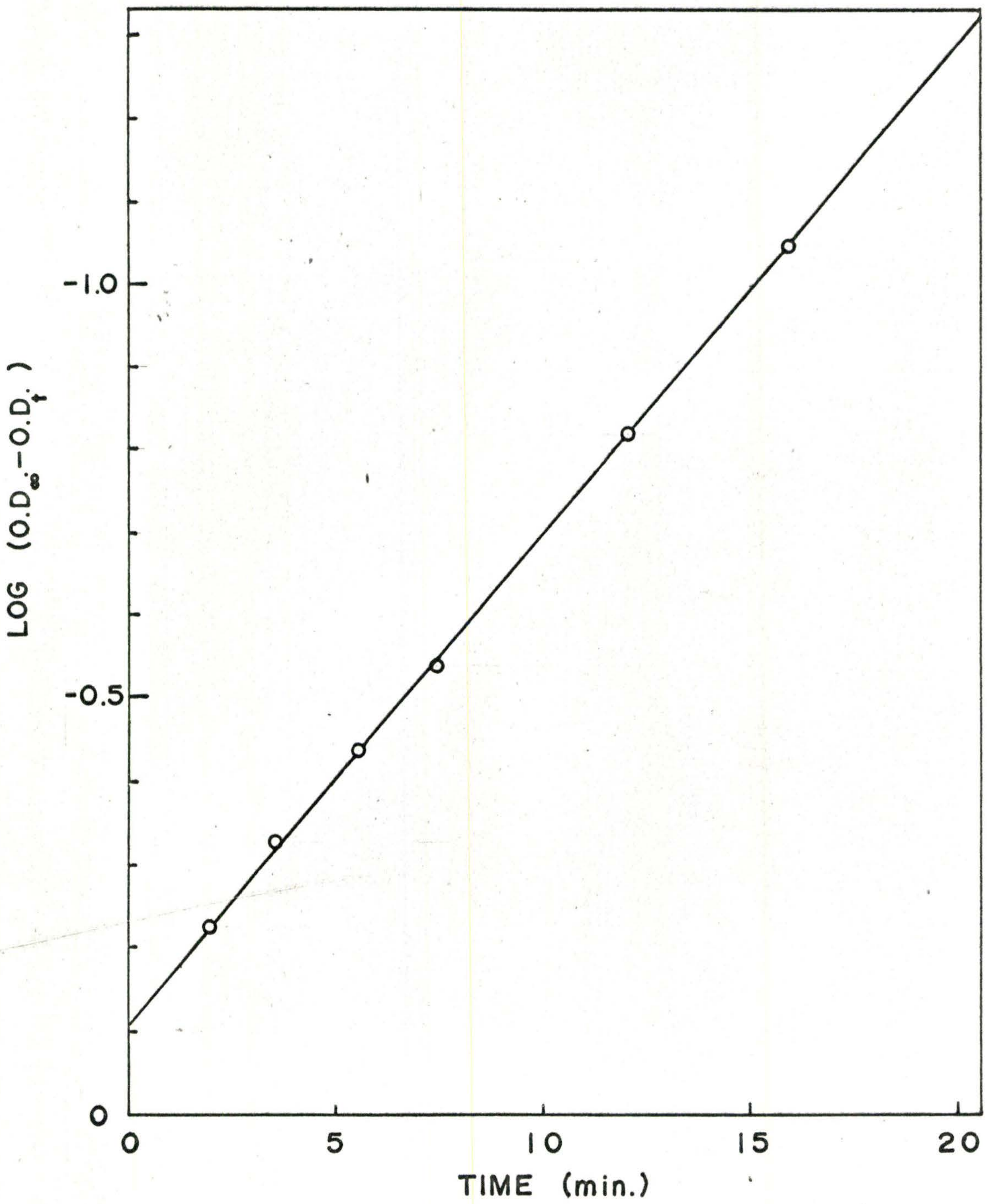

Fig. 23. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXX FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 25° C.

