

β -HYDROGEN ISOTOPE EFFECTS IN THE ELIMINATION REACTION
OF threo-1,2-DIPHENYL-1-PROPYLTRIMETHYLAMMONIUM IODIDE.

β -HYDROGEN ISOTOPE EFFECTS IN THE ELIMINATION REACTION
OF threo-1,2-DIPHENYL-1-PROPYLTRIMETHYLAMMONIUM IODIDE.

by

LAWRENCE LAU, B.Sc. Hons.

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

April 1974

MASTER OF SCIENCE (1974)
(Chemistry)

McMASTER UNIVERSITY
Hamilton, Ontario.

TITLE: β -Hydrogen Isotope Effects in the
Elimination Reaction of threo-1,2-Diphenyl-
1-propyltrimethylammonium Iodide.

AUTHOR: Lawrence Lau, B.Sc. Hons. (University of Singapore)

SUPERVISOR: Dr. A.N. Bourns

NUMBER OF PAGES: viii, 124

SCOPE AND CONTENTS:

α -Epimerisation has been found to be absent in the reactions of threo-1,2-diphenyl-1-propyltrimethylammonium ion and its -2-d₁ analogue with t-butoxide ion in t-butyl alcohol at 30°C. The formation of trans- α -methylstilbene, cis- α -methylstilbene and threo-N,N-dimethyl-1,2-diphenyl-1-propylamine has been associated with anti-elimination, syn-elimination and with nucleophilic substitution at a N-methyl carbon atom, respectively, and interpreted in terms of structural and medium features of the reactions. The β -hydrogen isotope effects for anti- and syn-elimination have been associated with reactant-like and product-like transition states, respectively, for these reaction modes.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. A.N. Bourns for his supervision of this research. He also wishes to thank Dr. A.C. Frosst for his special assistance.

The author is grateful to Dr. R.F. Childs, Dr. John Warkentin, Dr. N.H. Werstiuk and Dr. Peter Schmid for their helpful suggestions, and to Mr. Brian Sayer for recording the 100 MHz Proton Magnetic Resonance spectra.

This research was supported by the Chemistry Department, the Ontario Government and the National Research Council.

TABLE OF CONTENTS

	Page
GENERAL INTRODUCTION	1
HISTORICAL INTRODUCTION	6
A - Mechanisms of Elimination Reactions	
of $H - C_{\beta} - C_{\alpha} - X$ Systems	6
Determination of β -Elimination Mechanism	13
B - Isotope Effects	
General	18
Isotope Effects in a Simple Bond Breaking	
Process	19
Hydrogen Isotope Effects	21
Theoretical Calculations of Isotope Effects in	
β -Elimination Reactions	23
C - The Nature of the Transition State in	
E2 Processes	27
D - A Short Note on the <u>Syn-Anti</u> Dichotomy	52
RESULTS AND DISCUSSION	65
EXPERIMENTAL	
The Synthesis of <u>threo</u> -1,2-Diphenyl-1-propyltrimethyl-	
ammonium Iodide	90
The Synthesis of <u>threo</u> -1,2-Diphenyl-1-propyltrimethyl-	
ammonium-2- <u>d</u> ₁ Iodide	97
Purification of Solvent and Preparation of Base	
Purification of <u>t</u> -Butyl Alcohol	100
Preparation of Potassium <u>t</u> -Butoxide in <u>t</u> -Butyl	
Alcohol Solutions for Kinetic Measurements and	
Reaction Product Analyses	100

Test for Isomerisation of <u>cis</u> - α -Methylstilbene to	
<u>trans</u> - α -Methylstilbene	102
Test for Epimerisation at the α -Carbon Atom	102
Product Analyses by Gas-Liquid Partition Chromatography	103
Internal Standardisation for Gas-Liquid Partition	
Chromatographic Product Analysis	105
Determination of the Product Distributions associated with	
the Reactions of the Undeuteriated and Deuteriated Quaternary	
Ammonium Salts with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl	
Alcohol at 30°C.	105
Kinetic Studies	
General	107
Kinetic Measurements	108
APPENDIX	
Kinetic Data and Plots of Kinetic Experiments for the Reactions	
of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide and	
<u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide	110
REFERENCES	118

LIST OF TABLES

Number	Title	Page
I	β -Hydrogen Isotope Effects and Hammett Reaction Constants for the Reaction of 2-Phenylethyl Derivatives with Sodium Ethoxide in Ethanol at 30°C.	31
II	Isotope Effects for Reactions of 2-Phenylethyl Derivatives with Hydroxide Ion in Water	32
III	Isotope Effects in the E2 Reactions of Ethyltrimethylammonium and 2-Phenylethyltrimethylammonium Ions at 60°C.	34
IV	Isotope Effects for the E2 Reactions of 2-Arylethyltrimethylammonium Ions with Sodium Ethoxide in Ethanol at 40°C.	35
V	Hammett Correlations and Isotope Effects in the Reactions of Ethyltrimethylammonium Ion and 2-Phenylethyltrimethylammonium Ion with Ethoxide Ion and <i>t</i> -Butoxide Ion	36
VI	Eliminations from 2-Hexyl Halides at 100°C.	48
VII	Mechanism of Hofmann Elimination of Cycloalkyltrimethylammonium Hydroxides	53
VIII	Stereochemistry of E2 Reactions of Acyclic Quaternary Ammonium Salts	60
IX	Eliminations from PhCHDCHDX using <i>t</i> -Butoxide	62
X	Proton Magnetic Resonance Integrations for α -Hydrogen and Phenyl-Hydrogens of <u>trans</u> - α -Methylstilbene and Recovered Olefin from α -Epimerisation Test ..	68
XIa	Product Analyses of the Reactions of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <i>t</i> -Butoxide in Anhydrous <i>t</i> -Butyl Alcohol at 30°C. using <u>trans</u> -Stilbene as Internal Standard	69
XIb	Product Analyses of the Reactions of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide with Potassium <i>t</i> -Butoxide in Anhydrous <i>t</i> -Butyl Alcohol at 30°C. using <u>trans</u> -Stilbene as Internal Standard	69

Number	Title	Page
XII	Extrapolated Product Compositions of Olefins and Tertiary Amine for Reactions of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Ion and its <u>-2-d</u> Analogue with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	76
XIII	Rate Constants and β -Hydrogen Isotope Effects for <u>Syn</u> - and <u>Anti</u> -Elimination and "Substitution Isotope Effect" for Nucleophilic Substitution Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	77
XIV	Ultraviolet Absorption of the α -Methylstilbenes	108
XV	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	110
XVI	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	111
XVII	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	112
XVIII	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2- <u>d</u> Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	115
XIX	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2- <u>d</u> Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	116
XX	Kinetic Data for the Reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2- <u>d</u> Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	117

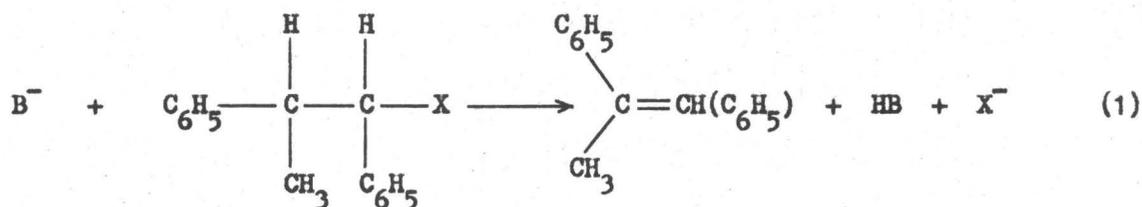
LIST OF FIGURES

1	A Plot of Energy against Reaction Coordinate for a Simple Bond Breaking Process	15
2	A Plot of (k^H/k^D) against Extent of Proton Transfer ..	22

Number	LIST OF FIGURES	Page
3	A plot of (k^H/k^D) against Extent of Proton Transfer and A	25
4	The Effects of a Linear Perturbation on the Parallel and Perpendicular Motions of the Transition State	37
5	P.E. Surfaces for the "Normal" and "E1cB-like" E2 Transition States	41
6a	Plot of % Yield of <u>cis</u> - α -Methylstilbene against Concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide	70
6b	Plot of % Yield of <u>cis</u> - α -Methylstilbene against Concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide	71
7a	Plot of % Yield of <u>trans</u> - α -Methylstilbene against Concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide	72
7b	Plot of % Yield of <u>trans</u> - α -Methylstilbene against Concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide	73
8a	Plot of % Yield of <u>threo</u> -N,N-Dimethyl-1,2-diphenyl-1-propylamine against concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide	74
8b	Plot of % Yield of <u>threo</u> -N,N-Dimethyl-1,2-diphenyl-1-propylamine-2-d ₁ against concentration of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide	75
9	Apparatus for Preparation of Potassium <u>t</u> -Butoxide Solution	101
10	Plot of the kinetic data given in Table XVI for a typical experiment for the reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	113
11.	Plot of the kinetic data given in Table XX for a typical experiment for the reaction of <u>threo</u> -1,2-Diphenyl-1-propyltrimethylammonium-2-d ₁ Iodide with Potassium <u>t</u> -Butoxide in Anhydrous <u>t</u> -Butyl Alcohol at 30°C.	114

GENERAL INTRODUCTION

In 1927, Hanhart and Ingold (1) formulated the anti-rule for E2 bimolecular elimination reactions of $H - C_{\beta} - C_{\alpha} - X$ systems, according to which, the E2 transition state has an anti-periplanar (2) orientation of the β -hydrogen atom and the leaving group, X. So convincing was the evidence (3-14) and so few were the exceptions (15-19) that the anti-rule was considered until about 1966 to be almost inviolable. Included in the evidence supporting this mode of elimination was the work, in 1956, of Cram, Greene and DePuy (7) who, in one of the most thorough studies of the stereochemistry of elimination, observed that, with only one exception, the erythro and the threo diastereomers of 1,2-diphenyl-1-propyl derivatives undergo exclusive anti-elimination with alkoxide ion in alcohol to give cis- and trans- α -methylstilbene, respectively, when the leaving groups were bromide, chloride and trimethylammonio. The exception was the reaction of the



trimethylammonium salt ($X = \overset{+}{N}Me_3$) with potassium t-butoxide in t-butyl alcohol where both diastereomers gave trans- α -methylstilbene. Since the cis-olefin was found not to isomerise to the trans-olefin under the reaction conditions, it was considered that the elimination from the erythro reactant was a syn-process. At that time, however, the precon-

ception against the syn-pathway was such that the anomalous behaviour of the erythro reactant was rationalised in terms of either an epimerisation at C_{α} followed by elimination or an E1cB elimination via a carbanion that inverts faster than it decomposes to olefin.

At the time of this writing, the syn-pathway is no longer considered to be an anomalous mechanism. Indeed, since about 1966, the application of new analytical techniques, notably gas-liquid partition chromatography, has opened up a new dimension in the study of β -elimination reactions. The work of Sicher and his associates (20-37), that of Saunders and his associates (38-42), that of DeFuy and his associates (19,43) and that of Coke and his associates (44,45) indicate that syn-elimination reactions are more general than had been supposed. Their investigations show that syn- and anti-pathways do occur concurrently in some elimination reactions and that by a judicious manipulation of substrate structure and reaction conditions, it is possible to make syn-elimination the dominant or even exclusive reaction pathway. Sicher and his associates called such a hitherto unobserved phenomenon the Syn-Anti Dichotomy to which the work of this thesis provides, in part, another piece of supporting evidence.

Another very important aspect of the study of β -elimination reactions with which this thesis is concerned is related to the extent to which reacting bonds are broken at the transition state. According to Ingold (46) and Bunnett (47), an E2 transition state is highly variable ranging from a carbanion-like (E1cB-like) extreme characterised by extensive $C_{\beta}-H$ bond breaking and a little $C_{\alpha}-X$ bond breaking, to a central or E2 transition state in which both bonds are equally broken, to a carbonium ion-like (E1-like) extreme in which the $C_{\alpha}-X$ bond

is broken extensively and the $C_{\beta}-H$ bond essentially intact. Furthermore, Bunnett envisions that the actual position of the transition state is dependent upon such factors as reaction conditions and substrate structure. Of particular interest has been Bunnett's view that any factor which facilitates the breaking of one bond will cause that bond to be stretched more at the transition state with a concomitant reduced stretching of the other reacting bond. Accordingly, at the transition state, the $C_{\beta}-H$ bond will be lengthened monotonically and the $C_{\alpha}-X$ bond shortened when a substrate undergoes elimination with a series of bases of increasing strength, or when a series of related substrates having electron-withdrawing substituents of increasing strength undergo elimination with the same base. According to Thornton (48), a bond that is made easier to break will be less stretched at the transition state with a parallel decreased stretching of the other reacting bond. Thus, Thornton, in contrast with Bunnett, envisions that strong bases and electron-withdrawing substituents of increasing strength, which facilitate the breaking of the $C_{\beta}-H$ bond, will shorten monotonically both the $C_{\beta}-H$ and the $C_{\alpha}-X$ bonds at the transition state, giving rise to transition states which are becoming increasingly "reactant-like". Surprisingly, both Bunnett (49) and Thornton (50) were able to provide evidence in support of their conflicting views.

For the assessment of the effects of substrate structure and reaction conditions on the positions of a transition state in the E1cB-like - E2 - E1-like spectrum of transition states, a number of tools are available. These include studies of the effects of structural and configurational changes of reactants on product composition, determination of Hammett ρ values, and measurement of primary and secondary isotope effects. Of these

tools, the one that affords the most direct way of determining transition state structure is the measurement of primary kinetic isotope effects. That this is so can be seen from the fact that for the E2 process involving the $\text{H}-\text{C}_\beta-\text{C}_\alpha-\text{X}$ system, the β -hydrogen isotope and the leaving group isotope effects associated with $\text{C}_\beta-\text{H}$ and $\text{C}_\alpha-\text{X}$ bond breaking, respectively, are interpretable in terms of the extents of breaking of the two bonds.

Heretofore, kinetic isotope effect studies have been applied almost exclusively to the anti-mode of elimination, although some measurements of β -hydrogen isotope effects associated with syn-processes have recently been published (19,22,38,44,45,51,52). Because of the established generality of the syn-mode of elimination, however, it is now clearly desirable to extend these studies to the determination of both β -hydrogen and leaving-group isotope effects in syn-reactions, and, particularly, to compare the magnitudes of these effects for syn- and anti-eliminations from either the same reactant or from reactants of similar structure.

The purpose of the overall investigation initiated by the present study was first to determine whether the formation of trans- α -methylstilbene in the reaction of erythro-1,2-diphenyl-1-propyltrimethylammonium iodide with potassium t-butoxide in t-butyl alcohol arises from a syn-E2 process or is an anti-elimination preceded by inversion at either the α - or β -carbon atom. If the reaction turned out to be a syn-process, it was then planned to apply kinetic isotope effect studies on both the threo and erythro compounds to compare the extents of bond breaking in the two reaction modes.

This thesis reports on the first stage of the overall study of syn- and anti-elimination of the 1,2-diphenyl-1-propyltrimethylammonium

system. It is restricted to the threo diastereomer for a number of reasons. First, the threo compound is the easier compound to synthesise in labelled form. Also, since the erythro and threo compounds are of comparable thermodynamic stability (7) and have exhibited approximately equal rates of elimination with t-butoxide ion in t-butyl alcohol (7), it is reasonable to assume that the occurrence of epimerisation, identifiable by hydrogen-deuterium exchange, at the α -carbon atom of the threo compound would be sufficient indication of epimerisation at the α -carbon atom of the erythro quaternary ammonium salt.

Early in the course of this work, it was learned that Borchardt and Saunders (53) were conducting a concurrent study on the erythro compound at the University of Rochester. Both their work and our work indicated the absence of epimerisation at the α -carbon atom. The test for an E1cB exchange was not carried out since it was found by Borchardt and Saunders that E1cB exchange did not occur in the erythro compound.

The second phase of the present study was the determination of the kinetic hydrogen isotope effect for the elimination reaction of the threo isomer. It was observed that, in addition to an anti-elimination giving trans- α -methylstilbene, there was an accompanying syn-elimination as well as nucleophilic displacement at an N-methyl carbon atom giving threo-N,N-dimethyl-1,2-diphenyl-1-propylamine. The latter assumed considerable importance with the deuteriated compound because of the isotope effect associated with the elimination reactions. In order to determine the β -hydrogen isotope effect accurately, it was necessary to do a careful product analysis. In addition to obtaining the β -hydrogen isotope effect for anti-elimination, it was possible as well to obtain a value for the syn-elimination although not with great accuracy.

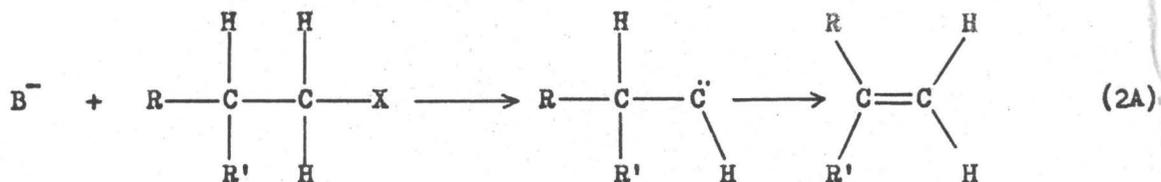
HISTORICAL INTRODUCTION

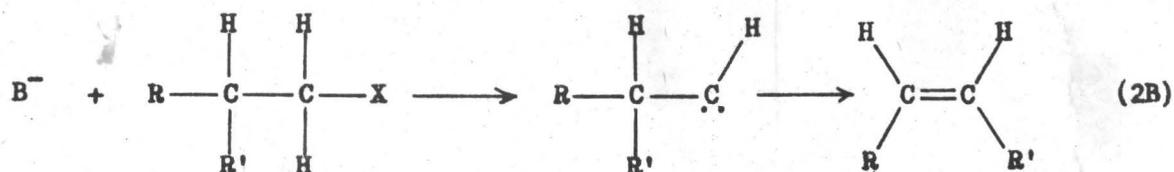
A. Mechanisms of Elimination Reactionsof H — C_β — C_α — X Systems

There are three major pathways of elimination reactions, as have been described in several comprehensive reviews (11,12,32,47). The elimination reactions considered here are the α -, $\alpha'\beta$ -, and β -elimination reactions, of which the last one is the most common. All these reactions are base-initiated reactions that proceed with resulting formation of a carbon to carbon double bond.

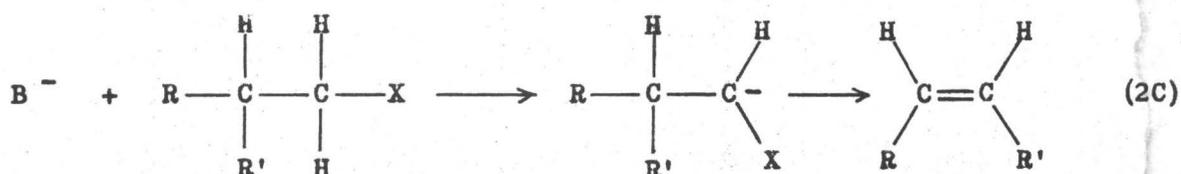
 α -Elimination Mechanism

This mechanism proceeds through a carbene intermediate formed initially by base abstraction of an α -hydrogen and the departure of the leaving group from the α -carbon atom. The β -hydrogen atom (equation (2A)) or some substituent from C_β (equation (2B)) then migrates to C_α. The necessary conditions are strong bases and aprotic media.





A reaction mechanism involving an α -carbanion rather than a carbene intermediate might be envisioned to arise by the abstraction of an α -hydrogen atom followed by the migration of a β -hydrogen atom or some substituent from the β -carbon atom either before or concurrent with the loss of the leaving group: but such a mechanism is considered to be

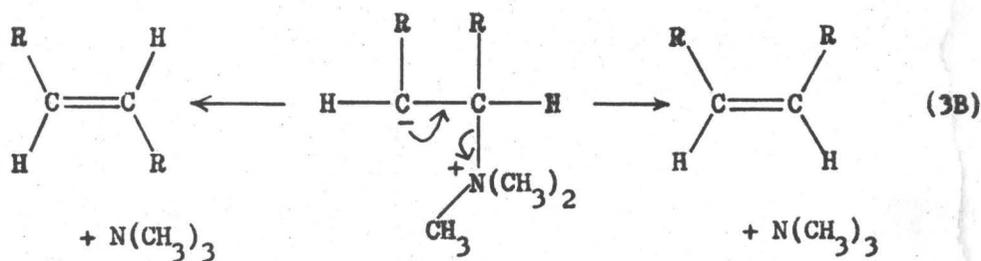
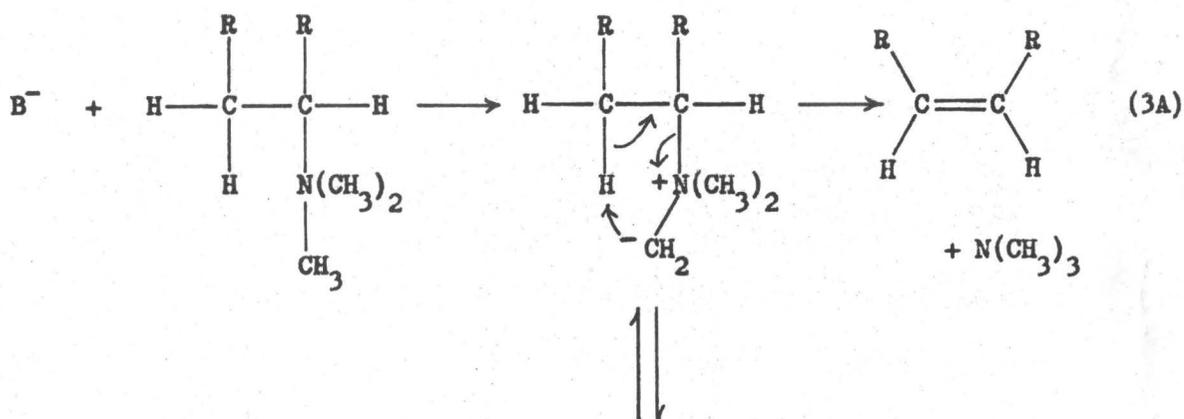


unlikely because it involves the migration of a β -hydrogen atom or some substituent from the β -carbon atom to a carbanion centre, a circumstance which has not been observed (11).

α' - β -Elimination Mechanism

This mechanism, first proposed by Wittig (54), is so called because a β -hydrogen atom is removed by the α' -carbon atom. As in the α -elimination mechanism, the necessary conditions are provided by strong bases and aprotic media. In this mechanism, a dipolar ylide is produced

by base abstraction of an α -hydrogen atom of an 'onium salt. The negative end of the dipolar ylide then abstracts a β -hydrogen atom from another branch of the substrate by means of a cyclic transition state. The decomposition of the ylide can be either a one- or two-step process.



In the one-step mechanism, syn-elimination must occur, but the two-step mechanism will have an overall orientation dependent on the stability of the second carbanion, equation (3B). If the carbanionic species is stable, permitting free rotation, the product distribution will depend upon the relative rates of formation of the two olefins. That this is true is illustrated in the work of Wittig and Polster (55) who found that the reaction of trimethylcyclooctylammonium bromide with phenyllithium in diethyl ether gave an olefin mixture containing 88% cis-olefin, but that

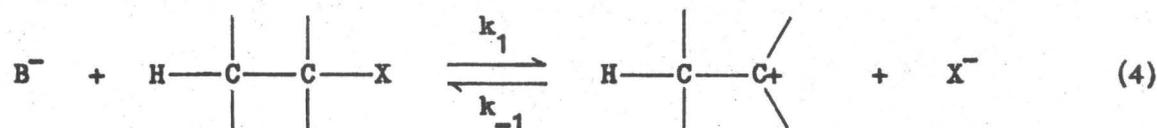
with potassium amide in liquid ammonia, the trans-olefin predominated (85%). Also, in the recent work of Bach and Andrzejewski (52) involving the elimination of cyclooctylammonium salts in liquid ammonia, cis- and trans-olefins were formed.

β -Elimination Mechanisms

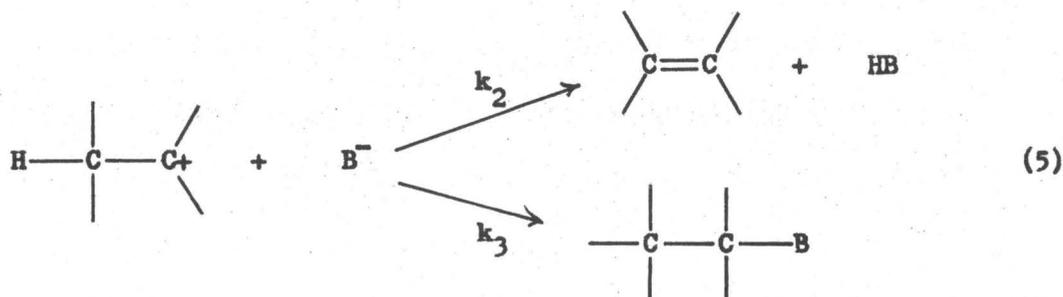
The three well-known mechanisms of β -elimination are the E1, E2, and E1cB mechanisms, and they differ in the timing of the breaking of the $C_\alpha-X$ bond before (E1), during (E2) or after (E1cB) the breaking of the $C_\beta-H$ bond.

The E1 Mechanism

This mechanism, first proposed by Hughes (56), consists of a rate determining step in which the carbon-leaving group bond is broken to form a carbonium ion as shown in equation (4). The carbonium ion then, in a



fast step, loses a proton to a base, usually the solvent, to form an olefin, or reacts with available nucleophile (S_N1).



The full kinetic expression for the formation of olefin is given by

$$\text{Rate of Elimination} = \frac{k_1 k_2 [\text{Reactant}][\text{B}^-]}{k_{-1}[\text{X}^-] + (k_2 + k_3)[\text{B}^-]} \quad (6)$$

If $k_{-1}[\text{X}^-]$ is large with respect to $(k_2 + k_3)[\text{B}^-]$, equation (6) reduces to

$$\text{Rate of Elimination} = \frac{k_1 k_2 [\text{Reactant}][\text{B}^-]}{k_{-1}[\text{X}^-]} \quad (7)$$

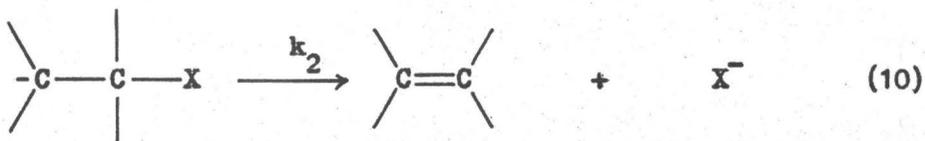
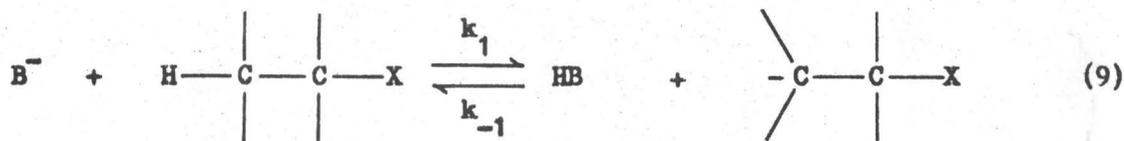
from which it is seen that the reaction follows second order kinetics.

If, however, as is usually the case, $k_{-1}[\text{X}^-]$ is small with respect to $(k_2 + k_3)[\text{B}^-]$, the reaction follows first order kinetics for which the rate expression becomes

$$\text{Rate of Elimination} = \frac{k_1 k_2 [\text{Reactant}]}{(k_2 + k_3)} \quad (8)$$

The E1cB Mechanism

This mechanism, first proposed by Ingold (57), has been found to occur with reactants having strongly electron-withdrawing substituents at the β -carbon atom. The name E1cB derives from the fact that it is the conjugate base of the substrate that gives up the leaving group. This mechanism is illustrated by equations (9) and (10).



A carbanion is formed first, which can then either lose the leaving group to form an olefin or recapture a proton and revert to the reactant.

The full kinetic expression for this reaction scheme is given by equation (11).

$$\text{Rate of Elimination} = \frac{k_1 k_2 [\text{Reactant}][B^-]}{k_2 + k_{-1} [HB]} \quad (11)$$

If $k_{-1} [HB]$ is large with respect to k_2 , the

$$\text{Rate of Elimination} = \frac{k_1 k_2 [\text{Reactant}][B^-]}{k_{-1} [HB]} \quad (12a)$$

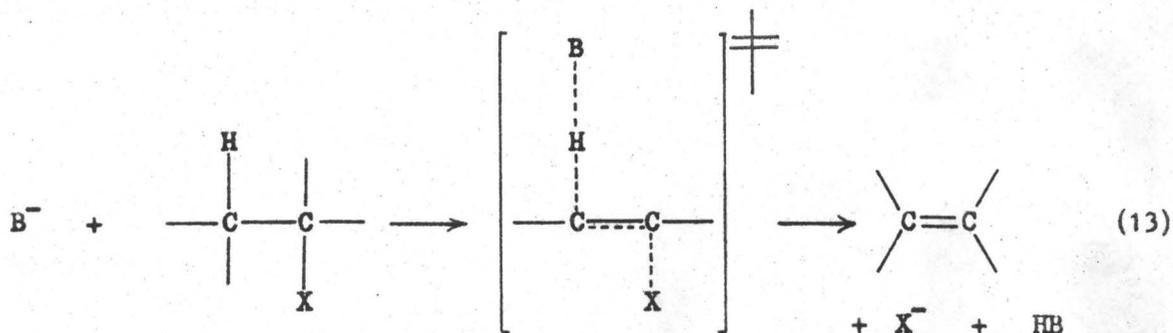
and the E1cB reaction will follow second order kinetics and exhibit specific lyate catalysis (14,58-61). However, when k_2 is large with respect to $k_{-1} [HB]$, the

$$\text{Rate of Elimination} = k_1 [\text{Reactant}][B^-] \quad (12b)$$

and the E1cB reaction will then exhibit general base catalysis (14,58-61).

