MASS SPECTROMETRY OF SOME MODEL AROMATIC AND ANTIAROMATIC SYSTEMS

A THESIS

SUBMITTED TO THE

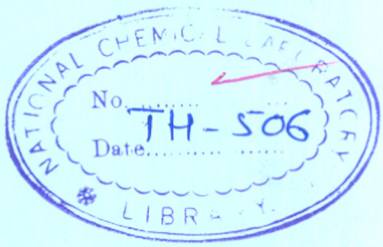
UNIVERSITY OF POONA

IN PARTIAL FULFILMENT

FOR THE DEGREE OF

MASTER OF SCIENCE

(IN CHEMISTRY)



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PUNE - 411 008

SEPTEMBER 1986

DEDICATED TO MY

PARENTS AND ELDEST BROTHER

CERTIFICATE

It is certified that the work incorporated in the thesis "Mass spectrometry of some model aromatic and antiaromatic systems" by Mr. S.P. Mirajkar of National Chemical Laboratory, Poona, was carried out by the candidate under my supervision. Such material as has been obtained from other source has been duly acknowledged in the thesis.

P. S. Kulkarni.

August, 1986

(Dr. P.S. Kulkarni)
Research Guide

ACKNOWLEDGEMENT

I wish to express my deep gratitude to Dr. P.S. Kulkarni, Scientist, Physical Chemistry Division, National Chemical Laboratory, Pune. for his guidance and keen interest during the course of the entire work.

I am grateful to Dr. N.R. Ayyangar, for gift of some compounds and suggesting methods of synthesis of azepines described in the thesis.

My thanks also go to Dr. K.P. Madhusudanan of C.D.R.I., Lucknow, for recording chemical ionization mass spectra.

I would like to thank Dr. C.A. Chinchwadkar, Dr. V.M. Kapoor, Mr. M.B. Shinde and Mr. I.S. Mulla for their help at various stages.

Finally, I sincerely thank the Director, National Chemical Laboratory, Pune, for allowing me to submit this work in the form of a thesis.

Mirajkar

(S.P. Mirajkar)

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CHAPTER I

IONIZATION IN THE GASEOUS PHASE AND MASS SPECTROMETRY TECHNIQUES

1.1 INTRODUCTION

Information on the structures of organic compounds can be obtained by a variety of analytical techniques such as NMR and mass spectral data. During the last two decades there has been almost tremendous growth in the use of these techniques to solve structural problems of great complexity. Mass spectra of a variety of organic compounds have been examined both for the purpose of understanding the mechanism of fragmentation of molecular ion and also with a view to attempt the inverse operation of using the cracking pattern to determine the molecular structure.[1,2,3]

Over the past few years a number of methods for ionization of organic molecule have been developed in the field of organic mass spectrometry. This chapter deals with mass spectrometric instrumentation, some aspects of electron ionization (EI), chemical ionization (CI) techniques and metastable ions.

1.2 MASS SPECTROMETRIC INSTRUMENTATION

There are four operations involved in any mass spectrometric experiment, namely (1) sample introduction, (2) ion production (ionization), (3) separation of ions according to their mass to charge m/z ratio and (4) detection.

(1) Sample introduction

There are several means of introducing samples into mass spectrometer ionization chamber and the inlet system used will normally depend on the volatility of the sample. These are (a) cold inlet, (b) hot inlet, (c) direct inlet and (d) gaschromatographic inlet.

A mass spectrometer is an instrument which produces gaseous ions from a substance, separates according to their mass to charge ratios and records their masses and relative abundances. The process by which an electrically neutral atom or molecule becomes charged, due to loss or gain of one or more electrons is called 'ionization'. The focusing and separation of ions is achieved by forces acting in electrostatic and magnetic fields. There are two types of geometries. In Nier-Johnson[4] geometry (Fig. 1) the deflection of the ions in the electrostatic and magnetic fields are in same direction whereas in Mattauch-Herzog[5] geometry (Fig. 2) they are in opposite direction.

(2) The ion source

The most common technique for the production of positive ions in the mass spectrometer is electron bombardment. The substance to be examined is

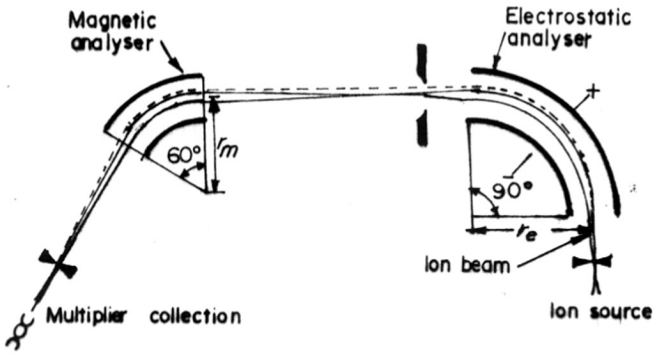


FIG. 1.

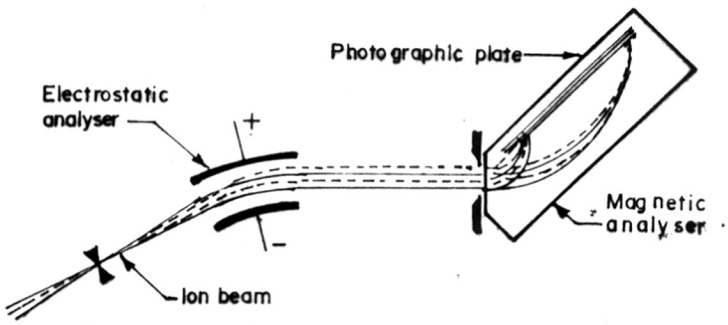


FIG. 2.

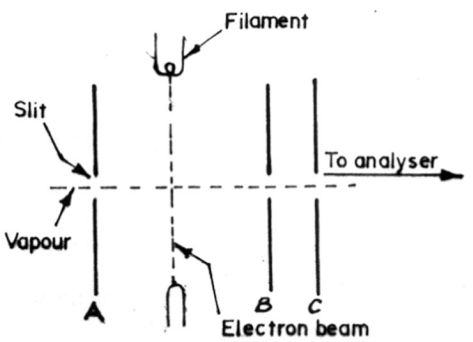


FIG. 3.

introduced as a vapour into the ion source at its operating pressure (ca. 10^{-6} mm Hg). The vapour is allowed to pass through a slit into the ionization chamber (Fig. 3) where it is bombarded with a beam of electrons emitted from a hot filament. The energy of electron beam can be varied from 0-100 eV. The ionization potential corresponds to the energy required to remove an electron from the highest occupied molecular orbital and the reaction is represented by eq. (1).

$$M + e \longrightarrow M^{+\bullet} + 2e \qquad (1)$$

Ionization energy of most of the organic molecules fall in the range 7-13 eV.

(3) Separation of ions

According to Wiens[6] a beam of positive ions could be deflected by both electric and magnetic fields. Thomson[7] built the instrument to analyse positive ions. Aston[8] and Dempster[9] built similar instruments independently. In early stages of its discovery the mass spectrometer was mainly used for the accurate measurement of the masses and relative abundances of isotopes.

Ions produced in the ionization chamber are accelerated by applying the acceleration potential (2 to 8 KV). These ions then enter the mass analyser which differentiates them on the basis of their mass to charge ratio (m/e) by electric and magnetic field. The two functions of a mass analyser are to resolve the ion beam into its components and to focus the resolved ions. The kinetic energy of an ion with charge 'e' and accelerating potential 'V' is 'eV'. The kinetic energy of an ion of mass 'm' moving with the velocity 'v_1' is $1/2\ mv_1^2$.

$$eV = 1/2\ mv_1^2 \qquad (2)$$

The centripetal force due to the magnetic field on the ion Hev_1 is balanced by the centrifugal force mv_1^2/R (where 'R' is the radius of the ion path and 'H' is the magnetic field).

$$Hev_1 = \frac{mv_1^2}{R} \quad \therefore \quad v_1 = \frac{HeR}{m} \qquad (3)$$

Elimination of v_1 between (2) and (3) results in the fundamental equation for a single focusing mass spectrometer

$$m/e = \frac{H^2R^2}{2V} \qquad (4)$$

Thus the radius of the path 'R' can be varied by changing 'H' or 'V'. Generally 'H' is varied but for very fast scanning 'V' is varied.

(4) Ion detector

The ions which are separated by the analyser are detected and measured either electrically or photographically. In the electrical detection the spectrum is scanned by varying the magnetic field. The ions pass through a collector slit one after the other and fall on electron multiplier. The electron currents are amplified and recorded either with a strip chart recorder or using a fast scanning oscillograph. In the photographic plate recording, the magnetic field is fixed and the ions are recorded on a photographic plate placed at the focal plane of the ions. In the Nier-Johnson geometry it is possible only to record spectrum electrically. However, in the Mattauch-Herzog geometry the spectrum can be recorded both electrically and photographically.

1.3 ELECTRON IMPACT IONIZATION

It has been pointed out[10] that 50 eV electron has a velocity of 4.2×10^8 cm/s and will traverse molecular diameter of a few $\mathring{A}$ in around 10^{-16} seconds.

The fastest vibrations found in organic molecules, (C-H) stretching vibrations, are almost 10^2 times slower and therefore the position of the nuclei in the molecule being ionized will not change during the time that the bombarding electron is in the vicinity of the molecule. Thus, when the electron bombardment process results in the removal of a valence electron to give a molecular ion, the process will occur without changes in internuclear distances. The transition will follow the Frank-Condon rule which requires that the configuration and momenta of the nuclei do not alter during the transition. If we use potential energy diagrams applicable to diatomic molecules to illustrate the principle of Frank-Condon rule with reference to polyatomic molecules (Fig. 4) then the ionization process would be represented by vertical transition. Hence, ionization under electron impact is a vertical process.

$$M + e \rightarrow M^{+\bullet} + 2e$$

Depending upon the interaction of the electron with the molecules, molecular ions are produced with internal energies varying from zero to (70 - I.P.) of the molecule (Fig. 5). As there are no collisions, intermolecular energy transfer does not take place

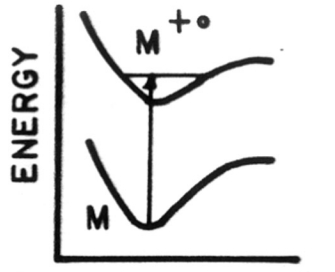


FIG - 4

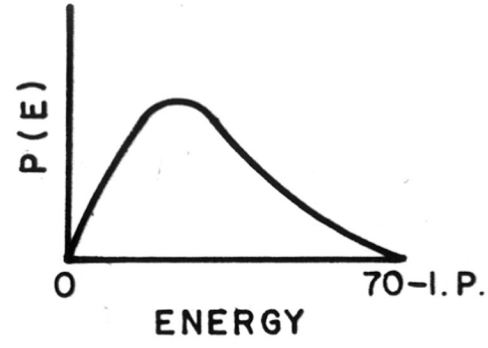


FIG-5

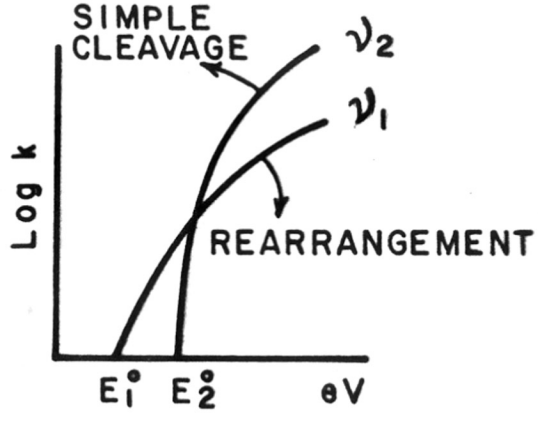


FIG-6

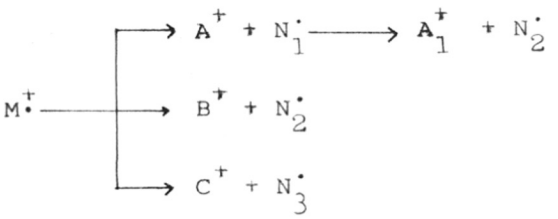
and hence the initial energy distribution is fixed and does not change on the mass spectrometer time scale. According to the quasi-equilibrium theory,[11] the molecular ions formed with varying internal electronic excitation energies do not decompose immediately into various fragments.

The initial excitation energy of the molecular ion is thought to be distributed randomly over all the molecular degrees of freedom in a short time compared to a dissociation process. Fragmentation occurs if a sufficient amount of energy is accumulated in one bond. It is further assumed that during these vibrations there is a high probability of radiationless transitions among the many potential surfaces of the ion. The general expression for the rate constant of the ionic dissociation process is given in eq. (5).

$$K = \nu \left(\frac{E-E_o}{E} \right)^{s-1} \qquad (5)$$

The rates of decomposition 'K' are described in terms of internal energy 'E' of the decomposing ion, the activation energy E_o for the fragmentation process, the frequency factor ν and s is the effective number of oscillators which is given by 3n-6 where

n is the number of atoms in the molecule. For a simple cleavage reaction where the internal energy is extremely large, reaction will occur in one vibration and $K \simeq \nu \simeq$ vibrational frequency of the bond in question (10^{13}-10^{14} s^{-1}). The molecular ion undergoes competing and consecutive unimolecular fragmentation reactions as given by QET rate expression.



For the rearrangement reaction it is not sufficient condition for a reaction to take place merely that the energy of activation for reaction be collected in the appropriate coordinates. The transition state with the formation of a new bond must take up a specific orientation with respect to the atom which is to receive it. The relatively low probability of attaining such a specific orientation lowers the reaction rate and therefore rates of such rearrangement reaction do not approach bond vibrational frequencies even when the internal

energies are extremely high. The situation is analogous to the negative entropies of activation for the formation of highly order transition state in ordinary thermal kinetics.

Competing Simple Cleavage and Rearrangement Reactions

If the molecular ion undergoes competing fragmentations involving simple cleavage and rearrangement, then the activation energies and frequency factors will be different for the two processes. For the rearrangement process involving bond formation, frequency factor and activation energies will be lower than for simple bond cleavages. This will lead to K versus E curves of the type shown in Fig. 6. Although it is difficult to predict quantitatively the variation of the ion abundance ratio of rearrangement and simple bond cleavage ions (R/c) with electron energy, useful generalisation can be made from the shapes of the K versus E curves shown in Fig. 6. As the electron energy is reduced to threshold values, the ion abundance ratio (R/c) should increase. All investigations on competitive simple cleavage versus rearrangement reactions have shown that this generalisation is valid.[12]

This theory is moderately successful in predicting the mass spectra of alkanes, but fails in the case of complex compounds. Some of the guidelines for understanding mass spectrometric fragmentation reactions are based mainly on empirical rules. Yeo and Williams[13] have calculated the ion abundance in the mass spectra of organic compounds undergoing two consecutive reactions using the simplified rate expression (5). In doing this it was assumed that the actual number of oscillators is a function of the internal energy of the ion and that it varies from one fifty at the threshold to one half of the total number of oscillators when the ion has 10 eV excess energy. Good agreement between calculated and observed ion abundance is claimed in the spectra of mono- and di-substituted benzenes.[14]

Types of Ions

The different types of ions usually met with in mass spectrometry are (1) molecular ion, (2) fragment ion, (3) rearrangement ion, (4) metastable ion, (5) multiple charged ion, (6) isotope ions, (7) negative ion, (8) odd and even electron ion and (9) ions formed by ion-molecule reaction.

(1) Molecular Ion

Molecular ions as parent ions are formed by the removal of one electron from the parent molecules.

$$M + e \rightarrow M^{+\bullet} + 2e$$

(2) Fragment Ion

The excited molecular ion undergoes many competing and consecutive unimolecular ion decompositions to give rise to a variety of fragment ions. Fragment ions are formed by both heterolytic and homolytic cleavage of bonds induced by active sites such as, radical and cationic. They are formed by simple cleavage and rearrangement processes. The formation of fragment ions by simple cleavage is a high energy process while formation of rearrangements is a low energy process.

(3) Rearrangement Ion

Fragment ions formed by intramolecular reorganization processes involving the migration of hydrogen and other atoms or groups are referred to as rearrangement ions.

(4) Metastable Ion

Ions decomposing unimolecularly outside the ionization chamber of a mass spectrometer are termed

"metastable ions". Depending on the internal energy and geometry of the instrument, metastable ions have life times in the range of 10^{-6} to 10^{-5} s.

(5) Multiple Charged Ion

The removal of two or more electrons from a molecule without fragmentation is possible in the case of organic compounds with aromatic rings and compounds containing conjugated systems. The doubly charged parent ions are formed by the loss of two electrons. They appear at half the mass of the molecular ion. A triply charged ion formed by the loss of three electrons from the neutral molecule will occur at one-third of its actual mass since it carries three positive charges (m/3).

(6) Isotope Ions

Most elements are mixtures of two or more stable isotopes differing by one or two mass units. Elements like carbon, hydrogen, oxygen, sulphur, etc. have one major isotope which is more than 90% abundant and a minor isotope. Chlorine and bromine have two isotopes (35,37 and 79,81) in the ratios 3:1 and 1:1 respectively. The isotopes ions are very helpful in determining the presence of such elements in the molecule.

(7) Negative Ion

Negative ions are formed from neutral molecules upon electron impact by the resonance capture of an electron ($AB + e \rightarrow AB^{-}$) or by dissociative resonance capture of an electron ($AB + e \rightarrow A + B^{-}$) as by ion pair production. ($AB + e \rightarrow A^{+} + B^{-} + e$). The efficiency of negative ion formation is lower by about a factor of thousand that of positive ion.

(8) Odd and Even Electron Ions

Odd ions contain an unpair electron while in even electron ions the electrons are paired. The molecular ion is an example of odd electron ion ($M^{+}\cdot$).

(9) Ions formed by Ion-Molecule Reactions

Generally mass spectral reactions are intramolecular. Intermolecular reactions between ions and neutral molecules take place when a sample pressure is very high. These reactions are termed as ion-molecule reactions. The simplest example is the protonation of molecular ion which results in the formation of the $(M + 1)^{+}$ peak.

Disadvantages of Electron Impact

Although electron impact serves as a good general ionization technique, it suffers from certain specific disadvantages. Most of these arises from the unknown high amount of energy deposited in the molecule upon ionization.

1. Internal Energy Distribution

The exact internal energy distribution of the ions produced by electron impact is generally unknown.

2. Unstable Molecular Ion

For certain classes of compounds, $M^{+\bullet}$ is unstable with respect to dissociation even at low internal energy. In such cases almost all $M^{+\bullet}$ ions fragment in the source with subsequent loss of high mass and molecular weight information.

3. Isomerization versus Decomposition

Because the rate of decomposition of ions is slow compared with that for energy randomisation, ions may isomerise prior to decomposition. This is not in general a problem although isomeric samples often yield identical electron impact spectra.

4. Stereochemistry

Because of internal energy randomisation

prior to decomposition, stereochemical information may be lost if electron impact is used to produce the ions.

5. Involatile and Thermally Unstable Compounds

Due to the prerequisite of sample vaporisation, compounds which either do not easily vaporise or decompose upon vaporisation cannot be fully analysed by electron impact.

1.4 CHEMICAL IONIZATION

Under EI conditions sample molecules vaporized in the ion source under high vacuum (10^{-5} to 10^{-6} torr) and are ionized by impact of a energetic (> 50 eV) electron beam. During this ionization process, the ion produced acquires average energy in the range of 1-8 eV and the ion undergoes extensive fragmentation. Since high vacuum is employed in EI conditions ion-molecule collisions are effectively precluded. The internal energy of the ions therefore remains in non-equilibrium distribution from the instant of ionization. In some cases molecular ions are not observed. Chemical ionization technique was developed to overcome this limitations and first described by Munson and Field.[15]

Hydrogen, methane, isobutane, water and ammonia have been employed as the reactant gases. The formation of major ions and proton affinity of the above gases are given in Table 1. In CI conditions only the reagent gas is ionized by EI and sample molecules are ionized by ion-molecule reactions. To achieve this, a sample to be analysed is added to the reaction gas at much lower pressure (about 10^{-3} torr). The stable ions of the reaction gas (at 1 torr) then react with the sample producing the quasi-molecular ions which fragment further. The ionization occurs by either proton transfer or hydride abstraction from the sample molecules.

$$R + e \rightarrow R^{+\bullet} \qquad (6)$$

(excited primary reactant gas ion)

$$R^{+\bullet} + R \xrightarrow{\text{collisional}} R^{+\bullet} + R \qquad (7)$$

(deactivation mechanism)

(equilibrium secondary reactant gas ion)

Proton transfer

$$M + RH^{+} \rightarrow (M+H)^{+} + R \qquad (8)$$

TABLE - 1

	Reagent Gas	Reaction Plasma	Proton Affinity[16] P.A. (A) kJ mol^{-1}
1.	Hydrogen H_2	$H_2 + e \longrightarrow H_2^{+\cdot} + 2e$	535
		$H_2^{+\cdot} + H_2 \longrightarrow H_3^{+} + H^{\cdot}$	
		$H_2^{+\cdot} \longrightarrow H^{+} + H^{\cdot}$	
		$H_2 + H^{+} \longrightarrow H_3^{+}$	
2.	Methane CH_4	$CH_4 + e \longrightarrow CH_4^{+}, CH_3^{+}, CH_2^{+}$	706
		$CH_4^{+\cdot} + CH_4 \longrightarrow CH_5^{+} + CH_3^{\cdot}$	
		$CH_3^{+} + CH_4 \longrightarrow C_2H_5^{+} + H_2$	
		$CH_2^{+\cdot} + CH_4 \longrightarrow C_2H_3^{+} + H_2 + H^{\cdot}$	
		$C_2H_3^{+} + CH_4 \longrightarrow C_3H_5^{+} + H_2$	
3.	Isobutane C_4H_{10}	$i\text{-}C_4H_{10} + e \longrightarrow C_4H_{10}^{+\cdot} + 2e$	755
		$i\text{-}C_4H_{10} \longrightarrow i\text{-}C_4H_9^{+} + H^{\cdot}$	
		$i\text{-}C_4H_{10}^{+} \longrightarrow C_3H_7^{+} + CH_3^{\cdot}$	
4.	Water H_2O	$H_2O + e \longrightarrow H_2O^{+\cdot} + 2e$	689
		$H_2O^{+\cdot} + H_2O \longrightarrow H_3O^{+} + OH^{\cdot}$	
5.	Ammonia NH_3	$NH_3 + e \longrightarrow NH_3^{+\cdot} + 2e$	840
		$NH_3^{+\cdot} + NH_3 \longrightarrow NH_4^{+} + HN_2^{\cdot}$	
		$M + RH^{+} \longrightarrow MH^{+} + R$	
		ΔH + P.A. (R) — P.A. (M)	

Hydride transfer

$$M + RH^{+} \rightarrow (M-H)^{+} + R + H_2 \quad (9)$$

$$(M \pm H)^{+\bullet} + RH \rightarrow (M \pm H)^{+} + RH \quad (10)$$

Since the exothermicity of gas phase proton transfer and hydride abstraction reaction is usually low (0-3 eV) the resulting even electron ions are relatively stable towards further decomposition. The opportunity for the sample ion to undergo stabilizing collisions (eq. 10) with neutral reagent gas molecules under CI conditions also contributes to the reduced fragmentation observed in the CI mode.

