Sec. 1

A STUDY OF THE MECHANISM OF A γ-ELIMINATION REACTION

A STUDY OF THE MECHANISM OF THE γ-ELIMINATION REACTION OF 3-PHENYLPROPYLTRIMETHYLAMMONIUM IODIDE

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SCOPE AND CONTENTS:

Deuterium tracer studies, kinetic isotope effect measurements and product composition studies in both ammonia and ammonia-$\underline{d}_3$ have been used to elucidate the mechanism of the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide in liquid ammonia at -55°. Deuterium tracer studies involving the products from the reaction of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide have excluded the carbene and ylide mechanism. A deuterium exchange test involving the deuterated quaternary salt in ammonia demonstrated that a γ-carbanion is formed during the reaction. In addition, a large γ-hydrogen isotope effect ($^{k_H}/_{k_D} > 22$) and a large nitrogen isotope effect ($\frac{k^{14}}{k^{15}} = 1.022$) were observed for the reaction. These results are consistent with either an Elcb mechanism in which the rates of ring closure and of return of the carbanion are of comparable magnitudes or a concerted mechanism accompanied by an irrelevant exchange reaction at the γ-carbon. The latter has been eliminated on the basis of a deuterium exchange test involving the undeuterated quaternary salt in ammonia-$\underline{d}_3$ and the relative rates of γ- and β-elimination of the deuterated and undeuterated quaternary salts in both ammonia and ammonia-$\underline{d}_3$.

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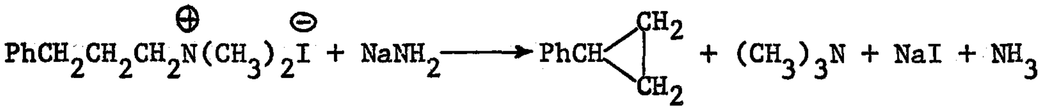
GENERAL INTRODUCTION

Elimination reactions are processes in which two atoms or groups are removed from the reacting molecule to produce, in most cases, a multiply-bonded linkage or a cyclic structure. β-Elimination reactions, in which the atoms or groups are removed from adjacent atoms of the reacting molecule and a multiply-bonded product is formed, is by far the most commonly encountered type of elimination process. Although β-elimination reactions have been used extensively in synthetic organic chemistry for well over 100 years, it is only in the last few decades that chemists have become interested in the mechanisms of this important class of reactions. A vast body of work dealing with the detailed pathways of β-elimination reactions has been published in recent years and, today, both the mechanisms and the factors which affect them are well understood.

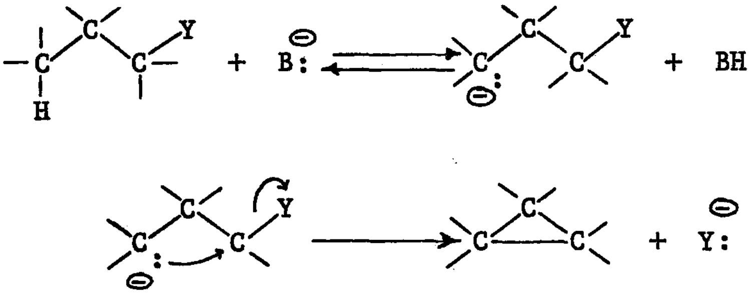
In the past decade considerable attention has been given to the elucidation of the mechanisms of γ-elimination reactions in which the two atoms or groups are removed from atoms that are separated by a third atom. The product of these reactions is generally a cyclopropane derivative. In 1958 C. L. Bumgardner (1) reported that γ-elimination reactions can compete successfully with the normal β-elimination processes when quaternary ammonium salts with β-benzyl or β-benzhydryl groups are treated with strong bases. Indeed, in the reaction of 3-phenylpropyltrimethylammonium iodide with sodium amide in liquid ammonia, the only product detected was that formed in a γ-elimination reaction (2), equation 1.



$$\mathrm{PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_2\overset{\ominus}{I} + NaNH_2 \longrightarrow PhCH{<}\,\overset{CH_2}{\underset{CH_2}{|}} + (CH_3)_3N + NaI + NH_3} \qquad (1)$$

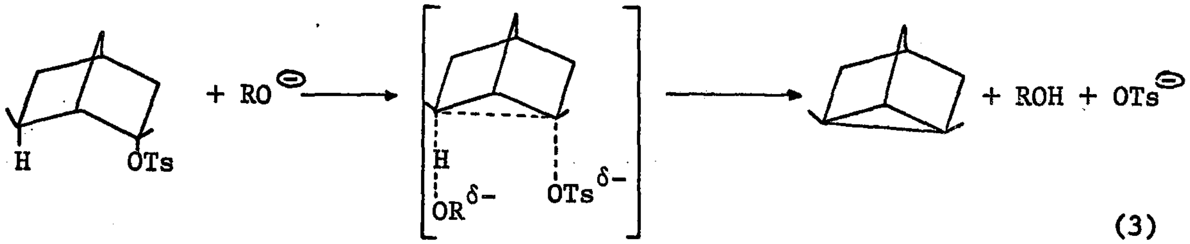
This study was begun in an effort to determine the mechanism of this new type of elimination reaction of quaternary ammonium salts.

Several reaction pathways have been identified in previously studied γ-elimination processes. Compounds containing strongly activating groups on the γ-carbon such as carbonyl (3) and sulphonyl (4) which can conjugate with a carbanionic centre, have been found to proceed by the so-called Elcb mechanism in which a γ-carbanion is a reaction intermediate, equation 2.



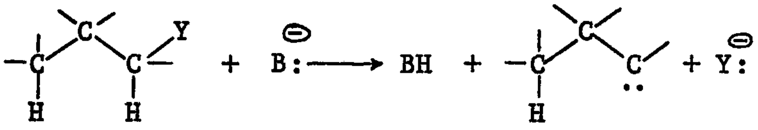
(2)

The γ-elimination reactions of bicyclic compounds, on the other hand, often proceed by way of a one-step or concerted pathway. Examples are the reactions of norbornyl tosylates (5,6) chlorides (7) and p-bromobenzenesulfonates (8) with alkoxide ions, equation 3.



(3)

Cyclopropanes are also formed in reactions proceeding by way of a carbene intermediate. The first stage in this mechanism is the formation of a divalent, electron-deficient carbene intermediate in an α-elimination reaction, equation 4.



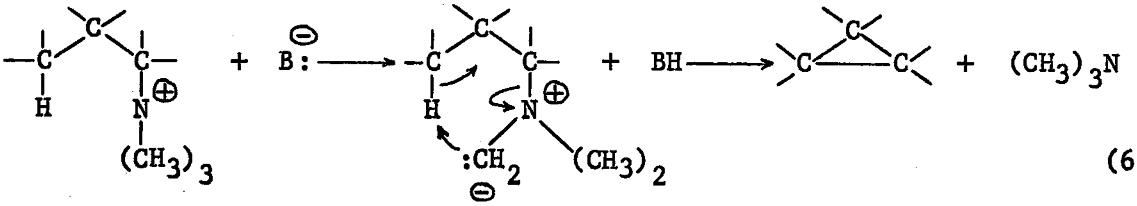
(4)

One of the important reactions of alkyl carbenes with three or more carbons is insertion into a C_γ-H bond to form a cyclopropane derivative, equation 5.

(5)

This mechanism has been observed when alkyl halides are treated with very strong bases in aprotic solvents (9,10).

Finally, a possible pathway for the γ-elimination reaction is one involving an ylide intermediate. The carbanionic centre of the ylide intermediate acts as the base in the γ-elimination reaction, equation 6.



(6)

This mechanism has occasionally been encountered in the β-elimination reactions of ammonium and sulfonium salts, particularly in the presence of strong base. Although this mechanism has not been observed for a γ-elimination process, it cannot be excluded *a priori* for the γ-elimination reaction of β-benzyl quaternary ammonium salts.

Bumgardner (11) has proposed that this elimination reaction could proceed either by a concerted or a carbanion (E1cb) mechanism. The necessity of using a strong base in order to make the γ-elimination competative with the β-elimination process suggested to Banthorpe (12) that the carbene mechanism was the more likely pathway.

The present study was undertaken in an attempt to elucidate the mechanism of the reaction of 3-phenylpropyltrimethylammonium ion with amide ion in liquid ammonia and, specifically, to distinguish between the four reaction pathways summarized in the preceeding paragraphs. The investigation involved deuterium tracer experiments, deuterium exchange tests, γ-hydrogen and nitrogen isotope effect measurements, and a study of the effect of deuterium substitution in the substrate and solvent on the relative rates of the competing β- and γ-elimination processes.

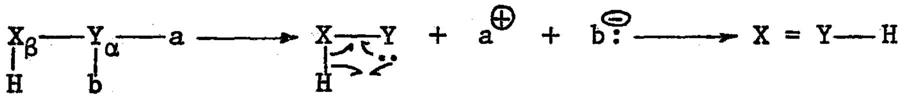
HISTORICAL INTRODUCTION

The first section of this thesis will be devoted to a review of elimination reactions. The section will begin with a brief discussion of the mechanisms of elimination reactions which produce olefins and will include an examination of the methods that have been used to distinguish between these mechanisms. The section will close with a more detailed review of γ-elimination reactions and their mechanisms.

The elimination reaction, which involves the removal of two atoms or groups from the reacting molecule, is one of the most important transformations of organic chemistry. Usually the atoms or groups that are eliminated are on adjacent atoms in the molecule and a multiple linkage is formed. This process is referred to as a β-elimination reaction, equation 7.

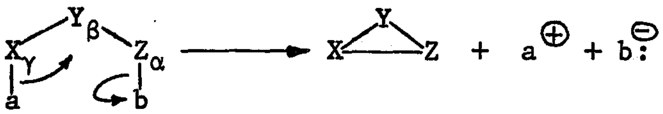
$$a\text{—}X_{\beta}\text{—}Y_{\alpha}\text{—}b \longrightarrow a^{\oplus} + b{:}^{\ominus} + X{=}Y \qquad (7)$$

Less commonly encountered are elimination processes in which atoms or groups are lost from the same atom, α-elimination, or from more distant atoms, γ- and δ-eliminations. The divalent species formed in an α-elimination can react in several ways, one of which is the migration of a hydrogen from the β- to the α-atom to produce a multiple linkage between the α- and β-atoms, equation 8.



$$\underset{\displaystyle H}{X_{\beta}}\text{—}\underset{\displaystyle b}{Y_{\alpha}}\text{—}a \longrightarrow \underset{\displaystyle H}{X}\text{—}\ddot{Y} + a^{\oplus} + b{:}^{\ominus} \longrightarrow X = Y\text{—}H \qquad (8)$$

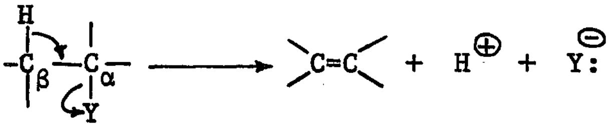
The γ- and δ-elimination reactions usually result in the formation of a ring, equation 9.



(9)

Mechanisms of β-Elimination Reactions

β-Elimination reactions are the most important and have been thoroughly studied from the point of view of reaction mechanism. Although there are several types of β-elimination reactions the discussion, for the most part, will be limited to the type where hydrogen and some group or atom Y are removed from adjacent carbon atoms to generate an olefin, equation 10.



(10)

The most frequently encountered leaving groups are halogen (13-17), dialkylsulfonium (18), trialkylammonium (19,20), and arylsulfonate (16,21).

A more extensive treatment of β-elimination reactions may be found in several excellent reviews (12,22-28) which discuss the mechanisms and stereochemistry, as well as the effects of changes in substrate structure, base and solvent on the rates and mechanisms of these processes.

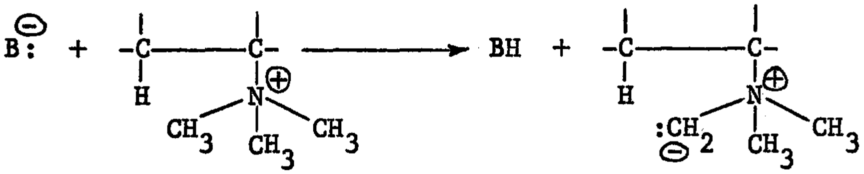
Four mechanisms have been found for β-elimination reactions. Three of these mechanisms involve the removal of only the β-hydrogen and the leaving group, Y, equation 10. These three mechanisms, which differ only in the timing of the rupture of the C_β-H and C_α-Y, bonds are:

(a) the E1 mechanism, where the rupture of the C_α-Y bond precedes the abstraction of the β-hydrogen by a base;

(b) the E2 mechanism, where the C_α-Y and the C_β-H bonds break simultaneously;

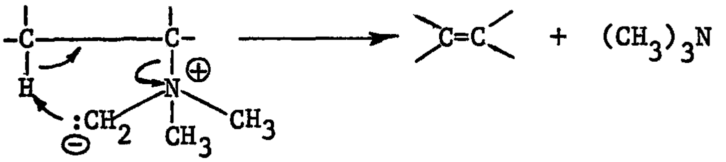
(c) the E1cb mechanism, where a hydrogen is removed from the β-carbon to produce a carbanion which subsequently decomposes to product by the breaking of the C_α-Y bond.

The fourth mechanism referred to as the α'β- or ylide mechanism involves the removal of a proton from a carbon α- to a positively charged nitrogen or sulfur atom of an 'onium salt, equation 11.



(11)

The carbanionic centre of the dipolar intermediate, called an ylide, acts as the base and initiates an intramolecular β-elimination reaction, equation 12.

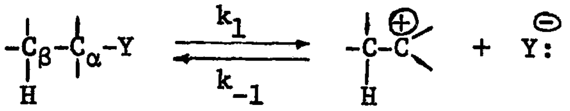


(12)

This mechanism is less common and has been found in only a few special cases.

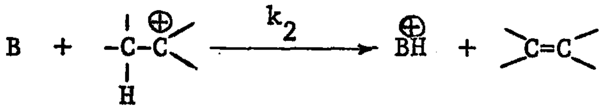
E1 Mechanism

The E1 mechanism is a two step process. The first step is the formation of a carbonium ion by the rupture of the C_α-Y bond, equation 13.



(13)

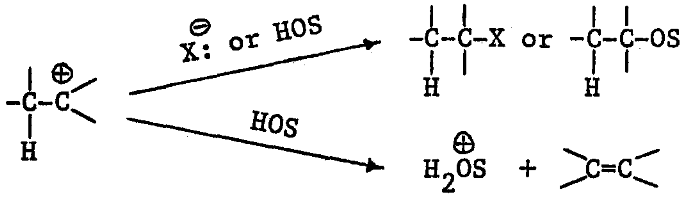
The carbonium ion then loses a proton and forms an olefin, equation 14.



(14)

This type of elimination reaction may exhibit either first or second-order kinetics. If carbonium ion formation is the rate determining step (k_2 is large relative to $k_{-1}[\overset{\ominus}{Y:}]$) first-order kinetics will be observed. If $k_{-1}[\overset{\ominus}{Y:}]$ is very much greater than k_2, the decomposition of the carbonium ion will be rate determining and second-order kinetics will be found. Carbonium ion formation is the slow step in most E1 elimination reactions.

In 1935, Hughes (29) proposed the E1 mechanism to explain why olefins accompanied the substitution products obtained in an S_N1 (unimolecular nucleophilic substitution) reaction. The first step is common to both the E1 and the S_N1 reactions. The resulting carbonium ion will be partitioned between reaction with an added nucleophile or solvent to form substitution products and reaction with a proton acceptor to form an olefin, equation 15.



(15)

This mechanism has been found when the leaving groups were halogen (30), dialkylsulfonium (31), arylsulfonate (32), and trialkylammonium (33,34).

Alpha-alkyl, vinyl, or aryl groups stabilize the carbonium ion intermediate and increase the probability that a unimolecular substitution and elimination reaction will occur.

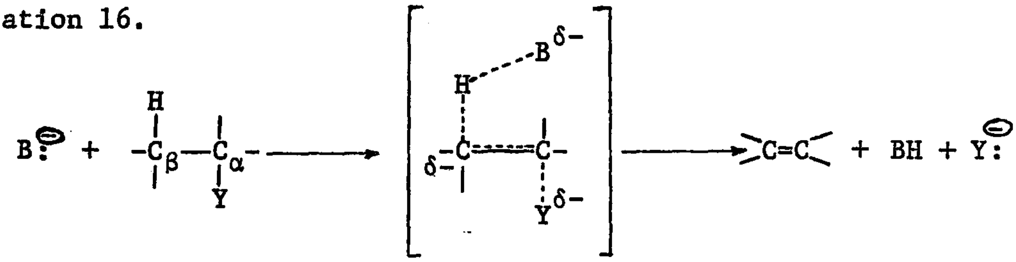
Substitution of alkyl or aryl groups at either the α- or β-carbon leads to an increased amount of elimination products. This increased amount of elimination has been attributed to two different factors. Ingold (35) suggests that the increase in elimination is a result of the increased stability of the olefin product. If the olefin is more stable, the transition state for olefin formation will be of lower energy and more elimination will occur. Brown (36,37), on the other hand, argues that these observations are best explained by steric effects. When the sp_2 hybridized carbonium ion reacts with a nucleophile to form an sp_3 hybridized substitution product steric crowding will increase. As the carbonium ion becomes more highly substituted at the α- and β-carbons the steric crowding associated with the formation of the substitution products will increase. This will make substitution less favourable and the amount of elimination will increase.

Although the rate of reaction can be expected to depend on the nature of the leaving group, the relative amounts of substitution and elimination products should be independent of the leaving group because these are reactions of the carbonium ion. This has been shown to be the case when reactions are carried out in ionizing solvents (30,38,39). It has been found, however, that in less dissociating, less nucleophilic solvents such as ethanol and acetic acid, which favour the existance of ion pairs, the product ratio can be very dependent on the leaving group (40).

A molecule which reacts via an E1 mechanism with first-order kinetics can be made to react in a bimolecular elimination process by adding a sufficient amount of strong base (41).

E2 Mechanism

The E2 mechanism (bimolecular elimination) is a one-step process involving simultaneous rupture of the C_β-H and C_α-Y bonds, equation 16.

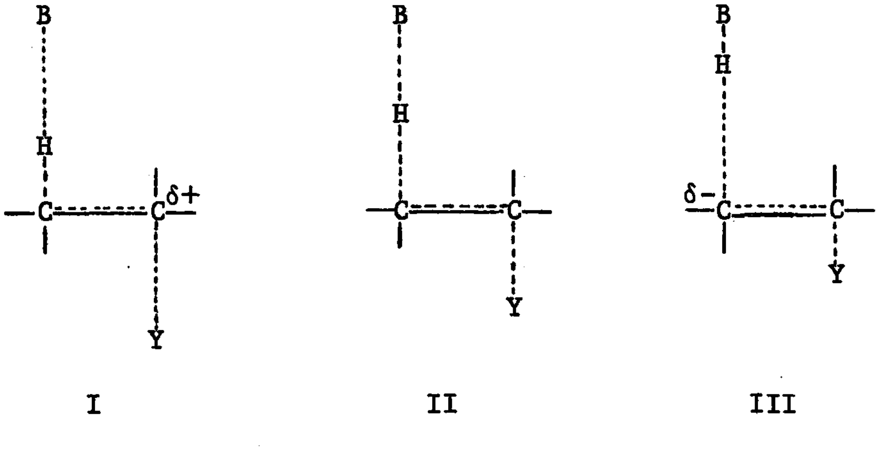


(16)

The elimination is first-order in base and first-order in reactant.

The E2 mechanism, proposed by Ingold in 1927 (19), is the normal pathway for base-promoted β-elimination reactions and there are many examples in the literature of reactions proceeding by this mechanism. The E2 mechanism has been found with charged and neutral bases of widely different strengths, with charged and neutral leaving groups, in solvents of widely different polarities and solvating power, and with molecules whose stereochemistry and structure have been widely varied.

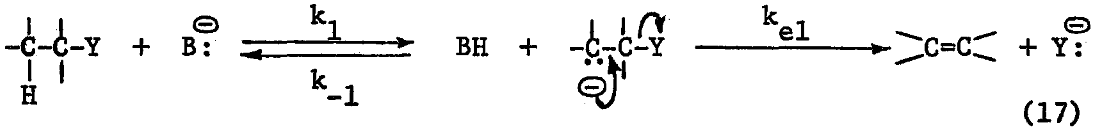
Although Ingold in his original paper suggested that the C-H and C-Y bond ruptures need not be fully synchronous, this seems to have been lost sight of in many of the subsequent papers emanating from the University College school and from other laboratories. During the past ten years, however, a number of investigators have clearly demonstrated that there is a spectrum of E2 transition states varying from the nearly E1, where the C-Y bond rupture is far advanced over C-H bond rupture, I, through the synchronous, where the C-H and C-Y bonds are ruptured to an equal degree, II, to the nearly E1cb, where the C-H bond rupture is well advanced in comparison with the C-Y bond rupture, III. While there is little double bond character in transition states I and III, the double bond is well developed in II.



The transition state of an E2 elimination reaction will be E1 like if the reacting molecule has α-alkyl, α-aryl or β-alkyl groups which stabilize the carbonium ion-like transition state. A weakly basic (good) leaving group also leads to an E1-like transition state. The transition state will be carbanion-like if the reactant contains a β-aryl or a β-electron withdrawing group, or a strongly basic (poor) leaving group (42,43).

Elcb Mechanism

The Elcb mechanism (unimolecular elimination of the conjugate base of the reactant) is a two-step process. In the first step the base produces a carbanion by abstracting a β-hydrogen from the reactant. The electrons of this carbanion displace the leaving group, Y, and form the double bond in the second step, equation 17.



$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{|}{C}}-Y + \overset{\ominus}{B:} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + -\overset{|}{\underset{\ominus\,\cdot\cdot}{C}}-\overset{|}{C}-Y \xrightarrow{k_{el}} >C=C< + \overset{\ominus}{Y:}$$

(17)

Application of the steady state treatment to the process represented in equation 17 enables the rate of β-elimination to be expressed in terms of the rate constants of the individual steps, equation 18.

$$\text{Rate} = \frac{k_{el}\ k_1[\overset{\ominus}{B:}][\text{Reactant}]}{k_{-1}[BH] + k_{el}} \qquad (18)$$

The Elcb elimination, like the E2 elimination, follows second-order kinetics whether the first step, the second step or both the first and second steps are rate determining. The free energy profile for these three alternatives, as well as that for an E2 elimination reaction are shown in figure 1.

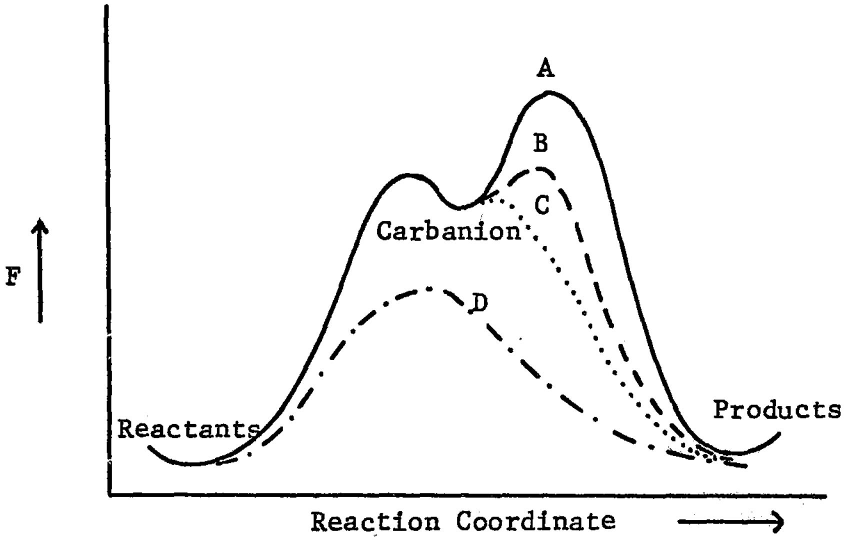
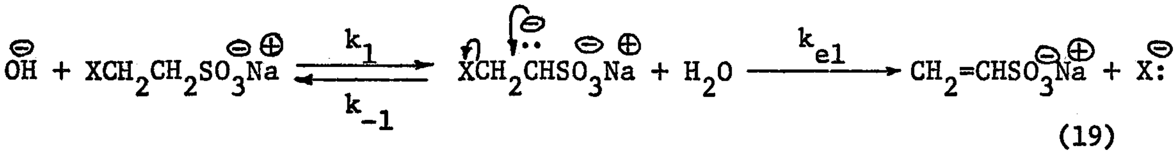


Fig. 1. A free energy plot for an E1cb process with the second step rate determining (curve A), for an E1cb process with both the first and second steps rate determining (curve B), for an E1cb process with the first step rate determining (curve C), and for an E2 process (curve D).

The partial removal of the β-proton in the transition state of an E2 elimination is facilitated by partial formation of the double bond and partial rupture of the C_{α}-Y bond. These factors, which assist the removal of the proton in an E2 elimination, are absent during carbanion formation in an E1cb elimination and the activation energy for carbanion formation is usually greater than the activation energy for the formation of an E2 transition state. Calculations by Cristol (44) have shown that the activation energy normally can be expected to be between 7 and 14 kcal/mole higher in a reaction proceeding by an E1cb mechanism than would be the case if the departure of the leaving group and double bond formation were to accompany the proton abstraction. The E1cb mechanism is found only when special structural features are present in the molecule or when the stereochemistry makes the E2 pathway a very high energy process.

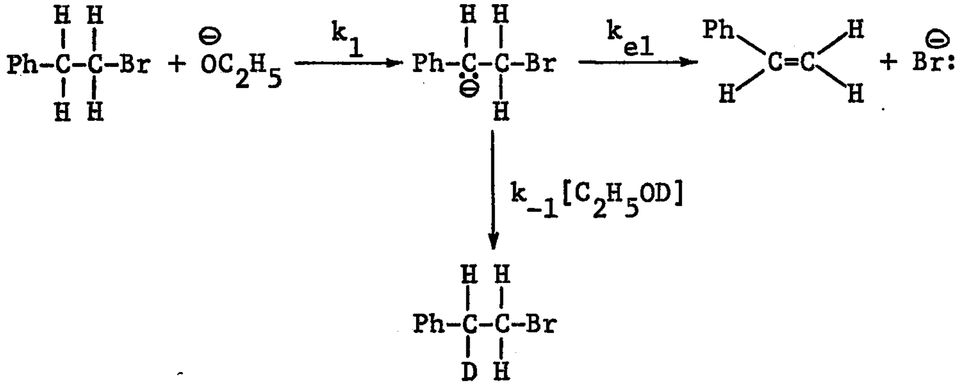
Although Ingold (45) proposed the E1cb mechanism over thirty years ago, it was only in 1946 that the first carbanion elimination was reported. Whitmore et al. (46) observed that the activation energies of the second-order dehydrohalogenations of 2-haloethylsodium sulfonates, equation 19, were independent of the halogen.



$$\overset{\ominus}{OH} + XCH_2CH_2\overset{\ominus\oplus}{SO_3Na} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} XCH_2\overset{\ominus}{C}HSO_3^{\ominus}Na^{\oplus} + H_2O \xrightarrow{k_{el}} CH_2{=}CHSO_3^{\ominus}Na^{\oplus} + \overset{\ominus}{X:} \qquad (19)$$

Since the activation energies of E2 elimination reactions were known to be dependent on the leaving group, they concluded that the C-X bond was being broken in a fast step and that the elimination reaction was an E1cb process with $k_{el} >> k_{-1}[H_2O]$.

Skell and Hauser (47) were the first to apply the deuterium exchange test for the E1cb mechanism. They allowed 2-phenylethylbromide to react with sodium ethoxide in C_2H_5OD until approximately 55 per cent of the reactant had been converted to styrene, equation 20. The unreacted bromide was recovered and examined for deuterium.

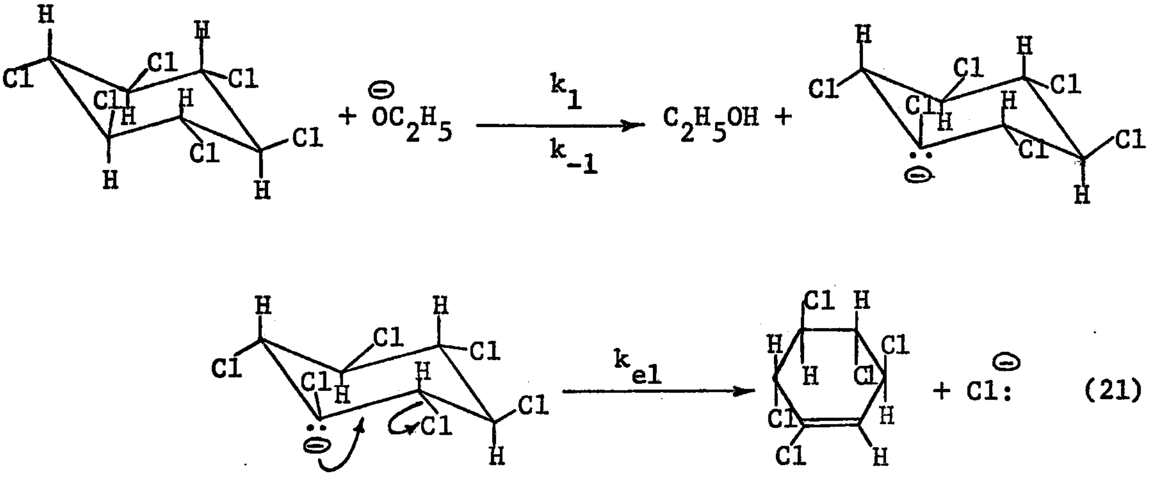


$$PhCH_2CH_2Br + \overset{\ominus}{O}C_2H_5 \xrightarrow{k_1} Ph\overset{\ominus}{C}HCH_2Br \xrightarrow{k_{el}} PhCH{=}CH_2 + \overset{\ominus}{Br:}$$

$$Ph\overset{\ominus}{C}HCH_2Br \xrightarrow{k_{-1}[C_2H_5OD]} PhCHDCH_2Br \qquad (20)$$

Skell and Hauser did not observe any incorporation of deuterium and concluded that the elimination reaction was a concerted process. Although this reaction is undoubtedly an E2 process, the failure to detect any deuterium in the molecule does not rule out the Elcb mechanism because deuterium would not be incorporated into the molecule if the elimination were an Elcb process with $k_{el} >> k_{-1}[C_2H_5OD]$.

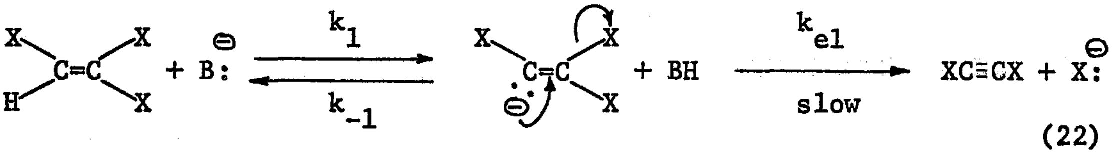
The demonstration of exchange at the β-position has been accepted as proof of an Elcb mechanism in many systems (48-58). Cristol and Fix (49) were the first to detect deuterium exchange in an elimination reaction. They found that a small amount of deuterium was incorporated into the molecule during the cis-dehydrohalogenation of the β-isomer of hexachlorocyclohexane, equation 21, and concluded that the elimination was an Elcb process with $\frac{k_{el}}{k_{-1}[C_2H_5OH]} \approx 150$.



(21)

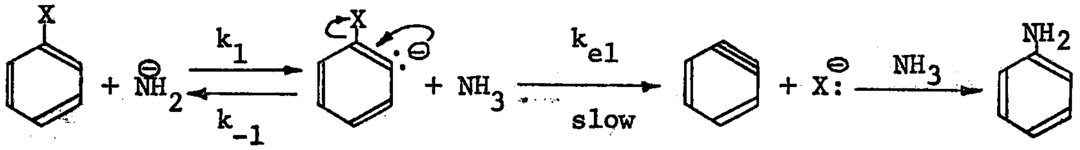
The authors suggested that the reaction was an Elcb process because the stereochemistry of the elimination made the E2 pathway a high energy process.

The dehydrohalogenation of vinyl halides has been found to be an Elcb process. Deuterium exchange has been observed in the dehydrohalogenation of both di- and trihaloethylenes (50-52), equation 22.



(22)

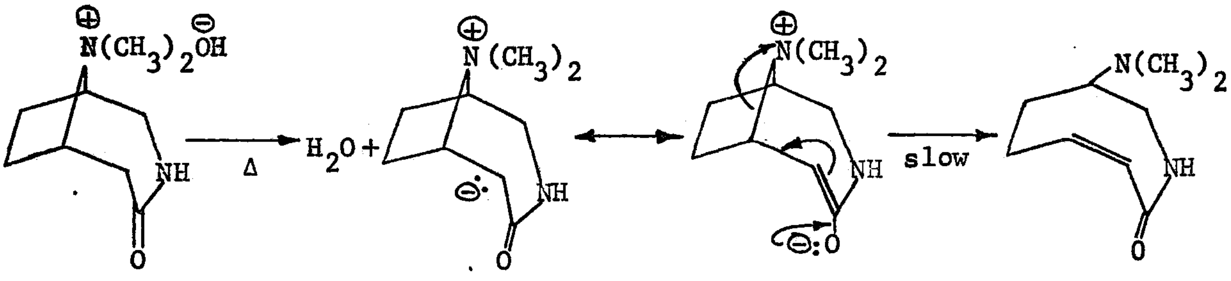
The formation of benzyne intermediates by dehydrohalogenation of halobenzenes (53) is also an Elcb process, equation 23.



(23)

Hine (54,55) observed that the rate of deuterium exchange is greater than the rate of elimination of hydrofluoric acid from 1,1,1-trifluoro-2,2-dihaloethanes and concluded that the reaction was an Elcb process. He suggests that the mechanism of a β-elimination reaction will be Elcb when the carbanion intermediate is highly stabilized $(CF_3\overset{\ominus}{\ddot{C}}Cl_2)$ and when the leaving group is poor $(\overset{\ominus}{F:})$.

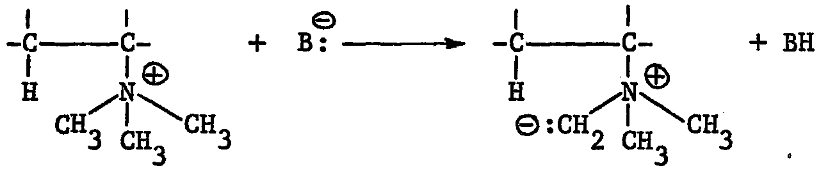
Deuterium exchange has been detected in β-elimination reactions of compounds with a β-carbonyl containing function. In these systems, the carbanion intermediate is stabilized by conjugation with the carbonyl group. The products are α,β-unsaturated acids (56), amides (57), and ketones (58). An example is shown in equation 24.



E1cb elimination reactions in which the carbanion is stabilized by conjugation with a β-p-nitrophenyl group (59) or a β-nitro group (60) also have been reported.

Ylide Mechanism

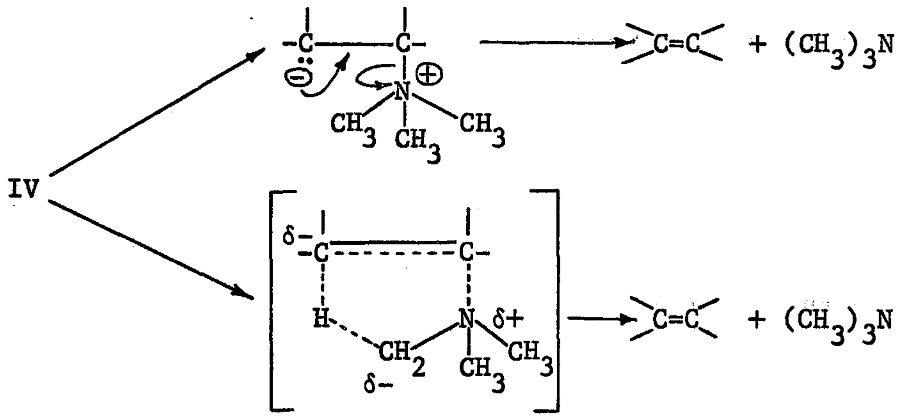
Although elimination reactions of ammonium and sulfonium ions normally proceed by the E2 mechanism, a different reaction pathway involving an intermediate dipolar species called an ylide has been observed in elimination reactions with strong bases and, less frequently, in reactions between weaker bases and molecules having structural features which inhibit a concerted process. The ylide intermediate, IV, is formed by abstraction of a proton from the carbon alpha to the 'onium atom, equation 11.



(11)

IV

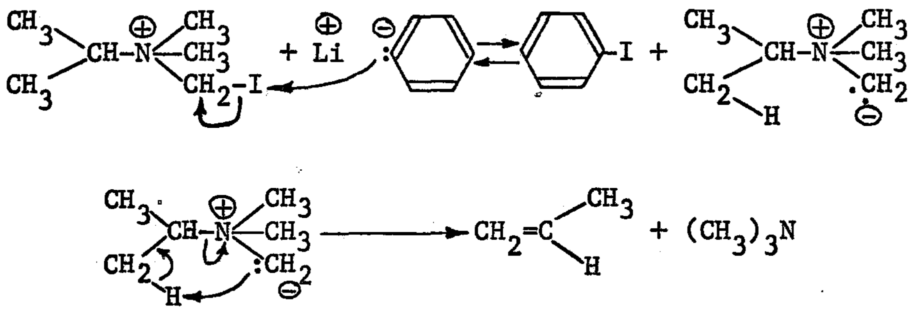
The ylide can be converted to β-elimination products in either a one or a two-step process. In the two-step process, the carbanionic centre abstracts the β-hydrogen forming a β-carbanion which is transformed into olefin in the second step. In the one-step process the abstraction of the β-hydrogen proceeds simultaneously with the departure of the leaving group, equation 25.



(25)

The formation of phosphonium and sulfonium ylides, where the α-carbanionic centre is stabilized by overlap with vacant low energy d orbitals on the 'onium atom, is relatively easy. Nitrogen has no low energy d orbitals and can only stabilize the α-carbanionic centre by electrostatic interaction with its negative charge (61). Nitrogen ylides are less stable and harder to produce than the corresponding sulfur and phosphorus ylides and, therefore, have been shown to be intermediates in only a few β-elimination reactions.

Several diagnostic tests have been used for the ylide mechanism. In 1956, Wittig (62) reported a 71 per cent yield of iodobenzene from the reaction of dimethyliodomethylisopropylammonium iodide with phenyllithium in diethylether. He concluded that this product could only have been formed by a reaction resulting in an ylide, equation 26.

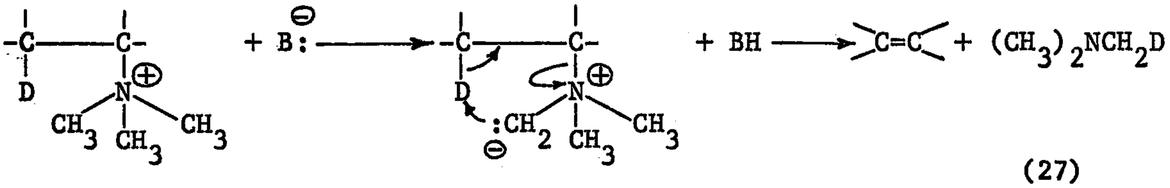


(26)

Wittig and co-workers (63,64) used this approach to show that ylide intermediates were produced in the β-elimination reactions of other quaternary ammonium salts with phenyllithium.

Product studies (65,66) have been used to demonstrate that the elimination from cyclooctyltrimethylammonium salts proceeds by an ylide mechanism when the base is an organolithium salt but not when the base is either potassium amide or hydroxide. The elimination with organolithium salts gave mainly _cis_-cyclooctene formed in a _cis_-elimination, whereas the products from the reaction with hydroxide or amide were mainly _trans_-cyclooctene formed in a _trans_-elimination.

The most definitive test for the ylide mechanism involves a tracer technique in which the β-hydrogens of the reacting molecule are labeled with either deuterium or tritium. If the α'-carbanionic centre of the ylide intermediate abstracts the β-hydrogen in a β-elimination reaction, the label will appear in the trimethylamine, equation 27.

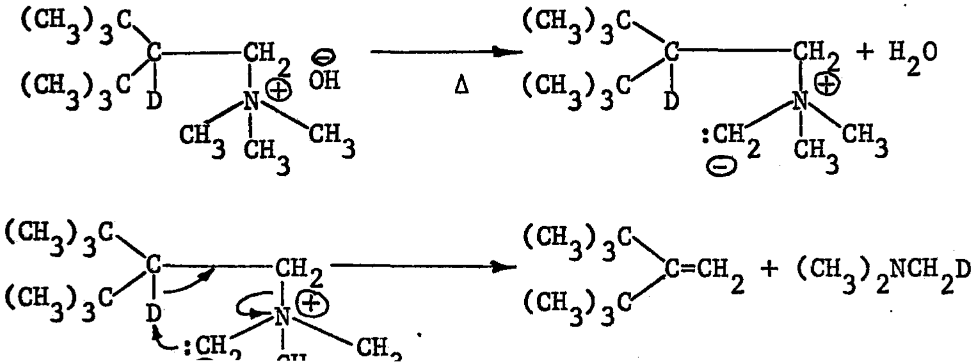


(27)

In recent years many investigators have used this test in order to determine if a β-elimination reaction proceeds by way of an ylide mechanism (48,67-72). This work has confirmed the results of the product studies which, as already stated, have shown that the ylide mechanism is favoured by the use of very strong bases, such as organolithium compounds in aprotic solvents, while the E2 pathway is followed when weaker bases are used in protic solvents (48,62-65,67, 68,73). For example, Cope (68), using the tracer test, found that the β-elimination reaction of 1-deuterocyclohexylmethyltrimethylammonium hydroxide under ordinary Hofmann conditions is exclusively E2, whereas the reaction proceeds almost completely by an ylide mechanism when the base is phenyllithium.

Bumgardner (74) replaced an N-methyl group of cyclooctyltrimethylammonium bromide with an N-benzyl group so as to increase the acidity of the α'-hydrogens. The reaction of this compound with sodium amide gave pure *cis*-cyclooctene, while cyclooctyltrimethylammonium bromide under essentially the same conditions gave 85 per cent *trans*-cyclooctene. This change in product composition when the α'-hydrogens are made more acidic was attributed to a change from an E2 to an ylide mechanism.

Although quaternary ammonium salts usually undergo an E2 elimination under Hofmann conditions, Cope (70) demonstrated that elimination can occur by way of an ylide mechanism if the normal *trans*-elimination is made less favourable. He found that 75 per cent of the trimethylamine recovered from the pyrolysis of N,N,N-trimethyl-2-*t*-butyl-3,3-dimethylammonium hydroxide-2-$\underline{d}_1$, equation 28, contained a deuterium atom indicating that at least 75 per cent of the elimination proceeded by an ylide mechanism.



(28)

Steric hindrance between the two t-butyl groups and the trimethylammonium group make the normal trans-E2 elimination a very high energy process and the ylide pathway becomes the favoured route for the elimination.

Differentiation of the E2 and Elcb Mechanisms

Until recently it has been impossible to unequivocally distinguish between the kinetically equivalent E2 and Elcb mechanisms. Although several E2 elimination reactions have been positively identified, the problem of distinguishing between these two mechanisms is not completely solved. The methods which have been used to distinguish between these two mechanisms will be discussed in this section of the thesis.

Deuterium Exchange Test

The exchange test first applied by Skell and Hauser (47) has demonstrated the presence of β-carbanions in a number of systems undergoing β-elimination reactions. Although the existence of these carbanions cannot be doubted, Breslow (75) has recently questioned whether the detection of β-carbanions is conclusive evidence for an Elcb mechanism. Breslow argues that while the formation of a carbanion may require less free energy than that required to produce an E2 transition state, this does not necessarily mean that the free energy for an E2 elimination is greater than for an Elcb elimination. In figure 2, the second step of the Elcb process is rate determining. The elimination reaction will proceed via an E2 mechanism because the free energy of the transition state for the E2 elimination is less than the free energy of the transition state for the slow step of the Elcb elimination. Deuterium exchange will occur because the transition state for carbanion formation requires less free energy than the transition state for either the Elcb or E2 eliminations.

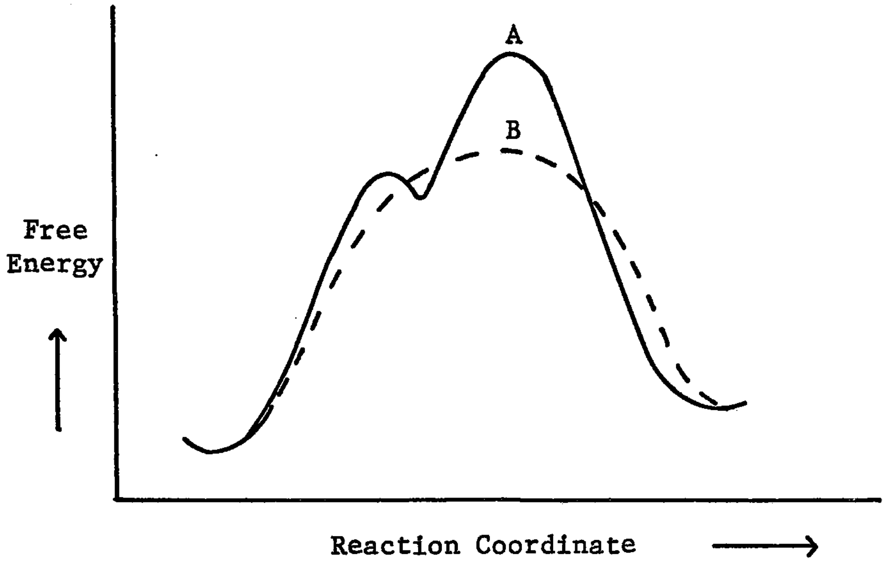
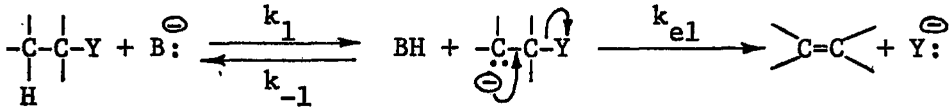


Fig. 2. A free energy plot for the Elcb mechanism (curve A) and for the E2 mechanism (curve B).

Hine (55) argues that if a partial freeing of the electrons of the C_β-H bond in an E2 reaction is sufficient to cause elimination, the fully developed negative charge of the carbanion in an Elcb reaction must be much more effective in causing elimination. The carbanion, which is in a potential energy well, must exist long enough to attain any orientation required for elimination. Since the carbanion has the ability to undergo elimination and can attain a stereochemistry suitable for elimination, it would appear that carbanions would readily be converted to elimination products and that the demonstration of deuterium exchange is probably a sufficient criterion for the E1cb mechanism.