The E2 Mechanism

In the E2 mechanism, first proposed by Hanhart and Ingold (1), the β -hydrogen atom and the leaving group X depart simultaneously. It is seen from equation (14) that the reaction exhibits second order kinetics, first order in substrate and first order in base.



$$\text{Rate of Elimination} = k [\text{Reactant}][\text{B}^-]. \quad (14)$$

This reaction is distinguishable from the E1cB reaction in that it exhibits general base catalysis rather than the specific lyate catalysis of the E1cB reaction (14,58-61).

Determination of β -Elimination Mechanisms

A variety of tools have been used to distinguish the E1, E1cB and E2 mechanisms from one another. Generally, the E1 is distinguishable from the E1cB and E2 mechanisms on the basis that a reaction proceeding by the E1 pathway exhibits first order kinetics.

Kinetically, the E1cB is distinguishable from the E2 mechanism if there is a preequilibrium between the reactant and the carbanion such that equation (12a) is valid. In this case, the E1cB reaction will exhibit specific lyate catalysis rather than the general base catalysis of the E2 (14, 58-61). The two mechanisms, however, become indistinguishable kinetically when the carbanion formed in the E1cB reaction eliminates faster than it reprotonates to starting material, that is, when k_2 is very much larger than $k_{-1}[\text{HB}]$.

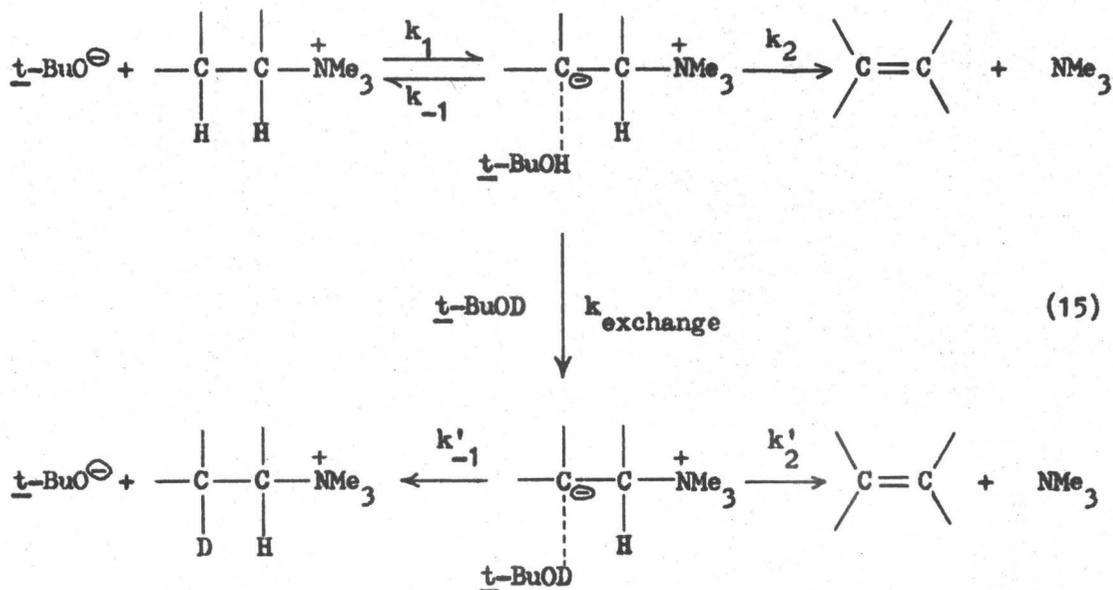
Since only the E1cB mechanism produces a carbanion, an acceptable criterion for the E1cB mechanism appears to be the exchange of the β -hydrogen atoms of the reactant when the reaction is conducted in a deuterated solvent (62,63). That is, the identification of carbanion formation should suffice to exclude the E2 mechanism. However, this does not necessarily follow since the possibility exists that the elimination reaction mechanism may well be E2 with carbanion formation being an irrelevant side reaction (62,64). Furthermore, it has been shown that the incorporation of deuterium by a carbanion will not be observed if the ratio $\frac{k_2}{k_{-1}[\text{HB}]}$ is greater than about 100 (65). Since neither the evidence of deuterium incorporation establishes an E1cB mechanism nor the absence of deuterium pick-up proves an E2 reaction, additional information must be obtained before it is possible to distinguish conclusively the E1cB mechanism from the E2.

In this regard, β -hydrogen isotope effects and leaving-group isotope effects are particularly informative. Since an atom exhibits an isotope effect only when a bond to that atom is stretched or broken in the rate determining step of a reaction, the mechanism of the elimination of a $\text{H}-\text{C}_\beta-\text{C}_\alpha-\text{X}$ system must be E2 if the reaction exhibits substantial β -hydrogen and leaving-group isotope effects. This must be so since the substantial isotope effects clearly indicate that the $\text{C}_\beta-\text{H}$ and $\text{C}_\alpha-\text{X}$ bonds are broken simultaneously in the same rate determining step of the reaction.

An E1cB reaction which does not exhibit hydrogen-deuterium exchange may, however, be distinguished from an E2 reaction by the relative magnitude of the isotope effect associated with the elimination of the leaving group. In the case of an E1cB reaction in which $k_2 \gg k_{-1}[\text{HB}]$, the breaking of the $\text{C}_\alpha-\text{X}$ bond occurs in a fast step and the isotope effect associated with the leaving group should be small or zero. If the elimination is an E2 process, the $\text{C}_\alpha-\text{X}$ bond is broken at the transition state of the rate determining step and a significant isotope effect should result.

An E1cB mechanism which is consistent with no hydrogen-deuterium exchange and a normal leaving-group isotope effect is shown in equation (15). Such a mechanism involves the formation of a carbanion which is specifically hydrogen-bonded to the molecule of say, *t*-butyl alcohol, formed by abstraction of the β -hydrogen atom by *t*-butoxide ion.

If k_2 is much larger than k_{exchange} but smaller than k_{-1} , exchange with deuteriated solvent molecules would be observed but a normal



leaving-group isotope effect would result. The β -hydrogen isotope effect for this particular E1cB process would be small or even inverse because it results from an equilibrium proton transfer between a carbanion and an alkoxide ion (66,67). In an E2 process, on the other hand, a large β -hydrogen isotope effect should be found because the $\text{C}_\beta\text{---H}$ bond is breaking at the transition state in the rate determining step.

Once the mechanism of a given reaction has been ascertained to be E2, the next level of understanding relates to the geometry of the transition state, that is, to the extent to which the transfer of the β -hydrogen atom to the base and the breaking of the bond between the departing atom and C_α have proceeded at the transition state. For this purpose, a number of kinetic methods have been employed. These kinetic methods involve the determination of the following kinetic parameters such as the ratio $k_{\text{t-BuS}^-}/k_{\text{EtO}^-}$, the Bronsted β coefficient, the Hammett ρ coefficient, and the ratio $k_{\text{OTs}^-}/k_{\text{Br}^-}$.

The determination of the ratio $k_{\text{t-BuS}^-}/k_{\text{EtO}^-}$ (68,69) involves measuring the relative rates of reaction with t-butyl thiolate and ethoxide ions for a family of compounds of varying reactivity. The determination of the Bronsted β coefficient involves measuring the rates of proton abstraction from a common substrate by a series of structurally similar bases. The determination of the Hammett ρ coefficient involves measuring the rates of elimination of a series of β -aryl-substituted reactants with a common base. The greater the magnitude of the ratio (68,69), or of the Bronsted β coefficient, or of the Hammett ρ coefficient, the greater is the extent of bonding between the transferred proton and the base at the transition state. That is, a relatively large value of any of these kinetic parameters can be taken to indicate extensive C_β -H bond breaking at the transition state with a relatively large degree of carbanion character at C_β . Finally, the ratio $k_{\text{OTs}}/k_{\text{Br}}$ may be determined by measuring the relative rates of elimination of tosylate and bromide substrates with a common base. The significance of the ratio $k_{\text{OTs}}/k_{\text{Br}}$ (70) is that large magnitudes of the ratio are associated with a large extent of C_α -X bond breaking at the transition state. Low values of $k_{\text{OTs}}/k_{\text{Br}}$, on the other hand, indicate transition states with small C_α -X bond breaking. It must be noted, however, that several complications in the interpretation of this ratio have been pointed out (71).

Implicit in the use of these kinetic methods is the assumption that the kinetic response of the reaction to substrate structure and reaction conditions (structural and environmental changes) depends on the nature of the transition state. It must not be overlooked, however, that the nature of the transition state may well be altered by the structural change or the environmental change itself. For an unambiguous study of the transition

state, recourse must be made to methods that utilise structural and environmental changes that do not alter appreciably the nature of the transition state. Since isotopic substitution is the subtlest change possible at the reaction site, β -hydrogen isotope effects (k^H/k^D), and leaving-group isotope effects (k_N^{14}/k_N^{15} , k_S^{32}/k_S^{34}) provide the most direct approach to elucidating the nature of the transition state in an elimination reaction.

B. Isotope Effects

General

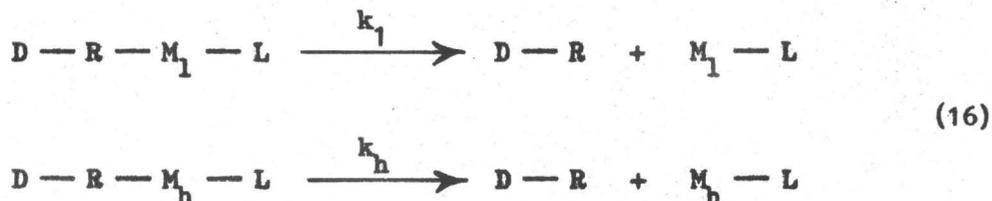
In the treatment of isotope effects, it is assumed that the Born-Oppenheimer Approximation (72) is valid, that is, all isotope effects arise from differences in the motion of the atoms or molecules of different masses upon identical potential energy surfaces.

On this basis, the magnitude of an isotope effect associated with an atom is related to the extent of motion of the atom, or equivalently, to the extent to which the force constants of the atom are weakened as the reaction proceeds from the initial state to the transition state. In an E2 elimination of a $\text{H} - \text{C}_\beta - \text{C}_\alpha - \text{X}$ system, the breaking of the $\text{C}_\alpha - \text{X}$ bond is not accompanied by the formation of a new bond to the departing leaving-group atom, with the result that the leaving-group isotope effect increases monotonically with the extent of $\text{C}_\alpha - \text{X}$ bond breaking at the transition state. In contrast, concurrent with the breaking of the $\text{C}_\beta - \text{H}$ bond is the formation of a bond between the hydrogen atom and the base with the result that the β -hydrogen isotope effect is at its maximum (ca. 7) if the partial bonds of hydrogen to the reactant and the base are of equal strength and less than 7 if the hydrogen atom is more strongly attached to either the base or to the reactant.

An elucidation of these relationships follows.

Isotope Effects in a Simple Bond Breaking Process

Let us consider two simple bond breaking processes associated with two isotopically labelled molecules in which M_1 and M_h are the lighter and the heavier isotopes, respectively, equation (16). The



zero point energy of each of the molecules is given by

$$E^0 = \sum \frac{1}{2} h\nu \tag{17}$$

where h = Planck's constant, ν = frequency of a particular vibrational mode and the summation is taken for all the vibrational modes of all the atoms in the molecule. Since the heavier isotope has a lower vibrational frequency, the zero point energy of the molecule with the heavier isotope is lower than that of its lighter counterpart.

Thus the change in energy of each of the molecules in traversing from the initial state to the transition state is given in Figure 1 from which it is seen that the zero point energy difference of the isotopically labelled transition states is less than the zero point energy difference of the reactant molecules. The decrease in zero point energy difference arises from the fact that the transition states have lost a vibrational mode associated with the isotopic atom. This vibration is replaced, in each case, by an internal translation that leads to formation of products. It is this loss in the zero point energy at the

transition state that results in a higher energy of activation for the molecule with the heavier isotope, thereby making the primary kinetic isotope effect, k_1/k_h , greater than unity.

In any detailed calculation of the kinetic isotope effect associated with an atom in a multi-atom system, it is necessary to consider

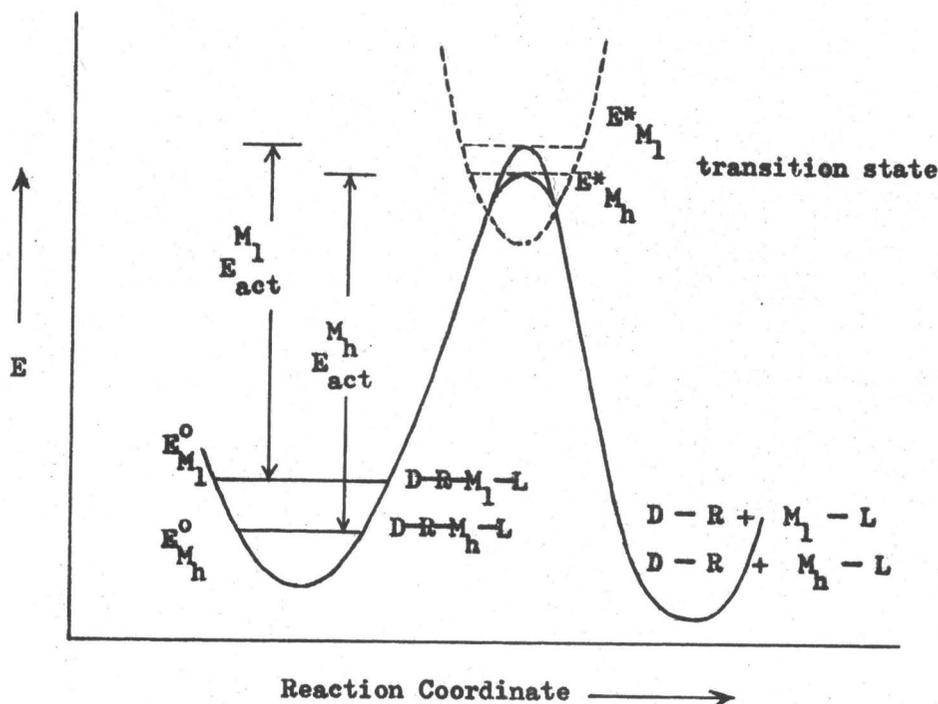


Figure 1.

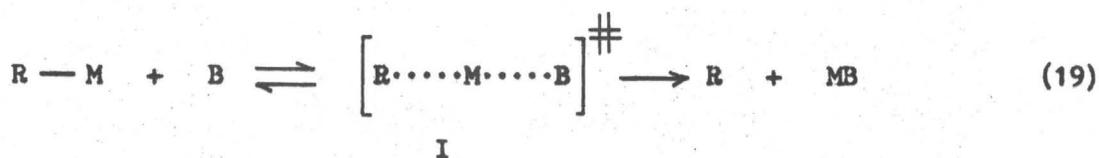
all the stretching and bending vibrations of the initial and transition states. Using the methods of statistical mechanics to derive equations for the calculation for the ratio of the rate constants for the reaction of isotopic molecules from vibrational frequency data, Bigeleisen (73) has formulated equation (18) where ν_1^* is the imaginary frequency

$$\frac{k_1}{k_h} = \frac{S_1 S_2^*}{S_2 S_1^*} \frac{\nu_1^*}{\nu_2} \left[1 + \frac{G(u_i)}{2u_i} \left(\frac{hc}{kT} \right)^2 \sum \left(\frac{1}{m_{1j}} - \frac{1}{m_{2j}} \right) (a_{ii} - a_{ii}^*) \right] \quad (18)$$

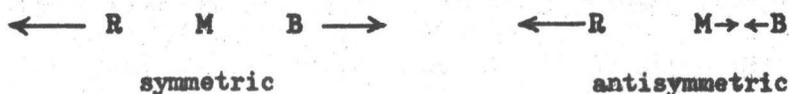
corresponding to translation of the molecule with the lighter isotope, m_{ij} are the masses of the atoms in the molecule, u_i is the reduced mass term, S_1 and S_1^* are the symmetry numbers of the initial and transition states, and a_{ii} and a_{ii}^* are the bond force constants. Equation (18) shows that the ratio k_1/k_h increases as a_{ii}^* decreases. That is, the leaving-group isotope effect arising from a simple bond breaking process increases monotonically as the force constant of the $C_\alpha-X$ bond decreases at the transition state.

Hydrogen Isotope Effects

Consider a three-centre transition state such as is operative in a reaction involving the transfer of a hydrogen atom or ion from one species to another, equation (19), where M is the isotopic atom, hydrogen or deuterium. For simplicity, the transition state is treated as a linear, one dimensional species, thereby ignoring bending vibrations. Associated with the transition state are a symmetric vibration and an antisymmetric



vibration, both vibrations being stretching vibrations. The symmetric vibration is a genuine vibration which contributes to the zero point energy of the transition state, whereas the antisymmetric vibration is a translational mode that leads to products. In the so-called symmetric



vibration, the partial bonds of M to R and B are of equal strength with the result that the isotopic atom M is motionless midway between R and B regardless of whether M is hydrogen or deuterium. Thus the zero point energy of the isotopically labelled transition states vanishes, and the entire zero point energy difference of the ground state vibrational stretching modes contributes to the activation energy difference for the reaction of the isotopic molecules, Figure 2. Consequently, the kinetic isotope effect is large. If, however, the isotopic atom is attached more strongly to either A or B, it will be in motion at the transition state, and the frequency of the symmetric vibration (which contributes to the zero point energy of the transition state) will depend on whether hydrogen or deuterium was present. Thus, in contrast to the preceding case, the zero point energy difference of the isotopic transition states will decrease the contribution to the zero point energy difference of the molecules in the initial state to the activation energy difference for the reaction of the isotopic molecules, thereby reducing the isotope effect. Thus, as indicated in Figure 2,

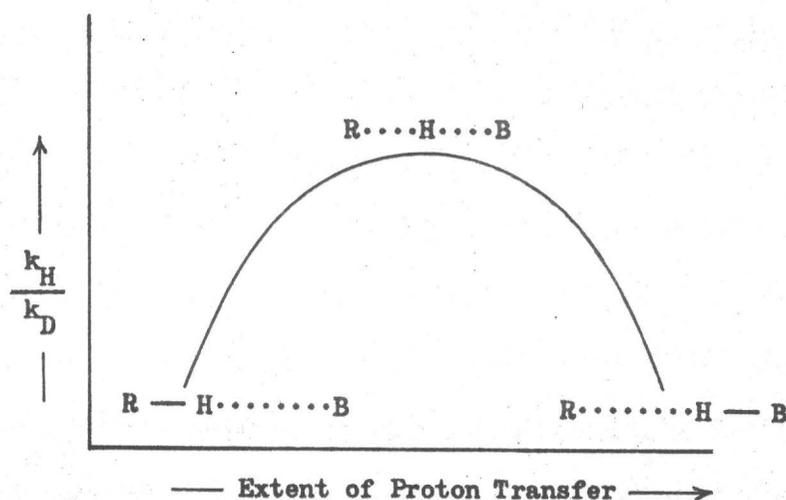


Figure 2.

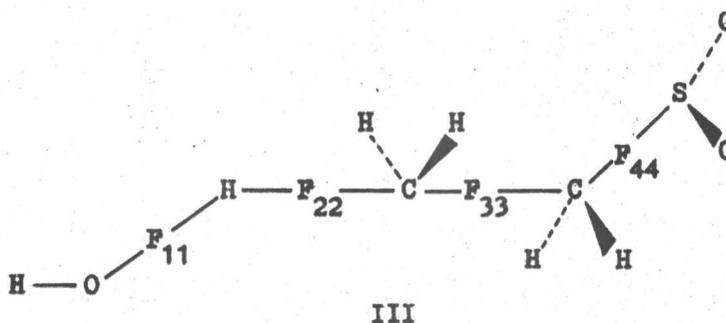
the kinetic isotope effect is at its maximum for a transition state in which hydrogen is half-transferred, and less for a transition state in which the hydrogen atom is more or less than half-transferred from the reactant to the base.

The foregoing results have been put on a mathematical basis by Westheimer (74) who used an essentially simplified version of the works of Johnston (75) and Bigeleisen (73).

Theoretical Calculations of Isotope Effects
in β -Elimination Reactions

Using the Wolfsberg-Schachtschneider FG Matrix Program (76) for calculating vibrational frequencies, Katz and Saunders (77) have calculated hydrogen and sulfur isotope effects associated with the E2 reaction at 25°C. of ethyldimethylsulfonium ion with hydroxide ion.

The transition state model below was used, the stretching and



bending force constants of the reacting bonds were arbitrarily varied, both separately and simultaneously to determine their effects on the

magnitudes of the hydrogen and sulfur isotope effects, and the off-diagonal elements, equation (20), defined in terms of the stretching force constants of the individual reacting bonds were applied to determine the extent to which the reacting bonds were coupled to each other.

$$\begin{aligned} F_{12} &= A(F_{11}F_{22})^{\frac{1}{2}} \\ F_{23} &= B(F_{22}F_{33})^{\frac{1}{2}} \\ F_{34} &= C(F_{33}F_{44})^{\frac{1}{2}} \end{aligned} \quad (20)$$

The calculations show that the hydrogen isotope effect is not at its maximum at half-transfer of the proton, and that an increase in A, which of itself must increase with the extent of proton transfer, increases the hydrogen isotope effect without affecting significantly the sulfur isotope effects. Thus Katz and Saunders suggest that the Westheimer three-centre model (Figure 2) clearly oversimplifies the real situation of an invariant maximum value of k_H/k_D and that the hydrogen isotope effect is not a reliable measure of the extent of proton transfer at the transition state. However, they also explain that if the contribution of A to the hydrogen isotope effect is not large relative to that arising from proton transfer, the overall variation of the hydrogen isotope effect with the extent of proton transfer was in agreement with the Westheimer model. This may be illustrated by Figure 3 where the effect of A for a hypothetical system is about 1/4 as important as that arising from half-transfer of the proton.

The ratio C/B which is a measure of the relative extents to which the C—S and C—H stretches, respectively, are coupled to the C—C contraction in the transition state was found to have

no significant effect on either the hydrogen or sulfur isotope effect. But, as expected, it was found that as C/B increases, that is, as the C — S stretching contributes increasingly to the coordinate motion, the sulfur isotope effect increases and the hydrogen isotope effect decreases.

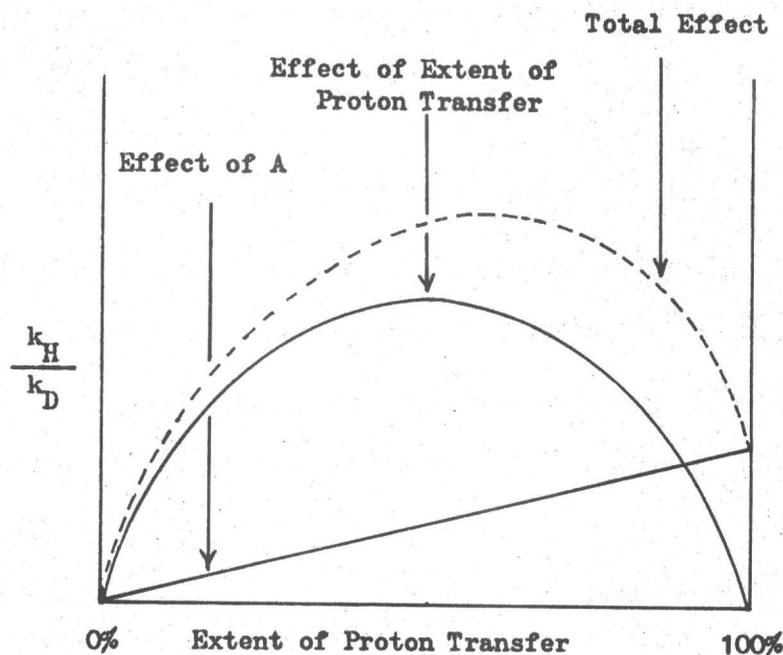


Figure 3.

Of particular interest is the conclusion that, except when a bond is more than 90% broken at the transition state, the extent of C — S bond weakening has no effect on the magnitude of the hydrogen isotope effect and the extent of proton transfer has no effect on the sulfur isotope effect.

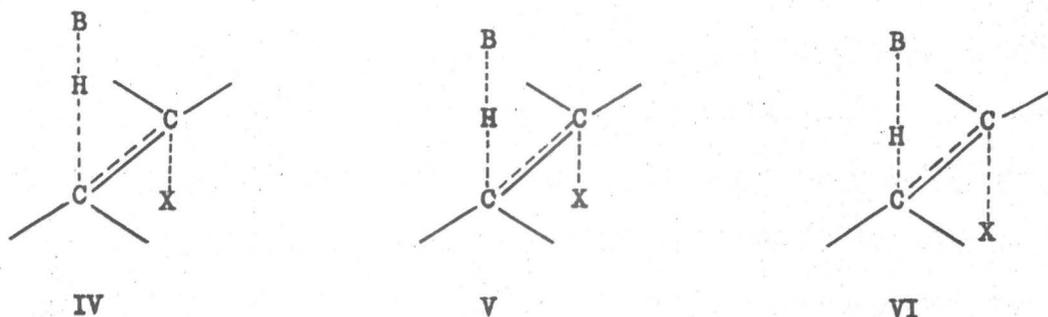
Particularly surprising, however, is the effect of changes in bond strength at the transition state on the sulfur isotope effect, which appears to become significant only when the C — S bond is more than half broken. This conclusion implies that small leaving-group

isotope effects can be associated with reactions in which the C — X bond breaking is well-advanced at the transition state.

From this study it is evident that a number of parameters can alter the isotope effect. Katz and Saunders themselves have acknowledged that parameters able to be treated as independent variables in the calculations are most probably interdependent in an actual physical situation. Accordingly, they conclude that a qualitative interpretation of isotope effects should be possible, but only when systematic changes in some structural or environmental feature of a reaction (basicity of reagent, for example (78,79)) are made, and that isotopic substitution in a number of different positions in the molecule may even yield semi-quantitative information about the transition state structure under favourable conditions.

C. The Nature of the Transition State in E2 Processes

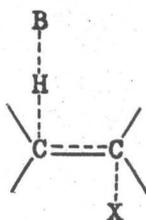
It is generally recognised that although the breaking of the $C_\beta-H$ and $C_\alpha-X$ bonds in an E2 bimolecular elimination reaction are simultaneous, the timing need not be synchronous. Accordingly, there is a continuum of transition states ranging from an E1cB-like extreme, IV, characterised by extensive $C_\beta-H$ bond breaking and a little $C_\alpha-X$ bond breaking, to a central or E2 transition state, V, in which the two reacting bonds are equally broken, to an E1-like extreme, VI, in which $C_\alpha-X$ bond breaking is well advanced over $C_\beta-H$ bond breaking.



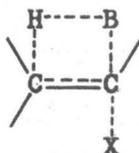
The actual position of a transition state in this continuum is determined by the relative extents of $C_\beta-H$ and $C_\alpha-X$ bond breaking and $C=C$ double bond character. These in turn are dependent upon substrate structure and reaction conditions which may affect the two bonds differently.

For many years, it had been presumed that the base must attack the β -hydrogen atom. However, only relatively recently (80,81), it was recognised that some bases which are weak toward hydrogen but are strong nucleophiles toward carbon may interact simultaneously with the β -hydrogen atom and nucleophilically assist the fission of the $C_\alpha-X$ bond, thereby causing elimination. These bases, such as halide anions, presumably utilise the

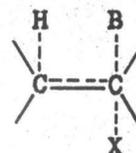
E2C transition state, VIII, whereas strong bases such as alkoxides which are poor carbon nucleophiles utilise the E2H transition state, VII, or an E2H-like transition state, IX. Thus it would appear that the continuum



VII

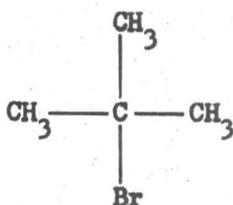


VIII

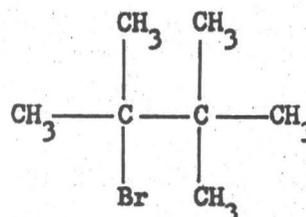


IX

of transition states with varying relative extents of $C_{\beta}-H$ and $C_{\alpha}-X$ bond breaking must be modified to include consideration of the position of the base relative to C_{α} and the β -hydrogen atoms. Such a modification, however, appears to be unnecessary because a recent observation of Eck (82) has shown that there is no nucleophilic interaction between the base and C_{α} . Eck reasons that if indeed there is nucleophilic interaction between a base such as Cl^{-} and C_{α} in X, the rate of elimination should be depressed by several powers of ten on replacing a methyl group in X with a *t*-butyl group to make XI in which C_{α} is rendered less accessible sterically. Since the rate was depressed by only a factor of five, Eck



X



XI

concludes that the E2C mechanism should be discarded.

Thus, the range of possible transition states in concerted elimination reactions is best illustrated by IV, V, and VI. The relative extents of $C_\beta-H$ and $C_\alpha-X$ bond breaking, that is, the nature of the transition state, is affected by many factors (47,49), including particularly the following: the ease or difficulty of detaching the leaving group; the strength of the base; substituents on C_β ; substituents on C_α ; the leaving-group inductive effect; and, the solvent.

In the study of the nature of the transition state as it is affected by the factors listed above, a variety of tools have been used. Principal among these tools have been: primary or (or β -) hydrogen and leaving-group isotope effects, secondary isotope effects, positional and geometrical isomerism of olefin products, Hammett ρ values, studies of stereochemistry, and studies of eclipsing effects. Of these, it has been found that primary hydrogen isotope and leaving-group isotope effects in combination with either secondary isotope effects or Hammett ρ values provide the most direct approach to the elucidation of transition state geometry associated with concerted bimolecular elimination reactions.

