Rearrangement of Organo-Nitrogen Anions in the Gas Phase

A Thesis submitted for the Degree of Doctor of Philosophy in the Department of Organic Chemistry

by

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"The greatest reward for a man's toil is not what he receives for it, 
but rather what he becomes by it"

C. R. Swindoll
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Publications
Statement

This thesis contains no material which has been submitted for the award of any other degree or diploma in this or any other University. To the best of my knowledge, this thesis contains no material previously published or written by any other person, except where due reference is made in the text.

Greg William Adams

NAME: MR GREG WILLIAM ADAMS COURSE: Ph.D.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

SIGNED: DATE: 11/10/91
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Abstract

This thesis investigates the rearrangement of organo-nitrogen anions in the gas phase. The collisional activation mass spectra of three classes of organo-nitrogen species are reported:

(i) the substituted ammonia derivatives of carbonyl compounds, viz: oximes, α-oximino ketones, hydrazones, amidoximes and semicarbazones,
(ii) heteroatom substituted amides, viz: hydroxamic acids and hydrazides,
(iii) heterocyclic systems containing two heteroatoms.

In the condensed phase the above species undergo a variety of carbanion rearrangements or rearrangement processes involving migration to an electron-deficient nitrogen atom. For example, the Beckmann rearrangement involves the acid catalysed conversion of an oxime to an amide; α-oximino ketones undergo a “second order” Beckmann rearrangement to produce a carboxylic acid and a nitrile, and the Lossen rearrangement involves the transformation of hydroxamic acids to isocyanate derivatives in the presence of base.

This thesis investigates the fragmentation behaviour of organo-nitrogen anions in order to determine whether there is any correlation between the products produced in the gas and condensed phase reactions of the various species. The fragmentation mechanisms have been studied using deuterium labelling experiments, and wherever possible, the structures of various product ions have been confirmed by triple sector MS/MS/MS techniques.

The collisional activation mass spectra of deprotonated oximes are discussed in Chapter 2, ions such as Me₂C=NO⁻, undergo a facile elimination of H₂O to yield the ion CH₂=C=NCH₂⁻, the mechanism of this fragmentation is suggested to be analogous to the Beckmann rearrangement of oximes in solution.

The fragmentation pathways of anions related to oximes (e.g. hydrazones and
semicarbazones) are studied, in order to determine to what extent the negative ion Beckmann rearrangement occurs in the gas phase. For example, the negative ion Beckmann rearrangement does not occur for semicarbazones, the major fragmentation of the general semicarbazone \([R_2C=NNHCONH_2 - H^+]^-\) is initiated by simple cleavage to eliminate \(R_2C=NNH_2\) and form \(NCO^-\).

The complex rearrangement reactions of deprotonated \(\alpha\)-oximino ketones are described in Chapter 4. The general \(\alpha\)-oximino ketone \([R^1COC(=NOH)R^2 - H^+]^-\) undergoes four different competitive rearrangements to eliminate HCN, \(H_2O\), \(R^2NO\) and form \(R^1CO_2^-\). The rearrangement to form \(R^1CO_2^-\) produces the widest dish-shaped peaks yet recorded in negative ion collisional activation mass spectra.

The gas phase reactivity of deprotonated hydroxamic acids, hydrazides and their various substituted derivatives is compared to the behaviour of the analogous species in the condensed phase. For example deprotonated benzohydroxamic acid \([PhCONHOH - H^+]^-\) rearranges via a Lossen rearrangement to yield PhNH\(^-\) in both the gas and condensed phases.

The Tiemann rearrangement in the condensed phase involves the base catalysed transformation of substituted amidoximes \([R^1(NH_2)C=NOR^2]\) to ureas \([R^1NHCONH_2]\). In contrast, deprotonated amidoximes, in the gas phase, undergo only minor reaction through Tiemann intermediates. Instead the major fragmentation is elimination of hydroxylamine \([NH_2OH]\) and it is proposed that a solvated ion complex \([\{(MeCN) NH_2O^-}\] is the key intermediate in this reaction.

The collisional activation mass spectra of deprotonated heterocyclic compounds containing two heteroatoms \([O,N,S]\) are discussed in Chapter 7, in order to investigate whether the deprotonated parent heterocyclic anions
undergo the characteristic ring opening reactions of the analogous species in solution, and to ascertain whether the interconversion of the isomeric ring systems (e.g. thiazole $\rightarrow$ isothiazole) which occurs in solution, also occur in the gas phase. The spectra exhibit characteristic retro-cleavages when deprotonated at the 5-position of the heterocyclic ring, or alternative ring-opening reactions when deprotonation occurs at the 2-, 3-, or 4-positions.
CHAPTER 1
An Introduction to Negative Ion Mass Spectrometry

“I pass with relief from the tossing sea of cause and theory to the firm ground of result and fact”

Sir Winston Churchill

1.1 History of Mass Spectrometry

Amidst discoveries and inventions in 1886, namely the automobile and the formulation of Coca-Cola, 1886 also heralded the beginnings of mass spectrometry when Goldstein\(^1\) detected "Kanalstrahlen" (positive rays) in a glow discharge tube. Later, Wein\(^2\) showed that these rays were in fact beams of ions which could be deflected by electric or magnetic fields. Thomson\(^3\) extended this work when two stable isotopes of neon were detected, their existence arose from the dissociation of the ions in a flight tube. This discovery permitted separation of ions according to their mass to charge ratio (i.e. \(m/z\)); and the term "mass spectrograph" was subsequently used by Aston (1919)\(^4\) to describe the photographic image produced by the ions.

The existence of stable gas phase negative ions has been known since the earliest days of mass spectrometry. For example, in 1928, Hogness and Harkness\(^5\) reported the formation of \(I_2^-\) and \(I_3^-\) in iodine vapour subjected to electron impact.

Throughout the early to mid 20\(^{th}\) century mass spectral studies of positively charged ions progressed rapidly\(^6,7\), whereas the field of negative ion mass spectrometry received much less attention\(^8\). While electron impact ionisation gave strong positive ion signals, early studies in negative ion mass spectrometry showed a low and structure dependent sensitivity for negative ion production.
and a strong dependence of negative ion spectra on the electron beam energy\textsuperscript{9-10}. Hence the development of negative ion mass spectrometry as an analytical technique was delayed until technology enabled suitable means of producing stronger negative ion signals\textsuperscript{11-15}.

The technique of ionising a sample of molecules by ion/molecule reactions was reported by Munson and Field\textsuperscript{16} in 1966; this technique became known as chemical ionisation. After von Ardenne\textsuperscript{11} (1973) produced negative ions using reagent gases in a chemical ionisation source, the structure and ion/molecule reactions of gas phase anions received considerable attention\textsuperscript{17-21}.

During the early 1970's collisional activation\textsuperscript{21-23} was used more effectively to induce and investigate fragmentation mechanisms and ion structure. Thomson and Aston\textsuperscript{24} had actually detected anomalous fragmentation ions produced from energetic collisions between ions and background gases; such ion/molecule reactions arose due to the poor vacuum conditions in the very earliest mass spectrometers. Collisionally induced dissociation (CID), the reaction of an ion with a neutral gas molecule, is now used routinely to induce fragmentation of stable gas phase ions in a mass spectrometer.

Nowadays, a variety of ionisation techniques are being used to prepare ions of interest\textsuperscript{25}. Examples are: chemical ionisation (CI)\textsuperscript{18}, electron impact (EI)\textsuperscript{7}, fast atom bombardment (FAB)\textsuperscript{26,27}, secondary ion mass spectrometry (SIMS)\textsuperscript{28-30}, laser desorption\textsuperscript{31,252} Cf plasma desorption\textsuperscript{32} and several nebulisation techniques such as thermospray\textsuperscript{33} and electrospray\textsuperscript{34}.

The array of ionisation techniques is also matched by the number of instruments now commercially available to study gas phase organic reactions. The title "mass spectrometer" now covers instrumentation such as magnetic/electric
sector instruments, quadrupole mass filters, flowing afterglow, time of flight, ion trap and ion cyclotron resonance mass spectrometers.

In this thesis sector mass spectrometers have been used extensively to probe fragmentation mechanisms and ion structure of organic ions.

### 1.2 Principles of Mass Spectrometry

#### 1.2.1 Tandem Mass Spectrometry

A "sector mass spectrometer" is an instrument that analyses charged particles using magnetic and/or electric fields. The very first mass spectrometers had only a magnetic sector, and the application to ion analysis was limited not only by resolution and sensitivity, but also because spectra contained peaks corresponding to i) singly and multiply charged ions, and ii) product ions formed by ion/molecule reactions occurring within the ionisation source. However, the coupling of two single sector instruments brought about a new era in mass spectrometric research. The term "tandem mass spectrometry" is now used to describe mass spectrometers having two or more mass analysing sectors.

Mattauch and Herzog produced the first tandem mass spectrometer (1934) which incorporated an electrostatic followed by a magnetic sector, and various other instruments followed, such as the double focussing instrument developed by Nier and Johnson (1953).

Instruments such as the VG ZAB 2HF mass spectrometer (Figure 1.1) have a reverse Nier-Johnson geometry in which the magnetic sector precedes the electric sector. For reverse sector mass spectrometers the acronym mass spectrometry/mass spectrometry or MS/MS is used to describe an instrument which utilises mass spectrometry for both mass separation and identification. In such an MS/MS experiment the fragmentation of a parent ion generates
daughter ions with different momentum and kinetic energies than that of the parent ion, and it is the mass to charge ratio \((m/z)\) of the various daughter ions that is physically measured (more specifically, it is the energy of the daughter ion that is measured, from which the mass of the ion is obtained). A tandem mass spectrometer focusses ions according to both momentum and kinetic energy, but the ions can be separated according to their \(m/z\) ratio in either the magnetic or electric sector. The double focussing of ions increases both the sensitivity and the resolution of the ion signal.

![Figure 1.1](image)

**Figure 1.1.** Schematic representation of the VG ZAB 2HF mass spectrometer. Redrawn from ref. 47.

The theory of unimolecular reactions is often referred to as the Quasi equilibrium theory\(^{49,50}\). The Quasi equilibrium theory of mass spectrometry attempts to i) rationalise how parent ions (which are formed with an internal energy in excess of the ground state) can decompose to form fragment ions and neutral species, and ii) how a parent ion may fragment by more than one pathway. The assumption that energy is randomised throughout the ion prior to
fragmentation has important implications. The daughter ion spectrum of a mass selected parent ion is determined by the energy dependent rate constants of possible reaction pathways, the time required for the reaction to occur and the internal energy distribution of the ions.

A mass spectrum is a recording of a series of competing consecutive unimolecular or collision induced decompositions of a parent ion. Ions are initially produced in various electronic, vibrational and rotational energy levels, but rapid transitions (without energy release) lead to randomisation of the energy and the formation of vibrationally excited ground state ions which undergo fragmentation. Mass spectra therefore depend upon the initial transfer of energy and not upon the method by which the energy is transferred.

1.2.2 Ion Formation and Detection

After a molecule has been ionised, the ions produced in the source are accelerated through a potential voltage difference (V). Assuming that the ion is formed with negligible kinetic energy, the accelerated ion beam enters the magnetic field with a kinetic energy equal to the accelerating potential, this kinetic energy is defined in equation 1.1

\[ ZeV = \frac{1}{2} mv^2 \]  \hspace{1cm} (1.1)

where m is the mass of the ion, z the charge of the ion, and e is the charge of an electron. Furthermore, a charged particle traversing a magnetic field experiences a centripetal force (i.e. angular momentum), \( mv^2/r \) and a centrifugal force \( ZevB \), and for energetic stability the two forces experienced by the ion in the magnetic field are equated i.e.
By rearranging eqn 1.2 the following expression for the radius of curvature is obtained.

\[
\frac{mv^2}{r} = BzeV \quad 1.2
\]

\[
r = \frac{mv}{zeB} \quad 1.3
\]

i.e. the ions traverse in a circular path of radius \( r \) while in the magnetic field \( B \). The mass to charge ratio (m/z) of an ion traversing in a fixed radius is also related to the magnetic field and accelerating potential by the equation

\[
\frac{m}{ze} = \frac{r^2 B^2}{2V} \quad 1.4
\]

Eqn 1.3 indicates that the radius of curvature of an ion is proportional to its momentum \( (mv) \), implying that the magnetic sector is a momentum analyser.

As the instrument has a fixed radius of curvature, either the magnetic field or the accelerating potential must be scanned to record the spectrum. This is shown by eqn 1.4, ions of different mass to charge \((m/z)\) ratios are dependent on \( B \) and \( V \). However, the quality of the mass spectrum in terms of ion abundance and ion focus is dependent on the accelerating voltage, therefore variation of the accelerating voltage causes defocussing of the ions and a general loss of sensitivity, hence in the magnetic sector, ions are more appropriately scanned by variation of the magnetic field. Ions which have the same mass, charge and kinetic energy are focussed at one point after leaving the magnetic sector and can be analysed.
A reverse sector double focussing mass spectrometer has an electric sector following the magnetic sector. When ions leave the magnetic sector, ions of identical mass but with different kinetic energies are not focussed at a single point, this spread in kinetic energies reduces the resolution of the m/z ratio of the ions in the spectrum.

By passing the ions through two charged plates of potential E in an electric sector, the ions are focussed according to their m/z ratio as shown in eqn 1.5.

\[ \frac{mv^2}{r} = eE \]

Therefore the radius of the ion is dependent on charge but not mass; this implies ions of the same kinetic energy have the same radius of flight path and are brought to a common focus, i.e. the electric sector is a kinetic energy analyser.

A double focussing instrument thus focusses ions according to both momentum and kinetic energy, but the ions can be separated by their m/z ratio in either the magnetic or electric sector. Mass spectrometers such as the the ZAB 2HF instrument have a reversed Nier-Johnson geometry in which the magnetic sector precedes the electric sector, i.e. the ions are initially separated by momentum and analysed in terms of kinetic energy, this allows a mass analysed ion kinetic energy spectrum (MIKES) to be recorded.
1.2.3 Scanning Techniques

1.2.3.1 Mass Analysed Ion Kinetic Energy Mass Spectrometry

The advantage of reverse sector (BE) instruments over conventional tandem (EB) or single sector instruments is the ability to mass select the parent ion prior to dissociation. The reverse sector instrument is designed with a collision cell in the field free region between the magnetic and electric sectors. The magnetic field is set such that ions of the desired mass-to-charge ratio travel through the magnetic sector to reach the collision cell. Ions of other mass-to-charge ratios have different trajectories and collide with the walls of the mass spectrometer.

The parent ion of mass $M_p$ enters the collision cell, where the ion is collisionally activated. The parent ion then decomposes into various daughter ions of mass $M_d$. Since the parent ion has dissociated in transit after acceleration the daughter ions are essentially metastable ions\(^{50}\), the daughter ions that form after collisional activation are then detected using the electric sector. When a parent ion fragments to a daughter ion and a neutral molecule, the internal energy of the parent ion is shared between the daughter ion and the neutral molecule, and hence the daughter ion has a kinetic energy that is less than that of its parent ion. The daughter ion will have a kinetic energy corresponding to a value of $E_d = E \times M_d/M_p$, where $E$ is the energy necessary to transmit the main ion beam, and by scanning the electric sector from the value $E$ to zero, the kinetic energies of all daughter ions will be detected as peaks in the spectrum. As the electric sector is used to detect the kinetic energy of the ions, the spectrum is therefore calibrated in energy, and the mass of the ions formed are calculated from the above equation i.e. $M_d = M_p \times E_d/E$. The mass of the parent ion is known from the magnetic sector and the value of $E_d$ is recorded in the spectrum, hence the recorded spectrum is called a Mass Analysed Ion Kinetic Energy Spectrum (MIKES)\(^{51,52}\).
Anomalous peaks occasionally form in MIKES experiments; these artifact ions\textsuperscript{53,54} result from higher mass ions which fragment, either in the ion source or prior to the magnetic sector, to form daughter ions which have identical momentum to the parent ion and hence these artifact ions traverse through the magnetic sector. As the magnetic field focusses the ion beam into a narrow energy range any ions that formed prior to the magnet and have the appropriate momentum to traverse the magnetic sector are highly resolved, therefore artifact peaks are readily identified in an MS/MS spectrum as the peaks are usually narrow relative to the daughter ion peaks. However if the artifact ion fragmented after passing through the magnetic sector, artifact daughter ions would be indistinguishable from true daughter ions.

1.2.3.2 Linked Scanning Techniques

The previous discussion outlined the use of a MIKES scan to provide a daughter ion MS/MS spectrum, this is an E type scan in which the ions are mass analysed before entering the electric sector. In a double focussing mass spectrometer there are three parameters which control the type of mass spectrum recorded, V the accelerating voltage, E the electric field strength and B the magnetic field strength.

Linked scans\textsuperscript{55,56} provide methods of scanning V, E and B in which two of the fields are scanned simultaneously. This type of scan is used to investigate the decomposition products formed in either the first or second field free regions of the mass spectrometer. The basis of a linked scan is that the velocity of the daughter ion is the same as that of the parent ion, thus maintaining the ratio of the B and E fields such that the velocity required for the ion to pass through both sectors is constant enables the daughter ion spectrum to be recorded.
### The B/E Linked Scan\(^{57,58}\)

In this scan V is held constant and B and E are scanned simultaneously such that the ratio B/E remains constant throughout the scan. Since E is now proportional to E, B/E is constant, and as B is scanned downwards, the scan passes through B\(_1\) and E\(_1\) allowing the ion m\(_1^-\) to be detected; at different values of B\(_n\) and E\(_n\), different ions m\(_n^-\) are transmitted through the two sectors giving rise to the daughter ion spectrum. The B/E scan gives spectra with increased mass resolution over MIKES spectra as the peaks in a B/E scan are much narrower because only a small range of velocities can pass through both sectors, consequently, any kinetic energy release associated with the formation of daughter ions is not detected in this type of scan.

### The B\(^2\)/E Linked Scan\(^{57,59}\)

This linked scan gives a mass spectrum of parent ions which fragment to give a chosen daughter ion. By equating equations 1.3 and 1.5 in section 1.2.2, the velocity term is eliminated and only a mass term remains i.e.

\[
m = \frac{B^2}{E}
\]

Thus in maintaining the ratio of E to B\(^2\) constant, all ions that dissociate to a given daughter ion are detected. The B\(^2\)/E scan detects dissociations that occur in the field free region (i.e. before the magnetic sector). Since both fields are scanned proportional to the velocity squared, the magnetic sector does not filter out part of the velocity spread and hence the mass resolution is decreased (relative to a B/E scan), and any kinetic energy released upon dissociation is recorded in the spectrum.
The \( B^2E \) Linked Scan\(^6\)

The \( B^2E \) linked scan can only be used with reverse sector instruments, it also differs from other linked scans as this scan detects dissociations that occur in the second field free region, i.e. between the magnetic and electric sectors (cf. B/E and \( B^2E \) linked scans which detect first field free region dissociations). In this scan the ratio of \( B^2E \) is constant, and in contrast to the \( B^2E \) linked scan the \( B^2E \) scan increases mass resolution and contains kinetic energy release information.

The Constant Neutral Loss Scan\(^6\)

For any given fragmentation, \( m_p^- \rightarrow m_d^- + m_n \), the B/E scan selects \( m_p^- \) and detects product ions arising from the dissociation of the parent ion; the \( B^2E \) scan selects \( m_d^- \) and detects parent ions that produce the chosen daughter ion. The constant neutral loss scan thus complements these two scans as it allows the selection of the neutral fragment \( m_n \) and investigates dissociations in which a neutral of mass \( m_n \) is eliminated. When \( B^2(1 - E)/E \) is constant throughout the scan, daughter ions \( m_d^- \) are transmitted by the two sectors only when the chosen neutral of mass \( m_n \) is lost in the fragmentation.

The four linked scanning techniques discussed provide different methods of investigating the ion intensity at different points of the ion's flightpath within the mass spectrometer and hence provide additional or complementary information to the normal MIKES scan.

1.2.4 Triple Sector Mass Spectrometry

The triple sector mass spectrometer\(^6\) is a further step in the development of MS/MS. The earliest triple sector instruments were assembled by the addition of a third sector, magnetic, electric or occasionally a quadrupole, to a double focussing mass spectrometer\(^6\); these instruments led to the commercial
availability of triple sector mass spectrometers. The triple sector mass spectrometer at the University of Lincoln-Nebraska\textsuperscript{65} is depicted in Figure 1.2.

![Diagram of a Kratos triple sector mass spectrometer](image)

\textit{Figure 1.2.} Schematic representation of a Kratos triple sector mass spectrometer. Redrawn from ref.65.

The instrument is an EBE design, the first two sectors comprise a standard Kratos MS-50 double focussing mass spectrometer\textsuperscript{66} coupled with an additional collision cell and electric sector. Such an instrument has unique capabilities over the standard tandem mass spectrometer. Triple sector instruments have increased mass resolution, hence the decompositions of a highly resolved parent ion can be investigated, which has direct application to analysis of complex mixtures containing ions of the same nominal mass\textsuperscript{67}. The additional electric sector eliminates the need to link-scan to obtain daughter ion spectra using EB geometry instruments. Daughter ion spectra are obtained by
selecting the parent ion with the EB sectors (hence the increased mass resolution) and scanning through the second electric sector to observe fragmentations induced in the second collision cell.

The triple sector mass spectrometer is also used in the analysis of sequential chemical reactions of ions which can be observed in the field free regions between the sectors. This type of experiment is termed a MS/MS/MS experiment, as the spectra recorded is a "grand daughter" spectrum of the initial parent ion. i.e.

$$M_p^+ \rightarrow \text{CID} \rightarrow M_d^+ \rightarrow \text{CID} \rightarrow \text{grand-daughter ions}$$

The reaction sequence is outlined in Figure 1.3.

![Figure 1.3. Schematic representation of the reaction sequence of a MS/MS/MS experiment. Redrawn from ref.67.](image)

The parent ion produced in the ion source is collisionally activated in the first collision cell (before the first electric sector), the daughter ion of interest is selected by the electric sector (\(E_d = E_m/d/m_p\)), focussed by the EB sectors and the collisionally activated in the second collision cell. The "grand-daughter" ions are then detected using the second electric sector.

The MS/MS/MS technique is particularly useful in the elucidation of mechanistic problems, the structure of an ion produced in an MS/MS experiment can only
be postulated, whereas triple sector mass spectrometry enables the spectrum of the ion to be investigated and structural information is thus obtained.

1.3 The Production of Negative Ions

1.3.1 Ion formation by Electron Impact

Negative ions may be formed by electron impact ionisation, using this technique a variety of organic molecules can be ionised. The ions formed are dependent on the energy of the electron beam and the nature of the molecule. There are three main processes which are classified as:

(i) Resonance Capture

\[ \text{AB} + e^- \rightarrow \text{AB}^- \]

The process involves capture of low energy electrons (0-10 eV) by the molecule, providing the molecule has a positive electron affinity. In the presence of a non-reactive gas (e.g., N\(_2\)) or at high sample pressures the process is more important as the excited species may be stabilised by collision with a neutral molecule or by radiation, otherwise the captured electron is expelled. Dissociation of \(\text{AB}^-\) into \(\text{A}^-\) and \(\text{B}^-\) will occur if the captured electron has enough energy to produce an electronic transition to a higher energy level than that of the required dissociation energy.

(ii) Dissociative Resonance Capture

\[ \text{AB} + e^- \rightarrow [\text{AB}^-] \rightarrow \text{A}^- + \text{B}^* \]

Dissociative capture occurs when AB captures an electron and undergoes an electronic transition to give \(\text{A}^-\) and the radical \(\text{B}^*\). It is an important process if the electron energy is less than 15 eV and provided the molecular anion (\(\text{AB}^-\)) readily fragments.
(iii) Ion Pair Formation

\[
AB + e^- \longrightarrow A^- + B^+ + e^-
\]

Ion pair formation occurs when the molecule receives sufficient energy after electron impact to dissociate into A\(^-\) and B\(^+\), both of which may be in an excited state. The process is a non-resonance process which occurs when the electron energy is greater than 10ev.

Under normal operating conditions in an electron impact source, all three processes may occur. As the processes are pressure and energy dependent, the intensity of the ion signal will change with sample pressure. Although dependent upon the nature of the sample molecule, the intensity of negative ions is generally a factor of 10\(^3\) lower than the intensity of positive ions under similar conditions. Electron energies in the range 40-70eV have also been used to generate negative ions in electronic ground states, formed by processes (i) and (ii). This energy range often gives more abundant negative ions, as in this range anions are formed by capture of secondary electrons, originating either at metal surfaces or from gas phase positive ionisation.

1.3.2 Ion formation by Chemical Ionisation

The technique of ionising a sample of molecules by gas phase ion/molecule reactions was reported by Munson and Field\(^\text{16}\) in 1966. The initial work in chemical ionisation mass spectrometry utilized positive ion/molecule reactions\(^\text{21}\), and the last 15 years have seen an increased interest in negative ion/molecule reactions and negative ion chemical ionisation (NICI)\(^\text{73}\). Chemical ionisation involves ionising a reagent gas\(^\text{74-76}\) (present in a large excess) such as H\(_2\)O or NH\(_3\) by electron impact, this primary ion (H\(_2\)O\(^-\) or NH\(_2\)\(^-\)) then reacts with the sample via ion/molecule reactions to produce negative ions.
Many types of reagent gases are available to produce reagent ions that act as Brönsted bases. In our studies reagent gases $H_2O$ or $NH_3$ are used extensively. The reactions of $OH^-$ with organic molecules such as carboxylic acids$^{77}$, alcohols$^{78}$, esters$^{79}$, ketones$^{80}$ and amino acids$^{81}$ have been studied and in all cases the $(M-H^+)^-$ ion forms in high yield. Scheme 1.1 illustrates the mechanism by which $HO^-$ is formed from $H_2O$ by electron impact. *

\[
\begin{align*}
H_2O + e^- & \rightarrow H^- + HO^- \\
H^- + H_2O & \rightarrow H_2 + HO^- 
\end{align*}
\]

Scheme 1.1

Other examples of Brönsted base type reagent ions are $MeO^-$ (produced from $MeONO$)$^{82}$, $O^-$ (from $N_2O$)$^{83}$ and $F^-$ (from $NF_3$)$^{84}$.

The various ion/molecule reactions that occur between a reagent ion and the sample molecule can be divided into four categories.

(i) Proton Transfer,

(ii) Charge Exchange,

(iii) Nucleophilic addition,

(iv) Nucleophilic Displacement.

(i) Proton Transfer (Deprotonation)$^{21}$

The proton transfer reaction

\[
R^- + MH \rightarrow M^- + RH 
\]

will be exothermic if the gas phase proton affinity of $R^-$$^{**}$ is greater than the gas phase proton affinity$^{85}$ of $M^-$. Proton transfer reactions have been studied

* It should be noted that $H^-$ and $O^-$ (from $O_2$) are also present and these ions also contribute to the formation of $(M-H^+)^-$ ions.

** $R^-$ is the ion formed from ionisation of the reagent gas, i.e. $HO^-$ or $NH_2^-$. 
extensively, such reactions form an important class of NCl as many organic molecules contain acidic hydrogens which are easily deprotonated by reagent ions such as $\text{HO}^-$ or $\text{NH}_2^-$ to give $(\text{M-H}^+)^-$ ions which are important in obtaining molecular weight information.

(ii) Charge Exchange Reactions\(^{86}\)

\[
\text{R}^- + \text{M} \rightarrow \text{M}^- + \text{R} \quad 1.12
\]
Charge exchange reactions will occur if the electron affinity of M is greater than the electron affinity of R.

(iii) Nucleophilic Addition\(^{87}\)

\[
\text{R}^- + \text{M} \rightarrow \text{MR}^- \quad 1.13
\]
Complexes such as $\text{MR}^-$ in eqn 1.13 occasionally form in a Cl source. The addition complex may either be a covalently bound adduct or a solvated ion pair\(^{88}\).

(iv) Nucleophilic Displacement\(^{89,90}\)

\[
\text{R}^- + \text{MX} \rightarrow \text{M}^- + \text{RX} \quad 1.14
\]
Nucleophilic displacement reactions are an important method of ion formation. The reaction may occur if:

(1) The reaction is exothermic or thermoneutral, or (2) there are no competing proton transfer reactions.

The reaction can be used to form novel anions\(^91\) (eqn 1.15) or similarly using a displacement reaction to form a specific anion in a molecule where there may be a more acidic hydrogen atom.

\[
\text{Nu}^- + \text{Me}_3\text{SiCH}_2\text{CH}_2\text{CHO} \rightarrow \text{CH}_2\text{CH}_2\text{CHO}^- + \text{Me}_3\text{SiNu} \quad 1.15^*
\]

* The species $[\text{CH}_2\text{CH}_2\text{CHO}]$ is unstable and rapidly rearranges to yield the acetone enolate ion (see eqn 1.48)\(^91\).
1.4 Elucidation of ion structure and fragmentation mechanism of ions in the gas phase

The previous discussion outlined how an organic molecule can be simply ionised by chemical ionisation (CI) to produce a high yield of stable negative ions. Chemical ionisation is a "soft" ionisation technique, ions are normally formed from thermal ion/molecule reactions and the technique often provides molecular weight information with few fragmentations. Chemical ionisation may be used to impart as little internal energy to the ion as possible and hence minimise to fragmentations occurring in the ion source. Collisional activation mass spectrometry (CA/MS) is a standard technique\textsuperscript{22,23} used to induce fragmentation of stable gas phase ions.

1.4.1 Collisional Activation Mass Spectrometry

Many modern commercial mass spectrometers\textsuperscript{47,48} are equipped with "collision cells" to enable the production of collisional activation mass spectra. In such instruments, ions are accelerated from the ion source to a high translational energy (e.g. 8keV). The collision cell is placed in a field free region of the mass spectrometer and contains an inert gas (e.g. Helium, Argon). When the ion enters the collision cell, a collision between the inert gas atom and the ion occurs. Conditions are generally controlled so that the measured pressure just outside the collision cell is approximately 5x10\textsuperscript{-7} Torr, under these conditions the ion collides (on average) only once with an inert gas atom, and the intensity of the ion beam is reduced by 10\%. This collision results in some translational energy of the ion being converted to internal energy, in the form of vibrational, rotational and perhaps electronic energy, which is spread uniformly over the whole ion\textsuperscript{16,22,64,92-93}. 
The mechanism for collision induced dissociation (CID) occurs in two steps\textsuperscript{94,95}. The process involves collisional activation of the parent ion, followed by dissociation i.e.

\[ \text{M}_p^- \rightarrow [\text{M}_p^-]^+ \rightarrow \text{M}_d^- + \text{M}_n \]  

where \([\text{M}_p^-]^+\) is the activated parent ion. The overall energy equation of the CID process is:

\[ q + \text{M}_p^- + \text{N} = \text{M}_d^- + \text{M}_n + \text{N}' + T \]

where \(q\) is the amount of energy converted from translational energy into internal energy, \(\text{N}'\) is the target gas molecule after collision, and \(T\) is the kinetic energy released in the unimolecular dissociation (kinetic energy release is discussed in section 1.4.3.2). The internal energy of the activated parent ion \([\text{M}_p^-]^+\) appears as \(T\) and the internal energy of \(\text{M}_d^-\) and \(\text{M}_n\) after dissociation.

Ions that are collisionally activated fragment according to quasi equilibrium theory\textsuperscript{96-98}; the excited ion has no memory of how energy was transferred to the molecule and the parent ion dissociates from an excited state.

The internal energy of \([\text{M}_p^-]^+\) is spread uniformly over the whole ion and as the activated parent ion is in an excited state, this excess internal energy:

i) causes the ion to fragment, therefore releasing energy through exothermic fragmentations,

ii) intensifies existing fragmentations,

iii) allows reaction pathways which have normally large activation barriers to occur.

The last point is of particular interest, as some reaction pathways have been observed in the gas phase which would not occur in the condensed phase,
solely because the activation barrier is too large. The collisional activation technique has been applied to many negative ion mass spectra, in order to give analytical information (e.g. in peptide studies)⁹⁹ or to give mechanistic information in gas phase physical organic chemistry.

### 1.4.2 Charge Reversal Mass Spectrometry

When a non decomposing negative ion with a high translational energy (e.g. 7keV) undergoes a collision with a non reactive neutral molecule, some of the translational energy is converted to internal energy (cf. collisional activation). If this occurs, the negative ion must liberate excess internal energy by one of a number of processes (e.g. radiation or fragmentation). Alternatively, during the collision process some ions will obtain sufficient energy to undergo processes that will alter the nature of the charge associated with the ion⁵⁰ (i.e. the charge is inverted).

A non decomposing negative ion may be converted into a positive ion via the following process.

\[
R^- + N \rightarrow [R^-]^* \rightarrow R^+ + N' + 2e^- \tag{1.18}
\]

The energy required to form a stable parent ion \(R^+\) is equal to the sum of the electron affinity of \(R\) and the ionisation energy of \(R\) (this energy is produced from a decrease in the translational energy of \(R^-\) during the collision process). Ions \(R^+\) are generally formed in electronically excited states and fragment to produce an intense spectrum of positive ions¹⁰⁰. As the electric sector is analysing positive ions produced from the charge reversal process, and since the source and magnetic sector are transmitting negative ions, the polarity of the electric
sector is reversed and hence the spectra were originally termed +E spectra (using the Cooks/Beynon nomenclature)\textsuperscript{101}.

The charge reversal spectrum of a negative ion has a number of applications. In general, negative and positive ions fragment differently, thus the charge reversal technique gives information complementary to that provided by the normal negative ion CA MIKE spectrum of \( R^- \). The charge reversal technique may also be used to form particular positive ions which cannot be formed by conventional ionisation techniques\textsuperscript{102}.

\subsection*{1.4.3 Neutralisation-Reionisation Mass Spectrometry}

Neutralisation-reionisation mass spectrometry\textsuperscript{103} is a technique used to probe the structure of a neutral formed in a fragmentation process by reionising the neutral molecule through reaction with collision gas molecules in the second collision cell of a triple sector mass spectrometer (see Figure 1.2). By applying a potential voltage\textsuperscript{47} across the second collision cell larger than the accelerating voltage of the daughter ions, only the neutral molecules enter the collision cell and collide energetically with the collision gas. The neutral molecules are ionised by electron detachment to give \( N^+ \) species and the second electric sector is the scanned to provide a spectrum of the reionised neutral(s). This method can be used to study ion structures of reactive or unstable neutrals and to elucidate the structure of a neutral molecule associated with a particular fragmentation.
1.4.4 Energetics of fragmentation

1.4.4.1 Unimolecular v Collision induced Dissociations

In MS/MS experiments there are two commonly observed fragmentation pathways

(i) Unimolecular dissociation

(ii) Collision induced dissociation

Unimolecular dissociations can occur in the ion source or in either of the field free regions of the mass spectrometer, whereas those ions that undergo collision induced dissociation are generally ions that would normally be stable, they would not dissociate without collisional activation.

A MIKE spectrum of a collisionally activated parent ion is essentially a recording of metastable ions produced by the parent ion, as by definition metastable ions are ions that are produced from dissociations that occur after acceleration outside of the ion source.

In a collisionally activated mass spectrum it is possible that both unimolecular and collision induced dissociations occur simultaneously in the one spectrum. There is a simple experiment to distinguish between the two processes, by applying a potential voltage $V'$ (say 1000 volts) across the collision cell, the kinetic energy of the daughter ions will differ depending upon whether dissociation occurs in the collision cell or the field free regions outside of the collision cell. The ions that are formed in the collision cell are shifted from the original energy $[(M_d/M_p)V]$ to a value of $[(M_d/M_p)(V-V')]$, ions that form in the outer field free regions are unaffected by the potential applied to the collision cell.
In a reverse sector mass spectrometer, any unimolecular dissociation that occurs in the ion source or prior to the magnetic sector is not detected under normal conditions, thus ions formed by unimolecular dissociation detected in the spectrum are formed from reactions that occur outside of the collision cell in the second field free region.

There is a possibility that some reactions may occur between ions and neutral gas molecules due to leakage of gas from the collision cell. In general, ions formed "outside" of the collision cell are thus a combination of unimolecular and collision induced dissociations. Morgan has calculated the relative probabilities of ion/molecule reactions occurring in the various regions of the mass spectrometer. At a pressure of 1x10^-3 Torr of argon*, there is a 90% probability of collision occurring within the cell, 3.9% in the field free region prior to the cell and 1% in the field free region between the collision cell and the electric sector.

1.4.4.2 Kinetic Energy Release

In a dissociation of a singly charged polyatomic anion i.e.

\[ M_p^- \rightarrow M_a^- + M_n \]  

some fraction of the internal energy in excess of the ground state products is partitioned into the kinetic energy involved in the separation of the ion and neutral after fragmentation. The potential energy of a basic dissociation (e.g eqn 1.19) is depicted in Figure 1.4.

---

* In this thesis, the pressure of collision gas just outside the cell is maintained between 5x10^-7 - 1x10^-6 Torr. The actual pressure in the collision cell will be greater than the 'measured' value.
The kinetic energy released in the dissociation can arise from two sources.

(i) The excess energy $e^+$ of the activated ion which is partitioned between the internal energies of the products and the translational energy released in the separation of the products, and

(ii) The reverse activation energy $e_{R0}$ which is also partitioned between internal and translational energy.

i.e. $T_{\text{total}} = T^R + T^\dagger$

Where $T^R$ is the contribution from reverse activation energy and $T^\dagger$ from the excess energy of the activated complex.

The major contribution to kinetic energy release is generally due to reverse activation energy; the reverse activation energy of a reaction is the energy difference between the ground state of the products and the critical energy for the fragmentation. Figure 1.4 shows schematically the origin of the kinetic energy.
energy release $T$ for a fragmentation with a large reverse activation energy, i.e. a reaction in which the ground state of the products is significantly lower than that of the activated complex. Gas phase dissociations generally occur with little excess energy in the transition state, and the reaction proceeds to give the product ions with no further release in energy, i.e. there is no reverse activation energy barrier for the fragmentation. When a reaction has a significant reverse activation energy barrier, the fragmentation will be accompanied by a relatively large kinetic energy release.

When the dissociation occurs in the collision cell in the second field free region, the products can be analysed in terms of kinetic energy by scanning the voltage using the electric sector. In the absence of any kinetic energy release, the observed peak width of the daughter ion is equal to $(M_d/M_p)E_p$ where $E_p$ is the energy of the parent ion. This is the general case for most dissociations and the peak shape of the daughter ion is gaussian. Similarly, if there is no translational energy contribution to the reverse activation energy, there is little or no kinetic energy released upon dissociation and the peak shape is again gaussian\textsuperscript{108}. Figure 1.5 shows a three dimensional representation of a dissociation of a parent ion in the second field free region of a mass spectrometer.

\textbf{Figure 1.5}, Dissociation of a parent ion in the second field free region of a mass spectrometer. Open circles represent daughter ions, closed circles represent the neutral fragment. Redrawn from ref.108. When kinetic energy release accompanies dissociation the ion and neutral repel one another and move in the direction of the vectors as shown. When no kinetic energy is released the ion and neutral separate without repulsion and move in the direction of the ion beam.
Peak shapes in ion kinetic energy spectra are heavily influenced by the magnitude and distribution of kinetic energy release upon dissociation. Figure 1.6 outlines the peak shapes of ions corresponding to the dissociation of ions as represented in Figure 1.5.

*Figure 1.6a*  
*Figure 1.6b*  
*Figure 1.6c*  
*Figure 1.6d*  

*Figure 1.6*, Figure 1.6(a), gaussian peak, Figures 1.6(b) – (d) show the change in peak shape as the amount of kinetic energy released upon dissociation increases. Note change from gaussian to "flat-topped" to "dish" shaped peaks with increasing kinetic energy release. Redrawn from ref.108.
When kinetic energy is released upon dissociation the daughter ion and neutral repel each other, decompositions occurring from orientation A in Figure 1.5 give rise to fragment ions with slightly higher momentum as the ion is "pushed" along the ion beam (i.e. the x direction) due to the repulsive forces, similarly an ion decomposing in orientation B (Figure 1.5) are pushed in a direction opposing the ion beam. Ions in orientation A appear at a slightly higher m/z value, consequently ions in orientation B appear at a slightly lower m/z value, hence the gaussian peak begins to broaden. Dissociations from intermediate orientations C, D and E (not in the plane of the ion beam) produce a three dimensional spread of energies due to the kinetic energy released. The resultant peak shape is a flat topped peak as shown in Figure 1.6(b). In cases where the kinetic energy released is very large, the peak shape changes from flat-topped to dish-shaped as the focussing slit prior to the electric sector is aligned in length along the z direction, thus in extreme cases of kinetic energy release, the ions in orientation C (i.e separating in the z direction) are unable to pass through the slit and hence a section of the ion beam is not detected and a dish-shaped peak results\textsuperscript{103,110}.

Figure 1.7 gives an example of flat-topped and dish-shaped peaks recorded in negative ion collisional activation spectra (CA/MS). The average value of the kinetic energy released in a dissociation, $T^\text{av}$, is calculated from the width at half-height of the peak\textsuperscript{*}(113-115). Figure 1.7(a) illustrates an example of a flat-topped peak with a half-height of 100 volts\textsuperscript{111}, whereas Figure 1.7(b) illustrates an example of a dish shaped peak with a half-height of 116 volts\textsuperscript{91}; thus it is apparent that peak shapes contain valuable information concerning the kinetic energy released upon dissociation.

\textsuperscript{*} In this thesis the width at half-height of the peak is quoted in electron volts, measured directly from the spectrum, this value is not the kinetic energy released upon fragmentation, however the value of KER is simply calculated from the half-height width in electron volts.
The major contribution to kinetic energy release is generally due to reverse activation energy. Gas phase dissociations generally do not have an appreciable reverse activation barrier, however, fragmentations that have a reverse activation energy, or in cases when the dissociation is appreciably
exothermic (i.e. energy is released) the daughter ion(s) will have an excess energy; such fragmentations will often be characterised by flat-topped or dish-shaped peaks for the reaction.

1.4.4.3 An Introduction to Kinetic Isotope Effects

Isotope effects can be an essential tool in the understanding the details of a reaction mechanism. Isotope effects have been observed in both condensed and gas phase reactions, and may be observed whenever an atom is substituted by one of its isotopes, e.g. H/D, ¹²C/¹³C, ¹⁶O/¹⁸O and others.