The mass spectra produced in this way by chemical reaction are usually quite different from those obtained by electron impact. Generally, the relative abundance of fragment ions is much smaller in the case of chemical ionization mass spectra. Therefore, this method seems to be very promising for the analysis of complicated mixture of organic components.

Although the formation of $(M+H)^{+}$ is usually the major reaction when methane, isobutane and ammonia are used as reagent gases, peaks due to

addition reactions may also be observed under appropriate conditions. In methane, low intensity $(M + C_2H_5)^+$ and $(M + C_3H_5)^+$ ions may be observed and in isobutane $(M + C_3H_7)^+$ and $(M + C_4H_9)^+$ ions may be observed. The proton affinities of most oxygen containing organic compounds fall in the range of 710-830 kJ mol^{-1}[16]. Proton attachment to such compounds by NH_4^+ is therefore endothermic although for many compounds NH_4^+ attachment to give $(M + NH_4)^+$ is exothermic. Therefore, as a general rule NH_4^+ will protonate compounds containing nitrogen such as amines and will form attachment ions $(M + NH_4)^+$ with oxygen containing compounds such as sugars.

1.5 METASTABLE IONS

The origins of metastable peaks

If a singly charged molecular ion of mass m_1 does not dissociate before arriving at the collector, it is recorded as a molecular ion or parent ion. If the reaction $m_1^+ \rightarrow m_2^+$ occurs in the source then m_2^+ may travel the whole of the analyser region as a mass m_2^+ and recorded as m_2^+ daughter ion. However, it is possible that the transition $m_1^+ \rightarrow m_2^+$ will occur after the source slit but before arrival at the collector. The ions can decompose in

the source region (A) before acceleration, in the first field free region (B) after acceleration, in the electric sector (C), in the second field free region (D) before the magnetic sector or in the magnetic sector (E). Ions undergoing such transitions are called metastable ions (Fig. 7). These ions do not have full accelerating kinetic energy. The K.E. is reduced by a factor of m_2/m_1 after metastable decomposition.

Molecular ions with internal energies less than the activation energies E_o will not decompose no matter what the frequency factor are in the reaction coordinate. These ions will be stable enough to be carried to the analyser and will be recorded as molecular ions.

Decomposition in the second field free region

Ions which have been accelerated may decompose in the magnetic sector region. These ions will not be recorded.[17] Ions which decompose in the second field free region $D(m_1^+ \rightarrow m_2^+ + N)$ will be recorded as small diffuse peaks at non-integral masses.

$$m^* = \frac{m_2^2}{m_1} \qquad (11)$$

These peaks are called metastable peaks.

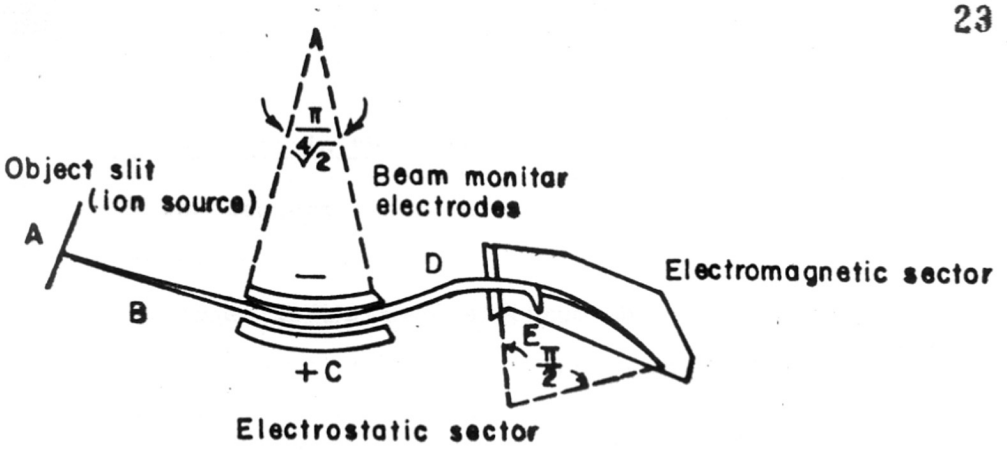

Object slit
(ion source)
A
B
Beam monitar
electrodes
D
Electromagnetic sector
+C
Electrostatic sector

FIG.- 7


Gaussiun
Flat – topped
Dish shaped

FIG.– 8

Decompositions in the first field free region

The daughter ions resulting from the decompositions in the first field free region are not recorded in the mass spectrum when the instrument is set for normal operation. The kinetic energy of the daughter ions is reduced to m_2/m_1 of the full acceleration energy when the decomposition takes place in the first free region. These ions cannot follow the central path along with the ions decomposing in the source. They generally strike the metal places and are lost. These ions can be made to follow the central path by increasing the ion accelerating voltage by the ratio of the masses of the precursor to the daughter ion m_1/m_2. This method of observation of metastable transitions is known as metastable defocussing technique which is developed by Elliott and Barber.[18] The method has the disadvantage that as the ion accelerating voltage is changed, the optimum tuning conditions within the source are altered, owing to change in the field penetration and also that voltage cannot be changed by more than a factor of four. This limits the ratio of the precursor to daughter ions which can be studied.

The advantages of using first free region for the study of metastable transitions are:

(i) each transition is unequivocally identified in terms of the mass of parent and daughter ions;

(ii) all the precursor ions of m_2 may rapidly be found in one scan of the accelerator voltage;

(iii) normal ions do not interfere; and

(iv) in the absence of normal ions, the electron multiplier can be increased and so weak transitions may be detected.

Methods of observing metastable transitions and their applications

In double focussing instruments, the three possible variables are E, the electric sector voltage, V, the accelerating voltage and B the magnetic field strength. These may be scanned in various ways to allow the collection of daughter ions formed in the metastable transition which occur in the field free region between the source and the first sector and between the two sectors. The major characteristics of the five methods which have so far been used are summarised in Table 2. In

TABLE - 2

Characteristics of different methods for observations of Metastable Transitions

	Scan	Fixed	Ease of assignment	KE Release	Feature
1.	E	V, B	i) Difficult ii) Usually to nearest nominal mass.	Yes	i) E preceeds B: gives all m_1/m_2 ratios without mass analysis. Requires EN between sectors. ii) B preceeds E: gives all m_2^+ from selected m_1^+. Wide range; constant source conditions.
2.	V	E, B	Usually to nearest nominal mass	Yes	Gives all m_1^+ of selected m_2. Range limited by practical V_1/V_0 ratio. Source conditions vary during scan.
3.	B	V, E	Often difficult	Yes	Gives m_2^2/m_1 ratio. Low intensity relative to normal peaks. Overlap problems.
4.	$V^{1/2}/E$	B	Good; peaks narrow	No	Gives all m_2^+ from selected m_1^+. Range limited to m_1/m_2 Source conditions vary during scan.
5.	B/E	V	Good, narrow peaks	No	Gives all m_2^+ from selected m_1^+. Wide range, constant source conditions.

discussing these methods, it will be assumed, unless otherwise stated, that the mass spectrometer has a geometry in which the electric sector preceeds the magnetic sector.

Metastable transition is used in (1) ion structure elucidation from metastable ion abundances; (2) identification of rearrangement process of kinetic energy release measurement, (3) measurement of isotope effect, (4) determination of extent of scrambling and (5) collisional activation studies to gain information on ion structure.

The analysis of metastable peak shapes is one of the most powerful tool for the investigation of reaction mechanism. Upon decomposition, part of the excess energy of an ion is released as kinetic energy T, leading to a range of translational energies in the ion beam. The kinetic energy released upon metastable ion decomposition can be detected from the peak broadening.[19] Small average T-values lead to narrow, Gaussiun shaped peaks, whereas flat-topped or dish shaped peaks are observed for large T values (Fig. 8). Measurement of kinetic energy in metastable ion transition helped in ion structure studies[20-22] as they afford

information concerning the energetics and mechanism of ion decomposition reactions.[23-25] Holmes et al[22] have examined metastable peaks for the fragmentation of $C_2H_4O^{+\cdot} \rightarrow C_2H_3O^{+} + H^{\cdot}$ in the first field free region. Three isomeric $C_2H_4O^{+\cdot}$ ions were generated (a) $CH_2\text{-}CH_2^{+\cdot}$ (O), (b) $CH_3CHO^{+\cdot}$ and (c) $CH_2 = CHOH^{+\cdot}$ from ethylene oxide, acetaldehyde and vinyl ether respectively and found each fragment is producing a different m^* peak having a characteristic shape and kinetic energy release.

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CHAPTER II

REACTIVITY OF SOME π ELECTRON SYSTEMS, SYNTHESIS OF AZEPINES AND ISOMERIC CARBAMATES

2.1 GAS PHASE ANALOGY AND DIFFERENCE WITH SOLUTION PHASE

Introduction

Many reactions which occur in solution phase do occur in gas phase and vice versa. The fundamental factors that influence reaction rates cannot be studied in solution phase because the solvent molecule themselves interact strongly with the reacting species. If the solvent could be totally removed, the intrinsic reactivity of the bare reactant could be measured and distinguished from the effect attributable to solvation.

Non-ionic reactants have been known to be converted into non-ionic product through transient ionic reactive intermediates in acid catalysed solvent in solution phase. The development of super acid have made it possible to produce stable alkyl carbonium ions in solution and directly observe them with analytical instrumentation made available such as ^{13}C NMR at present time. Ionic species in the gas phase react three billion times faster than the same species do in acetone and a million billion (10^{15}) times faster than in water. In the gas phase well established mass spectrometric methods such as electron

impact and chemical ionization allow the study of the reactivityof gaseous ions. These reactivity studies can be further supported by more sophisticated techniques such as, mass analysed ion kinetic energy and collision activation technique.

Gas phase acid catalysed Beckmann, Pinacol, Wagner-Meerwien, Claisen, Cope rearrangements, Fischer indol synthesis, aldol condensation have been shown to be analogous to known reaction in solution.[1] Gas phase electrophilic and nucleophilic substitution reactions are also observed to be analogous to their counterparts in solution.[2] Hoffman et al[3] have examined methyl substituted hexadiens and cyclobuten isomeric pairs and showed mass spectral reactions to be analogous to photochemical and thermal process.

A short review of these analogies of similarity of ionic reactions in the solution and gas phase reported in literature is illustrated with examples.

2.2 REARRANGEMENTS

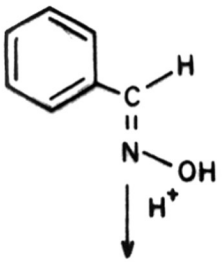
Beckmann Rearrangement

Aliphatic and aromatic oximes are known to undergo Beckmann rearrangement in acidic solutions.

Maquestiau and co-workers[4] have reported the occurance of the Beckmann rearrangement of $(M+H)^+$ ions of oximes in the gas phase by using the combined technique of chemical ionization (methane) and collision induced dissociation in the mass spectrometer. The $(MH-H_2O)^+$ ions were selected by the magnet of a reversed geometry mass spectrometer for the study of collision induced dissociations in the second field free region.

The fragmentation of the $(MH-H_2O)^+$ (m/z 104) ions of syn- and anti-benzaldoximes are quantitatively different. Analysis of the peaks at m/z 89 and m/z 91 allows the differentiation of the ions, a more intense m/z 91 $(C_6H_5N)^{+\bullet}$ ion is observed for the syn-isomer 1, while the m/z 89 $(C_7H_5)^{+\bullet}$ ion prevails in the case of anti-benzaldoxime 2. These results indicate, therefore, that m/z 104 ions formed from the protonated oximes 1 and 2 are dissimilar. Moreover, the great similarity of the CID spectra of these $(MH-H_2O)^+$ ions from 1 and 2 to those of the protonated molecular ions of phenylisocyanide (a) and benzonitrile (b) respectively, leads to the conclusion that the water loss is concerted with a stereospecific migration of the anti-substituent (Scheme 1).

1



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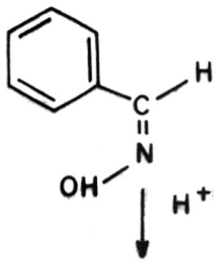
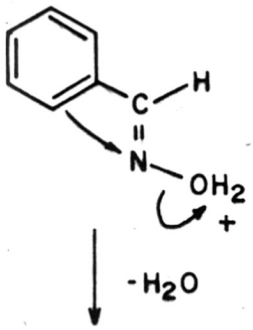
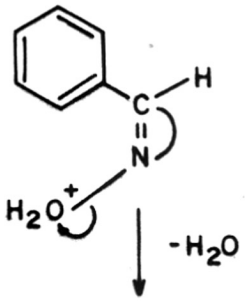
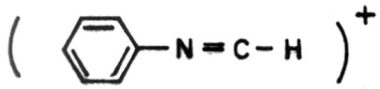
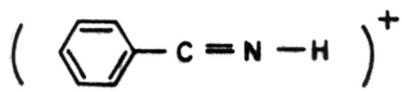






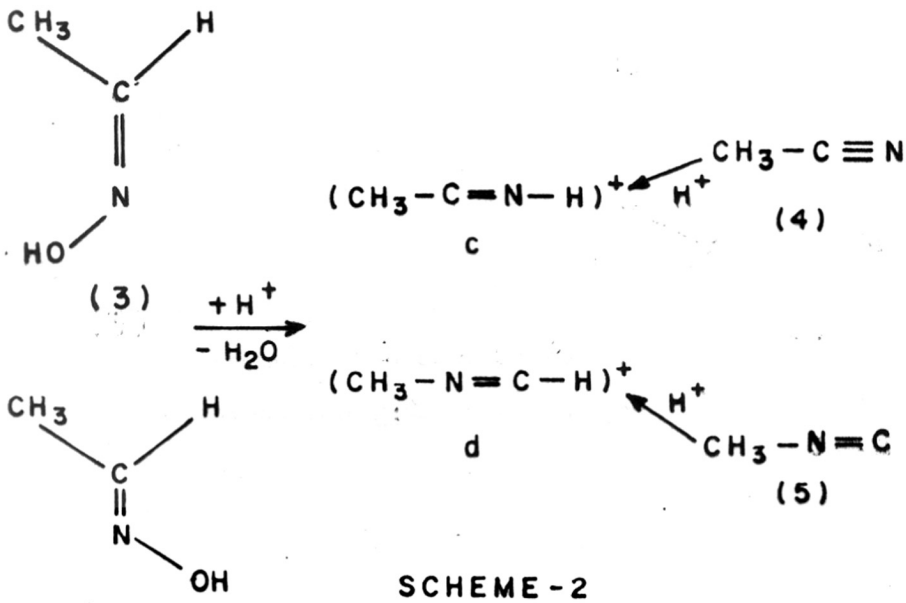


a



b

SCHEME – 1



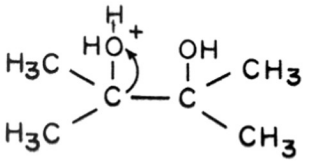
SCHEME-2

The CID spectra of the $(MH-H_2O)^+$ fragment ions from acetaldoxime 3 and the nitrilium ions obtained by protonation of methylisocyanide 5 and acetonitrile 4. The results are compatible with a mixture of nitrilium c and isonitrilium d cations for these fragment ions (Scheme 2).

In conclusion, the results show that the protonated aromatic aldoximes and ketoximes rearrange into nitrilium cations with a stereospecific migration of the anti-group with respect to the hydroxyl function. Even with mixtures of aliphatic oximes, it is possible to show that the loss of water is concerted with the specific Beckmann rearrangement.

Pinacol-Pinacolone Rearrangement

Aqueous solutions of pinacol under acidic conditions are known to rearrange to pinacolone. Glish and Cooks[5] first reported the occurance of similar rearrangement in the gas phase under chemical ionization (CI. Butane) conditions. The protonated molecular ion 6 eliminates water, giving rise to carbonium ion intermediate 7. Methyl migration to the carbonium ion center produces protonated pinacolone ion 8 as shown in Scheme (3). The MIKE



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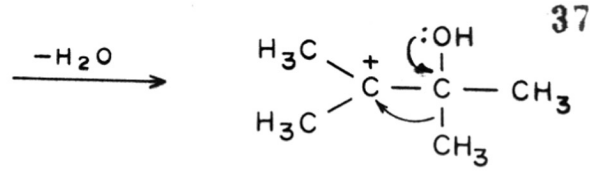

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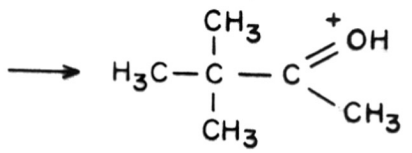
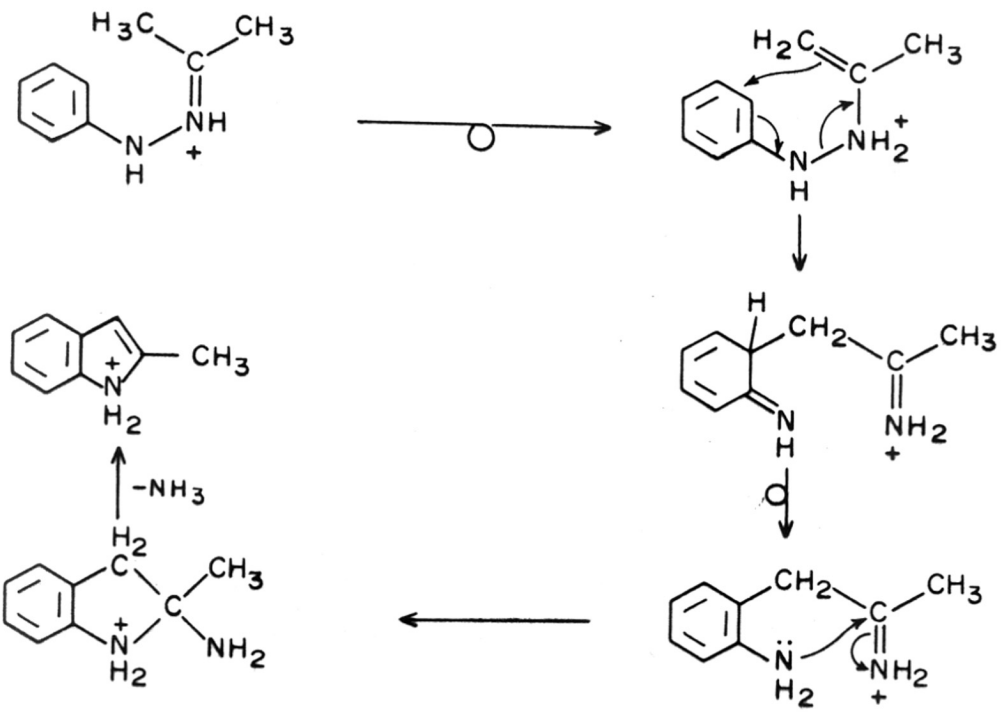


(MIKE)

(8)

SCHEME 3



SCMEME 4

spectrum of this dehydration product of protonated pinacolone 6, was identical to that of authentic protonated pinacolone indicating that similar pinacol - pinacolone rearrangement is occurring in the gas phase. Maquestiau et al[6] have reported similar rearrangements for other pinacols under CI (isobutane) conditions.

Fischer Indole Synthesis

Glish and Cooks[5] first reported that the gas-phase acid-catalysed elimination of NH_3 from protonated phenylhydrozones is analogous to a solution reaction. They employed MIKE measurements in conjunction with isotope labelling to support their observations.

The chemical ionization mass spectrum (isobutane reagent gas) of acetone phenylhydrazone shows a prominent ion due to the protonated molecule, m/z 149, as well as peaks at m/z 109 (protonated phenylhydrazine), m/z 59 (protonated acetone). In addition, to these peaks an ion of low abundance (0.9% of $(M+H)^+$) occurs at m/z 132. The presence of this ion in the mass spectrum provides necessary but not sufficient evidence that an NH_3 elimination

reaction, which may be analogous to the Fischer indole synthesis (Scheme 4) may be occurring in the gas phase.

The protonated molecule m/z 149 was selected and the resulting ions formed by collision of $(M+H)^+$ with nitrogen were analysed and found loss of 17 a.m.u. (NH_3) from the protonated molecule is a major process. Such a reaction is not expected for protonated acetone phenylhydrazone and a rearrangement of the ion, prior or subsequent to collision is indicated. It should be noted that the major reactions of this species, the formation of m/z 93, 92, 77, 65 and 58 are expected for the protonated hydrozone structure. Further, confirmation that the elimination of 17 mass unit does indeed correspond to ammonia loss comes from MIKE spectrum of the hydrazone formed from acetone-d_6. A clean loss of 19 mass unit is observed that is NHD_2 is lost. This result shows that interchange (scrambling) of hydrogen atoms between the ring, the amino hydrogens, and the methyl hydrogen does not occur in $(M+H)^+$ ion.

In the MIKE spectra of authentic protonated 2-methylindole and acetone hydrazone, elimination

product were compared.[6] The good correspondance observed points to the presence of protonated 2-methylindole in the m/z 132 ion beam of acetone-hydrazone and thus confirms the overall reaction sequence shown in Scheme (4).