As was shown in the preceding section, the leaving-group isotope effect increases monotonically with the extent of $C_\alpha-X$ bond breaking at the transition state. Consequently, if a structural or environmental change increases the leaving-group isotope effect associated with the elimination of a particular $H-C_\beta-C_\alpha-X$ system, the increase in the isotope effect must be due to the change extending the $C_\alpha-X$ bond more at the transition state. As was also shown previously, the primary hydrogen isotope effect (β -hydrogen isotope effect) can be expected to

be largest when the proton is half-transferred and to be small if it is more or less than half-transferred to the base at the transition state. Consequently, if a structural or environmental change causes a lowering of the β -hydrogen isotope effect, there is ambiguity in interpreting the decrease in the isotope effect with respect to whether the change has induced greater or less C_β -H bond breaking at the transition state. Likewise, there is ambiguity in interpreting the relative magnitudes of β -hydrogen isotope effects of a reaction series with respect to whether the proton is increasingly or decreasingly transferred along the reaction series. Therefore, in the absence of other information relating to the extent of proton transfer, β -hydrogen isotope effects alone cannot be applied to determine the effects of structural and environmental changes on the nature of the transition states associated with concerted elimination reactions.

The first detailed β -hydrogen isotope effect study on elimination reactions was carried out by Saunders and Edison (83) who measured the effect of changes in the leaving group on the β -hydrogen isotope effect in the reaction of a series of 2-phenylethyl derivatives with ethoxide ion in



ethanol, equation (21). Their results, together with the Hammett ρ values associated with a reaction series of ring-substituted compounds corresponding to each leaving group as reported by a number of investigators, appear in Table 1, page 31.

The relative magnitudes of the β -hydrogen isotope effects, by themselves, may be taken to indicate either increasing or decreasing proton

transfer to base along the series of leaving groups, I, Br, OTs, Cl, $\overset{+}{S}(\text{CH}_3)_2$, F, and $\overset{+}{N}(\text{CH}_3)_3$. However, the use of rho values which gives a measure of the carbanionic charge on C_β at the transition state, allows a choice: a bigger rho value has been taken to mean more $\text{C}_\beta\text{—H}$ bond breaking. If this assumption is valid, it follows from the decreasing trend of the β -hydrogen isotope effects that the proton in this reaction series is more than half-transferred at the transition state with the

TABLE I

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

<u>X</u>	<u>Hammett rho</u>	<u>(Ref.)</u>	<u>$k^{\text{H}}/k^{\text{D}}$</u>
I	2.07	(84)	
Br	2.14	(84)	7.1
OTs	2.27	(85)	5.7
Cl	2.61	(85)	
$\overset{+}{S}(\text{CH}_3)_2$	2.75	(86)	5.1
F	3.12	(85)	
$\overset{+}{N}(\text{CH}_3)_3$	3.77	(87)	3.0*

* at 50°C.

extent of proton transfer increasing as the leaving group becomes poorer ($\overset{+}{N}(\text{CH}_3)_3$ poorer than OTs).

Although the use of Hammett ρ values has provided the right answer as will be evident shortly, their successful application here may well have been fortuitous, for ρ values may be more a measure of double bond character than of carbanionic charge on C_β . Also, an increase of carbanionic charge on C_β and of double bond character may be due more to a shortening of the $C_\alpha-X$ rather than a lengthening of the $C_\beta-H$ bond at the transition state. Therefore, the extent of proton transfer in the phenylethyl series of compounds must rest on firmer evidence before it is legitimate to place an interpretation of the relationship between the magnitude of the β -hydrogen isotope effects and the extent of proton transfer in the reaction series.

The extent of proton transfer in the elimination reactions of the phenylethyl compounds with ethoxide ion in ethanol was finally determined by Steffa and Thornton (50) who used the secondary isotope effect $k^{\overline{OD}}/k^{\overline{OH}}$,

TABLE II

Isotope Effects for Reactions of 2-Phenylethyl Derivatives
with Hydroxide ion in Water

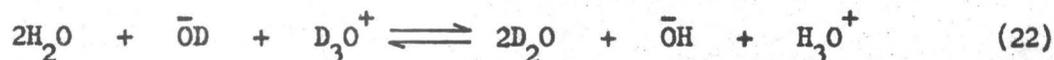
Substrate	$k^{\overline{OD}}/k^{\overline{OH}}$ ^a	k^H/k^D ^b
	at 80°C.	at 50°C.
$C_6H_5-CH_2-CH_2-\overset{\dagger}{N}(CH_3)_3$	1.79	3.02*
$p-Cl-C_6H_4-CH_2-CH_2-\overset{\dagger}{N}(CH_3)_3$	1.73	3.48*
$C_6H_5-CH_2-CH_2-\overset{\dagger}{S}(CH_3)_2$	1.57	5.05

^aSteffa and Thornton (50);

^bSaunders and Edison (83).

*Measured in 50% ethanol-water.

to establish that the proton was indeed more than half-transferred. Their results are presented in Table II, page 32. From a consideration of the exchange reaction, equation (22), Steffa and Thornton calculated



that the maximum value for the secondary isotope effect, $k^{\bar{\text{O}}\text{D}}/k^{\bar{\text{O}}\text{H}}$, is 1.88 at 80°C. for complete transfer of the proton to the base at the transition state, while for a reaction in which the proton is half-transferred at the transition state, the secondary isotope effect is the square root of the maximum value, or 1.37. The observed values of $k^{\bar{\text{O}}\text{D}}/k^{\bar{\text{O}}\text{H}}$ for 2-phenylethyltrimethylammonium, *p*-chloro-2-phenylethyltrimethylammonium and 2-phenylethyldisulfonium salts are 1.79, 1.73 and 1.57, respectively, indicating that the proton is more than half-transferred to the base at the transition state. Additional supporting evidence that the proton is more than half-transferred is provided by the relative magnitudes of the β -hydrogen isotope effects which decrease with increasing extent of proton transfer, Table II.

From the relative magnitudes and trend in the β -hydrogen isotope effects in Table II, it may be deduced that the coupling of the $\text{C}_\beta\text{—H}$ and O—H ($\text{B} = \bar{\text{O}}\text{C}_2\text{H}_5$) bonds at the transition state is relatively small. In other words, *A* (see discussion of Katz and Saunders' calculations, pages 23-26) which increases regularly with proton transfer, is probably not contributing substantially to the hydrogen isotope effect for the phenylethyl substrates. If the contribution of *A* was substantial, the β -hydrogen isotope effect would continue to increase with increasing extent of proton transfer, and it would not be possible to observe a lowering in the β -

hydrogen isotope effect when the *p*-chlorine atom in the trimethylammonium salt was replaced by a hydrogen atom.

Thus far it has been established that in the reactions of 2-phenylethyl substrates with ethoxide ion, the proton is more than half-transferred at the transition state with the extent of proton transfer increasing as the leaving group becomes poorer. To gain an insight into the effect of the β -aryl group on the relative timing of the $C_\beta-H$ and $C_\alpha-X$ bonds at the transition state, Smith (88) measured the nitrogen isotope effects associated with the E2 reactions of ethyltrimethylammonium and 2-phenylethyltrimethylammonium ions with sodium ethoxide in ethanol. His results, together with the corresponding k^H/k^D ratios obtained by Simon and Muellhofer (89) indicate that the effect of the β -aryl group is to decrease both the $C_\beta-H$ and $C_\alpha-X$ bond breaking in the same direction, Table III.

TABLE III

Isotope Effects in the E2 Reactions of Ethyltrimethylammonium
and 2-Phenylethyltrimethylammonium Salts at 60°C.

<u>Substrate</u>	<u>Reaction Conditions</u>	<u>$(k^{14}/k^{15} - 1)100$</u>	<u>k^H/k^D</u>
$CH_3-CH_2-\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.86 ^a	
	basic hydrate (vacuum)		3.0 ^c
	hydroxide in triethylene glycol		2.8 ^d
$C_6H_5-CH_2-CH_2-\overset{+}{N}(CH_3)_3$	ethoxide in ethanol	1.42 ^b	
	methoxide in methanol		4.2 ^c

^aSolvent: 95% ethanol;

^bSolvent: Absolute ethanol at 40°C.

^cSimon and Muellhofer (89)

^dSimon and Muellhofer(89)
from an experimental value of 1.23
at 130°C.

Smith has also measured the β -hydrogen isotope effects and nitrogen isotope effects associated with the E2 reactions of 2-(*p*-substituted) phenylethyltrimethylammonium bromides with sodium ethoxide in ethanol. His results, which appear in Table IV, show that as the substituent becomes more electron-withdrawing, both the $C_\beta-H$ and the $C_\alpha-N$ bonds are broken less at the transition state. Thus, again it was found that a structural change which decreases $C_\beta-H$ bond breaking at the transition state also decreases $C_\alpha-N$ bond breaking.

TABLE IV

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

<u>para-Substituent</u>	<u>$(k^{14}/k^{15} - 1)100$</u>	<u>k^H/k^D</u>
OMe	1.37	2.64
H	1.42 (1.33)*	3.23
Cl	1.14	3.48
CF ₃	0.88	4.15

* Redetermined by Smith and Bourns (63).

The conclusion that $C_\beta-H$ and $C_\alpha-N$ bond breaking parallel each other at the transition state has been reinforced by the work of Smith (88) and of Saunders, Bushman and Cockerill (87) on the effect of a stronger base, *t*-butoxide ion in *t*-butyl alcohol, on the nitrogen isotope effect associated with the reaction of ethyltrimethylammonium ion

and on the β -hydrogen isotope effect and Hammett ρ value for the reaction of 2-phenylethyltrimethylammonium ion. Their results which are presented in Table V show that the effect of the stronger base is to decrease both $C_\beta-H$ and $C_\alpha-N$ bond breaking at the transition state. Thus, it is evident that in the reactions of these quaternary ammonium salts, the effect of a structural or environmental change on the relative extents of $C_\beta-H$ and $C_\alpha-N$ bond breaking at the transition state is in the same direction.

TABLE V

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

<u>Substrate</u>	<u>Base/Solvent</u>	$(k^{14}/k^{15} - 1)100^a$	k^H/k^D	<u>ρ</u>
$CH_3-CH_2-\overset{+}{N}(CH_3)_3$	$EtO^-/95\% EtOH$	1.86		
$C_6H_5-CH_2-CH_2-\overset{+}{N}(CH_3)_3$	$EtO^-/EtOH$		2.98 ^b	3.86
$CH_3-CH_2-\overset{+}{N}(CH_3)_3$	$t-BuO^-/t-BuOH$	1.41		
$C_6H_5-CH_2-CH_2-\overset{+}{N}(CH_3)_3$	$t-BuO^-/t-BuOH$		6.97 ^c	3.04

^aSmith (88) at 60°C.

^bSaunders, Bushman and Cockerill (87) at 30°C.

^cSaunders, Bushman and Cockerill (87) at 50°C.

Thornton (48) has proposed a theory which may be used to predict the effects of substituents on the relative extents of $C_\beta-H$ and $C_\alpha-X$

bond breaking at the transition state. In this theory, the effect of a substituent is considered as linear perturbations of the vibrational potentials associated with the normal coordinate motions parallel and perpendicular to the reaction coordinate. This is illustrated by Figure 4. The parallel motion is analogous to Westheimer's antisymmetric stretch and is associated with a negative force constant, whereas the perpendicular motion is analogous to Westheimer's symmetric stretch and is associated with a positive force constant.

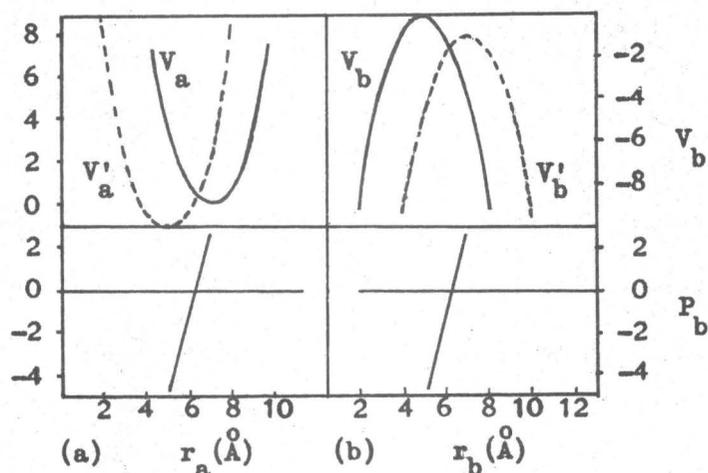


Figure 4. Plots of parabolic potentials, V , together with the perturbations, P , which, when added to V , give the new parabolic potentials, V' . Note that the slope of P'_a is exactly equal to the slope of P'_b .

(a) Effect expected for perpendicular motion; (b) Effect expected for parallel motion.

Consequently, the equilibrium bond distances, in particular the equilibrium bond distances associated with the atoms at the reaction site in the "perturbed" transition state are different from the bond distances in the normal transition state. Reflection reveals that the effect of a substituent on bond lengths in the parallel motion (Figure 4b) is opposite

to its effect on the bond lengths in the perpendicular motion (Figure 4a). Thus, Thornton formulated the following rule for predicting geometric changes at the transition state: "Any substituent which makes an increase (decrease) in the normal coordinate X of a molecule or transition state more difficult will lead to a perturbed equilibrium geometry in which X is decreased (increased) if the force constant for X motion is positive, but in which X is increased (decreased) if the force constant for X motion is negative".

Although the effect of a substituent on both the parallel and perpendicular motions must be considered in order to describe fully the change in the bond lengths at the transition state, it turns out, however, that in most cases, it is sufficient to consider only the effect on the parallel motion. This result is due to the circumstance that the change in coordinate X is inversely proportional to the force constant, or to the curvature of the potential energy surface in the region of energy maximum which curvature is, in most systems, smaller for parallel than for perpendicular motion. Consequently, Thornton predicts for most systems that a substituent change making a bond easier (or more difficult) to break will result in that bond being less broken (or more broken) at the transition state.

Thornton's theory is readily applicable to substituent effects in bimolecular elimination reactions where only the two reacting bonds closest to the substituent are considered, the others being assumed to "follow along". In the parallel motion which may be represented as



an electron-withdrawing substituent on C_β will weaken the $\text{C}_\beta\text{—H}$ bond

thereby making the motion extending this bond easier at the transition state. It will also make the compression of the $C_\beta - C_\alpha$ bond more difficult. The effect of $C_\beta - C_\alpha$ bond compression on the parallel motion is, however, relatively insignificant because the sigma bond already present prevents large changes in $C_\beta - C_\alpha$ bond length. Since the parallel motion is dominant in most cases and since for this motion a bond that is made easier to break will be less broken at the transition state, it follows that electron-withdrawing substituents at C_β will shorten the $C_\beta - H$ bond, lengthen the $C_\beta - C_\alpha$ bond with concomitant shortening of the $C_\alpha - X$ bond, thereby leading to a more reactant-like transition state. The reverse of the situation obtains for electron-releasing substituents at C_β . The theory also predicts that increasing the base strength (making the compression of the $B - H$ bond easier) will increase the $B - H$ bond length and shorten the $C_\beta - H$ and $C_\alpha - X$ bonds thereby making the transition state more reactant-like. All these predictions have been borne out by the work of Smith (88) and of Saunders, Bushman and Cockerill (87) as the results in Tables III, IV and V indicate.

Thornton's theory further predicts that a product-like transition state has relatively more carbanion than carbonium ion character. This prediction is based on a consideration of the relative extents of motion of the atoms associated with the reacting bonds along the reaction coordinate. Indeed, if H moves more relative to C_α , and C_β moves more relative to X, a transition state results in which there is more carbanion character at C_β than carbonium ion character at C_α . In other words, such a transition state is more E1cB-like. This prediction is supported by the relatively small β -hydrogen isotope effects ($k^H/k^D = 2.64-4.14$) observed by Smith (88) in the reactions of 2-arylethyltri-

methylammonium ions in ethoxide ion: the relatively small β -hydrogen isotope effects indicate extensive transfer of the proton to the base at the transition state. The nitrogen isotope effects (0.9-1.4%) for these reactions, on the other hand, would suggest that $C_{\alpha}-N$ bond breaking is substantial if the conclusions reached by Katz and Saunders (77) from their theoretical calculations of sulfonium salt elimination are equally applicable to trimethylammonium systems. If this assumption is valid, it follows that the transition state must be closer to E2 in contradistinction to the E1cB-like transition states as predicted by Thornton. However, the relatively large Hammett ρ value of 3.84 observed by Smith (88) is in support of Thornton and suggests that Katz and Saunders' (77) conclusions, although possibly valid for the sulfonium system, cannot be extended to reactions of trimethylammonium salts. Of this, more will be discussed later.

Another theory of β -elimination reactions and one which makes essentially the same predictions as Thornton's theory, although its rationale is different, is the theory of More O'Ferrall (90). Unlike Thornton, who considers the direct effect of substituents on the bond lengths of the transition state, O'Ferrall considers the effect of substituents on the energy of the reactants, products and intermediates which, in turn, affect the energy of the transition state. An important premise of this theory is that the Hammond's Postulate (91) that has been applied to the fission of a single bond is equally applicable to concerted processes and to the structures of carbanions and carbonium ions that appear in E1cB and E1 mechanisms.

O'Ferrall begins by stating that there is no continuity between the transition state of an E1cB-like E2 mechanism and the carbanion of an

E1cB-like E2 mechanism and the carbanion of an E1cB mechanism and that at the point of mechanistic change reaction by the two mechanisms can proceed concurrently through transition states, which although of the same energy, have quite different structures. As support for this view, O'Ferrall cites his work on the β -elimination of 9-fluorenylmethanol (92,93). Similarly, he concludes that there can be mechanistic discontinuity in the border region between the E1 and E2 pathways.

A major feature of the O'Ferrall theory is the representation of β -elimination reactions on a schematic potential energy surface which embraces the possibilities of reactions by both the concerted E2 mechanism and the stepwise mechanisms, as illustrated by Figures 5a and 5b. The

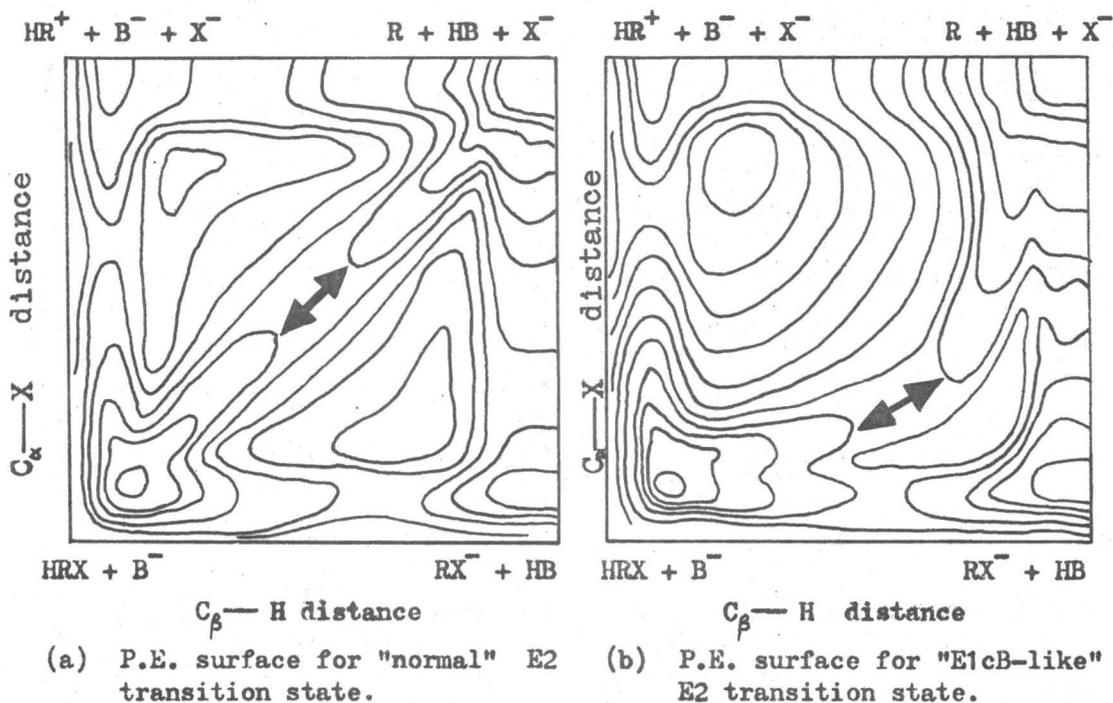


Figure 5.

surface is considered to be of such flexibility that the effects of

changes in energy in the stable species lying on the surface are transmitted across its entire length and breadth. Thus, the structure of the transition state for an E2 process is affected, not only by the stabilities of the reactants and products, but also by the stabilities of the carbanion and carbonium ion that would be formed if the mechanism were stepwise.

Inspection of Figure 5a reveals that an increase in stability of the product can be represented by a downward 'pull' (into the plane of the paper) at the top right hand corner. The effect of this is transmitted in attenuated form along the length of the E2 reaction coordinate, leading to a relatively large decrease in energy at a point close to the products and to a small decrease in energy close to the reactants. The effect on the transition state is increased stability and a change to a more reactant-like transition state in accordance with the Hammond's Postulate. By contrast, an increase in the stability of the carbanion may be represented by a downward pull at the lower right hand corner of Figure 5b. Again, the energy of the transition state is reduced, but this time its structure is closer to that of the carbanion.

Thus, the effect of product stability on transition state structure is transmitted along the reaction coordinate whereas the effect of carbanion stability is transmitted from a direction perpendicular to the reaction coordinate. These correspond, respectively, to the parallel and perpendicular motions of the Thornton's theory. Thus, it can be seen that while Thornton assumes structural changes in most systems exert their major influence on the reaction coordinate motion, O'Ferrall suggests that the effect of structural change on carbanion stability at the transition state is exerted essentially through the perpendicular motion for a "normal"

E2 transition state.

The very nature of the potential energy surface requires that a substituent change affect the stability of more than one species, although not to the same extent. For example, it can be expected that electron-withdrawing substituents at C_β will increase considerably the stability of carbanion-like transition states more than they increase the stability of the corresponding reaction products. That this is so would seem to be indicated by the order of the substituent effects on the magnitude of k^H/k^D for the reaction of 2-arylethyltrimethylammonium salts with ethoxide ion, Table IV, page 35. Clearly, this order is not the order of product stability which, on the basis of λ_{\max} values for the substituted styrenes (88), would appear to be $p\text{-CH}_3\text{O} > p\text{-Cl} > p\text{-CF}_3 > \text{H}$. On the other hand, the order of isotope effect does, indeed, correspond to the order of substituent effects on carbanion stability.

Earlier, it had been demonstrated rather convincingly that electron-withdrawing substituents at C_β of 2-arylethyltrimethylammonium compounds have the effect of decreasing rather than increasing the extent of proton transfer to the base at the transition state. This observation agrees with Thornton's prediction that substituents exert their influence on the transition state primarily through their effect on the reaction coordinate motion, but disagrees with O'Ferrall's view that substituents exert their effect on the perpendicular motion.

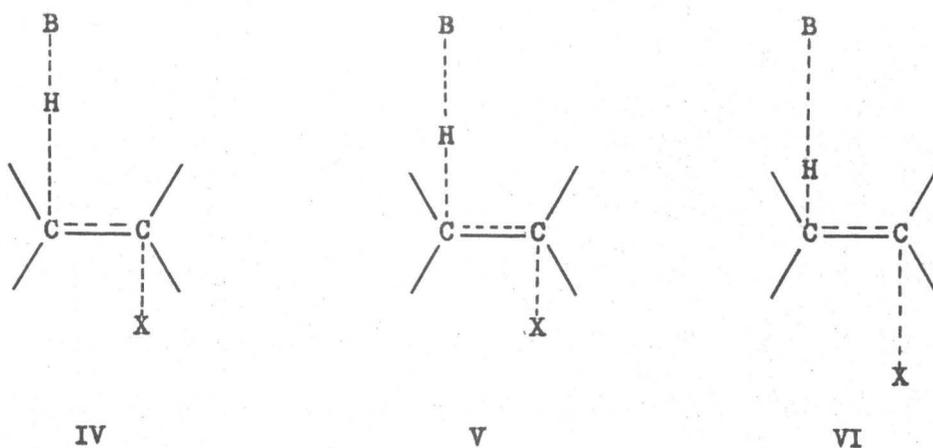
However, the decrease in the $C_\beta\text{—H}$ bond distances and the conclusions drawn from them can be reconciled with the O'Ferrall model if it is assumed that the potential energy surface for the β -elimination of 2-arylethyltrimethylammonium salts correspond to the E1cB-like surface,

Figure 5b. On this surface, the E2 transition state is highly carbanion-like and any variations in carbanion stability might be more strongly felt along the reaction coordinate than normal to it. This would, of course, lead to a decrease in $C_{\beta}-H$ bond distance with increasing carbanion stability.

This rationalisation of the β -hydrogen isotope effect results in terms of the O'Ferrall model leads to complications in interpreting the nitrogen isotope effects, Table IV, page 35, if it is assumed that the results of Katz and Saunders' theoretical calculations on the sulfur isotope effect are valid and equally applicable to the trimethylammonium system. According to Katz and Saunders, the sulfur isotope effect is relatively small unless the $C_{\alpha}-S$ bond is more than half-broken at the transition state. Thus, the relatively large nitrogen isotope effects of 0.9 to 1.4% must indicate that the $C_{\beta}-N$ bond at the transition state is appreciably broken. Such a situation is evidently untenable with the relatively small $C_{\alpha}-N$ bond lengths for the E2 process indicated in Figure 5b. Thus, there is no way in which the O'Ferrall model can be reconciled with both the β -hydrogen isotope effects and the nitrogen isotope effects found in Smith's work. However, in view of the approximate nature of Katz and Saunders' calculations and the possibility that the dependence of the leaving-group isotope effect on the extent of $C_{\alpha}-X$ bond breaking may be quite different for the sulfonium and trimethylammonium salts, it appears that further studies are required before discarding the O'Ferrall model.

Despite the fact that Thornton's and O'Ferrall's theories of the transition state in β -elimination reactions are based on different rationale, they make the same prediction that the effects of substituent changes

are transmitted along the parallel and perpendicular motions. Yet another 'theory' of the transition state in β -elimination reactions and one which is based more on chemical intuition rather than on a consideration of the thermodynamic properties of the transition state species is the theory of Bunnett (47,49). According to Bunnett, there is a continuum of 'variable' E2 transition states ranging from an E1cB-like extreme, IV,



to a central or E2 transition state, V, to an E1-like extreme, VI, and the actual position of a given transition state in this continuum is determined by such factors as substituent changes and reaction conditions.

Unlike Thornton who predicts that, if a bond is made more difficult to break by a substituent change, that bond will be relatively more broken with a parallel increase in the breaking of the other reacting bond at the transition state, Bunnett envisions the converse situation wherein a bond that is made more difficult to break will be relatively less broken with an accompanying increase in the breaking of the other reacting bond.

Since the effect of a substituent change on the geometry of the transition state is different according to the two theories, it follows that the corresponding effect of the substituent change on the trend in

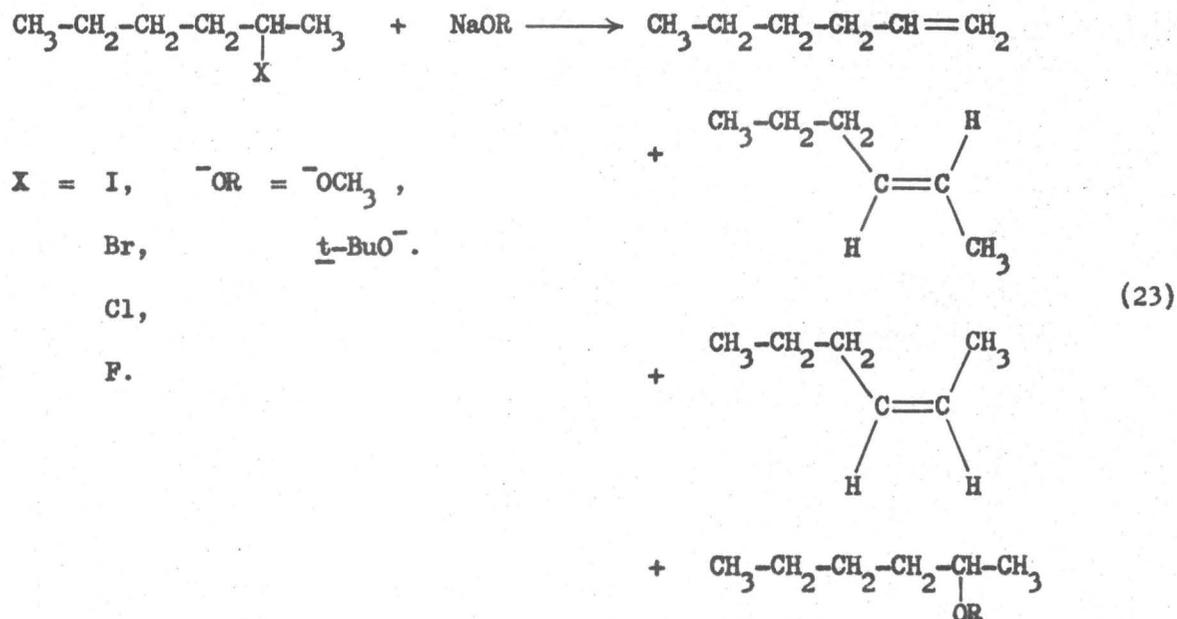
double bond formation is also different. Thus, Thornton predicts that a substituent change causing more $C_\beta-H$ bond breaking at the transition state gives rise to a "product-like" or carbanionic transition state wherein the double bond is relatively well-developed. By contrast, Bunnett requires that maximum double bond development occur at the central transition state wherein the two reacting bonds are equally broken and that double bond development decrease as the transition state becomes either more E1cB-like or E1-like. Thus, Bunnett expects that an increase in $C_\beta-H$ bond breaking at the transition state should result in decreased double bond formation when the transition state is central or carbanion-like.

Since the trend in double bond formation depends upon the nature of the transition state, the two theories may be evaluated by a consideration of the observed effects of substituents at C_β , of changes in the leaving group at C_α , and changes in the base strength on the nature of the transition state in a β -elimination reaction.

With regard to the effect of substituent changes at C_β , the secondary isotope effect studies of Steffa and Thornton (50) and the β -hydrogen and nitrogen isotope effect studies of Smith (88) on the β -elimination reactions of 2-arylethyltrimethylammonium salts, Tables II, III and IV, pages 32,34 and 35, have established that the change to a more electron-withdrawing substituent at C_β causes both the $C_\beta-H$ and $C_\alpha-N$ bonds to be relatively less broken at the transition state. These results agree with Thornton's but not with Bunnett's predictions.