Isotope effects are divided into three classifications:

i) Equilibrium isotope effects,

ii) Primary isotope effects,

iii) Secondary isotope effects.

We are concerned mainly with primary isotope effects, an isotope effect is called primary if at some stage of the reaction a bond to an isotopically substituted atom is either broken or formed in the rate determining step of the reaction. A secondary isotope effect refers to a reaction where no bonds to isotopically substituted atoms are directly involved in bond breakage or formation.

Zero Point Energy

The origin of an isotope effect lies in the difference in zero point energy (ZPE) of a species caused by isotopic substitution. Zero point energy is defined as:

\[ \varepsilon_0 = \frac{1}{2} \hbar \nu_0 \quad \text{(1.20)} \]

and

\[ \nu_0 = \frac{1}{2\pi} \sqrt{\frac{f^2}{m^*}} \quad \text{(1.21)} \]

therefore

\[ \varepsilon_0 = \frac{\hbar}{2\pi} \sqrt{\frac{f^2}{m}} \quad \text{(1.22)} \]
e is the ZPE, u is the vibrational frequency, \( m^* \) the effective mass and \( f \) is the force constant.

The force constant is a measure of the strength of a chemical bond and a measure of how the potential energy of a system changes with displacement of its atoms, however, the Born Oppenheimer approximation\(^{119}\) states that the potential energy surface of a reaction is not a function of isotopic substitution, therefore changes in ZPE by isotopic substitution are due to changes in effective mass (eqn 1.22).

In a diatomic system such as A-H where \( m_a >> m_h \) then the effective mass is given by eqn 1.23.

\[
m^* = \frac{m_A m_H}{m_A + m_H}
\]

therefore

\[
\frac{1}{m} = \frac{1}{m_A} + \frac{1}{m_H}
\]

in the case of hydrogen (\( m_h \)) being substituted for deuterium (\( m_d \)).

\[
\frac{1}{m} \approx \frac{1}{m_H} \quad \text{since} \quad \frac{1}{m_H} \gg \frac{1}{m_A}
\]

and hence for hydrogen isotopes the ZPE difference is

\[
\Delta \varepsilon_o = \Delta \varepsilon_o^H - \Delta \varepsilon_o^D = \frac{1}{2} \hbar (\nu_o^H - \nu_o^D)
\]

\[
= \frac{\hbar \sqrt{f}}{4\pi} \left( \frac{1}{\sqrt{m_H}} - \frac{1}{\sqrt{m_D}} \right)
\]

\[
= \frac{\hbar \sqrt{f}}{4\pi} \left( 1 - \frac{1}{\sqrt{2}} \right)
\]

Therefore the ZPE difference is proportional to the force constant, and hence the force constant controls the difference in ZPE between A-H and A-D, and the
difference in force constants between: i) reactant and transition state determines primary and secondary isotope effects, and, ii) reactant and products determines equilibrium isotope effects.

**Primary Kinetic Isotope Effects**

Kinetic isotope effects are expressed by the eqn:\n
\[ \frac{k_{h}}{k_{d}} = \text{MMI} \times \text{EXC} \times \text{TUN} \times \text{ZPE} \]  

1.28

The four contributions are:

(i) **MMI** - masses and moments of inertia contributions to the translation and rotational partition functions,

(ii) **EXC** - vibrational partition function which accounts for thermal excitation of low frequency vibrations,

(iii) **TUN** - tunnelling quantum mechanical correction to the reaction coordinate (large kinetic isotope effects (ca. \( k_{h}/k_{d} \approx 10 \)) have been attributed to significant tunnelling contributions),

(iv) **ZPE** - the differences in zero point energies of reactant and transition state.

For the reaction

\[ AH + B \rightarrow [A\cdots H\cdots B]^* \rightarrow A + BH \]  

1.29
the isotope effect is a function of the differences in force constant and there ZPE's of the reactant and transition state. The ZPE of the reactant can be easily calculated, but the ZPE of the transition state arises from the various degrees of freedom (3N-5). The transition state [A\cdots H\cdots B] has four degrees of freedom, 2 bending modes and 2 stretching vibrations. The stretching vibrations consist of a symmetric and an asymmetric vibration. The asymmetric vibration is along the reaction coordinate and has no restoring force (i.e. once the transition state forms it proceeds directly to products) and hence the vibration is not affected by isotopic substitution. The symmetric vibration is at right angles to the reaction coordinate and providing \( f_1 \) (force constant for A\cdots H) does not equal \( f_2 \) (force constant for H\cdots B) the symmetric vibration is isotopically sensitive. The value of
the isotope effect depends on the structure of the transition state and hence on 
f_1 and f_2.

This explanation of isotope effects is described using classical isotope effect 
theory, where the isotopic species will react having a Maxwell Boltzmann 
distribution of energy (i.e. in most condensed phase reactions), however, gas 
phase reactions do not always have Maxwell Boltzmann conditions. Thus 
simple classical isotope theory does not always predict the correct isotope effect 
for a gas phase reaction. In mass spectrometry, the "isotope effect" is measured 
in terms of ion abundances, not rate constants, and the relationship between 
rate constants and ion abundances has been shown by Derrick\textsuperscript{120}, and isotope 
effects are used in a qualitative fashion in our mechanistic studies.

1.5 Negative Ion Chemical Ionisation Mass Spectrometry of 
Organic Molecules

The earliest studies of even electron anions in the gas phase utilised electron 
impact ionisation, but it was found that the electron energies used in electron 
impact ionisation were generally not suitable for molecular weight or structure 
determination\textsuperscript{9}. During the 1970's and early 1980's the fragmentation 
behaviour of radical anions M^-* formed using electron capture of organic 
molecules were studied\textsuperscript{121}, but since that time the techniques of chemical 
ionisation and collisional activation have arguably provided more efficient 
means of producing negative ions derived from organic substrates. The 
development of these techniques has lead to a resurgence of negative ion 
mass spectrometry\textsuperscript{19,122}.

This discussion will be limited to even electron anions formed by negative ion 
chemical ionisation. Introduction of other ionisation techniques such as FAB\textsuperscript{26},
SIMS\textsuperscript{28}, laser induced mass spectrometry\textsuperscript{31}, \textsuperscript{252}Cf plasma spectroscopy\textsuperscript{32} and electrospray\textsuperscript{34} has also allowed the formation of deprotonated organic molecules to provide molecular weight and structural information. The fragmentation behaviour of organic functional groups analysed by NICI has recently been reviewed\textsuperscript{123}: a wide variety of functional groups such as hydrocarbons\textsuperscript{122}, alkoxides\textsuperscript{124}, ethers\textsuperscript{91}, enolates\textsuperscript{80}, acids\textsuperscript{77}, amines\textsuperscript{125}, amides\textsuperscript{111} and amino acids\textsuperscript{126} have been investigated.

1.5.1 Classification of fragmentation pathways of organic anions

From recent studies a number of simple rules for fragmentation of even electron species, including enolates, C\textsuperscript{−}, N\textsuperscript{−} and O\textsuperscript{−} species have been formulated\textsuperscript{123}, and most negative ion reactions fall into one of five main classification types:

i) loss of a radical to form a stabilised radical anion,

ii) direct fragmentation through an intermediate ion complex with subsequent elimination of a neutral molecule from the ion complex,

iii) fragmentation preceded by proton transfer from the initial site of deprotonation followed by elimination of a neutral molecule,

iv) charge remote fragmentations,

v) fragmentations which are preceded by skeletal rearrangement.

Examples of the five classifications are as follows:

1.5.1.1 Fragmentations involving radical loss

The majority of (M - H\textsuperscript{+})\textsuperscript{−} ions lose H\textsuperscript{+} to some extent, but in systems that can form stabilised radical anions, loss of hydrogen atom and alkyl radicals is often pronounced\textsuperscript{80} e.g.

\begin{equation}
\text{CH}_3\text{C} = \text{CH}_2 \quad \rightarrow \quad \text{CH}_3\text{C} = \text{O}^- \quad \rightarrow \quad \text{H}^+ \quad + \quad \cdot \text{CH}_2\text{C} = \text{CH}_2
\end{equation}
In other systems an apparent elimination of a higher alkyl radical (≥ Et) has been shown to occur by a two step process\textsuperscript{124, 127} e.g.

\[
\text{PhC} \text{(Et)}^+ \text{CH}_2\text{CH}_2^- \xrightarrow{\text{H}^+} \text{PhC} \text{CH}_2\text{CH}_3^- + \text{CH}_2=\text{CH}_2
\]

1.5.1.2 Fragmentations proceeding through an ion complex

Many fragmentations are initiated from the charged centre through an ion complex. The intermediate may be either an ion/neutral or radical/radical anion complex. Such ion complexes fragment via a number of pathways following the formation of the initial intermediate:

(i) direct displacement of the anion in the ion complex\textsuperscript{128} e.g.

\[
\text{PhC} \text{CHO}^- \xrightarrow{\text{MeCH}==\text{O}} \text{Ph}^- + \text{MeCHO}
\]

(ii) the bound anion of the ion complex deprotonates the neutral molecule of the complex\textsuperscript{125} e.g.

\[
\text{Me}_2\text{CH}==\text{NH}^- \xrightarrow{\text{MeCH}==\text{NH}} \text{CH}_4 + \text{MeCH}==\text{N}^-\]

(iii) the bound ion initiates an elimination reaction or a nucleophilic displacement\textsuperscript{129} e.g.

\[
\text{Et}_2\text{C}==\text{O} \xrightarrow{\text{MeO}^- \text{(Et}_2\text{C}==\text{C}==\text{O)}} \text{MeOEt} + \text{EtC}==\text{CO}^-
\]
Two interesting examples of reactions occurring through ion complexes are as follows:

1. Raftery\textsuperscript{120} has shown that the cyclohexanone enolate ion fragments by two specific losses of H$_2$, the hydride ion bound in the ion complex can deprotonate the intermediate cyclohex-2-ene-1-one at the 5-position (eqn 1.36) or 2-position (eqn 1.37), thus providing experimental evidence for the intermediacy of the anion/neutral complex.

\[
\begin{align*}
\text{Cyclohexanone enolate} & \rightarrow \text{Cyclohex-2-ene-1-one} + H_2 \\
\text{Cyclohexanone enolate} & \rightarrow \text{Cyclohex-2-ene-1-one} + HD
\end{align*}
\]

2. Sülzle and Schwarz\textsuperscript{131} have demonstrated that stereochemical criteria provide experimental evidence for stepwise decomposition of deprotonated isoborneols to enolate ions via the intermediacy of an ion complex, viz.

\[
\begin{align*}
+ \text{Isoborneol enolate} & \rightarrow \text{Isoborneol enolate} \\
\text{Isoborneol enolate} & \rightarrow \text{Isoborneol enolate} + H_2/HD
\end{align*}
\]
The ion $1a$ eliminates both H$_2$ and HD, if a concerted elimination of dihydrogen occurred (i.e. path A) only HD would be eliminated due to the stereochemical constraints of the isoborneol structure; however, experimentally it was found that both H$_2$ and HD are eliminated, thus fragmentation must be occurring via the ion/neutral complex $1b$ (path B) such that the hydride ion can deprotonate either the exo C-H or endo C-D bond. Analogous results occur for the exo C-D epimer.

### 1.5.1.3 Fragmentations following proton transfer to the initial ion

Fragmentations following proton transfer can occur via two pathways

i) reactions where direct neutral loss follows proton transfer, i.e. an elimination reaction

\[
\text{O} \quad \text{CH}_2 \quad \text{C} \quad \text{OH} 
\]

\[
\text{O} \quad \text{CH}_2 \quad \text{C} \quad \text{OH} + \text{C}_2\text{H}_4 
\]

ii) Alternatively the ion formed after proton transfer initiates fragmentation via an ion complex

\[
\text{Me}_2\text{CHCO}_2^- \quad \text{Me} \quad \text{C} \quad \text{OH} 
\]

\[
\text{Me}_2\text{CHCO}_2^- + \text{CH}_4 + \text{CH}_2=\text{C}\equiv\text{C} \quad \text{OH} 
\]

Proton transfer reactions to produce a different anion are common among negative ion fragmentations and occur when reactions outlined in sections 1.5.1.1 and 1.5.1.2 are or not possible or energetically unfavourable.
1.5.1.4 Charge remote fragmentations
This class of fragmentation differs from the preceding classes as charge remote fragmentations\textsuperscript{132} result in the loss of a neutral molecule from a position remote to the charge site, such fragmentations occur in both positive and negatively charged species. Charge remote fragmentations are common in collisional activation mass spectra (CI and FAB) of large even electron ions, particularly ions that contain long saturated alkyl chains. Such species eliminate the elements $C_nH_{2n+1}$ that originate from the alkyl terminus i.e.

\begin{equation}
\begin{array}{c}
\text{H} \quad \text{H} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{CO}_2^- \\
\rightarrow \\
\text{C}_\text{alkyl} + \text{CO}_2^- + \text{H}_2
\end{array}
\end{equation}

It is suggested that charge remote fragmentations are high energy processes\textsuperscript{132} and at low collision energies the fragmentation does not occur.

1.5.2 Rearrangement reactions of anions in the gas phase
Rearrangement reactions of anions in the gas phase form an interesting and important class of fragmentation pathways. Rearrangement reactions exhibit a rich ion chemistry; some reactions are unique to the gas phase, while other ions show analogy to the reactivity of the species under base catalysed conditions in solution.

1.5.2.1 Rearrangements unique to the gas phase
Collisional activation mass spectra often provide examples of unique and sometimes unusual gas phase rearrangements, e.g.

i) Deprotonated malonate esters\textsuperscript{133} show pronounced loss of methyl formate as outlined by the hydride transfer in eqn 1.44.
ii) A variety of rearrangements involving organometallic species have been investigated, an example of a trimethyl substituted arylcarboxylate ion$^{134}$ is given in eqn 1.45.

\[
\begin{align*}
\text{SiMe}_3 \text{SiMe}_2 & \rightarrow \text{SiMe}_2 \rightarrow \text{SiMe}_3 + \text{HCO}_2\text{Me} \quad 1.45
\end{align*}
\]

iii) "Three centre" rearrangements are not uncommon in gas phase anion chemistry, whereas analogous condensed phase reactions are uncommon: this is suggested to be due to orbital symmetry constraints$^{135}$. An example of such a reaction is given for deprotonated allyloxy carbamates$^{136}$ e.g.

\[
\begin{align*}
\text{MeOCON} & \rightarrow \text{MeOCON} \rightarrow \text{MeOCON} + \text{N}^+ \quad 1.46
\end{align*}
\]

The first step involves either a 1,2 or 2,3 nitrogen initiated Wittig rearrangement, the second step is a 1,2 anionic rearrangement.

iv) A further example of a rearrangement that occurs uniquely in the gas phase is that of unsaturated ethers. In solution ethers undergo elimination reactions with strong bases, this also occurs for deprotonated dialkyl ethers in the gas phase$^{137,138}$. Unsaturated ethers deprotonate at the allylic position in the gas phase$^{91}$, and the ions undergo proton transfer and an E$_{1cb}$ elimination, e.g.
Interestingly the ion $\text{CH}_2=\text{CHCH}(-)\text{OEt}$ eliminates ethene by a different pathway, the CA mass spectrum of this ion is shown in Figure 1.7(b) [pg.28]. By analogy with eqn 1.47, the product ion should be the allyloxy ion $\text{CH}_2=\text{CHCH}_2\text{O}^-$. However, CA and CR MS/MS/MS experiments have shown that the product ion has a structure consistent with the acetone enolate ion $\text{CH}_3\text{COCH}_2^-$. The mechanism which is consistent with experimental data is shown in eqn 1.48.

$$\text{CH}_2=\text{CHCH}_2\text{CHO} \rightarrow \text{CH}_3\text{COCH}_2^-$$

It is interesting to note the peak shape of the rearrangement ion in Figure 1.7(b) [page 28]. The dish-shaped peak has a width at half-height of 116eV. This kinetic energy release is consistent with the rearrangement process having a large reverse activation energy (cf. section 1.4.2).

### 1.5.2.2 A comparison of solution and gas phase rearrangements

Several classical condensed phase rearrangements\textsuperscript{139} have a direct analogy to rearrangements in the gas phase. Solution rearrangements that are acid catalysed have been shown to occur in the gas phase using positive ion mass spectrometry\textsuperscript{140}, likewise, base catalysed solution rearrangements have been studied using negative ion mass spectrometry\textsuperscript{123}. In addition this thesis presents an example of an acid catalysed solution rearrangement that has analogy to a negative ion gas phase rearrangement.
The following discussion outlines several negative ion gas phase rearrangements that also occur in solution.

i) Wittig Rearrangements

One of the better known carbanion rearrangements in solution is the Wittig rearrangement\textsuperscript{139}, the reaction converts an ether to an alkoxide, the rearrangement may either occur via an ion/neutral or radical/radical anion ion complex e.g.

\[
\begin{align*}
&\text{RCHO}^+ (R\text{CHO}) \\
\text{RCHO}^+ \quad \text{RCHO}^+ &\rightarrow \\
\text{RCHO}^+ \quad \text{RCHO}^+ &\rightarrow \\
\end{align*}
\]

ii) Sigmatropic Rearrangements

In solution diallyl ether gives hexa-1,5-dien-3-ol by a Wittig process\textsuperscript{141}, and on heating the alcohol gives hex-5-en-1-al via an oxy-Cope rearrangement\textsuperscript{142}. Deuterium labelling show that diallyl ether rearranges by both 1,2 or 2,3 Wittig process followed by oxy-Cope rearrangements in the gas phase\textsuperscript{143,144} e.g.

\[
\begin{align*}
\text{O}^- &\quad \text{O}^- \\
\text{O}^- &\quad \text{O}^- \\
\text{Wittig Rearrangements} &\rightarrow \\
\text{Oxy-Cope Rearrangements} &\rightarrow \\
\text{Oxy-Cope Rearrangements} &\rightarrow \\
\end{align*}
\]

1.49

1.50

1.51
Other sigmatropic rearrangements also occur in the gas phase, allyl vinyl ether rearranges by a Claisen process\textsuperscript{145}, and deprotonated allyl phenylacetates rearrange via a Claisen/Carroll rearrangement\textsuperscript{146,147} e.g.

\[
\begin{array}{c}
\text{Ph} & \text{O} \\
\text{CH}_2 & \text{CH}_2 \\
\text{O} & \text{O} \\
\text{Ph} & \text{O} \\
\end{array} \quad \text{1.52}
\]

\textbf{iii) Smiles Rearrangement}

In solution, species PhXCH\textsubscript{2}CH\textsubscript{2}Y\textsuperscript{−} rearrange to PhYCH\textsubscript{2}CH\textsubscript{2}X\textsuperscript{−} via spiro intermediates\textsuperscript{148}; the rearrangement requires i) electron withdrawing groups in either the ortho or para positions of the aromatic ring, ii) X to be a good leaving group and iii) Y to be a strong nucleophile\textsuperscript{149}. Gas phase ions PhO(CH\textsubscript{2})\textsubscript{n}O\textsuperscript{−} (n=2-5) fragment to give the phenoxide ion as the only product ion. When n=2, \textsuperscript{18}O and \textsuperscript{13}C labelling have shown that the reaction proceeds exclusively through the Smiles rearrangement\textsuperscript{150} e.g.

\[
\begin{array}{c}
\text{PhOCH}_2\text{CH}_2\textsuperscript{18}O\textsuperscript{−} \quad \text{1.53}
\end{array}
\]

\[
\begin{array}{c}
\text{PhO}− + \text{C}_2\text{H}_4\text{O} \\
\text{Ph}^{18}O\textsuperscript{−} + \text{C}_2\text{H}_4\text{O} \\
\end{array}
\]

\textbf{iv) Dieckmann Condensation}

One of the classical reactions of enolates in solution is the Dieckmann condensation\textsuperscript{151}, the condensation occurs in solution when an enolate anion of a diester can form a cyclic five or six membered β-ketoester as the product. The gas phase Dieckmann condensation of deprotonated adipates has been reported\textsuperscript{152-154} and is outlined in eq\textsuperscript{10} 1.55.

\[
\begin{array}{c}
\text{PhOCH}_2\text{CH}_2\text{O}^{18} & \quad \text{1.54}
\end{array}
\]

\[
\begin{array}{c}
\text{PhO}^{−} + \text{C}_2\text{H}_4\text{O} \\
\text{Ph}^{18}O^{−} + \text{C}_2\text{H}_4\text{O} \\
\end{array}
\]
A further class of rearrangement is one that occurs by a bimolecular reaction in the chemical ionisation source of the mass spectrometer. The MS50 triple sector instrument (see Section 1.2.4) has been used to investigate reactions such as the benzilic acid rearrangement\(^\text{155}\), aldol\(^\text{155}\) and Reformatsky\(^\text{157}\) condensations; in such reactions the reagent ion (e.g. \(\text{HO}^-\)) acts as a nucleophile rather than as a base and an adduct is formed between the sample molecule and the reagent ion.

**The Gas Phase Benzilic Acid Rearrangement**

When benzil is treated with potassium hydroxide in the condensed phase, the potassium salt of benzilic acid is obtained\(^\text{158-160}\) e.g.

\[
\begin{align*}
\text{Ph} & \text{C} = \text{O} \quad \text{KOH} \quad \text{Ph} & \text{C} = \text{O} \\
\text{Ph} & \text{C} = \text{OH} \quad \text{Ph} & \text{COCO}_2\text{H} \quad \text{Ph}_2\text{COCO}_2^-\text{K}^+ \\
\end{align*}
\]

In a high pressure chemical ionisation source, an adduct corresponding to \([\text{PhCOCOPh} + \text{HO}^-]\) is formed and the spectrum of this adduct is identical with that obtained from deprotonated benzilic acid\(^\text{155}\).
CHAPTER 2
Fragmentation and Rearrangement reactions of Collisionally Activated Oxime Anions

"Gather up the fragments, so that nothing may be lost" John 6:12.

2.1 Introduction

In section 1.5.2 the chemistry of anions that rearrange prior to fragmentation was discussed. Most rearrangement processes are in competition with normal fragmentation pathways, however there are some examples of ions that cannot fragment from the anion that is initially formed from deprotonation by the reagent ion. In general, the most acidic proton of a sample molecule is removed by the gas phase base. If the initially formed anion cannot fragment then it must proton transfer or rearrange to provide a different anion which can then effect fragmentation according to the general rules outlined in section 1.5.

One class of functional group that generally does not fragment through the initial anion is the carboxylate species. A proton transfer from the \( \alpha \) carbon to the carboxylate anion produces the enolate anion, viz.

\[
\text{RCH}_2\text{CO}_2^- \rightarrow \text{RCHCO}_2\text{H}
\]

The enolate anion is often responsible for the major fragmentations of the carboxylate species e.g.

\[
\text{RCH}_2\text{CO}_2\text{H} \rightarrow \left[ \text{HO}^- \left( \text{RCH}=\text{C}=\text{O} \right) \right] \rightarrow \begin{cases} \text{HO}^- + \text{RCHCO} \\ \text{H}_2\text{O} + \text{R}=\text{CO}^- \end{cases}
\]
The decarboxylation reaction (eqn 2.4) will only be detected when the electron affinity of \( R^- \) is positive. For most simple alkyl carboxylic acids the electron affinity of \( R^- \) is negative\(^{161} \) (i.e. the radical is more stable than the anion) and hence the decarboxylation reaction is not observed in the collisional activation mass spectra of these species. The only alkyl carbanions that have been detected from the decarboxylation reaction are \( R = \) methyl, neopentyl, 2- and 3-methylbutyl as well as several cyclic carbanions such as cyclopentylmethyl, 1- and 2-cyclopropylmethyl carbanions\(^{162} \).

\[
\text{RCO}_2^- \rightarrow R^- + \text{CO}_2 \tag{2.4}
\]

This chapter discusses the gas phase chemistry of anions that could behave somewhat akin to the carboxylate species, i.e. anions that must proton transfer or rearrange prior to fragmentation.

One example would be deprotonated oximes i.e.

\[
\begin{align*}
\text{R}^1\text{R}^1'&=\text{N}^=\text{OH} \\
\rightarrow & \\
\text{R}^1\text{R}^1'&=\text{N}^=\text{O}^- \\
\text{R}, \text{R}^1 &= \text{H, alkyl, aryl} \tag{2.5}
\end{align*}
\]

It is unlikely that fragmentation can be directly initiated through the \( O^- \) anion and either rearrangement or proton transfer would be expected to precede fragmentation. The proton transfer reaction (eqn 2.6) should be a facile process since the acidities of the oxyanion \( 2a \) and the carbanion \( 2b \) should differ only by some 30 kJmol\(^{-1} \).

\[
\begin{align*}
\text{R}^1\text{R}^1'&=\text{N}^=\text{O}^- \\
\rightarrow & \\
\text{R}^1\text{R}^1'&=\text{N}^=\text{OH} \\
\text{R}^1 & \tag{2.6}
\end{align*}
\]
For example the $\Delta H^o_{\text{acid}}$ values* for Me$_2$C=NOH$^{163}$ and (CH$_3$)$_2$C=NOMe$^{164}$ are 1532 and 1561 kJmol$^{-1}$ respectively. Under collisional activation conditions the energy required for proton transfer should be small enough such that proton transfer would give the carbanion and hence fragmentation through the $\alpha$ carbanion would seem likely to occur.

The fragmentations of alkyl and aryl ketoximes, ketoxime ethers, and alkyl and aryl aldoximes have been investigated and evidence in favour of a number of rearrangement reactions will be discussed in this chapter.

2.2 Results and Discussion

2.2.1 Alkyl Ketoximes

Oxime anions are produced by deprotonation of alkyl ketoximes with NH$_2^-$ To investigate the site of deprotonation in an oxime, the deuterium labelled oximes R$_2$C=NOD were prepared. Using NH$_2^-$ oximes such as R$_2$C=NOD yield both (M–H$^+$)$^-$ and (M–D$^+$)$^-$ ions. For acetoxime, Me$_2$C=NOD, the ratio of deprotonation:dedeuteration, i.e. (M–H$^+$)$^-$ : (M–D$^+$)$^-$ is approximately 4.5:1; a similar ratio is confirmed for other dialkyl ketoximes. This ratio reflects the acidities of the OH and CH=C=N$^-$ protons, the OH proton is the more acidic, but the two positions differ in acidity by only some 30 kJmol$^{-1}$.

---

* $\Delta H^o_{\text{acid}}$ is the energy required to effect the gas phase dissociation $\text{AH} \rightarrow \text{A}^- + \text{H}^+$. 
2.2.2 Collision Induced Dissociations of deprotonated Alkyl Ketoximes

The collisional activation mass spectra of deprotonated ketoximes are presented in Tables 2.1 and 2.2. All alkyl ketoximes behave similarly, and acetone ketoxime is the simplest case to explain the fragmentations in this series. Figures 2.1 and 2.2 illustrate the spectra of the (M–H+)− and (M–D+)− ions produced from deprotonated Me2C=NOD. The two spectra show similar fragmentations, the major fragmentations are the loss of H+, H2O and CH4 and formation of OH−. Less abundant peaks are observed for the loss of NOH+ and the formation of CNO−, −CH2CN, NO− and CN−. These fragmentations generally occur in all dialkyl ketoximes (see Tables 2.1 and 2.2). The characteristic decomposition of virtually all oximes is the loss of water, which generally gives the base peak in the spectra of ketoximes. This was somewhat unexpected, as loss of water is not a usual feature in negative ion spectra of anions containing O− functionality. The only cases that have been reported in which a species eliminates water to give the base peak of the spectrum occur when such a loss gives a stabilised anion (e.g. a conjugated or aromatic anion).

The spectrum of the (M–H+)− ion from Me2C=NOD (Figure 2) shows losses of H2O and HOD in the ratio of 6.5:1, similar results (Tables 2.1 and 2.2) are obtained from the (M–H+)− ion derived from Pr2C=NOD (ratio of H2O:HOD loss 2:1), and the (M−H+)− ion from (Me)(Et)C=NOD (ratio of H2O:HOD loss 2:1). Thus the loss of water from the deprotonated oxime is preceded by rapid interconversion between the carbanion and the oxyanion as shown in eqn 2.7.

\[
\begin{align*}
2a \\
-CH_2 & \quad \text{OD} \\
\text{CH}_3 & \\
2b \\
\text{CH}_2D & \quad \text{O}^- \\
\text{CH}_3 &
\end{align*}
\]
The data obtained from these three spectra imply that a loss of water may occur following \( H^+ \) (or \( D^+ \)) transfer and that a small isotope effect (\( H/D = 1.3 \)) operates in favour of elimination of \( H_2O \) rather than \( HOD \). It must be noted that in the case of unsymmetrical ketoximes [e.g. \( (\text{Me})(\text{Et})C=\text{NO}D \)] partial equilibration of the oxime anion occurs with both carbanion centres, but the extent of exchange is not the same in all cases, and no clear trend is apparent. A further point to note is that a small amount of a \( D_2 \) impurity will affect the observed \( H_2O/HOD \) ratio. For example \( R^1(R^2CHD)C=\text{NO}D \) will give mainly \( R^1(R^2CHD)C=\text{NO}^- \) and this ion may give different \( H_2O/HOD \) ratios than will the carbanion \( R^1(R^2CH^-)C=\text{NO}D \) unless complete equilibration has occurred. However in all cases shown in Tables 2.1 and 2.2, the loss of \( H_2O \) is always more pronounced than loss of \( HOD \) from the \( (M-H^+)^- \) ions from the \( D_1 \) labelled systems.

The following schemes outline the mechanisms proposed for the fragmentations of deprotonated acetone ketoxime.

The loss of \( H^+ \) is a major process in the fragmentation of ketoximes. Loss of a radical to form a stabilised ion radical is a common fragmentation of even electron anions\(^{111,128}\), and the hydrogen atom can be eliminated from either ion \( 2c \) or \( 2d \) to give the products shown in eqns 2.8 and 2.9.

\[
\begin{align*}
\text{CH}_2\text{C} (\text{Me}) \text{NO}^- & \quad \text{H}^+ \quad \text{Me}_2\text{C} = \text{N}^- \text{O}^- \\
\text{CH}_3 & \quad \text{CH}_2
\end{align*}
\]

\[
2.8 \quad 2c \quad 2d
\]

The eliminations of water, methanol and formation of hydroxide ion are proposed to occur from carbanion \( 2d \) via a negative ion Beckmann rearrangement, (see 2.2.2.1) i.e.
The competitive elimination of methane also occurs via a similar process, methyl anion migration may form the transient ion complex 2d and the methyl anion deprotonates the acidic proton attached to the oxygen atom (eqn 2.13).

The formation of NO\(^-\) may occur from ion 2c and the loss of NOH\(^+\) may occur through ion 2d as shown in eqn 2.14. The mechanisms for the formation of CN\(^-\) and CNO\(^-\) are not known.
Figure 2.1. CA mass spectrum of the ion $\text{Me}_2\text{C} = \text{NOD} - \text{H}^+$\textsuperscript{−}

Figure 2.2. CA mass spectrum of the ion $\text{Me}_2\text{C} = \text{NOD} - \text{D}^+$\textsuperscript{−}
<table>
<thead>
<tr>
<th>PARENT ION</th>
<th>H⁺</th>
<th>D⁺</th>
<th>Me⁺</th>
<th>CH₄</th>
<th>CD₄</th>
<th>H₂O</th>
<th>HOD</th>
<th>D₂O</th>
<th>Et⁺</th>
<th>NO⁺</th>
<th>NOD</th>
<th>MeOH</th>
<th>EtOH</th>
<th>PrOH</th>
<th>CNO⁻</th>
<th>CH₂CN⁻</th>
<th>CD₂CN⁻</th>
<th>NO⁻</th>
<th>CN⁻</th>
<th>HO⁻</th>
<th>DO⁻</th>
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<tr>
<td>Me₂CNOH - H⁺⁻</td>
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<td>15</td>
<td>85</td>
<td>70</td>
<td>6</td>
<td>2²a</td>
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<td>1</td>
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<tr>
<td>(CD₃)₂CNOD - D⁺⁻</td>
<td>100</td>
<td>10</td>
<td>70</td>
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<tr>
<td>Me₂CNOD - H⁺⁻</td>
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<td>14</td>
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<tr>
<td>Et₂CNOH - H⁺⁻</td>
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<tr>
<td>Pr₂CNOH - H⁺⁻</td>
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<td>8</td>
<td>65</td>
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<td>Pr₂CNOD - D⁺⁻ (c)</td>
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<td>100</td>
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<tr>
<td>Pr₉Pr₂CNOH - H⁺⁻</td>
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<td>15</td>
<td>67</td>
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<td>2</td>
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<tr>
<td>(CH₃CH₂CD₂)₂CNOD - D⁺⁻</td>
<td>20</td>
<td>100</td>
<td>38</td>
<td>3²d</td>
<td></td>
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<tr>
<td>(Pr)(CD₃CH₂CD₂)₂CNH - H⁺⁻</td>
<td>42</td>
<td>100</td>
<td>9</td>
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</table>

a) loss of MeOH yields -CH₂CN; b) CNO⁻ and -CD₂CN = 42 a.m.u.; c) the ion Pr₂CNOD - H⁺⁻ loses H₂O and HOD in the approximate ratio 2:1 (weak spectrum); d) in this case loss of CH₃CH₂CD₂OD gives m/z = 69 (3%); e) this spectrum shows two peaks in this region m/z = 102[30% (-CH₃CH₂⁺)], 99[10% (-CD₃CH₂⁺)].
2.2.2.1 The Beckmann Rearrangement

The rearrangement of a ketoxime to an amide was discovered in 1886 by Beckmann\textsuperscript{165}, the rearrangement is brought about by acids including Lewis acids (e.g. H\textsubscript{2}SO\textsubscript{4}, PCl\textsubscript{5}). Under non-isomerising conditions in solution, the mechanism consists of a simultaneous intramolecular migration of the group anti (or trans) to the departing protonated hydroxyl group with retention of configuration\textsuperscript{166}. The nitrogen atom is essentially electron deficient during the migration i.e.

\[
\begin{align*}
\text{R}^1\text{N}^+\text{OH} & \xrightarrow{\text{H}^+} \text{R}^1\text{N}^+\text{OH}_2^+ \xrightarrow{\text{O}} \text{R}^1\text{C}^=\text{NR}^1 \xrightarrow{\text{H}_2\text{O}} \text{R}\text{NHR}^1
\end{align*}
\]

For aldoximes, the conventional Beckmann rearrangement is known to be sluggish, and hydrogen only migrates under special catalytic conditions\textsuperscript{167}. Nitriles are often formed from aldoximes under the classical conditions of the Beckmann rearrangement\textsuperscript{168}.

This rearrangement does not occur under basic conditions, in alkaline base ketoximes are hydrolysed to the corresponding ketone. An anomalous reactions of an oxime (under basic conditions) was reported\textsuperscript{169} in 1949; reduction of acetophenone oxime with lithium aluminium hydride gave a mixture of phenylethylamine and N-ethylaniline (eqns 2.16). It was suggested that this may be a base catalysed Beckmann rearrangement. However, it has since been shown that the formation of the secondary amine arises from an electrophilic aluminium hydride catalysed Beckmann rearrangement, followed by reduction of the amide\textsuperscript{170,171}. Furthermore, hydroxylamines have been shown to be intermediates in the aluminium hydride reduction of oximes (with a milder reducing agent, e.g. diborane, oximes may be reduced to
hydroxylamines\textsuperscript{172}). There have been no reports in the literature of base-catalysed Beckmann rearrangements.

Beckmann rearrangements of molecular radical cations, formed via electron impact have been shown not to occur\textsuperscript{173,174}, except for some arylheterocyclic ketoximes\textsuperscript{175}. Beckmann rearrangements of oximes protonated (via methane chemical ionisation) do occur in the gas phase\textsuperscript{176,177}. The (M + H - H\textsubscript{2}O)+ ions of protonated syn and anti oximes of acetophenone oxime\textsuperscript{176} give different CID spectra e.g.

\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{\text{C}}\text{\text{H}}_{\text{3}} \quad \text{N} \quad \text{OH} & \xrightarrow{\text{H}^+} \quad \text{Ph} \quad \text{Me} \\
\text{\text{C}}\text{\text{H}}_{\text{3}} \quad \text{N} \quad \text{OH}_2^+ & \xrightarrow{\text{CID}} \quad \text{C}_6\text{H}_5\text{N}^+ \\
\text{Ph} & \quad \text{Me} \\
\text{\text{C}}\text{\text{H}}_{\text{3}} \quad \text{N} \quad \text{OH} & \xrightarrow{\text{H}^+} \quad \text{Ph} \quad \text{Me} \\
\text{\text{C}}\text{\text{H}}_{\text{3}} \quad \text{N} \quad \text{OH}_2^+ & \xrightarrow{\text{CID}} \quad \text{C}_7\text{H}_5^+ \\
\end{align*}

\textit{Scheme 2.2}
2.2.2.2 The Negative Ion Beckmann rearrangement

A proposed mechanism for the negative ion Beckmann rearrangement is shown in Scheme 2.3.

\[
\begin{align*}
\text{NH}_3 \xrightarrow{2e} & \quad \text{HO}^- + \text{CH}_2=\text{C} \equiv \text{NMe} \\
\text{OH}^- & \quad \text{H}_2\text{O} + \text{CH}_2=\text{C} \equiv \text{NCH}_2^- \\
\text{MeOH} + \text{CH}_3\text{CN} & \quad 2.21
\end{align*}
\]

Scheme 2.3

If the oxyanion 2c forms via initial deprotonation, proton transfer to the carbanion d will occur under the conditions of collisional activation, and this ion initiates the rearrangement in which a methyl anion migrates to the nitrogen atom to give the neutral species in the ion complex.

The equilibration between anions 2c and 2d has already been proposed, and it is further suggested that loss of water occurs through 2d via a negative Beckmann rearrangement; the rearrangement occurs via methyl anion migration to the nitrogen atom to give the ion complex 2e in which HO⁻ is solvated by CH₂=Ç=NMMe (Scheme 2.3).

Ion complex 2e may competitively decompose by

\begin{enumerate}
\item[i)] dissociation to give OH⁻, eqn 2.19
\item[ii)] elimination of H₂O, eqn 2.20
\item[iii)] an internal nucleophilic substitution reaction initiated by OH⁻ to give methanol and deprotonated acetonitrile, eqn 2.21
\end{enumerate}

In solution, the mechanism of the Beckmann rearrangement consists of the formation of an electron deficient nitrogen atom by the partial ionisation of the
oxygen-nitrogen bond (eqn 2.15). For the negative ion Beckmann rearrangement, the formation of an electron deficient nitrogen atom would imply a stepwise reaction pathway i.e.

\[
\text{The intermediate ion complex involves the migration of the methyl group to a nitrene. The formation of hydroxide ion from ion 2h to give the nitrene is termed an } \alpha \text{ effect}^{178} \text{ (in solution nucleophiles that contain a heteroatom adjacent to the reaction centre are found to be more reactive than would be expected from their basicity, this increased reactivity is called an } \alpha \text{-effect). However DePuy}^{179} \text{ has suggested that } \alpha \text{ effects do not occur for nucleophilic reactions in the gas phase, therefore it is possible that the Beckmann reaction is concerted in the gas phase (see Scheme 2.3).}
\]

The elimination of water (eqn 2.20) is the major fragmentation of virtually all deprotonated oximes. Comparison of the rearrangement of ion 2g (eqn 2.15, page 51) [i.e. the acid catalysed solution Beckmann rearrangement] and the rearrangement of ion 2e (Scheme 2.3) [i.e. the gas negative ion Beckmann rearrangement] clearly illustrates the similarities of the two processes. The comparison is especially interesting as it is one of the few examples of a solution phase rearrangement that occurs in solution only under acidic conditions whereas in the gas phase the same rearrangement occurs under both acidic and basic conditions.
2.2.2.3 The Beckmann Rearrangement of unsymmetrical ketoximes

The simplest example of an unsymmetrical ketoxime is butan-2-one ketoxime, the oxyanion $2i$ produced from this ketoxime can proton transfer to produce two distinct carbanions $2j$ and $2k$ (Scheme 2.4). Ion $2i$ also has a further resonance contributor $2l$. The resonance contributor $2l$ would imply that for unsymmetrical ketoximes, specific trans migration would not be expected since isomerisation of the carbon-nitrogen double bond should occur.

As the two carbanions are different this system would be expected to yield two Beckmann rearrangements, viz, the carbanion $2k$ will lead to ethyl migration to produce ion complex $2m$, and carbanion $2j$ will lead to methyl migration to produce ion complex $2n$ (Scheme 2.5). Deprotonation by $\text{HO}^-$ in the ion complexes then leads to the formation of the ions as shown in Scheme 2.5.
The product ions in eqns 2.23, 2.25 and 2.26 indicate that the HO⁻ ion could deprotonate the neutral species in complexes 2m and 2n at three different sites. The question arises as to where the hydroxyl ion actually does deprotonate the neutral and eliminate H₂O.

The spectra of the ions formed from the following ketoximes:

\[
\begin{align*}
CD_3(CH_3CD_2)C=NOD & \quad CD_3(CH_3CH_2CD_2)C=NOD & \quad CD_3(Me_2CD)C=NOD \\
(CD_3CH_2)_2C=NOD & \quad (CH_3CH_2CD_2)_2C=NOD
\end{align*}
\]

are shown in Tables 2.1 and 2.2, and the spectra of (Me)(Et)C=NO⁻ and CD₃(CH₃CD₂)C=NO⁻ are compared in Figures 2.3 and 2.4. The ions \(CD_3(EtCD_2)C=NO⁻\) and \((EtCD_2)_2C=NO⁻\) eliminate \(D_2O\) exclusively, and loss of \(D_2O\) is the base peak in both spectra. The ions \(CD_3(EtCD_2)C=NO⁻\) and \(CD_3(Me_2CD)C=NO⁻\) show a small loss of \(HOD\) (4 and 7\% respectively, loss of \(D_2O\) is still the base peak of both spectra). Additionally, the ion \(CH_3(CH_3CH_2)CN=O⁻\) losses \(H_2O\) exclusively, implying that:

i) the loss of water occurs with both hydrogen atoms originating from the α carbon atoms of the oxime,
ii) the process leading to formation of the ion $-\text{CH}_2\text{CH}=$C$=\text{NMe}$ and elimination of water (eqn 2.26) does not occur [this is in accord with the protons of the NMe group (eqn 2.25) having greater acidity].