Claisen Rearrangement

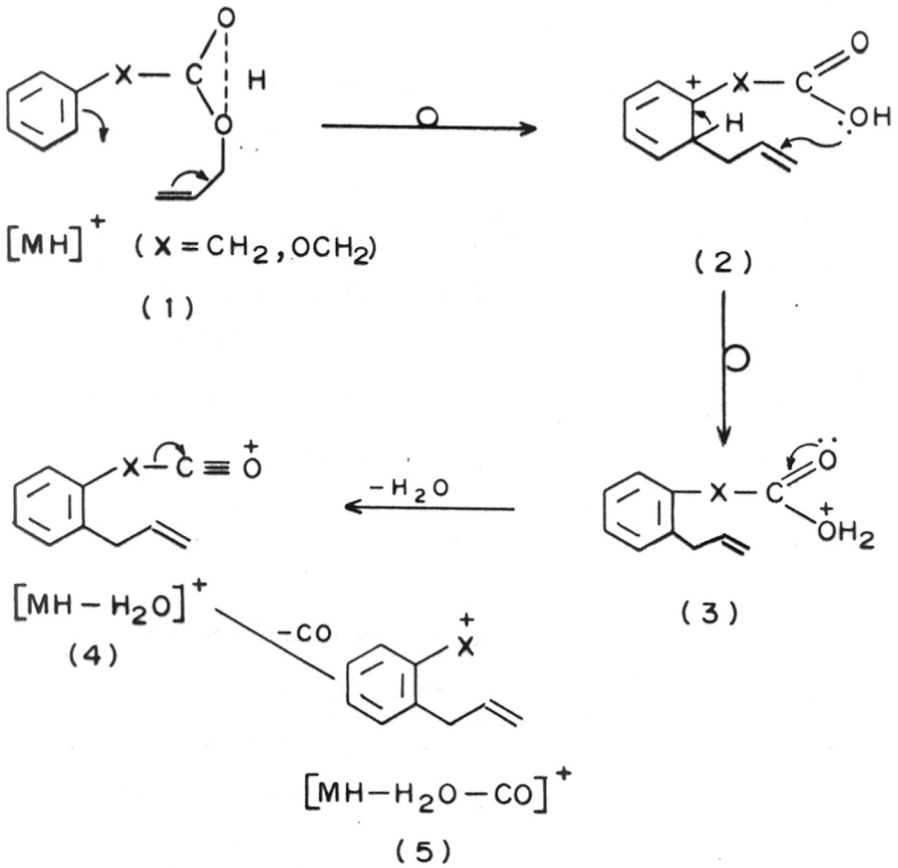
Phenylallyl ethers are known to undergo Claisen rearrangement in the solution leading to formation of o-allyl phenol.[7] Similar rearrangements were reported in the gas phase by Liehr et al.[8]

In the CI spectrum of allyl phenylacetate, the principal process corresponds to sequential loss of H_2O (m^*, m/e 142.8) followed by CO (m^*, m/e 108.1) from the protonated molecular ion, which requires skeletal rearrangement, is shown in Scheme (5).

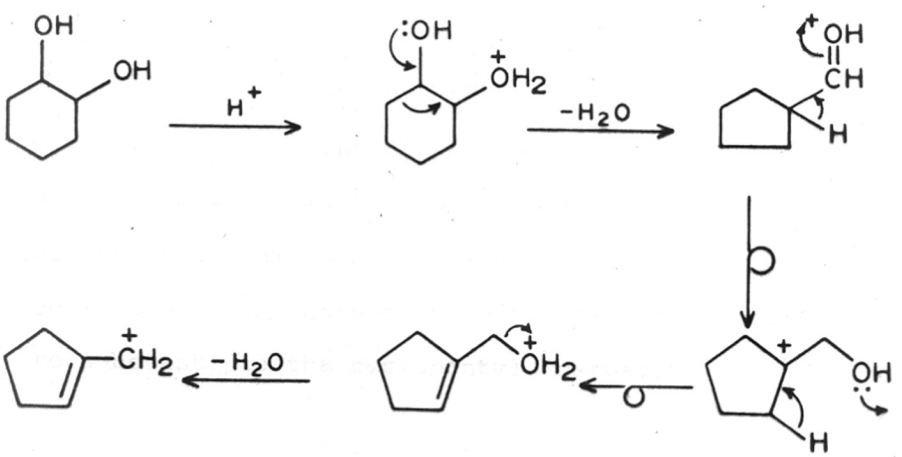
$(M+H)^+$	→	m/z 159	→	m/z 131
allyl phenylacetate		$(MH-H_2O)$		$(MH-H_2O-CO)$

The possibility of thermal rearrangement prior to protonation was excluded as a contributor to the formation of m/e 131 and 159, because of the

Claisen rearrangement



SCHEME-5



SCHEME-6

absence of analogous peaks in the EI spectrum which is constant over a range of temperature upto at least 250°C. Expulsion of H_2O from 3 and CO from 4 was initially interpretted in terms of allyl migration to phenyl ring in the protonated molecular ion. Therefore, after initial attack, abstraction of the o-hydrogen by the carboxyl group would lead to a highly favourable re-aromatization, thus completing an intramolecular extrophilic substitution.

The mechanism was supported by deuterium labelling in the ortho position and allyl phenoxyacetate using 2,4,6-trideuterio compound. The CIMS revealed the following sequence.

$(M+H)^+$	→	$(MH-HDO)^+$	→	$(MH-HDO-CO)$
m/z 196		m/z 177		m/z 149

Wagner-Meerwein Rearrangement

Wolfschurtz and co-workers[9] proposed a Wagner-Meerwein rearrangement in CI mass spectra of cyclohexanediols and have used collisionally activated dissociations and potential energy surfaces to substantiate the cyclopentyl carbaldehyde

structures of the $(MH-H_2O)^+$ ions from cis and trans-cyclohexane-1,2-diol. Mechanism is as shown in Scheme (6).

Cope Rearrangement

Kruger and co-workers[10] have proposed a Cope type rearrangement of $(M + C_3H_5)^+$ ions formed in the CI (Methane) mass spectra of nitrobenzene. The loss of NO_2 in these cases was collisionally activated.

Aldol Condensation

Wesdemiotis and McLafferty[11] have investigated the loss of water from the $(2M+H)^+$ ion of acetaldehyde in CI (methane). Collisionally activated dissociation studies support the proposed formation of protonated crotonaldehyde analogous to the Aldol condensation in solution.

2.3 THERMAL, PHOTOCHEMICAL AND ELECTRON IMPACT TRANSFORMATIONS - APPLICATION OF WOODWARD AND HOFFMANN RULES

Thermal and photochemical irradiation of molecules containing conjugated π electron systems is known to lead to the synthesis of a large number of novel compounds. In these systems a cyclic reorganization of bond occurs. In these reactions

an acyclic π system is converted into cyclic π system by formation of a single sigma bond between the termini of the cyclic system. The reverse ring opening reactions are also known. These transformations have been called electrocyclic reactions because the closure or opening involves the movement of electrons and atoms but no atoms are lost and gained. The other cyclical reorganization of bonds leading to novel synthesis are intramolecular cycloadditions and sigmatropic shifts. Both intermolecular and intramolecular additions are characterised by having a negative entropy of activation which is in keeping with formation of cyclic transition state. These reactions may be stereospecific and this stereospecificity may be explained by Woodward-Hoffmann rules. Woodward and Hoffmann rules rationalise the behaviour of many previously puzzling pericyclic reactions and predict with the remarkable accuracy, the outcome of hitherto unknown ones. These rules are based on the principle of the conservation of orbital symmetry.

The Woodward-Hoffmann rules divide the pericyclic processes into two categories; those

which are forbidden have high activation energies.

Selection Rules for Intramolecular Cyclo-additions and Cycloreversions

Number of π-electrons in cyclic member	Favoured process	
	Thermally	Photochemically
4n and 4n + 1	Conrotatory	Disrotatory
4n + 2 and 4n + 1	Disrotatory	Conrotatory

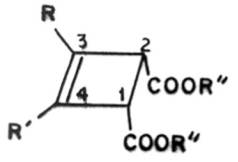
The essence of Woodward-Hoffmann rules is that during the course of pericyclic reaction, the symmetries of changing orbitals relative to the overall symmetry of the molecule must be retained from reactants through products.

The application of the Woodward and Hoffmann orbital symmetry rules to the radical cations generated in the mass spectrometer is of interest. Woodward and Hoffmann state[12] that orbital symmetry rules applicable to neutral systems containing even electrons should also hold for electrocyclic transformations within odd electron systems; the charged system should also behave in the same manner

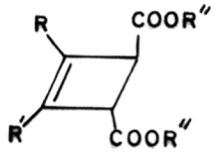
as neutral system containing the same number of electrons. This argument is supported by the investigations of several systems using extended Huckel theory.[13]

In order to gain a better understanding of the reactive states of ions, capable of undergoing electrocyclic transformations similar to those under photochemical and thermal conditions, various workers have examined mass spectral fragmentation of isomeric pairs of 2π, 4π and 6π electron systems. Comparison of normal mass spectral ion-abundance data, (I.P.-A.P.) measurements, metastable peak shapes and kinetic energy release data have been cited to seek correlations between electron impact and analogous photochemical and thermal behaviour.

Mandelbaum *et al*[14] compared the mass spectral behaviour of dimethyl esters of epimeric (*cis* and *trans*) cyclobut-3-ene-1,2-dicarboxylic acids (Ib, IIb) and the isomeric muconates (Vb, IIIb and IVb) (Scheme -7) respectively. The mass spectral fragmentation was entirely different in these isomers. Cyclobutene diesters undergo elimination of methanol and decarbonylation under electron impact



(I)



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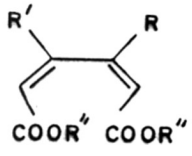

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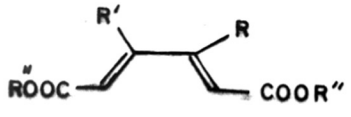

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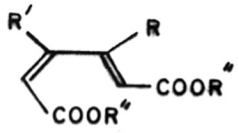


(V)

a) R = R' = R'' = H

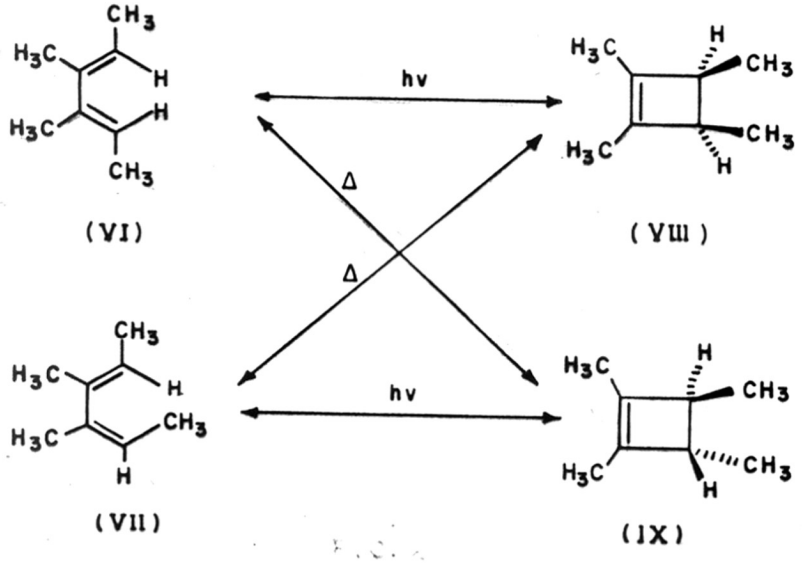
b) R = R' = H ; R'' = CH_3

c) R = R' = C_2H_5; R'' = CH_3

d) R = R' = n-C_3H_7 ; R'' = CH_3

e) R = CH_3; R' = n-C_3H_7; R'' = CH_3

SCHEME – 7



(VI) (VIII)

(VII) (IX)

VI) cis cis - 3,4 - Dimethyl - 2,4 - Hexadiene

VII) cis, Trans - 3,4 - Dimethyl - 2,4 - Hexadiene

VIII) cis 1,2,3,4 - Tetramethylcyclobutene

IX) Trans 1,2,3,4 – Tetramethylcyclobutene

SCHEME – 8

whereas these fragmentations are absent in the muconates. The most prominent ion in the spectra of muconates was formed by elimination of the $COOCH_3$ radical, whereas these $(M-59)^+$ ions were of low abundance in the spectra of substituted cyclobutene diesters. Mandelbaum et al therefore conclude that cyclobutene diesters (I,II) retain their cyclic structure and configuration upon ionization inspite of their low thermal stability. Concomitantly, the behaviour of 3,4-dialkyl-muconates (Scheme 7) indicate that their molecular ions retain the open chain structure before at least fragmentation takes place.

Hoffman et al[3] have examined mass spectra of acyclic 6π and 4π-electron systems and compared their behaviour with isomeric 4π and 2π-cyclic systems respectively accessible through electrocyclic transformations under photochemical and thermal conditions. The principal fragmentation routes of molecular ions of cis, cis-3,4-dimethyl-2,4-hexadiene (VI), cis, trans-3,4-dimethyl-2,4-hexadiene (VII) were compared with cis-1,2,3,4-tetramethylcyclobutene (VIII) and trans-1,2,3,4-tetramethylcyclobutene (IX) (Scheme 8). Loss of hydrogen, methyl radical

and hydrogen molecule from molecular ions were principal fragmentation modes. Kinetic energy released in these fragmentation modes was measured to probe the structures of fragmenting ions. For the loss of hydrogen and methyl radical processes, identical kinetic energy released values were observed for the isomers (VI and VIII) and (VII and IX). These isomers are interrelated by photochemically excited state disrotatory processes. For loss of hydrogen molecule from molecular ion, all the four isomers showed identical kinetic energy release values. This has been taken to indicate that all the isomers equilibrate to a common structure or a set of structures through vibrational and excited state pathways. Similarly, the principal decomposition routes of molecular ions of 6π electron octatriene and isomeric dimethyl cyclohexadiene were investigated by Hoffman et al.[15] The kinetic energy release in the fragmentation of molecular ions involving loss of hydrogen and methyl radical from isomeric pairs were compared. It was concluded that the loss of radicals from molecular ions proceeds from ground state since identical values were

observed in pairs that are reacting through a disrotatory (vibrational) pathway. Loss of neutral molecule such as H_2 from molecular ions seems to proceed from complete equilibration of structures, via both ground and electronically excited state pathways.

This short review shows that many physical organic concepts employed to rationalise organic reaction mechanism in solution phase are also useful in explaining ionic gas phase reactions. There are, however, important differences in the energetics of the two analogous processes due to the internal energies of the ions and solvation of reactants, transition states and products. In solution phase the abundant solvent molecules serve as an efficient energy sink and rapid multiple collisions remove any reaction exothermicity. This results in Maxwell-Boltzman distribution of internal energies of ions. The collision process deactivates the reactants and lowers the intrinsic reactivity. Solvation energies are high and differential solvation of reactants, transition states and products creates energy barriers to solution reactions. On the contrary, in the gas

phase there are few collisions and exact energy distribution of ions under electron ionization and chemical ionization is not known. The ionic and the neutral reactants approach along an attractive surface due to ion-permanent dipole and ion-induced dipole forces. The exothermicity of the reaction activates the reactive species to an energy state greater than many of the transition states of simple reactions along the reaction coordinate. The transition state energies are below the reactant energies and therefore gas phase ion-molecule reactions do not require an activation energy. Reaction exothermicity and strain energy often result in the fragmentation of the collision partners. The ion-dipole complexes appear to have moderately long lifetimes which allows extensive exploration of the reaction surface. These fragmentation processes often demonstrate striking selectivity from among a manifold of product channels. Some of these reaction channels show similarity to solution phase processes.

2.4 CHEMISTRY OF AZEPINES: SYNTHESIS AND REACTIVITY

Attempts have been made to correlate mass spectral reactions with thermally and photochemically analogous processes.[3,16,17] Mandelbaum[14] has compared mass spectral fragmentation of isomeric pairs of 2π, 4π and 6π electron systems and attempted to correlate the fragmentation modes from electrocyclic transformations in the system similar to those occurring under photochemical and thermal transformations in the neutral systems.

At present there is interest in the correlation of mass spectral reactions which are analogous to thermal and photochemical processes. Antiaromatic 8π electron heterocyclic azepine system is unstable and undergoes valence isomerization, dimerization and aromatization under photochemical,[18] thermal and acid-catalyzed[19-21] conditions respectively. There is no detailed comparative mass spectral study of this system. This study was done with a view to see whether transformations reported under photochemical, thermal and acid-catalysed conditions will also occur under mass spectral condition.

SYNTHESIS

N-phenylcarbamate 1a

This was prepared by the method described in the literature.[19,22] 9.3 g of aniline and 5.4 g of ethylchloroformate in 100 ml of tetrahydrofuran were stirred at room temperature for 30 minutes. The precipitated hydrochloric salt was removed by filtration and the filtrate was concentrated under reduced pressure to give 1a. Recrystallized from ether-hexane, m.p. 53°C. (Lit.[23] m.p. 53°C).

N-ethoxycarbonyl 1H-azepine 1b

The azepine 1b was prepared by the method described by Cottor et al.[24] A solution of 1.5 g of ethylazidoformate in 40 ml of benzene was placed in a sealed tube which was heated at 135°C for 5 hours. The benzene was subsequently removed under reduced pressure. The residue was chromatographed on 25 g of Florosil and elution with ether until yellow eluate no longer appeared; followed by fractional distillation of eluate under reduced pressure, gave N-ethoxycarbonyl 1H-azepine 1b, b.p. 54-55°C (0.1 mm) (Lit.[24] 55-56°C at 0.1 mm).

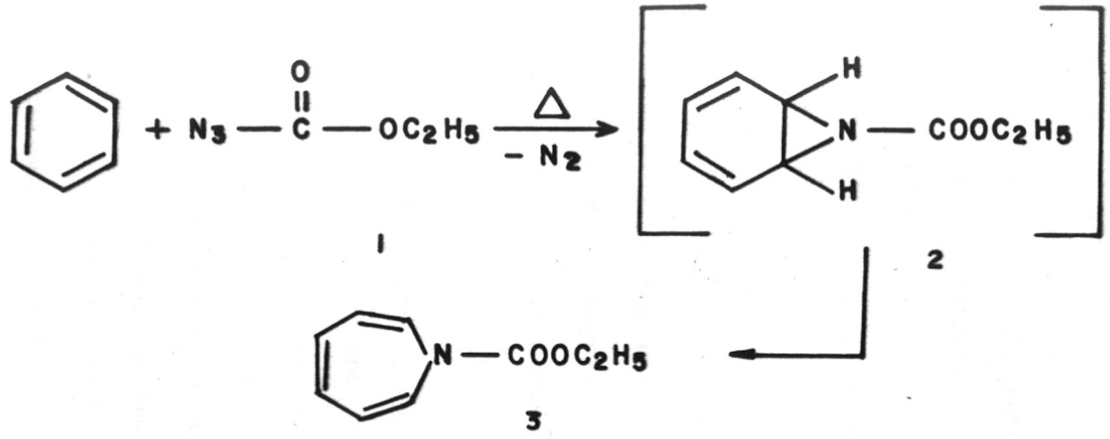
In this reaction, the formation of azanorcardiene derivative (2) was postulated as a probable intermediate which then rearranges to azepine 1b (Scheme 9).[25]

o-Methyl-N-phenylcarbamate 2a

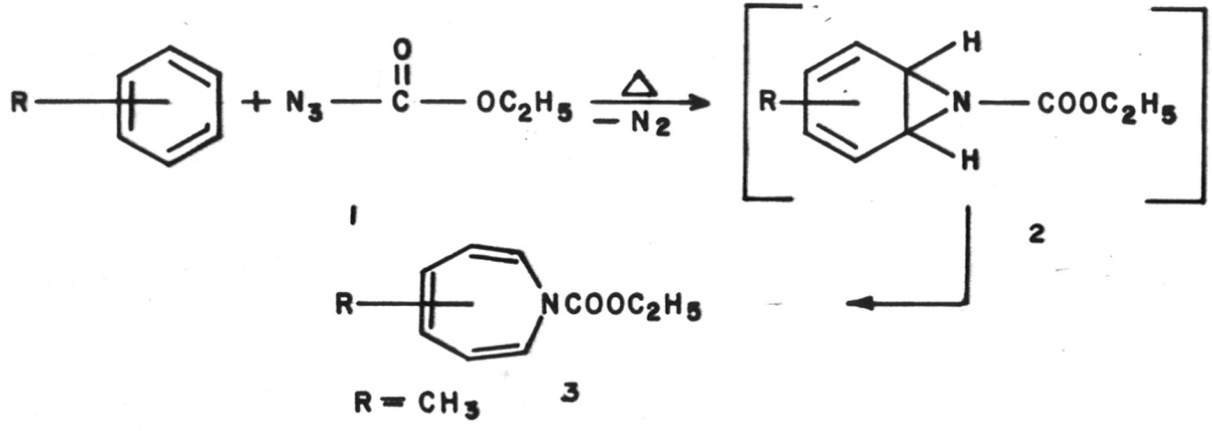
This was prepared by the method described in literature.[19,22] 10.7 g of o-toludine and 5.4 g of ethylchloroformate in 100 ml of tetrahydrofuran were stirred at room temperature for 30 minutes. The precipitated hydrochloride salt was removed by filtration and the filtrate was concentrated in vacuum to give 2a. Recrystallized from ether-hexane, m.p. 46°C (Lit.[26] m.p. 46°C).

Preparation of methyl-N-carbalkoxyazepines

Synthesis of substituted azepines has been reported by various workers by photolysis and pyrolysis[24,25] methods. The pyrolysis method involves generation of carbalkoxynitrene by thermolysis of alkyl azidoformates which adds to carbon-carbon bonds of aromatic nuclei. With substituted aromatics, carbalkoxynitrenes have been reported to add indiscriminately and do not show any selectivity. Hafner and colleagues[27]



SCHEME 9



SCHEME 10

report that 2,3 and 4-methyl-N-carbethoxyazepines are formed in the ratio of 1:1.2:1.3. Baldwin et al[27] report that methyl-N-carbomethoxyazepine isomers are formed in the ratios of 1.2:1:1.2. Carboethoxynitrene and carbomethoxynitrene therefore display no appreciable selectivity in reactions with toluene. Photis[28] also reports formation of the isomeric azepines with substituted aromatics and has developed a procedure for isolation of α-alkyl(2-alkyl)-N-carbethoxyazepine. The success of the reaction is attributed to a slower rate of hydrolysis of α-(2-alkyl) substituted isomer as a consequence of their steric hindrance about nitrogen and ester group.

Paquette et al[29] have also described preparation of specifically substituted 1H-azepines, which consists of electrophilic addition of iodineisocyanate to 1,4-dihydrotoluene derivative. Cyclization of the resulting iodoisocyanate or their derived carbamates with various bases gives rise to unsaturated aziridines which after bromination and dehydrobromination give the desired 1H-azepine. This method is reported[29] to give low yields of azepines.

2-Methyl-N-carbethoxyazepine 2b

We have prepared and isolated (2b) from the mixture of methyl substituted azepines by thermolysis of ethyl azidoformate in toluene by the method described by Photis[28] (Scheme 10).

2.5 g of ethyl azidoformate was added to 30 ml of toluene and the solution was heated under reflux to 125°C in an oil bath for two hours until the evolution of nitrogen ceased. Vacuum distillation of excess toluene left a viscous oily mixture of crude azepines. GC-MS of this crude mixture was carried out on SE-54 capillary column. Earlier workers[29] attempted separation of the mixture of azepines by preparative SF-96 column but attempts were not successful. No separation could be obtained on ordinary open tubular GC column of SE-30 or OV-17. The mixture could be separated on capillary column SE-54 under following conditions.