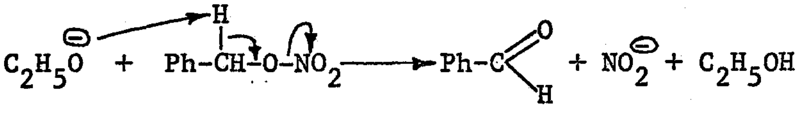
Isotope Effects

While the demonstration of deuterium exchange at the β-carbon is strongly indicative of the E1cb mechanism, the absence of detectable exchange does not establish the E2 reaction pathway. The lack of exchange can be a consequence either of a concerted process or of reaction by way of a carbanion which is converted into olefin very much faster than it abstracts a proton from solvent to regenerate reactant ($k_{el} >> k_{-1}[BH]$ in equation 17).



$$-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{|}{C}}-Y + B:^{\ominus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + -\overset{|}{\underset{\ominus}{\ddot{C}}}-\overset{|}{\underset{|}{C}}-Y \xrightarrow{k_{el}} {>}C{=}C{<} + Y:^{\ominus} \qquad (17)$$

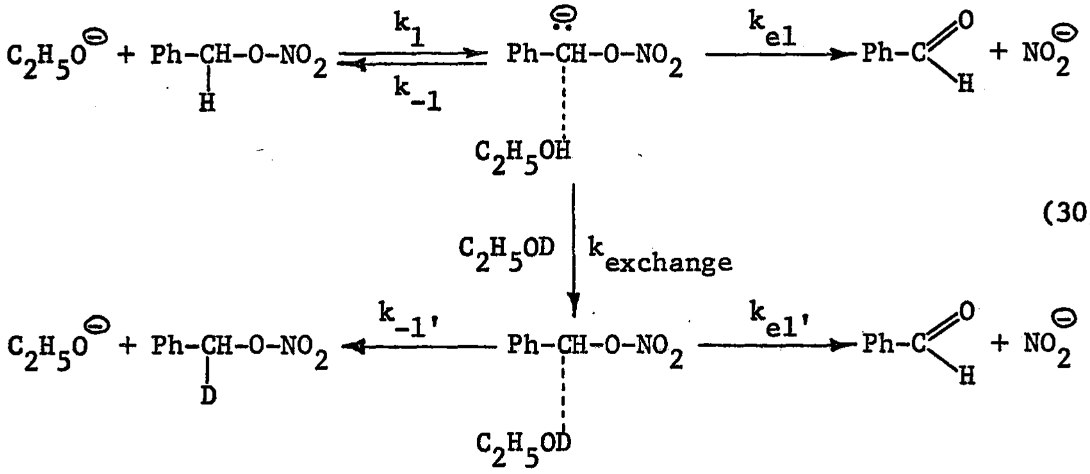
The isotope effect associated with the elimination of the leaving group has been used to help decide whether the mechanism of an elimination reaction showing no exchange is E2 or E1cb with $k_{el} >> k_{-1}[BH]$. If it is the latter, the C_α-Y bond is breaking in a fast step and little or no isotope effect associated with the leaving group should be found. If the elimination is an E2 process, the C_α-Y bond is partially broken in the transition state of the rate-determining step and a significant isotope effect should result. Bourns and Buncel (76) who studied the mechanism of the carbonyl elimination reaction of benzyl nitrate, equation 29, were the first to use this test.



$$C_2H_5O^{\ominus} + Ph-\overset{H}{\overset{|}{C}}H-O-NO_2 \longrightarrow Ph-C\overset{O}{\underset{H}{\lessgtr}} + NO_2^{\ominus} + C_2H_5OH \qquad (29)$$

No deuterium exchange was found in this system. The nitrogen isotope effect for the elimination was 2.0 per cent at 60°, indicating that the composite force constant associated with the O-N bond had greatly decreased at the transition state of the rate-determining step. The absence of deuterium exchange shows that a carbanion, if formed, would have to decompose to product very much faster than it abstracts a proton from solvent to regenerate reactant. This is excluded by the observation of a two per cent nitrogen isotope effect which requires the rupture of the C-N bond in a slow step. The reaction, therefore, cannot be following the Elcb pathway described in equation 17.

There is a modification of the Elcb mechanism which is consistent with no deuterium exchange and a normal nitrogen isotope effect. This is shown in equation 30 and involves the formation of a carbanion which is specifically hydrogen bonded to the molecule of ethanol formed by abstraction of the β-hydrogen



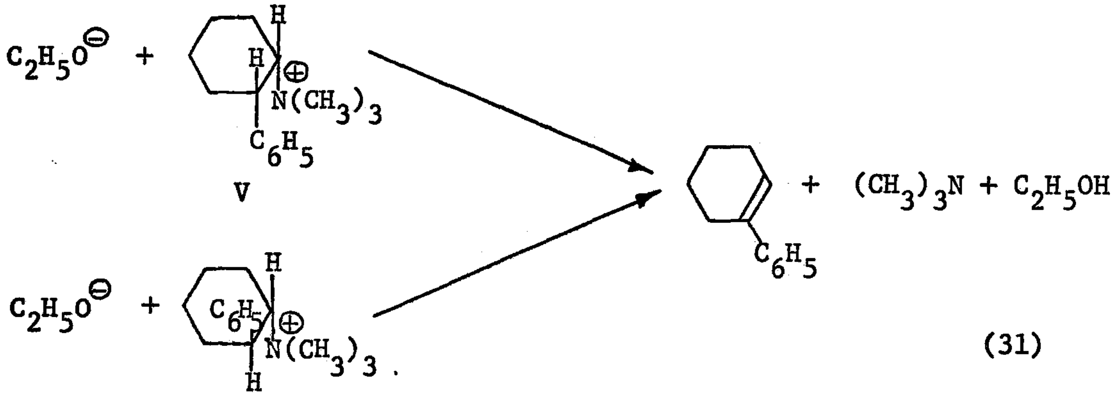
(30)

If k_{el} is much larger than $k_{exchange}$ but smaller than k_{-1}, exchange with deuterated solvent molecules would not be observed but a normal nitrogen isotope effect would result.

The β-hydrogen isotope effect can be used to distinguish between this mechanism and an E2 mechanism. The β-hydrogen isotope effect for the modified E1cb process would be small or even inverse because it results from an equilibrium proton transfer between a carbanion and an alkoxide ion (77). The E2 process, on the other hand, should give a large primary β-hydrogen isotope effect because the C_β-H bond is breaking in the transition state of the rate-determining step. Bourns and Buncel observed an isotope effect of 5.0 at 60°. This result, coupled with the large nitrogen isotope effect and the absence of deuterium exchange at the benzyl carbon, eliminates an E1cb mechanism as the reaction pathway and demonstrates unequivocally that the carbonyl elimination reaction of benzyl nitrate is an E2 process.

Bourns and co-workers have used these criteria to establish the E2 mechanism for the carbonyl elimination of fluorenyl nitrate with acetate ion (78) and for the reaction of several β-arylethylammonium salts with ethoxide ion (79,80).

Bourns and Ayrey (81) applied these diagnostic tests to the elimination reactions of cis- and trans-2-phenylcyclohexyltrimethylammonium salts V and VI. The major product of elimination from both of these compounds was 1-phenylcyclohexene, equation 31.



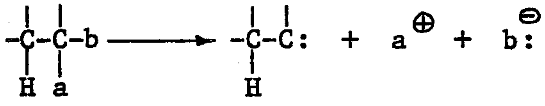
(31)

The cis-quaternary ammonium salt, V, forms 1-phenylcyclohexene in a normal trans-elimination. A β-hydrogen isotope effect ($\frac{k_H}{k_D}$ = 5.6 at 60°), a nitrogen isotope effect (1.2 per cent at 60°) and the lack of deuterium exchange at the β-carbon led these workers to conclude that the trans-elimination is a concerted E2 process.

The trans-quaternary ammonium salt, VI, forms 1-phenylcyclohexene in an unfavourable cis-elimination (82). Tracer studies have shown that 1-phenylcyclohexene was not formed in a trans-elimination after epimerization at the α-carbon (83), or from a tautomeric rearrangement of 3-phenylcyclohexene which could be formed in a normal trans-elimination (84). The ylide mechanism was also ruled out by tracer studies (69). Bourns and Ayrey did not find any deuterium exchange at the β-carbon. They did, however, find a primary β-hydrogen isotope effect ($\frac{k_H}{k_D}$ = 3 at 60°) and concluded that the reaction was either an E2 or an Elcb mechanism with $k_{el} >> k_{-1}[BH]$, equation 17. The nitrogen isotope effect was determined and found to have the extremely low value of 0.2 per cent. Although it is conceivable that the reaction is a one-step process in which the composite force constant associated with the C-N bond has changed so little at the transition state that there is essentially no isotopic dependence on the rate of reaction, a much more reasonable conclusion is that the reaction is an Elcb process with $k_{el} >> k_{-1}[BH]$.

Mechanisms of α-Elimination Reactions

Although a compound capable of reacting in a β-elimination process usually reacts in this manner, α-elimination reactions where two atoms or groups are removed from the same carbon to produce a divalent, electron-deficient species called a carbene, VII, equation 32, can become important when very strong bases are used in aprotic solvents.

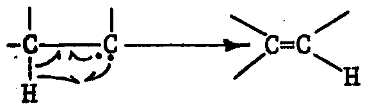


$$-\underset{H}{\overset{|}{C}}-\underset{a}{\overset{|}{C}}-b \longrightarrow -\underset{H}{\overset{|}{C}}-\overset{|}{C}: + a^{\oplus} + b:^{\ominus}$$

(32)

VII

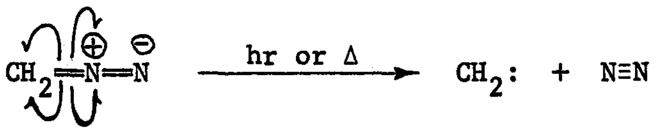
The transient carbene intermediate can transfer a β-hydrogen to the α-carbon and form an olefin, equation 33.



(33)

If a hydrogen is one of the atoms removed in the α-elimination, the olefin produced from the carbene intermediate is identical to that obtained from a normal β-elimination reaction.

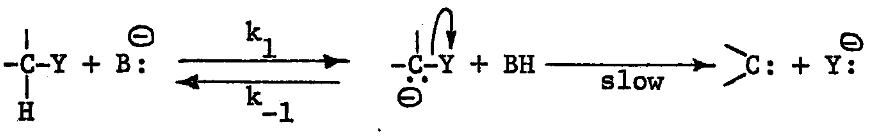
Carbenes have been generated by several methods. They have been prepared by photochemically and thermally induced homolytic decompositions of ketenes and diazo compounds, equation 34.



$$CH_2=\overset{\oplus}{N}=\overset{\ominus}{N} \xrightarrow{hr\ \text{or}\ \Delta} CH_2: + N\equiv N$$

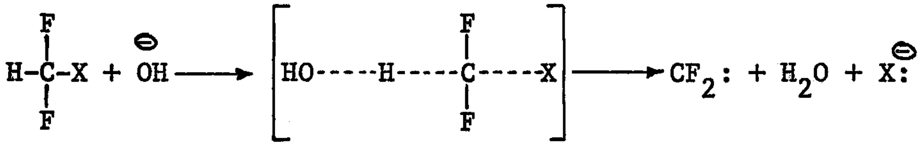
(34)

Hine (85) has found that di- and trihalomethanes react with hydroxide ion in an α-elimination reaction by either a one or a two-step mechanism. The two-step process shown in equation 35, is well documented (85-88), and appears to be the mechanism of most α-elimination reactions.



$$-\underset{H}{\overset{|}{C}}-Y + B:^{\ominus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} -\overset{|}{\underset{\ominus}{\ddot{C}}}-Y + BH \xrightarrow[\text{slow}]{} >C: + Y:^{\ominus} \qquad (35)$$

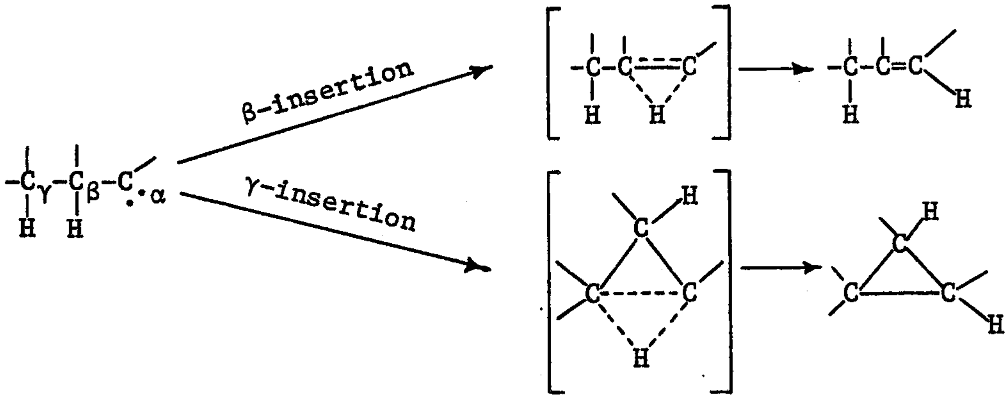
This mechanism has been observed when the leaving group, Y, is halogen (9,85,89), dimethylsulfonium (90,91), diphenylsulfonium (92,93), trialkylammonium (94), and thiophenolate (95). The α-elimination reaction of difluorohalomethanes with hydroxide, equation 36, has been found to be a concerted process (96).



$$H-\underset{F}{\overset{F}{C}}-X + \overset{\ominus}{O}H \longrightarrow \left[HO\text{-----}H\text{-----}\underset{F}{\overset{F}{C}}\text{-----}X\right] \longrightarrow CF_2: + H_2O + X:^{\ominus} \qquad (36)$$

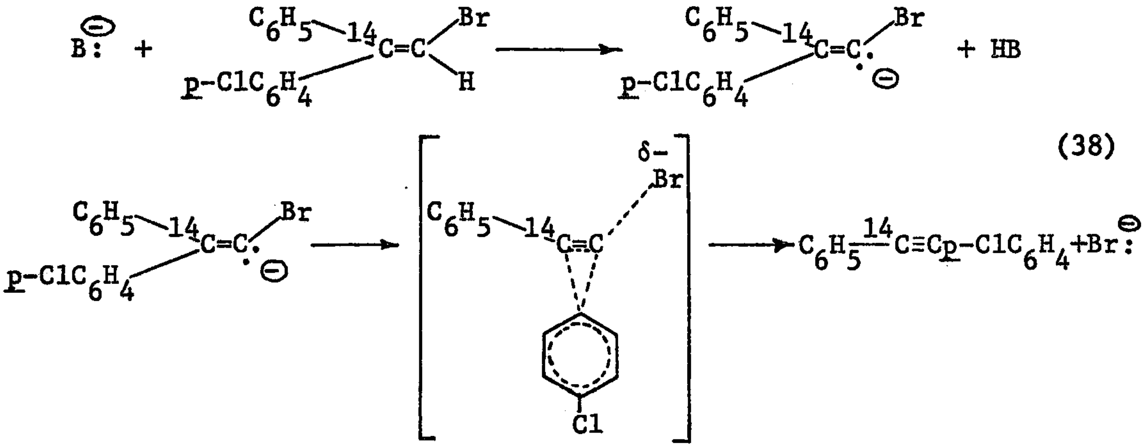
Hine suggests that the two fluorine atoms in the trihalomethane leads to a change in mechanism because the two fluorine atoms make the carbanion $(\overset{\ominus}{C}F_2X)$ relatively unstable and hence the two-step mechanism a high energy process, whereas they lower the energy for a concerted α-elimination by stabilizing the carbene-like transition state.

The major reactions of alkyl carbenes with at least three carbon atoms are insertion into a β-C-H or C-C bond to produce an olefin and insertion into a γ-C-H bond to form a cyclopropane ring, equation 37.



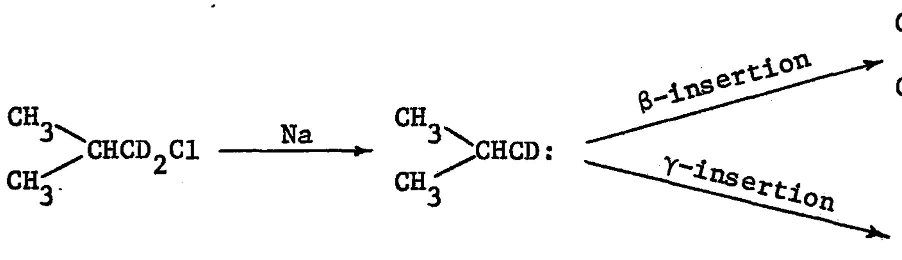
(37)

Bothner-By (97) and Curtin et al. (98) studied the α-elimination reaction of cis- and trans-2-phenyl-2-p-halophenylvinyl bromides-2-^{14}C, equation 38.

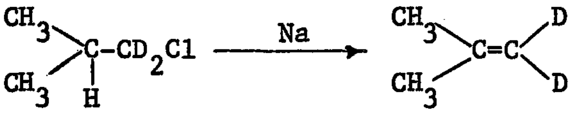

(38)

They found that the group trans- to the halogen in the vinyl bromide was almost exclusively on the unlabeled carbon of the product and concluded that insertion into the β-C-C bond and departure of the bromide ion were concerted. Although no proof has been provided both the β- and γ-insertions shown in equation 37 also could occur as the leaving group departs.

Tracer and product studies have been used to demonstrate that α-elimination competes successfully with β-elimination when very strong bases are used in aprotic solvents. Kirmse and Doering (10), using these techniques, were the first to demonstrate that α-elimination could predominate over β-elimination. They found that 67 per cent of the products from the reaction of sodium with isobutyl chloride-1,1-d_2 was formed in an α-elimination reaction, equation 39, while 33 per cent was formed in a β-elimination reaction, equation 40.



(39)



(40)

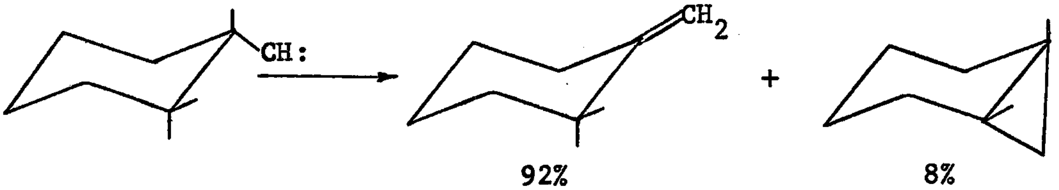
The products formed from the α-elimination reaction contained one atom of deuterium per molecule, while the olefin produced in the normal β-elimination had two atoms of deuterium per molecule. When phenylsodium was used as the base in this reaction, 89 per cent of the product was formed in an α-elimination reaction (9). n-Butyl, neopentyl and neohexyl halides were also found to react primarily by way of an α-elimination process when sodium metal or phenylsodium was the base (9,99,100).

The importance of a strong base was demonstrated by Friedman and Berger (9) who found that the amount of α-elimination from n-butyl chloride decreased from 94 per cent when phenylsodium was the base, to 30 per cent with amide ion, to only 10 per cent with methoxide ion. This trend has been observed in the reactions of other halides (9,99).

Alpha-elimination competes more successfully with β-elimination when a poor leaving group is present. When phenylsodium was the base the amount of α-elimination increased from 13 per cent with i-butyl-iodide, to 62 per cent with i-butyl bromide and to 89 per cent with i-butyl chloride (9).

Several factors influence the relative amounts of insertion into the β-C-H and γ-C-H bonds, equation 37. The inductive effect is important is determining the amount of γ-C-H insertion. Electron-withdrawing groups on the γ-carbon retard attack by the electron-deficient carbene (101), while both β- and γ-alkyl groups, which are electron-releasing, increase the amount of γ-C-H insertion (9,99, 102,103). When groups such as methoxy, which can stabilize positive charge, are on the β-carbon olefin formation by insertion into the β-C-H bond is increased with respect to insertion into the γ-C-H bond (104).

Insertion into the γ-C-H bond is the primary reaction when the bonds forming the cyclopropane ring are coplanar, while β-C-H insertion is the favoured reaction when coplanarity cannot be achieved (105,106). This was demonstrated in the reactions of cyclohexylcarbene, equation 41 and cyclopentylcarbene, equation 42.



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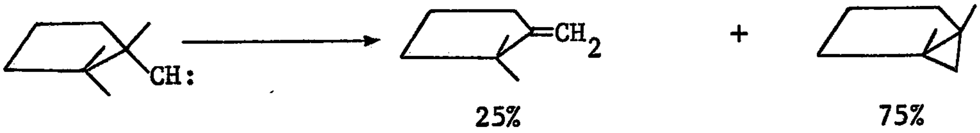
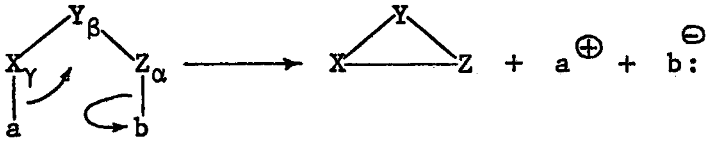


(42)

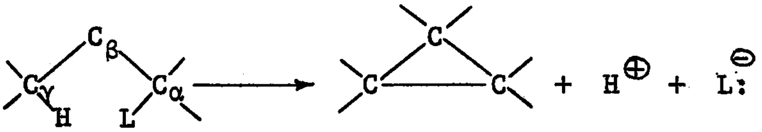
Mechanisms of γ-Elimination Reactions

A γ-elimination reaction, like the β-elimination reaction, involves the removal of two atoms or groups from the molecule. In a γ-elimination, however, the atoms or groups that are removed are not on adjacent atoms, as they are in a β-elimination reaction, but are on atoms that are separated by a third atom. The product is usually a three-membered ring, equation 9.



(9)

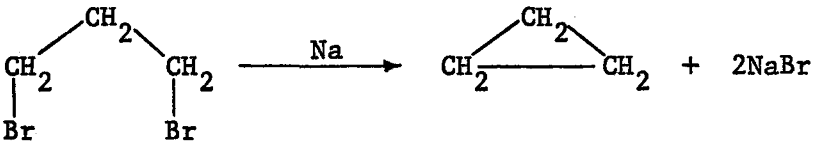
In most γ-elimination reactions X, Y and Z are carbon atoms and a cyclopropane ring is formed, equation 43, although γ-elimination reactions where Y is sulfur (107) and either X or Z is nitrogen (108) have been reported.



(43)

Usually hydrogen is one of the atoms removed. The other group or atom can be halogen (108-111), trimethylammonium (2,112), arylsulfonate (5,113), acetate (8) and sulphoxide (114).

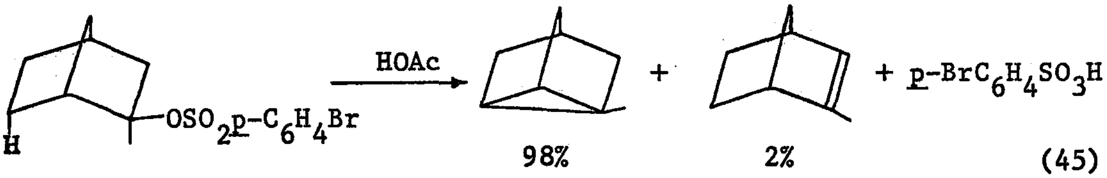
The first γ-elimination reaction was reported 85 years ago by Freund (115), equation 44.



(44)

From the time of Freund's report until approximately 1960 γ-elimination reactions were virtually ignored, and it is only in the last five or six years that the scope and mechanisms of these reactions have been investigated in any detail.

Although γ-elimination reactions often compete successfully with β-elimination reactions in bicyclic systems (5,6,116), equation 45, they normally do not in aliphatic systems.



(45)

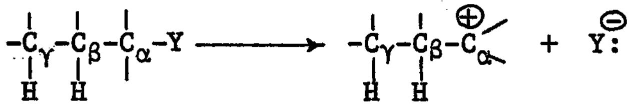
γ-Elimination reactions have been found in aliphatic systems only when β-elimination reactions are impossible (107,108,117) or when structural features which increase the rate of γ-elimination with respect to β-elimination are present in the molecule (2,11,110,113).

One difference between the β- and γ-elimination reactions has become apparent. The reacting α- and γ-carbon atoms are separated by a third atom and, as a result, changes in the bonding at the γ-carbon during movement along the reaction coordinate for γ-elimination has little or no effect on the bonding at the α-carbon and vice versa. Consequently, the two-step mechanisms of elimination, involving initial formation of a carbonium ion or a carbanion, would be expected to be more important in γ-elimination reactions than in β-elimination reactions where the reacting centres are joined together. Although concerted γ-elimination reactions have been observed in bicyclic systems, aliphatic systems appear to react by two-step mechanisms.

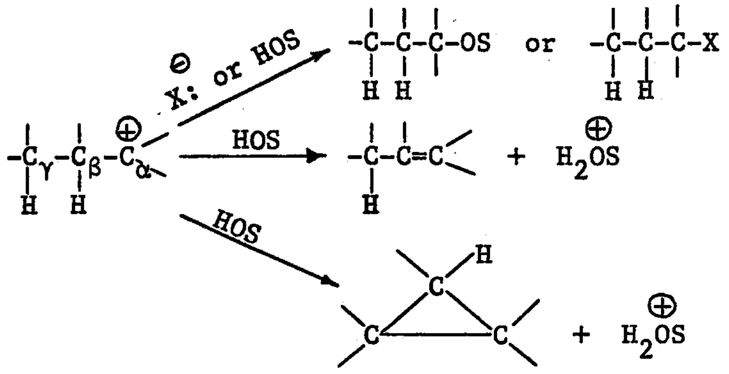
While γ-elimination reactions have not been as thoroughly studied from the point of view of reaction mechanism as β-elimination reactions, most of the mechanisms of β-elimination reactions have their counterparts in γ-elimination reactions. The terms E1, E2, E1cb and α-, which were used to describe the mechanisms of olefin-forming elimination reactions, are also used to describe the mechanisms of γ-elimination reactions because these terms refer to the mechanism and kinetic behaviour of the reaction rather than to the position of the atoms that are removed in the reaction.

E1 Mechanism

The E1 mechanism of γ-elimination is mechanistically identical to that described in the section on β-elimination reactions. The first step is the rupture of the C_α-Y bond to give a carbonium ion, equation 46, which can react with solvent or added nucleophile to give substitution products, or lose a proton to a molecule of base from either the β-carbon to form an olefin or from the γ-carbon to form a cyclopropane derivative, equation 47.



(46)

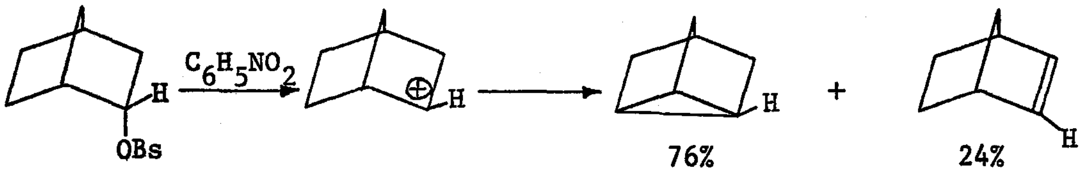


(47)

Cyclopropane derivatives have been found in low yields from several reactions which are known to proceed by way of a carbonium ion intermediate. Cyclopropanes have been produced when the leaving group, Y, is arylsulfonate (5,6,116), nitrogen from a diazonium ion (118-120) and carbon monoxide from an alkoxycarbene (121,122).

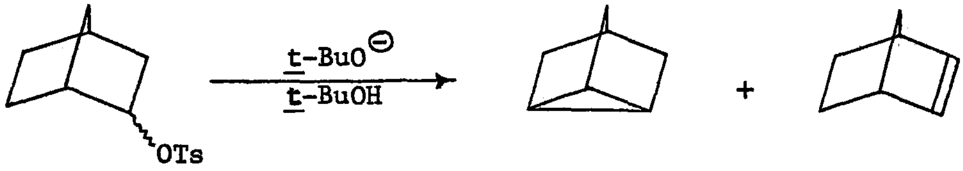
In bicyclic systems the major portion of the product from an E1 elimination reaction is a cyclopropane derivative formed in a γ-elimination reaction (112,123). In aliphatic systems on the other hand, the major product from an E1 elimination reaction is an olefin formed in a β-elimination reaction (124,125).

Winstein _et_ _al_. (116) found that 98 per cent of the elimination products from the acetolysis of _exo_-norbornyl-2-_p_-bromobenzenesulfonate is formed in a γ-elimination reaction while only two per cent is formed in a β-elimination reaction, equation 45. Sonnenberg and Stille (8) reported that 76 per cent of the elimination product formed in the solvolytic elimination of _endo_-norbornyl-2-_p_-bromobenzenesulfonate is formed in a γ-elimination reaction, equation 48.



(48)

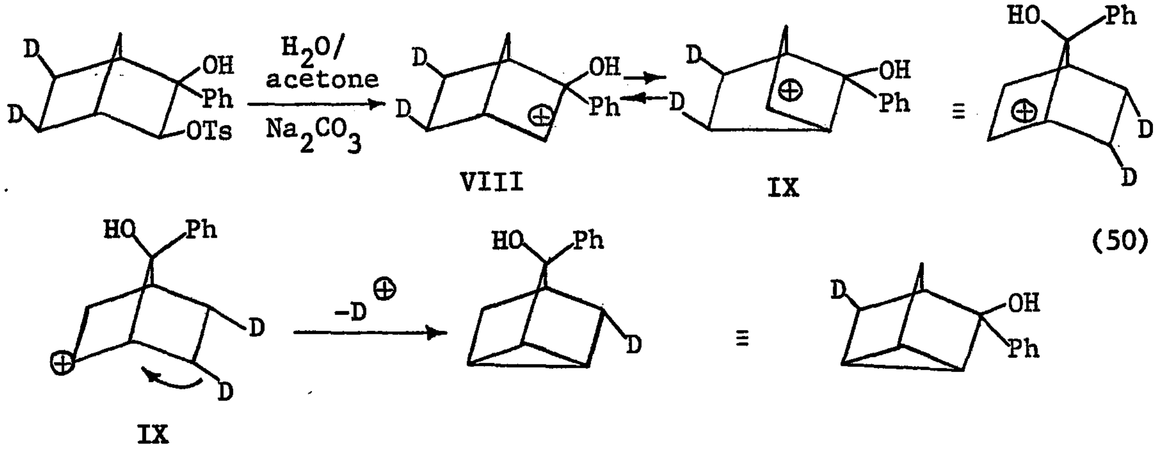
Nickon and Werstiuk (5,6) examined the reaction of both _endo_- and _exo_-norbornyl-2-tosylates in _t_-butoxide and _t_-butyl alcohol. They found that both reactions exhibited first-order kinetics when the base concentration was low, and concluded that both reactions involved the formation of a carbonium ion in the rate-determining step. Seventyfive per cent of the elimination product formed from the _exo_-isomer and 84 per cent of the elimination product from the _endo_-isomer was formed in a γ-elimination reaction, equation 49.



(49)

exo	75%	25%
endo	84%	16%

Collins and co-workers (126) studied the hydrolysis of _exo_-_exo_-5,6-dideutero-_exo_-3-hydroxy-3-phenyl-_exo_-2-norbornyl tosylate which cannot undergo an E1 β-elimination reaction. They obtained a 25 per cent yield of _exo_-5-deutero-_exo_-3-hydroxy-3-phenylnortricyclene which was formed in a stereospecific elimination reaction, equation 50.

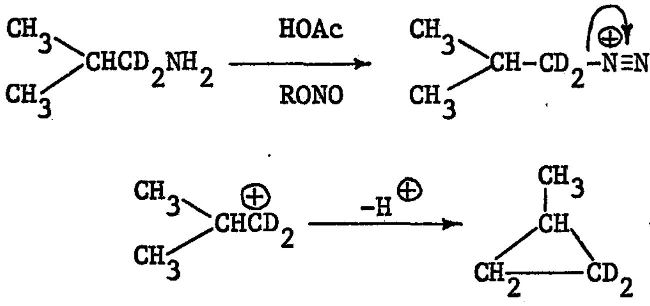


(50)

This reaction may involve a nonclassical carbonium ion rather than the two equilibrating carbonium ions VIII and IX.

Low yields of cyclopropane compounds are obtained from the decomposition of aliphatic diazonium ions. Friedman and Jurewicz

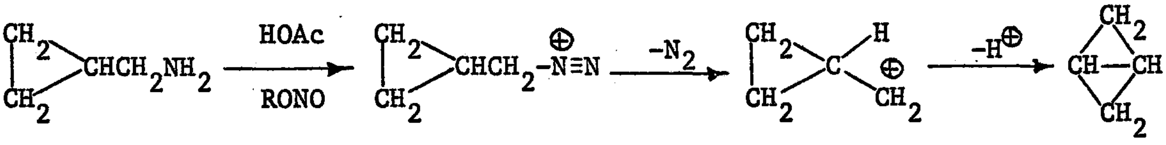
(119), using tracer techniques, showed that the cyclopropanes were not formed in a carbene insertion reaction. The methylcyclopropane produced in the reaction of i-butylamine-1,1-d_2 was almost completely dideuterated. The authors concluded that the methylcyclopropane was formed in an E1 γ-elimination reaction, equation 51.



+ olefins (51)

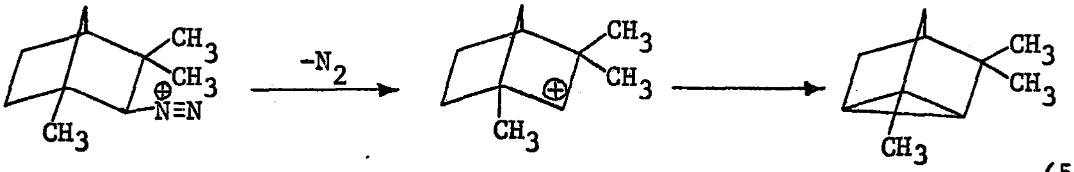
Only ten to fifteen per cent of the elimination product from the decomposition was formed in a γ-elimination reaction (118). The cyclopropane:olefin ratio was also very low in the decomposition of diazonium salts formed from other aliphatic amines, such as n-butyl, s-butyl, n-propyl and 3-methyl-2-butyl amines (124,125,127,128).

The major elimination product from the decomposition of diazonium salts involving cyclic structures is formed in a γ-elimination reaction. Smith et al. (123) obtained a 70-80 per cent yield of bicyclo[1,1,0]butane from the decomposition of cyclopropylcarbinyl and cyclobutyl diazonium ions, equation 52.



(52)

A twenty per cent yield of tricyclene was obtained from the diazonium salt of exo-fenchylamine which cannot undergo a β-elimination reaction (129), equation 53.



(53)

Skell and Starer (125) have reported that alkoxide ions react with dihalocarbenes to produce carbon monoxide and a carbonium ion, equation 54.

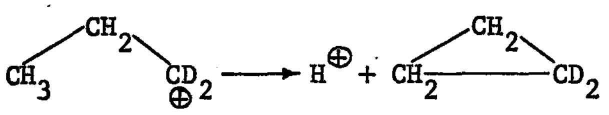
$$RCH_2O^{\ominus} + :CX_2 \longrightarrow RCH_2\text{-}\ddot{O}CX + \overset{\ominus}{X:} \longrightarrow \overset{\oplus}{RCH_2} + CO + \overset{\ominus}{X:} \tag{54}$$

The yields of the products from the carbonium ions generated from the alkoxide ions and from the corresponding diazonium ions were identical.

Skell and Starer (121) have shown that the cyclopropanes produced in this so-called deoxidation reaction are formed in an El elimination reaction rather than by a carbene insertion reaction. In the reaction of 1,1-dideuteropropanol, 94 per cent of the cyclopropane product was found to contain two atoms of deuterium per molecule, while the remaining six per cent was monodeuterated, equation 55.

$$CH_3CH_2CD_2O^{\ominus} + \ddot{C}X_2 \longrightarrow \overset{\ominus}{X:} + CH_3CH_2CD_2\ddot{O}CX \longrightarrow CH_3CH_2\overset{\oplus}{CD_2} + CO + \overset{\ominus}{X:}$$

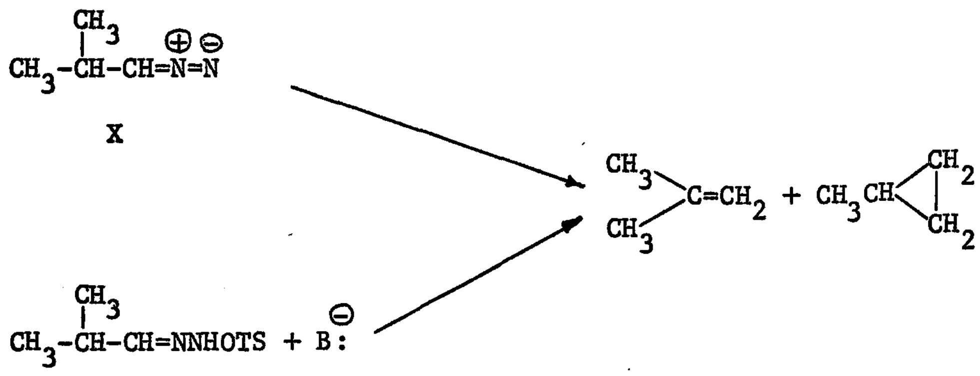
(55)



The authors suggested that the monodeuterated material was formed in a rearrangement reaction of the carbonium ion and that little or no cyclopropane had formed in a carbene insertion reaction.

Although cyclopropanes were obtained from n-propyl, n-butyl, i-butyl and 2-methylbutyl alcohols, the major elimination products from the deoxidation of these alcohols were olefins which were formed in a β-elimination reaction (122,125). The elimination product from the deoxidation of cyclopropylcarbinyl alcohol on the other hand, was mainly bicyclo[1,1,0]butane, which was formed in a γ-elimination process (123).

One of the products from the base-induced decomposition of tosylhydrazones (Bamford-Stevens reaction) is a cyclopropane derivative which can form in an E1 γ-elimination reaction. Friedman and Shechter (130) concluded that diazo compounds were intermediates in this reaction because they could detect small amounts of diazo compound when tosylhydrazones were decomposed in aprotic solvents and because they obtained a product of similar composition from the thermal decomposition of 1-diazo-2-methylpropane, X, and the base-induced decomposition of the tosylhydrazone of 2-methylpropanal, XI, equation 56.



X

XI

(56)

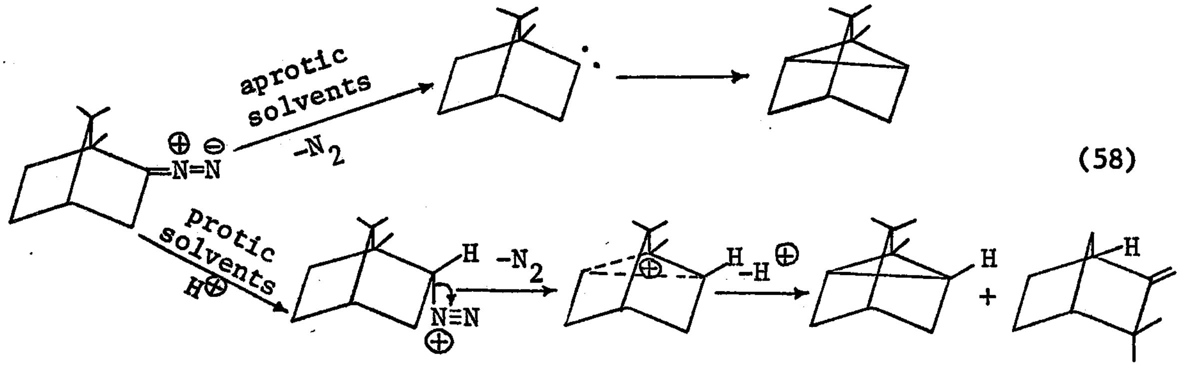
X	67%	33%
XI	62%	38%

Powell and Whiting (131) concluded that the rate-determining step in the Bamford-Stevens reaction is the conversion of the conjugate base of the tosylhydrazone to diazo compound since the rates of reaction of two entirely different compounds, camphor and cyclohexyl tosylhydrazones, are identical, equation 57.

$$R_2C{=}NNHOTs + \overset{\ominus}{B}: \rightleftarrows R_2C{=}N\overset{\ominus}{N}OTs + BH \xrightarrow{\text{slow}} R\ C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + \overset{\ominus}{O}Ts$$

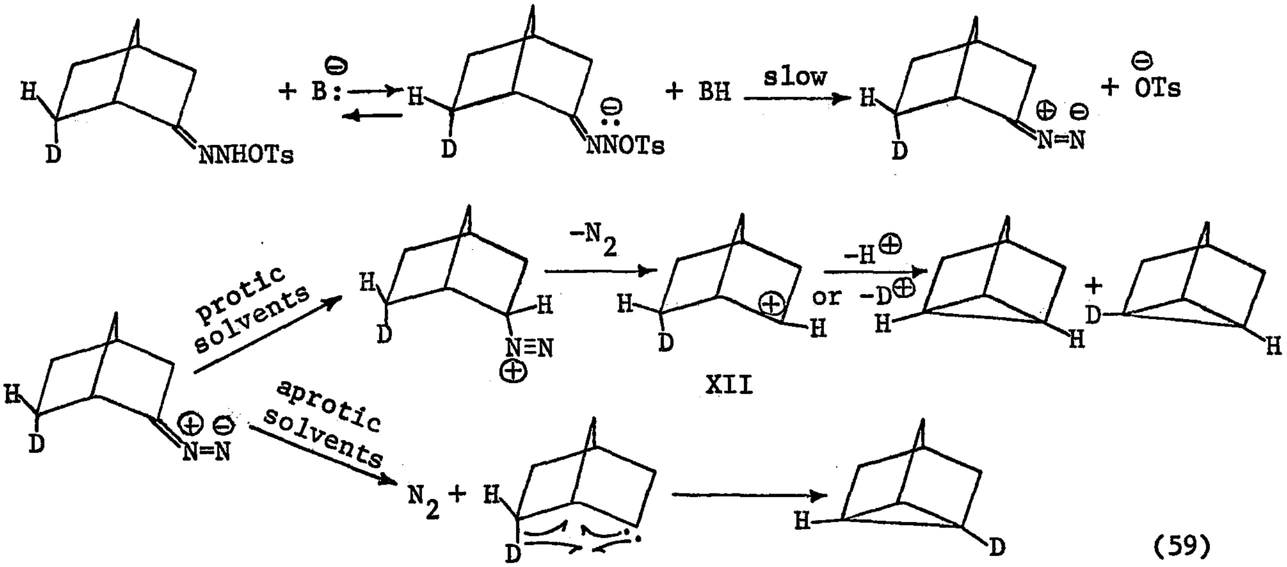
$$RCH{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \xrightarrow{\text{fast}} \text{Products} \qquad (57)$$

Powell and Whiting (131) found that the products from the decomposition of camphor tosylhydrazone are different in protic and aprotic solvents and proposed that the diazo intermediate decomposed by two mechanisms: homolytic decomposition to a carbene which inserts into the γ-C-H bond in aprotic solvents, or protonation to a diazonium ion which can undergo either a β- or γ-E1 elimination reaction in protic solvents, equation 58.



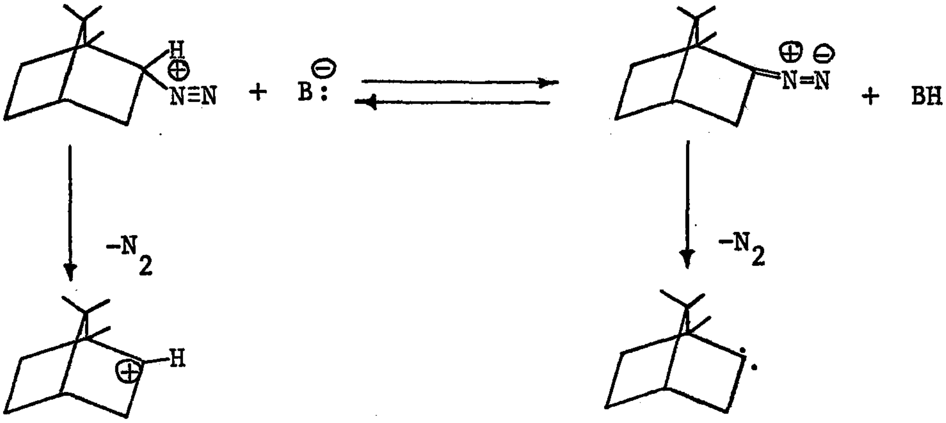
(58)

Nickon and Werstiuk (120) used tracer techniques to demonstrate that the diazo intermediate decomposes by both a carbonium ion and a carbene pathway. More than fifty per cent of the nortricyclene produced from <u>endo</u>-6-deuterionorbornan-2-one tosylhydrazone contained no deuterium when the reaction was carried out in protic solvents. All the tricyclene from this reaction had one deuterium per molecule when the reaction was carried out in aprotic solvents. This is consistent with a carbonium ion intermediate, XII, in protic solvents and a carbene intermediate in aprotic solvents, equation 59.



(59)

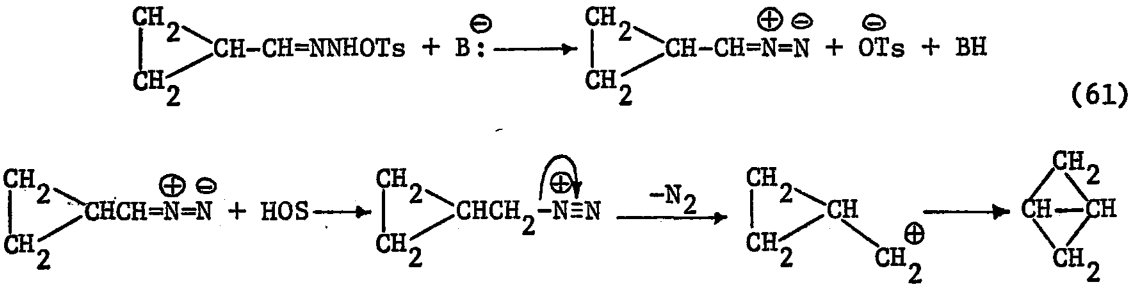
Shapiro et al. (132) have recently proposed that the relative contribution of the carbonium ion and carbene pathways in the Bamford-Stevens reaction is determined by the position of the equilibrium between the diazo and the diazonium ion intermediates, equation 60.



(60)

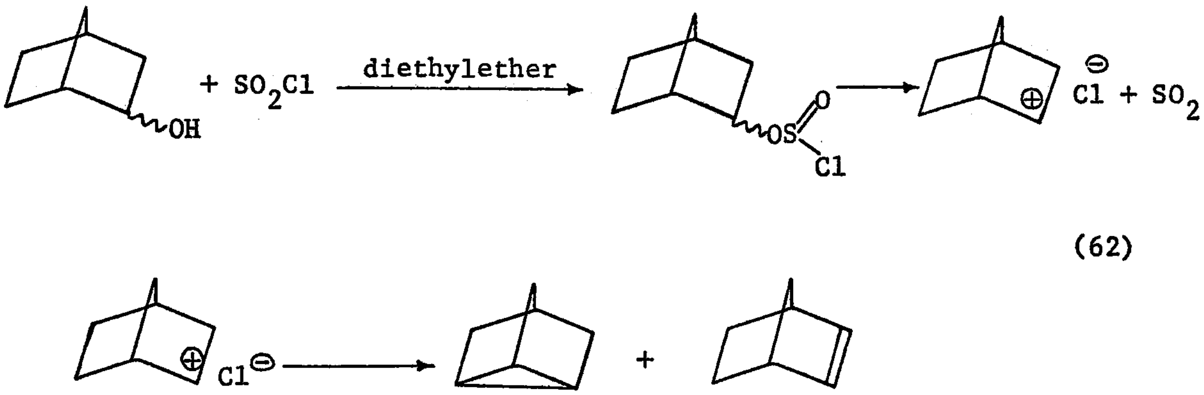
When a protic solvent is used the equilibrium is displaced towards the diazonium ion and the carbonium ion pathway is followed. When the solvent is aprotic, or when a large excess of base is used, the equilibrium is towards the diazo intermediate and the carbene pathway is followed. When less than one equivalent of base is used in the reaction, the diazo compound acts as a base, abstracts the proton from the tosylhydrazone and is converted into the diazonium ion which decomposes by the carbonium ion pathway.

