DEAMINATION AND HYDROLYSIS OF TERTIARY SYSTEMS

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by

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ABSTRACT

This thesis reports the aqueous nitrous acid deamination of two tertiary carbinamines; 2-amino-2-methylpropane and 3-amino-3-methylpentane (at 80°C, pH4). The hydrolysis (at 80°C, pH4) of the two corresponding alkyldimethyl sulphonium salts; dimethyl-(2-methyl-2-propyl)sulphonium perchlorate and dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate, is also reported. A comparison of the two types of reaction (deamination and hydrolysis) shows small but definite differences. Both deaminations produced a greater proportion of elimination than the corresponding hydrolyses. The deamination of 3-amino-3-methylpentane produced lower 2-ene/1-ene and trans/cis ratios than the corresponding hydrolysis.

It is suggested that the deamination carbocations are short-lived and shielding by the departing nitrogen prevents complete loss of the "excess" energy acquired from the irreversible decomposition of the diazonium ions. The "excess" energy of the deamination product precursors relative to the hydrolysis analogs makes the higher energy product-forming pathways more favourable in deamination than hydrolysis.

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INTRODUCTION

The nitrous acid deamination of primary amines continues to provide physical organic chemists with a problem although this reaction was first investigated at the end of the last century. When compared with the solvolysis of analogous alkyl substrates it was initially expected that the two types of reaction would produce the same carbocation intermediate and therefore the same product ratios. It was clear from the earliest days of these investigations that this is not so. Solvolysis and deamination of corresponding substrates (i.e. RX, RNH_2) generally produce markedly different product distributions.

The problem was then posed by the question, "if the solvolysis involves a 'normal' carbocation intermediate, what then is the nature of the 'abnormal' deamination intermediate?"

Current understandings of ion-pairing have joined numerous other suggestions put forward, and to a large extent their combined weight adequately explains many of the observations.

The large number of reported solvolyses and deaminations include only a few investigations of acyclic, tertiary aliphatic substrates. No deliberate comparison of the two reactions using tertiary alkyl substrates have been carried out in a suitably rigorous fashion. Reactions of tertiary substrates using water as the solvent may be expected to proceed via the free carbocation in each case. Similar product ratios may result if ion-pairing and conformational control (of elimination) are the main reasons for the solvolysis/deamination dichotomy. The practical work of this thesis is concerned with this comparative investigation using tertiary substrates.

A comparison of deamination and solvolysis encompasses a great deal of accumulated knowledge associated with each topic. Chapters 1 - 5 briefly survey the current knowledge that one should have in mind when conducting this comparative study.

Chapters 1 and 2 cover aspects of solvolysis and deamination respectively. Chapter 1 includes a survey of ion-pairing and elimination mechanisms relevant to this thesis. Chapter 2 includes a brief summary of the many reactions that produce diazonium ions and considers nitrous acid deaminations in rather more detail. Aromatic diazonium ions and nitrosations in basic solution are also very briefly considered.

Chapter 3 compares product distributions from solvolysis and deamination and summarises the mechanisms suggested to account for the experimental observations.

Chapter 4 summarises the field of nitrosation catalysis by halide ions, thiocyanate ion, aldehydes and ketones, thiourea and substituted thioureas, and micelles. Nitrosation inhibition is also very briefly considered. This chapter has little direct bearing on the practical work of this thesis but nevertheless this summary is an integral part of the field of deamination. Nitrosation catalysis is the subject of many reported nitrous acid deamination studies.

Chapter 5 considers micellar effects in deamination in particular and briefly also in some hydrolyses. Though absent in the systems studied in this thesis, micelles have been shown to exert a considerable influence on product ratios and stereochemistry in other reported studies.

Chapter 6 is an introduction to the experimental work of this thesis. It outlines the systems studied, in broad terms how it was done and describes some of the main problems that had to be overcome. It is designed to orientate the reader in the field of deamination as approached in this thesis and sets the scene for Chapters 7 - 10. These describe the reactions of the four compounds studied and their results. A section at the end of Chapter 6 outlines the structure of the experimental chapters and appendices in more detail.

Chapter 11 is the main discussion chapter and considers the experimental results and their implications.

From the oral examination

Throughout: The use of standard convention for prefixes *cis*- and *trans*- [(*E*)- and (*Z*)- are now used], *threo*-, *erythro*-, *syn*-, *anti*- etc. is ignored. These always appear italicized in print and are underline (or italicized) in a manuscript.

The same comment applies to the non-standard method used for reporting the literature citations.

Chapter One

Solvolysis

1.1 General

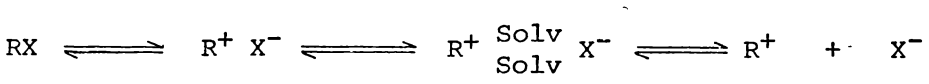
The practical work of this thesis investigates and compares the solvolysis (hydrolysis) and nitrous acid deamination of two simple, aliphatic, acyclic, tertiary systems; 2-methyl-2-propyl (dimethyl sulphonium salt and amine) and 3-methyl-3-pentyl (dimethyl sulphonium salt and amine). The products of these reactions arise from nucleophilic substitution by the solvent and elimination. The term "solvolysis" is used here in reference to the overall reaction and includes the elimination and rearrangement (where this occurs) components as well as the substitution by the solvent.

This chapter summarises the main aspects of the solvolysis mechanisms and the factors that influence them. Though different sections are devoted to different subjects, such as Leaving Group Effects and Solvent Effects for the sake of simplicity, it is recognised that the influences are, in reality, very much intertwined and often difficult to separate. Nucleophilic substitution and elimination mechanisms are considered in some detail. Rearrangement mechanisms are summarised rather more briefly since the practical aspects of this thesis do not include this type of reaction. Patterns of rearrangement are however, prominent in the discussions of Chapter 3.

1.2 General Principles in Nucleophilic Substitution

1.2.1 Ion-Pairs: General Points

It is usual in discussions of the mechanism of nucleophilic substitution to use the terminology proposed by Winstein[1]. This includes two intermediates; the intimate ion-pair (II) and solvent separated ion-pair (III) in addition to the free carbocation (IV).



$$RX \rightleftharpoons R^{+}X^{-} \rightleftharpoons R^{+}\,{}^{\mathrm{Solv}}_{\mathrm{Solv}}\,X^{-} \rightleftharpoons R^{+} + X^{-}$$

(I) (II) (III) (IV)

In this discussion the term "free carbocation" refers to the cation arising from dissociation of the solvent separated ion-pair. No effort is made to distinguish cations of varying solvations unless otherwise specified.

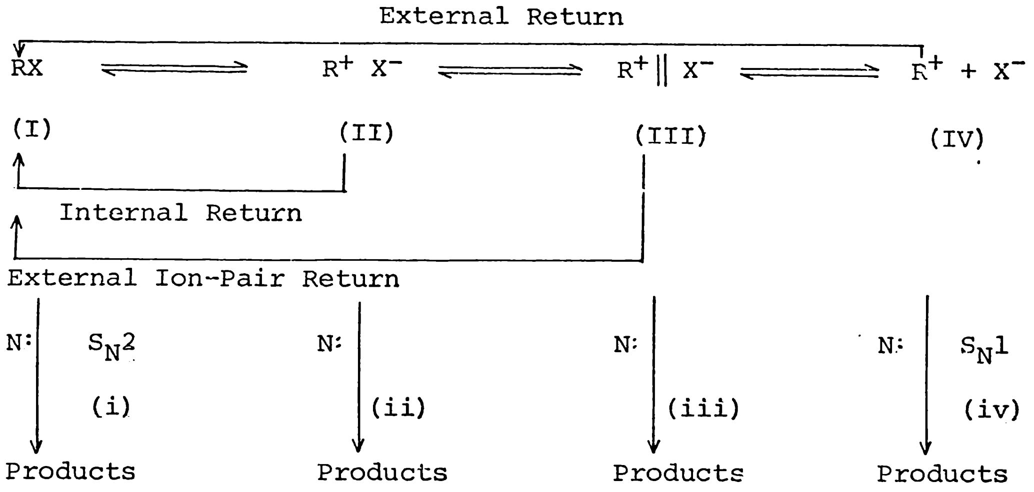
As implied by their names, the structures of (I) and (II) are considered to be different. Evidence for this comes from studies of reaction rates and stereochemistry, return pathways (Scheme I) and various measurement techniques[2] such as ESR, NMR, ultraviolet, infrared and raman spectroscopy and electrical conductance.

A scheme involving ion quadrapoles has been suggested by Ingold[3]. Though in many cases there is little reason to prefer the ion-pair hypothesis over quadrapoles, the former has been preferred and adopted by common usage[4].

McLennan has remained unconvinced and in a review has reconsidered the case for the concerted S_N2 mechanism of nucleophilic aliphatic substitution[5]. He concludes that much of the evidence for ion-pairing during nucleophilic substitution at a saturated carbon can equally well be explained by the S_N1/S_N2 mechanism. He also concludes that Sneen's[6] proposed universal unification of the

S_N1 and S_N2 mechanisms is not proven.

Scheme I shows terminology and pathways associated with ion-pairing.



Scheme I

The degree of dissociation is influenced by three factors:

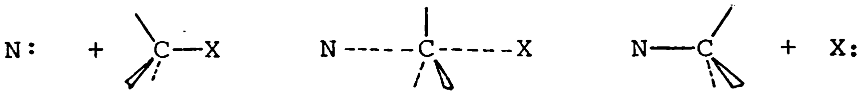
(a) The amount and type of added salts

(b) The nature of the substrate

(c) The solvent

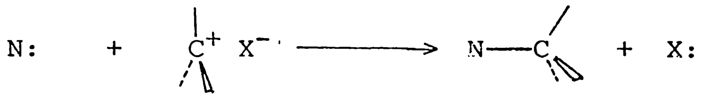
These factors will be discussed in Sections 1.2.2 to 1.2.5. Before doing so some general comments should be made about nucleophilic substitution reactions of the four species in Scheme I. The discussion of salt effects (Section 1.2.2) illustrates the importance of the return pathways.

(i) Neutral Substrate.



Reaction via this species (path (i), Scheme I) is typical of the bimolecular nucleophilic substitution mechanism (S_N2) and yields product with inverted configuration.

(ii) Intimate Ion-Pair.

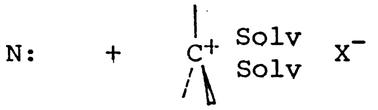


Sometimes called the close ion-pair, the intimate ion-pair mechanism (path (ii), Scheme I) gives predominant inversion of configuration in the product. Cation rotation may occur followed by internal return yielding varying degrees of racemisation in the starting substrate (RX).

Though often referred to as "the" intimate ion-pair, there is evidence for the existence of a number of intimate ion-pairs for a given substrate, that differ only in the position of the anion, with more than one of the positions resulting in an energy minimum[7-11].

(iii) Solvent Separated Ion-Pair.

(path (iii), Scheme I)

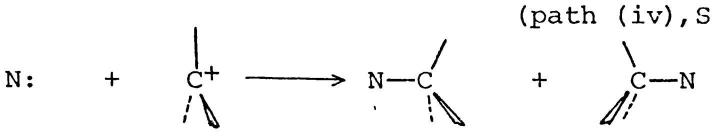


A mixture of inversion and retention of product configuration tends to occur, depending upon the nature of the substrate and reaction conditions. External ion-pair return may yield a change of stereochemistry in "unreacted" starting material. In solvolysis the nucleophile, N:, is also the solvent.

Various studies indicate that a discrete number of solvent molecules may differentiate intimate and solvent separated ion-pairs, possibly two to six[12]. Clearly this will depend upon the alkyl and leaving groups, also the solvent. A number of conformations with different anion positions may also be possible[13,14]. In solvolyses in mixed solvents such as EtOH/H_2O, both EtOH-separated and H_2O-separated ion-pairs have been postulated[15,16].

(iv) Free Carbocation.

(path (iv), Scheme I)



Substitution product formation solely via this intermediate (S_N1) tends to give racemic mixtures. This intermediate is considered to be free of the effects from the departed leaving group.

Carbocations may be solvated to varying degrees depending upon the solvent, alkyl group structure and leaving group[17]. In some cases where a very good leaving group is employed, such as nitrogen in the diazonium ion, carbocations with relatively little solvation have been postulated[17].

Carbocations are discussed further in the section on substrate structural effects (Section 1.2.3).

1.2.2 Salt Effects

Salt effects on nucleophilic substitution reactions afford a means of distinguishing between ion-pair and free carbocation mechanisms by influencing the extent of dissociation and return pathways (Scheme I).

Added salts may act in three ways:

(a) Ionic Strength Effects

(b) Common and Non-Common Salt Effects

(c) "Special" Salt Effects

(a) Ionic Strength Effects

Addition of non-reacting salts effectively increases the polarity of the solution. The result is the same as one would expect from a change to a more polar solvent and depends upon the charge type of the reaction (Section 1.2.4). The effect is quantitatively determined using the Bronsted equation (Bronsted Salt Effect)[18a].

Salts incapable of reaction with either the substrate or subsequent intermediate are used in ionic strength studies. Alkali metal perchlorates or tetrafluoroborates are often used since the anions are of very low nucleophilic power (Section 1.2.6).

Generally, substrates where the transition state of the slow step is more charged than the reagents experience enhanced rates on increasing the ionic strength.

(b) Common and Non-Common Salt Effects

Ionisation of a neutral substrate is generally reversible unless an unusually stable carbocation is formed.

$$RX \rightleftharpoons R^+ + X^-$$

Addition of a salt, with a common anion, X^-, tends to force the equilibrium in favour of the reagent causing a decrease in the rate of product formation through the carbocation. The rate enhancing ionic strength effect is usually less significant.

Addition of a non-common ion, such as azide (N_3^-), normally shows only an ionic strength effect on reaction rate.

The common ion rate depression is generally diagnostic of return from the free carbocation to a solvent separated ion-pair. Reactions proceeding by the latter intermediate do not show a common ion rate depression.

Product stereochemistry may also be expected to alter upon a change of mechanism (Section 1.2.1)[1].

Racemisation of starting material is also indicative of an ion-pair mechanism though this could conceivably also arise from carbocation-anion recombination. However, this is most unlikely since once separated, the anion is replaced by solvent present in vast excess.

(c) "Special" Salt Effects

The addition of a very small concentration of some inert salt, such as $LiClO_4$, to a solvolysis reaction, may give a very large rate increase - very much larger than would be expected from an increase in ionic strength.

It has been suggested[18b,19] that the "special" salt anion replaces the anion of the solvent separated ion-pair thereby stopping external ion-pair return. The resulting solvent separated ion-pair with the "special" salt anion is then committed to product formation. The rate of product formation is then closer to the rate of ionisation. The solvent separated ion-pair intermediate appears to be much more reactive towards the "special" salt than the intimate ion-pair. Therefore, while external ion-pair return is blocked, internal return continues so the rate of product formation, after "special" salt is added, is not exactly the rate of ionisation[19].

This "special" effect is therefore diagnostic of a solvent separated ion-pair mechanism and should show reduced racemisation of an optically active starting material.

Measurement of Return:

The rate constants for racemisation of a solvolysis substrate (k_{rac}) and isotope equilibration (k_{eq}) such as in arenesulphonate and benzoate esters provide a measure of the importance of return.

$$\mathrm{ROS\ {}^{18}O_2\ Ar} \xrightarrow{k_{eq}} \mathrm{R\ {}^{18}OS\ {}^{18}O_2\ Ar}$$

$$\mathrm{ROC\ {}^{18}O\ Ar} \xrightarrow{k_{eq}} \mathrm{R\ {}^{18}OC\ {}^{18}O\ Ar}$$

When using racemisation or isotope equilibration to measure ion-pair return, it is implicitly assumed that these processes are an integral part of the solvolysis reaction. However, this assumption might not always be valid. Hammett[20] has noted that alkyl bromides are racemised by bromide ion and alkyl iodides by iodide ion at a rate which is proportional to the concentration of the halide ion. In addition alkyl bromides undergo an exchange reaction with isotopically labelled bromide ion and alkyl iodides with iodide ion at a rate which is proportional to the concentration of the halide ion. Racemisation and equilibration may only provide a lower estimate of ion-pair return, since return with either retention of configuration or incomplete randomisation cannot be detected.

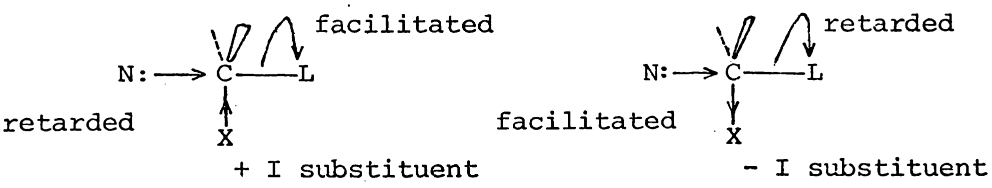
1.2.3 Alkyl Group Structural Effects

This discussion considers general principles and trends in substrate structural effects on the nucleophilic substitution mechanisms.

The effect of substrate structure on reactivity depends upon the reaction mechanism. The rate of an S_N1 type reaction depends upon the ease with which a substrate forms a carbocation. The rate of an S_N2 reaction depends upon the ease with which a nucleophile can attack a saturated carbon atom. The structural requirements of these two reactions are quite different:

Steric factors; Bulky substituents can enhance an S_N1 reaction since a change towards sp^2 hybridisation in the transition state and carbocation can relieve steric congestion. In S_N2 type reactions, increased branching generally tends to decrease the rate of substitution due to shielding of the reacting carbon. Tanida and Matsumura have investigated reactivity variations in the S_N2 reactions of crowded tertiary alkyl systems (α- aryldialkylcarbinyl and trialkylcarbinyl p-nitrobenzoates) with respect to rate enhancing relief of strain and rate-retarding steric hindrance to resonance stabilisation of the aryl group[21].

Electronic factors; Electron donating substituents tend to enhance carbocation stability by delocalising the charge to some extent. In S_N2 reactions structural influences on the rate are more difficult to predict than in S_N1 since both bond making and bond breaking are important in the transition state, and these processes have opposite electronic requirements as shown below (Isaacs)[18].



Carbocation stability has been mentioned and there are several ways of expressing relative stabilities[4];

(a) Comparative rates of ionisation of the parent compound as a measure of carbocation stability. This assumes that for a given type of parent compound a more stable ion will form more rapidly.

(b) Comparative reactivities towards a nucleophile as a measure of carbocation stability.

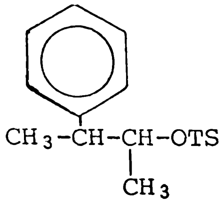
The rate at which a carbocation reacts with a nucleophile is determined by the difference in free energy between the carbocation and the nucleophile-carbocation transition state: the more reactive the carbocation, the smaller this Gibbs free energy difference[4].

Parent compound ionisation (a) measures the difference in free energy between the substrate and the transition state leading to the carbocation (free energy of activation). A comparison of rates of ionisation (a) provides a measure of carbocation stability if it is assumed that the difference between the Gibbs free energies of activation is largely due to the free energies of the transition states, and that these parallel those of the corresponding carbocation.

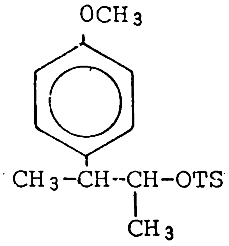
Therefore, (a) gives a measure of stability whilst (b) gives a measure of reactivity. Generally however, the less stable carbocations are more reactive, though this is not always so.

Generally speaking, for a series of simple primary, secondary and tertiary substrates the extent of dissociation increases along the series. However this trend is fairly rough and a relatively minor change near the reaction site can disrupt the relationship.

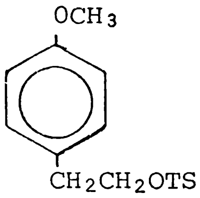
This is shown for the aromatic stabilised series overleaf[19].



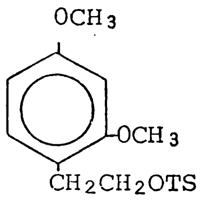
A



B



C



D

A and B give ion-pairs.

B gives a "special" salt effect indicating predominantly solvent separated ion-pairs.

A does not give a "special" salt effect indicating predominantly intimate ion-pairs.

C gives products from a solvent separated ion-pair and free carbocation (shows a common ion rate depression).

D gives products almost exclusively from a free carbocation.

1.2.4 Solvent Effects

When considering solvent effects on reaction rates and mechanisms a number of solvent properties must be taken into account;

(a) Polarity

(b) Nucleophilicity

(c) Ionising Power

These properties will be briefly defined and discussed before their effects on rates and mechanisms are explored.

(a) Solvent Polarity.

A term often used in qualitative discussions, usually referring to the ability of the solvent to solvate polar molecules and reaction intermediates:- ions and dipolar molecules are better solvated by more polar solvents.

The solvation of a solute is usually considered to involve electrostatic, ion-dipole or dipole-dipole interactions and perhaps also more specific types of interactions such as hydrogen bonding.

Since solvation is such a complex phenomenon, there is no single universal measure of solvent polarity. Various methods do, however, give reasonable indications in many instances[18c], these include; dielectric constants, the Winstein-Grunwald relationship, isomer ratios in a Diels-Alder reaction and solvent effects on solvatochromic dyes.

(b) Solvent Nucleophilicity.

In solvolysis reactions, the solvent molecule acts as a nucleophile. The inherent reactivity of a nucleophile, its nucleophilicity, has been defined as its kinetic affinity for a saturated carbon atom[4]. A measure of this is given by a displacement of the type:

$$\mathrm{N:} \quad + \quad \mathrm{RX} \longrightarrow \mathrm{RN} \quad + \mathrm{X:}$$

Schadt *et al.*[22] defined a solvent nucleophilicity scale (N) from rate data for methyl tosylate solvolysis and determined N values for a series of pure and mixed solvents.

Nucleophilicity versus Basicity.

Both terms refer to the tendency of a reagent to supply an unshared pair of electrons to form a covalent bond. However, basicity is used in a thermodynamic sense and applies to equilibrium conditions. Nucleophilicity refers to kinetic phenomena and is associated with reaction rates.

(c) Solvent Ionising Power.

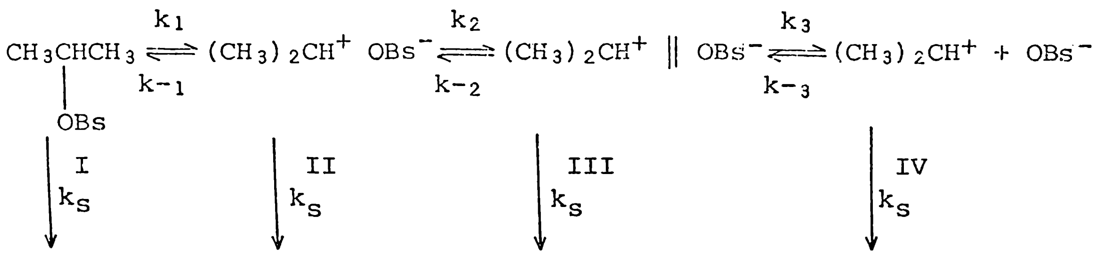
This property refers to the rate of substrate dissociation and is quite distinct from the ability of a solvent to dissociate ions.

This is apparent in the acetolysis of threo-3-p-anisyl-2-butyl brosylate as acetic anhydride is added to the solvent[1]. As the solvent changes from 100% acetic acid to 100% acetic anhydride the reaction changes from a solvent separated ion-pair to a free carbocation mechanism. Titrimetric and racemisation rate constant behaviour and salt effects indicate that acetic anhydride reduces the rate of formation of ionic intermediates (lower ionising power) but increases the extent to which they are dissociated. A measure of ionising power is provided by the racemisation rate constant, which gives a measure of external ion-pair and internal return (Section 1.2.2 (c)). However, nucleophilic reactions of the solvent must also be considered since a nucleophilic solvent can reduce the amount of ion-pair return by reacting with the intermediates.

(d) Solvent Effects on S_N Mechanisms.

An increase in solvent polarity tends to increase the degree of ion-pair dissociation. Increases in solvent nucleophilicity and ionising power tend to reduce the amount of ion-pair return[15]. As mentioned above, an increase in solvent nucleophilicity can also reduce or eliminate dissociation by providing a more facile, bimolecular product-forming pathway.

This has been shown for the solvolysis of 2-propylbrosylate[23].



Solvent	Slow Step	Product Determining Step	Nucleophilicity[24]
CF_3COOH	k_2	k_s^{III}	-5.55
CH_3COOH	k_1	k_s^{II}	-2.05
80% C_2H_5OH	k_s^{I}	k_s^{I}	0.00

S_N1 reactions are generally favoured by polar, protic solvents in which both the transition state and intermediate can be solvated.

$BuOH < EtOH < MeOH < H_2O < AcOH < HCOOH < CF_3CH_2OH < CF_3COOH$
$< H_2SO_4 < FSO_3H$

$\xrightarrow{\text{greater polarity}}$

Rappoport[25] has reported a detailed investigation of solvent effects on ion-pairing in several vinylic solvolyses. These effects have been discussed in terms of the solvent ionising power, dissociating power and nucleophilicity. Schadt *et al.*[26] have investigated solvent effects on aryl-assisted and aryl-unassisted pathways in the solvolyses of primary and secondary arylalkyl tosylates.

(e) Solvent Effects on S_N Rates.

The effect of the solvent upon nucleophilic substitution rates depends upon the mechanism and the change in charge between the transition state and reactants. This is summarised quantitatively in the Hughes-Ingold theory of solvent effects which is applicable to S_N1 and S_N2 mechanisms[3]. The theory considers solvation of the reactants and the transition states. It assumes that for a given solvent the degree of solvation will:

(i) increase with the magnitude of the charge on the solute.

(ii) decrease with increased distribution of a given charge.

These effects are summarised below:

Solvent Effects Predicted for S_N Reactions of Different Charge-types by the Hughes-Ingold Theory.

Mechanism	Reactants	Transition State	Charge in Transition State Relative To Reactants	Effect of an Increase in Polarity of Solvent On Rate
S_N2	$Y^- + RX$	$^{\delta-}\text{Y---R---X}^{\delta-}$	dispersed	small decrease
S_N2	$Y + RX$	$^{\delta+}\text{Y---R---X}^{\delta-}$	increased	large increase
S_N2	$Y^- + RX^+$	$^{\delta-}\text{Y---R---X}^{\delta+}$	decreased	large decrease
S_N2	$Y + RX^+$	$^{\delta+}\text{Y---R---X}^{\delta+}$	dispersed	small decrease
S_N1	RX	$^{\delta+}\text{R---X}^{\delta-}$	increased	large increase
S_N1	RX^+	$^{\delta+}\text{R---X}^{\delta+}$	dispersed	small decrease

Some specific examples of these influences have been summarised by Isaacs[18d]. Two are shown below.

$$\text{t-BuBr} + \text{SH} \longrightarrow \text{t-Bu-S} + \text{HBr}$$

SH:	EtOH	80% aq. EtOH	50% aq. EtOH	H_2O	HCOOH.
k_{relative}	1	10	29	1450	$1.2\text{x}10^5$

$$\text{t—Bu-}\overset{+}{\text{S}}\text{Me}_2 + \text{SH} \longrightarrow \text{t-Bu-S} + \text{SMe}_2 + \text{H}^+$$

SH:	EtOH	80% aq. EtOH	H_2O
k_{relative}	1	0.65	0.32

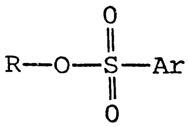
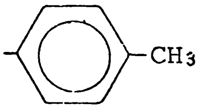
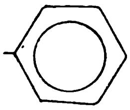
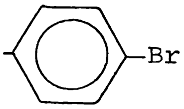
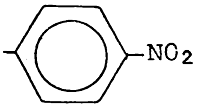
1.2.5 Leaving Ability of Groups

The rate of a substitution reaction occurring by either an S_N1 or S_N2 mechanism is sensitive to the nature of the leaving group. However, the influence of the solvent may substantially modify the influence of the leaving group. For example, see the cases of t-BuBr and $\text{t-Bu}\overset{+}{\text{S}}\text{Me}_2$ in section 1.2.4 (e). The product distribution of a solvolysis reaction may also depend upon the leaving group but once again the solvent has an important influence. Cocivera and Winstein[27] have solvolysed tertiary butyl chloride, bromide, iodide and the dimethyl sulphonium perchlorate salt in water, ethanol and acetic acid. In water the mole percent of elimination was the same for each leaving group. In ethanol the elimination decreased down the series;

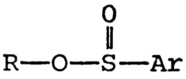
$$\text{Cl} > \text{Br} > \text{I} > {}^{+}\text{SMe}_2\text{ClO}_4^{-}$$

and this was even more pronounced in acetic acid solvent. These results are explained in terms of decreasing ion-pair dissociation as the solvent is changed from H_2O to EtOH to AcOH.

Solvolysis is facilitated by a weak carbon to leaving group bond and an increase in the ability of the leaving group to bear a negative charge. Chloride, bromide, iodide and perchlorate are inductively electron withdrawing while sulphonate and sulphinate groups involve both -I and -R effects making them better leaving groups.

Sulphonate Ester	Ar		
 $R-O-\overset{O}{\underset{O}{S}}-Ar$		p-toluene sulphonate	-OTs (tosylate)
		benzene sulphonate	-OBz
		p-bromobenzene-sulphonate	-OBs (brosylate)
		p-nitrobenzene - sulphonate	(nosylate)
also	$-CF_3$	trifluoromethane - sulphonate	(triflate)
	$-CH_3$	methane sulphonate	(mesylate)

Sulphinate Ester


$R-O-\overset{O}{S}-Ar$

Carboxylates and phenolates, heavily substituted with electron withdrawing groups are also used e.g. trifluoroacetate, 2,4-dinitrobenzoate (DNB) and picrate.

The preparation of unstable tosylates (tertiary alkyl groups and secondary alkyl groups with aromatic substituents) has been reported by Hoffmann[28] and Coates[29] while Crossland[30] reports the preparation of mesylates.

Leaving Groups, Mechanism and Products:

If RX is solvolysing through either the S_N2 or and ion-pair mechanism, changing the leaving group results in a changed product ratio, dependent upon the stability of the carbon to leaving group bond.

However, if RX solvolyses through the free carbocation, the product ratio should be independent of the leaving group.

A number of workers indicate that size seems to be a major factor in leaving group effects on ion-pair formation and return[31]. This may reflect differences in the solvation of the leaving groups[32,33] (see Section 1.2.6).

Roberts[31] has divided leaving groups into three sizes: small (e.g. chloride), medium (e.g. methanesulphonate) and large (e.g. arenesulphonate) and notes that large leaving groups tend to give less return than small leaving groups.

In mixed solvents such as EtOH/H_2O, where solvent separated ion-pairs are important, the product composition may depend upon the relative stabilities of the EtOH-separated and H_2O-separated species. The leaving group is important in this case. Solvolysis of a series of alkyl halides in EtOH/H_2O[15] gave an increase in the ROEt/ROH ratio with increased ion-pair stability. This was presumed to reflect the better nucleophilicity of EtOH compared with H_2O[23,24].

However, the ROEt/H_2O ratio for the 2-adamantyl arenesulphonate solvolysis decreases with increased ion-pair stability, reflecting preferential product formation through the H_2O-separated ion-pair[16].

The hydrolysis of aryldimethyl sulphonium salts is thought to involve an ion-dipole assemblage in place of the ion-pair[35]. Sneen envisages this assemblage as

$$ArCH_2^+ \text{---------} S(CH_3)_2$$

being a close analog of an ion-pair in which the dimethyl sulphide molecule interacts strongly with the carbocation centre. Ion-dipole collapse may occur rapidly though diffusion of the dimethyl sulphide into the bulk of the solvent would compete more effectively with collapse as the carbocation is made increasingly stable.

1.2.6 Nucleophiles

In solvolysis reactions the most abundant nucleophile is the solvent molecule. Aspects of its nucleophilicity have been discussed (Section 1.2.4). Other nucleophiles are also normally present; leaving groups, counter-ions from salt substrates (sulphonium and ammonium salts), added salts, acids and bases from pH adjustments and perhaps buffers. Since a discussion of nucleophile properties overlaps with previous discussions of salt and leaving group effects, only a brief outline follows.

Two aspects may be considered[4]:

(a) Basicity

(b) Polarisability

(a) Basicity:

As a general rule the strongest bases tend to be the most effective nucleophiles, but only then for those cases where the reacting atom remains the same, e.g. in the series of oxygen nucleophiles.

$$OH^- > OPh^- > OAc^- > H_2O > ClO_4^-$$

Any larger structural variation tends to lead to loss of correlation.

(b) Polarisability:

For reactions in protic solvents the following order of reactivity is commonly observed:

$I^- > CN^- > SCN^- > OH^- > N_3^- > Br^- > C_6H_5O^- > Cl^- > C_5H_5N > CH_3COO^- > H_2O$

The greater reactivity of the larger anion is assumed to reflect the greater ease with which its valence electrons are distorted (polarised) by the electrophilic centre of the substrate[36].

Summary: When the reacting atom is the same, the relative reactivities of the nucleophiles are determined by their basicity, otherwise the polarisability factor appears to be the more important.

Solvent Effect on Nucleophiles[4]:

In protic solvents the smaller anions tend to be more strongly solvated. Strong specific interactions with the solvent will reduce the reactivity of an anion. The higher reactivities of the larger nucleophiles, which have been discussed in terms of polarisability might be due, in part at least, to changes in solvation.

Ambident Nucleophiles[4]:

These are nucleophiles with more than one nucleophilic atom that may act as a reaction site, e.g. NO_2^-.

Silver nitrite reacts with alkyl halides to give mixtures of nitroalkanes and alkyl nitrites. The proportions vary with experimental conditions in such a way as to suggest that the oxygen atom is the preferred reaction site when the mechanism is S_N1.

1.3 Elimination Reactions

Theories of elimination reaction mechanisms are very much concerned with the unimolecular and bimolecular pathways, comparable to S_N1 and S_N2 in substitution reactions. However, unlike nucleophilic substitution, the role of ion-pairing is not so well understood. Consequently this discussion of elimination reactions will concentrate mainly on the E1 and E2 reactions with a brief summary of the role of ion-pairs. Though the solvolysis reactions with which we are concerned in this literature survey are generally devoid of appreciable quantities of strong nucleophiles, the E2 pathway is still considered in detail since knowledge of its mechanism contributes greatly to the overall understanding of elimination reactions.

Where necessary, reference should be made to the earlier discussions of solvent effects, leaving ability of groups and nucleophiles as they are equally applicable here.

1.3.1 Elimination Mechanisms

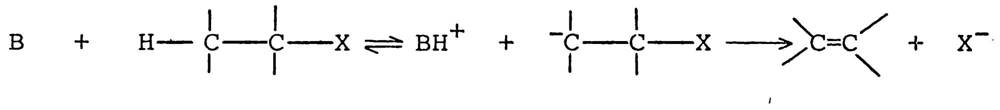
In order for elimination to occur during solvolysis, the substrate requires at least one hydrogen β to the leaving group. In some E1 reactions where rearrangements occur, an isomeric carbocation with a β-hydrogen may form from a substrate initially lacking a β-hydrogen.

There are two main elimination mechanisms:

(a) Unimolecular elimination (E1)
- loss of proton from a free carbocation

(b) Bimolecular elimination (E2)
- base abstracted proton loss from an undissociated substrate.

A possible alternative to the E2 reaction is the unimolecular elimination from the conjugate base (E1 cB)[37]. Instead of simultaneous removal of the β-proton and loss of the leaving group, the β-proton is removed first to give a carbanion intermediate, and the leaving group is lost in a subsequent step.



This mechanism requires a poor leaving group (e.g. alkoxyl) and a rather stable carbanion intermediate.

Reaction Conditions for E1 and E2:

E1: There are three main factors that favour this carbocation mechanism; a substrate that gives a relatively stable carbocation, an ionising solvent and the absence of strong bases or nucleophiles. Generally water, alcohols, mixtures of the two or carboxylic acids are used (Section 1.2.4).

E2: Generally water and alcohols are used as well as dipolar aprotic solvents. In protic solvents the strong base employed is usually the conjugate base of the solvent.

By altering the reaction conditions sufficiently, it is possible to make most substrates react by bimolecular mechanisms. However, many primary substrates cannot be made to react through unimolecular mechanisms.

1.3.2 Distinguishing Between E1 and E2

(a) By Reaction Rates

Both mechanisms are first order in substrate, but E2 is also dependent upon base concentrations. If only substrate and solvent are present, the mechanism could be E1 or E2 with the solvent acting as base. A distinction is usually made by adding a little of a stronger base such as the conjugate base of the solvent.

The rate equation for an E1 reaction may be complicated by reversible ionisation and ion-pairing[37a].

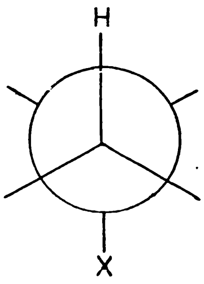
(b) By Product Ratios

If the substrate does not react at all in the absence of base, there can be no competing unimolecular reaction. If it does, lack of variations in product ratios over a range of base concentrations indicates that the unimolecular reaction either does not compete, at the base concentrations used, or else gives the same product ratios.

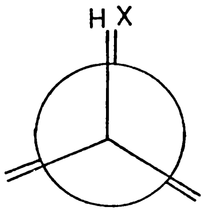
Generally E1 reactions give substantially lower proportions of elimination than E2 reactions of the same substrate[38].

1.3.3 Stereochemistry of E2 Reactions

In the transition state the leaving group and β-hydrogen can have two extreme positions with respect to each other: anti-periplanar[39] and syn-periplanar[39].



anti-



syn-

Intermediate positions (anti-clinal and syn-clinal) are also named but since they are experimentally difficult to distinguish from anti- and syn-periplanar, and the latter are theoretically preferred[37], the terms anti and syn are used in reference to the extremes. For electrostatic and steric reasons, elimination from the anti conformation is usually preferred[37,40]. Syn dominated eliminations occur in many ring systems and some aliphatic systems dependent also upon the base, size of leaving group and possible ion-pairing influences[26].

The terms trans and cis are often used in stereochemical discussions and refer to substrate and product carbon chain stereochemistries.

Amongst elimination products there are two major types of orientation possible:

(1) Positional Orientation, which gives isomers with the double bond in different positions in the carbon skeleton.

(2) Geometric Orientation, referring to trans and cis isomers of a disubstituted alkene.

In either case there is no necessary relation between product energies and product proportions[37b] (see Hofmann Rule). Since the ground state is common to all paths of reaction for a given reactant, the product ratios reflect the free energies of the various transition states. This is an advantage when one discusses the various paths available to the reactant under the specific reaction conditions employed. However, it makes it difficult to compare the results with those obtained for a different reactant, or the same reactant under different conditions such as a change of base or solvent. For example, an increase in the proportion of 1-butene from 2-butyl bromide might be due to an increased rate of 1-butene formation, a decreased rate of 2-butene formation, or an increase or decrease in both at the same time, but to different extents. This can only be resolved by considering orientation and overall rate data.

The Hofmann Rule

First advanced by Hofmann[41,42], this rule states that from some substrates, alkenes having the smallest number of alkyl groups about the double bond are preferred.

Explanations of this behaviour consider the increased acidity of the β-hydrogens by inductive effects from a positively charged leaving group[43,44] and steric effects[45,46].

Transition State: considered to have a carbanion character on the β-carbon with little overall double bond character.

This rule is followed by E2 reactions of trialkyl sulphonium and tetraalkyl ammonium salts[3].

The Saytzev Rule

Noted by Saytzev[47], this rule states that when elimination into different branches of an alkyl group is possible, the preferred product will be the most alkyl substituted alkene. This applies to both the E1 and E2 reactions of alkyl halides, but only to E1 reactions of sulphonium salts.

Transition State: tends to possess sufficient double bond character that they are stabilised by the same factors that stabilise the product alkenes.

1.3.4 Stereochemistry of E1 Reactions

In this mechanism, a slow dissociation step is followed by a rapid deprotonation though the order may be reversed for unusually stable carbocations.

Simple primary alkyl substrates seldom, if ever, react by the E1 mechanism, while it is often difficult to suppress with tertiary substrates even under conditions favouring the E2 mechanism[38].

Nearly all E1 reactions follow the Saytzev rule. Since alkyl substitution almost always increases alkene stability, the rule can be rephrased to predict preference for the thermodynamically more stable product(s)[37c].

As may be expected for a carbocation mechanism, the Saytzev-rule product is preferred regardless of the nature of the leaving group[48]. Preference for the more stable product is generally significantly more marked than in E2 reactions that follow the Saytzev rule[38,49,50], though E2 reactions tend to yield much lower substitution/elimination ratios overall[38].

1.3.5 Solvent Effects in Elimination

As in the case of S_N reactions, solvent effects depend upon the mechanism of reaction. In E2 reactions the base is also often changed with a change of solvent, making if difficult to differentiate whether a change in rate or product ratio is due to a change of base and/or solvent.

In E1 reactions, altering the solvent frequently leads to changes in ion-pairing. This is considered in Section 1.3.6.

In E2 reactions the strength of the base can change when the solvent changes even if the base species remains the same. For example, bases are generally considered to be stronger in DMSO than the corresponding alcohol[51]. DMSO is a weakly solvating medium[52].

In E2 reactions higher trans/cis-alkene ratios are generally observed in dipolar aprotic than in protic solvents[53].

The unimolecular solvolysis of erythro-3-D-2-butyl tosylate in nitrobenzene or acetic acid gave elimination products consistent with a syn elimination[54]. In more polar and basic solvents such as water or ? acetamide the same reaction gave products supporting an anti elimination. These observations have been explained in terms of the relative basicities of the solvent and the tosylate anion. Solvent participation in proton removal is minimal for the weakly basic solvents and the counterion removes the β-proton giving syn elimination. The more basic solvents simulate the base in an E2 reaction and anti elimination results[37d].

1.3.6 Ion-Pairing and Elimination

The discussion of nucleophilic substitution reactions (Section 1.2) indicates ample evidence for ion-pairing in solvolysis reactions. Since elimination reactions are an integral part of such processes, one would expect to see the influence of ion-pairing in elimination rates and product ratios. Relatively little work has gone into exploring this area, however, some aspects are summarised in this section.

In E2 reactions evidence from basicity functions such as of $KOBu_t$ compared with $NaOBu_t$ in t-BuOH[55], reaction rates[56,57] and conductance measurements[41] indicate that extensive ion-pairing of the base is possible in some E2 reactions.

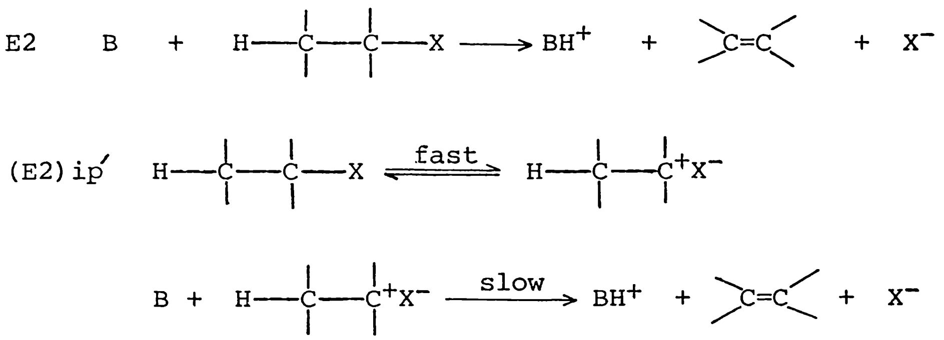
Ion-pairing may affect the amount of syn elimination with some substrates and bases in E2 reactions[37e].

Trans/cis and 2-ene/1-ene ratios are both markedly altered by the presence of base (e.g. $KOBu_t$) ion-pairs in E2 reactions. Reactions in DMSO (which tends to solvate cations and thereby weaken ion-pairs) show very much larger ratios than reactions in alcohol solvents[58-62].

Though it is not clear why ion-pairing should lower the trans/cis ratio to the extent it does in E2 reactions, it may relate to the greater steric requirements of the base ion-pair ($M^+ B^-$), or with the differing electrostatic interactions of the anionic base (B^-) and base ion-pair ($M^+ B^-$) with substrate[37f].

In E1 reactions both intimate and solvent separated ion-pairs may be involved. Under reaction conditions favouring ion-pairing, higher alkene yields are obtained from tertiary halides than when reaction is via the free carbocation mechanism[27]. The t-butyldimethyl sulphonium ion gave much the same proportion of alkene in water, ethanol and acetic acid as it presumably cannot give a reversible ion-pair intermediate[27].

Saunders has reviewed the methods of distinguishing between the E2 and the (E2)ip′ or ion-pair mechanisms[63].



He concludes that there are no definite cases of unequivocal ion-pair mechanism distinguishable from the E2 mechanism.

1.3.7 Leaving Group Effects

The types of leaving group have been mentioned (Section 1.2.5). In addition, dialkyl sulphide (from trialkyl sulphonium salts) and trialkyl ammonia (from tetraalkyl ammonium salts) are frequently encountered.

Changing the leaving group does not affect elimination occurring by the free carbocation mechanism but does have a marked effect upon concerted (E2) eliminations.

In E2 reactions the Hofmann rule has been found to apply to quarternary ammonium and sulphonium salts, while alkyl halides and sulphonate esters adhere to the Saytzev rule. It has been shown that the difference does not arise from the charge type of the leaving group[37g]. There are compounds with neutral leaving groups that follow the Hofmann rule and ones with positive leaving groups that follow the Saytzev rule. This is consistent with the Variable Transition State Theory[37h] which ascribes the major effect of the leaving group to the ease of bond cleavage between the α-carbon and the leaving group. This is not necessarily related to charge type.

The harder the bond is to break, the more negative charge builds up on the β-carbon in the transition state (Hofmann type transition state).

A steric explanation has been advanced by Brown and Wheeler[45]. The two theories have been compared and discussed by Saunders and Cockerill[37i].

Trans/cis Ratio Variations in E2 Reactions

Where 1,2-disubstituted alkenes are possible, the most common pattern of behaviour is for the more reactive leaving groups to give higher trans/cis ratios[37,45,49,58,59]. This is explainable by the variable transition state theory where better leaving groups give a transition state of more alkene-like character (Saytzev-type transition state). In E1 reactions the composition of a mixture of isomeric alkenes may be dependent upon leaving group where the reaction occurs through an ion-pair mechanism[64].

Some leaving groups such as tosylate, may form strong acids in solvolysis solutions. Weak bases such as 2,6-dimethylpyridine ~~2,6-lutidine~~ (dimethyl substituted pyridine) are often added to react with the strong acids thus preventing them from adding to or polymerising product alkenes. The base is itself too weak to take part in E2 reactions of the solvolysis substrate.

1.3.8 Competing Reactions

Generally E1 reactions give substantially lower proportions of elimination than E2 reactions of the same substrate[38].

In both E2-S_N2 and E1-S_N1 competitions the alkene yield increases in the alkyl group order; primary, secondary, tertiary.

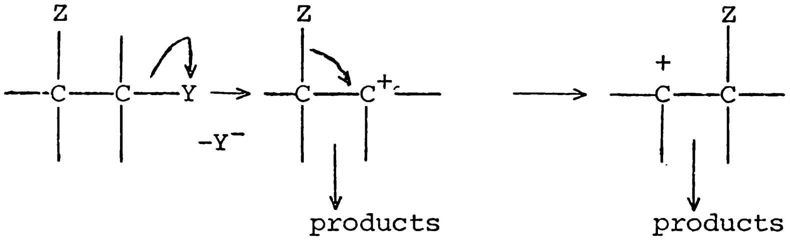
Increasing the temperature[65] and solvent polarity[66] tends to increase alkene yield in both unimolecular and bimolecular reactions.

1.4 Rearrangement Reactions in Solvolysis

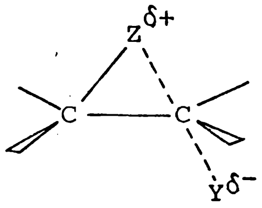
Kirmse[67] has recently published an extensive review of 1,2 rearrangements of carbocations in solution. He has also briefly summarised the chemistry of carbocations in the gas phase and in superacids since both provide information important in the consideration of rearrangements in solution. Rearrangements of higher order have been included in a review by Keating and Skell[17].

This section briefly presents the main aspects of carbocation rearrangement chemistry relevant to this thesis. Specific examples are presented in the course of Chapters 2, 3 and 5. The reader is referred to the review by Kirmse[67] for comprehensive details.

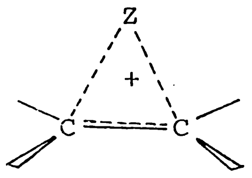
Rearrangement without change in the carbon skeleton: 1,2-hydride shifts frequently occur, generally with the formation of a more stable carbocation e.g. primary to secondary, secondary to tertiary. Rearrangements with a change in the carbon skeleton: shifts of alkyl or aryl groups occur, generally with the formation of a more stable carbocation.



A rearrangement reaction in which the migrating group assists in the departure of the leaving group by acting as an intra-molecular nucleophile is said to involve neighbouring group participation. The reaction proceeds through a bridged transition state[67]. When the reaction rate is increased by this affect, the reaction is said to be anchimerically assisted.



A bridged intermediate containing three partial bonds formed from one pair of delocalised sigma electrons (non-classical carbocation) is often invoked to explain rearrangement product ratios and stereochemistry[67].



Z = an aryl or alkyl group.

Bridged ions may form from neighbouring group assistance or after rate-determining ionization. The concept of bridged ions, first suggested by Wilson[68] has been supported by Winstein[69], Olah[70], and Kirmse[67] but has been strongly repudiated by H. C. Brown[71].

Rearrangements that take place after the formation of a carbocation may do so before it has reached conformational equilibrium. Conformational control leads to a variable degree of inversion at the migration terminus, depending upon the relative rates of rotation and rearrangement[17,67].

Carbocations normally rearrange in the direction of increasing stability, usually typified by primary to secondary and secondary to tertiary carbon transitions. "Degenerate" rearrangements from secondary to secondary carbon are also known in solvolyses[67]. Rearrangements from secondary to primary and tertiary to secondary or primary carbon are reported in nitrous acid deamination reactions[67] but not solvolyses[17].

Stereochemical control of rearrangement reactions may occur through the influence of ion-pairing and micelles (Chapter 5) in addition to conformational control, neighbouring group participation and bridged ions[67].

Chapter Two

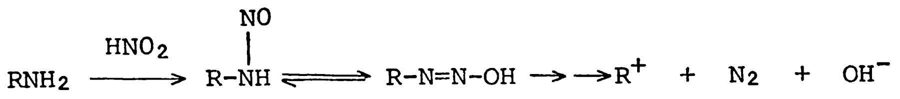
Deamination

2.1 General

In principle, the term "deamination" refers to a broad category of reactions that ultimately give rise to loss of an amino nitrogen[72]. These include numerous reactions yielding diazonium ions (Section 2.2), oxidative and reductive deamination[73] as well as enzyme reactions[74]. Though it has been suggested that the term ought to mean the replacement of an amino group with hydrogen[75], it is used in this thesis in reference to the nitrous acid reaction of amines and related reactions in which a diazonium ion takes part. Products may arise from substitution, elimination and rearrangement pathways.

A systematic nomenclature for substitution reactions was proposed by Bunnett[76] and adopted by Zollinger[77]. Regardless of the mechanism, all reactions in which both nitrogen atoms of an azo or diazo compound are replaced by another group are designated dediazoniations; this term being preceded by the name of the entering group (i.e. hydrolysis as hydroxydediazoniation). This nomenclature is not used here.

This literature survey is particularly concerned with the nitrous acid deamination reaction since it is the subject of the practical work of this thesis.



$$RNH_2 \xrightarrow{HNO_2} R\text{-}\overset{\overset{NO}{|}}{N}H \rightleftharpoons R\text{-}N{=}N\text{-}OH \rightarrow\rightarrow R^+ + N_2 + OH^-$$

While this reaction could conceivably produce a carbocation, other similar reactions where nitrogen is lost make different reactive intermediates accessible[78]. For example, diazeniates (I) yield carbanions in a step of the Wolff-Kishner reduction and related reactions, azo compounds (II) generate radicals[79] and the thermal or photochemical decomposition of diazo compounds (III) generate carbenes.

$$R{-}N{=}N^{-} \longrightarrow R^{-} + N_2 \qquad \text{(I)}$$

$$R{-}N{=}N{-}R \longrightarrow 2R\cdot + N_2 \qquad \text{(II)}$$

$$R_2C{=}N_2 \longrightarrow R_2C\colon + N_2 \qquad \text{(III)}$$

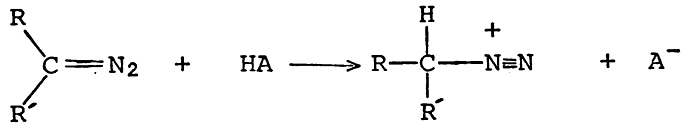
2.2 Types of Deamination Reaction

The nitrous acid deamination is one of a number of reactions in which molecular nitrogen is produced. Some of these reactions appear to have similar mechanisms to the nitrous acid deamination and are discussed in detail in later sections. A brief list of the diazonium ion producing reactions follows.

(a) Reactions of primary amines with nitrous acid[75,78].

Generally the nitrous acid is produced *in situ* by adding a mineral acid to an aqueous or acetic acid solution of sodium or potassium nitrite containing also the primary amine or amine salt.

(b) Reactions of diazo compounds with mineral acid[78,80].



Depending on the substituents, diazo compounds may be protonated under a wide variety of conditions and by various mechanisms[78,81]. Diazoalkanes may be protonated under mildly basic, neutral or acidic conditions[81]. Using the same reaction conditions, this reaction has been shown to yield product compositions identical to the nitrous acid deamination of analogous substrates (Section 2.5).

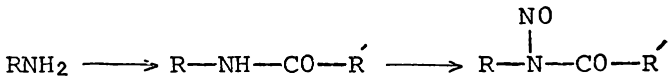
(c) Solvolysis of alkyl diazotates[78,82-86].

$$R{-}N{=}N{-}O^- \xrightarrow{H_2O} R{-}\overset{+}{N}{\equiv}N + 2OH^-$$

The decomposition of alkali salts of diazotic acids are a source of diazonium ions in basic media.

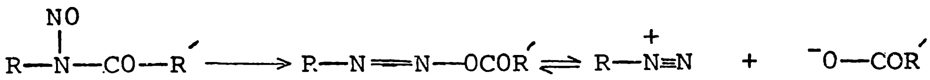
(d) Thermal decomposition of N-alkyl-N-nitrosoamides[87].

The deamination of aliphatic amines via the nitrosoamide is a useful variant of the nitrous acid method because of the wider range of temperatures and solvents that can be used and the greater control over the counterion that is possible[88]. The method involves acylation of the amine and nitrosation of the product amide.



$$RNH_2 \longrightarrow R{-}NH{-}CO{-}R' \longrightarrow R{-}\underset{}{\overset{NO}{N}}{-}CO{-}R'$$

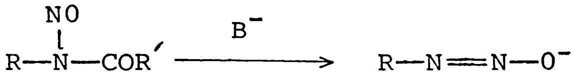
The thermal or acid catalysed reaction of nitrsoamides occurs via a diazonium-carboxylate ion-pair whose fate largely depends upon the solvent[78].



$$R{-}\overset{NO}{N}{-}CO{-}R' \longrightarrow R{-}N{=}N{-}OCOR' \rightleftharpoons R{-}\overset{+}{N}{\equiv}N + {}^-O{-}COR'$$

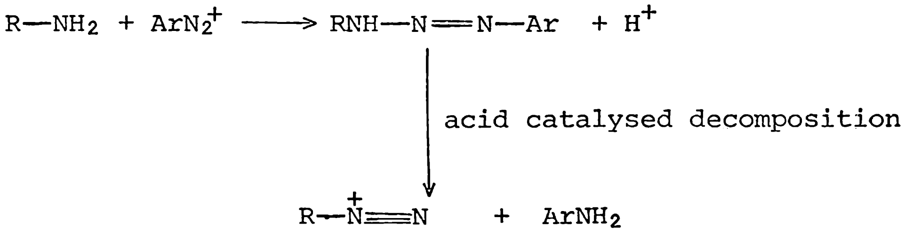
In polar solvents, product distributions similar to those from nitrous acid deamination and diazoalkane protonation are produced[78].

Alkali cleavage of N-nitrosoamides also occurs. The acyl group is removed by the base, forming alkane diazotates[78].



$$R{-}\overset{\displaystyle NO}{\underset{}{N}}{-}COR' \xrightarrow{B^-} R{-}N{=}N{-}O^-$$

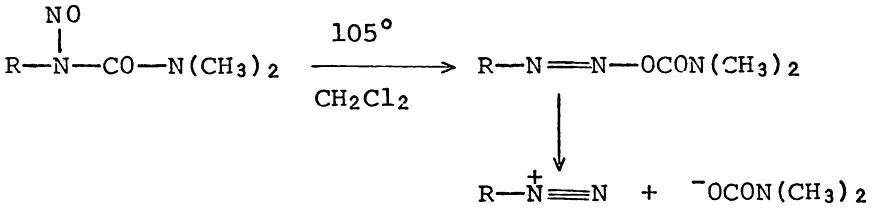
(e) Acid reactions of 3-alkyl-1-aryl triazenes[37,78,89,90].



$$R{-}NH_2 + ArN_2^+ \longrightarrow RNH{-}N{=}N{-}Ar + H^+$$

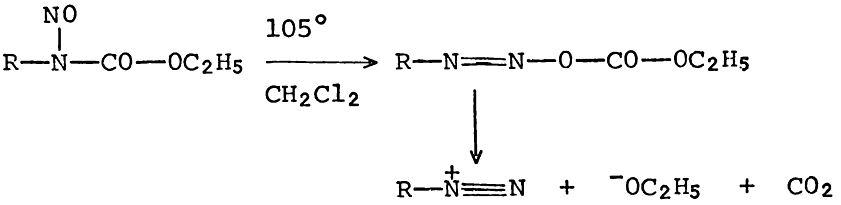
$$\xrightarrow{\text{acid catalysed decomposition}} R{-}\overset{+}{N}{\equiv}N + ArNH_2$$

(f) Thermal decomposition of substituted nitroso-ureas[91,92].



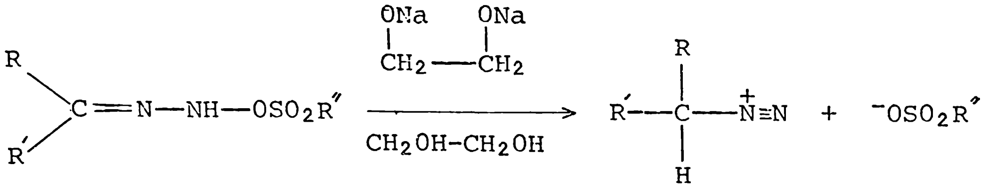
$$R{-}\overset{\displaystyle NO}{N}{-}CO{-}N(CH_3)_2 \xrightarrow[CH_2Cl_2]{105^\circ} R{-}N{=}N{-}OCON(CH_3)_2 \longrightarrow R{-}\overset{+}{N}{\equiv}N + {}^-OCON(CH_3)_2$$

(g) Thermal decomposition of substituted nitrosocarbamates[88,93].



$$R{-}\overset{\displaystyle NO}{N}{-}CO{-}OC_2H_5 \xrightarrow[CH_2Cl_2]{105^\circ} R{-}N{=}N{-}O{-}CO{-}OC_2H_5 \longrightarrow R{-}\overset{+}{N}{\equiv}N + {}^-OC_2H_5 + CO_2$$

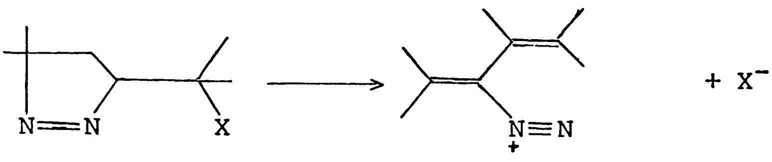
(h) Bamford-Stevens Reaction[92,94].



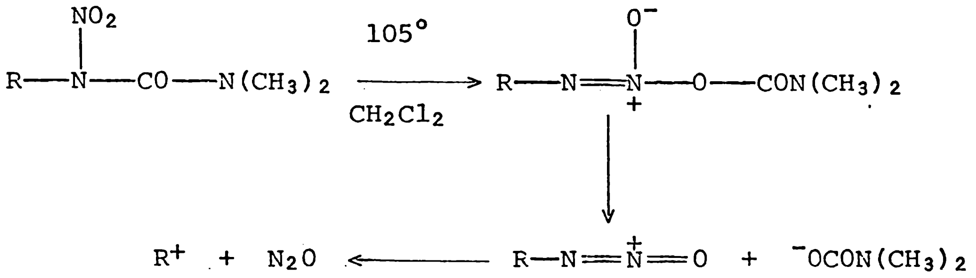
~~toluene-p~~-sulphonyl approx. 200°C

hydrazone

(i) Photolysis of pyrazolenine esters[80].



In addition to the nitroso (-NO) derivatives (d,f,g) their nitro ($-NO_2$) analogs have also been studied[88]. e.g. the decomposition of a nitro-urea,



In these compounds the leaving group is nitrous oxide. White and coworkers[95,96] have found that the same product distribution arises from analogous substrates when nitrogen and nitrous oxide are the leaving groups.