Bunnett, however, was able to furnish support for his theory by studying the effect in the change in the leaving group on the relative yields of products formed competitively in the elimination reactions of

2-hexyl halides, equation (23). His results, in conjunction with those obtained by Bartsch, appear in Table VI. Bunnett (49) proposes that although it is not possible to specify the exact location of any trans-



tion state in the continuum between the E1cB-like and E1-like extremes, that for the reaction of 2-hexyl iodide with methoxide ion in methanol is probably central. It follows from Bunnett's theory that as the leaving group becomes poorer along the series, $\text{I} > \text{Br} > \text{Cl} > \text{F}$, the transition state becomes more carbanion-like. Bunnett explains that since a central transition state calls for a rather high 2-hexene/1-hexene ratio (because of the favourable inductive interaction of a β -alkyl group with the considerably developed double bond) and also calls for a rather high trans/cis olefin ratio (because of the considerable degree of eclipsing of the methyl and n-propyl groups in the transition state to cis-2-hexene), there should be a decrease in the 2-hexene/1-hexene and trans/cis olefin ratios as the transition state becomes more carbanion-like. It is evident from Bartsch's

and Bunnett's results in Table VI that the predicted kinetic responses have indeed been observed.

TABLE VI

Eliminations from the 2-Hexyl Halides at 100°C.

Halogen	Reagent: $\text{OCH}_3/\text{CH}_3\text{OH}$ ^a		Reagent: $(\text{CH}_3)_3\text{CO}^-/(\text{CH}_3)_3\text{COH}$ ^b	
	Ratio of <u>2-hexene</u> 1-hexene	Ratio of <u>(trans/cis)</u> hexene	Ratio of <u>2-hexene</u> 1-hexene	Ratio of <u>(trans/cis)</u> hexene
I	4.2	3.6	0.45	1.8
Br	2.6	3.0	0.25	1.4
Cl	2.0	2.9	0.14	1.1
F	0.43	2.3	0.027	1.1

^aBartsch and Bunnett (94); ^bBartsch (95).

Bartsch and Bunnett's results, however, are at variance with Thornton's theory which requires that, as the transition state becomes increasingly carbanion-like, there should be an increase in double bond formation with consequent increases rather than decreases in the 2-hexene/1-hexene and trans/cis hexene ratios. Such increasing trends in the ratios are expected because of Thornton's prediction that, as the $\text{C}_\alpha\text{---X}$ bond is made more difficult to break it will be relatively more broken at the transition state with a parallel increase in the breaking of the $\text{C}_\beta\text{---H}$ bond.

However, Bunnett's theory is reinforced by Bartsch's results for the elimination of the 2-hexyl halides with t-butoxide ion in t-butyl

alcohol, Table VI. According to Bunnett, the elimination of the 2-hexyl halides in the new base-solvent medium should lead to even greater carbanion character at the transition state not only because $\underline{t}\text{-BuO}^-$ in $\underline{t}\text{-BuOH}$ is a stronger base than OMe^- in MeOH, but also because $\text{C}_\beta\text{-H}$ bond breaking is also enhanced by $\underline{t}\text{-BuOH}$ having a lesser capacity to weaken the $\text{C}_\alpha\text{-X}$ bond by solvation than the relatively more polar MeOH. The observed trends as well as the relatively smaller magnitudes of the ratios in Table VI are in agreement with Bunnett's predictions but disagree with Thornton's theory which requires that the stronger base should decrease carbanion character at the transition state with consequent increasing rather than decreasing trends in the 2-hexene/1-hexene and trans/cis hexene ratios.

On the other hand, the decreasing trend in the ratios may have been the result of increased steric hindrance at the transition state afforded by the relatively bulky \underline{t} -butoxide ion. If, indeed, an increase in base strength is the determinant for decreasing trends in the ratios, it follows that elimination of the halides with \underline{t} -butoxide ion in dimethyl sulfoxide should result in a further decrease in the ratios. This is to be expected for not only is $\underline{t}\text{-BuO}^-$ in DMSO a stronger base than $\underline{t}\text{-BuO}^-$ in $\underline{t}\text{-BuOH}$ but DMSO is also a poorer solvating medium than $\underline{t}\text{-BuOH}$. However, contrary to expectation, the observed 2-hexene/1-hexene and trans/cis hexene ratios were actually higher for elimination promoted by $\underline{t}\text{-BuO}^-$ in DMSO (96). This unexpected result casts doubt on the validity of this criterion of transition state. Nevertheless, this result may be rationalised by invoking the incursion of a trans-olefin forming syn mode of elimination when the elimination reactions were carried out with $\underline{t}\text{-BuO}^-$ in DMSO. Indeed, the incursion of a trans-olefin forming syn-elimination was invoked by Saunders and his associates to account for the increase in trans/cis

pentene ratios when 2-pentyltrimethylammonium (41) and 2-pentyldimethylsulfonium (42) salts were eliminated in a series of bases of increasing strength to give 1-pentene and isomeric alkylated 2-pentenes. They also point out that syn-elimination may compete significantly with the "normal" anti-elimination to increase the amount of trans-olefin relative to that of cis-olefin. Of the incursion of the syn-pathway in an elimination reaction, more details will be discussed under Syn-Anti Dichotomy in the next section.

To return to the discussion of the effect of base strength on the nature of the transition state, it should be noted that kinetic isotope effects have been used to determine the effect of a change from OEt^-/EtOH to $\text{t-BuO}^-/\text{t-BuOH}$ on transition state geometry in the elimination reactions of quaternary ammonium salts. The results (Table V, page 36) bear out Thornton's prediction that a stronger base causes less $\text{C}_\beta\text{---H}$ and $\text{C}_\alpha\text{---X}$ bond breaking at the transition state. Also, the Hammett ρ value is smaller for elimination with the stronger base, indicating less negative charge at C_β and less $\text{C}_\beta\text{---H}$ bond breaking at the transition state with the stronger base.

To conclude this section, it can be said there is sound experimental evidence in support of both Thornton's and Bunnett's theories. While Thornton's theory has been verified by studies on the elimination reactions of quaternary ammonium salts, that of Bunnett has been borne out by his work on neutral substrates. If all the tools that have been used to probe the nature of the transition state are reliable, it appears that the transition states of neutral and ionic substrates respond differently to substituent changes. Such a consideration is suggested by the O'Ferrall model. The transition states associated with the eliminations of 'onium

salts are believed to be carbanion-like and to have a potential energy surface resembling Figure 5b on page 41. Also, the effect of a substituent change on these transition states is expected to be felt most strongly in a direction perpendicular to the coordinate motion of the transition state. The transition states of the 2-hexyl halides, however, are believed to be less carbanion-like with a potential surface resembling that of Figure 5a. The effect of a substituent change on these transition states is expected to be felt strongly along the reaction coordinate.

D. A Note on the Syn-Anti Dichotomy

Until about 1966, it was generally believed that the preferred steric course of bimolecular elimination reactions is the trans-anti-departure of the β -hydrogen and the leaving group (3-14). A few exceptions to this anti-rule were observed and attributed to strong activation of the β -hydrogen atom by electron-withdrawing groups (19,98-103) or to the rigidity of cyclic systems (15-19) which hindered the torsional arrangement required for anti-elimination. Indeed, so strong was the presumption in favour of anti-elimination that Cram, Greene and DePuy (7) dismissed an apparent syn-elimination (the β -elimination of erythro-1,2-diphenyl-1-propyltrimethylammonium ion with t-butoxide ion in t-butyl alcohol) by assuming that the reaction resulted from epimerisation prior to or during the reaction.

From 1965 on, the "rate profile" studies of Sicher, Zavada and their associates on cyclic and acyclic substrates led to a reevaluation of accepted theories and generalisations concerning the stereochemistry of elimination (14,32). They found that, in some systems, cis-olefin was formed by anti-elimination and that trans-olefin was formed by syn-elimination and also that, under certain conditions, syn- and anti-eliminations occurred simultaneously. They called this phenomenon the "syn-anti dichotomy". They discovered that the propensity toward the syn-anti dichotomy was strongest with cyclic alkyl 'o n i u m salts (21-23,26) but was also observed with cyclic bromides (27) and cyclic tosylates (28). They also found that bromides and tosylates (neutral substrates) show an increasing tendency to eliminate according to the syn-

anti-dichotomy pattern with weak bases in non-polar solvents. Although the syn-anti dichotomy exhibited by the cyclic compounds are accountable from a consideration of the conformational features of the rings (26), the discovery by Cooke and Coke (44) of substantial syn-elimination with cyclobutyl-, cyclopentyl-, and cycloheptyl- (but not cyclohexyl-) trimethylammonium ions made it evident that syn-elimination was more general than was formerly supposed (see Table VII).

TABLE VII

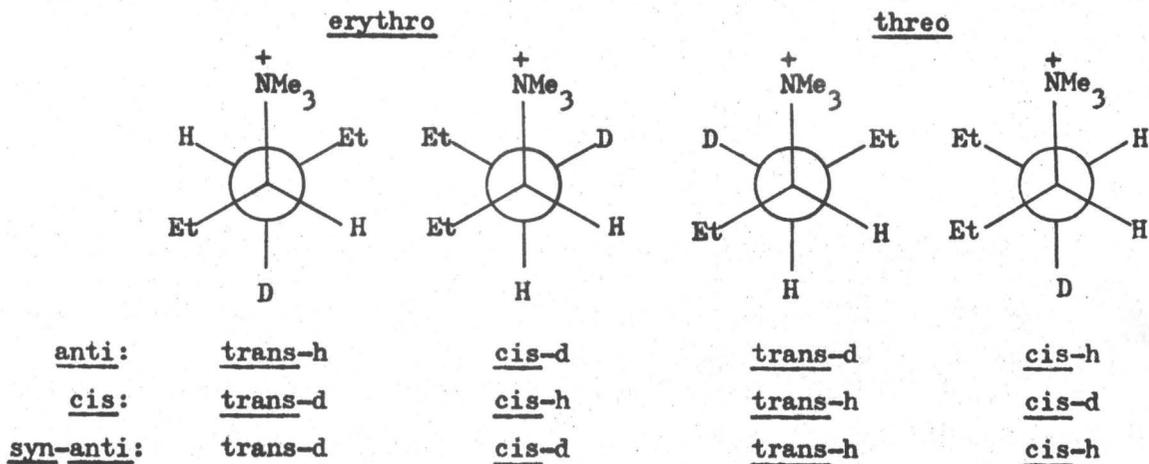
Mechanism of Hofmann Elimination of
Cycloalkyltrimethylammonium Hydroxides

<u>Ring Size</u>	% <u>syn</u> -Elimination	Ref.
4	90	(49)
5	46	(49)
6	4	(49)
7	31 - 37	(49)
8	100	(50)

Syn-elimination was also suggested by Zavada and Sicher (20) to be responsible for the high cis/trans olefin ratios observed in the elimination of quaternary ammonium salts, but this suggestion was not widely accepted until convincing evidence was obtained from the olefin compositions of the elimination of stereospecifically deuterium-labelled acyclic substrates (24,29). Again, as with the cyclic substrates, the same syn-anti dichotomy was observed, although in some cases not all of the trans-

olefin resulted from syn-elimination. The principle underlying the use of deuterium-labelled substrates is illustrated by Scheme 1. The syn-reaction of, for example, threo-3-hexyl-4-d₁ trimethylammonium ion to give trans-3-hexene involves the breaking of the C_β-D bond, whereas the formation of

Scheme 1

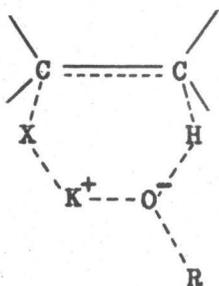


the same olefin by anti-elimination does not: the formation of trans-3-hexene from the threo-β-deuteriated substrate is therefore slowed down by the operation of a primary hydrogen isotope effect, its formation by the anti-route is not. Thus, if relative to the competing formation of cis- and trans-2-hexene, the proportion of trans-3-hexene from the threo-β-deuteriated substrate is found to be practically the same as that from the parent compound, one must conclude that the formation of trans-3-hexene from threo-3-hexyl-4-d₁ trimethylammonium ion has occurred by anti-elimination. If, however, the proportion of trans-3-hexene from the threo-β-deuteriated substrate is substantially lower than that from the parent compound, one must conclude that syn-elimination is partially or wholly responsible for the reaction. The ratio of the rate constants of the for-

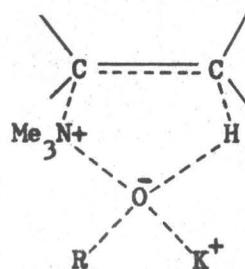
mation of trans-3-hexene from the non-deuteriated and mono-deuteriated hexyltrimethylammonium ions can be calculated from the product composition data. This ratio is the apparent kinetic isotope effect and may be used as a diagnostic tool for the occurrence of the syn-anti dichotomy. In the example cited, the apparent isotope effect should be greater than unity for syn-elimination while that for anti-elimination is about one. The extent to which the syn-anti dichotomy has occurred is given by the per cent of trans-olefin formed by syn-elimination.

Sicher, Zavada and Pankova (26), noting that when the syn-anti dichotomy operates only one of the two β -protons reacts, have speculated that the syn-anti dichotomy is the "consequence of an asymmetrically induced differential reactivity of the two hydrogens on C_β ". That is, the β -hydrogen atoms are said to be "diastereotropic" (26). But they gave no explanation for the diastereotropic nature of the β -hydrogen atoms. However, the following conclusions can be reached from their experiments. The syn-anti dichotomy is increasingly favoured over purely anti-stereochemistry for reactions of bromides < tosylates < quaternary ammonium salts; large rings \approx acyclic substrates < medium rings; polar solvents < non-polar solvents; and weak bases < strong bases.

Zavada and Sicher attribute the increasing importance of syn-elimination in non-polar solvents to ion-pairing phenomena (25,27,28,30). In accordance with their observations that the syn-pathway is favoured in non-polar solvents wherein the formation of contact ion-pairs is favoured, they propose the transition state, XII, for reactions with uncharged leaving groups, and the transition state, XIII, for reactions of substrates with charged leaving groups (26) in solvents that promote dissociation of the base into separate ions.



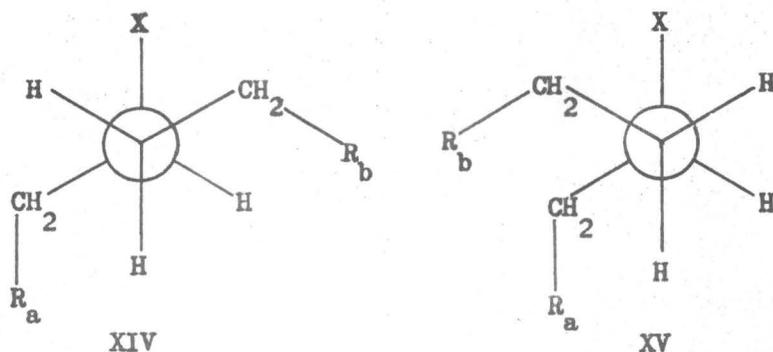
XII



XIII

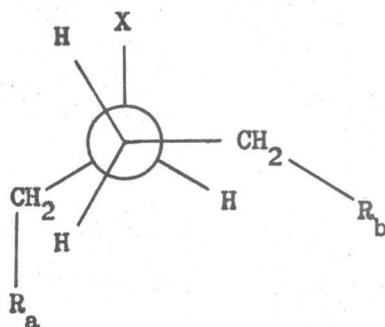
In order to explain the syn-anti dichotomy, Bailey and Saunders (38,39) have studied the stereochemistry of the formation of 2-hexene and 3-hexene from the E2 reactions of 3-hexyltrimethylammonium iodide and its erythro- and threo-3-hexyl-4-d₁ and -2-d₁ analogues. They found that the 3-hexyl-4-d₁ trimethylammonium ion reacted by syn-anti dichotomy (~80%) with t-alkoxides in t-alcohols but mainly by anti-elimination (~80%) with n-alkoxides in n-alcohols. Reactions with s-alkoxides in s-alcohols exhibited mixed behaviour. By contrast, the formation of 2-hexene from 3-hexyl-2-d₁ trimethylammonium ion did not follow exclusively the syn-anti dichotomy pattern even in tertiary base-alcohol systems. About 30% of the trans-2-hexene in the elimination of the 3-hexyl-2-d₁ trimethylammonium ion with t-amyloxyde in t-amyl alcohol was formed by anti-elimination.

Bailey and Saunders explain that the stereospecificity of the syn-anti dichotomy is determined by steric interactions between the base and the alkyl groups caused by a conformational bias due to interactions between the leaving group and the alkyl groups. This may be illustrated by XIV and XV. For example, when the leaving group X is large, R_a and R_b are expected to be repelled as far away as possible to minimise steric

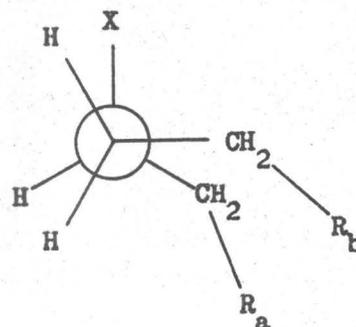


interactions. In the medium rings studied by Zavada and Sicher (21-23, 26-28) this arrangement is forced by conformational restrictions. Relative to the anti-proton in either XIV or XV, R_a is in a position analogous to a 1,3' diaxial position in a cyclohexane ring system and R_b is in a gauche position. The anti proton in structure XV leading to cis-olefin is less sterically hindered than the anti-proton in structure XIV leading to trans-olefin because the conformation leading to cis-olefin permits an angular approach of the base to the anti-proton on the side of the hydrogen atoms and away from the alkyl groups. This angular approach of the base is not possible for the removal of the anti-proton leading to the trans-olefin because the base is blocked on one side by R_a and on the other side by R_b. Thus, Bailey and Saunders predict that, in extreme cases, the anti-proton will be eliminated resulting in exclusive formation of the cis-olefin.

In order to explain the simultaneous operation of syn- and anti-eliminations, Bailey and Saunders postulate that the inherent energy difference (104,105) between a syn- and an anti-process is decreased as the transition state becomes more reactant-like. They point out that in favorable cases, syn-elimination may effectively compete with anti-elimination, and that in extreme cases, the syn-pathway may predominate. Thus, syn-elimination should lead mainly to the trans-olefin as is evident from the decreased steric interaction in XVI relative to that in XVII.



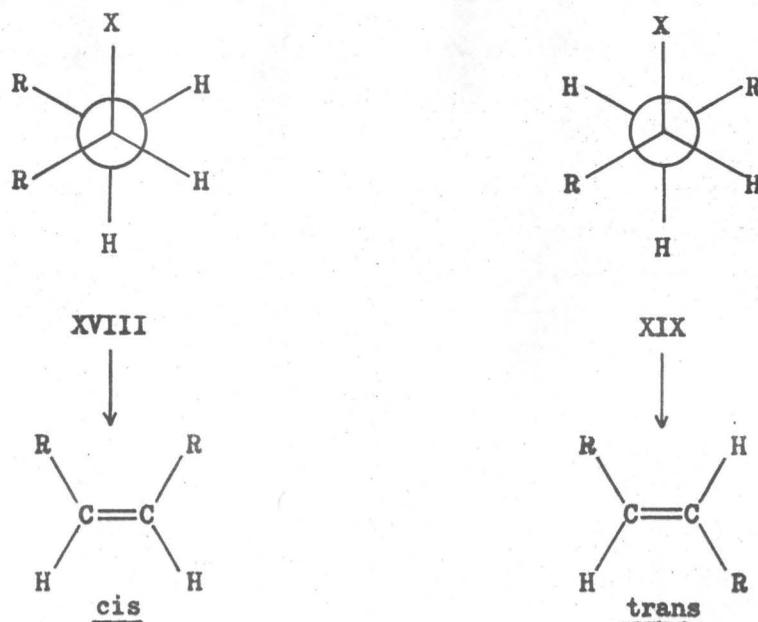
XVI



XVII

Bailey and Saunders claim their theory can be applied to explain the effect of the leaving group, base, solvent and alkyl groups on the stereochemical course of E2 reactions. The stereospecificity of anti-elimination requires the R groups to point away from the leaving group. The bigger the leaving group, the more the R groups will be affected. The syn-pathway is expected to be favoured by reactant-like transition states which are expected for E2 reactions involving poor leaving groups. Thus, the syn-anti dichotomy will be favoured when poor and bulky leaving groups are used, and the exclusive occurrence of the anti-process to form both cis- and trans-olefins will be favoured when good and small leaving groups are used. In this light, the increasing importance of the syn-anti dichotomy along the series $\text{Br} < \text{OTs} < \overset{\dagger}{\text{N}}(\text{Me})_3$ becomes evident.

Using an analogous argument, the syn-anti dichotomy is expected to be favoured by strong and bulky bases; the anti-process leading to both cis- and trans-olefins (107) as illustrated by XVIII and XIX should be favoured by weak and small bases. Thus, the increasing importance of the syn-anti dichotomy with strong bases is as expected.



With regard to the effect of the solvent, less polar solvents are expected to induce E2 reactions with more reactant-like transition states for substrates with uncharged leaving groups (12). As mentioned earlier, alkyl bromides and tosylates have shown an increasing tendency to react by the syn-anti dichotomy in less polar solvents.

Bailey and Saunders' theory is particularly successful in predicting the effect of R groups (see XIV and XV) on the stereochemical course of E2 reactions. It is predicted that a change in either R_a or R_b from H to Me should result in a large increase in the tendency of the reaction to proceed according to the syn-anti dichotomy pattern. Also, further increases from Me to larger alkyl groups should have only a minor effect since the added alkyl groups can then turn away from the anti-hydrogen atoms. Thus, only when R_a or R_b changes from methyl to a highly branched group such as t-butyl should there be a marked change in the stereochemical course of the reaction.

Table VIII shows the relative stereospecificity of E2 reactions of acyclic trimethylammonium salts with n- and t-butoxides in their respective alcohols as solvents.

TABLE VIII

Stereochemistry of E2 Reactions of
Acyclic Quaternary Ammonium Salts

<u>Compound</u>	<u>Olefin</u>	<u>Base</u> ^a	<u>R_a</u> ^b	<u>R_b</u> ^b	<u>% trans-olefin produced by syn-elimination</u>	<u>Reference</u>
$R-N^+(Me)_3$						
R =						
3-Hexyl	2-Hexene	<u>t</u> -AmO ⁻	H	Et	70	(39)
		MeO ⁻	H	Et	0	(39)
3-Hexyl	3-Hexene	<u>t</u> -AmO ⁻	Me	Me	90	(39)
		MeO ⁻	Me	Me	0	(39)
5-Decyl	5-Decene	<u>t</u> -BuO ⁻	<u>n</u> -Bu	<u>n</u> -Pr	87	(29)
		MeO ⁻	<u>n</u> -Bu	<u>n</u> -Pr	32	(29)
2,2-Di- methyl-4- nonyl	2,2-Di- methyl-4- nonene	<u>t</u> -BuO ⁻	<u>t</u> -Bu	<u>n</u> -Pr	100	(29)
		MeO ⁻	<u>t</u> -Bu	<u>n</u> -Pr	100	(29)

^aThe solvent is the corresponding alcohol.

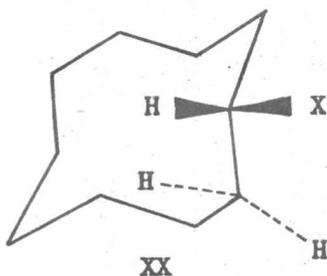
^bXIV and XV.

It is visible from the conformation for 3-hexyltrimethylammonium ion (this gives 3-hexene) that both R_a and R_b (see XIV and XV) are methyl groups. In the conformation leading to 2-hexene, R_a is H and R_b is ethyl. The prediction that 3-hexene would be formed by the syn-anti dichotomy

to a larger extent than 2-hexene is evident in Table VIII from the higher stereospecificity for the formation of 3-hexene in t-amyl alcohol. A comparison of the stereochemical course of the E2 reactions of the 3-hexyl and the 5-decyltrimethylammonium salts with methoxide ion in methyl alcohol shows that as R_a and R_b are changed from methyl to longer n-alkyl groups a slightly increasing tendency to react by syn-anti dichotomy was observed. It was also observed that when R_a was changed to the relatively bulky t-butyl group (as in 2,2-dimethyl-4-nonyltrimethylammonium ion) the reaction proceeded with a large increase in the syn-anti dichotomy specificity.

The same effect of alkyl chain length on stereochemistry occurs for reactions of acyclic quaternary ammonium salts with t-butoxide in dimethyl sulfoxide. It was found that 5-n-decyltrimethylammonium ion undergoes the E2 reaction in this base-solvent medium (29) mainly according to the syn-anti-dichotomy pattern, whereas the 2-butyltrimethylammonium ion forms both cis- and trans-2-butene mainly by an anti-process (40,107-109).

Bailey and Saunders' theory also explains the prevalence of the syn-anti dichotomy in medium-ring systems. The conformation of cyclodecane, XX, places anti-periplanar protons inside the ring. This restriction is



relaxed in the more flexible larger rings. Indeed, as observed by Zavada and Sicher (27), the syn-anti dichotomy was found to be relaxed in large-ring compounds.

Although Bailey and Saunders have demonstrated successfully that elimination by the syn-anti dichotomy is the result of steric interactions, it has been observed by Zavada, Pankova and Sicher (30) that the syn-anti dichotomy can occur even in the absence of the required steric interactions. It is also interesting to note that Bayne and Snyder (51) have observed substantial syn-elimination in the reactions of 2-phenylethyl-1,2- d_2 chloride and the corresponding tosylate in spite of the minimal steric interactions. Bayne and Snyder's results which appear in Table IX are in agreement with the conclusions of Sicher and his associates that contact ion pairs and the nature of the solvent are important in syn-elimination.

TABLE IX

Eliminations from PhCHDCHDX using t-Butoxide

<u>Diastereomer</u>	<u>X</u>	<u>Solvent</u>	<u>T°C.</u>	<u>% syn</u>	<u>% anti</u>	<u>(k^H/k^D)_{syn}</u>	<u>(k^H/k^D)_{anti}</u>
<u>threo</u>	OTs	<u>t</u> -BuOH	30	7	93	a	5.1
<u>threo</u>	OTs	<u>t</u> -BuOH	80	9	91	a	4.2
<u>threo</u>	OTs	DMSO	23	4 ^b	96	a	5.6
<u>threo</u>	OTs	Benzene	80	18	82	2.3	3.9
<u>threo</u>	OTs	Benzene	80	19	81	2.1	4.1
<u>erythro</u>	Cl	Benzene	80	25	75	2.9	4.8

^a Not reliable owing to large uncertainty value.

^b Values less than 5% syn-elimination are not experimentally distinguishable from 0%.

The dramatic increase in syn-elimination in entry 4 of Table IX is attributed to the prevalence of contact ion-pairs in the non-polar benzene solvent. That steric interactions is not the absolute determinant for the operation of the syn-anti dichotomy is also evident in a recent study by Pankova, Svoboda and Zavada (36) who found that regardless of the steric size of the leaving group, the elimination reactions of 5-decyl halides and the corresponding tosylate exhibited syn-anti dichotomy. On the basis of steric interactions of the alkyl groups in vicinal positions (see XIV and XV), the elimination of 2-butyl tosylate and 2-butyl trimethylammonium ion are expected to exhibit a syn-pathway leading to trans-butene. The search for this reaction pathway, however, had proved to be fruitless (40, 106-109). Thus, there is evidence to militate against the presumed overriding importance of steric interactions.

In retrospect, the reason for the former belief in the inviolability of the anti-rule for β -elimination is now evident. The early investigations of elimination reactions of cyclic reactants were done on cyclohexyl compounds (5). The cyclohexyl system is now considered a poor model for elimination reactions of other cyclic systems. Syn-elimination was not observed with cyclohexyl compounds because the energetically favoured chair-form of the cyclohexane ring precludes the attainment of syn-periplanar transition states which are available only when the highly unstable boat-form conformations are attainable (11).

With reference to acyclic molecules, it must be realised that much of the evidence for anti-elimination was based on the study of Pfeiffer (3) on the elimination of stilbene dibromide and on the study by Cram, Greene and DePuy (7) on the eliminations of 1,2-diphenyl-1-propyl compounds. The stereochemical conclusions based on these studies should not

be considered to be general. The virtual absence of syn-elimination in these studies may be attributed to the presence of bulky groups on C_α and C_β , a factor which would increase the energy required for syn-elimination (4). Furthermore, it is difficult to predict what influence the electronic effect of the phenyl rings will exert on the stereochemical course of the reaction.

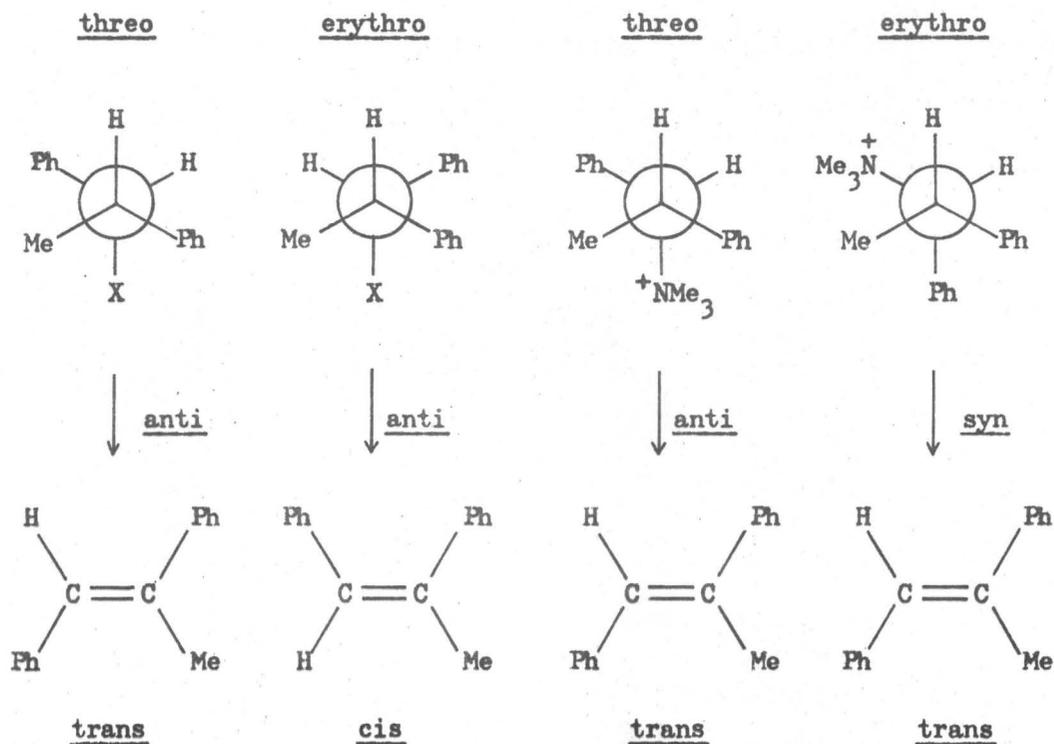
The study by Skell and Wall (10) on the stereochemistry of elimination of 2-butyl tosylate dispenses with these objections. The lack of bulky alkyl chains ($R_a, R_b = H, \dots$), however, renders the 2-butyl system a poor model for syn-elimination in acyclic compounds just as the cyclohexyl system was a poor model for syn-elimination in the alicyclic compounds.