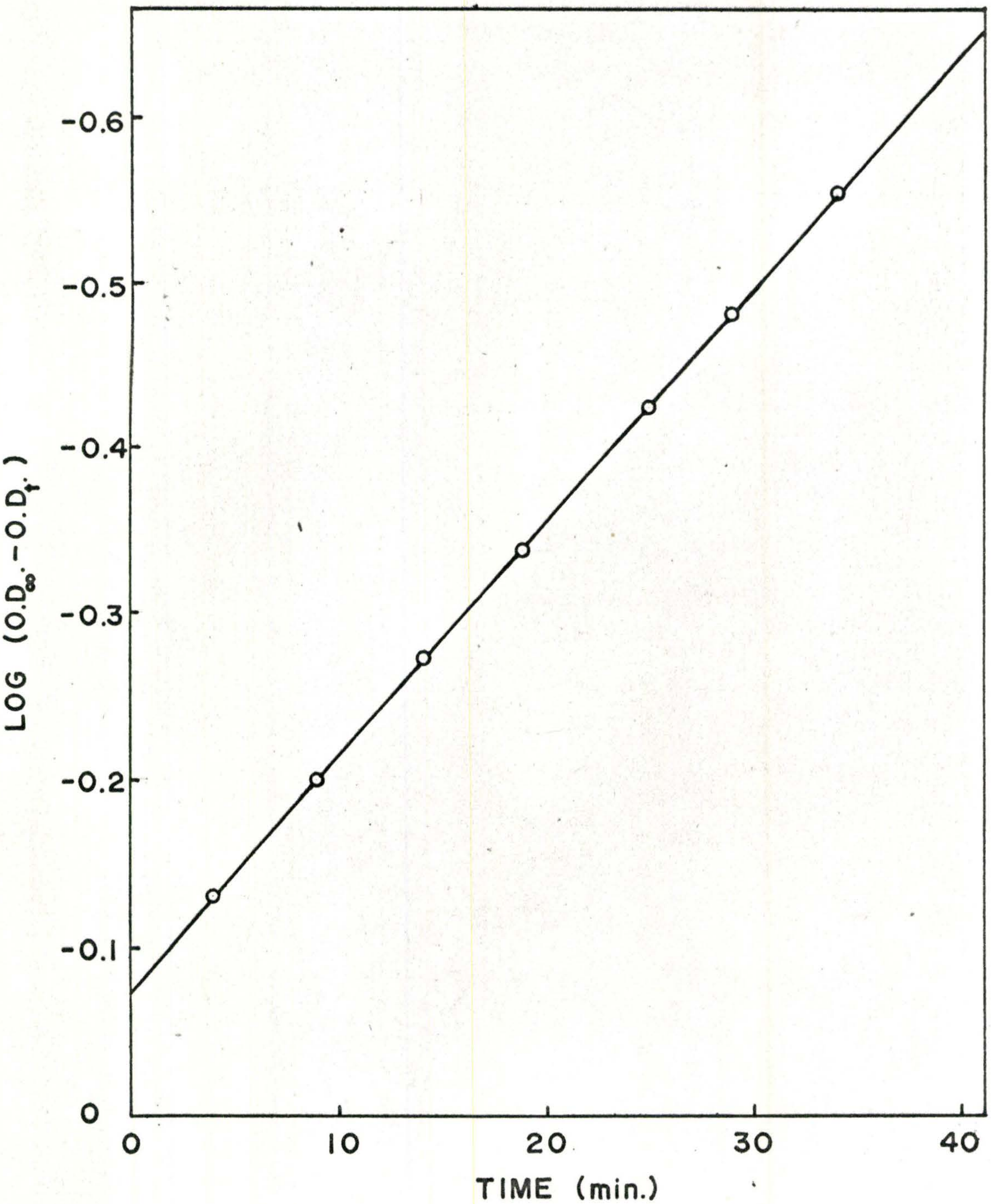

Fig. 24. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXI FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 15° C.