2.3 Deamination with Nitrous Acid

The deamination of simple aliphatic primary amines with nitrous acid, generally in water, acetic acid or aqueous acetic acid solutions has been reviewed on numerous occasions[17,67,75,78,80,81,87,97,99,100,101]. This section briefly summarises the main aspects of the topic.

Many species are present in acidified nitrite solution with the composition being dependent upon acidity[102]. The dominant nitrosating agent and rate determining step may therefore change with pH.

$$\begin{tikzcd}
2H^+(aq) \quad + \quad 2NO_2^-(aq) \arrow[r, leftrightharpoons] & 2HNO_2(aq) \arrow[r, leftrightharpoons] \arrow[d, leftrightharpoons, "H^+"] & N_2O_3(aq) \quad + \quad H_2O \\
& 2\;H_2NO_2^+(aq) \arrow[r, leftrightharpoons] & 2\;NO^+(aq) \quad + \quad 2\;H_2O
\end{tikzcd}$$

The suggested order of reactivity of the nitrosating agents is[97,102];

$NO^+ > NO{\cdot}OH_2^+ > N_2O_3 > NO{\cdot}OH$

Low Acidities: $[H^+] < 10^{-2}M$

All the nitrous acid deaminations referred to in this thesis fall into this category.

In the absence of catalysts such as halide ions (Chapter 5), the nitrosating agent is nitrous anhydride (N_2O_3, dinitrogen trioxide)[100].

$$H^+(aq) + NO_2^-(aq) \rightleftharpoons HNO_2(aq)$$

$$2\,HNO_2(aq) \rightleftharpoons N_2O_3(aq) + H_2O$$

$$RNH_2(aq) + N_2O_3(aq) \xrightarrow{slow} R\overset{+}{N}H_2NO(aq) + NO_2^-(aq)$$

$$R\overset{+}{N}H_2NO(aq) \rightleftharpoons RNHNO(aq) + H^+(aq)$$

$$v = k\,[RNH_2]\,[HNO_2]^2$$

The reaction has to be performed in a relatively narrow pH range (pH 3-5 for alkylamines) since both the free amine and nitrous acid must be present

Intermediate Acidities: $[H^+]$ $10^{-2}$to 10^{-1}M

While the reaction is second order in nitrous acid at low acidities, at intermediate acidities it is first order in nitrous acid. The nitrous acidium ion ($H_2NO_2^+$) is the nitrosating agent[97].

$$HNO_2(aq) + H^+(aq) \overset{fast}{\rightleftharpoons} H_2NO_2^+(aq)$$

$$H_2NO_2^+(aq) + RNH_2(aq) \xrightarrow{slow} R\overset{+}{N}H_2NO(aq) + H_2O$$

$$R\overset{+}{N}H_2NO(aq) \rightleftharpoons RNHNO(aq) + H^+(aq)$$

$$v = k\,[RNH_2]\,[HNO_2][H^+]$$

Moderate Acidities $[H^+]$ 0.1 - 6.5M

At these acidities, the nitrosating agent may be both the nitrous acidium ion and the nitrosonium ion (NO^+). Reaction may occurwith both the free amine (with $H_2NO_2^+$) and the protonated form (with NO^+)[97].

$$H^+(aq) + HNO_2(aq) \rightleftharpoons H_2ONO^+(aq) \rightleftharpoons H_2O + NO^+(aq)$$

Concentrated Acids

In most concentrated acids the reactive species is the nitrosonium ion (NO^+) and proton loss after nitrosation is rate limiting rather than the nitrosation step. The process is shown for aromatic amines[100].

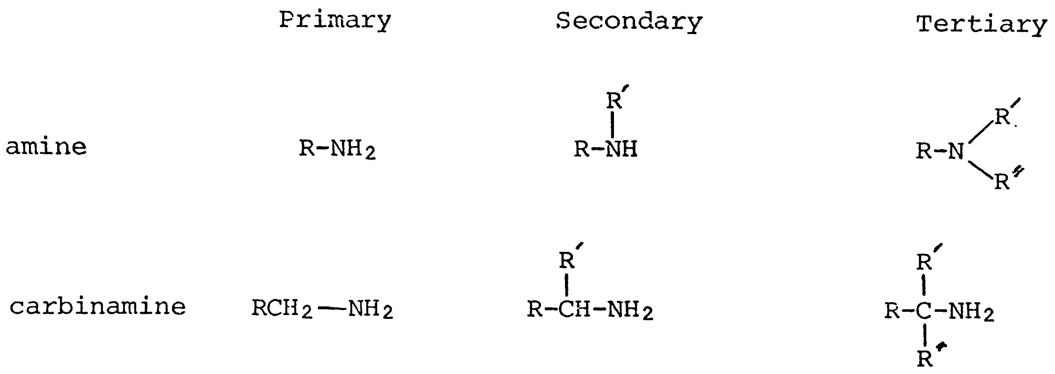
$$NO^+ + Ar\overset{+}{N}H_3 \xrightleftharpoons{\text{fast}} Ar\overset{+}{N}H_2NO + H^+$$

$$Ar\overset{+}{N}H_2NO + B: \xrightleftharpoons{\text{slow}} ArNHNO + BH^+$$

In catalysed nitrous acid reactions (Chapter 4) other nitrosating agents operate such as nitrosyl halides (NOCl, NOBr) and nitrosyl thiocyanate (NOSCN). Deaminations in solvents of low polarity may use a variety of nitrosating agents (alkyl nitrites and nitrosonium salts)[78,81] while gaseous nitrous anhydride (N_2O_3) and nitrogen tetroxide (N_2O_4) have been employed with aqueous systems[103-105].

Deamination with nitrous acid occurs only with primary amines. Secondary amines generally stop at the nitrosoamine because of the inability of the latter to tautomerise to the diazotic acid[103-105]. Tertiary amines generally do not react with nitrous acid though cleavage reactions to a secondary amine and aldehyde are reported[106,107].

A distinction should be made here between amines and carbinamines. Primary, secondary and tertiary amines refer to the nature of the substituents on the nitrogen while the same divisions of carbinamines refer to the nature of the alkyl group of primary amines.



Aromatic amines react rapidly, often producing stable diazonium salts. Reactions of these substrates are discussed briefly in Section 2.7.

Primary, aliphatic systems lack the stabilisation present in aromatic diazonium ions so products arise from dissociation beyond the diazonium ion.

$$RNH_2 + HNO_2 \longrightarrow \longrightarrow R—N{=}N—OH$$

$$R—N{=}N—OH \rightleftharpoons R—\overset{+}{N}{\equiv}N\ {}^{-}OH \longrightarrow R^{+}\ N{\equiv}N\ {}^{-}OH \longrightarrow R^{+} + N_2 + OH^{-}$$

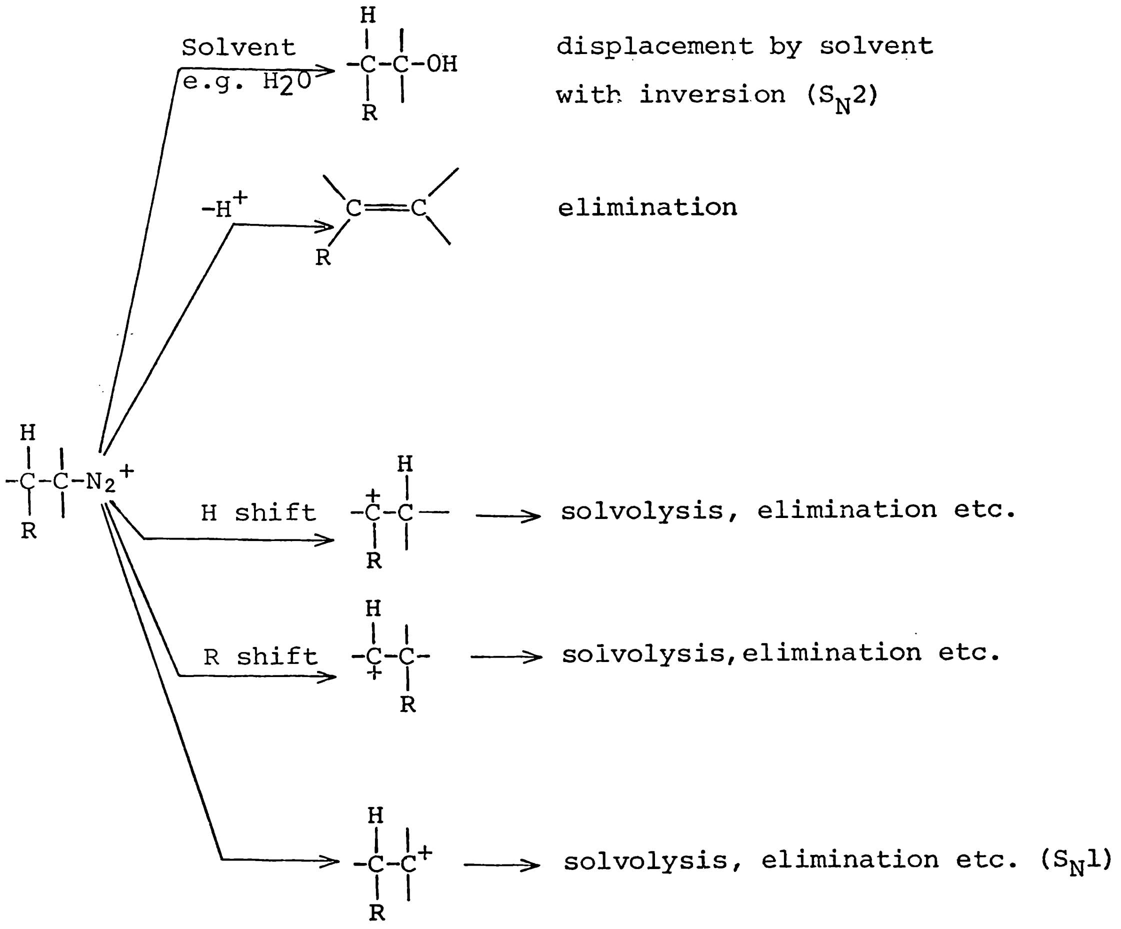
The diazotic acid (RNNOH) can dissociate to the ionic species shown above before product formation. The extent of dissociation depends upon the alkyl group structure and the reaction conditions.

Since nitrosation is the rate determining step, evidence for the nature of the product precursor must come from product ratios and stereochemistry rather than kinetic studies. This is in marked contrast to the usefulness of kinetic studies in solvolysis and nucleophilic substitution reactions (Chapter 1).

2.4 Products From the Nitrous Acid Deamination

Nucleophilic substitution, elimination and rearrangement all occur in deamination reactions. Frequently the latter two are more prominent in deamination than analogous solvolysis, this is discussed in Chapter 3.

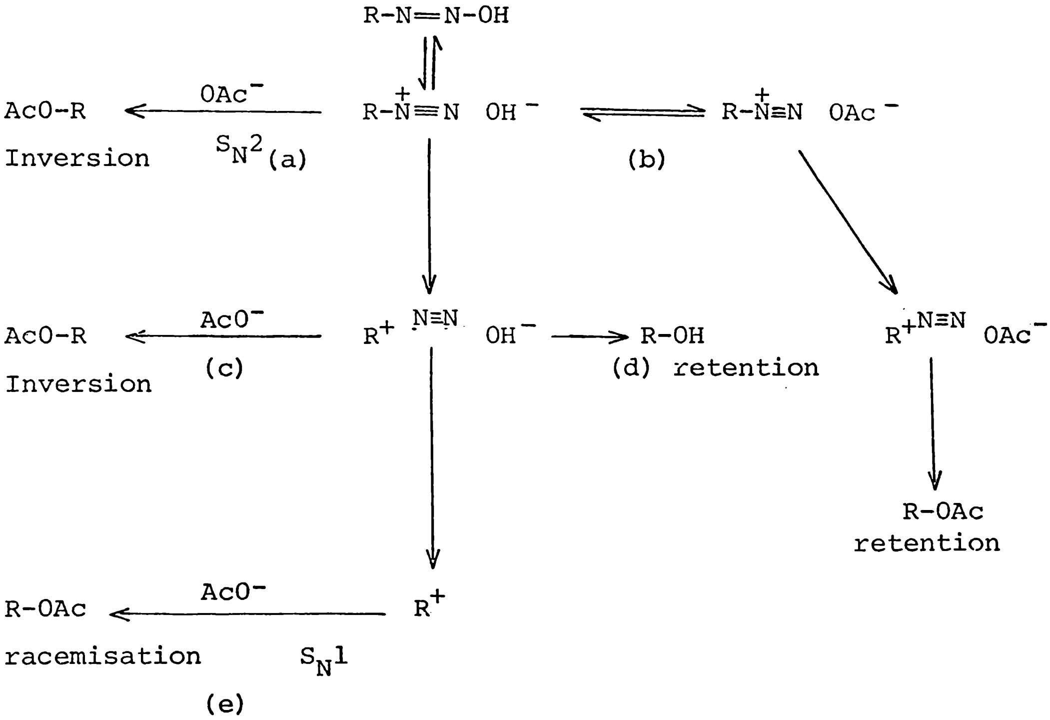
Product forming pathways in deamination have been reviewed[37,75,78,87,101]; a brief summary follows.



Competing Reactions in Product Formation
from an Acyclic Diazonium Ion[101]

2.4.1 Nucleophilic Substitution

Ion-pairing (Chapter 3) plays an important part in any consideration of substitution pathways in deamination. A great deal of information has come from the N-nitrosoamide studies of White and Woodcock[87]. In the nitrous acid deamination, a number of substitution pathways exist. The scheme below shows the pathways for reaction of an optically active substrate in acetic acid solvent.



(a) Backside attack by solvent on the diazonium ion-pair leading to inverted product.

(b) Front-side solvent exchange with the counterion which may lead to ion-pair collapse and a product with retained configuration.

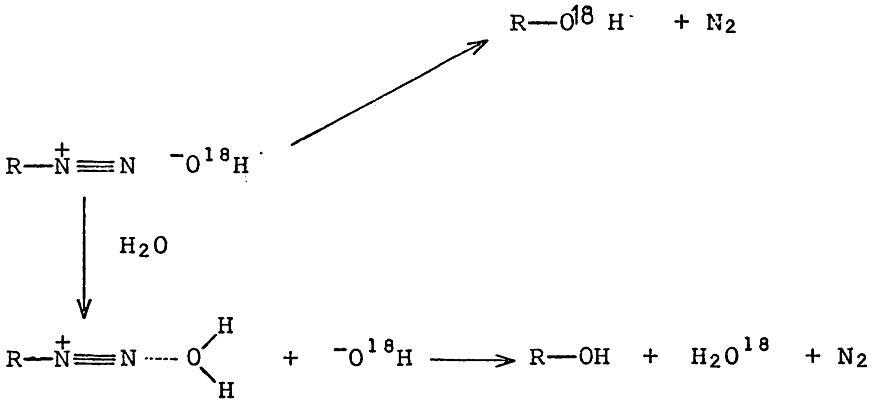
(c) Backside attack by solvent on the cation of the nitrogen separated ion-pair. Rotation of the cation before substitution may lead to product with less inversion than pathway (a).

(d) Ion-pair collapse giving alcohol with retention.

(e) Substitution via the fully dissociated cation giving racemic product.

The pathway dominant in any given system depends upon the nature of the alkyl group and reaction conditions. Generally primary substrates give substitution with inversion while tertiary substrates give racemic products. Secondary substrates vary widely between these extremes.

In nitrous acid deamination, most of the substitution occurs by the nucleophilic activity of the solvent. The hydroxide counterion in the diazonium ion-pair is generally replaced by a solvent molecule so it makes only a small contribution to the substitution with the formation of an alcohol. When water is the solvent, alcohol is the major substitution product. Minor substitution products may form from other nucleophiles present, such as nitrite[108]. The alcohol is formed by two pathways;



Boutle and Bunton[109] used sodium nitrite labelled with oxygen-18 in the aqueous deamination of cyclohexylamine. The results indicated a 10% incorporation of the labelled oxygen[80] showing that most of the alcohol is formed by solvolysis. Moss[82-86] has carried out similar studies using H_2O^{18} and diazotate substrates.

When glacial acetic acid is the solvent, the alkyl acetate is the major substitution product with a small percentage of alcohol being formed by the ion-pair collapse.

In aqueous acetic acid solvents a mixture of alkyl acetate and alcohol is found with the composition depending upon the solvent mixture[110].

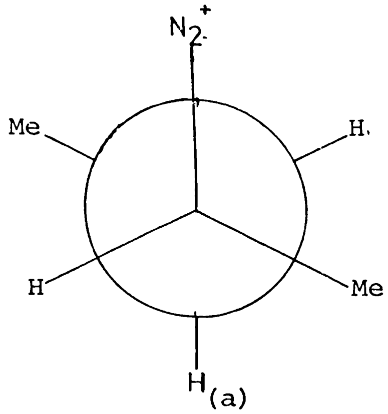
2.4.2 Elimination

Many nitrous acid deaminations have been observed to give elimination product ratios substantially different from similar solvolyses (Chapter 3). Not only does the overall proportion of elimination differ but also the ratios of positional and geometrical isomers[37].

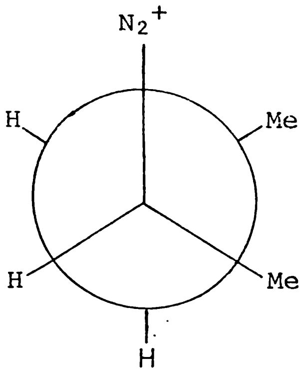
The different alkene compositions suggest that the elimination precursor in the nitrous acid deamination is substantially different from that involved in the solvolysis.

A concerted elimination from the diazonium ion was proposed by Streitwieser[101]. Conformational effects would be important since concerted eliminations generally result in the removal of hydrogens antiperiplanar ~~trans~~ to the leaving group. Decomposition of the diazonium ion is thought to be of comparable rate to C—C bond rotation.

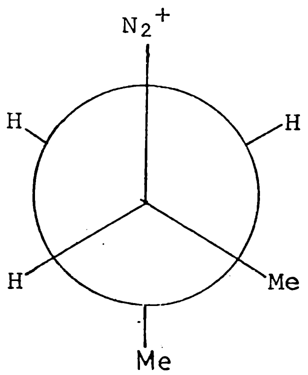
Hence for 2-butylamine, three conformations are important; (a), (b), (c)[101].



(a)



(b)



(c)

(b) is expected to be less populated than (a) or (c). Only (a) and (b) can eliminate an ~~trans-3~~ antiperiplanar hydrogen; this is consistent with the observed results where cis-2-butene (from (b)) is formed to a lesser extent than trans-2-butene (from (a)).

Few, if any, deaminations are reported where elimination solely from the free carbocation can be certain. If this occurs it may be expected that the elimination mechanism would be similar to that described for E1 reactions in Solvolyses (Chapter 1.3.1-1.3.7). An investigation of this subject is the practical work of this thesis.

2.4.3 Rearrangement

Rearrangement mechanisms have been described briefly in Chapter 1.4. Rearrangement reactions in deamination have been extensively reviewed[17,37,67,75,80,87,100]. Deaminations characteristically produce not only a greater proportion of rearrangement products than solvolysis, but also a different ratio of rearrangement products (Chapter 3).

Cyclopropane intermediates are frequently invoked by Kirmse to account for product ratios from aqueous nitrous acid deaminations[67]. These intermediates have also been implicated in the aqueous nitrous acid deamination of γ-butylamine-1-^{14}C [111].

2.5 Counterion Effects in Deamination

In solvolysis reactions the leaving group generally becomes the counterion except in the solvolysis of sulphonium and quarternary ammonium salts. In reactions where a diazonium ion is produced, nitrogen is the leaving group in all cases and the counter ion, X^-, is dependent upon the mode of diazonium ion formation and solvent used.

RY   Y = leaving group e.g. Halide, sulphonyl ester.

RYX   e.g. R Me_2SI

Me_2S = leaving group.

I^- = counter ion.

R—N=N—X   N≡N = leaving group.

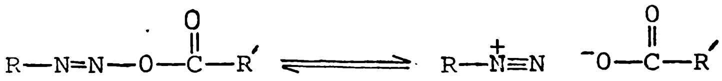
RYX X^- = counter ion.

Nitrous acid deaminations give diazotic acid then a diazonium ion-pair dissociation.

$$R{-}N{=}N{-}OH \rightleftharpoons R{-}\overset{+}{N}{\equiv}N \quad OH^-$$

counter ion = hydroxide ion.

The thermal decomposition of N-alkyl-N-nitrosoamides give diazo esters then a diazonium ion and carboxylate counterion.



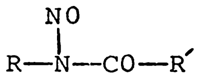
$$R{-}N{=}N{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R' \rightleftharpoons R{-}\overset{+}{N}{\equiv}N \quad {}^-O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R'$$

The reaction of diazo compounds with mineral acid and the acid catalysed decomposition of triazenes produce diazonium ions with counterions dependent upon the acid and solvent used.

The solvolysis of alkyl diazotates also yieldsdiazotic acid.

Many instances are reported in the literature where alkyl diazonium ions are generated by a number of the above methods and the product distributions compared. These results have led to conclusions about the similarities of the mechanisms involved, and also the nature of the product precursor, in cases of nitrous acid deamination. This section briefly surveys such comparisons.

Nitrosoamide:



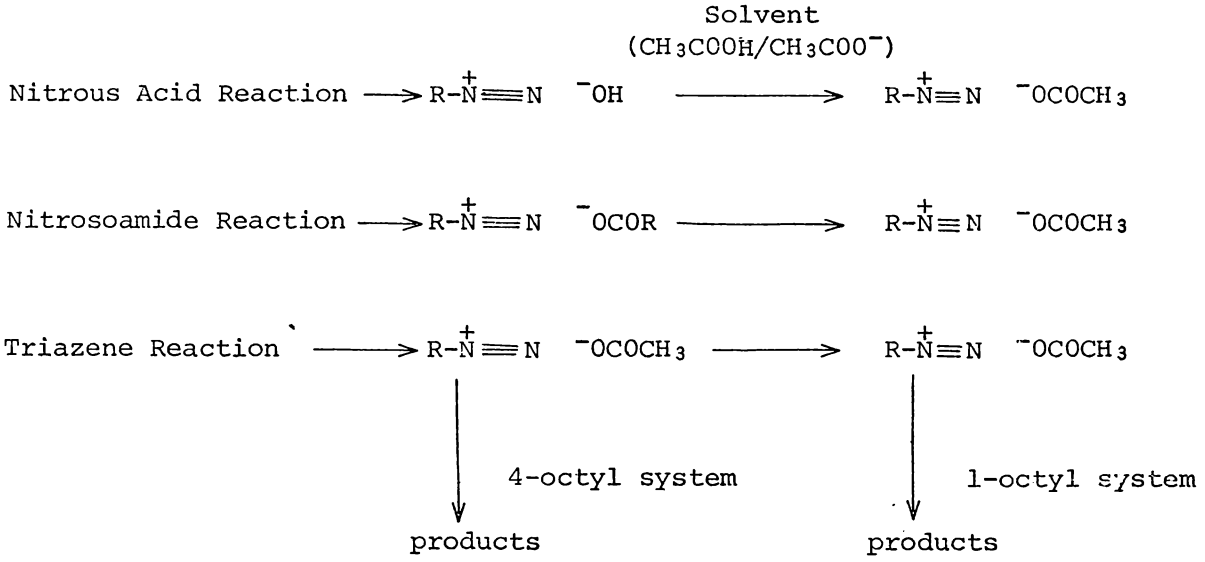
$$R{-}\overset{\displaystyle NO}{\overset{|}{N}}{-}CO{-}R'$$

In the reaction of N-nitrosoamides, when R is a primary group, products have been shown to arise from a diazo intermediate[37k]. However, in polar solvents, nitrosoamides with secondary or tertiary R groups do not decompose via diazo alkanes (Chapter 3.3.8) so are more comparable with nitrous acid deaminations[80].

The deamination of 1-aminooctane with nitrous acid, by the nitrosoamide reaction and by the triazene reaction (using aniline and p-nitroaniline as sources of diazonium ion) all in acetic acid solvent, has been studied by Whiting and coworkers[90]. The product proportions were almost the same for all three methods. However, when the same series of reactions was carried out with the 4-octyl system the results varied markedly and gave substantial yields of the products of ion-pair collapse.

These results may reflect a relatively long lived diazonium ion in reactions of the 1-octyl system where the counterions initially present ($^-$O-COR in nitrosoamide reaction, $^-$OH in nitrous acid reaction) are replaced by a solvent molecule or lyate ion (CH_3COO^-). The product precursors are therefore the same in each reaction.

The 4-octyl system may produce a relatively short lived diazonium ion. Subsequent product formation may therefore take place under the influence of the counterions that have not had time to be replaced by a solvent nucleophile.



Further examples of similar product ratios and stereochemistries from secondary and tertiary systems subjected to nitrous acid and nitrosoamide reactions are reviewed by White and Woodcock[87].

In making conclusions as to whether similar mechanisms are involved in these diazonium ion generating reactions it is clear that different product ratios do not necessarily indicate different product forming mechanisms. The same mechanism may prevail but the initial counter ion in the diazonium ion-pair may exert a strong influence. Similar product ratios would seem to indicate similar mechanisms, in which the counter ion has little influence or is exchanged by a solvent nucleophile prior to product formation.

2.6 Solvent Effects in Deamination

The effect of changing solvent composition on the substitution products has been mentioned (Section 2.4) with respect to glacial acetic acid, aqueous acetic acid, water. In highly polar media, by analogy with solvolytic reactions, ion-pairs should play a very small role (Chapter 1.2.5). The extent of ion-pair involvement will alter the stereochemistry of the substitution products (Chapter 1).

Rearrangement decreases as the solvent polarity decreases. This behaviour has been observed in numerous nitrous acid and nitrosoamide reactions, many of which are summarised by Keating and Skell[17].

Solvent effects on elimination are summarised in Chapter 1. In deamination the diazonium ion may influence the elimination pattern by conformational control particularly in those systems (primary carbinamine) where this intermediate is important. Increased ion-pairing in lower polarity solvents may enhance this effect.

2.7 Aromatic Diazonium Ions

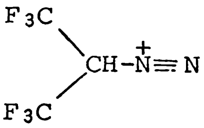
The chemistry of aromatic diazonium compounds has been comprehensively reviewed in a recent series edited by Patai[112]. Zollinger has reviewed the effect of solvents on reactions of aromatic diazonium ions[77]. A few basic points are noted here for comparison with aliphatic diazonium ions.

There is a marked difference in stability between aromatic and aliphatic diazonium ions. Many aromatic diazonium salts have been isolated since being first prepared by Griess last century[113].

In contrast, only few aliphatic diazonium ions are detectable even by spectroscopy. These include the 2,2,2-trifluoroethanediazonium ion[114] (IV), the hexafluoropropane diazonium ion[115] (V) and the 2-oxocyclohexane diazonium ion[116] (VI).

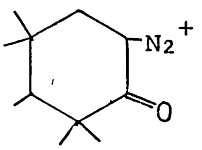
$F_3C{-}CH_2{-}\overset{+}{N}{\equiv}N$

(IV)



$(F_3C)_2CH{-}\overset{+}{N}{\equiv}N$

(V)



(VI)

These species contain powerfully electron-withdrawing substituents which destabilise the corresponding carbocation and oppose unimolecular decomposition.

Generally the existence of alkyl diazonium ions as an intermediate in nitrous acid deaminations is based on rate data and product analysis studies[100,117].

The greater ease with which the diazonium nitrogen is released from an (sp^3) carbon as compared with an (sp^2) (aryl) carbon atom can be explained by several factors[78];

(a) Aromatic diazonium ions are stabilised by interaction between the Π-systems of the rings and the diazonium group.

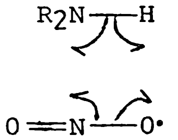
(b) The high energy of aryl cations impedes the expulsion of nitrogen from aromatic diazonium ions.

(e) The difficult nature of bimolecular substitution of arenes stabilises arenediazonium ions relative to their aliphatic analog.

2.8 Nitrosation in Basic Solutions

In aqueous nitrous acid deaminations with low acidities (Section 2.3) the nitrosating agent is nitrous anhydride (N_2O_3). This nitrosating agent forms from nitrous acid so acidic conditions are required where a significant proportion of the total nitrite is present as undissociated nitrous acid (pH < 5).

However, nitrosation of a range of amines using gaseous nitrous anhydride (N_2O_3) and nitrogen tetroxide (N_2O_4) has been accomplished in aqueous solutions from pH 7 to 14 at 25°C[103-105]. Various aromatic and secondary amines were nitrosated yielding diazonium ions and nitrosoamines respectively. These reactions were observed to be fast, insensitive to amine basicity and not inhibited by hydroxide ion. A radical mechanism was considered likely.



Nitrous acid reactions have been catalysed by aldehydes and ketones (see Chapter 4) resulting in an intramolecular nitrosation mechanism competing with the NOX nitrosation. The intramolecular mechanism uses unprotonated nitrite so occurs readily in basic conditions.

The nitrosonium salt, disodium pentacyanonitrosylferrate ("sodium nitroprusside") transfers its nitroso group to amines at pH 9 - 11 but decomposes at higher pH values[118]. Amines nitrosated by this method include; benzylamine, allylamine, cyclohexylamine, 2-aminooctane, 1-aminobutane and diethylamine.

Other sources of diazonium ions in basic media include the aqueous decomposition of diazotates ($R\text{-}N = NO^{-}M^{+}$)[72,82-86] and a photochemical variation of the Bamford-Stevens reaction[119], which involves the photolysis of sulfonyl hydrazones or their anions ($R_2C{=}N\text{-}\bar{N}\text{-}SO_2R$).

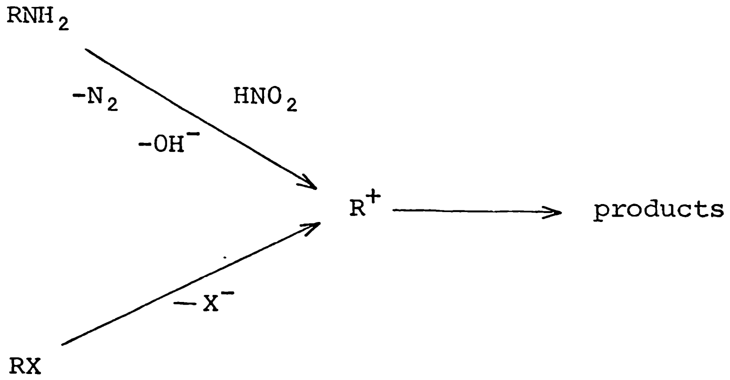
Chapter Three

The Mechanism of Nitrous Acid Deamination

- A Comparison of Solvolysis and Deamination -

3.1 General

A simple approach to deamination and solvolysis would indicate the involvement of a common intermediate. Therefore one might expect the same product ratios and stereochemistry in both reactions.



It has been abundantly apparent however, that analogous deaminations and solvolyses of primary and secondary alkyl substrates, under similar reaction conditions, do not generally give similar product ratios and stereochemistry. Suggestions forwarded to account for these observations included the belief that a carbocation is produced in both cases, but that from deamination differed from the solvolysis cation in some way, perhaps in its solvation, energy, or structural conformations. Relatively compressed energy profiles for product forming pathways from the deamination cation have also been suggested. A further suggestion that perhaps a common carbocation is not involved arose with Streitwieser's[101] hypothesis that the diazonium ion is the precursor to the deamination products. More recently, applications of the ion-pairing concept to solvolysis and deamination have accounted for many of the observed differences.

Since this subject has already received considerable attention from reviewers (Chapter 2.3) the following sections give only a selection of examples of some different results and summarise the suggested explanations in more detail.

3.2 Comparison of Deamination and Solvolysis Product Ratios

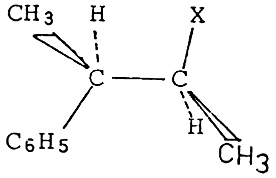
3.2.1 Rearrangement

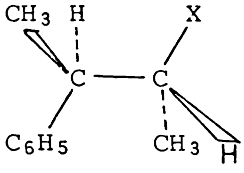
The most marked differences between deamination and solvolysis occur in the rearrangement product ratios. More rearrangement is observed in deamination and also a markedly different migration pattern is observed. In solvolysis reactions rearrangement is generally only encountered in the presence of non-nucleophilic reagents such as Friedel-Crafts catalysts ($AlCl_3$) where substitution is slower than rearrangement, or in poorly ionising solvents of low nucleophilicity such as glacial acetic acid[37l]. In glacial acetic acid, ionisation of the C—X bond is aided by migration of an alkyl or aryl group or a hydride transfer from the adjacent β-carbon.

The yield of isopropyl acetate in the acetolysis of i-~~n~~-propyl tosylate is 2.5% while the nitrous acid deamination of i-~~n~~-propyl amine in acetic acid produces 32% isopropyl ester[101].

Marked differences in the migratory aptitudes of phenyl and methyl groups during deamination and tosylate acetolysis of the 3-phenyl-2-butyl system have been noted by Cram[120] and discussed by Saunders and Cockerill[37m]. The following table compiled from Cram's work shows the rearrangement patterns leading to the product alcohols.

Source of the Product Alcohols From Reactions
of 3-Phenyl-2-Butyl Systems[120]



	Phenyl Shift	Methyl Shift	Hydride Shift
(threo-)			
$X = -NH_2$	44%	32%	24%
$X = -OTs$	89%	0%	11%
 (erythro-)			
$X = -NH_2$	74%	6%	20%
$X = -OTs$	94%	0%	6%

The deamination of 3-methyl-2-butylamine involves both hydride and methyl shift[121] while the solvolysis of the tosylate proceeds almost exclusively with hydride shift[122].

Recently Kirmse has examined the 3-methyl-2-phenyl-1-butyl system and obtained evidence for rearrangements via bridged carbocations[123]. Solvolysis of the tosylate gave only phenyl migration while the nitrous acid deamination gave products from phenyl, isopropyl and hydride shifts.

Rearrangements involving hydride, alkyl and aryl migrations in aliphatic acyclic and norbornyl systems have been studied and reviewed by Collins[75].

The results of solvolyses and deaminations of numerous butyl and pentyl systems have been summarised by Keating and Skell[17].

3.2.2 Elimination

Ratios of elimination products vary markedly between deamination and solvolysis. Deaminations of 2-aminoalkane systems tend to produce less of the highly substituted 2-ene than the corresponding solvolyses but tend to produce proportionately more 1-ene.

Although deamination cations are not much influenced by the relative stability of the incipient alkene when eliminating a proton, they are much more selective than solvolysis cations in giving trans rather than cis isomers[17]. The trans/cis ratios have been linked to the ground state populations of conformations (Chapter 2.4.2).

Keating and Skell[17] have summarised the results of solvolyses and nitrous acid deaminations for the following systems; 1-propyl, 1- and 2-butyl, 2-methyl-1-propyl (iso-butyl), 1- and 2-pentyl, 3-methyl-1-butyl (iso-pentyl), 3-methyl-2-butyl, 2-methyl-1-butyl, 2-methyl-2-butyl (tert -pentyl). Frequently different solvents have been used for deamination and solvolysis so caution must be exercised when making comparisons.

3.3 Suggested Deamination Mechanisms

The suggested mechanisms for the decomposition of diazonium ions aim to explain the different product distributions from deamination and solvolysis. The deamination reactions of primary and secondary carbinamines was first thought to proceed via a carbocation but the range of products was ~~soon~~ seen to exceed that of the postulated carbocation generated by the solvolysis of alkyl esters and halides.

$$R-\overset{+}{N}\equiv N \longrightarrow R^{+} + N_2 \longrightarrow \text{products}$$

3.3.1 The "Hot" Carbocation

To explain the experimental observations it was suggested that elimination of nitrogen from aliphatic diazonium ions should lead to high energy, "hot", carbocations[124]. The description means an intermediate still possessing excess energy arising from its exothermic mode of formation and not in thermal equilibrium with its environment[78]. Such an ion is supposed to have sufficient energy to cross energy barriers which blocked some reactions of the energetically "normal" species.

3.3.2 Compressed Energy Profiles

Huisgen[125] suggested that in the decomposition of diazonium ions there is a compression of the energy profile relative to the solvolysis reactions, leading to smaller differences in the energy of activation for several possible processes. This suggestion can be regarded as replacing a "high energy reactant" by a "low energy reaction". Support for this concept comes from Collins[75] who has studied rearrangement patterns in a number of aryl-substituted aliphatic systems and the cyclic norbornyl systems.

3.3.3 The Diazonium Ion as Product Precursor

The "hot" carbocation hypothesis was challenged by Streitwieser[101] who considered that the diazonium ion is the product precursor in deaminations. This would appear to be the case in reactions of primary carbinamines. The primary carbocation has yet to be demonstrated to take part in solvolyses so it seems reasonable that it will be formed slowly, if at all, in diazonium ion decompositions[99]. However, in the study of secondary acyclic and cyclic systems, Collins[75] concludes that the diazonium ion is not the product precursor and hence responsible for the rearrangement patterns observed.

3.3.4 Conformational Effects

The populations of ground state conformations of diazonium ions and subsequent carbocations have been successfully used as explanations for elimination trans/cis and 2-ene/1-ene ratios and migration ratios in rearrangements during nitrous acid deaminations. In a recent review, Kirmse includes a summary of this topic[67]. Though conformational arguments are often successful in these areas, the overall amounts of elimination and rearrangement have been tied to the lower activation energy of diazonium ion decomposition.

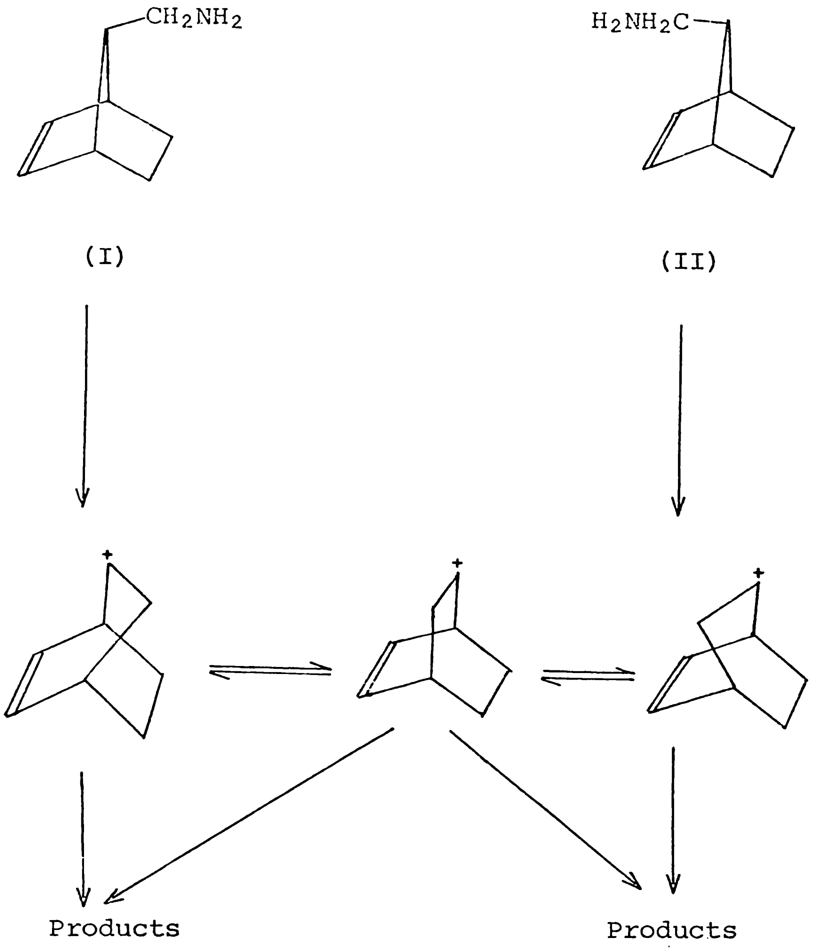
Differences in Transition State Structure Versus the "Hot" Carbocation

Though deamination generally gives product distributions markedly different to solvolysis, this is not always the case (Section 3.4). In the light of such findings Kirmse[78] suggests that the use of the term "hot" in connection with the intermediates of diazonium ion decomposition should be abandoned. He further suggests that energy differences are less significant than differences in the structure of the transition states and intermediates of the various cation-forming reactions. Diazonium ion decomposition requires far less assistance from neighbouring groups or external nucleophiles than the dissociation of alkyl halides or sulphonic esters. Ion-pairing and micelle formation need to be considered as well as neighbouring group effects.

3.3.5 Ion-Pairs

Ion-pairing in deaminations has been reviewed in detail by numerous authors[37,78,80,87,99,121], and is now well established in this type of reaction. The stereochemistry of substitution products is well explained by the influence of the counterion within an ion-pair (Chapters 1 and 2). The influence of the counterion has even been maintained after several Wagner-Meerwein shifts in some norbornyl systems[75].

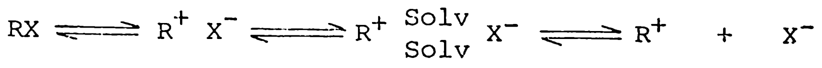
In considering the difference between solvolysis and deamination Berson[126] noted a "transference of unusual behaviour" from amine to intermediate and labelled this phenomenon a "Memory Effect". This originally referred to the "twisted ions" obtained in the deaminations of (I) and (II).



Collins has reconsidered Berson's argument and adequately explained the experimental results in terms of stereochemical control by ion-pairing[127].

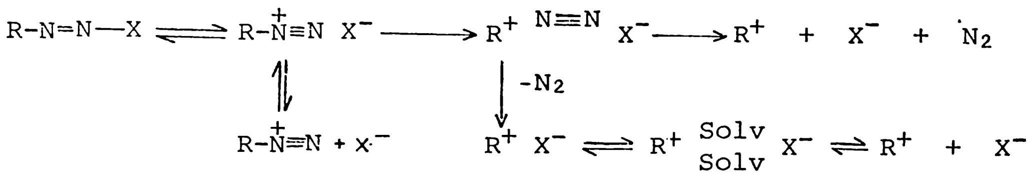
Unlike ion-pairing in most solvolyses, the carbocation and counterion formed in deamination are, initially at least, separated by a neutral molecule. The nitrogen separated ion-pair (or inert gas separated ion-pair) is believed to be enclosed within a solvent cage[99]. It has been shown that the nitrogen may be lost with little disruption of the ion-pair[80]

Solvolysis



$$RX \rightleftharpoons R^+ X^- \rightleftharpoons R^+ \begin{matrix}\text{Solv}\\ \text{Solv}\end{matrix} X^- \rightleftharpoons R^+ + X^-$$

Deamination



Products may arise from an S_N1 type displacement of nitrogen from the diazonium ion or S_N1 reaction from the carbocation as well as the nitrogen separated ion-pair. Products from the intimate and solvent separated ion-pairs shown may also be possible under some circumstances. Heterolysis of the C—N bond is likely to be irreversible, so capture of nitrogen by the carbocation is unlikely to be important[128]. A reversible C—N fission has been reported with arenediazonium ions in trifluoroethanol but this was under 300 atm of labelled nitrogen[129].

The isolation of alcoholic products, with predominant retention of configuration, from nitrous acid deaminations in glacial acetic acid[37,99], product stereochemistries in alicyclic deaminations[37,99] and nitrosoamide reactions[87] as well as numerous isotope labelling studies[80,87,126] provide conclusive evidence for ion-pairs in deamination. Moss[82-84,130] has reported detailed studies of ion-pairing in alkane diazotate reactions (using H_2O^{18})

while le Noble *et al.* report the affect of pressure (up to about 5000 atm) on the stereochemistry of ion-pair collapse in the N-nitrosoamide deamination[131].

3.3.6 Micelle Formation

The formation and affect of alkyl ammonium micelles on deaminations of appropriate substrates is discussed in Chapter 5. As one might expect, a micelle markedly alters the environment of a reacting molecule. Product distributions in micelle phase reactions tend to be markedly different from deaminations of the same substrate as a monomer. If the reactant is incorporated in micelles in either deamination or solvolysis a different product distribution would be expected. If both reacted through the micellar phase the product proportions would depend upon the relative natures of the micelles.

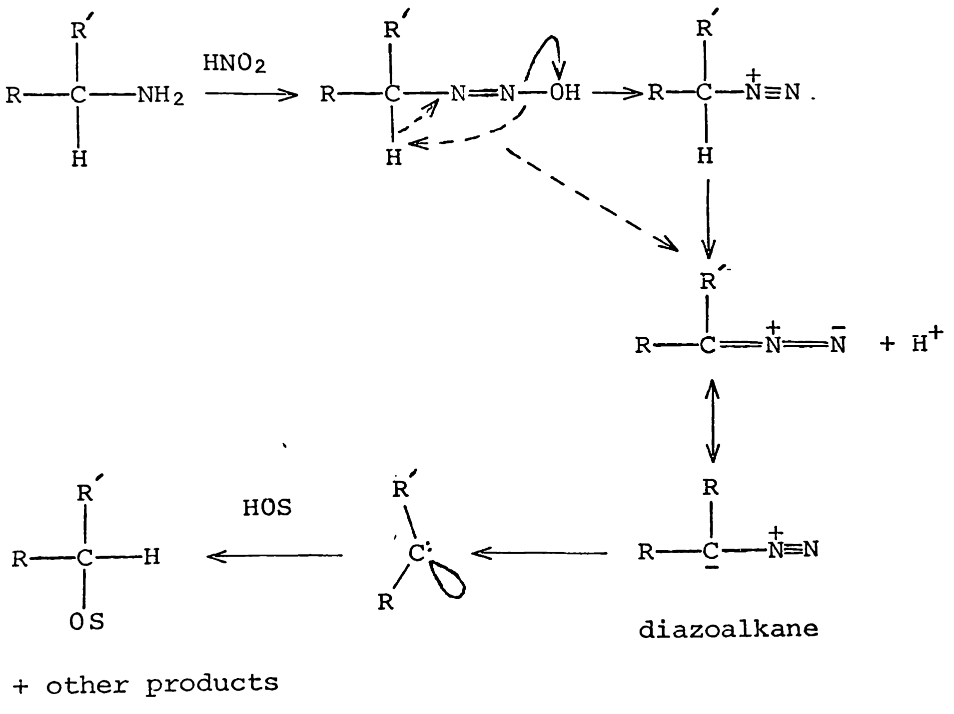
3.3.7 Neighbouring Group Effects

Carboxylate (in amino acids) and alkoxide substituents on amines may provide neighbouring group assistance in deaminations. The alkoxide groups tend to react via a pinacol rearrangement. Some cyclic and acyclic systems are discussed by Kirmse[78] who concludes that stereochemical studies and product analyses can only hint at the occurrence of neighbouring group effects. Since kinetic data are generally not available for diazonium ion decompositions, alternative interpretations cannot be definitely ruled out.

Kirmse[78] discusses the behaviour of norbornane diazonium ions which permit a reasonable distinction between alternatives.

3.3.8 Diazoalkane Intermediates

It is possible that differences between the products of deamination and solvolysis reactions arise as the deamination may occur via carbenoid reactions of diazoalkanes. This mechanism (shown below) was excluded in deaminations of ethylamine and 1-amino-2-methylpropane in polar solvents such as water and acetic acid but may occur with some amines in aprotic solvents[37n].



HOS = protic solvent

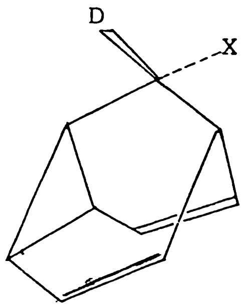
3.4 Similar Product Ratios From Deamination and Solvolysis

(i) 2-Methyl-2-propyl System[108]

The aqueous nitrous acid deamination of 2-amino-2-methylpropane gave 5.83% elimination while the hydrolysis of the corresponding dimethyl sulphonium salt gave 4.32%. (Experimental problems with this work may cast some doubt on these results. This system has been reexamined in the practical work of this thesis).

(ii) "Barbaralyl" System[78]

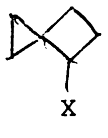
Barbaralyl tosylate was labelled with deuterium. After several rearrangements the label had migrated to a number of positions. Decomposition of the labelled barbaralane diazonium ion gave the same deuterium distribution.

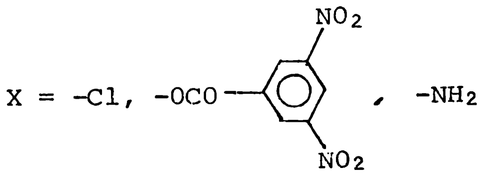


$X = -OTs, -N_2^+$

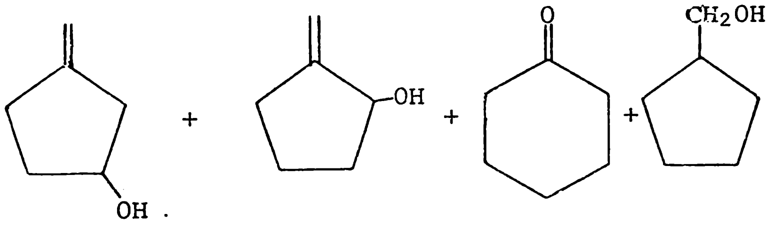
(iii) 4 and 5 - Spirohexyl Systems[132]

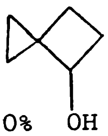
The hydrolyses of 4-spirohexyl chloride and the 3,5-dinitrobenzoate give product proportions similar to the aqueous nitrous acid deamination of 4-aminospirohexane.





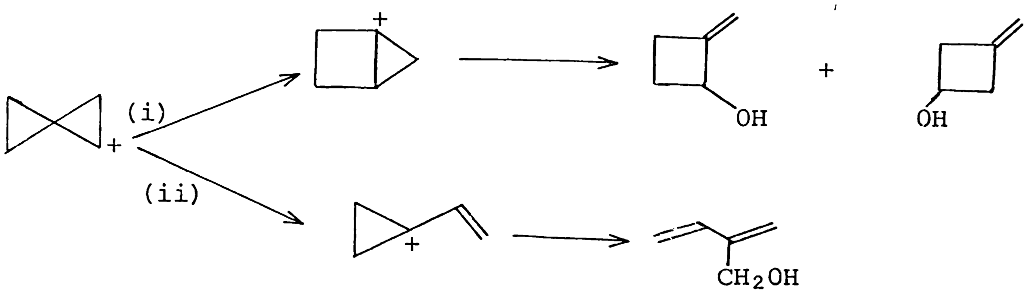
Products



Hydrolysis	52-64%	6-15%	4%	0-5%
Deamination	53%	10%	5%	+  + unknowns
				10% · 10%

The deamination of 5-aminospirohexane gives only unrearranged spirohexan-5-ol, exactly the same as obtained in the hydrolysis of 5-chlorospirohexane.

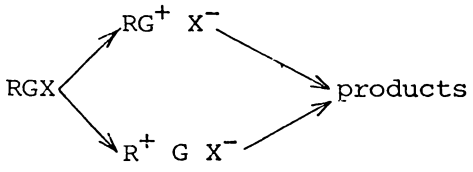
In marked contrast to the spirohexyl system, deamination of spiropentylamine (pathway (i)) and the hydrolysis of chlorospiropentane (pathway (ii)) give products by apparently different routes.



The explanation for the spirohexyl-spiropentyl difference in behaviour is the subject of further investigation.

3.5 Reactive Carbocations by Other Routes[133]

The loss of nitrous oxide from nitro-substituted amines was shown to give product distributions similar to deaminations, where nitrogen is lost (Chapter 2.2). Other analogies between the loss of nitrogen in deaminations and the losses of CO, CO_2, SO_2, SO_3 sulfoxides and metals from a variety of carbocation precursors has been suggested. Beak[133] has examined the similarities between silver-assisted reactions of chloroformates and deamination and discusses the results in terms of the characteristics attributed to "hot" carbocations.



$G = N_2, CO, CO_2, N_2O, SO_2, SO_3, SOR_2$, metal

Chapter Four

Nitrosation Catalysis

4.1 General

Nitrosation catalysis specifically refers to the following reaction;

$$\mathrm{RR'NH} \xrightarrow[+\text{"}\mathrm{NO^{+}}\text{"}]{-\mathrm{H^{+}}} \underset{\text{nitrosoamine}}{\mathrm{RR'N{-}{-}{-}NO}}$$

If the amine is aliphatic and primary, deamination will subsequently occur, otherwise the nitrosoamine is the end product. The term "nitrosation catalysis" should not be confused with the term "deamination catalysis" that frequently occurs in the literature. The latter refers to the removal of the amino group, but not necessarily via a nitrosoamine and diazonium ion.

The rate determining step of the nitrous acid deamination of aliphatic primary amines at pH3-5 is the initial nitrosation of the neutral amine by a nitrosyl species (NOX), nitrous anhydride ($NO-NO_2$).

Catalysis may be effected by an anion that gives a more reactive nitrosyl species or by changing the mechanism to a rate determining intra-molecular nitrosation. Micellar catalysis is also briefly considered. Much of the work summarised here has been investigated by researchers with an interest in carcinogens and the catalysis of carcinogenic nitrosoamine formation. Nitrosation inhibitors have also been investigated and are briefly considered at the end of this chapter.

4.2 Nitrosyl Species: Halide Ion Catalysis

Iodide, bromide and chloride ions catalyse amine nitrosation relative to the action of nitrous anhydride[134-137]. The nitrosyl halide (NOI, NOBr, NOCl) is the nitrosating agent. No rate enhancement is observed with the fluoride ion. Nitrosyl halides are thought to form in acidified nitrite solutions by halide ion attack on the nitrous acidium ion (H_2ONO^+)[97,100]. In these solutions, nitrosation by nitrosyl halide competes with nitrous anhydride (nitrosyl nitrite).

$$H_2ONO^+ + X^- \rightleftharpoons NOX + H_2O$$

$$RNH_2 + NOX \xrightarrow{\text{slow}} RNH\text{-}NO + X^- + H^+$$

Nitrosyl halides, like nitrous anhydride may be prepared independently and added to the reaction mixture as a gas[103-105]. Nitrosation reactions carried out in this way tend to be rapid compared with *in situ* production of the nitrosyl species due to the higher concentrations of NOX. These reactions may be conducted in alkaline conditions (since no H_2ONO^+ is required) where there is a high concentration of neutral amine[103-105].

It has been suggested that the perchlorate ion also acts as a catalyst[138] while the thiocyanate ion gives rate enhancements greater than the halide ions[139].

The acidic nitrosation of phenylhydrazine in the presence of sodium chloride, bromide and thiocyanate showed catalysis in the sequence; $SCN^- \gg Br^- > Cl^-$ [139].

Nitrosation by nitrosyl halides has been recently reviewed by Ridd in a paper on diffusion control and pre-association in nitrosation, nitration and halogenation[140].

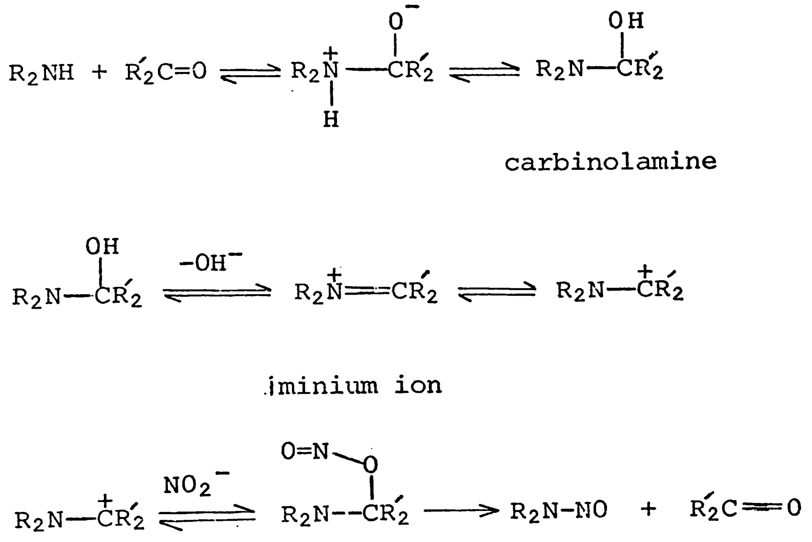
4.3 Nitrosyl Species: Thiocyanate Ion Catalysis

Catalysis by the thiocyanate ion has been observed in the nitrosations of phenylhydrazine[139] and isobutylamine[141] and involves nitrosyl thiocyanate (NOSCN). Boyland and Walker[142] studied the affect of various quantities of thiocyanate ion on the nitrosation of N-methylaniline in nitrous acid at various pHs. While uncatalysed nitrosation was found to be maximum at pH3, the thiocyanate ion had a maximum catalytic effect at pH1-2. In this range an amine/thiocyanate mole ratio of 1/10 increased the reaction rate 550 times compared with the uncatalysed reaction.

4.4 Catalysis by Aldehydes and Ketones

Aldehydes and ketones change the rate determining nitrosation from an intermolecular to an intramolecular process.

Using formaldehyde as the catalyst in neutral and basic media, Keefer and Roller have proposed the following mechanism[143];



$$R_2NH + R'_2C{=}O \rightleftharpoons R_2\overset{+}{N}H{-}C(O^-)R'_2 \rightleftharpoons R_2N{-}C(OH)R'_2$$

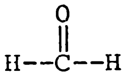
$$R_2N{-}C(OH)R'_2 \xrightleftharpoons{-OH^-} R_2\overset{+}{N}{=}CR'_2 \rightleftharpoons R_2N{-}\overset{+}{C}R'_2$$

$$R_2N{-}\overset{+}{C}R'_2 \xrightleftharpoons{NO_2^-} R_2N{-}C(O{-}N{=}O)R'_2 \longrightarrow R_2N{-}NO + R'_2C{=}O$$

Nitrosation of diethylamine at pH 6.4-11.0 is catalysed by formaldehyde though no reaction was detected at pH > 7.5 in the absence of the catalyst[143]. Archer *et al.* also investigated this reaction at pH4[144]. At this pH the initial rate of nitrosation was approximately doubled with an aldehyde/amine mole ratio of 1/1.

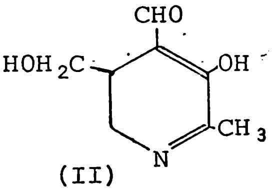
Types of Carbonyl Catalyst

A range of carbonyl catalysts was investigated by Archer *et al.*[144]. Formaldehyde (I) was the best catalyst for diethylamine nitrosation (pH4) and pyridoxal (II) the best for morpholine nitrosation (pH6.5). Other catalysts with lesser activity were; chloral (III), hexafluoroacetone (IV), hexachloroacetone (V), benzaldehyde (VI), p-nitrobenzaldehyde (VII), 2,4-dinitrobenzaldehyde (VIII) and dimethylaminobenzaldehyde (IX). Acetone and acetaldehyde had no catalytic effect.

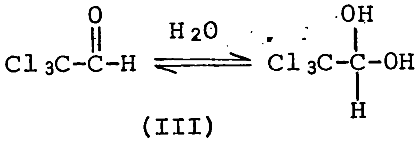


$\mathrm{H{-}C({=}O){-}H}$

(I)

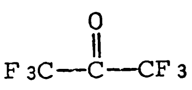


(II)



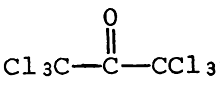
$\mathrm{Cl_3C{-}C({=}O){-}H} \xrightleftharpoons{H_2O} \mathrm{Cl_3C{-}C(OH)(OH){-}H}$

(III)



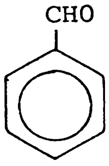
$\mathrm{F_3C{-}C({=}O){-}CF_3}$

(IV)

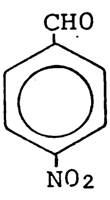


$\mathrm{Cl_3C{-}C({=}O){-}CCl_3}$

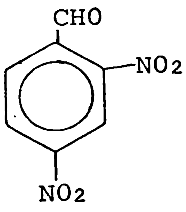
(V)



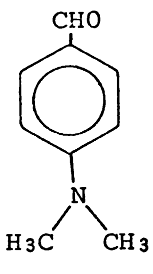
(VI)



(VII)



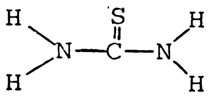
(VIII)



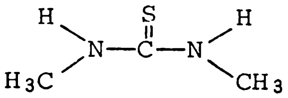
(IX)

4.5 Catalysis by Substituted Thioureas

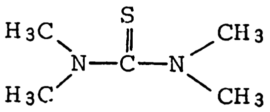
Matsui *et al.* have reported the catalysis of dimethylamine nitrosation by thiourea (X), N,N-dimethylthiourea (XI) and tetramethylthiourea (XII)[145].



(X)



(XI)



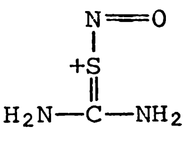
(XII)

The reactions were carried out at pH4 and 30°C and showed a catalytic effect in the order;

XII > X > XI

While aldehydes and ketones catalyse nitrosation by an intra-molecular rate determining step, it appears that thiourea and its derivatives form nitrosyl species that subsequently nitrosates the amine but the mechanism has yet to be confirmed.