The spectrum of deprotonated butan-2-one ketoxime shows the elimination of both methanol and ethanol (eqns 2.24 and 2.27). This substantiates that both methyl and ethyl groups migrate to the nitrogen atom. The ratio of ethanol loss to methanol is 4:1 [EtOH:MeOH]. For other unsymmetrical ketoximes (Table 2.2) the larger alkanol is lost preferentially, e.g. (Me)(Pr)C=NO$^-$ [PrOH:MeOH, 5:1], (Et)(Pr)C=NO$^-$ [PrOH:EtOH, 6:5] and (Me)(Bu)C=NO$^-$ loses only butanol to give $-\text{CH}_2\text{CN}$. These values are unlikely to mirror the relative migratory aptitudes of the various substituents, the trend is more likely to reflect the thermochemistry of the competing processes, i.e. elimination of the larger alkanol is more favoured.

There is a possibility that there may be an alternative mechanism to consider. This is the Neber rearrangement$^{180}$, which (in solution) is typified by the base catalysed conversion of O-sulfonyl oximes to $\alpha$-amino ketones via azirines$^{181}$ i.e.

\[
\begin{array}{cccccc}
\text{RCH}_2\text{C=NO} & \rightarrow & \text{RCH} & \rightarrow & \text{RCH} & \rightarrow \\
\text{NOSO}_2\text{Ar} & \text{NOSO}_2\text{Ar} & \text{H}_2\text{O} & \text{H}_2\text{O} & \text{R} & \text{R} \\
\end{array} \quad 2.28
\]

For the case of deprotonated acetone oxime, this alternative 1,2 rearrangement would involve direct attack of the methylene anion at nitrogen i.e.

\[
\begin{array}{cccccc}
\text{CH}_3 & \text{CH}_3 & \text{CH}_2\text{C=NO} & \rightarrow & \text{CH}_2\text{C=NO} & \rightarrow \\
\text{N} & \text{N} & \text{C} & \rightarrow & \text{C} & \rightarrow \\
\text{OH} & \text{OH} & \text{H}_2\text{O} & \text{H}_2\text{O} & \text{CH}_2\text{C} & \text{NCH}_2^- \\
\end{array} \quad 2.29
\]
In considering this mechanism as an alternative to the Beckmann rearrangement, although consistent with most of the deuterium labelling data, the mechanism would seem a less likely possibility, given the relative instability of an azirine ring, and in any case the Neber rearrangement ultimately produces the same product ion as the Beckmann rearrangement (eqn 2.29). Nevertheless, such a possibility cannot be totally excluded on available evidence.
Figure 2.3. CA mass spectrum of the ion Me(Et)C=NOH - H⁺⁻

Figure 2.4. CA mass spectrum of the ion CD₃(CH₃CD₂)C=NOD - D⁺⁻
Table 2.2. Collision Activation Mass Spectra of deprotonated unsymmetrical ketoximes

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<thead>
<tr>
<th>PARENTION</th>
<th>H'</th>
<th>D'</th>
<th>Me*</th>
<th>CH4</th>
<th>CD4</th>
<th>H2O</th>
<th>HOD</th>
<th>D2O</th>
<th>El*</th>
<th>Pr*</th>
<th>MeOH</th>
<th>EtOH</th>
<th>PrOH</th>
<th>C3H6</th>
<th>CNO^-</th>
<th>-CH3CN</th>
<th>-CHDCN</th>
<th>-CD2CN</th>
<th>NO^-</th>
<th>CN^-</th>
<th>HO^-</th>
<th>DO^-</th>
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<tbody>
<tr>
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<td>100</td>
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<td>0.5</td>
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<td>Et(Pr)CNOO - H'^-</td>
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<tr>
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<td>15^e</td>
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<td>Me(Bu)CNOO - H'^-</td>
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<td>100</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.2</td>
<td>9</td>
<td></td>
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<tr>
<td>(sec Pr)CNOO - H'^-</td>
<td>24</td>
<td>6</td>
<td>100</td>
<td>100</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.2</td>
<td>9</td>
<td></td>
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<tr>
<td>CD3(Me2CD)CNOO - D'^-</td>
<td>20</td>
<td>6</td>
<td>7</td>
<td>100</td>
<td>4</td>
<td>3^f</td>
<td>4^f</td>
<td>4^f</td>
<td>1</td>
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</tr>
<tr>
<td>Me(secBu)CNOO - H'^-</td>
<td>29</td>
<td>100</td>
<td>14</td>
<td>100</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.4</td>
<td>0.2</td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>Me(terBu)CNOO - H'^-</td>
<td>31</td>
<td>32</td>
<td>100</td>
<td>100</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
<td>0.5</td>
<td>51</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et(Pr)CNOO - H'^-</td>
<td>21</td>
<td>30</td>
<td>100</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

a) Loss of EtOH yields -CHDCN m/z = 41, loss of EtOD yields -CH2CN m/z = 40; b) Loss of CD3CH2OD yields -CD2CN m/z = 42 (see point c); c) CNO^- and -CD2CN m/z = 42 a.m.u.; d) Loss of PrOH yields -CH2CN m/z = 40; e) in this case the peak at m/z = 56 corresponds to loss of C3H6D3; f) in this case the peak at m/z = 56 corresponds to loss of C3H5D2; g) in this case the peak at m/z = 42 corresponds to loss of Me2CDOD (see point c).
2.2.3 The elimination of $R^+$ from the $(RCH_2)_2C=NO^-$ species

For deprotonated ketoximes such as $\text{Me}(RCH_2)C=NO^-$ and $(RCH_2)_2C=NO^-$, where $R \geq \text{Et}$, a $\beta$ cleavage (to the trigonal carbon) occurs which involves loss of the elements of an alkyl radical.

The data in Table 2.2 shows that $\text{Me}(\text{Et})C=NO^-$ has a small loss of Me $^+$ (cf. loss of H $^+$ eqns 2.8, 2.9), whereas the ions $\text{Me}(\text{Pr})C=NO^-$ [loss of $\text{C}_2\text{H}_5$, 30%], $\text{Me}(\text{Bu})C=NO^-$ [loss of $\text{C}_3\text{H}_7$, 18%], $\text{Et}(\text{Pr})C=NO^-$ [loss of $\text{C}_2\text{H}_5$, 30%] show substantial losses of either $\text{C}_2\text{H}_5^+$ or $\text{C}_3\text{H}_7^+$. Labelling studies in cognate systems$^{77,124}$ have shown that the process does not involve simple cleavage of the alkyl radical $R^+$: in the systems $(\text{CH}_3\text{CH}_2)(\text{CD}_3\text{CH}_2)\text{CHCO}_2^-$ and $\text{PhC}^-(\text{CH}_3\text{CH}_2)(\text{CD}_3\text{CH}_2)$ the loss of $'\text{C}_2\text{H}_5^+$ involves initial loss of $\text{H}^+$ followed by ethene. The elimination of $'\text{C}_2\text{H}_5^+$ from $\text{Et}_2\text{CHCO}_2^-$ and $\text{PhC}^-(\cdot)\text{Et}_2$ have $\text{H}/\text{D}$ isotope effects of 1.98 and 2.25 respectively. The large deuterium isotope effect associated with each terminal methyl group implies that the rate determining step involves either loss or transfer of a terminal hydrogen atom. This primary isotope effect is indicative of a stepwise reaction pathway i.e. initial loss of $\text{H}^+$ followed by elimination of ethene. This stepwise process is apparently more favoured than processes which involve simple alkyl cleavage. Eichinger$^{127}$ has proposed that initial homolytic cleavage of a C–H bond results in the formation of a stabilised intermediate which in effect increases the rate of reaction with respect to both simple radical loss and with other competing reactions. In several cases loss of $(\text{C}_2\text{H}_4 + \text{H}^+)$ produces the base peak of the spectrum. Furthermore, the unsymmetrical oxime $\text{Et}(\text{Pr})C=NO^-$ undergoes pronounced loss of $'\text{C}_2\text{H}_5^+$ but no loss of Me $^+$.

The spectrum of the ion $\text{Pr}(\text{CD}_3\text{CH}_2\text{CH}_2)C=NO^-$ is shown in Figure 2.5. Losses of both $'(\text{CH}_3\text{CH}_2)^+$ and $'(\text{CD}_3\text{CH}_2)^+$ are observed. The ratio of $(\text{CH}_3\text{CH}_2)^+:(\text{CD}_3\text{CH}_2)^+$ loss is 100:33, implying a primary isotope effect $\text{H}/\text{D} = 3.0$, indicating
that the rate determining step involves either loss or transfer of a terminal hydrogen atom.

![Diagram of chemical reactions involving nitro compounds.]

**Scheme 2.6**

The Eichinger model suggests that the incipient radical $2\sigma$ ($2\sigma'$) is stabilised by interaction of the semi occupied $p$ orbital with the antibonding $\pi^*$ orbital of the oxime which results in endocyclic ring closure to give the intermediates $2\rho$ ($2\rho'$). This intermediate is stabilised by delocalisation of the carbon centred radical with the non bonding fully occupied $p$ orbitals. The intermediates $2\rho$ ($2\rho'$) the fragment to eliminate $C_2H_4$ and $C_2H_2D_2$ as shown in Scheme 2.6. This mechanism is consistent with the previously cited examples$^{77,124}$, and illustrates the stepwise loss of $H^+ + C_2H_4$. 
Figure 2.5. CA mass spectrum of the ion \( \text{Pr}((\text{CD}_3\text{CH}_2\text{CH}_2)\text{C}=\text{NOH} - \text{H}^+)^{-} \)
2.2.4 Collision Induced dissociations of O-Alkyl Ketoxime Ethers

Deprotonation of ketoxime alkyl ethers, such as acetone O-methyl ketoxime, by $\text{NH}_2^-$ gives the ion $\text{-CH}_2(\text{Me})\text{C}=\text{NOMe}$. This ion is analogous to ion $d_2$, the precursor ion to the Beckmann rearrangement. If the proposed mechanism for the rearrangement described above is correct, then the ion $\text{-CH}_2(\text{Me})\text{C}=\text{NOMe}$ should both produce $\text{MeO}^-$ and eliminate $\text{MeOH}$. The spectra of various oxime ethers are listed in Table 2.3: the loss of $\text{ROH}$ and the formation of $\text{RO}^-$ [from the ion $\text{-CH}_2(\text{Me})\text{C}=\text{NOR}$] are the major fragmentation processes. For example, the spectra of deprotonated O-methyl and O-ethyl acetophenone ketoxime show major losses of methanol and ethanol respectively. These fragmentations are rationalised by the Beckmann process (for acetone O-methyl ketoxime) i.e.

\[
\text{MeO}^- + \text{CH}_2=\text{C}=\text{NMe} \quad 2.32
\]

\[
\text{MeOH} + \text{CH}_2=\text{C}=\text{NCH}_2^- \quad 2.33
\]

Scheme 2.7

The Beckmann rearrangement product of deprotonated acetone ketoxime should be the ion $\text{CH}_2=\text{C}=\text{NCH}_2^-$ $(m/z=54$, eqn 2.20, Scheme 2.3) and the ion from the rearrangement of deprotonated acetone O-methyl ketoxime should also produce the same ion (eqn 2.33, Scheme 2.7). The collisional activation and charge reversal (positive ion) spectra (MS/MS/MS) of $m/z=54$ are recorded in Table 2.4. The spectra are consistent with the structure $\text{CH}_2=\text{C}=\text{NCH}_2^-$ (both CA and CR spectra show pronounced loss of $\text{CH}_2$). Secondly, the spectra (CA and CR MS/MS/MS) of the ion $m/z=54$ derived from the two different parent ions are identical, i.e. the respective losses of $\text{H}_2\text{O}$ and $\text{MeOH}$ from deprotonated ketoximes and ketoxime O-methyl ethers yield the same product ion.
Table 2.3. Collision Activation Mass Spectra of deprotonated ketoimine Q-alkyl ethers

<table>
<thead>
<tr>
<th>PARENT ION</th>
<th>H'</th>
<th>Me'</th>
<th>Et'</th>
<th>Pr'</th>
<th>MeOH</th>
<th>EtOH</th>
<th>PrOH</th>
<th>PhCH₂OH</th>
<th>C₆H₅</th>
<th>PhCH₂*</th>
<th>PhCH₂⁻</th>
<th>C₆H₅⁻</th>
<th>PhCH₂O⁻</th>
<th>PrO⁻</th>
<th>EtO⁻</th>
<th>MeO⁻</th>
<th>CH₂CN</th>
<th>CN</th>
</tr>
</thead>
<tbody>
<tr>
<td>~CH₂(Me)C=NOMe</td>
<td>84</td>
<td>5</td>
<td>100</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>~CH₂(Me)C=NOEt</td>
<td>88</td>
<td>15</td>
<td>100</td>
<td>1</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>100</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>~CH₂(Me)C= NOPr</td>
<td>22</td>
<td>11</td>
<td>70</td>
<td>1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>100</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>~CH₂(Me)C= NOBz</td>
<td>80</td>
<td>28</td>
<td>5</td>
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<td></td>
<td></td>
<td></td>
<td>8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>~CH₂(Ph)C=NOMe</td>
<td>100</td>
<td>16</td>
<td>99</td>
<td>6</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>18</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>~CH₂(Ph)C= NOEt</td>
<td>100</td>
<td>30</td>
<td>27</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>2</td>
<td>100</td>
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</tr>
</tbody>
</table>

Chapter 2
Table 2.4. Collisional Activation (CA) and Charge Reversal (CR) mass spectra (MS/MS/MS) of Beckmann Product ions from Me₂C=NO⁻ and -CH₂(Me)C=NOMe

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>PRODUCT ION</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM [m/z (abundance)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂C=NOH - H⁺⁻</td>
<td>CH₂=C=NCH₂⁻</td>
<td>CA MS/MS/MS</td>
<td>40(100)</td>
</tr>
<tr>
<td></td>
<td>(- H₂O, m/z 54)</td>
<td>CR MS/MS/MS</td>
<td>54(4), 53(26), 52(100), 51(32), 40(24), 39(33), 38(14), 37(5), 28(31), 27(32), 26(38), 25(5), 14(4)</td>
</tr>
<tr>
<td>Me₂C=NOMe - H⁺⁻</td>
<td>CH₂=C=NCH₂⁻</td>
<td>CA MS/MS/MS</td>
<td>40(100)</td>
</tr>
<tr>
<td></td>
<td>(- MeOH, m/z 54)</td>
<td>CR MS/MS/MS</td>
<td>54(3), 53(24), 52(100), 51(31), 40(26), 39(35), 38(15), 37(5), 25(35), 27(30), 26(38), 25(5), 14(4)</td>
</tr>
</tbody>
</table>
2.2.5 Collision induced dissociations of Aryl Ketoximes

The spectra of deprotonated aryl ketoximes are listed in Table 2.5. The behaviour of alkyl aryl ketoximes and alkyl oximes is similar. Deprotonated acetophenone, propiophenone and butyrophenone ketoximes show pronounced loss of H⁺ and H₂O. Deuterium labelling data for acetophenone ketoxime indicates that elimination of H₂O is likely to occur following a Beckmann rearrangement. However, the migrating group is Ph (rather than methyl) as is illustrated by the following mechanism.

\[
\begin{align*}
\text{Ph} & \quad \text{CD₃} \\
\text{N} & \quad \text{O} \\
\downarrow & \quad \text{C} \\
\text{CD₂} & \quad \text{C} \quad \text{N(C₆H₅)} \\
\end{align*}
\]

The fragmentations of deprotonated ketoximes of the series Me[Ph(CH₂)ₙ]C=NOH (n=1..4) show several interesting processes as the chain length increases. When n=1, the ion Me(PhCH₂)C=NO⁻ loses H⁺ and undergoes the Beckmann rearrangement to eliminate H₂O as the major process, minor processes involve formation of PhCH₂⁻ and Ph⁻. For Me(PhCH₂CH₂)C=NO⁻ (n=2), the major fragmentation is the formation of the benzyl anion, PhCH₂⁻. The ratio of PhCH₂⁻ formation against H₂O elimination is 2:1, i.e. the formation of PhCH₂⁻ is more favourable than the Beckmann rearrangement in this system.

The spectrum of deprotonated Me(PhCH₂CH₂CH₂)C=NO⁻ (n=3) emphasises the ready proton transfer reactions of anions in the gas phase\(^{77,112}\). The spectra of deuterium labelled analogues of this ion are listed in table 2.5, and the particular example of Me(PhCD₂CH₂CH₂)C=NO⁻ is illustrated in Figure 2.6. In this case, the Beckmann rearrangement is suppressed by more favourable
fragmentations. The labelling studies suggest that proton transfer from O⁻ (via a cyclic six membered transition state to the benzylic position) yields ion 2p, which eliminates styrene to form deprotonated acetone ketoxime (eqn 2.35). Alternatively proton transfer from O⁻ to the α position gives ion 2q which fragments to give the benzyl anion (eqn 2.36) and also to eliminate toluene (eqn 2.37).

All aryl ketoximes so far considered have had an α sp³ carbon containing acidic hydrogen's, a necessary prerequisite to enable the Beckmann rearrangement to occur (cf. Scheme 2.2). In contrast, deprotonated benzophenone ketoxime cannot undergo the negative ion Beckmann rearrangement. Loss of H₂O is not observed (see Table 2.5); major fragment ions are formed by competitive losses of H⁺, H₂, C₆H₆ and the formation of PhO⁻. The formation of PhO⁻ must involve
a phenyl group migration to oxygen as shown in eqn 2.38 (it is possible that this migration may involve the ipso Smiles intermediate\textsuperscript{149}). The elimination of benzene is rationalised by the process shown in eqn 2.39 (in this case C\textsubscript{6}H\textsubscript{5}\textsuperscript{-} is a strong enough base to deprotonate PhCNO [\(\Delta\text{H}\textsubscript{acid}^{\circ} \text{PhH} = 1677 \text{ kJmol}^{-1}\)]\textsuperscript{183}.

\[
\begin{align*}
\text{Ph} & \xrightarrow{N} \text{Ph} \xrightarrow{-} \text{Ph} \xrightarrow{-} \text{PhO}^- \xrightarrow{\text{PhCN}} \xrightarrow{-} \text{PhO}^- + \text{PhCN} \quad 2.38 \\
\text{Ph} \xrightarrow{N} \xrightarrow{\text{PhCN}} \xrightarrow{-} \text{Ph} \xrightarrow{-} \text{(C\textsubscript{6}H\textsubscript{5})}^- \text{CNO} + \text{PhH} \quad 2.39
\end{align*}
\]

Figure 2.6. CA mass spectrum of the ion PhCD\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}(Me)C=NOH -H\textsuperscript{+}\]

* The alternative elimination of phenol is minor in comparison because PhO\textsuperscript{-} is not a strong enough base [\(\Delta\text{H}\textsubscript{acid}^{\circ} \text{PhOH} = 1461 \text{ kJmol}^{-1}\)]\textsuperscript{182} to efficiently deprotonate benzonitrile (see Table 2.5)
Table 2.5. Collision Activation Mass Spectra of deprotonated aromatic ketoximes

<table>
<thead>
<tr>
<th>Parention</th>
<th>Loss</th>
<th>Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H+</td>
<td>D+</td>
</tr>
<tr>
<td>Ph(PhCD2)CH2CNOH- H+]</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Ph(CD3)CH2CNOH- H+]</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Ph(PhCH2)CNOH- H+]</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>Ph(PhCD2)CH2CNOH- H+]</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Ph2CNOH- H+]</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>Ph(PhCH2)CNOH- H+]</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>47</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>Ph(Me)CH2CNOH- H+]</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

a) there is also a loss of NOD' (13%); b) in this case loss of PhCH2D; c) loss of PhCH=CH2 (100%), loss of PhCD=CH2 (91%); d) in this case formation of PhCD2-; e) in this case loss of PhCD=CH2; f) this spectrum also has peaks at m/z = 117 [22%, (Me2CH=NOH)], 156 [6% (-MeOH)].
2.2.6 Collision Induced dissociations of Aldoximes

The Beckmann rearrangement of aldoximes in the condensed phase occurs at a much slower rate compared to that of ketoximes, and various catalysts must be employed for the reaction to proceed\(^{167}\) (under normal acidic conditions of the ketoxime Beckmann rearrangement, nitriles often form from aldoximes\(^{168}\)). Hence alternative reaction pathways to the negative ion Beckmann rearrangement may occur with anions derived from aldoximes. One of the known alternative rearrangement pathways of aldoximes in solution is illustrated in eqn 2.40, i.e. when activated benzaldoximes are treated with dilute alkaline solution the oxime is dehydrated to the nitrile\(^{184,185}\). Similar results have been found for aromatic oxime ethers when the methine hydrogen is activated\(^{186}\).

\[
\begin{align*}
\text{o-NO}_2\text{C}_6\text{H}_4\text{C}=\text{NOH} \rightarrow & \text{NaOH} & \text{o-NO}_2\text{C}_6\text{H}_4\text{C}=\text{N} + \text{H}_2\text{O} \\
\end{align*}
\]

2.40

The spectra of deprotonated alkyl aldoximes and their labelled derivatives show many features in common with the ketoximes discussed in section 2.2.2. However, there are several features of the aldoxime spectra which are different to the ketoxime spectra described previously. The spectra of some deprotonated aldoximes are listed in Table 2.6, and examples of deprotonated MeCH=NOH and MeCD=NOH are illustrated in Figures 2.8 and 2.9. The characteristic fragmentations noted in Figure 2.8 are the formation of HO\(^{-}\), and the losses of H\(^{+}\) and H\(_2\)O, minor processes involve formation of CNO\(^{-}\) and CN\(^{-}\).

The differences between ketoxime and aldoxime spectra are illustrated for the formation of HO\(^{-}\). The peak profiles for the formation of HO\(^{-}\) from acetone ketoxime and acetaldoxime are shown in Figure 2.7, the peak from deprotonated acetone ketoxime is gaussian with no fine structure, whereas the corresponding peak from ethanaldoxime is composite, with a sharp peak
superimposed on a dish-shaped peak. The dish-shaped peak is characteristic of a fragmentation having a substantial reverse activation energy on fragmentation (see section 1.4.3.2). The dissociation is accompanied by an appreciable release of kinetic energy, whereas the sharp gaussian peak suggests a decomposition which occurs with minimal release of kinetic energy.

(a) Peak shape for formation of $\text{HO}^-$ from $[\text{Me}_2\text{C} = \text{NOH} - \text{H}^+]^-$, peak width 59eV.
(b) Peak shape for formation of $\text{HO}^-$ from $[\text{MeCH} = \text{NOH} - \text{H}^+]^-$, peak width 97eV.

Figure 2.7

The composite peak observed for ethanaloxime is indicative of two modes of formation of $\text{HO}^-$ (cf. the gaussian peak for acetone ketoxime, implying a single mechanism for formation of $\text{HO}^-$). The gaussian component of Figure 2.7b is due to the Beckmann rearrangement involving hydrogen migration to nitrogen (eqns 2.41 and 2.42); the process giving dish-shaped component of figure 2.7b involves methine hydrogen transfer to oxygen to give ion 2r which then produces $\text{HO}^-$ and eliminates $\text{H}_2\text{O}$ (eqns 2.43 and 2.44).
In the case of deprotonated unlabelled acetaldoxime the two processes produce the same product ion and hence a composite peak is observed (Figure 2.8). It is of interest to note that in the spectrum of the (M - H+)− ion of CH₃CD=NOH (Figure 2.9), the peak shape of HO− is gaussian (pathway A, Scheme 2.9) and the peak shape of DO− is dish-shape (pathway B, Scheme 2.9). The deuterium labelling has separated the composite peak in Figure 2.7 into two different components when the ion is labelled at the methine position. The spectra of propionaldoxime and butanaldoxime also show composite peak profiles for the formation of HO−; they also show respective losses of 'C₂H₅' and 'C₃H₇' yielding the radical anion 'CH₂CH=NO−' (these processes are analogous to that described in section 2.1.3).
Figure 2.8. CA mass spectrum of the ion $\text{CH}_3\text{CH}=\text{NOH} - \text{H}^+$

Figure 2.9. CA mass spectrum of the ion $\text{CH}_3\text{CD}=\text{NOH} - \text{H}^+$
Figure 2.10. CA mass spectrum of the ion syn PhCH=NOH – H+\]^−\)

Figure 2.11. CA mass spectrum of the ion anti PhCH=NOH – H+\]^−\)
The last aldoxime to be discussed is deprotonated benzaldoxime. Benzaldoxime exists as separable syn and anti isomers, whereas most aldoximes and ketoximes exist as a mixture of syn and anti isomers in solution. The MIKE spectra of the two isomers are illustrated in Figures 2.10 and 2.11. The spectra are identical, implying that the syn and anti isomers isomerise prior to fragmentation, in accord with the earlier postulate concerning isomerisation about the double bond (see ion 2, Scheme 2.4). Linked scan B/E spectra of the two isomers were also identical.

Benzaldoxime is similar to benzophenone ketoxime in the sense that it cannot fragment via the negative ion Beckmann rearrangement (see discussion in section 2.2.2.1). The major fragmentation of deprotonated benzaldoximes involves statistical loss of H⁺ from the phenyl ring, while the formation of HO⁻ and elimination of H₂O occur as minor fragmentations. The peak profile for the formation of HO⁻ is shown in Figure 2.12, in this case the peak is dish-shaped having no observable superimposed gaussian peak.

Peak shape for formation of HO⁻ from [PhCH=NOH - H⁺]⁻, peak width 113eV.

*Figure 2.12*
Labelling studies (Table 2.6) show that the formation of HO\(^-\) specifically involves the methine hydrogen, and that loss of this hydrogen together with statistical loss of a ring hydrogen constitutes the loss of H\(_2\)O. Scheme 2.10 summarises these processes, and it is process 2.45 (which is analogous to eqn 2.44) which gives rise to the dish-shaped peak shown in Figure 2.12.

\[
\text{PhC:N} + \text{DO}^- \rightarrow \text{PhC\textequiv N + DO}^- \quad 2.45
\]

\[
\text{PhCD\equiv NO}^- \rightarrow \text{Ph\textcircled{\text{C\equiv N}} + [PhC\equiv N \text{ DO}^-]} \rightarrow \text{C\equiv N} + \text{HOD} \quad 2.46
\]

*Scheme 2.10*

The spectrum of deprotonated benzophenone ketoxime exhibits formation of PhO\(^-\) (eqn 2.38). This ion does not occur in the spectrum of benzaldoxime hence for this reaction, the migratory aptitude of H is greater than that of phenyl.

2.3 Conclusions

The major fragmentation in the collisional activation mass spectra of deprotonated oximes is loss of water. We propose that the loss of water is best rationalised by a negative ion Beckmann rearrangement. This 1,2 anionic rearrangement occurs for all deprotonated oximes when an anion can form at the \(\alpha\) carbon. Deprotonated benzophenone oxime is the only species that does not undergo the negative ion Beckmann rearrangement, and in this case a different migration occurs. Deprotonated aldoximes eliminate water through two competitive mechanisms that are dependent upon the position of deprotonation. For example, deprotonation at the \(\alpha\) carbon leads to fragmentation via the Beckmann rearrangement, whereas deprotonation at the methine position and consequent elimination of water produces a dish shaped peak for this process. In all cases the products of the negative ion Beckmann rearrangement exhibit gaussian peak shapes.
### Table 2.6. Collision Activation Mass Spectra of deprotonated aldoximes

<table>
<thead>
<tr>
<th>PARENTION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCH=NOCHD</td>
<td>H*</td>
<td>23a</td>
</tr>
<tr>
<td>MeCH=NOH</td>
<td>D*+</td>
<td>32b</td>
</tr>
<tr>
<td>MeCD=NOH</td>
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<td>28b</td>
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<td>CD3CH=NOH</td>
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<tr>
<td>EtCH=NOH</td>
<td>H*</td>
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<tr>
<td>PrCH=NOCHD</td>
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<td>H*+</td>
<td>100c</td>
</tr>
<tr>
<td>EtCD2CH=NOH</td>
<td>D*+</td>
<td>67</td>
</tr>
<tr>
<td>BuCH=NOCHD</td>
<td>D*+</td>
<td>67</td>
</tr>
<tr>
<td>Me2CH=NOH</td>
<td>H*+</td>
<td>100c</td>
</tr>
<tr>
<td>syn PhCH=NOH</td>
<td>D*+</td>
<td>100</td>
</tr>
<tr>
<td>anti PhCH=NOH</td>
<td>D*+</td>
<td>100</td>
</tr>
<tr>
<td>syn PhCD=NOH</td>
<td>H*+</td>
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</tr>
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<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>100</td>
<td>23a</td>
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<td>32b</td>
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</tr>
<tr>
<td>2</td>
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</table>

- a) loss of CH4 gives CNO-; b) loss of CH3D or CD3H (as appropriate) gives CNO-; c) D2O and CD3H m/z = 20 a.m.u.; d) this spectrum also shows a peak at m/z = 52 (35%) corresponding to loss of (H2O + H2); e) this spectrum shows the following peaks in this region m/z = 52 (20%, - H2O), 67 (17%, - H2O + H2) and 66 (19%, - (HOD + H2) and/or - (H2O + HD)); f) in this case the peak at m/z = 52 corresponds to - (H2O + CH3D) and/or - (HOD + CH4); g) also peaks at m/z = 67 [25%, - (HOD + H2)] and 66 [12%, - (HOD + HD)]; h) peaks in this region are m/z = 53 [27% - (HOD + CH3)] and 52 [41%, - (HOD + CH3)]; i) this spectrum also shows a peak at m/z = 53 (33%) corresponding to loss of (H2O + H2).
CHAPTER 3  
Does the Negative ion Beckmann Rearrangement Occur in  
Deprotonated Semicarbazones, Hydrazones and Related Species?

3.1. Introduction

The results outlined in Chapter 2 have shown that deprotonated oximes undergo a collision induced loss of water and it has been proposed that this fragmentation is best rationalised in terms of a negative ion Beckmann rearrangement [e.g. route A, eqn 3.1]. The Neber process [e.g. route B, eqn 3.1] is an alternative but less likely process.

\[
\text{Beckmann} \quad \xrightarrow{A} \quad \text{H}_2\text{O} + \text{CH}_2=\text{C}=\text{CH}_2^- \\
\text{N} \quad \xrightarrow{B} \quad \text{HO}^-\left(\text{CH}_2=\text{C}=\text{C}=\text{Me}\right)
\]

The reaction has been shown to occur for the general species \([R^1R^2C=NX - H^+]^-\) when \(X=\text{OH}\) (i.e. oximes), and \(X=\text{OMe}\) (i.e. oxime ethers). What is the extent of such 1,2 anionic rearrangement processes? There are several species related to oximes and it is possible that these species may undergo an analogous reaction. Species such as semicarbazones \((X=\text{NHCONH}_2)\), hydrazones \((X=\text{NH}_2)\) and methyl substituted hydrazones \((X=\text{NHMe}, \text{NMe}_2)\) may behave like simple oxime anions and undergo a negative ion Beckmann rearrangement. The collisional activation mass spectra of deprotonated semicarbazones and hydrazones are discussed in this chapter.
3.2 Collisional Activation Mass Spectra of Deprotonated Semicarbazones

If deprotonated semicarbazones undergo the negative ion Beckmann rearrangement, the expected fragmentation mechanism would be as follows:

\[
\text{Me}_2\text{NCONH}_2 \xrightarrow{\text{CH}_2} \text{Me}_2\text{NCONH}_2 \xrightarrow{\text{Me}} \text{CH}_2=\text{C}=\text{NMe} \xrightarrow{\text{NHCONH}_2} \left[\text{CH}_2=\text{C}=\text{NMe} \xrightarrow{\text{NHCONH}_2}\right]
\]

Thus we would predict that acetone semicarbazone would eliminate or form deprotonated urea (eqns 3.2 and 3.3). It is possible that reaction 3.3 may not occur, even under collisional activation, since urea is a relatively weak base, \(\Delta H^{\circ}_{\text{acid}} \text{NH}_2\text{CONH}_2 = 1486 \text{ kJmol}^{-1}\) \(^{187}\); cf. the bases HO\(^-\), \(\Delta H^{\circ}_{\text{acid}} \text{H}_2\text{O} = 1600 \text{ kJmol}^{-1}\) \(^{188}\), and MeO\(^-\), \(\Delta H^{\circ}_{\text{acid}} \text{MeOH} = 1580 \text{ kJmol}^{-1}\) \(^{189}\) which are known to deprotonate the neutral species of the Beckmann intermediate [i.e. CH\(_2\)=C=NMe]. Hence, the formation of NH\(_2\)CONH\(^-\) in the collisional activation mass spectra of deprotonated semicarbazones may suggest the operation of a negative ion Beckmann rearrangement.

The collisional activation mass spectra of deprotonated semicarbazones are recorded in Table 3.1: The CA mass spectrum of \(^2\text{H}_6\) acetone semicarbazone is also shown in Figure 3.1.
Acetone semicarbazone fragments via elimination of $H^+$, $H_2$, HNCO and formation of the radical anion $'NHCONH$ and the ion NCO$^-$. The major fragmentation is the formation of NCO$^-$, which is consistent with all other ketone semicarbazone spectra. Deprotonated aldehyde semicarbazones (Table 3.1) show analogous behaviour to ketone semicarbazones. In all examples studied the ion $NH_2CONH^-$ is not formed, therefore the anionic Beckmann rearrangement does not occur in this case. The fragmentation mechanisms of acetone semicarbazone are summarised in Scheme 3.1. Fragmentation proceeds via radical cleavage, with loss of $H^+$ (eqn 3.4) or loss of Me$_2$C=NNH$^+$ (eqn 3.5). Alternatively fragmentation through ion complex 3b produces Me$_2$C=NNH$^-$ (eqn 3.6) and NCO$^-$ (eqn 3.7).

Scheme 3.1

MS/MS Studies show that the structure of the product ion in eqn 3.7 is NCO$^-$ rather than the isomeric ion CNO$^-**$. For semicarbazones such as Me(RCH$_2$)C=NNHCONH$_2$, the cleavage of the alkyl radical $R'$ to the trigonal carbon is a major reaction, this elimination is most prominent when $R$=Et. This is probably a standard two step process as discussed in Section 2.2.3.

---

* it is possible that the product ion in reaction 3.4 is Me$_2$C=N(-)CONH$^+$.

** Charge reversal spectrum of authentic NCO$^-; M^+(m/z)42: spectrum m/z(abundance) 30(25), 28(95), 26(100), 16(5), 14(25); major peaks are CN$^+$ (m/z 28) and CO$^+$ (m/z 28).
The reactions in Scheme 3.1 show that all fragmentations may be rationalised by decomposition of the anion formed on the terminal nitrogen. If the semicarbazone is unable to form the anion on the terminal nitrogen, it may be possible that the negative ion Beckmann rearrangement may then occur. The N,N dimethylsemicarbazones R₂C=NNHCONMe₂ deprotonate to give R₂C=NN⁻CONMe₂: the collisional activation mass spectra of such anions are listed in Table 3.2 while that of [Me₂C=NNHCONMe₂ − H⁺]⁻ is illustrated in Figure 3.2.

The major fragmentation involves loss of dimethylamine, together with minor formation of the ions Me₂NCONH⁻ and NCO⁻. The elimination of dimethylamine is shown in eqn 3.8, i.e.

\[
\begin{align*}
\text{Me}_2\text{C}=\text{NNCONMe}_2 & \rightarrow \left[\left(\text{Me}_2\text{C}=\text{NNCO} \right)^- \text{NMe}_2\right] \rightarrow \text{H}_2\text{C}(\text{Me})\text{C}=\text{NNCO} + \text{Me}_2\text{NH} \\
\end{align*}
\]

3.8

The formation of the ion Me₂NCONH⁻ can be rationalised in terms of a negative ion Beckmann rearrangement as shown in eqn 3.9. This fragmentation is a minor process, however.

\[
\begin{align*}
\text{Me}_2\text{C}=\text{NNCONMe}_2 & \rightarrow \text{Me}_2\text{C}=\text{NNCONMe}_2 \rightarrow \left[\left(\text{CH}_2=\text{C}=\text{NMe} \right)^- \text{NHCONMe}_2\right] \rightarrow \text{CH}_2=\text{C}=\text{NMe} + \text{NHCONMe}_2 \\
\end{align*}
\]

3.9
Figure 3.1. CA mass spectrum of the ion \((\text{CD}_3)_2\text{C}=\text{NNCONH}_2 - \text{H}^+\)^–

Figure 3.2. CA mass spectrum of the ion \(\text{Me}_2\text{C}=\text{NNCONMe}_2 - \text{H}^+\)^–
Table 3.1. Collision Activation Mass Spectra of Deprotonated Semicarbazones

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H⁺</td>
<td>Me⁺</td>
</tr>
<tr>
<td>MeCH=NNHCONH₂ - H⁺⁻     a</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>EtCH=NNHCONH₂ - H⁺⁻</td>
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<td>8</td>
</tr>
<tr>
<td>PrCH=NNHCONH₂ - H⁺⁻</td>
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<td>85</td>
</tr>
<tr>
<td>PhCH=NNHCONH₂ - H⁺⁻</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Me₂C=NNHCONH₂ - H⁺⁻</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Me(Et)C=NNHCONH₂ - H⁺⁻</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>Me(Pr)C=NNHCONH₂ - H⁺⁻</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Pr₂C=NNHCONH₂ - H⁺⁻</td>
<td>35</td>
<td>98</td>
</tr>
<tr>
<td>Me(Ph)C=NNHCONH₂ - H⁺⁻</td>
<td>100</td>
<td>98</td>
</tr>
</tbody>
</table>

a) CA mass spectrum of MeCH=NNDCOND₂ − D⁺⁻. m/z (loss) abundance:101 (H⁺)5, 100 (D⁺)25, 50 (MeCH=N⁺)15, 58 (DNCO)5, 42 (MeCH=NDN₂)100.

Table 3.2. Collision Activation Mass Spectra of Deprotonated N,N-dimethyl Semicarbazones

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H⁺</td>
<td>Me₂NH</td>
</tr>
<tr>
<td>Me₂C=NNHCONMe₂ - H⁺⁻</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Me(Ph)C=NNHCONMe₂ - H⁺⁻</td>
<td>100</td>
<td>10</td>
</tr>
</tbody>
</table>
3.3 CA mass spectra of deprotonated hydrazones

The collisional activation mass spectra of a variety of deprotonated hydrazones and methyl substituted hydrazones, viz. \( R_2C=NNH_2 \), \( R_2C=NNHMe \) and \( R_2C=NNMe_2 \) are listed in Tables 3.3-3.5 respectively, or illustrated in Figures 3.3-3.8. The spectra of unlabelled species were measured with the MS 50 TA mass spectrometer, while the deuterium labelled derivatives were recorded using the VG ZAB 2HF instrument. Tandem mass spectra (MS/MS/MS) of selected daughter ions are collated in Tables 3.6-3.7. All hydrazone anions have the general structure \([R^1R^2C=NR - H^+]^-\) where \( R^1 \) and \( R^2 \) are H, alkyl or aryl and \( R \) corresponds to \( NH_2 \), NHMe or NMe_2.

Hydrazone anions are produced by deprotonation with MeO^- and NH2^- respectively in the MS 50 TA and VG ZAB instruments. For the ion \([R^1R^2C=NNMe_2 - H^+]^-\), when \( R^1 \) and \( R^2 \) are alkyl, deprotonation occurs exclusively at the \( \alpha \) carbon substituent of \( R^1 \) and/or \( R^2 \). For example, the species \((MeCD_2)C=NNMe_2\) yields only an \([M-D+]^-\) ion (Figure 3.5). When \( R^1 = H \), \( R^2 = \text{alkyl} \) and \( R = NH_2 \), NHMe or NMe_2, deprotonation again occurs predominantly on \( R^2 \); only minor deprotonation occurs at \( R^1 \) or \( R \) (generally less than 15%), for example, deprotonation of CD_3CH=NNMe_2 yields \([M-H^+]^-: [M-D+]^-\) ions in the ratio 10 : 1.

Using the ion \([Me_2C=NR - H^+]^-\) as a prototypical example of a deprotonated hydrazone, the data listed in Tables 3.3-3.5 illustrate that the main collision induced dissociations of the three species are:

i) \([Me_2C=NNH_2 - H^+]^-\); elimination of \( H^+ \), \( H_2 \), \( NH_2^+ \), MeNH_2 and loss of \( NH_3 \),

ii) \([Me_2C=NNHMe - H^+]^-\); elimination of \( H_2 \), \( CH_4 \), \( CH_2=NH \), Me_2NH and minor formation of Me^-,

iii) \([Me_2C=NNMe_2 - H^+]^-\); elimination of \( H_2 \), \( CH_4 \), \((CH_4+H_2)\), \( CH_2=NMe \), Me_3N, and minor loss of Me_2NH and formation of Me^-.
Figure 3.3. CA mass spectrum of the ion $\text{Me}_2C=\text{NNHMe} - \text{H}^+)^-$

Figure 3.4. CA mass spectrum of the ion $(\text{CD}_3)_2C=\text{NNMe}_2 - \text{D}^+)^-$
Figure 3.5. CA mass spectrum of the ion CD₃CH=NNHMe – D⁺⁻

Figure 3.6. CA mass spectrum of the ion CH₃CD=NNHMe – H⁺⁻
Several of the above fragmentations are unexpected, for example, the loss of methane when \( R = \text{NMe}_2 \). Deuterium labelling experiments show that the loss of \( \text{CH}_4 \) occurs solely from \( R \); this fragmentation often yields the base peak of the spectrum. The majority of the dissociation processes of the three species are inter-related, furthermore, several fragmentations are analogous to the fragmentation processes of deprotonated oximes. Rather than rationalise the three series of spectra individually, the major fragmentation pathways will be summarised and significant features of these spectra will be illustrated with reference to particular spectra. The fragmentations of deprotonated hydrazones can be separated into two categories:

i) rearrangement processes, and ii) simple cleavage and related processes.