Bicyclo[1,1,0]butane is formed in 70-80 per cent yields in an El γ-elimination reaction of the diazonium salt produced when cyclopropylcarboxaldehyde tosylhydrazone is treated with base in protic solvents (133), equation 61.



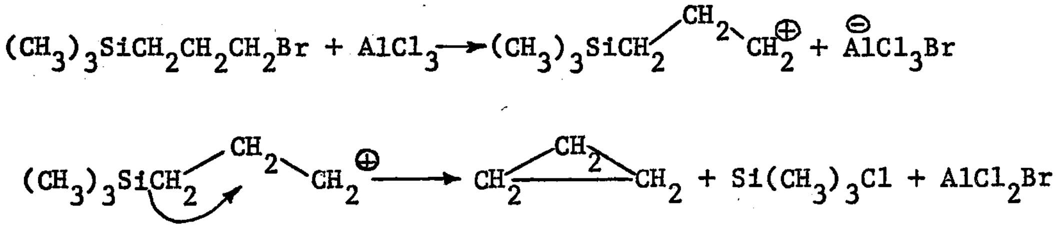
(61)

Sonnenberg and Stille (134), during studies on the SNi chlorination reactions which are known to involve carbonium ion intermediates, found that 85-100 per cent of the elimination product from the reaction of either exo- or endo-2-norborneol with thionyl chloride in aprotic solvents, was formed in a γ-elimination reaction, equation 62.



(62)

Whitmore _et_ _al_. (135) reported that γ-bromopropyltrimethylsilane gives a high yield of cyclopropane when treated with aluminum chloride under Friedel-Crafts conditions. The authors suggested that the reaction was an E1 γ-elimination reaction, equation 63.

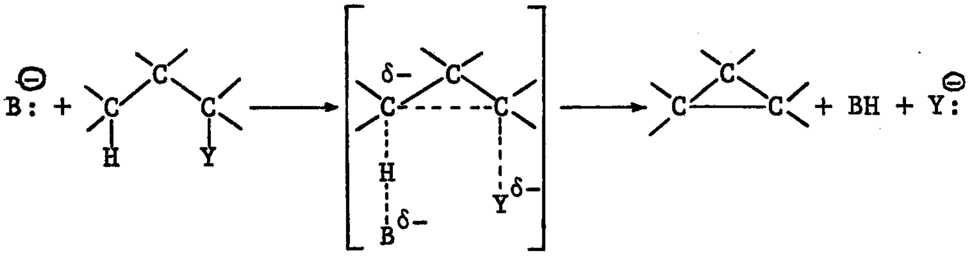


$$(CH_3)_3SiCH_2CH_2CH_2Br + AlCl_3 \longrightarrow (CH_3)_3SiCH_2\overset{CH_2}{\wedge}\overset{\oplus}{CH_2} + \overset{\ominus}{AlCl_3Br}$$

$$(CH_3)_3SiCH_2\overset{CH_2}{\wedge}\overset{\oplus}{CH_2} \longrightarrow CH_2\overset{CH_2}{\triangle}CH_2 + Si(CH_3)_3Cl + AlCl_2Br \qquad (63)$$

E2 Mechanism

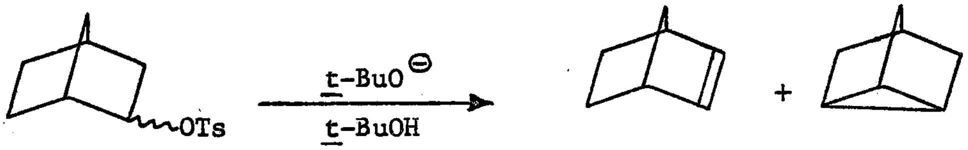
The E2 mechanism of γ-elimination is a one-step bimolecular process in which the C_γ-H and C_α-Y bonds break simultaneously, equation 64.



(64)

The E2 mechanism, which is the normal pathway for β-elimination reactions, appears to be the least common pathway for γ-elimination reactions. Only a few E2 γ-elimination reactions have been observed and very little is known about the factors which influence the structure of the transition states of these reactions. The E2 mechanism has been found in rigid bicyclic systems where the reacting bonds are coplanar and it is probably the mechanism of the Neber rearrangement and other similar reactions.

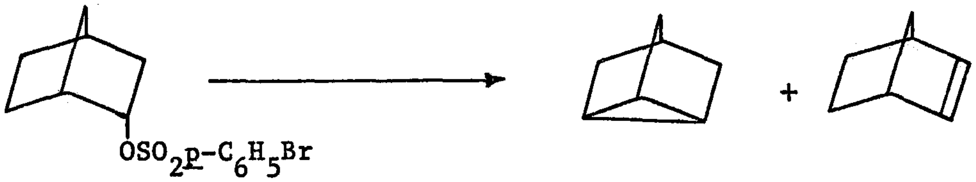
When both the β- and γ-elimination reactions in bicyclic systems are E2 processes, the product formed in the β-elimination reaction usually predominates. This is in contrast to E1 elimination reactions in such systems. Nickon and Werstiuk (5,6) found that both the exo- and endo-2-norbornyl tosylate, which react by way of an E1 mechanism when the base concentration is low, react by way of an E2 process at high base concentrations. Under "high base" conditions β-elimination is the major reaction of both isomers. The authors found (136) that the amount of product formed in the γ-elimination reaction decreased from 75 per cent to 37 per cent of the total elimination products from the exo-isomer and from 84 per cent to 27 per cent in the endo-isomer when the mechanism changed from E1 to E2, equation 65.



(65)

E1 mechanism	exo	25%	75%
	endo	16%	84%
E2 mechanism	exo	63%	37%
	endo	73%	27%

Stille and Sonnenberg (8) observed that when endo-2-norbornyl p-bromobenzenesulfonate is treated with strong bases the amount of β-elimination increases sharply from that obtained under solvolytic conditions, equation 66.

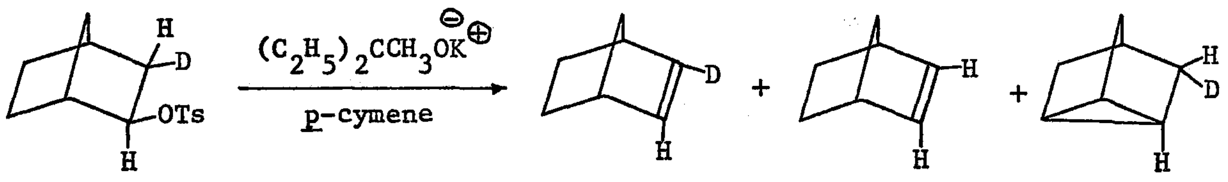


(66)

solvolytic conditions	76%	24%
$(C_2H_5)_2CCH_3\overset{\ominus}{O}K^{\oplus}$ in $(C_2H_5)_2CCH_3OH$	7%	93%

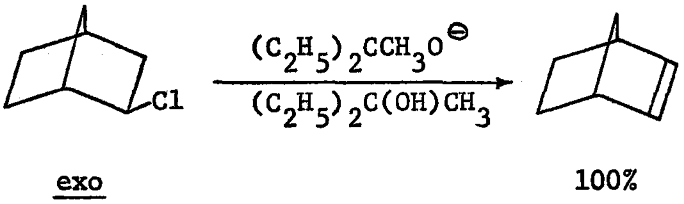
The increase in β-elimination is probably a result of a change in mechanism from E1 under solvolytic conditions to E2 when strong bases are present.

Kwart et al. (137) found that the reaction of exo-2-norbornyl tosylate with 3-methyl-3-pentoxide proceeds primarily by an E1 mechanism when the reaction is carried out in 3-methyl-3-pentanol, but becomes an E2 process in non-polar, aprotic solvents where the alkoxide is a stronger base and where ionization of the leaving group is more difficult. Ninety-five per cent of the elimination product formed in this reaction was formed in a β-elimination reaction, equation 67. Although no proof has been advanced, it is likely that the γ-elimination is also an E2 process.

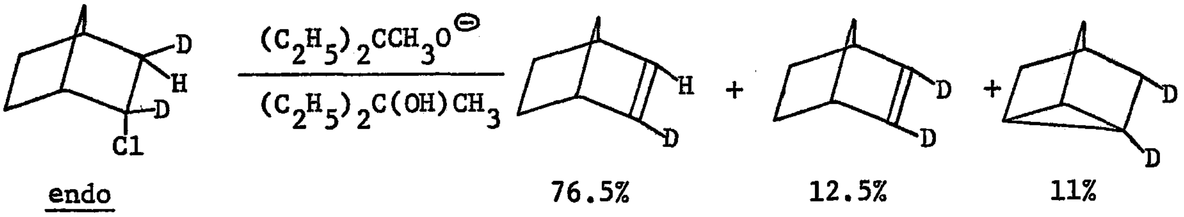


(67)

The predominance of β-elimination products in E2 processes was also noted by Sonnenberg and Stille (7) who found that 100 per cent and 89 per cent of the elimination product from the exo- and endo-2-norbornyl chlorides, respectively, is formed in a β-elimination reaction, equations 68 and 69.



(68)

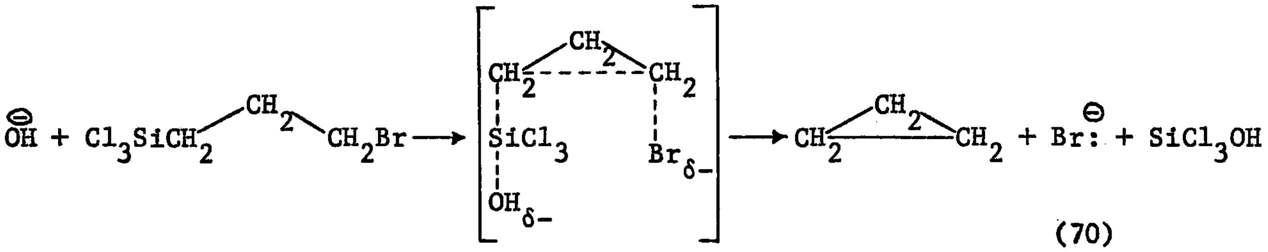


(69)

The authors suggest that the γ-elimination reaction competes more successfully with the β-elimination reaction in the endo-isomer than in the exo-isomer because the former can only react in slow trans- or endo-cis-β-elimination processes, while the latter reacts in a facile exo-cis-β-elimination reaction. Nickon and Werstiuk (136) on the other hand, found that γ-elimination competes more successfully with β-elimination in the E2 reaction of the exo-isomer of 2-norbornyl tosylate than in the E2 reaction of the endo-isomer, equation 65. Kwart (137) has suggested that β-elimination in the exo-isomer is slow because the exo-tosyl group sterically hinders the attack of the base. This steric hindrance enables the γ-elimination to compete more successfully with the β-elimination in the exo-isomer. The endo-isomer, which probably reacts in a trans-β-elimination reaction (see equation 69), would not be sterically hindered and would react at the normal rate. The slowing of the β-elimination reaction in the exo-isomer would account for the opposite effect observed by Nickon and Werstiuk.

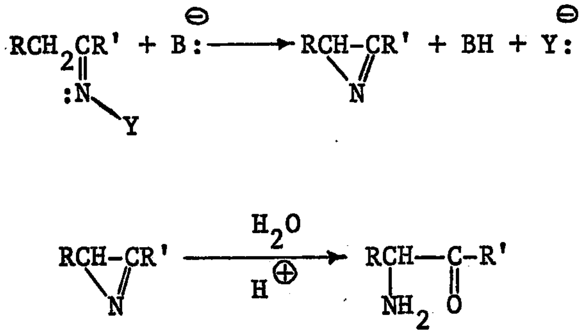
Sonnenberg and Stille (8) noted that the amount of β-elimination from endo-2-norbornyl p-bromobenzenesulfonate, equation 66, increases as the steric requirements of the base increase. The product produced in a β-elimination reaction increases from 62 per cent to 93 per cent of the elimination product when the base is changed from t-butoxide to 3-methyl-3-pentoxide. Nickon and Werstiuk (6) have found that the favoured stereochemistry in the E2 γ-elimination of endo-2-norbornyl tosylate is that in which the γ-hydrogen and the tosyl group are endo. This preference should also exist in the reaction of endo-2-norbornyl brosylate. As the size of the base increases, the favoured pathway of E2 γ-elimination becomes higher in energy while the β-elimination, which is probably almost completely a trans-elimination, should not be affected. The decrease in the rate of the γ-elimination reaction as the size of the base increases would lead to the observed increase in the amount of product formed in a β-elimination reaction.

Whitmore et al. (1935) have been the only workers to suggest that a γ-elimination could proceed by way of an E2 mechanism in an aliphatic system. They proposed that the γ-elimination reaction of γ-bromopropyltrichlorosilane, which gives cyclopropane as the only product, is an E2 process. The elimination was believed to have been initiated by attack of hydroxide on the electrophilic silicon atom, equation 70.



(70)

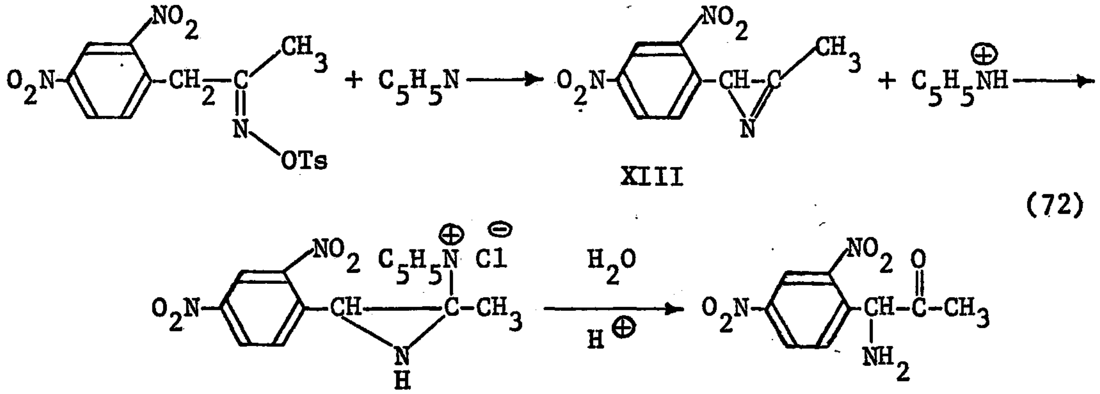
The first step in the Neber rearrangement and other similar reactions, equation 71, is a γ-elimination reaction which would seem to be an E2 process.



(71)

While the leaving group, Y, in the Neber rearrangement (138-142) is tosylate, the same reaction seems to occur when the leaving group is the nitrogen of an azide (143,144), trimethylammonium (145,146), chloride (147-150) and hydroxide (151).

The Neber rearrangement has been studied by several workers. Cram and Hatch (139,140) found that the Neber rearrangement occurs only when a methylene group is alpha to the carbon-nitrogen double bond and that the rearrangement is possible whether the tosyl group is <u>cis</u>- or <u>trans</u>- to the methylene group. They were also able to isolate two intermediates from the reaction of the oxime tosylate of 2,4-dinitrophenylacetone and pyridine, equation 72. These intermediates were identified as 2-(2,4-dinitrophenyl)-3-methyl azirine XIII and its addition product, the azirine-pyridine hydrochloride complex XIV.

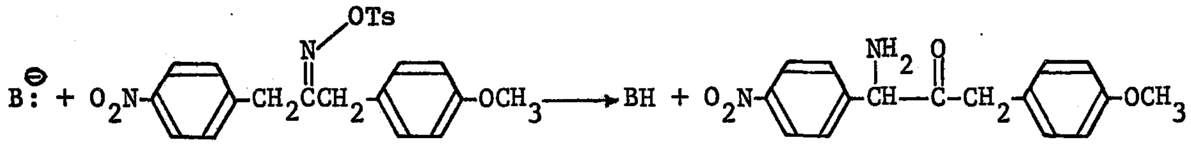


XIII

XIV

(72)

The isolation of these intermediates suggested that a γ-elimination reaction, which would lead to the azirine, was the first step in the rearrangement. Later, House and Berkowitz (141) demonstrated that if two methylene groups are alpha to the carbon-nitrogen double bond the rearrangement is to the more acidic methylene group, equation 73.

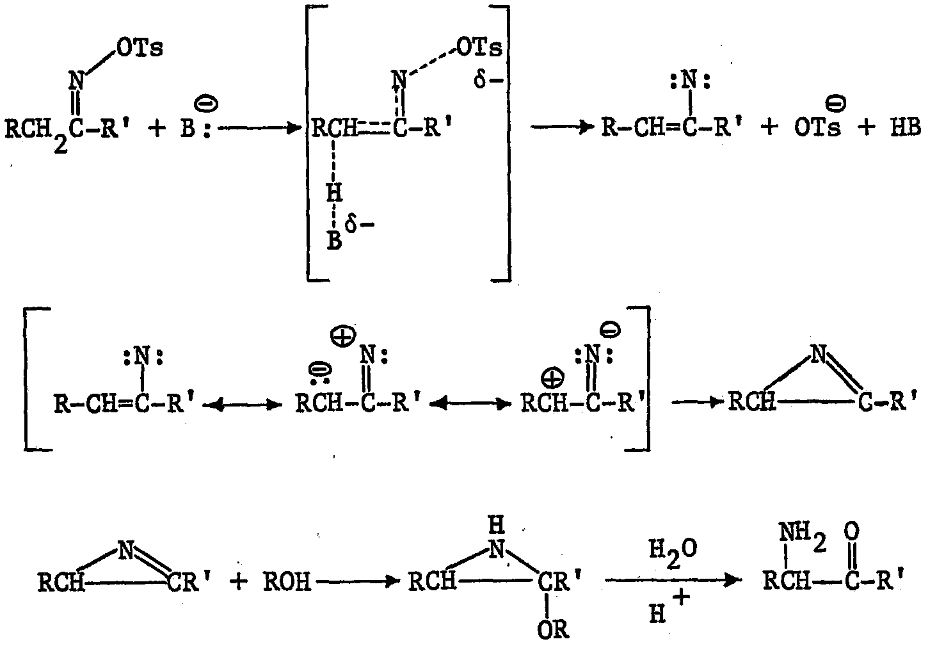


(73)

This preference for the more acidic methylene group suggests that the base is used to abstract a methylene proton.

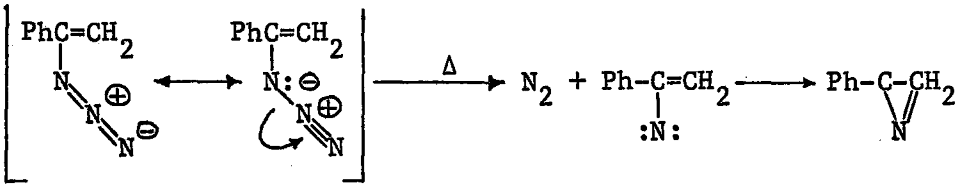
Since the stereochemical relationship between the tosyl and methylene groups is not important in the Neber rearrangement it seems probable that the tosyl group is lost in a step prior to, rather than during the formation of the azirine ring.

The experimental data do not distinguish between an E2 and an E1cb γ-elimination reaction. The concerted mechanism is favoured, however, because it seems more likely that the electrons of a carbanion generated on the α-carbon would delocalize into the carbon-nitrogen double bond and displace the tosyl group rather than remain solely on the α-carbon. The proposed mechanism of the Neber rearrangement is shown in equation 74.



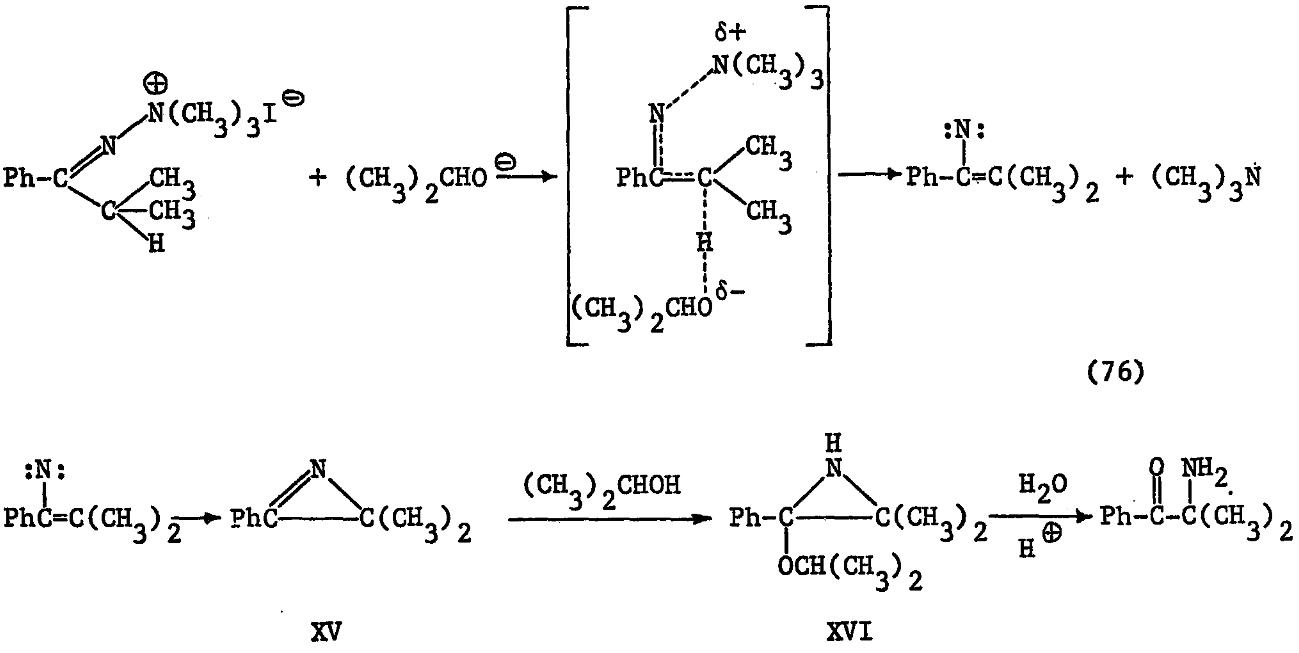
(74)

Neber type intermediates have been isolated from the reactions of compounds whose structure is similar to the oxime tosylates, equation 74. 2-Phenylazirine was isolated from the pyrolysis of α-azidostyrene (143,144), equation 75. The authors suggested that a vinyl nitrene is an intermediate in this reaction.



(75)

Both the azirine, XV, and the aziridine, XVI, intermediates have been isolated from the base-promoted decomposition of dimethylhydrazone methiodides (146). The mechanism of this reaction, equation 76, is thought to be identical to that of the Neber rearrangement.

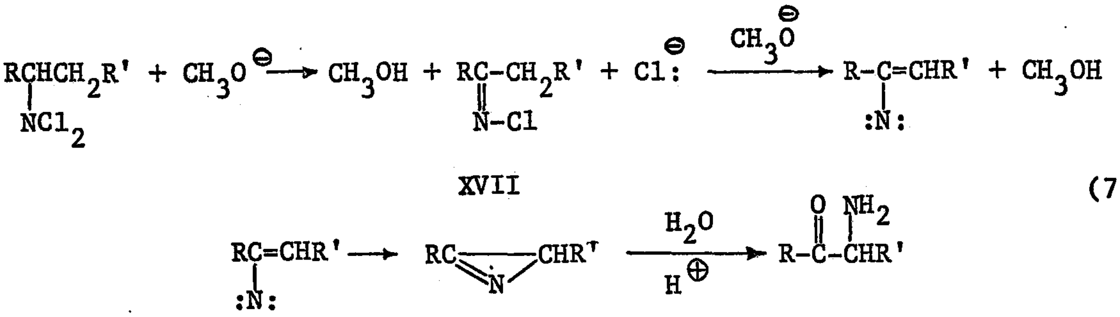


(76)

XV

XVI

N,N-Dichloro-sec-alkylamines are thought to react by the same mechanism, equation 77, even though none of the Neber intermediates have been isolated from these reactions.

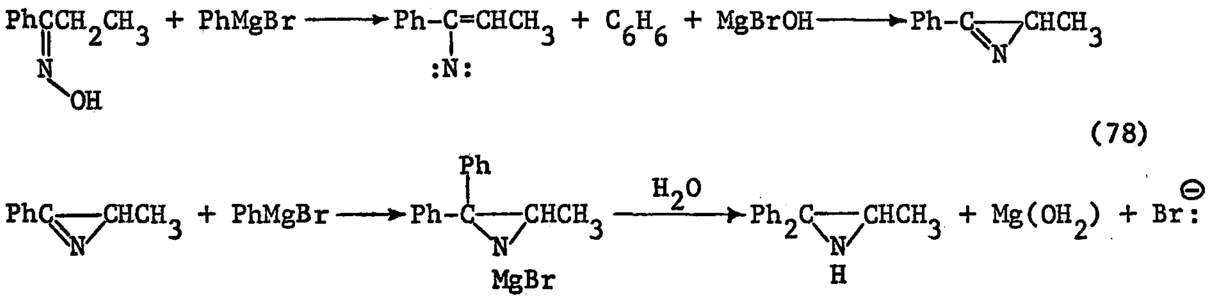


XVII

(77)

The intermediate XVII, which is similar in structure to compounds which react in a Neber rearrangement, has been isolated in several reactions involving N,N-dichloro-sec-alkylamines (148-150).

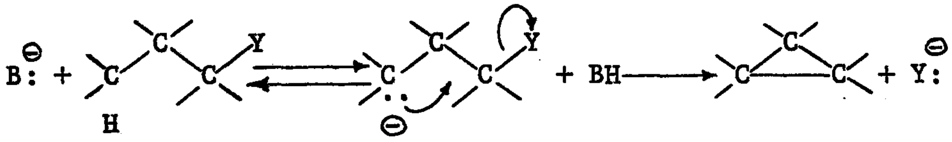
An aziridine is produced when the oxime of phenyl ethyl ketone is treated with a Grignard reagent (151). Cram (152) has suggested that this reaction proceeds by the same mechanism as that proposed for the Neber rearrangement, equation 78.



(78)

Elcb Mechanism

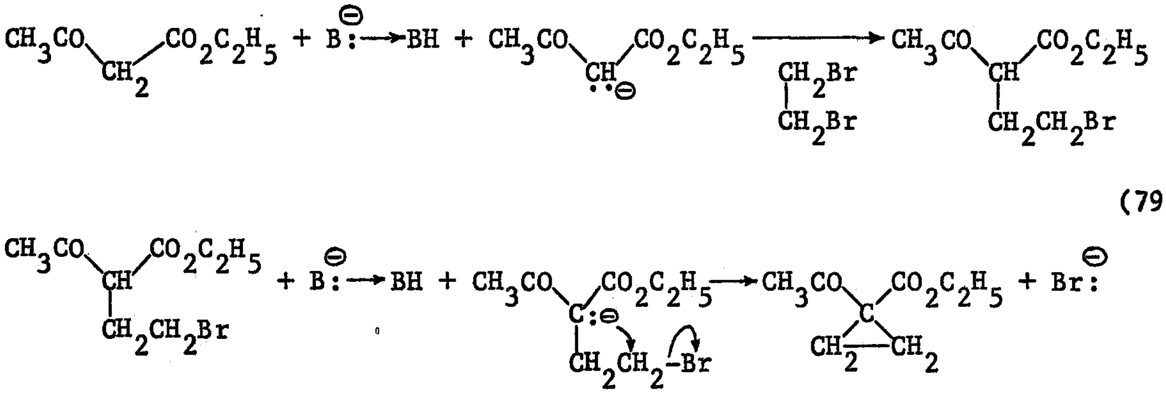
The first step in the Elcb γ-elimination reaction is the formation of a γ-carbanion. Attack of the γ-carbanionic centre at the α-carbon displaces the leaving group and forms the carbon-carbon bond of the cyclopropane ring in the second step, equation 2.



(2)

Either the first or the second step of this reaction can be rate determining.

The first Elcb γ-elimination reaction, which is shown in the second part of equation 79, was reported by Freer and Perkin in 1887 (153).



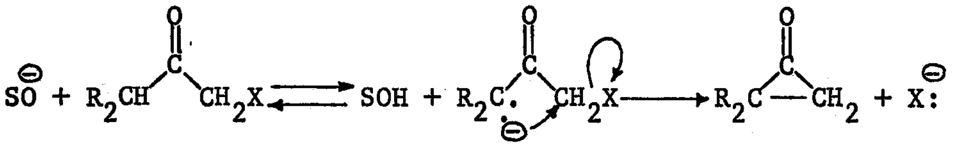
(79)

Subsequently, several other γ-elimination reactions involving active methylene compounds and 1,2-dihaloalkanes have been observed (154).

Almost all of the γ-elimination reactions in aliphatic systems and many of the γ-elimination reactions in cyclic systems have been shown to be Elcb processes, and as more and more results have been published it has become apparent that the Elcb mechanism is the normal pathway of γ-elimination reactions.

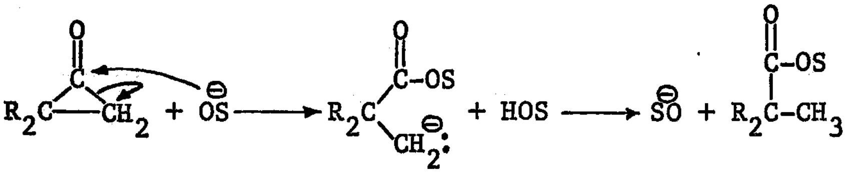
γ-Elimination is observed only when β-elimination is impossible, or when structural features in the molecule enhance the rate of the γ-elimination reaction. Groups which are capable of delocalizing the negative charge on the γ-carbanion facilitate the removal of the γ-hydrogen and increase the rate of γ-elimination. Carbonyl (154), sulphonyl (4,155,156), nitro (111), cyano (157) and aryl (110,113,117) groups give sufficient stabilization to the γ-carbanion to make the Elcb mechanism the favoured pathway.

The γ-carbanion is stabilized by a carbonyl containing group in many γ-elimination reactions. The Favorskii rearrangement (152, 158), the first step of which is considered to be an Elcb γ-elimination reaction, equation 80, is the most studied of these reactions.



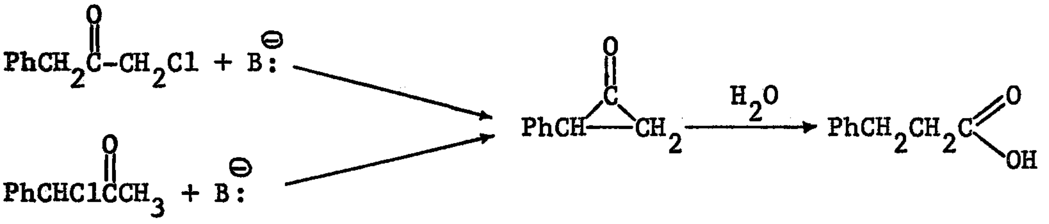
(80)

In the second step the unstable cyclopropanone ring is opened by nucleophilic attack at the carbonyl carbon, equation 81.



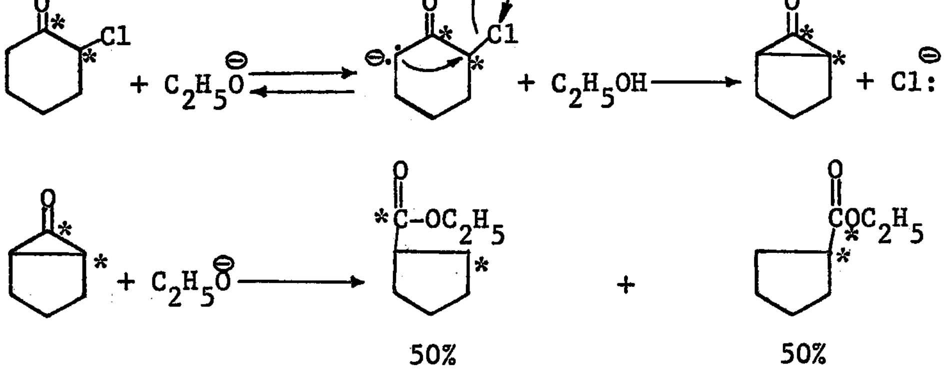
(81)

The intermediacy of the cyclopropanone has been indicated by the observation that the same product is obtained whether the halogen is removed from the α- or the α'-carbon of the haloketone (159-161), equation 82.



(82)

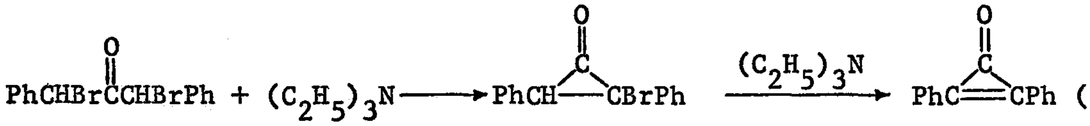
The equivalence of the α- and α'-carbons has been elegantly demonstrated by Loftfield (162,163) in an experiment using carbon-14 labeled 2-chlorocyclohexanone, equation 83.



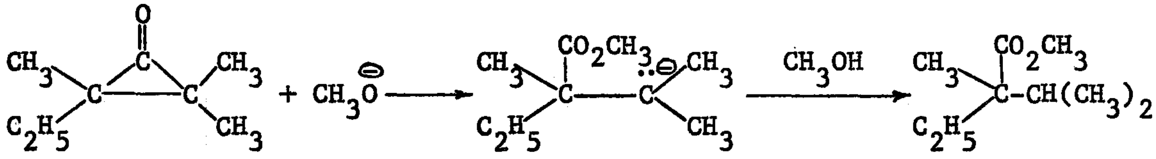
(83)

These products are consistent only with a process where the α- and α'-carbons have become equivalent and the results, therefore, strongly support the intermediacy of the cyclopropanone.

Breslow _et al_. (164) have obtained cyclopropenones from the reaction of α,α'-dihaloketones and triethylamine. They suggested that these products are produced when the cyclopropanone undergoes a β-elimination reaction rather than the usual ring opening, equation 84.

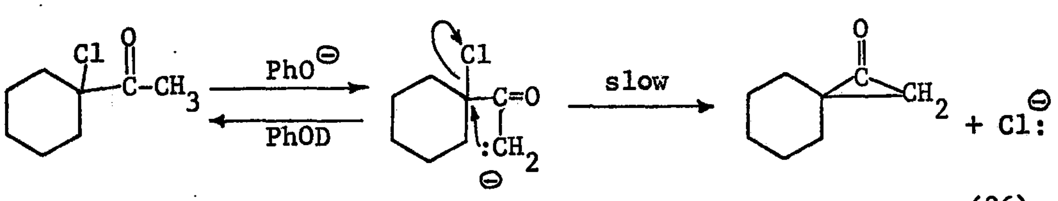

(84)

Strong evidence for the cyclopropanone intermediate was provided by Turro and Hammond (165), who showed that a quantitative yield of Favorskii products are obtained when a cyclopropanone is treated with base, equation 85.


(85)

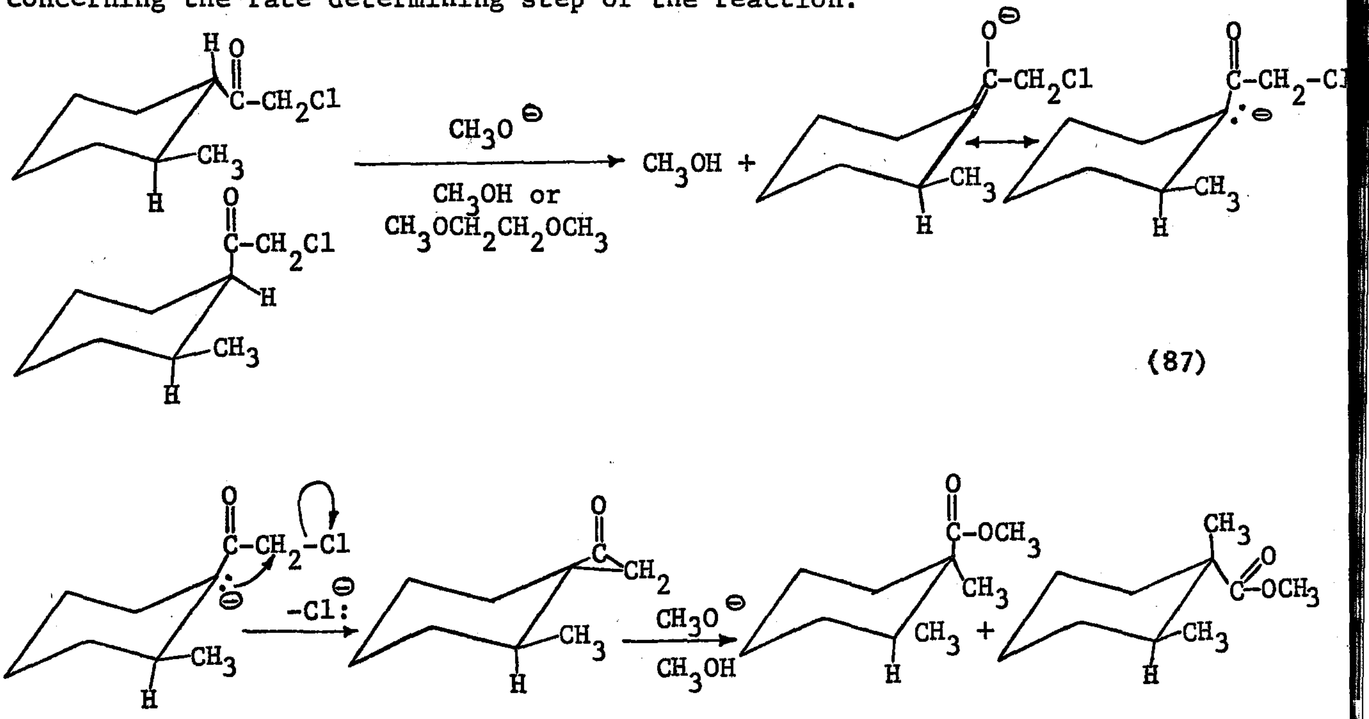
Rappe and co-workers (166,167) have proposed that the most stable carbanion is formed when the cyclopropanone ring is opened by attack of a nucleophile, equations 81, 82 and 85.

The γ-elimination reaction in the Favorskii rearrangement has been studied in considerable detail. Several workers (3,168-170) have found deuterium exchange at the carbon from which the hydrogen has been removed, and they have concluded that the ring closure is the slow step of the γ-elimination reaction, equation 86.



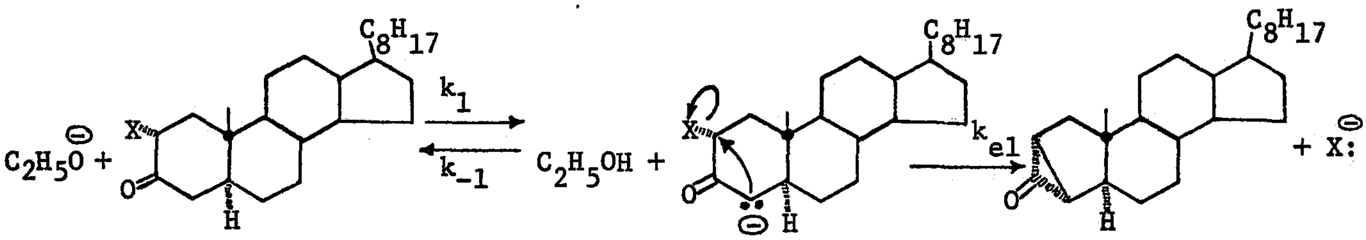
(86)

House and Richey (171) obtained products of identical composition from the reaction of cis- and trans-2-methylcyclohexyl chloromethyl ketone with methoxide ion in both protic and aprotic solvents, and they concluded that these reactions involve a common intermediate. They suggested that this intermediate is the planar enolate anion shown in equation 87 but they drew no conclusion concerning the rate determining step of the reaction.

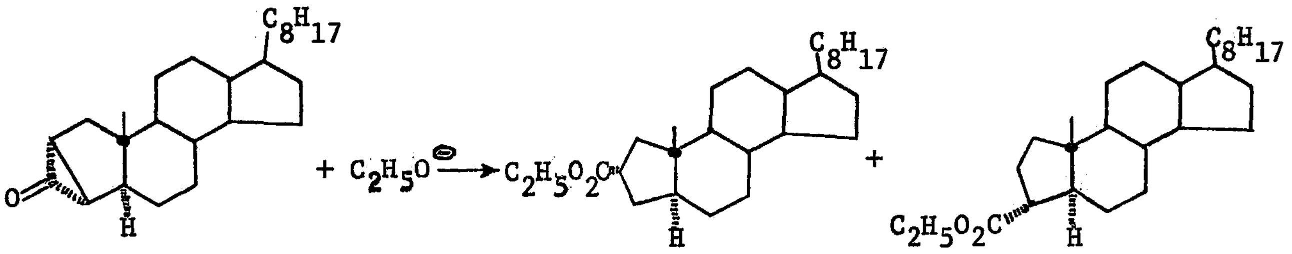


(87)

Nace and Olsen (3) examined the Favorskii rearrangement of 2α-chloro-, bromo- and iodocholestan-3-ones, equation 88, and their 2,4,4-trideuterated analogues.

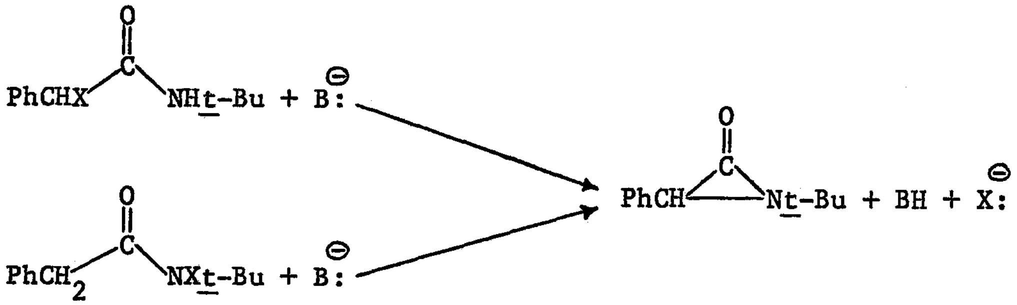


(88)



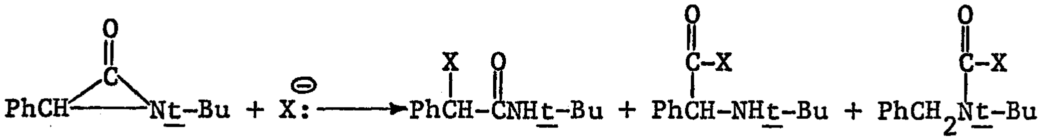
They found that the reactions of all three halides show a hydrogen isotope effect of at least four or five, indicating that the proton is removed in a slow step. While the deuterium at the two position exchanges rapidly with the solvent in all three compounds, the deuterium at the four position exchanges much more slowly. Only twenty per cent of the deuterium was lost from this position when the chloride was reacted to one half life, while little or no exchange was observed with the bromide or iodide. The authors concluded that the γ-elimination reaction is an Elcb process with $k_{-1} \approx k_{el}$ for the chloride and $k_{el} > k_{-1}$ for the bromide and iodide, equation 88.

α-Lactams can be produced from either α-haloamides or N-haloamides in a base-induced γ-elimination reaction (172-174), equation 89.



(89)

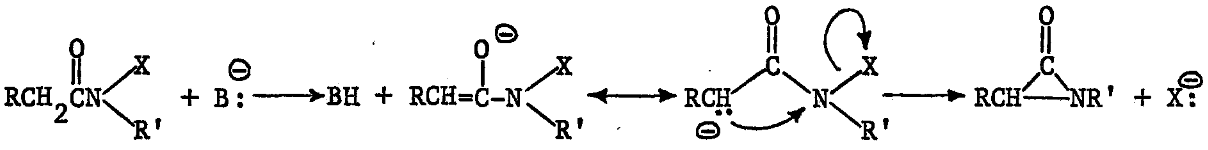
The relatively unstable α-lactam reacts with nucleophiles at either the α-carbon (172,173) or the carbonyl (175,176), equation 90.



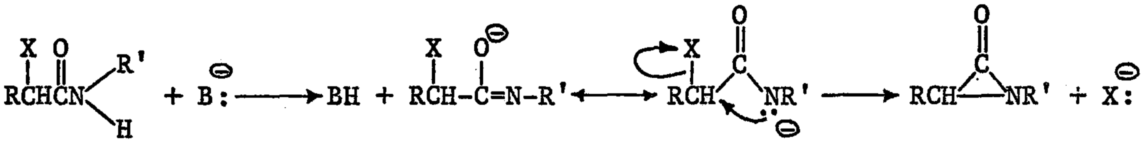
(90)

α-Lactams have been isolated or identified in several reactions of N-haloamides and α-haloamides (172,173,176,177).

Although no attempt has been made to determine the mechanism of these γ-elimination processes, it seems likely that the carbonyl of the amide group would stabilize the anions and make the E1cb mechanism the favoured route of reaction (176), equations 91 and 92.

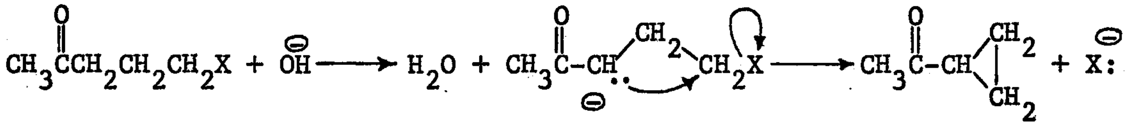


(91)



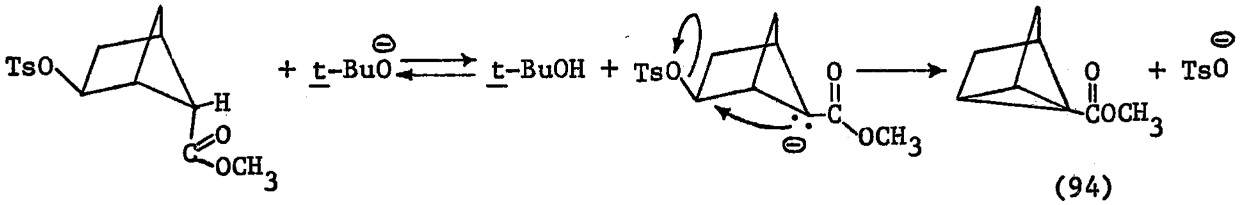
(92)

Certain other γ-elimination reactions, where a carbonyl group stabilizes the carbanion, give products that are stable under the reaction conditions. The reaction of 1-halopentan-4-one with hydroxide ion (178), equation 93, is an example of this type of reaction.

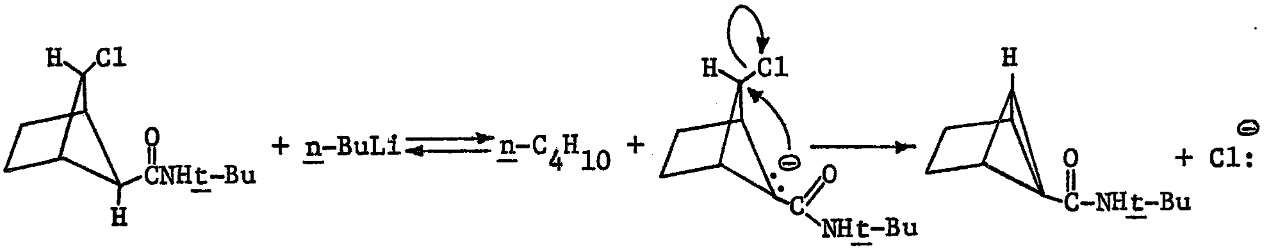


(93)

γ-Elimination reactions where the carbanion is stabilized by the carbonyl of an ester (179), equation 94, or an amide group (180), equation 95, have been found in bicyclo[2.1.1]hexane systems.