In conclusion, the syn-anti dichotomy is now a well-documented phenomenon (32,39-43,106). The foregoing discussion has shown that syn-elimination is a more frequent reaction mode than has previously been assumed. Both anti- and syn-elimination reactions should be looked upon as "normal", that is, frequent modes in bimolecular elimination reactions, the operation of the one or the other process or of both processes simultaneously depending upon the structural features of the reactants (substrate and base) as well as on the nature of the solvent.

RESULTS AND DISCUSSION

It will be recalled that Cram, Greene and DePuy have observed, in their study of the stereochemistry of elimination of erythro- and threo-1,2-diphenyl-1-propyl-X derivatives ($X = \text{Br}, \text{Cl}, \text{and } \overset{+}{\text{NMe}}_3$) in various alkoxide-alcohol media, that the erythro and threo diastereomers gave cis- and trans- α -methylstilbene, respectively. The stereospecificity of these reactions indicates that the reaction pathway was anti-elimination (see Scheme 2). One exception, however, was noted in that the elimination reactions of both erythro- and threo-1,2-diphenyl-1-propyl-trimethylammonium ion with t-butoxide ion in t-butyl alcohol gave trans- α -methylstilbene.

Scheme 2



Since the cis-olefin was found not to isomerise to the trans-olefin under the reaction conditions, this seemingly anomalous result was indicative of syn-elimination for the reaction of the erythro compound. The presumption, however, in favour of anti-elimination was so strong at that time that it was assumed, without proof, that the reaction resulted from rapid epimerisation at C_{α} or inversion at C_{β} via a carbanion mechanism prior to or during the reaction.

McLennan (14) has suggested that a carbanion mechanism was a strong possibility in the reactions of the quaternary ammonium salts. In making this suggestion he recalls the fact that the elimination reactions of the diastereomeric quaternary ammonium salts exhibited stereoconvergency at virtually identical rates (7) in the medium t-butoxide-in-t-butyl alcohol and that the approximately equal stability (110) of the diastereomeric quaternary ammonium salts would give rise to transition states of comparable energy. He also points out that a carbanion mechanism is favoured by the structural features of the reactants, the strength of the base and the nature of the solvent. McLennan, however, was uncertain whether the formation of the carbanion in the overall syn-elimination (of the erythro reactant) occurred in a syn-stereospecific step or by removal of the proton anti to the leaving group followed by rotation about the C_{α} — C_{β} bond. Noting that anti-stereospecificity was restored in the medium ethoxide-ethanol wherein the threo ion reacted 57 times faster than the erythro, McLennan points out that, " the reactions in t-butyl alcohol warrant further investigation and studies of isotope and phenyl-substituent effects could prove fruitful."

Accordingly, a study was undertaken to determine whether the

formation of the trans-olefin from the elimination of the erythro quaternary ammonium salt resulted from epimerisation followed by elimination or from a syn-E2 process. The original project was, if the reaction turned out to be a syn-E2 process, to determine by β -hydrogen isotope effect and leaving-group nitrogen isotope effect measurements the relative extents of C_β -H and C_α -N bond breaking associated with the elimination reactions of the diastereomeric quaternary ammonium salts. For reasons already given in the General Introduction, the present study is concerned only with the reaction of the threo reactant with t-butoxide ion in t-butyl alcohol.

Since the diastereomeric quaternary ammonium salts are of approximately equal stability, it is reasonable to assume that if epimerisation does occur at C_α or if an E1cB hydrogen-deuterium exchange does occur at C_β in the elimination reaction of one of the diastereomeric quaternary ammonium salts, it would also occur in the elimination reaction of the other diastereomer. Accordingly, the threo quaternary ammonium salt was reacted with t-butoxide ion in t-butyl alcohol- $O-d_1$ at $60 \pm 0.1^\circ C$. and the recovered olefin was tested for deuterium pick-up at C_α by proton magnetic resonance spectroscopy. The results of this experiment are presented in Table X. The results show that, within the limits of detection of the proton magnetic resonance spectrometer ($\pm 5\%$), epimerisation did not occur at C_α . Thus, one may also infer that α -epimerisation should be absent in the elimination reaction of the erythro compound. Indeed, this view has been verified by Borchardt and Saunders (53) who found that the elimination of erythro-1,2-diphenyl-1-propyltrimethylammonium ion and its $-1-d_1$ analogue with t-butoxide ion in t-butyl alcohol- $O-d_1$ and with t-butoxide ion in t-butyl alcohol, respectively, involved no

TABLE X

Proton Magnetic Resonance Integrations
for α -Hydrogen and Phenyl-Hydrogens of trans- α -Methylstilbene
and Recovered Olefin from α -Epimerisation Test at $60 \pm 0.1^\circ\text{C}$.

<u>trans</u> - α -Methylstilbene			Recovered Olefin		
<u>Phenyl-H's</u>	<u>α-H</u>	<u>α-H/ Phenyl-H's</u>	<u>Phenyl-H's</u>	<u>α-H</u>	<u>α-H/ Phenyl-H's</u>
11.55	1.10	0.095	11.65	1.20	0.103
9.80	1.00	0.102	11.90	1.15	0.097
11.15	1.10	0.099	11.30	1.15	0.102
9.70	0.95	0.098	9.50	0.90	0.095
9.40	0.90	0.096	10.45	1.00	0.096
11.25	1.10	0.098	11.75	1.15	0.098
		<u>0.098 \pm 0.002</u>			<u>0.098 \pm 0.003</u>

hydrogen-deuterium exchange at C_{α} . The test for an E1cB hydrogen-deuterium exchange was not carried out because Borchardt and Saunders (53) have observed that there was no E1cB hydrogen-deuterium exchange in the elimination of the $-2-d_1$ analogue of the erythro diastereomer with t-butoxide ion in t-butyl alcohol. The exchange tests performed by Borchardt and Saunders were carried out to one half-life at 35°C . The absence of an E1cB hydrogen-deuterium exchange in the reaction of the erythro quaternary ammonium salt may be taken to indicate the absence of an E1cB hydrogen-deuterium exchange in the reaction of the threo quaternary ammonium salt with the same base-solvent system.

Our results and those of Borchardt and Saunders exclude α -epimerisation if it is assumed that reprotonation at the α -carbanion centre does not occur by internal return of the proton from the t-butyl alcohol formed initially by proton or deuterium abstraction. If, likewise, it is also assumed that internal return of the deuterium is absent in the elimination of the $-2-d_1$ analogue of the erythro quaternary ammonium salt, Borchardt and Saunders' results are compatible with syn-elimination of the erythro reactant. However, their results still do not unequivocally exclude the possibility of an E1cB mechanism in the reaction of either quaternary ammonium salt.

In order to determine whether the reaction mechanism associated with the elimination of the diastereomeric quaternary ammonium salts is stepwise or concerted it is necessary to measure the β -hydrogen isotope effects for $C_{\beta}-\text{H}$ bond breaking and the nitrogen isotope effects for $C_{\alpha}-\text{N}$ bond breaking at the transition state. The utility of isotope effect measurements is not merely limited to determination of reaction

mechanism. Indeed, a comparison of the β -hydrogen isotope effects and the nitrogen isotope effects associated with the elimination reactions of the erythro and threo quaternary ammonium salts, respectively, will provide an insight into the nature of the transition states associated with syn- and anti-elimination of these reactants.

The determination of the β -hydrogen isotope effect associated with the elimination of the threo quaternary ammonium salt entailed measuring the rates of elimination of the undeuteriated and deuteriated threo quaternary ammonium salts as well as determining the compositions of the products of these reactions. The kinetic studies were conducted at the relatively low substrate concentration of 6.89×10^{-5} M in 0.220N potassium t-butoxide in t-butyl alcohol at 30°C. in order to obtain good first order kinetics. The temperature of 30°C. was used because at higher temperatures the rate of elimination of the undeuteriated quaternary ammonium salt was too fast to be measured conveniently. The reaction products resulting from the elimination of each quaternary ammonium salt were found by gas-liquid partition chromatography and proton magnetic resonance spectroscopic analyses to consist of trans- α -methylstilbene, cis- α -methylstilbene and threo-N,N-dimethyl-1,2-diphenyl-1-propylamine. The amounts of reaction products resulting from the elimination of the isotopic quaternary ammonium salts at the concentration of substrate used in the kinetic studies were too low to enable reliable determination of the product compositions. These product compositions were obtained, however, by extrapolation from the product compositions associated with the reactions of the substrates at three higher concentrations, Tables XIa, XIb, Figures 6a-8b and Table XII.

The formation of trans- α -methylstilbene from the threo-quaternary ammonium salt evidently resulted from anti-elimination as was observed

TABLE XIa

Product Analyses of the Reactions of
threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide
 with Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at $30 \pm 0.02^\circ\text{C}$.
 using trans-Stilbene as Internal Standard.

Concentration of t-BuOK = 0.22 m./l.

Conc. of Q.A.S. (mg. per 100 ml.)	%	%	%
	<u>cis</u> - α - Methylstilbene	<u>trans</u> - α - Methylstilbene	<u>threo</u> -N,N-Dimethyl- 1,2-diphenyl-1-propylamine
6	(2.2 \pm 0.1)	(90.8 \pm 1.3)	(6.9 \pm 0.3)
12	(2.5 \pm 0.2)	(89.9 \pm 1.2)	(7.6 \pm 0.8)
24	(3.9 \pm 0.2)	(87.9 \pm 1.1)	(8.9 \pm 0.2)

TABLE XIb

Product Analyses of the Reactions of
threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide
 with Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at $30 \pm 0.02^\circ\text{C}$.
 using trans-Stilbene as Internal Standard.

Concentration of t-BuOK = 0.22 m./l.

Conc. of Q.A.S. (mg. per 100 ml.)	%	%	%
	<u>cis</u> - α - Methylstilbene	<u>trans</u> - α - Methylstilbene	<u>threo</u> -N,N-Dimethyl- 1,2-diphenyl-1-propylamine-2-d ₁
6	(5.1 \pm 0.2)	(55.4 \pm 0.8)	(39.0 \pm 2.0)
12	(5.5 \pm 0.2)	(52.6 \pm 1.7)	(41.3 \pm 1.9)
24	(6.2 \pm 0.3)	(47.6 \pm 1.3)	(45.2 \pm 1.5)

TABLE XII

Extrapolated Product Compositions of Olefins and Tertiary Amine for
 Reactions of threo-1,2-Diphenyl-1-propyltrimethylammonium Ions at $30 \pm 0.05^\circ\text{C}$.
 with Potassium t-Butoxide in Anhydrous t-Butyl Alcohol.

$$([\text{Q.A.S.}]^a = 6.89 \times 10^{-5} \text{ m./l. ; } [\text{t-BuO}^-] = 0.220 \text{ m./l.}).$$

<u>Quaternary</u> <u>Ammonium Salt</u>	% <u>cis-α-^b</u> <u>Methylstilbene</u>	% <u>trans-α-^b</u> <u>Methylstilbene</u>	% <u>threo-N,N-Dimethyl-^b</u> <u>1,2-diphenyl-1-propylamine</u>
<u>threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide</u>	1.8	91.5	6.6
<u>threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide</u>	4.9	56.9	37.9

^a
 Concentration of quaternary ammonium salts at which kinetic data were obtained. At this concentration, it was not possible to determine product compositions with accuracy. $[\text{Q.A.S.}] = 2.63 \text{ mg./100 ml.}$

^b
 These results were obtained by extrapolation from product compositions of reactions of quaternary ammonium salts at higher concentrations, Table XIa and Table XIb.

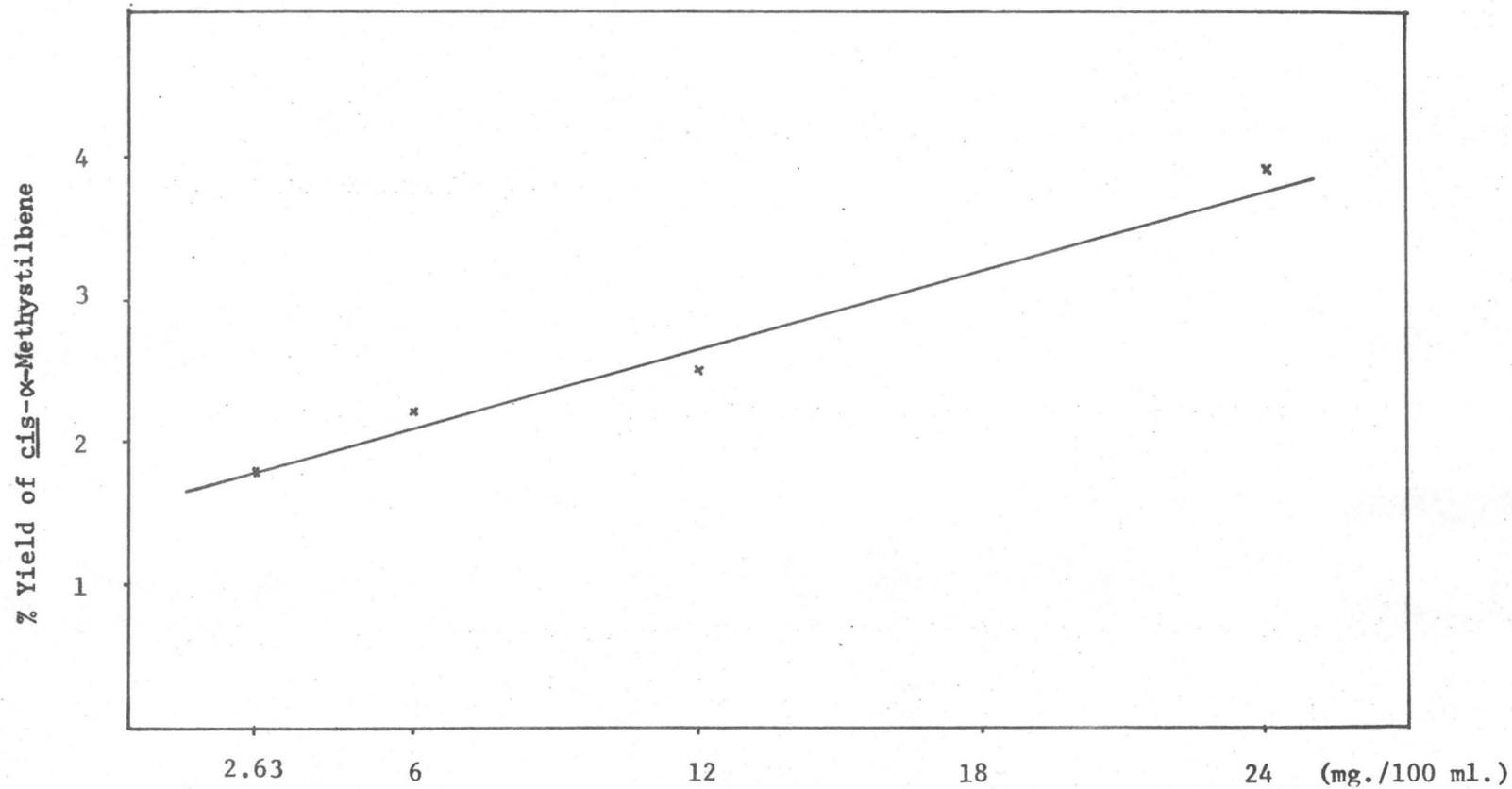


Figure 6a.

Plot of % cis- α -Methylstilbene

Vs. Conc. of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide

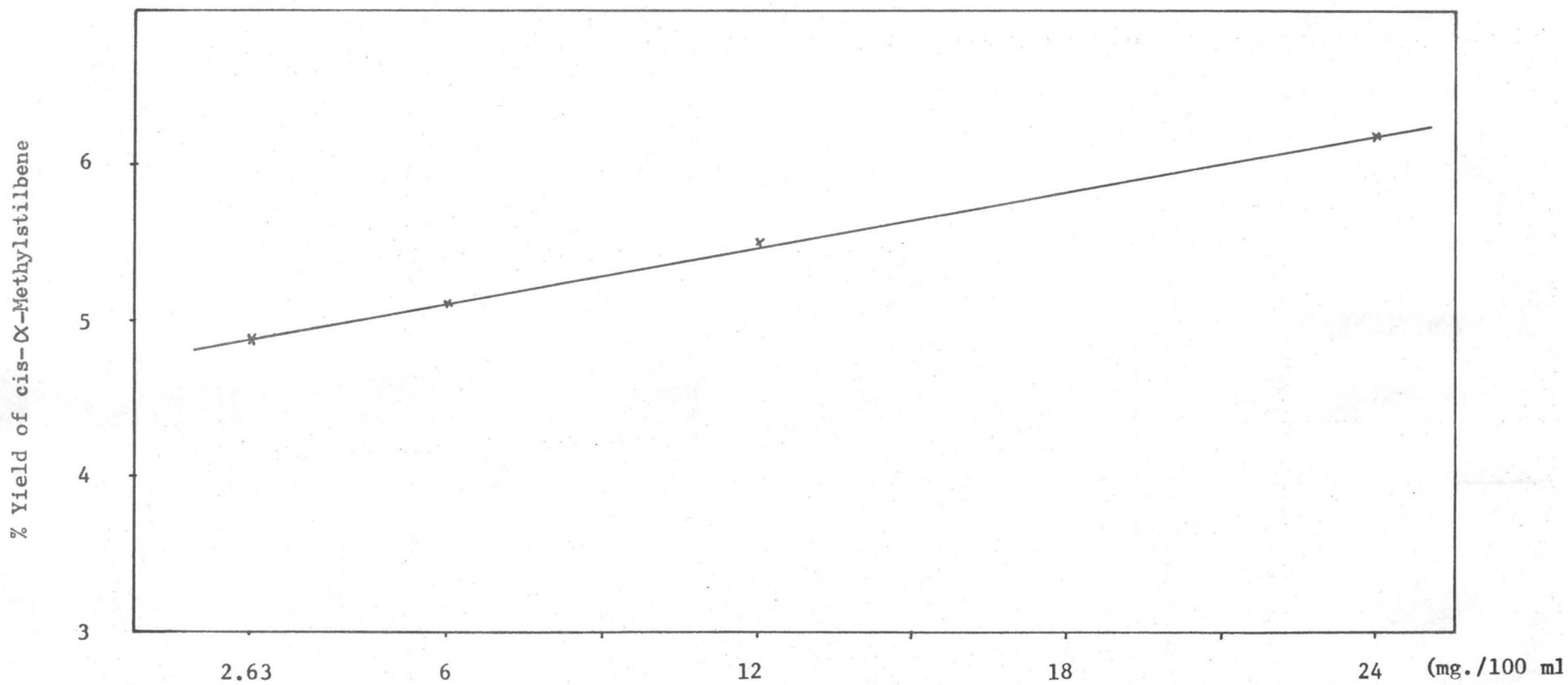


Figure 6b.

Plot of % *cis*- α -Methylstilbene

Vs. Conc. of *threo*-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide

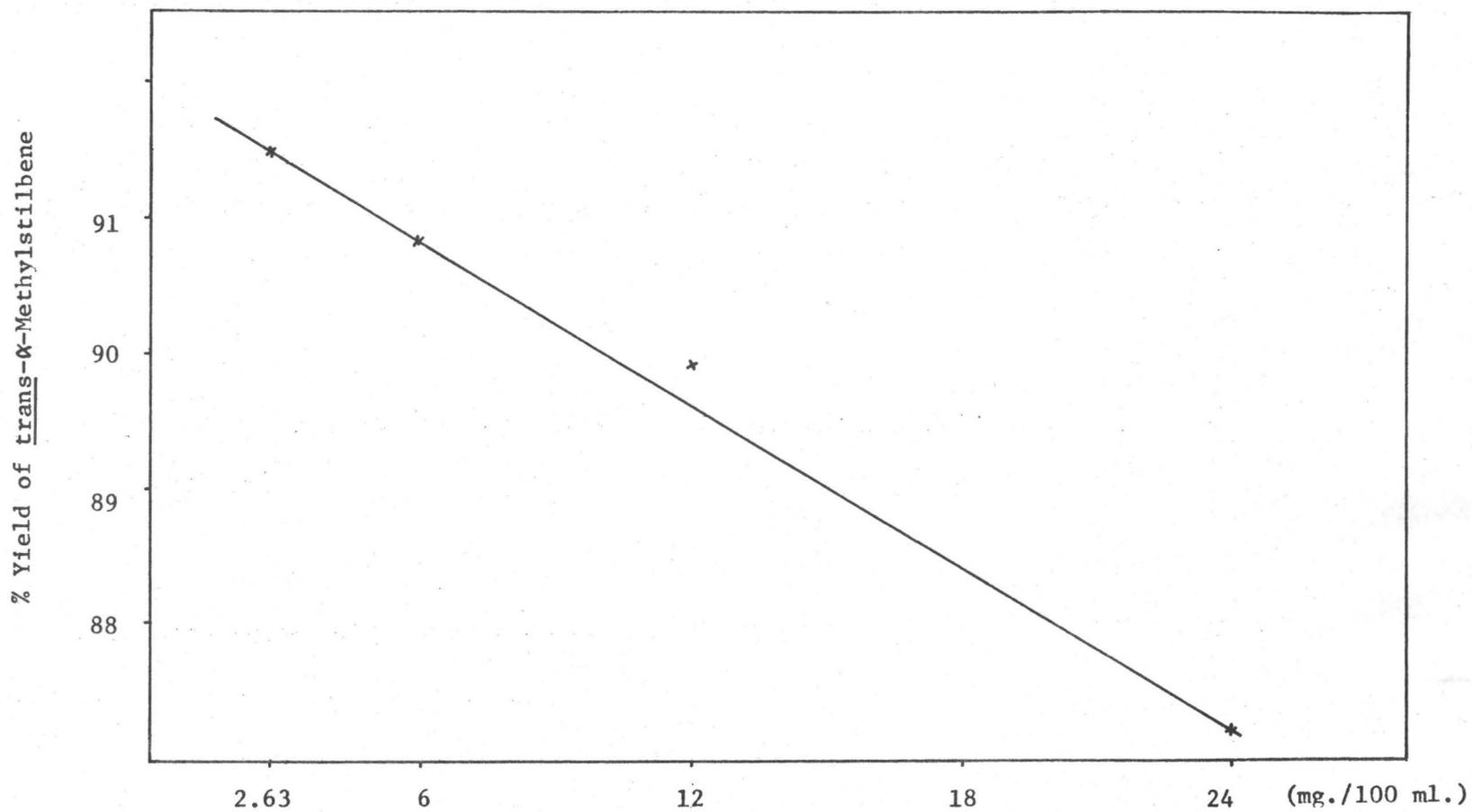


Figure 7a.

Plot of % trans- α -Methylstilbene

Vs. Conc. of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide

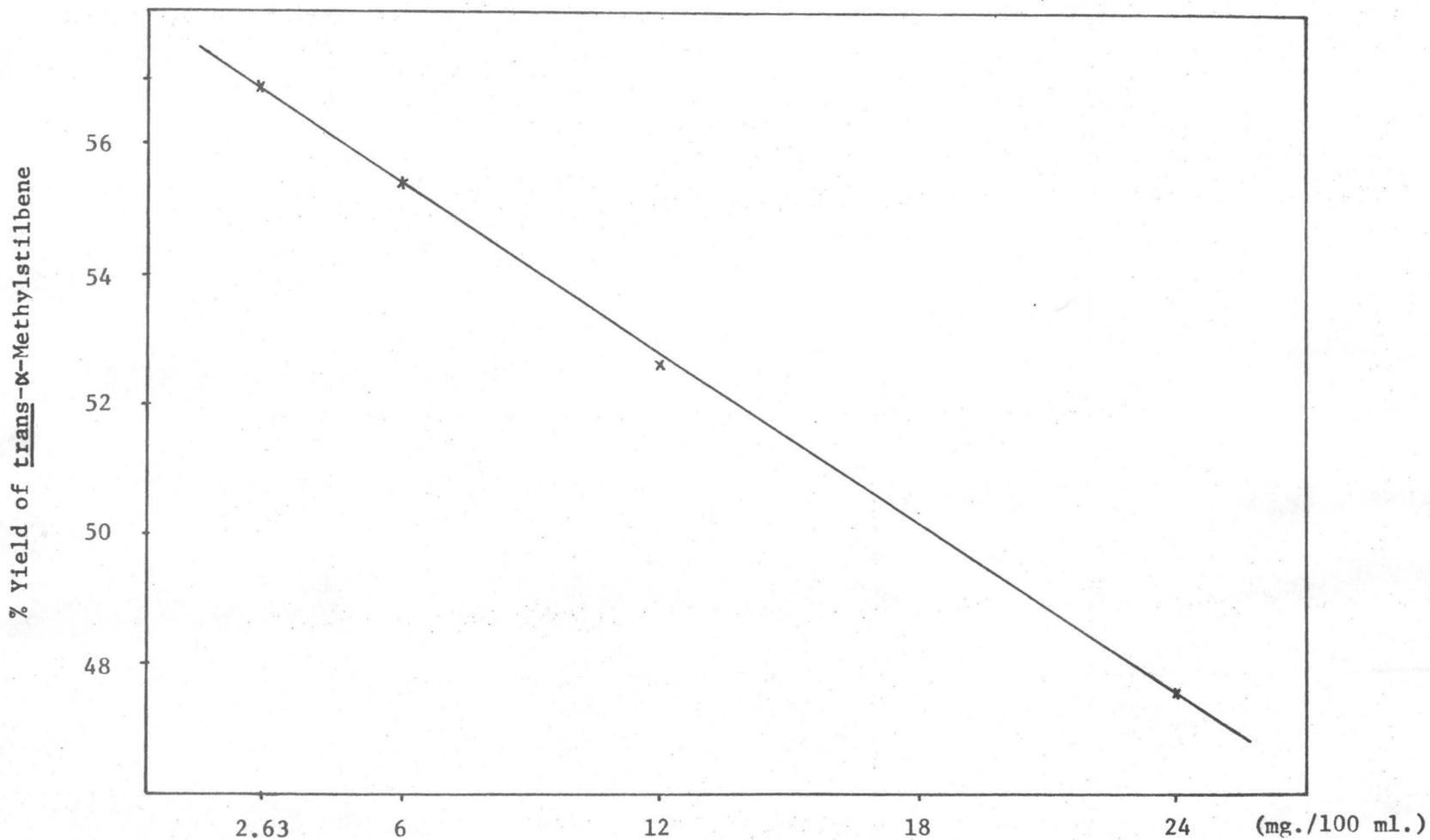


Figure 7b.

Plot of % trans- α -Methylstilbene

Vs. Conc. of threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide

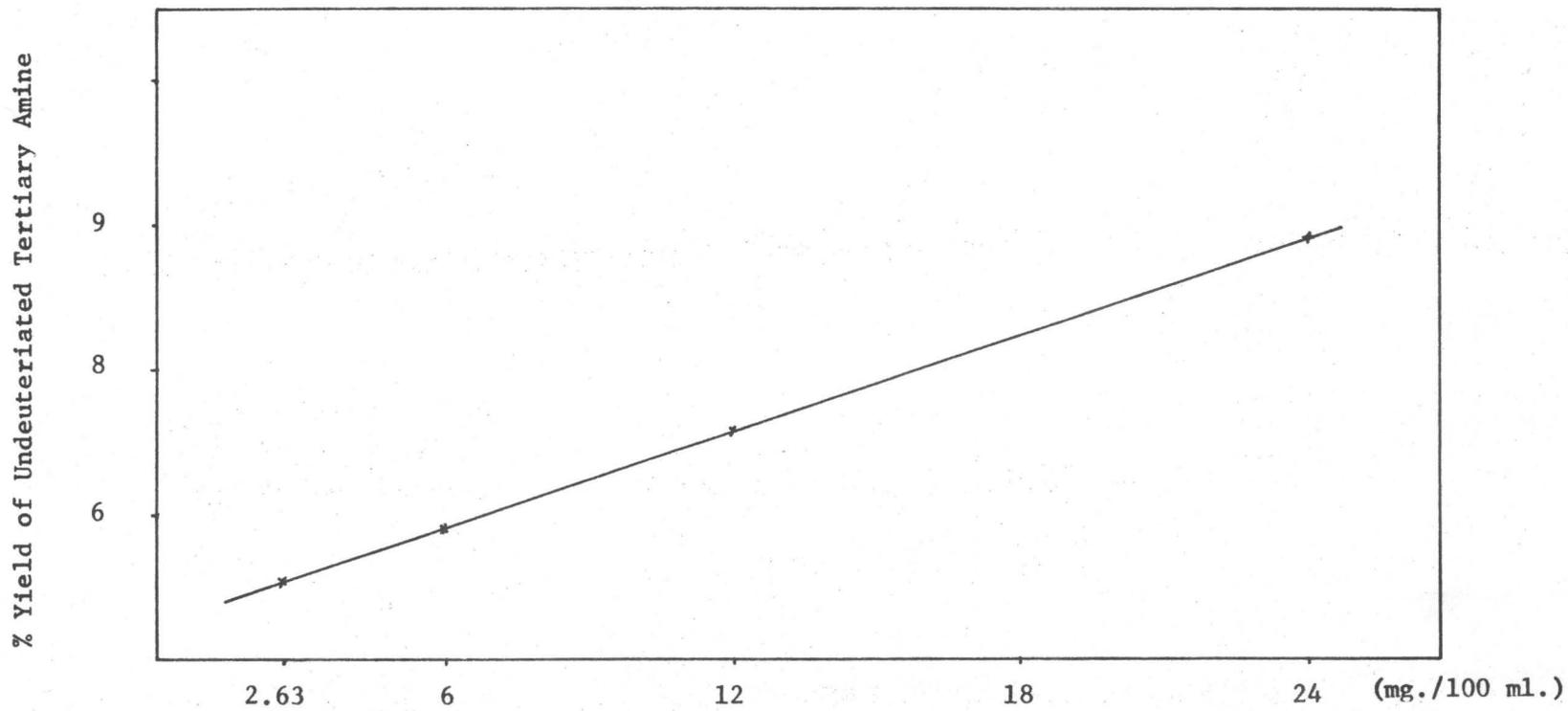


Figure 8a.