The reaction of various alkyl thioureas and thiourea with nitrous acid has been investigated by Collins *et al.*[146,147]. A yellow species (XIII) derived from S-nitrosation was identified while N-nitrosation of thiourea produced nitrogen and thiocyanic acid.



$H_2N-C(=S^{+}-N=O)-NH_2$

(XIII)

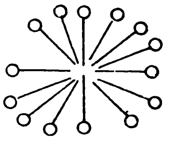
$$CS(NH_2)_2 \xrightarrow{NOX} NH_2{-}CS{-}NHNO \longrightarrow NH_2{-}CS{-}N{=}N{-}OH$$

$$NH_2{-}CS{-}N{=}N{-}OH \longrightarrow H^+ + HNCS + N_2 + OH^-$$

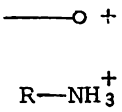
Masui *et al.*[145] showed that the thiocyanate ion does not catalyse the nitrosation of dimethylamine at pH4. Surprisingly, these authors seem to be unaware of the numerous reports of catalysis by aldehydes and ketones and have made the statement that "pronounced catalysis by a neutral species is not known" in reference to the nitrosation process[145].

4.6 Micellar Catalysis of Nitrosation

Studies of micellar chemistry have become widespread[148,149] and their affect on the aqueous nitrous acid deamination has been investigated in recent years[78,150,151]. The affect of alkyl ammonium micelles on product distribution and stereochemistry are discussed in Chapter 5. Their kinetic effect is considered here.



micelle



monomer

Aqueous nitrous acid deaminations of alkylamines occurs by rate limiting nitrosation of the neutral amine. It is suggested[150] that the electrostatic interactions between the positive ammonium head groups of the micelles destabilise the protonated amine relative to the monomer. Hence $K_a^{RNH_3^+}$ is increased upon micellisation of the alkyl ammonium ions and the overall reaction rate increases due to the greater availability of neutral amine;

$$Ka^{RNH_3^+} = [RNH_2][H^+]/[RNH_3^+]$$

At alkylammonium concentrations greater than the critical micelle concentrations (Chapter 5), deaminations may be treated as sums of micellar (m) and nonmicellar (f) processes[150]:

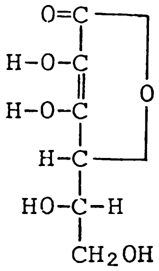
$$\text{rate} = k^{obs}[RNH_3^+]_{total} = k_m[RNH_3^+]_m + k_f[RNH_3^+]_f$$

Hutchinson and Stedman have reported the bromide and thiocyanate ion catalysed deaminations of long chain O-alkylhydroxylamines above and below their critical micelle concentrations (CMC, see Chapter 5)[152]. The bromide catalysed reaction showed a greater increase in rate above the CMC than the thiocyanate catalysed reaction[152]. The anion catalysed deamination of dodecylamine was enhanced by thiocyanate ion above the CMC and inhibited by bromide ion[153].

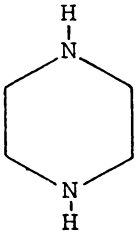
4.7 Nitrosation Inhibition

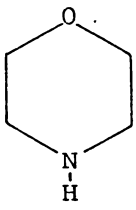
In contrast to nitrosation catalysis, cancer researchers concerned with N-nitrosoamines have also investigated inhibitors in order to prevent the in vivo formation of carcinogenic nitrosoamines from drug ingestion. The inhibitors thus far found to be successful with respect to a number of amines, appear to work providing a substrate more easily nitrosated than the target amine. Both C- and N-nitrosation occur .

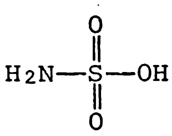
The best results were achieved with the ascorbate anion which had a marked inhibitory effect upon the nitrosation of piperazine (XIV), morpholine (XV), N-methylaniline, methylurea and dimethylamine at pH3.0 and pH4.0[154,155]. However it has little effect at pH2.0 and is even a little catalytic at pH1.0[154]


Ascorbic Acid

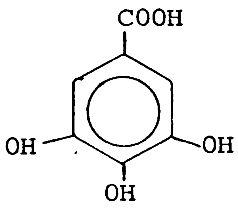
Other inhibitors with lesser effects were; sodium azide, sodium sulphite, sulphamic acid (XVI), hydrazine hydrochloride, gallic acid (XVII), tannin, hexamethylene tetrazine (XVIII) and cysteine hydrochloride (XIX).

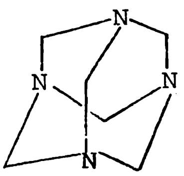

(XIV)

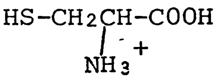

(XV)


$H_2N-S(=O)_2-OH$

(XVI)


(XVII)


(XVIII)


$HS-CH_2CH(NH_3^+)-COOH$

(XIX)

Chapter Five

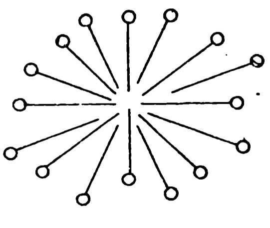
Micelles in Deamination and Solvolysis

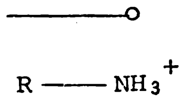
5.1 Micellar Effects in the Nitrous Acid Deamination

Micellar catalysis of the aqueous nitrous acid deamination was discussed briefly in Chapter 4.6. Here we consider micelle effects on product distribution and stereochemistry.

In deaminations with nitrous acid (pH3-5) alkylamines exist mainly as alkylammonium ions. These may aggregate into micelles which significantly alter the physical properties of solutions when the critical micelle concentration (CMC) is exceeded[148,149,156,157]. The physical properties affected have been reviewed[148,149,156] and include the electrical conductance and refractive index. Some parameters affecting the value of the CMC are briefly summarised[67]: The longer the total carbon chain length of the monomeric amphiphile, the lower the CMC becomes. Additional polar groups, C=C double bonds, and chain branching tend to increase the CMC, but changes in the hydrophilic part of the amphiphile generally have insignificant effects. The CMC is also affected by temperature, pressure, and by the addition of both ionic and non-ionic solutes.

In aqueous alkyl ammonium systems, the hydrophobic alkyl groups point to the interior of the micelles, while the hydrophilic ammonium groups are orientated to the surface.





The extent to which water penetrates the hydrocarbon core is not readily evaluated. However, water is considered, at present, to penetrate micelles only up to distances of approximately three to six carbon atoms[67]. The interior of the micelle is inferred to be hydrocarbon-like from ESR and NMR spectroscopy and from the utilization of fluorescent probes[67].

Acid-base equilibration between neutral amine and alkyl ammonium ions is fast compared with mass transfer between the micelle and solution[78,156]. (There is a dynamic exchange of amphiphiles between the micelle and solution, the extent of which is dependent upon the concentrations of amphiphile and added salts[148,149]). Above the CMC, nitrosation and diazonium ion decomposition occurs in both the micellar and solution phases. The micellar reaction generally produces a product distribution and stereochemistry markedly different from the reaction of the monomer[78,150,151].

Micellar control of the stereochemistry of nucleophilic substitution reactions was first recognised in the nitrous acid deamination of 2-aminooctane[150]. Below the CMC of 2-octylammonium perchlorate, octan-2-ol is formed with inversion. In the presence of micelles, backside attack by the solvent is impeded so inversion decreases with increasing substrate concentration until retention is finally observed. A linear relationship was found to exist between the micelle content of the solution and stereochemistry of the product, suggesting solution and micelle components in the overall reaction.

Moss[150] also investigated comicellisation of 2-octylammonium ions with; (i) 2-decylammonium (ii) 2-butylammonium ions, at 2-aminooctane concentrations normally giving substitution with partial inversion. The 2-decyl system gave 2-octanol with retention - consistent with reaction in a mixed micelle while the 2-butyl system gave 2-octanol with partial inversion indicating the absence of micelles.

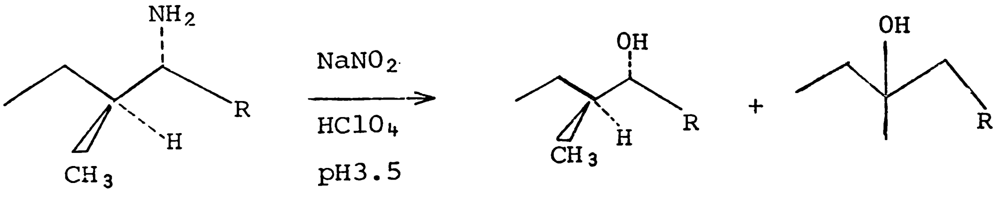
In contrast to 2-aminodecane, 2-aminobutane does not self-micellise in solutions below approximately 2 molar[158] though its presence dropped the CMC of the 2-octylammonium ions.

In micellar solutions, substitution product stereochemistry is critically dependent upon the nature of the counterion (from $RNH_3^+X^-$)[150]. Though catalysis is observed, bromide, chloride, nitrite and acetate counterions result in the disappearance of the micellar control of stereochemistry; i.e. though micelles are present, the substitution stereochemistry is the same as from reaction below the CMC. On the other hand, camphorsulphonate, fluoroborate, p-tosylate and perchlorate all assist in the display of micellar stereochemical control. The anions which are effective in stereochemical control are relatively hydrophobic and are expected to bind strongly to alkyl ammonium micelles. They therefore afford larger, more effectively charge-neutralised, denser and less aqueous micelles in which substitution stereochemistry moves toward retention[150].

Kirmse[67] has proposed that the increased retention observed in micelle-perchlorate deaminations might be attributed to a "double-inversion" process. The tightly bound perchlorate might displace nitrogen with inversion to give an alkyl perchlorate which undergoes rapid, inverting hydrolysis. Evidence for this process was taken from the micellar hydrolyses of 2-octyl substrates[67].

The low concentration of water in the micelle also favours increased elimination and rearrangement at the expense of direct substitution. It is known that homogeneous deamination reactions give increasing retention as the medium is altered from water to less polar solvents[67]. The micellar influence may also be due to the restrictions placed upon the substitution pathway by the micellar environment.

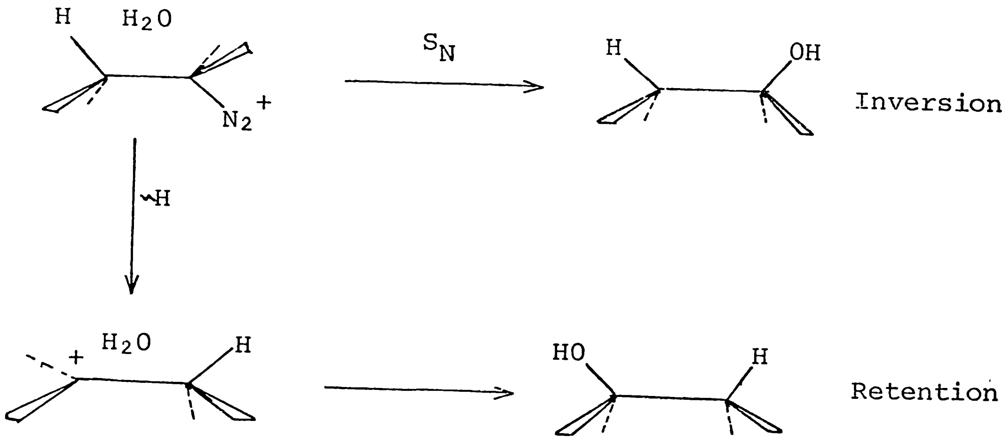
The stereochemistry of the products of 1,2-hydrogen shifts also depends upon micelle formation. Kirmse[151] has investigated the aqueous nitrous acid deaminations of a series of 4-amino-3-methylalkanes. The major products were alkenes (55% - 60%), 3-methyl-4-alkanols (15-20%) and 20 - 30% 3-methyl-3-alkanols (by 1,2-H shift).



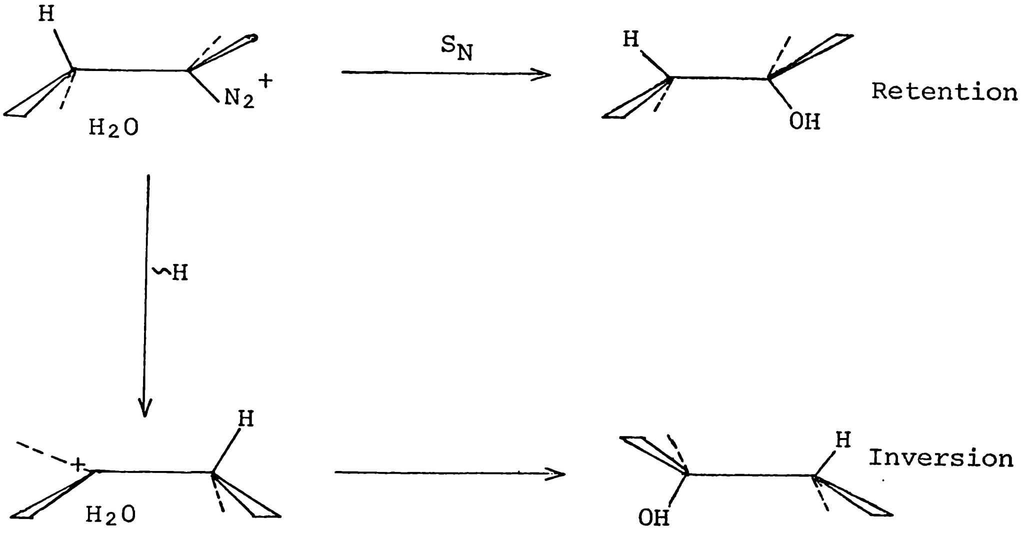
R = C_2H_5, n-C_4H_9, n-C_6H_{13}, $CH_2CH_2CH(CH_3)_2$

The stereochemistry of the products of 1,2-H shifts alters from retention in dilute solution to inversion in the micelle. It is suggested that this is due to asymmetric solvation[151] as outlined overleaf[78].

Reaction in solution:



Micelle reaction:

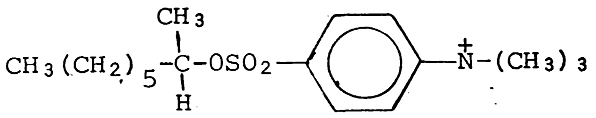


5.2 Micellar Effects in Hydrolyses

This topic has been reviewed by Fendler[148] and Cordes[149] and more recently by Brown[157]. Some aspects will be briefly summarised here for comparison with Section 5.1.

In hydrolysis, micelles may be formed from the micellisation of the hydrolysis substrate, or more frequently, by the addition of a known surfactant. The hydrolysis substrate may therefore be solubilised in an anionic or cationic micelle depending upon the surfactant used. These generally influence the hydrolysis in markedly different ways. Cationic micelles are often produced using hexadecyltrimethylammonium bromide (CTAB) while sodium lauryl (dodecyl) sulphate (NaLS) produces anionic miscelles.

In the hydrolysis of 2-octyl p-trimethylammonium benzenesulphonate (I)[159] the presence of cationic micelles (either of the reactant itself or CTAB) did not change the rate of hydrolysis nor did they affect the stereochemistry (100% inversion). However, anionic micelles (NaLS) strongly inhibited the hydrolysis reaction and modified the stereochemistry to a value as low as 54% inversion.



(I)

The stereochemical change was shown to arise from direct attack of the surfactant head group upon (I) leading to a short-lived covalent dialkyl sulphate intermediate.

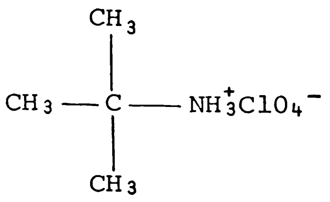
The rate of 2-octyl triflate hydrolysis was inhibited by both cationic and anionic micelles, and the stereochemistry changed from 70% inversion in pure water to 48% net retention in CTAB and 27% net retention in NaLS[160].

In Section 5.1 it was noted that the substitution product stereochemistry in aqueous deaminations is critically dependent upon the nature of the counterion. It would be interesting to see if this is also the case in the micellised hydrolyses of the corresponding (2-octyl) sulphonium salts. Such a study has apparently not yet been reported.

Chapter Six

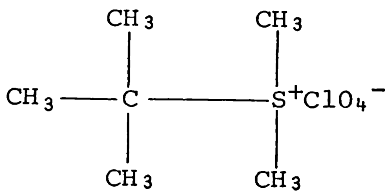
Introduction to the Experimental Work

The following chapters report the aqueous nitrous acid deaminations of two acyclic, aliphatic, tertiary carbinamines and the hydrolyses of the two corresponding alkyl dimethyl sulphonium salts.



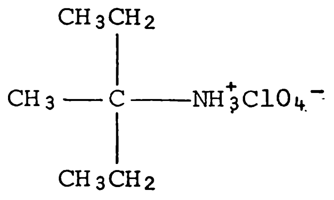
$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-NH_3^+ClO_4^-$$

2-amino-2-methylpropane
(perchlorate salt)



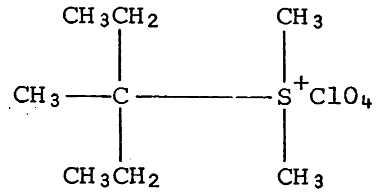
$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{S^+}}ClO_4^-$$

dimethyl-(2-methyl-2-propyl)-
sulphonium perchlorate



$$CH_3-\overset{\displaystyle CH_3CH_2}{\underset{\displaystyle CH_3CH_2}{C}}-NH_3^+ClO_4^-$$

3-amino-3-methylpentane
(perchlorate salt)



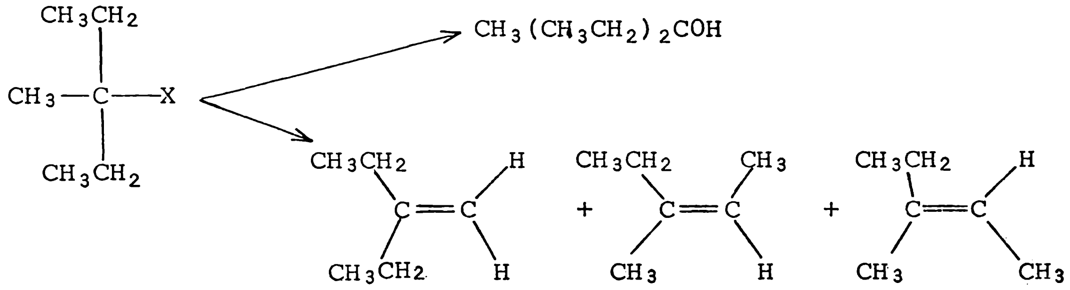
$$CH_3-\overset{\displaystyle CH_3CH_2}{\underset{\displaystyle CH_3CH_2}{C}}-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{S^+}}ClO_4$$

dimethyl-(3-methyl-3-pentyl)-
sulphonium perchlorate

The aim of the work was to investigate the nature of the deamination intermediate that is the product precursor. This was done by comparing the product distributions obtained from deamination and hydrolysis using reaction conditions as similar as possible. Primary and secondary alkyl substrates have been extensively studied (Chapter 3) while few tertiary systems have been investigated. The specific advantages of using tertiary substrates, from a mechanistic point of view, are discussed in Chapter 11.

The 2-methyl-2-propyl (tert-butyl) substrate was chosen since it is the simplest of the tertiary alkyl compounds. The deamination and hydrolysis produced essentially only two products (2-methylpropan-2-ol and 2-methylpropene) from the reaction of the alkyl group. This deamination was used as the model system for developing appropriate reaction procedures and methods of analysis.

Reactions of the 3-methyl-3-pentyl system produced three isomeric alkenes in addition to the substitution product. This enabled more subtle differences between the deamination and hydrolysis to be observed than was possible for the 2-methyl-2-propyl system.



Reactions of optically active substrates and those in which rearrangements may be expected would provide additional information but fall outside the scope of this thesis.

The sulphonium salt was chosen for the hydrolyses since the other commonly used substrates such as the halides and sulphonate esters are generally insoluble in water. Some sulphonate esters of tertiary substrates (e.g. 2-methyl-2-propyl tosylate) are also very difficult to prepare and readily decompose[28]. The quarternary ammonium salt could also have been used for the aqueous reactions.

Both the hydrolysis of the sulphonium salt and the deamination reaction involve a neutral molecule as the leaving group.

$$R\text{—}\overset{+}{S}Me_2\ X^- \longrightarrow R^+\ SMe_2\ X^-$$

$$R\text{—}\overset{+}{N}\equiv N\ X^- \longrightarrow R^+\ N_2\ X^-$$

In order to make the reaction conditions as similar as possible the hydrolyses were carried out in acidified ($HClO_4$) sodium nitrite solution (pH4).

Two aqueous deamination studies of 2-amino-2-methylpropane have been reported by Burgess (1953)[108] and Cannell (1956)[141]. The lack of accurate analytical techniques, rigorous experimental procedures and the presence of thiocyanate ion in Cannell's work made a re-examination of this system worthwhile in itself.

The reaction procedures developed in the work reported here were based upon the system used by Moss and coworkers[150] to study deaminations of octyl compounds. Maskill has pointed out that the mechanistic interpretation of aqueous nitrous acid deaminations is often difficult because nitrous acid reacts with alkenes and alcohols (the major products) and the product recovery is usually low[161]. The main emphasis of the experimental work described in the following chapters was to obtain complete product recovery and analysis. Possible secondary reactions of the products with nitrous acid was the subject of numerous control experiments. An accurate method for determining the amount of unreacted amine was developed (Appendix 2) and enabled accurate mass balances to be obtained for deaminations at 25°C. At higher reaction temperatures this determination was less accurate due to interferences.

Emphasis was placed upon product analyses during the first 20% of reaction. After more extensive reaction, secondary processes may become important. Complete recovery of the small amounts of products involved was a major task in developing the reaction procedures. While deaminations could be conveniently started and stopped by manipulating the pH, the hydrolyses could only be started and stopped by altering the reaction temperature. As a result, many experimental problems needed to be overcome in the hydrolysis studies.

Chapters 7 to 10 describe the reactions of the four substrates studied and summarise their results. The discussions at the end of each section in these chapters consider the control experiments as well as the quality and trends within each set of results.

Chapter 11 is the main discussion and considers the implications arising from the results, particularly with respect to the introductory chapters (Chapters 1 to 5). A brief discussion of other interesting features arising from supporting work is also included.

Appendices 1 and 2 summarise details and control experiments to do with the analyses of the reaction products and starting materials. This work has been placed in the appendices in order to keep Chapters 7 - 10 as simple as possible.

Appendix 3 summarises supporting details to do with the GLC work. This technique was used for all the quantitative analyses except for that of the nitrite ion.

Appendices 4 and 5 describe supporting studies to do with nitrous acid decomposition (A4) and the possible presence of micelles in the deamination solutions (A5).

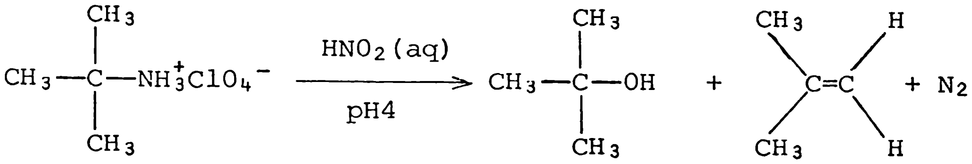
Appendix 6 summarises the preparations and characterisations of the starting materials, expected products and nitroaromatics made for use in a GLC stationary phase.

Chapter Seven

Deamination of 2-Amino-2-methylpropane

7.1 General

The perchlorate salt of 2-amino-2-methylpropane was prepared (Appendix 6.1) and deaminated in acidified (perchloric acid) sodium nitrite solution (pH4) at 80, 50 and 25°C.



Deaminations were initially carried out at 25°C but the hydrolysis of the analogous sulphonium salt (Chapter 8) was later found to be extremely slow at this temperature so both systems were re-examined at 50°C. Experimental difficulties required the deamination and hydrolysis of the 3-methyl-3-pentyl derivatives to be carried out at 80°C (Chapters 9 and 10). For comparison the 2-methyl-2-propyl system was also re-examined at this temperature. Some experimental modifications were required as the temperature was increased and these changes are described in the following sections. The reactions at 80°C are described first since their results are the most important in the overall comparison (see Chapter 11).

The initial reagent concentrations and quantities are summarised overleaf.

Temperature ($^\circ$C)	Amine Salt Concentration (mole l^{-1})	Quantity (mmole)	Sodium Nitrite Concentration (mole l^{-1})	Quantity (mmole)
80°	0.250	6.00	0.500	12.00
50°	0.250	6.00	0.500	12.00
25°	0.500	12.00	1.00	24.00

The analogous sulphonium salt was found to be only partially soluble when 12.00 mmole was used (at 25°C) so the quantities were halved for the higher temperature studies.

In all deaminations and hydrolyses, water was the only solvent.

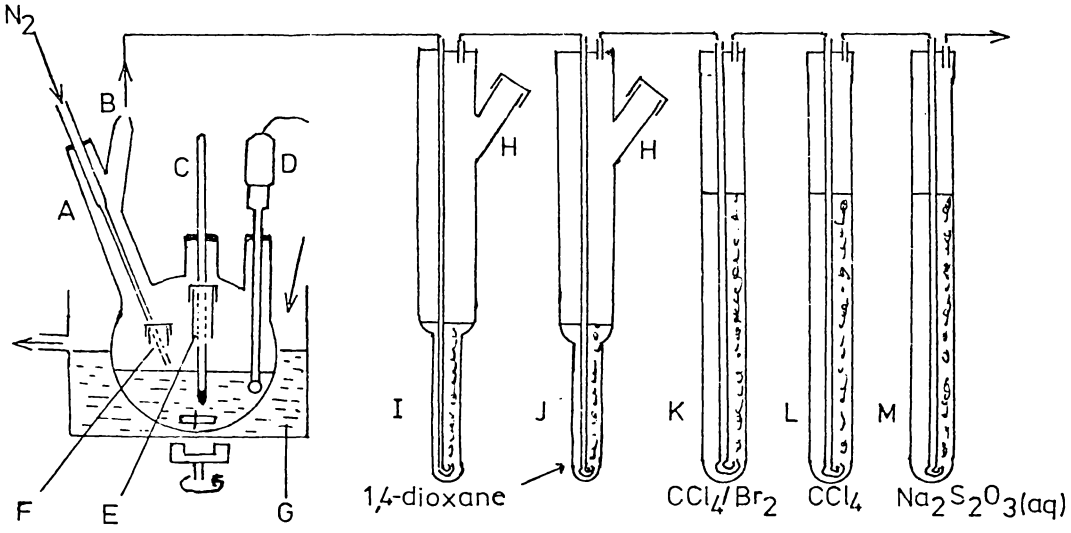
7.2 Deamination at 80°C

7.2.1 Apparatus and Procedure

Diagram 1 shows the apparatus used for deaminations at 80 and 50°C. 1,4-Dioxane bubblers were used to trap product alcohol (2-methylpropan-2-ol, bp. 82.2°C) evaporated from the reaction vessel. The elimination product (2-methylpropene, bp. -6.9°C) was trapped as the dibromo derivative in a tetrachloromethane/bromine (liq) bubbler. Some alkene was also trapped in the dioxane bubbler. This was removed by adding water to the dioxane (final dioxane concentration of 45% v/v) at the end of the reaction and bubbling with nitrogen (20 min) to transfer the product to the CCl_4/Br_2 mixture.

DIAGRAM 1

Apparatus for Deaminations at 80 and 50°C



A : Inlet for nitrogen carrier gas (30 ml/min).

B : Carrier gas exist to bubblers I-M.

C : Thermometer to monitor solution temperature.

D : Combined pH electrode. Radiometer GK2321C.

E : Neck with suba seal for acid and base injections.

F : Neck with septum seal for sample removal for GLC analysis.

G : Bath for temperature control: Various temperatures; room temperature while reagents are mixed, 80°C during reaction, -105°C (MeOH slush) for cooling at the end of the reaction, 0°C (ice bath) while the elimination product was flushed from the dioxane bubblers.

H : Necks with suba seals for water injection (20 ml) at the end of the reaction.

I + J : 1,4-Dioxane (15 ml) bubblers with narrow lower sections to give a reasonable depth of solvent.

K : Tetrachloromethane (20 ml)/liquid bromine (2 ml) bubbler.

L : Tetrachloromethane (20 ml) bubbler to trap any product carried over from K.

M : Sodium thiosulphate (1.00M) bubbler to remove bromine from the carrier gas effluent. PVC tubing was used to connect the various vessels.

Procedure:

2-Amino-2-methylpropane perchlorate salt (15.0 ml, 0.400M, 6.00 mmole) and sodium nitrite (8.40 ml, 1.500M, 12.00 mmole) solutions were added to a 100 ml, five-necked, round-bottomed flask fitted out as shown in DIAGRAM 1 (the thermometer was removed to allow addition of the reagents). The apparatus was purged with carrier gas (30 ml/min, 5 min, room temperature) and a sample of the reaction mixture removed for GLC analysis (see Appendix 1.2.2 for column type and conditions) to obtain a zero percent reaction baseline.

The constant temperature bath was filled (80°C) and the reaction mixture heated (75-78°C). Perchloric acid (0.25 ml, 4.22M) was added by syringe to adjust the acidity to pH4 (from approximately pH 6.5). The reaction time was started at this point (t_o). Further aliquots of acid were injected as necessary to maintain the reaction pH in the range 3.9-4.1.

Sodium hydroxide solution (5.0M approx. 0.20 ml) was injected after the appropriate reaction time (TABLE 1) to adjust the pH to about 9 (t_{final}). The 80°C water bath was replaced by a cold bath (-105°C, MeOH slush) and the solution temperature rapidly lowered to 0°C with stirring of both the reaction mixture and cold bath. The reaction vessel was then immersed in an ice bath. Water (20 ml) was added to each dioxane bubbler and the apparatus flushed with carrier gas for a further 20 minutes. The carrier gas flow was stopped and the pressure bled from the apparatus beginning at M (DIAGRAM 1) and working back to the reaction vessel using syringe needles to perforate the connecting PVC tubing and septum seals on I and J.

The tubing connecting the reaction vessel to bubbler (I) was cut at the bubbler and water (10 ml) flushed back to the flask to recover any condensed product alcohol. All fittings to the reaction vessel were rinsed with water (5 ml) when being removed. Water (2 ml) was also flushed through the delivery tube into bubbler (I).

Propan-1-ol (GLC internal standard, 100 µl, 1.357 mmole) was added to the reaction solution and both dioxane/water mixtures prior to their analysis by GLC (see Appendix 1.2.2).

1,3-Dibromopropane (GLC internal standard, 50 µl, 0.4918 mmole) was added to the contents of bubblers K and L. The tetrachloromethane mixtures were then washed with sodium thiosulphate solution and water before analysis by GLC (Appendix 1.2.1).

Two aliquots of reaction mixture were also taken for analyses of unreacted sodium nitrite (1.0 ml, see Appendix 2.2) and unreacted amine (5.0 ml, see Appendix 2.1.1).

Notes on the Procedure:

(i) The deamination is dependent upon the presence of nitrous acid (pKa 3.35 at 20°C) so the reaction rate may be controlled by manipulating the pH of the reaction mixture. The initial amine salt/sodium nitrite solution was at pH 6.0 - 6.5. Amine and nitrite analyses on samples of this solution showed no deamination at this acidity, as may be expected. The two reagents could therefore be safely mixed in the reaction vessel without loss of volatile products before the system was closed. The reaction could also be conveniently stopped by making the solution basic.

(ii) Analyses of the dioxane/water mixtures (by GLC, Appendix 1.2.2) showed that all the alkene had been removed after 20 minutes of bubbling with nitrogen (30 ml/min). This period also ensured the removal of all the alkene from the head space of the reaction vessel.

(iii) Care was taken to ensure that the reaction vessel was only immersed in the cold bath (-105°C, MeOH slush) to the depth of the reaction mixture in the flask. This minimised the possibility of condensing any gaseous alkene on the cold glass surface. This consideration was of particular importance in the reactions of the 3-methyl-3-pentyl compounds where the product alkenes have very much higher boiling points than 2-methylpropene.

(iv) The total volume of the quenched (basic) reaction mixture was measured for use in calculations of unreacted amine and sodium nitrite.

(v) A precolumn coated with 10% w/w $CoCl_2.6H_2O$ was required for the GLC analysis of the aqueous reaction mixture. Details are discussed in Appendices 1.2.2 and 3.2.

7.2.2 Results

The results of the deaminations of 2-amino-2-methylpropane carried out at 80°C are summarised in TABLES 1 and 2 while FIGURES 1 and 2 show plots of product quantity versus percentage of reaction. A brief discussion follows in Section 7.2.3 while control experiments are described in Section 7.2.4.

TABLE 1

Results of 2-Amino-2-methylpropane

Deaminations at 80°C

Reaction Time (sec)	Percentage of Reaction (Amine Analysis)	(Product Sum)	% Substitution	% Elimination
10	4.07	4.28±0.02	91.8±0.5	8.2±0.2
15	10.4	7.7±0.2	91.±3	8.3±0.2
28	15.0	9.0±0.1	91.±1	8.7±0.2
55	22.7	18.0±0.1	90.±1	9.6±0.9
75	32.3	27.5±0.2	90.3±0.8	9.7±0.3

mean % substitution 91±1

mean % elimination 8.9±0.4

TABLE 2

Results of 2-Amino-2-methylpropane Deaminations at 80°C

Percentage of Reaction (Product Sum)	Product Alcohol (mole $\times 10^{-4}$)	Product Alkene (mole $\times 10^{-5}$)
4.28±0.02	2.36±0.01	2.11±0.04
7.7±0.2	4.2±0.1	3.83±0.06
9.0±0.1	5.67±0.07	5.4±0.1
18.0±0.1	9.74±0.08	10.27±0.06
27.5±0.2	14.9±0.1	15.9±0.5

Notes on the Results:

(i) Errors;

The errors shown in TABLES 1 and 2 reflect only the reproducibility of the GLC analyses of the aqueous reaction mixture (for 2-methylpropan-2-ol) and the tetrachloromethane mixtures in the alkene traps.

Each solution was sampled 4 - 6 times and the mole of product calculated from each chromatogram. A mean and standard deviation was then calculated for the product in each solution.

$$\text{standard deviation} = \left[\frac{\Sigma(x-\bar{x})^2}{n}\right]^{\frac{1}{2}} = \sigma_1$$

Though only a small number of samples were taken from each solution, the error obtained nevertheless gives a measure of the reproducibility of the actual GLC analyses.

When comparing individual experiments (different extents of reaction), variation in the results outside the errors shown is then due to differences in the way the experiments behaved or possibly reflects an inadequacy in the product trapping procedure used. Control experiments were carried out to investigate the efficiency of the experimental procedure used (see the following sections of this chapter and Appendix 1).

The errors listed in all the tables of results, including those in Chapters8-10, reflect only the reproducibility of the GLC analyses.

(ii) Percentage of Reaction;

The percentage of reaction was calculated from a quantitative analysis of unreacted amine (Appendix 2) and also from the sum the moles of 2-methylpropan-2-ol and 2-methylpropene.

The discrepancy between the results of the two methods is probably due to some interference in the amine analysis since control experiments have indicated a complete product analysis (see the following sections of this chapter and Appendix 1).

FIGURE 1

Deamination of 2-Amino-2-methylpropane at 80°C

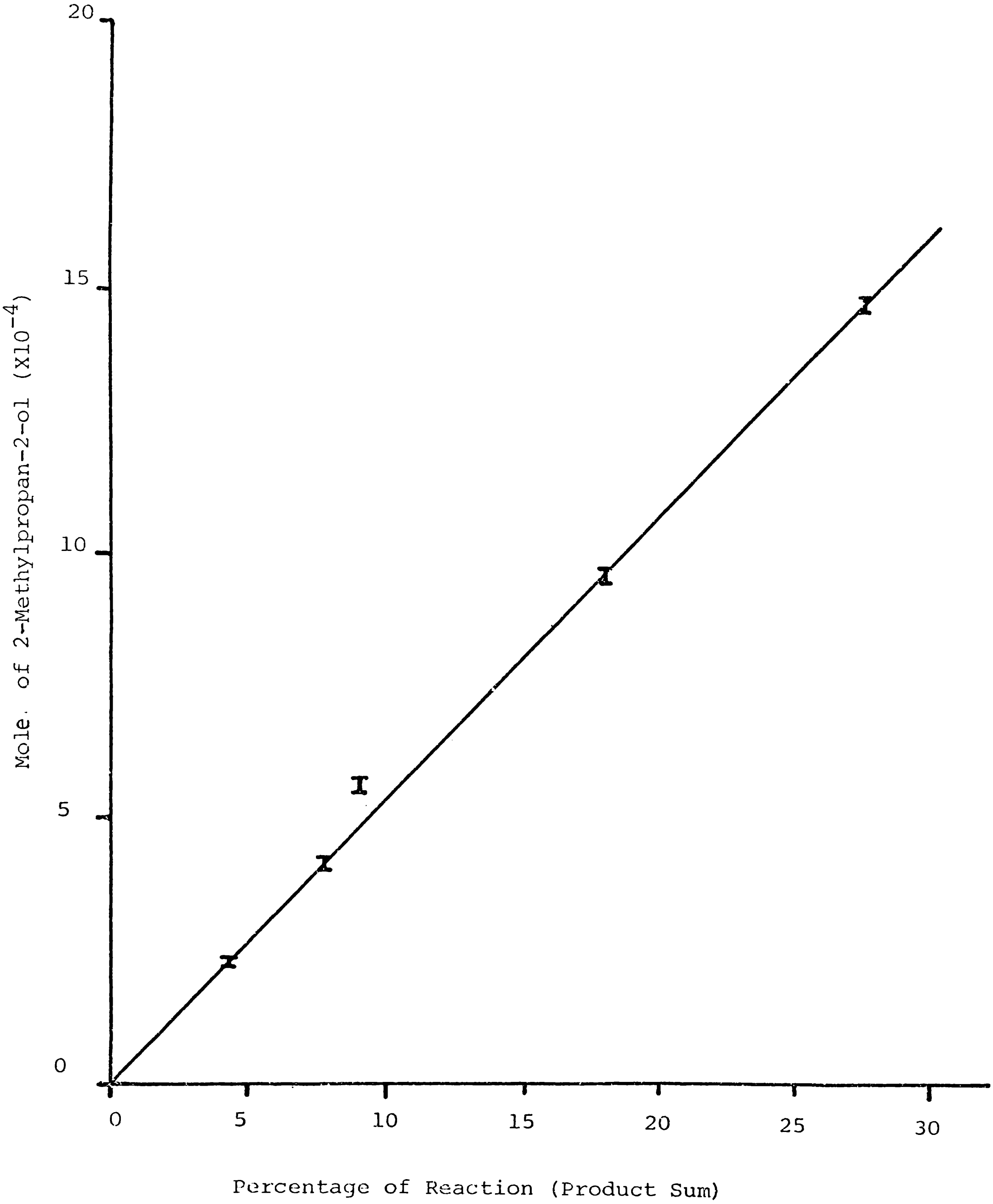
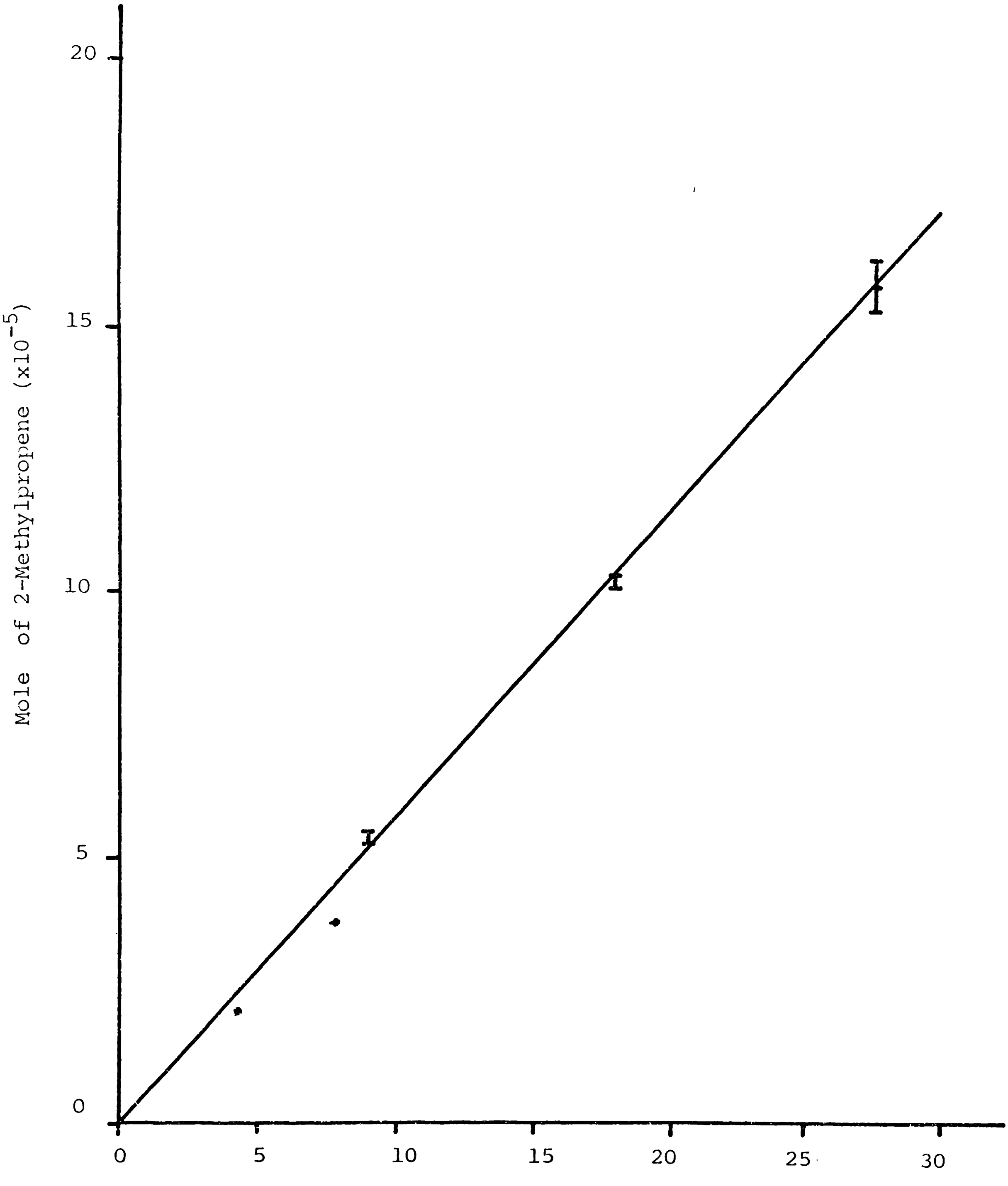


FIGURE 2

Deamination of 2-Amino-2-methylpropane at 80°C



Percentage of Reaction (Product Sum)

7.2.3 Discussion

The proportion of elimination shows a gradual decrease with decreasing extent of reaction. This probably reflects experimental error in the lower values where particularly small quantities of alkene are involved. Such quantities approached the maximum sensitivity of the analysis procedure.

A control experiment (Section 7.2.4) has shown that 2-methylpropan-2-ol is not dehydrated or nitrosated by the nitrous acid at 78°C. No 2-methyl-2-nitropropane or 2-methyl-2-propyl nitrite was detected. These had been reported as products from 2-amino-2-methylpropane deamination in a similar study by Burgess[108].

FIGURES 1 and 2 show plots of the mole of 2-methylpropan-2-ol and 2-methylpropene (respectively) against the percentage of reaction. FIGURE 1 would indicate major fluctuations in the proportion of substitution in each reaction. This plot is rather insensitive to such variations however, since the percentage of reaction is calculated from the sum of the products and substitution is the major component in this. Contamination of the starting material (amine salt) with 2-methylpropan-2-ol would not show up in FIGURE 1 but this was checked by analysing a sample of reaction mixture (by GLC) before the deamination was started by perchloric acid addition.

The plot of elimination product against percentage of reaction (FIGURE 2) acts as a more sensitive indicator of variations in the proportions of alkene observed since such fluctuations have little influence on the calculated percentage of reaction.

The plots indicate a reasonably accurate product determination and no loss of either product through secondary reactions. For example, a secondary reaction in which the alcohol was dehydrated would result in a negative deviation in FIGURE 1 and a positive deviation in FIGURE 2.

Similar plots are shown for all the sets of deaminations and hydrolyses reported in this chapter and Chapters 8 - 10.

7.2.4 Control Experiments

A number of control experiments relevant to this section are described in the next section concerning deaminations at 50°C (Section 7.3). The reaction apparatus and procedure were the same for both series.

In addition, a control experiment was conducted at 80°C to check for dehydration or other secondary reactions of the product alcohol (2-methylpropan-2-ol) by the nitrous acid.

A "deamination" was set up in the usual manner (Section 7.2.1) except that the amine salt was replaced by sodium perchlorate. When the reaction mixture was at 78°C and pH4 2-methylpropan-2-ol (100 μl, 35°C, 1.06 mmole) was added (by syringe) and the reaction continued for 9 minutes before base (NaOH) addition. The system was flushed with carrier gas and analysed in the normal way. Results; all the alcohol was detected (1.05 ± 0.01 mmole) with no evidence of dehydration product (2-methylpropene) in the alkene trap.

7.3 Deamination at 50°C

7.3.1 Apparatus and Procedure

APPARATUS: The apparatus was essentially the same as that described for deaminations at 80°C but with the following differences;

(i) A microburette (1.00 ml) containing perchloric acid (4.22M) for pH control during reaction was used in place of the thermometer (item C, DIAGRAM 1).

(ii) The water bath was filled at a constant 50.0°C instead of 80.0°C during the reaction.

(iii) An ice-bath was used to cool the reaction mixture in place of the MeOH slush (-105°C) bath.

PROCEDURE: Apart from the differences described above, the procedure was the same as described for the reaction at 80°C (Section 7.2.1).

7.3.2 Results

The results of the deaminations of 2-amino-2-methylpropane carried out at 50°C are summarised in TABLES 3 and 4 while FIGURES 3 and 4 show plots of product quantity versus percentage of reaction. A brief discussion follows in Section 7.3.3 while control experiments are described in Section 7.3.4.

TABLE 3

Results of 2-Amino-2-methylpropane Deaminations at 50°C

Reaction Time (min)	Percentage of Reaction (Amine Analysis)	(Product Sum)	% Substitution	% Elimination
2.5	6.52	6.52±0.08	93±2	7.4±0.2
5.0	10.47	11.0±0.2	92±2	7.7±0.5
11.0	19.11	19.0±0.2	92±1	7.8±0.1
15.0	23.67	23.0±0.3	91±2	9.1±0.2
20.0	27.07	25.0±0.2	93±1	6.68±0.07
31.0	32.33	31.5±0.3	91±1	9.3±0.1
53.5	-	31.8±0.5	91±2	9.1±0.5

mean % substitution 92±2%

mean % elimination 8.2±0.8%

TABLE 4

Results of 2-Amino-2-methylpropane Deaminations at 50°C

Percentage of Reaction (Product Sum)	Product Alcohol (mole x 10^{-4})	Product Alkene (mole x 10^{-5})
6.52±0.08	3.62±0.05	2.90±0.08
11.0±0.02	6.11±0.09	5.1±0.3
19.0±0.2	10.50±0.09	8.89±0.09
23.0±0.3	12.5±0.2	12.6±0.2
25.0±0.2	14.01±0.04	10.02±0.05
31.5±0.3	17.1±0.2	17.6±0.1
31.8±0.5	17.4±0.3	17.4±0.9

FIGURE 3

Deamination of 2-Amino-2-methylpropane at 50°C

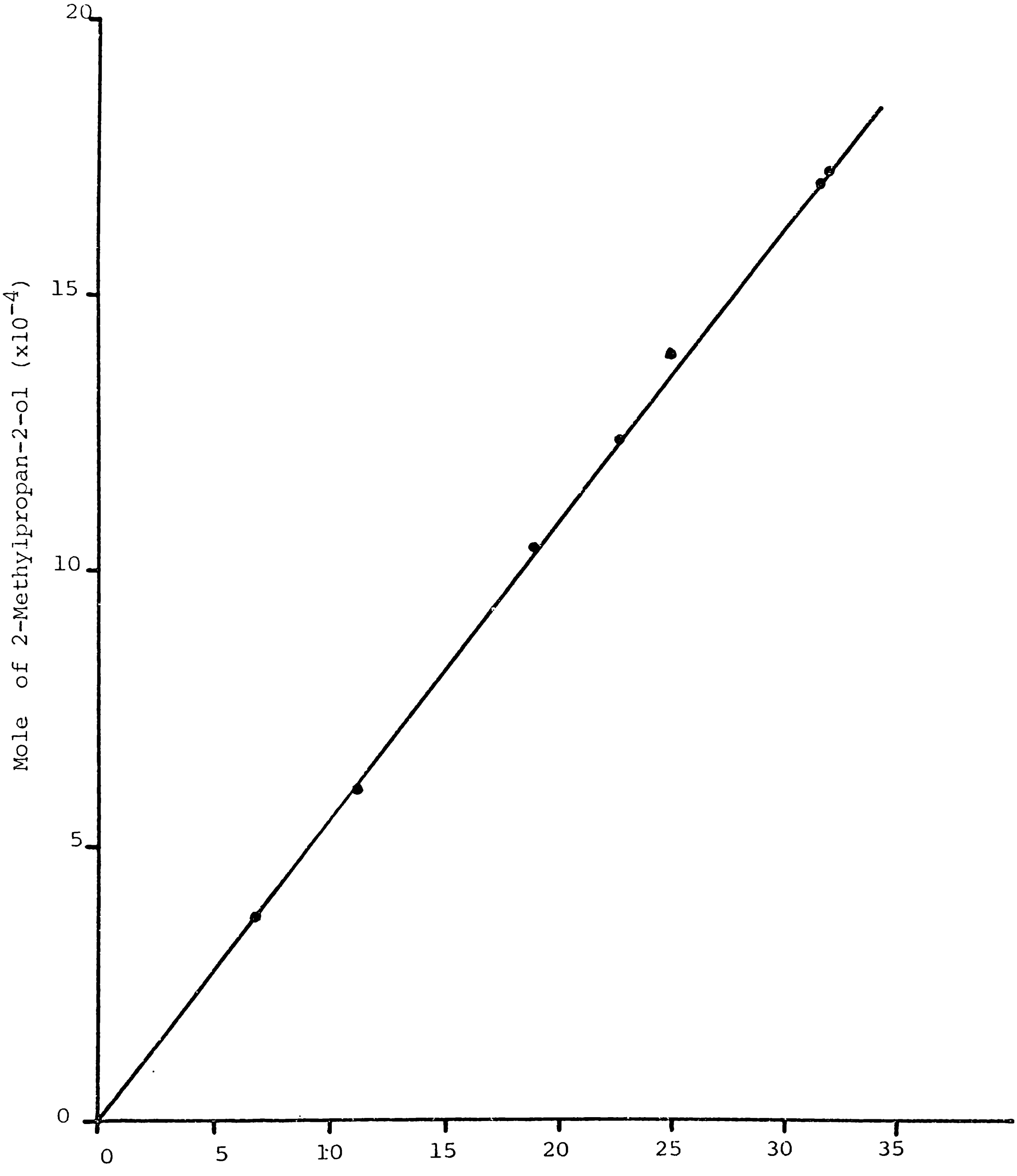
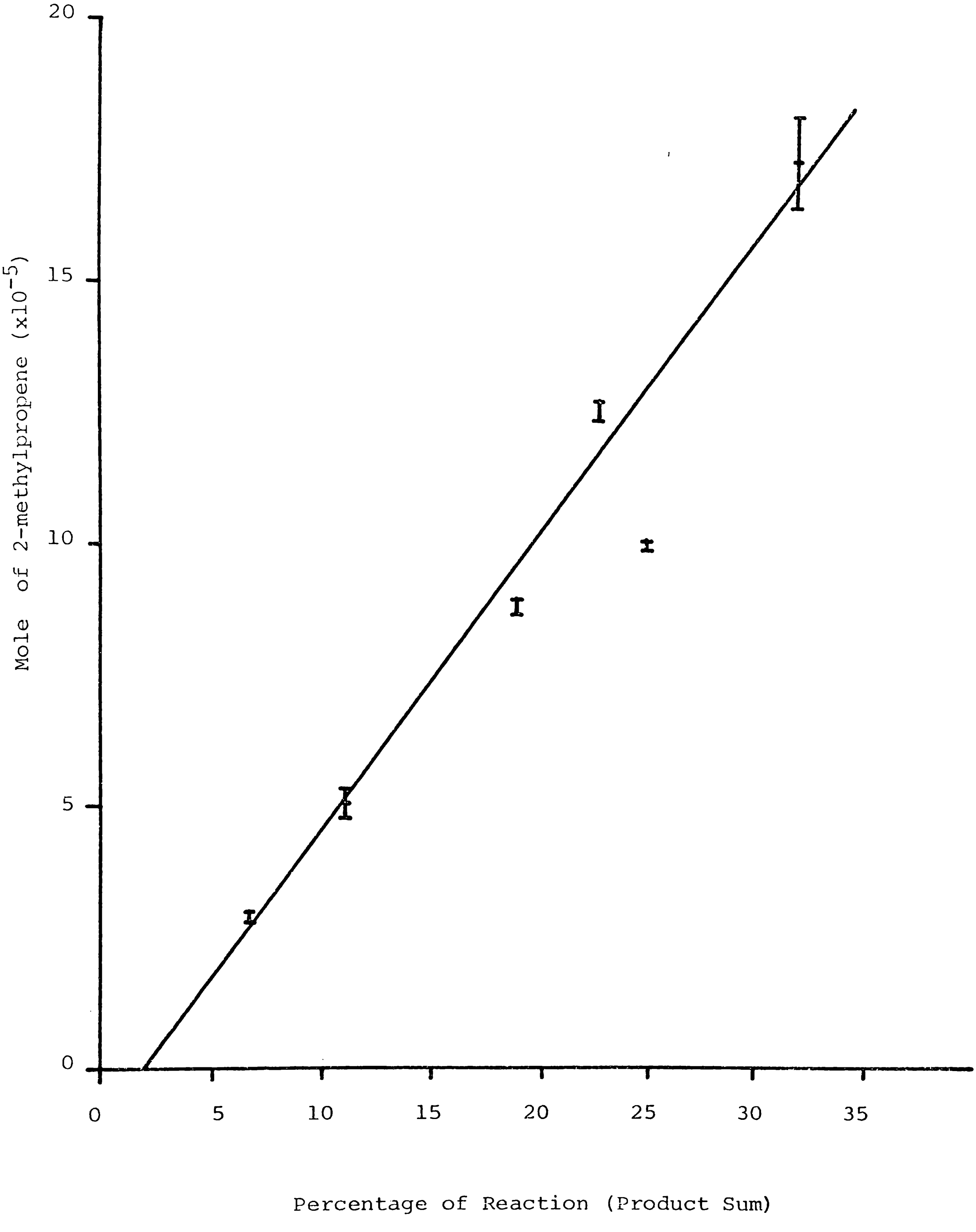


FIGURE 4

Deamination of 2-Amino-2-methylpropane at 50°C



7.3.3 Discussion

Comments concerning the errors, percentages of reaction and FIGURES have been made Sections 7.2.2 and 7.2.3.

FIGURE 4 shows rather more fluctuation in the proportions of elimination than occurred in the 80°C reactions.

In addition to the experiments listed in TABLES 3 and 4 a deamination was carried out at 50°C using 12.00 mmole of amine salt and 24.0 mmole of sodium nitrite. The reaction time was 9.75 minutes and the results were:

% substitution	91.5±0.3%	
% elimination	8.44±0.03%	
% reaction	38.00±0.08%	- Product sum
	37.9%	- Amine analysis

Comparison with the data from reactions at 25°C (Section 7.4.2) shows that increasing the reaction temperature from 25 to 50°C has resulted in a ten fold rate enhancement.

Likewise the increased initial reagent concentrations (two fold) compared with the other reactions at 50°C has resulted in a two fold rate enhancement.

The experiment also shows that the product distribution is not significantly affected by the reaction temperature (in the range 25 - 50°C) and reagent concentrations (in the range considered).

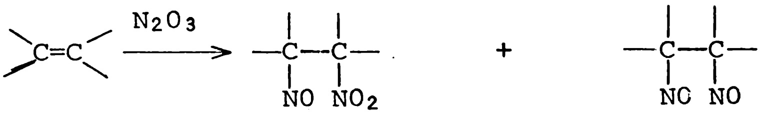
Deamination Products

2-Methylpropan-2-ol and 2-methylpropene were the main products in the deaminations. A trace of 2-methyl-2-propyl nitrite was also observed but no 2-methyl-2-nitropropane. Both have been reported as products in this reaction during a similar study by Burgess[108]. The alkyl nitrite and nitroalkane were prepared (Appendix 6) and their GLC retention times determined (see Appendix 1 for column details and GLC conditions).

The origin of the alkyl nitrite is discussed in Chapter 9.2.3 in reference to the 3-methyl-3-pentyl nitrite found in the deamination of 3-amino-3-methylpentane. The points made in the discussion of Chapter 9.2.3 are equally applicable to this system.

Secondary products from the reaction of the product alkene with nitrosating agents may also be envisaged.

Park and Williams[162] have studied the mechanism of dinitrogen trioxide (N_2O_3, nitrous anhydride) reaction with 2-methylpropene. The main product was shown to be the nitronitrosoalkane (a nitrosite) though the nitroso dimer also forms.



Though not specifically looked for in this deamination, the mass balance evident in TABLE 3 shows that these products were insignificant if present at all. Little reaction of the product alkene would be expected since, once formed it should leave the reaction mixture rapidly under the reaction conditions employed (water solvent, 50°C, alkene bp. - 6.9°C) thereby minimising contact with nitrosating agents.

The reaction of aromatic diazonium compounds with alcohols to give ethers is well known[163]. Though the conditions employed in such reactions are very different to our deamination (the former often have the alcohol as solvent), the precedent is set for similar processes to occur. The postulated diazonium ion in our deamination is present only as a transient intermediate (Chapter 2.7) and the alcohol product is in very dilute solution so the ether-forming pathway may be expected to have little significance. Again, the good mass balance obtained when considering only product alcohol and alkene supports this view though di-tert-butyl ether was not specifically looked for.

The perchlorate anion is a weak nucleophile and its concentration during deamination is small compared with the water. Little or no alkylperchlorate product was expected. Under the circumstances the preparation of a reference sample of this covalently bonded organic perchlorate was not warranted.

7.3.4 Control Experiments

Control experiments checked for the complete recovery of the reaction products. The controls associated directly with actual GLC analyses of the various solutions and mixtures obtained from each reaction are described in Appendix 1.

Trapping of the deamination products:

(i) 2-Methylpropan-2-ol

A trapping system was designed to prevent evaporated 2-methylpropan-2-ol from reaching the tetrachloromethane/liquid bromine bubbler. Controls had shown that only approximately half of the alcohol placed in the bubbler was detected as the alkyl bromide (the principal product of the reaction between the alcohol and bromine in tetrachloromethane) with the remainder being lost during the sodium thiosulphate/water washing procedure (see Appendix 1.2.1). Further tests had shown that 2-bromo-2-methylpropane was not affected by the sodium thiosulphate washing procedure.

The dioxane bubblers described in Section 7.2.1 were found to be the most efficient alcohol traps though it was necessary to add water at the end of the reaction to remove dissolved 2-methylpropene. Water bubblers were found to be less efficient while the GLC retention time of other organic solvents (with respect to the reaction products and internal standard) and their immiscibility with water precluded their use. This included tetrahydrofuran diethyl ether, pentane, hexane, and the chlorinated solvents.

Generally little or no 2-methylpropan-2-ol was found in the second 1,4-dioxane bubbler.

(ii) 2-Methylpropene

Control experiments and tests associated with the alkene trapping and GLC analysis have been mentioned in Section 7.2.1 and Appendix 1.2.1.

The good agreement between percentages of reaction calculated from the analysis of unreacted amine and summation of the products indicates a complete product recovery and analysis.

Gas Leaks in the Apparatus: With five bubblers in series a positive pressure built up in the apparatus. Immersion of the reaction vessel and fittings in water indicated no gas leaks (nitrogen carrier gas flow 30 ml/min).

7.4 Deamination at 25°C

7.4.1 Apparatus and Procedure

APPARATUS: The apparatus used differed from that employed for the deaminations at 50°C only in the alcohol trapping system. A single bubbler with water (20 ml) was used in place of the two dioxane units (less alcohol evaporated at 25°C so the water bubbler was quite adequate).

PROCEDURE: Deaminations were typically carried out by the method used for reactions at 50°C, however with the following differences;

(i) Amine salt solution, 15.0 ml, 0.800M, 12.00 mmole
(c.f. 15.0 ml, 0.400M, 6.00 mmole)

Sodium nitrite solution, 8.40 ml, 3.00M, 24.0 mmole
(c.f. 8.40 ml, 1.500M, 12.00 mmole)

(ii) After the reactants were added to the reaction vessel the apparatus was purged with carrier gas (nitrogen, 30 ml/min) for 15 minutes, before acidification.

(iii) During the reaction samples (5 μl) were removed for GLC analysis (see Appendix 1) to monitor the production of alkyl nitrite, alcohol and nitroalkane.

(iv) After the deamination was stopped, the apparatus was flushed with nitrogen for 10 minutes instead of 20 minutes.