As the main focus is to investigate whether deprotonated hydrazones behave like deprotonated oximes and undergo a negative ion Beckmann (or Neber) type rearrangement, initial discussion will centre on the rearrangement processes.

### 3.3.1 Rearrangement processes of deprotonated Hydrazones

All spectra show peaks which are formed following rearrangement of the \([\text{R}_1\text{R}_2\text{C}=\text{NR} - \text{H}^+]^-\) system. Such fragmentations include the losses of \( \text{R}^* \), \( \text{CH}_2=\text{NH} \) and \( \text{CH}_2=\text{NMe} \) (when \( R = \text{NHMe} \) and \( \text{NMe}_2 \)), elimination of "\( \text{R}_1\text{R}_2^* \)" and "\( \text{R}_2\text{R}^* \)" and minor loss of \( \text{RH} \) (see Tables 3.3-3.5 and Figures 3.3-3.8).

We propose that these fragmentations proceed via a Beckmann rearrangement. The various reactions are illustrated in Scheme 3.2 for the specific example of \([\text{Me}_2\text{C}=\text{NNMe}_2 - \text{H}^+]^-\).
The Beckmann rearrangement yields an ion complex which may be represented by contributing structures 3c and 3d. The intermediate complex \([3c \leftrightarrow 3d]\) may eliminate \(\text{Me}_2\text{N}^+\) (eqn 3.10), undergo deprotonation to eliminate \(\text{Me}_2\text{NH}\) (eqn 3.11), hydride transfer from the amine ion* (eqn 3.12) or effect the \(\text{S}_n2\) reaction to eliminate \(\text{Me}_3\text{N}\) as shown in eqn 3.13. The reactions of hydrazone anions decomposing through Beckmann intermediates are somewhat different to those illustrated for oxime anions [compare eqns 3.10-3.13 in Scheme 3.2 to eqns 2.19-2.21 in Scheme 2.3 (page 53)]. Consider the Beckmann intermediate \([\text{CH}_2\text{C}=N\text{Me} \text{HO}^-]\) formed from \([\text{Me}_2\text{C} = \text{NOH} - \text{H}^+]^-\). This species eliminates \(\text{H}_2\text{O}\) to give the base peak of the spectrum, while the \(\text{S}_n2\) process involving loss of \(\text{MeOH}\) is minor in comparison (<5%). Furthermore, the Beckmann intermediate \([\text{CH}_2\text{C} = \text{NMe} \text{MeO}^-]\) formed from \(\text{O}-\text{methyl oxime ether}[\text{Me}_2\text{C} = \text{NOMe} - \text{H}^+]^-\) also eliminates \(\text{MeOH}\) to give the base peak of the spectrum and in this case, the \(\text{S}_n2\) reaction to eliminate \(\text{MeOMe}\) does not occur. In contrast, the general hydrazone Beckmann intermediate \([\text{CH}_2\text{C} = \text{NMe} \text{R}^-]\) undergoes a facile \(\text{S}_n2\) displacement reaction to eliminate \(\text{MeR}\), and in several cases the elimination produces the base peak of the

* Simple amine anions are known to fragment through neutral/hydride ion complexes.\(^{125}\)
The ion \([\text{Me}_2\text{C} = \text{NMe}_2 - \text{H}^+]^-\) undergoes a major \(\text{S}_\text{n}2\) reaction (eqn 3.13), whereas the deprotonation reaction is a minor process. In fact, of all the spectra listed in Tables 3.3-3.5 only two spectra, those of \([\text{Me}_2\text{C} = \text{NNH}_2 - \text{H}^+]^-\) and \([\text{CD}_3\text{C} = \text{NNMe}_2 - \text{H}^+]^-\) (Figure 3.4) exhibit elimination of RH. In addition, oxime and O-alkyl oxime ether Beckmann intermediates do not lose \(\text{HO}^+\) or \(\text{MeO}^+\), whereas loss of \(\text{R}^+\) is a standard reaction of hydrazone anions.

<table>
<thead>
<tr>
<th>(\Delta H^0\text{_acid (kJmol}^{-1})</th>
<th>(\text{H}_2\text{O})</th>
<th>(\text{MeOH})</th>
<th>(\text{NH}_2)</th>
<th>(\text{MeNH}_2)</th>
<th>(\text{Me}_2\text{NH})</th>
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</thead>
<tbody>
<tr>
<td>(\text{Me}_2\text{C} = \text{NMe}_2 - \text{H}^+)</td>
<td>1635(^{188})</td>
<td>1595(^{189})</td>
<td>1688(^{190})</td>
<td>1687(^{190})</td>
<td>1628(^{190})</td>
</tr>
<tr>
<td>(\text{Me}_2\text{C} = \text{NNH}_2 - \text{H}^+)</td>
<td>176(^{188})</td>
<td>151(^{189})</td>
<td>72(^{190})</td>
<td>43(^{190})</td>
<td>37(^{190})</td>
</tr>
</tbody>
</table>

Table 3.8

The fact that the amine anion does not readily deprotonate the neutral species in the Beckmann ion complex cannot be attributed to the basicity differences of the various anions (see Table 3.8) since the amine anions are stronger bases than \(\text{H}_2\text{O}\) or \(\text{MeOH}\). Consideration of the data in Table 2.3 (page 50), Table 2.4 (page 64) and Tables 3.3-3.5 shows that \(\text{MeO}^-\) deprotonates the Beckmann neutral \([\text{CH}_2 = \text{C} = \text{NMe}]\) more readily than \(\text{HO}^-\) or the amine anions. The methoxide ion is the weakest base of the five anions (see Table 3.8).

As the deprotonation of the Beckmann neutral is apparently not dependent on the basicity of the anion, the deprotonation reaction must be a function of the decomposing intermediate, the structure of which depends to a major extent upon the electron affinities of the two parts of that intermediate. For the oxime, the electron affinity of \(\text{HO}^+\) is relatively high (Table 3.8) so the intermediate is likely to have a structure resembling an anion/neutral ion complex i.e. \([\text{CH}_2 = \text{C} = \text{NMe}]\text{HO}^-\). Similarly for the oxime ether, \(\text{MeO}^+\) has a high electron affinity and the ion complex is also expected to have an anion/neutral structure.
However, the electron affinities of the various amine radicals are at least 100 kJmol\(^{-1}\) lower than that of HO\(^{\ddagger}\) (see Table 3.8). This may imply that the intermediate in Scheme 3.2 is more likely to resemble the radical anion/radical (i.e 3g) rather than the anion/neutral structure (i.e 3d). If the hydrazone Beckmann intermediate has appreciable radical anion/radical nature, this may be the reason for the differences in the reactivity of the ion complexes for oximes and hydrazones.

It is of interest now to consider reactions analogous to the \(S_n2\) reaction shown in eqn 3.13 for hydrazones with alkyl groups other than methyl. For the series \([R^1R^2C=NNH_2 - H^+]-\) and \([R^1R^2C=NNMe_2 - H^+]-\), the relative losses of \(R^1R\) and \(R^2R\) follow a trend that is dependent upon the nature of \(R^1\) and \(R^2\). For example, when \(R^1 = \text{Me}\) and \(R^2 = \text{Et}\), the loss of \(\text{EtR}\) is approximately five times greater than the loss of \(\text{MeR}\). However, the ratio of loss of \(R^2R : \text{MeR (R^2>Et)}\) [see Tables 3.3-3.5] decreases with elaboration of \(R^2\). It seems unlikely that this effect is a function of the migratory aptitudes of the various alkyl substituents. Further information is obtained from the spectrum of the ion \([\text{CH}_3\text{CH}_2(\text{CD}_3\text{CH}_2)C=NN\text{Me}_2 - H^+]-\) (Figure 3.6), where it can be seen that the losses of \(\text{CH}_3\text{CH}_2\text{R}\) and \(\text{CD}_3\text{CH}_2\text{R}\) are accompanied by an appreciable deuterium isotope effect (\(H/D \sim 2.0\)). This data implies that the process involves the removal of a hydrogen from a terminal methyl group in the rate determining step of the reaction. Thus when \(R^1\) and/or \(R^2>\text{Et}\) it seems that an \(E_2\) reaction (eqn 3.14) operates in competition with the \(S_n2\) reaction (cf. eqn 3.13).

\[
\begin{align*}
\text{MeCH} & \text{N-NMe}_2 \\
\text{MeCH}_2 & \rightarrow [\text{MeCH=C=NNCH}_2\text{CH}_2\text{H} \text{NMe}_2] \\
\text{MeC} & \text{NMe}_2 \\
\text{MeCH}_2 & + \text{C}_2\text{H}_4 + \text{HNMe}_2 \tag{3.14}
\end{align*}
\]
The relative ratios of the $S_N^2$ and $E_2$ reactions for those ions listed in Tables 3.3-3.5 are not known, the magnitude of the isotope effect (cf. $H/D = 2$) at least in one case suggests that the $E_2$ reaction is slightly more favoured than the $S_N^2$ reaction. However, it is of interest to discuss the thermodynamics of the two reactions in order to distinguish which process is more favoured.

Consider for example, the $E_2$ and $S_N^2$ reactions of $[Et_2C=NNH_2 - H^+]^-$, eqns 3.15 and 3.16. The $S_N^2$ reaction is 56 kJmol$^{-1}$ more favoured than the $E_2$ process*, yet the $E_2$ process is clearly operating. The analogous $E_2$ and $S_N^2$ reactions of the deprotonated oxime $[Et_2C=NOH - H^+]^-$ are shown in eqn 3.17 and 3.18. The $S_N^2$ reaction is again more favoured by 46 kJmol$^{-1}$.

As the $S_N^2$ reaction is thermodynamically more favoured for both the deprotonated hydrazone and oxime, the ratio of loss of MeNH$_2$ : R$^2$NH$_2$ from MeR$^2$C=NNH$_2$ (or MeOH : R$^2$OH from MeR$^2$C=NOH) should increase with elaboration of R$^2$ (i.e R$^2$ = Et, Pr, iso Pr, Bu or sec Bu) if the reaction is thermodynamically controlled. However, for the deprotonated oxime $[MeR^2C=NOH - H^+]^-$ as R$^2$ increases from Et to Pr the ratio of MeOH : R$^2$OH loss decreases, and when R$^2$ = Bu, BuOH is eliminated exclusively. Thus it

\* $\Delta H^{\text{f}}$ values of EtNH$_2$, EtOH, C$_2$H$_4$, NH$_3$ and H$_2$O are -49.6, -235.3, +52.1, -45.8, -241 kJmol$^{-1}$ respectively. $\Delta H^{\text{f}}$ Heat of formation$^{190a}$. 

---

\[ 
\text{Et}_{\text{Me}}\text{CHC} = \text{N}\begin{array}{c} \text{H}^- \end{array} \rightarrow \begin{cases} \text{MeCHC} = \text{NCH}_2\text{CH}_3^{-} \text{NH}_2^- & \text{MeCHC} = \text{N} + \text{C}_2\text{H}_4 + \text{NH}_3 \addtocounter{equation}{1} \\ \text{MeCHC} = \text{N} + \text{CH}_3\text{CH}_2\text{NH}_2 & \addtocounter{equation}{1} \end{cases} \]  

\[ 
\text{Et}_{\text{Me}}\text{CHC} = \text{N}^{-} \rightarrow \begin{cases} \text{MeCHC} = \text{NCH}_2\text{CH}_3^{-} \text{HO}^- & \text{MeCHC} = \text{N} + \text{C}_2\text{H}_4 + \text{H}_2\text{O} \addtocounter{equation}{1} \\ \text{MeCHC} = \text{N} + \text{CH}_3\text{CH}_2\text{OH} & \addtocounter{equation}{1} \end{cases} \]
seems in this case the extent of the E2 reaction increases with elaboration of R^2. For the deprotonated hydrazone [MeR^2C=NNH_2 - H^+] when R^2 changes from Et → Bu, the ratio of MeOH : R^2OH loss varies from 1 : 8 (R^2 = Et) to 1 : 2 (R^2 = Bu). Taking into account the isotope effect determined for the reaction, the above data suggests that:

i) For deprotonated oximes, the E2 process is the major pathway for elimination of R^2OH, (R^2≥Et) and

ii) for deprotonated hydrazones, both S_n2 and E2 processes operate when R^2≥Et, with the E2 reaction being a major process.

Furthermore, since the E2 reaction predominates (even though the S_n2 reaction is favoured thermodynamically) the E2 reaction must be more kinetically favoured than the S_n2 process. Thus it appears that the kinetic product is formed in the gas phase reaction.

The selectivity of the intramolecular E2 reaction in the above examples is analogous to the results of intermolecular reactions recently reported by Ellison^{191} and DePuy^{192}. Ellison investigated the reaction of methoxide ion and 1-bromopropane and concluded that the E2 reaction was the sole reaction pathway (eqn 3.20), although ΔH°_1 values show that the S_n2 reaction (eqn 3.19) is more favoured thermodynamically by 57 kJmol⁻¹ over the E2 reaction.

\[ \text{MeO}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OMe} + \text{Br}^- \quad 3.19 \]

\[ \text{MeO}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{MeOH} + \text{CH}_3\text{CH}==\text{CH}_2 + \text{Br}^- \quad 3.20 \]

DePuy also found similar results in a study of the reactions of alkyl halides with a variety of nucleophiles, DePuy concluded that "E2 reactions are favoured over S_n2 reactions in the gas phase when both processes are structurally and thermodynamically accessible because the E2 transition state is a looser
transition state and so favoured entropically”. Hence in all of the above examples, the reaction appears to be kinetically controlled; i.e. the E2 transition state is more accessible than the $S_{n2}$ transition state.
3.3.2 Simple Cleavage Processes and Related Reactions

The spectra of the various hydrazone anions are dominated by the losses of $H^+$, $H_2$ and $CH_4$. Whenever $R^1$ and $R^2$ are both alkyl, loss of $H^+$ is always pronounced. Examination of Tables 3.3-3.5 and the spectrum of $[(MeCD_2)_2C=NNMe_2- H^+]^-$ (Figure 3.7) indicates the formation of a stabilised radical anion of the type shown in eqn 3.21. Other radical cleavages occur whenever $R^1$ and $R^2$ are alkyl and either substituent $\geq$Pr, $\beta$-cleavage occurs to the double bond, this elimination is most prominent for the ion $[Pr_2C=NNMe_2- H^+]^-$: This is probably a standard two step reaction [eqn 3.22 (cf. Section 2.2.3)].

The elimination of $H_2$ is observed in each of the three series of spectra, however when $R^1 = H$ or alkyl and $R = NHMe$, loss of $H_2$ occurs to the exclusion of $H^+$ loss. Labelling studies (see e.g. Figures 3.5a, 3.5b and Table 3.6) indicate that this loss of $H_2$ comes predominantly from the MeNH group. It is proposed that this process proceeds through the hydride ion intermediate 3e as shown in eqn 3.23.
Figure 3.7a. CA mass spectrum of the ion CD$_3$CH=NNMe$_2$ – D$^+$ –

Figure 3.7b. CA mass spectrum of the ion CH$_3$CD=NNMe$_2$ – H$^+$ –
Figure 3.8a. CA mass spectrum of the ion \((\text{CH}_3\text{CD}_2)\text{C}=\text{NNMe}_2 - \text{D}^+\)\(^-\)

Figure 3.8b. CA mass spectrum of the ion \((\text{CD}_3\text{CH}_2)(\text{Et})\text{C}=\text{NNMe}_2 - \text{H}^+\)\(^-\)
When \( R = \text{NMe}_2 \) the base peak of the spectrum is usually produced by loss of methane. In order to elucidate the mechanism of this fragmentation, the spectra of several deuterium labelled derivatives (Tables 3.3 and 3.5, Figures 3.4, 3.7-3.8), and MS/MS/MS data for a variety of daughter ions formed by loss of methane were investigated (Table 3.7). The deuterium labelling experiments suggest a similar mechanism to the loss of \( \text{H}_2 \) described above. Whenever \( R = \text{NMe}_2 \), loss of methane occurs exclusively through that group (see Figures 3.4, 3.6, 3.8a-b), but when \( R = \text{NHMe} \) and \( R^1 = \text{H} \), both groups are involved, for example the spectrum of \([\text{CH}_3\text{CD}=\text{NNHMe} - \text{H}^+]^-\) shows elimination of \( \text{CH}_3\text{D} \) (Figure 3.7b). A likely rationale is that the parent ion decomposes through ion complex 3f, to form \( \text{Me}^- \) (eqn 3.24) or eliminate methane to yield 3g (eqn 3.25). The mass spectrum of ion 3g is listed in Table 3.6, the characteristic loss of \( \text{NH}^+ \) (to form \( -\text{CH}_2\text{CN} \)) is in accord with structure 3g.

When \( R = \text{NMe}_2 \), methane is eliminated via a similar pathway to produce ion 3h as shown in eqn 3.27. The only difference between this and the previous example is the site of deprotonation. The CA MS/MS/MS data for daughter ions formed from elimination of \( \text{CH}_4 \) from ions \([\text{R}^1\text{R}^2\text{C}=\text{NNMe}_2- \text{H}^+]^-\) are recorded in Table 3.7. For example, the loss of \( \text{CH}_4 \) from \([\text{CH}_3\text{CH}=\text{NNMe}_2- \text{H}^+]^-\) produces ion 3h as shown in Scheme 3.3, upon collisional activation this ion loses \( \text{CH}_2\text{N}^+ \) (eqn 3.28) and \( \text{H}_2 \) (eqn 3.29). Loss of \( \text{H}_2 \) from the daughter ions listed in Table 3.7 is a facile process, and in fact sequential loss of \( \text{H}_2 \) from the loss of methane is observed in the spectra of dimethylhydrazones themselves [see the \((\text{CH}_4+\text{H}_2)\) fragments listed in Table 3.5 and Figures 3.5, 3.6 and 3.8, and loss of \((\text{CH}_4+\text{HD})\) in Figures 3.4 and 3.8b].
3.5 Conclusions

Deprotonated semicarbazones do not undergo the negative ion Beckmann rearrangement, instead, simple cleavage processes dominate the spectra of such ions. When the terminal amino group is substituted, the Beckmann rearrangement may occur, but it is a minor process.

The negative ion Beckmann rearrangement does occur for deprotonated hydrazones and the most favoured reactions resulting from this rearrangement are the internal $S_N2$ and $E2$ reactions illustrated in eqns 3.13 and 3.14 respectively. This result is in contrast with the behaviour of deprotonated oximes: such ions undergo the $S_N2/E2$ elimination to a minor extent, it is proposed that the differences in the Beckmann processes of deprotonated hydrazones and oximes is that the Beckmann intermediate for oximes is an anion/neutral ion complex whereas the analogous hydrazone intermediate is a radical anion/radical ion complex. Deprotonated hydrazones also undergo a number of simple cleavage rearrangements, in particular the loss of methane which involves the terminal NHMe or NMe$_2$ substituents.
<table>
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<tr>
<th>PARENT ION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
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<td>R¹ R²</td>
<td>H⁺ H₂ NH₂⁺ NH₃ Et⁺ Pr⁺ R¹NH₂ R²NH₂</td>
<td>CN⁻ NH₂⁻</td>
</tr>
<tr>
<td>Me Me</td>
<td>18 75 32 12 100</td>
<td>8 10</td>
</tr>
<tr>
<td>Me Et</td>
<td>78 92 19 15 100</td>
<td>8 8</td>
</tr>
<tr>
<td>Me Bu</td>
<td>32 73 28 22 48 100</td>
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<tr>
<td>Pr Bu</td>
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<td>4 2</td>
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Table 3.4. Collision Activation Mass Spectra of Deprotonated Methylhydrazones

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<td>Bu</td>
<td>100</td>
</tr>
<tr>
<td>Me</td>
<td>sec Bu</td>
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Table 3.5. Collision Activation Mass Spectra of Deprotonated Dimethylhydrazones

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### Table 3.6. Collisional Activation MS/MS/MS data For Product Ions in the Mass Spectra of Deprotonated Hydrazones

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<tr>
<th>PRECURSOR ION</th>
<th>( m/z )</th>
<th>PRODUCT ION</th>
<th>LOSS m/z</th>
<th>PRODUCT ION SPECTRUM ([m/z \ (loss) \ abundance])</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCH=NNMe(_2) - H(^+) (^-) ( (85))</td>
<td></td>
<td>Me(_2)N(^+) ( (41))</td>
<td></td>
<td>40 (H(^+))100.</td>
</tr>
<tr>
<td>Me(Pr)C=NNMe(_2) - H(^+) (^-) ( (127))</td>
<td></td>
<td>Me(_2)N(^+) ( (83))</td>
<td></td>
<td>40 (C(_3)H(_7))100.</td>
</tr>
<tr>
<td>Pr(_2)C=NNMe(_2) - H(^+) (^-) ( (155))</td>
<td></td>
<td>Me(_3)N ( (68))</td>
<td></td>
<td>67 (H(^+))25, 66 (H(_2))100, 52 (CH(_4))78.</td>
</tr>
<tr>
<td>PrC=N - H(^+) (^-) ( (68))</td>
<td></td>
<td>Me(_2)(Pr)N ( (68)) (^a)</td>
<td></td>
<td>67 (H(^+))28, 66 (H(_2))100, 52 (CH(_4))71.</td>
</tr>
<tr>
<td>Bu(_2)C=NNMe(_2) - H(^+) (^-) ( (183))</td>
<td></td>
<td>Me(_2)(Pr)N ( (82))</td>
<td></td>
<td>81(H(^+))20, 80 (H(_2))100, 52 (C(_2)H(_6))78.</td>
</tr>
<tr>
<td>BuC=N - H(^+) (^-) ( (82))</td>
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<td></td>
<td></td>
<td>81(H(^+))18, 80 (H(_2))100, 52 (C(_2)H(_6))88, 39 (C(_3)H(_7))1, 26 (C(_4)H(_8))1.</td>
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</table>

### Table 3.7. Collisional Activation MS/MS/MS data of Product Ions formed by loss of Methane from Deprotonated Hydrazones

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>( m/z )</th>
<th>PRODUCT m/z</th>
<th>PRODUCT ION SPECTRUM ([m/z \ (loss) \ abundance])</th>
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<tr>
<td>MeCH=NNHMe - H(^+) (^-) ( (71))</td>
<td></td>
<td>(55)</td>
<td>54 (H(^+))8, 53 (H(_2))18, 40 (NH(^+))100, 26 (C(_2)H(_3))N17.</td>
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<tr>
<td>MeCH=NNHMe - H(^+) (^-) ( (85))</td>
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<td>(69)</td>
<td>67 (H(_2))100, 41 (CH(_2)N(^+))70.</td>
</tr>
<tr>
<td>Me(Pr)C=NNMe(_2) - H(^+) (^-) ( (127))</td>
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<td>(111)</td>
<td>109 (H(_2))100, 95 (CH(_4))18, 83 (CH(_2)N(^+))68.</td>
</tr>
<tr>
<td>Me(Bu)C=NNMe(_2) - H(^+) (^-) ( (141))</td>
<td></td>
<td>(125)</td>
<td>123 (H(_2))100, 109 (CH(_4))8, 97 (CH(_2)N(^+))28.</td>
</tr>
<tr>
<td>Me(sec Bu)C=NNMe(_2) - H(^+) (^-) ( (141))</td>
<td></td>
<td>(125)</td>
<td>123 (H(_2))100, 109 (CH(_4))8, 97 (CH(_2)N(^+))27.</td>
</tr>
</tbody>
</table>
CHAPTER 4
The Collisional Activation Mass Spectra of deprotonated α-Oximino ketones

"All things must change, to something new, to something strange"
Henry W. Longfellow, Kéramos.

4.1. Introduction
Beckmann\textsuperscript{165} discovered the rearrangement of a ketoxime to an amide in 1886, and variations on this reaction have been known for nearly a hundred years\textsuperscript{193}. One such variation occurs when α-oximino ketones are treated with acid or base; instead of giving the normal amide product of the Beckmann rearrangement, the α-oximino ketone is cleaved to a carboxylic acid and a nitrile\textsuperscript{194,195}. Such rearrangements have been referred to as "abnormal"\textsuperscript{195,196} or "second order"\textsuperscript{197} Beckmann rearrangements. The first order rearrangement of a simple oxime involves the concerted departure of the leaving group, X, and migration of the trans group R with its bonding pair of electrons. Eqn 4.1 outlines the second order Beckmann rearrangement for \textit{anti} α-oximino ketones\textsuperscript{198}.

\[ \begin{align*}
R^1\overset{\text{HO}^-}{\longrightarrow} & \quad \left[ R\overset{+}{\underset{\text{C}=\text{O}}{\text{C}}}=\text{N} + R^1\text{C}=\text{N} + X^- \right] \\
& \downarrow_{\text{H}_2\text{O}} \\
& \quad \text{RCO}_2\text{H}
\end{align*} \tag{4.1} \]

However the \textit{syn} α-oximino ketones react in a slightly different manner as shown in eqn 4.2.
The rearrangement in eqn 4.2 involves migration of the R¹ group to nitrogen and an isonitrile is eliminated. In contrast, the anti α-oximino ketone eliminates a nitrile. In support of the mechanism proposed in eqn 4.1, the reaction of anti PhCOC(=NOH)Ph with an alkaline solution of benzene sulphonyl chloride yields the expected benzoic acid and phenylacetonitrile, together with a third product PhCOC(=NOCOPh)Ph. The final product arises from the combination of the carbonium ion PhCO⁺ (eqn 4.1) and the oxime anion PhCOC(=NO⁻)Ph.

The only reported fragmentation of a corresponding negatively charged species in the gas phase is shown in eqn 4.3*. In this case the molecular radical anion undergoes rearrangement to yield the benzoic acid molecular radical anion which in turn decomposes to give the benzoate ion.

* A major fragmentation of [R¹COC(=NOH₂)R²]⁺ ions in the gas phase is the formation of R¹CO⁺: for example the collisional activation MS/MS data for [MeCOC(=NOH₂)⁺]⁺ is [m/z (loss, relative abundance): 87(H)100, 70(H₂O)37, 46(CH₂CO)43, 43(HCN + H₂O)34 and 28(CH₂CO + H₂O)8.
This chapter investigates the fragmentation behaviour of deprotonated \( \alpha \)-oximino ketones in order to determine whether there is any correlation between the products produced in the gas and condensed phase reactions of \( \alpha \)-oximino ketones.

### 4.2 Deprotonation of \( \alpha \)-Oximino ketones

\( \alpha \)-Oximino ketone anions are produced in the gas phase by deprotonation with \( \text{NH}_2^- \) or \( \text{HO}^- \). For example, deprotonation of \( \text{CH}_3\text{COC}(=\text{NOH})\text{CH}_3 \) can give three different anions i.e. \( \text{-CH}_2\text{COC}(=\text{NOH})\text{CH}_3, \text{CH}_3\text{COC}(=\text{NO}^-)\text{CH}_3 \) and \( \text{CH}_3\text{COC}(=\text{NOH})\text{CH}_2^- \). The deprotonation centres differ in acidity by approximately 30 kJmol\(^{-1} \). For example, the gas phase \( \Delta H^a_{\text{acid}} \) values for \( \text{Me}_2\text{C}=\text{NOH}^{163}, (\text{CH}_3)_2\text{C}=\text{NOMe}^{164} \) and \( \text{CH}_3\text{COR}^{201} \) are 1532, 1561, and ca.1544 kJmol\(^{-1} \) respectively. Deprotonation should thus occur preferentially at the oximino position to yield \([\text{CH}_3\text{COC}(=\text{NO}^-)\text{CH}_3] \). However the amide ion is a strong enough base to deprotonate the other two carbanion sites to yield \([\text{-CH}_2\text{COC}(=\text{NOH})\text{CH}_3] \) and \([\text{CH}_3\text{COC}(=\text{NOH})\text{CH}_2^-] \). Under conditions of collisional activation it is probable that facile proton transfer may occur between all three centres as shown in eqn 4.4 (cf. oximes Section 2.2.2).

\[
\begin{align*}
\text{NOH} & \quad \text{NO}^- \quad \text{NOH} \\
\text{CH}_3\text{COC}=\text{NOH} & \quad \text{CH}_3\text{COC}=\text{NO}^- & \quad \text{CH}_3\text{COC}=\text{NOH} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

The following experiments were investigated to confirm the site of deprotonation. When biacetyl monoxime, \( \text{CH}_3\text{COC}(=\text{NOH})\text{CH}_3 \) is reacted with \( \text{D}_2\text{O} \) in the heated septum inlet of the mass spectrometer (and the deuterium incorporation determined by positive-ion mass spectrometry, using the procedure developed by Shannon\(^{202} \)) one hydrogen is totally exchanged within
30 seconds of the injection of D$_2$O, and three other hydrogens are partially exchanged within 3 minutes. Secondly, the reaction of CD$_3$COC(=NOH)CH$_3$ with NH$_2^-$ yields at least 80% of an [M − H$^+$]$^-$ ion. A more accurate estimate cannot be obtained since a fully labelled neutral species cannot be synthesised (i.e. the incorporation is $^2$H$_3 = 90\%$, $^2$H$_2 = 10\%$). Finally, the spectra of [CD$_3$COC(=NOH)CH$_3$ − H$^+$]$^-$ and [CD$_3$COC(=NOH)CH$_3$ − D$^+$]$^-$ are identical within experimental error: this result implies that equilibration between three anionic centres must occur prior to fragmentation.

4.3 Fragmentation and Rearrangement reactions of Deprotonated $\alpha$-Oximino ketones

The collisional activation mass spectra of deprotonated $\alpha$-oximino ketones are presented in Tables 4.1 and 4.2. The particular examples of [CD$_3$COC(=NOH)CH$_3$ − H$^+$]$^-$ and [CH$_3$COC(=NOH)Pr − H$^+$]$^-$ are illustrated in Figures 4.1 and 4.2. The mass spectra of the product ions in this spectrum (i.e. CA and CR MS/MS/MS spectra) are recorded in Table 4.3.

Deprotonated $\alpha$-oximino ketones undergo four different rearrangement processes.

For the general case [R$^1$COC(=NOH)CH$_2$R − H$^+$]$^-$ these processes are:

(i) the formation of R$^1$CO$_2^-$ and loss of R$^1$CO$_2$H,
(ii) the losses of HNO, R$^1$NO, and RNO,
(iii) the loss of HCN when R$^1$ = Me, and R = H or Me,
(iv) the loss of H$_2$O, particularly when R$^1$ = Ph.

4.3.1 The Formation of R$^1$CO$_2^-$ and loss of R$^1$CO$_2$H

The carboxylate ion R$^1$CO$_2^-$ is formed from all deprotonated $\alpha$-oximino ketones. For a simple case, e.g. [CH$_3$COC(=NOH)CH$_3$ − H$^+$]$^-$, five mechanisms need to be considered for the formation of CH$_3$CO$_2^-$ and the associated loss of CH$_3$CO$_2$H. These mechanisms are summarised in Scheme 4.1.
Figure 4.1. CA mass spectrum of the ion $\text{CD}_3\text{COC(=NOH)}\text{CH}_3 - H^+ \sim (-\text{NOH})$.

Figure 4.2. CA mass spectrum of the ion $\text{MeCOC(=NOH)}\text{Pr} - H^+ \sim (-\text{Et}^*)$. 

$\text{MeCO}_2^- 59$  
$\text{69} (-\text{EtNO})$  
$\sim (-\text{HNO}) 97$  
$\sim 83 \text{PrC}_2\text{O}^-$  
$\sim 113$  
$\sim 128$  
$\sim 99 (-\text{Et}^*)$
Scheme 4.1

Chapter 4

[Chemical reaction images and structures]
The first mechanism shown is the negative ion Beckmann type rearrangement (eqn 4.5). In this case proton transfer from the oxyanion 4a to form the carbanion 4b precedes the negative ion Beckmann rearrangement (the group migrating to nitrogen is MeCO). Alternatively, ion 4b may undergo a Neber rearrangement. Here, the carbanion directly attacks the nitrogen centre. In either reaction, nucleophilic displacement initiated by the hydroxide ion in the initial ion complex may produce the ion complex 4d, which may decompose to give both CH₃CO₂⁻ and -CH₂CN. If the reaction is thermodynamically controlled the predominant process would be formation of CH₃CO₂⁻, as -CH₂CN is a stronger base than the acetate ion (ΔH°acid values for CH₃CN and CH₃CO₂H are 1561 and 1457 kJmol⁻¹ respectively). The Beckmann/Neber rearrangements cannot be distinguished by available experimental data.

In the third mechanism (eqn 4.7), the oxyanion 4a initiates a cyclisation to the carbonyl group through a four centre transition state. The major product ion of this rearrangement should be CH₃CO₂⁻: for the acetate ion to deprotonate acetonitrile in the ion complex of eqn 4.7, the ion complex would need an excess energy of some 105 kJmol⁻¹ (i.e. the difference in acidities of CH₃CO₂H and CH₃CN).

The fourth mechanism involves the complex cyclisation initiated from the carbanion 4c. Following cyclisation, the hydroxide ion attacks the carbonyl group to form ion complex 4e, in which the acetic acid enolate ion [ΔH°acid CH₃CO₂H = 1527 kJmol⁻¹] could deprotonate acetonitrile if the ion complex 4e forms with an excess energy of at least 34 kJmol⁻¹. Thus CH₃CO₂⁻ could be formed via ion complex 4f (eqn 4.8). Alternatively, ion complex 4e could be formed following cleavage of 4c to form the disolvated ion complex 4g; which could react as illustrated in eqn 4.9.
Deuterium labelling and product ion studies have been used to consider the above mechanisms. Firstly, MS/MS/MS data in Table 4.3 confirm the product ion to be the acetate ion, $\text{CH}_3\text{CO}_2^-$, and not the acetic acid enolate ion, $-\text{CH}_2\text{CO}_2\text{H}$. The CA MS/MS/MS spectrum of the ion $[(\text{CH}_3\text{CO}(-\text{NOH})\text{CH}_3 - \text{H}^+ ) - \text{CH}_3\text{CN}]^-$ shows loss of $\text{H}^+$, $\text{H}_2\text{O}$ and $\text{CO}_2$, while the corresponding charge reversal spectrum exhibits major formation of $\text{CO}_2^{++}$ and $\text{Me}^{++}$. The CA and CR MS/MS data for the possible product ions are as follows, $\text{CH}_3\text{CO}_2-$: CA MS/MS, loss of $\text{H}^+$, $\text{H}_2\text{O}$ and $\text{CO}_2$; CR MS/MS, formation of $\text{CO}_2^{++}$ and $\text{Me}^{++}$; $-\text{CH}_2\text{CO}_2\text{H}$: CA MS/MS, loss of $\text{H}^+$ and $\text{H}_2\text{O}$; CR MS/MS loss of $\text{H}^+$ and formation of $\text{H}_2\text{C}_2\text{O}^+$ and $\text{CH}_2^{++}$.

Secondly, consider the spectrum of the ion $[\text{CD}_3\text{CO}(-\text{NOH})\text{CH}_3 - \text{H}^+]^-$, illustrated in Figure 4.1. The mechanisms in eqn 4.5, 4.6 and 4.7 will yield $\text{CD}_3\text{CO}_2^-$ as the product ion, whereas the corresponding product ion from eqn 4.8 is $\text{CD}_2\text{HCO}_2^-$ (see eqn 4.10).

\[
\text{CH}_2\text{DCO}_2^- + \text{CH}_2\text{DCN} \rightarrow \left[ -\text{CH}_2\text{CN} \left( \text{CH}_2\text{DCO}_2\text{D} \right) \right] \rightarrow \left[ -\text{CD}_2\text{CO}_2\text{D} \left( \text{CH}_3\text{CN} \right) \right] 4.10
\]

The product ion shown in the spectrum of $[\text{CD}_3\text{CO}(-\text{NOH})\text{CH}_3 - \text{H}^+]^-$ is specifically $\text{CD}_3\text{CO}_2^-$. Therefore process 4.8 does not occur in this instance.

The Beckmann/Neber type rearrangements (eqns 4.5 and 4.6) require the formation of a carbanion $\alpha$ to the oxime group. For the $\alpha$-oximino ketone $\text{R}^1\text{COC}(-\text{NOH})\text{R}^2 [\text{R}^2 = \text{H}, \text{COMe} \text{or Ph}]$, no such carbanion can form but dish
shaped-peaks due to \( \text{R}^1\text{CO}_2^- \) are still observed in these spectra. \( \text{R}^1\text{CO}_2^- \) ions are formed in all spectra, and all the resulting peaks are broad and dish-shaped. Figure 4.3 illustrates the peak shapes for the formation of \( \text{RCO}_2^- \) ions from two different \( \alpha \)-oximino ketones (also see Figures 4.1–4.6, Tables 4.2 and 4.3). The peak width for the formation of \( \text{CD}_3\text{CO}_2^- \) from \( [\text{CD}_3\text{COC(=NOH)}\text{CH}_3 - \text{H}^+]^- \) (Figure 4.3a) is \( 228\pm2 \text{eV} \), the widest peak width yet recorded for a negative ion dissociation. Broad peaks are often associated with reactions having tight transition states and appreciable reverse activation energies. Thus, there must be a high probability that all \( \text{R}^1\text{CO}_2^- \) ions are formed by the same overall mechanism. If this is so, then the formation of \( \text{R}^1\text{CO}_2^- \) is independent of the nature of \( \text{R}^2 \), thus the Beckmann/Neber type rearrangements cannot be the operative mechanism(s). Therefore, it appears that the formation of \( \text{R}^1\text{CO}_2^- \) ions (and subsequent losses of \( \text{R}^1\text{CO}_2\text{H} \)) arise via the four-centre cyclisation shown in eqn 4.7.

All \( \alpha \)-oximino ketones eliminate \( \text{R}^1\text{CO}_2\text{H} \) to yield the deprotonated nitrile to some extent, in general the ratio of formation of \( \text{R}^1\text{CO}_2^- \) : formation of \( [\text{R}^2\text{CN} - \text{H}^+]^- \) is \(~3:1\). For \( \text{R}^1\text{CO}_2\text{H} \) to be eliminated as shown in eqn 4.7, the acetate ion must deprotonate acetonitrile. As previously mentioned, for this reaction to occur the ion complex must have an excess energy of at least 105 kJmol\(^{-1} \). There is a significantly large amount of kinetic energy released upon dissociation (as is evident from the peak shapes in Figures 4.1-4.6). However, in general, reactions having such large activation barriers are expected to be unfavourable and so it is not unusual that the loss of \( \text{R}^1\text{CO}_2\text{H} \) is not one of the major losses noted in these spectra (cf. Table 4.1).
(a) Peak shape for the formation of $\text{CD}_3\text{CO}_2^-$ from $[\text{CD}_3\text{COC}(=\text{NOH})\text{CH}_3 - \text{H}^+]^-$, peak width $228\pm2$ eV.

(b) Peak shape for the formation of $\text{PhCO}_2^-$ from $[\text{PhCOC}(=\text{NOH})\text{CH}_3 - \text{H}^+]^-$, peak width $177\pm2$ eV.

*MS/MS/MS studies have shown that the structure of the ion $[(\text{PhCOC}(=\text{NOH})\text{CH}_3 - \text{H}^+) - \text{CH}_3\text{CN}]^-$ (Figure 4.2b) is $\text{PhCO}_2^-$ [the CA MS/MS/MS of $[(\text{PhCOC}(=\text{NOH})\text{CH}_3 - \text{H}^+) - \text{CH}_3\text{CN}]^-$ shows loss of $\text{H}^+$, $\text{CO}_2$, and formation of $\text{C}_6\text{H}_4^-$; the CA MS/MS of authentic deprotonated benzoic acid shows analogous fragmentations].
4.3.2 The elimination of RNO or RON

The second major pathway of fragmentation involves a rearrangement that eliminates the elements R1NO, HNO or RNO from the general α-oximino ketone [R1COC(=NOH)CH2R − H+]− (R = H, alkyl or aryl). There are two types of rearrangement resulting in the loss of RON/RNO and R1ON/R1NO. Both processes involve migration of a hydrogen or alkyl group to either oxygen or nitrogen of the oxime group. This process occurs in the majority of spectra, e.g. the losses of "CD3NO" (Figure 4.1), "EtNO" (Figure 4.2), and "HNO" (Figure 4.4) to yield the ions 55, 83, and 111 respectively.*

The first rearrangement involves migration of R1; R1 can migrate to oxygen (eqn 4.11) and eliminate the alkoxy nitrene R1–O–N:, alternatively R1 can migrate to nitrogen (eqn 4.12) and eliminate the alkyl nitroxyl species R1–N=O.

![Scheme 4.1](image)

![Scheme 4.2](image)

* The notation "RNO" is used to imply loss of either R–N=O or loss of R–O–N:.
** in this scheme R2 refers to the group CH2R.
Experimentally we cannot distinguish between the two processes, the mechanism involving loss of R\textsuperscript{1}NO (eqn 4.12) is favoured thermodynamically. \textit{Ab initio} calculations\textsuperscript{204} have shown that hyponitrous acid HNO\textsubscript{2} is 177.9 kJmol\textsuperscript{-1} more stable than hydroxynitrene HON\textsuperscript{+}, however it is possible that the alternative process, loss of RON\textsuperscript{+} is kinetically favoured.

The loss of "HNO" occurs for all \(\alpha\)-oximino ketones whenever the carbon \(\alpha\) to the oxime bears at least one hydrogen. In Figure 4.1 the loss of "HNO" from the ion [CD\(_3\)COC(=NOH)CH\(_3\) - H\(^+\)]\(^-\) gives the base peak of the spectrum: again, the elimination may proceed via migration to oxygen (eqn 4.13, \(R = H\), and eliminate HON\textsuperscript{+}), or via migration to nitrogen (eqn 4.14, \(R = H\), and eliminate HNO). Both processes give the same product ion 4h.

The MS/MS/MS spectra of product ion 4h (\(R^1 = CH_3\)) are listed in Table 4.2. The fragmentation data are consistent with this structure. The major collision induced dissociations are loss of Me\textsuperscript{*} and C\(_2\)H\(_4\) as rationalised in eqns 4.15 and 4.16, while the corresponding charge reversal spectrum exhibits major loss of CH\(_4\) and formation of MeCO\textsuperscript{+}. 