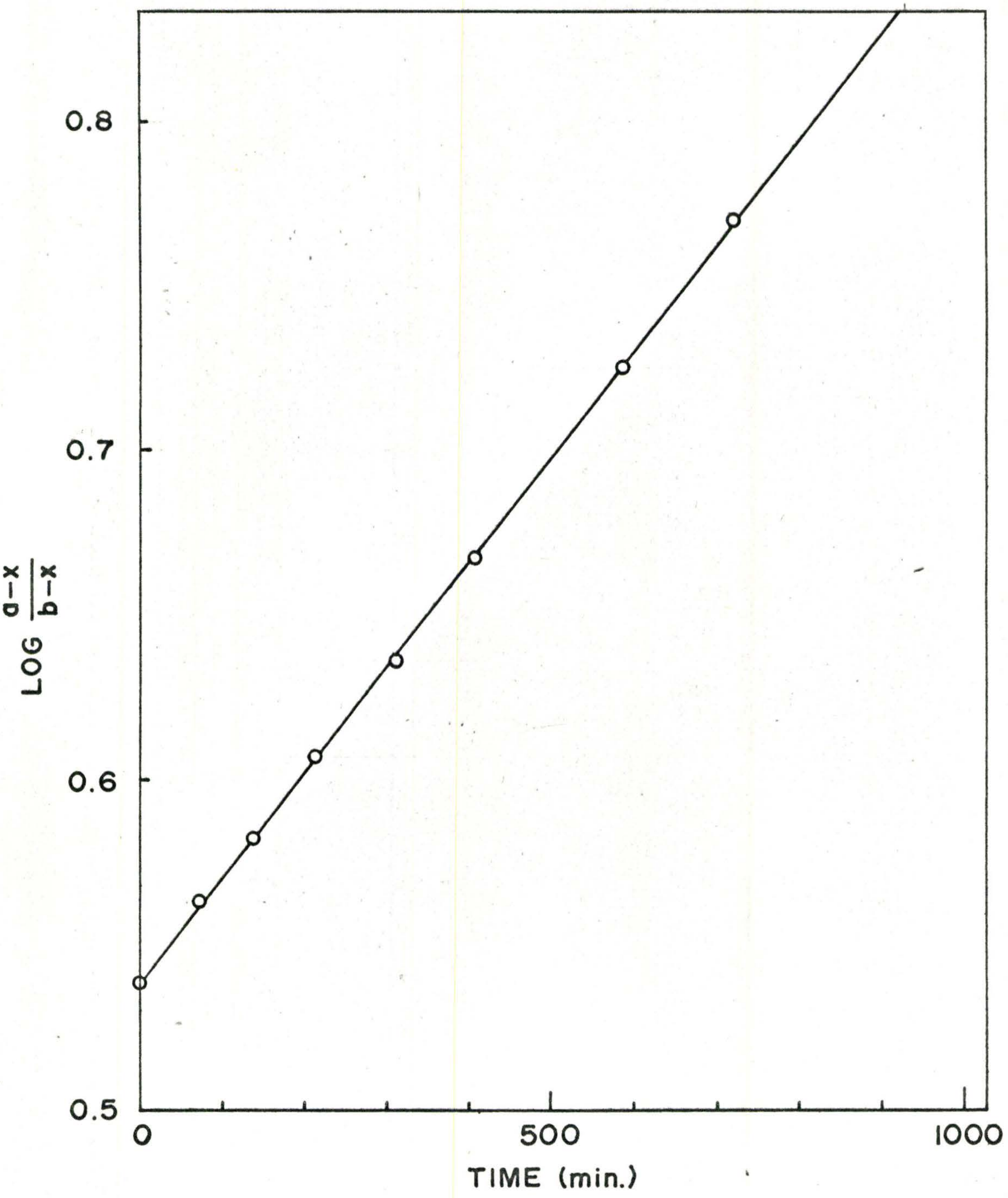

Fig. 25. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXII FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-PHENYLETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