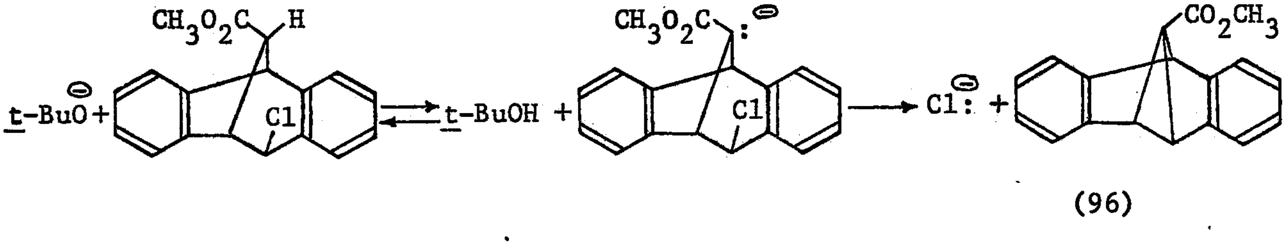
(94)



(95)

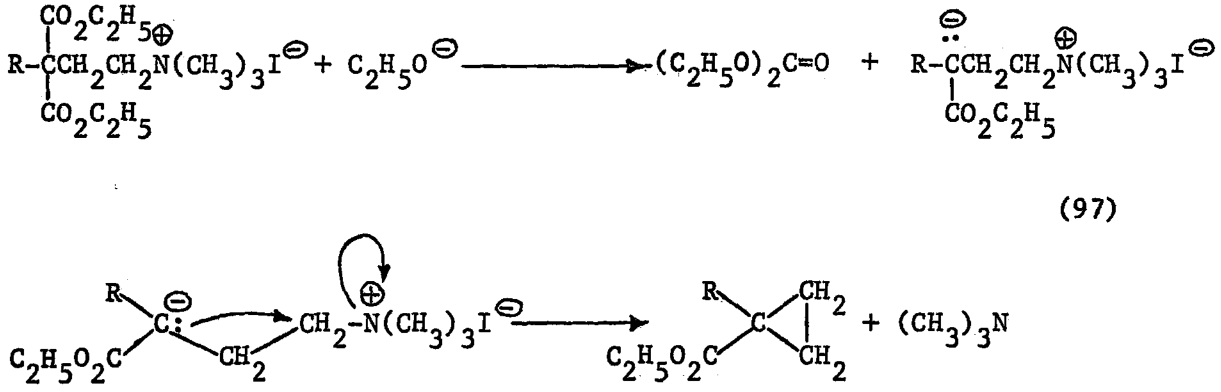
Although no proof has been advanced, it seems probable that both these reactions are E1cb processes.

Cristol and Jarvis (181) found that exo-4-chloro-anti-8-carbmethoxydibenzobicyclo[3.2.1]octadiene reacted with t-butoxide in dimethyl sulfoxide to give a tricyclic compound in what is probably an E1cb γ-elimination reaction, equation 96.



(96)

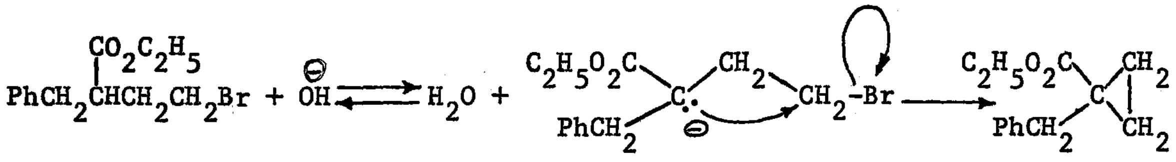
Weinstock (112) demonstrated that cyclopropanes, not olefins (182,183), are obtained from the reaction of γ,γ-dicarbethoxy quaternary ammonium salts with ethoxide ion. The quaternary ammonium salt decarboxylates to give a γ-carbanion which is stabilized by the remaining ester group. The electrons of this carbanion displace the leaving group and form the cyclopropane ring in a subsequent step, equation 97.



(97)

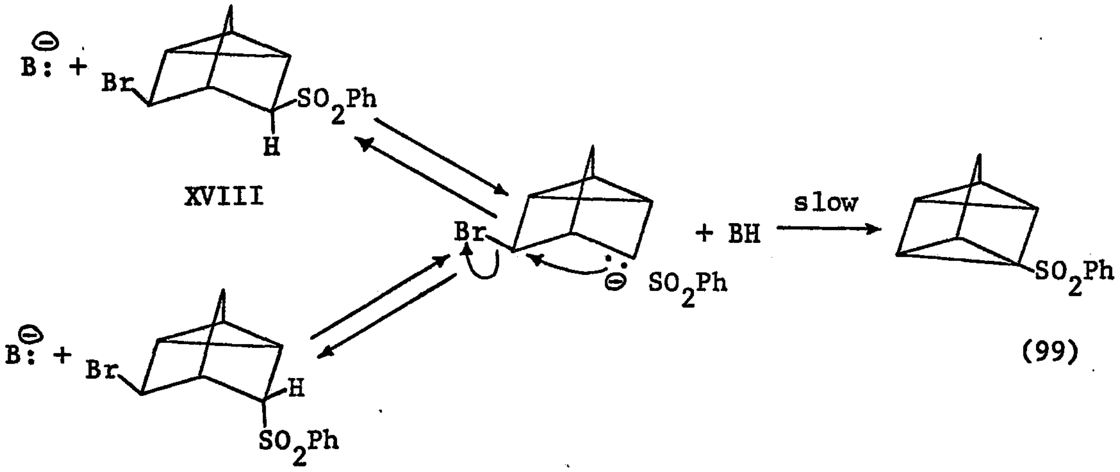
This reaction has been observed when R is benzyl or acetamido.

Weinstock (112) has suggested that a similar reaction, which Ingold and Rogers had interpreted as a β-elimination reaction (184), was in reality a γ-elimination reaction, equation 98.



(98)

E1cb γ-elimination reactions have been found in systems where the γ-carbon is bonded to a sulfonyl group. Cristol and co-workers have demonstrated that the γ-elimination reaction of γ-halosulfones is an Elcb process and they have attempted to determine the stereochemistry of the ring closure. They found that exo-5-bromo-exo-3-nortricyclyl phenyl sulfone, XVIII, is converted into 2-quadricycloheptyl phenyl sulfone when treated with base (109). Since exo-5-bromo-exo-3-nortricyclyl phenyl sulfone, XVIII, was found to be in rapid equilibrium with exo-5-bromo-endo-3-nortricyclyl phenyl sulfone, XIX, the authors concluded that a γ-carbanion was formed and that this carbanionic centre displaced the bromide in the rate-determining step, equation 99.



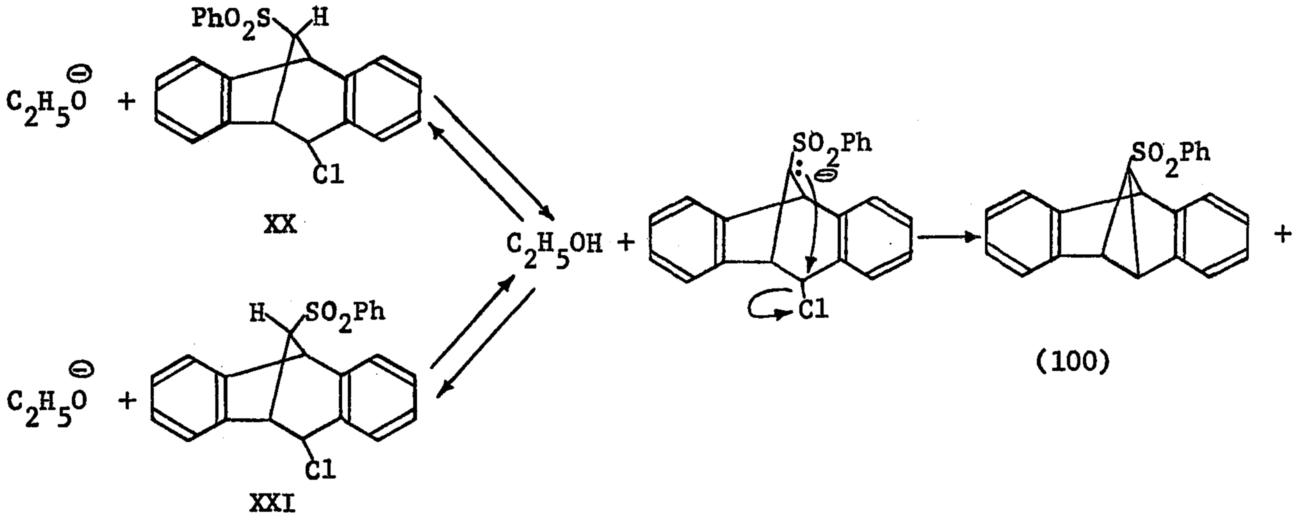
XVIII

XIX

(99)

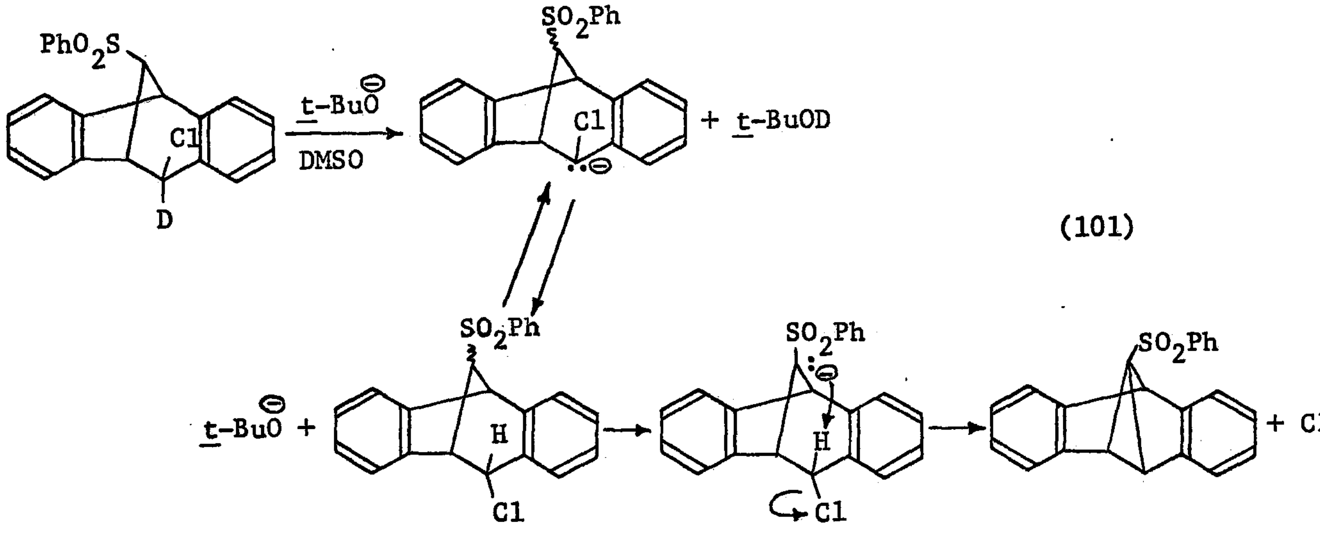
The endo-5-bromo-exo-3-nortricyclyl phenyl sulfone does not undergo a γ-elimination reaction even though a deuterium exchange test showed that a γ-carbanion is formed. The Elcb γ-elimination reaction apparently proceeds only when inversion of configuration can occur at the α-carbon.

Cristol and Jarvis (156,181) studied the γ-elimination reaction of endo-4-chloro-anti-8-phenylsulfonyldibenzobicyclo-[3.2.1]octadiene, XX, with ethoxide ion, equation 100. They established the presence of a preequilibrium between the phenyl sulfone and its conjugate base and found that only the *endo*-chlorides, XX and XXI, form a cyclopropane derivative in a γ-elimination reaction. The ring closure therefore, occurs with inversion of configuration at the α-carbon.



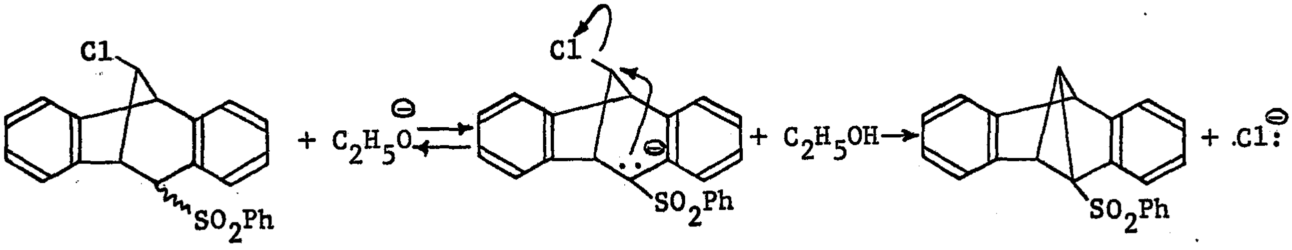
(100)

The *exo*-4-chloro isomers, which do not undergo a γ-elimination reaction with ethoxide, do react to form cyclopropane derivatives when stronger bases are used. The authors suggested that the *exo*-chloride is converted to the *endo*-chloride which undergoes the γ-elimination reaction. This suggestion is supported by the observation that the cyclopropane obtained from the reaction of *exo*-4-chloro-4-deutero-*anti*-8-phenylsulfonyldibenzobicyclo[3.2.1]octadiene and *t*-butoxide does not contain any deuterium, equation 101.



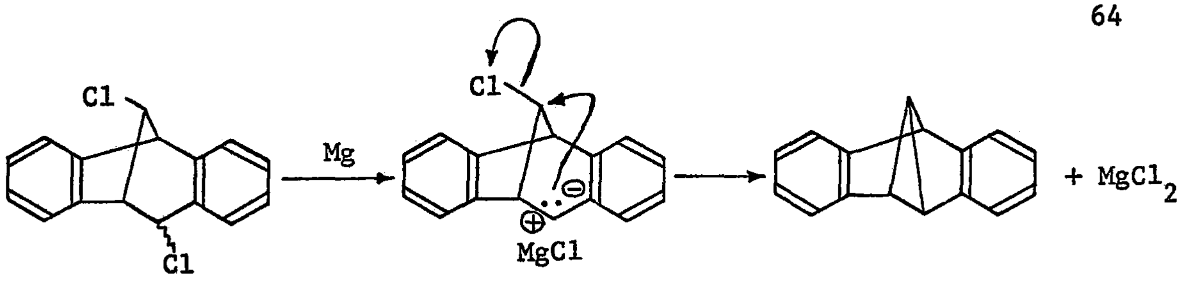
(101)

Inversion of configuration at the α-carbon has been found in several other systems which react by way of an Elcb mechanism (156). While both anti-8-chloro-exo-4-phenylsulfonyl- and anti-8-chloro-endo-4-phenylsulfonyldibenzobicyclo[3.2.1]octadiene undergo a γ-elimination reaction with ethoxide ion, equation 102, the syn-8-chloro-isomers do not give any cyclopropanes.



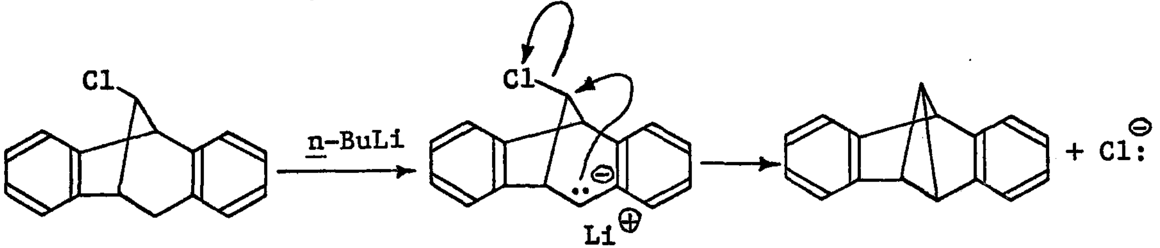
(102)

The same results were obtained with the 4,8-dichloro-isomers of the same compound. Both exo- and endo-4-chloro-anti-8-chlorodibenzobicyclo[3.2.1]octadiene react with magnesium to form the tricyclic product, equation 103, while the syn-8-chloro-isomers fail to undergo a γ-elimination reaction even though the γ-carbanion does form (156).



(103)

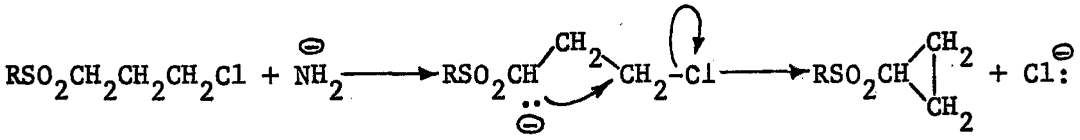
The preference for inversion of configuration at the α-carbon in an Elcb γ-elimination reaction is also found in the reaction of anti-8-chlorodibenzobicyclo[3.2.1]octadienes with n-butyllithium in tetrahydrofuran, equation 104.



(104)

The syn-8-chloride does not react in a γ-elimination reaction.

Truce and Lindy (185) found that aliphatic γ-chlorosulfones reacted with strong bases in either protic or aprotic solvents to form cyclopropylsulfones, equation 105.

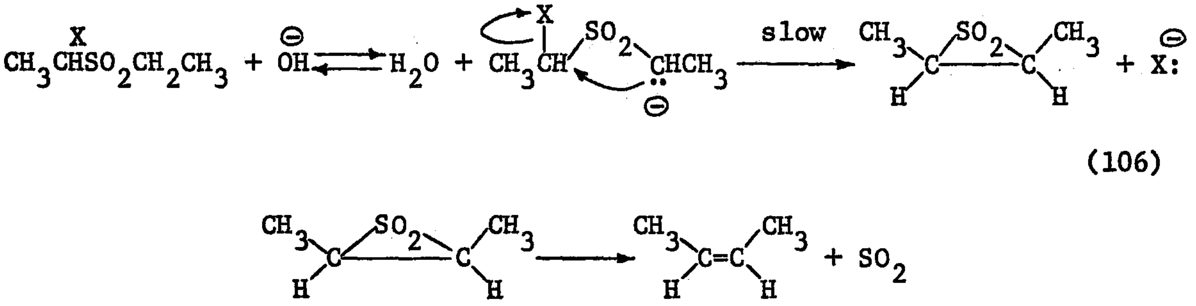


$$RSO_2CH_2CH_2CH_2Cl + \overset{\ominus}{NH_2} \longrightarrow RSO_2\underset{\ominus}{\ddot{C}H}\diagup^{CH_2}\diagdown CH_2\text{-}Cl \longrightarrow RSO_2CH\left<\begin{array}{l} CH_2 \\ \mid \\ CH_2 \end{array}\right. + Cl\overset{\ominus}{:}$$

(105)

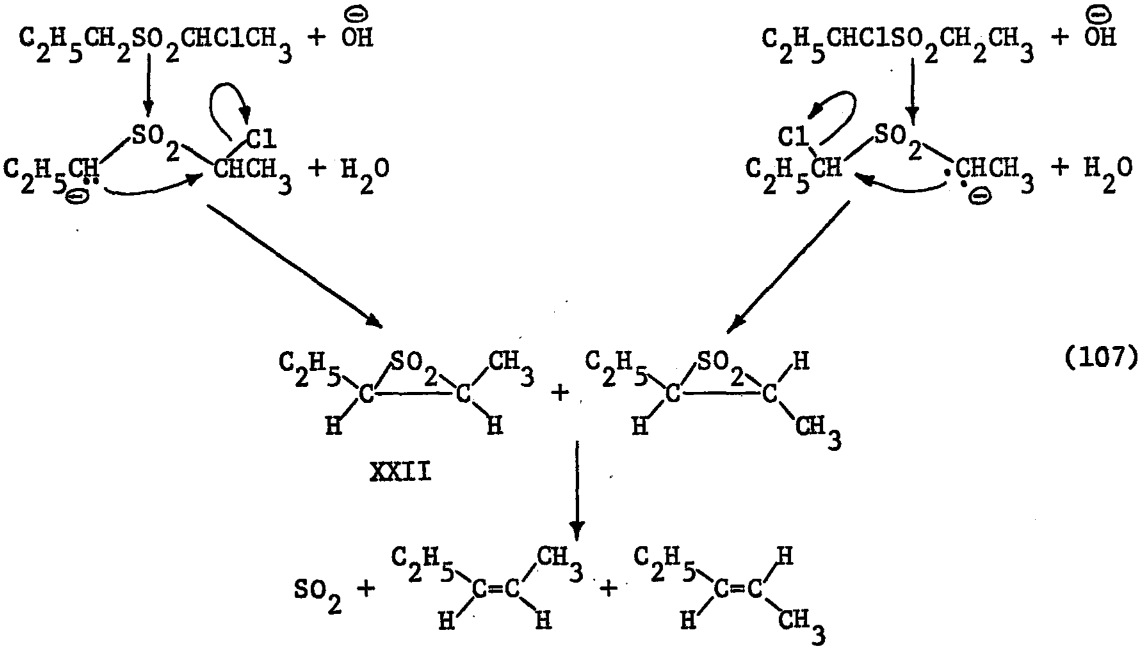
This ring closure has been found when R is methyl, t-butyl, benzyl, phenyl and p-tolyl. Zimmerman and Thyagarajan (186) prepared phenyl cyclopropyl sulfone from phenyl γ-chloropropyl sulfone and t-butoxide in t-butyl alcohol.

An E1cb γ-elimination reaction is the first step in the Ramberg-Backländ rearrangement, equation 106.



(106)

The intermediacy of the episulfone in the reaction is indicated by the observation of Neureiter and Bordwell (4) that a product of the same composition is obtained whether the halogen is displaced from the α- or α'-carbon of the sulfone, equation 107.



XXII

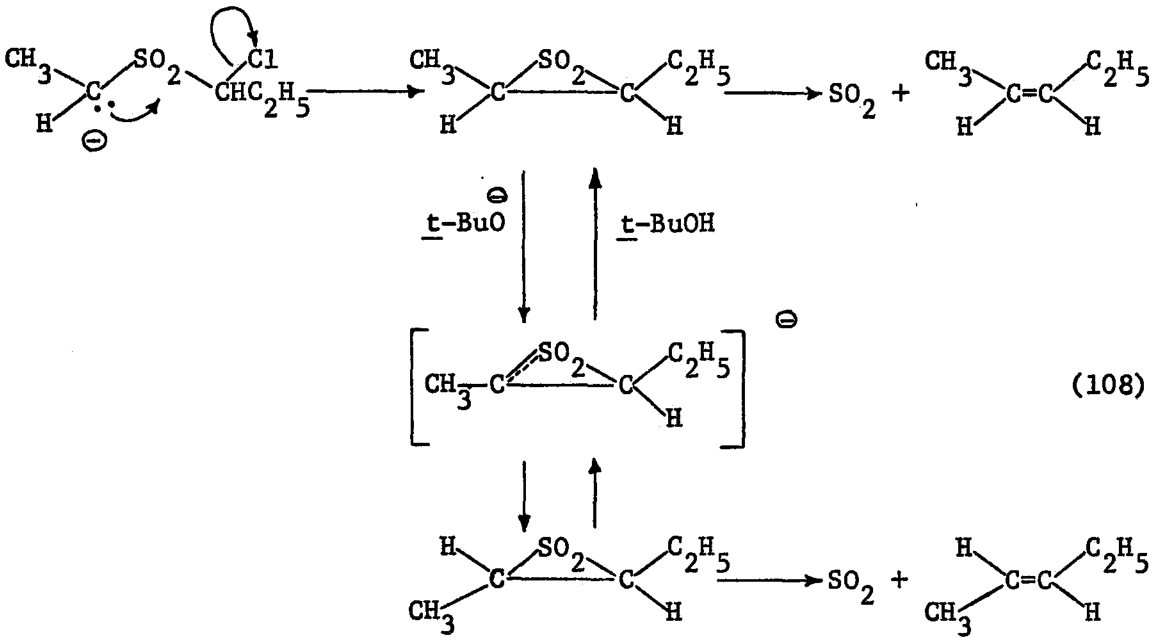
(107)

Additional support for the episulfone intermediate was provided by these same workers who prepared the cis-episulfone, XXII, equation 107, and showed that it decomposed stereospecifically to cis-2-pentene under the conditions of the Ramberg-Backländ rearrangement.

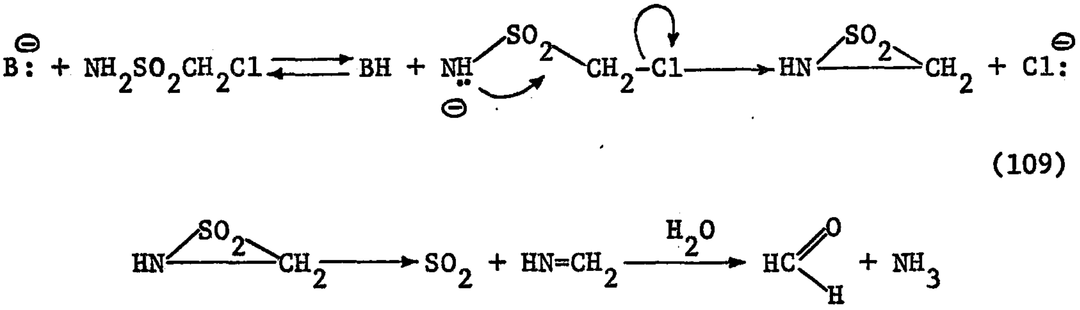
Bordwell and Cooper (187) found that the production of halide ion, which is first order in sulfone and in base, is slower from chloromethyl methyl sulfone than the rate of hydrogen exchange from dimethyl sulfone, and they concluded that the formation of the episulfone is the rate-determining step in the E1cb γ-elimination reaction, equation 106. This was confirmed by Neureiter and Bordwell (4,155), who showed that the α- and α'-hydrogens are completely exchanged when the reaction is carried out in deuterated solvents. Neureiter (155) observed that the rate of γ-elimination is dependent on the halogen while the composition of the product is not. This is consistent with the proposed mechanism since the product composition depends on the relative amounts of _cis_- and _trans_-episulfones and not on the rate of formation of these episulfones.

Neureiter (155) also noted that less of the _cis_-olefin, and therefore less of the _cis_-episulfone, is produced as the size of the groups on the α- and α'-carbons of the sulfone increase and he suggested that steric hindrance in the _cis_-episulfone makes its formation a high energy process.

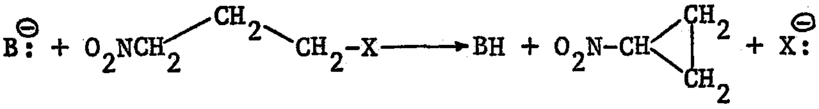
The amount of _trans_-olefin is also increased when the reaction is carried out with stronger bases such as _t_-butoxide, because the kinetically-controlled _cis_-episulfone equilibrates to the more stable _trans_-episulfone (4,155), equation 108.


(108)

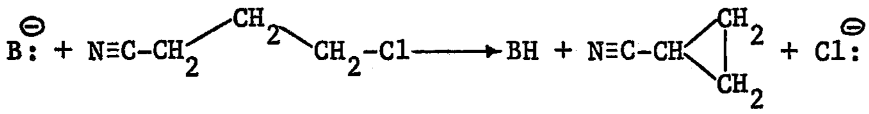
Bordwell and Cooper (187) suggested that the base-induced rearrangement of chloromethylsulfonamide to formaldehyde (188) has a mechanism identical with that of the Ramberg-Backländ rearrangement, equation 109.


(109)

γ-Elimination reactions have also been found in systems where a γ-carbanion can be stabilized by a nitro or a cyano group. Bay (111) reported that γ-nitro-α-halopropanes are converted to cyclopropane compounds when treated with base, equation 110.


(110)

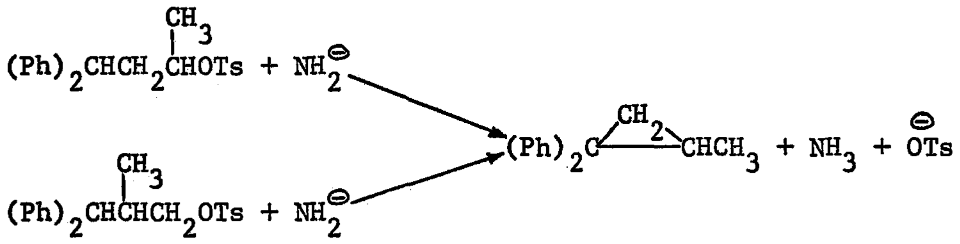
Cloke and co-workers (157,189) obtained cyanocyclopropanes when γ-cyano-α-chloropropanes were treated with base, equation 111.



(111)

The yield of γ-elimination products from both these reactions increases as the strength of the base is increased. Although no mechanistic studies have been attempted in either of these systems, the Elcb mechanism would appear to be the favoured pathway since the nitro and cyano groups are strongly electron withdrawing and the γ-hydrogen would be easily removed.

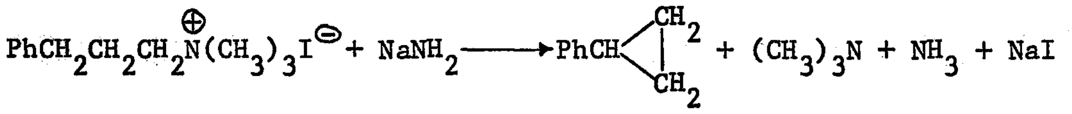
γ-Elimination reactions compete successfully with β-elimination reactions when the γ-carbon is substituted with one or more aryl groups. Pitt and Walborsky (113) found less than one per cent of β-elimination products from the reaction between amide ion and either 3,3-diphenyl-2-butyl tosylate or 3,3-diphenyl-2-methylpropyl tosylate, equation 112.



(112)

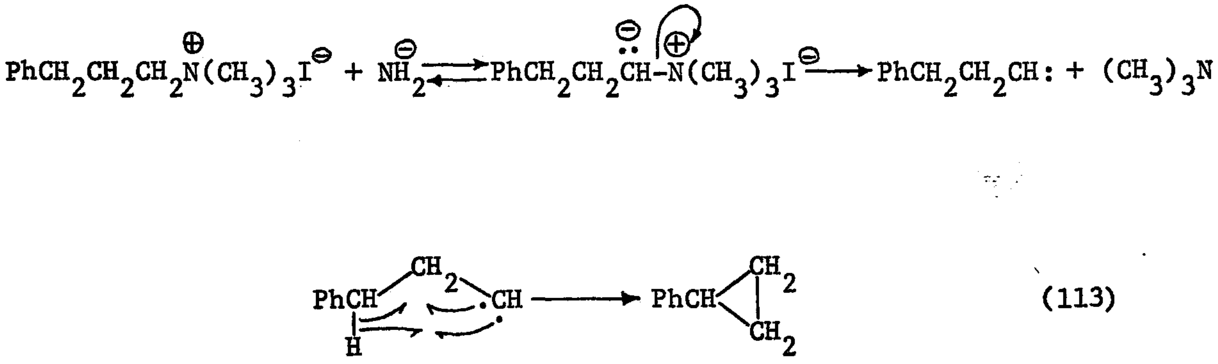
Although the mechanism of these reactions is not known, the Elcb mechanism appears to be more likely because the reaction is carried out in strong base and the aryl groups would aid γ-carbanion formation.

C. L. Bumgardner began what has been the most extensive study of γ-elimination reactions in 1958. He obtained (1,2) an eighty per cent yield of cyclopropanes when either 3-phenylpropyl- or 3,3-diphenylpropyltrimethylammonium iodides were treated with sodium amide in liquid ammonia, equation 1.



$$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} + NaNH_2 \longrightarrow PhCH\langle(CH_2)_2 + (CH_3)_3N + NH_3 + NaI \quad (1)$$

Bumgardner (11) originally suggested that this γ-elimination reaction proceeds either by the E1cb mechanism or is an E2 process in which the transition state has a considerable degree of carbanion character. Banthorpe (12), on the other hand, suggested that the phenylcyclopropane could be formed when a carbene, which is produced in an α-elimination reaction, inserts into the γ-C-H bond, equation 113.

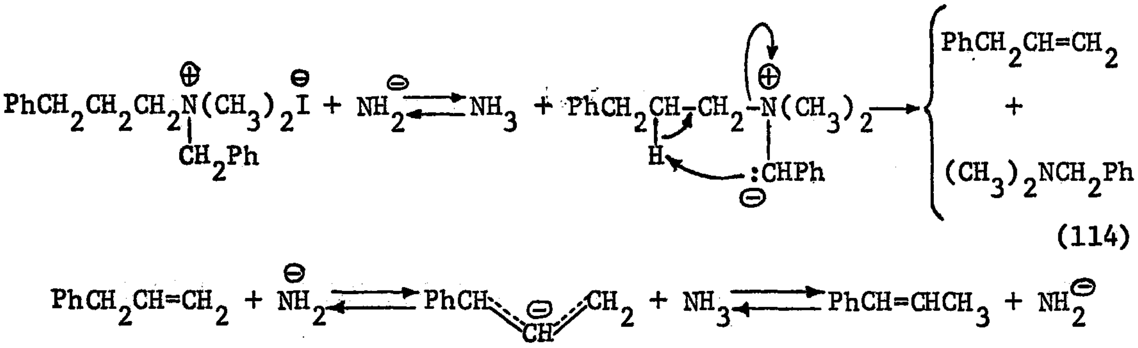


$$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} + \overset{\ominus}{N}H_2 \rightleftharpoons PhCH_2CH_2\overset{\ominus}{\ddot{C}}H-\overset{\oplus}{N}(CH_3)_3I^{\ominus} \longrightarrow PhCH_2CH_2CH: + (CH_3)_3N$$

(113)

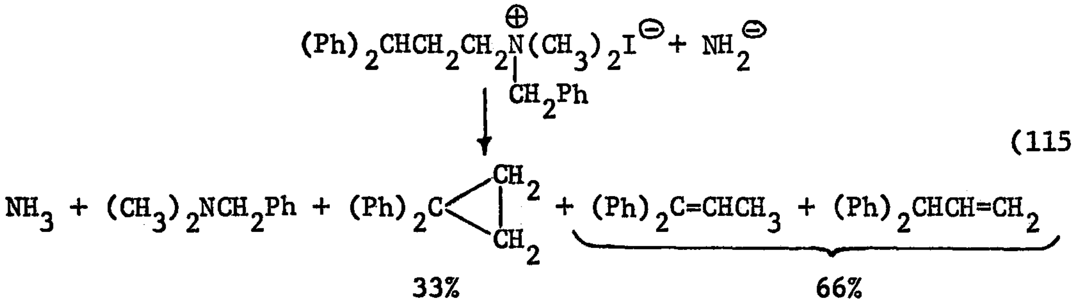
The work presented in this thesis was begun in an effort to distinguish between these mechanistic possibilities.

Bumgardner (2) demonstrated that the acidity of the γ-hydrogens is important in the γ-elimination reaction. When an N-methyl group of 3-phenylpropyltrimethylammonium iodide was replaced with an N-benzyl group the only product from reaction with amide ion was an olefin which Bumgardner suggested was produced in an α'β elimination reaction, equation 114.



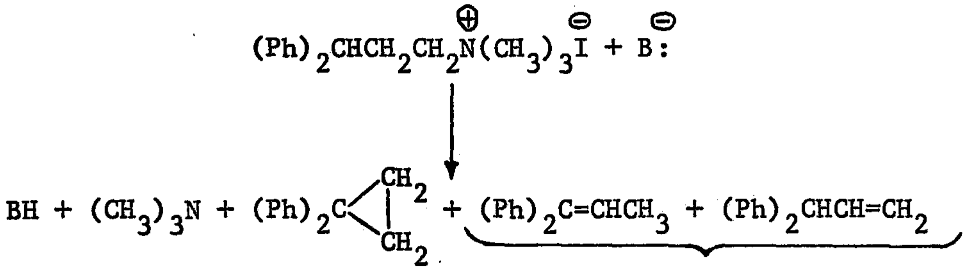
(114)

When the acidity of the γ-hydrogen is increased by replacing a γ-hydrogen with a second phenyl group, equation 115, the amount of γ-elimination increases from zero to 33 per cent.



(115)

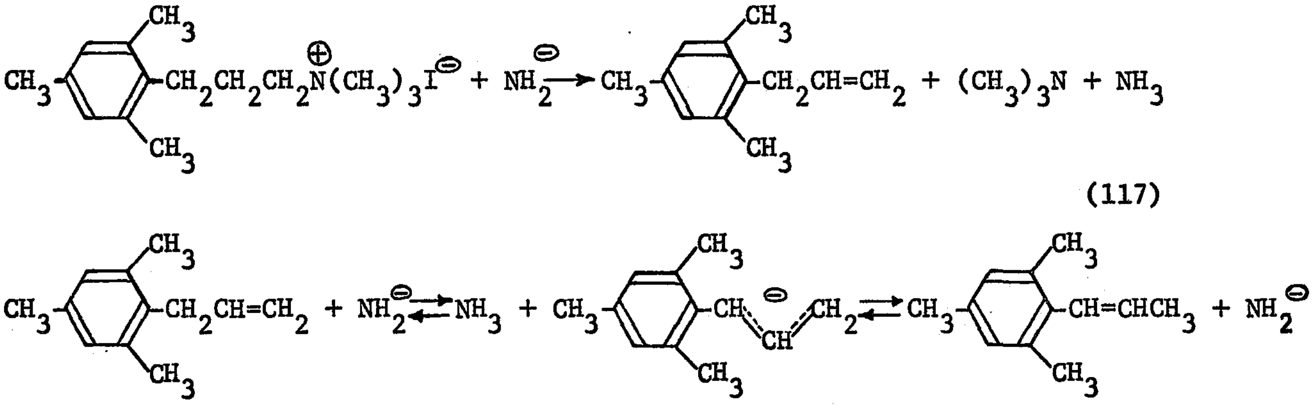
Bumgardner (11) found that γ-elimination increases at the expense of β-elimination when stronger bases are used in the reaction, equation 116.



$B:^{\ominus} = OH^{\ominus}$ (Hofmann conditions) 28% 72% (116)

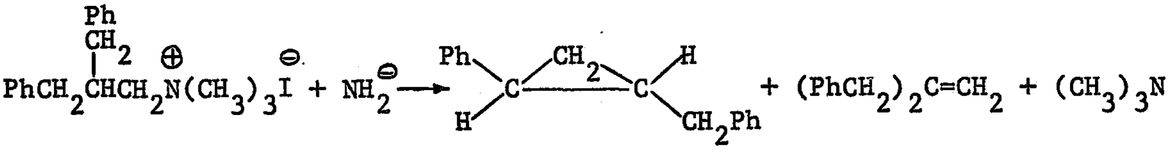
$B:^{\ominus} = NH_2^{\ominus}$ in NH_3 100% 0%

Bumgardner (11) also demonstrated that the formation of the cyclopropane ring is susceptible to steric effects. Both 3-phenylpropyl- and 3-o-tolylpropyltrimethylammonium iodides give only γ-elimination products when treated with amide ion, while the more bulky 3-mesitylpropyltrimethylammonium iodide does not give any γ-elimination products under essentially the same conditions, equation 117. Bumgardner suggests that the lack of γ-elimination is a result of steric hindrance to formation of the cyclopropane ring rather than steric hindrance to abstraction of the γ-proton because the γ-proton is abstracted by base when the olefin formed in the β-elimination reaction isomerizes to its conjugated isomer.



(117)

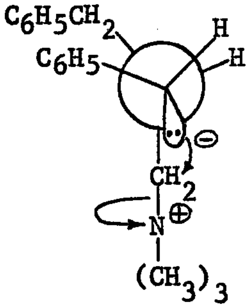
Bumgardner and Iwerks (190) found that the orientation of the substituents of the β- and γ-carbons are important in the formation of the cyclopropane ring. Trans-2-benzyl-1-phenylcyclopropane is the only γ-elimination product from the reaction of 2-benzyl-3-phenylpropyltrimethylammonium iodide and sodium amide, equation 118.



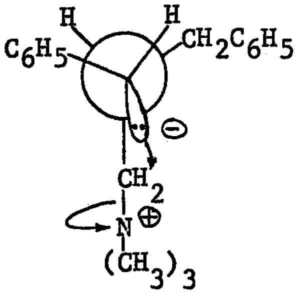
61% γ-elimination 39% β-elimination

(118)

The authors suggested that the transition state for ring closure is much less sterically crowded and therefore of lower energy for the trans-cyclopropane than for the cis-cyclopropane. Formulas XXIII and XXIV show the difference between the steric crowding in the carbanion conformations required for formation of the cis- and trans-cyclopropane, respectively. Similar conformations would be required if the abstraction of the γ-proton and departure of the trimethylamine were concerted.

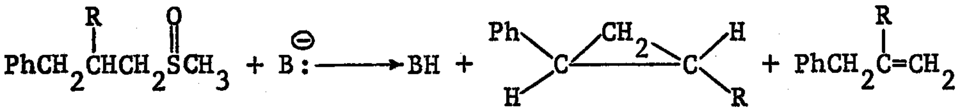


XXIII



XXIV

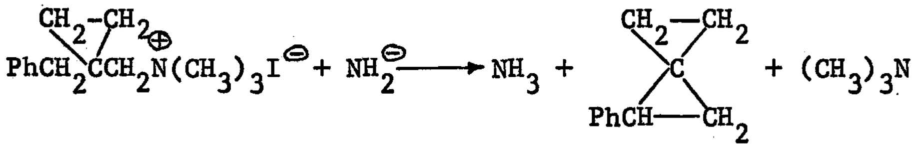
Baker and Spillett (114) also obtained only trans-cyclopropanes from the γ-elimination reaction of 2-alkyl-3-phenylpropyl methyl sulfoxides with either amide ion in triethylamine or the sodium salt of the anion of dimethyl sulfoxide in dimethyl sulfoxide, equation 119. Even when R in equation 119 is as small as methyl, the only product of γ-elimination is the trans-compound.



(119)

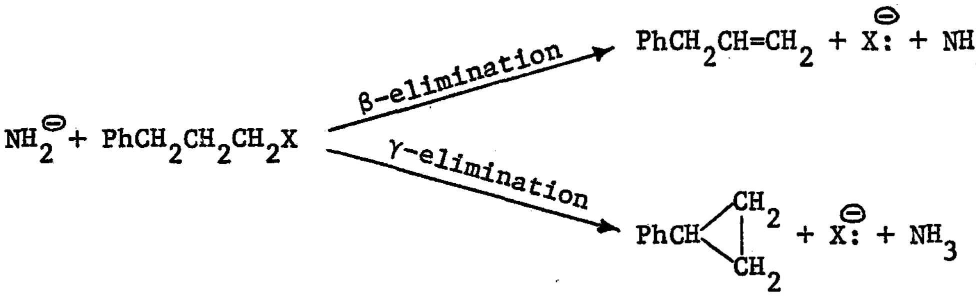
Although the mechanisms of the sulfoxide reactions are not known, the authors suggest that the γ-elimination reactions are Elcb processes and that the β-elimination reactions are E2 processes. The yields of cyclopropanes are higher when the reaction is carried out in dimethyl sulfoxide, which favours ionic reactions, than in less polar trimethylamine. This may be a result of either a solvent effect and or a base strength effect.

Bumgardner (117) found that a γ-elimination reaction that produces a highly strained cyclopropane can occur if the β-elimination reaction is impossible. A fifty per cent yield of phenylspiropentane is obtained from the reaction of (1-benzylcyclopropyl) carbinyltrimethylammonium iodide and sodium amide, equation 120.



(120)

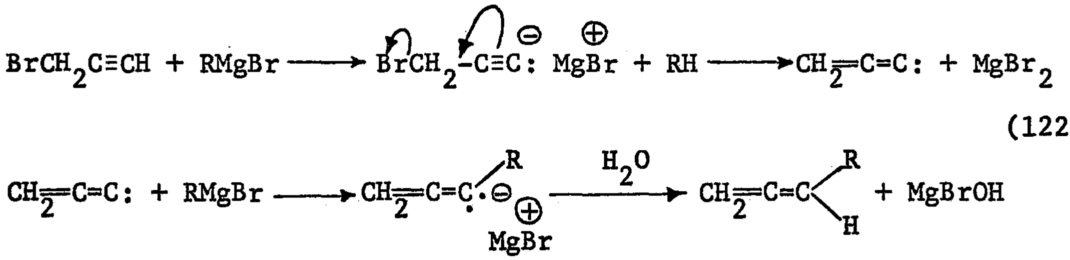
Bumgardner (110) has also examined the effect of the leaving group on the ratio of β:γ-elimination from the reaction of 3-phenylpropyl derivatives with sodium amide in liquid ammonia, equation 121.



(121)

The product changed from olefin when bromide was the leaving group, to a mixture of olefin and cyclopropane with chloride, to only cyclopropane with fluoride. Bumgardner suggests that while both the β- and γ-elimination reactions are slowed by a poorer leaving group, the β-elimination reaction is more sensitive to changes in the leaving group than is the γ-elimination reaction. As a result, the amount of γ-elimination increases when poorer leaving groups are used. Only cyclopropanes are produced when the leaving group is either trimethylamine (a poor leaving group) or tosylate (normally a good leaving group).

Serratosa (191) found that α-bromomethylacetylene can react with Grignard reagents to form an allene carbene in what is probably an Elcb γ-elimination reaction, equation 122. The carbene reacts with another molecule of the Grignard reagent to form an allene.



$$BrCH_2C\equiv CH + RMgBr \longrightarrow BrCH_2-C\equiv C:^{\ominus}\ \overset{\oplus}{MgBr} + RH \longrightarrow CH_2=C=C: + MgBr_2$$

(122)

$$CH_2=C=C: + RMgBr \longrightarrow CH_2=C=\overset{R}{C}{:}^{\ominus}\ \overset{\oplus}{MgBr} \xrightarrow{H_2O} CH_2=C=C\genfrac{}{}{0pt}{}{R}{H} + MgBrOH$$

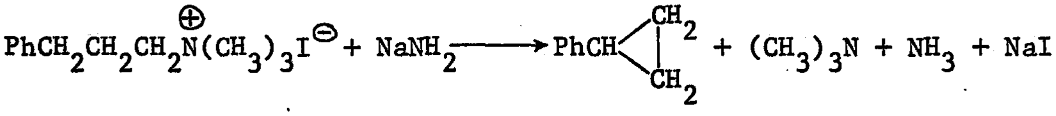
As R becomes more basic this route of reaction becomes increasingly important.

Other γ-Elimination Processes

Other types of γ-elimination reactions have been reported. Acetates (8,192), halides (193,194), pyrazolines (195) and amine oxides (196) react in pyrolytic γ-elimination reactions to produce cyclopropane derivatives. Cyclopropanes are also obtained from free radical (197,198) and Wurtz-type reactions of 1,3-dihalides (199). These reactions are, however, outside the scope of this thesis and will not be discussed.