I and W fused silica capillary column.

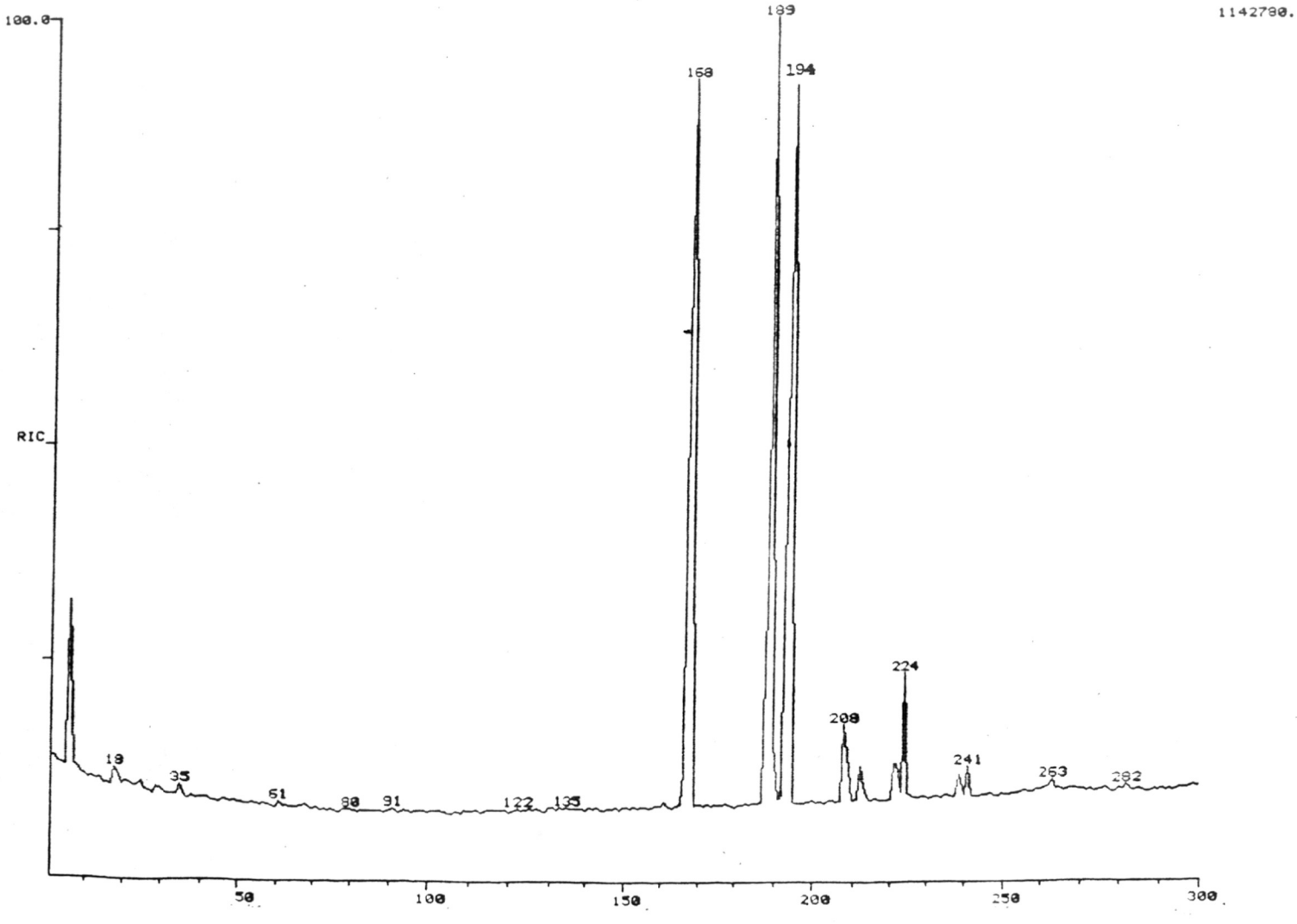
Column dimensions	:	15 M x 0.285 mm
Liquid phase	:	SE-54
Film thickness	:	0.25 μM
Helium gas flow	:	25 ml/min.

Column temperature : Initial temperature 75°C, programming 5°C/min., final temperature 230°C., zone temperature 160°C.

Split/sweep valve time : 40.0 sec.

The GC chromatogram (Fig. 1) showed three major peaks, namely, scan numbers 168, 189 and 194 in ratio 1:1:1 and mass spectral fragmentation and molecular weight 179 was consistant with the expected fragmentation of methyl substituted N-carboethoxyazepines. This shows that the addition of nitrene occurs indiscriminately and there is no selectivity. Earlier workers' observation on the ratio of the three isomeric mixtures were based on the analysis of NMR signals. Our results were based on separation of isomers by capillary gas chromatography.

The mixture of crude azepine was dissolved in 20 ml of 95% ethanol. 6.0 g potassium hydroxide was then added and the mixture was stirred at room temperature for six hours. The dark coloured solution was then poured in 100 ml of water and extracted three times with 30 ml portions of ether.


100.0
RIC
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189
168
194
224
208
241
253
282
19
35
51
88
91
122
125
50
100
150
200
250
300

FIG. 1.

The residue from evaporation of the dried ether extract was chromatographed on alumina. Elution with hexane first removed excess toluene and then eluted with benzene gave azepine (2b) fraction. NMR analysis was consistant with that reported in the literature.[28]

PMR ($CDCl_3$): δ 2.06(s), CH_3 S-alkyl substituted.

Ethyl N-(2,5-dicarbmethoxyphenyl)carbamate 3a

The carbamate 3a was prepared by the method described in the literature.[30] 2-Aminoterephthalic acid dimethyl ester (0.1 g), ethyl chloroformate (100 ml) and sodium carbonate (0.1 g) was refluxed for 16 hours. Ethyl chloroformate was removed under reduced pressure and ethyl N-(2,5-dicarbmethoxyphenyl)-carbamate was recrystallized from petroleum ether, white needles m.p. 134°C (Lit.[30] m.p. 134°C).

1-Ethoxycarbonyl-2,5-dicarbmethoxy-1H-azepine 3b

This was prepared by the method described in the literature.[30] Dimethylterephthalate (4.0 g) and acetic anhydride (14.0 g) were heated at 125°C under stirring. Ethylazidoformate (0.4 g) was added gradually under stirring over a period of 30 minutes.

The reaction mixture was maintained at the same temperature for two hours. After completion of the reaction, acetic anhydride was removed under reduced pressure. Unreacted dimethyl terephthalate was removed by repeated crystallization in benzene. The total quantity of dimethylterephthalate was 3.0 g. The remaining residue was adsorbed on silica gel column. Initial elution with petroleum ether gave unreacted dimethylterephthalate (0.05 g). Next elution with petroleum ether:benzene (1:1) gave 1-ethoxycarbonyl-2,5-dicarbmethoxy-1H-azepine 3b. Recrystallized from petroleum ether, deep yellow crystals, m.p. 93°C (Lit.[30] m.p. 93°C). Rest of the fractions were not isolated.

The sulfonanilides 4a, 5a and sulfonylazepines 4b, 5b were purified by recrystallization. These four compounds were gifted from Dr. N.R. Ayyangar, Scientist, Organic Chemistry Division, N.C.L., Pune. Purity of the compounds was checked by TLC and melting points by literature.

p-Toluenesulfonanilide 4a was recrystallized from petroleum ether:benzene (1:1), white needles m.p. 103°C (Lit.[31] m.p. 103°C).

N-p-toluenesulfonyl-1H-azepine 4b was recrystallized from petroleum ether:benzene (1:1), colour pale yellow, m.p. 167°C (Lit.[32] m.p. 169°C).

p-Bromobenzenesulfonanilide 5a was recrystallized from petroleum ether, reddish brown crystals, m.p. 117°C (Lit.[33] m.p. 119°C).

N-p-bromobenzenesulfonyl-1H-azepine 5b was recrystallized from petroleum ether, m.p. 131°C (Lit.[29] m.p. 131°C).

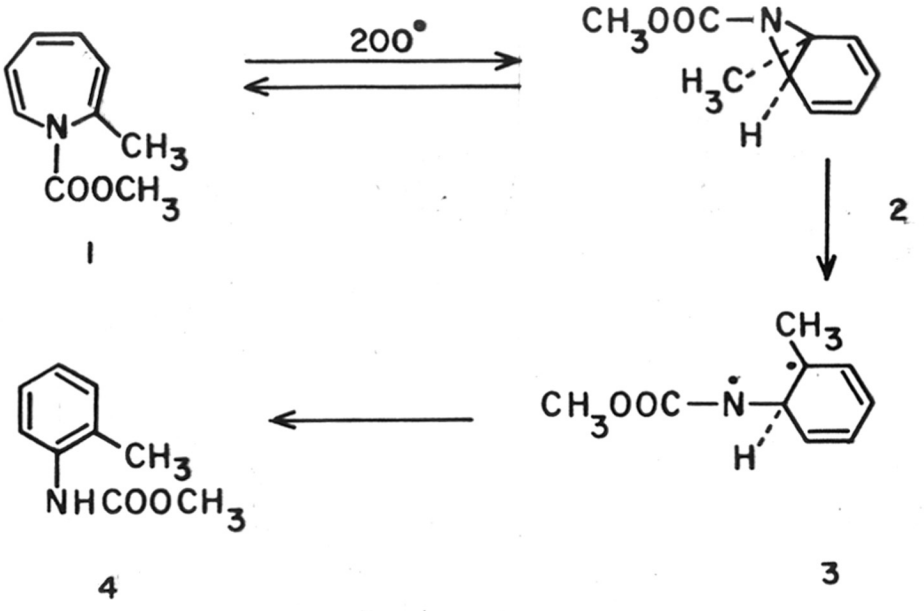
STRUCTURE AND REACTIVITY OF AZEPINES

The heterocyclic seven-membered azepine system contains cyclic array of 8π-electrons. The absence of a driving force for delocalization in this system leads to decreased π electron stability relative to open chain congeners. Huckel's rule predicts marked anti-aromatic polyene character.[34] X-ray studies have indicated that the molecule is not planar and exists in a boat conformation. The reactive nature of azepines is due to this anti-aromatic 8π electron cyclic array driving the system to electrocyclic transformations in the ground and excited states. It therefore,

readily undergoes valence isomerization, dimerization and aromatization under photochemical, thermal and acid catalysed conditions. Alkyl groups on the ring and substituents on nitrogen can have effect on these reactions. The chemistry of azepine has been investigated by Paquette et al.[19,20] This is described briefly below.

Thermal rearrangement: Paquette et al[19,20] reported that N-carbalkoxy-1H-azepines and their 3,4-methyl derivatives undergo dimerization at elevated temperature, 2-methyl-N-carbomethoxy azepine and a number of disubstituted and annelated congeners aromatize or rearrange when heated. They also reported that this behaviour is not shared by 2,7-dimethyl-N-carbomethoxyazepine which is stable upto 250°C but decomposes above that temperature.

Heating of 2-methyl-N-carbomethoxyazepine 1 at 130°C for a period of 2 hr results no reaction, but at 200°C 1 was converted in 64% yield to give aromatic urethane 4 which is shown in (Scheme 11) and as reported by Paquette et al[19]. In this transformation the termini of the π electron system are joined resulting in the formation of benzaziridine



THERMAL REARRANGEMENT OF MONOCYCLIC 1H-AZEPINES

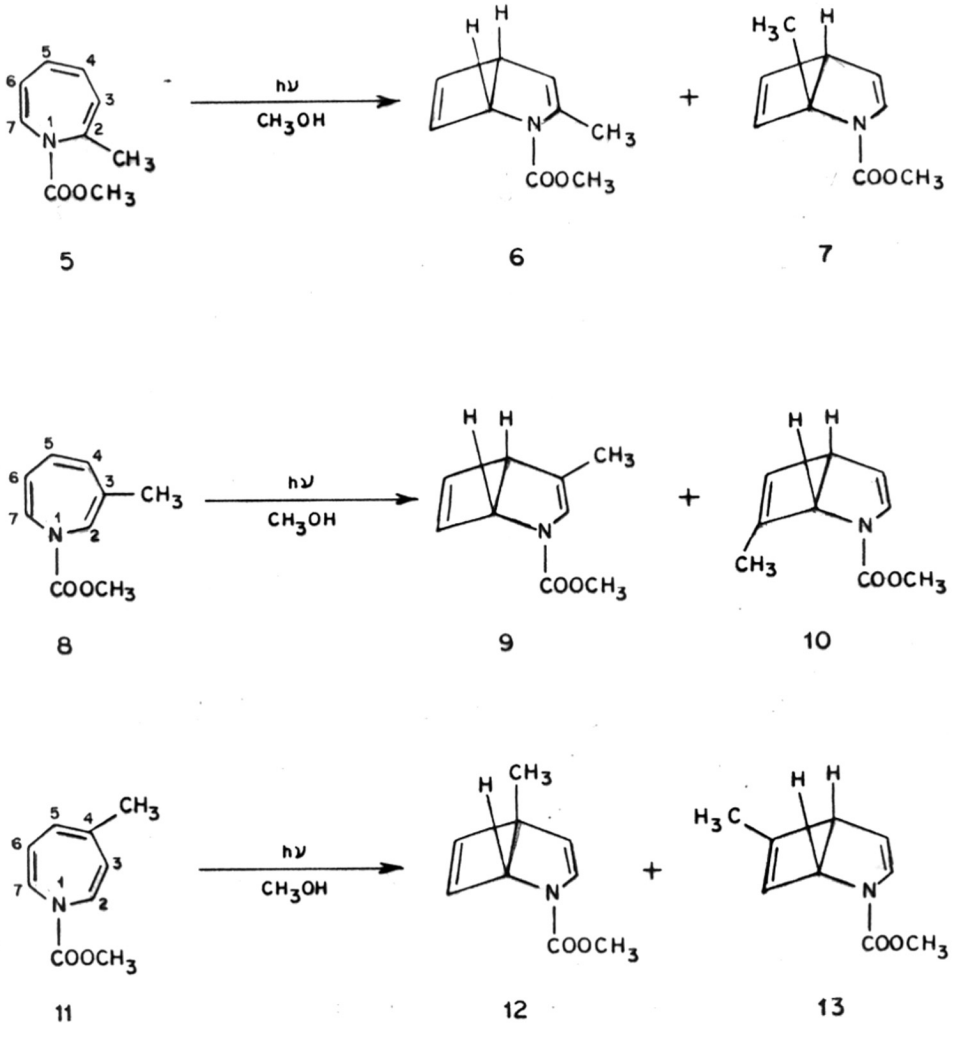
SCHEME-II

intermediate 2. Ring opening following sigmatropic shift of hydrogen results in the formation of 2-methylcarbamate 4. The N-alkoxyazepine are also reported to undergo intermolecular $6\pi + 4\pi$ thermal cycloaddition. The nature of the dimeric products are complex and depend on temperature. Similarly, N-methane sulfonyl-1H-azepines have also been reported[20] to undergo $4\pi + 2\pi$ thermal cycloaddition reaction.

Photochemical transformation: Paquette et al[18] also reported that the irradiation of methanol solution of 2,3 and 4-methyl-N-carbomethoxyazepines with a 450 W mercury arc under nitrogen gives two components mixture containing both possible bicyclic valence tautomers, which is shown in Scheme 12.

Irradiation of 5 was seen to be quite selective leading to 6 and 7 in the ratio of 14:1. However, as reported by Paquette et al, irradiation of 3-methyl isomer 8 gave 9 and 10 in equimolar quantities and photolysis of 11 gave 12 and 13 in the ratio 1.5:1.

8 produces both isomers 9 and 10 in equal amount was not unanticipated, since the photoisomers



5 6 7

8 9 10

11 12 13

PHOTOREARRANGEMENTS OF

2,3 AND 4 METHYL-N-CARBOMETHOXY AZEPINE

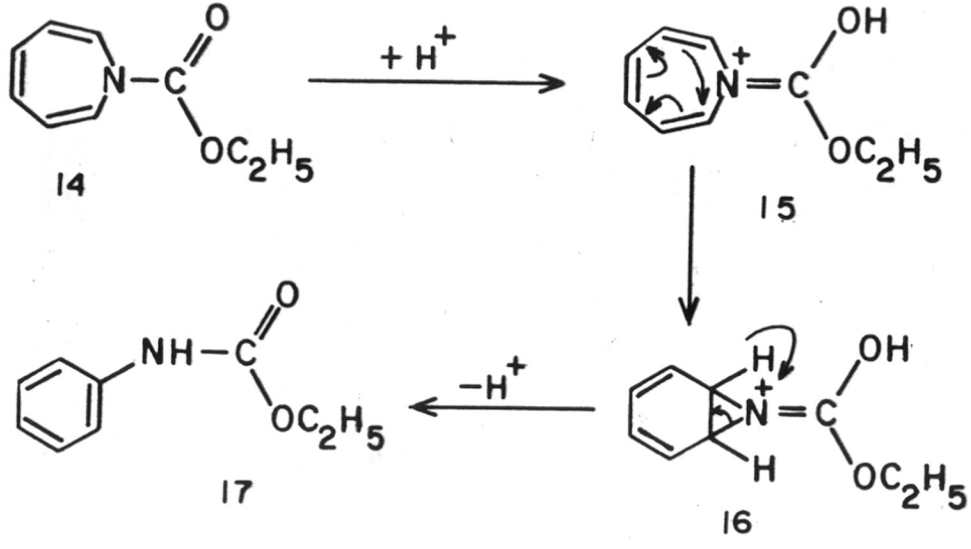
SCHEME-12

are not expected to differ measurably in strain energy. Significantly, however the 4-methyl function in 11 does not exert on overwhelming directive influence in the course of the photoreaction, despite the fact that in 12 the alkyl group is located at an angular position.

Hence they conclude that the presence of a methyl group at an angular position alone does not constitute a significantly strong deterrent to product formation. Rather the selectivity noted in the cyclization of 5 is rationalized on the basis of serious non-bonded interactions between the methyl group and rather bulky substituent on nitrogen as distortion leading to 7. Such a repulsive forces, which are absent in the alternative electrocyclization are apparently sufficient to cause the preferred formation of 6. In contrast the photorearrangement of 8 and 10 are not affected by non-bonded interactions and selectivity is not observed.

Acid catalysed rearrangement: Paquette et al[19] also discussed the acid catalysed rearrangements of these same azepines. Hafner[21] has noted that reaction of N-carbethoxyazepine 14 with dilute acids leads rapidly

to N-phenylcarbamate 17 which is shown in Scheme 13. The transformation proceeds by initial protonation of carbonyl oxygen function followed by formation of aziridine 16 intermediate. Ring opening followed by sigmatropic shift leads to irreversible formation of phenylcarbamate 17.



ACID CATALYSED REARRANGEMENTS

OF 1 H-AZEPINES

SCHEME-13

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CHAPTER III

MASS SPECTROMETRY OF SOME MODEL ANTIAROMATIC AZEPINES AND THEIR AROMATIC ANALOGUES

3.1 INTRODUCTION

Although there are some reports on the mass spectral fragmentation of alkoxycarbonylazepines,[1] isomeric aromatic carbamates,[2,3] sulfonylazepines[4] and aromatic sulphonalides,[5] there has not been a systematic attempt to correlate the mass spectral fragmentations of the isomeric pairs. This is necessary since the antiaromatic azepines are known to undergo bicyclic valence tautomerization,[6] dimerization[7] and aromatization[8] under photochemical, thermal and acid catalysed conditions respectively.

The present work reports on the mass spectra of ethoxycarbonylazepines, sulfonylazepines and their aromatic substrates. The purpose of the study was to examine whether the transformations of azepines reported under photochemical, thermal and acid-catalyzed conditions also occur under mass spectral conditions. The results are supported by electron ionization (E.I.), chemical ionization (C.I.) and low electron voltage, metastable ions and shift techniques in the electron ionization mode.

The isomeric pairs belonging to these classes are reported[5-13] to be thermally unstable and give

complex reaction products in the presence of traces of acids and bases. This creates problems in the identification of these compounds by gas chromatography and mass spectrometry. In the present studies, care was taken to record the mass spectra at as low a temperature as possible and under identical conditions to avoid these complications.

.2 EI AND CI MASS SPECTRAL STUDIES

EI mass spectral fragmentation of N-phenylcarbamate 1a and isomeric N-ethoxycarbonyl-1H-azepine 1b, 2-methyl-N-phenylcarbamate 2a and isomeric 2-methyl-N-ethoxycarbonyl 1H-azepine 2b.