Plot of % threo-N,N-Dimethyl-1,2-diphenyl-1-propylamine
Vs. Conc. of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide

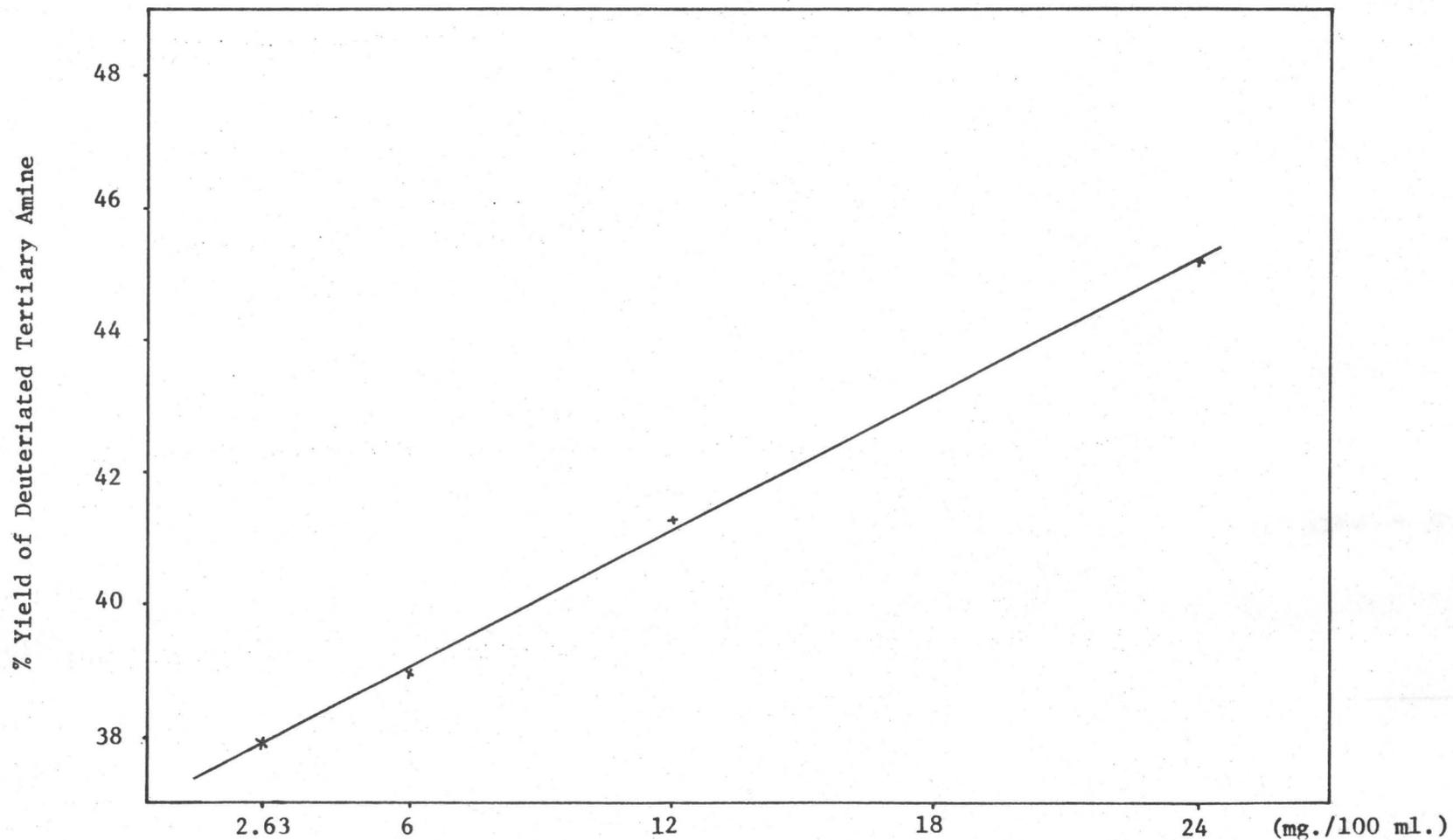


Figure 8b.

Plot of % threo-N,N-Dimethyl-1,2-diphenyl-1-propylamine-2-d₁
Vs. Conc. of threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide

by Cram, Greene and DePuy who, however, did not detect the formation of the cis-olefin and the tertiary amine. It is significant to note that the trans-olefin recovered from the elimination of the deuteriated quaternary ammonium salt was found by proton magnetic resonance spectroscopy to contain no deuterium at C_{α} . In view of the fact that an α -mechanism is a possibility with a strong base in an aprotic solvent, conditions approximated by t-butoxide ion in t-butyl alcohol, the absence of deuterium on C_{α} shows the absence of an α -elimination besides giving further support for the absence of α -epimerisation. The presence of the cis-olefin is evidently due to the incursion of a syn-elimination, a probable occurrence in view of the established generality of syn-elimination. The formation of the tertiary amine resulted most probably from nucleophilic attack of the quaternary ammonium salt by the base at a N-methyl carbon atom.

The second order rate constants for anti-elimination and syn-elimination of the undeuteriated and deuteriated quaternary ammonium salts, respectively, were obtained by multiplying the observed rate of elimination of each quaternary ammonium salt by the corresponding per cent yields of the trans-olefin and the cis-olefin of the reaction, Table XIII, page 80. The β -hydrogen isotope effects associated with anti- and syn-elimination were then calculated, Table XIII. Of the two isotope effects, the more reliable is that for anti-elimination because the relatively large amounts of the trans-olefin formed enabled accurate determination of the absolute amounts of the trans-olefin. By contrast, the β -hydrogen isotope effect for syn-elimination has a relatively substantial uncertainty value because it was not possible to determine accurately the absolute amounts of the relatively small quantities of the cis-olefin.

TABLE XIII

Rate Constants and β -Hydrogen Isotope Effects for Anti- and Syn-Elimination of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide with Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at $30 \pm 0.05^\circ\text{C}$. (Conc. of Q.A.S. = 6.89×10^{-5} m./l.; Conc. of Base = 0.220 m./l.).

$(k^{\text{H}})^{\text{a}}$ <u>obs.</u>	$(k^{\text{H}})^{\text{b}}$ <u>anti</u>	$(k^{\text{H}})^{\text{c}}$ <u>syn</u>
----- ($\times 10^4$ mole ⁻¹ sec ⁻¹) -----		
13.24 \pm 0.07	12.11	0.24
13.21 \pm 0.07	12.08	0.24
13.29 \pm 0.09	12.16	0.24
<u>13.25 \pm 0.08</u>	<u>12.12 \pm 0.05</u>	<u>0.24</u>
$(k^{\text{D}})^{\text{a}}$ <u>obs.</u>	$(k^{\text{D}})^{\text{b}}$ <u>anti</u>	$(k^{\text{D}})^{\text{c}}$ <u>syn</u>
----- ($\times 10^4$ mole ⁻¹ sec ⁻¹) -----		
3.41 \pm 0.01	1.94	0.17
3.39 \pm 0.02	1.93	0.17
3.41 \pm 0.02	1.94	0.17
<u>3.40 \pm 0.02</u>	<u>1.94 \pm 0.01</u>	<u>0.17</u>
$(k^{\text{H}}/k^{\text{D}})_{\text{anti}} = 6.25 \pm 0.04^{\text{d}}; \quad (k^{\text{H}}/k^{\text{D}})_{\text{syn}} = 1.41^{\text{e}}$		

^aThe rate error limit for each kinetic run was given by least squares calculations, and that for the mean of a series of runs is the standard deviation.

^b $(k)_{\text{anti}} = (k)_{\text{obs.}} \times \% \text{ Yield of trans-olefin}$ }
^c $(k)_{\text{syn}} = (k)_{\text{obs.}} \times \% \text{ Yield of cis-olefin}$ } See Table XII for % Yields of olefins.

^dDeviation = $\pm (k^{\text{H}}/k^{\text{D}}) \left[(r^{\text{H}}/k^{\text{H}})^2 + (r^{\text{D}}/k^{\text{D}})^2 \right]^{\frac{1}{2}}$

^eIsotope Effect is associated with relatively large uncertainty value.

The relatively large β -hydrogen isotope effect for anti-elimination shows that the fission of the $C_{\beta}-H$ bond has occurred in the rate determining step. The relatively small β -hydrogen isotope effect for syn-elimination shows that $C_{\beta}-H$ bond breaking for this mode of elimination may be partly if not wholly rate determining.

Since the theoretical maximum hydrogen isotope effect for half-transfer of the proton to the base at the transition state is about 7 at 25°C., the observed β -hydrogen isotope effect of 6.25 at 30°C. (this will be a little larger than 6.25 at 25°C.) shows that the transfer of the proton to the base in the anti-mode of elimination of the quaternary ammonium salt may be a little more or a little less than half-complete. In the absence of further evidence, it is not possible to tell whether the proton is, in reality, more or less than half-transferred to the base at the transition state. However, it is interesting to speculate on what the extent of proton transfer may be by a consideration of the effects of substituents on C_{α} and C_{β} on the extent of bond breaking in the elimination of ethyltrimethylammonium ion.

It will be recalled that the proton is more than half-transferred to the base at the transition state in the elimination of 2-phenylethyltrimethylammonium ion with ethoxide ion in ethanol (50), and that the nitrogen isotope effect measurements of Smith (88) and the β -hydrogen isotope effect results of Simon and Muellhofer (89) clearly indicate that the effect of the β -phenyl substituent is to decrease the nitrogen isotope effect and to increase the β -hydrogen isotope effect. Thus, it is evident that the proton, in the elimination of ethyltrimethylammonium ion is more than half-transferred to the ethoxide ion, and that the effect

of the β -phenyl substituent is to bring about a shift toward a less product-like transition state. Again, it will be recalled that a change to a stronger base or to an electron-withdrawing substituent in the β -phenyl ring increases the β -hydrogen isotope effect and decreases the nitrogen isotope effect with a shift toward a less product-like transition state in the elimination of 2-phenylethyltrimethylammonium ion (87,88). Since a methyl group is electron-supplying in contradistinction to a β -phenyl group which is electron-withdrawing, it can be expected that the proton is further transferred to the base at the transition state in the elimination of 2-phenyl-1-propyltrimethylammonium ion than is the proton in the elimination of 2-phenylethyltrimethylammonium ion with the same base-solvent system. That the proton is indeed more than half-transferred is accessible from Storm's study (112,113) on the elimination reactions of undeuteriated and deuteriated m-Br substituted 2-phenyl-1-propyl bromides and tosylates with ethoxide ion in ethanol and with t-butoxide ion in t-butyl alcohol, respectively. Storm's study shows that the proton was more than half-transferred to the base at the transition state for the bromide. Since the extent of proton transfer increases as the leaving group becomes poorer (48,83), it follows that replacement of the bromide leaving group by trimethylammonio must further increase the extent of proton transfer with a shift toward a more product-like transition state.

The effect of an α -phenyl substituent on the β -hydrogen isotope effect may be deduced from Smith and Tsui's (114) study on the elimination reactions of 1-arylethyltrimethylammonium salts with ethoxide ion in ethanol to be that it decreases the extent of proton transfer with a shift toward a less product-like transition state. Thus, it can be expected

that the β -hydrogen isotope effect associated with anti-elimination of threo-1,2-diphenyl-1-propyltrimethylammonium ion should be greater than that for the elimination of 2-phenyl-1-propyltrimethylammonium ion with the same base-solvent system. It is not possible to deduce, however, whether the α -phenyl substituent has exerted sufficient influence to more than offset the effect of the β -methyl group, thereby causing the proton to be less than half-transferred to the base at the transition state. Nevertheless, if one accepts the view that the proton is considerably more transferred to the base than the proton in 2-phenylethyltrimethylammonium ion when these quaternary ammonium salts are eliminated with, say, ethoxide ion in ethanol, the α -phenyl substituent cannot be expected to cause the proton in the elimination of threo-1,2-diphenyl-1-propyltrimethylammonium ion to be less than half-transferred to the ethoxide ion at the transition state. Thus, it can be expected that the proton is still more than half-transferred to the base at the transition state in the elimination of the threo quaternary ammonium salt with ethoxide ion in ethanol.

This intuitive result may be tested immediately by measuring the β -hydrogen isotope effects and the nitrogen isotope effects for the reactions of the threo-quaternary ammonium salt with ethoxide ion in ethanol and with t-butoxide ion in t-butyl alcohol. If the proton is more than half-transferred to the base for the reaction in ethanol, the β -hydrogen isotope effect and the nitrogen isotope effect for this reaction should be smaller and greater, respectively, than the corresponding β -hydrogen isotope effect and the nitrogen isotope effect for the reaction in t-butyl alcohol. If this is so, the β -hydrogen isotope effect for the elimination of the threo-quaternary ammonium salt with t-butoxide ion in dimethyl sulfoxide should be greater than the β -hydrogen isotope effect

for the reaction with t-butoxide ion in t-butyl alcohol since the former is the stronger base. If, however, the β -hydrogen isotope effect turns out to be smaller or almost unchanged, it is possible that the proton has become less than half-transferred to the base for the reaction in dimethyl sulfoxide. In this case, the nitrogen isotope effect should be less than that for the reaction in t-butyl alcohol.

Apart from studying the change in the β -hydrogen isotope effects and nitrogen isotope effects in various base-solvent systems, one may also study the trend in these isotope effects on changing to electron-withdrawing substituents of increasing strength on either the α - or β -phenyl substituent. If, in the elimination of the parent compound, the proton is more than half-transferred to the base at the transition state, the β -hydrogen isotope effects should increase and the nitrogen isotope effects should decrease with the strength of the electron-withdrawing substituent. Also, if the series of compounds studied are eliminated in two base-solvent systems, the Hammett ρ value for elimination with the stronger base should be smaller than that for elimination with the weaker base.

One may also determine the extent of proton transfer by measuring the β -hydrogen isotope effects associated with the elimination, with the same base-solvent system, of threo-1,2-diphenyl-1-propyl-X derivatives ($X = \text{Br}, \text{OTs}, \text{Cl}, \text{SMe}_2^+, \text{NMe}_3^+$). If the proton is already more than half-transferred in the reaction of the trimethylammonium salt, the β -hydrogen isotope effect should increase as X is replaced by a better leaving group (see Table I, page 31).

In all the measurements of the isotope effects mentioned in the preceding paragraphs, it has been assumed that the predicted trends in the isotope effects would indeed be observed. However, this assumption is

valid only in the absence of proton-tunnelling (115-117) and if the effect of the perpendicular motion of Thornton's and O'Ferrall's theories on the nature of the transition state remains subordinate to the effect of the parallel motion. Also, the effect of A (see Katz and Saunders' theoretical calculations (77)) on the magnitude of the hydrogen isotope effect must not be appreciable.

As indicated earlier, the magnitude of 6.25 for the β -hydrogen isotope effect associated with the anti-mode of elimination of the threo-quaternary ammonium salt with t-butoxide ion in t-butyl alcohol shows that the proton at the transition state is rather close to the point of half-transfer between the base and the reactant. Therefore, the transition state associated with the reaction of the threo-quaternary ammonium salt in t-butyl alcohol may still be described as "reactant-like". Indeed, on the basis of $(k_{\text{threo}}/k_{\text{erythro}})$ ratios (interpreted as measures of the extent to which C_{α} and C_{β} -substituents are eclipsed at the transition state), Cram and his co-workers (7) have proposed a reactant-like transition state for the reaction in t-butyl alcohol wherein $(k_{\text{threo}}/k_{\text{erythro}}) = 1.1$ and a product-like transition state for the reaction in ethanol wherein $(k_{\text{threo}}/k_{\text{erythro}}) = 57$. The reactant-like nature of the transition state is attributable partly to the strength of the t-butoxide base in t-butyl alcohol (87) and partly to the effect of the α -phenyl substituent (114). That the α -phenyl substituent does indeed cause the transition state to be less product-like has also been observed by Gripenburg (124) who has studied the elimination reactions of 2-substituted 1,2-diphenylethyl chlorides with ethoxide ion in ethanol. Gripenburg found that the Hammett ρ values associated with these reactions were less than those for the reactions of 2-phenylethyl bromides (84) and 2-phenylethyl chlorides (85). Gripenburg

proposes that the change to a more reactant-like transition state is due to the effect of the α -phenyl substituent on the breaking of the leaving-group bond, a proposition in agreement with the prediction of Bunnett (47).

To return to the significance of the magnitude of the β -hydrogen isotope effect for the anti-mode of elimination, it can be said that the substantial value of 6.25 removes the possibility of an E1cB mechanism with a preequilibrium step or an E1cB mechanism in which the abstracted proton reattaches itself to C_β by internal return (66,67) because the β -hydrogen isotope effects associated with these mechanisms are expected to be relatively small (14,66,67,111). However, the relatively large magnitude of the β -hydrogen isotope effect does not exclude an E1cB mechanism in which carbanion-formation is rate-determining. In order to determine whether the reaction is E1cB or E2, it will be necessary to measure the nitrogen isotope effect for the breaking of the C_α -N bond at the transition state. If a relatively substantial nitrogen isotope effect is found, the reaction is E2. Otherwise, an E1cB mechanism is indicated.

The formation of the cis-olefin in the elimination of the threo quaternary ammonium salt with t-butoxide ion in t-butyl alcohol is evidently due to the incursion of a syn-elimination. As indicated in the concluding portion of the last section, the syn-anti dichotomy is expected to operate when steric interactions reducing the accessibility of the anti-proton increases beyond a certain limit. It is probable that the incursion of a syn-elimination is aided, in part, by the attraction between the oppositely charged base and the leaving group as well as by the strength of the t-butoxide base reducing the stereoelectronic preference for the anti-mode of

elimination (38). Since in the syn-mode of elimination of the threo quaternary ammonium salt, non-linear approach of the base to the syn-proton from the side remote from the cis-oriented phenyl groups is possible, one would expect more syn-elimination to have occurred than was actually observed. That the syn-mode of elimination is only slightly favoured may be attributed to the unfavourable steric interactions of the cis-oriented phenyl groups increasing the energy required for syn-elimination to occur. If this assumption is valid, the elimination of the erythro quaternary ammonium salt with t-butoxide ion in t-butyl alcohol via a syn-pathway wherein the phenyl groups are trans to each other is quite understandable. On the other hand, the formation of the cis-olefin may be due to the operation of an α' - β mechanism. This possibility is by no means remote because the base, t-butoxide ion, and the solvent, t-butyl alcohol, approximate conditions required for the operation of the α' - β mechanism. Also, the incursion of an α' - β mechanism has been suspected to be responsible for the anomalously high cis/trans olefin ratios observed in the elimination reactions of some sulfonium salts (42) with t-butoxide ion in t-butyl alcohol. In order to test for the incursion of an α' - β mechanism, it will be necessary to test the trimethylamine resulting from the elimination of the threo- β -deuteriated quaternary ammonium salt for deuterium pick-up (55).

The relatively small magnitude of the β -hydrogen isotope effect associated with the syn-mode of elimination of the threo quaternary ammonium salt with t-butoxide ion in t-butyl alcohol indicates that the transfer of the proton to the base at the transition state is probably more than half-complete. This is to be expected because the higher energy required for

syn-elimination requires that the $C_{\beta}-H$ and the $C_{\alpha}-N$ bonds be stretched more at the transition state than would be necessary for the anti-mode of elimination. Such a view is in accord with the Hammond's Postulate (91) and the Principle of Least Motion (105). Indeed, Bayne and Snyder (51) have found that the hydrogen isotope effects associated with the syn-mode of elimination are smaller than the hydrogen isotope effects for the anti-mode of elimination of threo-2-phenylethyl-1,2- d_2 chloride and the corresponding tosylate with t-butoxide ion in t-butyl alcohol. It is tempting to speculate from the magnitudes of the hydrogen isotope effects associated with the anti-mode of elimination of these compounds that the proton is more than half-transferred to the base at the transition state, Table IX, page 62.

In order to determine whether the proton is more than half-transferred to the base at the transition state in the syn-mode of elimination of the threo-quaternary ammonium salt, one may observe the trend in the β -hydrogen isotope effects on changing to stronger bases or on changing to electron-withdrawing substituents of increasing strength on C_{α} or C_{β} . In each of these cases, the β -hydrogen isotope effects should exhibit an increasing trend if the proton in the syn-mode of elimination of the threo-quaternary ammonium salt is more than half-transferred to the base at the transition state.

The formation of threo-N,N-dimethyl-1,2-diphenyl-1-propylamine is evidently the result of nucleophilic attack by the base at a N-methyl carbon atom. It is conceivable that this reaction is aided by the attraction between the negatively charged base and the slightly positively charged N-methyl carbon atoms.

Since the deuterium atom in the deuteriated quaternary ammonium salt is relatively distant from the N-methyl carbon atoms, the rate constant for the formation of the tertiary amine from the deuteriated quaternary ammonium salt should be equal to the rate constant for the formation of the amine from the undeuteriated quaternary ammonium salt. The larger amount of the tertiary amine resulting from the deuteriated reaction is evidently due to a higher concentration of the deuteriated quaternary ammonium salt available for nucleophilic attack by the base. This is readily understandable because the reaction of the deuteriated quaternary ammonium salt is slower by a factor of 6.

From the above discussion, one would normally expect the "substitution isotope effect", $(k^H/k^D)_{\text{sub.}}$, obtainable from equation (24)

$$(k^H/k^D)_{\text{sub.}} = \frac{(k^H)_{\text{obs.}} \times \% \text{ tertiary amine from undeut. Q.A.S.}}{(k^D)_{\text{obs.}} \times \% \text{ tertiary amine from deut. Q.A.S.}} \quad (24)$$

to be unity since there is no effect on the N-methyl substitution reaction with isotopic substitution at the β -carbon atom. Instead of being equal to unity, however, the "substitution isotope effect" was found to be 0.67. This departure from unity is felt to be the result of experimental errors associated with determining the relatively small amount of the undeuteriated tertiary amine (6.6%). In the glpc analyses, the peak shape for the tertiary amine recorded on the chart paper was very broad with considerable tailing. It was difficult, therefore, to determine accurately the absolute amount of the tertiary amine resulting from the elimination of the undeuteriated quaternary ammonium salt.

E X P E R I M E N T A L

THE SYNTHESIS OFTHREO-1,2-DIPHENYL-1-PROPYLTRIMETHYLAMMONIUM IODIDE

G e n e r a l

Although threo-1,2-diphenyl-1-propyltrimethylammonium iodide had been prepared by Cram, Greene and DePuy (7) in 1956, an altogether different synthetic route which includes two stereospecific reactions was used in this investigation, resulting in relatively higher product yields.

trans-Stilbene was converted by reaction with dimethyl sulfinyl carbanion to trans- α -methylstilbene which was then converted to erythro-1,2-diphenyl-1-propanol by hydroboration. Nucleophilic displacement by azide anion in dimethyl sulfoxide on the corresponding tosylate gave threo-1,2-diphenyl-1-propylazide which was then reduced with lithium aluminium hydride in diethyl ether to threo-1,2-diphenyl-1-propylamine. The primary amine was methylated by an Eschweiler-Clarke reaction to form threo-N,N-dimethyl-1,2-diphenyl-1-propylamine which was then quaternised with methyl iodide in acetonitrile to give the desired product.

All melting points are corrected; all boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Proton magnetic resonance spectra are reported in parts per million from tetramethylsilane.

Preparation of *trans*-1,2-Diphenylpropene (*trans*- α -methylstilbene)

This compound was prepared by the action of dimethyl sulfinyl carbanion (118) on *trans*-stilbene. A 57% oil-dispersion of sodium hydride (Metal Hydrides Incorporated), 44 g. (1.05 mole), was placed in a one-litre, three-necked, round-bottomed flask and washed three times with 100 ml. portions of sodium-dried petroleum ether (b.p. 40°C.). The mineral oil and petroleum ether washes were removed by suction through a filter-stick. The flask was then fitted with a nitrogen inlet, a mercury-seal stirrer, a pressure-equilibrated dropping funnel, and a nitrogen outlet and flushed with dry nitrogen. The flow of nitrogen was maintained throughout the remainder of the procedure.

Dimethyl sulfoxide, 800 ml. (b.p. 90°C./20 mm.), freshly distilled from calcium hydride, was added and the temperature of the solution raised to and maintained at 75°C. in a water-bath until the evolution of hydrogen had ceased. The solution was then cooled to room temperature with ice-water. Upon the addition of *trans*-stilbene (Eastman), 100 g. (0.556 mole), the dimethylsulfinyl carbanion solution quickly changed from yellow-grey to blood-red with an accompanying evolution of heat. The reaction mixture was cooled and maintained at 30°C. for 25 minutes and then poured into 300 ml. of crushed ice and water. The resulting yellowish mixture was extracted with 40 ml. portions of methylene dichloride, and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent at the rotary evaporator yielded a residue which crystallised in part. The residue was dissolved in 95% ethanol, and the solution was clarified with Norit A Decolourising Carbon. Evaporation of the solvent yielded crude

trans- α -methylstilbene, 61.4 g. (61%). Recrystallisation from aqueous ethanol twice and finally over anhydrous petroleum ether (b.p. 40°C.) gave trans- α -methylstilbene, 50.4 g. (47%), m.p. 79-81°C. Pmr (CCl₄), 7.58-7.08 δ (multiplet, 10 H), 6.8 δ (unresolved quartet, J = 2 Hz, 1 H), 2.17 δ (doublet, J = 2 Hz, 3 H). ((Feldman, Danishefsky and Levine (118) m.p. 78-80°C., Pmr (CCl₄), 7.58-7.08 δ (multiplet, 10 H), 6.8 δ (unresolved quartet, J = 2 Hz, 1 H), 2.17 δ (doublet, J = 2 Hz, 3 H)).

Preparation of erythro-1,2-Diphenyl-1-propanol

This compound was prepared by Brown's (119) method of hydroboration. trans-1,2-Diphenylpropene, 39 g. (0.201 mole), and sodium borohydride (British Drug House), 5.7 g. (0.151 mole), were mixed in 100 ml. of bis(2-methoxyethyl) ether (Eastman), freshly distilled from lithium aluminium hydride under reduced pressure (b.p. 73°C./30 mm.). The reaction mixture was placed in a 500 ml., three-necked, round-bottomed flask fitted with a nitrogen inlet, a mercury-seal stirrer, and a pressure-equilibrated dropping funnel fitted with a nitrogen outlet. After flushing the flask thoroughly with dry nitrogen, a solution of freshly distilled boron trifluoride etherate (Eastman), 31.8 g. (0.201 mole), in 30 ml. of bis(2-methoxyethyl) ether (diglyme) was added slowly. The resulting solution was stirred for three hours at room temperature and then hydrolysed by the dropwise addition of 5 ml. of water. When hydrogen was no longer evolved, 30 ml. of 3N sodium hydroxide was added. This was followed by the dropwise addition of 40 ml. of 30% hydrogen peroxide solution with constant stirring. The reaction mixture was cooled in an ice-water bath, stirred for 1 hour at 15°C. and for an additional hour at room temperature. Water (200 ml.) was

then added very slowly. The product, which separated as an upper layer, was removed and the aqueous layer was extracted with three 40 ml. portions of ether. The product and the ether extracts were combined and washed with three 40 ml. portions of ice water to remove diglyme, then dried over anhydrous sodium sulfate. Removal of the ether and the diglyme by distillation under reduced pressure gave a colourless oily liquid which gradually turned to a waxy solid, 38.0 g. (89%). This crude product was dissolved in petroleum ether (b.p. 40°C.) and chromatographed through a deactivated (10% water) alumina column using petroleum ether as eluent. Evaporation of the solvent under reduced pressure yielded a white waxy solid, 35.0 g. (82%), m.p. 50-51°C. (Cram and Elhafez (120), m.p. 50.5-51.5°C.).

Preparation of erythro-1,2-Diphenyl-1-propyl p-Toluenesulfonate

This compound was prepared by the method of Tipson (121). erythro-1,2-Diphenyl-1-propanol, 35.0 g. (0.166 mole), was dissolved in 150 ml. of dry pyridine (Fisher Certified Reagent) which had been purified by refluxing for 8 hours over barium oxide followed by distillation. The solution was cooled to -5°C. in an ice-salt bath, and freshly recrystallised p-toluenesulfonyl chloride*, 69.0 g. (0.361 mole), was added with shaking to effect solution. The reaction mixture was left in the refrigerator for 14 days, during which time, the solution turned slowly from

* The p-toluenesulfonyl chloride, (75 g.), purified immediately before use, was dissolved in 150 ml. of chloroform and the solution diluted to 800 ml. with 30-60°C. petroleum ether. The resulting solution was treated with Norit A Decolourising Carbon and filtered. The volume of the filtrate was reduced to 140 ml. on a rotary evaporator and the p-toluenesulfonyl chloride was allowed to crystallise from the concentrated solution.

a faint yellow to a pinkish-purple colour as long needles of pyridine hydrochloride formed. The mixture was then poured onto 300 ml. of ice and water. The tosylate that precipitated out was filtered immediately, and additional tosylate was recovered from the filtrate by three extractions with 50 ml. portions of chloroform. The combined tosylate was then recrystallised from benzene to give erythro-1,2-diphenyl-1-propyl p-toluenesulfonate, 32.1 g. (52.7%), m.p. 84-85°C. (Cram and Elhafez (120), m.p. 84-85°C.).