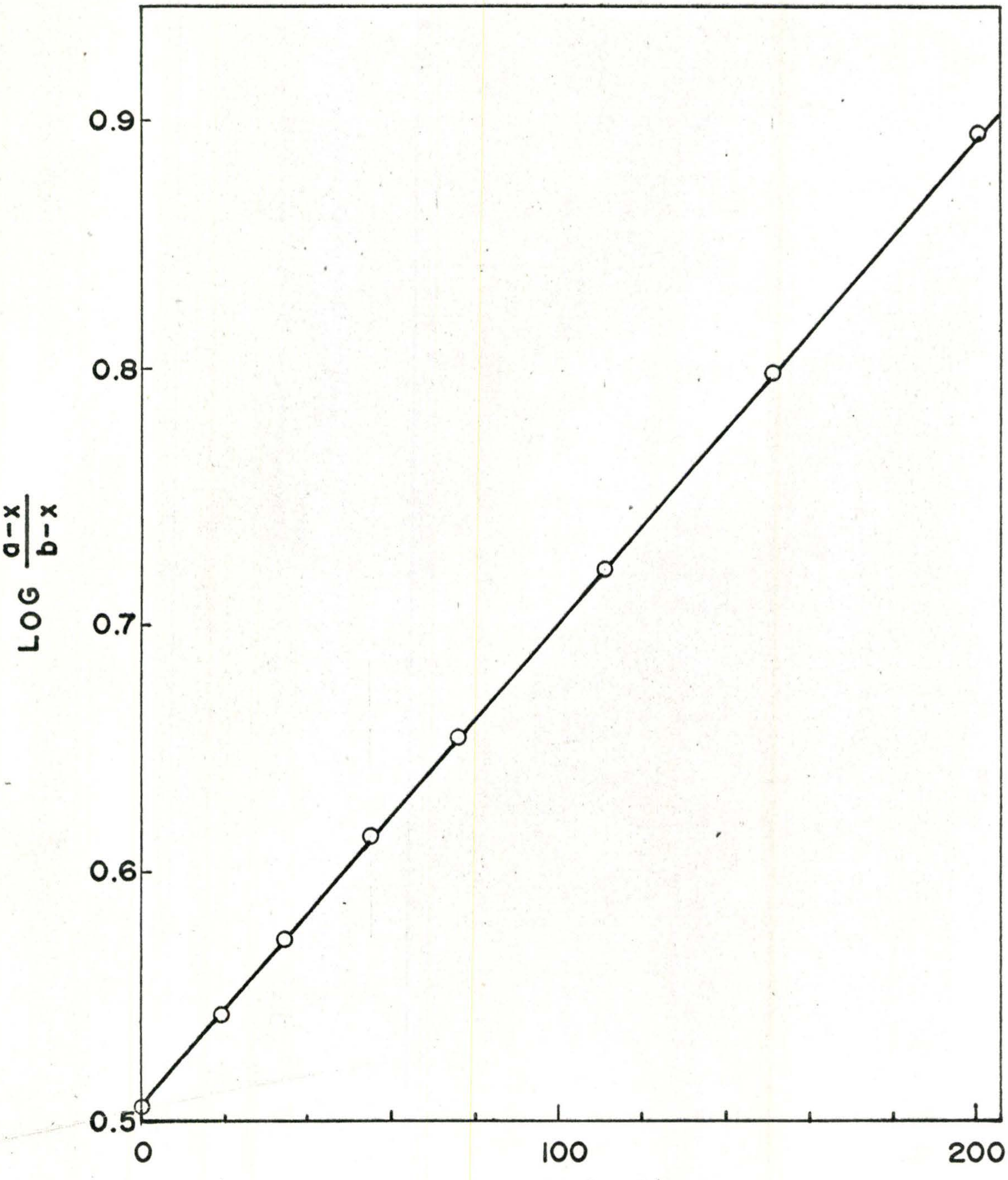

Fig26 . PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXIII FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-CHLOROPHENYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