Figures (1 and 2) show the 70 eV mass spectra of 1a, 1b and 2a, 2b. The mass spectra of carbamates 1a, 2a and isomeric azepines 1b, 2b show significant differences. The molecular ion abundances at m/z 165 and m/z 179 in the mass spectra of carbamates 1a, 2a were greater than that of the isomeric azepines 1b and 2b respectively at 70 eV and lower electron volts (Tables 1 and 2). This is ascribed to the greater stability of 6π electron aromatic carbamates 1a, 2a than the antiaromatic 8π electron azepines 1b, 2b. Most of the fragmentation could be ascribed to the localization

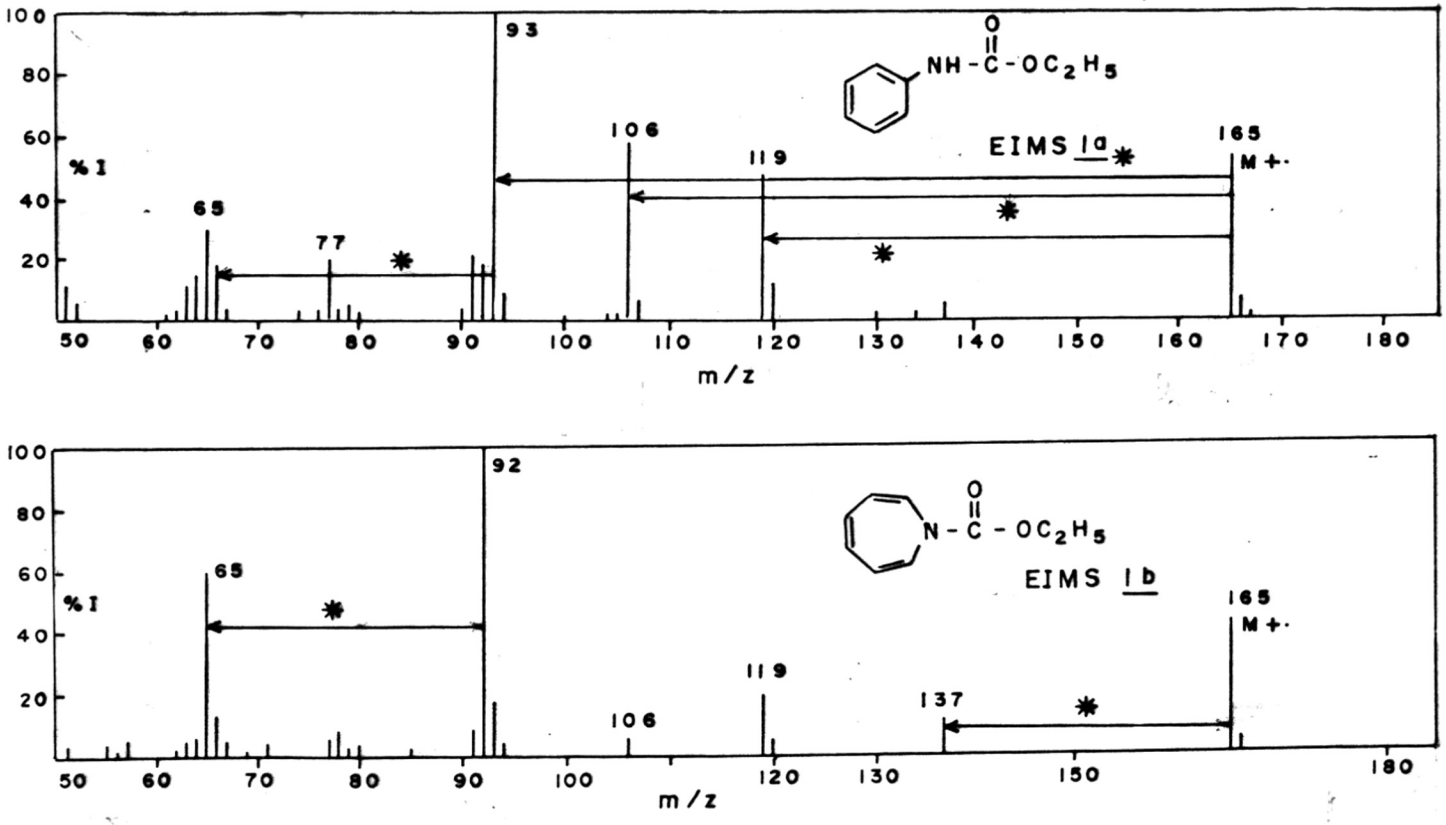


FIGURE -1. EIMS OF N-PHENYLCARBAMATE 1a AND N-ETHOXYCARBONYL -1H-AZEPINE 1b

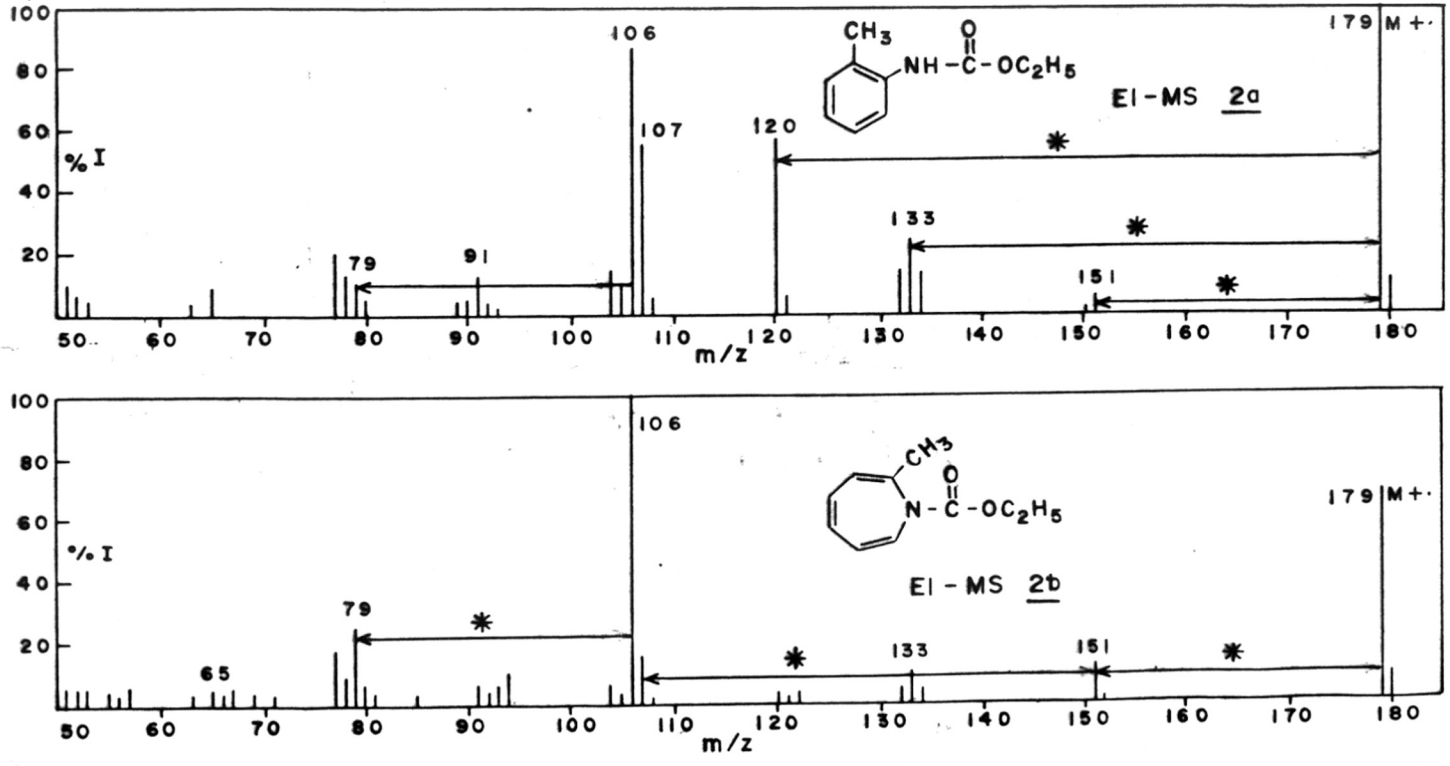


FIGURE-2. EIMS OF ORTHOMETHYL-N-PHENYL CARBAMATE (2a) AND 2-METHYL-N-ETHOXYCARBONYL-1H-AZEPINE (2b)

TABLE - 1

Low electron volts EI mass spectral fragmentation of carbamate 1a and azepine 1b

m/z	70 eV		30 eV		15 eV	
	% I 1a	% I 1b	% I 1a	% I 1b	% I 1a	% I 1b
166	7.0	4.0	8.0	6.0	10.0	9.0
165	53.0	42.0	60.0	50.0	100.0	55.0
137	5.0	12.0	5.0	14.0	5.0	13.0
120	12.0	6.0	10.0	6.0	8.0	5.0
119	47.0	19.0	40.0	19.0	24.0	18.0
107	6.0	-	5.0	-	4.0	3.0
106	58.0	6.0	50.0	6.0	46.0	6.0
94	9.0	4.0	8.0	3.0	5.0	6.0
93	100.0	17.0	100.0	25.0	59.0	24.0
92	19.0	100.0	20.0	100.0	5.0	100.0
91	22.0	8.0	20.0	9.0	3.0	14.0
80	2.0	4.0	-	4.0	-	6.0
79	5.0	3.0	5.0	3.0	-	6.0
78	3.0	8.0	3.0	7.0	-	10.0
77	19.5	6.0	18.0	5.0	-	3.0
71	-	4.0	-	-	-	5.0
67	3.0	6.0	3.0	7.0	-	12.0
66	18.0	13.0	18.0	14.0	4.0	24.0
65	30.0	61.0	27.0	50.0	3.0	52.0
64	15.0	7.0	10.0	5.0	-	6.0
63	11.0	5.0	5.0	-	-	-
57	-	5.0	-	5.0	-	10.0
52	6.0	3.0	-	-	-	4.0
51	12.0	4.0	9.0	3.0	-	3.0
50	6.0	3.0	5.0	3.0	-	3.0

TABLE - 2

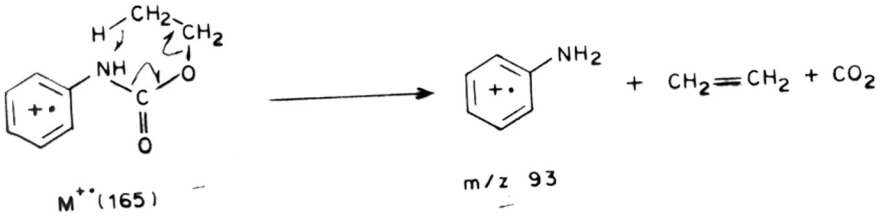
Low electron volts EI mass spectral fragmentation of carbamate 2a and azepine 2b

m/z	70 eV		30 eV		15 eV	
	% I 2a	% I 2b	% I 2a	% I 2b	% I 2a	% I 2b
180	12.0	8.0	12.0	9.0	12.0	9.0
179	100.0	58.0	100.0	60.0	100.0	67.0
151	6.0	12.0	6.0	12.0	4.0	15.0
134	14.0	2.0	13.0	4.0	6.0	4.0
133	24.0	10.0	60.0	15.0	29.0	13.0
132	14.0	5.0	17.0	6.0	6.0	5.0
121	6.0	2.0	6.0	-	6.0	5.0
120	58.0	3.0	62.0	3.0	32.0	-
108	6.0	2.0	6.0	3.0	5.0	-
107	55.0	15.0	45.0	18.0	41.0	19.0
106	86.0	100.0	78.0	100.0	60.0	100.0
105	9.0	3.0	14.0	3.0	6.0	3.0
104	14.0	6.0	28.0	6.0	7.0	6.0
94	-	10.0	3.0	10.0	-	9.0
93	2.0	6.0	3.0	6.0	-	7.0
92	3.0	4.0	3.0	6.0	-	4.0
91	18.0	6.0	16.0	6.0	7.0	6.0
80	4.0	7.0	3.0	8.0	-	9.0
79	11.0	25.0	9.0	30.0	3.0	19.0
78	13.0	8.0	14.0	9.0	3.0	3.0
77	20.0	18.0	16.0	20.0	-	5.0
67	-	6.0	-	5.0	-	5.0
65	9.0	5.0	8.0	3.0	-	-
63	4.0	2.0	3.0	2.0	-	-
57	-	6.0	-	6.0	-	-
53	4.0	6.0	3.0	4.0	-	-
52	7.0	6.0	5.0	3.0	-	-
51	10.0	7.0	7.0	3.0	-	-
50	4.0	3.0	-	-	-	-

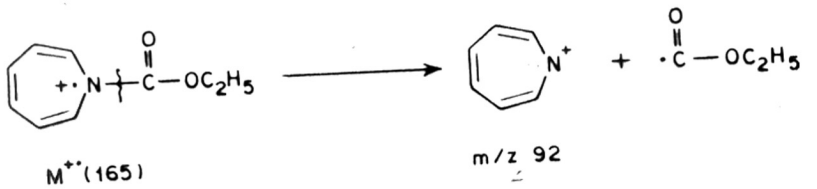
of charge on the nitrogen atom or on the oxygen atom of the carbonyl group. The comparison of the mass spectra reveals that isomers fragment by simple cleavage, hydrogen rearrangement and skeletal rearrangement processes.

Simple cleavage reactions: In the mass spectra of azepines 1b, 2b the base peak is due to azatropylium ions at m/z 92 and m/z 106 respectively resulting from the simple cleavage of N-C bond with the loss of ethoxycarbonyl radical (Schemes 2 and 6). No metastable peaks were observed for the genesis of these ions from molecular ions. These ions fragment further by loss of HCN and C_2H_2. Similar simple cleavage process is not very significant in the spectrum of carbamate 1a and 2a.

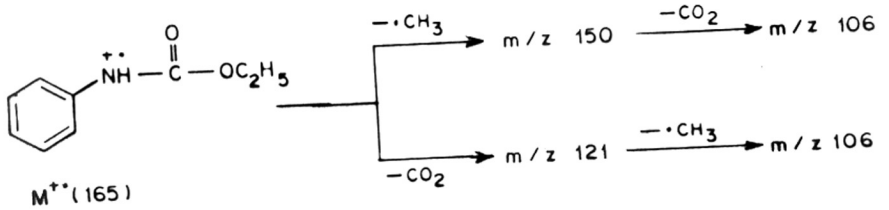
Rearrangements: The comparison of the mass spectral fragmentation processes in the two isomers reveals that simple cleavage of C-N bond competes with hydrogen transfer process. In the mass spectra of the carbamates 1a and 2a, strong peaks at m/z 93 (100%) and m/z 107 (56%) respectively, are due to hydrogen transfer to nitrogen via six-membered transition states. These McLatterty rearrangements



SCHEME – 1



SCHEME – 2



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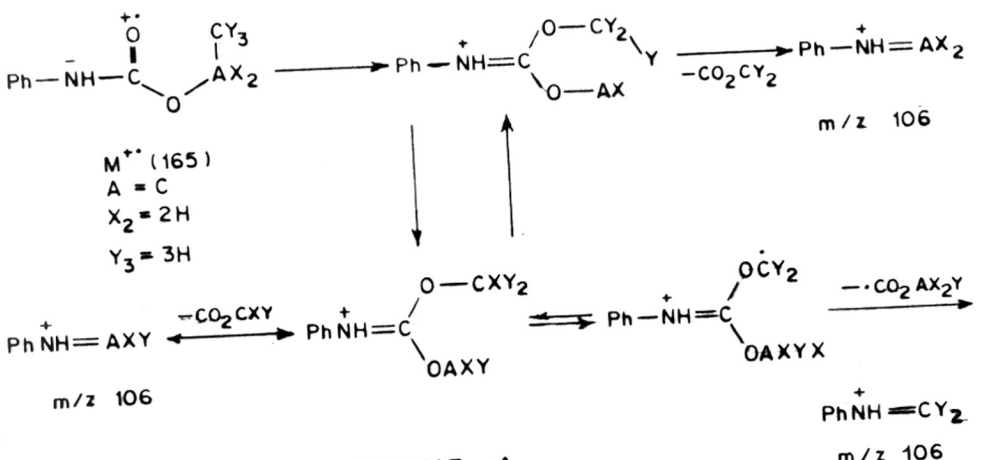

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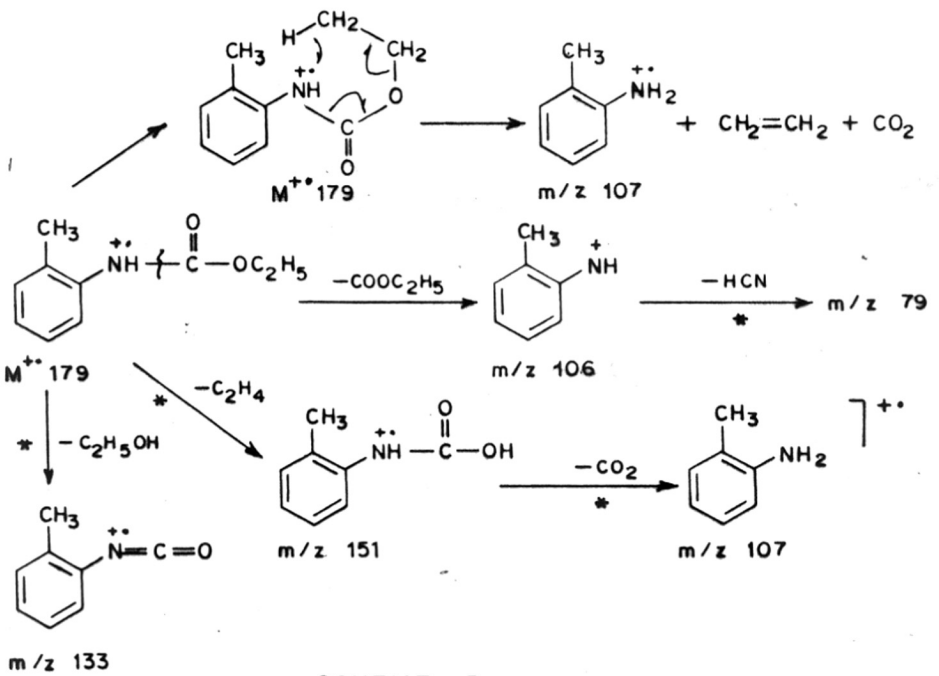

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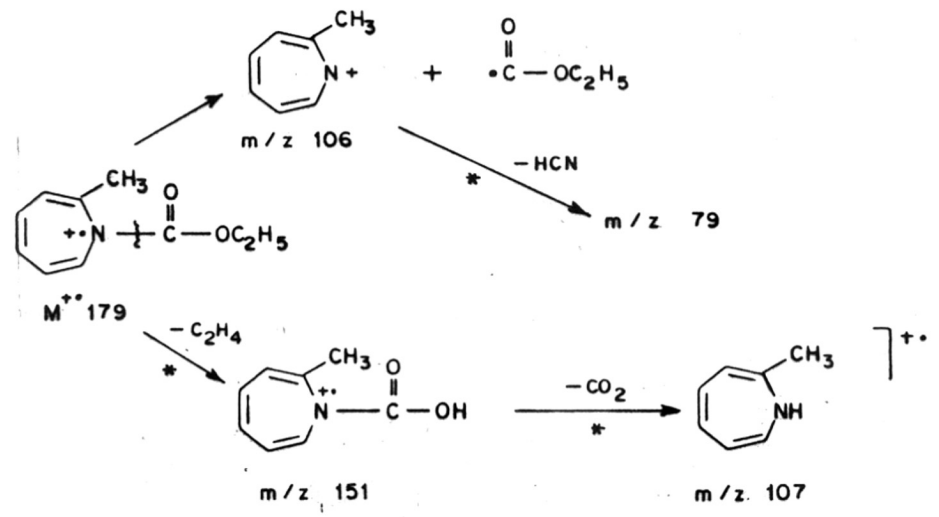


SCHEME – 6.

are favoured in carbamates, whereas they are relatively suppressed in azepines which favour simple cleavage processes. The ratio of intensities of rearrangements and simple cleavage ions in the two isomers are as follows:

m/z 93 (%)/ m/z 92 (%)	1a = 5.0, 1b = 0.2
m/z 107 (%)/ m/z 106 (%)	2a = 0.57, 2b = 0.12

This favoured rearrangement process in the carbamates is ascribed to the stability of the parent and daughter ions in carbamate which correspond to 6π electron aromatic amines, whereas similar hydrogen transfer process in azepines 1b and 2b would lead to antiaromatic 1H-azepinium ions. These azepinium ions are unstable and hence hydrogen transfer is not favoured. The striking difference in the relative intensity ratios of simple cleavage/hydrogen rearrangement ions in the isomeric pairs indicates that thermal or electron impact induced isomerization to common intermediates or equilibration of structures does not occur prior to fragmentation.

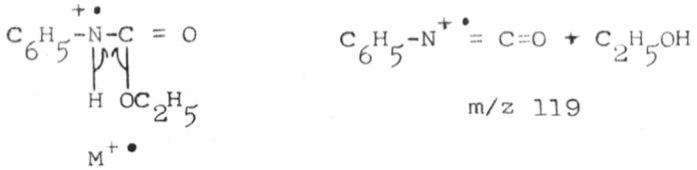
The mass spectra of the isomeric pairs that have been examined in the present studies show peaks

at m/z 93 ($C_6H_7N^{+\bullet}$) and/or m/z 92 ($C_6H_6N^+$). These ions fragment further by loss of HCN and C_2H_2. The structures of these ions are of interest and have been investigated theoretically and experimentally by labelling studies. Dougherty[14] on the basis of analogy between toluene and aniline, has theoretically predicted that the odd electron $C_6H_7N^{+\bullet}$ aniline ion being aromatic should be more stable than antiaromatic azepine ion. Aniline ion therefore should not rearrange to azepine until after β-cleavage which forms protonated even electron nitrene $(C_6H_6N)^+$ ion. These theoretical predictions have been experimentally verified by Djerassi et al[15,16] and Rinehart and coworkers.[17] The mass spectra of 1-^{13}C-aniline, aniline-^{15}N, metastable scans and high resolution studies[15-17] were carried out by these workers to determine the extent of skeletal rearrangements of the C_6H_7N and C_6H_6N ion species. Their studies reveal that the odd electron ion C_6H_7N is nearly unrearranged while the even electron ion C_6H_6N could be largely rearranged. This result is ascribed to the electronic nature of the species viz. the even electron character of the C_6H_6N ion, an even electron ion which would correspond to the tropylium ion.

In view of this extensive studies on these ions we have not investigated the structures of these ions further and assumed that similar conclusions apply to m/z 93 and m/z 92 ions observed in present series.

Polyfunctional molecules containing an ester function have been reported[18-21] to eliminate a molecule of alcohol under electron impact or chemical ionization conditions. The elimination can occur by four or six-membered transition states. In the mass spectra of stereoisomers of bycyclo(4.3.0)-3-nonene skeleton ring annulation and geometric arrangement of bonds have been shown to influence the elimination of alcohols from bicyclic keto esters and related compounds.[19] The hydrogen transferred to the oxygen of the ether moiety could be preceded by cleavage of the ring and this cleavage could be assisted by the π electron system of the molecule.[18,19] In chemical ionization spectra of esters, elimination of alcohol when it competes with loss of other groups such as acid, it has been shown that anchimeric assistance. proton affinity of the departing neutral and steric hindrance influence the fragmentation processes.[19,20]

The mass spectra of isomeric pairs showed loss of 46 mass units corresponding to elimination of ethanol from molecular ions. This could arise by consecutive losses of ethoxyl ($\dot{O}C_2H_5$) and hydrogen radical $^{\cdot}H$ respectively or direct loss of ethanol. Most probably amide hydrogen is involved in elimination of ethanol via four-membered transition state to the ether oxygen since this is supported by metastable transition.



The driving force for this fragmentation is the formation of stable phenylisocynate ion. Similar ethanol elimination from azepine molecular ion is less pronounced. This could be due to abstraction of hydrogen atom from α or β positions of the azepine ring via five or six-membered transition states respectively and formation of less stable product ion. The metastable peak shapes for loss of ethanol from isomeric molecules of carbamate and azepine isomers (1a, 1b), (2a, 2b)

were different indicating that no isomerization to common intermediates has occurred prior to fragmentation.