Preparation of threo-1,2-Diphenyl-1-propylazide

erythro-1,2-Diphenyl-1-propyl p-toluenesulfonate, 32.1 g. (0.087 mole), was placed in a 500-ml., round-bottomed flask and dissolved in dry dimethyl sulfoxide, freshly distilled from calcium hydride. Sodium azide (Fisher Purified), 28.3 g. (0.435 mole), was added with stirring, and the flask was stoppered with a drying tube and then heated to 60°C. for 48 hours. The reaction mixture was cooled, poured into 200 ml. of cold water, and extracted four times with 40 ml. portions of ether. The ether extract was dried over anhydrous sodium sulfate, then evaporated under reduced pressure to give crude threo-1,2-diphenyl-1-propylazide, 19.7 g. (95%).

Preparation of threo-1,2-Diphenyl-1-propylamine

threo-1,2-Diphenyl-1-propylazide, crude, 19.7 g. (0.083 mole), was dissolved in 50 ml. of anhydrous ether and added dropwise via a pressure-equilibrated dropping funnel to a slurry of lithium aluminium

hydride, 2.83 g. (0.083 mole), in 50 ml. of anhydrous ether in a 250 ml. round-bottomed flask. The dropping funnel was replaced by a drying tube, and the reaction mixture was stirred with a magnetic stirrer for 7 hours. The excess lithium aluminium hydride was hydrolysed by the dropwise addition of 3N sodium hydroxide. The ether layer was separated, and the aqueous layer was extracted with three 30 ml. portions of ether. The combined ether solution was then dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, distillation gave a colourless liquid, threo-1,2-diphenyl-1-propylamine, 13.0 g. (74.2%), b.p. 78-80°C./0.1 mm.

Preparation of threo-N,N-Dimethyl-1,2-diphenyl-1-propylamine

This compound was prepared by the Eschweiler-Clarke reaction. threo-1,2-Diphenyl-1-propylamine, 13.0 g. (0.062 mole), was added dropwise to a solution containing 37% formaldehyde solution, 15.6 g. (0.192 mole), and 90% formic acid, 16.4 g. (0.320 mole). The reaction mixture was stirred until the evolution of carbon dioxide had ceased, and then it was refluxed for 8.5 hours. The mixture was cooled to room temperature, concentrated hydrochloric acid, 15 ml., was added, and the excess formic acid was removed by distillation under reduced pressure. Water, 50 ml., was then added, followed by 40 ml. of 5N sodium hydroxide to render the solution basic. The resulting solution was extracted four times with 40 ml. portions of ether, and the combined ether extracts were dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, distillation gave threo-N,N-dimethyl-1,2-diphenyl-1-propylamine, 7.8 g. (53%), b.p. 82-84°C./0.1 mm.

Preparation of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide

threo-N,N-Dimethyl-1,2-diphenyl-1-propylamine, 7.8 g. (0.033 mole), and methyl iodide (Fisher Certified Reagent), 23.1 g. (0.164 mole), were dissolved in 50 ml. of dry and freshly distilled acetonitrile in a 100-ml. Erlenmeyer flask. After three hours, anhydrous ether was added dropwise until precipitation ceased. The crude quaternary ammonium salt was collected and recrystallised twice from acetonitrile-diethylether to yield threo-1,2-diphenyl-1-propyltrimethylammonium iodide, 7.8 g. (63%), m.p. 175-176°C. (dec.). (Cram, Greene and DePuy (7), m.p. 174-176°C. (dec.)).

Anal. calcd. for $C_{18}H_{24}IN$: C, 56.68; H, 6.35; N, 3.67; Found: C, 56.85; H, 6.42; N, 3.64.

Nmr (DMSO- d_6): 7.16 δ (multiplet, 10 H); 5.28 δ (doublet, $J = 8$ Hz, 1 H); 4.08 δ (quintet, $J = 8$ Hz, 1 H); 3.22 δ (singlet, 9H); 1.53 δ (doublet, $J = 8$ Hz, 3 H).

THE SYNTHESIS OFTHREO 1,2-DIPHENYL-1-PROPYLTRIMETHYLAMMONIUM-2-d₁ IODIDE

G e n e r a l

threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ iodide was prepared by Brown's (119) method of hydroboration using sodium borodeuteride. The preparative procedures for each of the succeeding steps were essentially identical with those of the corresponding unlabelled analogue, and the product yields were comparable.

All melting points are corrected; all boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee; deuterium analyses were determined using the falling drop method by J. Nemeth at the University of Illinois. Proton magnetic resonance spectra are reported in parts per million from tetramethylsilane.

Preparation of erythro-1,2-Diphenyl-1-propanol-2-d₁

This compound was prepared by the method described for its corresponding unlabelled analogue. Sodium borodeuteride (Merck, Sharpe and Dohme), 3.15 g. (0.075 mole), and trans-1,2-diphenylpropene, 19.5 g. (0.103 mole), were dissolved in 50 ml. of bis(2-methoxyethyl) ether and treated with a solution of boron trifluoride etherate, 15.9 g. (0.112 mole), in 15 ml. of diglyme, to yield erythro-1,2-diphenyl-1-propanol-2-d₁

15.2 g. (80%), m.p. 48.5–49.5°C. (undeuteriated compound, m.p. 50–51°C.).

Preparation of erythro-1,2-Diphenyl-1-propyl-2-d₁ p-Toluenesulfonate

This compound was prepared in the same way as for its corresponding unlabelled analogue. erythro-1,2-Diphenyl-1-propanol-2-d₁, 15.2 g. (0.072 mole), was dissolved in 70 ml. of dry pyridine and treated with p-toluenesulfonyl chloride, 29.4 g. (0.143 mole), at 0°C. and placed in the refrigerator for 14 days. The work-up gave erythro-1,2-diphenyl-1-propyl-2-d₁ p-toluenesulfonate, 15.3 g. (59%), m.p. 82–83°C. (undeuteriated compound, m.p. 84–85°C.).

Preparation of threo-1,2-Diphenyl-1-propylazide-2-d₁

erythro-1,2-Diphenyl-1-propyl-2-d₁ p-toluenesulfonate, 15.2 g. (0.041 mole), and sodium azide, 14.6 g. (0.225 mole), were reacted in 250 ml. of dry dimethyl sulfoxide at 60°C. for 60 hours to yield crude threo-1,2-diphenyl-1-propylazide-2-d₁, 9.1 g. (90%).

Preparation of threo-1,2-Diphenyl-1-propylamine-2-d₁

This compound was prepared by the procedure described previously for the undeuteriated compound. threo-1,2-Diphenyl-1-propylazide-2-d₁, 9.1 g. (0.025 mole), was reduced with lithium aluminium hydride, 1.0 g. (0.026 mole), in anhydrous ether. After the work-up, distillation gave threo-1,2-diphenyl-1-propylamine-2-d₁, 3.5 g. (59%), b.p. 78–80°C./0.1 mm. (undeuteriated compound, b.p. 78–80°C./0.1 mm.).

Preparation of *threo*-N,N-Dimethyl-1,2-diphenyl-1-propylamine-2-d₁

This compound was prepared in an identical fashion as for the undeuteriated compound. A reaction mixture of *threo*-1,2-diphenyl-1-propylamine-2-d₁, 3.5 g. (0.017 mole), 37% formaldehyde solution, 3.58 g. (0.044 mole), and 90% formic acid, 3.76 g. (0.073 mole), was refluxed for 7.5 hours to yield *threo*-N,N-dimethyl-1,2-diphenyl-1-propylamine-2-d₁, 1.8 g. (26%), b.p. 80-82°C./0.1 mm. (undeuteriated compound, b.p. 82-84°C./0.1 mm.).

Preparation of *threo*-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide

This compound was prepared by the procedure described previously for the undeuteriated compound. *threo*-N,N-Dimethyl-1,2-diphenyl-1-propylamine-2-d₁, 1.8 g. (0.0075 mole), was treated with methyl iodide, 10.7 g. (0.075 mole), in 40 ml. of dry acetonitrile in a 100 ml. Erlenmeyer flask. Eight recrystallisations from acetonitrile-diethyl ether gave *threo*-1,2-diphenyl-1-propyltrimethylammonium-2-d₁ iodide, 0.6 g. (21%), m.p. 172.5-173.5°C. (dec.), (undeuteriated compound, m.p. 175-176°C. (dec.)). Anal. calcd. for C₁₈H₂₃DIN: C, 56.54; H+D, 6.61; N, 3.66; Found: C, 56.45; H+D, 6.69; N, 3.64. Deuterium analyses indicated that this compound had 0.99 atom of deuterium per molecule (4.12 atom per cent excess deuterium). Pmr (DMSO-d₆): 7.17 δ (multiplet, 10 H); 5.21 δ (singlet, 1 H); 3.18 δ (singlet, 9 H); 1.51 δ (singlet, 3 H); (undeuteriated compound, Pmr (DMSO-d₆): 7.16 δ (multiplet, 10 H); 5.28 δ (doublet, J = 8 Hz, 1 H); 4.08 δ (quintet, J = 8 Hz, 1 H); 3.22 δ (singlet, 9 H); 1.53 δ (doublet, J = 8 Hz, 3 H).

Purification of Solvent and Preparation of Base

Purification of *t*-Butyl Alcohol

t-Butyl alcohol (Fisher Certified), 4.5 litres, was refluxed with calcium hydride (Ventron Metal Hydrides), 14 g. (0.333 mole), in a five-litre flask for 24 hours and then distilled through a 1.7 cm. x 35 cm. glass column packed with glass helices. This was followed by two more successive distillations from potassium metal. In each case, the first 200 ml. of azeotrope and the last 200 ml. of residual alcohol in the flask were rejected.

Preparation of Potassium *t*-Butoxide in *t*-Butyl Alcohol Solutions for Kinetic Measurements and Reaction Product Analyses

Anhydrous *t*-butyl alcohol (160 ml.) was placed in a vessel illustrated in Figure 6 and warmed to about 40°C. in a heating mantle. Purified nitrogen (122) was bubbled through the alcohol for 2 hours. Potassium metal, 5.25 g. (0.134 mole), was cleaned thoroughly in anhydrous *t*-butyl alcohol and added in small portions to the reaction vessel. The mixture was allowed to stand until all the potassium had dissolved (10 hours). The resulting base, after equilibrating to 30°C., was standardised using bromothymol blue as indicator.

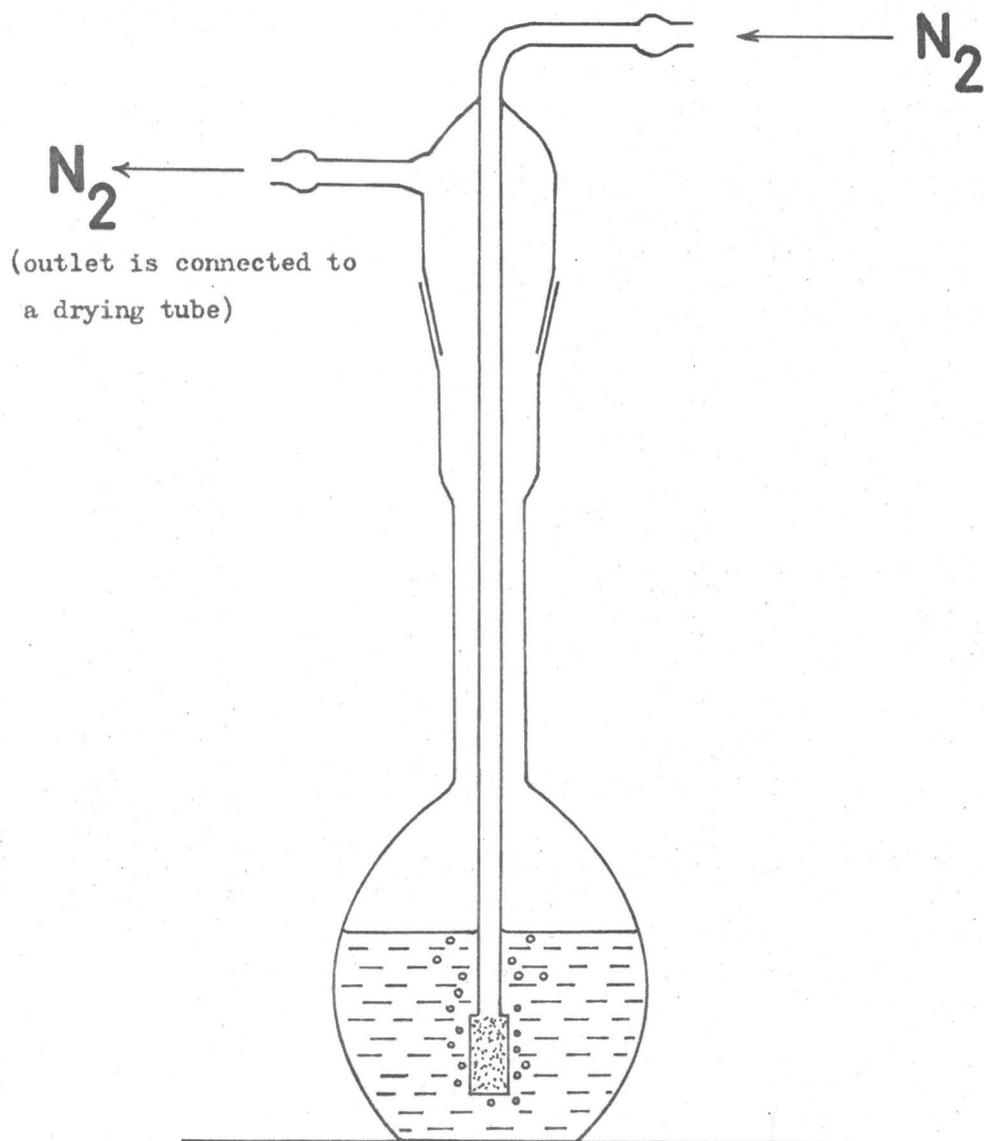


Figure 9. Apparatus for Preparation of Potassium t-Butoxide Solution.

Test for the Isomerisation of
cis- α -Methylstilbene to trans- α -Methylstilbene

trans- α -Methylstilbene, 50.0 mg. (2.58×10^{-4} mole), and cis- α -methylstilbene, 50.1 mg. (2.58×10^{-4} mole), were dissolved in 50 ml. of 0.2N potassium t-butoxide in t-butyl alcohol and warmed to and maintained at 40°C. for 48 hours. A one-millilitre aliquot was withdrawn at the start of the heating period, diluted with 95% ethanol, and its ultra violet spectrum was determined using a Cary 14 UV-VIS Spectrophotometer. Likewise, the ultra-violet spectra were determined for aliquots taken at 12, 24, 36 and 48 hours, respectively. It was found that the optical density of the solutions, measured at 273 nm, remained constant over the time period.

Borchardt and Saunders (52) observed that isomerisation did not occur at 30°C. even when a stronger base, made by adding tetra-n-butyl-ammonium bromide to potassium t-butoxide in t-butyl alcohol was used. These results agree with the absence of isomerisation observed by Cram, Greene and DePuy (7), who attempted the isomerisation of the olefins in p-toluenesulfonic acid.

Test for Epimerisation at the α -Carbon Atom

threo-1,2-Diphenyl-1-propyltrimethylammonium iodide, 180 mg. (4.72×10^{-4} mole), was dissolved in 100 ml. of 0.1 N potassium t-butoxide in t-butyl alcohol-O-d₁ and heated at 60°C. for 72 hours. The solution was cooled, poured into 150 ml. of cold water and extracted with 30 ml. portions of petroleum ether (b.p. 40°C.), then dried over anhydrous potassium carbonate. After removal of the solvent at the

rotary evaporator, the olefin was washed once with 5 ml. of petroleum ether (b.p. 40°C.) and dried in vacuo to give a white solid, 76 mg. (85%), m.p. 77-80°C., (trans- α -methylstilbene, m.p. 79-81°C.).

Proton magnetic resonance spectra and integrations for the α -hydrogen and the phenyl hydrogen atoms at 6.8 δ and 7.35 δ , respectively, for trans- α -methylstilbene and the recovered olefin were recorded using a Varian T60 NMR Spectrometer.

The data for this experiment are presented in the Results and Discussion, Table X.

Product Analyses by Gas-Liquid Partition Chromatography

threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ iodide, 300 mg. (7.87×10^{-4} mole), was dissolved in 250 ml. of 0.2N potassium t-butoxide in t-butyl alcohol. The reaction mixture was heated to 40°C. in a constant temperature bath for 84 hours, then cooled and poured into 300 ml. of water. The resulting solution was extracted with six 30 ml. portions of petroleum ether (b.p. 40°C.). The combined petroleum ether extracts were dried over anhydrous potassium carbonate, then filtered into a 300-ml. flask. The solution was concentrated to about 90 ml. by evaporating the solvent through a 1.7 cm. x 25 cm. glass column packed with glass helices, then transferred to a 100 ml. flask and evaporated to about 2 ml. Spectrograde carbon disulfide (46.2°C.) was added via the glass column to increase the volume of the solution to about 20 ml. when again it was reduced to about 2 ml. The alternate addition and evaporation of the carbon disulfide was repeated

four times in order to displace the petroleum ether.

The proton magnetic resonance spectrum of the concentrated solution was recorded with a Varian HA 100 NMR Spectrometer, and it indicated clearly the presence of more than one product. The product solution was separated on an Aerograph A90-P3 Chromatograph using a $\frac{3}{8}$ " x 7' stainless steel column packed with 10% QF1* on 60-80 mesh Chromosorb W. At a column temperature of 140°C. and a helium input pressure of 24 p.s.i., three products having retention times of 7, 18, and 24 minutes, respectively, were found. The second and third products were shown by proton magnetic resonance analyses to be threo-N,N-dimethyl-1,2-diphenyl-1-propylamine and trans- α -methylstilbene, respectively. The first product was obtained in too small an amount for identification by proton magnetic resonance spectroscopy, but it was shown to be cis- α -methylstilbene by comparing its retention time with that of a known sample.

In a similar fashion, but without doing proton magnetic resonance analyses, the products arising from the reaction of the undeuteriated quaternary ammonium salt with potassium t-butoxide in t-butyl alcohol were identified from their retention times to be cis- α -methylstilbene, threo-N,N-dimethyl-1,2-diphenyl-1-propylamine, and trans- α -methylstilbene.

* QF1 is a fluorinated silicone oil (FS 1265).

Internal Standardisation for
Gas-Liquid Partition Chromatographic Analysis

Standard 50 ml. solutions, each containing 1×10^{-3} mole of cis- α -methylstilbene (194 mg.), trans- α -methylstilbene (194 mg.), threo-N,N-dimethyl-1,2-diphenyl-1-propylamine (239 mg.), and trans-stilbene (180 mg.), in t-butyl alcohol were prepared in four 50 ml. volumetric flasks. Ten-millilitre aliquots of each of the solutions were mixed and a sample of the solution mixture was analysed using an Aero-graph A204 Chromatograph fitted with a $\frac{1}{8}$ x 7' stainless steel column packed with 10% QF1 on 60-80 mesh Chromosorb W. At a column temperature of 120°C. and a helium input pressure of 26 p.s.i., cis- α -methylstilbene, threo-N,N-dimethyl-1,2-diphenyl-1-propylamine, trans- α -methylstilbene and trans-stilbene had retention times of 8, 16, 22 and 28 minutes, respectively. Six sets of four full-size peak areas were cut out and weighed to determine the peak areas from which peak area ratios were calculated.

The peak area ratios of cis- α -methylstilbene, threo-N,N-dimethyl-1,2-diphenyl-1-propylamine and trans- α -methylstilbene with respect to an equivalent amount (in moles) of trans-stilbene were found to be 1.08, 1.06 and 1.08, respectively, with the standard deviation in each case equal to ± 0.02 .

Determination of the Product Distributions associated with the
Reactions of the Undeuteriated and Deuteriated Quaternary Ammonium Salts
with 0.22N Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.

Preliminary tests indicated that the relative yields of the three reaction products were dependent upon salt concentration and that the low

concentration of salt ($10^{-5}M$) required for good first order kinetics was too low to permit accurate product analyses. Accordingly, product distributions were determined at several different higher concentrations and extrapolated to the low concentration used in the kinetic studies.

A 100 ml. stock solution of threo-1,2-diphenyl-1-propyltrimethylammonium iodide, 60 mg. (1.573×10^{-4} mole), in t-butyl alcohol was prepared in a volumetric flask. Aliquots of 10 ml., 20 ml., and 40 ml., were pipetted into three 100 ml. volumetric flasks, each containing 60 ml. of anhydrous t-butyl alcohol. After equilibration to $30^{\circ}C$. in a constant temperature bath (1 hour), 25 ml. of 0.88N potassium t-butoxide in t-butyl alcohol, temperature-equilibrated at $30^{\circ}C$., was added and the resulting solution was made up to the calibration mark by the addition of a small amount of t-butyl alcohol. The solutions were shaken briefly and maintained at $30^{\circ}C$. for 24 hours. Each solution was then poured into a separatory funnel containing about 140 ml. of water. To each of the resulting solutions, an appropriate aliquot from a $1.573 \times 10^{-4} M$ stock solution of the internal standard trans-stilbene in t-butyl alcohol was added to provide trans-stilbene equivalent to 100 per cent yield of trans- α -methylstilbene from each reaction. The resulting solutions were extracted with six 30 ml. portions of petroleum ether (b.p. $30-60^{\circ}C$.). The petroleum ether extracts were dried over anhydrous potassium carbonate, filtered and evaporated at the rotary evaporator to about 2 ml.

The concentrated solutions were analysed on an Aerograph A204 Chromatograph using $\frac{1}{8}$ " x 7' stainless steel column, packed with 10% QF1 on 60-80 mesh Chromosorb W. At a column temperature of $120^{\circ}C$. and a helium input pressure of 26 p.s.i., cis- α -methylstilbene, threo-N,N-dimethyl-1,2-diphenyl-1-propylamine, trans- α -methylstilbene and trans-stilbene had retention times of 8, 16, 22 and 28 minutes, respectively.

Reactions of the deuteriated quaternary ammonium salt were carried out in a similar way but with a reaction time of 72 hours. Analyses of the concentrated solutions were performed as previously described.

The results of the reaction products analyses for the quaternary ammonium salts are presented in Table XIa and Table XIb.

Kinetic Studies

General

A slight modification of a spectroscopic method, described by Cockerill, Rottschaefer and Saunders (123) was used. Briefly the method involved following simultaneously the rates of the elimination reactions of the undeuteriated and the deuteriated quaternary ammonium salts under identical conditions in stoppered cells placed in a thermostatted cell-holder of a Hitachi Perkin-Elmer 139 UV-VIS Spectrophotometer.

The kinetic studies were carried out at a relatively low concentration (ca. $7 \times 10^{-5}M$) of quaternary ammonium salt in order to obtain good first order kinetics. Higher concentrations of quaternary ammonium salt were not used because of the incursion of salt effects which precluded first order kinetics.

At the relatively low concentration of quaternary ammonium salt used in the kinetic studies, the absolute amounts of reaction products could not be reliably determined. However, they were obtained by extrapolation from product distributions for higher concentrations of salt.

The first order rate constant was determined by multiplying the observed rate constant by the fraction of trans- α -methylstilbene formed in the reaction. The second order rate constant was then obtained by dividing the first order rate constant by the concentration of the base.

Both λ_{\max} and the molar extinction coefficient at λ_{\max} for trans- α -methylstilbene used in the work of this thesis were found to be identical with the values reported by Cram, Greene and DePuy (7), Table XIV.

TABLE XIV

Ultra-Violet Absorption of the α -Methylstilbenes

<u>Olefin</u>	λ_{\max} nm	<u>Molar Extinction Coefficient</u>
<u>trans</u> - α -methylstilbene	273	19,750
<u>cis</u> - α -methylstilbene	262	11,700

Kinetic Measurements

Ten ml. of standard solutions of undeuteriated and deuteriated quaternary ammonium salts in t-butyl alcohol (ca. 7×10^{-5} M), equilibrated to 30°C. in a constant temperature bath, were transferred into 100 ml. volumetric flasks and diluted with temperature-equilibrated t-butyl alcohol to approximately 70 ml. To each solution, 25 ml. of temperature-equilibrated standard base solution (0.880N) was added, and the solutions were made up to the calibration mark.

Small portions of each solution were transferred immediately into separate Hellma Quartz cells, previously equilibrated to $30 \pm 0.05^\circ\text{C}$. in the

thermostatted cell-holder of a Hitachi-Perkin Elmer 139 UV-VIS Spectrophotometer. A third Hellma Quartz cell containing anhydrous t-butyl alcohol at 30°C. was in the cell-holder.

At regular intervals, the optical densities of the two reaction mixtures were determined at 273 nm.

For all kinetic runs, pseudo-first order conditions with t-butoxide ion in greater than ten thousand-fold excess were employed. The pseudo-first order rate constant, k_1 , is given by the expression

$$k_1 = \frac{1}{t} \ln \left(\frac{O.D.\infty - O.D.o}{O.D.\infty - O.D.t} \right) \quad (25)$$

where $O.D.\infty$ is the optical density of the solution at $t = \infty$,

$O.D.o$ is the optical density of the solution at $t = 0$,

$O.D.t$ is the optical density of the solution at time t .

The rate constant k_1 was calculated using a Hewlett Packard 9810A computer programmed for least squares calculations. The second order rate constant, k_2 , was calculated by dividing k_1 by the concentration of potassium t-butoxide.

Data for the kinetic experiments for each compound and the appropriate plots of the data are presented in the Appendix.

TABLE XV

Kinetic Data for the Reaction

of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide withPotassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	$OD_{\infty} - OD_t$	$\ln (OD_{\infty} - OD_t)$
10	0.249	1.041	+ 0.04018
13	0.310	0.980	- 0.02020
16	0.358	0.932	- 0.07042
19	0.399	0.891	- 0.11541
22	0.447	0.843	- 0.17079
25	0.492	0.798	- 0.22565
27	0.523	0.767	- 0.26527
30	0.560	0.730	- 0.31471
33	0.593	0.697	- 0.36097
36	0.630	0.660	- 0.41552
39	0.666	0.624	- 0.47160

Calculation of the rate constant:

$$k_1 = (29.12 \pm 0.15) \times 10^{-5} \text{ sec}^{-1}.$$

$$k_2 = (13.24 \pm 0.07) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

TABLE XVI

Kinetic Data for the Reaction

of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide withPotassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	$OD_{\infty} - OD_t$	$\ln (OD_{\infty} - OD_t)$
10	0.189	1.091	+ 0.08709
13	0.245	1.035	+ 0.03440
16	0.301	0.979	- 0.02122
19	0.350	0.930	- 0.07527
22	0.398	0.882	- 0.12556
25	0.443	0.837	- 0.17793
28	0.482	0.798	- 0.22565
31	0.522	0.758	- 0.27707
34	0.565	0.715	- 0.33547
37	0.595	0.685	- 0.37834
41	0.646	0.634	- 0.45571
43	0.670	0.610	- 0.49430

Calculation of the rate constant:

$$k_1 = (29.07 \pm 0.15) \times 10^{-5} \text{ sec}^{-1}.$$

$$k_2 = (13.21 \pm 0.07) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

TABLE XVII

Kinetic Data for the Reaction
of threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide with
Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.
(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	$OD_{\infty} - OD_t$	$\ln (OD_{\infty} - OD_t)$
10	0.145	1.135	+ 0.12663
13	0.205	1.075	+ 0.07232
16	0.260	1.020	+ 0.01980
19	0.310	0.970	- 0.03046
22	0.353	0.927	- 0.07580
25	0.402	0.878	- 0.13011
28	0.450	0.830	- 0.18633
31	0.493	0.787	- 0.23953
34	0.528	0.752	- 0.28502
37	0.575	0.705	- 0.34956
40	0.610	0.670	- 0.40048

Calculation of the rate constant:

$$k_1 = (29.23 \pm 0.20) \times 10^{-5} \text{ sec}^{-1}$$

$$k_2 = (13.29 \pm 0.09) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

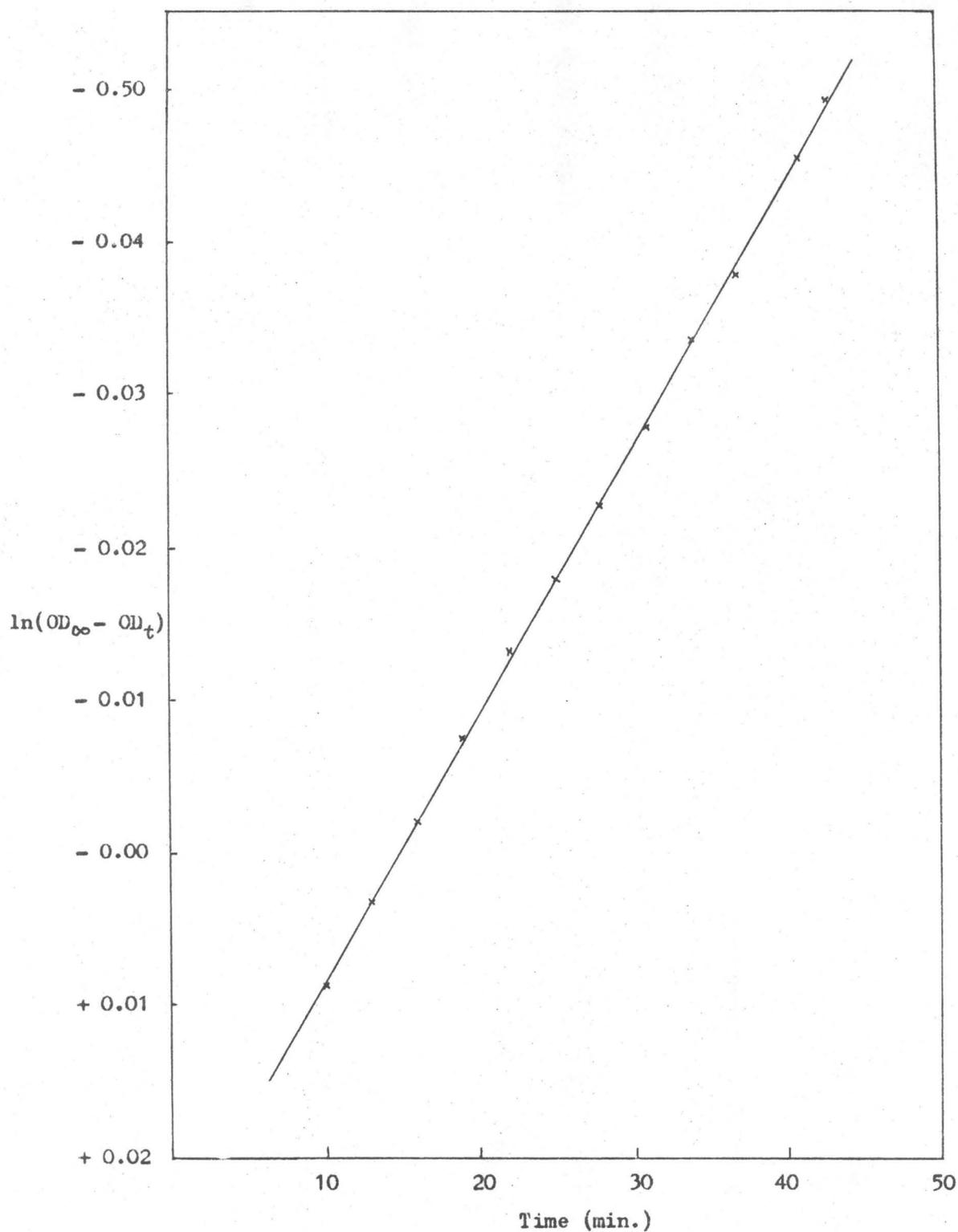


Figure 10.