(v) No cooling (-105°C cold bath or ice-bath) was necessary at the end of the reaction.

(vi) The fittings to the reaction vessel were not rinsed with water as was the case for the 80 and 50°C deaminations.

7.4.2 Results

Deaminations were carried out with varying reaction times. The results are summarised in TABLES 5 and 6 while FIGURES 5 and 6 show plots of product quantity versus percentage of reaction. Deamination catalysis by the thiocyanate ion was also briefly investigated (Section 7.4.4).

TABLE 5

Results of 2-Amino-2-methylpropane

Deaminations at 25°C

Reaction Time (min)	Percentage of Reaction (Amine Analysis)	(Product sum)	% Substitution	% Elimination
15.5	4.9	4.99±0.06	93±2	6.7±0.2
14.5	6.3	5.6±0.3	93±6	7.9±0.4
20.0	6.2	5.8±0.2	93±4	6.9±0.2
27.0	7.1	7.7±0.3	92±4	7.4±0.3
31.0	11.8	11.7±0.5	93±6	6.9±0.3
30.25	12.5	12.5±0.3	92±4	8.0±0.2
62.0	16.8	16.0±0.8	92±6	8.2±0.4
123.0	24.4	23.7±0.4	92±2	8.3±0.2

mean % substitution	93±4%
mean % elimination	7.5±0.6%

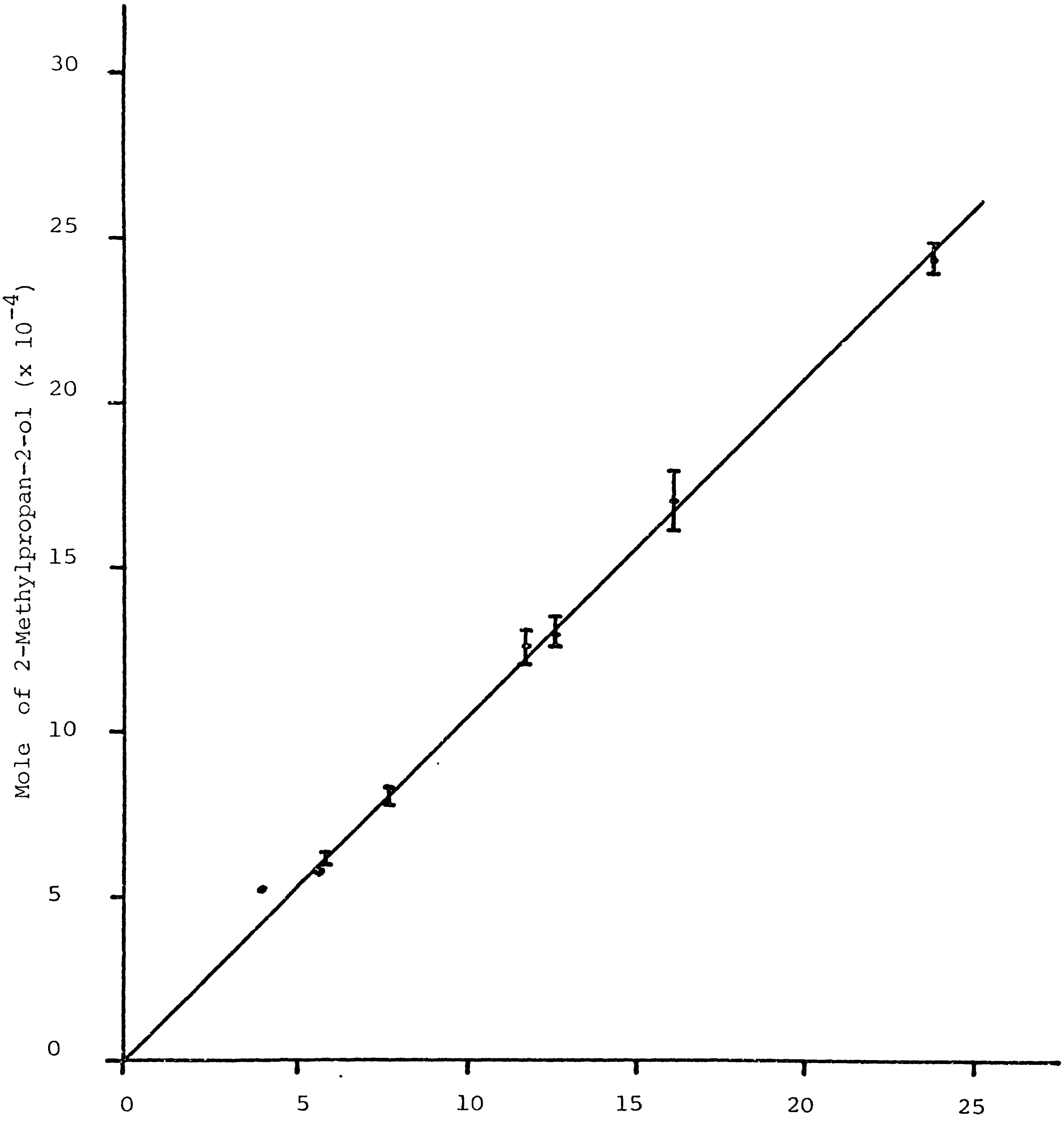
TABLE 6

Results of 2-Amino-2-methylpropane Deaminations at 25°C

Percentage of Reaction (Product Sum)	2-Methylpropan-2-ol (mole x 10^{-4})	2-Methylpropene (mole x 10^{-5})	Alkyl nitrite (mole x 10^{-5})	% RONO wrt. substitution
4.99±0.06	5.34±0.07	4.0±0.1	2.5	4.2
5.6±0.3	5.9±0.3	5.27±0.07	2.9	4.3
5.8±0.2	6.2±0.2	4.79±0.08	1.5	2.2
7.7±0.3	8.1±0.3	6.85±0.08	4.4	4.8
11.7±0.5	12.7±0.6	9.62± -	2.7	1.9
12.5±0.3	13.2±0.4	12.0±0.1	5.9	3.9
16.0±0.8	17.2±0.9	15.8± -	4.1	2.1
23.7±0.4	24.7±0.5	23.58±0.08	13.0	4.6

FIGURE 5

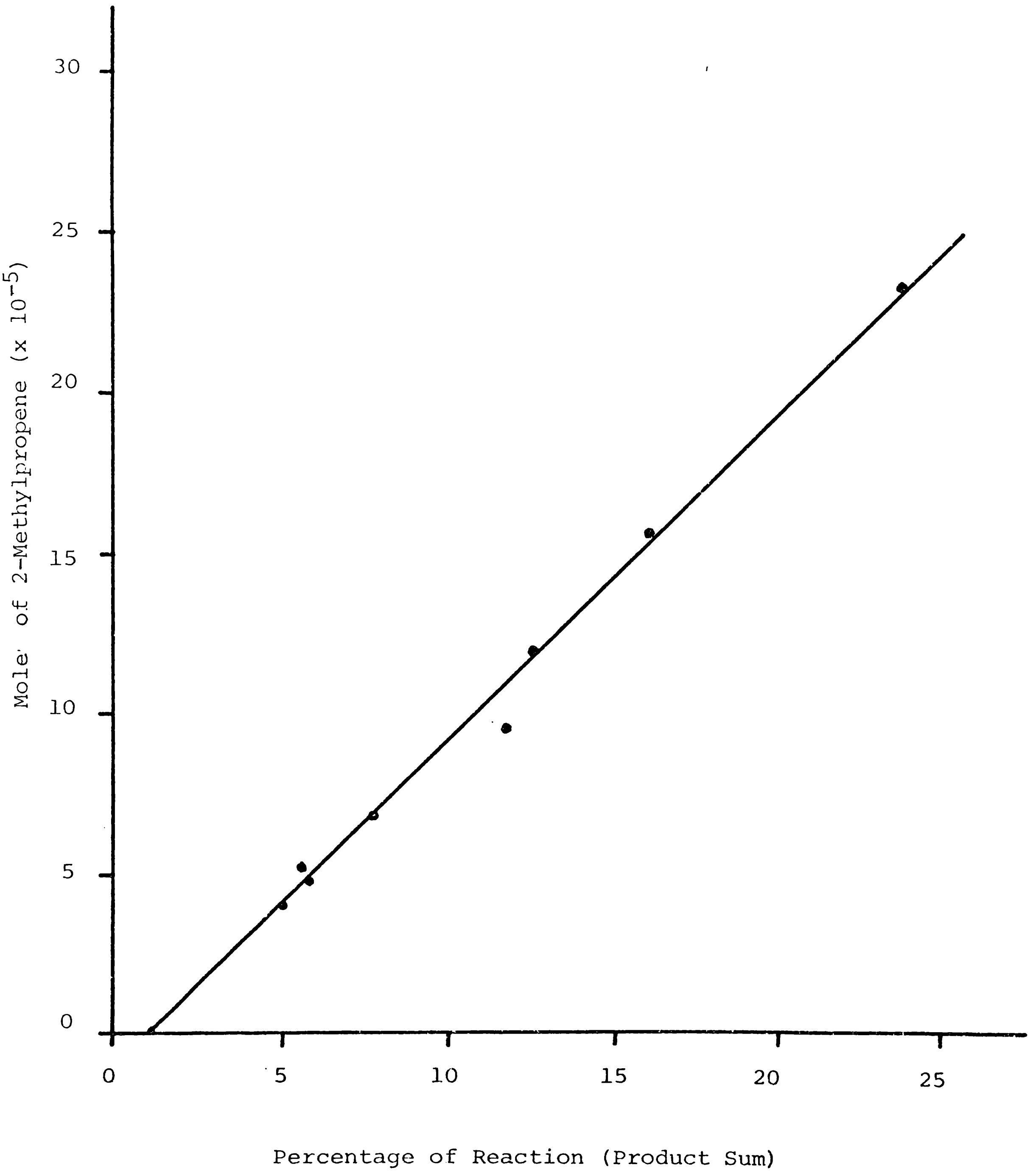
Deamination of 2-Amino-2-methylpropane at 25°C



Percentage of Reaction (Product Sum)

FIGURE 6

Deamination of 2-Amino-2-methylpropane (25°C)



7.4.3 Discussion

Deamination at 25°C produced significant amounts of 2-methyl-2-propyl nitrite (TABLE 6) while only a trace was observed at 50°C and none at 80°C. This was expected since the alkyl nitrite was found to hydrolyse to the alcohol in water at 25°C

$$RONO + H_2O \longrightarrow ROH + HNO_2$$

The hydrolysis would be expected to be more rapid at higher reaction temperatures. Brown nitrogen dioxide gas was observed during tests of the alkyl nitrite hydrolysis (25°C). This was probably due to decomposition of the nitrous acid product. Allen[164] has reported the acid-catalysed hydrolysis of 2-methyl-2-propyl nitrite in 72.5% (w/w) dioxane/water (0°C). Hydrolysis using H_2O^{18} enriched water showed that the reaction proceeds exclusively by nitrosyl-oxygen fission. It was therefore concluded that alkyl-oxygen fission is extremely unlikely in the hydrolysis of any simple alkyl nitrite under similar conditions.

$$R{-}O \not{-} N{=}O + H_2O^{18} \longrightarrow ROH + ONO^{18}H$$

No alkene (2-methylpropene) was detected by methods sensitive to as little as 0.1% of this product. The alkene would be expected as a product if alkyl-oxygen fission occurred.

The alkaline hydrolysis of alkyl nitrites was also studied by Allen[164] and more recently by Oae *et al.*[165], again using oxygen-18 methods. Hydrolysis also proceeds exclusively with nitrosyl-oxygen fission under these conditions.

The alkyl nitrites reported in the deaminations and hydrolyses of this thesis may also hydrolyse with nitrosyl-oxygen fission(Section 9.2.3 discusses the possible sources of these alkyl nitrites; 2-methyl-2-propyl nitrite and 3-methyl-3-pentyl nitrite).

They are subjected to both acidic (during the deaminations and hydrolyses) and basic (NaOH quenching at the end of each reaction) conditions.

In the reactions in this thesis the alkyl nitrites may be secondary products from the reaction of product alcohol with the nitrous acid solution. It was possible that the subsequent hydrolysis of the alkyl nitrite would yield products of elimination as well as substitution (alcohol). In the case of the 3-methyl-3-pentyl system, elimination from the alkyl nitrite could produce the three isomeric alkenes (Chapters 9 and 10) in different ratios to the initial deamination and sulphonium salt hydrolysis. Since elimination is the minor product forming pathway in the latter reactions, contribution from alkyl nitrite hydrolysis was potentially a serious complication.

Control experiments in which product alcohols were added to nitrous acid solutions (Section 7.2.4, Chapter 9.2.3) then quantitatively analysed for complete recovery of the alcohols and possible alkyl nitrites, nitroalkanes and elimination products showed no alkenes were produced though 3-methyl-3-pentyl nitrite was definitely present when 3-methylpentan-3-ol was used (Chapter 9.2.3). This shows that the production and hydrolysis of the alkyl nitrites does not interfere with the deamination and sulphonium salt hydrolysis product distribution and supports the nitrosyl-oxygen bond fission mechanism.

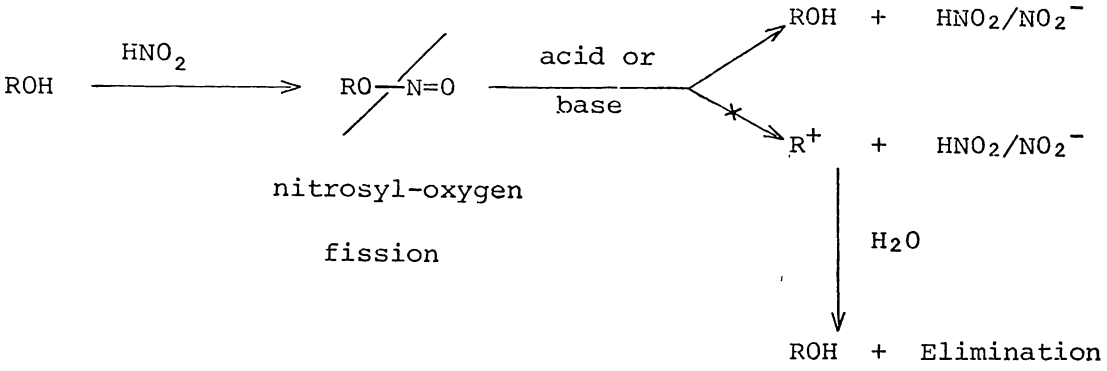


FIGURE 6: The failure of the plot to pass through the origin probably reflects a systematic error in the product recovery and analysis. At the lower percentages of reaction (less than 10%) the amount of 2-methylpropene produced in each reaction approached the minimum limit below which the product recovery method and GLC analysis was not 100% accurate.

7.4.4 Deamination Rate Enhancement by NaSCN

The thiocyanate ion is known to catalyse the nitrosation of amines (Chapter 4). In the deamination of primary aliphatic amines by nitrous acid the nitrosation step is rate-limiting (Chapter 2).

A single deamination of 2-amino-2-methylpropane at 25°C in the presence of NaSCN is described here.

Sodium thiocyanate (0.973g, 12.0 mmole) was added to a deamination carried out in the standard fashion.

Result: Chromatograms of the aqueous reaction mixture contained a number of peaks not present in uncatalysed deaminations. These were probably the alkyl thiocyanate (RSCN) and alkyl isothiocyanate (RCSN). Cannell[141] has identified these products in a study of various isomeric butylamine deaminations in the presence of the thiocyanate ion.

The proportions of substitution and elimination were estimated from the alkene and unreacted amine analyses.

Reaction time	30.25 minutes
Percentage of reaction	36.4% (c.f. 12.5% without NaSCN, TABLE 5)

Substitution 91.3%, Elimination 8.7%
c.f. 92±4% and 8.0±0.2% respectively in the absence of NaSCN (TABLE 5).

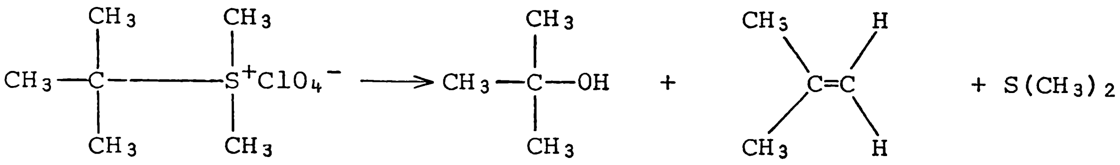
The rate enhancement may be due, in part, to ionic strength effects. In the absence of control experiments to test for salt effects and the influence of NaSCN upon the amine analysis, conclusive statements cannot be drawn from these results. Since this experiment was conducted out of interest only the additional work was not carried out. The experiment is reported here for future reference.

Chapter Eight

Hydrolysis of Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate

8.1 General

Dimethyl-(2-methyl-2-propyl)sulphonium perchlorate was prepared (Appendix 6.3) and hydrolysed in acidified (perchloric acid) sodium nitrite solution (pH4) at 80 and 50°C.

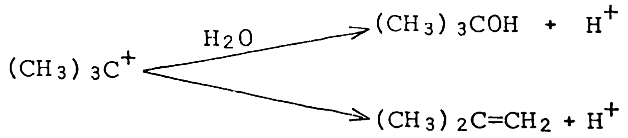


Attempts to study the hydrolysis at 25°C showed that little or no reaction occurs at this temperature even after one or two hours. However, the extremely slow rate of reaction at 25°C made it possible to control the extent of reaction at higher temperatures by simply cooling the reaction vessel. Stopping the reaction by cooling also prevented further hydrolysis during the time taken to analyse the reaction mixture.

The hydrolyses were carried out in acidified sodium nitrite solution to make the reaction conditions as similar as possible to those encountered in the deamination of 2-amino-2-methylpropane.

An advantage of this system was the nitrite ion/nitrous acid buffer effect. Both substitution and elimination pathways in hydrolysis produce hydrogen ions so in the absence of a buffer the reaction solution acidity rapidly increases (hence titrimetric analyses have been used in many rate studies).

$$(CH_3)_3C\overset{+}{-}S(CH_3)_2 \longrightarrow (CH_3)_3C^+ \;+\; S(CH_3)_2$$



Acidified sodium nitrite solution is a poor buffer system since the decomposition of the nitrous acid to nitrogen oxides reduces the hydrogen ion concentration[166].

$$NO_2^- + H^+ \rightleftharpoons HNO_2$$

$$4HNO_2 \longrightarrow 2NO + 2H_2O + N_2O_4$$

In the hydrolysis reactions the opposing effects result in an acidity easily maintained at pH4, the same as in deamination.

Solubility of the Sulphonium Salt:

At 25°C, 12.0 mmole of sulphonium salt was only partially soluble so in all reactions at 80 and 50°C only 6.00 mmole was used. The amount of sodium nitrite used was also halved to maintain a sulphonium salt: sodium nitrite mole ratio of 1:2.

8.2 Hydrolysis at 80°C

8.2.1 Apparatus and Procedure

APPARATUS: The apparatus employed was the same as that used for deaminations at 80°C (Chapter 7.2.1).

PROCEDURE: The deamination reactions were started and stopped by controlling the pH. The hydrolyses were started and stopped by manipulating the temperature. This difference was reflected in the reaction procedures. The hydrolyses were carried out in basically the same way as the deaminations (Chapter 7.2.1) at 80°C except for the following differences;

(i) Solid sulphonium salt (1.322 g, 6.00 mmole) and water (15.0 ml) were used instead of a prepared solution. This minimised decomposition of the starting material before use.

(ii) Perchloric acid (4.22M,0.25 ml) was added to the reaction mixture at room temperature and the water bath then filled at 80°C. The beginning of the reaction time was taken at the point when the water bath was filled.

(iii) After the appropriate reaction time the 80°C bath was emptied and replaced by the cold bath (-105°C , MeOH slush) to rapidly cool the reaction mixture and stop the hydrolysis. The final reaction time was taken at the point when the cold bath was applied.

(iv) After cooling the reaction mixture to 0-5°C the pH was adjusted to about pH 10.

(v) Water (20 ml) was added to the dioxane bubblers and thereafter the procedure was as previously described (Chapter 7.2.1).

Note on the Procedure:

See the "Notes on the Procedure" in Chapter 7.2.1. The use of a 10% w/w $CoCl_2.6H_2O$ precolumn was described for the analysis of the aqueous reaction mixture from the deamination. This was not used in the analysis of the hydrolysis reaction mixture since the injector temperature (on the Gas Chromatograph) was found to be an important factor in obtaining a clear baseline on the chromatograms. A "Celite" precolumn (10 cm) was used (new packing for each sample containing involatile salts) with an injector temperature of 70°C (see Appendix 1.3).

8.2.2 Results

The results of hydrolyses carried out at 80°C are summarised in TABLES 7 and 8 while FIGURES 7 and 8 show plots of product quantities versus percentage of reaction. A brief discussion follows in Section 8.2.3.

TABLE 7

Results of Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate Hydrolyses at 80°C

Reaction Time (min)	Percentage of Reaction ($S(Me)_2$)	(Product Sum)	% Substitution	% Elimination
3	1.35±0.07	1.57±0.02	97±2	3.02±0.07
5	5.3±0.1	6.0±0.1	96±2	3.6±0.1
6.5	8.3±0.5	9.5±0.1	96±2	3.80±0.09
9.5	11.5±0.2	12.5±0.1	96±1	3.94±0.09
12.5	18.7±0.5	19.7±0.2	96±1	4.25±0.04

mean % substitution 96±2

mean % elimination 3.7±0.4

TABLE 8

Results of Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate Hydrolyses at 80°C

Percentage of Reaction (Product Sum)	2-Methylpropan-2-ol (mole x 10^{-4})	2-Methylpropene (mole x 10^{-5})
1.57±0.02	0.91±0.01	0.284±0.006
6.0±0.1	3.47±0.06	1.28±0.03
9.5±0.1	5.46±0.07	2.16±0.04
12.5±0.1	7.23±0.07	2.97±0.06
19.7±0.2	11.3±0.1	5.02±0.03

FIGURE 7

Hydrolysis of Dimethyl-(2-methyl-2-propyl)-sulphonium Perchlorate at 80°C

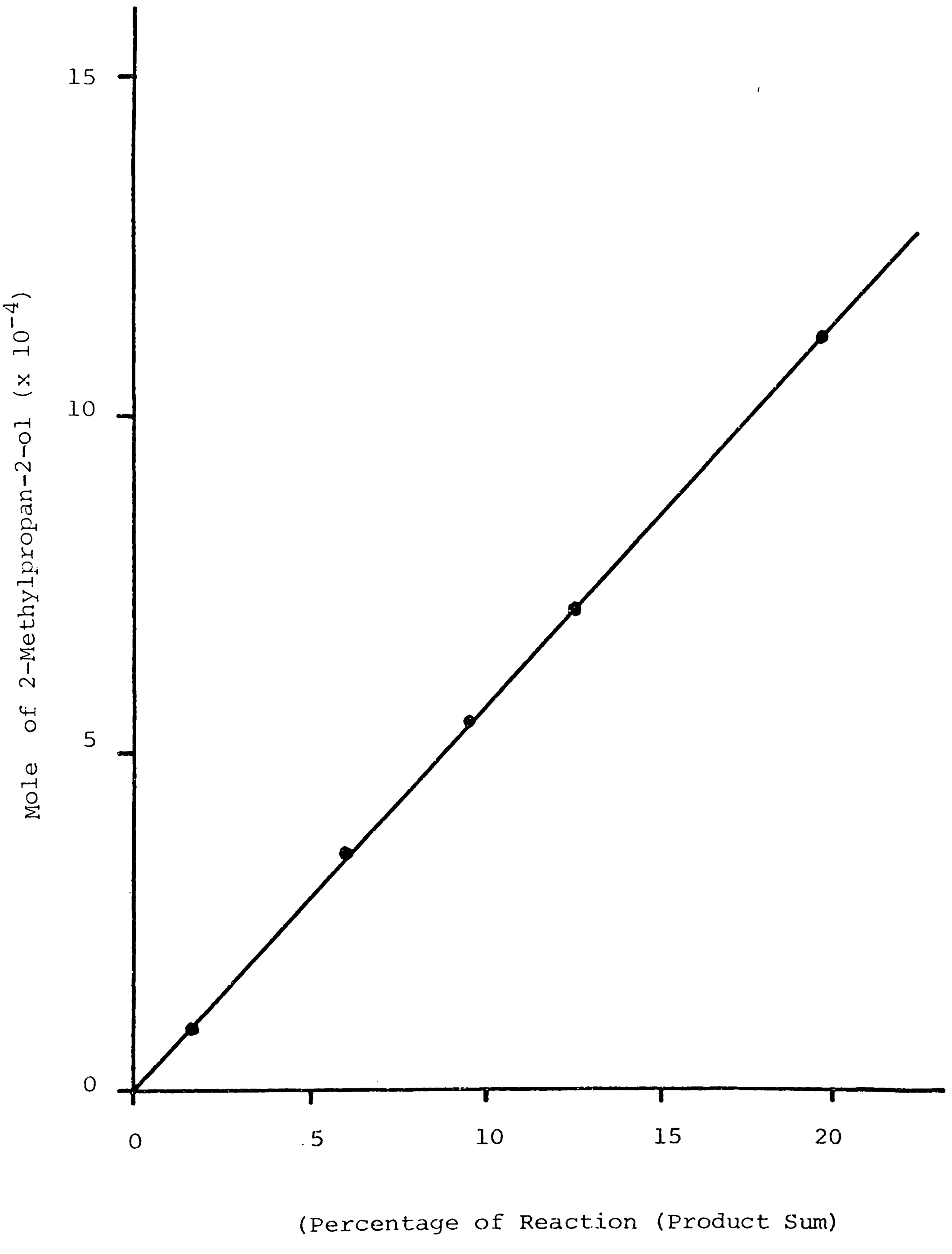
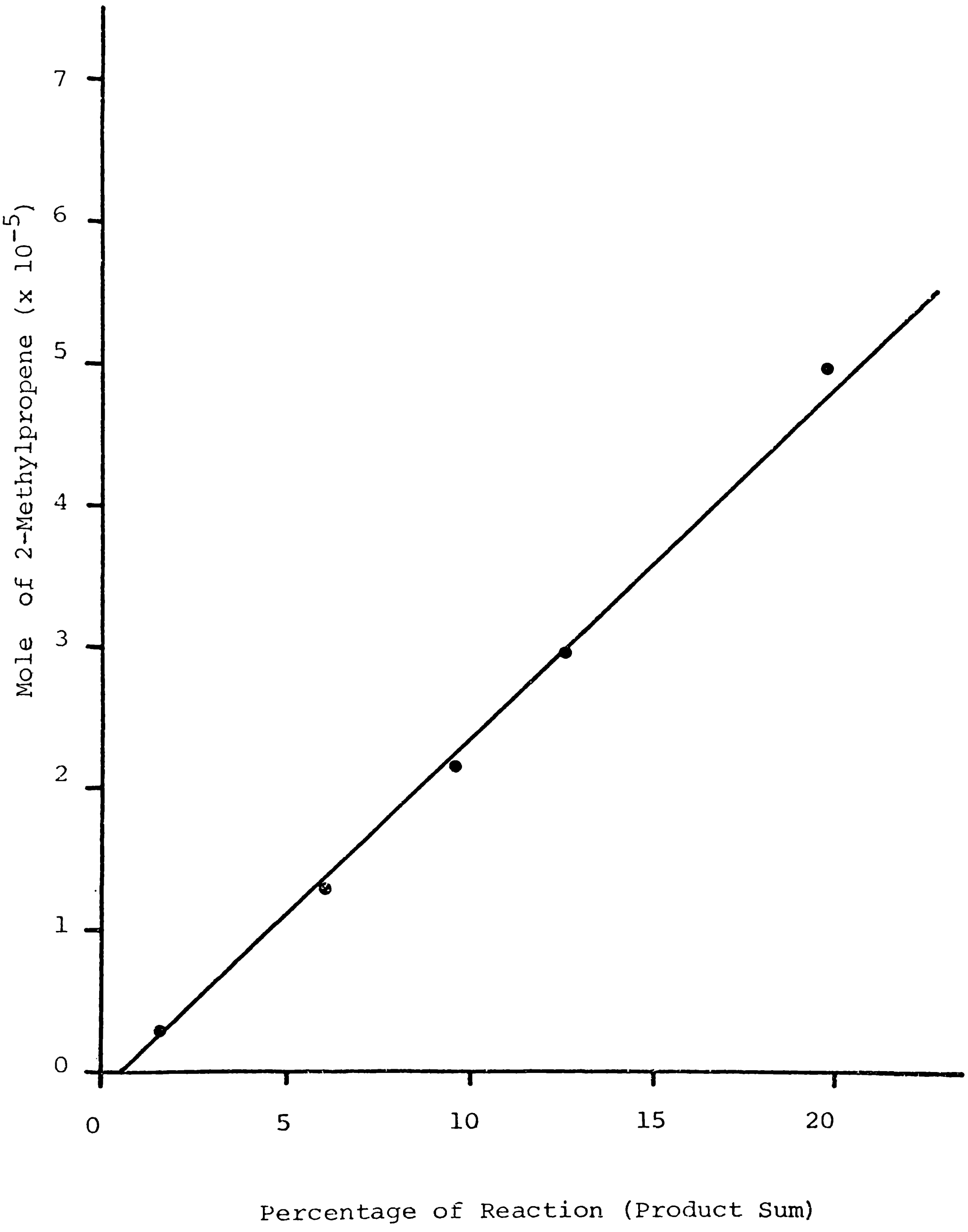


FIGURE 8

Hydrolysis of Dimethyl-(2-methyl-2-propyl)-

sulphonium Perchlorate at 80°C



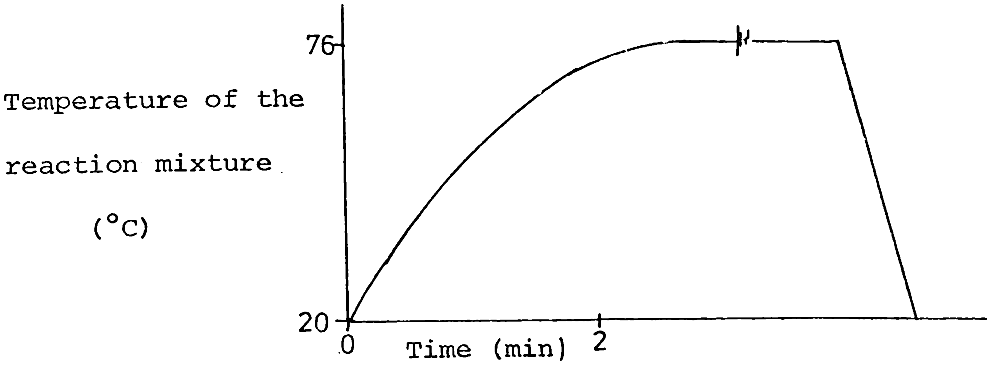
8.2.3 Discussion

Proportion of Elimination: The data in TABLE 7 shows a clear trend in the percentage of elimination. Though this may reflect some mechanistic change it is more probable that it is due to inaccuracies involved in trapping and analysing such small quantities of alkene. The amounts involved are close to the minimum that can be detected by the system used. With large sample injections of tetrachloromethane (from the CCl_4/Br_2 bubbler) of 10-12 µl, the gas chromatograph (Varian GC 3700) was operating on the maximum sensitivity of the flame ionisation detector.

Similar trends were observed in the deamination of 2-amino-2-methylpropane, particularly at the percentages of reaction with comparable amounts of elimination product.

The possibility of dehydration of the 2-methylpropan-2-ol contributing to the detected alkene was ruled out by a control experiment described in Chapter 7.2.4.

Reaction Temperature: All the hydrolysis reactions described in this thesis were started and stopped by controlling the reaction temperature. The variation of temperature with time is illustrated below:



The length of the plateau relative to the heating and cooling steps depends upon the reaction time. The cooling step was very much more rapid than the heating step since a very low temperature (-105°C) coolant was used while an 80°C bath was used for heating the solution.

It was possible that hydrolysis during the heating and cooling steps was contributing a different product distribution than hydrolysis in the plateau region. The results of hydrolyses at 50°C (Section 8.3) show essentially the same product ratio as the hydrolyses at 80°C. In addition, as the temperature drops the rate of hydrolysis decreases rapidly so the contribution from the hydrolysis at less then 75-78° would have been small (hydrolysis at 50°C is about 40 times slower than at 80°C - see TABLES 7 and 9).

Calculation of the Percentage of Reaction:

(i) Product sum :

$$\frac{\text{mole of 2-methylpropan-2-ol + mole of 2-methylpropene}}{\text{mole of starting material}} \times 100$$

(ii) $S(Me)_2$: Dimethyl sulphide was produced in a 1:1 mole ratio with the reaction of the sulphonium salt. Though no trapping system was specifically incorporated to account for this product, it was found to be effectively trapped in the dioxane bubblers (DIAGRAM 1, Chapter 7.2.1) and a small amount retained in the reaction vessel. The calculated percentages of reaction (TABLE 7) are somewhat lower than those obtained from the product sum, possibly due some loss of this water - insoluble product during opening of the reaction vessel at the end of the reaction and a small loss in the gas stream during the reaction.

Very large discrepancies were observed for hydrolyses at 50°C where very long reaction times were involved during which time much of the dimethyl sulphide was lost in the carrier gas stream.

8.2.4 Control Experiments:

No control experiments were required specifically for the hydrolysis at 80°C since most aspects were covered by those described for the deaminations (Chapter 7) and hydrolyses at 50°C (Section 8.3)

8.3 Hydrolysis at 50°C

8.3.1 Apparatus and Procedure

APPARATUS: The apparatus was the same as that used for the deamination of 2-amino-2-methylpropane at 50°C.

PROCEDURE: The procedure was basically the same as that used for the 80°C hydrolysis with the following differences;

(i) The carrier gas flow was reduced to approximately 10 ml/min after 40 minutes of reaction and restored to 30 ml/min about 10 minutes before the hydrolyses were stopped.

This was done to prevent excessive loss of bromine from the alkene trap and loss of product alcohol dissolved in the dioxane bubblers.

(ii) The reactions were cooled using an ice-bath instead of the MeOH slush bath.

8.3.2 Results

The results of the hydrolyses of dimethyl-(2-methyl-2-propyl)sulphonium perchlorate at 50°C are summarised in TABLES 9 and 10 while product quantities are plotted against percentage of reaction in FIGURES 9 and 10.

TABLE 9

Results of Dimethyl-(2-methyl-2-propyl)-
sulphonium Perchlorate Hydrolyses at 50°C

Reaction Time (min)	Percentage of Reaction	% Substitution	% Elimination
120	4.81±0.07	96±2	4.0±0.2
250	9.3±0.3	96±4	3.4±0.2
367	13.0±0.3	96±4	3.7±0.1
600	15.5±0.1	97±1	3.37±0.07

mean % substitution 96±3%

mean % elimination 3.6±0.3%

TABLE 10

Results of Dimethyl-(2-methyl-2-propyl)-
sulphonium Perchlorate Hydrolyses at 50°C

Percentage of Reaction	2-Methylpropan-2-ol (mole x 10^{-4})	2-Methylpropene (mole x 10^{-5})
4.81±0.07	2.78±0.04	1.17±0.07
9.3±0.3	5.4±0.2	1.9±0.1
13.0±0.3	7.4±0.2	2.84±0.06
15.5±0.1	8.83±0.08	3.06±0.06

FIGURE 9

Hydrolysis of Dimethyl-(2-methyl-2-propyl)-

sulphonium Perchlorate at 50°C

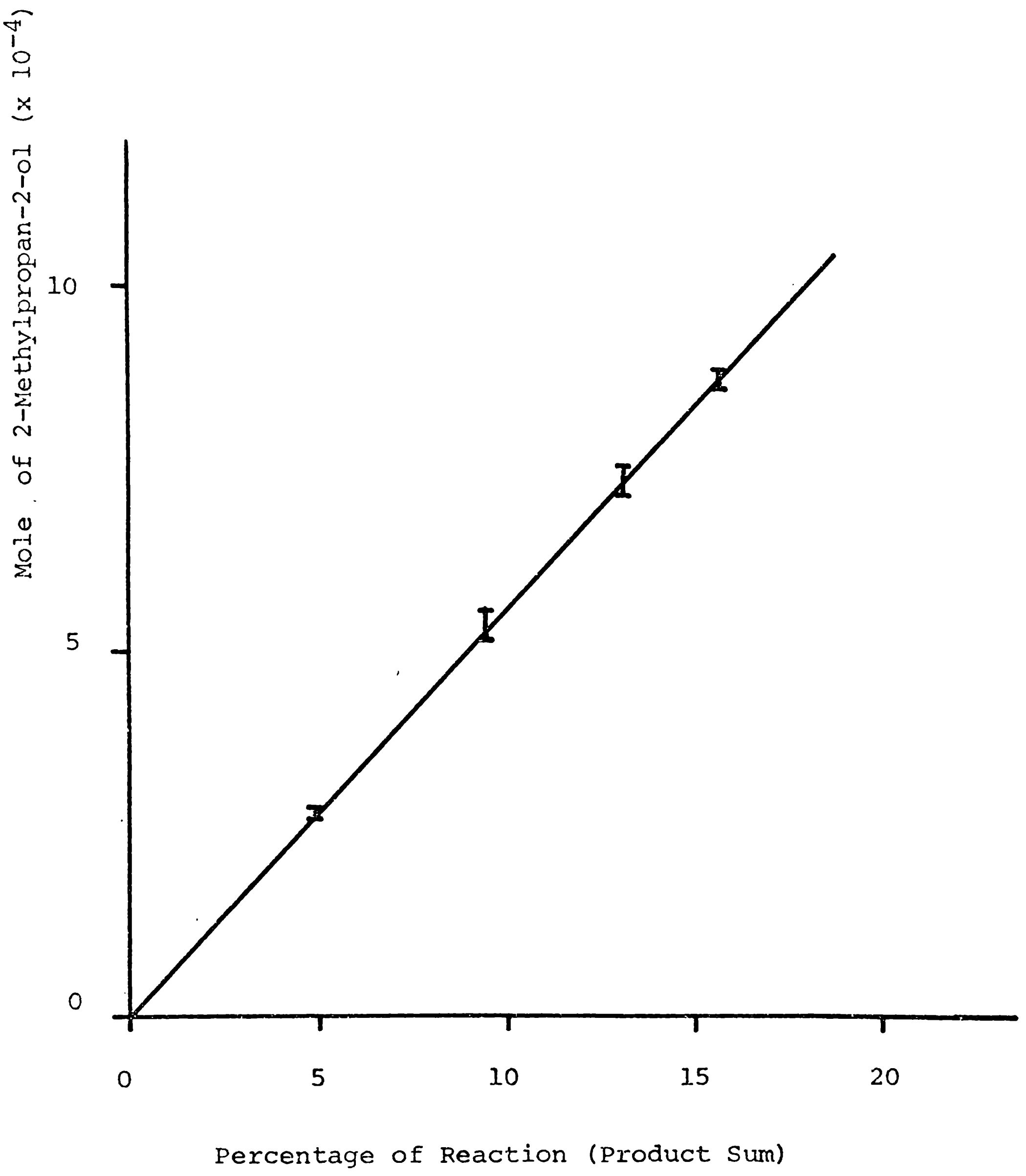
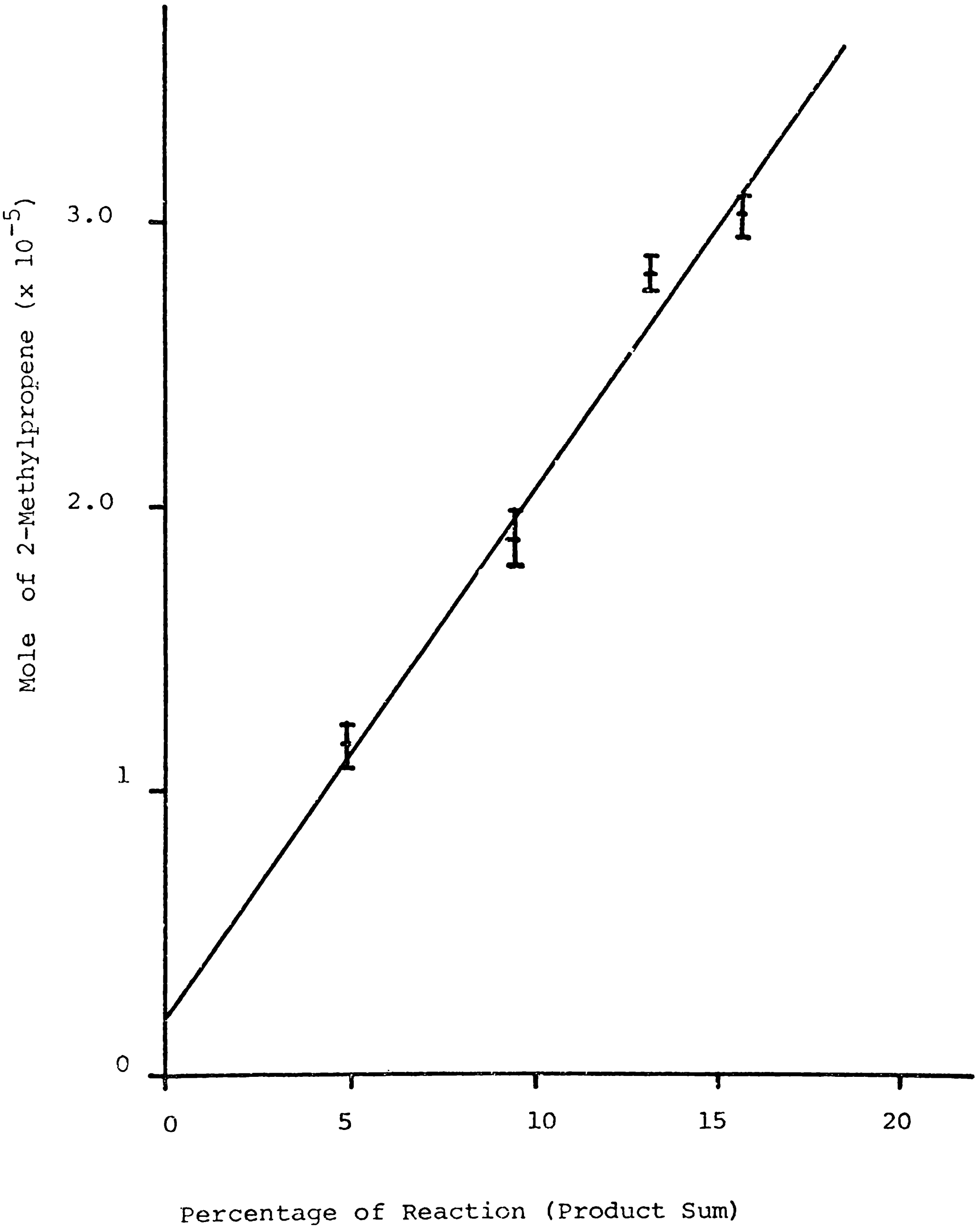


FIGURE 10

Hydrolysis of Dimethyl-(2-methyl-2-propyl)-
sulphonium Perchlorate at 50°C



8.3.3 Discussion

A detailed comparison of the 2-amino-2-methylpropane deamination and this hydrolysis, and the implications arising from this, is left to Chapter 11. However, it is clear that the deamination proceeds with more elimination than the corresponding hydrolysis.

Deamination at 50°C	substitution	92±2%
	elimination	8.2±0.8%
Hydrolysis at 50°C	substitution	96±3%
	elimination	3.6±0.3%

This difference may reflect a mechanistic difference (Chapter 11) or some experimental inequality. The reaction conditions were made as similar as possible with the latter possibility in mind. However, two aspects have been checked.

(a) Dimethyl sulphide was a product in the hydrolysis but not in the deamination. It may in some way have influenced the products in the hydrolysis to give the result observed. To test for this, a deamination (11.8% reaction) was carried out in which dimethyl sulphide (amount equivalent to that produced in 10% of hydrolysis) was added. The reaction is described in Section 8.3.4. The results clearly show no effect of the dimethyl sulphide on the deamination and analyses of the product alcohol and alkene. Since the same products, reaction conditions and analysis procedure occur in the hydrolysis, it can be said that the dimethyl sulphide product had no affect on the hydrolysis product analysis.

(b) More nitrogen oxides are expected to be present in the hydrolysis than in deamination. In deamination the nitrous acid can react by two pathways; (i) nitrosation of the amine and (ii). non-deaminative decomposition to nitrogen oxides. In hydrolysis only the decomposition pathway is available.

A hydrolysis was carried out using twice the amount of sodium nitrite (24.0 mmole) normally used. When acidified this would produce more nitrogen oxides. This reaction (described in Section 8.3.4) gave 4.7% elimination. Had the low proportion of elimination in the hydrolysis reaction been due to interference by nitrogen oxides one would have expected less than 3.6% elimination in this control. As it was, the proportion was slightly higher than usual.

2-Methyl-2-propyl nitrite and dimethyl sulphide could not be quantitatively determined under the method used for this hydrolysis at 50°C. The two compounds coincided on the chromatogram obtained from the aqueous phase, thus ruling out an assessment of the alkyl nitrite. The total dimethyl sulphide was distributed over the reaction vessel and all the bubblers with some passing out of the system in the effluent gas stream.

Failure to determine the amount of alkyl nitrite produced was not a serious problem as little was expected in an aqueous reaction at 50°C. Only a small trace was found in deaminations at 50°C. Tests with independently prepared alkyl nitrite (Appendix 6.5) showed that it hydrolysed rapidly to the alcohol even at 25°C. Should a significant amount actually be present it would add to the overall amount of substitution observed and further lower the proportion of elimination.

8.3.4 Control Experiments

(a) Product Analysis in the Presence of Dimethyl Sulphide.

2-Amino-2-methylpropane was deaminated at 50°C in the standard fashion (Chapter 7.3.1) except that dimethyl sulphide (44 µl, 0.600 mmole) was added to the reaction mixture before initial acidification.

Results; reaction time, 5.25 minute ; percentage of reaction, 11.8±0.2 (product sum); substitution, 92±2%; elimination, 8.5±0.2%; 2-methylpropan-2-ol, $(6.5\pm0.1) \times 10^{-4}$ mole ; 2-methylpropene, $(6.0\pm0.1) \times 10^{-5}$ mole .

The extent of reaction determined from the analysis of unreacted amine (13.4%) was probably in error due to interference in the analysis by dimethyl sulphide which is a base.

The results are consistent with those obtained from deamination in the absence of dimethyl sulphide where the 5 minute reaction gave the following results (TABLE 3, Chapter 7.3.2); percentage of reaction, 11.0±0.2 (product sum); substitution, 92±1%; elimination 7.7±0.5%.

(b) Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate, Hydrolysis at 50°C with 24.0 mmole of Sodium Nitrite.

A hydrolysis was carried out in the standard fashion, however with double the usual amount of sodium nitrite present (8.40 ml, 3.00M, 24.0 mmole).

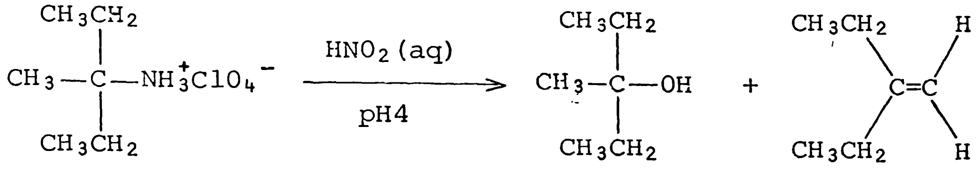
Results; reaction time, 120 minute ; percentage of reaction, 4.3% (product sum); substitution, 95.3%; elimination, 4.7%.

Chapter Nine

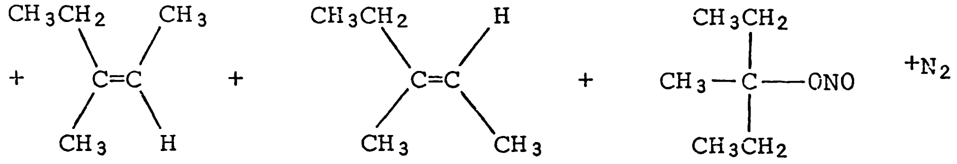
Deamination of 3-Amino-3-Methylpentane

9.1 General

3-Amino-3-methylpentane was prepared as the perchlorate salt (Appendix 6.8) and deaminated in acidified (perchloric acid) sodium nitrite solution (pH4) at 80 and 50°C.



3-methylpentan-3-ol   2-ethylbut-1-ene



cis-3-methylpent-2-ene   trans-3-methylpent-2-ene   3-methyl-3-pentyl nitrite

Deaminations of 3-amino-3-methylpentane were carried out in essentially the same way as described for deaminations of 2-amino-2-methylpropane but with differences in the trapping system used. The procedure for deaminations at 50°C was developed first but was such that the corresponding sulphonium salt could not be hydrolysed by the same method:- the reaction vessel was flushed with carrier gas (nitrogen, 100 ml/min) for 30 minutes at 50°C to transfer the product alkenes to the alkene traps at the end of the deamination. In hydrolysis, such a step would need to be done at

0-3°C since the reaction would otherwise continue. Control experiments with the deamination showed that alkene trapping was incomplete if the reaction vessel was less than 50°C during the flushing period.

Deaminations were conducted at 80°C so that the alkenes would be swept from the reaction vessel immediately after formation so that little would remain when the reaction mixture was rapidly cooled. Such a procedure did not require the lengthy high temperature flushing step so could also be used to study the hydrolysis of dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate (Chapter 10).

The initial reagent concentrations were the same as used in the deaminations of 2-amino-2-methylpropane at 80 and 50°C :

Amine Salt : 0.250M, 6.00 mmole
Sodium Nitrite : 0.500M, 12.00 mmole.

Error noted from the examination.

Bromination of the trans and cis isomers would give products that are diastereoisomers. Although these have different physical properties a system where the alkenes are trapped directly was used.

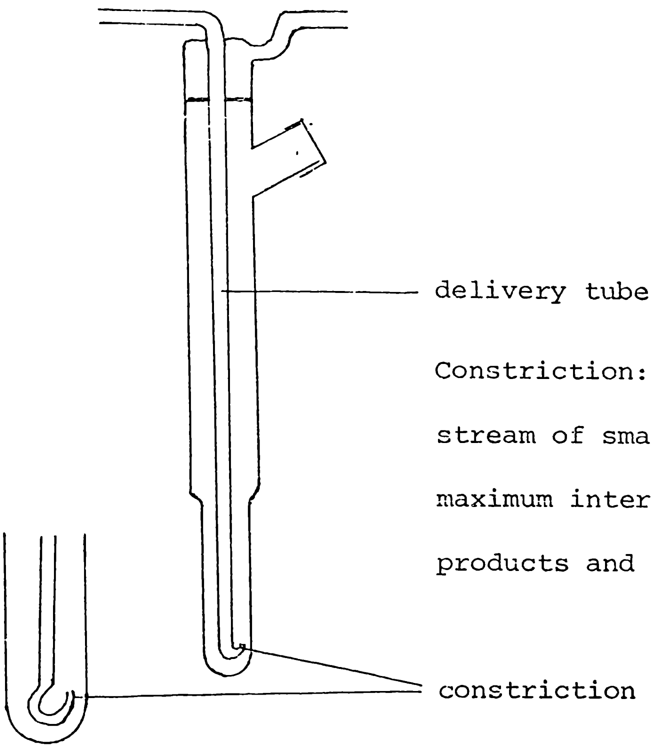
9.2 Deamination at 80°C

9.2.1 Apparatus and Procedure

APPARATUS: The apparatus used was based upon that shown in DIAGRAM 1 (Chapter 7.2.1). The modifications reflect the difference in the elimination products obtained from the 2-methyl-2-propyl and 3-methyl-3-pentyl systems. The latter produces three isomeric alkenes (see Section 9.1) with boiling points in the range 64-71°C/1 atm compared with -6.9°C/1 atm for 2-methylpropene. A higher carrier gas flow was used in reactions of the 3-methyl-3-pentyl system to ensure a rapid transfer of the alkenes to the traps.

Two cold traps in series (-105°C, MeOH slush) containing diethyl ether (20 ml) were used in place of the dioxane, tetrachloromethane/bromine and tetrachloromethane bubblers. ~~The alkenes could not be brominated since a common derivative would form from the cis and trans isomers.~~ The cold traps collected evaporated 3-methylpentan-3-ol and 3-methyl-3-pentyl nitrite in addition to the elimination products.

A condenser was mounted on the carrier gas exit from the reaction vessel and a "U" tube (immersed in ice/water) inserted between the condenser and the first cold trap. These were designed to condense water evaporated from the reaction solution which would otherwise freeze in the delivery tube of the first cold trap and possibly block the constriction at the end of the tube (DIAGRAM 2).



Constriction: designed to produce a stream of small bubbles and give maximum interaction between the gaseous products and solvent.

DIAGRAM 2

PROCEDURE: The procedure was basically the same as that described in Chapter 7.2.1 with the following differences:

(i) 3-Amino-3-methylpentane perchlorate salt solution (15.0 ml, 0.400M, 6.00 mmole) was generally used though solid salt (1.2099 g, 6.00 mmole) and water (15 ml) was also used on occasions.

(ii) At the end of the reaction when the reaction mixture had been cooled to 0-3°C, the carrier gas was flushed through the system for a further 5 minutes (100ml/min).

(iii) An ice-bath was used for cooling the reaction mixture after the deamination had been stopped instead of the cold bath (-105°C).

(iv) The tube connecting the condenser to the first cold trap was detached at the condenser and diethyl either (15 ml) flushed down the tube into the first cold trap (still at 105°C). This transferred any condensed product to the trap.

(v) Water (20 ml) was flushed down the condenser into the reaction vessel to collect any condensed product and the fittings to the reaction vessel were removed as previously described (Chapter 7.2.1). Aliquots of propan-1-ol (100 µl, 1.357 mmole, GLC internal standard) were added to the reaction vessel and to each cold trap. These were then analysed as described in Appendix 1.4. Samples of reaction mixture were also taken for the analysis of unreacted amine (5.0 ml, Appendix 2.1.1) and sodium nitrite (1.0 ml, Appendix 2.2.1).

Some deaminations were carried out with slightly different procedures to check aspects of the technique and these are described and discussed in Sections 9.2.3 and 9.2.4.

9.2.2 Results

The results of the deaminations of 3-amino-3-methylpentane carried out at 80°C are summarised in TABLES 11 and 12 while FIGURES 11 and 12 show plots of product quantity versus percentage of reaction. A brief discussion follows in Section 9.2.3 while control experiments are described in Section 9.2.4.

TABLE 11

Results of 3-Amino-3-methylpentane Deaminations at 80°C

Reaction Time	Percentage of Reaction						
(sec)	(Amine Analysis)	(Product Sum)	% Substitution[a]	% Elimination	% 1-ene	% cis 2-ene	% trans-2-ene
20	4.09	6.7±0.2	83±3	17.8±0.5	16±1	27.5±0.8	55±1
15[b]	-	7.8±0.1	77±2	23.0±0.9	15.7±0.5	30±2	55±3
35	11.0	10.0±0.3	77±4	22.7±0.8	17.1±0.5	26.8±0.5	56.0±0.5
30	17.4	14.5±0.2	77±1	22.4±0.3	19.5±0.5	28.9±0.3	51.8±0.6
45	13.6	15.7±0.3	80±3	20.5±0.7	17±1	27±1	56±2
-[c]	15.3	16.3±0.3	81±3	18.8±0.6	16.4±0.6	29±1	55±3
-[d]	18.3	21.2±0.1	79.8±0.7	20.2±0.4	16.3±0.8	28.4±0.9	55±2
-[e]	29.1	31.3±0.2	78.3±0.4	21.8±0.5	17.3±0.8	27±2	56±3
120	32.5	35.2±0.2	77±2	23.3±0.5	16.5±0.5	28.1±0.8	55±2

Notes (a) - (e) overleaf

Notes (TABLE 11):

(a) 3-Methylpentan-3-ol was the major substitution product but 3-methyl-3-pentyl nitrite was also produced. This is discussed in Section 9.2.3.

(b) 6.770 mmole of amine salt was used instead of the standard 6.00 mmole.

(c) The reaction mixture was acidified while at 6°C then heated to 70°C (water bath, 80°C) and finally cooled to 18°C (-105°C, MeOH slush bath) before the addition of base (NaOH, 5M). Reaction time from the beginning of the heating to the application of the cold bath was 3 minutes.

(d) The deamination was initiated at 80°C with perchloric acid (4.22M) but cooled (ice-bath) after 1 minute before addition of base (NaOH,5M) at 1 minute 25 seconds.

(e) The reaction mixture was acidified at room temperature then heated (water bath, 80°C) to 75°C before being slowly cooled (water bath, 20°C then an ice-bath) to 8°C over 7 minutes. Base was added to the cold reaction mixture.