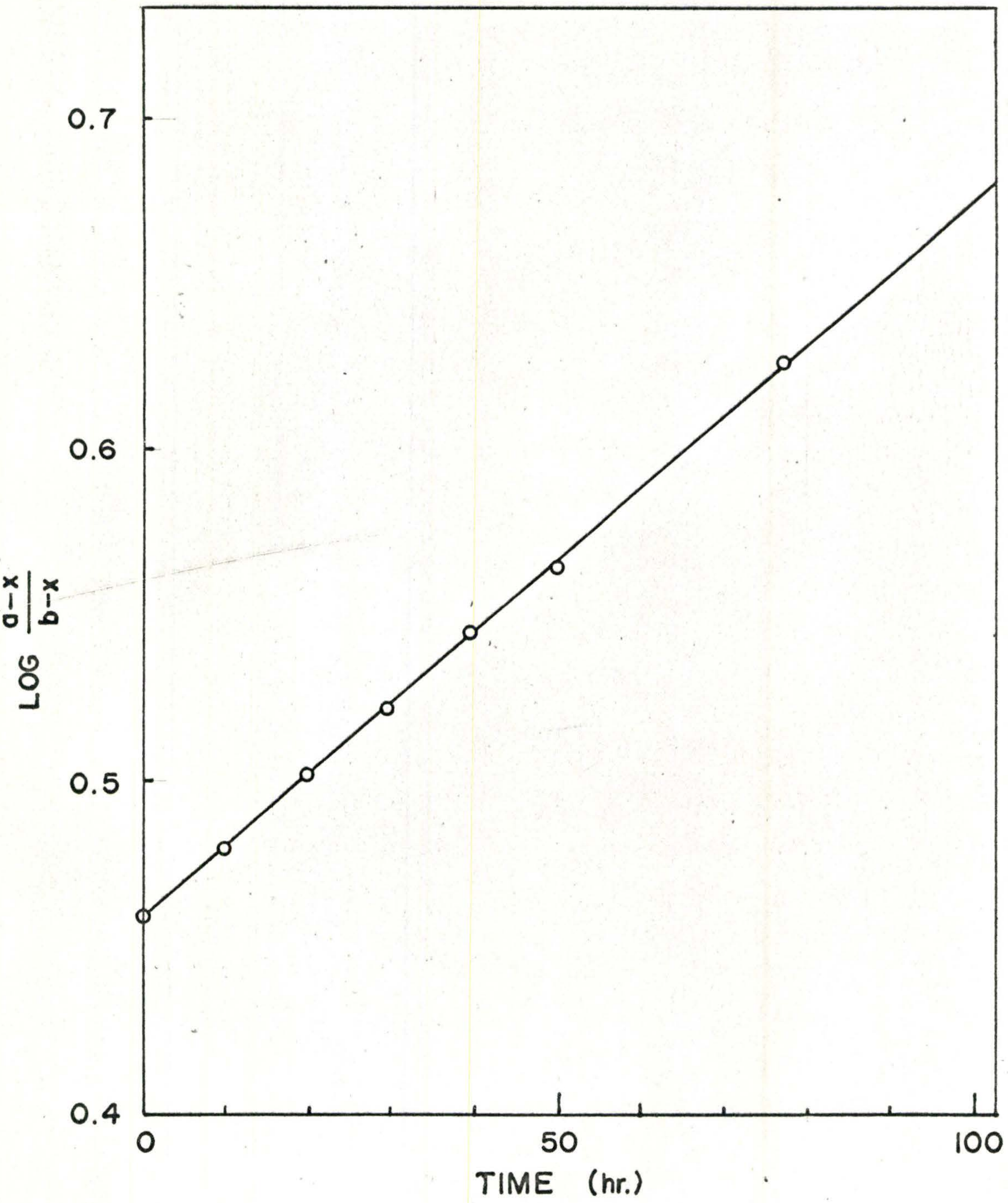

Fig. 27. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXIV FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-ANISYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

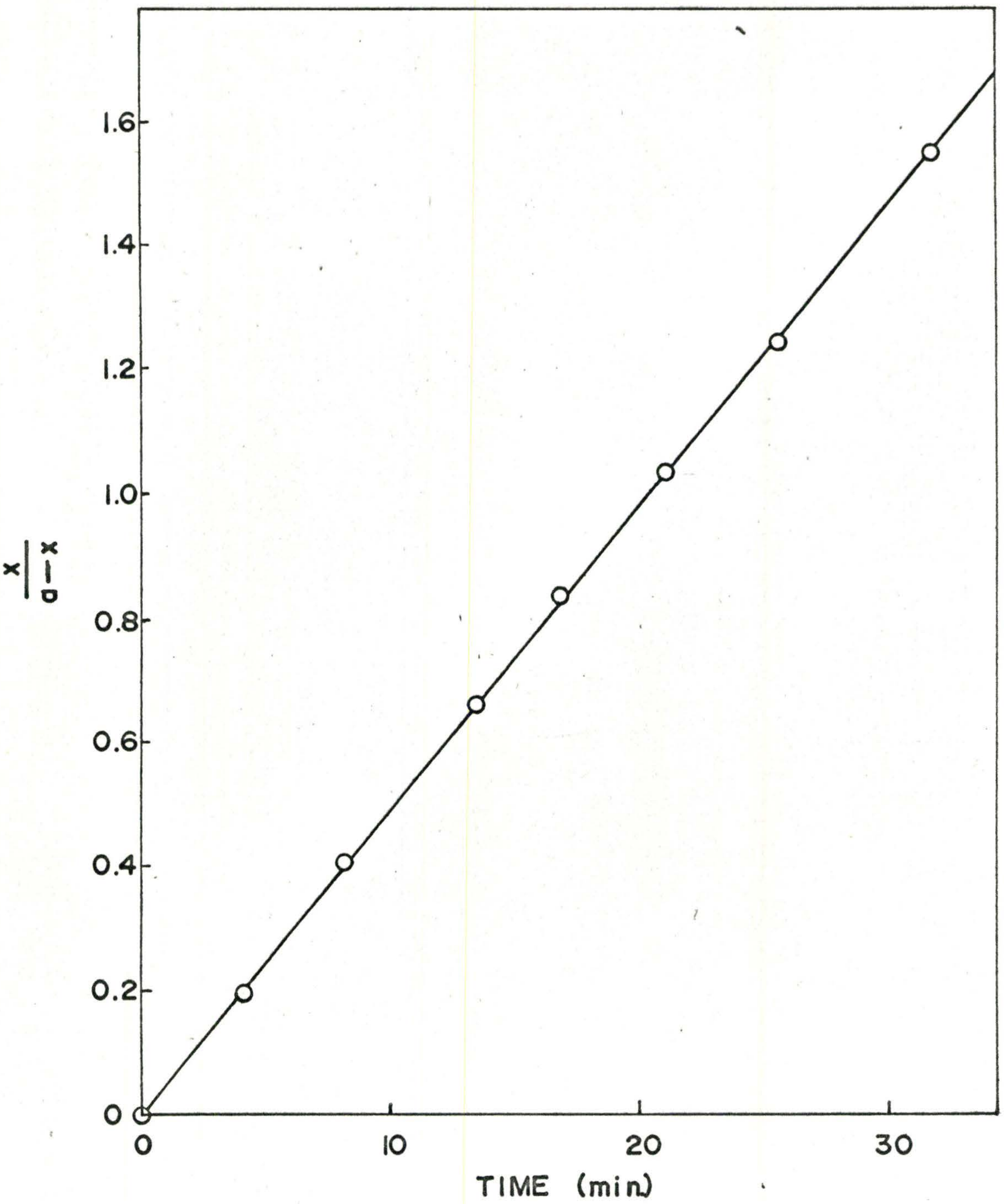

Fig. 28. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXV FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 40° C.