RESULTS AND DISCUSSION

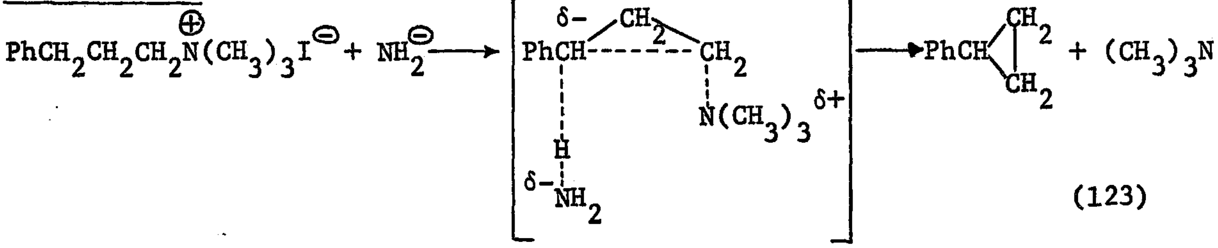
C. L. Bumgardner, in his original papers (2,11), reported that several quaternary ammonium salts undergo γ-elimination reactions when treated with sodium amide in liquid ammonia. Three of the compounds Bumgardner studied were reported to undergo only a γ-elimination reaction. The simplest of these compounds, 3-phenylpropyltrimethylammonium iodide, equation 1, was chosen as the model compound for this study.



$$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} + NaNH_2 \longrightarrow PhCH\begin{matrix}CH_2\\ |\\ CH_2\end{matrix} + (CH_3)_3N + NH_3 + NaI \quad (1)$$

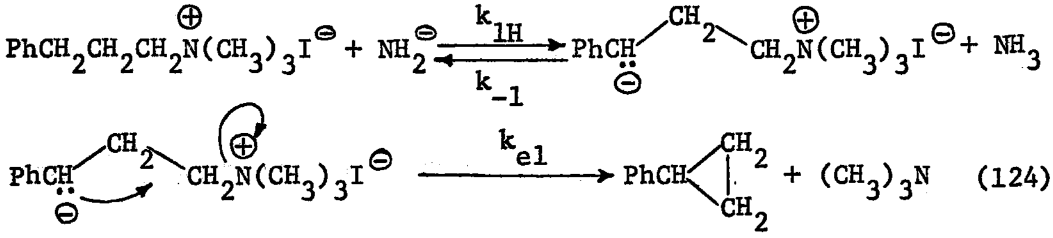
As stated in the Historical Introduction, three mechanism have been suggested for this reaction. They are an E2 process in which the transition state has a considerable degree of carbanion character (11), equation 123, an Elcb process (11), equation 124, and a carbene mechanism (12), equation 113. An ylide mechanism, equation 125, although less likely, cannot be ruled out *a priori* and was also considered as a possible pathway for the γ-elimination reaction.

E2 Mechanism



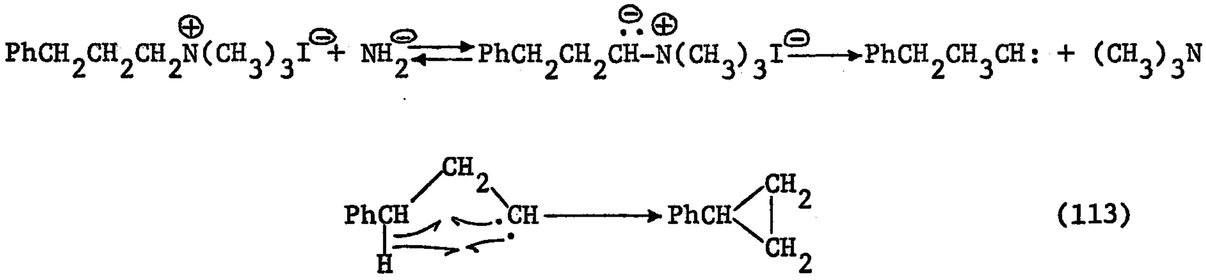
(123)

Elcb Mechanism



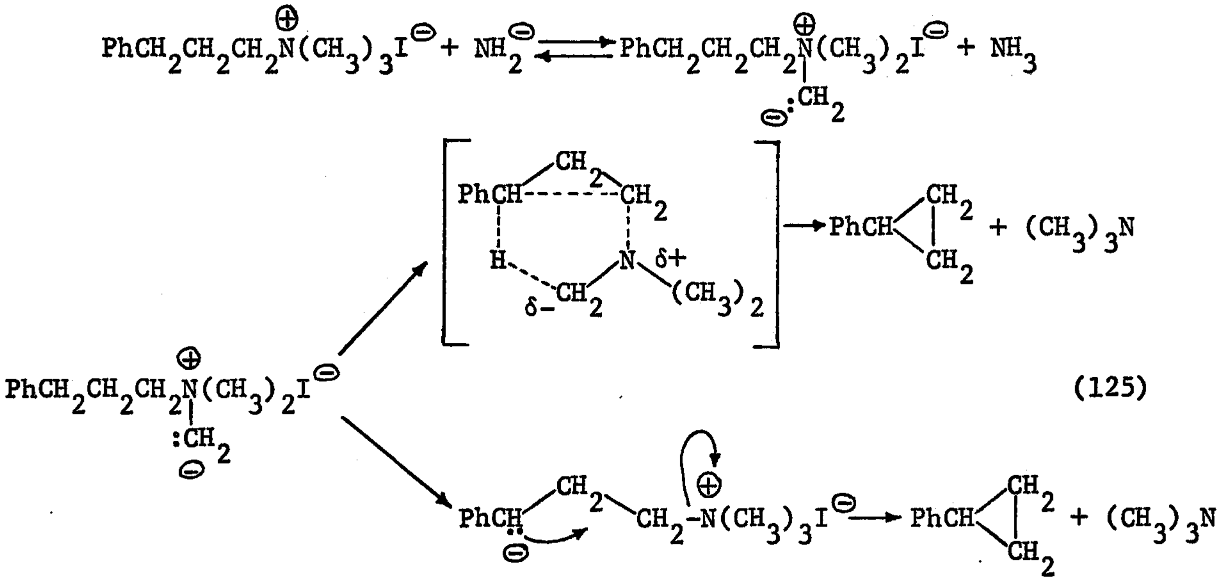
(124)

Carbene Mechanism



(113)

Ylide Mechanism



(125)

The work described in this thesis was begun in an effort to distinguish between these four mechanistic possibilities.

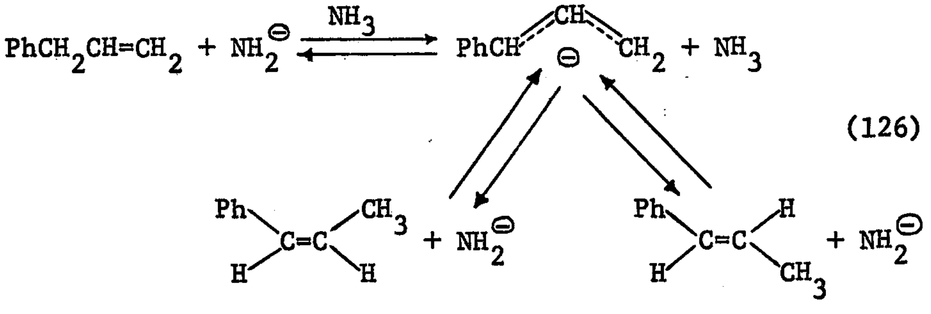
Reaction Conditions

Since sodium amide is virtually insoluble in liquid ammonia (200), the reactions carried out by Bumgardner proceeded under heterogeneous conditions. In the present study it was hoped that kinetic isotope effects could be used to obtain information about the mechanism of the reaction. It, therefore, was necessary to find conditions such that the reactants are completely in solution and the rate is sufficiently slow for kinetic measurements. Although the reaction occurs under homogeneous conditions when the base is potassium amide, the reaction is too fast to control kinetically at -33°, the temperature employed by Bumgardner. The reaction was slowed to a measurable rate by lowering the temperature from -33° to -55°. A preliminary investigation showed that the hydrocarbon product from the reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide at -55° is essentially the same as the product obtained when the reaction is carried out under the conditions employed by Bumgardner (sodium amide at -33°). All the reactions discussed in this thesis have been carried out at -55° using potassium amide as the base.

Product Identification and Analysis

Bumgardner reported that only phenylcyclopropane, the product of γ-elimination, is produced when 3-phenylpropyltrimethylammonium iodide reacts with sodium amide in liquid ammonia at -33° (2). In the present study, a gas chromatographic analysis of the product formed in the reaction of the quaternary salt with potassium amide in liquid ammonia at -55° showed two small peaks in addition to that attributed to phenylcyclopropane. The amounts of these minor products, however, were too small to permit identification. These compounds were found to constitute a very much larger fraction of the total product when the reaction was carried out on 3,3-dideutero-3-phenylpropyltrimethylammonium iodide, persumably because of the kinetic isotope effect on the γ-elimination reaction. Identification studies were made, therefore, on the products formed from the deuterated quaternary ammonium salt.

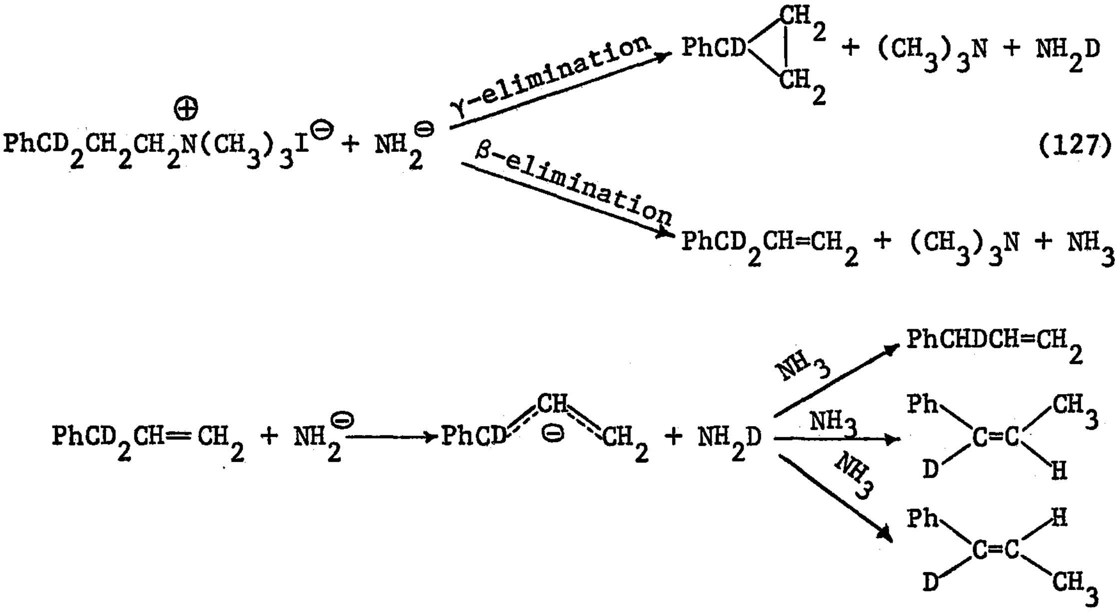
It was suspected that these other products were a result of a competing β-elimination reaction. Several workers (201-203) have shown that when 3-phenylpropene, the product formed in the β-elimination reaction, is treated with alkali metal amides in liquid ammonia, it isomerizes by way of a reddish brown allyl carbanion (202,203) to a mixture of *cis*- and *trans*-β-methyl styrene and 3-phenylpropene, equation 126.



(126)

cis-β-methyl styrene *trans*-β-methyl styrene

It was found that the reaction mixture is indeed a reddish brown colour when either the deuterated or the undeuterated quaternary ammonium salts are treated with potassium amide in liquid ammonia. This suggested that the isomerization of 3-phenylpropene is occurring and that there are competing β- and γ-elimination reactions with both quaternary salts, equation 127.



(127)

The products from the reaction of the deuterated quaternary ammonium salt were identified by comparison with known compounds, spectroscopic analysis and gas chromatography. A sample of 3-phenylpropene was converted into a mixture of 3-phenylpropene and cis- and trans-β-methyl styrene by treatment with potassium amide in liquid ammonia (201). The products from this isomerization were examined by gas chromatography and found to have retention times identical to the retention times of the products from the reaction of the deuterated quaternary ammonium salt. In addition, the retention times of trans-β-methyl styrene and phenylcyclopropane were found to be identical under the conditions of the analysis. The three peaks found in the gas chromatographic analysis of the product of the reaction of the deuterated quaternary ammonium salt were tentatively attributed to the following components:

(1) 3-phenylpropene

(2) a mixture of trans-β-methyl styrene and phenylcyclopropane

and (3) cis-β-methyl styrene.

The hydrocarbon mixture from the deuterated quaternary salt was separated by preparative gas chromatography and the two largest components, (1) and (2), collected. Component (1), which had a retention time on the v.p.c. identical to the retention time of 3-phenylpropene, was examined by infra-red spectroscopy. The spectrum of component (1) was identical with that of 3-phenylpropene except for a peak at 2150 cm^{-1}, and the absence of a peak at 1440 cm^{-1}. The new peak at 2150 cm^{-1} is caused by the C-D stretching vibration (204-206), while the absorption caused by the bending vibration of the methylene group at 1440 cm^{-1} (204) is absent in the deuterated compound, see equation 127.

Component (2) could not be separated on a preparative scale by gas chromatography and as a result, the compounds in component (2) had to be identified in the mixture. The infra-red and N.M.R. spectra of component (2) are consistent with a mixture of trans-β-methyl styrene and phenylcyclopropane. The presence of these two compounds in the mixture was confirmed by the following experiments. The mixture was assumed to consist of only trans-β-methyl styrene and phenylcyclopropane and the percentage of each compound was determined (a) by the area under the peaks in a gas chromatographic analysis*, (b) from the integration of the N.M.R. spectrum of the mixture, and (c) by ultraviolet spectroscopy at 250 millimicrons in 95 per cent ethanol. A sample of component (2) obtained when the deuterated quaternary salt was reacted 66 per cent to completion, was analyzed by N.M.R. and gas chromatography. Both methods of analysis showed that 71 per cent of the mixture was phenylcyclopropane, Table I. Another sample of component (2) that was obtained from an identical reaction, was analyzed by N.M.R. and ultraviolet spectroscopy. The N.M.R. analysis showed that phenylcyclopropane represented 72 per cent of the mixture, while the analysis by ultraviolet spectroscopy indicated that only 68 per cent of the mixture was phenylcyclopropane, Table I. The latter analysis was the least accurate because the analysis was performed with a very small amount of material. The agreement between the three methods of analysis is quite good, and since each method of analysis is based on different properties of the molecules it is inconceivable that component (2) is not comprised of _trans_-β-methyl styrene and phenylcyclopropane. Throughout this thesis the composition of component (2) obtained when the deuterated quaternary salt is reacted 66 per cent to completion, will be taken to be 71 per cent phenylcyclopropane and 29 per cent _trans_-β-methyl styrene.

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* Varian Aerograph attempted to separate the compounds in component (2) by gas chromatography. While even a partial separation was impossible on a preparative scale, they were able to partially resolve very small samples of component (2) (less than ten microliters) by using temperature programming and a 40 foot, 1/4 inch column with five per cent Ucon polar as the liquid phase. The separation, while not complete, was sufficient to allow the percentage of phenylcyclopropane in the mixture to be determined.

Table I. The Per Cent Phenylcyclopropane in Component (2) when the Deuterated Quaternary Salt is Reacted 66 Per Cent to Completion

Sample	Per Cent Phenylcyclopropane by N.M.R.	Per Cent Phenylcyclopropane by v.p.c.	Per Cent Phenylcyclopropane by u.v.
1	71.2	71[a]	-
2	71.6	-	68[b]

a. Analysis done by Varian Aerograph.

b. The u.v. analysis was, in this instance, felt to be the least accurate of these analyses.

Although the amount of component (3) was not sufficient for a positive identification, there is little doubt but that component (3) is cis-β-methyl styrene.

The relative amounts of β- and γ-elimination from both the deuterated and undeuterated quaternary ammonium salts were determined by gas chromatographic and spectroscopic analysis of the products. A gas chromatographic analysis using the internal standard technique (207) showed that the thermal conductivity of 3-phenylpropene, trans-β-methyl styrene and phenylcyclopropane are identical. It was assumed that the thermal conductivity of cis-β-methyl styrene is identical to that of the other isomers. Since all the products have the same thermal conductivity, the relative amounts of the three components of the product (3-phenylpropene, cis-β-methyl styrene and a mixture of phenylcyclopropane and trans-β-methyl styrene) can be determined from the peak areas on the gas chromatograph. The phenylcyclopropane-trans-β-methyl styrene mixture was separated from the other products by preparative gas chromatography, collected and analyzed by ultraviolet spectroscopy, N.M.R. spectroscopy and gas chromatography as previously described.

Control experiments with synthetic mixtures showed that the styrenes do not polymerize either during the reaction or during the recovery and the analysis.

The amounts of each product obtained from the reaction of the deuterated and undeuterated quaternary ammonium salts with potassium amide in liquid ammonia at -55° are given in Table II.

Table II. Product Ratios from the Reaction of the Deuterated and Undeuterated Quaternary Ammonium Salts with Potassium Amide in Liquid Ammonia at -55°

Quaternary Salt	Per Cent *Cis*-β-Methyl Styrene	Per Cent *Trans*-β-Methyl Styrene	Per Cent 3-Phenylpropene	Per Cent β-Elimination	Per Cent Phenylcyclopropane	γ-Elimination / β-Elimination
Deuterated I[a]	2.4	23.3	21.7	47.4	52.6	
Deuterated II[a]	2.1	21.5	22.6	46.2	53.8	
Deuterated Average[a]				46.8 ± 0.6	53.2 ± 0.6	53/47
Undeuterated I	-	0.7	2.8	3.5	96.5	
Undeuterated II	-	2.0	2.5	4.5	95.5	
Undeuterated Average				4.0 ± 0.5	96.0 ± 0.5	96/4

[a] These product ratios are obtained when the reaction has gone 66 per cent to completion.

Deuterium Tracer Studies

3,3-Dideutero-3-phenylpropyltrimethylammonium iodide, which was found to contain at least 1.96 deuteriums per molecule ($\geq$ 98 per cent dideuterated)*, was used in the deuterium tracer studies. These tracer studies were used to test for both the carbene and ylide mechanisms as well as to determine if the γ-hydrogens exchange with solvent.

A Test for the Carbene Mechanism

The test for the carbene mechanism involved a tracer study which was based on the number and position of deuterium atoms in the phenylcyclopropane produced from 3,3-dideutero-3-phenylpropyltrimethylammonium iodide. If the phenylcyclopropane is formed by insertion of a carbene intermediate into the γ-C-D bond, it would contain two atoms of deuterium per molecule. One of the deuteriums would be on the carbon bearing the phenyl group and the other would be on one of the methylene carbon atoms of the cyclopropane ring, equation 128.

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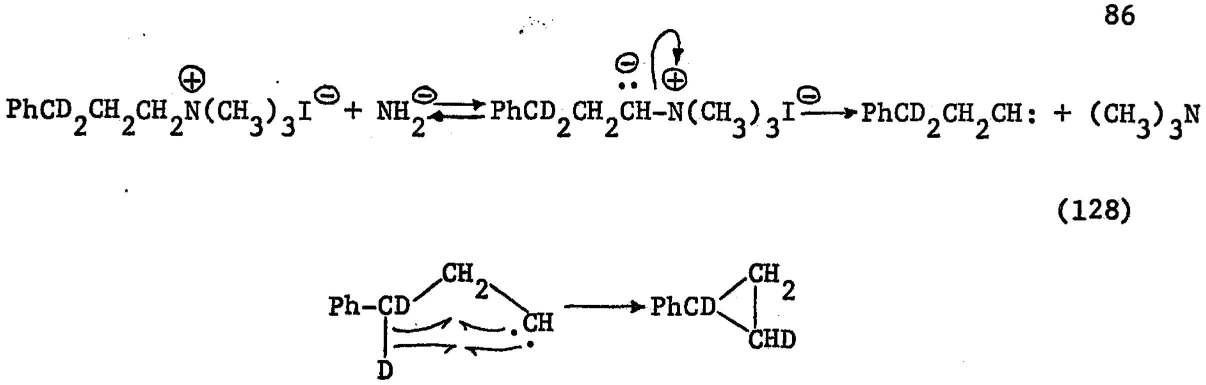
* Unless otherwise stated, the deuterium analyses were performed by Mr. J. Nemeth, 303 W. Washington St., Urbana, Illinois. The deuterium content appears to be at least two per cent low when the analysis, which is done by the falling drop method, is performed on quaternary ammonium salts. In other work in this laboratory (208) it was observed that several tertiary amines which have been shown to be more than 99 per cent dideuterated by N.M.R., gave quaternary ammonium salts which Nemeth found to be only 94 to 98 per cent dideuterated. Since it is highly unlikely that deuterium is lost during the quaternization, it is probable that the analyses by Nemeth gives results which are from two to six per cent low for quaternary ammonium halides. This means that the 3,3-dideutero-3-phenylpropyltrimethylammonium iodide is probably very nearly 100 per cent deuterated at the γ-position.



$$\mathrm{PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} + NH_2^{\ominus} \rightleftharpoons PhCD_2CH_2\overset{\ominus}{\ddot{C}}H\text{-}\overset{\oplus}{N}(CH_3)_3I^{\ominus} \longrightarrow PhCD_2CH_2CH\colon + (CH_3)_3N}$$

(128)

As reported in the previous section, the phenylcyclopropane obtained from this reaction could not be separated on a preparative scale by gas chromatography from <u>trans</u>-β-methyl styrene which is also produced in the reaction. As a result, the determination of the number and position of the deuterium atoms in the cyclopropane had to be carried out on the phenylcyclopropane-<u>trans</u>-β-methyl styrene mixture.

This mixture was examined by N.M.R. spectroscopy and mass spectrometry. Two things were immediately apparent when the N.M.R. spectrum of the mixture, figure 3, was compared with the spectrum of undeuterated phenylcyclopropane, figure 4. The broad absorption associated with the methine proton of phenylcyclopropane (1.55-2.10 p.p.m.) was absent, and the complex multiplets caused by the two methylene groups of the cyclopropane ring (0.45-1.1 p.p.m.) were reduced to two broad lines. These changes in the N.M.R. spectrum of phenylcyclopropane are consistent with replacing the hydrogen on the carbon bearing the phenyl group with a deuterium.

The ratio of phenyl:methylene protons in the phenylcyclopropane can be calculated from the integration of the N.M.R. spectrum of the mixture. The absorption caused by the phenyl protons of

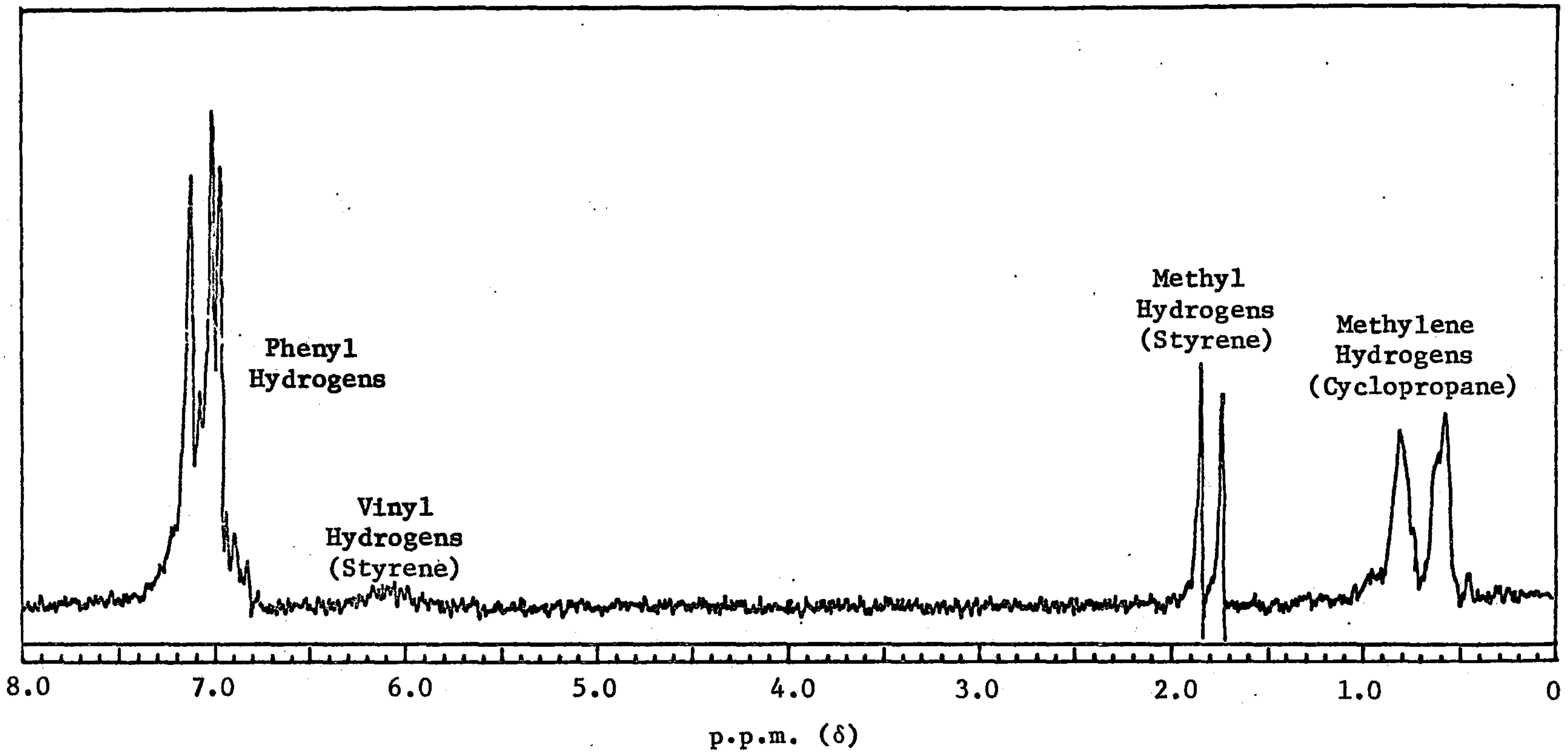


Fig. 3. N.M.R. spectrum of 1-deutero-1-phenylcyclopropane and trans-β-methyl styrene.

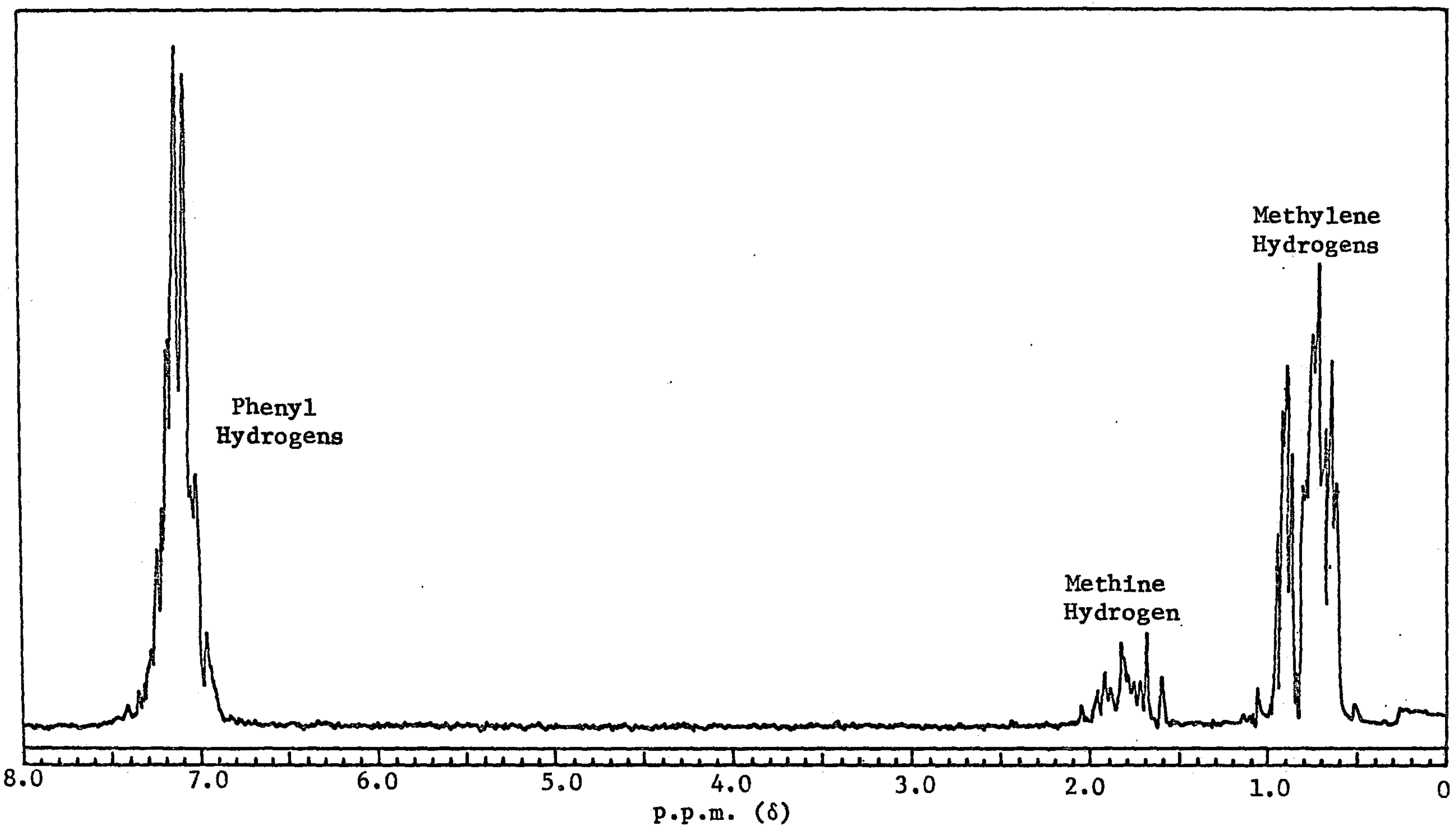


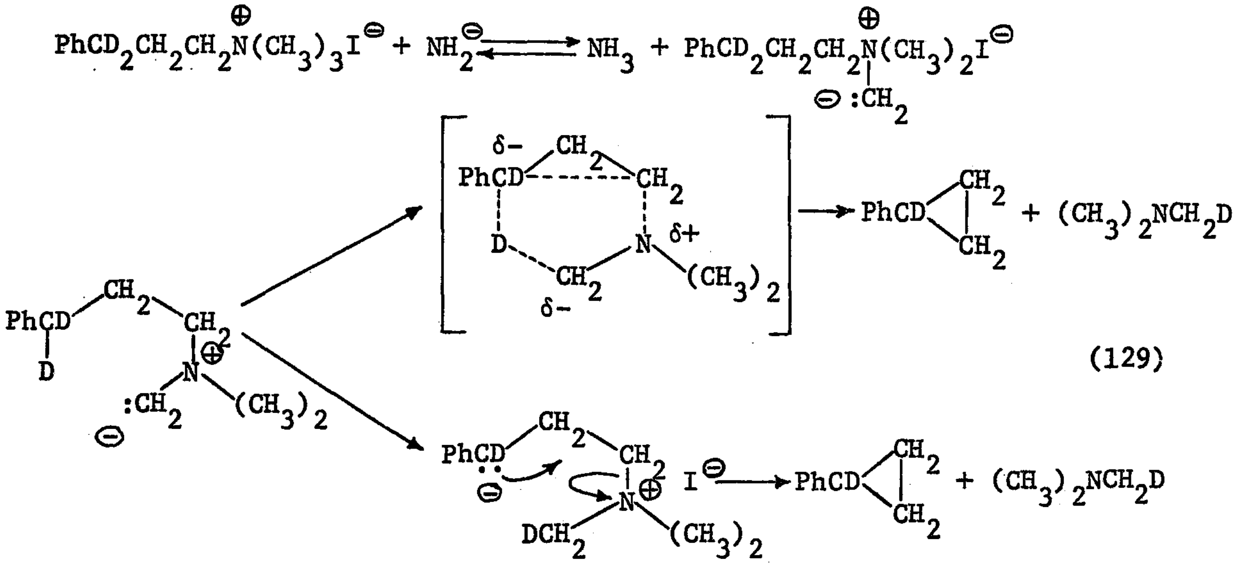
Fig. 4. N.M.R. spectrum of phenylcyclopropane.

phenylcyclopropane is not resolved from the absorption caused by the phenyl protons of trans-β-methyl styrene. The absorption caused by the phenyl protons of phenylcyclopropane can be found by subtracting the contribution of the phenyl protons of trans-β-methyl styrene from the total absorption caused by phenyl protons. The portion of the absorption caused by the phenyl protons of trans-β-methyl styrene is 5/3 times the absorption caused by the methyl protons of trans-β-methyl styrene. The absorption caused by the phenyl protons of phenylcyclopropane can be compared directly with the absorption caused by the protons on the secondary carbons of the cyclopropane ring to show that the ratio of phenyl:methylene protons in the phenylcyclopropane from the deuterated quaternary ammonium salt is phenyl:methylene = 5.0:4.0. This shows that the phenylcyclopropane is monodeuterated and that there is little or no deuterium on the methylene carbons of the cyclopropane ring.

These results were confirmed by mass spectrometry. The phenylcyclopropane-trans-β-methyl styrene mixture was found to be 94.4 per cent monodeuterated, 5.5 per cent undeuterated and 0.1 per cent dideuterated. The virtual absence of dideuterated material, coupled with the presence of a deuterium on the carbon bearing the phenyl group as shown by N.M.R., demonstrates conclusively that there is no deuterium on the methylene carbons of the cyclopropane ring. It therefore can be concluded that the γ-elimination reaction does not proceed by a carbene mechanism.

A Test for the Ylide Mechanism

A deuterium tracer study based on the deuterium content of the trimethylamine produced in the reaction of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide with amide ion was used to test for an ylide intermediate in the γ-elimination reaction. If an ylide intermediate were involved in the γ-elimination reaction it would abstract the γ-deuterium atom, equation 129. Although this could be accomplished by either a one or a two-step mechanism, both pathways lead to the incorporation of deuterium in the trimethylamine.



(129)

The trimethylamine from the reaction of the deuterated quaternary ammonium salt and potassium amide in liquid ammonia was distilled along with the solvent into an excess of concentrated hydrochloric acid. This solution was taken to dryness under reduced pressure giving a mixture containing one part of trimethylammonium chloride to 2500 parts of ammonium chloride. Extraction of the hydrochloride salts with absolute ethanol and chloroform gave a product which was approximately 99 per cent trimethylammonium chloride (209). Trimethylamine was liberated by adding base to an ethanolic solution of the salt, purified by gas chromatography and analyzed for its deuterium content by the mass spectrometric method devised by Cope and Mehta (70,210). The analysis of the trimethylamine involved comparing the relative heights of the molecular ion and fragment ion peaks from a sample of undeuterated trimethylamine and the trimethylamine formed in the reaction of the deuterated quaternary ammonium salt. If the trimethylamine isolated from the reaction mixture were even slightly deuterated, the relative heights of the molecular ion and fragment ion peaks would be quite different from those of the undeuterated trimethylamine. Cope and Mehta (210) determined the relative heights of the molecular ion and fragment ion peaks of trimethylamine and trimethylamine-$\underline{d}_1$ using a C.E.C. 21-130 mass spectrometer. The values obtained, relative to the molecular ion peak which is given a height of one hundred, are shown in Table III. The relative peak heights obtained for trimethylamine on the Hitachi Perkin-Elmer R.M.U.-6A mass spectrometer used in this study are in good agreement with those reported by Cope and Mehta. Although a sample of trimethylamine-$\underline{d}_1$ was not available, the excellent agreement between the results for trimethylamine suggest that the relative heights of the peaks which would be obtained for trimethylamine-$\underline{d}_1$ on our mass spectrometer would be almost identical to those reported by Cope and Mehta.

The peak heights observed for the trimethylamine produced in the reaction of the deuterated quaternary salt with amide ion are also shown in Table III. Within experimental error these are identical to those obtained for trimethylamine. The relative heights of the mass peaks of mixtures containing one per cent and one-half

Table III. Relative Heights of Molecular Ion and Fragment Ion Peaks of Trimethylamine and Trimethylamine-$\underline{d}_1$

Mass Peak	Reported[a] $(CH_3)_3N$	Reported[a] $(CH_3)_2NCH_2D$	$(CH_3)_3N$ Found	Trimethylamine from $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus}$	1% $(CH_3)_2NCH_2D$ 99% $(CH_3)_3N$ Calc.[b]	0.5% $(CH_3)_2NCH_2D$ 99.5% $(CH_3)_3N$ Calc.[b]
60	4.1	100	3.3	3.4	4.3	3.7
59	100	223	100	100	100	100
58	245	37.8	251	251	246	248
57	18.0	6.15	17.6	17.5	17.4	17.5

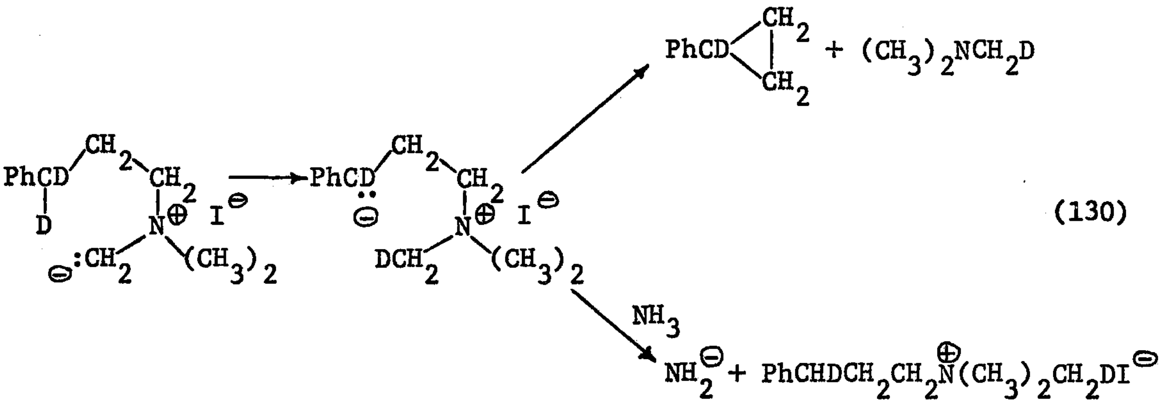
a. Reference 210.

b. Calculated from the Peak Heights for $(CH_3)_3N$ Found and Reported $(CH_3)_2NCH_2D$.

a per cent of trimethylamine-$\underline{d}_1$ were calculated using the peak heights observed by Cope and Mehta for trimethylamine-$\underline{d}_1$ and those obtained in this study for trimethylamine. From a comparison of the heights of the mass peaks calculated for these mixtures and the heights of the observed mass peaks, it was concluded that the trimethylamine from the deuterated quaternary salt was definitely less than one per cent trimethylamine-$\underline{d}_1$ and probably less than one-half a per cent.

While the mass spectrometric analysis clearly demonstrates that there is little or no deuterium in the trimethylamine from the deuterated quaternary salt, the significance of this result is more difficult to assess. Analysis of the products from the deuterated quaternary salt showed that the ratio of γ-elimination : β-elimination was 53:47. The trimethylamine produced in the β-elimination reaction cannot be deuterated and, therefore, a maximum of 53 per cent of the trimethylamine would be deuterated if the γ-elimination reaction proceeds by a concerted ylide mechanism, equation 129 (page 90). Since less than one per cent of the trimethylamine contains a deuterium atom less than two per cent of the γ-elimination reaction is proceeding by this mechanism.

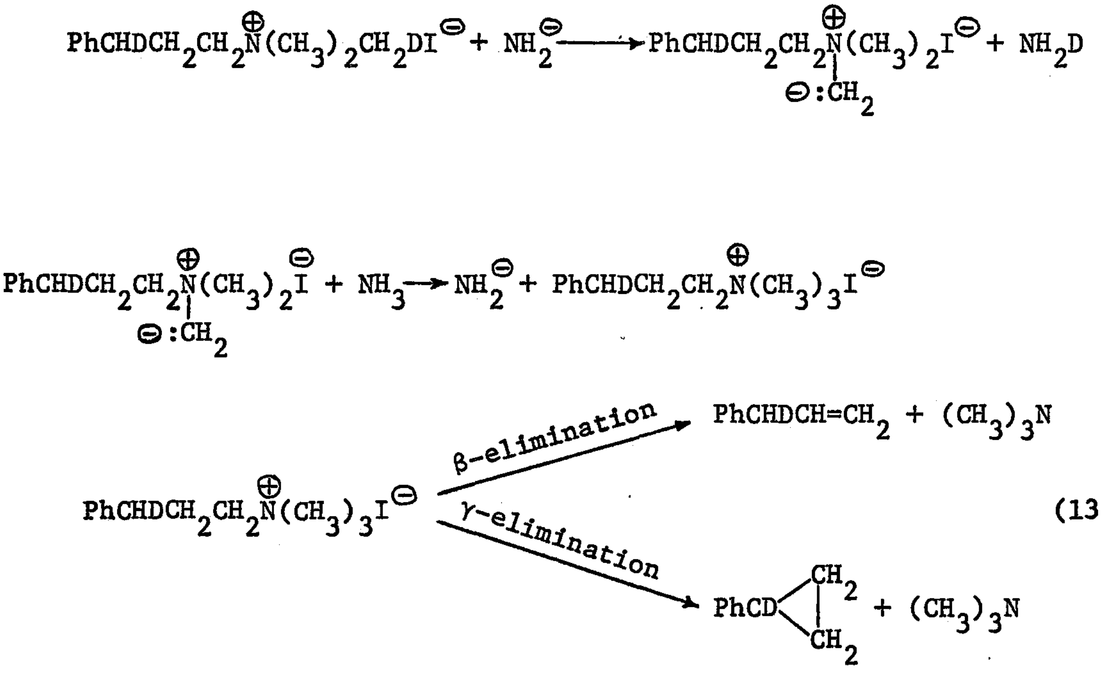
On the other hand, the two-step ylide mechanism described in equation 129, cannot be completely ruled out by the results of the tracer study. The γ-carbanion, which is produced when the ylide intermediate abstracts the deuterium, could abstract a proton from solvent and produce the dideuterated quaternary ammonium salt, XXV, equation 130.



(130)

XXV

If the deuterium in the trimethylammonium group of XXV exchanges with solvent before the trimethylammonium group is displaced in either a β- or a γ-elimination reaction, the trimethylamine would be free of deuterium, equation 131.



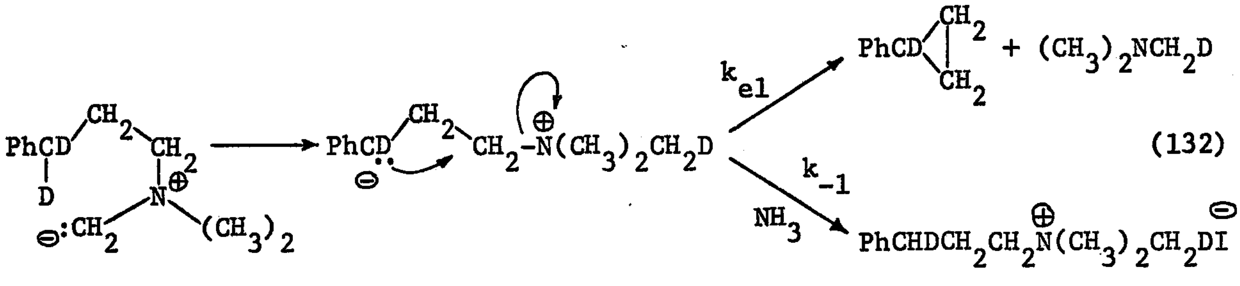
$$\mathrm{PhCHDCH_2CH_2\overset{\oplus}{N}(CH_3)_2CH_2DI^{\ominus} + NH_2^{\ominus} \longrightarrow PhCHDCH_2CH_2\underset{\ominus:CH_2}{\overset{\oplus}{N}}(CH_3)_2I^{\ominus} + NH_2D}$$

$$\mathrm{PhCHDCH_2CH_2\underset{\ominus:CH_2}{\overset{\oplus}{N}}(CH_3)_2\overset{\ominus}{I} + NH_3 \longrightarrow NH_2^{\ominus} + PhCHDCH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus}}$$

(131)

An experiment in which 3-phenylpropyltrimethylammonium iodide was reacted with potassium amide-$\underline{d}_2$ in ammonia-$\underline{d}_3$ showed that approximately fifty per cent of the N-methyl hydrogens have exchanged with solvent when the γ-elimination has proceeded eleven per cent to completion. Since the exchange of the N-methyl hydrogens is rapid compared to the γ-elimination reaction, a significant amount of any deuterium in the trimethylammonium group of quaternary salt XXV would be exchanged for a hydrogen from solvent before trimethylamine is produced in an elimination reaction. Any loss of deuterium from the trimethylammonium group of XXV would lower the amount of deuterium found in the trimethylamine and make the test for the ylide mechanism less sensitive.

Later in this thesis it will be shown that the ratio of the rates of reaction of undeuterated and γ,γ-dideuterated quaternary salts is greater than 6.4. It will also be shown that an isotope effect of this magnitude can be accommodated by a mechanism involving a γ-carbanion intermediate only if the relative rates of the two processes designated by the rate constants k_{-1}* and k_{el} in equation 132 are less than fifteen.



(132)

XXV

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* The rate constant k_{-1} contains $[NH_3]$, the concentration of solvent which is constant throughout the reaction.

Since $\frac{k_{-1}}{k_{el}}$ cannot exceed fifteen for the mechanism under discussion, it follows that at least 6.7 per cent of the γ-carbanions must decompose directly to trimethylamine-$\underline{d}_1$ and phenylcyclopropane rather than abstract a proton from solvent and form the dideuterated quaternary salt XXV. As a result, a minimum of $\frac{6.7}{100} \times 53 = 3.6$ per cent of the trimethylamine produced from the dideuterated quaternary salt would contain a deuterium atom. Since this amount of deuterated trimethylamine would have been easily detected in the mass spectrometric analysis, it can be concluded that the two-step ylide mechanism is not the major pathway of the γ-elimination reaction.

A Test for Exchange at the γ-Carbon

Since the carbene and ylide mechanisms have been ruled out by the deuterium tracer studies, the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide must be either an E2 or an Elcb process, as Bumgardner originally suggested. A deuterium exchange test was performed in an effort to detect the presence of a γ-carbanion.

3,3-Dideutero-3-phenylpropyltrimethylammonium iodide was reacted with potassium amide in liquid ammonia until the reaction had gone approximately 66 per cent to completion. The unreacted quaternary salt was recovered, purified and analyzed for deuterium. Deuterium analysis of the unreacted quaternary ammonium salt showed that a significant amount of the deuterium bonded to the γ-carbon had exchanged with hydrogen from the solvent, see Table IV.

The percentage composition of a deuterated mixture can be calculated from equation 133.

$$\text{Per Cent Excess Deuterium} = \frac{\Sigma_i\, y_i\ (\text{Number of Deuterium Atoms/Molecule})_i}{\text{Total Number of Hydrogen and Deuterium Atoms/Molecule}} \tag{133}$$

where y_i is the percentage of each component in the mixture. The percentage composition of the starting material and the unreacted salts were calculated on the assumption that these mixtures consisted of only mono- and dideuterated quaternary salts. For these mixtures equation 133 reduces to

$$x = \frac{z(2) + (100-z)(1)}{20} = \frac{z + 100}{20} = \frac{z}{20} + 5.0$$

$$\text{or} \qquad z = 20x - 5.00 \tag{134}$$

where x is the per cent excess deuterium and z is the percentage of dideuterated quaternary salt. The values obtained from equation 134 and the percentage of the dideuterated quaternary salt that has exchanged a γ-deuterium for a hydrogen from the solvent after 66 per cent reaction, are shown in Table IV.