![Scheme 4.3](Image)
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The loss of "HNO" from the deuterium labelled derivatives of MeCOC(=NO⁻)Et support the mechanisms given in eqns 4.13 and 4.14. However, the data in Table 4.1 show that although the ions CH₃COC(=NO⁻)CH₂CD₃ and CD₃COC(=NO⁻)CH₂CH₃ lose "HNO" specifically, the ion CH₃COC(=NO⁻)CD₂CH₃ loses "HNO" and "DNO" in almost equal amounts. Thus, in this case, processes 4.13 and 4.14 must have a deuterium isotope effect, which causes the competitive transfer of a proton from the terminal methyl group. This is a process which is not observed for other labelled analogues.

For the various cases when R ≥ Me, in addition to the elimination of "HNO", an analogous, competitive cyclisation involving the various β substituents to eliminate the species "RNO" (Scheme 4.4). For example:

i) The spectrum of MeCOC(=NO⁻)n Pr, (illustrated in Figure 4.3), shows losses of "HNO" and "EtNO" (i.e. R = H or Et) to give ions m/z 97 and 69 respectively, whereas the isomer MeCOC(=NO⁻)iso Pr (Table 4.1) shows losses of "HNO" and "MeNO".

ii) MeCOC(=NO⁻)sec Bu (Figure 4.4) shows losses of "HNO", "MeNO" and "EtNO" (i.e. R = H, Me, Et) to give ions m/z 111, 97 and 83 respectively.

** Similar behaviour has been noted previously, e.g. in studies of deuterium labelled ketones."
iii) The spectrum of CD$_3$COC(=NO$^-$)CH$_2$CH$_3$ (Table 4.1) eliminates "CD$_3$NO" (eqns 4.11 or 4.12, Scheme 4.2), "HNO" and "MeNO" (eqns 4.17 or 4.18, Scheme 4.4).

![Scheme 4.4](image)

\[ R^1 \text{C}=\text{O} \leftarrow \text{R} \text{N}^+ \xrightarrow{\alpha \beta} \xrightarrow{\text{R}} \xrightarrow{\text{R}^1} \xrightarrow{\text{CH}_2\text{C}=\text{O}^-} + \text{RON}^+ \]

\[ \text{R}^1 \text{N}^+ \xrightarrow{\alpha \beta} \xrightarrow{\text{R}} \xrightarrow{\text{R}^1} \xrightarrow{\text{CH}_2\text{C}=\text{O}^-} + \text{R}^1 \text{N}^+ = \text{NO} \]

\[ \text{MeCO}_2^- \quad 59 \]

\[ (-\text{EtNO}) \quad 83 \]

\[ (-\text{MeNO}) \quad 97 \]

\[ (-\text{HNO}) \quad 111 \]

\[ (-\text{HCN}) \quad 115 \]

\[ (-\text{H}_2\text{O}) \quad 124 \]

\[ \text{MeCO}_2^- \quad 59 \]

\[ (-\text{EtNO}) \quad 83 \]

\[ (-\text{MeNO}) \quad 97 \]

\[ (-\text{HNO}) \quad 111 \]

\[ (-\text{HCN}) \quad 115 \]

\[ (-\text{H}_2\text{O}) \quad 124 \]

\[ \text{MeCO}_2^- \quad 59 \]

\[ (-\text{EtNO}) \quad 83 \]

\[ (-\text{MeNO}) \quad 97 \]

\[ (-\text{HNO}) \quad 111 \]

\[ (-\text{HCN}) \quad 115 \]

\[ (-\text{H}_2\text{O}) \quad 124 \]

\[ \text{Figure 4.4. CA mass spectrum of the ion MeCOC(=NOH)sec Bu -- H}$^+$\]
Table 4.1. Collision Activation Mass Spectra of deprotonated α oximino ketones

<table>
<thead>
<tr>
<th>R'COOH/BoH</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>H' D' Me' D' CD' H' Dod' HCN' DNO' MeNO' CD'NO' E'NO' P'NO' R'CO2H'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me Me</td>
<td>75 3 48 100 3</td>
<td>25</td>
</tr>
<tr>
<td>CD3 Me</td>
<td>40 2 39(180) 0</td>
<td>12 15</td>
</tr>
<tr>
<td>Me Et</td>
<td>60 8 27(179) 65</td>
<td>36</td>
</tr>
<tr>
<td>CD3 Et</td>
<td>100 3 26 84</td>
<td>25 26 12</td>
</tr>
<tr>
<td>Me CD2CH3</td>
<td>100 20 12 3 24^f</td>
<td>32 28 54</td>
</tr>
<tr>
<td>Me CH2CD3</td>
<td>100 3 15^g 15^h 25^c</td>
<td>73 22 18</td>
</tr>
<tr>
<td>Me Pr</td>
<td>45 2 54^e</td>
<td>51 9 48 &lt;10^-4</td>
</tr>
<tr>
<td>Me isoPr</td>
<td>20 5 2 45 65</td>
<td>25</td>
</tr>
<tr>
<td>Me Bu</td>
<td>33 7 34 2 450 1^a 12 16</td>
<td></td>
</tr>
<tr>
<td>Me isoBu</td>
<td>35 100 43 15 56 8</td>
<td></td>
</tr>
<tr>
<td>Me secBu</td>
<td>30 2 100^h 100^h 93 51 22 &lt;10^-4</td>
<td></td>
</tr>
<tr>
<td>Me CHMe</td>
<td>100 2 25</td>
<td></td>
</tr>
<tr>
<td>Et Me</td>
<td>65 9</td>
<td></td>
</tr>
<tr>
<td>Pr Et</td>
<td>60 5</td>
<td></td>
</tr>
<tr>
<td>Bu Pr</td>
<td>51 75</td>
<td></td>
</tr>
<tr>
<td>Me Pr</td>
<td>100 2 3 2 100</td>
<td>18</td>
</tr>
<tr>
<td>CD3 Pr</td>
<td>100 2 2 2 72 18</td>
<td></td>
</tr>
<tr>
<td>Ph Me</td>
<td>100 20 28</td>
<td></td>
</tr>
<tr>
<td>C6D5 Me</td>
<td>100 1 66</td>
<td></td>
</tr>
<tr>
<td>Ph Ph</td>
<td>100 32 2</td>
<td></td>
</tr>
<tr>
<td>C6D5 Ph</td>
<td>100 &lt;20^a 45 2</td>
<td></td>
</tr>
<tr>
<td>C6D5 Ph</td>
<td>100 30 2</td>
<td></td>
</tr>
</tbody>
</table>

values in brackets are peak widths at half height (volts ± 2)

(a) CD3 and H2O mz = 18 a.m.u.; (b) CNO- and DCO- mz = 42 a.m.u.; (c) composite peak - minor gaussian component superimposed on dish-shaped peak; (d) loss of R'CO2D in this case; (e) not fully resolved; (f) formation of R'CO2- corresponds to loss of RCN.
Table 4.2. Collision Activation Mass Spectra of deprotonated β-oxo aldoximes

<table>
<thead>
<tr>
<th>$R^1$CO$_2$(NOH)$_R$</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R$^1$</td>
<td>R</td>
</tr>
<tr>
<td>Me H</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Pr H</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>isoPr H</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>tertBu H</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Ph H</td>
<td>100</td>
<td>21</td>
</tr>
</tbody>
</table>

Values in brackets are peak widths at half height (volts ± 2)

a) Formation of $R^1$CO$_2^-$ corresponds to loss of HCN
4.3.3 The loss of HCN

The major fragmentation of species such as RCOC(=NO-)H (a β-oxo aldoxime) is elimination of HCN [see Table 4.2], a fragmentation analogous to that shown in eqn 4.7 (Section 4.3.1) i.e.

\[ \text{R}^1\text{COC(=NO-)CH}_2\text{R} \rightarrow \text{R}^1\text{CO}_2^- + \text{HCN} \]

The elimination of HCN also occurs for the general α-oximino ketone \( \text{R}^1\text{COC(=NO-)CH}_2\text{R} \), \( \text{R} = \text{H, alkyl} \). However, the fragmentation becomes less pronounced with the elaboration of \( \text{R} \) (see Table 4.1). This reaction is best illustrated in the spectrum (Figure 4.1) of CD₃COC(=NO-)CH₃, where loss of DCN produces a dish-shaped peak centred at \( m/z \) 75 [Figure 4.4 shows the peak shapes produced by elimination of HCN from two different α-oximino ketones; the peak widths are in the range 170–190 eV]. The spectrum depicted in Figure 4.1 is typical of most α-oximino ketones, it is a most unusual spectrum as it includes two very broad dish-shaped peaks arising from two different rearrangement processes. This is the first time such a result has been reported for negative ion collisional activation mass spectra.

The CA and CR MS/MS spectra of the source produced ion \( [(\text{CH}_3\text{COC(=NOH)}\text{CH}_3 \rightarrow \text{H}^+) - \text{HCN}]^- \) are illustrated in Figures 4.5a and 4.6a respectively. Also illustrated are the CA and CR MS/MS spectra of deprotonated propanoic acid. Comparison of the spectra in Figures 4.5 and 4.6 confirm that the structure of the source produced product ion is the propionate ion.
Figure 4.5a. CA mass spectrum of the ion CH$_3$CH$_2$CO$_2$H − H$^+$[−] −

Figure 4.5b. CA (MS/MS/MS) mass spectrum of the ion [(MeCOC(=NOH)Me − HCN) − H$^+$][−] −
Figure 4.6a. CR mass spectrum of the ion $\text{CH}_3\text{CH}_2\text{CO}_2\text{H} - \text{H}^+ \text{]}^-$

Figure 4.6b. CR (MS/MS/MS) mass spectrum of the ion $[(\text{MeCOC}(=\text{NOH})\text{Me} - \text{HCN}) - \text{H}^+]^-$
The major collision induced dissociations of the propionate ion are rationalised in eqns 4.20-22, while the corresponding charge reversal spectrum exhibits major loss of C\textsubscript{2}H\textsubscript{5} (m/z 44) and CO\textsubscript{2} (m/z 29) and formation of C\textsubscript{2}H\textsubscript{3}++ (m/z 27) and C\textsubscript{2}H\textsubscript{4}++ (m/z 28).

\[
\text{CH}_3\text{CH}_2\text{C}=\text{CO}^- \rightarrow \text{CH}_3^+ + \cdot\text{CH}_2\text{CO}^- 4.20
\]

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CO}^- + \text{HO}^- &\rightarrow \text{CH}_3\text{CH}_2\text{CO} + \text{HO}^- 4.21 \\
\text{CH}_3\text{CH}_2\text{CO}^- + \text{H}_2\text{O} &\rightarrow \text{CH}_3\text{C}=\text{CO}^- + \text{H}_2\text{O} 4.22
\end{align*}
\]

Deuterium labelling and MS/MS/MS studies show that the ion [[CD\textsubscript{3}COC(=NOH)CH\textsubscript{3} − H\textsuperscript{+}]− specifically eliminates DCN to yield the ion CH\textsubscript{3}CD\textsubscript{2}CO\textsubscript{2}−. The formation of the propionate ion as the product ion is an intriguing rearrangement; two possible reaction sequences are summarised in Scheme 4.5.

\[
\begin{align*}
\text{CD}_3\text{C}=\text{O} + \text{CD}_3\text{CH}_3 \rightarrow \text{CD}_3\text{CD}_2\text{CO}_2^- + \text{DCN} 4.23
\end{align*}
\]
The first reaction pathway, route A, involves an alkyl migration through a four-centre transition state, then nucleophilic displacement within the ion complex produces the cyanide ion, deprotonation generates the propionate ion and eliminates DCN (eqn 4.23).

The second reaction pathway, route B, follows the initial reaction shown in eqn 4.7 to give the ion CD₃CO₂N=CCH₃, (4i). The reaction sequence then proceeds as shown in eqn 4.24 with the final step involving a six-centre methyl rearrangement to an enolate ion.

Figure 4.7 illustrates the peak shapes produced by elimination of HCN from two α-oximino ketones [(CH₃COC(=NOH)CH₃) and (CH₃COC(=NOH)Pr)]. As the loss of HCN gives a dish-shaped peak, with wide peak widths (170-190eV), the similarities between eqn 4.24 and eqn 4.7 (i.e. both rearrangements occur through the same initial four-centre transition state) imply that of the two possible reaction pathways, route B (eqn 4.18) may be the more likely.

However, for the ion CH₃COC(=NO⁻)Pr, the peak resulting from loss of HCN is composite, with a narrow central gaussian peak superimposed on the dish shaped peak [as illustrated in Figure 4.7b]. The observance of a composite
peak is indicative of two modes of elimination of HCN. When $R^2 = Pr$ the product ion is the butyrate anion (see Table 4.3). MS/MS/MS Studies reveal that both modes of fragmentation give the same product ion [i.e. the composite peak due to $((\text{MeCOC}(=\text{NOH})\text{Pr} - \text{H}^+) - \text{HCN})^-$ is identical to the spectrum of authentic $\text{PrCO}_2^-$]. Therefore it seems likely that in the case where $R^2 = Pr$, both routes A and B may be operating.

(a) Peak shape for the ion $[(\text{MeCOC}(=\text{NOH})\text{Me} - \text{H}^+) - \text{HCN}]^-$; peak width 177±2eV.
(b) Peak shape for the ion $[(\text{MeCOC}(=\text{NOH})\text{Pr} - \text{H}^+) - \text{HCN}]^-$; peak width 175±2eV.

Figure 4.7
4.3.4 The loss of H$_2$O

Loss of H$_2$O is a minor process for aliphatic $\alpha$-oximino ketones (relative abundance $\{[(M - H^+) - H_2O]^- \ 2\text{-}10\%\}$, but is more pronounced for aryl $\alpha$-oximino ketones (see Figure 4.8). The process is most pronounced for the diaryl species PhCOC(=NOH)Ph. The deuterium labelled ion C$_6$D$_5$COC(NO$^-$)Ph shows loss of HOD, thus loss of water involves a hydrogen atom from each aromatic ring. Furthermore when $R_1 = \text{-}D_2$, HOD is also lost specifically, implying that the aromatic ring is preferentially deprotonated at either the ortho or para positions. A possible rationale is suggested in eqn 4.25.

![Diagram of possible fragmentation](image)

The MS/MS/MS studies of ion 4j (Table 4.3) are consistent with such a structure, the characteristic fragmentation is loss of CHO$^*$, whereas [C$_6$D$_5$CO(=NOH)Ph $- H^+$ $- \text{HOD}^-]$ loses mainly CDO$^*$.

---

* Losses of CHO$^*$ have been observed for cyclic systems containing CO functionality$^{205}$. 
4.3.5 Other fragmentations of $\alpha$-oximino ketones

The preceding sections have discussed the four competitive rearrangement processes of deprotonated $\alpha$-oximino ketones. In addition to these rearrangement reactions, several other reactions are observed in the spectra of deprotonated $\alpha$-oximino ketones which are standard fragmentations of even electron species in the gas phase (see Section 1.5).

For example:

i) the loss of H$^+$ to form a stabilised ion radical$^{127}$ is a major process which often gives the base peak, particularly for aryl $\alpha$-oximino ketones.

\[
\begin{align*}
\text{CH}_3\text{C}={\text{NO}}^- \quad &\rightarrow\quad \text{CH}_3\text{C}={\text{CHR}}^- + \text{H}^+ \quad \text{4.26} \\
\end{align*}
\]

ii) the loss of an alkyl radical R or [(alkyl - H$^+$) + H$^+$] when R $\geq$ Et (see Section 2.2.3 for cleavages of this type).

\[
\begin{align*}
\text{CH}_3\text{C}={\text{NO}}^- \quad &\rightarrow\quad \text{CH}_3\text{C}={\text{CHR}}^- + \text{R}^+ \quad \text{4.27} \\
\end{align*}
\]

iii) the formation of deprotonated ketene HC$_2$O$^-$.  

\[
\begin{align*}
\text{CH}_2\text{C}={\text{NOH}}^- \quad &\rightarrow\quad \text{CH}_2\text{CO} \left( \text{C(=NOH)} \right) \quad \rightarrow\quad \text{HC}_2\text{O}^- + \text{RCHNOH} \quad \text{4.28} \\
\end{align*}
\]
Figure 4.8. CA mass spectrum of the ion $\text{C}_6\text{D}_5\text{COC}(\text{=NOH})\text{Me} - \text{H}^+$
Table 4.3. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated α oximino ketones

<table>
<thead>
<tr>
<th>PRECURSOR ION m/z</th>
<th>PRODUCT ION m/z</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM [m/z (Abundance)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[MeCOC(NH)Me − H⁺]^−</td>
<td>100 − MeCN (59)</td>
<td>CA MS/MS/MS^a</td>
<td>58(100), 41(18), 15(20).</td>
</tr>
<tr>
<td>m/z 100</td>
<td>CR MS/MS/MS</td>
<td>45(25), 44(100), 43(30), 42(42), 41(19), 29(26), 28(24), 15(20), 14(15).</td>
<td></td>
</tr>
<tr>
<td>MeCO₂⁻</td>
<td>m/z 59</td>
<td>CA MS/MS</td>
<td>58(100), 44(0.5), 41(13), 15(15), 14(1).</td>
</tr>
<tr>
<td>m/z 59</td>
<td>CR MS/MS</td>
<td>45(27), 44(100), 43(36), 42(46), 41(16), 31(4), 29(26), 28(30), 16(1), 15(31), 14(18), 13(3), 12(1).</td>
<td></td>
</tr>
<tr>
<td>&quot;CH₂CO₂⁻</td>
<td>m/z 59</td>
<td>CA MS/MS</td>
<td>58(60), 44(0.8), 41(100), 17(0.6), 15(6), 14(0.6).</td>
</tr>
<tr>
<td>m/z 59</td>
<td>CR MS/MS</td>
<td>45(65), 44(18), 42(100), 41(22), 31(23), 29(49), 28(21), 17(5), 15(4), 14(26), 13(6), 12(4).</td>
<td></td>
</tr>
<tr>
<td>100 − NOH (69)</td>
<td>CA MS/MS/MS</td>
<td>67(18), 54(100), 41(27).</td>
<td></td>
</tr>
<tr>
<td>m/z 59</td>
<td>CR MS/MS/MS</td>
<td>54(20), 53(42), 51(21), 50(14), 43(100), 39(18), 27(22), 26(25), 15(19).</td>
<td></td>
</tr>
<tr>
<td>100 − HCN (73)</td>
<td>CA MS/MS^b</td>
<td>72(100), 71(20), 58(8), 55(20), 44(5), 27(1), 17(0.2).</td>
<td></td>
</tr>
<tr>
<td>m/z 73</td>
<td>CR MS/MS^b</td>
<td>57(2), 56(2), 55(2), 53(2), 45(24), 44(100), 42(20), 29(30), 28(48), 27(63), 26(35), 17(1), 16(1), 15(1), 14(1).</td>
<td></td>
</tr>
<tr>
<td>CH₂CO₂⁻</td>
<td>CA MS/MS</td>
<td>72(100), 71(22), 58(8), 55(28), 44(7), 27(1), 17(0.3).</td>
<td></td>
</tr>
<tr>
<td>m/z 73</td>
<td>CR MS/MS</td>
<td>57(2), 56(2), 55(2), 53(2), 45(28), 44(100), 42(22), 29(48), 28(47), 27(59), 26(32), 17(1), 16(1), 15(1), 14(1).</td>
<td></td>
</tr>
<tr>
<td>&quot;CH₂CO₂CH₃</td>
<td>CA MS/MS</td>
<td>56(7), 41(100), 31(4).</td>
<td></td>
</tr>
<tr>
<td>m/z 73</td>
<td>CR MS/MS</td>
<td>59(6), 57(2), 44(10), 42(100), 31(6), 29(30), 27(15), 15(17), 14(8), 13(3).</td>
<td></td>
</tr>
</tbody>
</table>

(a) weak spectrum m/z = 44 is not detected because of baseline noise; (b) The MS/MS/MS data are lost in baseline noise, the spectra recorded are those of the appropriate species formed by dissociation of the (M − H⁺)^− in the ion source.
Table 4.3. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated α oximino ketones

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>PRODUCT ION</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM ( m/z ) (Abundance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{MeCOC(NOH)Ei} - \text{H}^+])</td>
<td>114 - HCN</td>
<td>CA MS/MS(^3)</td>
<td>86(100), 85(6), 71(31), 69(16), 56(56), 44(4), 41(3), 27(1).</td>
</tr>
<tr>
<td>(m/z) 114</td>
<td>CA MS/MS(^3)</td>
<td>86(1), 71(2), 69(3), 55(9), 53(31), 45(26), 44(100), 43(58), 41(4), 39(94)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR MS/MS(^3)</td>
<td>29(24), 26(31), 27(46), 26(26).</td>
<td></td>
</tr>
<tr>
<td>(\text{PhCO}_2^-)</td>
<td>(m/z) 87</td>
<td>CA MS/MS</td>
<td>86(1), 71(3), 69(3), 55(11), 53(31), 45(26), 44(100), 43(62), 41(91), 39(96)</td>
</tr>
<tr>
<td></td>
<td>CR MS/MS</td>
<td>29(20), 26(28), 27(48), 26(22).</td>
<td></td>
</tr>
<tr>
<td>([\text{MeCOC(NOH)Ph} - \text{H}^+])</td>
<td>162 - PhCN (59)</td>
<td>CA MS/MS(^3)</td>
<td>58(100), 41(14), 15(28).</td>
</tr>
<tr>
<td>(m/z) 162</td>
<td>CA MS/MS</td>
<td>58(100), 44(0.6), 41(13), 15(13), 14(1).</td>
<td></td>
</tr>
<tr>
<td>(\text{MeCO}_2^-)</td>
<td>CR MS/MS</td>
<td>45(27), 44(100), 43(36), 42(46), 41(18), 31(4), 29(28), 28(30), 16(1).</td>
<td></td>
</tr>
<tr>
<td>(m/z) 59</td>
<td>15(31), 14(18), 13(3), 12(1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>([\text{PhCOC(NOH)Ph} - \text{H}^+])</td>
<td>224 - H(_2)O (206)</td>
<td>CA MS/MS(^3)</td>
<td>205(100), 177(10), 154(0.5), 130(1), 102(2), 90(1).</td>
</tr>
<tr>
<td>(m/z) 224</td>
<td>CA MS/MS(^3)</td>
<td>120(100), 77(96), 75(18).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>105(14), 77(100), 51(65), 50(50), 44(4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{PhCO}_2^-)</td>
<td>CR MS/MS</td>
<td>120(100), 77(94), 75(17).</td>
<td></td>
</tr>
<tr>
<td>(m/z) 121</td>
<td>CR MS/MS</td>
<td>105(12), 77(100), 51(67), 50(41), 44(6).</td>
<td></td>
</tr>
<tr>
<td>([\text{C}_6\text{H}_5\text{COC(NOH)Ph} - \text{H}^+])</td>
<td>229 - H(_2)O (208)</td>
<td>CA MS/MS(^3)</td>
<td>209(200), 181(1), 180(5), 134(0.5), 102(1), 90(1).</td>
</tr>
<tr>
<td>(m/z) 229</td>
<td>CA MS/MS(^3)</td>
<td>124(46), 82(100), 82(8).</td>
<td></td>
</tr>
</tbody>
</table>

(b) The MS/MS/MS data are lost in baseline noise, the spectra recorded are those of the appropriate species formed by dissociation of the \((\text{M} - \text{H}^+)\)\(^-\) in the ion source.
4.4. Rearrangement reactions of α-Oximino ketone

O-Methyl ethers

The majority of the rearrangement reactions of α-oximino ketones proceed through the NO centre, viz. the formation of R¹CO₂⁻ (eqn 4.7), the elimination of RNO or RON (eqns 4.11–14) and the elimination of HCN (eqn 4.19). Such rearrangements cannot occur for O-methyl ethers, such as R¹COC(=NOMe)R², as the anion cannot form at the NO position. Depending on the nature of R¹ and R², deprotonation can only occur at these centres and the subsequent fragmentations should differ substantially from those described for the unsubstituted α-oximino ketones.

The collisional activation mass spectra of deprotonated O-methyl ethers R¹COC(=NOR³)R², (R³ = Me or CD₃), are listed in Table 4.4. The characteristic fragmentations are losses of R³* and R³OH, and formation of [(R²–H)CN]⁻ and R³O⁻. For example, the appropriate processes for the ion [CH₃COC(=NOCD₃)CH₃–H⁺]⁻ are loss of CD₃* and CD₃OH, and formation of –CH₂CN and MeO⁻.

For the species CH₃COC(=NOMe)CH₃, deprotonation should occur preferentially at the enolate position. For example the gas phase ΔH°acid values for CH₃COR¹⁶² and (CH₃)₂C=NOMe¹⁶⁴ are ca. 1544 and 1561 kJmol⁻¹ respectively. Deuterium labelling studies show that when CH₃COC(=NOMe)CH₃ is allowed to react with NH₂⁻, the ratio of formation of the ions –CH₂COC(=NOMe)CH₃ : CH₃COC(=NOMe)CH₂⁻ is approximately 4 : 1 (Table 4.4, Figures 4.9, 4.10).
4.4.1 The formation of [(R²-H)CN]- ions

All deprotonated α-oximino ketone O-methyl ethers, [R¹COC(=NOMe)R² - H+]⁻, form an ion [(R²-H)CN]⁻ and this ion yields the base peak of the spectrum. There are several mechanisms that need to be considered for the formation of the deprotonated nitrile. The first possibility to be considered is whether the ions are formed by either Beckmann or Neber rearrangements [eqns 4.29 and 4.30, Scheme 4.6].

\[
\begin{align*}
\text{Beckmann} & : & \text{CH}_3\text{CO}_2\text{Me} + \text{CH}_2\text{CN} & \rightarrow & \left[ \text{CH}_3\text{CON}=\text{C}=\text{CH}_2 \right]^{-} \text{MeO}^- & \text{4.29} \\
\text{Neberr} & : & \text{CH}_3\text{CO}_2\text{Me} & \rightarrow & \left[ \text{CH}_3\text{CON}=\text{C}=\text{CH}_2 \right]^{-} \text{MeO}^- & \text{4.30}
\end{align*}
\]

*Scheme 4.6*

The following observations can be made from consideration of the data in Table 4.4.

i) The Beckmann/Neber rearrangement requires the formation of a carbanion α to the methoxyimino group, i.e. [R¹COC(=NOMe)(R² - H⁺)]⁻. When R² = H or Ph, no such carbanion can form, however both species give the ion [(R²-H)CN]⁻ as the base peak. These ions *cannot* be formed from Beckmann/Neber rearrangements, and

ii) the neutral species must be able to deprotonate at the enolate position, i.e. [(R¹ - H⁺)COC(=NOMe)R²]⁺, to produce the ion [(R²-H)CN]⁻. For example, when R¹ = Ph the reaction does not occur.
As the formation of the \([(R^2-H)CN]^-\) ion is independent of the nature of \(R^2\), let us therefore explore the proposal that \([(R^2-H)CN]^-\) ions are formed solely from the enolate ion.

The neutral CH₃COC(=NOMe)CH₃ and its three deuterated analogues (Table 4.4, Figures 4.9, 4.10) best illustrate the formation of \(^{-}\text{CH}_2\text{CN}\). Possible fragmentations of the enolate ion are outlined in Scheme 4.7.

\[
\begin{align*}
\text{Scheme 4.7}
\end{align*}
\]
Chapter 4

The first possibility is via route A to give the bisolvated ion complex, \(4k\), which could decompose to yield \(-\text{CH}_2\text{CN}\) (eqn 4.31). Alternatively, this process could be concerted (route B, eqn 4.32). Other possibilities involve cyclisation to \(4l^*\), which can either deprotonate and undergo a retro reaction (eqn 4.33) or undergo internal nucleophilic attack at the carbonyl group and elimination to give \(4m\), which could decompose to the products shown in eqn 4.34.

All four processes give the same product ion, and in this case deuterium labelling does not provide a means to distinguish between the various mechanisms. In order to differentiate between the four processes, we attempted to detect the eliminated neutral(s) by a neutralisation/reionisation experiment (see Section 1.4.3) as three of the processes involve elimination of ketene and methanol, whereas in the fourth process (eqn 4.34) methyl acetate is formed. The neutralisation/reionisation mass spectrum obtained was very weak and the only peaks of relevance were due to \text{MeOH}^{+*}\ and its decomposition products. No peaks corresponding to either \text{CH}_2\text{CO}^{+}\ or \text{CH}_3\text{CO}_2\text{CH}_3^{+}\ were detected, although any small peaks could be lost amongst the background noise. The detection of the peak corresponding to methanol fails to shed any light on the problem as loss of methanol is itself observed in the spectrum (Table 4.4, Figures 4.9, 4.10).

* This intermediate was postulated for the formation of \(\text{RCO}_2^+\) ions from \(\alpha\)-oximino ketones (eqn 4.8), but was eliminated as a possibility in that case.
However, consideration of the relative acidities of the product ion/neutrals does assist in differentiating between certain mechanisms. The gas phase acidities and electron affinities of the relevant species are:

<table>
<thead>
<tr>
<th>Neutral</th>
<th>$\Delta H^\circ_{\text{acid}}$ (kJmol$^{-1}$)</th>
<th>$E_A$ (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$CO</td>
<td>1527$^{206}$</td>
<td>2.350 (HC$_2$O$^-$)$^{206}$</td>
</tr>
<tr>
<td>CH$_3$CO$_2$CH$_3$</td>
<td>1557$^{163}$</td>
<td>1.80 (CH$_2$CO$_2$CH$_3$)$^{206}$</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>1560$^{163}$</td>
<td>1.543 (CH$_2$CN)$^{208}$</td>
</tr>
</tbody>
</table>

*Table 4.5. Thermodynamic data of possible product ions formed in Scheme 4.6.*

Fragmentation through the bisolvated ion complex 4$k$, i.e. [(CH$_2$CO)(CH$_3$CN) MeO$^-$], is not plausible since such an intermediate should undergo competitive deprotonation processes to yield both HC$_2$O$^-$ and $^-$CH$_2$CN. In fact formation of HC$_2$O$^-$ should predominate as ketene is more acidic than acetonitrile and HC$_2$O$^+$ has a larger electron affinity than $^-$CH$_2$CN (Table 4.5). In Figure 4.9 the ion HC$_2$O$^-$ gives a peak less than 5% in abundance, whereas $^-$CH$_2$CN is the base peak (see Table 4.4). In contrast the concerted process (eqn 4.32) yields $^-$CH$_2$CN directly, and deprotonated ketene cannot form via this reaction pathway.

Using a similar argument, fragmentation via ion complex 4$m$ may also be discounted. Methyl acetate and acetonitrile have almost the same acidity and the appropriate radicals have only a small difference in electron affinity. This would suggest that an ion complex such as [CH$_2$CO$_2$CH$_3$ (CH$_3$CN)] should decompose to give appreciable amounts of both $^-$CH$_2$CO$_2$CH$_3$ and $^-$CH$_2$CN. Experimentally $^-$CH$_2$CO$_2$CH$_3$ is not formed from any deprotonated $\alpha$-oximino ketone O-methyl ether.
Therefore, if the enolate ion is the sole precursor of $\text{CH}_2\text{CN}$, the mechanism may involve either the concerted process (eqn 4.32) or the cyclisation/retro process (eqn 4.33). Closer inspection of the deprotonation of the cyclic neutral by MeO$^-$ in ion complex 4l (as illustrated in Scheme 4.8) reveals that this reaction may yield both HC$_2$O$^-$ and $\text{CH}_2\text{CN}$.

\[ \text{Scheme 4.8} \]

The methoxide ion can deprotonate the cyclic neutral at either of two positions:

i) the exo methyl group, to give ion 4n, this ion undergoes a retro reaction to yield $\text{CH}_2\text{CN}$ as the product ion (eqn 4.35), or

ii) the endo methylene position to give ion 4o, this ion undergoes a different retro reaction to give HC$_2$O$^-$ as the product ion (eqn 4.36).

Experimentally, the ratio of $\text{CH}_2\text{CN}$ to HC$_2$O$^-$ is ca. 20 : 1. Although this argument does not disprove the formation of ion 4l, the formation of $\text{CH}_2\text{CN}$ by the concerted process (eqn 4.28) seems the more likely process on available evidence.
The preceding discussion has argued that if the enolate ion is the sole precursor of $-\text{CH}_2\text{CN}$, then the formation of this ion is most likely to occur through the concerted process (eqn 4.32). The assumption that the enolate ion was the sole precursor to the fragmentation was made as a generality to account for cases when a Beckmann/Neber rearrangement can occur.

The situation concerning the decompositions of $[\text{MeCOC(=NOMe)Me} - \text{H}^+]^-$ ions is much more complex. Definitive information is obtained from the $[\text{M} - \text{H}^+]^-$ and $[\text{M} - \text{D}^+]^-$ ions derived from $\text{CD}_3\text{COC(=NOMe)CH}_3$ and $\text{CH}_3\text{COC(=NOMe)CD}_3$ (Table 4.4, Figures 4.9, 4.10). The major parent ions are the enolate ions $-\text{CD}_2\text{COC(=NOMe)CH}_3$ and $-\text{CH}_2\text{COC(=NOMe)CD}_3$ [ratio of formation of enolate : carbanion parent ions (using $\text{NH}_2^-$ as the deprotonating agent) is 5 : 1 and 3 : 1 respectively]. The enolate ion $-\text{CD}_2\text{COC(=NOMe)CH}_3$ fragments to form $-\text{CH}_2\text{CN}$ specifically and $-\text{CH}_2\text{COC(=NOMe)CD}_3$ fragments to form $-\text{CD}_2\text{CN}$ specifically.

In contrast the carbanions $\text{CD}_3\text{COC(=NOMe)CH}_2^-$ and $\text{CH}_3\text{COC(=NOMe)CD}_2^-$ yield $-\text{CH}_2\text{CN}/-\text{CHDCN}$ and $-\text{CD}_2\text{CN}/-\text{CHDCN}$ respectively, implying that some $\text{D}^+$ (or $\text{H}^+$ as appropriate) transfer has preceded or accompanied fragmentation.

This evidence indicates that when the parent ion is the enolate ion, it is the sole precursor of $-\text{CH}_2\text{CN}$ (or $-\text{CD}_2\text{CN}$) [fragmenting via route B, eqn 4.32]. When the parent ion is the carbanion, proton/deuterium transfer precedes fragmentation and hence the situation is more complex.
Consider the fragmentation of the carbanion CD$_3$COC(=NOMe)CH$_2^-$, \ref{eq:4.9}; here proton transfer gives enolate ion \ref{eq:4.9}, and if fragmentation then proceeds solely through the enolate ion then $^-$CH$_2$CN and $^-$CHDCN should form in the ratio 1 : 2 in the absence of an isotope effect. Similarly, CH$_3$COC(=NOMe)CD$_2^-$ should form $^-$CD$_2$CN/$^-$CHDCN in the ratio 2 : 1. Experimentally, the ratio from both ions is precisely 1 : 0.82 (Table 4.4, Figures 4.9, 4.10). These ratios can be rationalised by two competing reactions (originating from the carbanion as parent ion) producing the same product ion i.e.

i) the major reaction which is proceeding through the enolate ion, following initial D$^+$ (or H$^+$) transfer from the carbanion (eqns 4.37, 38), and

ii) a minor process requiring no D$^+$ (or H$^+$) transfer, i.e. a Beckmann or the alternative Neber rearrangement.

The Beckmann/Neber rearrangements cannot be distinguished: either process may form the product ion by deprotonation/elimination (i.e. to form $^-$CH$_2$CN + CD$_2$CO + MeOD, eqn 4.39) or by nucleophilic displacement (yielding CH$_3$CO$_2$CH$_3$ + $^-$CH$_2$CN, eqn 4.40).

The deprotonation/elimination process (eqn 4.39) would be favoured over nucleophilic displacement as the displacement process produces an ion complex, [(CH$_3$CO$_2$CH$_3$) $^-$CH$_2$CN], which would be expected to dissociate to give both $^-$CH$_2$CO$_2$CH$_3$ and $^-$CH$_2$CN. The ion $^-$CH$_2$CO$_2$CH$_3$ is not detected in the spectrum indicating that the nucleophilic displacement reaction does not occur.

The experimental abundance ratios suggest the competitive enolate decomposition (eqns 4.37, 38) and Beckmann/Neber processes (eqns 4.39, 40) occur in the approximate ratio 2 : 1.
4.4.2 The loss of MeOH

The data in Table 4.4 indicate that there are several different mechanisms operating for the loss of MeOH (or MeOD). For example, PhC(-)OC=NOCH₃ loses MeOH as shown in eqn 4.41.

\[
\text{PhCOO}^-\text{NOMe} \rightarrow \left[\left(\text{PhCO}≡\text{N}\right)\text{MeO}^-\right] \rightarrow (\text{C}_6\text{H}_4^-)\text{COC}≡\text{N} + \text{MeOH} \quad 4.41
\]

However, the most interesting case is that of CH₃COC(=NOMe)CH₃. The spectra of the labelled derivatives show specific loss of MeOH and MeOD from the carbanions, CD₃COC(=NOMe)CH₂⁻ and CH₃COC(=NOMe)CD₂⁻, respectively. Conversely, the enolate ions, -CD₂COC(=NOMe)CH₃ and -CH₂COC(=NOMe)CD₃, lose both MeOH and MeOD.
This evidence implies, that for the loss of MeOH, it is the carbanion, \( \text{CH}_3\text{COC(=NOMe)CH}_2^- \), that is the decomposing ion, and the enolate ion, \( \text{CH}_2\text{COC(=NOMe)CH}_3 \), must undergo \( H^+ \) (or \( D^+ \)) transfer prior to loss of MeOH. It is proposed that Beckmann (eqn 4.42) or Neber (eqn 4.43) rearrangements may occur in this case.

The enolate ions, \( \text{CH}_2\text{COC(=NOMe)CH}_3 \) and \( \text{CH}_2\text{COC(=NOMe)CD}_3 \), lose MeOH and MeOD in the respective ratios 1 : 1.4 and 1 : 0.35 [for no isotope effect, the respective statistical values are 1 : 2 and 2 : 1 for either mechanism]. These values are consistent with the operation of a small deuterium isotope effect.

Scheme 4.10. See Scheme 4.9 For the Beckmann/Neber intermediate ion complexes

The CA mass spectrum of the (source formed) product ion \( m/z 82 \) formed in the spectrum of \( \text{CH}_2\text{COC(=NOMe)CH}_3 \) is \( [m/z(\text{loss})\text{abundance}] : 41(\text{CH}_3\text{CN}) \) and 40(\( \text{CH}_2\text{CO}\))100. This is consistent with either of the product ions shown in eqns 4.42 or 4.43. For example, see eqns 4.44 or 4.45.
4.5 Conclusions

The condensed phase Beckmann rearrangement of α-oximino ketones in solution produces a carboxylic acid and a nitrile (eqn 4.1 and 4.2), and a carboxylic acid is indeed a major rearrangement product in the gas phase. However, the mechanism for formation of the carboxylate ion in the gas phase is not analogous to the condensed phase Beckmann rearrangement of α-oximino ketones; instead rearrangement proceeds via a characteristic four-centre cyclisation (eqn 4.7).

The rearrangements of α-oximino ketones presented in this chapter are probably the most complex fragmentations yet recorded for any closed shell negative ions. In several cases it has not been possible (with available experimental evidence) to determine an exclusive mechanism for a specific reaction, particularly the Beckmann and Neber rearrangements which are indistinguishable. In summary, the competitive rearrangements of the ion \([\text{CD}_3\text{COC}(\equiv\text{NOH})\text{CH}_3 - \text{H}^+]^{-}\) are losses of HNO (eqn 4.14), CD$_3$NO (eqn 4.12), the formation of CD$_3$CO$_2^-$ (eqn 4.7) and elimination of DCN to form CH$_3$CD$_2$CO$_2^-$ (eqn 4.23). The formation of CD$_3$CO$_2^-$ and CH$_3$CD$_2$CO$_2^-$ yield the broadest dish-shaped peaks yet recorded for negative ions. In both cases the rearrangement proceeds via a cyclic four-centred transition state. The large kinetic energy release of these processes is presumably a function of:

i) the four centre transition state as fragmentations that proceed through small cyclic transition states are in general, accompanied by a large release of kinetic energy. This observation can be rationalised by assuming that smaller transition states are "tighter\(^{50}\)", and therefore less effective in partitioning internal energy into vibrational modes of the products, instead
more internal energy is partitioned into the energy of separation and hence kinetic energy is released*, and

ii) the large reverse activation energy of the process that is primarily due to the large electron affinity of RCO2* [e.g. $E_A (MeCO_2^*) = 3.32eV$]**.

In contrast to the behaviour of α-oximino ketones, the corresponding deprotonated α-oximino ketone O-methyl ethers appear to fragment via a negative ion Beckmann (or related Neber) rearrangement, although the rearrangement is not the dominant decomposition pathway. For example, MeCOC(=NOMe)Me deprotonates to form $-CH_2COC(=NOMe)Me$ and MeCOC(=NOMe)CH$_2^-$ in the ratio 3 : 1. The enolate ion $-CH_2COC(=NOMe)Me$ fragments principally to yield $-CH_2CN$ [eqns 4.32 or 4.33], while the carbanion MeCOC(=NOMe)CH$_2^-$ loses MeOH, via a Beckmann (or Neber) rearrangement [eqns 4.42 or 4.43]. The product ions give gaussian peaks as the change in electron affinities is much smaller than those of the carboxylate species outlined above [e.g. $E_A (-CH_2CN) = 1.543eV$].

---

* There are however exceptions, the reaction illustrated in eqn 4.23 proceeds through a four-centre transition state, yet in certain cases, a gaussian peak is produced as shown in Figure 4.7b.

** Calculated by the thermodynamic cycle$^{209}$. $\Delta H_{\text{acid}} (MeCO_2H) = DE (MeCO_2-H) + IE (H^+) - E_A (MeCO_2^*)$. Thus $1457187 = 443.5^{210} + 1312^{211} \cdot E_A$. $E_A = 299 \text{ kJmol}^{-1} = 3.32eV$. 
Figure 4.9. CA mass spectrum of the ion CH$_3$COC(=NOMe)CD$_3$ - H$^+$.  