Skeletal rearrangement: The genesis of the common ion peak at m/z 106 and m/z 120 in the mass spectra of 1a, 1b and 2a, 2b respectively is of interest. Lewis[2] indicated that m/z 106 probably arises due to two processes, viz. loss of carbon dioxide from the molecular ion followed by loss of methyl or loss of methyl followed by carbon dioxide (Scheme 3). We investigated genesis of this ion by metastable technique. No metastable peaks were observed to support the genesis of common ion m/z 106 from either m/z 150 or m/z 121. However, a metastable peak was observed at m/z 68 (Table 3) to support the genesis of this ion from molecular ion. Wunsche[3] has examined the genesis of this ion by deuterium and ^{13}C labelling. The molecular ion undergoes complex rearrangement (Scheme 4) and m/z 106 has multiple precursors. The process is initiated by methyl transfer to the oxygen atom followed by hydrogen exchange. According to Wunsche[3] CH_2 moiety in $C_6H_5NH=CH_2$ is contributed by the both carbon atoms and two of the five hydrogen atoms of OC_2H_5 group.

TABLE - 3

Metastable studies

S.No.	Name of the compound	Metastable transition	Calculated	Observed
1.	N-Phenylcarbamate 1a	$165^{+\bullet} \rightarrow 119^{+} + 46$	85.80	86.0
		$165^{+\bullet} \rightarrow 106^{+} + 59$	68.10	68.0
		$165^{+\bullet} \rightarrow 93^{+} + 72$	52.40	52.5
		$93^{+\bullet} \rightarrow 66^{+\bullet} + 27$	46.80	47.0
2.	N-Ethoxycarbonyl-1H-azepine 1b	$165^{+\bullet} \rightarrow 137^{+} + 28$	113.80	114.0
		$92^{+} \rightarrow 65^{+} + 27$	45.90	46.0
3.	2-Methyl-N-phenyl carbamate 2a	$179^{+\bullet} \rightarrow 151^{+} + 28$	127.40	128.0
		$179^{+\bullet} \rightarrow 133^{+} + 46$	98.80	99.0
		$179^{+\bullet} \rightarrow 120^{+} + 59$	80.50	80.0
		$151^{+} \rightarrow 107^{+} + 44$	75.80	75.5
		$106^{+} \rightarrow 79^{+} + 27$	58.90	59.0
4.	2-Methyl-N-ethoxy carbonyl-1H-azepine 2b	$179^{+\bullet} \rightarrow 151^{+} + 28$	127.40	127.5
		$151^{+} \rightarrow 107^{+} + 44$	75.80	75.5
		$106^{+} \rightarrow 79^{+} + 27$	58.90	59.0
5.	Ethyl-N-(2,5-dicarb-methoxyphenyl) carbamate 3a	$281^{+\bullet} \rightarrow 235^{+} + 46$	196.50	196.0
		$281^{+\bullet} \rightarrow 209^{+} + 72$	155.40	155.5
		$250^{+} \rightarrow 178^{+} + 72$	126.70	127.0
6.	1-Ethoxycarbonyl-2,5-dicarbmethoxy-1H-azepine 3b	$281^{+\bullet} \rightarrow 209^{+} + 72$	155.5	156.0

TABLE -3 (contd.)

7.	p-Toluenesulfonanilide 4a	$247^{+\bullet} \rightarrow 183^{+} + 64$	135.60	135.0
		$247^{+\bullet} \rightarrow 168^{+} + 79$	114.30	114.5
		$155^{+} \rightarrow 91^{+} + 64$	53.40	53.5
8.	p-Toluenesulfonyl-1H azepine 4b	$92^{+} \rightarrow 65^{+} + 27$	45.90	46.0
9.	p-Bromobenzene--sulfonanilide 5a	$311^{+\bullet} \rightarrow 247^{+} + 64$	196.20	196.5
		$92^{+} \rightarrow 65^{+} + 27$	45.90	46.0
10.	p-Bromobenzene sulfonyl-1H-azepine 5b	$92^{+} \rightarrow 65^{+} + 27$	45.90	46.0

Similarly in the spectra of 2a and 2b the common ion peak at m/z 120 as stated above probably arises due to two processes, viz. loss of CO_2 from the molecular ion followed by loss of methyl or loss of methyl followed by loss of CO_2. No metastable peaks were observed to support the genesis of this ion m/z 120 from either m/z 164 or m/z 135, however a metastable peak was observed at m/z 80 (Table 3) to support the genesis of this ion from molecular ion m/z 179.

EI mass spectral fragmentation of ethyl-N-(2,5-dicarbomethoxyphenyl)carbamate 3a and 1-ethoxycarbonyl-2,5-dicarbmethoxy-1H-azepine 3b

Figure 3 shows 70 eV mass spectra of carbamate 3a and azepine 3b. The mass spectra show significant differences in the fragmentation pattern. The greater stability of the aromaticcarbamate 3a as compared to isomeric antiaromatic azepine 3b is reflected in the greater molecular ion abundance [3a $M^{+\bullet}$(40%), 3b $M^{+\bullet}$(8%)] and also the percentage of the total ion current [3a % $M^{+\bullet}$(11.0), 3b % $M^{+\bullet}$(3.0)] in the former. The carbamate function contains active amide hydrogen atom and under electron impact

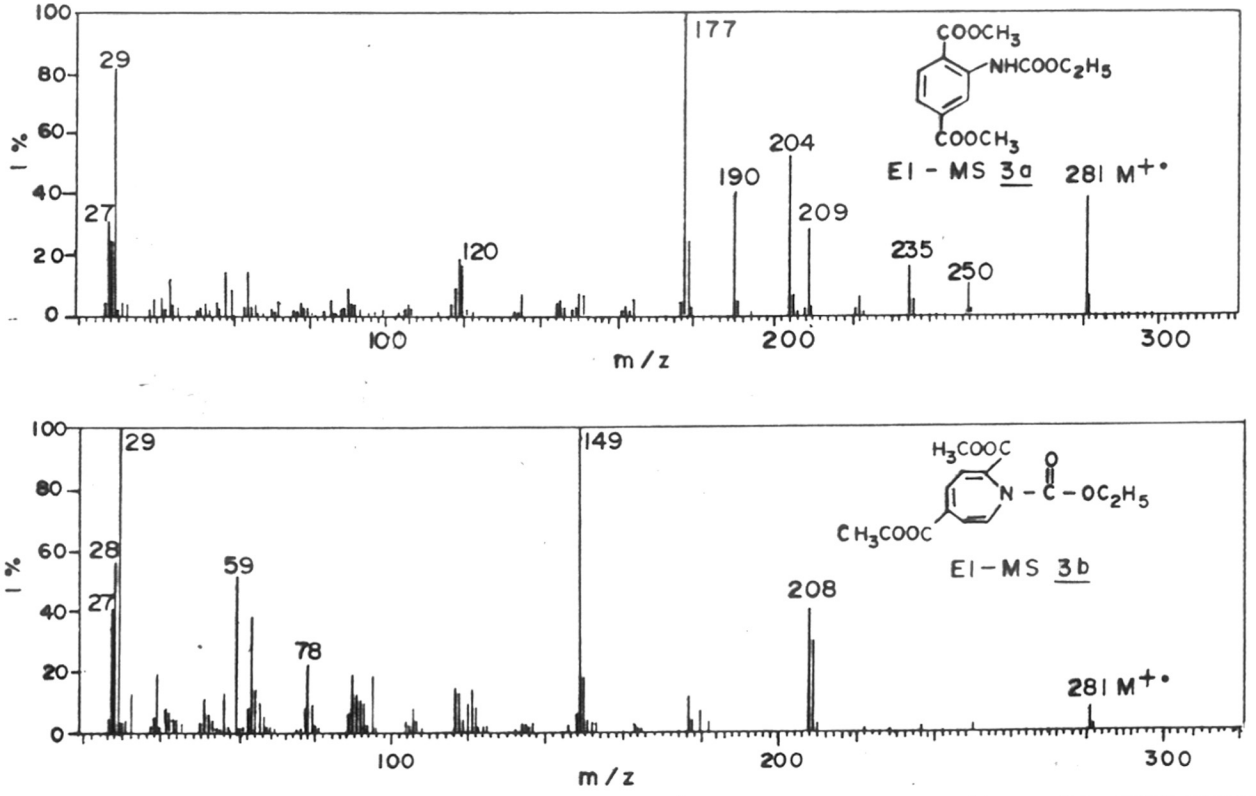
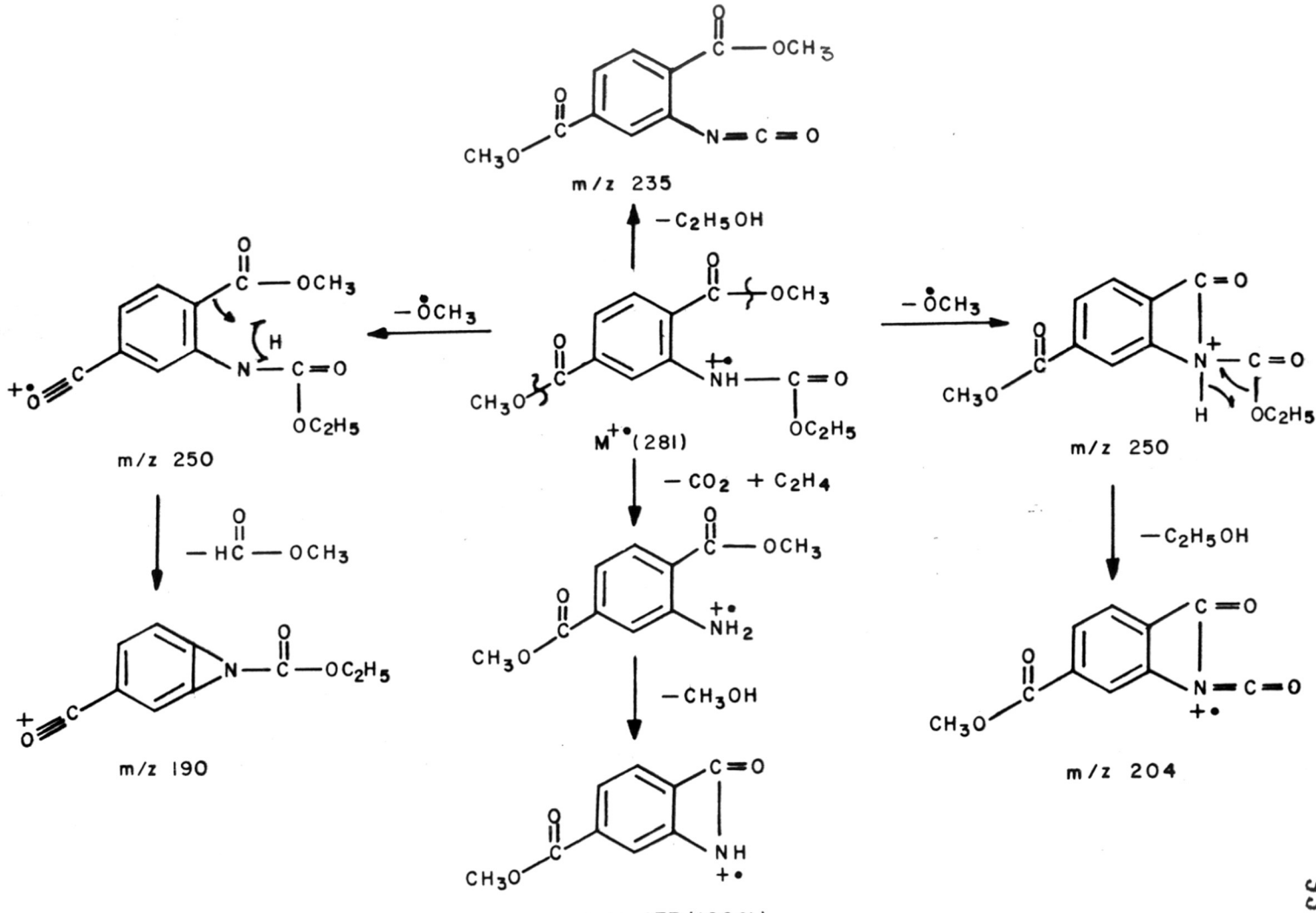


FIGURE-3-EIMS OF ETHYL-N-(2,5-DICARBMETHOXY)PHENYL) CARBAMATE 3a, 1-ETHOXYCARBONYL -2,5-DICARBMETHOXY-1H-AZEPINE 3b

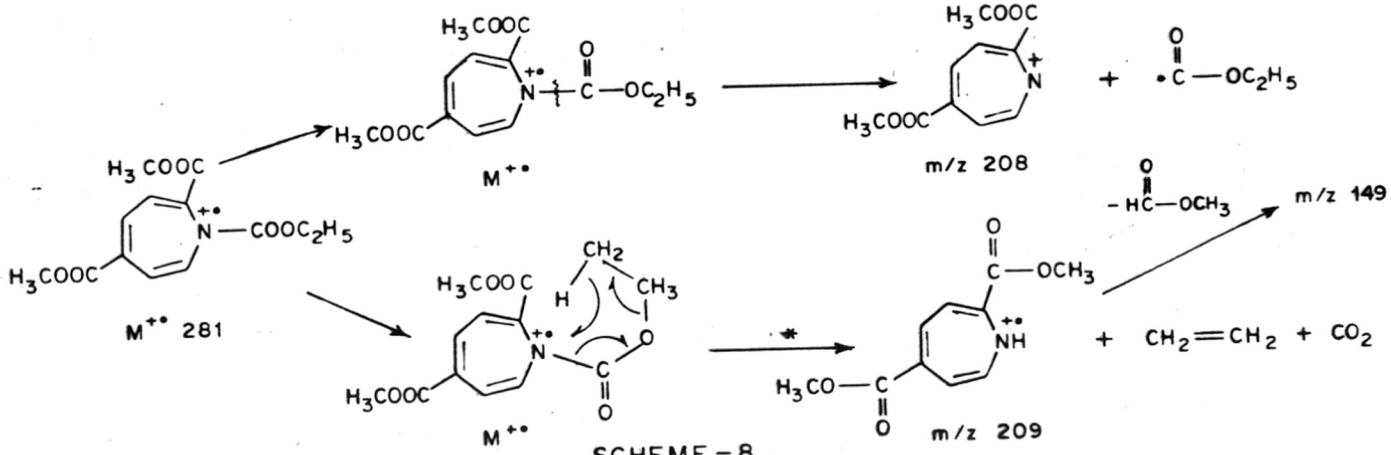
and chemical ionization conditions has been observed to eliminate neutral molecules via a variety of ways similar to thermolytic behaviour of carbamates.[21] The substituted carbamate in addition has two carbomethoxy groups at 2 and 5 positions. One could therefore expect the molecular ion to lose these radicals from 2(ortho) or 5 position resulting in fragment ions to be stabilized by cyclization or quinoid type conjugation. This expectation is realised by the observed fragmentation by loss of methoxyl radical from 2 or 5 position leading to a significant peak at m/z 250 which is stabilized by cyclization or conjugation. Elimination of ethanol further from this ion leads to another significant peak at m/z 204, whereas elimination of $HCOOCH_3$ leads to a strong peak at m/z 190. Methyl hydrogen transfer to amide nitrogen with elimination of $CO_2 + C_2H_4$ from m/z 250 gives rise to m/z 178. Both these elimination reactions involve amide hydrogen atom. The molecular ion also eliminates ethanol leading to substituted phenylisocyanate ion at m/z 235, whereas methyl hydrogen transfer to nitrogen via six-membered transition state with elimination of $CO_2C_2H_4$ leads to m/z 209 which again eliminates methanol to produce base peak at m/z 177. It seems that

mass spectral reactivity is strongly determined by active amide hydrogen as this hydrogen is involved in the elimination reactions leading to the formation of ions at m/z 235, 204, 190 and 177 respectively (Scheme 7). Absence of amide hydrogen atom in azepine leads to different fragmentation pattern. Simple cleavage of N-C bond leading to formation of strong peak at m/z 208 competes with methyl hydrogen transfer to nitrogen leading formation of azepinium ion at m/z 209 (Scheme 8) followed by loss of formate $HCOOCH_3$ to give base peak at m/z 149. The $COOCH_3$ function and hydrogen radical involved in the elimination reaction could arise either from C-2 and C-3 or C-4 and C-5 atoms of the azepine ring respectively. Other peaks at m/z 29 $(C_2H_5)^+$, 59 $(COOCH_3)^+$ might arise from simple cleavage and are not of diagnostic value.

The mass spectral fragmentation analysis of carbamate (1a, 2a, 3a) and isomeric azepine (1b, 2b, 3b) indicates that the intensities of common ion vary significantly and hence we conclude that azepines do not isomerize to carbamates prior to fragmentation.


m/z 235
$-C_2H_5OH$
$-\dot{O}CH_3$
$-\dot{O}CH_3$
m/z 250
$M^{+\bullet}$ (281)
m/z 250
$-CO_2 + C_2H_4$
$-HC(=O)-OCH_3$
$-C_2H_5OH$
m/z 190
$-CH_3OH$
m/z 204
m/z 177 (100%)

SCHEME — 7



SCHEME-8

EI mass spectral fragmentation of p-toluenesulfonanilide 4a and isomeric p-toluenesulfonyl-1H-azepine 4b, p-bromobenzenesulfonanilide 5a and isomeric p-bromobenzenesulfonyl-1H-azepine 5b

The 70 eV EIMS of 4a, 4b and 5a, 5b are shown in Figs. 4 and 5 respectively. The mass spectra of sulfonanilides and isomeric sulfonylazepines show significant differences. In the mass spectrum of sulfonanilide 4a, the molecular ion abundance [4a $M^{+\bullet}$(27.0%), 4b $M^{+\bullet}$(10.0%)] and the total ion current carried by molecular ion [4a % $M^{+\bullet}$(10.0), 4b % $M^{+\bullet}$(5.0)] was greater than that of azepine 4b at 70 eV and lower electron volts (Table 4). Similarly, in the spectrum of sulfonanilide 5a, the molecular ion abundance [5a $M^{+\bullet}$(40.0%), 5b, $m^{+\bullet}$(0.0%)] and the total ion current carried by molecular ion [5a % $M^{+\bullet}$(14.0), 5b % $M^{+\bullet}$(0.0)] was greater than that of azepine 5b. This is ascribed to the greater stability of aromatic sulfonanilide than the antiaromatic sulfonylazepines. The comparison of mass spectra reveals that isomers fragment by simple cleavage and skeletal rearrangement processes.

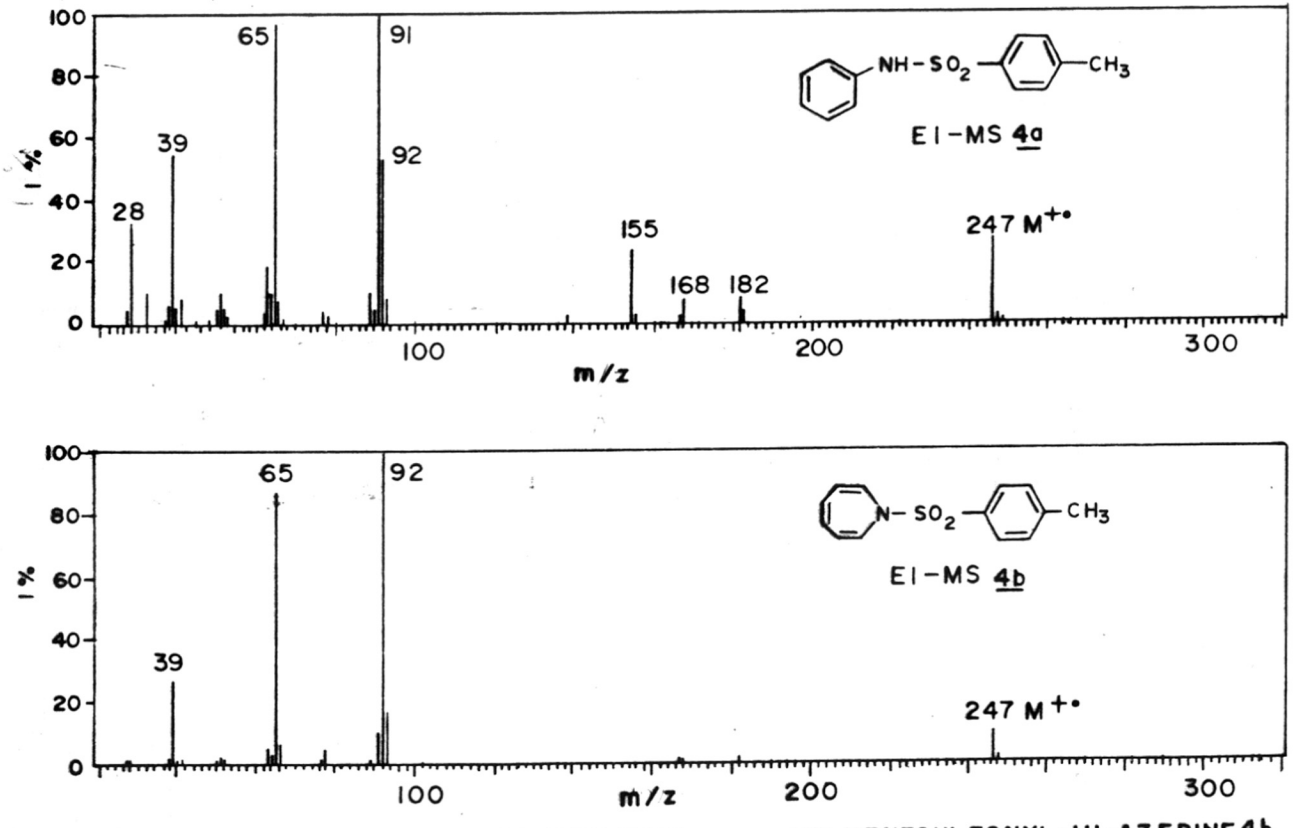


FIGURE 4 - EIMS OF p-TOLUENESULFONANILIDE 4a AND p-TOLUENESULFONYL-1H-AZEPINE 4b

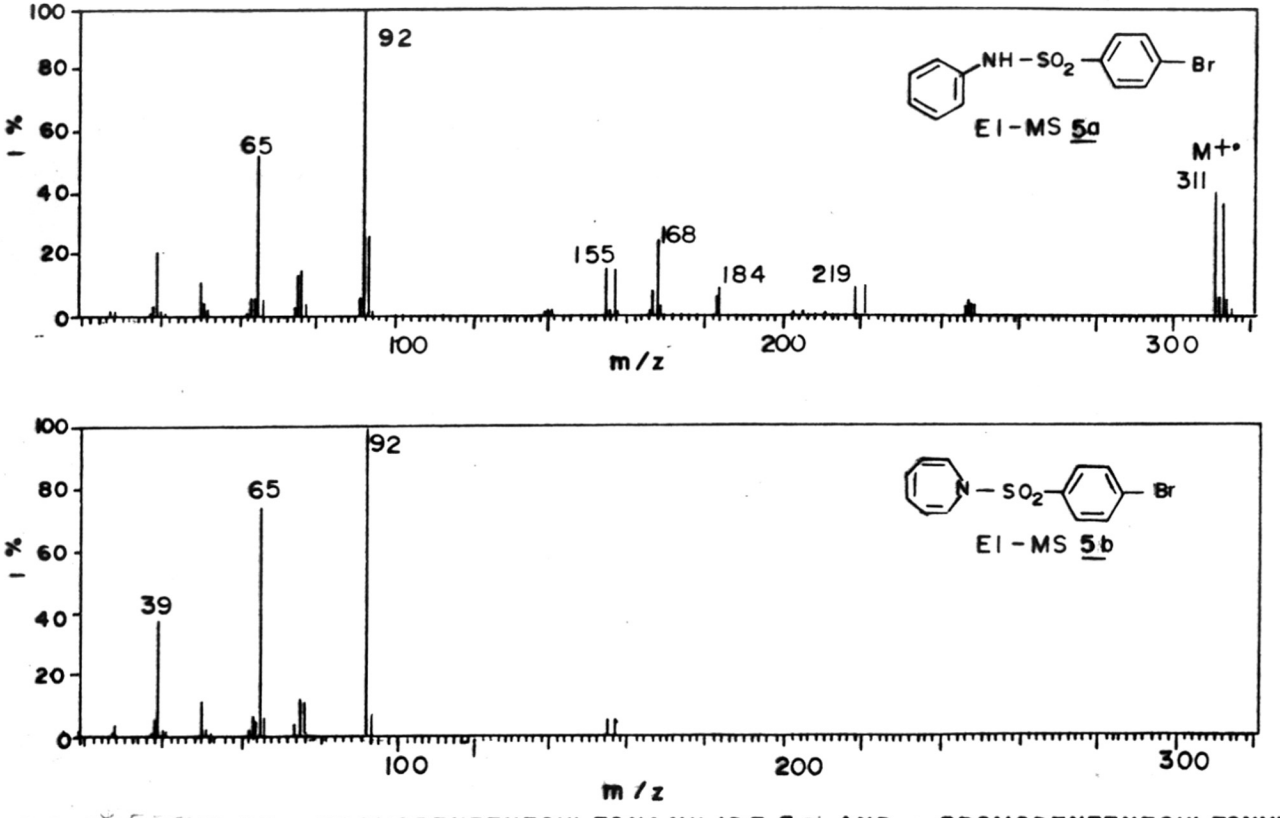


FIGURE 5. EIMS OF p-BROMOBENZENESULFONANILIDE 5a AND p-BROMOBENZENESULFONYL -1H-AZEPINE 5b .