Plot of the kinetic data given in Table XVI for a typical kinetic experiment for the reaction of threo-1,2-diphenyl-1-propyltrimethylammonium iodide with potassium t-butoxide in anhydrous t-butyl alcohol at 30°C.

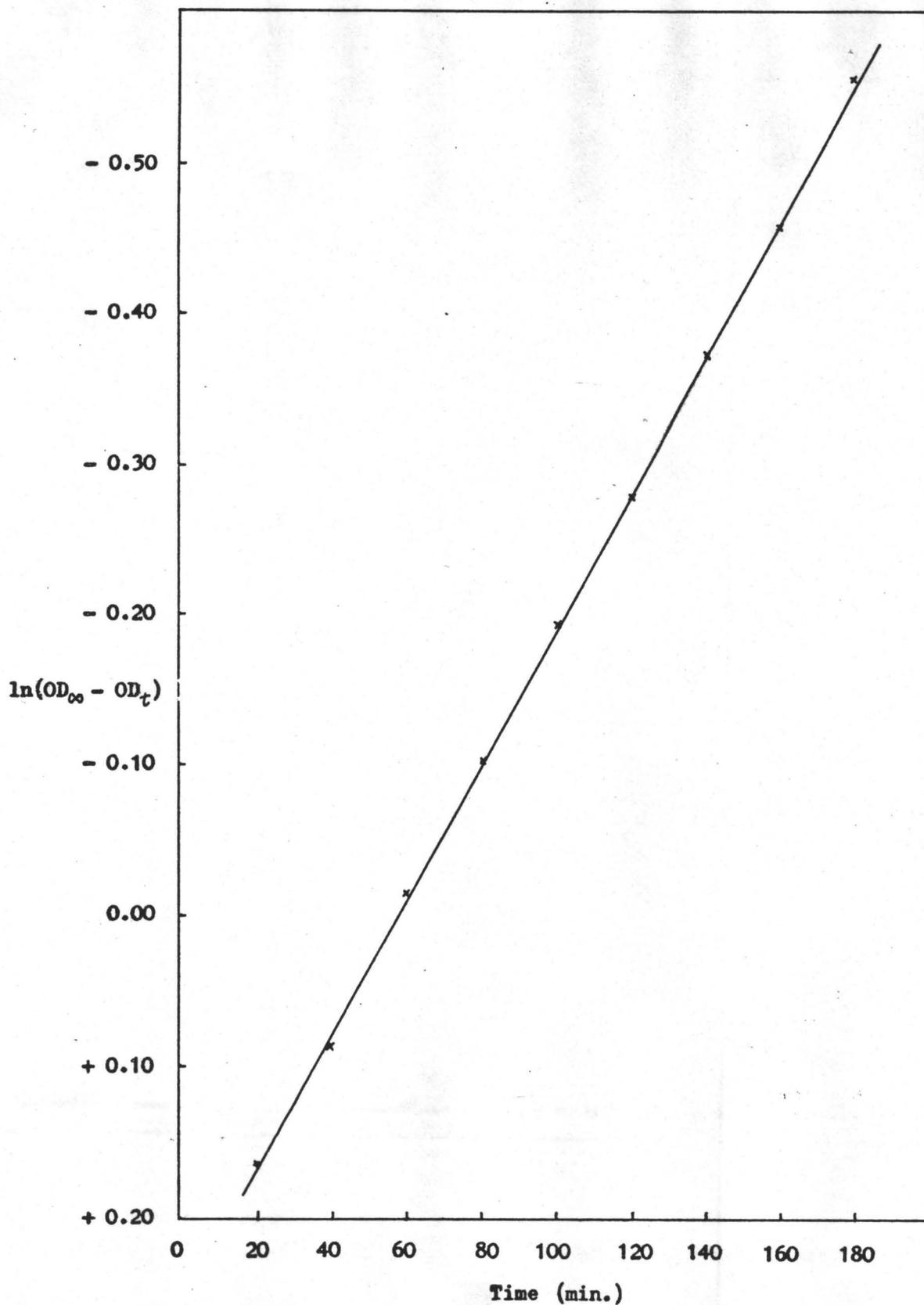


Figure 11.

Plot of the kinetic data given in Table XX for a typical kinetic experiment for the reaction of threo-1,2-diphenyl-1-propyltrimethylammonium-2- d_1 iodide with potassium t-butoxide in anhydrous t-butyl alcohol at 30°C.

TABLE XVIII

Kinetic Data for the Reaction

of threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide withPotassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	$OD_{\infty} - OD_t$	$\ln (OD_{\infty} - OD_t)$
20	0.165	0.625	- 0.47000
40	0.220	0.570	- 0.56212
60	0.271	0.519	- 0.65585
80	0.314	0.476	- 0.74234
100	0.355	0.435	- 0.83241
120	0.393	0.397	- 0.92382
140	0.425	0.365	- 1.00786
160	0.458	0.332	- 1.10262
180	0.487	0.303	- 1.19402

Calculation of the rate constant:

$$k_1 = (75.04 \pm 0.26) \times 10^{-6} \text{ sec}^{-1}$$

$$k_2 = (3.41 \pm 0.01) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

TABLE XIX

Kinetic Data for the Reaction

of threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide withPotassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	$OD_{\infty} - OD_t$	$\ln (OD_{\infty} - OD_t)$
20	0.113	0.677	- 0.39008
40	0.175	0.615	- 0.48613
60	0.227	0.563	- 0.57448
80	0.273	0.517	- 0.65971
100	0.317	0.473	- 0.74866
120	0.358	0.432	- 0.83933
140	0.396	0.394	- 0.93140
160	0.431	0.359	- 1.02443
180	0.459	0.331	- 1.10564

Calculation of the rate constant:

$$k_1 = (74.59 \pm 0.35) \times 10^{-6} \text{ sec}^{-1}.$$

$$k_2 = (3.39 \pm 0.02) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

TABLE XX

Kinetic Data for the Reaction
of threo-1,2-Diphenyl-1-propyltrimethylammonium-2-d₁ Iodide with
Potassium t-Butoxide in Anhydrous t-Butyl Alcohol at 30°C.
(Init. concs: Q.A.S. = 6.89×10^{-5} m./l.; t-BuOK = 0.220 m./l.)

Time Min.	Optical Density	OD _∞ - OD _t	ln (OD _∞ - OD _t)
20	0.065	0.715	- 0.33547
40	0.119	0.661	- 0.41400
60	0.183	0.597	- 0.51584
80	0.233	0.547	- 0.60331
100	0.281	0.499	- 0.69515
120	0.322	0.458	- 0.78089
140	0.363	0.417	- 0.87467
160	0.396	0.384	- 0.95711
180	0.431	0.349	- 1.05268

Calculation of the rate constant:

$$k_1 = (74.91 \pm 0.47) \times 10^{-6} \text{ sec}^{-1}.$$

$$k_2 = (3.41 \pm 0.02) \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}.$$

REFERENCES

1. W. Hanhart and C.K. Ingold, *J. Chem. Soc.*, 997 (1927).
2. W. Klyne and V. Prelog, *Experientia*, 16, 521 (1960).
3. P. Pfeiffer, *Z. Physik. Chem. (Leipzig)*, 48, 40 (1904).
4. W. Huckel, W. Tappe and G. Legutke, *Ann.*, 543, 191 (1940).
5. S.J. Cristol, N.L. Hause and J.S. Meek, *J. Am. Chem. Soc.*, 73, 674 (1951).
6. E.D. Hughes, C.K. Ingold and J.B. Rose, *J. Chem. Soc.*, 3839 (1953).
7. D.J. Cram, F.D. Greene and C.H. DePuy, *J. Am. Chem. Soc.*, 78, 790 (1956).
8. C.K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York, 1957, Chapter 8.
9. T.H. Brownlee and W.H. Saunders, Jr., *Proc. of Chem. Soc.*, 314 (1961).
10. P.S. Skell and W.L. Hall, *J. Am. Chem. Soc.*, 85, 2851 (1963).
11. D.V. Banthorpe, "Elimination Reactions", Elsevier Pub. Co., New York, 1963, Chapter 1.
12. W.H. Saunders, Jr., "The Chemistry of Alkenes", S. Patai Ed., Wiley Interscience, London, 1964, Chapter 2.
13. M.A. Baldwin, D.V. Banthorpe, A.G. Loudon and F.D. Waller, *J. Chem. Soc. (B)*, 509 (1967).
14. D.J. McLennan, *Quarterly Reviews*, 21, 490 (1967).
15. S.J. Cristol and N.L. Hause, *J. Am. Chem. Soc.*, 74, 2193 (1952).
16. S.J. Cristol and E.F. Hoeffler, *J. Am. Chem. Soc.*, 79, 3438, (1957).
17. N.A. Lebel, P.D. Beirne, E.R. Karger, J.C. Powers and P.M. Subramaniam, *J. Am. Chem. Soc.*, 85, 3199 (1963).

18. N.A. Lebel, P.D. Beirne and P.M. Subramaniam, *J. Am. Chem. Soc.*, 86, 4144 (1964).
19. C.H. DePuy, G.F. Morris, J.S. Smith and R.J. Smat, *J. Am. Chem. Soc.*, 87, 2421 (1965).
20. J. Zavada and J. Sicher, *Collect. Czech. Chem. Comm.*, 30, 438 (1965).
21. J. Sicher, J. Zavada and J. Krupicka, *Tetrahedron Letters*, 1619 (1966).
22. J. Zavada, M. Svoboda and J. Sicher, *ibid.*, 1627 (1966).
23. J. Zavada and J. Sicher, *Collect. Czech. Chem. Comm.*, 32, 3701 (1967).
24. M. Pankova, J. Sicher and J. Zavada, *Chem. Comm.*, 394 (1967).
25. J. Zavada, J. Krupicka and J. Sicher, *Chem. Comm.*, 66 (1967).
26. J. Sicher and J. Zavada, *Collect. Czech. Chem. Comm.*, 33, 1278 (1968).
27. J. Zavada, J. Krupicka and J. Sicher, *ibid.* 1393 (1968).
28. M. Svoboda, J. Zavada and J. Sicher, *ibid.* 1415 (1968).
29. M. Pankova, J. Zavada and J. Sicher, *Chem. Comm.*, 1142 (1968).
30. J. Zavada, M. Pankova and J. Sicher, *ibid.* 1145 (1968).
31. J. Sicher, M. Svoboda, M. Pankova and J. Zavada, *Collect. Czech. Chem. Comm.*, 36, 3633 (1971).
32. J. Sicher, *Angew. Chem. Internat. Edit.*, 11, 200 (1972).
33. J. Zavada and J. Svoboda, *Tetrahedron Letters*, 23 (1972).
34. M. Svoboda, J. Hapala and J. Zavada, *Tetrahedron Letters*, 265 (1972).
35. J. Zavada, M. Svoboda and M. Pankova, *Tetrahedron Letters*, 711 (1972).
36. M. Pankova, M. Svoboda and J. Zavada, *Tetrahedron Letters*, 2465 (1972).
37. M. Pankova and J. Zavada, *Tetrahedron Letters*, 2237 (1973).
38. D.S. Bailey and W.H. Saunders, Jr., *Chem. Comm.* 1598 (1968).
39. D.S. Bailey and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, 92, 6904 (1970).
40. D.S. Bailey, F.C. Montgomery, G.W. Chodak and W.H. Saunders, Jr., *ibid.* 6911 (1970).
41. I.N. Feit and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, 92, 5615 (1970).

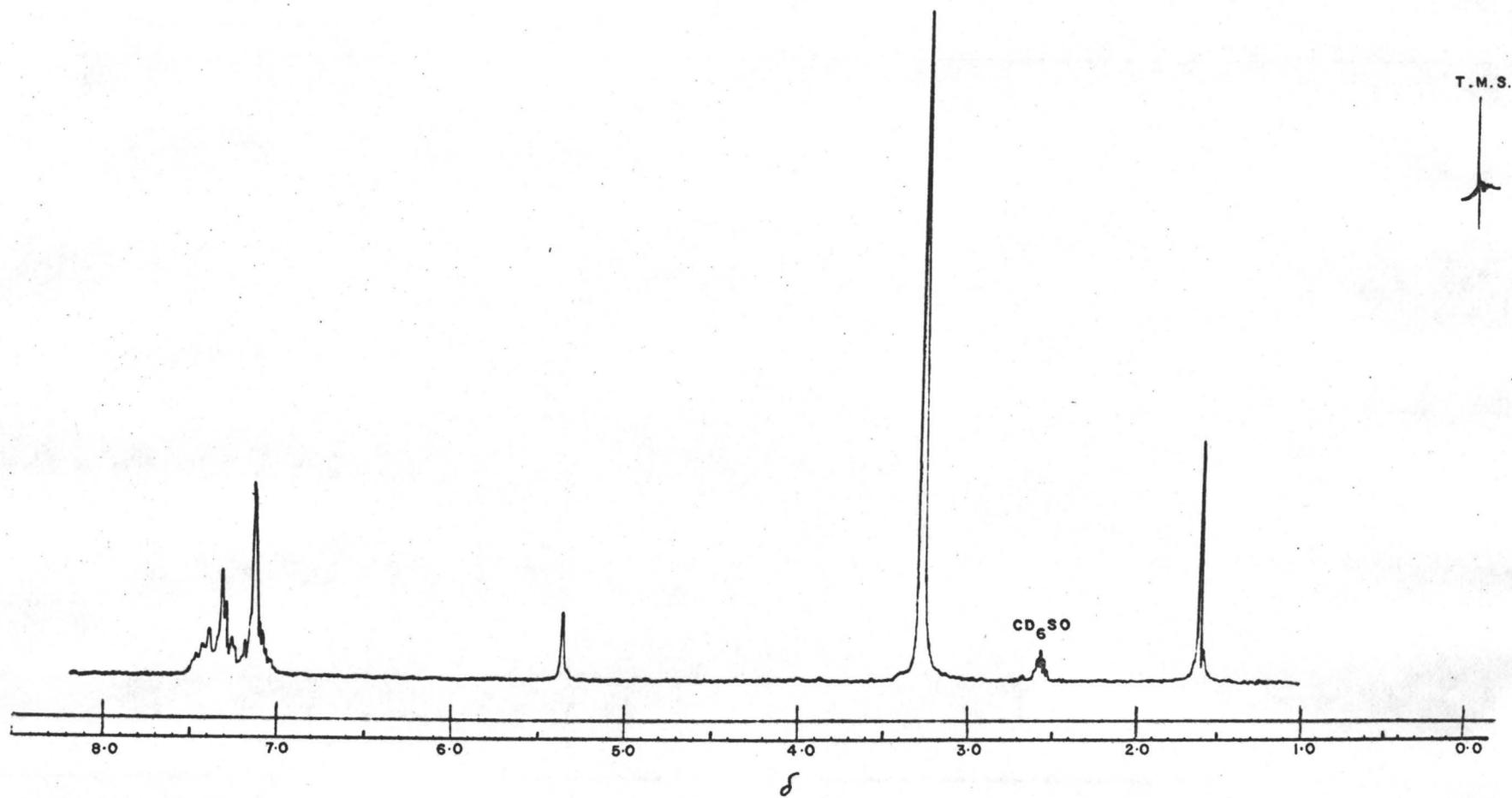
42. I.N. Feit, F. Schadt, L. Lubinkowski and W.H. Saunders, Jr.,
J. Am. Chem. Soc., 93, 6606 (1971).
43. C.H. DePuy, C.G. Naylor and J.A. Beckman, J. Org. Chem., 35, 2751 (1970).
44. M.P. Cooke, Jr., and J.L. Coke, J. Am. Chem. Soc., 90, 5556 (1968).
45. J.L. Coke and M.C. Mourning, *ibid.*, 5561 (1968).
46. C.K. Ingold, Proc. of Chem. Soc., 265 (1962).
47. J.F. Bunnett, Angew. Chem. Internat. Edit., 1, 225 (1962).
48. E.R. Thornton, J. Am. Chem. Soc., 89, 2915 (1967).
49. J.F. Bunnett, Survey of Progress in Chemistry, 5, 53 (1969).
50. L.J. Steffa and E.R. Thornton, J. Am. Chem. Soc., 89, 6149 (1967).
51. W.F. Bayne and E.I. Snyder, Tetrahedron Letters, 571 (1971).
52. R.D. Bach and D. Andrzejewski, J. Am. Chem. Soc., 93, 7118 (1971).
53. J.K. Borchardt and W.H. Saunders Jr., Private Communication.
54. G. Wittig and R. Polster, Ann., 599, 13 (1956).
55. G. Wittig and R. Polster, Ann., 612, 102 (1957).
56. E.D. Hughes, J. Am. Chem. Soc., 57, 708 (1935).
57. E.D. Hughes, C.K. Ingold and C.S. Patel, J. Chem. Soc., 526 (1933).
58. T. Crowell, R. Kemp, R. Lutz and A. Wall, J. Am. Chem. Soc., 90, 4638 (1968).
59. L. Fedor, J. Am. Chem. Soc., 91, 908 (1969).
60. F. Bordwell, K. Yee and A. Knipe, J. Am. Chem. Soc., 92, 5945 (1970).
61. F. Bordwell, M. Vestling and K. Yee, *ibid.*, 5950 (1970).
62. H. Hine, R. Wiesboeck and O. Ramsay, J. Am. Chem. Soc., 83, 1222 (1961).
63. F.J. Smith and A.N. Bourns, Can. J. Chem., 48, 125 (1970).
64. R. Breslow, Tetrahedron Letters, 399 (1964).
65. V.J. Shiner, Jr., and M.L. Smith, J. Am. Chem. Soc., 80, 4095 (1958)
66. D.J. Cram, D.A. Scott and W.D. Nielsen, J. Am. Chem. Soc., 83, 3696
(1961).

67. A. Streitwieser, Jr., W.C. Langworthy and D.E. Van Sickle, *J. Am. Chem. Soc.*, 84, 251 (1962).
68. J.F. Bunnett and E. Bacchioci, *J. Org. Chem.*, 32, 11 (1967).
69. P.D. Buckley, B.D. England and D.J. McLennan, *J. Chem. Soc. (B)*, 98 (1967).
70. H.R.M. Hoffman and G.M. Fraser, *J. Chem. Soc. (B)*, 425 (1967).
71. A.F. Cockerill, *Tetrahedron Letters*, 4913 (1969).
72. M. Born and R. Oppenheimer, *Ann. Phys. (Leipzig)*, 84, 457 (1927).
73. J. Bigeleisen and M.G. Mayer, *J. Chem. Phys.*, 15, 261 (1947).
74. F.H. Westheimer, *Chem. Review*, 61, 265 (1961).
75. D.J. Wilson and H.S. Johnston, *J. Am. Chem. Soc.*, 79, 29 (1957).
76. M. Wolfsberg and M.J. Stern, *Pure App. Chem.*, 8, 725 (1964).
77. A.M. Katz and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, 91, 4469 (1969).
78. A.F. Cockerill and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, 4985 (1967).
79. A.F. Cockerill, *J. Chem. Soc. (B)*, 964 (1967).
80. D. Winstein, D. Darwish and N.J. Holness, *J. Am. Chem. Soc.*, 78, 2915 (1956).
81. A.J. Parker, M. Ruane, G. Biale and S. Winstein, *Tetrahedron Letters*, 2113 (1968).
82. D. Eck and J.F. Bunnett, *J. Am. Chem. Soc.*, 91, 3099 (1969).
83. W.H. Saunders and D.H. Edison, *J. Am. Chem. Soc.*, 82, 138 (1960).
84. C.H. DePuy and D.H. Froemsdorf, *J. Am. Chem. Soc.*, 79, 3710 (1957).
85. C.H. DePuy and C.A. Bishop, *J. Am. Chem. Soc.*, 82, 2532 (1960).
86. W.H. Saunders and R.A. Williams, *J. Am. Chem. Soc.*, 79, 3712 (1957).
87. W.H. Saunders, Jr., D.G. Bushman and A.F. Cockerill, *J. Am. Chem. Soc.*, 90, 1775 (1968).

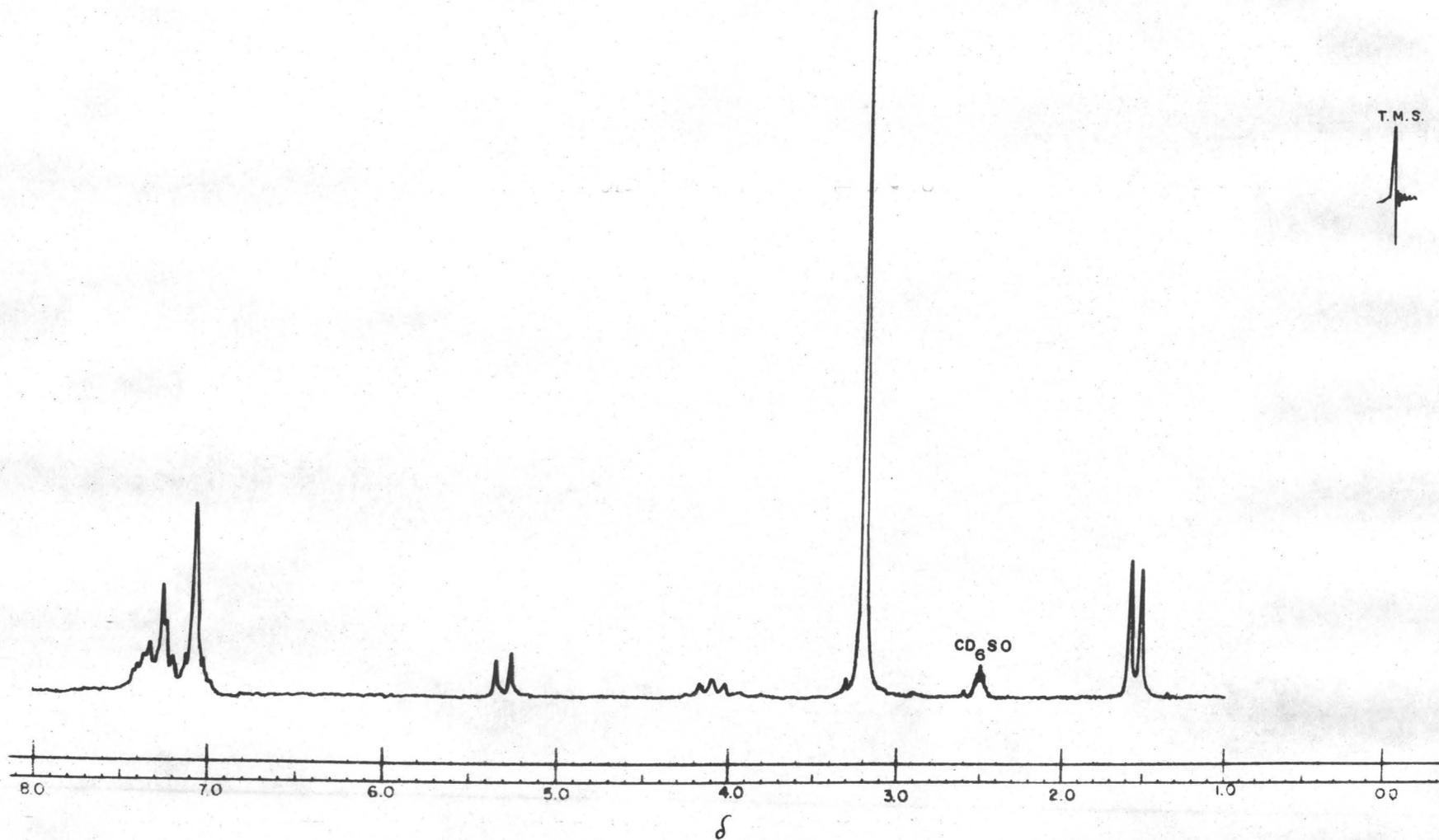
88. P.J. Smith, Ph.D. Thesis, "Isotope Exchange and Kinetic Isotope Effect Studies on the Elimination Reactions of 2-Arylethylammonium Salts", McMaster University, Hamilton, Ontario, 1965.
89. H. Simon and G. Muellhofer, Chem. Bericht, 97, 2202 (1964).
90. R.A. More O'Ferrall, J. Chem Soc. (B), 274 (1970).
91. G.S. Hammond, J. Am. Chem. Soc., 77, 334 (1955).
92. R.A. More O'Ferrall and S. Slae, J. Chem. Soc. (B), 260 (1970).
93. R.A. More O'Ferrall, *ibid.*, 268 (1970).
94. R.A. Bartsch and J.F. Bunnett, J. Am. Chem. Soc., 91, 1376 (1969).
95. R.A. Bartsch, Ph.D. Dissertation, Brown University, Providence, Rhode Island, 1967.
96. R.A. Bartsch and J.F. Bunnett, J. Am. Chem. Soc., 91, 1382 (1969).
97. J. Hine, "Physical Organic Chemistry", 2nd. Edit., McGraw Hill Co., New York, 1962, Chapter 8.
98. J. Weinstock, R.G. Pearson and F.G. Bordwell, J. Amer. Chem. Soc., 76, 4748 (1954).
99. R.T. Arnold and P.N. Richardson, J. Am. Chem. Soc., 76, 3649 (1954).
100. J. Weinstock and F.G. Bordwell, J. Am. Chem. Soc., 77, 6706 (1955).
101. S.J. Cristol and F.R. Stermitz, J. Am. Chem. Soc., 82, 4692 (1960).
102. A.C. Cope, G.A. Berchtold and D.L. Ross, J. Am. Chem. Soc., 83, 3859 (1961).
103. C.H. DePuy, R.D. Thurn and G.F. Morris, J. Am. Chem. Soc., 84, 1314 (1962).
104. A.E. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, "Conformational Analysis", Interscience Publishers, New York, 1965.
105. J. Hine, J. Am. Chem. Soc., 88, 5525 (1966).

106. D.H. Froemsdorf, W. Dowd, W.A. Gifford and S. Myerson, *Chem. Comm.*, 449 (1968).
107. D.H. Froemsdorf, H.R. Pinnick, Jr., and S. Myerson, *ibid.*, 1600 (1968).
108. R.A. Bartsch, *Tetrahedron Letters*, 297 (1970).
109. R.A. Bartsch, *J. Org. Chem.*, 38, 840 (1973).
110. F.A. Abd. Elhafez and D.J. Cram, *J. Am. Chem. Soc.*, 75, 339 (1953).
111. F.G. Bordwell, *Accounts of Chemical Research*, 5, 374 (1972).
112. D.L. Storm, Ph.D. Thesis, Iowa State University of Science and Technology, Ames, Iowa, 1967. Number 67-8938, University Microfilms Inc., Ann Arbor, Michigan.
113. C.H. DePuy, D.L. Storm, J.T. Frey and C.G. Naylor, *J. Org. Chem.*, 35, 2746 (1970).
114. P.J. Smith and S.K. Tsui, *Tetrahedron Letters*, 917 (1972).
115. G. Gamow, *Structure of Atomic Nuclear Transformations*, Oxford Press, 1935, Chapter 5.
116. R.P. Bell, T.A. Fendley and J.R. Hulett, *Proc. of Roy. Soc.*, A235, 453 (1956).
117. L.H. Funderburk and E.S. Lewis, *J. Am. Chem. Soc.*, 86, 2531 (1964).
118. M. Feldman, S. Danishefsky and R. Levine, *J. Org. Chem.*, 31, 4322, (1966).
119. H.C. Brown and B.C. Subha Rao, *J. Am. Chem. Soc.*, 81, 6428 (1959).
120. D.J. Cram and F.A. Abd. Elhafez, *J. Am. Chem. Soc.*, 74, 5851 (1952).
121. R.S. Tipson, *J. Org. Chem.*, 9, 235 (1944).
122. A.I. Vogel, *Practical Organic Chemistry*, 3rd. Edit., Longmans, Toronto, 1956, page 186.
123. A.F. Cockerill, S. Rottschaefer and W.H. Saunders, Jr., *J. Am. Chem. Soc.*, 89, 901 (1967).

124. J.V. Griepenburg, Ph.D. Thesis, "Kinetics of Elimination Reactions of 1,2-Diphenylethyl Chlorides", University of Rochester, Rochester, New York, 1970.



Proton Magnetic Resonance Spectrum of
threo-1,2-Diphenyl-1-propyltrimethylammonium Iodide
(see page 96)



Proton Magnetic Resonance Spectrum of
threo-1,2-Diphenyl-1-propyltrimethylammonium-2d₁ Iodide
(see page 99)

SL126