Figure 4.10. CA mass spectrum of the ion CH$_3$COC(=NOMe)CD$_3$ - D$^+$. 
### Table 4.4. Collision Activation Mass Spectra of deprotonated α-oximino ketone O-methyl ethers

<table>
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<th>LOSS</th>
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<td>$R_3^{R_2}$</td>
<td>Parent ion</td>
</tr>
<tr>
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<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
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<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Me</td>
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</tr>
<tr>
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<td>Me</td>
<td>Me</td>
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<tr>
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<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>Ph$_3$</td>
<td>D</td>
<td>Me</td>
</tr>
</tbody>
</table>
**CHAPTER 5**

The Gas Phase Lossen Rearrangement

Fragmentation and Rearrangement reactions of Collisionally Activated Hydroxamic Acid and Hydrazide Anions

"It all comes to the same thing in the end"

Robert Browning

### 5.1 Introduction

In solution chemistry, there are several well known rearrangements involving migration to an electron-deficient nitrogen atom. Rearrangements such as the Hoffmann, Lossen, Curtius and Schmidt reactions are illustrated in Scheme 5.1.

\[ \text{Hoffmann:} \quad \text{RCONH}_2 + \text{BrO}^- \rightarrow \text{RCON}=\text{O} \]

\[ \text{Lossen:} \quad \text{RCNOCOR} \rightarrow \text{RCON}=\text{O} \]

\[ \text{Curtius:} \quad \text{RCONHNH}_2 + \text{NaN}_2 \text{HCl} \rightarrow \text{RCON}=\text{O} \]

\[ \text{Schmidt:} \quad \text{RCO}_2 \rightarrow \text{RCON}=\text{O} \]

**Scheme 5.1**

All the rearrangements shown in Scheme 5.1 involve migration of an alkyl, aryl or acyl group, R, from carbon to nitrogen to produce an isocyanate...
intermediate$^{213,214}$. The intermediate isocyanate reacts readily with a variety of oxygen or nitrogen nucleophiles to produce functionalised ureas, esters or amides. Hydrolysis of the isocyanate with acid or base yields the amine$^{214}$. The rearrangements generally proceed with retention of optical and geometrical configuration$^{215}$.

In solution, the Lossen rearrangement$^{214,215}$ occurs when an O-acylated hydroxamic acid is treated with base to produce the isocyanate intermediate (eqn 5.5). Base is not always necessary for the Lossen rearrangement; in selected cases heating alone can also cause rearrangement$^{212}$.

\[
\text{R NHOH} + \text{HO}^- \rightarrow \text{R NOH} + \text{R-CO}^-
\]

Salts of O-acylated hydroxamic acids can be isolated and they often rearrange spontaneously or on mild heating$^{217}$. Non-acylated hydroxamic acids do not rearrange when treated with base, due to the hydroxide group being a poor leaving group. If the nitrogen atom is substituted with an alkyl or aryl group the Lossen rearrangement does not proceed$^{218}$.

In the gas phase a number of intramolecular rearrangements of even-electron anions have been reported. Several of these rearrangements were discussed in Section 1.5.3.2 and some examples are the Wittig$^{141}$, Oxy-Cope$^{142}$, Claisen$^{145}$ and Smiles$^{150}$ rearrangements; often such reactions have analogies with base catalysed reactions which occur in solution. In addition, Chapter 2 discussed the Beckmann rearrangement of deprotonated oximes; an acid catalysed solution rearrangement that has analogy to a negative ion gas phase rearrangement.
This chapter investigates whether the Lossen rearrangement of deprotonated hydroxamic acids and hydrazides occurs in the gas phase. If the Lossen rearrangement (eqn 5.2, Scheme 5.1) occurs in the gas phase, then the ion/molecule complex 5a (eqn 5.6) would be produced. Such a species should be easily identified by its fragmentation behaviour.

\[
\begin{align*}
\text{R-NHOH} + \text{HO}^{-} & \xrightarrow{\text{Lossen}} \text{R-NHO} \quad \left[ \text{R-N=C=O} + \text{HO}^{-} \right] \\
\end{align*}
\]

5.2 Collisional Activation Mass Spectra of Deprotonated Hydroxamic acids

In solution, the site of deprotonation and the structure of the hydroxamate ion has been debated for 50 years\textsuperscript{214,216}. Hydroxamic acids have a relatively high acidity, several reviews assume that the hydroxamic acid is ionised on the oxygen atom\textsuperscript{214}, however, recent investigation of equilibrium acidities of various hydroxamic acids in dimethyl sulphoxide\textsuperscript{219} and gas phase proton transfer studies\textsuperscript{220} have suggested that that hydroxamic acids behave essentially as an NH acid in both condensed and gas phases.

Hydroxamic acids should deprotonate preferentially on nitrogen, as can be seen from the following cognate acidity values: MeCONH\textsubscript{2} (\(\Delta H^\circ_{\text{acid}} = 1430\) kJmol\textsuperscript{-1})\textsuperscript{163}, PhCONH\textsubscript{2} (\(\Delta H^\circ_{\text{acid}} = 1452.5\) kJmol\textsuperscript{-1})\textsuperscript{163}, CH\textsubscript{3}CONMe\textsubscript{2} (\(\Delta H^\circ_{\text{acid}} = 1569.5\) kJmol\textsuperscript{-1})\textsuperscript{163}, NH\textsubscript{2}OH (\(\Delta H^\circ_{\text{acid}} = 1629\) kJmol\textsuperscript{-1})\textsuperscript{19}, [\(\Delta H^\circ_{\text{acid}}\) of RCONHOH should be somewhat lower than that of NH\textsubscript{2}OH]. When CD\textsubscript{3}CONHOH is

\(^*\) \textit{Ab initio} calculation\textsuperscript{221}. 
treated with $\text{HO}^-$ or $\text{NH}_2^-$ in the gas phase only a $[\text{M} - \text{H}^+]^-$ species is formed, in accord with the above prediction. Recently, the gas phase acidities of acetohydroxamic acid and O-methyl acetohydroxamic acid were reported\textsuperscript{220}, $\Delta G^0_{\text{acid}}$ values for $\text{MeCONH}_2\text{OH}$ and $\text{MeCONHOMe}$ are 1418 and 1437 kJmol\textsuperscript{-1} respectively.

The collisional activation mass spectra (MS/MS) of deprotonated hydroxamic acids are listed in Table 5.1 or illustrated in Figures 5.1-2. The mass spectra (MS/MS/MS) of certain product ions are recorded in Table 5.2. Consider $[\text{MeCONH}_2\text{OH} - \text{H}^+]^-$ as a prototypical example: its collisional activation mass spectrum shows competitive elimination of $\text{H}^+$, $\text{NH}_2^+$, $\text{NH}_3^+$, $\text{CH}_4$, $\text{H}_2\text{O}$, $\text{HNO}$, $\text{NH}_2\text{OH}$ and formation of $\text{NCO}^-$. These processes are best explained using the example $\text{CD}_3\text{CON}^-\text{HO}$ as illustrated in Figure 5.1.

Of all fragmentations, the only reactions which appear to occur following proton transfer to the nitrogen anion from the methyl group involve minor formation of $\text{DC}_2\text{O}^-$ (eqn 5.7) and $\text{CHD}_2\text{CO}^-$ (eqn 5.8).

\[
\text{DC}_2\text{O}^- + \text{ND}_2\text{OH} \quad 5.7
\]

\[
\text{CHD}_2\text{CO}^- + \text{DNO} \quad 5.8
\]

The two reactions are especially interesting as the ion in ion complex $5\text{b}$ is the hydroxylamine anion, $-\text{NHOH}^-$. This ion is thought to be unstable\textsuperscript{221}, as the electron affinity of $-\text{NHOH}$ is calculated to be $-17$ kJmol\textsuperscript{-1}. Thus $-\text{NHOH}$ should be unstable with respect to its radical, but experimentally it appears that the ion may be stabilised in an ion/molecule complex (cf. eqn\textsuperscript{s} 5.7, 5.8). A similar
situation occurs for $^-\text{CH}_2\text{OH}$ which cannot be detected directly, but reacts when stabilised in an ion/molecule complex$^{222}$ (see eqn 5.17).

The hydroxylamine anion, $^-\text{NHOH}$, reacts via two pathways from ion complex $5b$, i) the deprotonation reaction (eqn 5.7) to produce DC$_2$O$^-\ [^-\text{NHOH} \text{ is a}
\text{powerful base, } \text{NH}_2\text{OH } \Delta H^\circ_{\text{acid}} = 1670^{221} \text{ kJmol}^{-1} \text{ cf. } \text{CH}_2\text{CO } \Delta H^\circ_{\text{acid}} = 1526^{206} \text{ kJmol}^{-1}\text{)], and, ii) the hydride transfer reaction (eqn 5.8) to produce the acetyl anion CD$_2$HCO$^-$ and eliminate DNO. The structure of this ion is confirmed by the MS/MS/MS data collated in Table 5.2. The charge reversal (CR) mass spectrum of the source produced ion m/z 43 shows major loss of H', Me' and CO, as does the CR MS/MS spectrum of the acetyl anion MeCO$^-\text{*}$. All other fragmentations may be rationalised by initiation from the nitrogen anion. Loss of a hydrogen or deuterium radical occurs by the processes shown in eqns 5.9 and 10.

\[
\begin{align*}
\text{CD}_3\text{CONOH} & \longrightarrow \text{CD}_2\text{COH} + \text{H'} & \text{5.9} \\
\text{CD}_3\text{CONOH} & \longrightarrow \text{CD}_2\text{CONOH} + \text{D'} & \text{5.10}
\end{align*}
\]

Loss of methane is a major fragmentation, this fragmentation may occur through the ion complex $5c$. Alternatively, if a transient methyl anion migrates from carbon to nitrogen, the methyl anion could deprotonate the proton on oxygen to eliminate CD$_3$H and form the oxyisocyanate ion OCNO$^-\text{*}$. The structure of this ion is confirmed by the MS/MS/MS data in Table 5.2$\text{*}$.

* The acetyl anion$^{223}$ is formed by the $S_n2$ (S) reaction:

\[
\text{Me}_3\text{SiCOMe} + \text{F}^- \longrightarrow \text{MeCO}^- + \text{Me}_3\text{SF}
\]

* The ONCO$^-$ ions formed from CD$_3$CON$^-\text{OH}$ and HON$^-\text{CO}_2\text{Me}^{224}$ exhibit identical CR spectra, viz. loss of N, O, CO and CO$_2$.
Figure 5.1. CA mass spectrum of the ion CD$_3$CONH$_2$OH – H$^+$]$^-$

Figure 5.2. CA mass spectrum of the ion PhCONH$_2$OH – H$^+$]$^-$
The ions HO\textsuperscript{−}, NCO\textsuperscript{−}, and -CD\textsubscript{2}NCO are rationalised as forming via Lossen ion complex 5d [eqns 5.12 – 5.14 (Scheme 5.2)].

\[
\begin{align*}
\text{HO}^- + \text{CD}_3\text{NCO} & \quad \text{eqn 5.12} \\
\text{CD}_3\text{H} + \text{ONCO}^- & \quad \text{eqn 5.11} \\
\text{CD}_3\text{OH} + \text{NCO}^- & \quad \text{eqn 5.14}
\end{align*}
\]

\textbf{Scheme 5.2}

The Lossen ion complex 5d could form directly from CD\textsubscript{3}CON\textsuperscript{−}OH or via ion complex 5c [CD\textsubscript{3}\textsuperscript{−} (OCNOH)]. It may decompose to produce HO\textsuperscript{−} (eqn 5.12), and deprotonated methyl isocyanate, -CD\textsubscript{2}NCO (eqn 5.13). It may also undergo an internal nucleophilic substitution reaction to produce the isocyanate ion, NCO\textsuperscript{−} (eqn 5.14), as a major product ion. The data in Table 5.2 indicate that the product ion of eqn 5.14 is the isocyanate ion (NCO\textsuperscript{−}) rather than the isomeric cyanate ion (-CNO\textsuperscript{−}). The isocyanate and cyanate ions can be distinguished from their characteristic charge reversal mass spectra. For example NCO\textsuperscript{−} shows major loss of N, O and CO, whereas CNO\textsuperscript{−} shows losses of C, O, and CN [see Table 5.2].
In a recent FT-ICR study of deprotonated acetohydroxamic acid\textsuperscript{220}, the (low energy, multiple collision) CID mass spectrum of \([\text{CH}_3\text{CONHOH} - \text{H}^+]^-\) gave an ion \(m/z = 42\) as the sole product ion. The authors concluded that the structure of the ion \(m/z = 42\) was the cyanate ion (-CNO): an unlikely result since formation of such an ion would require oxygen transfer from carbon to nitrogen.

The elimination of NH and NH\textsubscript{2}* produce MeCO\textsubscript{2}^- and \((\text{CH}_2\text{CO}_2)^-\), respectively. The formation of these ions is rationalised by proton transfer (eqn 5.15) and a three centre rearrangement (eqn 5.16) [Scheme 5.3].

\[\begin{align*}
\text{CD}_3\text{CONHOH} & \rightarrow \text{CD}_3\text{N}=\text{O}^- \rightarrow \text{CD}_3\text{CO}_2^-=\text{NH}^- \rightarrow \text{CD}_3\text{CO}_2^- + \text{NH}^+ \quad 5.15 \\
\text{CD}_3\text{CO}_2\text{NH}^- & \rightarrow \text{CD}_2\text{CO}_2\text{NHD} \quad 5f \\
& \rightarrow \left[\left(\text{CD}_2\text{CO}_2\right)^+ \text{NHD}^-\right] \quad 5g \\
& \rightarrow \left[\left(\text{CD}_2\text{CO}_2\right)^- \text{NHD}^+\right] \quad 5.16 \\
& \rightarrow (\text{CD}_2\text{CO}_2)^+ + \text{NHD}^* 
\end{align*}\]

\textbf{Scheme 5.3}

The process in eqn 5.16 is particularly interesting. It is proposed that ion complex 5f undergoes electron transfer to furnish 5g which dissociates to give the radical ion \((\text{CD}_2\text{CO}_2)^-\). The structure of this radical anion is consistent with the data in Table 5.2. For example, the CR MS/MS/MS spectrum of \((\text{CD}_2\text{CO}_2)^+\) exhibits loss of CD\textsubscript{2} (to form CO\textsubscript{2}**) (see Table 5.2).
Radical/radical anion intermediates have been proposed previously, e.g. for alkoxide decompositions and the Wittig rearrangement\(^{141}\) (cf. eqn 1.51). Negative ion decompositions are generally assumed to proceed in a stepwise manner\(^{123,131,225}\), and the concept of an anion/neutral complex is generally used for convenience\(^{123}\). In many cases the true nature of the "ion complex" may well be intermediate between the two extremes, i.e. 5f and 5g are really contributors to a resonance hybrid. The actual structure will depend upon a number of factors including the electron affinities of the species contained in the ion complex. In simplistic terms, for an ion complex \([A \text{ (neutral )}]-\), if the electron affinity of \(A^+\) is more positive than that of the neutral, the reactive intermediate would be more like \([A-(\text{neutral})]\). However, if the situation is reversed, i.e. the electron affinity of the neutral is more positive than that of \(A\), then \([A^+ \text{ (neutral)}]^-\) may be the major contributor. Nevertheless, there are documented cases when even in the later situation, the ion complex appears to react as \([A^-(\text{neutral})]\). For example, the ion -CH\(_2\)OH\(^{222}\) may react when stabilised in an ion/molecule complex as in eqn 5.17, even though the electron affinity of \(^{1}CH_2OH\) is calculated to be \(-36.8\) kJmol\(^{-1}\) (i.e. \(^{1}CH_2OH\) is unstable with respect to its radical). In the particular case of the complex 5g, the electron affinity of NH\(_2^+\) is \(74^{226}\) kJmol\(^{-1}\), and although the electron affinity of (CH\(_2\)CO\(_2\)) is not known, the radical anion is known to be stable\(^{203}\), and thus fragmentation through complex 5g is certainly a possibility.

\[
\text{DOCH}_2\text{CH}_2\text{O}^- \rightarrow \left[ \text{DOCH}_2^- \left(\text{CH}_2\text{O}\right) \right] \rightarrow \text{CH}_3\text{O}^- + \text{HDCO} \quad 5.17
\]
When the alkyl substituent R is ≥ Et, the intermediate analogous to 5f (5q) may also eliminate ammonia (eqn 5.18).

\[
\text{CH}_3\text{CH}_2\text{NOH} \rightarrow \text{CH}_3\text{C}\text{HCO}_2\text{NH}_2 \rightarrow \left(\text{CH}_3\text{CHCO}_2\right)^{\text{NH}_2^-} \\
\text{CH}_2=\text{CHCO}_2^- + \text{NH}_3
\]

The reaction illustrated in eqn 5.19 occurs when R ≥ Pr. It has been shown previously that such reactions are two step processes; where initial loss of a terminal hydrogen atom is followed by elimination of ethene (cf. Section 2.2.3). The CR MS/MS/MS of the product ion (eqn 5.19) is consistent with the structure \(^{t}\text{CH}_2\text{CON}^-\text{OH}\). For example, the spectrum exhibits major losses of NO and \(^{t}\text{NOH}\) (see data in Table 5.2).

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{NOH} \rightarrow \text{CH}_2\text{CO}_2\text{NOH} + (\text{C}_6\text{H}_4^- + \text{H}^+)
\]

Deprotonated aryl hydroxamic acids also undergo a Lossen rearrangement to form ONCO\(^-\), NCO\(^-\) and (\(\text{C}_6\text{H}_4^-\))CNO (cf. Scheme 5.2). Further fragmentation occurs to produce Ph\(^-\) (cf. 5q, eqn 5.11\(^*\)), PhNH\(^-\) and and elimination of NH via a three centre rearrangement (cf. eqn 5.15) yields PhCO\(_2^-\). The peak corresponding to PhNH\(^-\) is pronounced, whereas deprotonated alkyl hydroxamic acids do not produce RNH\(^-\). Initial reaction involves formation of the Lossen ion complex, 5h, and the formation of PhNH\(^-\) is summarised in eqn

\[
\text{Dissociation of the ion complex} \ [\text{R}^-(\text{ONCOH})] \longrightarrow \text{R}^+ + \text{ONCOH} \text{ is not detected for simple alkyl derivatives due to the low or negative electron affinities of R}^+. \text{In contrast} \ E_A \text{ Ph}^+ = 87227 \text{kJmol}^{-1}.
\]
5.20. The complex $5h$ may react via nucleophilic attack of $\text{HO}^-$ onto the carbon of the isocyanate, proton transfer from oxygen to nitrogen yields the carboxlate ion and decarboxylation yields the amine ion $\text{PhNH}^-$. The formation of this ion is important since the solution rearrangement of benzohydroxamic acid with hydroxide gives aniline as a major rearrangement product$^{213,216}$. 

\[
\begin{align*}
\text{Ph-N=O-} + \text{HO}^- &\rightarrow \text{Ph-NHCO}_2^- + \text{CO}_2 \\
\text{Ph-NH}^- &\rightarrow \text{Ph-NCO} \\
\end{align*}
\]
Table 5.1. Collision Activation Mass Spectra of deprotonated hydroxamic acids, O-alkyl hydroxamic acids, hydrazides and N,N dimethyl hydrazides

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<th>Neutral Precursor</th>
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</tr>
<tr>
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</tr>
<tr>
<td>CD$_3$CONHNNH$_2$</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>EICONHNNH$_2$</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>PrCONHNNH$_2$</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>PhCONHNNH$_2$</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>BzCONHNNH$_2$</td>
<td>95</td>
<td>22</td>
</tr>
<tr>
<td>MeCONHNNMe$_2$</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>EICONHNNMe$_2$</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>PrCONHNNMe$_2$</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

(a) loss of $\text{NH}_2^+ = \text{CH}_4$ both $m/z = 16$ a.m.u.; (b) loss of $\text{H}_2 = \text{D} m/z = 2$ a.m.u.; (c) loss of HOD in this case; (d) loss of CD$_3$H to give OCNO$^-$ = loss of HOD to give "CD$_2$NCO, m/z OCNO" = "CD$_2$NCO m/z = 58 a.m.u.; (e) loss of NHDOH to give DC$_2$O$^-$ = formation of NCO$^-$, m/z DC$_2$O$^- = \text{NCO}^- = 42$ a.m.u.; (f) this spectrum shows loss of EtOH; (g) this spectrum also has a peak corresponding to loss of CHO$^-$.
Table 5.2. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated aliphatic hydroxamic acids

<table>
<thead>
<tr>
<th>Precursor Ion (m/z)</th>
<th>Product Ion (m/z)</th>
<th>Spectrum Type</th>
<th>Spectrum m/z (loss) relative abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCONH2 - H+</td>
<td>HCOO- (41)</td>
<td>CR</td>
<td>40(H)100, 28(CH)90, 25(O)70, 13(CO)60.</td>
</tr>
<tr>
<td>[74]</td>
<td>NCOO- (42)</td>
<td>CR</td>
<td>30(C)25, 28(N)80, 26(O)100, 16(CH)5, 14(CO)10.</td>
</tr>
<tr>
<td>NCOO- [42]</td>
<td>MeOO (43)</td>
<td>CR</td>
<td>43(100), 42(H)95, 29(CH)270, 28(Me)30, 26(OH)20, 15(CO)70, 14(CH2O)30.</td>
</tr>
<tr>
<td>MeCOO- [43]</td>
<td>(CH2CHO)2-</td>
<td>CR</td>
<td>43(100), 42(H)95, 41(H2)42, 29(CH2)244, 28(Me)15, 27(O)16, 26(OH)19, 25(H2O)9, 15(CO)70, 14(CH2O)30, 13(CH2O)4.</td>
</tr>
<tr>
<td>MeCOO- [43]</td>
<td>(CD2CHO)2-</td>
<td>CR</td>
<td>43(100), 42(H)95, 41(H2)44, 29(CH2)250, 28(Me)37, 27(O)10, 26(OH)10, 25(H2O)6, 15(CO)25, 14(CH2O)12, 13(CH2O)4.</td>
</tr>
<tr>
<td>CD3CONH2 - H+</td>
<td>OCNO- (58)</td>
<td>CR</td>
<td>44(N)15, 42(O)100, 30(CO)30, 28(NO)35, 14(CO2)3.</td>
</tr>
<tr>
<td>[58]</td>
<td>OCNO-</td>
<td>CR</td>
<td>44(N)13, 42(O)100, 30(CO)32, 28(NO)35, 14(CO2)3.</td>
</tr>
<tr>
<td>OCNO- [58]</td>
<td>(CD2CO)2-</td>
<td>CR</td>
<td>44(CD2, O)100, 42(DO)35, 40(D2O)2, 30(CIDO)30, 28(CD2O)20, 16(CO2)10.</td>
</tr>
<tr>
<td>(CD2CO)2- [60]</td>
<td>CR</td>
<td>44(CD2, O)100, 42(DO)30, 40(D2O)5, 30(CIDO)25, 28(CD2O)28, 16(CO2)5.</td>
<td></td>
</tr>
<tr>
<td>PrCONH2 - H+</td>
<td>CH2CONOH (73)</td>
<td>CR</td>
<td>43(NO)35, 42(NOH)100, 30(MeCO)40.</td>
</tr>
</tbody>
</table>

The MS/MS/MS data are lost in baseline noise, the spectra recorded are those of the appropriate species formed by dissociation of the (M – H+) in the ion source; all of the charge reversal (positive ion) spectra are weak and 'noisy' – abundances are correct to within ±5%.
The MS/MS/MS data are lost in baseline noise, the spectra recorded are those of the appropriate species formed by dissociation of the (M – H^+)^- in the ion source; all of the charge reversal (positive ion) spectra are weak and 'noisy' – abundances are correct to within ± 5%.

Table 5.3. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated aryl hydroxamic acids

<table>
<thead>
<tr>
<th>Precursor Ion (m/z)</th>
<th>Product Ion (m/z)</th>
<th>Spectrum Type</th>
<th>Spectrum m/z (loss) relative abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCONHOH - H^+^-</td>
<td>PhCO_2^- (121)</td>
<td>CA</td>
<td>120(H^+)100, 77(CO_2)96, 76(CO_2+H^+)15, 75(CO_2+H_2)9, 44(Ph^+)2.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>105(O)10, 77(CO_2)100, 75(CO_2+H_2)26, 51(CO_2+C_2H_2)75, 51(CO_2+C_2H_2)50, 50(CO_2+C_2H_3^-)61, 44(Ph^+)6.</td>
</tr>
<tr>
<td>PhCO_2^- (121)</td>
<td>CA</td>
<td>120(H^+)100, 77(CO_2)96, 76(CO_2+H^+)18, 75(CO_2+H_2)8, 44(Ph^+)2.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>105(O)12, 77(CO_2)100, 75(CO_2+H_2)30, 51(CO_2+C_2H_2)67, 50(CO_2+C_2H_3^-)61, 44(Ph^+)6.</td>
<td></td>
</tr>
<tr>
<td>PhNH^- (92)</td>
<td>CA</td>
<td>91(H^+)100, 90(H_2)16.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>91(H^+)10, 76(NH_2^-)10, 65(HCN)80, 64(HCN+H^-)72, 53(HCN+H_2)45, 51(C_2H_3N)100, 39(C_3H_3N)55, 38(C_3H_4N)45, 26(C_5H_6)16.</td>
<td></td>
</tr>
<tr>
<td>PhNH^- (92)</td>
<td>CA</td>
<td>91(H^+)63, 76(NH_2^-)27, 65(HCN)100, 64(HCN+H^-)63, 63(HCN+H_2)56, 51(C_2H_3N)57, 39(C_3H_3N)47, 38(C_3H_4N)52, 26(C_5H_6)14.</td>
<td></td>
</tr>
</tbody>
</table>
5.3 Rearrangements of deprotonated O-alkyl substituted Hydroxamic acids

Deprotonated hydroxamic acid O-methyl or O-ethyl ethers show reactions analogous to those of the unsubstituted hydroxamic acids. The collisional activation mass spectra of several hydroxamic acid ethers are listed in Table 5.1. The spectrum of the ion \( \text{CH}_3\text{CON}(-)\text{OCH}_3 \) is illustrated in Figure 5.3. This ion shows losses of \( \text{H}^+ \), \( \text{Me}^+ \) and \( \text{MeO}^- \), and formation of \( \text{-CH}_2\text{NCO} \), \( \text{NCO}^- \), \( \text{MeO}^- \), and \( \text{H}_2\text{CN}^- \). It is suggested that the major losses occur via a Lossen rearrangement with the main processes proceeding through a radical/radical anion ion complex (eqn 5.21–23).

\[
\begin{align*}
\text{CH}_3\text{CONOMe} & \xrightarrow{\text{Lossen Rearrangement}} \left[ \left( \text{CH}_3\text{NCO} \right)\text{MeO}^- \right] \\
& \xrightarrow{\text{MeO}^- + \text{CH}_3\text{NCO}} \left[ \left( \text{CH}_3\text{NCO} \right)\text{MeO}^- \right] \\
& \xrightarrow{\text{-CH}_2\text{NCO} + \text{MeOH}} \left[ \left( \text{CH}_3\text{NCO} \right)^{-} \text{MeO}^- \right] \\
& \xrightarrow{\left( \text{CH}_3\text{NCO} \right)^{-} + \text{MeO}^-} \left( \text{CH}_3\text{NCO} \right)^{-} + \text{MeO}^- 
\end{align*}
\]

The three centre rearrangements illustrated in Scheme 5.3 for deprotonated hydroxamic acids do not occur for the O-methyl ethers as the rearrangement outlined in eqn 5.15 is initiated from the \( \text{O}^- \) centre of the unsubstituted hydroxamic acid.
Figure 5.3. CA mass spectrum of the ion CH$_3$CONHOCH$_3$ – H$^+$.
5.4 Rearrangement of deprotonated Hydrazides

The solution reaction of hydrazides (RCONHNH₂) with nitrous acid, yields the isocyanate intermediate (RNCO) via a Curtius rearrangement.\(^{228,229}\)

\[
\begin{align*}
\text{O} & \quad \text{NHNH}_2 \\
\text{R} & \quad \text{NaNO}_2, \text{HCl} \\
\rightarrow & \quad \text{O} \\
\text{R} & \quad \text{N}^+ \\
\rightarrow & \quad \text{N}^+ \\
\text{R} & \quad \text{N} \rightarrow \text{N}^+ \\
\text{N} & \quad \text{N} \rightarrow \text{C} = \text{O} \\
\end{align*}
\]

The reaction of a hydrazide and strong aqueous base in solution does not lead to a Lossen rearrangement; instead, hydrolysis is noted.\(^{229}\) It has been shown that deprotonated hydroxamic acids rearrange readily in the gas phase. Do deprotonated hydrazides exhibit similar behaviour?

The collisional activation mass spectra of a number of ions, RCON(-)NH₂, are listed in Table 5.1, and the spectrum of CD₃CON(-)NH₂ is illustrated in Figure 5.4. This species fragments via fewer pathways than the cognate hydroxamic acid. The deprotonated hydrazide fragments by loss of H⁺, CD₃H and CD₃NH₂ (cf. eqns 5.9, 11 and 14). There are no fragments due to loss of D⁺, NH, NH₃, N₂H₂ and no formation of NH₂⁻ (cf. eqns 5.10, 15, 18, 7 and 12). The major fragmentations of CD₃CON(-)NH₂ are summarised in Scheme 5.4.
The processes resulting in losses of H\textsuperscript{+} and CD\textsubscript{3}H are shown in eqns 5.25 and 5.26: the latter process\textsuperscript{*} produces the amidoisocyanate ion, OCNNH\textsuperscript{−}. The structure of this ion is confirmed by the MS/MS/MS data in Table 5.2\textsuperscript{**}. It is proposed that NCO\textsuperscript{−} may be formed via a Lossen ion complex 5i. MS/MS/MS studies show that the loss of NH\textsubscript{2}\textsuperscript{−} from CD\textsubscript{3}CON(\textsuperscript{−})N\textsubscript{H}\textsubscript{2} yields (CD\textsubscript{3}NCO)\textsuperscript{−}\textsuperscript{•} rather than (CD\textsubscript{2}CO\textsubscript{2})\textsuperscript{−}\textsuperscript{•} (cf. eqn 5.16). The formation of (CD\textsubscript{3}NCO)\textsuperscript{−}\textsuperscript{•} may form via the Lossen radical/radical anion complex 5j (eqn 5.28). Alternatively NCO\textsuperscript{−} could be formed by a radical reaction through radical/radical anion complex 5i.

Other deprotonated hydrazides react similarly. Points of interest are i) when R = Pr, the elimination of (C\textsubscript{2}H\textsubscript{4} + H\textsuperscript{+}) is again prominent, and ii) the spectrum of PhCON(\textsuperscript{−})N\textsubscript{H}\textsubscript{2} (Table 5.2) lacks the pronounced peak due to PhNH\textsuperscript{−}, which is observed in the spectrum of PhCON(\textsuperscript{−})OH (cf. Figure 5.2 and eqn 5.20).

\textsuperscript{*} Dissociation of the ion complex in eqn 5.25 occurs when the electron affinity of R\textsuperscript{+} is positive, e.g. Ph\textsuperscript{+}, or PhCH\textsubscript{2}\textsuperscript{+} (see Table 5.2).

\textsuperscript{**} The OCNNH\textsuperscript{−} ions formed from CD\textsubscript{3}CON(\textsuperscript{−})N\textsubscript{H}\textsubscript{2} and H\textsubscript{2}NN(\textsuperscript{−})CO\textsubscript{2}Et\textsuperscript{224} exhibit identical CR mass spectra, viz. major elimination of NH\textsubscript{2}, O, CO/N\textsubscript{2}, N\textsubscript{2}H and NCO.
5.5 Rearrangement of deprotonated N'-substituted Hydrazides

Deprotonated N',N' dimethylhydrazides exhibit several reaction pathways typical of a gas phase Lossen rearrangement. The prototypical example of [CH$_3$CONHNMe$_2$ – H$^+$]$^-$ is illustrated in Figure 5.5, other spectra are listed in Table 5.1. The ion CH$_3$CON(–)NMe$_2$ fragments via loss of H$^*$, Me$^*$ and CH$_4$, and formation of CH$_3$CONH$^-$, (CH$_3$NCO)$^-$ and NCO$^-$. Proposed mechanisms accounting for the major fragmentations are summarized in Scheme 5.5.

\[
\text{CH}_3\text{CON}(-)\text{NMe}_2 \xrightarrow{\text{Lossen Rearrangement}} [\text{CH}_3\text{CONNMe}_2^-] \rightarrow \text{NCO}^- + \text{Me}_2\text{N} \quad 5.31
\]

\[
5k [\text{CH}_3\text{CONNMe}_2^-] \rightarrow (\text{CH}_3\text{NCO})^+ + \text{Me}_2\text{N}^- \quad 5.32
\]

\[
\text{CH}_3\text{CONHNMe}_2 \rightarrow \text{CH}_3\text{CONH}^- + \text{CH}_3\text{N}=\text{CH}_2 \quad 5.33
\]

Scheme 5.5
The reactions in eqn 5.29 and 31 are analogous to the radical cleavages of hydrazides and hydroxamic acids. Likewise, the formation of (CH₃NCO)⁻* and NCO⁻ appear to occur via a radical/radical anion complex 5k. The formation of CH₃CONH⁻ is proposed to form following proton transfer to carbon and elimination of CH₃N=CH₂, via a six-centre transition state (eqn 5.33).
Figure 5.4. CA mass spectrum of the ion CD₃CONHNH₂ - H⁺]⁻

Figure 5.5. CA mass spectrum of the ion CH₃CONHNMe₂ - H⁺]⁻
The MS/MS/MS data are lost in baseline noise, the spectra recorded are those of the appropriate species formed by dissociation of the (M – H⁺)⁻ in the ion source; all of the charge reversal (positive ion) spectra are weak and ‘noisy’ – abundances are correct to within ± 5%.

<table>
<thead>
<tr>
<th>Precursor lon (m/z)</th>
<th>Product lon (m/z)</th>
<th>Spectrum type</th>
<th>Spectrum m/z (loss) relative abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3CONHNH2 - H⁺⁻</td>
<td>OCNNH⁻ (57)</td>
<td>CR</td>
<td>56(H⁺)20, 43(N)10, 42(NH)72, 41(O)18, 29(CO, N2)60, 28(N2H, CHO)100, 13(N2O)6.</td>
</tr>
<tr>
<td>OCNNH⁻ [57]</td>
<td>CR</td>
<td>56(H⁺)32, 43(N)23, 42(NH)100, 41(O)22, 41(HO)6, 29(CO, N2)46, 28(N2H, CHO)81, 15(NCO)4, 13(N2O)8, 12(NH2O)2.</td>
<td></td>
</tr>
<tr>
<td>(CD2NCO)⁻⁻ (60)</td>
<td>CA</td>
<td>42(CD3⁺)100.</td>
<td></td>
</tr>
<tr>
<td>(CD2NCO)⁻⁻ (60)</td>
<td>CR</td>
<td>58(D⁺)15, 46(N)45, 44(O)50, 42(CD3⁺)1100, 30(C2D⁺)60, 28(CD2N)20, 18(NCO)25, 16(CD3NC)8, 14(CD3CO)5.</td>
<td></td>
</tr>
<tr>
<td>¹CH2CONNH₂⁻⁻ [90]</td>
<td>CR</td>
<td>55(NH3)20, 43(N2H⁺)50, 42(N2H2)100, 29(MeCO⁺)80, 28(CH4N2, C2H₄O)95.</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 6

The Collisional Activation Mass Spectra of Deprotonated Amidoximes: Does the Tiemann Rearrangement Occur in the Gas Phase?

6.1 Introduction

In chapter 2, the collision induced loss of water from deprotonated oximes in the gas phase was discussed; this fragmentation is rationalised by a negative ion Beckmann rearrangement as illustrated in eqn 6.1. In certain cases, a deprotonated oxime does not undergo the gas phase Beckmann rearrangement, and the ion rearranges via a different process. For example:

i) When proton transfer to the \( O^- \) centre cannot occur, migration of another group may be observed (e.g. eqn 6.2), and

ii) as discussed in chapter 4, \( \alpha \)-oximino ketones undergo the cyclisation/dissociation reaction shown in eqn 6.3, even when a competitive proton transfer to \( O^- \) is possible.

\[
\begin{align*}
\text{CH}_{3}\text{N:C-Me} & \xrightarrow{\text{O}} [\text{HO}^- (\text{CH}_2=\text{C}=\text{NMMe})] \xrightarrow{} \text{H}_2\text{O} + \text{CH}_2=\text{C}=\text{NCH}_2^- \quad 6.1 \\
\text{Ph}_2\text{C}=\text{NO}^- & \xrightarrow{\text{O}} \text{PhC}=\text{NOPh} \xrightarrow{} \text{PhO}^- + \text{PhCN} \quad 6.2 \\
\text{Me}\text{C}=\text{NMe} & \xrightarrow{\text{O}} \text{RCO}_2^- + \text{MeCN} \quad 6.3
\end{align*}
\]
In solution, suitably substituted amidoxime derivatives undergo a base catalysed rearrangement which is comparable to the proposed gas phase negative ion Beckmann rearrangement. The Tiemann rearrangement\(^\text{230}\) of amidoximes to ureas was reported in 1891, five years after Beckmann discovered the rearrangement of oximes to amides. The Tiemann rearrangement is summarised in eqn \(^\text{6.4}\).\(^\text{231-234}\)

\[
\begin{align*}
\text{R} & \equiv \text{NOSO}_2\text{Ph} \\
\text{H}_2\text{N} & \rightarrow \text{i) base} \\
& \rightarrow \text{ii) H}_2\text{O} \\
& \rightarrow \text{R} \text{NH}^- \text{NH}_2 \\
\end{align*}
\]

If this reaction occurs for deprotonated amidoximes in the gas phase, then it is analogous to the negative ion Beckmann rearrangement and a major fragmentation should be loss of water as proposed in eqn \(^\text{6.5}\).

\[
\begin{align*}
\text{R} \equiv \text{NOH} & \rightarrow [\text{H}_2\text{N} \equiv \text{C} \equiv \text{NR}] \text{HO}^- \\
& \rightarrow [\text{RN} \equiv \text{C} \equiv \text{NH} - \text{H}^+] + \text{H}_2\text{O} \\
\end{align*}
\]

This chapter investigates the collisional activation mass spectra of deprotonated amidoximes and cognate systems in order to determine whether there is a correlation between the gas and condensed phase reactivities of deprotonated amidoximes.
Figure 6.1. CA mass spectrum of the ion Me(NH$_2$)C=NOH – H$^+$]

Figure 6.2. CA mass spectrum of the ion Ph($^{15}$NH$_2$)C=NOH – H$^+$]
6.2 Results and Discussion

6.2.1 Collisional Activation Mass Spectra of Deprotonated Amidoximes

The collisional activation mass spectra (MS/MS) of deprotonated unsubstituted and N-alkyl substituted amidoximes and O-alkyl amidoxime ethers are recorded in Tables 6.1 and 6.2. The spectra of \([\text{Me}(\text{NH}_2)\text{C}=\text{NOH} - \text{H}^+]\) and \([\text{Ph}(15\text{NH}_2)\text{C}=\text{NOH} - \text{H}^+]\) are illustrated in Figures 6.1 and 6.2. Tandem mass spectra (MS/MS/MS) of selected daughter ions are collated in Table 6.3.

Amidoxime anions are produced by deprotonation with \(\text{NH}_2^-\). The \(\Delta H^\circ_{\text{acid}}\) values of the three positions at which deprotonation can occur are not known, but relative values can be estimated. For example, i) \(\Delta H^\circ_{\text{acid}}\) of \([\text{CH}_3(\text{NH}_2)\text{C}=\text{NOH}]\) would be similar to \(\Delta H^\circ_{\text{acid}}\) of a primary amide or urea, cf. \([\text{MeCONH}_2]^{187} = 1510 \text{ kJmol}^{-1}\), ii) the \(\Delta H^\circ_{\text{acid}}\) of \([\text{CH}_3(\text{NH}_2)\text{C}=\text{NOH}]\) can be compared to the value for \([\text{Me}_2\text{C}=\text{NOH}]^{163} = 1532 \text{ kJmol}^{-1}\), and iii) \(\Delta H^\circ_{\text{acid}}\) of \([\text{CH}_3(\text{NH}_2)\text{C}=\text{NOH}]\) will be similar to that of \([\text{[(CH}_3)_2\text{C}=\text{NOH}]^{164} = 1560 \text{ kJmol}^{-1}\). Therefore \(\text{NH}_2^- [\Delta H^\circ_{\text{acid}} (\text{NH}_3) = 1689 \text{ kJmol}^{-1}]^{190}\), will in principle, deprotonate the neutral amidoxime to form the ions \([\text{CH}_3(\text{NH}^-)\text{C}=\text{NOH}] \text{ 6a}, [\text{CH}_3(\text{NH}_2)\text{C}=\text{NO}^-] \text{ 6b} \) and \([-\text{CH}_2(\text{NH}_2)\text{C}=\text{NOH}] \text{ 6c} \). The relative acidities of the three positions suggest that deprotonation should primarily occur at the amido position to produce \(\text{6a}\) as the most prevalent parent ion. In addition, it is possible that the ions \(\text{6a}, \text{6b}\) and \(\text{6c}\) will interconvert, by proton transfer, under conditions of collisional activation (similar results were found for deprotonated oximes (Section 2.2.1) where the oxyanion and the carbanion of the oxime undergo rapid interconversion prior to fragmentation).