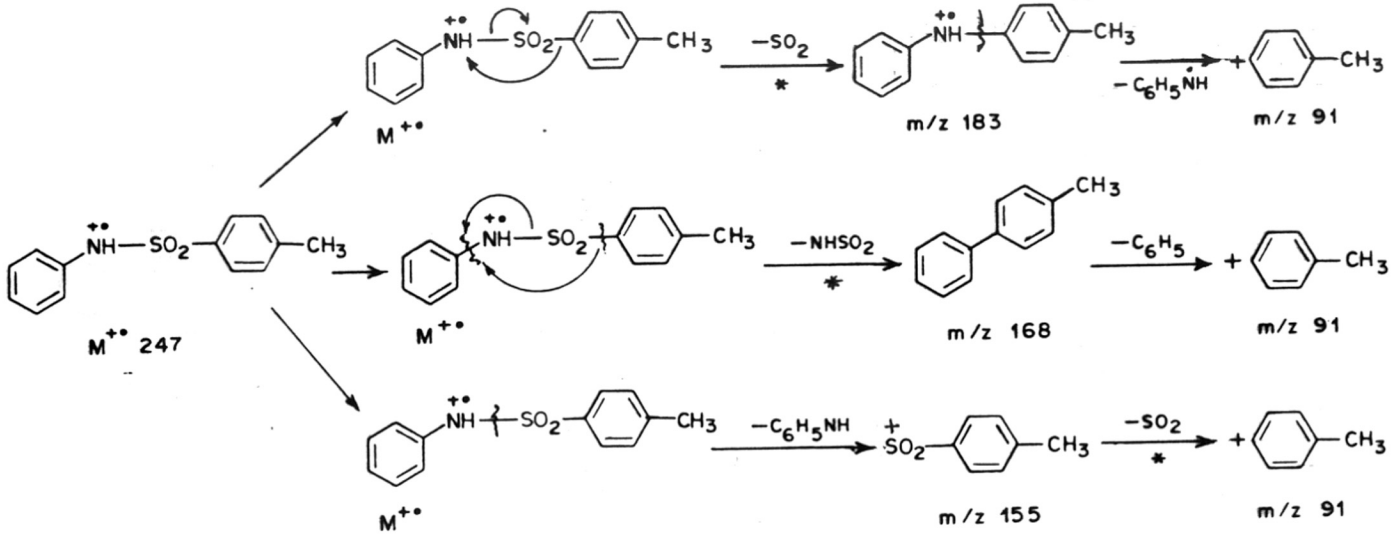
TABLE - 4

Low electron volts EI mass spectral fragmentation of sulfonanilide 4a and sulfonylazepine 4b

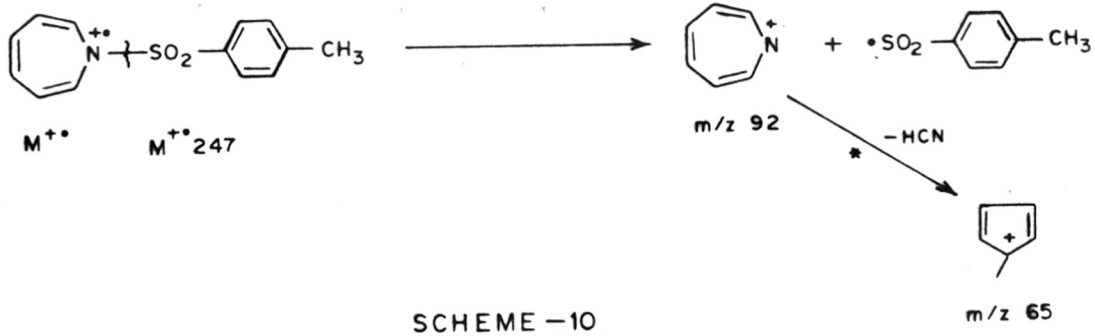
m/z	70 eV		30 eV		15 eV	
	% I 4a	% I 4b	% I 4a	% I 4b	% I 4a	% I 4b
248	3.0	0.0	11.0	9.0	4.0	-
247	30.0	10.0	33.0	15.0	33.0	18.0
183	3.0	-	4.0	-	4.0	-
182	8.0	2.0	20.0	-	15.0	-
168	8.0	2.0	5.0	-	2.0	-
167	3.0	2.0	4.0	-	2.0	-
166	-	-	2.0	-	-	-
155	23.0	-	49.0	3.0	24.0	-
93	8.0	16.0	11.0	9.0	12.0	8.0
92	53.0	100.0	63.0	100.0	70.0	100.0
91	100.0	10.0	100.0	11.0	100.0	3.0
78	2.0	5.0	-	6.0	-	6.0
77	2.0	2.0	3.0	2.0	-	-
67	2.0	-	-	2.0	-	-
66	5.0	5.0	4.0	6.0	3.0	-
65	96.0	86.0	37.0	54.0	29.0	9.0
64	10.0	3.0	3.0	2.0	-	-
63	18.0	5.0	3.0	-	-	-

In the mass spectra of all these compounds a significant peak at m/z 92 is observed which further fragments by loss of HCN followed by C_2H_2 resulting in peaks at m/z 65 and 39 respectively. These m/z 92 ions in the spectra of sulfonanilides are produced by simple cleavage of N-S bond most probably have phenylamine $C_6H_5NH^+$ structure initially, which rearrange to azatropylium ion and those in azepines 4b, 5b could form azatropylium ion structures directly.

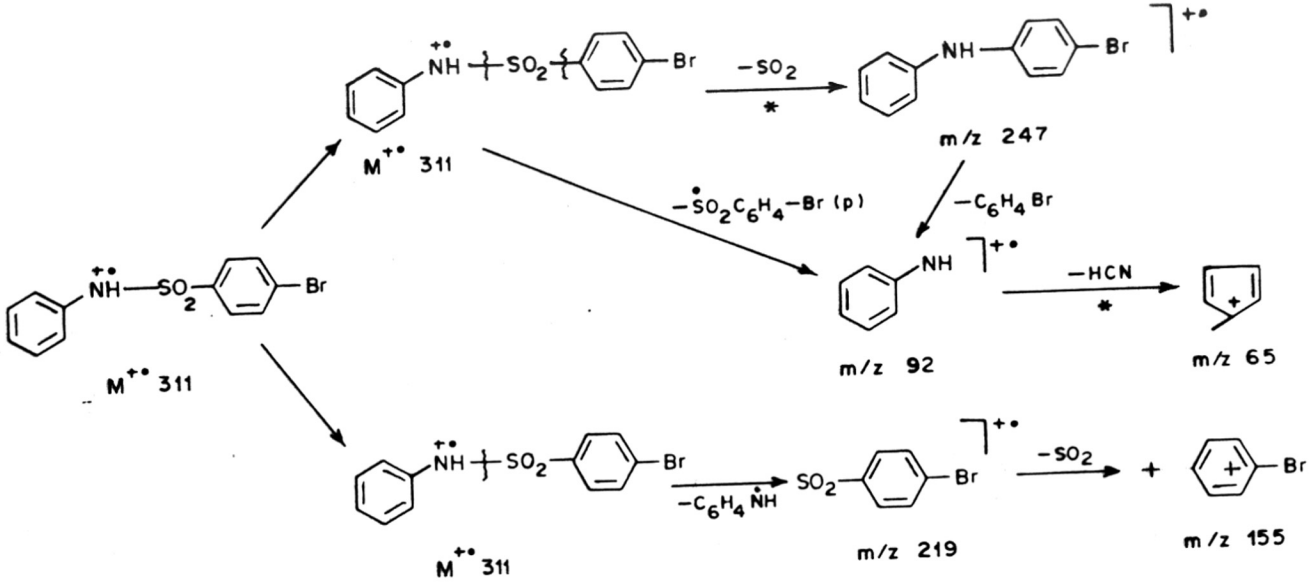
The EIMS of sulfonylazepines show only m/z 92, 65 and 39 significant peaks (Schemes 10 and 12). Other peaks due to hydrogen rearrangement and skeletal rearrangement are absent. In contrast, spectrum of aromatic sulfonanilides shows peaks arising due to loss of SO_2 and HSO_2. In the mass spectrum of 4a, the peaks at m/z 183 and 168 are due to elimination of SO_2 and $NHSO_2$ from molecular ion m/z 247 (Scheme 9). A metastable peaks at m/z 135 and 114.5 was observed to support the losses of SO_2 and $NHSO_2$ from molecular ion (Table 3). The peak at m/z 155 is resulting from simple cleavage of N-S bond with the loss of C_6H_5NH which further looses SO_2 to give base peak at m/z 91 (Scheme 9).



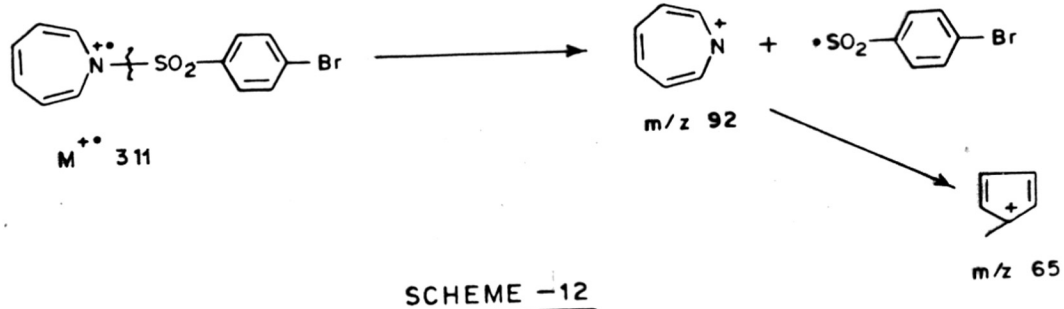
SCHEME – 9



SCHEME – 10



SCHEME — 11



SCHEME —12

A metastable peak at m/z 53.5 (Table 3) was observed to support the loss of SO_2 from m/z 155 to give base peak at m/z 91. The peak at m/z 91 is very small in the spectrum of azepine 4b.

In the spectrum of 5a, SO_2 elimination from molecular ion m/z 311 results peak at m/z 247 which further looses bromine followed by loss of C_6H_4 to give peaks at m/z 168 and 92 respectively (Scheme 11). A metastable peak at m/z 196.5 is observed to support the loss of SO_2 from molecular ion (Table 3). The peak at m/z 219 is resulting from loss of C_6H_5NH from molecular ion which further looses SO_2 to give peak at m/z 155 (Scheme 11). The skeletal rearrangement involve migration of aryl groups via 3 or 4 membered transition states. Similar observations have been noted on elimination of SO_2 ions in the spectra of sulfonylureas[22], sulphonamides[23] and sulfones.[24] The aryl analogs exhibited peaks in their mass spectra corresponding to skeletal rearrangements involving aryl migration with elimination of SO_2 from their molecular ions, but this fragmentation is absent in alkyl analogs.[24] This is due to the nature of migrating

groups which migrates as a nucleophile to the electrophilic centre in the molecule. In the present system SO_2 elimination from the molecular ion of sulfonylazepines 4b and 5b could not be observed. This is ascribed to the electronic nature of migrating species namely azepine which is antiaromatic in character.

The mass spectral analysis indicates that the intensities of common ion vary significantly and showed different fragmentation pattern. Hence, it is concluded that sulfonylazepines do not isomerize to sulfonanilides prior to their principle fragmentation and retain their antiaromatic character.

Metastable ion studies

The metastable transitions reported in Table 3 were recorded on CEC-21-110B Mass spectrometer. They occur in the second field free region of the mass spectrometer. They were recorded in order to characterise parent/daughter ion relationship and to gain information on the structures of the fragmenting ion. Most of the metastable transitions were associated with hydrogen rearrangement and skeletal rearrangement processes. Peak shapes have

not been given here. The peak shapes associated with common fragmentation modes in isomeric pairs were different indicating that no isomerization to common intermediates takes place.

Chemical ionization mass spectral fragmentation of N-phenylcarbamate 1a and isomeric N-ethoxycarbonyl-1H-azepine 1b, 2-methyl-N-phenylcarbamate 2a and isomeric 2-methyl-N-ethoxycarbonyl-1H-azepine 2b.

N-phenylcarbamate 1a has also been named in literature as phenylurethane, ethyl phenylcarbamate and ethyl carbanilate.[12,13] Compounds belonging to this class have been reported to produce complex reaction products on pyrolysis. Carbamates decompose to phenylisocyanate, aniline and alcohol when heated to 200°C. The phenylisocyanate further react producing dimers, trimers, biurates, allophanates, etc. depending on the nature of the substance, temperature and presence of basic or acidic catalysts.[12,13]

The chemical ionization mass spectra were recorded on JEOL D-300 instrument. An attempt was made to record the spectra at lowest temperatures. However, in this instrument the CI spectra could only

be recorded above source temperature of 150°C. Due to this temperature limitation and presence of acidic species in the chemical ionization plasma, the CI-MS spectra were complex due to thermal decomposition products. The CI-MS of carbamate 1a was simple and showed base peak at m/z 166 due to protonated molecular ion which fragments by loss of ethoxycarbonyl function to produce aniline ion at m/z 93. Small peaks at m/z 106 and m/z 272 [MH^+ + 106] are due to the thermal decomposition and ion-molecule reactions respectively. The CI-MS of azepine 1b in contrast, was complex due to the thermal instability of azepines at high temperatures and in acid catalysed reactions. According to Paquette et al,[6,7] azepines undergo thermal dimerization reactions by cycloadditions and the nature of products depend on the temperature and substituents. The CI-MS of azepine 1b showed significant protonated molecular ion at m/z 166 and another strong peak base peak at m/z 332. Thermal dimerization of neutral azepine (MW 165) followed by protonation should produce a peak at m/z 331. However, peak at m/z 331 was very small and the base peak was observed at m/z 332. This

corresponds to the dimerization of protonated molecular ion [M+H 166], which is not likely. Most probably protonated azepine molecular ion seems to have undergone acid catalysed isomerization to phenylcarbamate which decomposes to phenylisocyanate. The phenylisocyanate then dimerizes and reacts with aniline producing biurate MW 331. The peak at m/z 332 is due to protonated biurate. The sequence of reactions is represented by the following steps. Formation of biurate from phenylcarbamate by thermal reactions has been reported in literature.[12]

Protonated azepine $\xrightarrow{O}$ Protonated carbamate $\xrightarrow[\Delta]{200^{\circ}}$

phenylisocyanate $\rightarrow$ Dimeric product $[C_6H_5\text{-}N{=}C{=}O]_2$ $\xrightarrow[\Delta + \text{Amine}]{160^{\circ}}$

Biurate $C_6H_5\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}N(C_6H_5)\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}C_6H_5$ (MW 331)

The CI-MS behaviour carbamate 2a and azepine 2b was similar. The carbamate 2a showed the expected protonated molecular ion at m/z 180 but strong peak at m/z 181 (100%) is difficult to explain. Other peaks in the CI-MS of 2a were insignificant. Similarly, azepine 2b showed expected protonated molecular ion at m/z 180 (100%). The peaks at m/z 181 and m/z 360 were also strong and indicate

thermal dimerization reactions. The peak at m/z 360 could be due to protonated biurate

(CH_3)-C_6H_4-NH-C(=O)-N(C_6H_5)-C(=O)-NH-C_6H_4-(CH_3) MW 359.

The fragmentation of these two species 2a and 2b was complex due to thermal decomposition and ion-molecule reactions and conventional CI-MS technique is not suitable to gain structural information of these isomers. Recently, Cairns et al[21] have recommended chemical ionization of carbamate under LC-MS conditions and thermospray techniques, to overcome some of these difficulties.

CI mass spectral fragmentation of ethyl-N-(2,5-dicarbmethoxyphenyl)carbamate 3a and 1-ethoxycarbonyl-2,5-dicarbmethoxy-1H-azepine 3b

The methane CI mass spectra of the carbamate 3a and azepine 3b are shown in Fig. 6. Both of them show significant protonated molecular ions.

Site of initial protonation: Since the molecules contain six oxygen atoms and one nitrogen atom, initial protonation on these heteroatoms leading to a mixture of heterogeneous protonated quasimolecular ions is quite possible. The relative abundance of the $[M+H]^+$ ions is due to the different stabilities

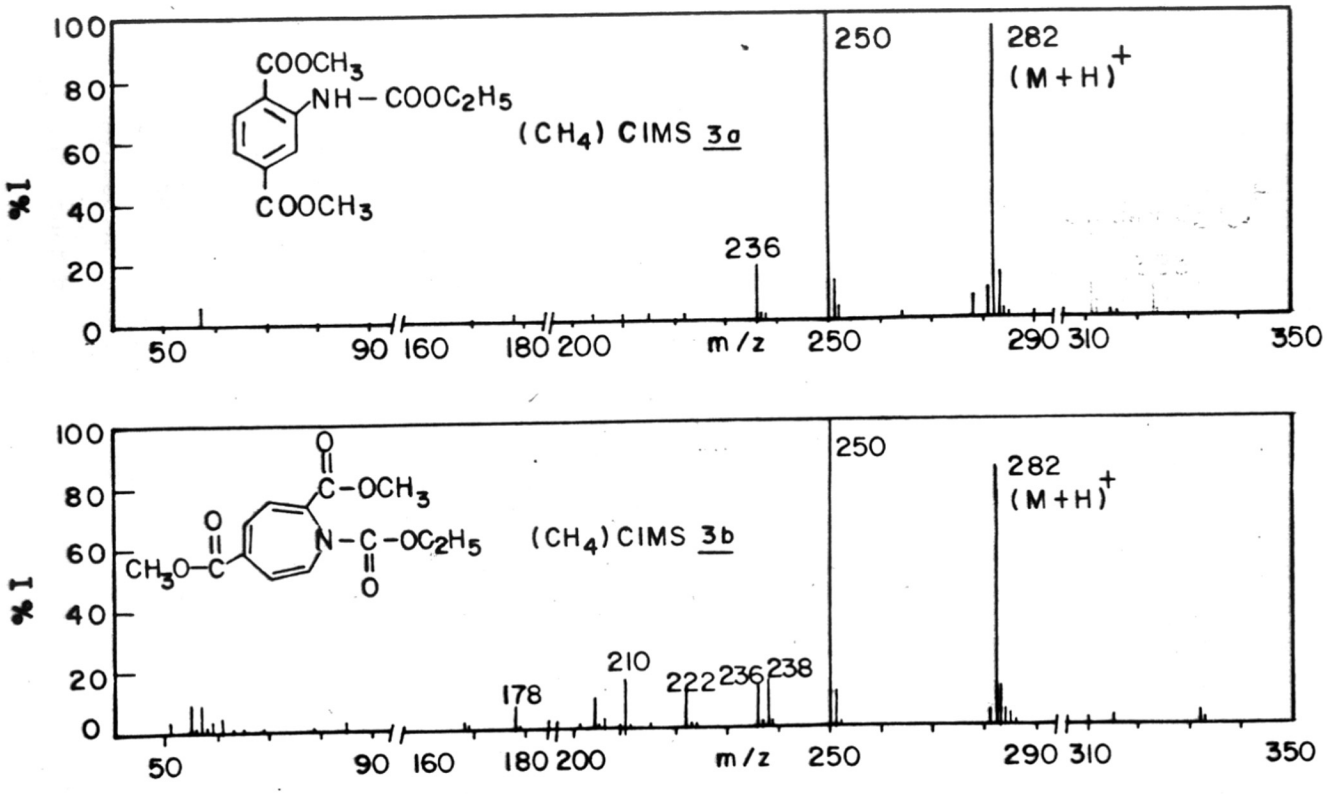


FIGURE 6. METHANE CI MASS SPECTRA OF ETHYL-N-(2,5-DICARBMETHOXY PHENYL) CARBAMATE 3a AND 1-ETHOXYCARBONYL-2,5-DICARBMETHOXY-1H-AZEPINE 3b

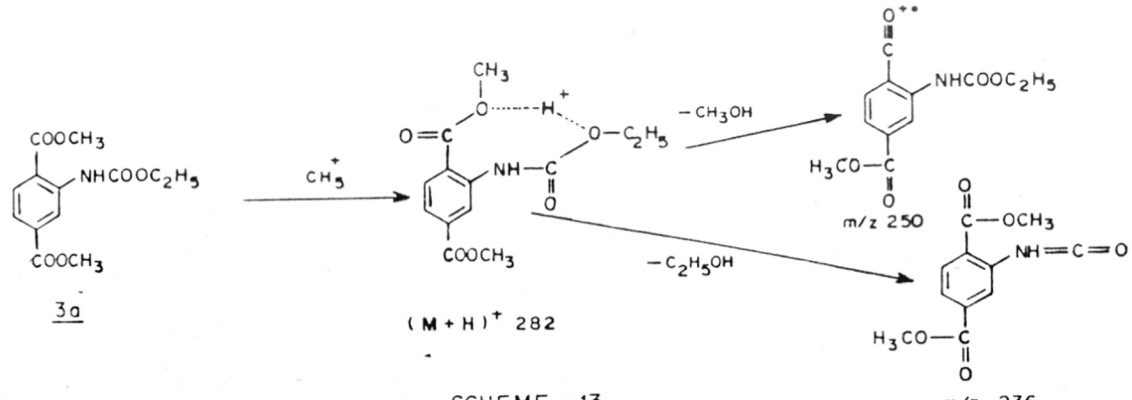
of these heterogeneous quasimolecular ions and different exothermicities of the localised proton transfer reactions. The exothermicities of the proton transfer depend on the differences between proton affinity values of the functional groups and conjugate base of the reagent ion. This concept of initial proton transfer at various sites which initiates localised fragmentation is helpful in the identification of functional groups. Hydrogen bonding in protonated molecular ions of specific bifunctional compounds has also been ascribed to greater relative quasi-molecular ion abundances.[25] The proton transferred can link two functional groups forming a stable cyclic structure and makes the proton affinity of the molecule greater than that of either mono-functional compound. In conformationally mobile systems, macrocyclic structures with proton bridged structures as large as fortynine-membered rings have been indicated[26] to be formed under CI-MS conditions. In the present system of carbamates and azepines the greater stability of protonated molecular ions could be due to such several ring structures formed due to hydrogen bonding between the proton transferred and ether oxygen atoms of the two carbomethoxy groups

and ester functions (Scheme 13).