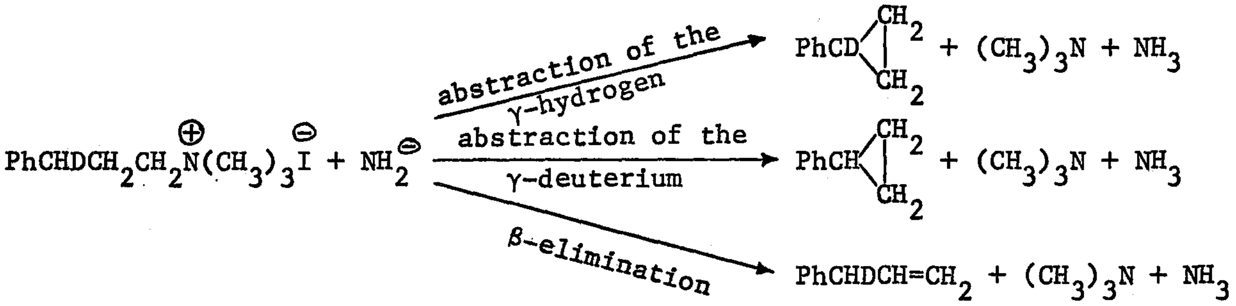
The results demonstrate that an average of 10.8 ± 0.7 per cent of the dideuterated material has exchanged a γ-deuterium for a hydrogen from solvent after 66 per cent reaction. Control experiments showed that deuterium was not lost during the recovery and purification of the unreacted quaternary ammonium salt. This exchange experiment demonstrates that γ-carbanions are formed and that some of these carbanions abstract a proton from solvent and produce 3-deutero-3-phenylpropyltrimethylammonium iodide, equation 135.

$$\text{PhCD}_2\text{CH}_2\text{CH}_2\overset{\oplus}{\text{N}}(\text{CH}_3)_3\overset{\ominus}{\text{I}} + \text{NH}_2^{\ominus} \longrightarrow \text{Ph}\overset{\overset{\ominus}{\ddot{}}}{\text{C}}\text{DCH}_2\text{CH}_2\overset{\oplus}{\text{N}}(\text{CH}_3)_3\overset{\ominus}{\text{I}} + \text{NH}_2\text{D} \xrightarrow{\text{NH}_3} \text{PhCHDCH}_2\text{CH}_2\overset{\oplus}{\text{N}}(\text{CH}_3)_3\overset{\ominus}{\text{I}} \tag{135}$$

Table IV. Results of the Deuterium Exchange Test on 3,3-Dideutero-3-phenylpropyltrimethylammonium Iodide

Per Cent Reaction	Per Cent Excess Deuterium In Starting Material	$\frac{\text{Dideuterated}}{\text{Monodeuterated}}$ Quaternary Salt In Starting Material	Per Cent Excess Deuterium In Unreacted Quaternary Salt	$\frac{\text{Dideuterated}}{\text{Monodeuterated}}$ Quaternary Salt In Unreacted Material	Per Cent of Dideuterated Quaternary Salt Exchanged After 66 per cent Reaction
64.9	9.78 ± 0.03	95.6/4.4	9.23 ± 0.03	84.6/15.4	11.50
66.7	9.77 ± 0.04	95.4/4.6	9.29 ± 0.04	85.8/14.2	10.06

The monodeuterated quaternary salt can undergo either a β-elimination reaction or a γ-elimination reaction in which either the γ-deuterium or the γ-hydrogen can be abstracted by base, equation 136.



(136)

Product analysis and tracer studies have shown that a large hydrogen isotope effect is associated with the removal of the γ-proton. As a result, the exchanged quaternary salt, which has a γ-hydrogen which can be abstracted in the γ-elimination reaction, will be consumed much faster than the dideuterated quaternary salt and would not be expected to accumulate to a major extent during the reaction. The extent of isotopic exchange is, therefore, considerably greater than that indicated by the amount of monodeuterated quaternary salt in the unreacted material.

While the existence of a γ-carbanion is consistent with an Elcb γ-elimination reaction, the E2 mechanism cannot be ruled out solely because a γ-carbanion is formed. Breslow (75) has suggested that the carbanion may not be on the reaction coordinate and that an elimination reaction may be concerted even though hydrogen exchange is observed. Hine, on the other hand, has argued (55) that the existence of a carbanion is sufficient evidence for an Elcb mechanism in β-elimination reactions because the fully developed negative charge of a carbanion would be much more effective in displacing the leaving group than the partially developed negative charge that is formed in an E2 β-elimination reaction. While it is unlikely that carbanion formation is only a side reaction in β-elimination reactions, it is conceivable that γ-carbanion formation could be a side reaction accompanying a concerted γ-elimination reaction. If the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide were a stereospecific E2 process, the conformation required for elimination would be achieved only infrequently because of free rotation about the C_α-C_β and C_β-C_γ bonds. If the reacting orbitals were not in the proper orientation for elimination when the γ-proton is being abstracted by amide ion, a carbanion would be produced. This carbanion could abstract a proton from solvent giving the exchanged material rather than react in a γ-elimination reaction. If the carbanion reacts with solvent very much faster than it achieves the specific orientation required for the γ-elimination reaction, the γ-elimination reaction would not occur by way of an Elcb mechanism and essentially all of the elimination product would be formed by the concerted E2 process.

Kinetic Isotope Effects

As stated in the Historical Introduction, kinetic isotope effect measurements provide the best means for distinguishing between the Elcb and E2 mechanisms. Since both the hydrogen and leaving group isotope effects are required if any firm conclusions are to be reached, both the hydrogen and nitrogen kinetic isotope effects were determined for the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide.

Hydrogen Isotope Effect

It was noted during the product analysis and deuterium tracer studies that the deuterated quaternary ammonium salt reacts more slowly and gives much less γ-elimination product than the undeuterated quaternary salt. These observations indicate that there is a large primary hydrogen isotope effect associated with the abstraction of the γ-proton.

There were several problems associated with the determination of an accurate kinetic isotope effect by independent measurement of the rates of reaction of the deuterated and undeuterated quaternary salts. The major problem was that the amount of base was not known precisely. Kinetic control of the very fast reaction required that the base be present in a very low concentration with the result that traces of water, carbon dioxide or oxygen present either in the reaction system or in the ammonia could significantly alter this concentration. Also, without developing fairly elaborate techniques for rate measurements, it was not convenient to make more than a single kinetic measurement in an individual experiment. Consequently, the γ-hydrogen isotope effect was evaluated by the isotopic competative method (211).

A mixture of approximately equal amounts of deuterated and undeuterated quaternary ammonium salts was prepared and reacted in the usual manner. The reaction was stopped when, on the basis of crude rate measurements, it was estimated that approximately 85 per cent of the undeuterated compound would have reacted. The unreacted quaternary salts were recovered and purified. The overall extent of reaction (57.7 per cent) was determined from the amount of recovered unreacted quaternary ammonium salt. Both the starting mixture and the mixture of unreacted quaternary ammonium salts were analyzed for deuterium, Table V.

Table V. Per Cent Excess Deuterium in the Starting Mixture and in the Mixture of Unreacted Quaternary Salts

Per Cent Excess Deuterium In Starting Material	Per Cent Excess Deuterium In Unreacted Material
4.75 ± 0.01	8.48 ± 0.02

The hydrogen isotope effect for the disappearance of the undeuterated and dideuterated quaternary ammonium salts (k_H/k_D) can be calculated from the expression derived by Bigeleisen and Wolfsburg (211), equation 137.

$$k_H/k_D = 1.00 + \frac{\log\left(\dfrac{\text{salt}_{Ht}/\text{salt}_{Dt}}{\text{salt}_{Ho}/\text{salt}_{Do}}\right)}{\log(1-f)\left(\dfrac{1 + \text{salt}_{Ho}/\text{salt}_{Do}}{1 + \text{salt}_{Ht}/\text{salt}_{Dt}}\right)} \qquad (137)$$

where $\text{salt}_{Ht}/\text{salt}_{Dt}$ is the ratio of the undeuterated : dideuterated quaternary ammonium salt after time t, $\text{salt}_{Ho}/\text{salt}_{Do}$ is the ratio of the undeuterated : dideuterated quaternary ammonium salt in the starting mixture and f is the mole fraction that has reacted at time t.

The value of $\text{salt}_{Ho}/\text{salt}_{Do}$ can be calculated using equation 133,

$$\text{Per Cent Excess Deuterium} = \frac{\Sigma_i \, y_i \text{ (Number of Deuterium Atoms/Molecule)}_i}{\text{Total Number of Hydrogen \& Deuterium Atoms/Molecule}} \tag{133}$$

where y_i is the percentage of each component in the mixture. The starting mixture consists only of dideuterated and undeuterated quaternary salt and, therefore, equation 133 becomes

$$\text{Per Cent Excess Deuterium} = 2p/20$$

where p is the percentage of dideuterated quaternary salt in the starting mixture. Substituting 4.75 (Table V) for the per cent excess deuterium and solving for p gives p = 47.5 per cent, from which it follows that $\text{salt}_{Ho}/\text{salt}_{Do} = 52.5/47.5$.

It is not possible to determine the exact value of $\text{salt}_{Ht}/\text{salt}_{Dt}$. The deuterium exchange test demonstrated that when the dideuterated quaternary salt is reacted part way to completion the unreacted material contains an appreciable amount of monodeuterated quaternary salt. Since approximately twenty per cent of the dideuterated quaternary salt in the starting mixture of the hydrogen isotope effect experiment has reacted, the mixture of unreacted quaternary salt must also contain some monodeuterated material. Although the actual amount of monodeuterated material in the mixture of unreacted quaternary salts cannot be estimated, an upper and a lower limit can be placed on the amount of this salt in the mixture. The ratio of monodeuterated : dideuterated quaternary salt, which is zero in the starting mixture, will increase to some steady state value during the reaction. This ratio can be expected to be lower in the mixture of unreacted salts isolated from the hydrogen isotope effect experiment, where only approximately twenty per cent of the deuterated quaternary salt has reacted, than in the unreacted material from the exchange test, where 66 per cent of the deuterated material had disappeared. The deuterium exchange test showed that when 66 per cent of the deuterated compound had reacted 10.8 per cent of the unreacted material was 3-deutero-3-phenylpropyltrimethylammonium iodide. It follows that the maximum value for the ratio of monodeuterated : dideuterated quaternary salt in the unreacted material from the hydrogen isotope effect experiment will be 10.8/89.2. When this ratio of monodeuterated : dideuterated quaternary salt is used equation 133 becomes

$$8.48 = \frac{\frac{89.2}{100} \times q \times 2 + \frac{10.8}{100} \times q \times 1}{20}$$

where q is the percentage of deuterated quaternary salt in the unreacted mixture of quaternary salts from the hydrogen isotope effect experiment and 8.48 is the per cent excess deuterium found in the unreacted salt (Table V). It follows that

$$q = \frac{20 \times 8.48}{1.784 + 0.108} = 89.6 \text{ per cent}$$

The undeuterated quaternary salt represent (100.0-89.6) = 10.4 per cent of the unreacted mixture, while $\frac{89.2}{100} \times 89.6 = 79.9$ per cent of the unreacted mixture is dideuterated quaternary salt. The value of

${}^{\text{salt}}{}_{\text{Ht}}/\text{salt}_{\text{Dt}}$ is, therefore, $\frac{10.4}{79.9}$. Since some of the unreacted material is monodeuterated quaternary salt, the actual extent of reaction of the dideuterated and undeuterated quaternary salt is greater than the 57.7 per cent estimated from the total quaternary salt recovered from the reaction. In this particular case,

$$\left(\frac{100.0}{10.4 + 79.9}\right) \times 57.7\% = 63.9 \text{ per cent of the}$$

dideuterated and undeuterated quaternary salt has reacted and f is 0.639. Substituting this value of f along with ${}^{\text{salt}}{}_{\text{Ho}}/\text{salt}_{\text{Do}} = \frac{52.5}{47.5}$ and ${}^{\text{salt}}{}_{\text{Ht}}/\text{salt}_{\text{Dt}} = 10.4/79.9$ in equation 137 gives ${}^{k}{}_{H}/k_{D} = 6.4$ for the hydrogen isotope effect for the disappearance of the undeuterated and dideuterated quaternary ammonium salts. A lower limit for the ratio of monodeuterated : dideuterated quaternary salts in the unreacted mixture is zero (no monodeuterated quaternary salt in the unreacted mixture). Table VI gives the hydrogen isotope effects calculated for several values of monodeuterated : dideuterated quaternary salt.

Table VI shows that the hydrogen isotope effect for the disappearance of the undeuterated and dideuterated quaternary salts is between 7.5 (no monodeuterated quaternary salt in the unreacted mixture) and 6.4 (the monodeuterated : dideuterated ratio observed after 66 per cent reaction in the deuterium exchange test). Although it is impossible to place narrower limits on the value of the hydrogen isotope effect, the small extent of reaction of the deuterated compound (approximately twenty per cent) would suggest that the ratio of monodeuterated : dideuterated quaternary salts would not be as large as was found after 66 per cent reaction and, therefore, that the

Table VI. Hydrogen Isotope Effect in the Disappearance of the Undeuterated and Dideuterated Quaternary Ammonium Salts for Several Ratios of Monodeuterated : Dideuterated Quaternary Salts in the Unreacted Material.

$\frac{\text{Monodeuterated}}{\text{Dideuterated}}$ in Mixture of Unreacted Quaternary Salts	$\text{salt}_{Ht}/\text{salt}_{Dt}$	f	k_H/k_D
0/100	15.2/84.8	0.577	7.5
3/97	13.9/83.5	0.592	7.2
4/96	13.5/83.0	0.598	7.0
5/95	13.0/82.6	0.604	6.9
6/94	12.6/82.2	0.609	6.8
9/91	11.2/80.8	0.627	6.6
9.8/90.2	10.8/80.5	0.632	6.5
10.8/89.2	10.4/79.9	0.639	6.4

hydrogen isotope effect would be greater than 6.4. Since some monodeuterated material must be present in the unreacted mixture, the hydrogen isotope effect must be less than 7.5. This places an upper and lower limit on the value of the isotope effect for the disappearance of the undeuterated and dideuterated quaternary salts. In subsequent calculations, a value of 7.0 will be used for this isotope effect, although it must be kept in mind that this is subject to an uncertainty within the limits stated.

Both the dideuterated and undeuterated quaternary ammonium salts are being consumed in a β- as well as in a γ-elimination reaction. In addition, the dideuterated quaternary salt is consumed in an exchange reaction. As a result, the hydrogen isotope effect for the disappearance of the undeuterated and dideuterated quaternary salts ($^{k_H}/k_D = 7$) depends on several rate constants, and is not the isotope effect for any particular reaction. The significance of this hydrogen isotope effect will be discussed later in this section of the thesis.

The isotope effect obtained by the competative method expresses the relative rates of disappearance of the undeuterated and dideuterated quaternary salts. Of even greater interest is the isotope effect associated with the γ-elimination reaction. A lower limit of this isotope effect is provided by comparing the relative amounts of γ- and β-elimination products from the reactions of the dideuterated and undeuterated quaternary salts, Table II, page 84.

Since both the β- and γ-elimination reactions are bimolecular processes involving the quaternary salt and amide ion, the product ratios are identical to the ratios of the rate constants for the two reactions. Ninety-six per cent of the reaction of the undeuterated quaternary salt is γ-elimination while four per cent is β-elimination, Table II. It follows that $^{k_{\gamma H}}/k_{\beta H} = {}^{96}/4 = 24$, where $k_{\gamma H}$ and $k_{\beta H}$ are the rate constants for the γ- and β-elimination reactions, respectively. For the dideuterated quaternary salt, 53 per cent of the product is phenylcyclopropane and 47 per cent is phenylpropenes. If there were no exchange at the γ-position giving monodeuterated quaternary salt then $^{k_{\gamma D}}/k_{\beta D} = {}^{53}/47 = 1.1$, where $k_{\gamma D}$ is the rate constant for the direct formation of phenylcyclopropane from the dideuterated quaternary salt and $k_{\beta D}$ is the rate constant for the corresponding β-elimination reaction. Since $k_{\beta D} = k_{\beta H}$ to a close approximation, it follows that

$$\frac{^{k_{\gamma H}}/_{k_{\beta H}}}{^{k_{\gamma D}}/_{k_{\beta D}}} = {}^{k_{\gamma H}}/k_{\gamma D} = \frac{24}{1.1} = 22 \qquad (138)$$

This value of $^{k_{\gamma H}}/_{k_{\gamma D}} = 22$ is, however, the lower limit of the hydrogen isotope effect for the γ-elimination reaction. The observation of hydrogen exchange at the γ-position establishes that a significant amount of the dideuterated quaternary salt is converted to the monodeuterated quaternary salt which subsequently reacts with amide ion to form the elimination products. This means that the product ratio of 1.13 is actually a composite of the ratio of γ-elimination : β-elimination for the dideuterated and monodeuterated quaternary salts. Since the monodeuterated quaternary salt, by virtue of the large hydrogen isotope effect associated with the abstraction of the γ-proton, will undergo a γ-elimination reaction much faster than the dideuterated quaternary salt, its ratio for γ-elimination : β-elimination will be considerably larger than the same ratio for the dideuterated quaternary salt. The composite ratio of γ-elimination : β-elimination, therefore, must also be larger than the ratio for the elimination products formed directly from the dideuterated quaternary salt. Consequently, the isotope effect of 22, obtained by substituting the product ratios in equation 138, is a minimum value for the isotope effect for the γ-elimination reaction. This is a large isotope effect, even when taking into account the low temperature of -55° at which these reactions were carried out, and it suggests the possibility of tunnelling. This will be discussed in more detail later in this section.

Nitrogen Isotope Effect

The importance of the leaving group isotope effect in distinguishing between an Elcb and an E2 process was demonstrated by the studies that were reported in the Historical Introduction. Since the hydrogen isotope effect has shown that the C_γ-H bond is breaking in a rate-determining step, it was important to determine if the C_α-N bond is breaking in a fast or a slow step.

Several samples of 3-phenylpropyltrimethylammonium iodide were reacted with potassium amide at -55° to extents of reaction varying from 53 to 94 per cent of completion. The unreacted quaternary salts from each reaction were recovered from the reaction mixture, purified and decomposed to ammonium sulfate by the Kjeldahl technique. The ammonium salts were subsequently oxidized to nitrogen by treatment with sodium hypobromite. The (N^{14}/N^{15}) mass ratio of the nitrogen from these samples was determined on a mass spectrometer capable of measuring the isotopic ratios with a precision of ±0.02 per cent. The same experimental procedures were used to convert several samples of the starting material to nitrogen for isotopic analysis.

The nitrogen isotope effect was calculated using equation 139 (211).

$$k^{14}/k^{15} = 1.00 + \frac{\log(R_f/R_o)}{\log(1 - f)\left(\frac{1 + R_o}{1 + R_f}\right)} \tag{139}$$

where R_f is the (N^{14}/N^{15}) mass ratio of the nitrogen from the unreacted quaternary salt, R_o is the (N^{14}/N^{15}) mass ratio of the nitrogen from the starting material and f is the mole fraction of the quaternary salt that has reacted. The latter was estimated from the amount of unreacted quaternary ammonium salt that was recovered from the reaction mixture.

The values of the nitrogen isotope effect calculated for the various extents of reaction are shown in Table VII. The average value of the nitrogen isotope effect for the reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide in liquid ammonia at -55° is 2.20 ± 0.092 per cent. The error limits are given as the standard deviation.

While these results show that there is a primary nitrogen isotope effect in the γ-elimination reaction, the significance of the actual value of the observed isotope effect is not immediately

Table VII. Nitrogen Kinetic Isotope Effect for the Reaction of 3-Phenylpropyltrimethylammonium Iodide with Potassium Amide in Liquid Ammonia at -55°

Experiment Number	Extent of Reaction	Nitrogen Isotope Effect $({}^{k_{14}}/_{k_{15}} - 1)100\%$
1	53	2.13
2	70	2.15
3	80	2.32
4	82	2.08
5	84	2.21
6	94	2.32
	Mean	2.20 ± 0.092[a]

[a] the error limits are given as the standard deviation.

apparent. An insight into the amount of C_α-N bond rupture in the transition state can be obtained by comparing this nitrogen isotope effect with the nitrogen isotope effects of β-elimination reactions of quaternary ammonium salts. The β-elimination reactions of quaternary ammonium salts have been studied extensively in these laboratories and the relative degree of C-N bond rupture in the transition states of these reactions is known. Several of the nitrogen isotope effects found for β-elimination reactions at 60° are given in Table VIII.

The magnitude of the nitrogen isotope effect for the reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide must be estimated at 60° in order that a comparison with the nitrogen isotope effects for the β-elimination reactions in Table VIII can be made. The nitrogen isotope effect for the γ-elimination reaction can be estimated in two ways. First, it can be assumed that the temperature dependence of the nitrogen isotope effect of the γ-elimination reaction is similar to that observed in the β-elimination reactions of quaternary ammonium salts. The best data for the latter were obtained in a recent study of the nitrogen isotope effect in the _trans_-β-elimination reaction of _cis_-2-phenylcyclopentyltrimethylammonium iodide with ethoxide ion in ethanol (213) and are shown in Table IX.

Table VIII. Nitrogen Isotope Effects for Some E2 β-Elimination Reactions of Quaternary Ammonium Salts at 60°

Quaternary Ammonium Salt	Base/Solvent	Temperature	$(k^{14}/k^{15} - 1)100$	Reference
Ethyltrimethylammonium	$C_2H_5\overset{\ominus}{O}/C_2H_5OH$	60°	1.86	212
Ethyltrimethylammonium	*t*-Bu$\overset{\ominus}{O}$/*t*-BuOH	60°	1.41	212
2-Phenylethyltrimethylammonium	$C_2H_5\overset{\ominus}{O}/C_2H_5OH$	60°	0.99	213
cis-2-Phenylcyclohexyltrimethylammonium	$C_2H_5\overset{\ominus}{O}/C_2H_5OH$	60°	1.23	81
cis-2-Phenylcyclopentyltrimethylammonium	$C_2H_5\overset{\ominus}{O}/C_2H_5OH$	60°	1.08	213

Table IX. The Influence of Temperature on the Nitrogen Isotope Effect for the Trans-β-Elimination Reaction of Cis-2-Phenylcyclopentyltrimethylammonium Iodide

Temperature °C	$(^{k^{14}}/_{k^{15}} - 1)$ 100%
60	1.08
45	1.17
30	1.26

These results show that the nitrogen isotope effect decreases by 0.09 when the temperature is increased by fifteen degrees. Assuming that this temperature dependence remains constant over the region from -55° to 60°, the 2.20 per cent nitrogen isotope effect at -55° would be equivalent to an isotope effect of approximately 1.5 per cent at 60°.

The nitrogen isotope effect at 60° can also be estimated by assuming that the isotope effect at -55° and 60° will be the same percentage of the theoretical maximum isotope effect for the rupture of a $C-N^{\oplus}$ bond at these temperatures. An estimate of the maximum isotope effect at any temperature can be obtained from equation 140 (214), which is derived by assuming that the difference between the zero point energies of the stretching vibrations of the isotopically substituted bonds disappears in going from the initial state to the transition state.

$$^{k^{14}}/_{k^{15}} = {}^{s^{14}s^{\ddagger 15}}/_{s^{15}s^{\ddagger 14}}\, e^{[^{hc}/_{2kT}\,(\bar{\nu}_{14} - \bar{\nu}_{15})]} \qquad (140)$$

where h is Planck's constant, c is the velocity of light, k is the Boltzmann constant, T is the absolute temperature, $\bar{\nu}_{14}$ and $\bar{\nu}_{15}$ are the stretching frequencies of the $C-N_{14}^{\oplus}$ and $C-N_{15}^{\oplus}$ bonds, respectively, and the S terms are symmetry numbers for the initial state and transition state. A $C-N_{15}^{\oplus}$ stretching frequency of 940.2 cm^{-1} was calculated from the $C-N_{14}^{\oplus}$ stretching frequency of 955 cm^{-1} (215) and the reduced masses of the atoms in the reacting bonds. The maximum nitrogen isotope effect was found to be 5.00 per cent at -55° and 3.25 per cent at 60°. On the assumption that the isotope effects at -55° and 60° will be the same percentage of the maximum isotope effect at these temperatures the 2.20 per cent isotope effect at -55° would be equivalent to an isotope effect of y, where

$$\frac{y}{3.25\%} = \frac{2.20\%}{5.00\%}$$

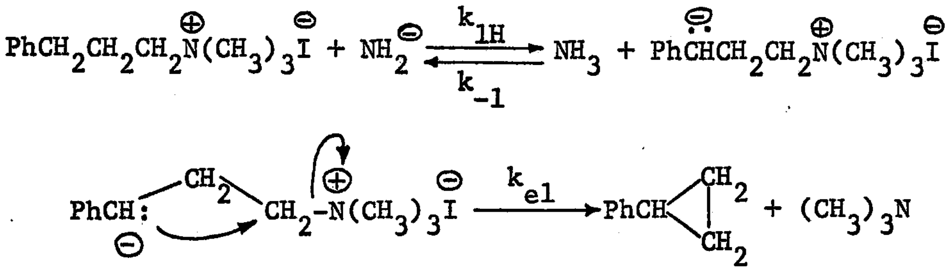
$$\text{or } y = \frac{2.20 \times 3.25\%}{5.00} = 1.43 \text{ per cent at } 60°$$

Since these two methods of estimating the isotope effect are in good agreement, it seems probable that the nitrogen isotope effect of 2.20 per cent at -55° would be approximately 1.4-1.5 per cent at 60°. This nitrogen isotope effect for the reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide is larger than the nitrogen isotope effects found for most concerted β-elimination reactions at the same temperature (see Table VIII). Only the isotope effect for the β-elimination reaction of ethyltrimethylammonium iodide with ethoxide ion in ethanol is larger.

The γ-elimination reaction is accompanied by a β-elimination reaction and, therefore, the observed isotope effect of 2.20 per cent at ~-55° (1.4-1.5 per cent at 60°) is actually a composite of the isotope effects for the two processes. No correction is needed, however, to translate the observed isotope effect into the nitrogen isotope effect for the γ-elimination reaction since the β-elimination reaction, which accounts for only four per cent of the reaction, would have a nitrogen isotope effect which would be very close to that observed for the overall process (see Table VIII).

The 2.20 per cent nitrogen isotope effect indicates that there is a considerable decrease in the composite force constant of the C_α-N bond in the transition state of a rate-determining step of the γ-elimination reaction.

The observation of large primary hydrogen and nitrogen isotope effects for the γ-elimination reaction is, of course, consistent with the concerted mechanism in which both the C_γ-H and C_α-N bonds are breaking in the transition state. These results also can be accommodated by the Elcb mechanism, equation 124, provided that certain restrictions are placed upon the relative rates with which the intermediate is converted to phenylcyclopropane or reverts to reactant by abstracting a proton from the solvent.

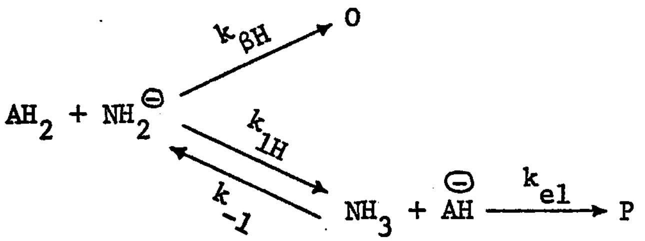


$$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I} + NH_2^{\ominus} \underset{k_{-1}}{\overset{k_{1H}}{\rightleftarrows}} NH_3 + Ph\overset{\ominus}{C}HCH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$$

$$Ph\overset{\ominus}{C}H\!:\,CH_2CH_2\text{-}\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I} \xrightarrow{k_{el}} PhCH\langle(CH_2)_2 + (CH_3)_3N \qquad (124)$$

If $k_{el} >> k_{-1}$ virtually every carbanion formed is converted to product. Carbanion formation, therefore, is rate-determining and the C_α-N bond is breaking in a fast step. This is, of course, inconsistent with the observed primary nitrogen isotope effect and must be discarded. On the other hand, if $k_{el} << k_{-1}$ the carbanion is formed in what is essentially a pre-equilibrium step. The C_α-N bond rupture process is rate-determining and a nitrogen isotope effect will result. This realtionship of k_{el} and k_{-1}, however, makes it difficult to account for the large hydrogen isotope effect observed in the competative experiment. The following kinetic derivations demonstrate this point.

Consider first the reaction of the undeuterated quaternary salt (AH_2) which gives phenylpropenes (O) and phenylcyclopropane (P). The latter is formed from the intermediate γ-carbanion ($\overset{\ominus}{AH}$).



Applying the steady state approximation to $[\overset{\ominus}{AH}]$, it follows that

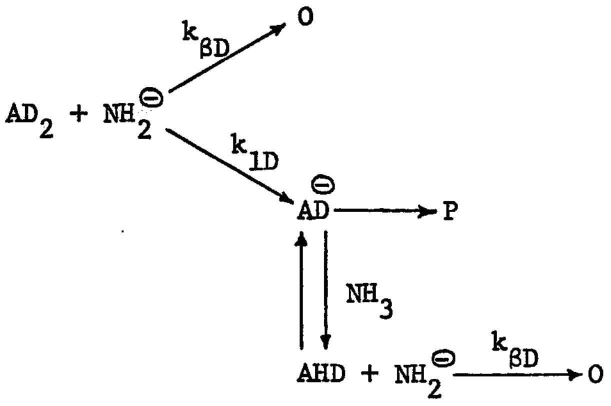
$$\frac{-d[AH_2]}{dt} = (k_{\beta H} + \frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}})\ [AH_2][NH_2^{\ominus}]$$

$$\text{Also} \qquad \frac{-d[AH_2]}{dt} = k_H[AH_2][NH_2^{\ominus}]$$

where k_H is the overall rate constant for the disappearance of the undeuterated quaternary salt. It follows that

$$k_H = k_{\beta H} + \frac{k_{el}\, k_{1H}}{k_{el} + k_{-1}}$$

Similarly for the reaction of the dideuterated quaternary salt (AD_2),



where $\overset{\ominus}{AD}$ is the γ-carbanion and AHD is the monodeuterated quaternary salt. It can be seen that

$$\frac{-d[AD_2]}{dt} = (k_{\beta D} + k_{1D})[AD_2][NH_2^{\ominus}]$$

Since only a very small secondary isotope effect will be associated with the β-elimination reaction, it can be assumed that $k_{\beta D} = k_{\beta H}$, hence

$$k_D = k_{\beta H} + k_{1D}$$

where k_D is the overall rate constant for the disappearance of the dideuterated quaternary salt. The isotope effect found in the competative experiment ($^{k_H}/k_D$) can be expressed in terms of the contributing rate constants as follows

$$^{k_H}/_{k_D} = \frac{k_{\beta H} + \frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}}}{k_{\beta H} + k_{1D}} \qquad (141)$$

It can be readily shown that the ratio of β-elimination : γ-elimination ($\frac{[O]}{[P]}$) from the undeuterated quaternary salt is given by

$$\frac{[O]}{[P]} = \frac{k_{\beta H}}{\frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}}}$$

which on rearranging gives

$$k_{\beta H} = \frac{[O]}{[P]} \left(\frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}}\right)$$

Substituting for $k_{\beta H}$ in equation 141 gives

$$^{k_H}/_{k_D} = \frac{\left(\frac{[O]}{[P]} + 1\right)\left(\frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}}\right)}{\frac{[O]}{[P]}\left(\frac{k_{el}\ k_{1H}}{k_{el} + k_{-1}}\right) + k_{1D}} \qquad (142)$$

The value of $^{k_H}/_{k_D}$ found in the competative experiment is approximately seven. The product analysis of the reaction of the undeuterated quaternary salt with potassium amide gave an $\frac{[O]}{[P]}$ ratio of $\frac{4}{96}$, Table II. Introducing these quantities into equation 142 and rearranging gives

$$^{k_{1H}}/_{k_{1D}} = 9.3\ (^{k_{-1}}/_{k_{el}} + 1) \qquad (143)$$

It is apparent that large values of $^{k_{-1}}/_{k_{el}}$ will give rise to an unrealistically large hydrogen isotope effect for the abstraction of the γ-proton. Even if the ratio of $^{k_{-1}}/_{k_{el}}$ were only as large as fifteen the hydrogen isotope effect for γ-proton abstraction would be 150. An isotope effect of this magnitude seems very unlikely even if tunnelling, which is a very real possibility at the low temperature used in this study, were important in the γ-proton abstraction. It, therefore, can be concluded that the γ-elimination reaction does not proceed by an Elcb mechanism in which $k_{-1} >> k_{el}$.

Although the Elcb mechanism with $k_{el} >> k_{-1}$ has been ruled out on the basis of the large nitrogen isotope effect and an Elcb mechanism with ${}^{k_{-1}}/k_{el} > 15$ has been ruled out because of the unrealistically large hydrogen isotope effect that would be required, an Elcb mechanism in which k_{-1} and k_{el} are of comparable magnitudes is compatible with the results obtained. Both a normal hydrogen and a normal nitrogen isotope effect would be observed because the reactions involving the rupture of the C_{γ}-H and C_{α}-N bonds would each be partially rate determining. Only two mechanisms then, a concerted and an Elcb in which k_{-1} and k_{el} are of comparable magnitudes, are consistent with the existence of both a large hydrogen and a large nitrogen isotope effect.

Studies in Ammonia-$\underline{d}_3$

While the tracer and isotope effect studies have demonstrated that several of the mechanisms that have been suggested for the γ-elimination reaction can be ruled out, the results of these experiments do not distinguish between a concerted mechanism accompanied by an irrelevant hydrogen exchange at the γ-position and an Elcb mechanism in which $k_{-1} \approx k_{el}$. The reaction of both the undeuterated and deuterated quaternary salts was carried out in liquid ammonia-$\underline{d}_3$ in an effort to distinguish between these two mechanistic possibilities.

The deuterium exchange test demonstrated that a γ-carbanion was formed during the reaction of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide with potassium amide in liquid ammonia. Only a small amount of exchanged material was found in this experiment even though it was probable that a large portion of the γ-carbanions abstracted a proton from ammonia. This was because the γ-elimination reaction of the exchanged quaternary salt was much faster than that of the dideuterated quaternary salt. It was reasoned that if this exchange test was carried out by reacting the undeuterated quaternary salt in deuterated solvent, the monodeuterated salt formed when the γ-carbanion abstracted a deuterium from ammonia-$\underline{d}_3$ would react more slowly than the undeuterated quaternary salt and would tend to accumulate during the reaction. This experiment, therefore, was expected to give a much better estimate of the amount of exchange that occurs during the γ-elimination reaction.

Since the amount of exchange was expected to be quite large, the undeuterated quaternary salt was reacted only eleven per cent to completion in ammonia-$\underline{d}_3$. The unreacted quaternary salt was recovered, purified, and examined by infra-red and N.M.R. spectroscopy. None of the absorptions associated with the presence of deuterium at the γ-position (2180 cm^{-1}, 2110 cm^{-1} and 983 cm^{-1}) could be detected in the infra-red spectrum of the unreacted quaternary salt, figure 5. In addition, the intensity of the strong C_{γ}-H absorption at 770 cm^{-1} was identical to that of the infra-red spectrum of the starting material and it was concluded that very little exchange had occurred at the γ-position during the reaction.

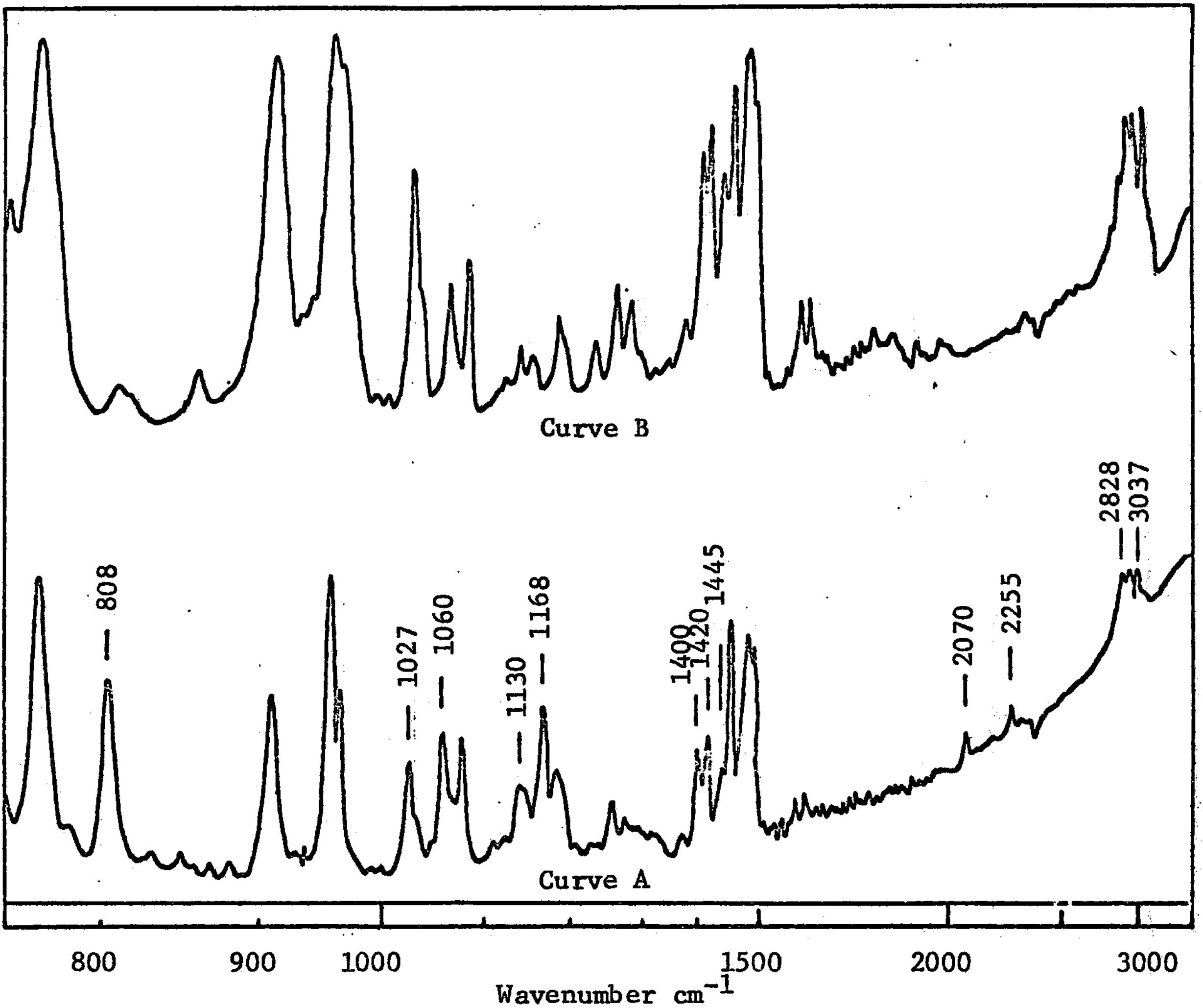


Fig. 5. The infra-red spectrums of 3-phenylpropyltrimethylammonium iodide (Curve B), and the unreacted quaternary salt from the reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide-$\underline{d}_2$ in ammonia-$\underline{d}_3$ (Curve A).

Although there were no changes in the spectrum of the unreacted quaternary salt that could be attributed to the substitution of deuterium at the γ-position, the spectrum of the unreacted quaternary salt was quite different from that of the starting material, figure 5.

Young et al. (215) have reported the infra-red absorption frequencies of the C-H bonds of tetramethylammonium ions, Table X. All the absorptions associated with the N-methyl C-H bonds were identified in the infra-red spectrum of 3-phenylpropyltrimethylammonium iodide, although those at 1289 cm^{-1} and 1173 cm^{-1} were very weak. The infra-red absorptions associated with these bonds were much less intense in the spectrum of the unreacted quaternary salt recovered from the exchange experiment in ammonia-$\underline{d}_3$ than in the spectrum of the undeuterated salt. The intensity of two other absorptions in the starting material (1400 cm^{-1} and 1027 cm^{-1}) were also lower in the spectrum of the unreacted quaternary salt. These absorptions, which are present in the spectrum of ethyltrimethylammonium bromide*, were attributed to the C_α-H bonds. The infra-red spectrum of the unreacted salt had some absorptions that were not present in the spectrum of the starting material, Table X. These new absorptions result because substituting a deuterium for a hydrogen reduces the absorption frequency by $\sqrt{2} = 1.41$. If the bond in which this substitution is made is vibrationally coupled with other bonds the reduction in the

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* The spectrum of this compound was recorded in a potassium bromide disc.

Table X. Infra-red Absorption Frequencies that have a Different Intensity in the Unreacted Quaternary Salt from the Reaction of 3-Phenylpropyltrimethylammonium Iodide in Ammonia-$\underline{d}_3$ than in the Starting Material

Reported Absorption Frequencies of the C-H bonds in Tetramethylammonium Ions in Cm^{-1}	Absorptions whose Intensity was Lower in the Unreacted Quaternary Salt than in the Starting Material in Cm^{-1}	Absorptions in Unreacted Quaternary Salt not Present in the Starting Material in Cm^{-1}	$\frac{\text{C-H absorption frequency}}{\text{C-D absorption frequency}}$
3037	3037	2255	1.34
2930	2930	-	-
2828	2828	2070	1.37
1455	1445	1168-1130	1.24-1.25
1418	1420	1168-1130	1.24-1.25
-	1400	1168-1130	1.24-1.25
1289	-	-	-
1173	-	-	-
-	1027	808	1.27

absorption frequency is less than $\sqrt{2}$ (205). The ratios of the related C-H and C-D absorption frequencies are also given in Table X. The absorptions at 2255 cm^{-1} and 2070 cm^{-1} are the C-D non-symmetrical and symmetrical stretching frequencies corresponding to the C-H absorptions at 3037 cm^{-1} and 2828 cm^{-1}, respectively. The broad peaks in the region between 1130 cm^{-1} and 1165 cm^{-1} are attributed to the non-symmetrical and symmetrical deformation frequencies. The corresponding C-H frequencies are at 1400, 1420 and 1445 cm^{-1}. Although the absorptions at 808 cm^{-1} and 1027 cm^{-1} could not be identified, the absorption at 808 cm^{-1} appears to be the deuterated analogue of the absorption at 1027 cm^{-1}. The decreased intensity of the absorptions caused by the N-methyl C-H and the C_α-H bonds, as well as the new absorptions caused by the N-methyl C-D bonds indicate that considerable exchange has occurred at these positions during the reaction.

The conclusions drawn from the examination of the infra-red spectra were confirmed by N.M.R. spectroscopy. Integration of the 100 Mc. spectrum of the unreacted quaternary salt showed that fifty per cent of the N-methyl hydrogens and 35 per cent of the α-hydrogens had been exchanged for deuterium from the solvent. No deuterium was observed at either the β- or the γ-position, Table XI.

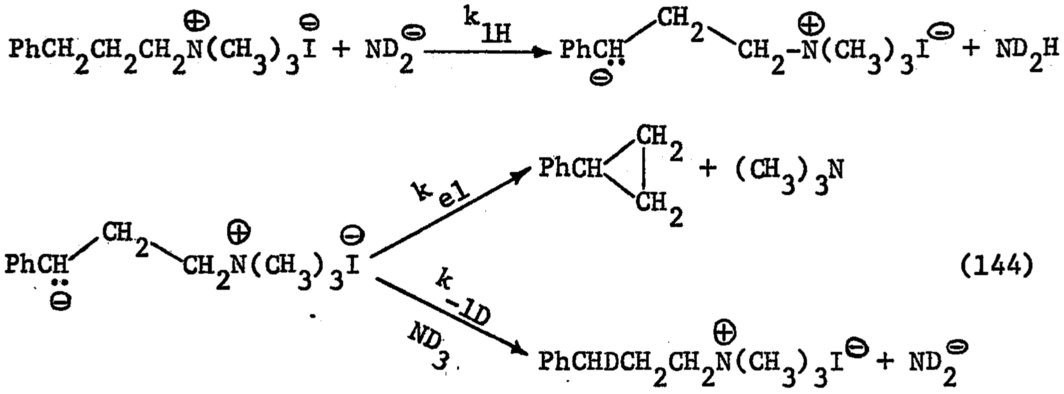
The large amount of exchange of the N-methyl and α-hydrogens was not surprising because the protons at these positions are the most acidic protons in the molecule. The N-methyl protons would be expected to undergo exchange faster than the α-protons because they are less sterically hindered to attack by base and because the electron-releasing alkyl substituent on the α-carbon would lower the acidity of

Table XI. The Percentage of α-, β-, γ- and N-Methyl Protons that have Exchanged when 3-Phenylpropyltrimethylammonium Iodide is Reacted Eleven Per Cent to Completion with Potassium Amide-$\underline{d}_2$ in Ammonia-$\underline{d}_3$

Position of the Protons	Number of Protons In the Starting Material	Number of Protons in the Unreacted Quaternary Salt	Per Cent Exchange
α	2.0	1.3	35
β	2.0	2.0	0
γ	2.0	2.1	0
N-methyl	9.0	4.5	50

the α-protons.

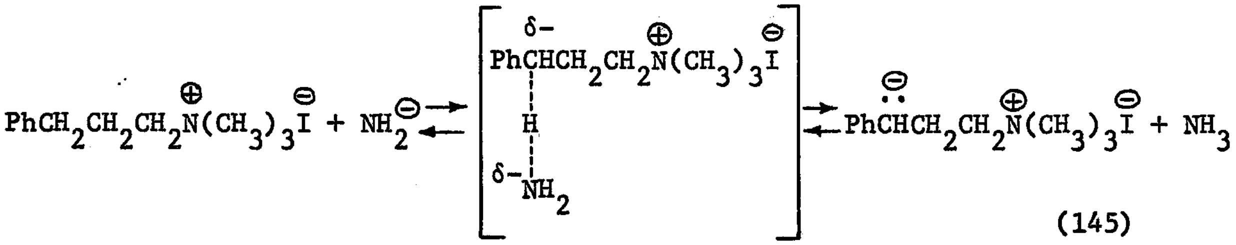
The failure to detect any deuterium at the γ-position in the unreacted material indicates that very few of the γ-carbanions formed in this reaction abstract a deuterium from ammonia-$\underline{d}_3$ and produce 3-deutero-3-phenylpropyltrimethylammonium iodide, equation 144.



(144)

Since the deuterium exchange test demonstrated that a large portion of the γ-carbanions formed in undeuterated solvent abstract a hydrogen from ammonia and revert to quaternary salt, it must be concluded that the γ-carbanion abstracts a deuterium from ammonia-$\underline{d}_3$ much more slowly than it abstracts a hydrogen from ammonia and that there is a large primary hydrogen isotope effect associated with the abstraction of a proton from the solvent. This primary hydrogen isotope effect, of course, is to be expected because the N-H bond rupture must be occurring in the transition state of this one-step, proton-transfer reaction.