Deamination of 3-Amino-3-methylpentane (80°C)

mean % substitution	79±2
mean % elimination	21±2
Ratio of Isomeric Alkenes:	
mean % 2-ethylbut-1-ene	17±1
mean % cis-3-methylpent-2-ene	28±1
mean % trans-3-methylpent-2-ene	55±2

TABLE 12

Results of 3-Amino-3-methylpentane Deaminations at 80°C

% Reaction (Product Sum)	Substitution Products (mole x 10^{-4})	1-ene (mole x 10^{-5})	cis-2-ene (mole x 10^{-5})	trans-2-ene (mole x 10^{-5})	total elimination (mole x 10^{-4})
6.7±0.2	3.3±0.1	1.16±0.08	1.95±0.05	3.90±0.09	0.71±0.01
7.8±0.1	4.1±0.1	1.92±0.02	3.6±0.2	6.7±0.3	1.22±0.04
10.0±0.3	4.6±0.2	2.32±0.07	3.64±0.07	7.62±0.04	1.36±0.01
14.5±0.2	6.7±0.1	3.8±0.1	5.64±0.04	10.1±0.1	1.95±0.01
15.7±0.3	7.5±0.2	3.2±0.2	5.2±0.2	10.9±0.2	1.93±0.04
16.3±0.3	7.9±0.2	2.98±0.08	5.2±0.2	10.0±0.5	1.82±0.05
21.2±0.1	10.16±0.06	4.2±0.2	7.3±0.2	14.2±0.4	2.57±0.05
31.3±0.2	14.72±0.00	7.1±0.3	11.1±0.6	23±1	4.1±0.1
35.2±0.2	16.2±0.3	8.1±0.2	13.8±0.3	27.3±0.9	4.92±0.09

FIGURE 11

Deamination of 3-Amino-3-methylpentane at 80°C

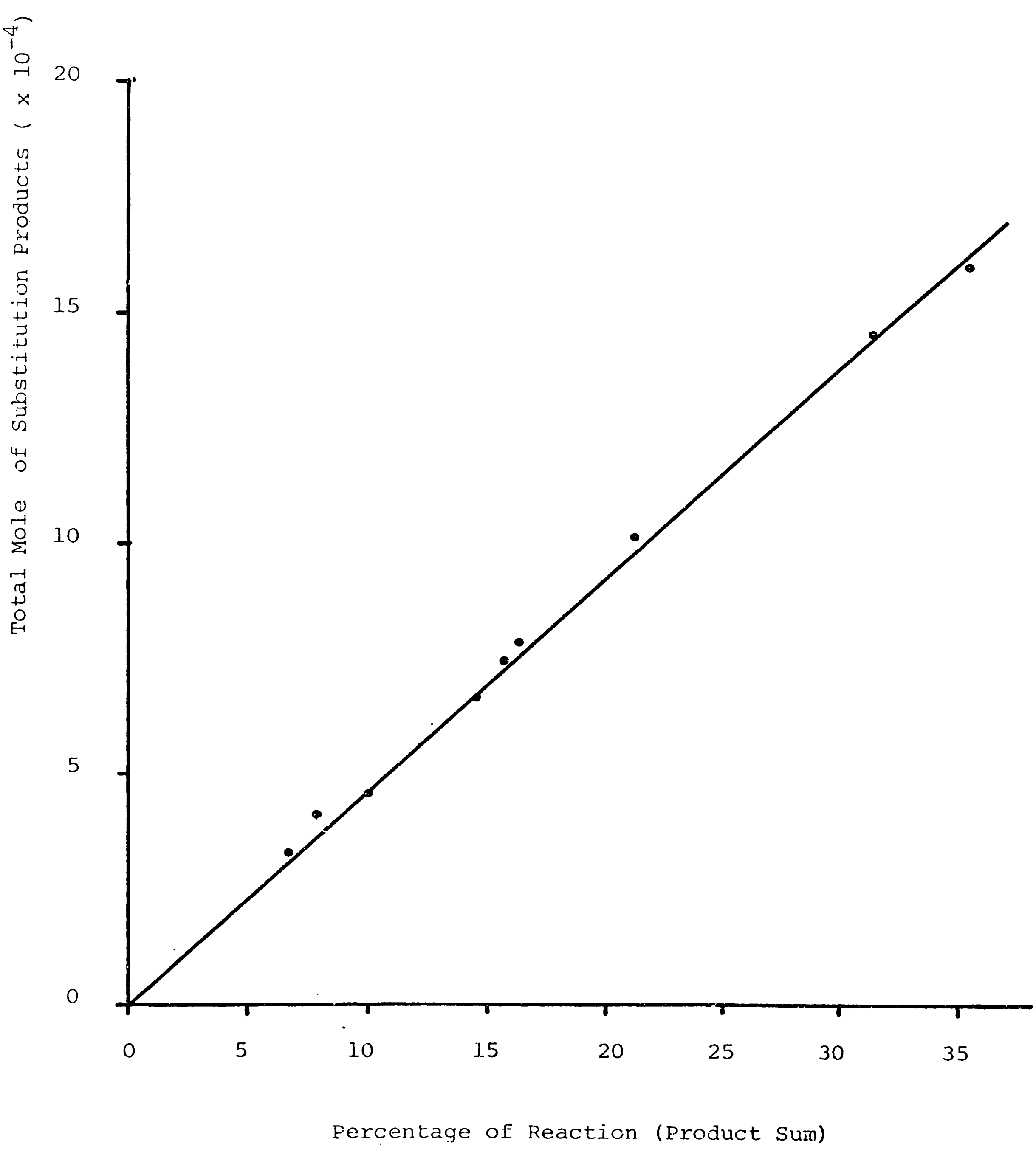
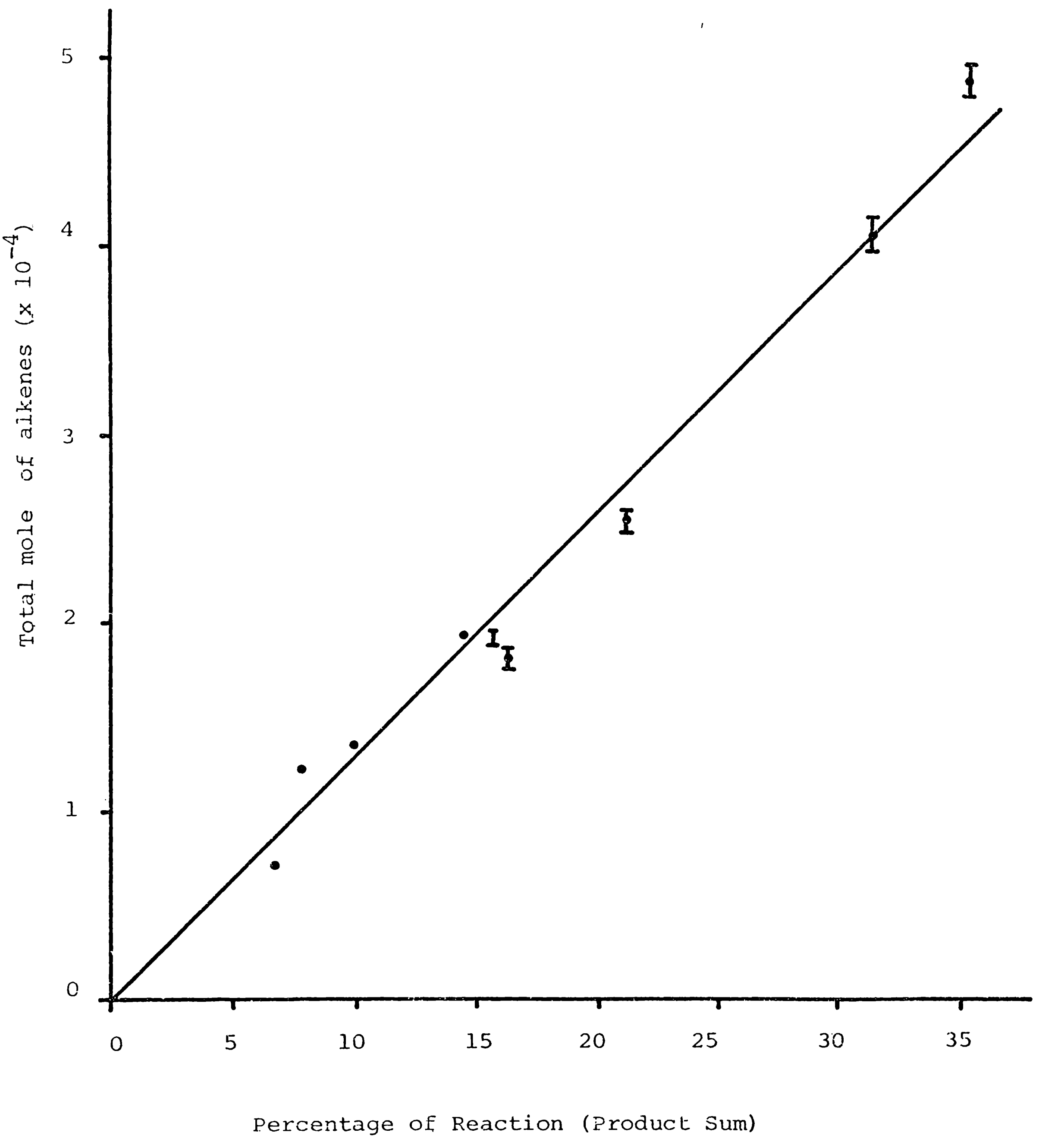


FIGURE 12

Deamination of 3-Amino-3-methylpentane at 80°C



9.2.3 Discussion

(a) Deaminations Started and Stopped by Temperature Changes.

Two deaminations were carried out in which the reaction was stopped by cooling the reaction mixture (see Notes attached to TABLE 11). One reaction was rapidly cooled using a methanol slush bath (-105°C) while the other was slowly cooled (reactions labelled c and e respectively). Experiment (c) (TABLE 11) was acidified at 6°C and the reaction started by heating the reaction mixture to 70°C (80°C water bath).

The hydrolysis reactions with which the deamination results are to be compared were also started and stopped by varying the reaction temperature (see Chapter 8.2.3). Deaminations (c) - (e) (TABLE 11) tested whether the product analyses or product ratios were affected by the temperature variation. The results are consistent with the normal acid-base controlled deaminations (TABLE 11). It was therefore expected that the different methods used to start and stop the deamination (acid-base) and hydrolysis (temperature variation) reactions did not influence the results from the point of view of the trapping and analysis of the products.

A consideration that remained however, was how the product ratio from the hydrolysis would be affected by the variations in reaction temperature. This is discussed in Chapter 10.2.3.

(b) Substitution Products.

The alcohol (3-methylpentan-3-ol) was the major substitution product, comprising 90-98% of the total substitution. The remainder was 3-methyl-3-pentyl nitrite. The nitrite appeared only in the first cold trap (20 ml diethyl ether at -105°C), not the reaction vessel, and rapidly decomposed to the alcohol on standing over a period of hours. This was shown by the concurrent decrease of the alkyl nitrite peak and increase of the alcohol peak.

The alkyl nitrite may arise as a primary reaction product or from the secondary reaction of the product alcohol with the acidified sodium nitrite solution. Since alkyl nitrites are insoluble in water even a small amount formed would tend to evaporate at 80°C or hydrolyse back to the alcohol (see Chapter 7.4.3).

That the alkyl nitrite may be formed from the alcohol was shown in control experiments designed to test for the efficiency of the product alcohol analysis (see Sections 9.2.4 and 9.3.4). In the experiment described in Section 9.2.4, a known quantity of 3-methylpental-3-ol was added to an acidified sodium nitrite solution ($HClO_4$, pH4, 80°C) in the reaction apparatus. Subsequent analyses showed alkyl nitrite in the first cold trap in approximately the ROH/RONO proportion observed in the deaminations. The alkyl nitrite was also observed in deaminations at 50°C and during the control experiments at 50°C (Section 9.3).

The source of the 3-methyl-3-pentyl nitrite, therefore remains uncertain.

Since the amount of the compound produced was also uncertain due to its rapid hydrolysis the substitution data are given as product alcohol plus alkyl nitrite. An unknown amount of the nitrite may have been hydrolysed in the reaction vessel if it was a primary product.

No nitro alkane product was observed.

Product Stability During the Reactions:

3-Methylpentan-3-ol: In addition to the conversion of product alcohol to the alkyl nitrite it was possible for dehydration to also occur under the high temperature, acidic conditions employed. If so, this could have seriously interfered with the analysis of elimination from the deamination since the two processes would be expected to produce isomeric alkenes in different ratios. The alcohol was the major product so even 5-10% of alcohol dehydration would alter the overall alkene ratios observed. A control experiment, described in Section 9.2.4 showed that no alcohol dehydration occurred under the reaction conditions.

Elimination Results:

The complete recovery of product alkenes and their stability under the reaction conditions was tested by a control experiment described in Section 9.2.4.

The experiment showed that the alkene trapping system and reaction procedure recovered all the product alkenes.

No significant change in the isomer ratios was observed with respect to the alkene mixture initially injected into the experiment.

Cold Traps:

The choice of two diethyl ether (20 ml) cold traps (methanol slush, -105°C) to trap the evaporated alkenes was the result of a number of trials using different solvents, temperatures and the number of traps in series. These are mentioned further in Section 9.3.

Only one deamination at 80°C used four diethyl ether cold traps in series (35 second reaction) and no alkenes were found beyond the second trap.

Rearrangement in Deamination:

No rearrangement products were detected in any of the deaminations of 2-amino-2-methylpropane or 3-amino-3-methylpentane. Any rearrangements occurring would involve the formation of a secondary or primary carbocation but such endothermic rearrangements are known in deamination studies. Authentic samples of all the possible rearranged products were not prepared and their retention times determined (2-methylpropan-1-ol and butan-2-ol were checked for the 2-methyl-2-propyl system). Retention times relative to the unrearranged products could be estimated and the chromatograms showed no significant unknown peaks to indicate that rearrangement was occurring.

9.2.4 Control Experiments

(i) Test for 3-Methylpentan-3-ol Stability and Analysis Under the Reaction Conditions (80°C).

The apparatus was arranged in the manner typical for a reaction at 80°C. Sodium perchlorate solution (15.0 ml, 0.400M, 6.00 mmole) and sodium nitrite solution (8.40 ml, 1.500M, 12.00 mmole) were added to the reaction vessel and the thermometer replaced. 3-Methylpentan-3-ol (100 µl, 0.817 mmole) was injected into the solution after acidification and the mixture heated (water bath 80°C) to 75°C and allowed to react for 9 minutes before cooling (methanol slush bath, -105°C) The subsequent product analysis found 0.83±0.02 mmole of alcohol and alkyl nitrite. The alkyl nitrite comprised 10% of the total.

No alkenes were detected indicating that the alcohol was not dehydrated under the reaction conditions.

(ii) Test for Alkene Stability and Analysis Efficiency Under the Reaction Conditions (80°C).

A reaction was carried out in the same way as control experiment (i) except that a mixture of the isomeric alkenes was injected into the nitrous acid solution at 23°C. After 2 minutes at 70-75°C the reaction mixture was cooled.

The analyses of the cold traps showed 99% recovery of the alkenes with no significant alteration of the isomer ratios.

	Initial Percentage	Isomer percentages after Control Experiment
1-ene	63.4%	61±4%
cis-2-ene	22.0%	21±1%
trans-2-ene	14.6%	17.9±0.7%

A small amount of 1-ene ⟶ trans-2-ene conversion was evident, however, deamination produces only 17% (TABLE 11) 1-ene so this was not likely to be important.

Curiously, after standing for two days at room temperature the traps showed the following alkene proportions; 1-ene 60.3%; cis-2-ene, 15.5%; trans-2-ene, 24.2%. Significant cis-2-ene ⟶ trans-2-ene conversion had taken place possibly with the involvement of dissolved nitrogen oxides[167].

9.3 Deamination at 50°C

9.3.1 Apparatus and Procedure

The apparatus and procedure were basically the same as described for deamination at 80°C except that the reaction vessel was flushed with carrier gas (nitrogen, 100 ml/min) for 30 minutes at 50°C after base addition to transfer the product alkenes to the cold traps. The thermometer previously used to measure the solution temperature was replaced by a microburette (1.0 ml) containing perchloric acid (4.22M) used to maintain the reaction pH in the range pH 3.9-4.1.

9.3.2. Results

Only two deaminations were conducted by the procedure described above before it was realised that hydrolyses could not be done by the same procedure (see Section 9.1). The results of the two reactions are summarised in TABLES 13 and 14.

TABLE 13

Results of 3-Amino-3-methylpentane Deaminations at 50°C

Reaction Time (min)	Percentage of Reaction (Amine Analysis)	(Product Sum)	% Substitution	% Elimination	% 1-ene	% cis-2-ene	% trans-2-ene
4	10.9	9.8	77	23	15	26	59
11	24.9	21.2	81	19	16	26	58

TABLE 14

% Reaction (Product Sum)	Substitution Products (mole x 10^{-4})	1-ene (mole x 10^{-5})	cis-2-ene (mole x 10^{-5})	trans-2-ene (mole x 10^{-5})	total elimination (mole x 10^{-4})
9.8	4.55	1.98	3.55	8.03	1.36
21.2	10.3	3.97	6.23	14.0	2.42

9.3.3 Discussion:

The procedure for carrying out deaminations of 3-amino-3-methylpentane at 50°C (Section 9.3.1) was developed from a method used for a series of reactions that produced results indicating incomplete analysis of product alkenes. A series of control experiments indicated that the current procedure and apparatus gives alkene analyses of 97-99.5% efficiency, and alcohol+alkyl nitrite analyses of 99-100% efficiency.

9.3.4 Control Experiments

The control experiments were directed towards establishing a trapping and reaction procedure that would give 100% recovery of the reaction products. Three types of control experiment of increasing complexity were involved.

(a) Simulated deamination reaction using sodium perchlorate and sodium chloride solutions in place of the amine salt and sodium nitrite respectively. This tested the efficiency of the nitrogen flow, temperature and time involved in the product recovery.

(b) Simulated reaction using sodium perchlorate and sodium nitrite solutions at pH4. This tested the effect of nitrous acid on the reaction products as well as the efficiency of product recovery from the apparatus.

(c) A deamination was conducted using a 2-amino-2-methylpropane at 50°C. Known quantities of 3-amino-3-methylpentane deamination products (alcohol and alkenes) were added and assessed.

Method (c) had the advantage of recreating, as closely as possible, the conditions of the actual deamination being studied. In particular, considerable amounts of gas;nitrogen, nitrogen oxides and volatile organic products were evolved from the reaction mixture and this may have affected the extent to which the reaction products were evaporated from the reaction vessel.

Numerous control experiments using known quantities of 3-methylpentan-3-ol or a mixture of the three isomeric alkenes were carried out with variations to the carrier gas flow rate, period of flushing of the reaction vessel, the cold trap solvents and temperature and the number of cold traps until the current system was found. Efficiencies varied from 35% to 99.3% recovery of added substrates. The final set of conditions were tested using the 2-amino-2-methylpropane background control.

Nitrogen (carrier gas) flow 100 ml/min

Flushing period; 30 minute at 50°C

Traps: 2 x 20 ml diethyl ether, -105°C (MeOH slush bath).

Test of the 3-Methylpentan-3-ol Analysis

The alcohol (50 µl, 0.41 mmole) was added to a 2-amino-2-methylpropane deamination (50°C, pH4) with the conditions listed above and reacted for 9 minutes before base addition and flushing of the reaction vessel.

Final analysis showed 0.39 mmole of alcohol giving a recovery efficiency of 96%. Deficiencies in the recognition and analysis of 3-methyl-3-pentyl nitrite make this efficiency closer to 100%.

Test of Elimination Product Analysis Efficiency

A mixture of the three isomeric alkenes was added to a 2-amino-2-methylpropane deamination as above, and reacted for 4 minutes.

Analysis showed a 99.4% recovery efficiency and no change in the ratio of the isomers.

Traps investigated included solvents such as propan-1-ol (acetone was the internal standard), and isooctane. The isooctane had the advantage of a long retention time on a 15% PPG (LB-550-X) GLC column and therefore it left the acetone and alkenes on a flat baseline, but it interfered with the propan-1-ol (internal standard for the substitution products), 3-methylpentan-3-ol and alkyl nitrite peaks. These three compounds had retention times considerably longer than diethyl ether. However, the isomeric alkenes had retention times that placed them on the tail of the diethyl ether solvent peak (see a diagram of the chromatogram in A1.5, P141 ~~Appendix 1.5~~). This was only a problem at very low concentrations of the alkenes (at less than 5% of deamination).

Ethyl acetate was originally used as the coolant (-85°C) for the cold traps but a methanol slush (-105°C) was found to give a considerable improvement in the alkene trapping efficiency.

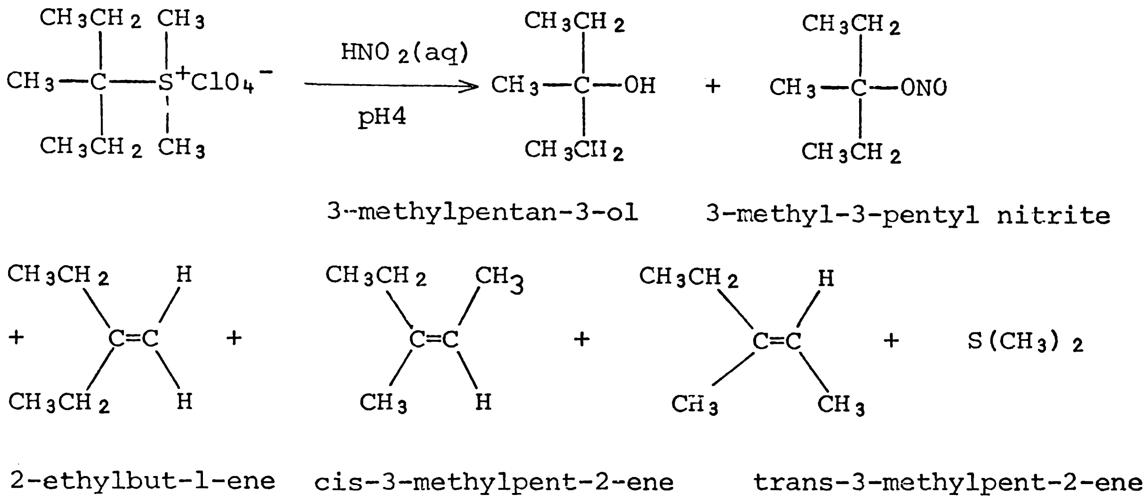
Attempts to use a system with no carrier gas flow through the apparatus, but rather an extraction procedure (diethyl ether) to remove the alkenes from the reaction vessel, gave no better than 50% recovery of the product alkenes.

Chapter Ten

Hydrolysis of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate

10.1 General

Dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate was prepared (Appendix 6.10) and hydrolysed in acidified (perchloric acid) sodium nitrite solution (pH4) at 80°C.



The reasons for carrying out the hydrolysis at 80°C have been explained in Chapter 9.1. Further relevant introductory comments have been included in Chapter 8.1. The products of this reaction are the same as those obtained from 3-amino-3-methylpentane deamination except that dimethyl sulphide is produced instead of nitrogen.

Initial reagent concentrations and quantities:

Sulphonium salt; 0.250M, 6.00 mmole.

Sodium nitrite; 0.500M, 12.00 mmole.

10.2 Hydrolysis at 80°C

10.2.1 Apparatus and Procedure

APPARATUS: The apparatus was identical to that used for the corresponding deaminations at 80°C (Chapter 9.2.1).

PROCEDURE: The procedure was basically the same as that described for the 3-amino-3-methylpentane deamination (c) at 80°C (see Chapter 9.2.1 and the Notes attached to TABLE 11) except with the following differences;

(i) Solid sulphonium salt (1.4805g, 6.00 mmole) and water (15.0 ml) were used instead of a prepared solution. This minimised reaction of the starting material before use.

(ii) After the solid sulphonium salt was added to the sodium nitrite solution and the reaction vessel was closed to the atmosphere, the mixture was allowed to stir at room temperature to dissolve most of the solid salt (2-3 min). A sample was removed (5 μl) and a chromatogram obtained to determine the amount of 3-methylpentan-3-ol contaminant in the 6.00 mmole of starting material used. This would later be deducted from the total amount of alcohol detected at the end of the reaction (see Section 10.2.3). Appendix 1.4.1 describes the GLC column and conditions used while the "Notes to the Procedure" in Chapter 8.2.1 discuss the use of a precolumn during the GLC analysis of the aqueous reaction mixture.

In one of the hydrolysis reactions carried out, the reaction mixture was sampled three times in succession (over 20 min) and only a small continuous increase in the amount of 3-methylpental-3-ol present was observed. This indicated that the hydrolysis was very slow at room temperature. Solutions of the sulphonium salt at

0-5°C(cold reaction mixtures after reaction) showed little or no reaction over a period of 2-3 hours.

(ii) Perchloric acid (4.22M, 0.25 ml) was added to the reaction mixture at room temperature and the water bath then filled at 80°C. The beginning of the reaction time was taken at the point when the water bath was filled.

(iv) After the appropriate reaction time the 80°C bath was drained and replaced by the cold bath (-105°C, MeOH slush) to rapidly cool the reaction mixture and stop the hydrolysis. (Stirring of the reaction mixture and the coolant was essential for rapid cooling). See also the "Notes on the Procedure" part (iii), Chapter 7.2.1. The final reaction time was taken at the point when the cold bath was applied.

(v) After cooling the reaction mixture to 0-5°C the pH was adjusted to about pH 10. The carrier gas was then flushed through the system for 5 minutes (100 ml/min) while the reaction vessel was stored in an ice-water bath.

The rest of the procedure is described in Chapter 9.2.1, procedure; parts (iv) and (v). The GLC analyses of reaction mixture and diethyl ether from the cold traps is described in Appendix 1.5.

10.2.2 Results

The results of the hydrolyses of dimethyl-(3-methyl-3-pentyl)-sulphonium perchlorate (80°C) are summarised in TABLES 15 and 16 while FIGURES 13 and 14 show plots of product quantity versus percentage of reaction. A discussion follows in Section 10.2.3.

TABLE 15

Results of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate Hydrolyses at 80°C

Percentage of Reaction						
$(S(CH_3)_2)$	(Product Sum)	% Substitution	% Elimination	% 1-ene	% cis-2-ene	% trans-2-ene
16.67±0.02	16.17±0.02	93±1	6.7±0.1	7.8±0.5	26.8±0.4	65±2
37.2±0.8	32±1	89±1	11.3±0.5	9.4±0.5	28.4±0.6	62±2
39±1	35±1	90±4	10.2±0.4	8.2±0.3	27±1	64±3
47±2	40.7±0.8	86±3	14.2±0.5	8.7±0.6	29±1	62±3
67±5	64±1	86±3	14.1±0.4	7.0±0.2	28±2	65±2
70±2	69.5±0.1	83.4±0.2	16.6±0.2	9.0±0.6	28.9±0.5	62±1
80±1	82±1	84±1	15.8±0.6	10.5±0.6	29±1	61±7

Hydrolysis of Dimethyl-(3-methyl-3-pentyl) sulphonium Perchlorate at 80°C

mean % substitution	85±2
mean % elimination	15±1

Ratio of Isomeric Alkenes:

mean % 2-ethylbut-1-ene	9±1
mean % cis-3-methylpent-2-ene	29±1
mean % trans-3-methylpent-2-ene	63±3

These values were calculated from the results of the experiments with greater than 40% reaction. The reasons for this are discussed in Section 10.2.3.

TABLE 16

Results of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate Hydrolyses at 80°C

% Reaction (Product Sum)	Substitution Products (mole x 10^{-3})	1-ene (mole x 10^{-5})	cis-2-ene (mole x 10^{-4})	trans-2-ene (mole x 10^{-4})	total elimination (mole x 10^{-4})
16.17±0.02	0.90±0.01	0.51±0.03	0.175±0.001	0.427±0.009	0.653±0.009
32±1	1.70±0.09	2.0±0.2	0.61±0.01	1.347±0.008	2.16±0.02
35±1	1.88±0.06	1.76±0.05	0.59±0.02	1.38±0.05	2.15±0.05
40.7±0.8	2.09±0.05	3.0±0.2	1.00±0.04	2.16±0.08	3.46±0.09
64±1	3.28±0.08	3.8±0.1	1.52±0.08	3.5±0.1	5.4±0.1
69.5±0.1	3.447±0.002	6.2±0.4	1.99±0.03	4.27±0.05	6.88±0.07
82±1	4.20±0.05	8.3±0.4	2.28±0.08	4.8±0.3	7.9±0.3

FIGURE 13

Hydrolysis of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate at 80°C

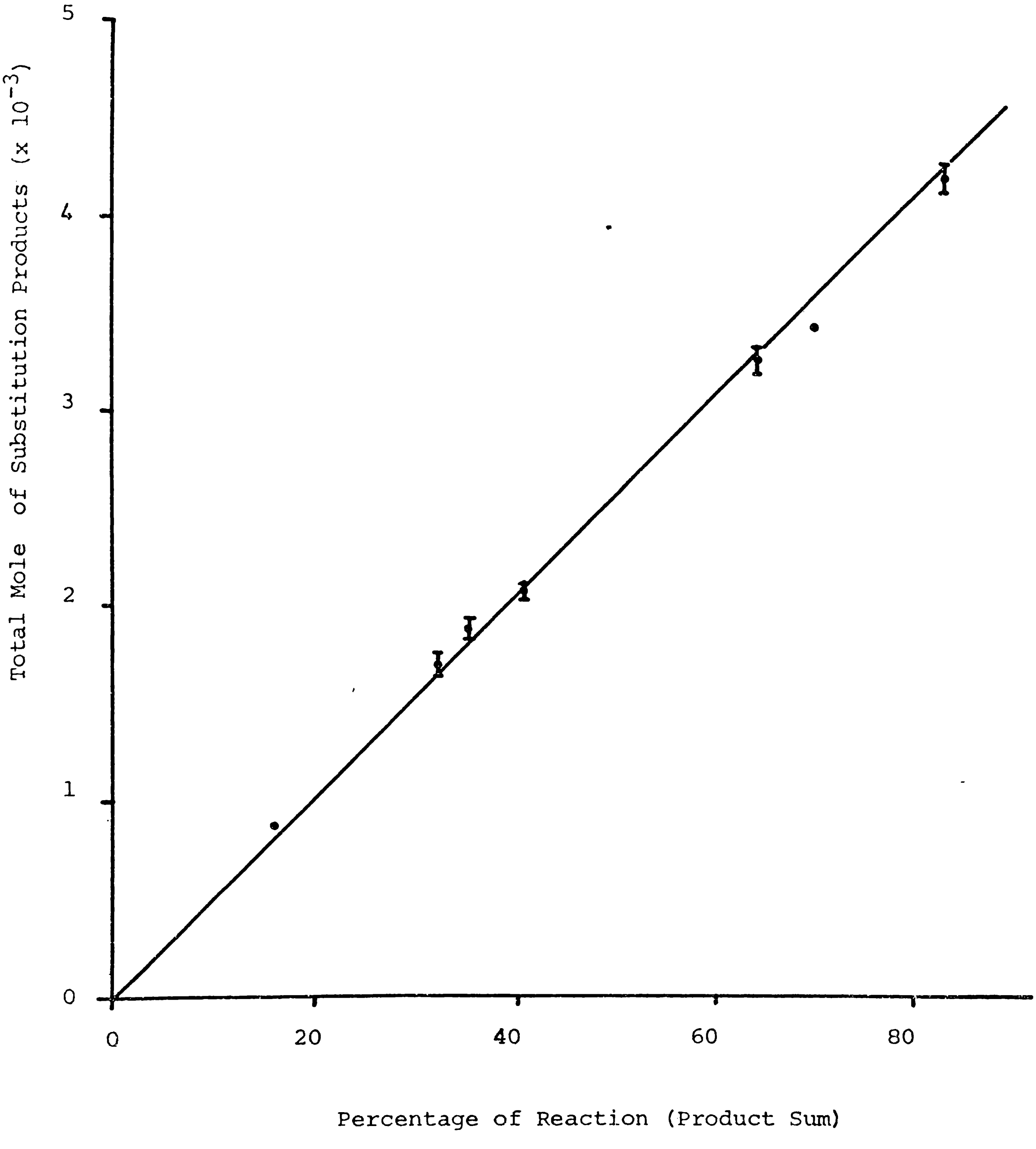
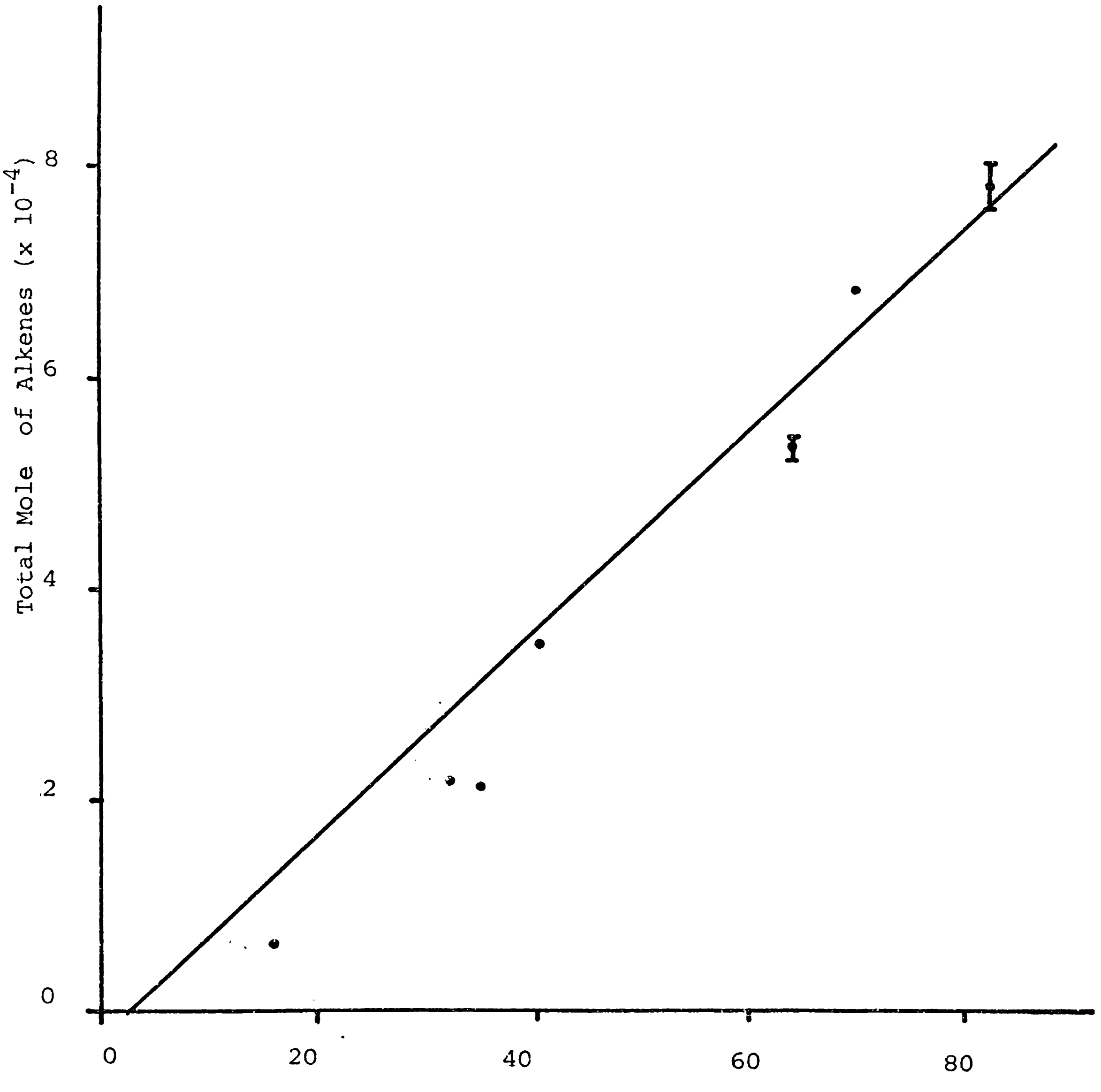


FIGURE 14

Hydrolysis of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate at 80°C



Percentage of Reaction (Product Sum)

10.2.3 Discussion

Calculation of Mean Results:

The results summarised in TABLE 15 show consistent proportions of alkene isomers but variable overall proportions of elimination. The experiments with less than 35% reaction had reaction times of 30-90 seconds. The heating rate of the reaction mixture (from room temperature) using the 80°C water bath was such that approximately 100 seconds was required for the reaction temperature to reach 70°C (see temperature profile, Chapter 8.2.3). At temperatures less than this it was shown (Chapter 9.1) that incomplete alkene recovery occurred. The results of the experiments with less than 36% reaction were therefore not used to calculate the mean results. Control experiments carried out in the course of developing a reaction procedure for 3-amino-3-methylpentane deamination at 50°C previously showed that incomplete recovery of the mixture of alkene isomers did not necessarily result in a change in the observed ratio of those alkenes compared with the mixture initially added to the experiment. This is consistent with the results of TABLE 15 where the ratio of isomeric alkenes is uniform even though product recovery was incomplete in some reactions.

The absence of marked trends in the proportions of elimination above 40% reaction, and the uniformity of the alkene ratios overall makes a comparison of the mean results with those from the deamination (Chapter 9.2.2) reasonable even though the deaminations were all at less than 36% reaction.

Deaminations were carried out in which the reactions were started and stopped by varying the temperature (TABLE 11, reactions (c) - (e)). These showed that product recovery was complete once the reaction mixture had reached 70°C.

It was possible that the variation in temperature during the hydrolysis reaction contributed to the difference observed between deamination and hydrolysis. This has been discussed in Chapter 8.2.3 with respect to the hydrolysis of dimethyl-(2-methyl-2-propyl)sulphonium perchlorate. In that reaction the proportion of elimination was the same for hydrolyses at 80°C (Chapter 8.2.2) and 50°C (Chapter 8.3.2). Dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate was hydrolysed with reliable product analysis only at 80°C. The experiments used to calculate the mean results had reaction times from 2-5 minutes. The proportion of the reaction time spent in the heating and cooling phases therefore decreased as the total reaction time increased. If significantly different product ratios were produced during the heating and cooling phases one would have expected to see a gradual change in the ratios as the percentage of reaction increased. This was not observed. Furthermore, the rate of hydrolysis decreases rapidly as the reaction temperature decreases so the contribution of hydrolysis during the heating and cooling phases may be expected to be relatively small.

Alkyl Nitrite:

3-Methyl-3-pentyl nitrite was observed in the first cold trap of each reaction as was the case in the deamination (Chapter 9). The proportion of the alkyl nitrite was about the same in both systems.

The origin of alkyl nitrite has been discussed (Chapter 9.2.3) while its influence on the product ratios was considered in Chapter 7.4.3.

Hydrolysis Starting Material:

Dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate (solid) decomposes slowly on standing (room temperature, over silica gel). A sample was recrystallised (absolute EtOH) and dried (room temperature, 30 mm Hg, over P_2O_5) 2-3 hours before use. Contamination by a small amount (approx. 5% mole/mole) of 3-methylpentan-3-ol (possibly from hydrolysis during the recrystallisation), was taken into account by analysing (GLC) the reaction mixture before the hydrolysis was started.

Percentage of Reaction by SMe_2 Analysis:

TABLE 15 shows some discrepancy between the percentage of reaction for the SMe_2 analysis and that from the product sum. This was probably due to the difficulties encountered in determining the amount of SMe_2 contaminating the starting material. This was done from the chromatogram of the reaction mixture taken before the hydrolysis was started. Some interference occurred from sulphonium salt decomposing in the injector portion of the GLC column.

10.2.4 Control Experiments

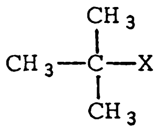
No control experiments other than those described in Chapter 9 were carried out.

Chapter Eleven

Discussion

Two simple, acyclic, tertiary aliphatic systems have been studied in this work. In each case the amino derivative has been deaminated with nitrous acid in water while the dimethyl sulphonium salt has been hydrolysed under reaction conditions as similar as possible to those of the deamination. The results (TABLE 17) show small but definite differences between the deamination and hydrolysis reactions of both systems studied.

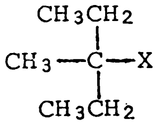
TABLE 17



$(CH_3)_3C{-}X$

$X = NH_2$, $-\overset{+}{S}Me_2ClO_4^-$

	% Substitution	% Elimination
Deamination (80°C)	91±1	8.9±0.4
Hydrolysis (80°C)	96±2	3.7±0.4
Deamination (50°C)	92±2	8.2±0.8
Hydrolysis (50°C)	96±3	3.6±0.3
Deamination (25°C)	93±4	7.5±0.6



$CH_3{-}C(CH_2CH_3)_2{-}X$

$X = -NH_2$, $-\overset{+}{S}Me_2ClO_4^-$

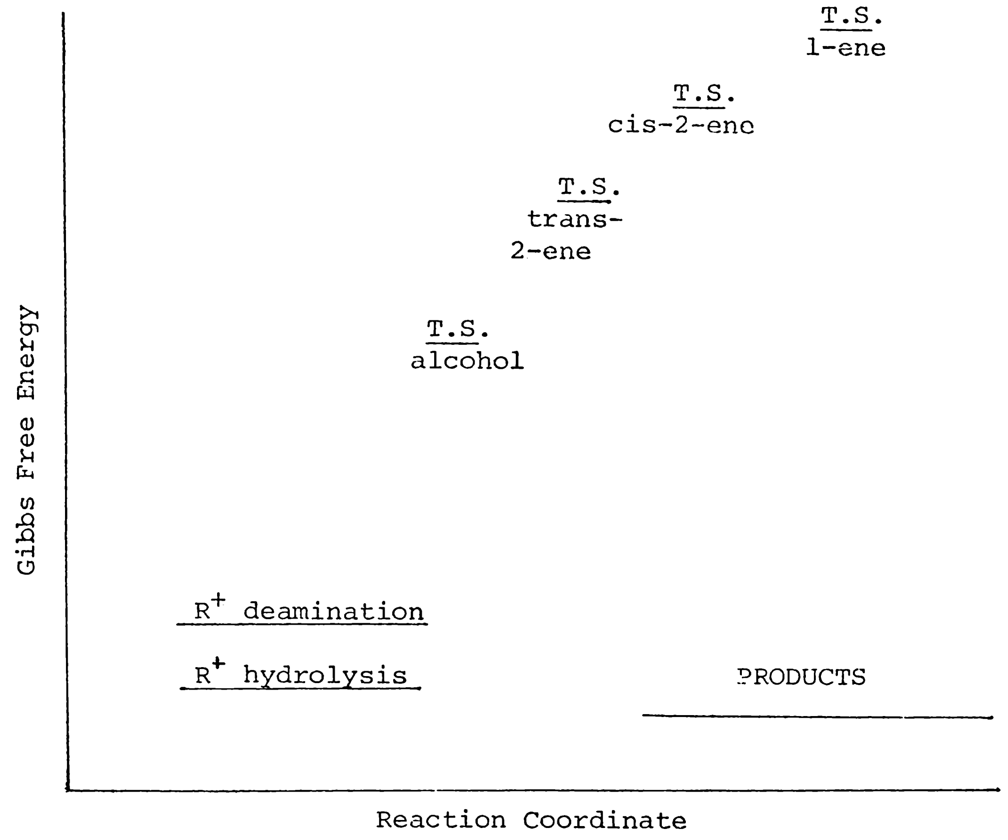
	% substitution	% elimination	% 1-ene	% cis-2-ene	% trans-2-ene
Deamination (80°C)	79±2	21±2	17±1	28±1	55±2
Hydrolysis (80°C)	85±2	15±1	9±1	29±1	63±3

In both systems the deamination produced more elimination than the corresponding hydrolysis. Elimination from the 3-methyl-3-pentyl systems was also different,with deamination producing a higher proportion of 2-ethylbut-1-ene but a lower proportion of trans-3-methylpent-2-ene.

If both alkyl systems dissociated to the free carbocations, free of the affects the leaving groups ($N_2$and SMe_2) and in equilibrium with the solvent, the product distributions from deamination and hydrolysis should have been the same. The results indicate that the leaving groups continue to exert an influence on the carbocation prior to product formation, possibly as the nitrogen separated ion-pair in deamination (Chapter 2.3) and the ion-dipole assemblage (ion-neutral molecule pair) in hydrolysis (Chapter 1.2.5).

$$\begin{array}{lcr} H_2O & & OH_2 \\ & R^+\ {}^{N\equiv N}\ {}^-OH & \\ H_2O & & OH_2 \end{array} \qquad\qquad \begin{array}{lcr} H_2O & & OH_2 \\ & R^+\ {}^{S(CH_3)_2} & \\ H_2O & & OH_2 \end{array}$$

Dissociation of a diazonium ion (R-$\overset{+}{N}$≡N) yields a carbocation of higher energy than the corresponding hydrolysis since C—N heterolysis is essentially irreversible and occurs with little or no solvent assistance. Had a free carbocation formed, it would be expected to be symmetrically solvated and the "excess" energy of the deamination carbocation would have been rapidly lost in collisions with solvent molecules. It is suggested that the deamination carbocations formed in the studies of this thesis are short-lived and shielding by the departing nitrogen prevents complete loss of the "excess" energy before product formation. The "excess" energy of the deamination carbocation relative to the hydrolysis analog makes the higher energy product-forming pathways more favourable in deamination than in hydrolysis.



As a result, more elimination occurs in the deamination. Where the isomeric alkenes were possible, lower trans/cis and 2-ene/1-ene ratios would be expected in deamination and these were observed.

	trans/cis	2-ene/1-ene
Deamination (80°C)	1.96	4.9
Hydrolysis (80°C)	2.17	10.1

The explanation for the deamination/hydrolysis difference is then a hybrid of the "hot" carbocation concept (Chapter 3.3.1) and the influence of the neutral molecule of the ion-pairs. The free (symmetrically) solvated carbocations do not appear to be involved even though the systems studied had tertiary alkyl groups and the solvent was water.

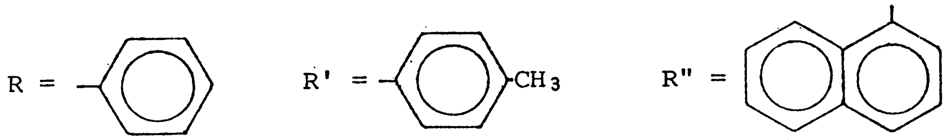
The Saytzeff rule products (Chapter 1.3.3) from the 3-methyl-3-pentyl system reactions are consistent with anti elimination (Chapter 1.3.3). Syn elimination would have been expected to give predominantly the cis-2-ene.

A suggested continuation of this work would be the deamination and hydrolysis of optically active tertiary substrates such as 3-amino-3-methylhexane and the corresponding dimethyl sulphonium salt. If the shielding by the neutral leaving groups also operates in these systems, it may be evident in the optical activity of the substitution product. Symmetrically solvated carbocations would be expected to give a racemic mixture of the product alcohol (in addition to the same product ratios for the two types of reaction). A shielding effect by the neutral molecules (N_2, SMe_2) would tend to give product alcohol with net inversion though this may depend upon the rate of rotation of the cation before nucleophilic attack by the solvent molecule.

Few tertiary acyclic carbinamines have been deaminated but these include the following examples. Arcus *et al.*[168] have found that the deamination of optically active phenylnaphthyltolylcarbinylamine yielded inactive alcohol (water as solvent).

$RR'R''C{-}NH_2$ (±)-α-carbinol

(+) amine-hydrochloride
optical purity 51%



The authors suggest that a symmetrically solvated carbocation is formed. Steric interactions between the bulky substituents would tend to enhance the formation of a planar sp^2 hybridised carbocation and stabilisation of the carbocation by the aromatic groups would encourage the formation of a symmetrically solvated cation. White and Stuber[169] deaminated the optically active amine (100% optically pure) 2-phenyl-2-butylamine by both the nitrous acid reaction and decomposition of N-(2-phenyl-2-butyl)-benzamide (Chapter 2.2 (d)) in glacial acetic acid as solvent. Predominant to complete retention of configuration occurred in the substitution products. This is not surprising since diazonium ion-pair mechanisms would be involved when glacial acetic acid is the solvent.

Silver[170] has studied the solvolysis of 2-methyl-2-butyl (tert-pentyl) halides and the nitrous acid deamination of 2-amino-2-methylbutane (tert-pentylamine) in aqueous acetic acid solutions. The elimination products showed that more 2-methylbut-1-ene was produced in deamination than the solvolysis.

Burgess[108] has studied the aqueous nitrous acid deaminations of 2-amino-2-methylpropane (tert-butylamine) and 2-amino-2-methylbutane (tert-pentylamine) and the hydrolyses of the corresponding dimethyl sulphonium salts (all at 25°C). The results are summarised below:

tert-butyl system	% elimination	tert-pentyl system	% elimination
deamination	5.83	deamination	7.48
hydrolysis	4.32	hydrolysis	11.08

It was concluded that the two reactions of both systems produced the same proportions of elimination within experimental error and that a free carbocation is involved. Experimental problems and restrictions imposed by the analytical techniques available at the time (1953) cast some doubt upon these results. Numerous experimental problems were encountered with the analyses of the isomeric alkenes from the tert-pentyl system.

Cocivera and Winstein[27] have reported the hydrolyses (25°C) of the 2-methyl-2-propyl halides (Cl, Br, I) and 2-chloro-2-methylbutane (tert-pentyl chloride). The 2-methyl-2-propyl halides all gave 4-5% of elimination indicating reaction by free carbocations. The hydrolysis of tert-pentyl chloride gave 8.9±0.4% of elimination which is close to the value obtained by Burgess[108].

Kinetics:

This thesis is concerned with the product distributions from the reactions studied,not the details of their kinetic behaviour. However, some experimental observations are considered below.

Reactions	Estimated time for 11% reaction from the tables of results (Chapters 7-10).
$(CH_3)_3CNH_2$ deamination	30 sec (80°C), 5 min (50°C) 30 min (25°C)
$(CH_3)_3C\overset{+}{S}(CH_3)_2ClO_4^-$ hydrolysis	8 min (80°C), 300 min (50°C)
$CH_3(CH_3CH_2)CNH_2$ deamination $CH_3(CH_3CH_2)C\overset{+}{S}(CH_3)_2ClO_4^-$ hydrolysis	both about 35 sec. (80°C)

Both deaminations react at about the same initial rate at 80°C. The rate determining nitrosation (at 80°C) is presumably not significantly affected by the small difference in amine basicity and the change of alkyl group. The hydrolysis of the 3-methyl-3-pentyl sulphonium salt is considerably faster than the hydrolysis of the 2-methyl-2-propyl analog. This may reflect greater steric interactions between the alkyl substituents of the diethyl methyl system than the trimethyl compound. The sulphonium salts were prepared from the alkyl iodides in nitromethane (Appendices 6.3 and 6.10). It was noted that dimethyl-(3-methyl-3-pentyl)sulphonium iodide was produced much more rapidly than the 2-methyl-2-propyl analog in the polar aprotic solvent used (CH_3NO_2). Furthermore, the dry, crystallised 3-methyl-3-pentyl salt decomposes on standing while the 2-methyl-2-propyl salt is quite stable (at room temperature). Both observations support a more reactive 3-methyl-3-pentyl substrate.

Micelles in Deamination:

The influence of micelles in deamination reactions has been considered in Chapter 5. A study was carried out to determine whether they are present in the reactions reported in this thesis (Appendix 5). No evidence was found for their presence, presumably because the substrates used were small, branched molecules (Chapter 5).

Limits of the Experimental Procedures Developed in this Thesis:

The procedures described for carrying out deaminations work well for systems producing relatively low boiling point alkenes (bp.<75°C) that can be readily flushed from the reaction vessel and trapped. Incomplete alkene analyses may occur with higher boiling point alkenes unless a modified product recovery system is developed.

The procedures have a limited use in solvolysis studies where the reactions are to be stopped at less than 100%. The rapid rate of the hydrolysis (at 80°C) of dimethyl-(3-methyl-3-pentyl)-sulphonium perchlorate placed this substrate at the limit of the experimental procedure and even so the results are not as accurate as those from the other three substrates studied.

Appendix One

Deamination and Hydrolysis Product Analyses

(Methods and Control Experiments)

A1.1 General

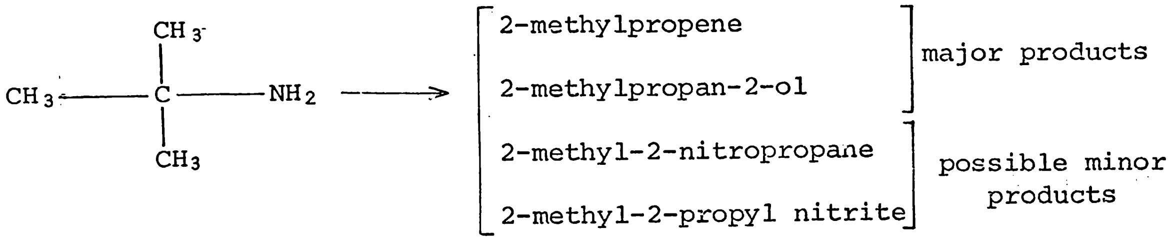
This appendix describes the quantitative analyses of the reaction products contained inthe aqueous reaction mixtures and various product traps. Control experiments are summarised while others have been described in Chapters 7 - 10.

All the reaction products were identified by comparing their GLC retention times with authentic samples (Appendix 6). Nitrogen from the deaminations was not quantitatively assessed.

Gas-liquid chromatography was used for all product analyses. Instruments; Varian GC3700, Pye Unicam Series 104 Chromatograph. Flame ionisation detectors were used in both cases.

Each solution or mixture analysed was sampled 4 - 10 times and a sampling error obtained.

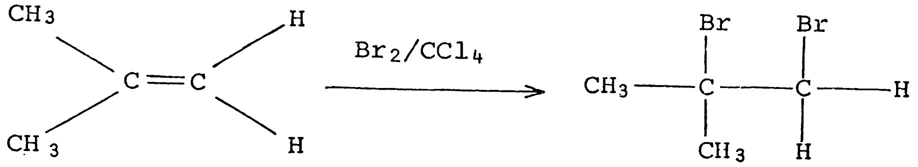
A1.2 Deamination of 2-Amino-2-methylpropane



$$(CH_3)_3C\text{-}NH_2 \longrightarrow$$

A1.2.1 2-Methylpropene

2-Methylpropene was trapped as 1,2-dibromo-2-methylpropane by reaction of the alkene with bromine (2 ml) in tetrachloromethane (20 ml).



1,3-Dibromopropane (50 µl, 0.492 ± 0.002 mmole) was added to the bromine mixture before it was washed (3 x 15 ml $Na_2S_2O_3$, 1.00M; 1 x 10 ml H_2O) to remove the excess bromine, and dried (anhyd. $MgSO_4$).

GLC Conditions:

Column; 10% w/w SE30, diatomite C-AW 100-120 mesh, 1.5 metre 6.23 mm o.d., glass. Carrier gas; nitrogen, 20 ml/min. Temperature; volume, 70°C for 4 minute ,80°C/min to 120°C; injector,100°C; detector, 150°C.

The amount of 1,2-dibromo-2-methylpropane was determined from the standard equation,

$$\text{mole of product} = \frac{\text{Peak Area (Product)}}{\text{Response Factor}} \times \frac{\text{mole of Internal Standard}}{\text{Peak Area (Int. Standard)}}$$

Mole of Internal Standard:

A constant volume of internal standard was taken 10 times and each injected into 20 ml of solvent (CCl_4 in this case) and weighed. The amount of internal standard was calculated for each weighing and a mean and standard error determined.

Response Factor (RF):

The response factor of the product relative to the internal standard was determined by preparing solutions of known product : internal standard composition then measuring the peak areas on a chromatogram and inserting the appropriate values into the equation above.

The RF value was found to be independent of the solvent used to make up the solution and the column stationary phase, as expected.

(Water, 55/45% water/ 1,4-dioxane, 1,4-dioxane, diethyl ether, chloroform, dimethylformamide and n-pentane were used a solvents during various response factor determinations.)

1,2-Dibromo-2-methylpropane : 1,3-Dibromopropane

RF = 1.27 ± 0.02

Control Experiments:

Controls were conducted to check for; (i) complete trapping of the alkene, (ii) removal of the brominated derivative from the trap in the carrier gas stream, (iii) loss of either the derivative or internal standard during the thiosulphate washing process.

(i) The alkene was generated by the process described in Appendix 6.6 and passed into two CCl_4/Br_2 bubblers in series (nitrogen flow, 30 ml/min). The mixtures were analysed in the usual way.

No bromination product was found in the second trap although much more alkene was generated than would be produced in a deamination reaction.

(ii) 1,2-Dibromo-2-methylpropane and 1,3-dibromopropane were added to tetrachloromethane (20 ml) and a chromatogram obtained. The mixture was then flushed with nitrogen (30 ml/min, 1 hour) and re-analysed. No loss of either compound was observed.

Considerable loss occurred when the experiment was repeated with a nitrogen flow of 100-120 ml/min.

(iii) A solution was prepared as in (ii) and bromine (2 ml) added. The mixture was washed (3 x 15 ml $Na_2S_2O_3$, 1.00M; 2 x 10 ml H_2O) and dried (anhyd. $MgSO_4$).

A comparison of the chromatograms obtained before bromine addition and after the washing procedure, indicated a 3% decrease in the calculated mole of 1,2-dibromo-2-methylpropane.

A1.2.2 2-Methylpropan-2-ol

Product 2-methylpropan-2-ol was found in the reaction vessel and alcohol traps (2 x 15 ml 1,4-dioxane for reactions at 50 and 80°C, 1 x 15 ml H_2O for reactions at 25°C). Propan-1-ol (100 µl, 1.357 ± 0.008 mmole) was the internal standard. All solutions were analysed on a 20% w/w Poly Ethylene Glycol Adipate (PEGA) column.

Reaction Vessel:

The aqueous reaction mixture was injected directly onto the column. A problem arose with the unreacted amine. Some of the amine salt was neutralised to the free amine upon injection and obscured a large part of the chromatogram. This problem was overcome by using a precolumn (10 cm) of 10% w/w $CoCl_2.6H_2O$ on celite 80-120 mesh. A fresh packing was required for each sample; this was inserted into the chromatograph immediately before sample injection. Prolonged drying of the precolumn by the injector heater (even at an injector temperature of 70°C) before sample injection reduced the effectiveness of the packing.

The cobalt salt complexed the free amine while control experiments showed that the reaction products and the internal standard were only slightly affected.

2-Methylpropan-2-ol : Propan-1-ol

RF = 1.47 ± 0.01 with $CoCl_2.6H_2O$ precolumn

RF = 1.45 ± 0.01 with an uncoated celite precolumn.

Control Experiments:

Possible substitution products were; 2-methylpropan-2-ol, 2-methyl-2-nitropropane and 2-methyl-2-propyl nitrite.

The following solutions were prepared:

(a) 2-methylpropan-2-ol + propan-1-ol + 20 ml water.

(b) 2-methyl-2-nitropropane + pentan-1-ol (internal standard) + chloroform (20ml). (The nitroalkane is insoluble in water and has the same retention time as 1,4-dioxane on a 20% PEGA column).

(c) 2-methyl-2-propyl nitrite + propan-1-ol + 1,4-dioxane (anhyd.) (20 ml). (The alkyl nitrite is insoluble in water.)

Each solution was analysed by GLC using columns with and without the $CoCl_2.6H_2O$ precolumn to test the effect of the $CoCl_2.6H_2O$ precolumn in the possible products.

Analysis of the Alcohol Traps:

Propan-1-ol (100 µl) was added to each trap and the contents analysed by GLC using a 20% PEGA column with an uncoated celite precolumn (10 cm).

GLC Conditions:

Column; 20% w/w PEGA (precolumns as described) on diatomite C-AW 100-120 mesh, 1.5 metre, 6.25 mm o.d., glass. Column Temperature; 80°C (5 minute for the reaction mixture, 4 minute for the trapping solutions), 80°C/min to 160°C.

Carrier gas; nitrogen, 20 ml/min.

Notes:

(a) It was most important to dry the columns at 160°C for 5 minutes between each aqueous sample. Moist columns were shown to give very low results with the alcohols used.

(b) It was most important to ensure complete trapping of the product alcohol before the CCl_4/Br_2 bubbler. A series of control experiments has shown that only about 50% alcohol entering this mixutre was converted to 2-bromo-2-methylpropane (the major product of this reaction) and finally detected. The rest was lost during the washing procedure which has little affect on the alkyl bromide.

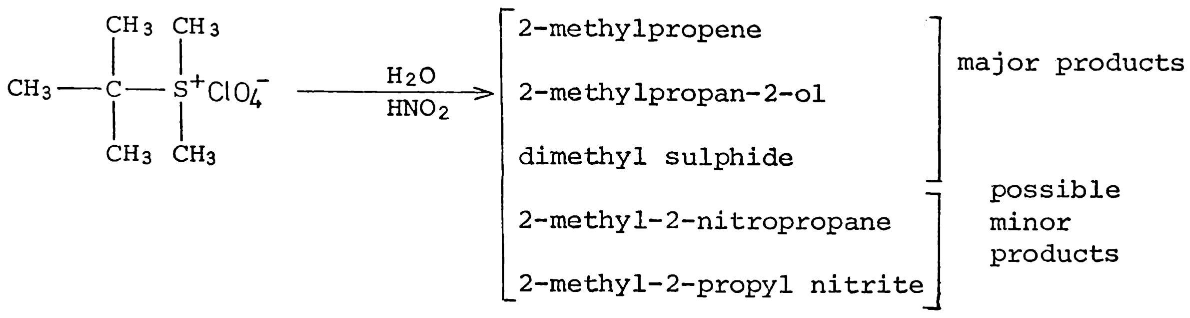
A1.2.3 2-Methyl-2-nitropropane, 2-Methyl-2-propyl Nitrite

Though reported as a product in a similar study by Burgess[108], 2-methyl-2-nitropropane was not produced in any of the deaminations reported in this thesis. A reference sample was, however, prepared (Appendix 6.4) and used in control experiments and to estimate the alkyl nitrite/propan-1-ol response factor.

2-Methyl-2-nitropropane : Propan-1-ol RF = 1.30 (diethyl ether solvent).

2-Methyl-2-propyl nitrite was produced as less than 5% of the products in 2-amino-2-methylpropane deamination at 25°C only. A sample sufficiently pure for a response factor determination could not be prepared (Appendix 6.5) so the ~~volume~~ value was estimated to be 1.30 by comparison with the nitro alkane.

A1.3 Hydrolysis of Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{CH_3}{S^+}}ClO_4^- \xrightarrow[HNO_2]{H_2O}$$

The hydrolysis shown above was carried out in the same apparatus and by the same procedure as described for the corresponding deamination. The products differed only in the production of dimethyl sulphide in the hydrolysis.

Dimethyl Sulphide : Propan-1-ol, RF = 0.66 ± 0.01

The dimethyl sulphide was measured quantitatively in hydrolyses at 80°C during analyses for the substitution products in the reaction vessel and the alcohol traps.

Note: The GLC injection temperature was important when sampling the reaction mixture containing unreacted sulphonium salt. At injection temperatures higher than 70°C broad peaks appear in the region of interest, possibly due to pyrolysis of the sulphonium salt. The baseline was undisturbed at 70°C. The cobalt salt precolumn used for the deamination reaction mixtures had no affect in this case.

FIGURES 15 - 17 illustrate the chromatograms obtained from the 2-methyl-2-propyl system reation mixture , the alcohol traps and the alkene trap respectively. The positions of the various compounds are shown although all may not occur at the same time, e.g. dimethyl sulphide (FIGURE 15) does not occur during the deamination reactions. The stationary phases used are noted in the FIGURES while the operating details have been described in the text.