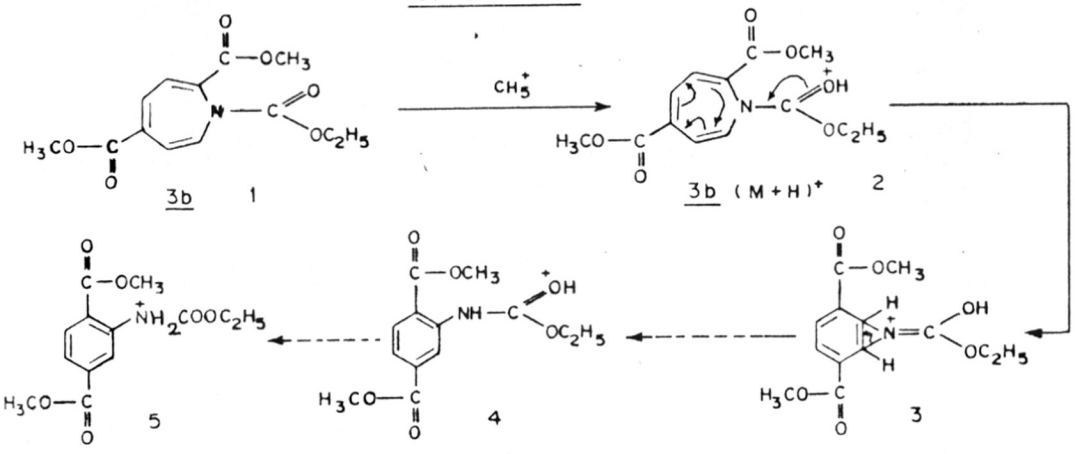
Protonated molecular ions in CI-MS have been observed to undergo elimination reactions. According to Field[27] the tendency of the protonated molecular ions to eliminate group XH is inversely correlated with the proton affinity of the departing neutral.

$$RXH^+ \rightarrow R^+ + XH$$

The extent of elimination reaction as measured by R^+/RXH^+ is inversely proportional to the proton affinity of the departing neutral XH. When several functional groups are present in a molecule, protonated molecular species can undergo competing elimination reactions. If Fields[27] correlation holds for competing elimination reactions, then greater fragmentation should be observed with elimination if larger proton affinity of the neutral molecule. This prediction has been found to be valid for competing elimination of neutral molecules under CI-MS conditions by Harrison et al.[28]



SCHEME — 13



SCHEME — 14

The principal fragmentation of the substituted carbamates and azepines is observed to be elimination of methanol and ethanol respectively (Scheme 13). Protonation of either of the two ether oxygen atoms of the 2,5-dicarbomethoxy groups or oxygen atom of $NH-\overset{O}{\overset{\|}{C}}-OC_2H_5$ function followed by heterolytic cleavage of the bond leads to the two elimination reactions. Recently Cairns *et al*[21] have reported CI-MS fragmentation of carbamates in which protonated departing neutral such as, alcohols and isocyanates were observed. The results were rationalised in terms of proton bound complex. The protonation of ether oxygen in the carbamate is followed by intramolecular amide hydrogen transfer. The proton bound bimolecular complex then adopts various potential neutral molecules prior to fragmentation.

In the present system, peaks corresponding to protonated methyl alcohol (CH_3-OH_2) and ethyl alcohol ($C_2H_5-OH_2$) were not observed and formation of proton bound bimolecular complex indicated by Cairns *et al*[21] is not indicated. The extent of methanol elimination as measured by

$$\frac{\% \text{ m/z } 250}{\% \text{ m/z } 282} = \frac{(MH-CH_3OH)^+}{(M+H)^+}$$

was greater than that of ethanol elimination.

$$\frac{\% \text{ m/z } 236}{\% \text{ m/z } 282} = \frac{(M-C_2H_5OH)^+}{(M+H)^+}$$

The values of methanol and ethanol elimination for the isomers are 3a, 1.05 and 0.21; 3b, 1.20 and 0.18 respectively.

The greater elimination of methanol is certainly due to the presence of two carbomethoxy groups which opens two channels for eliminations. However, it could be due to lower proton affinity,[29] of methanol (PA 757 K.J./mole) than that of ethanol (PA 787 K.J./mole) which explains the results according to Field's prediction.[27]

The CI mass spectral fragmentation of azepine 3b shows similar relative intensities of protonated molecular ions and product ions corresponding to the two elimination reactions. N-carboethoxy azepines are reported to isomerize to carbamate under acid catalysed conditions by Paquette et al[7] and Hafner and co-workers.[8] Since acid catalysed reactions in solutions have analogies to gas phase chemical ionization reactions,[25] probably isomerization of azepine 3b to carbamate 3a

by similar mechanism is possible (Scheme 14). The isomerization is initiated by the initial proton transfer to the carbonyl oxygen atom of the carbomethoxy group leading to aziridine intermediate 3. Sigmatropic shift of hydrogen atom followed by ring contraction leads to aromatization prior to fragmentation. Hence it is concluded that at least part of the fragmentation reactions of azepines occur after isomerization to carbamate.

CI mass spectral fragmentation of p-toluenesulfonanilide 4a and isomeric p-toluenesulfonyl-1H-azepine 4b, p-bromobenzenesulfonanilide 5a and isomeric p-bromobenzenesulfonyl-1H-azepine 5b

The CI-MS of 4a, 4b and 5a, 5b are shown in Figs. 7 and 8 respectively. In the CI-MS of all the compounds intense protonated molecular ion is observed.

Site of initial protonation: Since these molecules contain one nitrogen, one sulphur and two oxygen atoms together with heterocyclic rings, initial protonation on these sites leading to a mixture of heterogeneous protonated quasimolecular

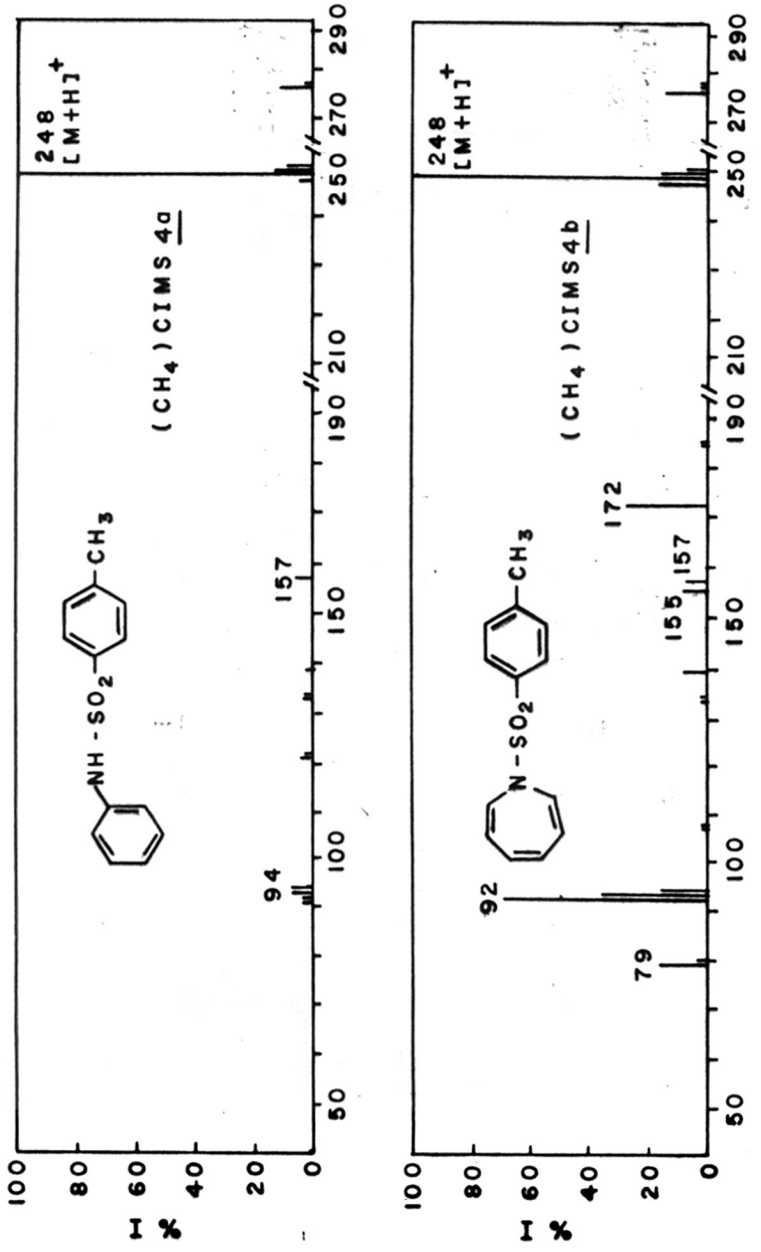


FIGURE 7. METHANE CI MASS SPECTRA OF p-TOLUENESULFONANILIDE 4a AND p-TOLUENESULFONYL-1H-AZEPINE 4b

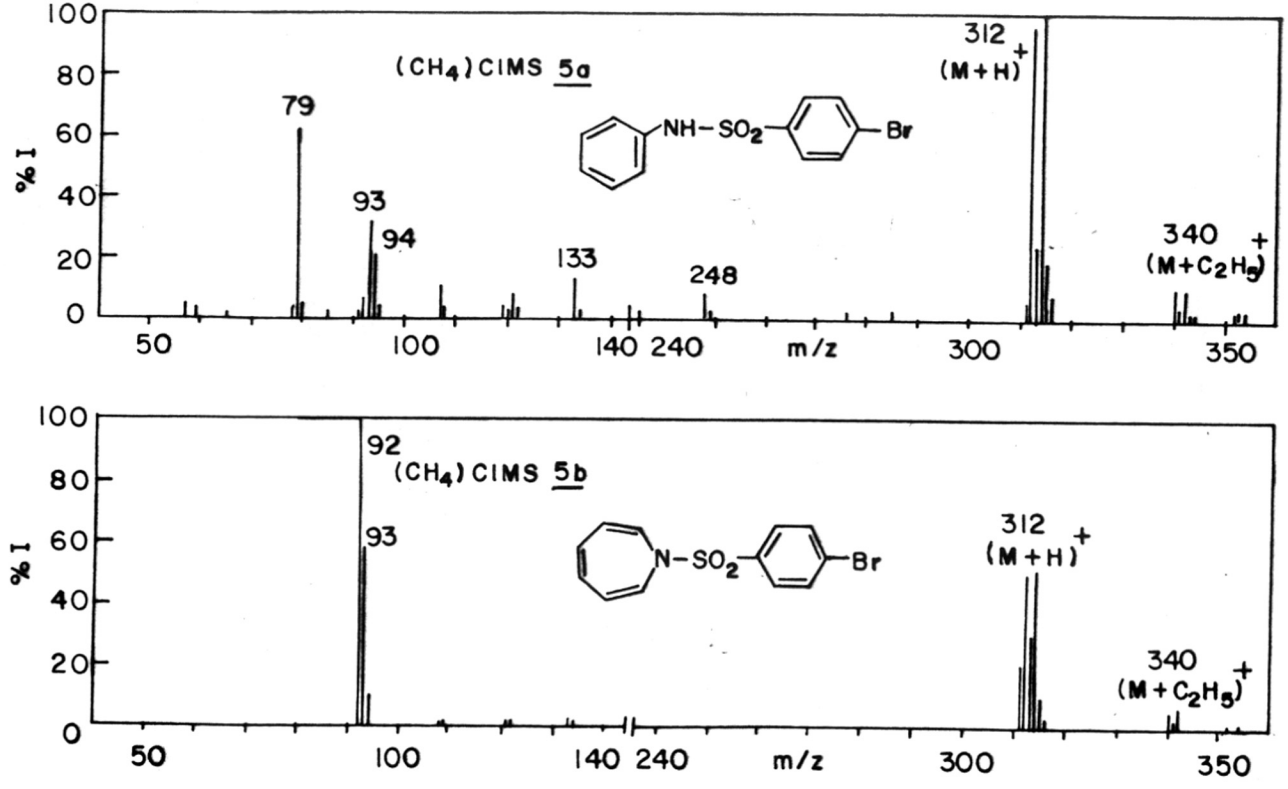
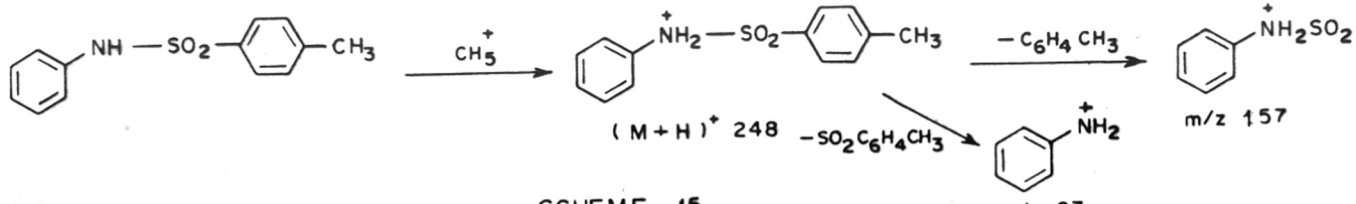


FIGURE 8. METHANE CI MASS SPECTRA OF p-BROMOBENZENESULFONANILIDE 5a AND p-BROMOBENZENESULFONYL-1H-AZEPINE 5b

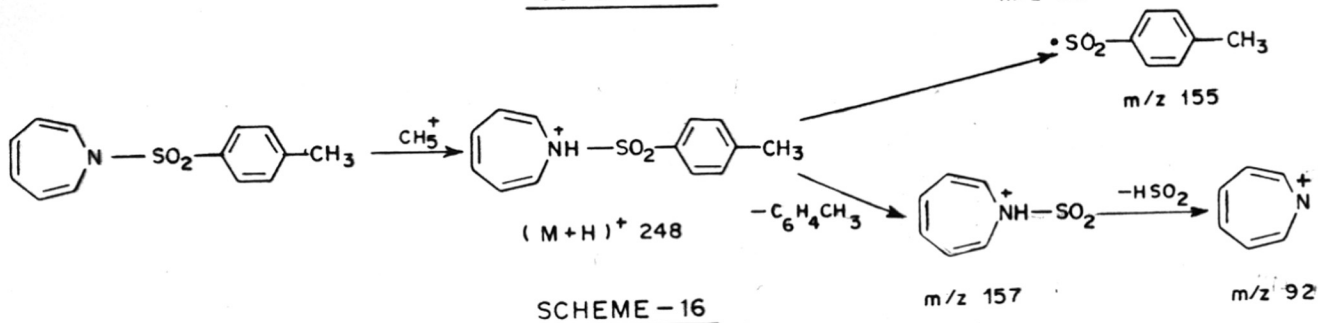
ions is quite possible. The stability of protonated molecular ion could be due to proton bridge between heteroatoms. These quasimolecular ions undergo localised fragmentation giving rise to different peaks.

In the spectra of sulfonylazepines intense peak at m/z 92 is observed. This could be due to initial protonation at sulphur or oxygen atom followed by expulsion of p-toluene or p-bromophenyl sulfonic acid resulting from simple cleavage of N-S bond to give azatropylium ion peak at m/z 92. Another possibility could be due to initial protonation on nitrogen followed by hydrogen transfer with expulsion of same species to give peak of azatropylium ion at m/z 92 (Schemes 16,18). This ion at m/z 92 is not significant in the spectra of sulfonanilides 4a and 5a.

In the spectra of sulfonanilides 4a and 5a initial protonation at nitrogen atom followed by simple cleavage of N-S bond with elimination of aryl sulfonyl radical leads to peak at m/z 93 (Schemes 15, 17). The peak at m/z 157 in 4a could be ascribed to the loss of p-tolyl radical



SCHEME −15.



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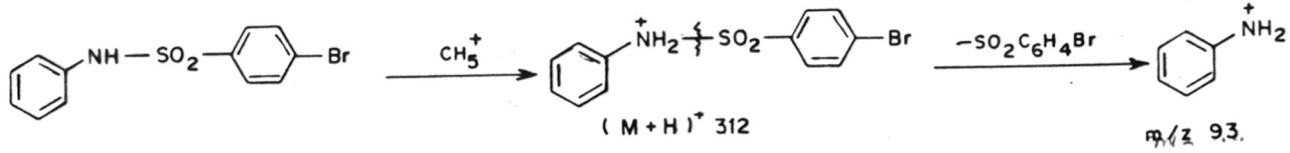
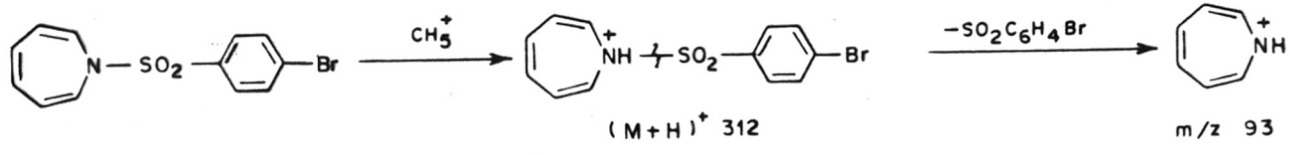


SCHEME −17



SCHEME − 18

C_6H_4-CH_3 from the protonated molecular ion which fragments further by loss of SO_2 to give peak at m/z 93. In the spectrum of 5a the peak at m/z 79 is not due to bromine ions as isotopic peak at m/z 81 is absent. This could be ascribed to formation of NH-SO_2 ion by complex skeletal rearrangement process.

The CI-MS analysis of sulfonanilides 4a, 5a and azepines 4b, 5b show significant differences hence it is concluded that sulfonylazepines do not isomerize to sulfonalides prior to principle fragmentation under methane CI conditions.

3.3 EXPERIMENTAL

The electron impact mass spectra were recorded on CEC-21-110B or MS-30 mass spectrometer at lowest temperature possible. Samples were introduced through direct inlet system and vaporized at minimum temperature. The other instrumental conditions are as follows:

Ion source temperature	40-120°C
Electron energy	15-70 eV
Source pressure	$\simeq 5 \times 10^{-6}$ torr.
Trap current	50-100 μA

The GC-MS experiments were performed on Finnigan Mat 1020B instrument. GC-MS sample was introduced through capillary SE-54 column with helium carrier gas. The details of instrumental conditions are stated in chapter 2.

The chemical ionization mass spectra were recorded on Jeol D-300 mass spectrometer attached to a JMA-2000 data system. Methane reagent gas used was greater than 99% purity. The other instrumental conditions are as follows:

Electron energy	200 eV
Source housing pressure	1.5×10^{-5} torr.
Emission current	600 μA
Source temperature	150-180°C

The electron ionization, chemical ionization mass spectra of azepines and their respective aromatic isomers were recorded under identical conditions. All the spectra were checked for reproducibility.

The synthesis of the compounds was done by known methods and purified by column chromatography, repeated crystallization and distillation process. Purity of all compounds was checked by TLC in two different solvent systems, melting and boiling points. They were unequivocally characterised by spectral and analytical methods.

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S U M M A R Y

SUMMARY

Substituted phenyl carbamates and isomeric azepines were synthesised by methods reported in literature. The product of thermolysis of ethyl-azidoformate and toluene was analysed on capillary SE-54 column GC-MS. The analysis reveal that all the three methyl substituted (2, 3 and 4) isomers are formed in equal proportions. This indicates that insertion of carbethoxynitrene in aromatics is not selective. The work regarding selectivity of carbethoxynitrene insertion reported earlier was based on NMR analysis. The present work is supported by separation on capillary column and mass spectral analysis of the three isomers.

Mechanisms for the fragmentation of simple cleavage, hydrogen and skeletal rearrangements in azepines and isomeric substrates were studied by metastable technique and electron impact at low and high electron volts. The intensities of common ion show significant differences. Simple cleavage reactions are preferred in azepines and rearrangements are preferred in aromatic analogues. The analysis reveals that the seven-membered 8π electron azepine skeleton is stable to electron ionization at moderate

temperatures and can be used to characterise azepine structure from mass spectral fragmentation.

The methane chemical ionization mass spectra of isomeric pairs show protonated molecular ions. However, due to thermal decompositions and presence of acidic species, the spectra of 1a, 1b and 2a, 2b are complex. The CI mass spectra of dicarbomethoxy substituted azepine 3b and carbamate 3a show elimination of alcohols. The relative intensities of the alcohol eliminated products are inversely proportional to proton affinities of the departing alcohol. Some acid catalysed rearrangements similar to that reported in solution phase is indicated. The CIMS of sulfonanilides 4a and 5a and sulfonylazepine 4b and 5b shows significant differences.

From this studies we conclude that at least to a large extent, azepines retain their unstable 8π electron seven-membered cyclic structure before principal fragmentation occurs. Concomitantly isomeric carbamates and sulfonanilides retain their aromatic structure and no ring expansion to azepinium structures occurs prior to their fragmentation.