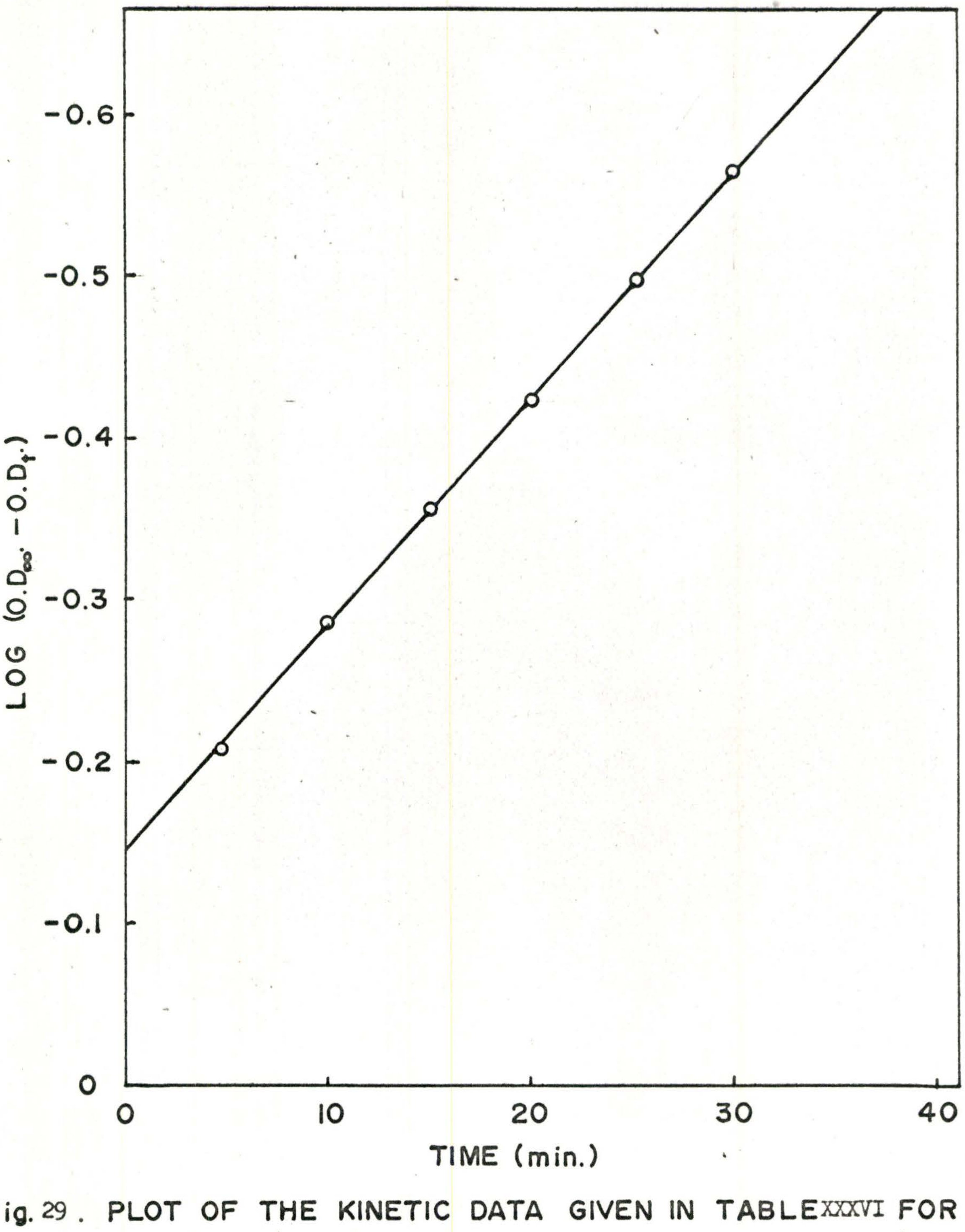

Fig. 29. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXVI FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 25° C.