Although it is impossible to determine the magnitude of the isotope effect associated with the abstraction of a proton from solvent, it would appear that it should be larger than the isotope effect associated with the abstraction of the γ-proton. A consequence of the principle of microscopic reversibility (216) is that the transition state for carbanion formation and for proton abstraction from solvent will be the same, equation 145.



$$\mathrm{PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}} + \mathrm{NH_2^{\ominus}} \rightleftarrows \left[\begin{array}{l} \overset{\delta-}{\mathrm{Ph}}\mathrm{CHCH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}} \\ \quad\vdots \\ \quad\mathrm{H} \\ \quad\vdots \\ \delta-\mathrm{NH_2} \end{array}\right] \rightleftarrows \mathrm{Ph\overset{\ominus}{\ddot{C}}HCH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}} + \mathrm{NH_3}$$

(145)

Since the transition state for these two reactions is the same, the magnitude of the hydrogen isotope effects for these processes will depend, to a first approximation, on the difference in the zero point energies of the X-H and X-D bonds, where X is either carbon or nitrogen. Calculations using equation 140,

$$^{k_H}/_{k_D} = {}^{s^Hs^{\ddagger D}}/_{s^Ds^{\ddagger H}} \; e^{[^{hc}/_{2kT}(\bar{\nu}_H - \bar{\nu}_D)]} \tag{140}$$

where $\bar{\nu}_H$ and $\bar{\nu}_D$ are the stretching frequencies of the X-H and X-D bonds, respectively, show that the maximum theoretical hydrogen isotope effects at -55° for the rupture of the C_γ-H bond (carbanion formation) and the rupture of the N-H bond (abstraction of a proton from solvent) are approximately 16.9 and 31.6, respectively. The absorption frequencies used in these calculations are respectively 2926 cm^{-1} (217) and 2160 cm^{-1}* for the C_γ-H and C_γ-D bonds of the

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* The absorption frequency of the C_γ-D bond was obtained from the infra-red spectrum of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide in a potassium bromide disc.

quaternary salt and 3577 cm^{-1} and 2652 cm^{-1} for the N-H and N-D bonds in ammonia (218).

Although these calculations are far from rigorous since they neglect secondary isotope effects associated with the proton transfer from ammonia and ammonia-$\underline{d}_3$, it would appear that the isotope effect for proton abstraction from solvent would be considerably larger than for the formation of the γ-carbanion.

The decrease in the amount of exchange at the γ-position when the solvent is changed from ammonia to ammonia-$\underline{d}_3$ is understandable provided that the γ-elimination reaction is an Elcb process with $k_{-1} \approx k_{el}$. The large primary hydrogen isotope effect associated with the abstraction of a proton from solvent means that the abstraction of a deuterium from ammonia-$\underline{d}_3$ will be much slower than ring closure and elimination of trimethylamine ($k_{-1D} << k_{el}$ in equation 144, page 127). As a result, essentially all the γ-carbanions formed during the reaction will be converted to phenylcyclopropane rather than abstracting a deuterium from ammonia-$\underline{d}_3$ to give 3-deutero-3-phenylpropyltrimethylammonium iodide, and the amount of deuterium incorporated at the γ-position would be small. When the exchange test is performed with deuterated quaternary salt in undeuterated solvent, the abstraction of the proton from solvent and ring closure and elimination of trimethylamine occur at comparable rates ($k_{-1} \approx k_{el}$) and a significant portion of the γ-carbanions formed during the reaction will be converted to 3-deutero-3-phenylpropyltrimethylammonium iodide.

While the results of the exchange experiments are compatible with an Elcb mechanism, they cannot be accommodated by a concerted γ-elimination reaction accompanied by an irrelevant exchange process. If the γ-carbanion only reacts with solvent and does not react to produce phenylcyclopropane, a deuterium must be abstracted from ammonia-$\underline{d}_3$ in spite of the large hydrogen isotope effect associated with this reaction. As a result, the amount of exchange at the γ-position should be essentially the same whether the reaction is performed in ammonia or ammonia-$\underline{d}_3$. Since a large amount of exchange occurred at the γ-position in undeuterated solvent, the failure to detect exchange at the γ-position when the undeuterated quaternary salt was reacted in deuterated solvent strongly indicates that the γ-elimination reaction is not a concerted process accompanied by an irrelevant exchange reaction. It must be pointed out, however, that the extent of reaction in the exchange test in ammonia-$\underline{d}_3$ was only eleven per cent compared to 66 per cent in ammonia and it is, therefore, impossible to completely rule out the concerted mechanism on the basis of the results of this deuterium exchange test alone.

The ratio of γ-elimination : β-elimination, which can be measured by analyzing the hydrocarbon products, was determined for the reactions of both the undeuterated and deuterated quaternary salts with potassium amide-$\underline{d}_2$ in liquid ammonia-$\underline{d}_3$ at -55° in an effort to confirm the conclusion based on the results of the deuterium exchange tests.

When the undeuterated quaternary salt was reacted eleven per cent to completion in the deuterium exchange experiment in ammonia-$\underline{d}_3$, the reaction mixture was colourless rather than the reddish-brown colour observed with the other reactions reported in this thesis. Since amide ion readily converts 3-phenylpropene, the product of the β-elimination reaction, to the reddish-brown allyl carbanion, the lack of colour in the reaction mixture indicates that very little 3-phenylpropene was formed during the reaction. A gas chromatographic analysis of the hydrocarbon product from this reaction also failed to detect any 3-phenylpropene and it was concluded that 3-phenylpropene represented less than 0.5 per cent of the product.

The amount of hydrocarbon from this reaction was too small to enable the analysis for trans-β-methyl styrene to be performed in the usual manner (ultra-violet spectroscopy). The hydrocarbon product, however, was examined by gas chromatography using a 25 foot column of five per cent Zonyl E-7 on chromosorb P, which is capable of separating very small quantities of phenylcyclopropane and trans-β-methyl styrene. No trans-β-methyl styrene could be detected and, therefore, this olefin must also represent less than 0.5 per cent of the product. As expected, there was no trace of cis-β-methyl styrene in the product.

The virtual absence of β-elimination products was confirmed by showing that a very definite colour results from the action of amide ion in liquid ammonia on a sample of phenylcyclopropane containing the amount of 3-phenylpropene that would have been present in the reaction mixture if 0.4 per cent of the hydrocarbon product had formed in a β-elimination reaction. Since the colour associated with the allyl carbanion could not be detected when the undeuterated quaternary salt was reacted in deuterated solvent, it was concluded that less than 0.4 per cent of the product was formed in a β-elimination reaction. The ratio of γ-elimination : β-elimination must, therefore, be greater than 250 : 1.

The hydrocarbon product from the reaction of the deuterated quaternary salt in deuterated solvent was recovered and analyzed in the usual manner. Neither 3-phenylpropene nor cis-β-methyl styrene could be detected in the product from this reaction and it was concluded that these compounds accounted for less than 0.5 per cent of the products. The amount of trans-β-methyl styrene in the product was found to be 2.3 per cent. Since control experiments showed that the styrene does not polymerize during either the reaction or the recovery and analysis, it was concluded that the ratio of γ-elimination : β-elimination for the reaction of the deuterated quaternary salt in ammonia-$\underline{d}_3$ was approximately 97.7 : 2.3 or 43 : 1.

This reaction was carried out for a considerably longer time than the other reactions in this study in order to ensure that the reaction had gone to completion. The 3-phenylpropene formed in the β-elimination reaction would, therefore, be converted to an equilibrium mixture of 3-phenylpropene and cis- and trans-β-methyl styrene before the reaction was stopped. Since only 2.3 per cent of the product is formed in a β-elimination reaction, the amount of 3-phenylpropene and and cis-β-methyl styrene at equilibrium would be below the level of detection (approximately 0.5 per cent).

The product ratios found in the experiments in deuterated solvent, as well as the product ratios obtained from the reactions of the deuterated and undeuterated quaternary salts in undeuterated solvent, are given in Table XII.

Table XII. Ratio of γ-Elimination : β-Elimination for the Reactions of the Deuterated and Undeuterated Quaternary Salts in Ammonia and Ammonia-$\underline{d}_3$

Quaternary Salt	Base and Solvent	Per Cent γ-Elimination / Per Cent β-Elimination	γ-Elimination / β-Elimination
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$	KNH_2 in NH_3	96 : 4	24 : 1
$PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$	KNH_2 in NH_3	53 : 47	1.1 : 1
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$	KND_2 in ND_3	>99.6 : 0.4	>250 : 1
$PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$	KND_2 in ND_3	97.7 : 2.3	43 : 1

The ratio of γ-elimination : β-elimination found in these different reactions will now be examined in relation to the two possible mechanisms for the γ-elimination reaction a) a concerted process accompanied by an irrelevant exchange reaction and b) an Elcb process with $k_{-1} \approx k_{el}$.

The effect of isotopic substitution at the γ-position and in the solvent on the ratio of γ-elimination : β-elimination will first be estimated for a concerted γ-elimination reaction. Earlier in this section, it was shown that a hydrogen isotope effect of at least 22 is associated with the abstraction of the γ-proton. Substitution of deuterium for the γ-hydrogens will, therefore, considerably decrease the rate of the γ-elimination reaction. The rate of the β-elimination reaction, on the other hand, will not be significantly altered by this substitution and, as a result, the ratio of γ-elimination : β-elimination will be greatly decreased whether the solvent is ammonia or ammonia-$\underline{d}_3$. When the solvent is ammonia the γ-elimination : β-elimination ratio decreases from 24 : 1 to 1.1 : 1 while it decreases from >250 : 1 to 43 : 1 when ammonia-$\underline{d}_3$ is the solvent. Both of these changes are in the direction predicted and are consistent with a concerted γ-elimination reaction.

A change in the isotopic nature of both the base and the solvent will have an effect on the rates of concerted β- and γ-elimination reactions. The solvent isotope effect, which results from a change in solvent from ammonia to ammonia-$\underline{d}_3$, should be small and, furthermore, would be expected to be in the same direction for both the β- and γ-elimination reactions since both reactions involve the conversion of a positively-charged quaternary salt and a negatively-charged base to neutral products. As a result, the solvent isotope effect should not significantly alter the ratio of γ-elimination : β-elimination.

The isotope effect associated with the change in base from $NH_2^{\ominus}$ to $ND_2^{\ominus}$ will probably be larger than the solvent isotope effects. Although neither the direction nor the magnitude of these secondary isotope effects on the β- and γ-elimination reactions are known, it is safe to assume that these isotope effects would be in the same direction and of almost identical magnitudes in the two concerted elimination reactions. As a result, the rates of the β- and γ-elimination reactions should change by approximately the same amount when the base is changed from $NH_2^{\ominus}$ to $ND_2^{\ominus}$ and the product ratio would not change significantly. It may be concluded then, that the change from $NH_2^{\ominus}$ in ammonia to $ND_2^{\ominus}$ in ammonia-$\underline{d}_3$ would not significantly alter the γ-elimination : β-elimination ratio if the γ- as well as the β-elimination reaction proceeds by a concerted mechanism.

The results show, however, that contrary to this prediction, there is a large increase in the γ-elimination : β-elimination ratio for the reaction of both the undeuterated and deuterated quaternary salts. The ratio increases from 24 : 1 to >250 : 1 when the undeuterated quaternary salt is the reacting species and from 1.1 : 1 to 43 : 1 when the reactant is the deuterated quaternary salt. Neither of these changes can be accommodated by a concerted mechanism.

It is of interest to compare the γ-elimination : β-elimination ratio for the reactions of the undeuterated quaternary salt in ammonia and the deuterated salt in ND_3. Since the γ-elimination : β-elimination ratio for a concerted process will be essentially unchanged when the base and solvent is changed from $NH_2^{\ominus}$ in ammonia to $ND_2^{\ominus}$ in ammonia-$\underline{d}_3$, the change in the product ratio will be that resulting from the isotopic substitution of the γ-carbon. It follows that the γ-elimination : β-elimination ratio should be markedly lower for the reaction of the deuterated quaternary salt in ammonia-$\underline{d}_3$ than for the reaction of the undeuterated quaternary salt in ammonia. In actual fact, the opposite was observed; the ratio increased from 24 : 1 to 43 : 1. This result is also incompatible with a concerted mechanism for the γ-elimination reaction.

Finally, a comparison can be made between the γ-elimination : β-elimination ratio for the reaction of the undeuterated quaternary salt in ammonia-$\underline{d}_3$ and that for the reaction of the deuterated quaternary salt in ammonia. Since only the substitution of deuterium at the γ-carbon will have a significant effect on the γ-elimination : β-elimination ratio if the γ-elimination reaction is concerted, one would expect the product ratio to be smaller in the latter system. This is indeed, observed, but the very large decrease from >250 : 1 to 1.1 : 1 seems much too large to have its origin solely in the primary isotope effect associated with the abstraction of the γ-proton.

A summary of the predicted effects of isotopic substitution in the substrate, base and solvent on the γ-elimination : β-elimination ratio for a concerted γ-elimination reaction is given in Table XIII, together with the observed results. It is seen that of the six comparisons, only two are of the magnitude and direction predicted on the basis of a concerted γ-elimination reaction. It must, therefore, be concluded that this is not the reaction pathway for the γ-elimination reaction.

It is now necessary to examine the effect of isotopic substitution in the substrate, base and solvent in relation to that predicted for a γ-elimination process proceeding by an Elcb mechanism in which $k_{-1} \ll k_{el}$. Substituting deuterium for the γ-hydrogens of 3-phenylpropyltrimethylammonium iodide, by virtue of the large hydrogen isotope effect associated with the abstraction of the γ-proton, should result in a large decrease in the rate of carbanion formation and, therefore, in the rate of the γ-elimination reaction, whether the solvent is ammonia or ammonia-$\underline{d}_3$. Since the rate of the β-elimination reaction will not be significantly altered by this substitution, the ratio of γ-elimination : β-elimination must be much

Table XIII. A Comparison of γ-Elimination : β-Elimination for the Deuterated and Undeuterated Quaternary Ammonium Salts in Ammonia and Ammonia-$\underline{d}_3$ Assuming that the γ-Elimination Reaction is a Concerted Process Accompanied by an Irrelevant Exchange Reaction at the γ-Position

Reactions Compared	Differences in Systems Compared and Effects of these Changes	Predicted Changes in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$	Observed Changes in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3	γ-deuterium lowers rate of γ-elimination reaction	large decrease	large decrease from 24 : 1 to 1.1 : 1*
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	γ-deuterium lowers rate of γ-elimination reaction	large decrease	large decrease from >250 : 1 to 43 : 1
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	change in solvent and base has approximately the same effect on the β- and γ-elimination reactions	little or no change	large increase from 24 : 1 to >250 : 1

Table XIII Continued

Reactions Compared	Differences in Systems Compared and Effects of these Changes	Predicted Changes in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$	Observed Changes in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$
$PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	change in solvent and base has approximately the same effect on the β- and γ-elimination reactions	little or no change	large increase from 1.1 : 1* to 43 : 1
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	(a) γ-deuterium lowers rate of γ-elimination reaction (b) change in solvent and base has approximately the same effect on the β- and γ-elimination reactions	(a) large decrease (b) little or no effect Overall Change: large decrease	increase from 24 : 1 to 43 : 1
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3	(a) γ-deuterium lowers rate of γ-elimination reaction (b) change in solvent and base has approximately the same effect on the β- and γ-elimination reactions	(a) large decrease (b) little or no change Overall Change: large decrease	extremely large decrease From >250 : 1 to 1.1 : 1*

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* This ratio would be considerably smaller if exchange had not occurred at the γ-carbon during the reaction of the deuterated salt in ammonia.

smaller when the deuterated quaternary salt is the reacting species. This is, in fact, what is actually observed. The γ-elimination : β-elimination ratio decreases from 24 : 1 to 1.1 : 1 in ammonia, and from >250 : 1 to 43 : 1 in ammonia-$\underline{d}_3$.

The changes resulting from isotopic substitution in the solvent are more complex because the primary hydrogen isotope effect associated with the removal of the proton from solvent by the carbanion is accompanied by secondary isotope effects that result from the change in the base and solvent. Earlier in this section of the thesis it was shown that the primary isotope effect associated with the abstraction of a proton from solvent is very large. As a result, fewer carbanions will revert to quaternary salt and more will be converted to phenylcyclopropane when ammonia-$\underline{d}_3$ is the solvent, equation 144 (page 127). It follows that the rate of the γ-elimination reaction from either the undeuterated or deuterated quaternary salts should be greater in ammonia-$\underline{d}_3$ than in ammonia, and the γ-elimination : β-elimination ratio should show a large increase.

It is of course, an oversimplification to consider only the primary isotope effect related to the relative acidity of ammonia and ammonia-$\underline{d}_3$. The solvent isotope effects associated with the change in solvent should be small however, and furthermore, should be in the same direction for the two elimination processes since they both involve the delocalization of charge in going from the initial state to the transition state. The solvent isotope effects, therefore, would not significantly alter the ratio of γ-elimination : β-elimination. Although the secondary isotope effects in carbanion formation and the β-elimination reaction, which result from the change in base from $NH_2^{\ominus}$ to $ND_2^{\ominus}$, should be much larger than the solvent isotope effects, they also should be in the same direction and of approximately the same magnitude because both reactions involve the abstraction of a proton from the quaternary salt. On the other hand, the secondary isotope effect caused by the change in acid from ammonia to ammonia-$\underline{d}_3$ in the return of the carbanion to reactant will have a significant effect on the γ-elimination : β-elimination ratio. This component of the overall isotope effect relating to the relative acidity of ammonia and ammonia-$\underline{d}_3$ will, however, be small compared to the primary isotope effect associated with the rupture of the N-H and N-D bonds and probably will be in the same direction. Since the effect on the product ratio caused by the secondary and solvent isotope effects associated with the change in base and solvent is small in comparison to that caused by the primary isotope effect, it follows that the change in the product ratio caused by replacing ammonia with ammonia-$\underline{d}_3$ can be closely approximated by considering only the primary hydrogen isotope effect. As a result, changing the solvent from ammonia to ammonia-$\underline{d}_3$ should result in a large increase in the γ-elimination : β-elimination ratio whether the undeuterated or deuterated quaternary salt is the reacting species. Reference to Table XII shows that when the solvent is changed from ammonia to ammonia-$\underline{d}_3$ the γ-elimination : β-elimination ratio increases from 24 : 1 to >250 : 1 when the undeuterated quaternary salt is the reacting species, and from 1.1 : 1 to 43 : 1 when the reactant is the deuterated quaternary salt. Both these changes are in the direction predicted and are consistent with an Elcb process in which

$k_{-1} \approx k_{el}$.

The ratio of γ-elimination : β-elimination may also be compared for the reaction of the undeuterated quaternary salt in ammonia and the deuterated quaternary salt in ammonia-$\underline{d}_3$. Deuteration at the γ-position should cause a large decrease in the γ-elimination : β-elimination ratio, while the primary isotope effect associated with the change in solvent to ammonia-$\underline{d}_3$ would cause a large increase in this ratio. The changes in the product ratio resulting from the two primary isotope effects should approximately cancel, and since the change in the product ratio resulting from the secondary and solvent isotope effects associated with the change in solvent should be relatively small, only a small change would be expected in the γ-elimination : β-elimination ratio. In fact, only a small increase from 24 : 1 to 43 : 1 is observed. This result is, therefore, also compatible with the E1cb mechanism.

A comparison can also be made between the γ-elimination : β-elimination ratio for the reaction of the undeuterated quaternary salt in ammonia-$\underline{d}_3$ with that of the deuterated quaternary salt in ammonia. Both the isotopic substitution of the γ-hydrogens, which slows the rate of formation of the γ-carbanion, and the change in solvent from ammonia-$\underline{d}_3$ to ammonia, which results in an increase in the rate of the k_{-1} step, will markedly decrease the rate of the γ-elimination reaction and cause a large decrease in the γ-elimination : β-elimination ratio. The secondary and solvent isotope effects associated with the change in solvent can again be assumed to have only a small influence on the magnitude of the change in the product ratio. As a result, a very large decrease in the γ-elimination : β-elimination ratio would be predicted since the overall isotope effect will be the product of two primary isotope effects operating in the same direction. This is what is observed; the product ratio decreases from >250 : 1 in the reaction of the undeuterated quaternary salt in ammonia-$\underline{d}_3$ to 1.1 : 1 in the reaction of the deuterated quaternary salt in ammonia.

A summary of the predicted effects and the observed effects of isotopic substitution at the γ-position of the quaternary salt and in base and solvent is given in Table XIV. In every case, the changes observed in the product ratio are of the magnitude and direction predicted. It is concluded, therefore, that the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide in liquid ammonia at -55° proceeds by way of an E1cb mechanism in which $k_{-1} \approx k_{el}$.

Now that the mechanism of the γ-elimination reaction has been established it is possible to estimate the value of the ratio of the rate constants for the return of the carbanion to quaternary salt and ring closure to phenylcyclopropane. An upper limit of the ratio of ${}^{k_{-1}}/k_{el}$ can be estimated from equation 143 and the maximum isotope effect for the abstraction of the γ-proton (${}^{k_{1H}}/k_{1D}$).

$$ {}^{k_{1H}}/k_{1D} = 9.3 \; ({}^{k_{-1}}/k_{el} + 1) \qquad (143) $$

The largest hydrogen isotope effect reported to date was found by Lewis and Funderburk (219) in the base-induced iodination of 2-nitropropane, equation 146.

Table XIV. A Comparison of γ-Elimination : β-Elimination for the Deuterated and Undeuterated Quaternary Ammonium Salts in Ammonia and Ammonia-$\underline{d}_3$ Assuming that the γ-Elimination Reaction is an Elcb Process with $k_{-1} \approx k_{el}$

Reactions Compared	Differences in the Systems Compared and Effects of these Changes	Predicted Change in $\frac{\text{γ-Elimination}}{\text{β-Elimination}}$	Observed Change in $\frac{\text{γ-Elimination}}{\text{β-Elimination}}$
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3	γ-deuterium slows carbanion formation and, therefore, decreases rate of γ-elimination reaction	large decrease	large decrease from 24 : 1 to 1.1 : 1*
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	γ-deuterium slows carbanion formation and, therefore, decreases rate of γ-elimination reaction	large decrease	large decrease from >250 : 1 to 43 : 1

Table XIV Continued

Reactions Compared	Differences in the Systems Compared and Effects of these Changes	Predicted Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$	Observed Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	(a) primary isotope effect resulting from deuterated solvent slows the k_{-1} step and increases the rate of the γ-elimination (b) secondary and solvent isotope effects have approximately the same effect on the rates of the β- and γ-eliminations	(a) large increase (b) small change Overall Change: large increase	large increase from 24 : 1 to >250 : 1
$PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	(a) primary isotope effect resulting from deuterated solvent slows the k_{-1} step and increases the rate of the γ-elimination (b) secondary and solvent isotope effects have approximately the same effect on the rates of the β- and γ-eliminations	(a) large increase (b) small change Overall Change: large increase	large increase from 1.1 : 1* to 43 : 1

Table XIV Continued

Reactions Compared	Differences in the Systems Compared and Effects of these Changes	Predicted Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$	Observed Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3	(a) γ-deuterium slows carbanion formation and decreases the rate of the γ-elimination reaction (b) primary isotope effect resulting from deuterated solvent slows the k_{-1} step and increases the rate of the γ-elimination (c) secondary and solvent isotope effects have approximately the same effect on the rates of the β- and γ-eliminations	(a) large decrease (b) large increase (c) small change Overall Change: small increase or a small decrease	small increase from 24 : 1 to 43 : 1

Table XIV Continued

Reactions Compared	Differences in the Systems Compared and Effects of these Changes	Predicted Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$	Observed Change in $\frac{\gamma\text{-Elimination}}{\beta\text{-Elimination}}$
$PhCH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in ND_3 with $PhCD_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I}$ in NH_3	(a) γ-deuterium slows carbanion formation and decreases the rate of the γ-elimination reaction (b) primary isotope effect in going from ND_3 to NH_3 increases the rate of the k_{-1} step and decreases the rate of the γ-elimination reaction (c) secondary and solvent isotope effects have approximately the same effect on the rates of the β- and γ-eliminations	(a) large decrease (b) large decrease (c) small change Overall Change: very large decrease	very large decrease from >250 : 1 to 1.1 : 1*

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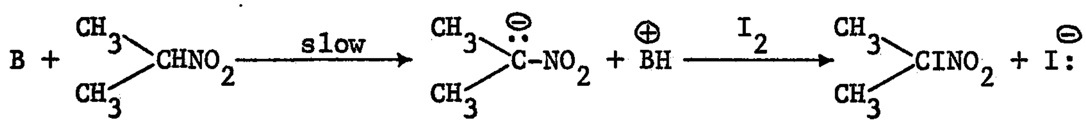
* This ratio would be considerably smaller if exchange had not occurred at the γ-position during the reaction of the deuterated quaternary salt in ammonia.



(146)

When the base was 2,4,6-trimethylpyridine the hydrogen isotope effect for this reaction (k_H/k_D) was 24.8 at 25°. These workers studied the temperature dependence of this isotope effect and concluded on the basis of a very small ratio of preexponential factors (A_H/A_D) and an extremely large activation energy difference (ΔEa), equation 147, that there is a significant amount of tunnelling in the proton transfer process (220).

$$k_H/k_D = A_H/A_D\ e^{\Delta Ea/RT} = 0.16\ e^{3006/RT} \qquad (147)$$

By substituting the temperature used in the present study (-55°C = 218°A), for T in equation 147 and solving for k_H/k_D, it can be shown that the isotope effect observed by Lewis and Funderburk (24.8 at 25°), would be equivalent to an isotope effect of 154 at -55°. Since the isotope effect observed by Lewis and Funderburk is the largest that has been found for proton abstraction reactions, it is reasonable to assume that the extrapolated isotope effect of 154 is close to the maximum isotope effect for the abstraction of the γ-proton in the present system. Substituting the value of 154 for k_{1H}/k_{1D} into equation 143, one obtains a value of k_{-1}/k_{el} = 15.5, which is probably close to the upper limit of this ratio.

A minimum value of the k_{-1}/k_{el} ratio can be estimated from the magnitude of the nitrogen isotope effect for the γ-elimination reaction $[(k^{14}/k^{15})_{obs}$ = 1.0220 at -55°] and the theoretical maximum isotope effect at -55°. It has been shown earlier that for a γ-elimination reaction proceeding by an Elcb mechanism that

$$k_{obs} = \frac{k_{el}\, k_{1}}{k_{el} + k_{-1}} \qquad (148)$$

It follows that the observed nitrogen isotope effect $(^{k^{14}}/_{k^{15}})_{obs}$ can be expressed in terms of the rate constants in equation 148.

$$(^{k^{14}}/_{k^{15}})_{obs} = \frac{k^{14}_{el}\, k^{14}_{1} \,/\, k^{14}_{el} + k^{14}_{-1}}{k^{15}_{el}\, k^{15}_{1} \,/\, k^{15}_{el} + k^{15}_{-1}} = \frac{k^{14}_{el}\, k^{14}_{1}}{k^{14}_{el} + k^{14}_{-1}} \cdot \frac{k^{15}_{el} + k^{15}_{-1}}{k^{15}_{el}\, k^{15}_{1}} \qquad (149)$$

Since the C-N bond is not involved in either the carbanion formation or the return to quaternary salt, k^{15}_{1} and k^{15}_{-1} are equal to k^{14}_{1} and k^{14}_{-1}, respectively, and equation 149 becomes

$$(^{k^{14}}/_{k^{15}})_{obs} = \frac{k^{14}_{el}(k^{15}_{el} + k^{14}_{-1})}{k^{15}_{el}(k^{14}_{el} + k^{14}_{-1})}$$

Dividing the top and bottom by k^{14}_{el} and rearranging gives

$$^{k^{14}_{-1}}/_{k^{14}_{el}} = \frac{(^{k^{14}}/_{k^{15}})_{obs} - 1}{^{k^{14}_{el}}/_{k^{15}_{el}} - (^{k^{14}}/_{k^{15}})_{obs}} = \frac{0.0220}{^{k^{14}_{el}}/_{k^{15}_{el}} - 1.0220} \qquad (150)$$

where $^{k^{14}_{el}}/_{k^{15}_{el}}$ is the nitrogen isotope effect for the ring closure reaction. The $^{k^{14}_{-1}}/_{k^{14}_{el}}$ ratio decreases as the nitrogen isotope effect for the ring closure increases and, therefore, the miniumum value of $^{k^{14}_{-1}}/_{k^{14}_{el}}$ occurs when the nitrogen isotope effect for ring closure is at a maximum. The theoretical maximum isotope effect at -55° was previously estimated to be 5.0 per cent. When this value for the isotope effect in the ring closure step is substituted in equation 150, the minimum value of k^{14}_{-1}/k^{14}_{el} is found to be 0.8.

It is highly improbable that the nitrogen isotope effect for the ring closure will be as large as the theoretical maximum and, therefore, the ratio of k_{-1}/k_{el} would be expected to be greater than 0.8.

The minimum value of the k_{-1}/k_{el} can also be estimated from the magnitude of the primary hydrogen isotope effect associated with the abstraction of the γ-proton. It was shown in the section on the hydrogen isotope effect that the γ-elimination reaction is 22 times slower with the deuterated quaternary salt than with the undeuterated quaternary salt. The hydrogen isotope effect associated with the abstraction of the γ-proton must, therefore, be greater than 22 and it follows from equation 143 that

$$k_{1H}/k_{1D} = 9.3\ (k_{-1}/k_{el} + 1) > 22$$

and hence k_{-1}/k_{el} must be greater than 1.4.

It is of interest to calculate, using equations 143 and 150, values for the nitrogen isotope effect, $(k^{14}_{el}/k^{15}_{el} - 1)100$, and the hydrogen isotope effect, k_{1H}/k_{1D}, corresponding to different values of k_{-1}/k_{el} over the range 0.8 to 15.5. These are given in Table XV.

Although a nitrogen isotope effect as large as five per cent is theoretically possible, it will be recalled that in the E2 reaction of 2-phenylethyltrimethylammonium ion the measured isotope effect was actually less than one-half the calculated maximum for a process involving carbon-nitrogen bond rupture. In the present system an unstable carbanion is decomposing into stable products and,

Table XV. The Hydrogen and Nitrogen Isotope Effects for the γ-Elimination Reaction of 3-Phenylpropyltrimethylammonium Iodide with Potassium Amide in Liquid Ammonia at -55°

k_{-1}/k_{el}	k_{1H}/k_{1D} [a]	$(k^{14}_{el}/k^{15}_{el} - 1)100\%$ [b]
0.8	17	5.0
1.37	22	3.8
2.0	28	3.3
3.0	37	2.9
5.0	56	2.6
6.0	65	2.6
7.0	74	2.5
8.0	84	2.5
9.0	93	2.4
10.0	102	2.4
11.0	112	2.4
12.0	121	2.4
13.0	130	2.4
14.0	140	2.4
15.0	149	2.3
15.5	154	2.3

a. Calculated from equation 143 (page 142).

b. Calculated from equation 150 (page 148).

on the basis of the Hammond thermal postulate (221), one would predict that bond rupture would not be well advanced at the transition state and a relatively small nitrogen isotope effect would result. It seems unlikely, therefore, that the nitrogen isotope effect for the ring closure step would be much more than half the theoretical maximum of five per cent. If this is so, then the minimum value for k_{-1}/k_{el} would be no less than three.

In conclusion, the γ-elimination reaction of 3-phenylpropyltrimethylammonium iodide with potassium amide in liquid ammonia at -55° has been found to proceed by way of an Elcb mechanism in which both the γ-carbanion formation and the ring closure and elimination of trimethylamine are partially rate determining. The ratio of k_{-1}/k_{el} in this reaction must be greater than 1.4 and probably lies within the limits of three and fifteen. The hydrogen isotope effect associated with the abstraction of the γ-proton is greater than 22, which would suggest that tunnelling is important in this reaction. The nitrogen isotope effect associated with the ring closure is greater than 2.20 per cent.

EXPERIMENTAL

The Synthesis of 3-Phenylpropyltrimethylammonium Iodide

3-Phenylpropyltrimethylammonium iodide was prepared by reacting methyl iodide with N,N-dimethyl-3-phenylpropylamine which was formed by the action of dimethylamine on the tosylate derived from 3-phenyl-1-propanol. This alcohol was prepared by reacting ethylene oxide with benzyl magnesium chloride.

Preparation of 3-Phenyl-1-propanol

This compound was prepared by the method described by Huston and Agett (222). A solution of 203 g. (1.58 mole), benzyl chloride (Fisher Certified Reagent) in 330 ml. of sodium dried ether was added dropwise with stirring to a mixture of 38.5 g. (1.58 mole), magnesium turnings (Shawinigan Reagent) and 50 ml. of ether. This mixture was stirred for ten hours, cooled to 0°, and a solution of 139 g. (3.16 mole), ethylene oxide (Eastman) in 237 ml. of ether was added dropwise with stirring. The cold bath was removed and the mixture was stirred overnight. The mixture was treated with 160 ml. of water and the ether layer separated. The water layer was acidified with 10% hydrochloric acid and extracted with three 100 ml. portions of ether. All the ether solutions were combined and dried over anhydrous sodium sulfate. The ether was removed on a rotary evaporator and the residue was distilled using a spinning band column to give 125 g. (58%) of 3-phenyl-1-propanol, b.p. 105-106°/5 mm., (Delépine and Hanegraaf (223), b.p. 114-118°/14 mm.), $n_D^{24.5}$ 1.5363 (Huston and Agett (222), n_D^{23} 1.5351).

Preparation of 3-Phenylpropyl p-Toluenesulfonate

The method described by Tipson (224) was used to prepare this compound. p-Toluenesulfonyl chloride*, 124.5 g. (0.653 mole) was dissolved in a solution of 80.6 g. (0.593 mole) of 3-phenyl-1-propanol in 810 ml. of pyridine** which had been cooled to -5° in an ice-salt bath. The solution was stirred for 11 hours at -5° and then water was added in volumes of 7.5, 7.5, 7.5, 15 and 37.5 ml. at 5 minute intervals so as to keep the temperature below 5°. An additional 750 ml. of water were added and the solution was extracted thrice with 500 ml portions of chloroform. These chloroform solutions were combined and extracted with a 10% solution of sulphuric acid until no odour of pyridine remained. The chloroform was extracted twice with 250 ml. of 5% sodium bicarbonate and twice with 250 ml. of water. The chloroform

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* The p-toluenesulfonyl chloride (Eastman) was purified immediately prior to use. A solution of 51 g. p-toluenesulfonyl chloride in 105 ml. chloroform and 495 ml. petroleum ether, b.p. 30-60°, was heated to boiling and treated with Norite A decolourizing carbon. The hot solution was filtered and concentrated to a volume of 100 ml. under reduced pressure. Cooling the concentrate gave 41 g. (81%) p-toluenesulfonyl chloride m.p. 69.5-70.5°, uncorrected.

** The pyridine (Fisher Certified Reagent) was refluxed over barium oxide for eight hours and distilled immediately prior to use.

solution was dried over anhydrous sodium sulfate. The chloroform was removed at room temperature under reduced pressure leaving the tosylate which was not purified.

Preparation of N,N-Dimethyl-3-phenylpropylamine

The amine was prepared using the method described by Cope and Bumgardner (225). The tosylate was mixed with 52.4 g. (1.19 mole) of anhydrous dimethylamine (Eastman) in 300 ml. sodium dried benzene. The mixture was left for one week at room temperature. The solution was extracted with three 500 ml. portions of 5% hydrochloric acid. The acid solution was made basic and extracted thrice with 100 ml. of ether. These ether solutions were combined and dried over anhydrous sodium sulfate. The residue obtained when the ether was removed under reduced pressure was distilled giving 66.2 g. (68%) N,N-dimethyl-3-phenylpropylamine, b.p. 93-95°/10 mm. (Cope and Bumgardner (225), b.p. 94-96°/10 mm.).

Preparation of 3-Phenylpropyltrimethylammonium Iodide

This compound was prepared using the method described by Senfter and Tafel (226). Methyl iodide, 115 g. (0.810 mole) was added to a solution of 66.1 g. (0.406 mole) of N,N-dimethyl-3-phenylpropylamine in 200 ml. of anhydrous ether. The mixture was left overnight in the dark. The quaternary salt was filtered and recrystallized to a constant melting point from ethanol and diethylether. All operations were performed in a darkened area because the quaternary salt decomposes readily in the light. This preparation gave 108.7 g. (74%) of 3-phenylpropyltrimethylammonium iodide m.p. 178-178.5°, uncorrected, (Cope and Bumgardner (225) m.p. 178.5-180°). Analysis*: Calculated for $C_{12}H_{20}NI$; C, 47.22%; H, 6.61%; N, 4.59%. Found: C, 47.22%; H, 6.73%; N, 4.43%.

The Synthesis of
3,3-Dideutero-3-phenylpropyltrimethylammonium Iodide

The first step in the synthesis of the dideuterated quaternary ammonium salt was the preparation of benzyl alcohol-α,α-$\underline{d}_2$ by the reduction of ethylbenzoate with lithium aluminum deuteride. The alcohol was converted to benzyl chloride-α,α-$\underline{d}_2$ by treatment with lucas reagent. This material was converted to the deuterated quaternary ammonium salt by the same sequence of reactions as were used for the preparation of the unlabelled salt.

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

This compound was prepared by the method described by Buncel and Bourns (76). A solution of 20.9 g. (0.139 mole) ethylbenzoate (Fisher) in 100 ml. of ether** was added dropwise with stirring to a solution of 2.98 g. (0.071 mole) lithium aluminum deuteride (Metal Hydride Inc.) in 300 ml. of ether**. The mixture was refluxed for four hours and then hydrolyzed by the dropwise addition of a 10% solution of sulfuric acid. The ether layer was separated and the

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

** Sodium dried ether was refluxed over lithium aluminum hydride for four hours and distilled prior to use.

aqueous solution was extracted with three 50 ml. portions of ether. The ether solutions were combined and the ether removed under reduced pressure. The residue was refluxed for 1.5 hours with aqueous alcoholic sodium hydroxide* to hydrolyze any unreacted ester. Twenty-five ml. of water was added and the resulting solution was extracted thrice with 50 ml. of ether. The ether solutions were combined and dried over anhydrous sodium sulfate. Distillation gave 12.0 g. (79%) benzyl alcohol-α,α-$\underline{d}_2$, b.p. 76-78°/5 mm. (Buncel and Bourns (76), b.p. 76°/5 mm.). An N.M.R. analysis of the product showed that the benzyl carbon was more than 99 per cent deuterated.

Preparation of Benzyl Chloride-α,α-$\underline{d}_2$

The method employed by Buncel and Bourns (76) was used to prepare this compound. Benzyl alcohol-α,α-$\underline{d}_2$, 11.8 g. (0.11 mole) was added dropwise with stirring over 50 minutes to 53 g. of lucas reagent (227) at 0°. The mixture was stirred at this temperature for one hour and then extracted with three 50 ml. portions of 1:1 diethylether-petroleum ether, b.p. 30-60°. The ether-petroleum ether solutions were combined and dried over anhydrous sodium sulfate. Distillation yielded 8.6 g. (62%) benzyl chloride-α,α-$\underline{d}_2$, b.p. 76-77°/25 mm. (Buncel and Bourns (76) b.p. 64°/12 mm.).

Preparation of 3,3-Dideutero-3-phenyl-1-propanol

This compound was prepared from benzyl chloride-α,α-$\underline{d}_2$ by the

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* This solution was prepared by adding 2.5 ml. of water to the sodium ethoxide produced from the reaction of 0.8 g. of sodium and 25 ml. of ethanol.

procedure described for the synthesis of 3-phenyl-1-propanol. Benzyl chloride-α,α-$\underline{d}_2$, 8.6 g., was reacted with 1.75 g. of magnesium and 6.3 g. of ethylene oxide in sodium dried ether to produce 5.8 g. (63%) of 3,3-dideutero-3-phenyl-1-propanol, b.p. 103-106°/5 mm. (Delépine and Hanegraaf (223), b.p. 114-118°/14 mm.).

Preparation of N,N-Dimethyl-3,3-dideutero-3-phenylpropylamine

The procedure described for the conversion of 3-phenyl-1-propanol to N,N-dimethyl-3-phenylpropylamine was used in the preparation of this compound. 3,3-Dideutero-3-phenyl-1-propanol, 5.8 g., was reacted with 9.0 g. of p-toluenesulfonyl chloride in 60 ml. of dry pyridine to give 3,3-dideutero-3-phenylpropyl p-toluenesulfonate. The crude tosylate was treated with 3.8 g. of anhydrous dimethylamine to form 4.9 g. (71%) of N,N-dimethyl-3,3-dideutero-3-phenylpropylamine, b.p. 96-98°/10 mm. (Cope and Bumgardner (225), b.p. 94-96°/10 mm.).

Preparation of 3,3-Dideutero-3-phenylpropyltrimethylammonium Iodide

This compound was prepared using the procedure described in the synthesis of the undeuterated quaternary salt. N,N-Dimethyl-3,3-dideutero-3-phenylpropylamine, 4.92 g., was reacted with 8.55 g. of methyl iodide in 50 ml. of ether. The deuterated quaternary salt was recrystallized from ethanol-diethylether to a constant melting point 178.0-178.5° (Cope and Bumgardner (225), m.p. 178.5-180°). The yield was 8.0 g. (91%).

The 60 Mc. N.M.R. spectrum of the quaternary salt was too complex to permit the extent of deuteration to be determined by this method. Deuterium analysis by Nemeth* indicated that this compound contained 1.96 atoms of deuterium per molecule, or was 98 per cent deuterated at the γ-position.

Elimination Reaction Conditions and Product Analysis

The reaction was performed by adding a solution of potassium amide to a solution of the quaternary ammonium salt in liquid ammonia. The base was generated from potassium metal and liquid ammonia immediately prior to use. In experiments where it was necessary to stop the reaction before completion, quenching was accomplished by the addition of excess ammonium chloride.

The products of the reaction were identified by a gas chromatographic analysis and by infra-red, N.M.R. and ultraviolet spectroscopy. The extent of reaction was estimated from the amount of hydrocarbon product by gas chromatography using the internal standard technique and from the amount of unreacted quaternary salt recovered from the reaction mixture. A quantitative analysis was accomplished by a gas chromatographic separation of the reaction product into three components: _cis_-β-methyl styrene, 3-phenylpropene and a mixture of _trans_-β-methyl styrene and phenylcyclopropane. The composition of the latter mixture was determined by ultraviolet spectroscopy although gas chromatography and N.M.R. spectroscopy were also used in one instance. The ultraviolet analysis was done at 250 mμ

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* The deuterium analysis was performed by Mr. J. Nemeth, 303 W. Washington St., Urbana, Illinois.

where the molar extinction coefficients of trans-β-methyl styrene and phenylcyclopropane were found to be 16,000 and 153, respectively.

General Experimental Procedure

The apparatus used to react the quaternary ammonium salt with potassium amide in liquid ammonia is shown in Figure 6. The nitrogen was purified by bubbling through two gas bottles of Fieser's solution (228) which absorbs oxygen, one bottle containing a saturated solution of lead acetate which traps hydrogen sulfide, one bottle of concentrated sulphuric acid to trap water and two bottles of potassium hydroxide pellets which absorb both water and carbon dioxide. The anhydrous ammonia was passed through two drying towers of barium oxide (B.D.H.) (229).

The apparatus consisted of two Flasks A and B connected by means of a rubber tube. Flask A contained a magnetic stirrer and was fitted with a dry ice-acetone condenser, D_1, and a vial, E_1, for adding potassium metal. Flask B was fitted with an airtight teflon stirrer, a dry ice-acetone condenser, D_2, and a vial, E_2, for the addition of ammonium chloride. Clamps C_1 and C_2 were placed on the rubber connections joining the vials to the reaction flasks. In preparation for an experiment a small crystal (approximately 10 mg.) of ferric nitrate nonahydrate was placed in Flask A and the whole apparatus was placed in a drying oven for 8 hours. On removal from the oven the apparatus was immediately connected to a three way stopcock, Z, joining the nitrogen and ammonia trains, and to a barium oxide drying tube, F, whose exit tube passed into a small beaker, H,

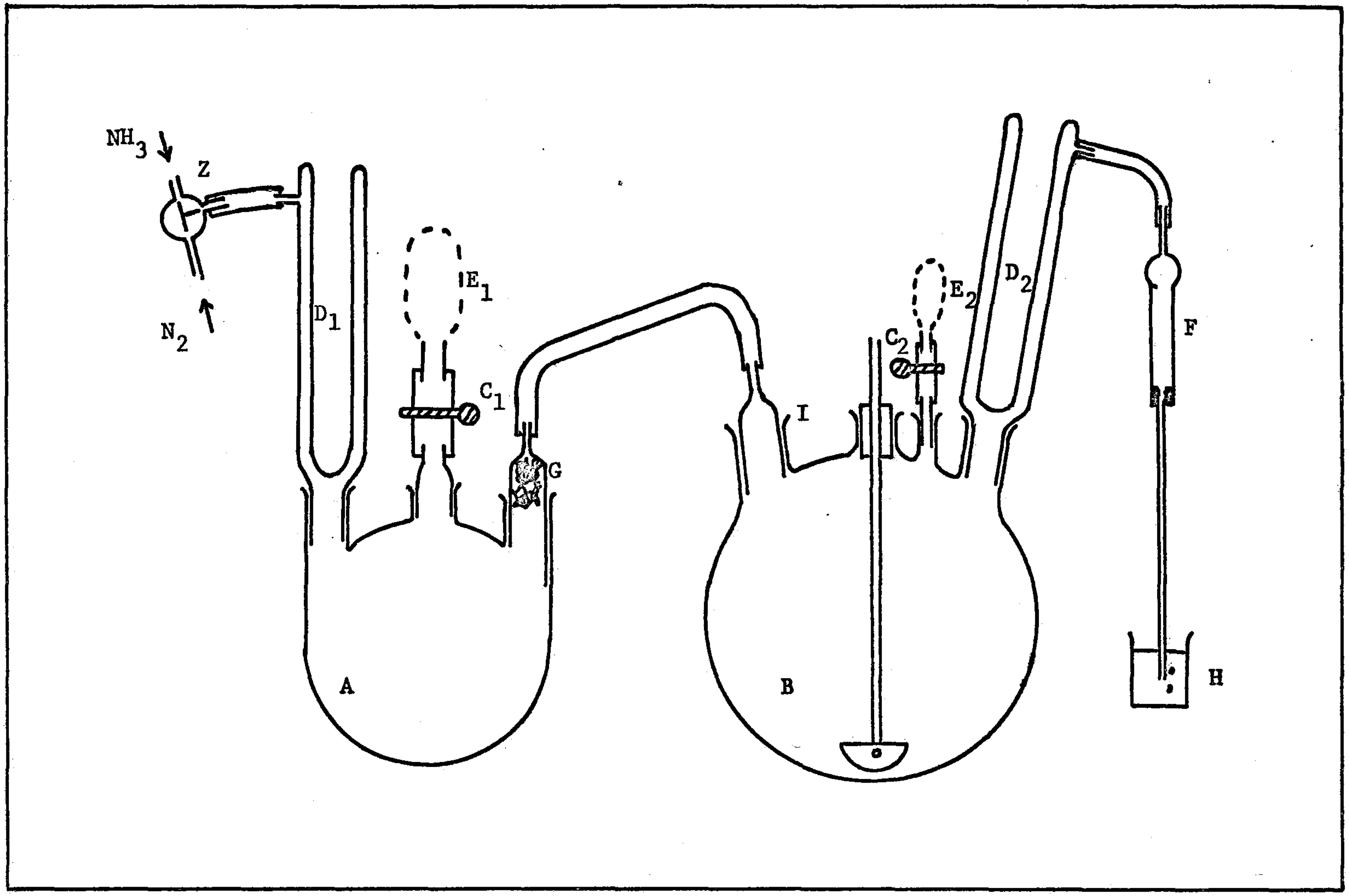

Fig. 6. Apparatus for the reaction of quaternary ammonium salts with potassium amide in liquid ammonia.

containing oil. After the apparatus was thoroughly flamed while flushing with both ammonia and nitrogen, D_2 was removed without interruption of the gas flow and the appropriate amount (usually 2 g.) of quaternary salt was added to Flask B as rapidly as possible. The condenser was replaced, flamed again and the apparatus was flushed with a slow flow of nitrogen overnight.