FIGURE 15

Aqueous Reaction Mixture

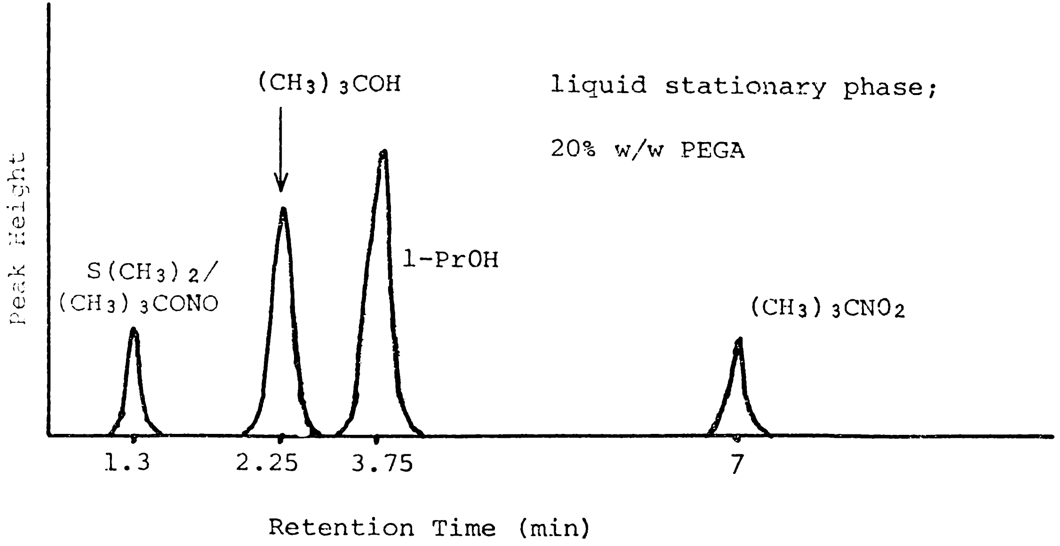


FIGURE 16

Alcohol Trap (1,4-Dioxane Solvent)

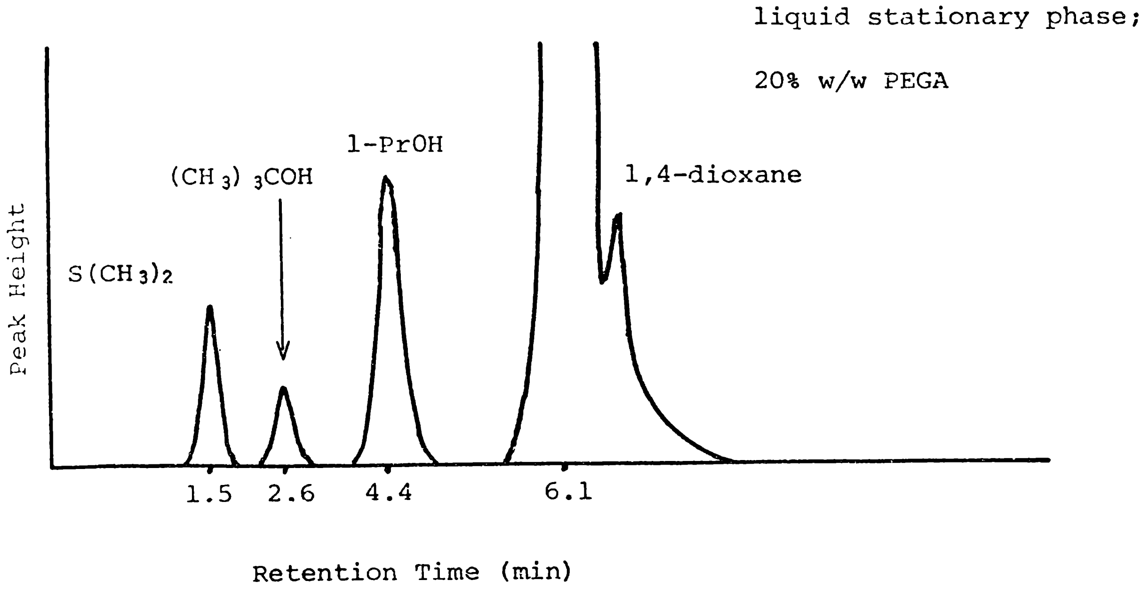
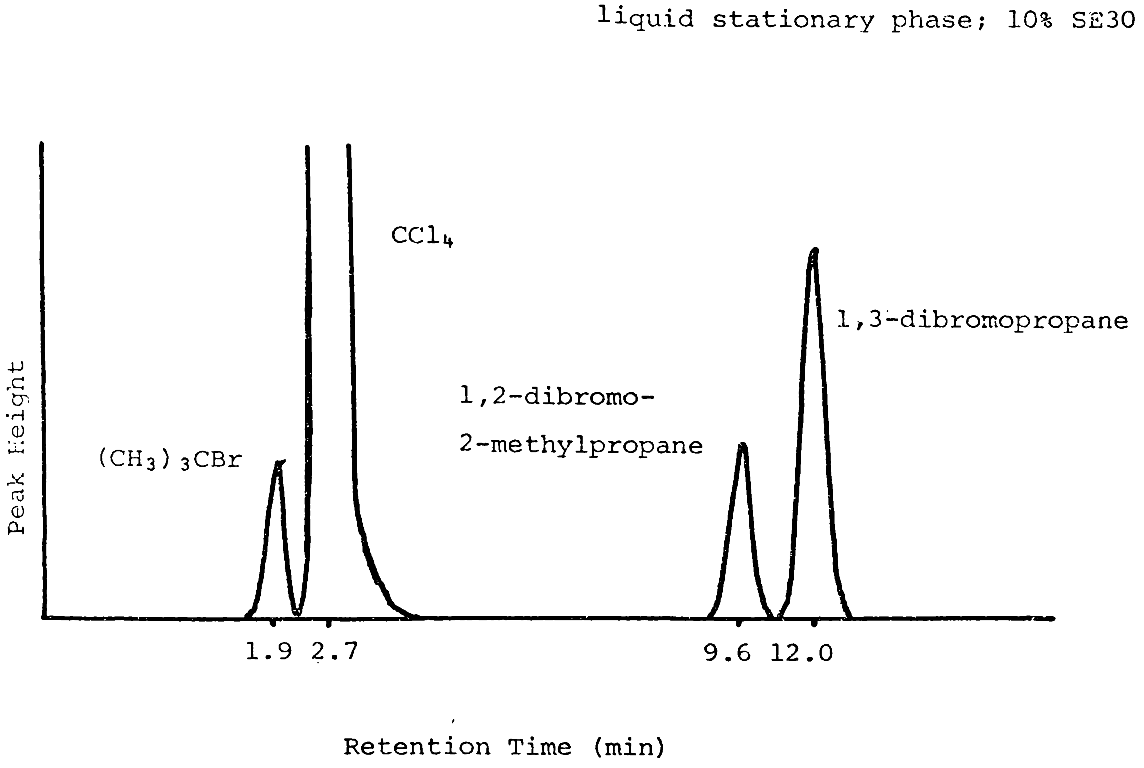
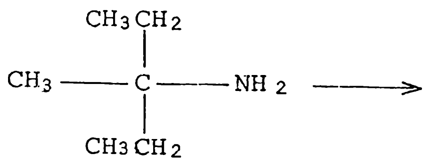


FIGURE 17

Alkene Trap (Tetrachloromethane Solvent)



A1.4 Deamination of 3-Amino-3-methylpentane



$$CH_3-\underset{CH_3CH_2}{\overset{CH_3CH_2}{\underset{|}{\overset{|}{C}}}}-NH_2 \longrightarrow$$

Products	
3-methylpentan-3-ol 2-ethylbut-1-ene cis and trans-3-methyl-pent-2-ene	major products
3-methyl-3-nitropentane 3-methyl-3-pentyl nitrite	possible minor products

A1.4.1 3-Methylpentan-3-ol

3-Methylpentan-3-ol was found in the reaction vessel (about 90%) and the first diethyl ether cold trap (about 10%).

The 10% w/w $CoCl_2.6H_2O$ precolumn (A1.2.2.) was again required for the analysis of the aqueous reaction mixture. Control experiments showed that the precolumn only slightly affected the passage of 3-methylpentan-3-ol and propan-1-ol.

Propan-1-ol was again the internal standard (100 µl, 1.357 ± 0.008 mmole).

3-Methylpentan-3-ol : Propan-1-ol

RF = 1.97 ± 0.02 with 10% w/w $CoCl_2.6H_2O$ precolumn

RF = 1.94 ± 0.02 with uncoated celite precolumn

Reaction Vessel:

GLC conditions: Column, 20% w/w PEGA on diatomite C-AW 100-120 mesh, 1.5 metre , 6.25 mm o.d., glass.

Precolumn, 10% w/w $CoCl_2.6H_2O$ on celite 80-120 mesh, 10 cm.

Temperature; Column, 80°C for 4 minute ,80°C/min to 130°C, Injector 70°C, Detector 150°C.

Carrier gas; nitrogen, 20 ml/min.

Note: It was most important to dry the columns at 160°C for 5 minutes between each aqueous sample.

Diethyl Ether Phases (Cold Traps):

The diethyl ether cold traps contained the elimination products as well as some 3-methylpentan-3-ol. A column with a stationary phase of poly propylene glycol (15% w/w) was used for the analyses since only this phase was capable of resolving the isomeric alkenes (Appendix 3).

Propan-1-ol was the internal standard.

GLC Conditions: Column, 15% w/w PolyPropylene Glycol (PPG) (LB-550-X) on chromosorb 80-100 mesh, 4 metre , 1/8 inch o.d., stainless steel.

Temperature: Column, 45°C for 18 minute ,80°C/min to 170°C, Injector 70°C, Detector 150°C.

Carrier gas; nitrogen, 12 ml/min.

A1.4.2 2-Ethylbut-1-ene, cis and trans-3-Methylpent-2-ene

The elimination products were trapped in diethyl ether cold traps (-105°C, MeOH slush). Propan-1-ol (100 µl, 1.357 ± 0.008 mmole) and acetone (100 µl, 1.372 ± 0.003 mmole) were used as the internal standard for deaminations at 80 and 50°C respectively. Dimethyl sulphide was found to have the same retention time as acetone on the PPG column so the acetone could not be used as an internal standard for the corresponding hydrolyses.

Response Factors;

The three isomeric alkenes could not be prepared individually so the response factors were determined using three mixtures of widely varying alkene composition.

A known weight of each mixture and the internal standard was added to diethyl ether (20 ml). The response factors for the alkene mixtures were determined. (The isomeric alkenes have the same molecular weight so the mole of alkene used was easily determined.) Each of the three mixtures gave the same (within the experimental errors of the RF values shown below) combined response factor despite the markedly different compositions. The response factor (relative to the internal standard) for each of the three isomers was therefore assumed to be the same as that of the mixtures.

The assumed response factors were used to calculate the compositions of the three mixtures involved.

No	1-ene	cis-2-ene	trans-2-ene
1	4.5%	26.5%	69%
2	12%	31%	57%
3	62%	23%	14%

Alkene : Propan-1-ol RF = 1.99 ± 0.06

Alkene : Acetone RF = 2.66 ± 0.05

GLC Conditions: the same as described for the diethyl ether phases in A1.4.1.

A1.4.3 3-Methyl-3-nitropentane

No nitro alkane was detected in any of the 3-methyl-3-pentyl reactions. A sample was prepared (Appendix 6.11) to determine the retention time and the response factor relative to propan-1-ol. This value was used as an estimate for the response factor of 3-methyl-3-pentyl nitrite relative to propan-1-ol since the alkyl nitrite could not be prepared sufficiently pure for a RF determination.

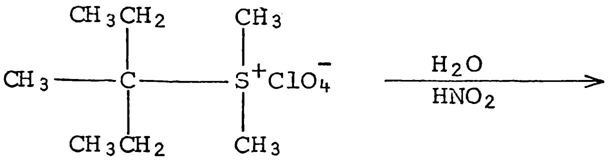
3-Methyl-3-nitropentane : Propan-1-ol, RF = 2.8 ± 0.1 (diethyl ether solvent)

A1.4.4 3-Methyl-3-pentyl Nitrite

3-Methyl-3-pentyl nitrite was detected in the first diethyl ether cold trap during deamination and the corresponding hydrolysis. Its response factor was assumed to be the same as that for 3-methyl-3-nitropentane. A sample of the alkyl nitrite was prepared (Appendix 6.12) but it was only in approximately 10% yield in unreacted alcohol.

3-Methyl-3-pentyl nitrite was quantitatively assessed at the same time as the product alkenes (present in the same solvent).

A1.5 Hydrolysis of Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate



$$CH_3\text{—}\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}\text{—}\overset{CH_3}{\underset{CH_3}{S^+}}ClO_4^- \xrightarrow[HNO_2]{H_2O}$$

products as shown in A1.4 with the addition of dimethyl sulphide.

The product analyses are the same as described in A1.4. However, dimethyl sulphide was also trapped in the diethyl ether cold traps as well as the reaction vessel. See the comments in A1.3 regarding the injection temperature.

FIGURES 18 and 19 illustrate the chromatograms obtained from the 3-methyl-3-pentyl system reaction mixtures and diethyl ether cold traps respectively. The stationary phases used are noted in the FIGURES while the operating details have been described in the text.

FIGURE 18

Aqueous Reaction Mixture

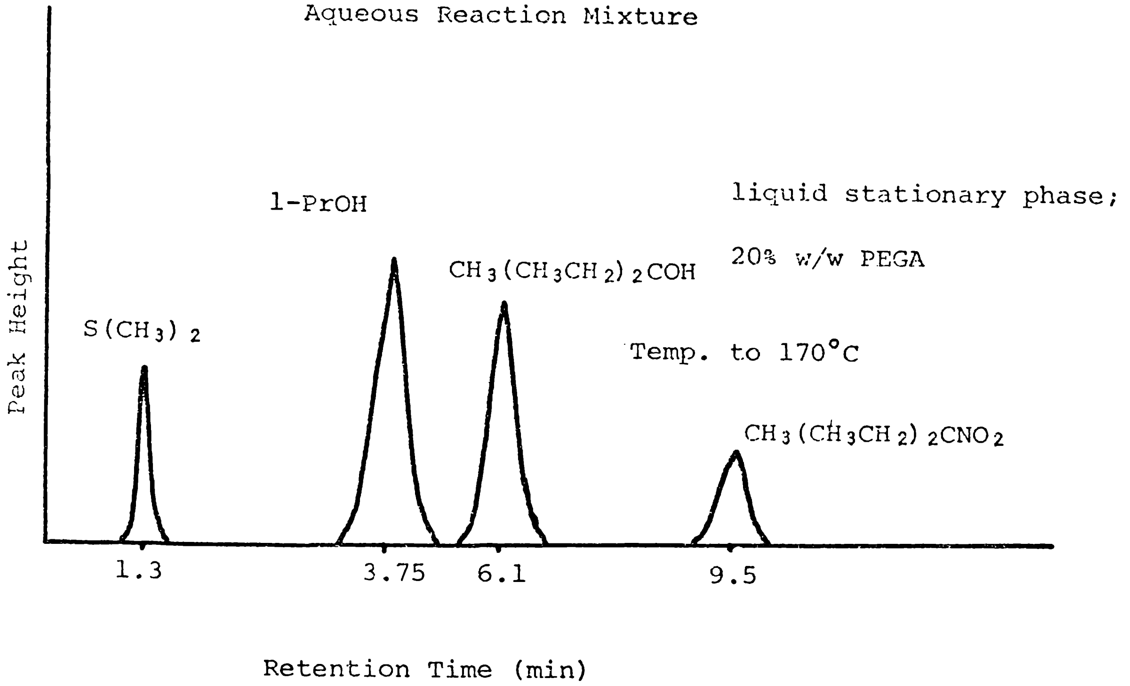
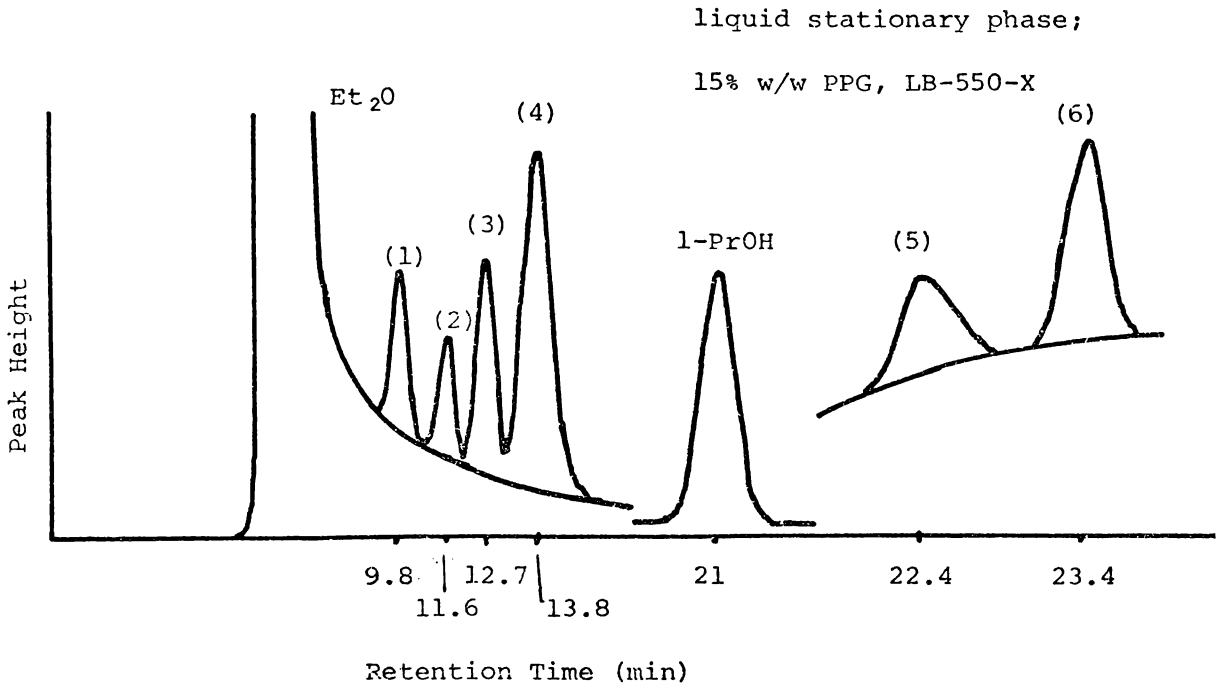


FIGURE 19

Cold Trap (Diethyl Ether Solvent)



(1) $S(CH_3)_2$, (2) 2-ethylbut-1-ene, (3) cis-3-methylpent-2-ene

(4) trans-3-methylpent-2-ene, (5) 3-methyl-3-pentyl nitrite,

(6) 3-methylpentan-3-ol.

Appendix Two

Measurement of Unreacted Amine And Sodium Nitrite

A2.1 Unreacted Amine

A number of methods for measuring unreacted amine have been investigated:

(i) Acid-base Titration

(ii) Gas-Liquid Chromatography

(iii) Ultra-Violet Spectroscopy.

A2.1.1 Acid-Base Titration

$$RNH_3^+(aq) + OH^-(aq) \rightleftharpoons RNH_2(\ell) + H_2O$$

$$RNH_2(aq) + H_3BO_3(aq) \rightleftharpoons RNH_3^+(aq) + H_2BO_3^-(aq)$$

$$H_2BO_3^-(aq) + H^+(aq) \rightleftharpoons H_3BO_3(aq)$$

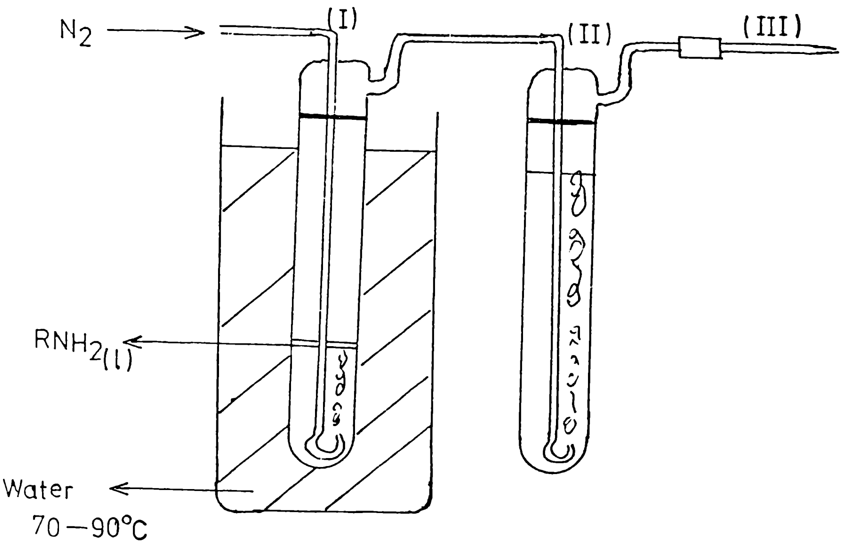
The procedure was modified from that described by Burgess[108].

An aliquot of the quenched deamination reaction mixture (5 ml) was placed in a bubbler vessel (DIAGRAM 3) and sodium hydroxide added (see note overleaf). Nitrogen (approx. 30 ml/min) was passed through the amine/base mixture and into a bubbler containing ortho-boric acid solution (25 ml, 0.500M) for 90 minutes.

The amine/base bubbler was immersed in hot water (70 - 90°C) to assist evaporation of the amine. The boric acid solution was then titrated with standardised hydrochloric acid (0.0636M) using bromocresol green/methyl red indicator (colour change; green to red).

DIAGRAM 3

Apparatus used in the Measurement of Unreacted Amine by Acid-Base Titration.



(I) Sodium hydroxide + amine solution.

(II) Boric acid solution.

(III) Capillary constriction that causes smaller bubbles in the gas stream.

Notes: 2-Amino-2-methylpropane deaminations;
25 and 50°C; 20 ml, 15M NaOH.
80°C; 2 g, NaOH pellets

All 3-Amino-3-methylpentane deaminations; 2 g, NaOH pellets.

A2.1.2 Control Experiments

(a) Indicators.

Control experiments using both 2-amino-2-methylpropane and 3-amino-3-methylpentane were conducted in which the titrations were monitored simultaneously by pH meter and colour change to ensure that the end-points coincided.

The sharp colour change accurately reflected the pH end-point (pH 5.2 - 5.3) in both cases.

(b) Boric Acid Solution Only.

The boric acid solution (0.005M) was only weakly acidic and in the absence of amine the indicators were at the point of colour change.

(c) Loss of Activity in the Nitrogen Flow.

Amine trapped in the boric acid solution may be lost in the nitrogen stream. 2-Amino-2-methylpropane was used in the following control experiment to test for this.

2-Amino-2-methylpropane (0.1708g, 2.34 mmole) was added to boric acid solution (60 ml, 0.500M) and two aliquots (25 ml) taken. One was bubbled with nitrogen (45 ml/min, 65 min) then titrated while the second was titrated directly as a standard. The titres were the same within experimental error (16.27 and 16.34 ml respectively) indicating that no amine was lost in the gas stream.

(d) Hydroxide Transfer to the Boric Acid Bubbler

A control experiment in which water (5 ml) was used in place of the reaction mixture showed that no sodium hydroxide was transferred to the boric acid bubbler in the gas stream.

(e) Interference by Sodium Nitrite and Reaction Products.

A series of control experiments were conducted using aliquots (5 ml) of 2-amino-2-methylpropane perchlorate solution (0.250M). Sodium nitrite, propan-1-ol, 2-methyl-propan-2-ol and 3-methylpentan-3-ol were added to the amine/base bubbler to test their affect on the amine analyses.

No interference was noted.

(f) Efficiency of the Method.

2-Amino-2-methylpropane; Known amounts of amine salt solution corresponding to 0-30% deamination, were analysed as described. The results showed the technique to be 99-100% efficient.

3-Amino-3-methylpentane; Solutions of the amine perchlorate salt, again corresponding to 0-30% deamination were analysed as described.

A maximum, consistent efficiency of 93.5-94.5% was found.

Numerous variations in the nitrogen flow rate, temperature, time and sodium hydroxide concentration failed to produce a significant improvement.

Freshly prepared salt solutions and the use of solid amine salt indicated there was no error in the initial amount of substrate taken.

A2.1.3 Gas-Liquid Chromatography

A GLC method in which a sample of aqueous reaction mixture could be analysed directly, without extraction procedures, was investigated with 2-amino-2-methylpropane. The technique finally developed however, was set aside in favour of the simpler, more rapid titration method except for some work reported in Appendix 4.

A number of difficulties arose:

(a) The reaction mixture contained inorganic salts ($NaClO_4$, $NaNO_2$) and base (NaOH) as well as product alcohol.

(b) When the deamination reaction was stopped by addition of base (pH 9) the amine was largely protonated in aqueous solution. The neutral amine had to be regenerated in a homogeneous solution in order to be analysed reproducibly by GLC.

In dilute aqueous solution it proved to be impossible to resolve the amine and 2-methylpropan-2-ol on the stationary phases at hand (polyethylene glycol adipate, SE30, polyethylene glycol, diisopropyl phthalate) so a procedure in which the alcohol was first extracted from a solution of the amine salt was adopted. 1,4-Dioxane was added to the reaction mixture (after extraction) to keep the solution homogeneous and the pH raised to pH 12.5 ($NaOH_{(aq)}$) to release the free amine. However, control experiments showed that the dioxane was reacting with the sodium hydroxide in the injector portion of the GLC column and the products of this interfered with the analysis. Subsequently, ammonia solution was used in place of dioxane.

PROCEDURE:

Reaction mixture (5.0 ml, pH 9) and water (5.0 ml) were mixed in a separating funnel (25 ml) and extracted (4 x 5 ml chloroform, 1 x 10 ml 2,2,4-trimethylpentane). Concentrated ammonia solution (10 ml) and sodium hydroxide solution (10 ml, 6M) were added and shaken. Pentan-1-ol (100 µl, GLC internal standard) was added to the basic (pH 12.5) solution which was then analysed by GLC.

Column; 10% SE30 on diatomite C-AW 100-120 mesh, 1.5 metre, 6.5 mm o.d.

Temperature; column 110°C (Isothermal)

Carrier gas; nitrogen, 18 ml/min at 110°C.

The solution was analysed ten times to check the reproducibility, the chromatograms analysed by cutting out and weighing the peaks and comparing with a standard plot of "Percentage of Deamination" versus "Amine/Internal Standard Ratio". New injector packing was required for each sample to avoid side reactions on the solid salts.

Notes:

(i) The use of ammonia helped to make the solution more basic as well as ensuring the homogeneity of the solution.

(ii) If more than 100 µl of pentan-1-ol was added it separated out of solution.

(iii) In the absence of a stationary phase specifically suited for amines a tailed amine peak could not be avoided when the amine was in aqueous solution.

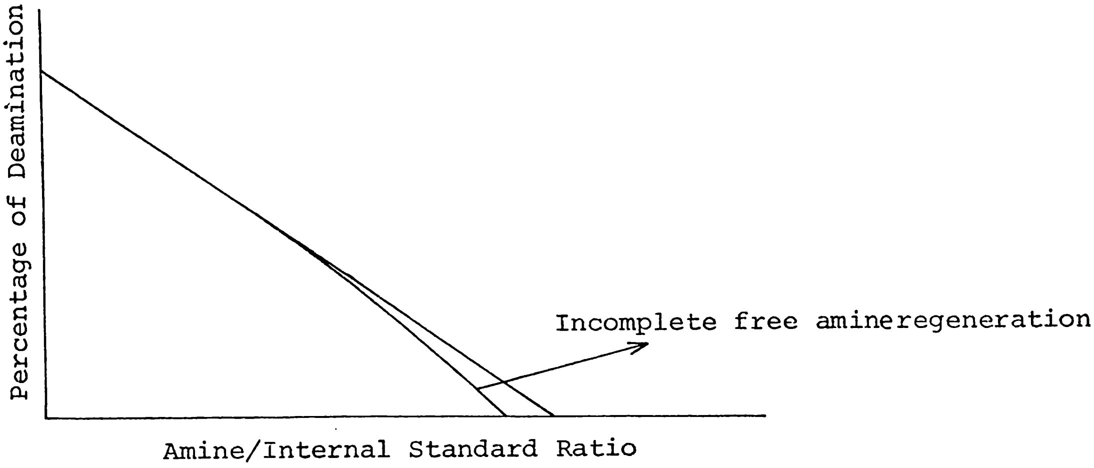
(iv) Chloroform was used for the extractions since its density allows for a number of extractions without need to transfer the aqueous phase.

(v) 2,2,4-Trimethylpentane (10ml) removed suspended chloroform but did not interfere in the chromatogram and is insoluble in water.

A2.1.4 Control Experiments

Numerous control experiments were conducted to check aspects of this procedure. Since the method was not employed in the major experiments of this thesis (Chapters 7 - 10) and the experiments in which it was used constitute only a small part of Appendix 4, the control experiments are only summarised. Extensive experimental detail is not included.

(a) Conc. Ammonia and Sodium Hydroxide Solutions:
A series of standards using known amounts of amine salt and less conc. ammonia (4 ml) and sodium hydroxide (10 ml, 5M) than usual indicated incomplete regeneration of the free amine by giving a negatively curved plot of "Percentage of Deamination" versus "Amine/Internal Standard Ratio". A straight line was observed when 10 ml of conc. ammonia solution and 6M sodium hydroxide solution was used.



(b) Amine Removal During Extractions: A simulated reaction solution was prepared and two aliquots (5 ml) taken, of which only one was extracted. A comparison of the amine analyses indicated no significant removal of amine during extraction.

(c) Efficiency of the Extraction Procedure: Amine salt solutions were prepared containing known amounts of 2-methylpropan-2-ol approximating alcohol concentrations at 4 - 5% and 40% deamination. Analyses of the combined extracts (+ 200 µl pentan-1-ol)by GLC indicated that 98% of the alcohol was removed from the 4 - 5% solution while 94% was removed from the 40% solution. Use of 6 x 5 ml chloroform instead of 4 x 5 ml in the latter case, increased the alcohol extraction to 99%. The 2,2,4-trimethylpentane removed only suspended chloroform, not alcohol.

Column: 20% Polyethylene glycol adipate, diatomite C-AW 100-120 mesh, 1.5 metre, 6.25 mm o.d., glass

Column Temperature: 70°C for 5 minute ,80°C/min, 120°C .

Carrier gas: nitrogen, 25 ml/min at 70°C .

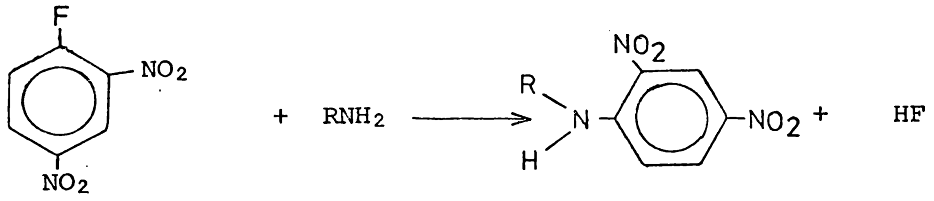
A2.1.5 Ultra-Violet Spectroscopy

Ultra-violet spectroscopy afforded the possibility of analysing the quenched reaction solution directly by taking an aliquot and measuring the absorption at an appropriate wavelength. Such a method was used to measure the unreacted sodium nitrite (A2.2). A number of methods were investigated but none proved to be viable.

(i) Direct Measurement of RNH_3^+/RNH_2

A test using 2-amino-2-methylpropane indicated no suitable absorption in the range 250 - 800 nm.

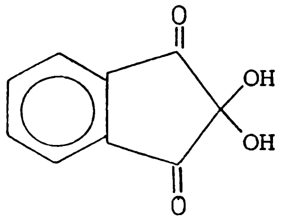
(ii) 2-Amino-2-methylpropane/ 2,4-Dinitro-1-fluorobenzene (DNFB).



2,4-dinitrophenyl derivative.

The reaction of DNFB with amino acids is well known so a similar reaction was investigated with 2-amino-2-methylpropane. Though an absorption at 292 nm was observed for RNH_2/DNFB/MeOH, subsequent tests indicated incomplete coupling under the aqueous reaction conditions.

(iii) 2-Amino-2-methylpropane/Ninhydrin



Ninhydrin

(triketohydrindene hydrate)

The reaction of ninhydrin with amino acids is widely known in biochemistry and geochemistry[171,172].

The method of Stevenson and Cheng was tried[172].Though a potentially useful absorption at 475 nm (weak) was noted, considerable refinement of the method would be required to develop a useful technique for tertiary carbinamines. This method was not pursued further.

A2.2 Unreacted Sodium Nitrite

A2.2.1 Procedure

A simple UV absorption method was used for quantitative analysis of unreacted sodium nitrite. The method used the strong nitrite ion absorption at 356 nm.

An aliquot of the reaction mixture (1 ml, pH 9) was diluted to 25 ml and its absorbance at 356 nm measured and compared with a standard solution.

Instrument: Pye-Unican SP 1800 Ultra-Violet Spectrophotometer.

A2.2.2. Control Experiments

(i) Interference by Inorganic Salts and Organic Compounds:
The absorbance at 356 nm was unaffected by perchlorate, sulphate or chloride anions; amine salts, propan-1-ol, product alcohols and alkenes and sulphonium salts.

(ii) Variable pH of Quenched Reaction Solutions:

The various reactions are quenched to approximately pH 9 though this may vary in the range 8 - 10.5. A series of sodium nitrite solutions with pHs in the range 6 - 10.5 had the absorption at 356 nm measured, and shown to be constant.

$$HNO_{2\,(aq)} \rightleftharpoons H^{+}_{(aq)} + NO_{2\,(aq)}^{-} \qquad pKa\ 3.35\ (25°C)^{173}$$

Appendix Three

Gas-Liquid Chromatography - Miscellaneous

This appendix briefly summarises a collection of GLC related studies conducted during the development of the techniques reported in Appendices 1 and 2. Brief summaries are reported for reference only.

A3.1 Methods of Chromatogram Analysis

Four methods were used at various times for quantitatively analysing GLC chromatograms;

(i) Integration
(ii) Planimetry
(iii) Cutting and Weighing
(iv) Peak Height - Retention Time Calculation

(i) Integration;

Instrument; Spectra - Physics Minigrator coupled to a Varian, Model 3700 Gas Chromatograph fitted with a flame ionisation detector.

This method was used in the studies of 2-amino-2-methylpropane (at 25 and 50°C) and dimethyl-(2-methyl-2-propyl)sulphonium perchlorate (at 50°C).

(ii) Planimetry;

Instrument; Koizumi, Type KP-27 Compensating Planimeter.

All chromatograms from reactions of the 3-methyl-3-pentyl system (Chapters 9 and 10) and associated control experiments were analysed by planimeter since the integrator could not reliably handle small samples on shifting baselines (the result of solvent tails and temperature programming). The detector system was being used close to its maximum sensitivity. Reproducibility - (Planimeter): peaks with large areas were found to be most suitable. A single, accurate scan of a peak was found to be just as accurate as averaging multiple scans and avoided laborious repetitions.

(iii) Cutting and Weighing;

This method was used only in early work reported in Appendix 4 and occassionally as a check on methods (i) and (ii).

Each chromatogram was Xerox copied five times and each copy cut and weighed. Variations in paper density are insignificant compared to the errors involved in the actual cutting and weighing. Reproducibility; most of the error involved was found to arise from the cutting operation. However, peaks with a large area/perimeter ratio (fast chart speed) could be repeatedly cut and weighed with an error of only ±0.5%.

(iv) Peak Height - Retention Time Calculation;

This method was used only in preliminary work. Except for peaks with a very small width compared to height (spiked peaks), peak height is not a good quantitative measure. The errors involved may, however, be cancelled out by ~~doing~~ performing analyses with reference to standards measured in the same way.

Comparison of the Methods:

A chromatogram was analysed by methods (i) - (iii) and the results compared. All the results were the same within a measurement error of ±3%.

A series of experiments analysed by the peak height - retention time method were reanalysed by cutting and weighing. The results differed only by about 5%.

A3.2 Precolumns in Deamination Analyses:

A short precolumn (10 cm) of 10% w/w $CoCl_2.6H_2O$ on celite 80-100 mesh, was used for GLC analyses of aqueous deamination reaction mixtures (A2.2) to retain free amine released upon injection of the reaction mixture onto the column.

Other transition metal salts (10% w/w $Ni(NO_3).6H_2O$, 10% w/w $MnSO_4.4H_2O$) were found to be slightly less efficient at complexing the free amine.

A precolumn of 10% w/w phthalic acid was partially successful but tended to also give unwanted decompositions of the compounds analysed. This precolumn worked by protonating the free amine.

A3.3 Resolution of 2-Ethylbut-1-ene, cis and trans-3-Methylpent-2-ene

The solid stationary phase, graphitized carbon black, has been reported to separate the cis and trans isomers of 3-methylpent-2-ene[174], however this phase was not available for our work.

A stationary phase of 15% w/w polypropylene glycol LB-550-X (A1.4.1) was found to adequately resolve 2-ethylbut-1-ene and cis and trans-3-methylpent-2-ene. Numerous other stationary phases were tried but none achieved any resolution at all, these included;

20% polyethyleneglycol adipate, 20% polyethyleneglycol 20M, 16% XE60, 5% Silar 10CP, 5% OV210 and 1% OV17, all on celite 80-120 mesh.

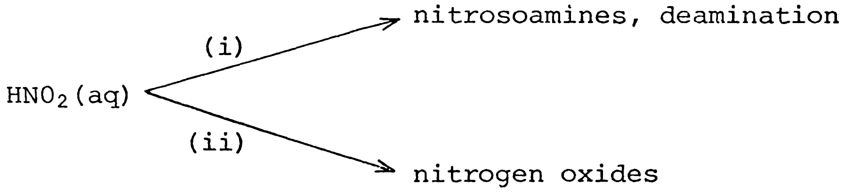
A ternary eutectic mixture of 2,4,6-trinitrotoluene (44% w/w), 1,3,5-trinitrobenzene (27% w/w) and 1,3-dinitrobenzene (29% w/w) has been used to separate isomeric octenes[175]. This stationary phase was prepared (27% w/w of the eutectic mixture on celite 80-120 mesh) but completely failed to resolve the six-carbon isomers. However cis and trans-oct-2-ene were partially resolved as expected.

The PPG, LB-550-X column used was a commercially prepared (Perkin-Elmer) analytical column. The neat stationary phase was not available to coat a preparative column for the collection of separate samples of 2-ethylbut-1-ene, cis and trans-3-methylpent-2-ene. In the absence of a suitable alternative the preparative column was not made.

Appendix Four

Non-Deaminative Decomposition of Nitrous Acid

In nitrous acid deaminations the acid, or species arising from it may react in two ways; (i) by nitrosating the amine, (ii) by decomposing to various nitrogen oxides (non-deaminative decomposition).



Pathway (i) has been the subject of the literature survey and the experimental work of this thesis. Aqueous nitrous acid decomposes to nitrogen oxides even at 25°C[102,166].

$$4\ HONO \rightleftharpoons 2N_2O_3 + 2H_2O$$

$$2\ N_2O_3 \rightleftharpoons N_2O_4 + 2NO$$

$$N_2O_4 + H_2O \rightleftharpoons HONO + HNC_3$$

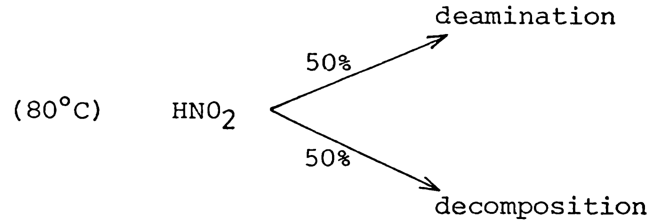
In the deaminations reported in this thesis, samples of reaction mixture (1.0 ml) were taken for the analysis of unreacted sodium nitrite. By comparing the amount of sodium nitrite reacted and the extent of deamination (product sum) it was possible to determine the importance of the non-deaminative decomposition of the nitrous acid during deaminations at 80, 50 and 25°C.

$$HNO_2 + RNH_2 \longrightarrow \text{products}$$

1 mole + 1 mole

Initial $NaNO_2:RNH_2$ mole ratio = 2:1 in deaminations. Therefore 20% of deamination will give 10% reaction of the sodium nitrite if there is no non-deaminative decomposition of the nitrous acid.

The deamination reactions carried out at 25°C and pH4 (Chapter 7.4) involved little or no non-deaminative decomposition. The reactions at 50 and 80°C gave increasing amounts of the side reaction so that deaminations at 80°C involved equal amounts of nitrosation and decomposition. At reaction pHs of less than 4.0, increasing amounts of non-deaminative decomposition occurred in a series of 2-amino-2-methylpropane deaminations at 25°C.



The amount of nitrous acid decomposition in deaminations at 80 and 50°C may be reduced if they were to be carried out at a pH > 4, however a decrease in deamination rate would also be observed.

The effect of the nitrogen oxides (NO, NO_2, N_2O_4) on the products of the deaminations was tested by a number of control experiments previously described in Chapters 7 to 10. Literature relevant to this area includes papers by Turney and Wright[102] (Nitrous Acid and Nitrosation), Beattie[176] (Dinitrogen Trioxide), Park and Williams[162] (Reaction of Dinitrogen Trioxide with 2-Methylpropene and other Alkenes), Komiyama and Inoue[177] (Reaction and Transport of Nitrogen Oxides in Nitrous Acid Solutions) and Ridd[140] (Diffusion Control and Pre-association in Nitrosation, Nitration and Halogenation).

Appendix Five

Micelles in Deamination

A5.1 General

Studies by Moss[150] and Kirmse[67] have shown that alkylammonium micelles may form in aqueous deamination reactions. Their presence markedly alters the product distribution compared with non-micellar deaminations (Chapter 5).

Preliminary deamination studies of 3-amino-3-methylpentane hydrochloride gave variable product ratios that were subsequently shown to be due to experimental error. However, the possibility of micellar intervention was also considered since the observed variations were consistent with reported micellar mechanisms. The reaction conditions of the published studies were similar to those employed in the deaminations of this thesis.

The presence of micelles affects many physical properties of solutions including the conductivity and the refractive index[148,149]. These two properties were measured for a number of amine salt and inorganic salt solutions.

3-Amino-3-methylpentane hydrochloride and 2-amino-2-methylpropane hydrochloride solutions were studied using concentrations spanning that used in the deamination reactions (up to 2.5M).

No micelles appeared to be present. Sodium chloride solutions were also measured to see whether the observed conductance behaviour was an artifact of the high salt concentrations used.

Sodium dodecyl (lauryl) sulphate is a well known surfactant for which the critical micelle concentration has been determined by conductance measurements[178]. These were reproduced to check the accuracy of the conductance technique employed here. The results are compared and discussed in Section 5.6.

A5.2 3-Amino-3-methylpentane Hydrochloride Salt

A5.2.1 Conductance Measurements (no added inorganic salts)

This work followed preliminary deamination studies using the amine hydrochloride salt rather than the amine perchlorate salt reported in Chapters 7 and 9. The former was synthesised (Appendix 6.8), solutions (25 solutions in the range 0.025-2.415M) prepared using doubly distilled water (conductance 2-3 $x10^{-6}$ ohm^{-1} cm^{-1} at 25.00±0.02°C) and the pH adjusted to pH 3.95-4.05 ($HClO_4$, 0.034M or NaOH, 0.025M as appropriate).

The solutions were equilibrated to 25.00±0.02°C (30 min) before use, the electrodes inserted and the resistance measured after further equilibration (15-20 min). All solutions were open to the atmosphere.

Instruments:

Philips Conductance Meter PR9500/02

Philips Conductance Cell 9510

Radiometer pH Meter 28

Radiometer Combined Electrode GK2321C
(potassium hydrogen phthalate buffer, pH 4.006 at 25.00°C).

Calculations:

The specific conductance (K) was calculated from the measured resistance values using the expression;

$K = k/R$ ohm^{-1} cm^{-1}, where k is the cell constant and R is the measured resistance (ohm).

The equivalent conductance (Λ) was obtained from the expression;

$\Lambda = 1000.K/C$ ohm^{-1} $mole^{-1}$ cm^2, C is the amine salt concentration.

Results: The specific and equivalent conductance values are summarised in TABLE 18 and are plotted in FIGURES 20 and 21 against concentration and square root of concentration respectively. The errors listed in TABLE 18 are reading errors only.

TABLE 18

Electrical Conductance of 3-Amino-3-methylpentane Hydrochloride Salt Solutions (25.00°C)

$[RNH_3^+Cl^-]$ (mole l^{-1}) (C)	R (ohm) (x 10^2)	% Reading Error in R (±)	$K_{RNH_3^+Cl^-}$ (ohm^{-1} cm^{-1}) (x 10^{-3})	Λ (ohm^{-1} mole^{-1} cm^2)	$(C)^{\frac{1}{2}}$
0.025	2.36	0.7	2.55	101.57	0.158
0.050	1.63	1.2	4.47	89.10	0.224
0.075	1.13	1.8	6.45	85.67	0.274
0.100	0.889	0.2	8.20	81.70	0.317
0.151	0.619	0.3	11.78	78.21	0.388
0.201	0.497	0.4	14.67	73.10	0.448
0.251	0.405	0.5	18.00	71.72	0.501
0.329	0.335	0.6	21.76	66.09	0.574
0.402	0.292	0.7	24.97	62.18	0.634
0.452	0.265	0.8	27.51	60.90	0.672
0.502	0.250	0.8	29.16	58.09	0.709
0.548	0.233	0.9	31.29	57.08	0.740
0.602	0.226	0.9	32.26	53.55	0.776
0.653	0.213	0.9	34.23	52.45	0.803
0.733	0.200	1.0	36.46	49.71	0.856
0.803	0.190	1.1	38.37	47.75	0.896
0.904	0.180	1.1	40.51	44.83	0.951
1.004	0.175	1.1	41.66	41.50	1.002
1.100	0.167	1.2	43.66	39.69	1.049
1.200	0.158	1.3	46.15	38.45	1.095
1.401	0.150	1.3	48.61	34.69	1.184
1.601	0.148	1.4	49.26	30.77	1.265
1.799	0.145	1.4	50.28	27.95	1.341
2.000	0.145	1.4	50.28	25.14	1.414
2.415	0.152	1.3	47.92	19.86	1.554

R = Sample + cell resistance.

$K_{RNH_3^+Cl^-}$ = Specific Conductance of the sample,

(K = k/R, k = cell constant)

Λ = Equivalent Conductance of the sample,

(Λ = 1000 x K/C, C = concentration of $RNH_3^+Cl^-$)

FIGURE 20

3-Amino-3-methylpentane Hydrochloride Solutions

pH 4.00±0.05, 25.00±0.02°C

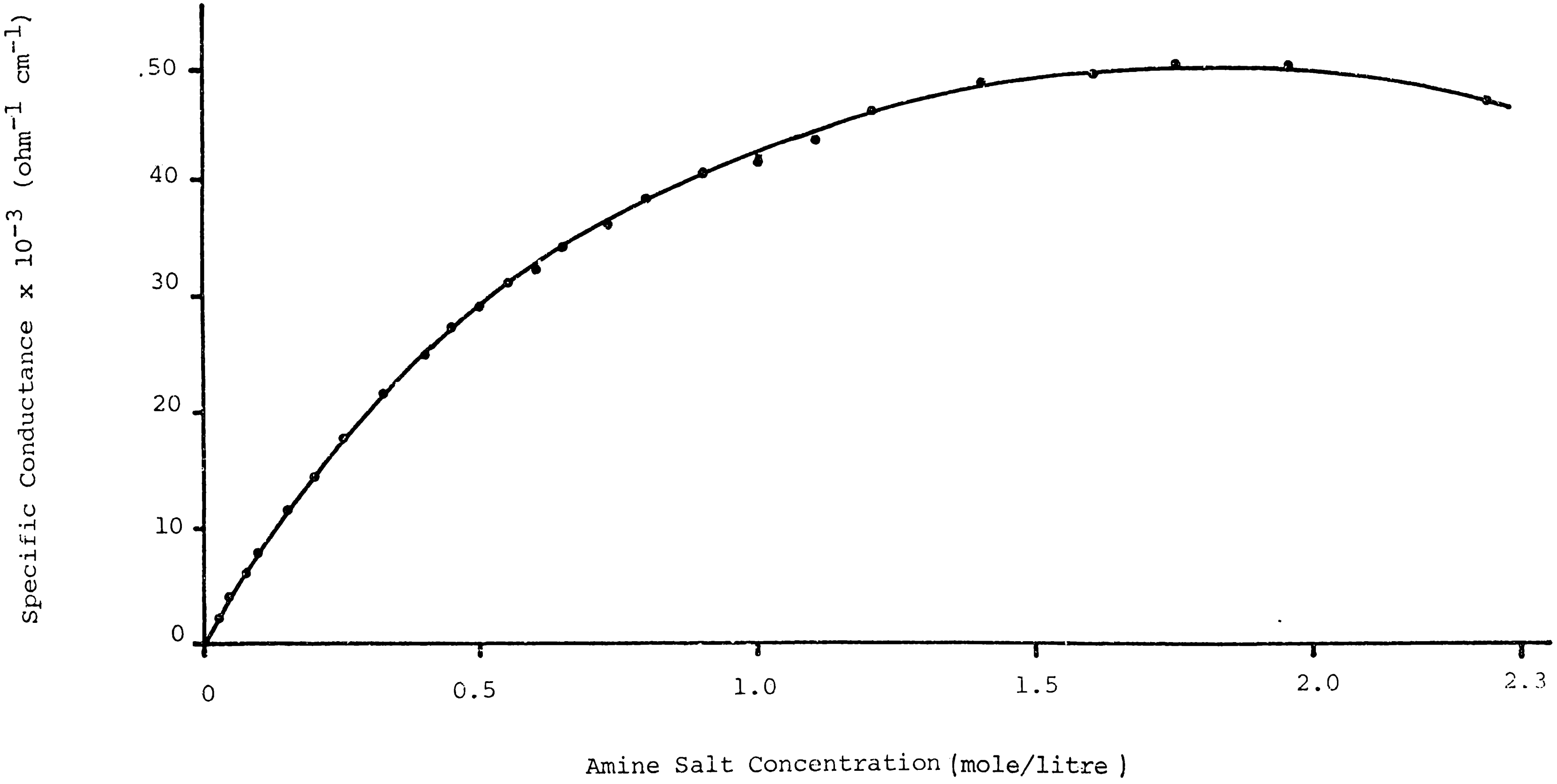
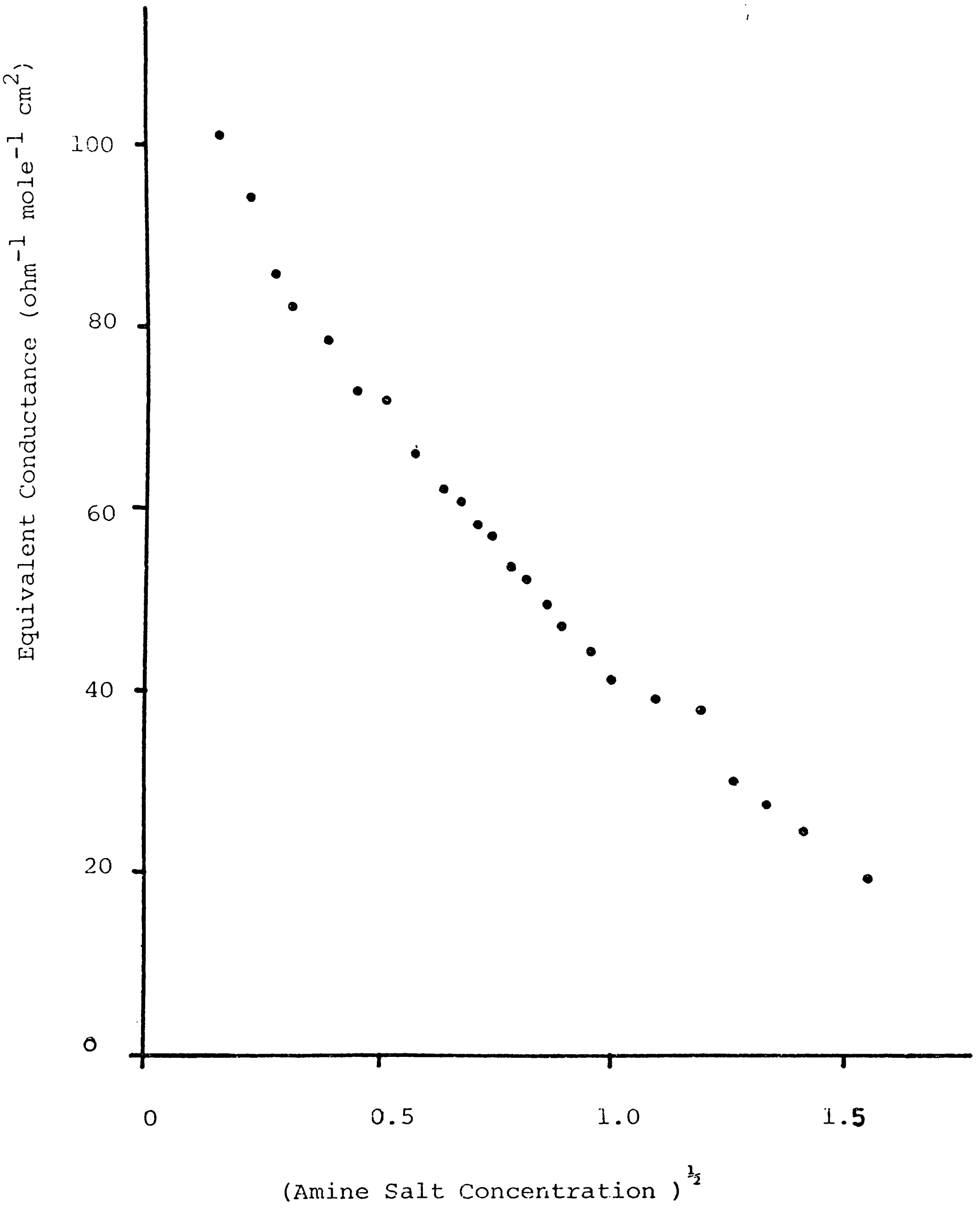


FIGURE 21

3-Amino-3-methylpentane Hydrochloride Solutions

pH 4.00±0.05, 25.00°C



A5.2.2 Refractive Index Measurements (no added inorganic salts)

Refractive indexes (24.90±0.02°C) were determined for solutions prepared in Section 5.2.1

Instrument: Atago Abbe Type, No 302 refractometer.

Results: The refractive indexes are listed in TABLE 19 and plotted in FIGURE 22 against the salt concentration.

TABLE 19

Refractive Indexes of Solutions of

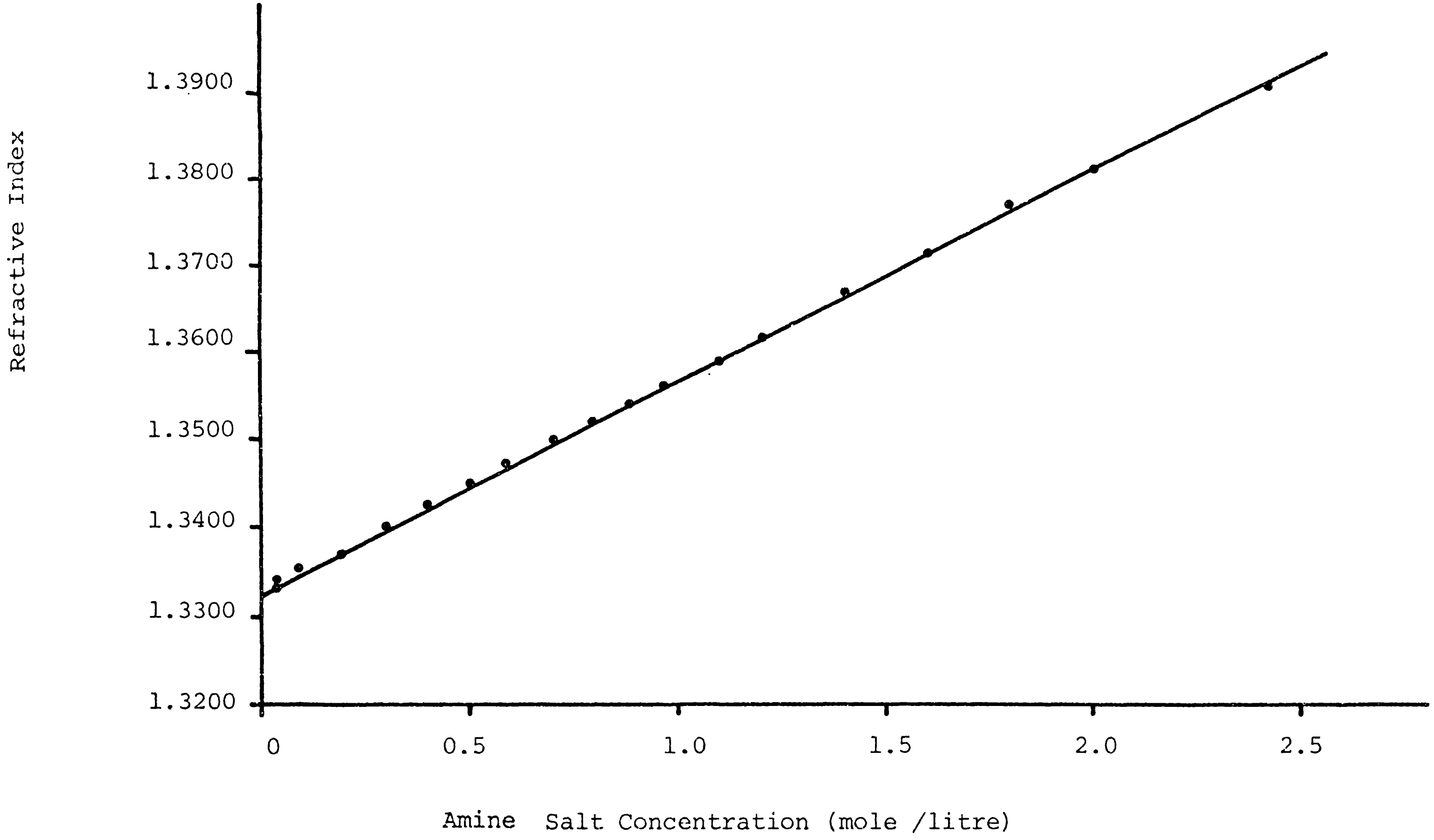
3-Amino-3-methylpentane Hydrochloride Salt

Salt Concentration (mole/litre)	Refractive Index (24.90±0.02°C)
0.0330	1.3342
0.0880	1.3354
0.1920	1.3370
0.2942	1.3403
0.3960	1.3427
0.4050	1.3451
0.5884	1.3474
0.7044	1.3499
0.7916	1.3523
0.8800	1.3541
0.9660	1.3563
1.100	1.3591
1.200	1.3619
1.401	1.3670
1.601	1.3715
1.799	1.3770
2.001	1.3809
2.415	1.3906
water (distilled)	1.3335

FIGURE 22

3-Amino-3-methylpentane Hydrochloride Solutions

pH 4.0, 24.9°C



A5.2.3 Conductance Measurements (added inorganic salts)

It is well known that added salts tend to lower the critical micelle concentrations of organic substrates[149]. The micelle study was directed towards deaminations at 25°C. These contained sodium nitrite (1.02M) and perchloric acid (0.0328M).

Amine salt solutions were prepared containing constant concentrations of sodium chloride (1.02M, in place of sodium nitrite[150]) and sodium perchlorate (0.0328M). The pH was adjusted to pH 3.95-4.05 and the conductance measured in the manner described in Section 5.2.1.

Notes: The amount of acid added to adjust the pH was very small compared with the mole, of sodium chloride and sodium perchlorate in each sample.

Sodium chloride was used to prevent reaction of the amine at pH4.

Results: The specific and equivalent conductance values are summarised in TABLE 20 and are plotted in FIGURES 23 and 24 against concentration and square root of concentration respectively.

TABLE 20

Electrical Conductance of 3-Amino-3-methylpentane Hydrochloride Solutions with Added NaCl and $NaClO_4$ (pH 4.0, 25.00°C)

$[RNH_3^+Cl^-]$ (mole l^{-1})	[Total Salt] (mole l^{-1})	R(ohm) (x 10^2)	% Reading Error in R (±)	$K_{RNH_3^+Cl^-}$ (ohm^{-1} cm^{-1}) (x 10^{-3})	Λ (ohm^{-1} mole^{-1} cm^2)	$[\text{Total Salt}]^{\frac{1}{2}}$
0.025	1.078	0.083	2.4	85±2	78.8	1.038
0.050	1.103	0.084	2.4	84±2	76 4	1.050
0.100	1.153	0.085	2.4	83±2	71.9	1.074
0.200	1.253	0.085	2.4	83±2	66.4	1.119
0.400	1.453	0.085	2.4	83±2	57.1	1.205
0.599	1.652	0.086	2.3	82±2	49.8	1.285
0.799	1.852	0.088	2.3	80±2	43.3	1.361
0.916	1.969	0.089	2.3	80±2	40.9	1.403
1.199	2.252	0.090	2.2	79±2	35.2	1.501
1.235	2.288	0.090	2.2	79±2	34.4	1.513
1.447	2.500	0.096	2.1	74±2	29.5	1.581
1.598	2.651	0.096	2.1	74±2	27.7	1.628
1.799	2.852	0.102	2.0	70±1	24.2	1.689
2.010	3.063	0.105	1.9	67±1	21.9	1.750
2.479	3.550	0.123	1.6	57±1	16.1	1.884

R = Sample + cell resistance.