As a prototypical example, the major fragmentations of deprotonated acetamidoxime \([\text{Me}(\text{NH}_2)\text{C}=\text{NOH} - \text{H}^+]\) are loss of \(\text{H}^+\) and the elements of hydroxylamine \([\text{NH}_2\text{OH}]\), there are also a number of minor fragmentations involving loss of water.
6.2.1.1 The loss of water

The loss of water is a minor process in the spectra of \([R^1(R^2R^3N)C=NOH- H^+]^{-}\) species (\(R^1 = \text{alkyl or aryl}, R^2, R^3 = \text{H or alkyl}\)). It is most pronounced for N-unsubstituted amidoximes, viz. \(R^1=\text{Me}, R^2=R^3=\text{H}\) [13\% (Table 6.1)] and for \(R^1=\text{Ph}, R^2=R^3=\text{H}\) [14\% (Table 6.1)]. The loss of water could occur via a Tiemann rearrangement through the ion complex 6d (eqn 6.6) or by a Beckmann type rearrangement through ion complex 6e (eqn 6.8). A process associated with the Tiemann ion complex 6d is the minor S\(_{\text{N}2}\) elimination of MeOH to form \(-\text{NHC}=\text{N}\) (eqn 6.7) [see Table 6.1].

\[
\text{HN=C=NM}_\text{e} \xrightarrow{\text{Tiemann}} \text{HN=C=NCNH}_2^- + \text{H}_2\text{O} \quad 6.6
\]

\[
\text{HN=C=NNH}_2^- + \text{MeOH} \quad 6.7
\]

\[
\text{HN=C=NNH}_2^- \xrightarrow{\text{Beckmann}} \text{HN=C=NCNH}_2^- + \text{H}_2\text{O} \quad 6.8
\]

\[
\text{Scheme 6.1}
\]

For the Tiemann rearrangement, the hydroxide ion deprotonates the neutral to produce \([\text{HN}=\text{C}=\text{N}=\text{Me} - \text{H}^+]^{-}\), while the Beckmann rearrangement should give \([\text{CH}_2=\text{C}=\text{N}=\text{NH}_2 - \text{H}^+]^{-}\). The MS/MS/MS data for the product ion \(m/z\) 55 due to loss of water is listed in Table 6.3. The CA MS/MS/MS spectrum shows loss

* The spectrum of \([\text{Me}(\text{ND}_2)C=\text{NOD} - \text{D}^+]^{-}\) (Figure 6.1) eliminates both HOD and D\(_2\)O in a 1 : 1 ratio, indicating the \(\text{HO}^-\) of the decomposing ion complexes 6d or 6e (Scheme 6.1) is effecting deprotonation at both carbon and nitrogen.
of \( H^* \), \( H_2 \), \( NH \) and formation of \( CN^- \), (the corresponding charge reversal spectrum exhibits major loss of \( H_2 \), \( CH_2/N \), \( NH \), \( C_2H_3 \), \( CH_2N \) and \( CH_3N \)). This data does not specifically confirm the structure to be \([HN=C=N-Me - H^+]^-\) or \([CH_2=C=N-NH_2 - H^+]^-\) and thus we cannot distinguish between the two structures.

In contrast, the ion \([Ph(NH_2)C=NOH - H^+]^-\) cannot undergo the Beckmann reaction. In this case the CA MS/MS/MS data for the ion \( m/z \) 117 (Table 6.3) is consistent with the structure of the Tiemann product ion i.e. \((C_6H_4)^-N=C=NH\) (cf. eqn 6.6). For example, the Tiemann product ion loses HCN (to form \( C_6H_4N^-\)) and \( C_6H_4 \) (to give \(-NHC≡N\)). As the elimination of water is only a very minor reaction, we can conclude that the Tiemann reaction is, at best, a minor process of deprotonated amidoximes in the gas phase.
6.2.1.2 Other Fragmentations: The loss of hydroxylamine and related processes

All deprotonated amidoximes eliminate hydrogen; deuterium labelling indicates that for $[\text{Me(ND}_2\text{)C=NOH - D}^+]^-$, loss of D* forms predominantly the resonance stabilised radical anion shown in eqn 6.9. Loss of H* from the methyl group is minor in comparison.

\[ \text{Me} \text{Me} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{H}_2\text{N} \]
\[ \text{HN} \]
\[ \text{O} \]
\[ \text{Me} \text{Me} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{H}_2\text{N} \]
\[ \text{HN} \]
\[ \text{O} \]

The most interesting fragmentation of deprotonated amidoximes is loss of NH$_2$OH and several related processes. For example, the spectrum of $[\text{Me(NH}_2\text{)C=NOH - H}^+]^-$ (Figure 6.1) exhibits major loss of NH$_2$OH, to produce the base peak in the spectrum, together with minor loss of HNO and the formation of a small peak at m/z 32. We propose that the three processes are inter-related and involve the formation of a deprotonated hydroxylamine ion complex, viz. $[(\text{MeCN})^-\text{NHOH}]$. A $^{15}$N labelled derivative is required to determine which nitrogen is lost in these processes. The most informative derivative would be $[\text{Me}^{(15)}\text{NH}_2\text{C}=\text{NOH - H}^+]^-$. Unfortunately we were unable to synthesise this neutral. However $[\text{Ph}^{(15)}\text{NH}_2\text{C}=\text{NOH - H}^+]^-$ also eliminates NH$_2$OH and HNO, and in this case the neutral was prepared. The spectrum of $[\text{Ph}^{(15)}\text{NH}_2\text{C}=\text{NOH - H}^+]^-$ eliminates NH$_2$OH and HNO specifically. Thus it is the nitrogen of the oxime group that is involved in each process.

The spectrum of the ion $[\text{Me(ND}_2\text{)C=NOH - D}^+]^-$ (Table 6.1) shows elimination of "HD$_2$NO" together with minor loss of "H$_2$DNO". MS/MS/MS Studies show that the structure of the product ion formed by loss of NH$_2$OH from of
[Me(NH₂)C=NOH – H⁺]⁻ is –CH₂CN* (see Table 6.3) The labelling data suggests that elimination of NH₂OH may occur as shown in Scheme 6.2: proton transfer from the imine position (route A) is the predominant process to yield the ion complex 6f. The associated hydride transfer involving loss of HNO₂, could occur from either complex 6f or 6g in Scheme 6.2.

\[ \text{Me} \quad \text{HN} \quad \text{N} \quad \text{OH} \quad \text{Me} \quad \text{HN} \quad \text{N} \quad \text{OH} \quad \equiv \quad \text{Me} \quad \text{HN} \quad \text{N} \quad \text{OH} \quad \text{Me} \quad \text{HN} \quad \text{N} \quad \text{OH} \]

\[ \text{6a} \]

\[ \text{MeCN} \quad \text{NHOH} \quad \equiv \quad \text{MeCN} \quad \text{NHOH} \]

\[ \text{6b} \]

\[ \left[ (\text{MeCN})^{-} \text{NHOH} \right] \quad \left[ (\text{CH₂C=} \text{CH₃})^{-} \text{NHOH} \right] \]

\[ \text{−CH₂CN} + \text{NH₂OH} \]

\[ 6.10 \]

Scheme 6.2

The product ion formed by loss of NH₂OH from [(Ph(NH₂)C=NOH – H⁺)]⁻ is (C₆H₄)⁻CN as evidenced by the data listed in Table 6.3. However, the spectrum of [(Ph(ND₂)C=NOD – D⁺)]⁻ shows elimination of "H₂DNO" and "HD₂NO" in an approximate 2 : 1 ratio (see Table 6.1). Thus the predominant fragmentation route for the methyl derivative (route A, Scheme 6.2) is the minor process for the phenyl analogue. The major process must involve proton transfer from the ring followed by a second proton transfer as shown in eq 6.11.

* The CA mass spectra of −CH₂CN and the ion [(Me(NH₂)C=NOH – NH₂OH) – H⁺]⁻ exhibit identical fragmentation, viz. loss of H⁺ and CH₂.
Small peaks at m/z 32 are observed in some amidoxime spectra (cf. Figure 6.1). This ion corresponds to a deprotonated hydroxylamine. The ion cannot have the structure \( -\text{NHOH} \), since the electron affinity of \( \text{NHOH} \) is negative (-17 kJmol\(^{-1}\))\(^{221} \). The species must be \( \text{NH}_2\text{O}^- \); this ion has been observed previously and the electron affinity of \( \text{NH}_2\text{O}^- \) is -1 kJmol\(^{-1}\)(\(^{221}\))\(^* \). This ion is presumably formed from an ion complex of the type shown in Scheme 6.2. For example, for \([\text{Me(NH}_2\text{)}\text{C}=\text{NOH} - \text{H}^+]^-\), the reaction may be:

\[
[\text{(MeCN)} -\text{NHOH}] \rightarrow [\text{-CH}_2\text{CN (NH}_2\text{OH)}] \rightarrow [(\text{MeCN}) \text{NH}_2\text{O}^-] \rightarrow \text{NH}_2\text{O}^- + \text{MeCN}.
\]

For this process to occur, the initial ion complex must have an excess energy of at least 70 kJmol\(^{-1}\) [i.e. the respective \( \Delta H^o \) \(_{\text{acid}} \) values of CH\(_3\)CN\(^{163}\), NH\(_2\)OH\(^{221}\), NH\(_2\)OH\(^{221}\) are 1560, 1670 and 1630 kJmol\(^{-1}\).

\(^*\) A similar situation was discussed in the fragmentations of deprotonated acetohydroxamic acid (Chapter 5). The ion \( -\text{CH}_2\text{NHOOH} \) fragments via the ion complex \([\text{(H}_2\text{C} - \text{C} - \text{O}^-) -\text{HNOH}] \) to eliminate \( \text{NH}_2\text{OH} \) and form \( \text{CH}_3\text{CO}^- \) by hydride transfer (see eq\(^\text{n}\) 5.7 and 5.8, page 148, cf. Scheme 6.2). In this example, no ion m/z 32 is detected in the spectrum of deprotonated acetohydroxamic acid.

\(^\star\) Ions that have electron affinities close to zero have been detected indirectly in other systems. For example, \( \text{Me}^+ \) is formed by decarboxylation of \( \text{MeCO}_2^- \)\(^{235}\). The electron affinity of \( \text{Me}^+ \) is determined experimentally to be +6 kJmol\(^{-1}\) \(^{236}\) yet the highest level \( ab\ initio \) calculations indicate a value close to zero\(^{221}\).
### Table 6.1. Collision Activation Mass Spectra of Deprotonated Amidoximes and N-alkyl Amidoximes

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>R²</td>
<td>R³</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H¹</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>H²</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H³</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

a) this spectrum also shows a peak corresponding to loss of CH₄ (1%). b) this spectrum also shows a peak corresponding to loss of Et⁺ (6%).
c) the spectrum of Ph(NH₂)C=NO⁻ [formed from Ph(NH₂)C=NOSIMe₃ by nucleophilic displacement with NH₂⁻] is as follows:
m/z (loss) abundance: 134 (H⁺)100, 117 (H₂O)8, 104(HNO)6, 102 (NH₂OH)62, 41 (C₆H₅)1.
d) The CA mass spectrum of the ion [CH₃(ND₂)C=NO⁻ – D⁺]⁻ is as follows; [m/z (loss) abundance]:
74 (H⁺)15, 73 (D⁺)92, 56 (HOD)8, 55 (D₂O)8, 43 (HNO)2, 42 (CH₃OD)3, 41 (H₂DNO)8, 40 (HD₂NO)100, 34 (CH₃CN), 26 (CH₃D₂NO)8, 18 (C₂H₃DN₂)0.8.
e) The CA mass spectrum of the ion [Ph(ND₂)C=NO⁻ – D⁺]⁻ is as follows; [m/z (loss) abundance]:
136 (H⁺)30, 135 (D⁺)100, 103 (H₂DNO)40, 40 (HD₂NO)23, 42 (C₆H₅ND₂) 0.3.
Figures 6.3a-c. CA mass spectra of methyl substituted acetamidoximes. 

Figure 6.3a, CA mass spectrum of the ion Me(\text{Me}_2\text{N})\text{C}=\text{NOH} - \text{H}^+\text{.}

Figure 6.3b, CA mass spectrum of the ion Me(\text{NH}_2)\text{C} = \text{NOMe} - \text{H}^+\text{.}

Figure 6.3c, CA mass spectrum of the ion Me(\text{Me}_2\text{N})\text{C} = \text{NOMe} - \text{H}^+\text{.}
6.2.2 Fragmentations of N-substituted Amidoximes

It is of interest now to investigate what happens when the amido group becomes progressively substituted. The spectrum of deprotonated N,N-dimethyl acetamidoxime \([\text{Me(Me}_2\text{N})\text{C}=\text{NOH} - \text{H}^+]\) (Figure 6.3a) does not eliminate \(\text{NH}_2\text{OH}\). This result is in accord with the mechanism proposed in eqn 6.9. For the elimination of hydroxylamine to proceed, deprotonation must occur at the amido nitrogen, hence in the case of \(\text{Me(Me}_2\text{N})\text{C}=\text{NOH}\) no such anion can form and loss of hydroxylamine is not observed. Other losses now become prominent and the spectra are dominated by radical losses; for example the loss of an alkyl radical from nitrogen to yield a stabilised radical anion (eqn 6.12). Loss of an amine is also observed, and formation of \(\text{HO}^-\). These processes can be rationalised by a Beckmann rearrangement as shown in eqns 6.13 and 6.14.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me}_2\text{N} & \quad \text{MeN} \\
\text{N} & \quad \text{N} \\
\text{O}^- & \quad \text{O}^- \\
\text{Me} & \quad \text{Me} \\
\text{Me}_2\text{N} \quad \text{MeN} & \quad \text{Me}^- \\
\end{align*}
\]

6.12

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me}_2\text{N} & \quad \text{MeN} \\
\text{N} & \quad \text{N} \\
\text{O}^- & \quad \text{O}^- \\
\text{Me} & \quad \text{Me} \\
\text{Me}_2\text{N} & \quad \text{MeN}^- \\
\end{align*}
\]

Beckmann

\[
\begin{align*}
\left(\text{HN}==\text{C}==\text{NNMe}_2\right)\text{HO}^- & \quad \left(\text{HN}==\text{C}==\text{NNO}^-\right)\text{Me}_2\text{N}^- \\
\text{HN}==\text{C}==\text{NNMe}_2 & \quad \text{HN}==\text{C}==\text{NO}^- & \quad \text{Me}_2\text{NH} \\
\end{align*}
\]

6.13

\[
\begin{align*}
\left(\text{HN}==\text{C}==\text{NNMe}_2\right)\text{HO}^- & \quad \left(\text{HN}==\text{C}==\text{NNO}^-\right)\text{Me}_2\text{N}^- \\
\text{HN}==\text{C}==\text{NNMe}_2 & \quad \text{HN}==\text{C}==\text{NO}^- & \quad \text{Me}_2\text{NH} \\
\end{align*}
\]

6.14

Scheme 6.3
6.2.3 Fragmentations of O-substituted Amidoximes

Deprotonated O-methyl amidoxime ethers such as Me(NH₂)C=NOMe should in principle eliminate methylhydroxylamine by the same mechanism that amidoximes eliminate hydroxylamine (i.e. eqn 6.10). The spectra of some deprotonated O-methyl amidoxime ethers are recorded in Table 6.3. The spectra are significantly different from the amidoxime spectra, and loss of the alkyl substituted hydroxylamine is a minor process [loss of "MeONH₂" from R¹=Ph, (abundance) 4%; R¹=Me, 3%]. The major fragmentations of [Me(NH₂)C=NOMe - H⁺]⁻ (Table 6.3) are also dominated by radical losses. viz, the loss of H⁺ and Me⁺ to yield stabilised radical anions (eqns 6.15 and 6.16). Rearrangement through the Tiemann reaction leads to elimination of MeOH and formation of -NHC≡N (eqns 6.17 and 6.18).

The reactions of [Ph(NH₂)C=NOMe - H⁺]⁻ (Table 6.2) are similar to those of O-methyl acetamidoxime; loss of Me⁺ is the major fragmentation pathway (cf. eqn 6.18) and elimination of methoxylamine occurs to a minor extent (3%). Further reaction through a Tiemann rearrangement produces the ion complex...
deprotonation by MeO− yields the ion HN=C=NC6H4− (eqn 6.19), whereas hydride transfer from MeO− produces HN=CH=NPh (eqn 6.20).

\[
\begin{align*}
\text{Ph} & \quad \text{Tiemann} \\
\text{HN} & \quad \text{OMe} \\
\end{align*}
\]

6.2.4 Fragmentations of N- and O-substituted Amidoximes

When both the oxime and amido positions are fully alkylated e.g. R1(Me2N)C=NOMe alternative reactions must occur. When R1=Ph, the parent ion cannot undergo the Tiemann reaction, and the spectrum (Table 6.2) is dominated by other rearrangement processes (eqn 6.21).

The spectrum of [Me(Me2N)C=NOMe − H+]− is illustrated in Figure 6.3c. The major fragmentation is formation of MeO−; this reaction is proposed to occur through a Beckmann rearrangement to produce ion complex 6i. Decomposition of 6i leads to formation of MeO− (eqn 6.22) and minor formation of CH2CN (eqn 6.23). Other major fragmentations proceed through ion complex 6k, viz. formation of Me2N− (eqn 6.24), loss of Me2NH (eqn 6.25) and a related loss of Me3N (eqn 6.26) as shown in Scheme 6.6.

* hydride addition reactions from methoxide ions have been observed in other systems238.
6.3 Conclusions
Deprotonated amidoximes undergo a gas phase Tiemann rearrangement to a minor extent. This rearrangement is characterised by loss of water from the deprotonated amidoxime. In contrast, the major fragmentation pathway of amidoxime anions is loss of hydroxylamine to form a nitrile anion. $^{15}$N Labelling studies have shown that this fragmentation proceeds through a double proton transfer rather than rearrangement of the parent ion. When either the oxygen or nitrogen atom of the amidoxime is substituted, loss of hydroxylamine does not occur and the spectra are dominated by losses of H$^+$ and the substituent attached to N (or O) to produce resonance stabilised radical anions. In certain cases the N (or O) substituted amidoxime rearrange via Tiemann or Beckmann intermediates, however such reactions are minor processes.
**Table 6.2. Collision Activation Mass Spectra of Deprotonated O-alkyl Amidoximes**

<table>
<thead>
<tr>
<th>NEUTRAL PRECURSOR (m/z)</th>
<th>SPECTRUM [m/z (loss or formation as appropriate) relative abundance]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(NH$_2$)C=NOMe (87)</td>
<td>86 (H$^+$)46, 72 (Me$^+$)100, 56 (MeO$^-$)4, 55 (MeOH$^-$)7, 41 ($^-$NHCN)$^3$, 40 ($^-$CH$_2$CN)$^3$, 31 (MeO$^-$)$^1$, 26 (CN$^-$)$^1$.</td>
</tr>
<tr>
<td>Me(Me$_2$N)C=NOMe (115)</td>
<td>114 (H$^+$)10, 100 (Me$^+$)11, 83 (MeOH$^-$)1, 70 (Me$_2$NH)$^1$, 55 (Me$_3$N)$^6$, 41/40 ($^-$NHCN, $^-$CH$_2$CN)$^8$, 31 (MeO$^-$)$^1$00.</td>
</tr>
<tr>
<td>Ph(NH$_2$)C=NOMe (149)</td>
<td>148 (H$^+$)46, 134 (Me$^+$)100, 119 (CH$_2$O)$^4$, 117 (MeOH$^-$)7, 104 (MeNO)$^4$, 102 (Me$_2$NO)$^5$, 77 (Ph$^-$)$^5$, 4 ($^-$NHCN)$^1$.</td>
</tr>
<tr>
<td>Ph(Me$_2$N)C=NOMe (177)</td>
<td>176 (H$^+$)86, 162 (Me$^+$)8, 147 (CH$_2$O)$^3$, 146 (MeO$^-$)$^5$, 91 [(C$_6$H$_4$)$^-$Me]$^1$, 42 (CNO$^-$)$^5$.</td>
</tr>
</tbody>
</table>

a) overlapping peaks - unresolved.
### Table 6.3. Fragmentation data (CA and CR) for Product Ions in the Mass Spectra of Deprotonated Amidoximes

<table>
<thead>
<tr>
<th>PARENT ION (m/z)</th>
<th>DAUGHTER ION ([m/z]; loss)</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM A</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CN - H⁺⁻ (40)</td>
<td>([55], H₂O)</td>
<td>CA</td>
<td>54 (H⁺) 10, 53 (H₂) 22, 40 (NH₂) 100, 26 (CH₃NO) 21.</td>
</tr>
<tr>
<td></td>
<td>([42], HNO)</td>
<td>CR</td>
<td>54 (18), 53 (100), 41 (40), 39 (18), 36 (14), 29 (15), 28 (38), 27 (26), 15 (6), 14 (5).</td>
</tr>
<tr>
<td></td>
<td>([40], NH₂OH)</td>
<td>CA †</td>
<td>42 (52), 41 (100), 40 (74), 39 (28), 38 (14), 28 (20), 27 (21), 26 (19), 25 (4), 15 (15), 14 (6).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>39 (H⁺) 100, 26 (CH₂) 14.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40 (100), 39 (45), 38 (30), 28 (4), 27 (1), 26 (16), 25 (2), 24 (1), 14 (1).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA</td>
<td>39 (H⁺) 100, 26 (CH₂) 9.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>40 (100), 39 (40), 38 (29), 28 (3), 27 (1), 26 (14), 25 (2), 24 (1), 14 (1).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph(NH₂)C=NOH - H⁺⁻ (135)</td>
<td>([117], H₂O)</td>
<td>CA †</td>
<td>116 (H⁺) 100, 90 (HCN) 68, 41 (C₆H₄) 45, 26 (C₆H₅N) 8.</td>
</tr>
<tr>
<td></td>
<td>([104], HNO)</td>
<td>CA †</td>
<td>102 (H₂) 100, 76 (CH₂N) 71.</td>
</tr>
<tr>
<td></td>
<td>([102], NH₂OH)</td>
<td>CA</td>
<td>101 (H⁺) 100, 26 (C₆H₃N) 20.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA</td>
<td>101 (H⁺) 100, 25 (C₆H₃N) 18.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>101 (80), 100 (20), 99 (18), 98 (24), 87, 86, 85 (15), 76 (57), 74 (100), 61, 62 (21), 50 (43), 37, 36 (12), 25, 26 (2).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>101 (80), 100 (15), 99 (18), 98 (23), 87, 86 (10), 76 (58), 74 (100), 61, 62 (20), 50 (40), 37, 36 (8), 25, 26 (2).</td>
</tr>
</tbody>
</table>

a) collisional activation [m/z (loss) abundance]; for charge reversal [m/z (abundance)]; b) spectrum very weak; c) formed from deprotonation of acetonitrile; d) the charge reversal spectra are very complex and are not recorded; e) prepared from deprotonation of benzonitrile; f) peaks are unresolved but of equal abundance.
CHAPTER 7

The Collisional Activation Mass Spectra of Deprotonated Heterocycles:

"Seek, and ye shall find; knock, and it shall be opened unto you"

Matthew 5:7

7.1 Introduction

This chapter discusses the collisional activation mass spectra of deprotonated heterocyclic compounds, namely the isothiazole, thiazole, isoxazole and oxazole ring systems, and investigates the correlation between the reactions of anionic heterocycles in solution and the fragmentation/rearrangement processes of the corresponding species in the gas phase.

The reactions of heterocyclic compounds containing one or two heteroatoms with various bases in the condensed phase are quite diverse. The anionic reactions of such heterocycles can be divided into two categories:

(i) deprotonation and subsequent electrophilic reactions, and

(ii) ring opening reactions.

7.1.1 Deprotonation of heterocyclic species in the condensed phase

Furan, thiophene and N-alkyl pyrroles react readily with butyl lithium to produce the 2-lithioheterocycle and the resulting carbanion undergoes electrophilic substitution to form substituted heterocycles in generally excellent yield\textsuperscript{239,240} (eq\textsuperscript{n} 7.1). Lithiation will generally occur preferentially at the 2-position, however, various factors including the nature of the solvent, reaction temperature and chelating agents can influence the direction of lithiation to the 3-position\textsuperscript{241}. 

temperature and chelating agents, can influence the direction of lithiation to the 3-position\textsuperscript{241}.

\[ \text{Oxazole} \xrightarrow{i) n-BuLi} \text{Oxazol-2-yl magnesium bromide} \]

The reactions of diheteroatom heterocycles, viz: thiazole/isothiazole, oxazole/isoazole, and imidazole/pyrazole with base are generally more complicated. For example, thiazole reacts with phenyl lithium at -60°C to afford the 2-lithioanion\textsuperscript{242}, whereas reaction with HO\textsuperscript{-} yields the 2- and 5-lithioanions in similar yield\textsuperscript{243} (Scheme 7.1). Reaction of thiazole with two equivalents of ethyl magnesium bromide at 30°C produces thiazol-2-yl magnesium bromide in almost quantitative yield\textsuperscript{244}. The isomeric isothiazole reacts with HO\textsuperscript{-} to form the 5-lithioanion\textsuperscript{245} but with butyl lithium the 3-lithioanion is produced\textsuperscript{246,247}.

Oxazole is preferentially deprotonated at the 2 position with minor reaction at the 5 position\textsuperscript{248,249}, whereas isoxazole is deprotonated at both the 3 and 5 positions\textsuperscript{250,251}.

\[ \text{Oxazole} \xrightarrow{n-BuLi} \text{Oxazol-2-yl anion} \]

\[ \text{Isotiazole} \xrightarrow{\text{HO}^-} \text{Isotiazol-5-yl anion} \]

\[ \text{Isoxazole} \xrightarrow{\text{HO}^-} \text{Isoxazol-3-yl anion} \]

\textit{Scheme 7.1}

\textbf{7.1.2 Ring opening reactions}

There are many cases in which metallation of a five membered heterocycle causes ring cleavage rather than formation of the metallated heterocycle\textsuperscript{252,253}.
The two most common types of anionic ring opening reactions of heterocycles are illustrated in Scheme 7.2.

\[
\begin{align*}
&\text{Scheme 7.2} \\
\text{eqn 7.5} &\quad \text{eqn 7.6}
\end{align*}
\]

The presence of electronegative atoms at positions A, B or D in the product anion \( Z_a \) (eqn 7.5) stabilise the open-chain species and hence favour ring opening in such cases\(^{254} \); whereas in eqn 7.6 the direction of ring opening will depend on the relative stabilities of the two open chain ions \( Z_b \) or \( Z_c \), but in neither intermediate is the delocalisation of charge as extensive as in the anion \( Z_a \). Therefore, ring opening reactions of 1,2-substituted diheteroatom heterocycles (where A and B are the heteroatoms, eqn 7.5) are more common than for 1,3-substituted heterocycles (eqn 7.6). Most 1,3-substituted heterocycles for stable anions that do not ring open when metallated at the 2- or 5-position\(^{253} \).

Cleavage of 1,2-Heterocycles

Isoxazoles unsubstituted in the 3 position are readily opened by base, for example, 5-phenylisoxazole ring opens to yield the sodium salt of benzoylacetonitrile in the presence of sodium ethoxide\(^{255} \).
Alternatively, when the 3 position is substituted, a different reaction occurs\textsuperscript{256} preceded by deprotonation at the 5-position (eqn 7.8). Furthermore, a leaving group at C3 can also change the course of the reaction\textsuperscript{257} (eqn 7.9).

Reaction of 4-methylthiazole with butyl lithium gives mainly the stable 5-lithioanion, but a minor product of the reaction involves lithiation at the 3-position and consequent ring opening\textsuperscript{257} i.e.

3-Unsubstituted pyrazoles are not easily ring opened by base, however electron-withdrawing groups at the 1- or 4-positions enhance ring cleavage\textsuperscript{258}.
Cleavage of 1,3 Heterocycles

Thiazoles unsubstituted at the 2 position form stable 2-lithioanions\textsuperscript{242} when treated with butyl lithium at \(-78^\circ C\) and do not undergo ring cleavage\textsuperscript{*}; similarly 2 substituted thiazoles yield stable 5-lithioanions\textsuperscript{242}.

The reactions of 2 unsubstituted oxazoles provide several interesting examples of ring opening reactions. For example, when 5-ethoxyoxazole is treated with \(n\)-butyl lithium at \(-78^\circ C\) for 5 minutes and quenched with \(D_2O\), the only product obtained is ethyl \(\alpha\)-deutero-\(\alpha\)-isocyanopropionate\textsuperscript{260}, i.e.

\[
\begin{align*}
\text{EtO} & \quad \xrightarrow{\text{Li}} \quad \text{EtO} & \quad \text{Li} \\
\text{N} & \quad \xrightarrow{\text{Li}} \quad \text{N} \\
\text{C} & \quad \xrightarrow{\text{Li}} \quad \text{C} \\
\end{align*}
\]

Such reactions are common for heterocyclic compounds with N3 lone pairs (with the exception of thiazole) and in such cases all species undergo fast thermal ring openings. The reaction is rapid as the lone pair on nitrogen facilitates the eliminative ring fission\textsuperscript{253,260}, i.e.

\[
\begin{align*}
\text{EtO} & \quad \xrightarrow{\text{Li}} \quad \text{EtO} & \quad \text{Li} \\
\text{N} & \quad \xrightarrow{\text{Li}} \quad \text{N} \\
\text{C} & \quad \xrightarrow{\text{Li}} \quad \text{C} \\
\end{align*}
\]

The reaction of 4-methyloxazole with butyl lithium at \(-78^\circ C\) results in an equilibrium mixture of the 4-methyl-2-lithiooxazole and the \(\alpha\)-isocyano enolate

\textsuperscript{*} 2-Lithiothiazole decomposes at temperatures > \(-50^\circ C\), whereas substituted 4 or 5 2-lithiothiazole species are stable up to temperatures of \(+5^\circ C\). Various temperature studies\textsuperscript{259} of the reactions of 2-lithiothiazole anions report "decomposition" products rather than "ring opened" products.
The ring opening reaction in this case is reversible, as the ring opened species can be trapped with trimethyl silylchloride to produce the enol ether (eqn 7.13), whereas reaction with benzaldehyde proceeds selectively to yield 2-(α-hydroxybenzyl)-4-methyloxazole (eqn 7.14). Furthermore, heating the enol ether at 100°C with potassium hydroxide induces cyclisation to produce 2-trimethylsilyloxazole (eqn 7.15).

7.1.3 Photochemical interconversion of heterocyclic species

One of the interesting features of the thiazole/isothiazole, oxazole/oxazoline ring systems are their photochemically induced transformations. For example, irradiation of isothiazole in the presence of a primary amine yields thiazole; it is suggested that the transformation occurs as illustrated in eqn 7.16. Similarly, isoxazole and oxazole interconvert via acyl azirines upon irradiation. 3-Methylisothiazole isomerises to yield 2 and 4-methylthiazole via a zwitterion mechanism (cf. eqn 7.17). 5-Methylisothiazole similarly isomerises to yield 2-methylthiazole and 3- and 4-methylisothiazole.
Similar interconversions of the molecular cations of isoxazoles have also been reported in the gas phase.\(^{266,267}\).

\[ \text{hv} \rightarrow \text{N} \rightarrow \text{N} \rightarrow \text{N} \]

This chapter discusses the complex and characteristic collision induced dissociations of the deprotonated species of five-membered heterocyclic systems containing two heteroatoms (N and O,N, or S) and investigates i) if the deprotonated parent heterocyclic anions undergo the characteristic ring opening reactions of the analogous species in solution, and ii) whether the interconversion of the isomeric ring systems (e.g. thiazole \(\rightarrow\) isothiazole) also occurs in the gas phase.

### 7.2 Results and Discussion

Simple aryl anions undergo little fragmentation upon collisional activation, for example, \(\text{C}_6\text{H}_5^-\) loses \(\text{H}^+\) and forms \(\text{C}_2\text{H}^+\), while \(\text{C}_5\text{H}_5^-\) loses \(\text{H}^+, \text{H}_2\) and forms \(\text{C}_3\text{H}_3^-\) and \(\text{C}_2\text{H}^-\). Heterocyclic anions should, in principle, fragment more readily than aryl anions. For example, the mass spectra of deprotonated
heterocycles containing one heteroatom exhibit major loss of H\(^+\) and minor loss of H\(_2\). Other fragmentations are minor in comparison, e.g. furan eliminates H\(_2\)O and C\(_2\)H\(_2\), thiophene eliminates C\(_2\)H\(_2\) while pyrrole eliminates HCN and C\(_2\)H\(_2\) and also forms CN\(^-\).

Guarna and Monete\(^2\) recently reported the collisional activation mass spectra of isoxazole and various methyl and phenyl substituted isoxazoles. Deprotonated isoxazole undergoes facile fragmentation to eliminate H\(^+\), H\(_2\), and H\(_2\)O. The elimination of H\(_2\)O is rationalised as shown in eqn 7.18.

\[
\begin{align*}
\text{CN} & \rightarrow \text{CN}^- + \text{H}_2\text{O} \\
\text{CN}^- + \text{OH}^- & \rightarrow \text{C}_2\text{CN} + \text{H}_2\text{O} \\
\end{align*}
\]

The following sections discuss the behaviour of thiazole/isothiazole, oxazole/isoxazole, and imidazole/pyrazole heterocyclic systems and in part their various methyl substituted derivatives.

### 7.2.1 CA mass spectra of deprotonated Thiazole and Isothiazole

Thiazole and isothiazole present the most complex fragmentation pathways of all the five-membered heterocycles: the spectra of deprotonated thiazole and isothiazole are illustrated in Figures 7.1a and 7.1b. The parent ions are formed by reaction with NH\(_2\)\(^-\). The collisional activation mass spectra of various deuterium labelled and unlabelled thiazole and isothiazole ions are listed in Table 7.1.
Figure 7.1a. CA mass spectrum of deprotonated thiazole

Figure 7.1b. CA mass spectrum of deprotonated isothiazole
Table 7.1. Collision Activation Mass Spectra of deprotonated isothiazole and thiazole

<table>
<thead>
<tr>
<th>PARENTION</th>
<th>LOSS</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H*</td>
<td>D*, H2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100 (31.2)a</td>
<td>76 (39.0)</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100 (31.8)</td>
<td>30 (37.4)</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>95</td>
<td>28 (37.2)</td>
</tr>
<tr>
<td>-H^+[-</td>
<td>100</td>
<td>6</td>
</tr>
</tbody>
</table>

a) Figures in brackets are peak widths at half height in volts (error ±0.5eV).
The spectra of thiazole and isothiazole are similar and produce identical fragment ions, the only difference in the spectra are the abundances of the peaks and for the ion \( m/z \ 57 \), the peak widths are different. Several of the fragmentations in the spectra of thiazole and isothiazole are very collision sensitive, particularly the formation of the ion at \( m/z \ 57 \), hence the collision gas pressure was carefully maintained at a pressure of \( 5 \times 10^{-7} \) Torr for all the spectra listed in Tables 7.1-7.6 in order to enable an accurate comparison of various spectra.

The collisional activation and charge reversal (MS/MS/MS) data for the product ions in the spectra of thiazole/isothiazole are listed in Table 7.2. The data indicates that the pairs of ions \( m/z \ 82 (-H_2) \), \( m/z \ 57 (-HCN) \), \( m/z \ 50 (-H_2S) \), \( m/z \ 33 (HS^-) \) and \( m/z \ 26 (CN^-) \) formed in each spectra have the same structure in each spectrum, whereas the two ions \( m/z \ 83 (-H^+) \) have similar but not identical spectra.

The three major product ions common to each spectrum are:

\[
\begin{align*}
\text{S} - \text{C} = \text{C} - \text{C} = \text{N} & \quad 7e \\
\text{HC} = \text{CS}^- & \quad 7f \\
\text{C} - \text{C} - \text{C} - \text{N} & \quad 7g
\end{align*}
\]

The product ion spectra confirm the structures of the ions \( 7e, 7f, \) and \( 7g \), for example:

i) Ion \( 7e \ (m/z \ 82, \text{ loss of } H_2) \) is characterised by loss of S in the CA spectrum (i.e. \( 7e \rightarrow 7g \)) and by losses of N, CN, S and CS (to form \( m/z \ 68, 56, 50 \)

\[
\begin{align*}
7e & \rightarrow 7g \\
& \rightarrow 68, 56, 50
\end{align*}
\]

* In some cases in Table 7.2 (and in other product ion spectra presented in this chapter) the only comparison of pairs of product ions is by the charge reversal spectra. The corresponding collisional activation spectra give weak spectra and the MS/MS/MS data is lost amongst the baseline noise. In cases where comparison is made solely from the charge reversal spectrum there is always a possibility that rearrangement of the positive parent ion occurs prior to fragmentation, however such cases are not common.
and 26 respectively) in the CR spectrum. It is also possible that the structure of ion \(7e\) is the isomeric isocyanate species, \(\text{-S--C\equiv C--\text{N}}_2\text{C}^+\), this structure seems less likely as it would involve complex rearrangement but it cannot be completely excluded on the available evidence.

ii) Ion \(7f\) (\(m/z\ 57\), loss of HCN) is characterised by losses of \(\text{H}^+\), \(\text{CH}\) and \(\text{C}_2\text{H}^+\)

(to give \(m/z\ 56, 44\) and 32 respectively) in the CR spectrum, and

iii) Ion \(7g\) (\(m/z\ 50\), loss of \(\text{H}_2\text{S}\)) is characterised by losses of \(\text{C}\), \(\text{N}\), \(\text{C}_2\) and \(\text{CN}^+\)

(to give \(m/z\ 38, 36, 26\) and 24 respectively) in the CR spectrum.

To identify the mode(s) of formation of these ions is difficult and the initial problem is to identify the site of deprotonation in the initial parent heterocycles. The deprotonation of thiazole and isothiazole in solution was discussed in section 7.1.1. The behaviour of the heterocycle with base in the condensed phase depends on the position of various substituents on the ring. For unsubstituted thiazole, deprotonation can occur at the 2 or 5-positions and isothiazole is deprotonated at the 3 or 5-positions. Deprotonation at the 3-position leads to a ring-opened intermediate.
Table 7.2. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated isothiazole and thiazole

<table>
<thead>
<tr>
<th>PRECURSOR ION (m/z)</th>
<th>PRODUCT ION (m/z)</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM { [m/z (Loss) Abundance] for CA }</th>
</tr>
</thead>
<tbody>
<tr>
<td>[- H'] (83)</td>
<td>CA</td>
<td>82(H')100, 56(HCN)4, 50(HS')2, 26(C2H2S)0.1.</td>
<td></td>
</tr>
<tr>
<td>[- H'] (83)</td>
<td>CR</td>
<td>82(100), 70(8), 68(26), 57(34), 56(57), 51(10), 50(10), 46(16), 45(18), 44(20), 39(5), 38(12), 32(14).</td>
<td></td>
</tr>
<tr>
<td>[- H3] (82)</td>
<td>CA</td>
<td>50(S)100.</td>
<td></td>
</tr>
<tr>
<td>[- H3] (82)</td>
<td>CR</td>
<td>70(26), 68(58), 56(100), 50(48), 44(45), 38(68), 32(28), 26(4), 24(4), 12(2).</td>
<td></td>
</tr>
<tr>
<td>[- HCN] (57)</td>
<td>CA</td>
<td>56(H')100.</td>
<td></td>
</tr>
<tr>
<td>[- HCN] (57)</td>
<td>CR</td>
<td>57(100), 56(95), 45(38), 44(56), 32(35), 25(13), 24(7), 12(2).</td>
<td></td>
</tr>
<tr>
<td>[- H2S] (50)</td>
<td>CR</td>
<td>50(100), 38(85), 36(65), 26(14), 24(26), 12(10).</td>
<td></td>
</tr>
<tr>
<td>[- H'] (83)</td>
<td>CA</td>
<td>82(H')100, 56(HCN)4, 50(HS')2, 26(C2H2S)2.</td>
<td></td>
</tr>
<tr>
<td>[- H'] (83)</td>
<td>CR</td>
<td>82(100), 71(4), 70(12), 68(4), 57(45), 56(45), 51(17), 45(49), 44(23), 39(6), 38(15), 32(12), 25(3).</td>
<td></td>
</tr>
<tr>
<td>[- H2] (82)</td>
<td>CA</td>
<td>50(S)100.</td>
<td></td>
</tr>
<tr>
<td>[- H2] (82)</td>
<td>CR</td>
<td>70(28), 68(50), 56(100), 50(42), 44(45), 38(68), 32(27), 26(4), 24(4), 12(2).</td>
<td></td>
</tr>
<tr>
<td>[- HCN] (57)</td>
<td>CA</td>
<td>56(H')100.</td>
<td></td>
</tr>
<tr>
<td>[- HCN] (57)</td>
<td>CR</td>
<td>57(100), 56(90), 45(42), 44(58), 32(29), 25(14), 24(7), 12(2).</td>
<td></td>
</tr>
<tr>
<td>[- H2S] (50)</td>
<td>CR</td>
<td>50(100), 38(87), 36(70), 26(14), 24(25), 12(9).</td>
<td></td>
</tr>
</tbody>
</table>
Figures 7.2a-c. CA mass spectra of the 3- (Figure 7.2a), 4- (Figure 7.2b), and 5- (Figure 7.2c) anions of isothiazole
7.2.2.1 Fragmentations of Isothiazole Anions

The simplest method to investigate the site of deprotonation of the isothiazole ring would be to label the isothiazole ring with deuterium at a specific position. Deprotonation or dedeuteration will thus produce an anion at a specific position on the isothiazole ring. However it is not easy to label the isothiazole ring with deuterium in specific positions. An alternative method of forming specific carbanions is by decarboxylation of an appropriate carboxylate anion in the ion source. Using this approach, the 3-, 4- and 5-isothiazole anions were formed from decarboxylation of the appropriate isothiazole carboxylic acid.

The spectra of the 3-, 4- and 5-isothiazole anions are illustrated in Figures 7.2a-7.2c and also listed in Table 7.2. Comparison of the three spectra with the spectrum of deprotonated isothiazole (Figure 7.1b) indicates that the major contribution to the isothiazole spectrum is the 5-anion $7h$ (Scheme 7.4). A minor contribution from the 3-anion cannot be excluded on the available evidence.

The major reactions of the 5-anion are summarised in Scheme 7.4, these fragmentations are:

i) elimination of HCN via the retro process shown in eqn 7.19 to form HC$_2$S$^-$ (m/z 57),

ii) formation of the hydride ion complex, $7h$, follows an analogous pathway to eqn 7.19. The hydride ion intermediate may undergo nucleophilic attack to form $^-S\leftrightharpoons CH\equiv CH\equiv C\equiv N$, $7i$. Proton transfer followed by elimination then produces a further ion complex which may react as shown in eqn 7.20 and 7.21 to form HS$^-$ (m/z 33) and $^-C_2CN$ (m/z 50). Alternatively, the hydride ion intermediate may effect deprotonation, eliminating H$_2$ to yield $^-SC_2CN$ (m/z 82) [eqn 7.22].
iii) the origin of the loss of H⁺ (to form m/z 83) is not known, loss from either the 3 or 4-position will produce a stabilised radical anion.