Dry ice and acetone were placed in condenser D_2 and 200 ml. of ammonia was condensed into Flask B. Condenser D_1 was cooled with dry ice and acetone and 100 ml. of ammonia was condensed into Flask A. Potassium (Baker), 0.57 g. (1.5×10^{-2} mole), cut and weighed in petroleum ether, was placed in vial E_1. Clamp C_1 was removed and the potassium was added one piece at a time with stirring to Flask A. The solution in Flask A was stirred for 30 minutes after the dark blue colour caused by the presence of potassium in ammonia had disappeared.

The dry ice-acetone condenser, D_1, was quickly changed for an adapter connected to the nitrogen train, and then both Flasks A and B were cooled to -55° in a bath of dry ice-diacetone alcohol. The flasks were stirred for 30 minutes after the cold baths had reached a constant temperature. Flask A was inverted and the potassium amide solution was pushed by nitrogen through a glass wool filter, G, into Flask B. The addition of base took between five and ten seconds. The temperature of the cold bath was maintained at -55° ± 1° during the reaction.

The reaction was stopped by removing the clamp, C_2, and adding 1.56 g. (0.030 mole) of ammonium chloride (Mallinckrodt) to the reaction mixture. The reddish brown colour caused by the allyl carbanion disappeared within ten seconds of adding the ammonium chloride indicating that the base was neutralized in less than ten seconds.

The cold bath was removed and adapter, I, was replaced with a water condenser connected to a gas washing bottle containing 100 ml. of diethyl ether. The gas washing bottle which was to trap any hydrocarbon product swept out of the reaction flask by the evaporating ammonia, was cooled in an ice-salt bath. The dry ice-acetone condenser, D_2, was replaced with a stopper. Finally, 200 ml. of ether was added carefully to the reaction flask and the ammonia was allowed to evaporate slowly. Ether was added occasionally to the gas washing bottle so the volume of ether remained close to 100 ml. during the evaporation of the ammonia. When all the ammonia had evaporated approximately 100 ml. of water was added and the salts in the reaction flask were taken into solution. The ether layer was separated and the water layer was then extracted with an additional 50 ml. of ether.

Identification of Products

The combined ether solutions were examined by gas chromatography using a 3/8 inch, 20 foot column of 30% SE-30* on 45/60 mesh chromosorb P at 150°. Three peaks were observed, but only one was present in sufficient quantity to enable an identification. After

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* The silicon oil, SE-30, was purchased from Varian Aerograph, 2700 Mitchell Drive, Walnut Creek, California.

most of the ether had been removed by distillation on a spinning band column, the major component of the product was separated by gas chromatography using the above conditions and condensed in a collection bottle cooled to 0° in an ice-water bath. The N.M.R. spectrum of the purified material was identical in every respect to that reported for phenylcyclopropane (230). The infra-red spectrum of this material was also consistent with phenylcyclopropane; strong absorptions at 3070 cm^{-1}, 2985 cm^{-1} and 1025 cm^{-1} are typical of the cyclopropyl group and the absorptions at 1125 cm^{-1}, 1082 cm^{-1}, 1050 cm^{-1}, 752 cm^{-1} and 695 cm^{-1} are characteristic of a monosubstituted phenyl group (231).

The products which were not present in sufficient quantity to be identified when the reactant was the undeuterated quaternary salt represented a much larger portion of the products when the deuterated quaternary salt was the reacting species. The experimental procedure used in the latter reaction was identical to that described in the previous section. As before, most of the ether was removed by distillation, the products were separated by gas chromatography and the two largest components were collected.

The retention time of component (1) on the gas chromatograph was found to be identical to that of 3-phenylpropene (Matheson, Coleman and Bell). The infra-red spectrum was superimposable on the spectrum of 3-phenylpropene except for a peak at 2150 cm^{-1} associated with the stretching frequency of the C_γ-D bond (204-206) and the disappearance of the peak at 1440 cm^{-1} which was attributed to the C_γ-H bending vibration (204).

The retention time of component (2) corresponded to that of phenylcyclopropane but its N.M.R. spectrum showed two absorptions, a doublet at 1.80 p.p.m. and a broad multiplet centred at 6.00 p.p.m., which are not found in the spectrum of this compound (see figures 3 and 4, pages 87 and 88). It was suspected that some of the 3-phenylpropene had isomerized during the reaction and that component (2) was a mixture of phenylcyclopropane and trans-β-methyl styrene.

In order to confirm this hypothesis, an authentic sample of trans-β-methyl styrene was prepared by the isomerization of 3-phenylpropene with potassium amide in liquid ammonia (201). A solution of potassium amide was prepared by adding 7.72 g. (0.20 mole) of potassium to 0.240 g. of ferric nitrate nonahydrate in 300 ml. of anhydrous liquid ammonia at its boiling point. The mixture was stirred for 30 minutes after the deep blue colour of potassium metal in liquid ammonia had disappeared. 3-Phenylpropene, 10.8 g. (0.091 mole), was added dropwise to the solution and the mixture was stirred for 45 minutes. Finally, 10.6 g. (0.20 mole) of ammonium chloride and 200 ml. of ether were added. After the ammonia had evaporated, most of the ether was removed on the rotary evaporator. The products of the isomerization were separated into three components by gas chromatography using a 3/8 inch, 20 foot column of 30% SE-30 on 45/60 mesh chromosorb P at 150° and the two largest components were collected in the usual manner. The component representing 20 per cent of the mixture was identified as 3-phenylpropene by its infra-red spectrum and its retention time on the gas chromatograph. The largest component, corresponding to 79% of the total product of the isomerization, was found to have an infra-red spectrum which was identical in every respect to that reported for trans-β-methyl styrene (232). Furthermore, its N.M.R. spectrum was consistent with that expected for this compound; a doublet at 1.80 p.p.m., a multiplet centered at 6.00 p.p.m. and a phenyl absorption at 7.07 p.p.m.

Since the N.M.R. absorptions of the synthetic trans-β-methyl styrene have the same chemical shift as the new absorptions in component (2) of the reaction product from the deuterated quaternary salt and, furthermore, since the v.p.c. retention times of the trans-β-methyl styrene and phenylcyclopropane were found to be identical, it seemed likely that component (2) was a mixture of these two compounds. This was confirmed when the composition of component (2) was found to be essentially the same by three different methods of analysis. These analyses were carried out on the assumption that component (2) was a mixture of only phenylcyclopropane and trans-β-methyl styrene.

One method of analysis was based on the integration of the N.M.R. absorptions associated with the methylene protons of phenylcyclopropane and the methyl protons of trans-β-methyl styrene. The ratio of the absorptions resulting from these protons is given by

$$\frac{\text{Absorption associated with the methylene protons}}{\text{Absorption associated with the methyl protons}} = \frac{\frac{y}{100} \times 4.0}{\left(\frac{100-y}{100}\right) \times 3.0}$$

where y is the percentage of phenylcyclopropane in component (2).

The composition of the mixture was also determined from the area under the peaks in a gas chromatographic analysis. Varian

Aerograph were able to accomplish a partial separation of the two components when very small samples (less than ten microlitres) were chromatographed using temperature programming and a 40 foot, 1/4 inch column of five per cent Ucon Polar*. This separation was sufficient to allow the composition of component (2) to be estimated.

Finally, analysis of the mixture was accomplished by determining the absorbance of a solution of known concentration of component (2) in 95% ethanol at 250 mμ on a Hitachi Perkin-Elmer model 139 u.v.-visible spectrophotometer. The molar extinction coefficients of the trans-β-methyl styrene and phenylcyclopropane were found to be 16,000 and 153, respectively, at this wavelength. Since the molecular weight of both compounds in component (2) is the same, the total molar concentration of the solution is known. Consequently, the percentage of phenylcyclopropane can be calculated from equation 151.

$$\text{Absorption} = \epsilon_{\text{sty.}} \left(\frac{100-y}{100}\right) [\text{Component (2)}] + \epsilon_{\phi\text{-}\triangleleft} \left(\frac{y}{100}\right) [\text{Component (2)}] \qquad (151)$$

where $\epsilon_{\text{sty.}}$ and $\epsilon_{\phi\text{-}\triangleleft}$ are the molar extinction coefficients of trans-β-methyl styrene and phenylcyclopropane, respectively, and y is the percentage of phenylcyclopropane in component (2).

The analysis involving u.v. spectroscopy is potentially the most accurate of the three methods for determining the composition of phenylcyclopropane-trans-β-methyl styrene mixtures and it was employed

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* Ucon Polar can be purchased from Varian Aerograph, 2700 Mitchell Drive, Walnut Creek, California.

throughout the investigation for this purpose. In the single instance of the analysis of component (2) from the reaction of the deuterated quaternary salt in ammonia, the amount of sample was very small and a weighing error could be expected to produce a rather large error in the results. Nevertheless, the agreement between the results of the three methods of analysis was such that it could be safely concluded that component (2) was indeed a mixture of phenylcyclopropane and trans-β-methyl styrene.

The smallest component of the product from the deuterated quaternary salt was found to have a v.p.c. retention time identical to that of the smallest component of the product from the isomerization of 3-phenylpropene. Although this component was not present in sufficient quantity to be recovered and positively identified, there seems little doubt but that it is cis-β-methyl styrene.

The Determination of the Extent of Reaction

The extents of reaction in experiments which were stopped before all the quaternary salt had reacted were measured in two ways: a gas chromatographic analysis using the internal standard technique (207) and recovery of unreacted quaternary salt.

In the gas chromatographic analysis a calibration curve was prepared by plotting the mole ratio of phenylcyclopropane to an internal standard (ethylbenzene) against the corresponding peak area ratio for several ether solutions containing different amounts of phenylcyclopropane and a fixed amount of ethylbenzene. 3-Phenylpropene-ethylbenzene and trans-β-methyl styrene-ethylbenzene solutions also gave points which fell on the phenylcyclopropane-ethylbenzene calibration curve and it was assumed that solutions of the minor component (cis-β-methyl styrene) would behave in the same way. Since the same concentrations of all the products from the reaction produce peaks of the same size, the ratio of the sum of the peak areas of all the products to the peak area of ethylbenzene can be used to determine the total amount of hydrocarbon formed in the reaction.

The actual analysis was carried out using the following procedure. Approximately 57 mg. of ethylbenzene was mixed with the ether solution of the reaction products and the solution was diluted with ether to a volume of 250 ml. so that the concentration of ethylbenzene would be similar to that used in the calibrating solutions. The ratio of the sum of the peak areas for the products to the peak area for ethylbenzene was determined by cutting out and weighing the peaks from seven separate chromatographs and averaging the results. The corresponding mole ratio was found from the calibration curve and the total number of moles of hydrocarbon product in the ether solution was then calculated. Control experiments in which the undeuterated quaternary salt was reacted to completion showed that the total recovered hydrocarbon product corresponded to 86 ± 2 per cent of the theoretical. It follows that the extent of reaction of the quaternary salt in any experiment will be $^{100}/86$ times the extent of reaction found in the gas chromatographic analysis.

The second method of determining the extent of reaction involved the recovery of unchanged quaternary salt. The water layer from the reaction mixture, which contained potassium iodide, potassium chloride, ammonium chloride and unchanged quaternary ammonium iodide, was taken nearly to dryness on a rotary evaporator to remove any ether or ammonia. The concentrated solution was diluted to a volume of approximately 125 ml. with water. The iodides in this solution were converted to chlorides by passing the solution through an anion exchange resin (Dowex 1-X8, $^{100}/200$ mesh, [Baker]) in the chloride form. The ion exchange column was washed with an additional 250 ml. of water. After the total eluant had been taken to dryness on a rotary evaporator, the flask containing the salts was rapidly transferred to a vacuum desiccator where the chloride salts were dried for five hours at a pressure of less than 0.1 mm. A few glass beads and three times the volume of anhydrous acetone (233) required to dissolve the unreacted quaternary salt* were added to the flask containing the chloride salts and the mixture was shaken for 12 hours at room temperature. The potassium and ammonium chlorides, which are essentially insoluble in anhydrous acetone (233,234), were removed by filtration. The acetone solution of the quaternary salt was taken to dryness on the rotary evaporator. The residue was dissolved in 50 ml. of water and the solution was again taken nearly to dryness under reduced pressure to ensure that all the acetone had been removed. Approximately 70 ml. of water and 2.25 times the amount of

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* The solubility of the quaternary ammonium chloride in anhydrous acetone was found to be 0.28 g. per 100 ml. The amount of unchanged quaternary salt was calculated from the results of the gas chromatographic analysis of the hydrocarbon product.

silver oxide (235) required to convert the quaternary salt to the quaternary ammonium hydroxide* were added to the concentrated solution. The mixture was stirred for 3.5 hours, filtered and the filtrate titrated to a P_H of approximately 5.5 with a dilute solution of hydriiodic acid (Fisher Certified). The solution was left overnight, filtered through a 984 H ultra glass fiber filter (Reeve Angel) and then taken to dryness on the rotary evaporator. The solid was dried for approximately 12 hours in a vacuum desiccator at a pressure of less than 0.1 mm. The extent of reaction was calculated from the weight of the crude quaternary ammonium iodide.

The agreement between the two methods of determining the extent of reaction was found always to be within seven per cent. The method involving the recovery of the unchanged quaternary salt was considered the more accurate for two reasons. First, the extent of reaction calculated from the results of the gas chromatographic analysis using the correction factor $^{100}/86$ referred to earlier, occasionally exceeded 100 per cent, even though some unchanged quaternary salt had been recovered. Clearly, the gas chromatographic method can lead to results which are too high. The second reason is that most of the reactions in this study were stopped at quite high extents of reaction and, since the amount of unchanged starting material is small under these circumstances, a large error in the

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* The amount of quaternary ammonium chloride was calculated from the results of the gas chromatographic analysis. The reaction was carried out by treating 0.28 g. of quaternary ammonium chloride with 0.655 g. of silver oxide.

recovery of unreacted quaternary salt leads to only a small error in the extent of reaction. Control experiments in which the quaternary salt was recovered from a solution of liquid ammonia containing more than twice the amount of ammonium and potassium iodide and chloride salts that would be present in reaction mixtures have shown that the error in the extent of reaction based on the recovery of unchanged quaternary salt would not exceed three per cent. For these reasons, the extents of reaction given throughout this thesis are those calculated from the amount of unchanged starting material.

Product Analysis

In all cases, except for the reaction of the deuterated quaternary salt in ammonia, the product composition was determined by gas chromatography and ultraviolet spectroscopy. Since the thermal conductivities of all the products are identical, the percentage of each product is directly proportional to the area under the peak in the gas chromatograph. The relative amounts of 3-phenylpropene, _cis_-β-methyl styrene and the _trans_-β-methyl styrene-phenylcyclopropane mixture were determined by weighing the peaks produced by these compounds.

Ultraviolet spectroscopy was used to determine the composition of the _trans_-β-methyl styrene-phenylcyclopropane mixture. The ether solution used in the gas chromatographic analysis was concentrated by distilling the ether on a spinning band column. The concentrated solution was separated into three components by gas chromatography and the _trans_-β-methyl styrene-phenylcyclopropane mixture was condensed in a collection bottle cooled to 0° in an ice-water bath.

The composition of the mixture was then determined by the ultraviolet analysis described in the section entitled Product Analysis.

Finally, the relative amounts of γ-elimination and β-elimination were calculated.

Deuterium Tracer Studies

A Test for the Carbene Mechanism Based on the Deuterium Content of Phenylcyclopropane

This test was carried out on the phenylcyclopropane-trans-β-methyl styrene mixture obtained from the reaction of the deuterated quaternary salt in liquid ammonia. The isolation and purification of this mixture is described in the previous section.

Approximately 150 mg. of the phenylcyclopropane-trans-β-methyl styrene mixture was added to 0.25 ml. of spectrograde carbon tetrachloride (Baker) and the 60 Mc. N.M.R. spectrum was recorded (Figure 3, page 87) and integrated. The absence of the absorption associated with the methine proton of phenylcyclopropane (1.55 - 2.10 p.p.m.) is consistent with the presence of deuterium on the carbon bearing the phenyl group. The ratio of methylene : phenyl protons of phenylcyclopropane was determined from the integration of this spectrum. Although the absorption associated with the phenyl protons of phenylcyclopropane was not resolved from those of trans-β-methyl styrene, it was possible to determine their absorptions. The portion of the phenyl absorption caused by trans-β-methyl styrene was 5/3 times that of the methyl protons of this compound. Subtraction of this from the total phenyl absorption gave the absorption associated with the phenyl protons of phenylcyclopropane. Finally, the ratio of the absorptions associated with the methylene and phenyl protons of phenylcyclopropane was found to be $^{4.0}/5.0$, indicating that there was no deuterium on the methylene carbons of the cyclopropane ring.

The deuterium content of the phenylcyclopropane-trans-β-methyl styrene mixture from the reaction of the deuterated quaternary salt in liquid ammonia was also determined by mass spectrometry using a Hitachi Perkin-Elmer R.M.U.-6A mass spectrometer. The analysis required the relative peak heights of the undeuterated mixture. Furthermore, since the molar ionization efficiency of trans-β-methyl styrene and phenylcyclopropane would undoubtedly be different, the relative peak heights of the undeuterated mixture had to be determined for a sample whose composition was identical to that of the deuterated phenylcyclopropane-trans-β-methyl styrene mixture. The relative intensities of the mass peaks observed for the deuterated mixture (71% phenylcyclopropane, 29% trans-β-methyl styrene) and the undeuterated mixture (71.6% phenylcyclopropane, 28.4% trans-β-methyl styrene) at an electrode voltage of 8.5 are given in Table XVI.

Table XVI. The Relative Intensities of the Molecular Ion and Fragment Ion Peaks of the Deuterated and Undeuterated Phenylcyclopropane-Trans-β-Methyl Styrene Mixtures at 8.5 Electron Volts

Mass Peak	Relative Intensities of the Mass Peaks in the Undeuterated Mixture	Relative Intensities of the Mass Peaks in the Deuterated Mixture
120	-	10.05
119	10.05	100.0
118	100.0	8.80
117	3.0	-

The peak heights of the 120, 119, and 118 mass peaks in the deuterated mixture can be expressed in terms of the relative amounts of the di-, mono-, and undeuterated species in the mixture if it is assumed that the fragmentation pattern for the mono- and dideuterated species is the same as that of the undeuterated species. It follows that

$$10.05 = \left(\frac{100.0}{100.0}\right) x + \left(\frac{10.05}{100.0}\right) y$$

$$100.0 = \left(\frac{100.0}{100.0}\right) y + \left(\frac{3.0}{100.0}\right) x + \left(\frac{10.05}{100.0}\right) z$$

$$8.80 = \left(\frac{100.0}{100.0}\right) z + \left(\frac{3.0}{100.0}\right) y$$

where x, y and z are the relative amounts of the dideuterated, monodeuterated and undeuterated species, respectively. Solving these equations and expressing the amount of each species as a percentage shows that less than 0.1 per cent of the <u>trans</u>-β-methyl styrene-phenylcyclopropane mixture is dideuterated while 94.4 per cent is monodeuterated and 5.5 per cent is undeuterated.

A Test for the Ylide Mechanism Based on the Deuterium Content of the Trimethylamine

The reaction involved in this study was performed using the procedure described in the section entitled General Experimental Procedure. The conditions of this reaction differed from those described in that the solution in Flask B consisted of 0.44 g. (1.4×10^{-3} mole) of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide in 45 ml. of liquid ammonia and the solution in Flask A was prepared by reacting 0.30 g. (7.7×10^{-3} mole) of potassium with 65 ml. of liquid ammonia. The reaction was carried out for 30 minutes and was quenched by adding 0.82 g. (1.5×10^{-2} mole) of ammonium chloride. One hundred ml. of ether was added and the ammonia and trimethylamine from the reaction were allowed to evaporate into one litre of concentrated hydrochloric acid which was stirred and cooled in an ice-water bath. The hydrochloride salts were recovered by removing the solvent under reduced pressure on a steam bath. After drying the salts for 8 hours in a vacuum desiccator over potassium hydroxide pellets, the trimethylammonium chloride, which is soluble in absolute ethanol and chloroform, was extracted from the large excess of ammonium chloride which is virtually insoluble in these solvents (209), by stirring the hydrochloride salts at room temperature with 600 ml. of absolute ethanol for 21 hours, and with two 550 ml. portions of chloroform for 24 hours. The combined ethanol and chloroform solutions were evaporated leaving an impure mixture of hydrochloride salts. This material was stirred at room temperature with 500 ml. of chloroform for 24 hours. The solid obtained on removal of the chloroform was dissolved in 10 ml. of cold ethanol and the solution made basic to phenolphthalien by adding a solution of sodium ethoxide in ethanol. The trimethylamine in this solution was separated from the small amount of ammonia (less than one per cent) using a ten foot 3/8 inch column of 20% Amine 220 on $^{60}/80$ mesh base washed Chromosorb W* at 55°. The trimethylamine from the gas chromatograph was collected in the apparatus shown in figure 7. The collection of the trimethylamine

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* The column and packing were purchased from Varian Aerograph, 2700 Mitchell Driver, Walnut Creek, California.

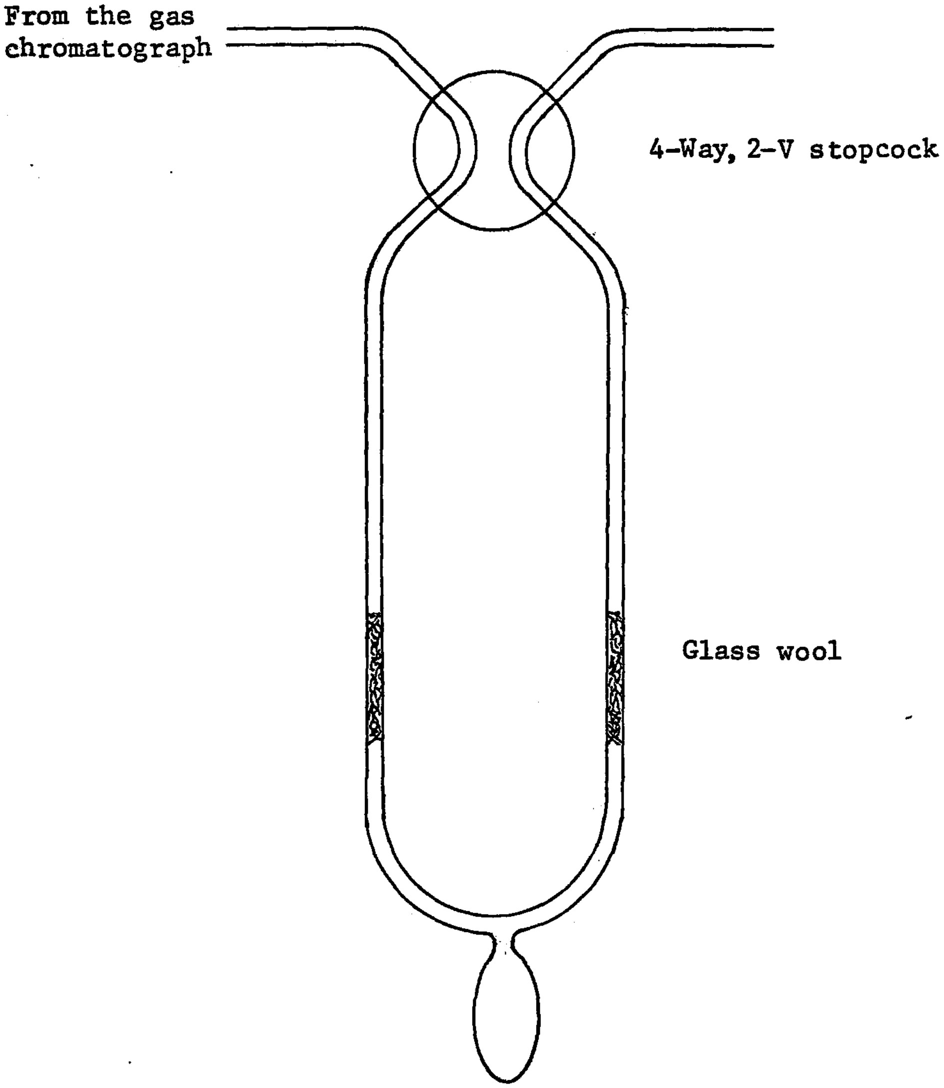

Fig. 7. The apparatus used to collect the trimethylamine for mass spectrometric analysis.

was accomplished by turning the 4-way, 2V stopcock so that effluent from the chromatograph passed through the lower portion of the collection apparatus which was immersed in liquid nitrogen. When the collection was complete one end of the apparatus was sealed and the other was joined to a vacuum line fitted with a break-seal tube. The trimethylamine was frozen by means of liquid nitrogen and the helium trapped in the lower portion of the collection apparatus was then removed by evacuation. The 4-way stopcock was closed, the liquid nitrogen bath removed and the system evacuated to a pressure of less than ten microns. After isolating the manifold of the vacuum line, the 4-way stopcock was opened and the trimethylamine was distilled over a period of 30 minutes into the break-seal tube cooled in liquid nitrogen. The break-seal tube was then sealed.

A sample of trimethylamine (Eastern) was purified by gas chromatography, collected and transferred to a break-seal tube using the procedure described above. This material was the standard sample of undeuterated trimethylamine in the mass spectrometric analysis.

The break-seal tubes were attached to the Hitachi Perkin-Elmer R.M.U.-6A mass spectrometer and the spectrum of both samples of trimethylamine were recorded at an electrode voltage of 80. The heights of the mass peaks were calculated relative to the mass 59 peak which was arbitrarily assigned a height of 100.

The amount of trimethylamine recovered from the reaction of the deuterated quaternary salt in liquid ammonia was estimated in the following manner. The trimethylamine that was not used in the mass spectrometric analysis was sublimed into the break-seal tube with liquid nitrogen. The break-seal tube was removed from the mass spectrometer, attached to a vacuum line and the trimethylamine distilled *in vacuo* into an excess of 0.01 N sulphuric acid. The amount of trimethylamine in the acid solution was determined by titrating the excess acid with 0.01 N sodium hydroxide. It was found that at least 38% of the trimethylamine produced in the reaction of the deuterated quaternary salt had been recovered.

A Test for Isotopic Exchange at the γ-Carbon

The two deuterium exchange tests involving the deuterated quaternary salts in liquid ammonia were performed using only 1.1 g. of quaternary salt. The procedure used in these tests was otherwise identical to that described in the section entitled General Experimental Procedure. Both reactions were allowed to proceed for nine minutes. The unreacted quaternary salt was recovered using the method described in the section headed The Determination of the Extent of Reaction. The two reactions, based on the recovered material, were 64.9 and 66.7% complete. The recovered quaternary salts were recrystallized to constant melting point (178.0-178.5°, uncorrected) from ethanol-diethyl ether. Both the recovered quaternary salt and the starting material were analyzed in Nemeth's laboratory for their deuterium content.

A control experiment, designed to establish the extent to which deuterium might be lost during the recovery and purification of the unreacted quaternary salt, was carried out as follows. A sample of deuterated quaternary salt was recovered from an ammonia solution containing a larger quantity of impurities than were present in the exchange reactions and purified by recrystallization. Both the recovered sample and a sample of the starting material were analyzed for deuterium. The deuterium content of the quaternary salt recovered from the synthetic mixture was found to be identical to that of the starting material, indicating that deuterium is not lost in either the recovery or the purification of the unreacted quaternary salt.

Kinetic Isotope Effects

Hydrogen Isotope Effect Using the Competative Method

This experiment was designed to determine the relative rates of reaction of the undeuterated and dideuterated quaternary salts. This was accomplished by reacting a sample consisting of both the dideuterated and undeuterated quaternary salts part way to completion. The relative rates of reaction of these two compounds were calculated from the amounts of each species recovered from the reaction.

The reactant used in this experiment was a mixture consisting of 47.5 per cent dideuterated and 52.5 per cent undeuterated quaternary salt. Although the procedure was identical to that used in the other reactions, the solution in flask B consisted of 0.753 g. (2.45×10^{-3} mole) of quaternary salt in 300 ml. of liquid ammonia and the solution in flask A was prepared from 0.309 g. (7.5×10^{-3} mole) of potassium and 150 ml. of liquid ammonia. On the basis of crude rate data, the reaction was quenched after 92 seconds by adding 1.2 g. (2.2×10^{-2} mole) of ammonium chloride. The unreacted quaternary salt was recovered, purified by the method described in the section entitled The Determination of the Extent of Reaction and analyzed for its deuterium content.

The hydrogen isotope effect associated with the disappearance of the dideuterated and undeuterated quaternary salts was calculated using equation 137 (page 102).

$$k_H/k_D = 1.00 + \frac{\log\left(\dfrac{\text{salt}_{Ht}/\text{salt}_{Dt}}{\text{salt}_{Ho}/\text{salt}_{Do}}\right)}{\log(1-f)\left(\dfrac{1 + \text{salt}_{Ho}/\text{salt}_{Do}}{1 + \text{salt}_{Ht}/\text{salt}_{Dt}}\right)} \qquad (137)$$

where $\text{salt}_{Ho}/\text{salt}_{Do}$ is the ratio of undeuterated to dideuterated salt in the starting material, $\text{salt}_{Ht}/\text{salt}_{Dt}$ is the corresponding ratio in the recovered quaternary salt and f is the total mole fraction of undeuterated and dideuterated quaternary salt that has reacted, including the dideuterated salt which had been converted to monodeuterated quaternary salt by exchange with solvent. Although $\text{salt}_{Ho}/\text{salt}_{Do}$ was known, it was impossible to establish the exact values of $\text{salt}_{Ht}/\text{salt}_{Dt}$ and f. The unreacted quaternary salt mixture consisted of di-, mono- and undeuterated quaternary salt and, as a result, $\text{salt}_{Ht}/\text{salt}_{Dt}$ could not be calculated from the per cent excess deuterium in the recovered material without a knowledge of the amount of monodeuterated salt present. As outlined in the section headed Hydrogen Isotope Effect (see page 103), values of $\text{salt}_{Ht}/\text{salt}_{Dt}$ were calculated from the observed deuterium content of the recovered quaternary salt for several different concentrations of monodeuterated salt ranging from zero to 10.8 per cent, the amount found in an exchange test carried to a greater extent of completion. The corresponding values of f were also calculated. These values of f and $\text{salt}_{Ht}/\text{salt}_{Dt}$ were substituted along with $\text{salt}_{Ho}/\text{salt}_{Do}$ into equation 137 and the isotope effects were calculated.

Nitrogen Isotope Effect

A kinetic isotope effect can be determined by comparing the isotopic ratios of the atom of interest in the initial reactant and the reactant recovered from a reaction which had been allowed to proceed to more than 50 per cent completion, or alternatively, by comparing the isotopic ratio in the reactant and the product formed during a relatively small extent of reaction. The former method was used in this case because it was impossible to recover the trimethylamine quantitatively from the large excess of ammonia. Several reactions were taken to extents of reaction varying from 53 to 94 per cent. The unreacted quaternary salt from these reactions was recovered and purified. Samples of the starting material and the unreacted starting material were decomposed in a Kjeldahl digestion which converted the nitrogen to ammonium sulfate. The ammonium salt was subsequently oxidized to nitrogen which was collected and examined by mass spectrometry. The nitrogen isotope effect was calculated from the isotopic ratios of the nitrogen from these samples.

The reactions involved in the determination of the nitrogen isotope effect were performed exactly as described in the section headed General Experimental Procedure. The unreacted quaternary salt was recovered and purified in the usual manner (see page 168).

Kjeldahl Digestion of 3-Phenylpropyltrimethylammonium Iodide

The iodide ion was oxidized to iodine which was removed by distillation prior to the Kjeldahl digestion since it had been previously observed (237) that it is impossible to obtain a quantitative conversion of the nitrogen to ammonium sulfate in the Kjeldahl digestion in the presence of halide ions. Between 0.061 and 0.068 g. (2×10^{-4} mole) of 3-phenylpropyltrimethylammonium iodide was weighed into a 25 ml. Kjeldahl flask and 1 ml. of water, 0.5 ml. of 30% hydrogen peroxide (Fisher Reagent) and 0.5 ml. of concentrated sulphuric acid were added. The mixture was boiled to expel the iodine and most of the water. One hundred milligrams of red mercuric oxide (Baker and Adamson), 1.5 g. of potassium sulfate (Analar) and 2.5 ml. of concentrated sulphuric acid were added and the mixture was refluxed for eight hours. The samples were cooled and transferred to a Kjeldahl distillation apparatus. The samples were made basic by adding 25 ml. of 40% sodium hydroxide containing 5% sodium thiosulfate (238,239) and the ammonia was distilled into an excess of 0.01 N sulphuric acid. The yield of ammonia was determined by titrating the excess acid with standard base using bromocresol green (a nitrogen-free compound) as the indicator. The samples were acidified immediately after the titration to prevent the loss of ammonia. The conversion to ammonium sulfate was 94% ± 3%.

Preparation of Nitrogen Samples for Mass Spectrometric Analysis

The high vacuum system used to prepare the nitrogen samples for mass spectrometric analysis is shown in figure 8. The ammonium

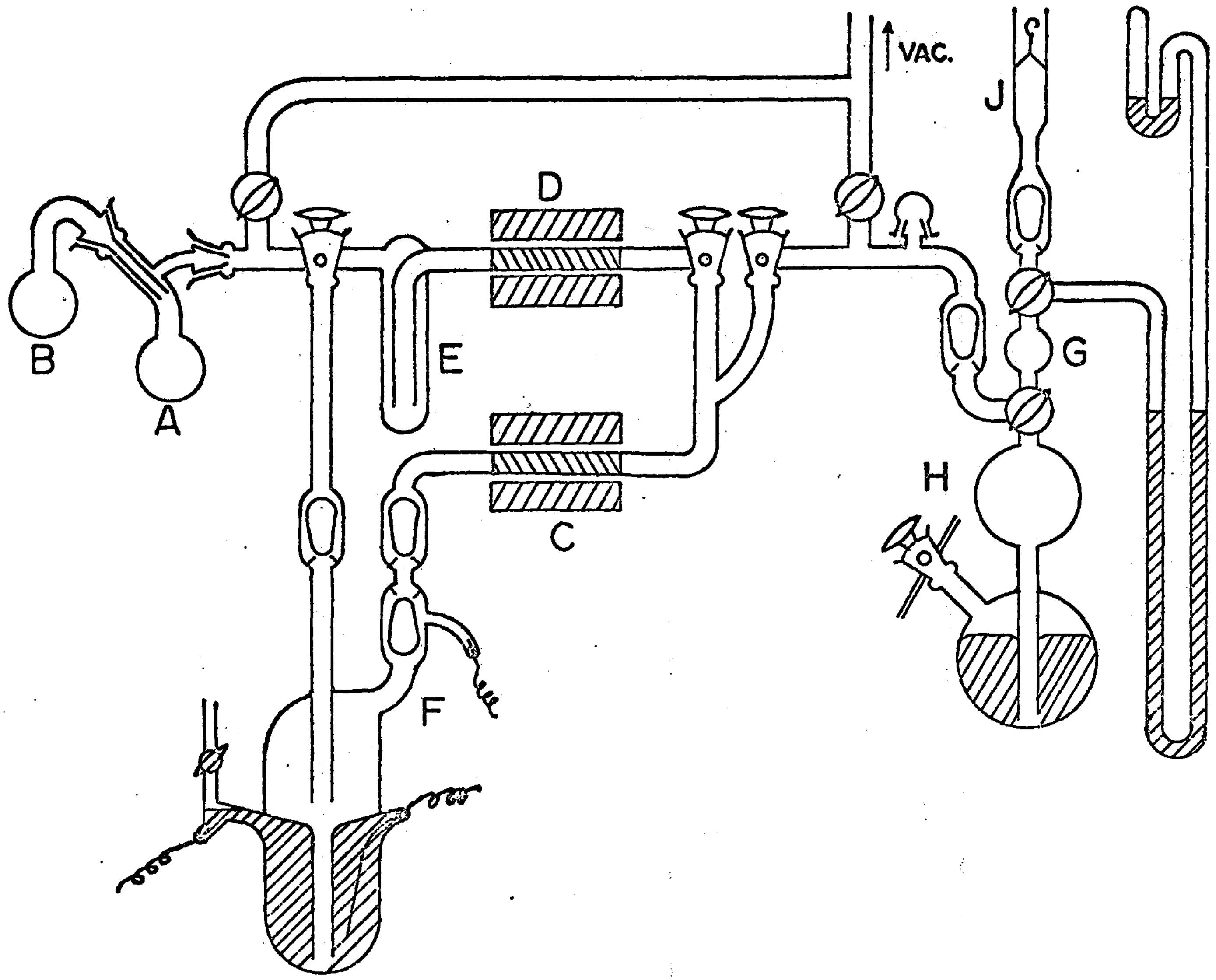

Fig. 8. Apparatus used for the preparation and purification of nitrogen samples.

sulfate solution was evaporated under reduced pressure to a volume of approximately five ml. This solution was transferred to flask A and concentrated to a volume of about 3 ml. Flask A and flask B, which contained 6 ml. of sodium hypobromite and 4 ml. of water, were inserted into the vacuum line and the system was partially evacuated. The solutions in both flasks were frozen with liquid nitrogen. After the flasks had been evacuated for five minutes, both solutions were melted. This degassing procedure was repeated two more times. Flasks A and B were isolated and the nitrogen liberated by inverting flask B so as to transfer the sodium hypobromite solution to flask A. Both flasks were frozen and the nitrogen was pumped into the purification system during 45 minutes by means of a Urry toeppler pump, F, (241). The gas was circulated through furnace C filled with copper wire (Baker Analyzed), furnace D containing copper oxide (British Drug Houses Microanalytical) (242) and micro silver wool (Fisher) at 750° and trap E cooled in liquid nitrogen. In this way carbon monoxide was oxidized to carbon dioxide by the hot copper oxide, halogen was removed by the hot silver wire and oxygen was converted to copper oxide by reaction with the hot copper. Carbon dioxide and water were removed in the liquid nitrogen trap E. After purification, the gas was transferred by means of a manual toeppler pump, H, to a calibrated blub, G, where the yield of nitrogen was determined from its temperature, pressure and volume. The nitrogen was then pushed into the break-seal tube, J, which was sealed. The yield of nitrogen in this process was 96% ± 4%.

Mass Spectrometric Analysis

The relative abundances of the nitrogen isotopes were measured using a 6-inch 90-degree simultaneous collection mass spectrometer similar to that described by Thode and Wanless (243). This instrument was capable of measuring changes in isotopic ratios with a precision of ±0.02 per cent. A standard nitrogen sample with a $^{28}/29$ mass ratio arbitrarily taken as 136.50 was used in all the analyses and the mass ratios of all the samples were determined relative to this arbitrary standard. The collector of a single beam instrument was modified so that ion currents resulting from ions of mass 28 and 29 could be simultaneously collected and measured by a null method. A magnetic valve system permitted rapid switching from the standard nitrogen to the unknown nitrogen sample. The measurements were made by amplifying the ion current produced by the mass 28 beam and applying it to a put-and-take potentiometer. A portion of the current from the potentiometer was balanced against the separately amplified ion current from the mass 29 beam and the balance point was recorded on a Minneapolis Honeywell Brown Electronik Recorder. This balance point varies as the isotopic ratio of the sample and, therefore, a shift in the balance point is a measure of mass $^{28}/29$ ratio relative to that of the standard sample. The ion current from the mass 28 beam was used as the reference voltage and was adjusted to the same value for both the standard and the sample by changing the gas pressure of the sample until the peak height of mass 28, measured on a single collection, was identical to 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 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 isotopic ratio of the sample relative to that of the standard. The N^{14}/N^{15} mass ratios were simply twice the observed N^{28}/N^{29} ratios.

The N^{14}/N^{15} ratios obtained in the mass spectrometric analysis are given in Table XVII. The nitrogen isotope effect was calculated from equation 139 (page 110).

$$k^{14}/k^{15} = 1.00 + \frac{\log R_f/R_o}{\log(1 - f)\left(\frac{1 + R_o}{1 + R_f}\right)} \tag{139}$$

where R_f is the N^{14}/N^{15} mass ratio of the nitrogen from the unreacted quaternary salt, R_o is the corresponding ratio in the starting material and f is the mole fraction of quaternary salt that has reacted. R_o was the average value of the N^{14}/N^{15} ratio observed for nine samples of quaternary salt. The R_f values were obtained from individual samples of quaternary salt.

A control experiment designed to determine the extent of fractionation of nitrogen isotopes in the recovery and purification of the unchanged quaternary salt and in the conversion of the quaternary salt to nitrogen gas is described below. Several samples of quaternary salt were recovered from ammonia solutions containing more than twice the amount of ammonium and potassium iodide and chloride salts that would be present in reaction mixtures, purified and decomposed to nitrogen which was examined on the mass spectrometer.

Table XVII. The $^{N^{14}}/_{N^{15}}$ Ratios and Nitrogen Kinetic Isotope Effect in the γ-Elimination Reaction of 3-Phenylpropyltrimethylammonium Iodide with Potassium Amide in Liquid Ammonia at -55°

Experiment Number	Extent of Reaction %	$^{N^{14}}/_{N^{15}}$ Ratio[a]	$^{k^{14}}/_{k^{15}}$ [b]
1	100	271.58	-
2	100	271.76	-
3	100	271.59	-
4	100	271.73	-
5	100	271.60	-
6	100	271.90	-
7	100	271.73	-
8	100	271.56	-
9	100	271.91	-
10	53	267.47	1.0213
11	70	264.93	1.0215
12	80	261.99	1.0232
13	82	262.37	1.0208
14	84	261.17	1.0221
15	94	254.94	1.0232
			mean = 1.0220 ± 0.001

a. The ratios are relative to the standard nitrogen sample whose $^{N^{28}}/_{N^{29}}$ ratio was arbitrarily taken as 136.50.

b. The limits shown are standard deviation.

The $^{N^{14}}/_{N^{15}}$ ratio in the recovered samples was found to be identical to that of the starting material indicating that there was no fractionation of nitrogen isotopes in either the recovery and purification of the quaternary salt or in the conversion of the quaternary salt to nitrogen.

Studies in Ammonia-$\underline{d}_3$

The reactions of the deuterated and undeuterated quaternary salts with potassium amide-$\underline{d}_2$ in ammonia-$\underline{d}_3$ were carried out using the method described in the section entitled General Experimental Procedure.

Reaction of 3-Phenylpropyltrimethylammonium Iodide in Ammonia-$\underline{d}_3$

The solution in flask B consisted of 1.105 g. (3.62 x 10^{-3} mole) of the undeuterated quaternary salt in 100 ml. of ammonia-$\underline{d}_3$ (Merck, Sharp and Dohme). The solution in flask A was prepared by reacting 0.114 g. (2.93 x 10^{-3} mole) of potassium with 75 ml. of ammonia-$\underline{d}_3$. Although the base was undoubtedly consumed in the first few minutes, the reaction was allowed to proceed for 45 minutes before 0.321 g. (6.0 x 10^{-3} mole) of ammonium chloride was added. The reaction mixture was completely colourless rather than the deep reddish brown colour observed in all the other reactions in this study.

The unreacted quaternary salt was recovered and purified using the method described in the section on The Determination of the Extent of Reaction. The amount of recovered quaternary salt indicated that the reaction had gone 11% to completion. The purified quaternary salt was examined both by N.M.R. and infra-red spectroscopy in an effort to detect exchange at the γ-position. The 100 Mc. N.M.R. spectrum was recorded on an HA 100 Varian Aerograph N.M.R. spectrometer. The percentage of α-, β-, γ- and N-methyl protons that had exchanged with solvent during the reaction was calculated from the integration of the N.M.R. spectrum. An estimate of the amount of exchange at these positions was also obtained from a comparison of the intensities of the infra-red absorptions of the starting material and the recovered quaternary salt.

A gas chromatographic analysis was carried out on the ether solution in an effort to detect 3-phenylpropene and cis-β-methyl styrene in the product. The method employed in this analysis was identical to that described in the section entitled Product Analysis. Neither 3-phenylpropene nor cis-β-methyl styrene could be detected in the product of this reaction. After this analysis had been completed, the ether solution was concentrated by distillation on a spinning band column. This reaction had been taken only 11% to completion and, therefore, the amount of product was much less than usual, with the result that it was not possible to determine the amount of trans-β-methyl styrene in the usual manner (purification of the trans-β-methyl styrene-phenylcyclopropane mixture by gas chromatography and analysis of the mixture by ultra violet spectroscopy). Consequently, a gas chromatographic analysis was performed on the residue from the distillation of the ether solution in an effort to detect trans-β-methyl styrene in the product. The separation of trans-β-methyl styrene and phenylcyclopropane was accomplished on a Model 204-B gas chromatograph fitted with a hydrogen-flame ionization detector and a 25 foot 1/4 inch column of 5% Zonyl E-7* on 60-80 mesh chromosorb P. Temperature programming from 60° to 150° at the rate of 2°/minute was employed. No _trans_-β-methyl styrene was detected in this analysis.

A control experiment was used to show that less than 0.4% of the product from the reaction of the undeuterated quaternary salt in ammonia-$\underline{d}_3$ was formed in a β-elimination reaction. A solution of potassium amide prepared by reacting 0.2 g. (5.1×10^{-3} mole) of potassium with 175 ml. of ammonia, became noticeably coloured when one drop (4.2×10^{-3} g.) of a phenylcyclopropane solution containing 4.4% 3-phenylpropene was added. This one drop of the phenylcyclopropane solution contained the same amount of 3-phenylpropene that would have been present in the reaction mixture if 0.4 per cent of the product from the reaction of the undeuterated quaternary salt in ammonia-$\underline{d}_3$ was formed in a β-elimination process. Since the control experiment gave a coloured solution while the reaction mixture was colourless, it was concluded that significantly less than 0.4 per cent of the product was produced in a β-elimination reaction when the undeuterated quaternary salt is treated with potassium amide-$\underline{d}_2$ in ammonia-$\underline{d}_3$.

Reaction of 3,3-Dideutero-3-phenylpropyltrimethylammonium Iodide in Ammonia-$\underline{d}_3$

In the reaction of the deuterated quaternary salt with

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* This material was purchased from Varian Aerograph, 2700 Mitchell Drive, Walnut Creek, California.

potassium amide-$\underline{d}_2$ in liquid ammonia-$\underline{d}_3$, flask B contained a solution of 0.97 g. (3.16 x 10^{-3} mole) of 3,3-dideutero-3-phenylpropyltrimethylammonium iodide in 100 ml. of ammonia-$\underline{d}_3$, while flask A contained a solution of potassium amide-$\underline{d}_2$ prepared from 0.35 g. (9.0 x 10^{-3} mole) of potassium and 75 ml. of ammonia-$\underline{d}_3$. The reaction was stopped after 90 minutes by adding 1.54 g. (2.68 x 10^{-2} mole) of ammonium chloride. The ratio of γ-elimination : β-elimination in the hydrocarbon product was determined by the method described in the section headed Product Analysis.

This reaction was allowed to proceed for a much longer time than the other reactions in this study and it seemed possible that some of the β-methyl styrene formed during the reaction could have polymerized thus causing an error in the product ratio. This was shown not to be the case by a control experiment in which 0.600 g. of a phenylcyclopropane solution containing 27.2% 3-phenylpropene was treated for 90 minutes with a solution of potassium amide prepared by reacting 0.395 g. (1.01 x 10^{-2} mole) of potassium with 175 ml. of liquid ammonia. The reaction was quenched by adding 0.54 g. (1.01 x 10^{-2} mole) of ammonium chloride. The percentage of olefins in the hydrocarbon product was determined in the usual manner. The product was found to be 27.0% olefin indicating that little or no β-methyl styrene polymerized during this experiment even though the concentrations of both the β-methyl styrene and potassium amide were higher than in the reaction of the deuterated quaternary salt in ammonia-$\underline{d}_3$.

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