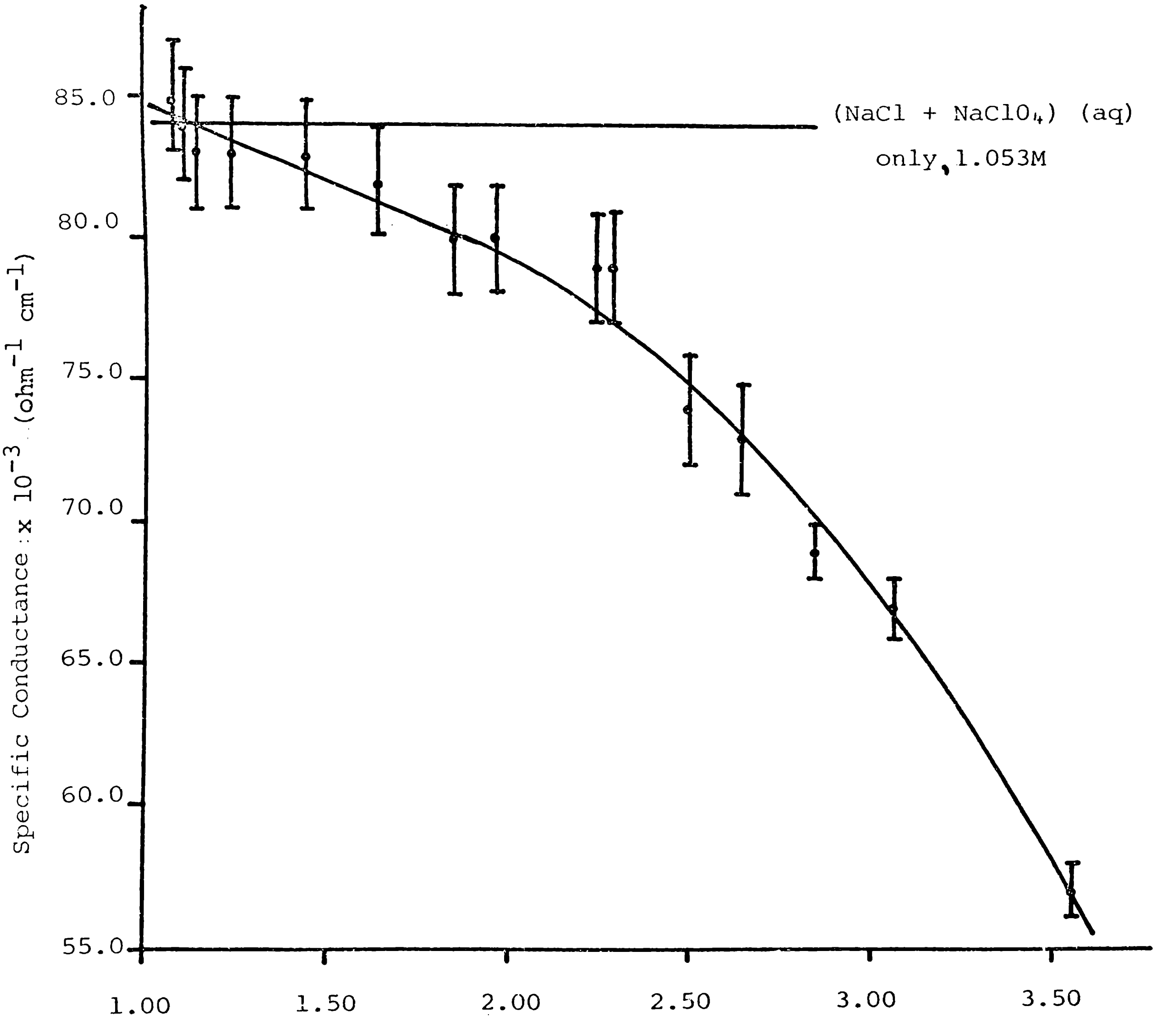
$K_{RNH_3^+Cl^-}$ = Specific Conductance of the sample.

Λ = Equivalent Conductance = 1000.K/[Total Salt].

FIGURE 23

Solutions Containing 3-Amino-3-methylpentane Hydrochloride, Sodium Chloride and Sodium Perchlorate

pH 4.0, 25.00°C



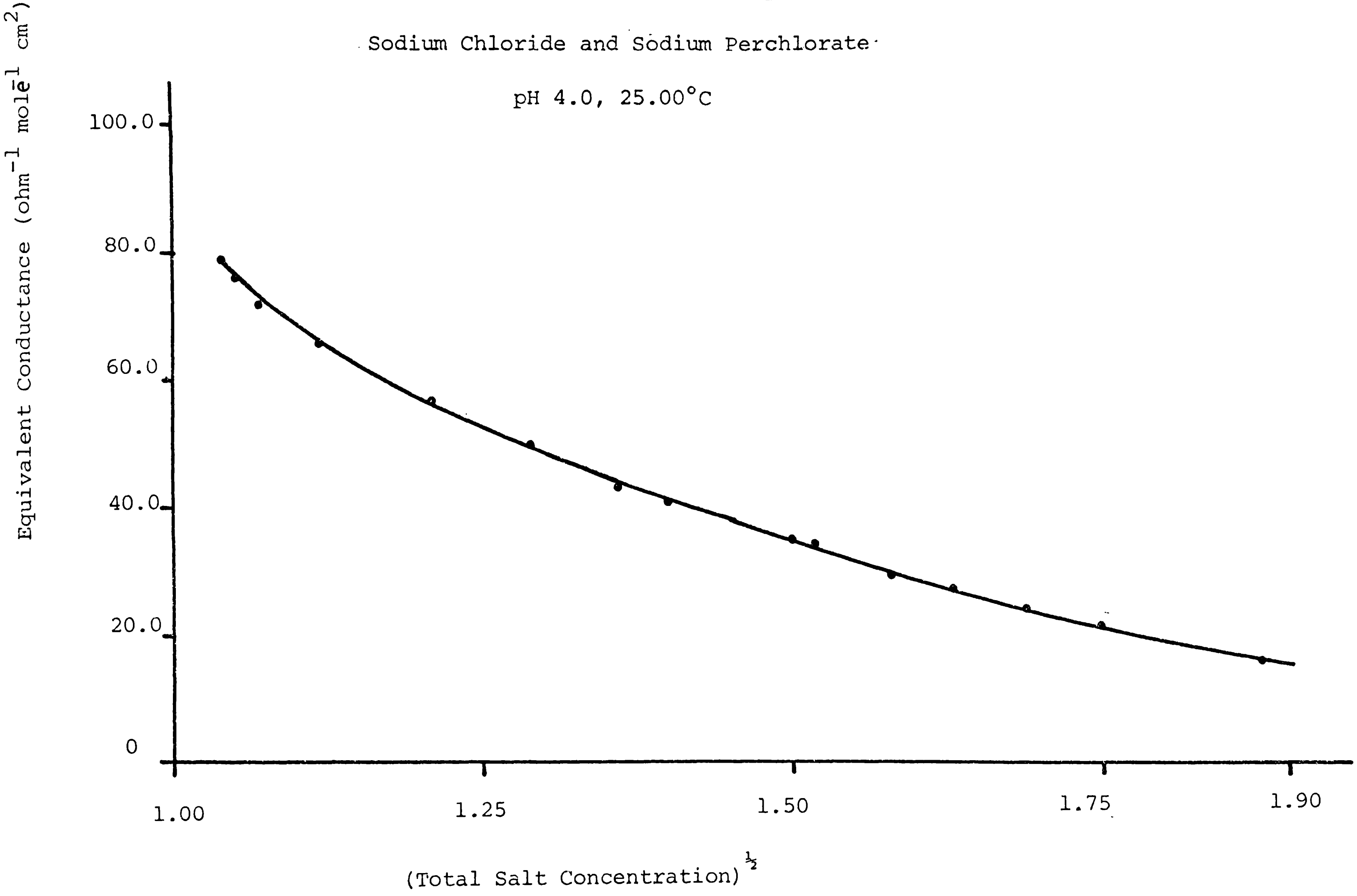
Total Salt Concentration (mole/litre)

FIGURE 24

Solutions Containing 3-Amino-3-methylpentane Hydrochloride,

Sodium Chloride and Sodium Perchlorate

pH 4.0, 25.00°C



A5.2.4 Refractive Index Measurements (added inorganic salts)

Refractive indexes (25.5±0.1°C) were determined for the solutions prepared in Section 5.2.3.

Results: The refractive indexes are summarised in TABLE 21 and plotted in FIGURE 25 which also includes data from TABLE 19 for comparison.

TABLE 21

Refractive Indexes of Solutions of
3-Amino-3-methylpentane Hydrochloride Salt
with added NaCl and $NaClO_4$

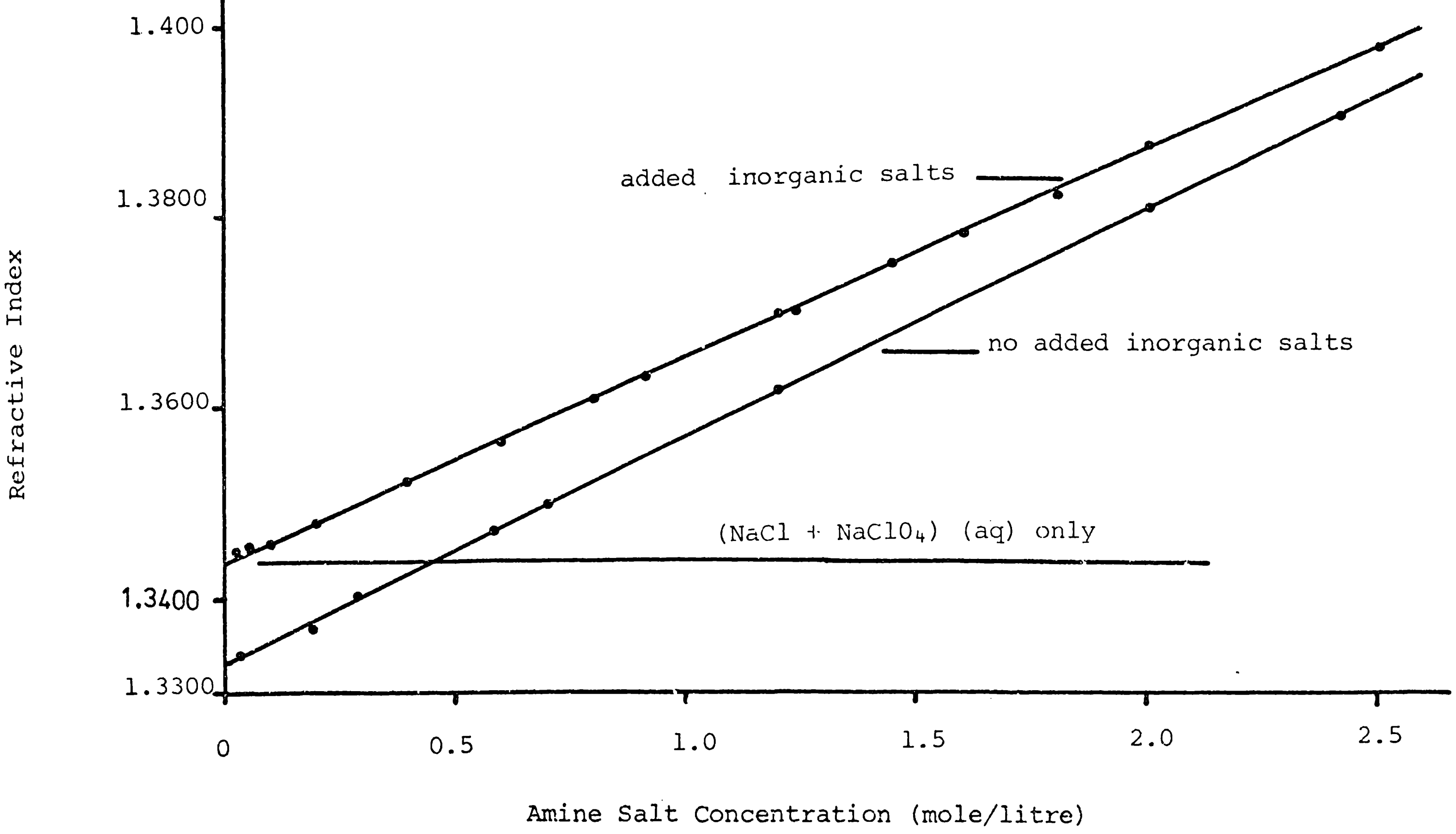
Amine Salt Concentration (mole/litre)	Refractive Index (25.5±0.1°C)
0.025	1.3449
0.050	1.3455
0.100	1.3462
0.200	1.3482
0.400	1.3523
0.599	1.3563
0.799	1.3608
0.916	1.3632
1.199	1.3698
1.238	1.3700
1.447	1.3747
1.598	1.3782
1.798	1.3821
2.010	1.3874
2.497	1.3979
water (distilled)	1.3342
($NaCl + NaClO_4$) (aq) pH 4.0	1.3438
($NaCl + NaClO_4$) (aq) pH 6.31	1.3439

FIGURE 25

Solutions Containing 3-Amino-3-methylpentane Hydrochloride,

Sodium Chloride and Sodium Perchlorate

pH 4.0, 25.5 0.1°C



A5.3 2-Amino-2-methylpropane Hydrochloride Salt

Conductance Measurements (no added organic salts)

Resistances of amine salt solutions (25°C) were measured in the same way as described in Section 5.2.1.

Results: The results are summarised in TABLE 22 while conductance and equivalent conductance are plotted against salt concentration and square root of salt concentration respectively in FIGURES 26 and 27.

TABLE 22

Electrical Conductance of 2-Amino-2-methylpropane Hydrochloride Solutions (25.0°C)

$[RNH_3^+Cl^-]$ (mole l^{-1}) (C)	R (ohm) ±0 .002 (x 10^2)	$K_{RNH_3^+Cl^-}$ (ohm^{-1} cm^{-1}) (x 10^{-2})	Λ (ohm^{-1} mole^{-1} cm^2)	$(C)^{\frac{1}{2}}$
0.125	0.660	1.08±0.02	86±2	0.35
0.250	0.363	1.95±0.04	78±2	0.50
0.500	0.210	3.38±0.07	68±1	0.71
0.600	0.185	3.83±0.08	64±1	0.77
0.800	0.153	4.64±0.09	58±1	0.89
1.00	0.135	5.3±0.1	53±1	1.00
1.500	0.107	6.6±0.1	44.0±0.9	1.22
2.00	0.102	7.0±0.1	35.0±0.7	1.41
2.50	0.100	7.1±0.1	28.4±0.6	1.58

R = Sample + cell resistance.

$K_{RNH_3^+Cl^-}$ = Specific Conductance of the sample.

Λ = Equivalent Conductance of the sample.

C = Amine salt concentration.

FIGURE 26

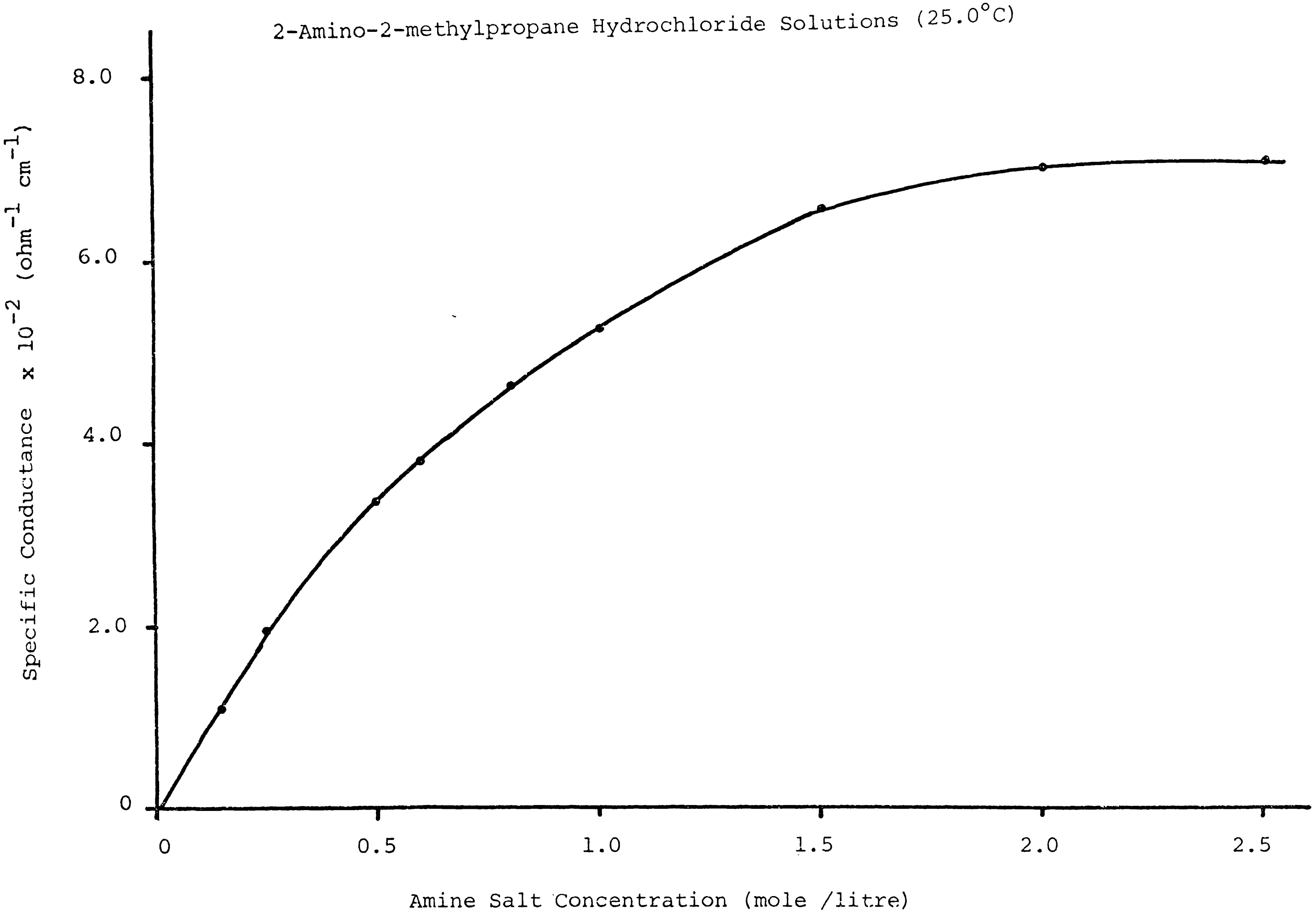
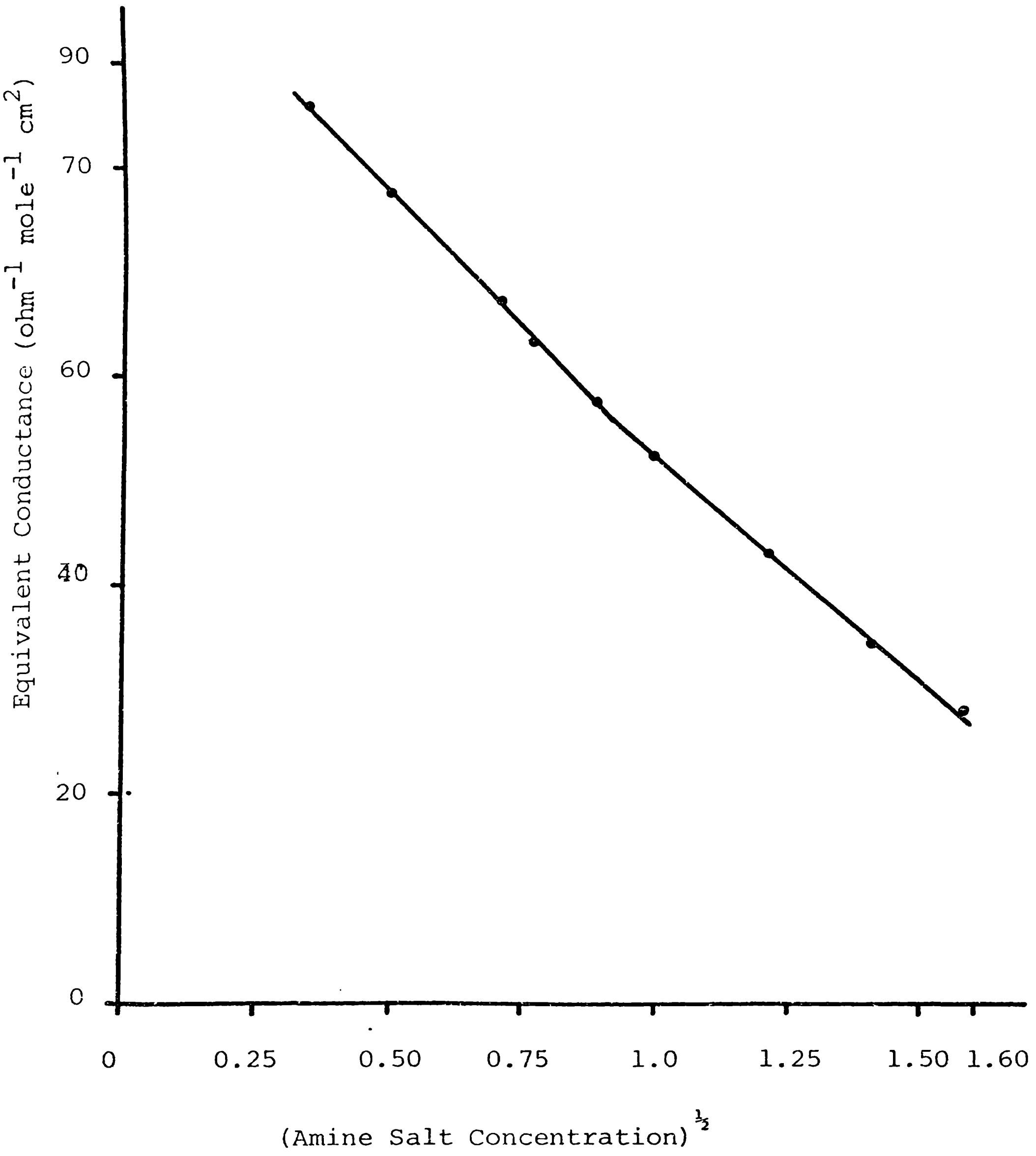

2-Amino-2-methylpropane Hydrochloride Solutions (25.0°C)
Specific Conductance x 10^{-2} (ohm^{-1} cm^{-1})
8.0
6.0
4.0
2.0
0
0
0.5
1.0
1.5
2.0
2.5
Amine Salt Concentration (mole /litre)

FIGURE 27

2-Amino-2-methylpropane Hydrochloride Solutions (25.0°C)



A5.4 Sodium Dodecyl Sulphate

A5.4.1 Conductance Measurements

Sodium dodecyl (lauryl) sulphate ($C_{12}H_{25}OSO_3Na$) solutions were prepared using doubly distilled water (conductance 1.13 x 10^{-6} ohm^{-1} cm^{-1} at 25.0°C). The reported critical micelle concentration is approximately 0.008M[178] so solutions were prepared in the range 2 x 10^{-2} to 1.000 x 10^{-3}M and their resistances measured at 25.05±0.02°C.

Specific and equivalent conductances were calculated as outlined in Section 5.2.1.

Note: The solution resistance slowly decreased during resistance measurements open to the atmosphere (possibly due to carbon dioxide absorption) so the cell was rinsed (3 times) with temperature equilibrated solution and a reading taken immediately.

Results: The specific and equivalent conductances are summarised in TABLE 23 and plotted in FIGURES 28 and 29.

Critical Micelle Concentration;

from FIGURE 28 (Specific Conductance vs Concentration)

CMC = 0.00815M at 25.05°C

from FIGURE 29 (Equivalent Conductance vs Square Root of Concentration)

CMC = 0.00745M at 25.05°C

compared with Mukerjee[178], CMC = 0.0081M at 25.0°C (from a plot of Equivalent Conductance vs Square Root of Concentration)

Material:

Sodium Dodecyl (Lauryl) Sulphate, BDH chemicals

Specifically purified for Biochemistry 99%

Maximum limit of impurities; chloride 0.01%, phosphate 0.0001%, lead 0.0002%

TABLE 23

Electrical Conductance of Sodium Dodecyl Sulphate Solutions (25.05±0.02°C)

[NaLS] (mole l^{-1}) ($\times 10^{-2}$)	R (ohm) ($\times 10^{3}$)	% Reading Error in R (±)	K_{NaLS} (ohm^{-1} cm^{-1}) ($\times 10^{-4}$)	Λ (ohm^{-1} $mole^{-1}$ cm^{2})	$[NaLS]^{\frac{1}{2}}$
0.0250	37.7	0.3	0.189	75.7±0.4	0.0158
0.0500	19.1	0.5	0.374	74.7±0.4	0.0224
0.100	9.75	0.5	0.732	73.2±0.4	0.0316
0.125	8.09	0.1	0.882	70.6±0.1	0.0354
0.200	5.15	0.2	1.386	69.3±0.2	0.0447
0.400	2.59	0.4	2.76	68.9±0.3	0.0632
0.500	2.08	0.5	3.43	68.6±0.4	0.0707
0.600	1.73	0.6	4.12	68.7±0.4	0.0775
0.800	1.34	0.7	5.33	66.6±0.5	0.0894
1.000	1.16	0.9	6.15	61.5±0.6	0.1000
1.400	1.01	1.0	7.07	50.5±0.5	0.1183
1.600	0.920	0.5	7.76	48 5±0.2	0.1265
1.800	0.865	0.6	8.25	45.8±0.3	0.1342
2.000	0.820	0.6	8.70	43.5±0.3	0.1414

R = Sample + cell resistance.

K_{NaLS} = Specific Conductance of the sample.

Λ = Equivalent Conductance of the sample.

FIGURE 28

Sodium Dodecyl Sulphate Solutions (25.05±0.02°C)

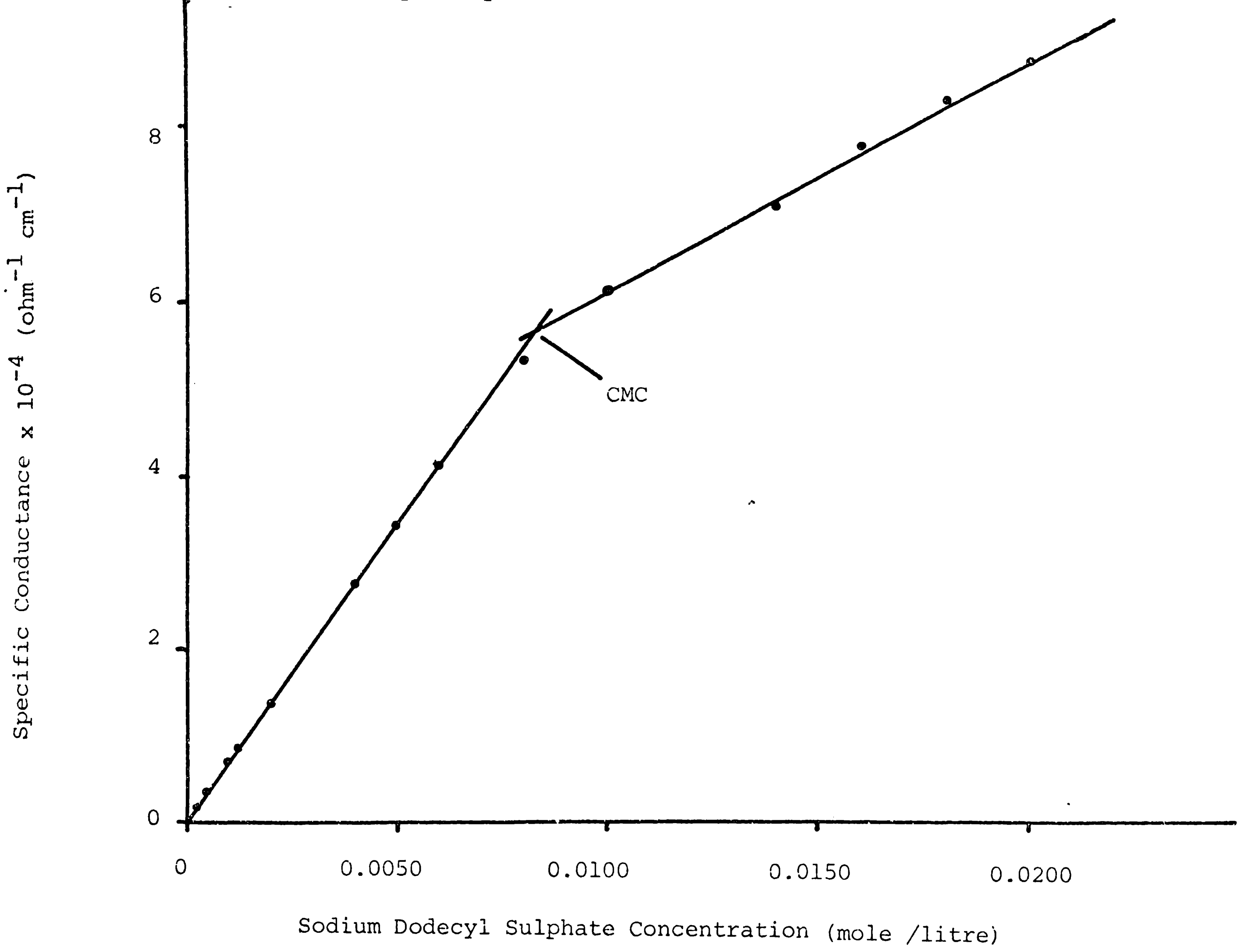
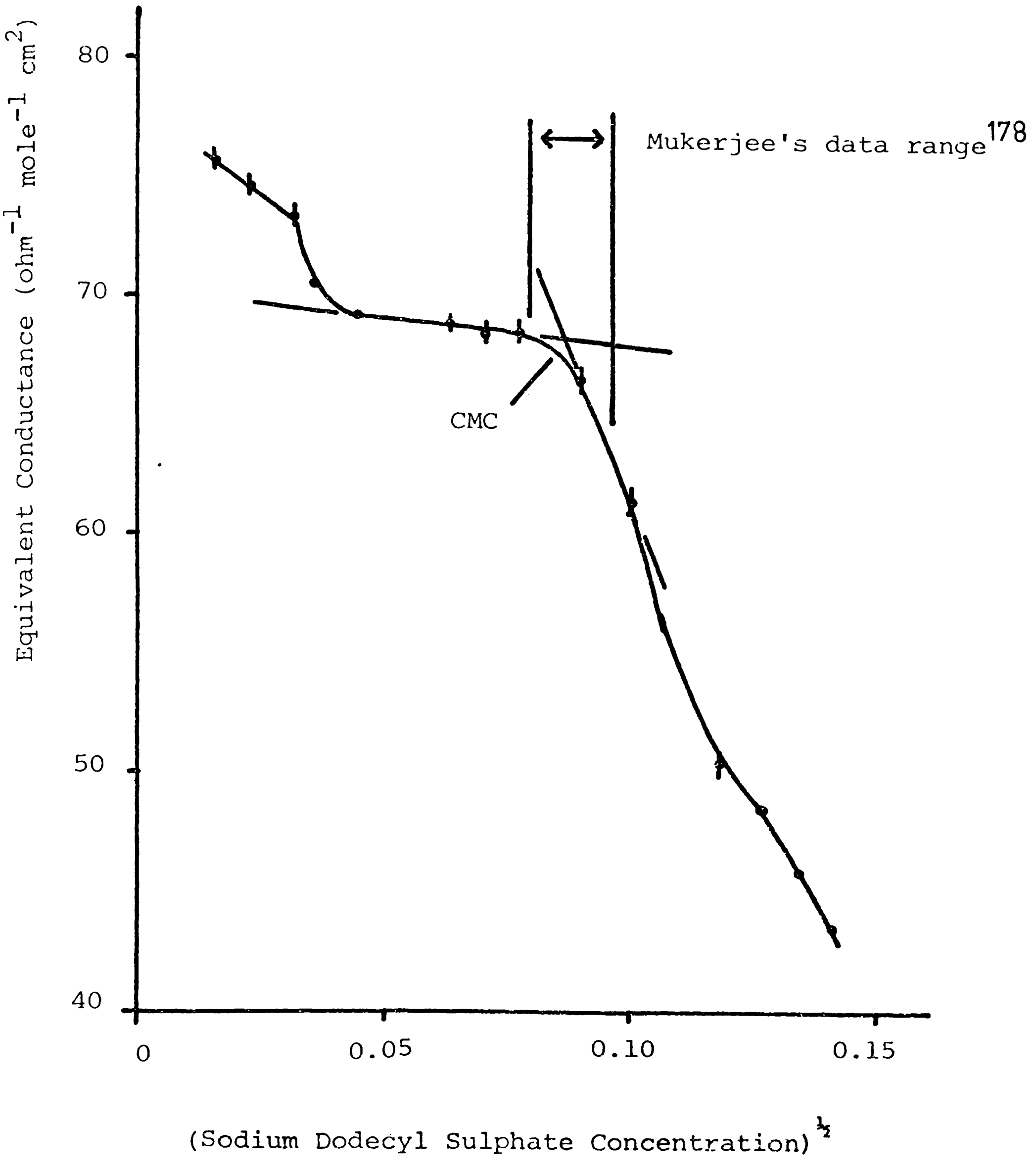


FIGURE 29

Sodium Dodecyl Sulphate Solutions (25.05±0.02°C)



A5.4.2 Refractive Index Measurements

Refractive indexes were determined for the solutions prepared in Section 5.4.1.

Results: The refractive indexes (25.65±0.02°C) were constant with a mean value of 1.3336±0.0003. Distilled water had a refractive index of 1.3337.

Clearly the method is insensitive to such low concentrations of solute.

A5.5 Sodium Chloride

A5.5.1 Conductance Measurements

Sodium chloride solutions (5.0 x 10^{-4}M to 3.000M) were prepared using doubly distilled water and the solution resistances measured in the manner described for sodium dodecyl sulphate (Section 5.4.1) at 25.05±0.02°C.

Results: The specific and equivalent conductances were calculated in the standard fashion (Section 5.2.1) and are summarised in TABLE 24. FIGURES 30 and 31 (Section 5.6) include plots of Specific Conductance vs Salt Concentration and Equivalent Conduct vs Square Root of Salt Concentration respectively.

TABLE 24

Electrical Conductance of Sodium Chloride Solutions (25.05 ± 0.02°C)

[NaCl] (mole l^{-1})	R (ohm) (x 10^{-1})	% Reading Error in R (±)	κ_{NaCl} (ohm^{-1} cm^{-1}) (x 10^{-2})	Λ (ohm^{-1} mole^{-1} cm^2)	[NaCl]$^{1/2}$
5 x 10^{-4}*	-	-	6.23 x 10^{-3}	124.5	0.0224
1 x 10^{-3}*	-	-	1.24 x 10^{-2}	123.7	0.0316
5 x 10^{-3}*	-	-	6.04 x 10^{-2}	120.7	0.0707
0.01 *	-	-	0.119	118.5	0.1000
0.0200 *	-	-	0.231	111.5	0.1414
0.0500	128	0.8	0.558	111.5	0.2236
0.100	67.8	0.1	1.053	105.3	0.3162
0.200	35.9	0.3	1.988	99.4	0.4472
0.400	19.1	0.5	3.74	93.4	0.6325
0.500	15.6	0.6	4.57	91.5	0.7071
1.000	8.76	0.1	8.15	81.5	1.000
1.200	7.53	0.1	9.48	79.0	1.095
1.400	6.72	0.1	10.62	75.9	1.183
1.800	5.57	0.2	12.81	71.2	1.342
2.000	5.18	0.2	13.78	68.9	1.414
2.400	4.59	0.2	15.55	64.3	1.549
2.700	4.27	0.2	16.71	61.9	1.643
3.000	3.97	0.3	19.98	59.9	1.732

* Literature values: see reference 184 p. D-132.

R = Sample and cell resistance.

κ_{NaCl} = Specific Conductance of the sample.

Λ = Equivalent Conductance of the sample.

A5.5.2 Refractive Index Measurements

Refractive indexes were determined for the solutions prepared in Section 5.5.1.

Results: The refractive indexes are summarised in TABLE 25.

TABLE 25

Refractive Indexes of Solutions of Sodium Chloride

Salt Concentration (mole/litre)	Refractive Index (24.95±0.02°C)
0.0500	1.3339
0.100	1.3342
0.200	1.3354
0.400	1.3373
0.500	1.3384
1.000	1.3431
2.000	1.3523
3.000	1.3610

A linear plot is achieved when the Refractive Index is plotted against Salt Concentration.

A5.6 Conclusions

No evidence was found for the presence of micelles in solutions of either 2-amino-2-methylpropane or 3-amino-3-methylpentane. The work with sodium dodecyl sulphate showed that the technique used was correct and the conductance plots for this system show the behaviour associated with the presence of micelles. The conductance measurements on the sodium chloride solutions indicate that the behaviour of the amine salts probably reflects interference in the ion mobilities by ion-ion interactions and possibly the formation of ion-pairs at the high salt concentrations used. FIGURES 30 and 31 compare the behaviour of the sodium chloride and amine salt solutions.

FIGURE 30

Conductance of Salt Solutions at High Concentrations

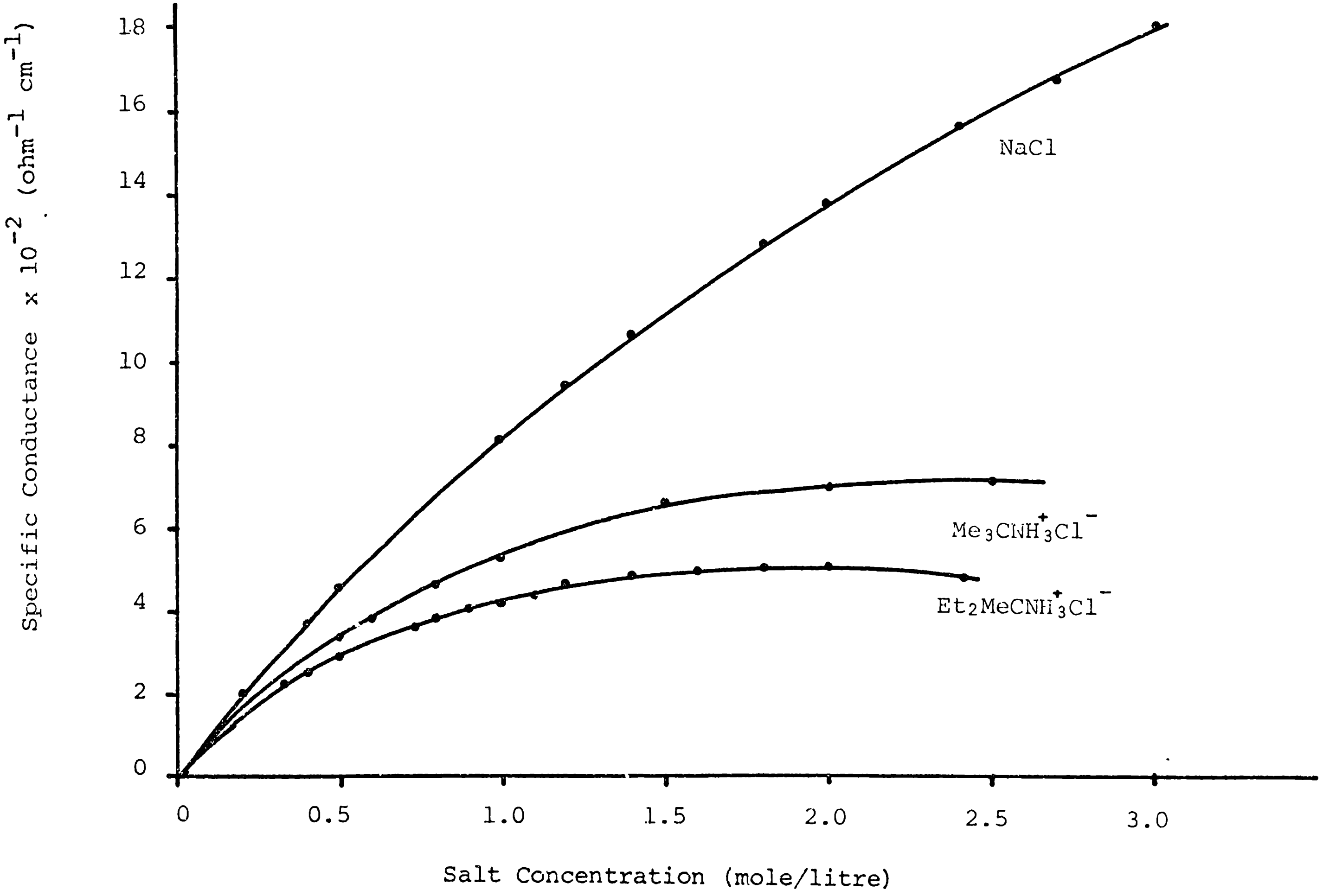
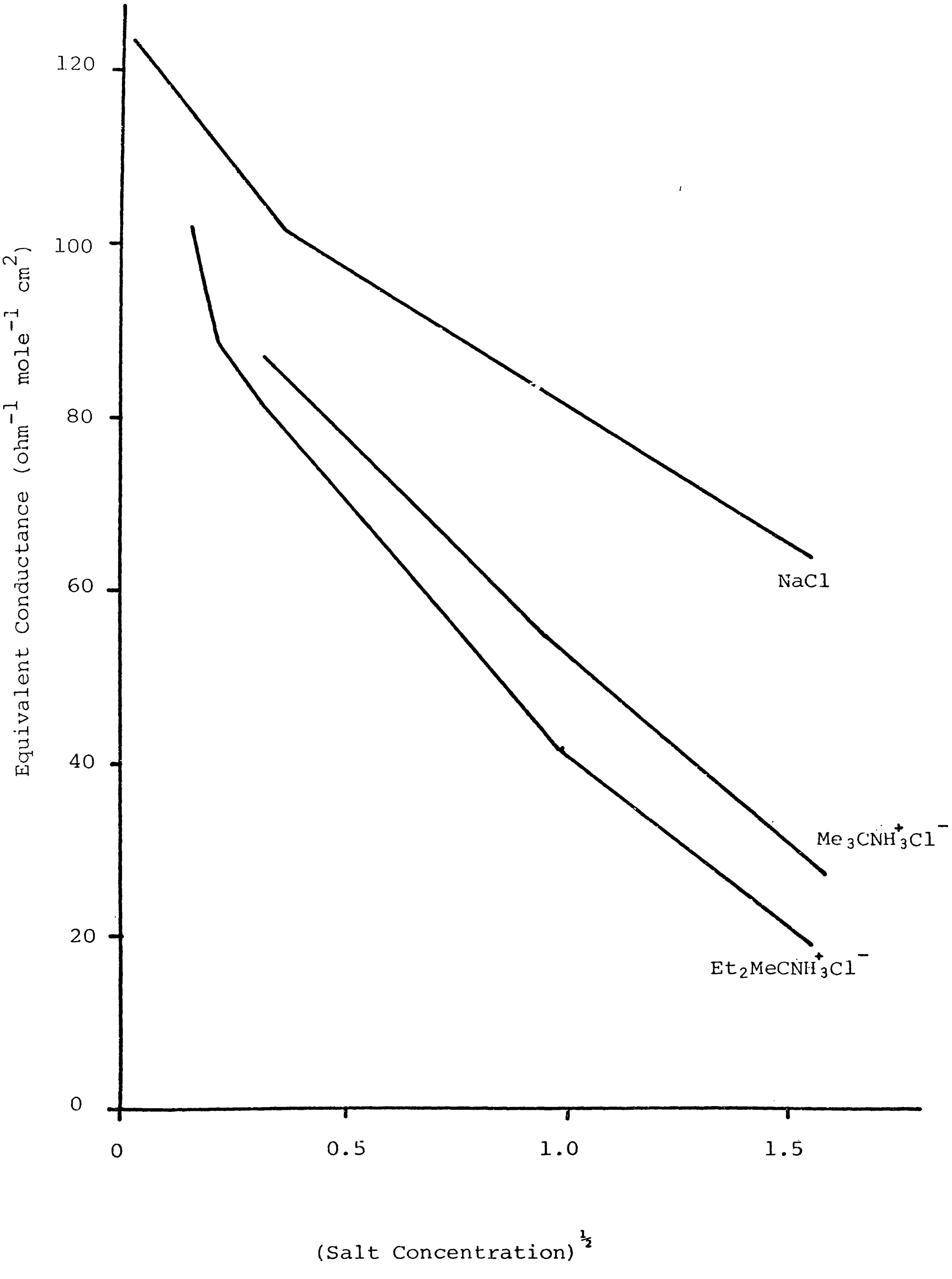


FIGURE 31

Conductance of Salt Solutions at High Concentrations (25.0°C)



Appendix Six

Syntheses and Characterisations

This appendix describes the synthesis and characterisation of the starting materials for the deaminations and hydrolyses, also the expected reaction products (for use in control experiments and response factor determinations) and aromatic compounds (A6.15 - A6.17) used in the preparation of a GLC stationary phase (Appendix 3).

2-Methylpropan-2-ol, 2-amino-2-methylpropane and dimethyl sulphide were obtained commercially and used without further purification.

A6.1	2 Amino-2-methylpropane, perchlorate salt.
A6.2	2-Iodo-2-methylpropane.
A6.3	Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate.
A6.4	2-Methyl-2-nitropropane.
A6.5	2-Methyl-2-propyl Nitrite.
A6.6	1,2-Dibromo-2-methylpropane.
A6.7	3-Methylpentan-3-ol.
A6.8	3-Amino-N-formyl-3-methylpentane 3-Amino-3-methylpentane, perchlorate salt.
A6.9	3-Iodo-3-methylpentane.
A6.10	Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate.
A6.11	3-Methyl-3-nitropentane.
A6.12	3-Methyl-3-pentyl Nitrite.
A6.13	cis and trans-3-Methylpent-2-ene.
A6.14	2-Ethylbut-1-ene.
A6.15	2,4,6-Trinitrotoluene.
A6.16	2,4,6-Trinitrobenzoic Acid.
A6.17	1,3,5-Trinitrobenzene.

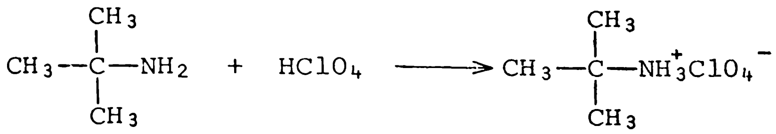
From the oral examination

Appendix 6 (Throughout): The convention adopted for reporting microanalytical data is:

New compound Found:........ $C_xH_yO_z$ requires.........

Known " Found:........ Calc. for $C_xH_yO_2$........

A6.1 2-Amino-2-methylpropane, perchlorate salt



$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}NH_2 + HClO_4 \longrightarrow CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}\overset{+}{N}H_3ClO_4^-$$

m.w. 173.5975

2-Amino-2-methylpropane (commercial, redistilled) was added to dilute perchloric acid (0.20M) until in mole excess and rotary evaporated to dryness. (Tests on a small amount of dry crystal had shown that this salt is not explosive when exposed to flame or shock).

The salt was recrystallised from 1,4-dioxane/diethyl ether (both solvents were sodium dried) and dried (30 mm Hg, room temperature, over P_2O_5).

Residual 1,4-dioxane was removed by dissolving the salt in water and extracting with chloroform. The solution was then rotary evaporated and dried as before. GLC analyses of subsequent amine salt solutions showed it to be free of chloroform and only a trace of 1,4-dioxane remained.

melting point: 130 - 135°C

Elemental analysis of the purified salt, $C_4H_{12}NO_4Cl$

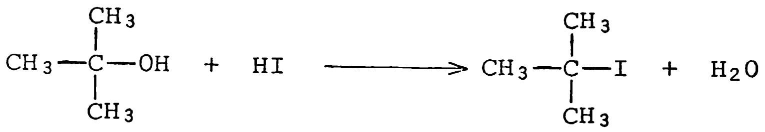
Found; C. 27.58%; H. 6.27%; N, 8.06%; Cl, 20.41%

Calcd.; C. 27.68%; H. 6.97%; N, 8.07%; Cl, 20.42%

All elemental analyses were ~~done~~ performed by Professor A. Campbell and his associates at the University of Otago.

A6.2 2-Iodo-2-methylpropane

2-Iodo-2-methylpropane was prepared as a starting material for the synthesis of dimethyl-(2-methyl-2-propyl)sulphonium perchlorate (A6.3).



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OH + HI \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{C}}-I + H_2O$$

2—Methylpropan-2-ol (92.7g, 1.25 mole) and hydriodic acid (150.5 ml, 2.0 mole, sp.grav. 1.7, 55%) were placed in a 500 ml flask fitted with a magnetic stirrer.

The cooled (water bath 15°C) mixture was saturated with hydrogen iodide (see note below for preparation) and stirred (1 hour) at room temperature.

The organic layer was separated, washed (water, dilute $NaHCO_3$ solution, dilute $NaHSO_3$ solution, water) and dried (anhyd. $MgSO_4$).

Since the iodoalkane decomposes on standing or heating, the crude product (clear, yellowish liquid) was immediately used in the preparation of the sulphonium salt (A6.3) without further purification. It probably contained some unreacted alcohol as an impurity.

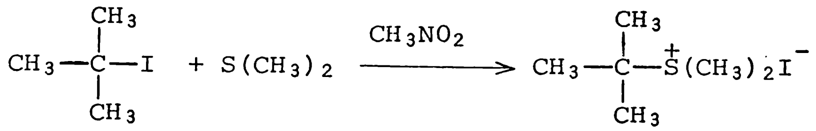
Note: Hydrogen iodide was generated from iodine, red phosphorus and hydriodic acid using the method described by Vogel[179]. The following quantities were used; iodine (100g. 0.79 mole), red phosphorus (21.6g. 0.70 mole), hydriodic acid (30 ml, 0.40 mole, sp.grav. 1.7, 55%).

A6.3 Dimethyl-(2-methyl-2-propyl)sulphonium Perchlorate

The sulphonium perchlorate salt was prepared in two steps from 2-iodo-2-methylpropane.

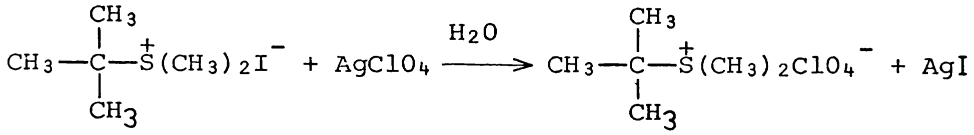
(i) Preparation of the sulphonium iodide salt[108,180].

(ii) Conversion of the iodide salt to the sulphonium perchlorate salt.



$$(CH_3)_3C{-}I + S(CH_3)_2 \xrightarrow{CH_3NO_2} (CH_3)_3C{-}\overset{+}{S}(CH_3)_2 I^-$$

m.w. 246.1556



$$(CH_3)_3C{-}\overset{+}{S}(CH_3)_2 I^- + AgClO_4 \xrightarrow{H_2O} (CH_3)_3C{-}\overset{+}{S}(CH_3)_2 ClO_4^- + AgI$$

m.w. 218.7018

(i) 2-Iodo-2-methylpropane (crude, freshly prepared (A6.2), 180 ml, approx. 1.36 mole (?)), dimethyl sulphide (100 ml, 1.36 mole) and nitromethane (100ml, 1.86 mole) were mixed and left to stand at room temperature in a stoppered flask. The sulphonium salt began crystallising after 48 hours. The first batch (51.39g, 0.209 mole) was filtered off after 72 hours, washed (diethyl ether) and dried (20 mm Hg, over silica gel.).

The salt continued to precipitate and a second batch was collected 5 days after initial mixing (78.97g, 0.321 mole).

Total yield; 130.36g, 0.53 mole, dark yellow crystals.

Elemental Analyses:

First batch,

Found; C, 28.71%; H, 6.20%; S, 13.93%; I,51,86%

Calcd; C, 29.28%; H, 6.14%; S, 13.03%; I, 51,25%

Second batch, mp., decomposes at 170°C (lit.[180], decomposes at 160°C)

Found; C, 29.16; H, 6.32%; S, 13.43%; I, 51.64%.

Calcd.; as above.

(ii) Dimethyl-(2-methyl-2-propyl) sulphonium iodide and silver perchlorate solutions (1.00:0.97 mole ratio) were mixed, the silver iodide precipitate filtered off and the filtrate rotary evaporated to dryness. The sulphonium salt was recrystallised (absolute ethanol) and dried (20mm Hg, over silica gel.).

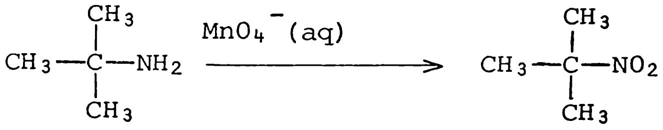
A sample of the sulphonium salt (white crystalline solid, decomposes over 200°C, melts and ignites at 220°C) was dissolved in water and added to sodium chloride solution. The absence of any precipitate indicated that the sulphonium salt was free of silver salts.

The proton NMR spectrum of the product (in D_2O) gave signals due only to the dimethyl-tert-butyl salt. No evidence was found for the trimethyl sulphonium salt which had been reported as a second product in the sulphonium iodide preparation[180]. No literature reference to the perchlorate derivative was found.

A6.4 2-Methyl-2-nitropropane

2-Methyl-2-nitropropane has been reported as a product in the aqueous deamination[108] of 2 amino-2-methylpropane so it was prepared as a reference sample.

The method described below was based on that reported by Kornblum *et al.*[181].



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-NH_2 \xrightarrow{MnO_4^-(aq)} CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-NO_2$$

Potassium permanganate (85.00g, 0.56 mole) and water (400 ml) were placed in a 500 ml flask fitted with a condenser, thermometer and magnetic stirrer. 2-Amino-2-methylpropane (20 ml, 13.92g, 0.19 mole) was added and the mixture stirred at room temperature for 14 hours, then 45-65°C for a further 4 hours.

The nitroalkane and unreacted amine were steam distilled from the mixture (external source of steam) and the organic phase of the distillate separated. The crude nitroalkane was washed (dilute acid, dilute $NaHCO_3$ solution) to remove unreacted amine and dried (anhyd. $MgSO_4$).

A chromatogram of the product in diethyl ether showed it to be free of unreacted amine, 2-methyl-2-propyl-nitrite and 2-methyl-propan-2-ol.

Yield 50%, mp 24.5-26.0°C (lit.[182], 26.23°C).

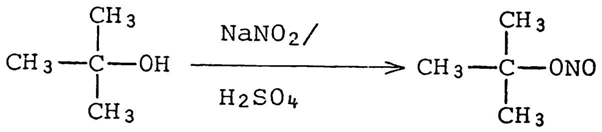
Note: GLC column: 20% PEGA, diatomite C-AW, 100-120M, 1.5M, 6.25mm o.d., glass.

Carrier gas: nitrogen 20 ml/min.

Temperature: Column 80°C for 5 minute,
80°C/min to 160°C.
Injector, 70°C; Detector (FID), 150°C

A6.5 2-Methyl-2-propyl Nitrite

2-Methyl-2-propyl nitrite was prepared by a method based upon the reported preparation of ~~n~~t-butyl nitrite[183].



$$\mathrm{CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-OH \xrightarrow[H_2SO_4]{NaNO_2/} CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-ONO}$$

Water (5 ml), sulphuric acid (conc., 6.8 ml, 0.13 mole) and 2-methylpropan-2-ol (23.50 ml, 0.25 mole) were mixed with cooling (ice-bath) and added to sodium nitrite solution (19.00g, 0.28 mole + water, 75 ml) at room temperature. Nitrogen oxides were rapidly evolved.

The organic phase (green) was quickly separated, washed (dilute $NaHCO_3$ solution) and dried (anhyd. $MgSO_4$). A colour change (green to yellow) occurred during the washing.

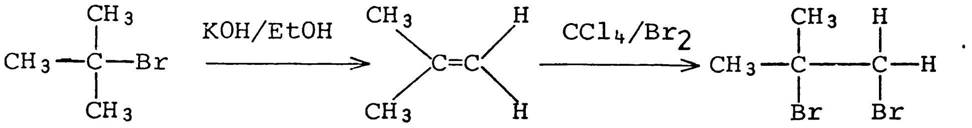
A chromatogram (see Notes in A6.4 for details) showed that the crude product was mainly unreacted alcohol with a host of products of which the alkyl nitrite was the major component. A fraction collected at bp. 63°C (the boiling point of 2-methyl-2-propyl nitrite[182]) was enriched in the major product.

Rapid reactions with slower mixing of the reagents and cooling, failed to produce an improved yield.

The alkyl nitrite decomposed on standing, at room temperature, with evolution of nitrogen oxides.

A6.6 1,2-Dibromo-2-methylpropane

1,2-Dibromo-2-methylpropane was the brominated derivative of 2-methylpropene in the deaminations (Chapter 7) and hydrolyses (Chapter 8) of the 2-methyl-2-propyl substrates. A reference sample of the dibromo derivative was prepared.



Potassium hydroxide (31g) was dissolved in aqueous ethanol (15 ml, 95% EtOH + 15 ml water) in a 100 ml flask fitted with a nitrogen gas inlet (gas flow, 30 ml/min), thermometer, magnetic stirrer and a condenser through which the gas exited to a cold (-85°C, ethyl acetate slush) tetrachloromethane (20 ml)/bromine (2 ml) bubbler.

2-Bromo-2-methylpropane (commercial, 20 ml, 0.18 mole) was added at room temperature and the mixture heated (55-60°C). A vigorous boiling ensued, lasting approximately 15 minutes.

The tetrachloromethane phase was washed ($Na_2S_2O_3$ solution (1.00M), water) to remove the free bromine, dried (anhyd. $MgSO_4$), and fractionated.

The 1,2-dibromo-2-methylpropane was collected at 150-153°C/1 atm ,(lit.[184], 149-151°C/1 atm). Refractive index 1.5059 (24.5°C),(lit.[184], 1.509).

A6.7 3-Methylpentan-3-ol

3-Methylpentan-3-ol was prepared by two grignard reactions. Preparation A used an ester while Preparation B used a ketone. The latter was employed for routine preparations of the alcohol.

Preparation A:

$$Mg + CH_3CH_2I \longrightarrow CH_3CH_2MgI$$

$$CH_3CO_2CH_2CH_3 + 2CH_3CH_2MgI \longrightarrow CH_3(CH_3CH_2)_2COH$$

Magnesium (60.77g, 2.5 mole, acetone washed) was placed in a 2 litre, three-necked flask fitted with a double surface reflux condenser (topped with $CaCl_2$ guard tube) and a nitrogen inlet; the apparatus was flushed with nitrogen and dried by heating with a bunsen (10 min). Diethyl ether (195 ml, Na dried) was added to the cooled flask and a mechanical stirrer inserted. Ethyl iodide (200 ml, 2.5 mole) in ether (300 ml, Na dried) was slowly added, reaction having been initiated by a crystal of I_2. (The reflux rate was controlled with an ice-bath). After addition was complete, the reaction mixture was warmed over a steam-bath (20 min). Ethyl acetate (122 ml, 1.25 mole, dried-anhyd. $MgSO_4$) in dry diethyl ether (124 ml) was slowly added to the cooled (ice-bath) grignard solution. (The reaction is highly exothermic). The reaction was completed over a steam-bath (1 hr). The cooled reaction mixture was added to H_2SO_4 (200 ml, 4M) and crushed ice (1 hr). The aqueous phase was extracted (2 x 150 ml diethyl ether), then discarded and the ethereal phase washed ($NaHCO_3$ solution then water) and dried (anhyd. K_2CO_3). Distillation yielded 3-methylpentan-3-ol (74 ml, 0.60 mole, 60% yield) at bp. 121-124°C/1 atm, lit.[184], 122.4°C/1 atm.

Preparation B;

$$CH_3CH_2Br + Mg \longrightarrow CH_3CH_2MgBr$$

$$CH_3CH_2COCH_3 + CH_3CH_2MgBr \longrightarrow CH_3(CH_3CH_2)_2COH$$

The apparatus was the same as for Preparation A. Magnesium (48.6g, 2.0 mole, acetone washed, dried as in Preparation B) and diethyl ether (300 ml, Na dried) were added to the flask then bromoethane (150 ml, 2.0 mole, dried-anhyd. $MgSO_4$, 12 hr) in dry ether (100 ml) was added slowly to the cooled (ice-bath) solution. The reaction was completed over a steam-bath (30 min). Butan-2-one (180 ml, 2.0 mole, dried-anhyd. $MgSO_4$, 12 hr) was added dropwise to the cooled solution. A further 200 ml of diethyl ether (Na dried) was added to prevent the reaction mixture turning solid. The reaction was completed over a steam-bath (30 min), then H_2SO_4 (200 ml, 4M) and ice, added. The product work-up was as for Preparation A. This preparation was carried out 5 times. All yields were approx. 65% (gas chromatography). 3-Methylpentan-3-ol was initially collected at bp. 120-124°C/1 atm but redistilled to give bp. 122.5-125°C/1 atm (about 99% pure, gas chromatopgraphy) lit.[184], bp. 122.4°C/1 atm.

A6.8 3-Amino-3-methylpentane

Tertiary alcohols can be converted to tertiary carbinamines by two methods;

(1) In a method reported by Hendrickson and Joffee[185] the alcohol is reacted with chlorosulphonyl isocyanate ($ClSO_2NCO$) to give the N-chlorosulphonylurethane which thermally decarboxylates, via a carbocation mechanism, to the monoalkyl sulphamyl chloride ($RNHSO_2Cl$) and carbon dioxide. The sulphamyl chloride is reduced using tert -butoxycarbonyl hydrazides ($H_2NNHCOO$-tert-Bu) and the derivative treated with lead tetraacetate. This process produces the amine hydrochloride salt.

$$ROH + ClSO_2NCO \longrightarrow ROCONHSO_2Cl$$

$$ROCONHSO_2Cl \longrightarrow RNHSO_2Cl + CO_2$$

$$RNHSO_2Cl \xrightarrow{\text{red. agent}} RN\overset{+}{H}_3\overset{-}{Cl} + SO_2$$

(2) The Ritter[186,187] reaction converts the alcohol to the N-formylamine derivative using concentrated sulphuric acid, glacial acetic acid and hydrogen cyanide (produced *in situ*). The formyl derivative is then hydrolysed to corresponding amine.