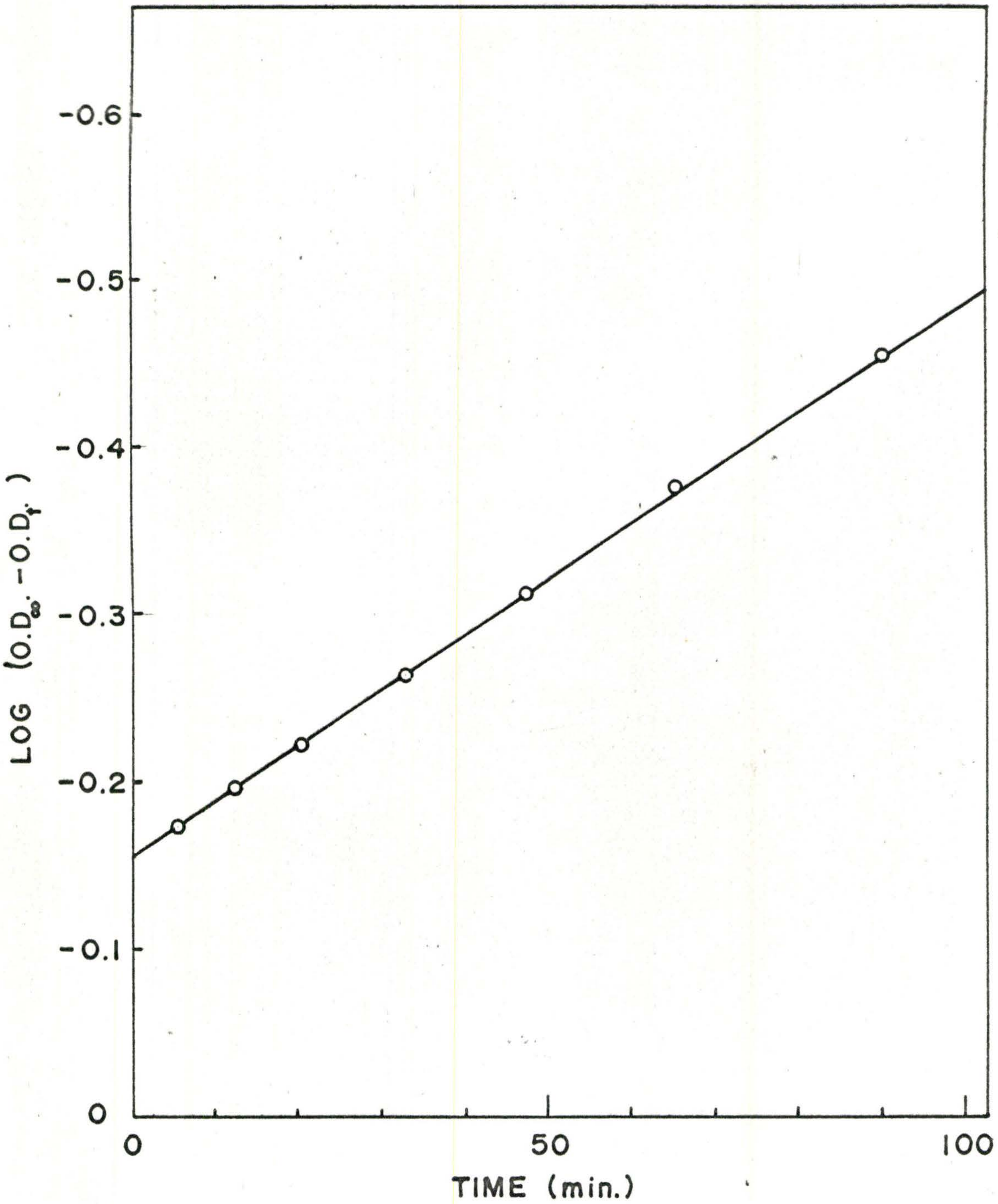

Fig. 30. PLOT OF THE KINETIC DATA GIVEN IN TABLE XXXVII FOR A TYPICAL KINETIC EXPERIMENT FOR THE REACTION OF 2-(p-TRIFLUOROMETHYLPHENYL)ETHYLTRIMETHYLAMMONIUM-2,2-d_2 BROMIDE AND SODIUM ETHOXIDE IN ANHYDROUS ETHANOL AT 15° C.

Table XXXVIII

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-Phenylethyltrimethylammonium Bromide with Sodium Ethoxide in Ethanol at 40°C

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	273.80	-
2	-	100	273.82	-
3	-	100	274.00	-
4	-	100	273.96	-
5	-	100	273.96	-
6	60	[d]100	273.90	-
7	60	[d]100	273.98	-
8	40	7.4	277.70	1.0143
9	40	14.3	277.40	1.0139
10	40	14.6	277.64	1.0148
11	40	23.8	277.20	1.0138
12	40	23.8	277.32	1.0143

mean = 1.0142 ± .0004

[a] Determined from 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 limits shown are the standard deviation.

[d] The trimethylamine was collected after 100 per cent reaction.

Table XXXIX

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-(p-Chlorophenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Ethanol at 40°C

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	273.66	-
2	-	100	273.40	-
3	-	100	273.44	-
4	-	100	273.40	-
5	40	17.1	276.28	1.0113
6	40	14.6	276.44	1.0118
7	40	16.3	275.96	1.0098
8	40	29	276.18	1.0118
9	40	29	276.28	1.0122
				mean = 1.0114 ± .0009

[a] Determined from 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 limits shown are the standard deviation.

TableXXXX

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-(p-Anisyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Ethanol at 40°C

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	273.00	-
2	-	100	273.26	-
3	-	100	273.32	-
4	-	100	273.08	-
5	40	4.9	276.52	1.0125
6	40	4.9	276.80	1.0135
7	40	8.1	276.90	1.0141
8	40	12.6	276.62	1.0137
9	40	23.2	276.34	1.0133
10	40	23.5	276.80	1.0153
				mean = 1.0137 ± .0009

[a] Determined from 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 limits shown are the standard deviation.

Table XXXXI

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-(p-Trifluoromethylphenyl)ethyltrimethylammonium Bromide with Sodium Ethoxide in Ethanol at 40°C

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	272.90	-
2	-	100	273.22	-
3	-	100	273.22	-
4	-	100	273.32	-
5	40	[d]100	273.52	-
6	40	[d]100	273.46	-
7	40	[e]23	275.32	1.0084
8	40	[e]17.3	275/48	1.0088
9	40	[e]46.2	275.10	1.0092
10	40	[e]43.6	275.16	1.0093
11	40	73	274.52	1.0093
12	40	60	274.58	1.0078
				mean = 1.0088 ± .0006

[a] Determined from the yield of trimethylamine.

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

[c] The limits shown are the standard deviation.

[d] The trimethylamine was collected after 100 per cent reaction.

[e] The amount of base corresponding to the desired extent of reaction was added.

Table XXXXII

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of 2-Phenylethyltrimethylammonium Bromide with Hydroxide Ion in Water at 97°C

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	273.80	-
2	-	100	273.82	-
3	-	100	274.00	-
4	-	100	273.96	-
5	-	100	273.96	-
6	60	[d]100	273.90	-
7	60	[d]100	273.98	-
8	97	8.1	275.56	1.0063
9	97	9.8	276.32	1.0090
10	97	31.6	276.24	1.0102
11	97	29.0	275.56	1.0072
12	97	13.5	275.80	1.0074
13	97	13.1	275.78	1.0073
14	97	13.1	275.88	1.0078
			mean =	1.0079 ± .0013

[a] Determined from 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 limits shown are the standard deviation.

Table XXXXIII

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of Ethyltrimethylammonium Iodide with Potassium Hydroxide in 95 per cent Ethanol at 60°

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	-	100	273.44	-
2	-	100	273.28	-
3	-	100	273.44	-
4	-	100	273.50	-
5	-	100	273.66	-
6	[d]60	100	273.60	-
7	[e]60	8.3	278.08	1.0173
8	60	8.3	278.44	1.0190
9	60	8.3	278.44	1.0190
10	60	8.3	278.26	1.0181
11	60	8.3	278.30	1.0184
				mean = 1.0186 ± .0004

[a] Determined from 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 limits shown are the standard deviation.

[d] Trimethylamine was collected from the complete reaction of ethyltrimethylammonium nitrate with t-butoxide in t-butanol.

[e] The Kjeldahl digestion was carried out on both the trimethylamine and the dimethylethylamine.

Table XXXXIV

N^{14}/N^{15} Ratios and Kinetic Isotope Effects in the E2 Reaction of Ethyltrimethylammonium Nitrate with Potassium t-Butoxide in t-Butanol at 60°

Expt. No.	Reaction Temp. °C	Extent of Reaction %[a]	N^{14}/N^{15} Ratios[b]	$\frac{k^{14}}{k^{15}}$[c]
1	[d] -	100	273.44	-
2	[d] -	100	273.28	-
3	[d] -	100	273.44	-
4	[d] -	100	273.50	-
5	[d] -	100	273.66	-
6	[e] 60	100	273.60	-
7	60	[f] 13.4	277.14	1.0145
8	60	[f] 13.8	277.08	1.0142
9	60	[f] 27.6	276.72	1.0139
10	60	[f] 27.6	276.76	1.0141
11	60	60	275.78	1.0138
				mean = 1.0141 ± .0003

[a] Determined from 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 limits shown are the standard deviations.

[d] From a Kjeldahl of ethyltrimethylammonium iodide.

[e] Trimethylamine was collected from the complete reaction of ethyltrimethylammonium nitrate with t-butoxide in t-butanol.

[f] The amount of base corresponding to the desired extent of reaction was added.

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