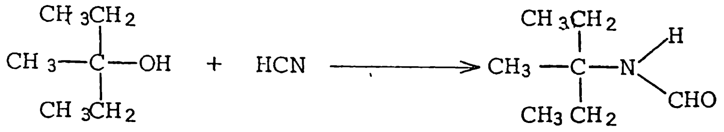
$$ROH + HCN \xrightarrow[CH_3COOH]{H_2SO_4} RNHCHO$$

$$RNHCHO \xrightarrow{NaOH} RNH_2 + HCOONa$$

Both methods are basically two step syntheses and rely on the formation of a carbocation so are particularly suitable for tertiary systems.

The Ritter reaction has been employed here to prepare 3-amino-3-methylpentane using a procedure based on the reported preparation of 2-amino-2-methyl-3-phenylpropane[186].

(a) 3-Amino-N-formyl-3-methylpentane



m.w. 129.2045

Acetic acid (glacial, 385 ml), sodium cyanide (85g, 1.73 mole) and a conc. H_2SO_4/glacial CH_3COOH mixture (400 ml, 1:1 mole ratio) were successively added to a two litre flask fitted with a mechanical stirrer, reflux condenser and addition funnel. Cooling (ice-bath) was required during the slow addition of the mixed acids. 3-Methylpentan-3-ol (190 ml, 1.54 mole) was added and reacted for 48 hours (room temperature) then ice-water added (2.5 litre) and nitrogen bubbled through the mixture to remove gaseous hydrogen cyanide. The mixture was neutralised with sodium bicarbonate (1 kg) and sodium hydroxide (5M, volume as required).

The aqueous phase was separated, extracted (600 ml, diethyl ether) and discarded. The organic phase was then dried (anhyd. $MgSO_4$) and fractionated.

The N-formylamine (yield 60%) was collected under reduced pressure; bp. 117.5-118.5°C/13.5 mm Hg, 122.5-123.5°C/16.0 mm Hg, 129.5-130.0°C/21.5 mm Hg, 237°C/1 atm.

Refractive index at 25°C; 1.4490

No literature reference to this compound was found.

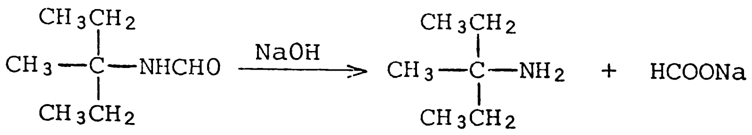
Elemental Analysis; $C_7H_{15}NO$

Found; C, 64.42%; H, 11.96%; N, 10.87%

Calcd.; C, 65.07%; H, 11.70%; N, 10.84%

Proton NMR spectra were obtained and are shown later in this section.

(b) 3-Amino-3-methylpentane, perchlorate salt



$$CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-NHCHO \xrightarrow{NaOH} CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-NH_2 + HCOONa$$

m.w. 101.20

$$RNH_2 + HClO_4 \longrightarrow RNH_3^+ClO_4^-$$

m.w. 201.653

3-Amino-N-formyl-3-methylpentane (110.2g, 0.83 mole) and sodium hydroxide (1 litre, 6.83M) were placed in a two litre flask fitted with a reflux condenser and mechanical stirrer and refluxed for eight hours.

The organic layer was separated and the aqueous phase extracted (diethyl ether). The ethereal phase was distilled and the combined crude amine dissolved in hydrochloric acid (1.41M) to separate it from unreacted starting material. The amine salt solution was rotary evaporated and the free amine regenerated with sodium hydroxide solution (15M) and dried (KOH pellets).

The amine was distilled (bp. 109.0-109.5°C/1 atm, refractive index (25°C) 1.4132), dissolved in water and perchloric acid (2.12M) added dropwise till the solution was neutral (pH meter), then rotary evaporated to dryness. The salt was recrystallised from super-dry ethanol/diethyl ether (sodium dried) and dried (30 mm Hg, over P_2O_5).

Yield, 64%, white crystals, mp. 175-177°C. (No literature values were found for this compound).

Elemental Analysis; $C_6H_{16}ClO_4N$

Found; C, 35.83%; H, 8.02%; N, 7.18%; Cl, 17.74%

Calcd.; C, 35.74%; H, 8.00%; N, 6.95%; Cl, 17.58%

The amine chloride salt had also been prepared.

Elemental Analysis: $C_6H_{16}ClN$, sublimes over 110°C.

Found; C, 52.50%; H, 11.95%; Cl, 26.06%; N, 9.95%

Calcd.; C, 52,35%; H, 11.72%; Cl, 25.76%; N, 10.18%

Proton NMR Spectra:

The proton NMR spectra of 3-amino-3-methylpentane and 3-amino-N-formyl-3-methylpentane have been recorded. The spectrum of 3-methylpentan-3-ol is also included for comparison. While the spectra are fully consistent with the compounds named, no effort is made here to undertake a detailed analysis of them. The spectra are included here for future reference when a detailed analysis may be made.

(i) 3-Amino-3-methylpentane (FIGURE 32)

Comparison with the spectrum of 3-methylpentan-3-ol (FIGURE 33) indicates that the down-field signal of the ethyl group triplet is superimposed on the methyl ($Et_2C(CH_3)NH_2$) group singlet.

(ii) 3-Amino-N-formyl-3-methylpentane (FIGURES 34 - 37)

FIGURES 34 and 35 show spectra of the neat compound. The amino proton (7.57ppm) was located by obtaining a spectrum of the compound in D_2O (FIGURE 37). The splitting of the aldehydic proton (8.15ppm) is lost as the sample temperature is raised from room temperature to 142°C (FIGURE 36).

FIGURE 32

Proton NMR Spectrum of 3-Amino-3-methylpentane

(Neat, room temperature, TMS internal reference)

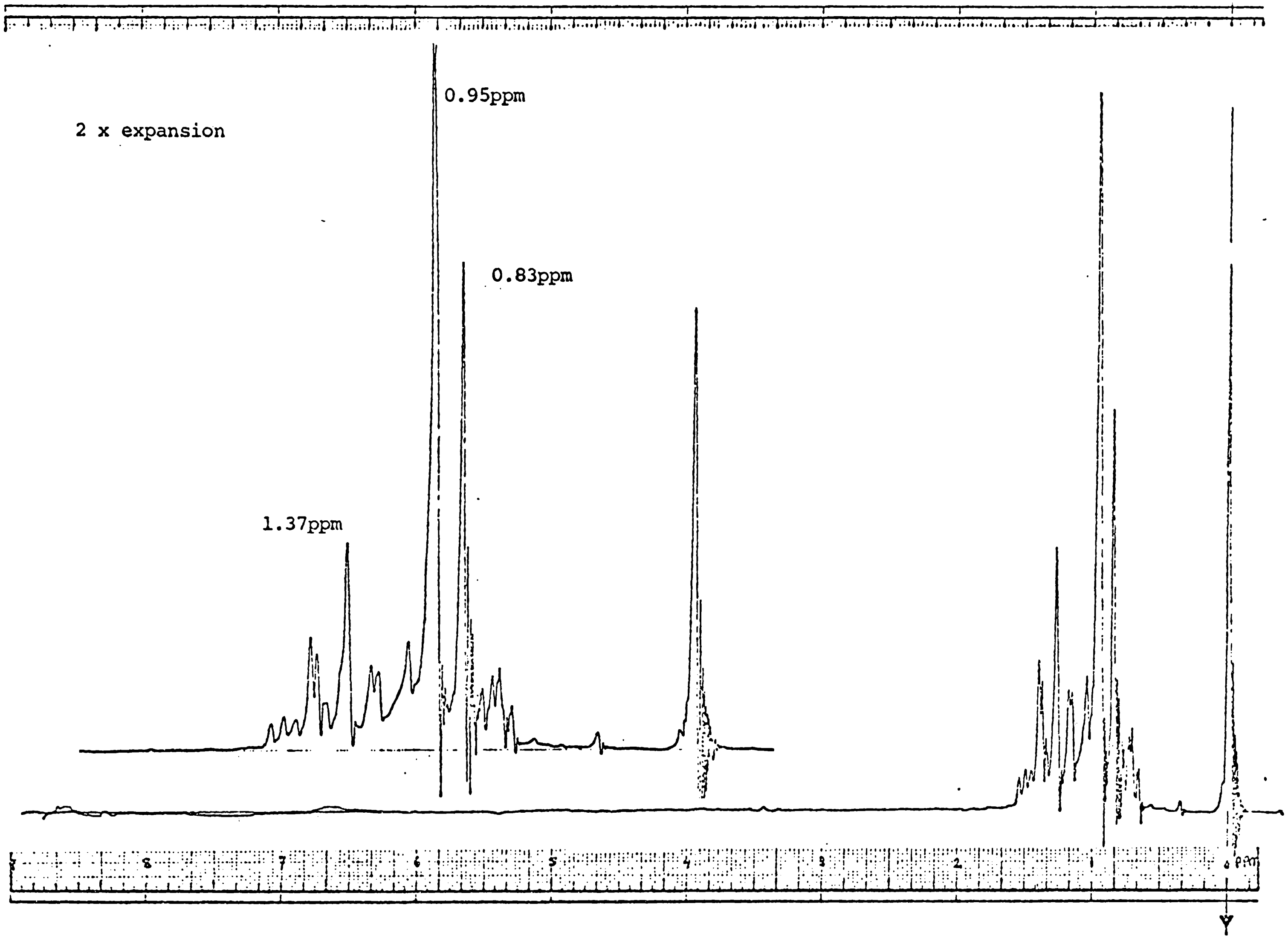


FIGURE 33

Proton NMR Spectrum of 3-Methylpentan-3-ol

(Neat, room temperature, TMS internal reference)

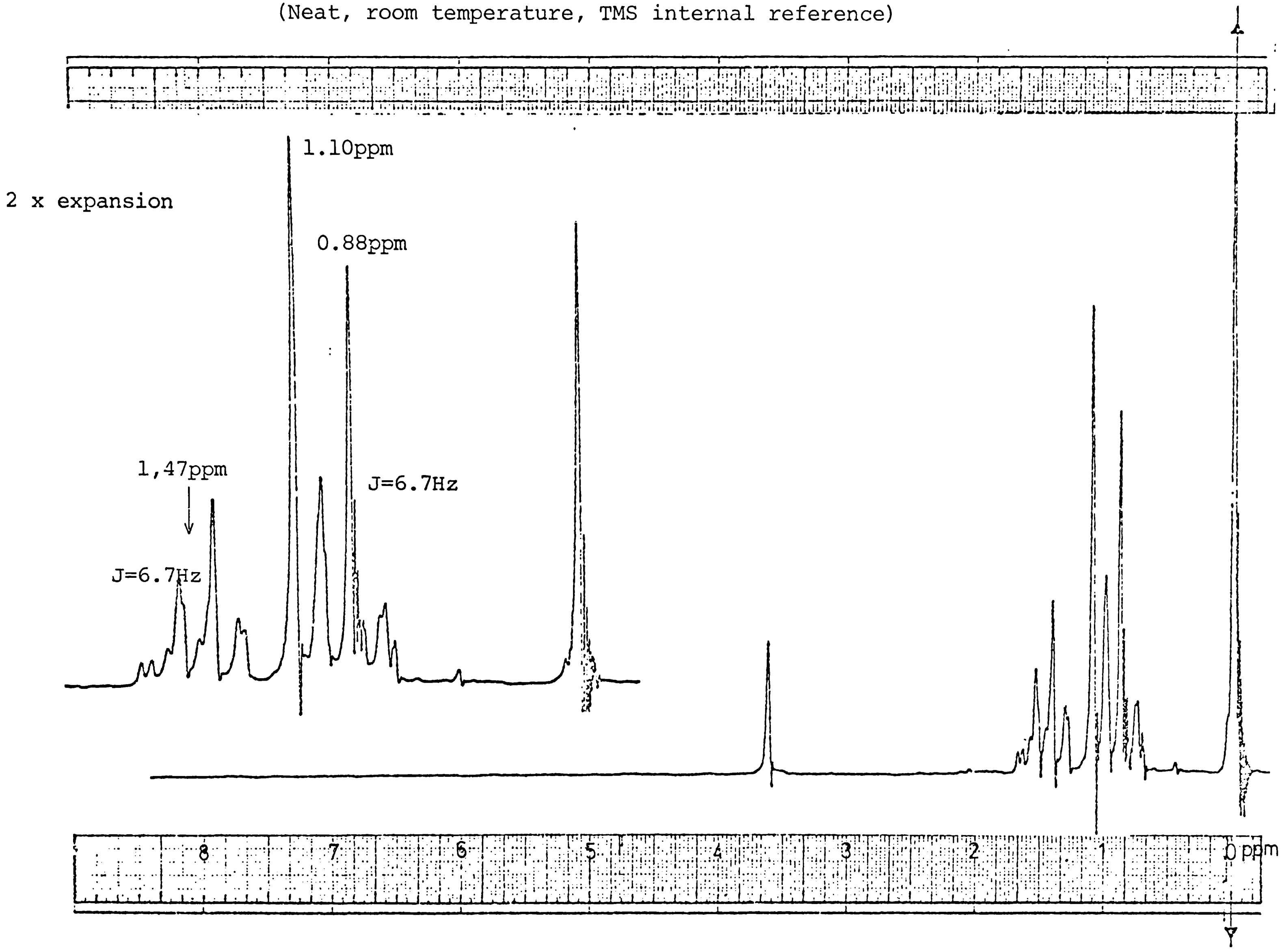


FIGURE 34

NMR Spectrum of 3-Amino-N-formyl-3-methylpentane

(Neat, room temperature, TMS internal reference)

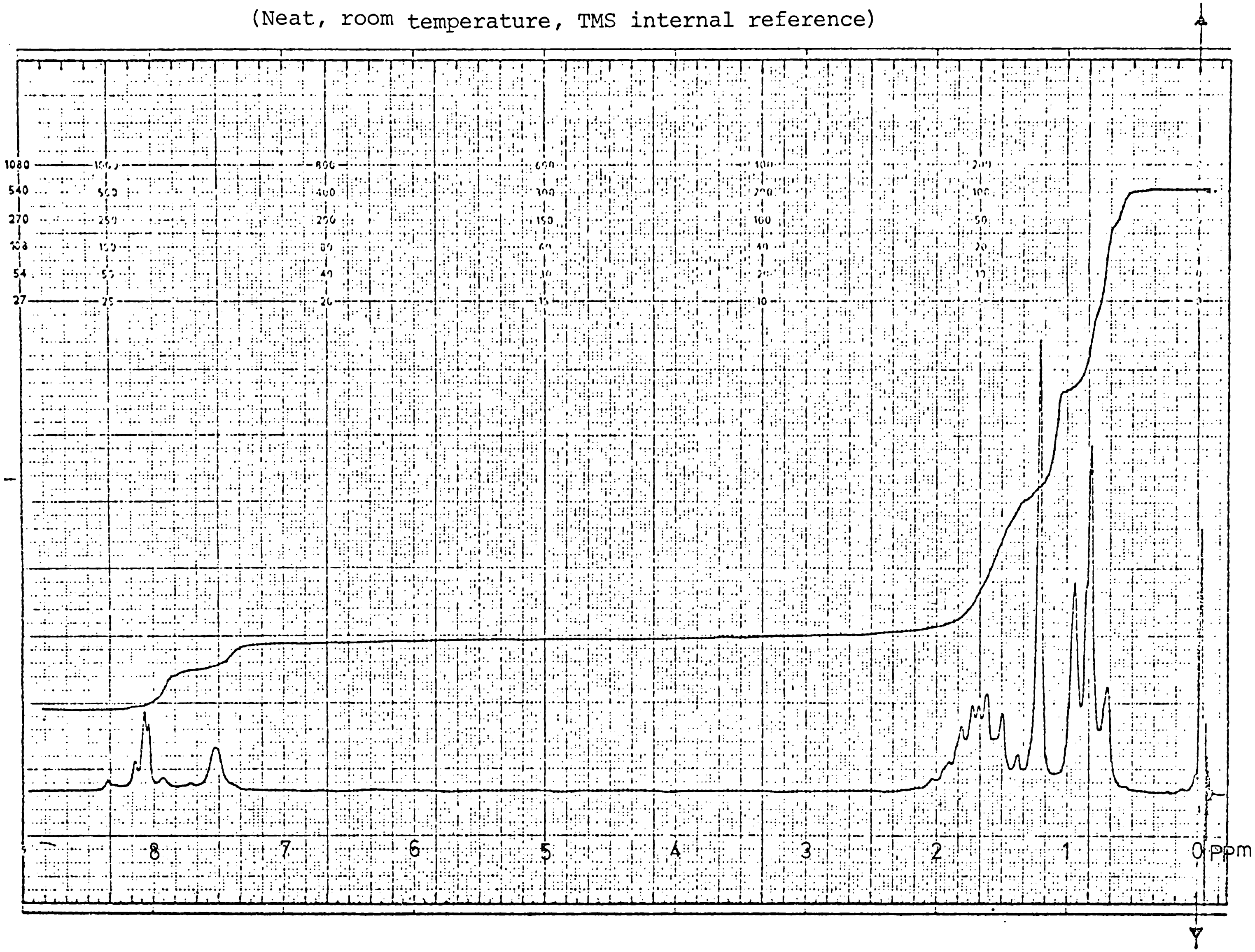


FIGURE 35

Proton NMR Spectrum of 3-Amino-N-formyl-3-methylpentane

(Neat, room temperature, TMS internal reference)

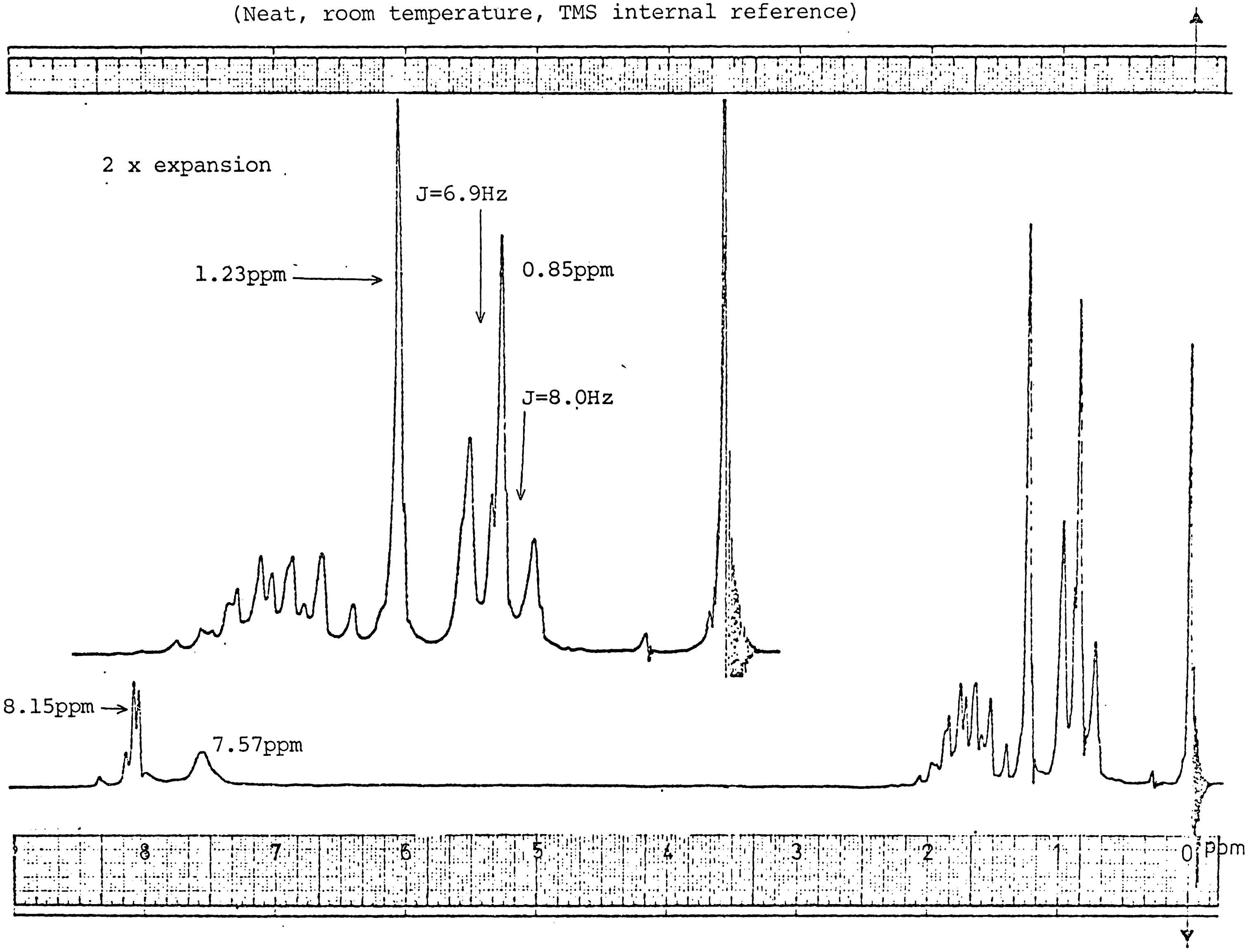
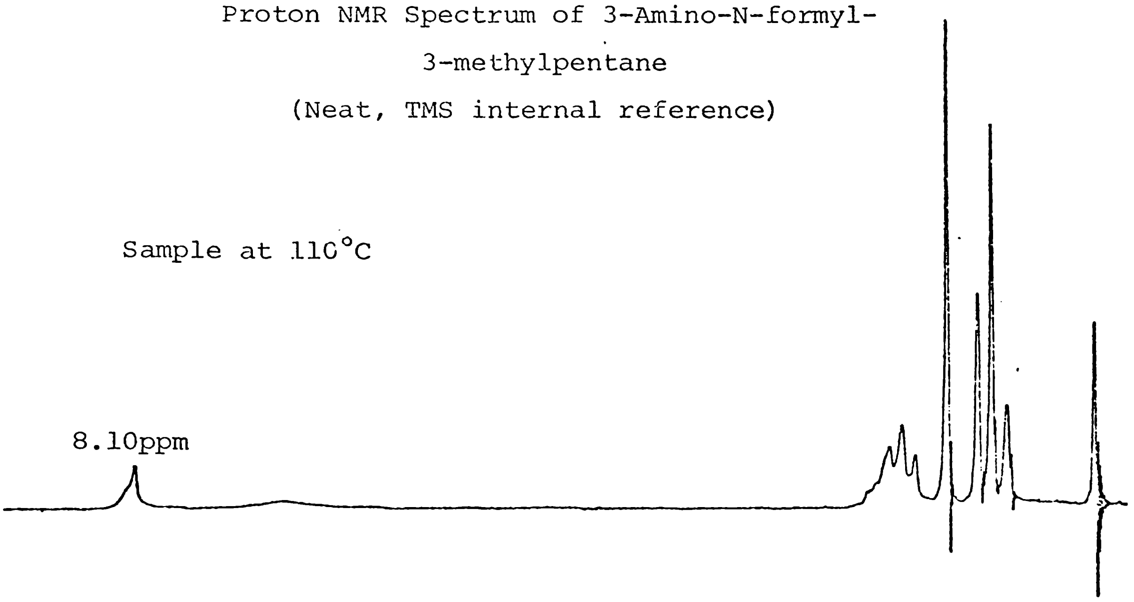


FIGURE 36

Proton NMR Spectrum of 3-Amino-N-formyl-
3-methylpentane
(Neat, TMS internal reference)

Sample at 110°C



Sample at 142 °C

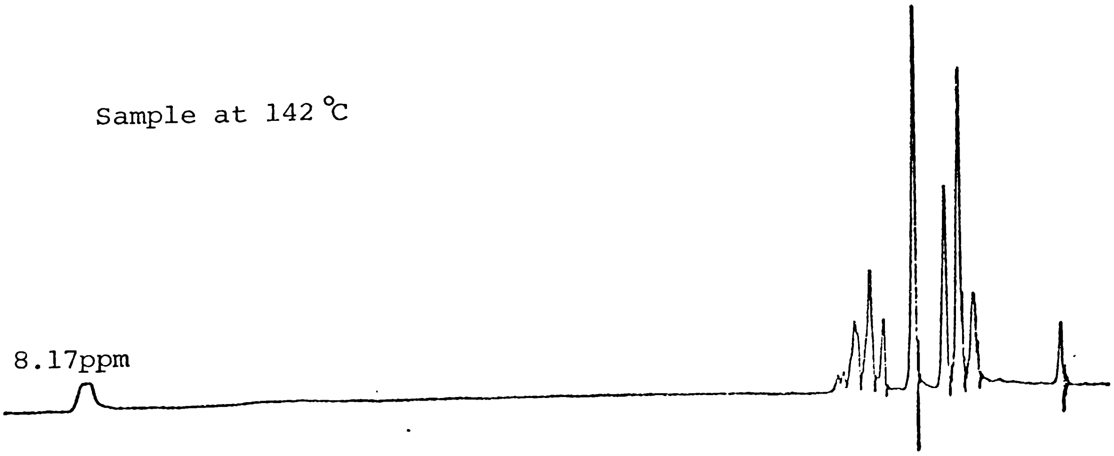
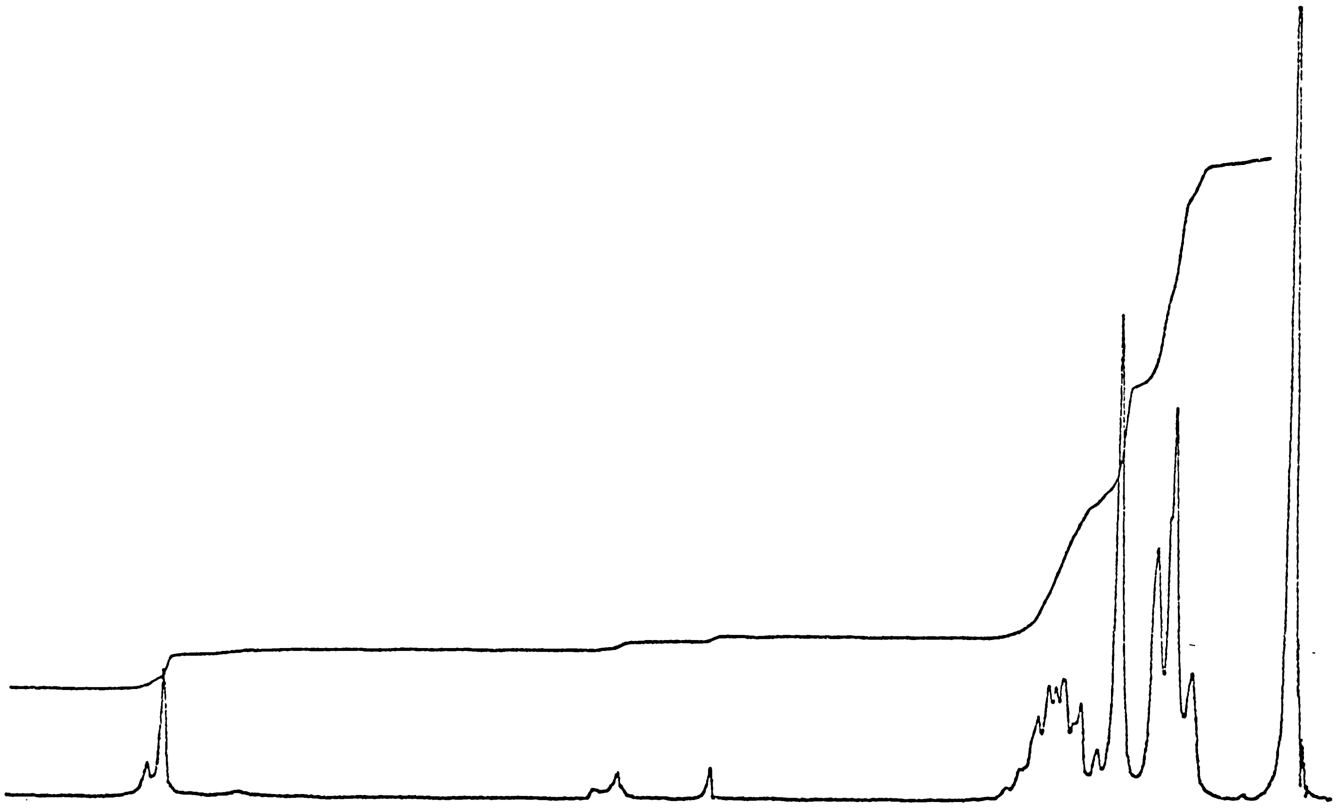


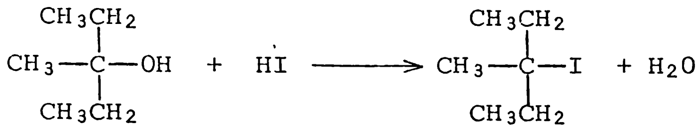
FIGURE 37

Proton NMR Spectrum of 3-Amino-N-formyl-3-methylpentane

(D$_2$O solvent, room temperature, TMS internal reference)



A6.9 3-Iodo-3-methylpentane

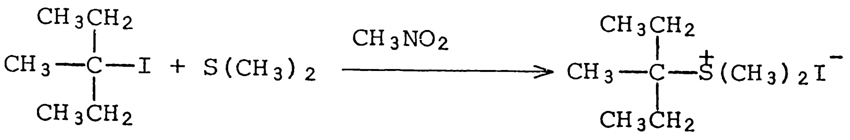


$$CH_3-\underset{CH_3CH_2}{\overset{CH_3CH_2}{\underset{|}{\overset{|}{C}}}}-OH \;+\; HI \longrightarrow CH_3-\underset{CH_3CH_2}{\overset{CH_3CH_2}{\underset{|}{\overset{|}{C}}}}-I \;+\; H_2O$$

3-Iodo-3-methylpentane was prepared as a starting material for the synthesis of dimethyl-(3-methyl-3-pentyl)sulphonium perchlorate (A 6.10). The procedure used was the same as that described in A6.2, except that 3-methylpentan-3-ol (150 ml, 1.25 mole) was used instead of 2-methylpropan-2-ol. The crude iodoalkane (theoretical yield, 1.25 mole) was immediately used in the preparation of the sulphonium salt.

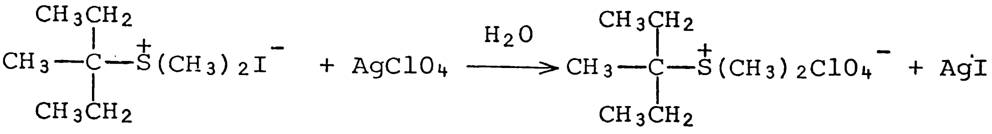
Yield, 125 ml of crude iodo alkane (plus unreacted alcohol).

A6.10 Dimethyl-(3-methyl-3-pentyl)sulphonium Perchlorate



$$CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-I + S(CH_3)_2 \xrightarrow{CH_3NO_2} CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-\overset{+}{S}(CH_3)_2I^-$$

m.w. 274.2100



$$CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-\overset{+}{S}(CH_3)_2I^- + AgClO_4 \xrightarrow{H_2O} CH_3-\overset{CH_3CH_2}{\underset{CH_3CH_2}{C}}-\overset{+}{S}(CH_3)_2ClO_4^- + AgI$$

m.w. 246.7562

The perchlorate salt was prepared by the two step method described in A6.3.

(i) Quantities used; iodoalkane (maximum 1.25 mole).
dimethyl sulphide (92 ml, 1.25 mole)
nitromethane (92 ml, 1.25 mole)

The sulphonium iodide salt began to crystallise rapidly 1½ hours after mixing (compared with 48 hours for the 2-methyl-2-propyl analog, A6.3). Batches of product were filtered off for up to 60 hours and further product crystallised upon addition of diethyl ether.

Yield; 164.6g, 0.60 mole.

White (colourless) crystals (platelets), melts and decomposes at 114-116°C. A sample of the sulphonium iodide was recrystallised (EtOH) and dried (30 mm Hg, over P_2O_5). This melted and decomposed at 108-110°C.

The product darkened and decomposed over a period of weeks with the liberation of dimethyl sulphide and iodine.

(ii) The sulphonium iodide was converted to the perchlorate salt as described in A6.3.

Product; white crystals, melts and decomposes at 95°C. Like the iodide salt, the perchlorate analog decomposed on standing at room temperature. Samples to be hydrolysed were recrystallised (absolute ethanol) shortly before use.

Elemental Analysis; $C_8H_{19}ClO_4S$

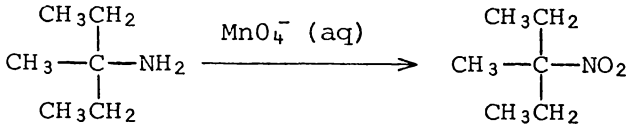
Found; C, 38.52%; H, 7.72%; Cl, 14.33%; S, 12.70%

Calcd.; C, 38.94%; H, 7.76%; Cl, 14.37%; S, 12.99%

No literature reference to either of the two compounds prepared above was found.

A6.11 3-Methyl-3-nitropentane

The method described for the preparation of 2-methyl-2-nitropropane (A6.4) was also used to prepare 3-methyl-3-nitropentane.



$$CH_3-\underset{\displaystyle CH_3CH_2}{\overset{\displaystyle CH_3CH_2}{C}}-NH_2 \xrightarrow{MnO_4^-\ (aq)} CH_3-\underset{\displaystyle CH_3CH_2}{\overset{\displaystyle CH_3CH_2}{C}}-NO_2$$

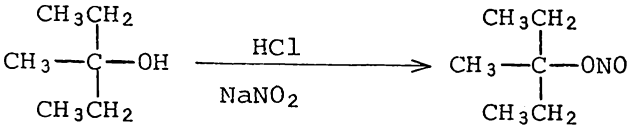
m.w. 131.182

Potassium permanganate (43g, 0.28 mole) and water (100 ml) were placed in a 150 ml flask fitted with a condenser and mechanical stirrer. 3-Amino-3-methylpentane (10g, 0.1 mole) was added and the mixture stirred for 13 hours at room temperature then 5 hours at 75-85°C.

The mixture was transferred to a 500 ml flask and steam distilled (external source of steam). Acid (dilute HCl) was added to the distillate to dissolve unreacted amine and the organic layer separated and dried (anhyd. $MgSO_4$). The crude nitro alkane was distilled. The product, presumed to be 3-methyl-3-nitropentane by analogy with A6.4, had a boiling point of 172-173°C/1 atm, and refractive index 1.4223 (24.5°C). Yield 80 %. (No literature values were available for comparison).

A sample of the nitroalkane was reduced to the hydroxylamine by reacting it with zinc powder and ammonium chloride in 50% ethanol (boiled for 5 minutes). Cuprous oxide was precipitated from Fehling's solution when the hydroxylamine/ethanol was added. No precipitate occurred when the nitro alkane was added to Fehling's solution and warmed.

A6.12 3-Methyl-3-pentyl Nitrite

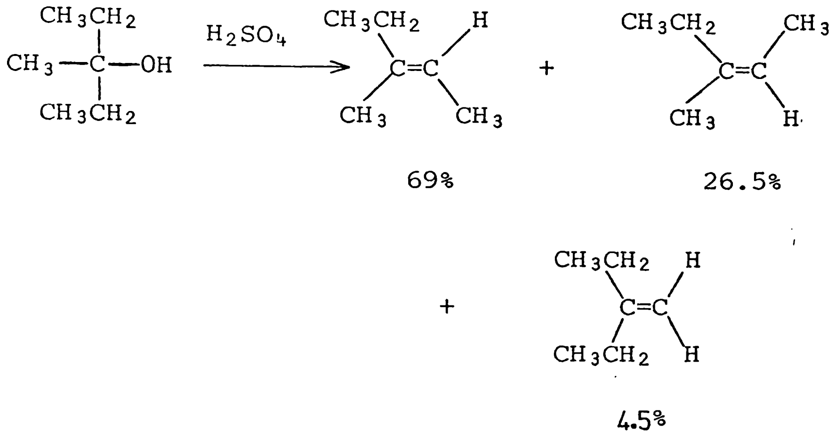


A cold (5°C) mixture of 3-methylpentan-3-ol (20 ml, 0.17 mole) and hydrochloric acid (75 ml, 5M) was added slowly to a cold (0-2°C, ice-salt bath) solution of sodium nitrite (30g, 0.42 mole, 100 ml water) with vigorous stirring. The organic layer (green) was separated from the aqueous phase (blue) and dried (anhyd. $MgSO_4$).

Chromatograms of the organic phase (on 20% PEGA and 15% PPG, LB-550-X) showed that it was approximately 85% unreacted alcohol. The single major product was presumably the alkyl nitrite; its retention time was consistent with that expected from a comparison of 2-methylpropan-2-ol and 2-methyl-2-propyl nitrite (Appendix 1). No attempt was made to isolate the product since experience with 2-methyl-2-propyl nitrite showed that these tertiary alkyl nitrites readily decompose. The preparation also produced a number (less than 10% of the products) of higher boiling point compounds.

A6.13 cis- and trans-3-Methylpent-2-ene

A mixture of cis and trans-3-methylpent-2-ene was prepared by dehydrating 3-methylpentan-3-ol with sulphuric acid.



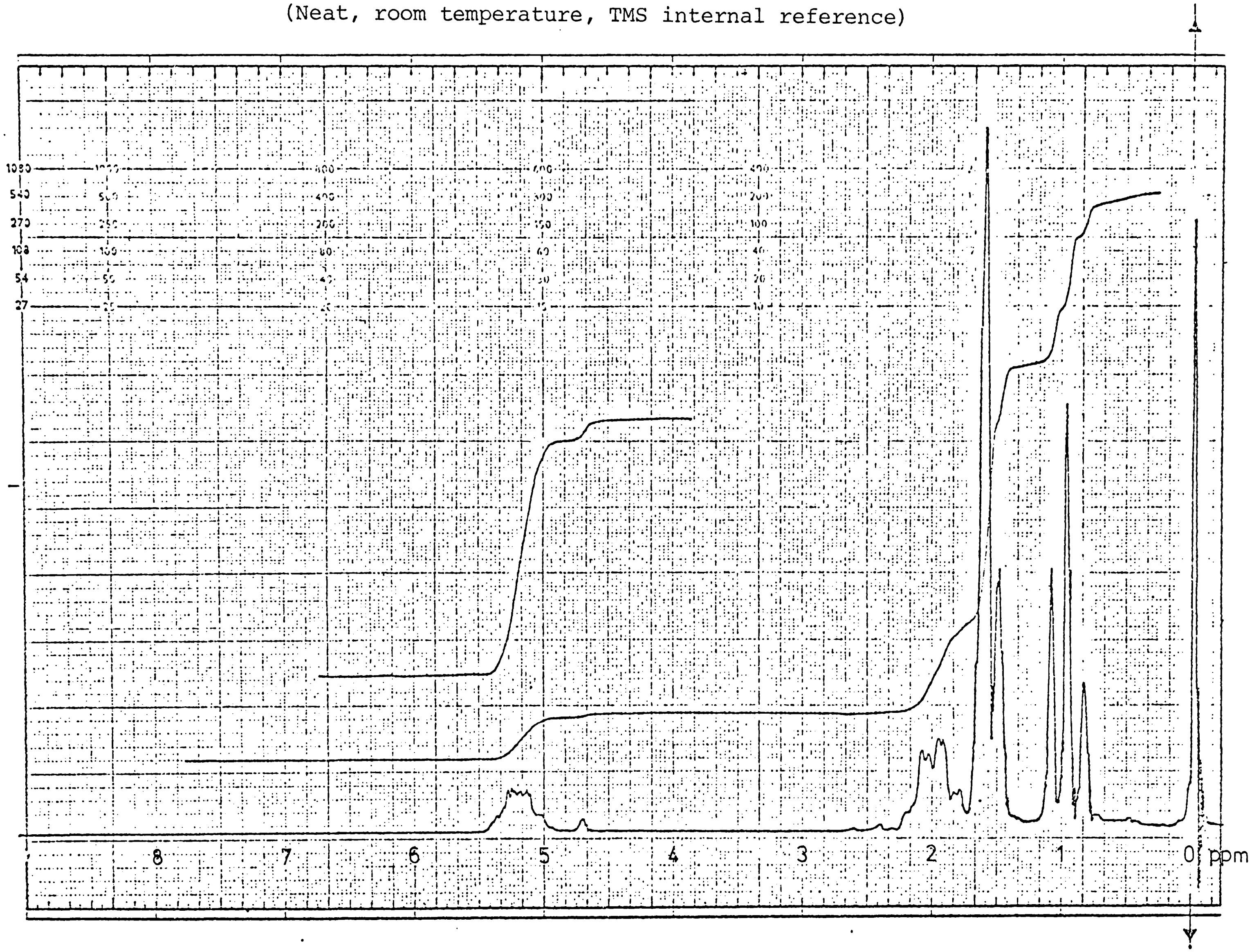
3-Methylpentan-3-ol (25 ml) and sulphuric acid (100 ml, 6M) were placed in a 250 ml flask fitted with a vigreux column (15 cm) and distillation apparatus. The mixture was heated and the alkenes collected (bp. 66-72°C) , washed (water) and dried (anhyd. $MgSO_4$) . The product mixture was analysed by GLC (see A6.14 for the operating conditions) and indicated the alkene composition shown in the reaction scheme above (the composition was determined using the assumed response factor described in Appendix 1.4.2) .

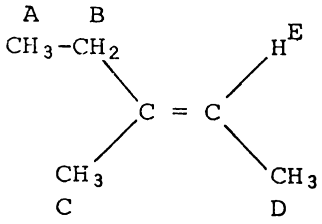
A proton NMR spectrum of the mixture was recorded (FIGURE 38) .

FIGURE 38

Proton NMR Spectrum of cis and trans-3-methylpent-2-ene

(Neat, room temperature, TMS internal reference)





A: triplet at 0.99ppm (J=6.8, 7.2Hz).

B: quartet of doublets by coupling to A and E at 2.00ppm. Quartet coupling constant J=7.2Hz.

C: singlet at 1.60ppm superimposed on the doublet of D.

D: doublet by coupling to E at 1.57ppm (J=5.5Hz).

E: multiplet at 5.23ppm.

The trans and cis isomers would be expected to give similar spectra. The mixture probably accounts for the relatively poor resolution. A small singlet at 4.73ppm indicates the presence of the 2-ethylbut-1-ene. This singlet, from the double bond protons, can be used to calculate the proportion of the 1-ene present in the mixture. The result of this calculation is close to the amount determined by GLC.

Distinguishing Between cis and trans-3-methylpent-2-ene:

(i) Stereospecific Synthesis

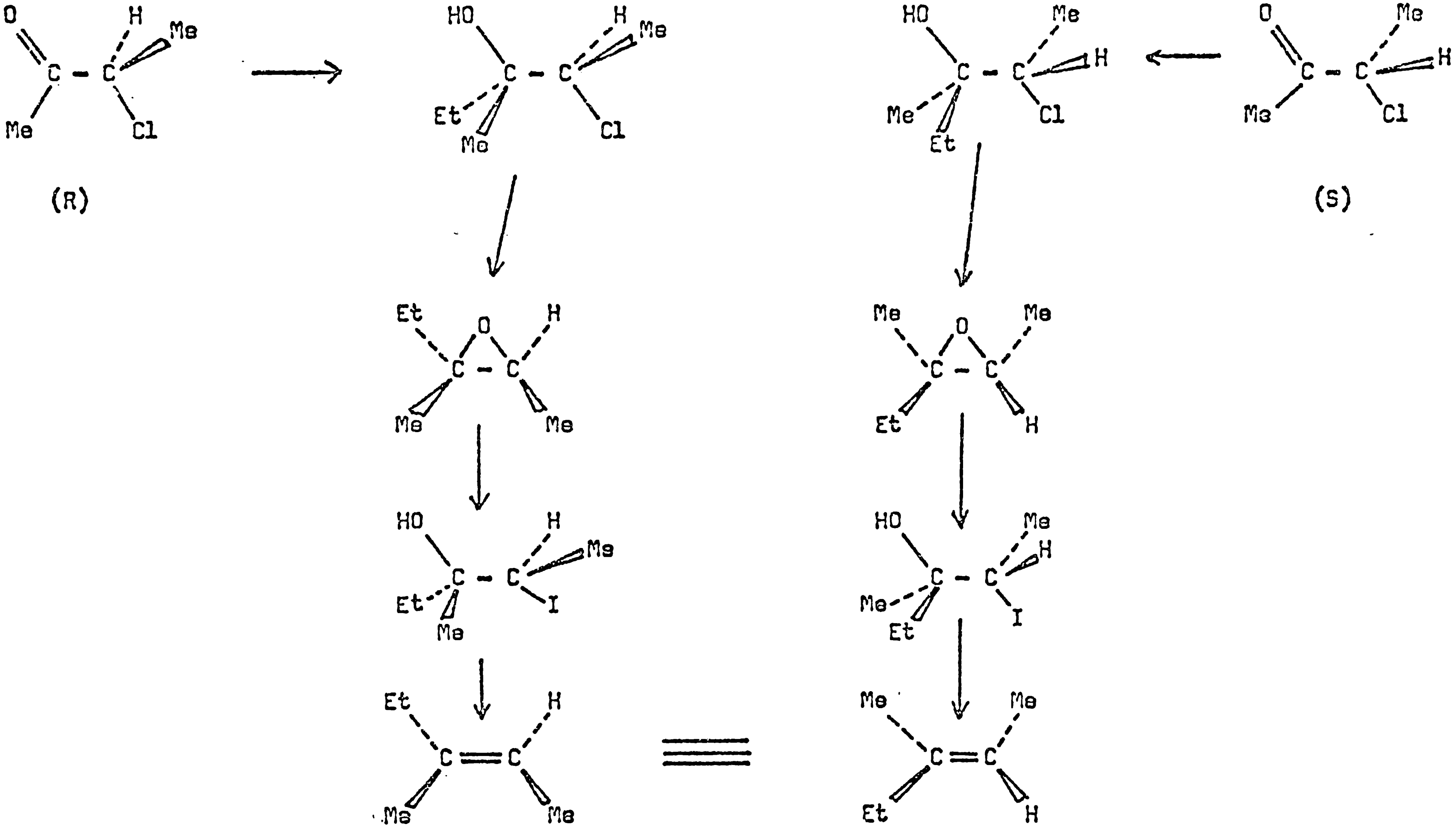
A stereospecific preparation of the trans isomer was carried out using the method reported by Cornforth *et al.*[188] (FIGURE 39). A mixture of 2-ethylbut-1-ene, cis-3-methylpent-2-ene and trans-3-methylpent-2-ene was obtained in the ratio; 10%, 29%, 61% respectively. The mixture was fractionated and chromatograms of the fractions clearly showed the trans isomer to have the higher boiling point (trans-2-ene, bp. 70-72°C/1 atm, cis-2-ene, bp. 69°C/1 atm[188]).

(ii) Dehydration of 3-Methylpentan-3-ol

The dehydration of 3-methylpentan-3-ol in an aqueous solution containing a strong mineral acid would be expected to give predominantly the thermodynamically more stable alkene[37]. Generally the most substituted alkene is the most stable and the trans isomer is preferred over the cis isomer.

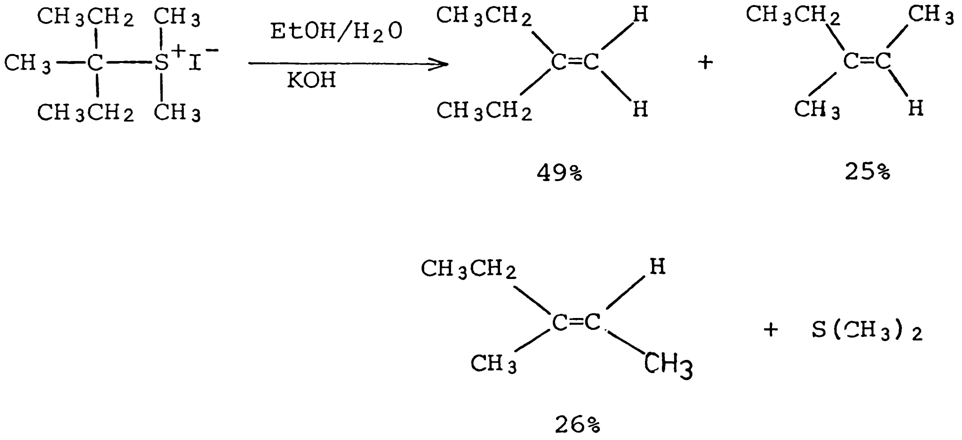
FIGURE 39

Stereospecific Preparation of trans-3-Methylpent-2-ene[188]



A6.14 2-Ethylbut-1-ene

Trialkyl sulphonium salts eliminate under E2 conditions to give predominantly the least substituted alkene[37]. This type of reaction was carried out with dimethyl-(3-methyl-3-pentyl)sulphonium iodide in order to obtain a mixture of alkenes sufficiently enriched in the 1-ene to allow it to be fractionated and an NMR spectrum obtained.



Potassium hydroxide (30g) was dissolved in 50% v/v aqueous ethanol (50 ml) in a 100 ml flask fitted with a vigreux column (15 cm) and distillation apparatus. Dimethyl-(3-methyl-3-pentyl)-sulphonium iodide (33.10g, 0.121 mole, prepared A6.10) was added, heated and the distillate collected (bp. 45-55°C) and dried (anhyd. $MgSO_4$). A GLC analysis of the distillate showed the following composition;

dimethyl sulphide	38%
2-ethylbut-1-ene	26%
cis-3-methylpent-2-ene	13%
trans-3-methylpent-2-ene	14%
ethanol	14%

(GLC; Column; 15% w/w PPG LB-550-X, chromosorb 80-100 mesh, stainless steel, 4 metres, 1/8 inch o.d.

Temperature; Column, 45°C, 18 minute , 80°C/min to 170°C

Injector 70°C, Detector 150°C

Carrier gas; nitrogen 12 ml/min.

The proportions of isomeric alkenes are shown in the reaction scheme above.

Fractionation of the product mixture on a spinning band distillation column gave the following fractions and compositions.

Fraction	Temperature (°C)	SMe_2 (%)	1-ene (%)	c-2-ene (%)	t-2-ene (%)	EtOH (%)
1	34 - 40	>97	-	-	-	-
2	37.5 - 57.0	27	41	10	5	17
3	56.5 - 58.5	1	48	18	11	23
4	57.5 - 58.5	-	40	20	15	25

Alkene Composition in the Fractions

Fraction	1-ene (%)	cis-2-ene (%)	trans-2-ene (%)
2	73	18	9
3	62	23	14
4	53	27	20

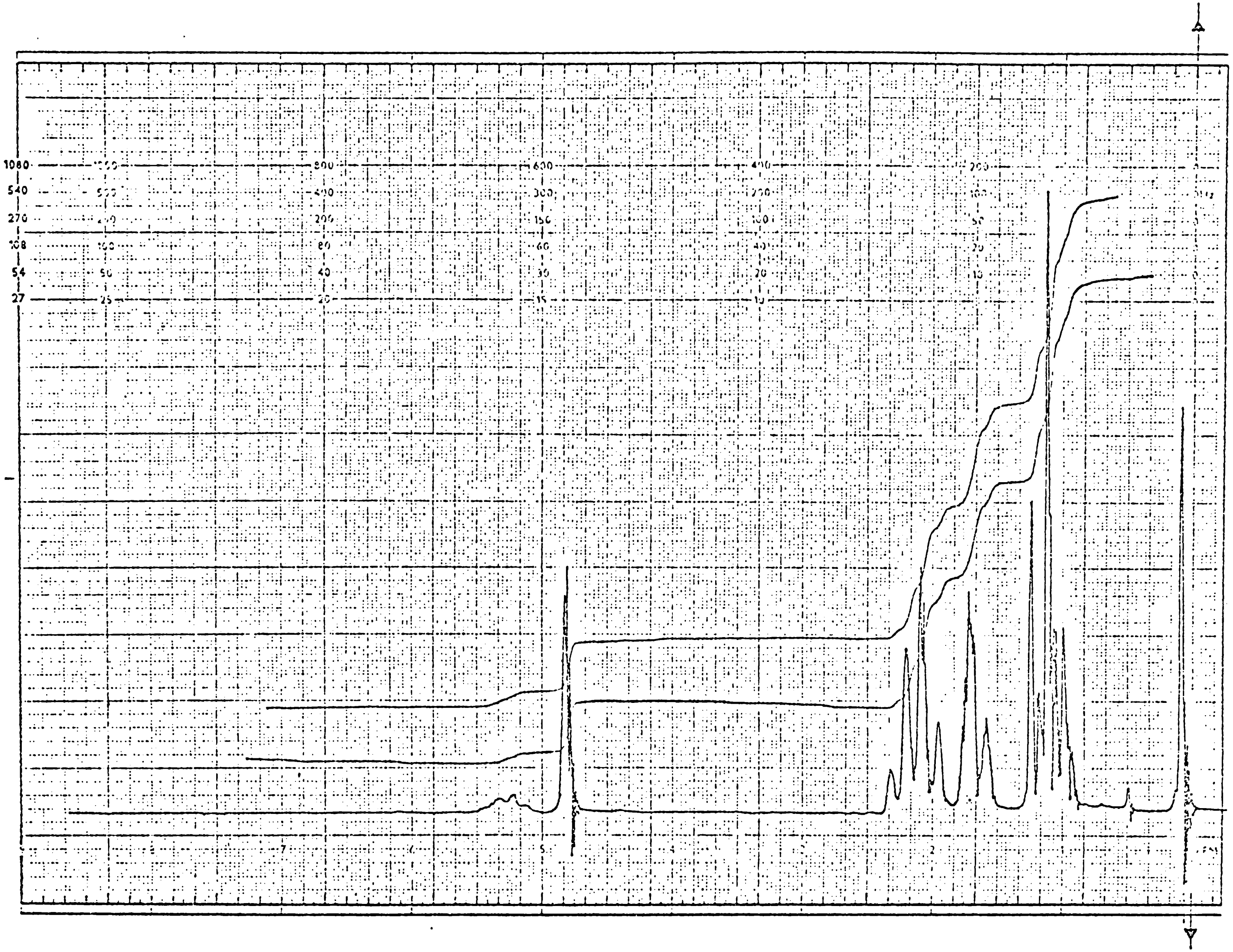
Fraction 3 was washed (water) to remove the ethanol and dried (anhyd. $MgSO_4$). The proton NMR spectrum of this mixture is shown in FIGURE 40.

As expected, the ethyl triplet and quartet from 2-ethylbut-1-ene are superimposed upon those from the 3-methylpent-2-ene isomers.

FIGURE 40

Proton NMR Spectrum of a Mixture of Alkenes (Fraction 3)

(Neat, room temperature, TMS internal reference)



$CH_3-(CH_2)$	triplet	1.03ppm	J = 6.8 and 8.0Hz
$-CH_2-$	quartet	2.05ppm	J = 7.2, 6.0 and 8.4Hz
H-	singlet	4.73ppm	

The remaining signals are from the 3-methylpent-2-ene double-bond proton and methyl substituents . The different coupling constants observed in the triplet and quartet are probably due to the sample being a mixture of alkenes, rather than indicating a second order spectrum.

Given that the sample contained 60% 2-ethylbut-1-ene and 40% 3-methylpent-2-ene the relative integrals for each signal can be predicted;

e.g. 2-ene double-bond proton, 1 x 0.4 = 0.4

1-ene double-bond protons, 2 x 0.6 =1.2

1-ene and 2-ene methylene protons;

(1-ene) 4 x 0.6 = 2.4 + (2-ene) 2 x 0.4 = 0.8

= 3.2

Proton	Calcd. Relative Integral	Measured Relative Integral
H-(2-ene)	1	1
H-(1-ene)	3	3.1
$(CH_3)-CH_2-$	8	8.2
CH_3-	6	6.1
$CH_3-(CH_2)-$	12	12.2

The broadening of the double-bond proton signal of 2-ethylbut-1-ene is probably due to weak coupling with the methylene protons.

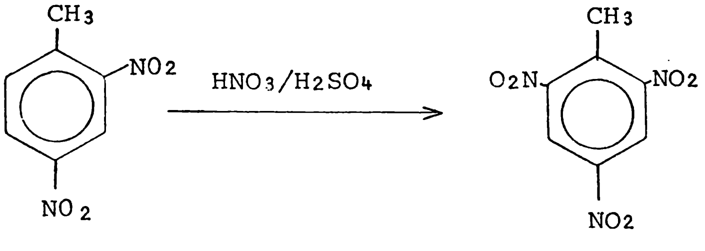
A6.15 2,4,6-Trinitrotoluene

2.4,6-Trinitrotoluene was prepared for use in a GLC stationary phase which was a ternary eutectic mixture of 1,3,5-trinitrobenzene, 2,4,6-trinitrotoluene and 1,3-dinitrobenzene (see Appendix 3). The preparation of 1,3,5-trinitrobenzene is described in A6.18.

2,4-Dinitrotoluene was the starting material. The nitration to give the trinitro derivative was found to produce the 2,4,6-substituted toluene only and was not noticeably exothermic. By contrast, the commercial preparation of TNT involves the reaction of toluene with fuming nitric and sulphuric acids, is highly exothermic and produces a range of substituted toluenes.

No difficulties beyond the normal hazards of handling hot (90°C) fuming nitric and sulphuric acids were encountered with the procedure described below.

In the absence of a published laboratory preparation the following procedure was based on details from an encyclopedia[189] and papers on industrial nitration processes by Albright[190,191].



m.w. 227.13

Fuming sulphuric acid (100 ml, 80% H_2SO_4, 20% free SO_3) was placed in a one litre flask fitted with a mechanical stirrer and nitrogen inlet (flow, 300 ml/min, dried with conc. H_2SO_4) with one neck open for further reagent additions, gas exit and temperature monitoring.

Freshly prepared fuming nitric acid (150 ml, bp. 75-78°C) was slowly added to the cooled sulphuric acid (ice-bath) with vigorous stirring. The addition was highly exothermic and large volumes of nitrogen dioxide were evolved.

2,4-Dinitrotoluene (20g, 0.111 mole) was added to the cooled (6°C, ice-bath) acid mixture (green). No temperature increase was noted.

The temperature was raised to 90°C over 20 minutes and maintained at 90-95°C for a further 30 minutes. The cooled mixture was poured into ice water (2 litre) and the precipitate (greenish-white crystals) filtered, washed (water, Na_2CO_3 solution, water) and dried (20 mm Hg, room temperature, over silica gel).

Yield; 87.0%, mp. 77-81°C (lit.[184], 80-82°C)

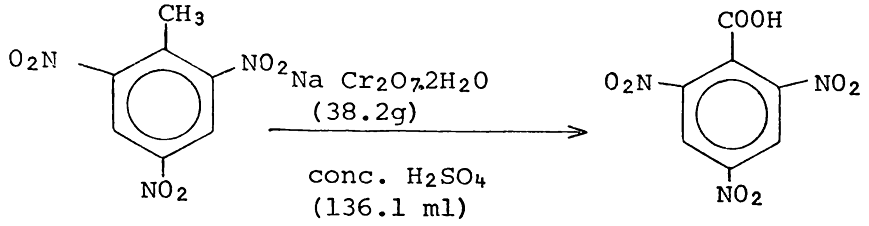
The crude 2,4,6-trinitrotoluene was recrystallised (absolute ethanol) to give light-yellow, needle-like crystals, mp. 79-80°C.

A proton NMR spectrum of the TNT in deuterated acetone (TMS internal reference) gave two singlets at 2.70 and 9.03ppm, with relative integrals of 3 and 2 respectively. No signals due to the starting material were detected.

Note: Fuming Nitric Acid was prepared by the method described by Vogel[179].

A6.16 2,4,6-Trinitrobenzoic Acid

2,4,6-Trinitrobenzoic acid was prepared from 2,4,6-trinitrotoluene using the method described by Vogel[179].



(25g, 0.110 mole) m.w. 257.12

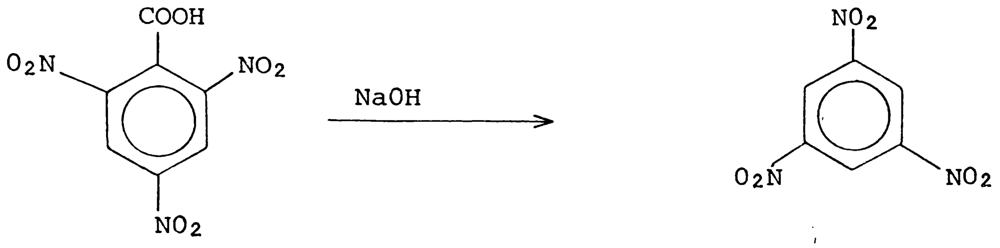
2,4,6-Trinitrobenzoic acid; melts and decomposes at 230-235°C (lit.[184], decomposes at 228.7°C) pale yellow crystals.Yield; 14.08g, 0.055 mole, 50%.

The following problem was noted;

Upon the addition of the sodium dichromate to the mixture of TNT and conc. sulphuric acid, the mixture changed to a thick green froth that filled the reaction vessel. The froth could not be stirred and consequently the temperature was very difficult to control. The mixture was quenched with ice and ice water 45 minutes after the initial additions of sodium dichromate and the product isolated as described by Vogel[179].

A6.17 1,3,5-Trinitrobenzene

1,3,5-Trinitrobenzene was prepared from 2,4,6-trinitrobenzoic acid using the method described by Vogel[179].



(11.82g,0.046 mole)

m.w. 213.11

Yield; 2.37g, 0.011 mole, 24%,white crystals

Exptl. mp 122-123°C, (lit.[184]121-122°C).

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