Consider now the spectra illustrated in Figures 7.2a-7.2c of the various isothiazole anions. The spectrum of the 5-anion is quite different from those of the 3- and 4-anions, and is almost identical to deprotonated isothiazole. Furthermore, the spectra of the 3- and 4-anions are virtually identical (even to the widths (at half-height) of the major peaks (see Table 7.1)). Equilibration of the 3- and 4-anions (Scheme 7.5) by 1,2 hydride transfer is unlikely as such a reaction is suggested to be symmetry forbidden135. Thus it seems likely that both ions are fragmenting via the common intermediate S-CH=CH-C≡N (Zl).
This species can form following direct cleavage of the 3-anion or from rearrangement of the 4-anion as shown in Scheme 7.5. The ion 7i was earlier proposed as an intermediate to account for several of the minor fragmentations of the 5-anion [see eqns 7.20 and 7.21, Scheme 7.4]. The same product ion is obtained as an intermediate when 4-substituted isothiazoles are treated with base in the condensed phase (cf. eqn 7.10).

Following formation of the ring-opened ion (7i), proton transfer and elimination produces a further ion complex which may react as shown in eqns 7.20 and 7.21 to form HS\(^-\) (m/z 33) and \(-\text{C}_2\text{CN}\) (m/z 50). In addition, the thiirene ion complex decomposes to form \(\text{CN}^-\) and eliminate HCN as shown in eqns 7.23 and 7.24. Elimination of \(\text{H}_2\) also occurs from 7i via the reaction 7.22 (Scheme 7.4).

\[
\begin{align*}
\text{4-anion} & \quad \text{4-anion} \\
\text{7i} & \quad \text{3-anion} \\
\text{7i} & \quad \text{7i}
\end{align*}
\]

Scheme 7.5
The ion S—CH=CH—C≡N, ZI, is a common intermediate from the 3-, 4- and 5-isothiazole anions. The majority of the fragmentations (apart from the retro reaction 7.19) of deprotonated isothiazole (Figure 7.1b) appear to proceed through this intermediate. Furthermore, Schemes 7.4 and 7.5 outline two mechanisms for the formation of HCN, viz. eqn 7.19 and 7.24, implying that even if the 5-anion is the exclusive deprotonation product of isothiazole, the peak at m/z 57 in Figure 7.1b (resulting from loss of HCN) must be formed by two processes, i.e.

i) the retro reaction 7.19 which is the major process giving the broad flat-topped peak, and

ii) reaction 7.22, a minor process giving the narrow gaussian peak [peak width 43±0.5eV] (cf. Figures 7.2a,b). The gaussian peak is not visible in the spectrum of the 5-isothiazole anion (or isothiazole) due to the wide peak width [105±0.5eV] of the retro process and the abundance of this peak.
Figures 7.3a-c. CA mass spectra of the [M-D+] – (Figure 7.3a) and [M-H+] – (Figure 7.3b) ions derived from 2-D-thiazole, and deprotonated thiazole (Figure 7.3c)
7.2.2.2 Fragmentations of Thiazole anions

The spectra of the $[M - H^+]^-$ and $[M - D^+]^-$ ions derived from 2-D-thiazole and the spectrum of deprotonated thiazole are illustrated in Figures 7.3a-7.3c. The $[M-D^+]^-$ ion (Figure 7.3a) produces the 2-anion of thiazole, whereas the $[M-H^+]^-$ ion (Figure 7.3b) is most likely to form the 5-anion.

Comparison of the spectra shown in Figure 7.3 suggests that thiazole is deprotonated by $\text{NH}_2^-$ to produce a combination of both the 2- and 5-anions. The major fragmentations are loss of HCN (to form m/z 57) and loss of H$_2$S (to form m/z 50).

The loss of HCN from deprotonated thiazole is sensitive to the collision gas pressure. Figure 7.4 illustrates the peak shape for loss of HCN at various collision gas pressures. At a pressure of $5 \times 10^{-7}$ Torr, the peak shape is flat-topped with a width at half-height of $129 \pm 0.5 \text{eV}$, while at $2 \times 10^{-6}$ Torr the peak shape becomes composite and the peak width increases to $141 \pm 0.5 \text{eV}$. The composite peak is indicative of two modes of elimination of HCN. Furthermore, the loss of HCN in the spectrum of the 5-anion (i.e. the $[M-H^+]^-$ ion, Figure 7.3b) is a flat-topped peak, with a width of $131 \pm 0.5 \text{eV}$, whereas the 2-anion (i.e. the $[M-D^+]^-$ ion, Figure 7.3b) yields a gaussian peak with a width of $43 \pm 0.5 \text{eV}$ (collision gas pressure $5 \times 10^{-7}$). The elimination of HCN from the $[M-D^+]^-$ ion is minor compared to the loss of H$_2$S (see Figure 7.3a). The two losses of HCN can be rationalised by eqns 7.25 and 7.27. The broad component is likely to be formed from the 5-anion by the retro process (eqn 7.25), while the narrow component is formed by rearrangement of the 2-anion to the intermediate $Z_i$; this ion then fragments via the thiirene ion complex to form CN$^-$ (eqn 7.26) and eliminate HCN (eqn 7.27). Further fragmentation of ion $Z_i$ follows after proton transfer to form HS$^-$ (eqn 7.28) and eliminate H$_2$S (eqn 7.29).
As the collision gas pressure increases, multiple collisions between ions and gas molecules increase as do fragmentations resulting from high activation/dissociation energy pathways. It seems likely that the rearrangement of deprotonated thiazole (eqns 7.26 and 7.27) would have a high activation energy, so as the collision gas pressure increases the rearrangement process will occur to a greater extent, hence the gaussian component of the composite peak (due to loss of HCN) increases relative to the flat-topped component.

In summarising the spectra of isothiazole and thiazole, we conclude from the above evidence that deprotonated isothiazole and thiazole do not equilibrate upon collisional activation. The S-anions of isothiazole and thiazole undergo retro-reactions to produce characteristic flat-topped peaks for this process. All other fragmentations of isothiazole and thiazole are rationalised as proceeding through the common intermediate $\text{S}^-$CH=CH=CCN.$
Figure 7.4. Effect of collision gas pressure on the peak shape of the m/z 57; Loss of HCN from thiazole. Figure 7.4a, collision gas pressure $6 \times 10^{-7}$ Torr, peak width 129eV; Figure 7.4b, collision gas pressure $1 \times 10^{-6}$ Torr, peak width 133eV; Figure 7.4c, collision gas pressure $5 \times 10^{-6}$ Torr, peak width 141eV.
Figures 7.5a-c. CA mass spectra of deprotonated 3-methylisothiazole (Figure 7.5a), 4-methylisothiazole (Figure 7.5b), and 5-methylisothiazole (Figure 7.5c).
7.2.3 CA Mass Spectra of deprotonated Methyl isothiazole and thiazole derivatives

The spectra of deprotonated 3-, 4-, 5-methylisothiazole and 2-, 4-, 5-methyl thiazole are compared in Figures 7.5a–c and 7.6a–c. The CA and CR (MS/MS/MS) spectra of various product ions are listed in Table 7.3.

7.2.3.1 Fragmentations of methylisothiazole anions

The three different methyl derivatives of isothiazole exhibit characteristic fragmentations that are dependent upon the position of the methyl group and the position of deprotonation. There appears to be no fragmentation that originates via a deprotonated methyl substituent, which is in accord with the solution behaviour of methylisothiazoles, viz. 4-methylisothiazole reacts with n-butyl lithium to form predominantly the 5-anion and a minor amount of the 3-anion (see eqn 7.10).

The characteristic fragmentations of 3-methylisothiazole are elimination of CH₄ and CH₃CN to form m/z 82 and 57 respectively. These fragmentations are analogous to the reactions of the 5-anion of isothiazole (Scheme 7.4), viz. loss of CH₃CN via a retro process (eqn 7.30, cf. loss of HCN from isothiazole) and loss of methane (eqn 7.31, cf. loss of H₂ from isothiazole). The only fragmentation of isothiazole that does not occur for 3-methylisothiazole is formation of HS⁻ and consequent elimination of H₂S. Elimination of H₂S is not possible because positioning of the methyl group prevents further reaction as proton transfer from the vinylic position cannot occur (see Scheme 7.4).
The 4-methylisothiazole isomer exhibits eliminations of CH₄, HCN and CH₂S (to form m/z 82, 57 and 52 respectively). Loss of HCN proceeds via a retro-reaction from the 5-anion (eqn 7.32). Rearrangement of the 5-anion to the intermediate $^\text{-S-}\text{CH=CH(Me)}\text{-C≡N}$ Zj is analogous to the rearrangement that yields $^\text{-S-}\text{CH=CH-C≡N}$ from isothiazole in Scheme 7.4 (the intermediate ion Zj also forms in the condensed phase when 4-methylisothiazole is treated with n-butyl lithium (eqn 7.10)). It is proposed that fragmentation to eliminate CH₄ and CH₂S proceeds through the ion Zj. Loss of methane occurs via the thiirene ion complex (eqn 7.33) whereas loss of CH₂S is rationalised by methyl migration to sulphur and consequent elimination as shown in eqn 7.34.
The fragmentations of 3- and 4-methylisothiazole appear to proceed solely via the 5-anion. The fragmentations of the 5-methyl isomer would be expected to be different from those of the other isomers as deprotonation at the 5-position is blocked by the methyl group. However, the fragmentations of 5-methyl isothiazole should, in principle, be analogous to those of the 3-anion of deprotonated isothiazole (see Scheme 7.5). The major fragmentations of 5-methylisothiazole are elimination of HCN, H₂S and formation of NCS⁻; these fragmentations are rationalised from the ring opening reaction of the 3-anion to produce the ion Zk. Elimination of HCN follows cyclisation of Zk to form the thiirene ion complex (eqn 7.35). Alternatively, proton transfer from Zk leads to the formation of HS⁻ and elimination of H₂S as shown in eqns 7.36 and 7.37 [cf. eqns 7.20 and 7.21, Scheme 7.5]. Loss of H⁺ from the product ion due to elimination of HCN [i.e. m/z 71, CH₃C≡CS⁻] produces the stabilised radical anion 'CH₂C≡CS⁻' (m/z 70). The elimination of HCN from 5-methylisothiazole is analogous to the loss of HCN from the 3-anion of isothiazole: in both spectra the fragmentation produces a gaussian peak (peak width 43±0.5eV).
An ion $m/z$ 58 is also formed. MS/MS/MS Studies confirm the structure of $m/z$ 58 to be the isothiocyanate ion NCS$^-$, rather than the isomeric thiocyanate ion CNS$^-$. For example, the charge reversal spectrum (Table 7.3) of NCS$^-$ shows characteristic elimination of N, NC, and S. The proposed mechanism for formation of NCS$^-$ is shown in eqn 7.38.
Table 7.3. Fragmentation data (CR) for product ions in the mass spectra of deprotonated 5-methylisothiazole and 5-methylthiazole

<table>
<thead>
<tr>
<th>PRECURSOR ION (m/z)</th>
<th>PRODUCT ION (m/z)</th>
<th>SPECTRUM TYPE &lt;sup&gt;a&lt;/sup&gt;</th>
<th>SPECTRUM [m/z (Loss) Abundance]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="5-methylisothiazole structure" /></td>
<td>NCS&lt;sup&gt;-&lt;/sup&gt; (58)</td>
<td>CR</td>
<td>58 (Parent) 100, 46 (C) 7, 44 (N) 25, 32 (NC) 35, 26 (S) 14, 14 (CS) 2, 12 (NS) 2.</td>
</tr>
<tr>
<td><img src="image" alt="5-methylthiazole structure" /></td>
<td>NCS&lt;sup&gt;-&lt;/sup&gt; (58)</td>
<td>CR</td>
<td>64 (Parent) 80, 63 (H&lt;sup&gt;+&lt;/sup&gt;) 45, 62 (H&lt;sub&gt;2&lt;/sub&gt;) 8, 51 (CH) 8, 50 (CH&lt;sub&gt;2&lt;/sub&gt;) 35, 49 (N) 12, 48 (NH) 7, 38 (CN) 45, 37 (HCN) 100, 36 (H&lt;sub&gt;2&lt;/sub&gt;CN) 6, 26 (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;, C&lt;sub&gt;2&lt;/sub&gt;N) 5, 25 (C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;N) 1.</td>
</tr>
<tr>
<td><img src="image" alt="5-methylisothiazole structure" /></td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;≡C-CN (64)</td>
<td>CR</td>
<td>58 (Parent) 100, 46 (C) 4, 44 (N) 26, 32 (NC) 38, 26 (S) 16, 14 (CS) 2, 12 (NS) 2.</td>
</tr>
<tr>
<td><img src="image" alt="5-methylthiazole structure" /></td>
<td>NCS&lt;sup&gt;-&lt;/sup&gt; (58)</td>
<td>CR</td>
<td>64 (Parent) 80, 63 (H&lt;sup&gt;+&lt;/sup&gt;) 49, 62 (H&lt;sub&gt;2&lt;/sub&gt;) 11, 51 (CH) 9, 50 (CH&lt;sub&gt;2&lt;/sub&gt;) 32, 49 (N) 10, 48 (NH) 8, 38 (CN) 48, 37 (HCN) 100, 36 (H&lt;sub&gt;2&lt;/sub&gt;CN) 8, 26 (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;, C&lt;sub&gt;2&lt;/sub&gt;N) 6, 25 (C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;N) 7.</td>
</tr>
<tr>
<td><img src="image" alt="5-methylisothiazole structure" /></td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;≡C-CN (64)</td>
<td>CR</td>
<td>58 (Parent) 100, 46 (C) 4, 44 (N) 17, 32 (NC) 27, 26 (S) 11, 14 (CS) 1, 12 (NS) 2.</td>
</tr>
</tbody>
</table>

a) MS/MS data for source formed ions; b) formed by the S<sub>n</sub><sup>2</sup> (Si) reaction: Me<sub>3</sub>SiNCS + NH<sub>2</sub><sup>-</sup> → NCS<sup>-</sup> + Me<sub>3</sub>SiNH<sub>2</sub>. 
Figures 7.6a-c. CA mass spectra of deprotonated 2-methylthiazole (Figure 7.5a), 4-methylthiazole (Figure 7.5b), and 5-methylthiazole (Figure 7.5c)
7.2.3.2 Fragmentations of methylthiazoles

In solution, 4-methylthiazole and 5-methylthiazole react with butyl lithium to form the 2-lithio anion exclusively, whereas 2-methylthiazole reacts with butyl lithium at -100°C to form the 5-lithio and the 2-lithiomethyl anions in almost equal amounts. At higher reaction temperatures the formation of the 5-lithioanion is favoured over formation of the deprotonated methyl species. 2-Methylthiazole or 5-methylthiazole react with butyl lithium to yield the 4-lithioanion as a minor product (~ 1-3%).

The spectrum of deprotonated 2-methylthiazole is recorded in Figure 7.6a. The characteristic fragmentation of 2-methylthiazole is elimination of HCN to form a composite peak centered on m/z 57. The broad component of this peak is due to a retro-reaction initiated by the 5-anion of 2-methylthiazole (eqn 7.39, Scheme 7.10). The gaussian component is suggested to arise from decomposition of the methyl deprotonated species. The fragmentations of the 2-methylanion are illustrated in eqns 7.40 and 7.41 (Scheme 7.10). The 2-methylanion fragments via the thiirene ion complex to form -CH₂CN (eqn 7.40) and eliminate MeCN (eqn 7.41) to produce the sharp gaussian component of m/z 57 in the spectrum of deprotonated 2-methylthiazole (Figure 7.6a). As the collision gas pressure increases the gaussian component of the composite peak (due to loss of HCN) increases relative to the flat-topped component.

```
\[ \text{Scheme 7.10} \]
```

\[ \text{\[7.39\]} \]

\[ \begin{align*}
\text{Me} & \quad \text{MeCN} \\
\text{S} & \quad \text{CS} \quad \text{+} \\
\text{N} & \quad \text{H} \\
\end{align*} \]

\[ \text{\[7.40\]} \]

\[ \begin{align*}
\text{CH₂CN} & \quad \text{+} \\
\text{C₂H₂S} & \quad \text{+} \\
\text{HC≡C} & \quad \text{+} \\
\text{S} & \quad \text{MeCN} \\
\end{align*} \]

\[ \text{\[7.41\]} \]

\[ \begin{align*}
\text{CH₂CN} & \quad \text{+} \\
\text{C₂H₂S} & \quad \text{+} \\
\text{HC≡C} & \quad \text{+} \\
\text{S} & \quad \text{MeCN} \\
\end{align*} \]
Figure 7.6b illustrates the spectrum of deprotonated 4-methylthiazole and Table 7.4 lists the spectra derived from 2-D-4-methylthiazole (dedeuteration will produce the 2-anion, whereas deprotonation is most likely to yield the 5-anion). Deprotonation in this case to give the 4-methyl anion is unlikely as the methyl anion is less stable than the 5-anion (in solution 4-methyl thiazole does not deprotonate at all on the methyl substituent). The major fragmentation of deprotonated 4-methylthiazole is the characteristic elimination of HCN from the 5-anion via the retro-reaction to produce a flat-topped peak (peak width $102\pm0.5\text{eV}$).

The $[\text{M}-\text{H}^+]^-$ and $[\text{M}-\text{D}^+]^-$ ions of 2-D-4-methylthiazole illustrate the origin of the remaining fragmentation pathways. The main fragmentation of the 5-anion of 2-D-4-methylthiazole is elimination of DCN via a retro-reaction to produce a flat-topped peak (eqn 7.42, peak width $102\pm0.5\text{eV}$). The major fragmentations of the 2-anion of 2-D-4-methylthiazole are the elimination of CH$_2$S and DCN. The rearrangement of the 2-anion to produce the ring opened intermediate $Z_I$ precedes the elimination of CH$_2$S as illustrated in eqn 7.43 [this reaction is analogous to the elimination of CH$_2$S from 4-methylthiazole (eqn 7.34, Scheme 7.8)]. The elimination of HCN from the $[2\text{-D-4-methylthiazole} - \text{H}^+]^-$ ion produces a gaussian peak at $m/z$ 71, and a further gaussian peak $m/z$ 70 that corresponds to a loss of (HCN + H$^+$). Loss of HCN in this case occurs from the ring opened ion $Z_j$ (eqn 7.44); loss of H$^+$ from the product ion in eqn 7.44 produces the stabilised radical anion $^*\text{CH}_2\text{C}==\text{CS}^-$ ($m/z$ 70).

The $[\text{M} - \text{H}^+]^-$ and $[\text{M} - \text{D}^+]^-$ ions derived from 2-D-4-methylthiazole illustrate that the wide flat-topped peak produced by elimination of HCN from deprotonated unlabelled 4-methylthiazole (Figure 7.6b) masks the smaller gaussian peak due to loss of HCN from the 2-anion of 4-methylthiazole (see Table 7.4). Therefore, there are two losses of HCN; the major process which is
the retro-reaction of the 5-anion that produces the flat-topped peak (eqn 7.42) and a minor process from the ring opened ion $\mathcal{Z}_i$ that produces the gaussian peak (eqn 7.44).

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{MeC=CS}^- & \quad + \quad \text{DCN} \\
\text{Me} \quad \text{CH}_{2} & \quad \text{CN} \\
\text{Me} & \quad ^{12}S \\
\text{Me} \quad \text{CH} & \quad \text{CHCN} \\
\text{Me} & \quad \text{C=CS}^- \\
\text{Me} & \quad \text{HCN}
\end{align*}
\]

\(7.42\)

\(7.43\)

\(7.44\)

Scheme 7.11

The fragmentations of 5-methylthiazole would be expected to be analogous to those of the 2-anion of thiazole (Figure 7.3a) as 5-methylthiazole would deprotonate to produce the 2-anion exclusively. The major fragmentations of 5-methylthiazole are loss of HCN (to produce a gaussian peak, m/z 71), loss of H$_2$S (m/z 64) and formation of NCS$^-$ (m/z 58). These fragmentations all proceed via the ring-opened intermediate $\mathcal{Z}_k$ (eqn 7.45-7.47, Scheme 7.12). There are no fragmentations that appear to proceed via the deprotonated methyl substituent. The most interesting fragmentation is formation of the ion m/z 58, identified as NCS$^-$ (rather than CNS$^-$, see Table 7.3). The ion m/z 58 has a composite peak shape resulting from two processes producing NCS$^-$. It is proposed that NCS$^-$ forms via two mechanisms as a consequence of two competitive ring cleavages, viz. cleavage of the 2-anion (eqn 7.48) as well as ring cleavage to ion $\mathcal{Z}_k$ and further reaction as shown in eqn 7.49.
It is of interest now to compare directly the spectra of the various methylthiazoles and methylisothiazoles. The spectra of 4-methylisothiazole and 4-methyl thiazole are characterised by retro-eliminations of HCN (both isomers produce a flat-topped peak with a peak width of 102±0.5eV), and the remaining fragmentations occur via the common intermediate \( \text{S}^\cdot\text{CH=C(Me)}=\text{C}^\equiv\text{N} \). Both 3-methylisothiazole and 2-methylthiazole exhibit retro-eliminations of MeCN (peak widths 99±0.5 and ±0.5eV) respectively. The spectra of 5-methyl isothiazole and 5-methylthiazole illustrate the facile ring opening cleavages of these species: both the 3-anion of 5-methylisothiazole and the 2-anion of 5-methyl thiazole rearrange to a common intermediate \( \text{N}^\equiv\text{C}^\cdot\text{CH=C(Me)}=\text{C}^\equiv\text{N} \) and fragmentation proceeds via this ion. There appear to be no major fragmentations which originate via a deprotonated methyl substituent, except in the case of 2-methylthiazole. Here, fragmentation of the 2-methyl anion is characterised by the formation of deprotonated acetonitrile, \( \text{CH}_2\text{CN}^- \). In principle, most of the other methyl derivatives could deprotonate on the methyl group, but in this happens, it appears that fragmentation through such ions are not as favourable as fragmentations of ring deprotonated ions.
Table 7.4. Collision Activation Mass Spectra of deprotonated deuterium labelled 4- and 5-methylthiazole

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>PARENT ION (m/z)</th>
<th>SPECTRUM ([m/z (Loss) Relative Abundance])</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Thiazole Structure]</td>
<td>[M - H]^- (99)</td>
<td>98(H') 75, 97(H2, D') 8, 84(Me') 4, 82(CH3D) 5, 71(DCN) 100^3, 53(46) 2, 52(47) 2, 26(C2H3OS) 2.</td>
</tr>
<tr>
<td>![Thiazole Structure]</td>
<td>[M - D]^- (98)</td>
<td>97(H') 100, 83(Me') 9, 82(CH4) 11, 71(HCN) 50^3, 70(H2CN) 35, 64(H2S) 4, 50(CH2S) 73, 50(48) 2, 33(C3H2CN) 2, 26(C2H3DS) 3.</td>
</tr>
<tr>
<td>![Thiazole Structure]</td>
<td>[M - H]^- (99)</td>
<td>98(H') 100, 72(HCN) 61^c, 65(H2S) 4, 64(HDS) 9, 58(C2H3D) 51, 52(47) 3, 34(C3H3N) 2. 33(C3H2DN) 2, 26(C2H3DS) 3.</td>
</tr>
<tr>
<td>![Thiazole Structure]</td>
<td>[M - D]^- (98)</td>
<td>97(H') 100, 83(Me') 18, 82(CH4) 9, 71(HCN) 35^d, 64(H2S) 61, 58(C2H4) 42, 52(46) 7. 33(C3H3N) 18, 26(C2H4S) 7.</td>
</tr>
</tbody>
</table>

a) Flat-topped peak, width at half height 105.0±0.5eV; b) Sharp gaussian peak, width at half height 55.2±0.5eV; c) Gaussian peak, width at half height 68.0±0.5eV; d) Gaussian peak, width at half height 57.0±0.5eV;
7.2.4 CA mass spectra of isoxazole and oxazole

The spectra of deprotonated isoxazole\textsuperscript{268} and oxazole are shown in Figure 7.7a-b, and the collisional activation and charge reversal (MS/MS/MS) spectra for the product ions in the two spectra are collated in Table 7.5. The spectra are very similar; both species eliminate H\textsuperscript{+}, H\textsubscript{2} and H\textsubscript{2}O. In addition, deprotonated oxazole eliminates C\textsubscript{2}H\textsubscript{2} to form NCO\textsuperscript{−}. The data in Table 7.5 indicates that the pairs of ions m/z 67 (−H\textsuperscript{+}), m/z 66 (−H\textsubscript{2}) and m/z 50 (−H\textsubscript{2}O) formed in each spectra have the same structure in each spectrum. The species m/z 66 and m/z 50 have the respective structures \textsuperscript{−}O=C≡C≡C≡N, \textit{Zl}, and \textsuperscript{−}C≡C≡C≡N \textit{Zm}. The structures of the two ions are confirmed by the product ion spectra viz:

(i) ion \textit{Zl} is characterised by loss of CO in the CA spectrum, and major losses of O, CO, CN and C\textsubscript{2}N in the CR spectrum,

(ii) ion \textit{Zm} is characterised by major losses of C, N and CN in the CR spectrum.

In the condensed phase, isoxazole deprotonates at both the 3 and 5-position, whereas oxazolone is preferentially deprotonated at the 2-position with only minor reaction at the 5-position. Similar behaviour is expected in the gas phase.

The fragmentation pathways of deprotonated isoxazole and oxazole are similar to those described for isothiazole and thiazole. The 3 and 5-anions of isoxazole (\textit{Zn}, \textit{Zq}) and the 2-anion of oxazole (\textit{Zp}) should all undergo ring cleavage or rearrangement to form the common intermediate, \textit{Zi}, which may eliminate H\textsubscript{2}O (eq\textsuperscript{n} 7.51) and to a lesser extent eliminate HCN (cf. the reactions of the analogous sulphur anion \textit{Zi} in Schemes 7.4 and 7.5). Hydride transfer to produce the ion complex \textit{Zr} precedes elimination of H\textsubscript{2} (eq\textsuperscript{n} 7.52). The oxazole anion \textit{Zp} also decomposes to NCO\textsuperscript{−} (eq\textsuperscript{n} 7.50).
It is interesting to compare the condensed phase behaviour of 5-substituted oxazoles with butyl lithium which gives a different ring cleavage product to the ion $Z_q$ which is formed in the gas phase (see eqn 7.11). e.g.

$$\text{Me} \quad \text{BuLi} \quad \text{Me} \quad \text{Li} \quad \text{Me}$$

It seems unlikely that the 2-anion of oxazole could effect such a transformation, but if it did, it would yield the isocyanate isomer to ion $Z_q$, which would lose H$_2$, H$_2$O and HCN to form $^+\text{C}==\text{C}^-\text{N}==\text{C}$, $^+\text{C}==\text{C}^-\text{N}==\text{C}$ and HCCO$^-$ respectively.
Figure 7.7a. CA mass spectrum of deprotonated oxazole

Figure 7.7b. CA mass spectrum of deprotonated isoxazole
Table 7.5. Fragmentation data (CA and CR) for product ions in the mass spectra of deprotonated oxazole and isoxazole

<table>
<thead>
<tr>
<th>PRECURSOR ION</th>
<th>PRODUCT ION</th>
<th>SPECTRUM TYPE</th>
<th>SPECTRUM (m/z (Loss) Abundance) for CA</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Oxazole Structure" /> - H⁺ (67)</td>
<td>CA 66(H⁺)100, 39(CO)2, 38(CH₂⁺)2, 28(C₂H₂O)1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR 66(H⁺)86, 65(H₂)24, 51(HO⁺)83, 50(H₂O)25, 41(HCN)16, 39(CO)100, 38(CH₂⁺)96, 29(C₂N)29, 28(C₂NH)14, 25(CHNO)13, 13(C₂HNO)3, 12(C₂H₂NO)3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Isoxazole Structure" /> - H⁺ (67)</td>
<td>CA 66(H⁺)100, 39(CO)2, 38(CH₂⁺)2, 28(C₂H₂O)1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR 66(H⁺)26, 65(H₂)24, 51(HO⁺)39, 50(H₂O)18, 41(HCN)13, 39(CO)65, 38(CH₂⁺)100, 29(C₂N)45, 28(C₂NH)8, 25(CHNO)5, 13(C₂HNO)3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Oxazole Structure" /> - H₂ (66)</td>
<td>CA 38(CO)100.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR 66(Parent)40, 54(C)3, 52(N)14, 50(O)32, 40(CN)10, 38(CO)100, 28(C₂N)7, 25(C₂O)3, 24(CNO⁺)7, 12(C₂NO)3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Isoxazole Structure" /> - H₂ (66)</td>
<td>CA 38(CO)100.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CR 66(Parent)35, 54(C)3, 52(N)16, 50(O)31, 40(CN)12, 38(CO)100, 28(C₂N)8, 26(C₂O)5, 24(CNO⁺)8, 12(C₂NO)4.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Oxazole Structure" /> - H₂O (50)</td>
<td>CA 50(Parent)100, 38(C)82, 36(N)53, 26(C₂)8, 24(CN)26, 12(C₂N)6.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Isoxazole Structure" /> - H₂O (50)</td>
<td>CA 50(Parent)100, 38(C)78, 36(N)57, 26(C₂)9, 24(CN)24, 12(C₂N)5.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Oxazole Structure" /> - C₂H₂ (42)</td>
<td>CA 30(C)38, 28(N)72, 26(O), 16(CN)5, 14(CO)12.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reactions of even electron anions in the gas phase fall into one of five main classification types. The majority of fragmentations involve either,

i) loss of a radical to form a stabilised radical anion, or

ii) direct fragmentation through an intermediate (i.e. an ion complex) with subsequent competitive fragmentation of that intermediate resulting in elimination of a neutral molecule.

When such reactions are either unfavourable or not possible, one of three processes generally occurs:

1) fragmentation preceded by proton transfer from the initial site of deprotonation followed by elimination of a neutral molecule,

2) fragmentations which are preceded by skeletal rearrangement.

3) charge remote fragmentations,

Proton transfer and rearrangement reactions have been observed in other systems, however in these cases (see Section 1.5) the reaction generally occurs in competition with simple cleavage processes. The projects described in this thesis were specifically chosen to investigate ions that cannot decompose by simple fragmentation, we expected these species to fragment by proton transfer/rearrangement or less likely by charge remote fragmentations. Charge remote fragmentations are described in Section 1.5.1.3 [page 37]. It is proposed that such fragmentations result in loss of a neutral molecule from a position remote to and uninfluenced by the charged site (see eqn 1.32).
One of the major areas of this thesis concerns the rearrangement processes of deprotonated oximes and related species. The results obtained have shown that when the initial anion cannot fragment simply, observed fragmentation pathways are often quite unpredictable.

Deprotonated oximes were shown to rearrange through a process analogous to the condensed phase Beckmann rearrangement. The condensed phase rearrangement involves migration of an alkyl or aryl group from the carbon to nitrogen atom of the oxime to produce an amide. This reaction does not occur in solution under base catalysed conditions, due to the hydroxide ion being a poor leaving group.

In order to determine to what extent the negative ion Beckmann rearrangement occurs in the gas phase, the fragmentation pathways of anions related to oximes were studied. Deprotonated semicarbazones do not undergo a negative ion Beckmann rearrangement, whereas deprotonated hydrazones do rearrange, however, in the later case, the rearrangement process is not the dominant fragmentation. In both cases, fragmentation may occur through simple cleavage processes [involving the functional group attached to the trigonal nitrogen (e.g. NHCONH₂ or NMe₂)], whereas such processes cannot occur for the oxime. It appears that the negative ion Beckmann rearrangement will be the major fragmentation when competitive simple cleavage reactions cannot occur.

The remaining discussion has focussed on the fragmentation behaviour of organo-nitrogen anions in order to determine whether there is any correlation between the products produced in the gas and condensed phase reactions of the various species.
The best correlation between the reactivity of a species in the condensed and gas phase involves hydroxamic acids. For example deprotonated benzohydroxamic acid \([\text{PhCONHOH} - \text{H}^+]\) rearranges via a Lossen rearrangement to yield PhNH\(^-\) in both the gas and condensed phases.

Several of the rearrangement processes discussed in this thesis were unexpected. In several cases it has not been possible (with available experimental evidence) to determine an exclusive mechanism for a specific reaction. However there appears no doubt than in all the studied cases the rearrangement is initiated via the initial anion (e.g. the Lossen rearrangement [Chapter 5], the Tiemann rearrangement [Chapter 6]) or the rearrangement is preceded by proton transfer from the charged site (e.g. the Beckmann rearrangement [Chapters 2 and 3]). All rearrangements have been rationalised in terms of the intermediacy of ion complexes. The reactions of the intermediate ion complex are dependent upon the electron affinities of the two parts of the ion complex. When the anion formed in the ion complex is particularly stable (i.e. when the “precursor” radical has, in this context, a high positive electron affinity) the ion complex may have a anion/neutral structure if both constituents of the ion complex have similar electron affinities.
"one of the greatest pains of human nature is the pain of a new idea", Walter Bagehot

8.1 General

The collisional activation (CA) and charge reversal (CR) MS/MS mass spectra described in this thesis were recorded on a Vacuum Generators ZAB 2HF reverse geometry mass spectrometer operating in the negative ionisation mode\(^{269}\). All slits were fully opened to maximise sensitivity and to reduce energy resolution effects\(^{270}\). The chemical ionisation slit was used in the ion source; ionising energy 70eV (tungsten or rhenium filament); ion source temperature 150°C; accelerating voltage −7kV.

Liquid samples were introduced through the septum inlet at 150°C; solids through the direct insertion probe (with heating whenever required). Deprotonation of all neutrals was effected by NH\(_2^−\) (from NH\(_3\)) or HO\(^−\) (from H\(_2\)O). The initial source pressure of NH\(_3\) (or H\(_2\)O) was 1x10\(^−5\) Torr (1 Torr = 133.332 Pa). The substrate pressure was typically 5x10\(^−7\). The estimated total pressure in the ion source is 10\(^−1\) Torr.

The pressure of Helium in the collision cell was 5x10\(^−6\) Torr measured by an ion gauge situated between the electric sector and the collision cell. These conditions produced a decrease in the main beam signal of approximately 10% corresponding to essentially single ion-helium collision conditions. Similar conditions were employed for the charge reversal spectra\(^{100−102}\) except that the polarity of the electric sector voltage was reversed. A voltage of ca. 1kV was applied to the collision cell\(^{47}\) to distinguish between unimolecular and collisionally activated dissociations\(^{103,104}\).
Experimental

Consecutive collisional activation (MS/MS/MS) and charge reversal (MS/MS/MS) mass spectra were measured with a Kratos MS50 TA instrument. Samples were introduced via an all glass heated inlet system at 100°C. The neutral samples were deprotonated by MeO⁻ (from MeONO) in a Kratos Mark IV chemical ionisation source, ion source pressure 100°C. The indicated source pressure of substrate was \(2 \times 10^{-5}\) and of methyl nitrite \(1 \times 10^{-6}\) giving an estimated total source pressure of ca. \(10^{-1}\) Torr. The indicated pressure of helium in the collision cells was \(2 \times 10^{-6}\) Torr giving an overall decrease in the main beam signal of 30%.

Electron impact (positive ion) mass spectra and accurate mass measurements were recorded on a AEI MS-30 mass spectrometer.

Proton magnetic resonance spectra were recorded on a Varian TS-60 (60 MHz) n.m.r. spectrometer. High field (300 MHz) \(^1\)H and \(^{13}\)C n.m.r spectra were recorded on a Bruker CXP300 or ACP300 n.m.r. spectrometer. The spectra were recorded in p.p.m. downfield from internal standard tetramethylsilane in CDCl₃ or CCl₄.

Melting points were measured on a Reichert-Kofler hot stage melting point apparatus and are uncorrected.

Microanalyses were carried out by the Canadian Microanalytical Service Ltd., Delta, British Columbia.

All solvents were purified by standard methods prior to use. Anhydrous diethyl ether and tetrahydrofuran were prepared by distillation from benzophenone ketal. Thin layer chromatography was performed on aluminium backed Merck Kieselgel 60 F₂₅₄ silica plates.
8.2 Synthetic Procedures used for Chapter 2

2.1 General Preparation of Aldoximes
The appropriate aldehyde (25 mmol) was added to a solution of hydroxylamine hydrochloride (30 mmol) and sodium hydroxide (30 mmol) in 30% methanol/water (30 ml). After stirring for one hour, the solution was extracted with diethyl ether (2x30 ml), the organic extracts were washed with saturated sodium chloride (30 ml) and dried (Na$_2$SO$_4$). Removal of the solvent and distillation gave pure aldoximes in yields of 55 –80%.

Ethanaloxime$^{271}$, propanaloxime$^{271}$, butanaloxime$^{271}$, 2-methylpropanaloxime$^{271}$ are all known compounds.

Syn and anti benzaldoximes were prepared using the procedure of Vogel$^{272}$.

2.2 General Preparation of Ketoximes
The ketone (25 mmol) was added to a solution of hydroxylamine hydrochloride (30 mmol) and sodium hydroxide (30 mmol) in 30% methanol/water (30 ml). The solution was heated at reflux for one hour, after extraction with diethyl ether (2 x 30 ml), the organic extracts were washed with aqueous sodium chloride (saturated, 30 ml) and dried (Na$_2$SO$_4$). Removal of the solvent followed by distillation gave pure aldoximes in yields of 60 - 85%.

Oximes of acetone$^{271}$, butan-2-one$^{3271}$, pentan-2-one$^{271}$, 3 methyl butan-2-one$^{272}$, 3 methyl pentan-2-one$^{273}$, 3,3 dimethyl butan-2-one$^{274}$, pentan-3-one$^{271}$, hexan-2-one$^{271}$, hexan-3-one$^{271}$, heptan-4-one$^{271}$, 2,4 dimethyl pentan-3-one$^{271}$, 3 phenylpropan-2-one$^{275}$, benzophenone oxime$^{276}$, phenyl benzyl ketoxime$^{274}$, acetophenone oxime$^{276}$, propiophenone oxime$^{276}$, butyrophenone oxime$^{276}$ are known compounds.
2.3 General Preparation of O–Oxime Ethers

Oxime ethers were prepared using the procedure of Vogel et al\textsuperscript{271}.

O–Methyl acetoxime ether\textsuperscript{271}, O–ethyl acetoxime ether\textsuperscript{271}, O–propyl acetoxime ether\textsuperscript{271}, O–benzyl acetoxime ether\textsuperscript{276}, O–methyl acetaldoxime ether\textsuperscript{276}, O–methyl acetophenoxime ether\textsuperscript{276} and O–ethyl acetophenoxime ether\textsuperscript{276} are known compounds.

2.4 General Preparation of O–Deuterated Oximes

O–Deuterated oximes were prepared by heating the oxime (0.3 ml) in deuterium oxide (1 ml) for 3–5 minutes at 60°C. The extent of deuterium incorporation was measured by positive ion mass spectrometry. When the incorporation was greater than 95\%, heating was stopped and the negative ion mass spectra of the (M – H\textsuperscript{+})\textsuperscript{−} and (M – D\textsuperscript{+})\textsuperscript{−} ions were recorded (see earlier experimental details).

2.5 Preparation of oximes with α, O protons labelled with deuterium

The appropriate ketone or aldehyde (1.0 g) was heated under reflux in deuterium oxide (5.0 ml) [to which sodium (10 mg) had been added previously] for 24 hours under an atmosphere of nitrogen. Hydroxylamine hydrochloride (1.2 mol eq.) and sodium hydroxide (1.2 mol eq.) were added to the solution and the mixture heated under reflux for a further one hour. After cooling the solution was saturated with sodium chloride, extracted with diethyl ether (2 x 10 ml), the combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}). Removal of solvent and distillation or recrystallisation as appropriate gave the required deuterium labelled oxime.
The following oximes were prepared using the above procedure: 2,2,2-\textsuperscript{2}H\textsubscript{3}-ethanaldoxime, 1,1,1,3,3,3-\textsuperscript{2}H\textsubscript{6}-acetoxime, 1,1,1,3,3-\textsuperscript{2}H\textsubscript{5}-butan-2-one oxime, 2,2-\textsuperscript{2}H\textsubscript{2}-butanaldoxime, 1,1,1,3-\textsuperscript{2}H\textsubscript{5}-pentan-2-one oxime, 1,1,1,3-\textsuperscript{2}H\textsubscript{4}-3 methylbutan-2-one oxime, 3,3,5,5-\textsuperscript{2}H\textsubscript{4}-heptan-4-one oxime, and 1,1,1-\textsuperscript{2}H\textsubscript{3}-acetophenoxime.

2.6 Preparation of deuterium labelled compounds

2.6.1 (Ethan-\textsuperscript{2}H\textsubscript{1}-)aldoxime

(i) 1,1-\textsuperscript{2}H\textsubscript{2}-Nitroethane

1,1-\textsuperscript{2}H\textsubscript{2}-Nitroethane was prepared using a modified procedure of based on that of Leitch\textsuperscript{278}.

A mixture of nitroethane (8 ml), deuterium oxide (8 ml) and sodium acetate (10 mg) was heated under reflux for 24 hours. After cooling to room temperature the upper layer of 1,1-\textsuperscript{2}H\textsubscript{2}-nitroethane was separated, dried (Na\textsubscript{2}SO\textsubscript{4}) and distilled.

Yield 90%; \textsuperscript{2}H\textsubscript{2} = 95%, \textsuperscript{2}H\textsubscript{1} = 5%; b.p. 112–115 °C/760 mm Hg, (Lit\textsuperscript{279} 114°C/760 mm Hg); N.M.R (CDCl\textsubscript{3}) : \delta 1.55(s).

(ii) Ethan-\textsuperscript{2}H\textsubscript{1}-al

Ethan-\textsuperscript{2}H\textsubscript{1}-al was prepared using a modified procedure based on that of Leitch\textsuperscript{278}.

1,1-\textsuperscript{2}H\textsubscript{2}-Nitroethane (4.0 ml) was dissolved in aqueous sodium hydroxide (10%, 25 ml) and added dropwise to a ice cold solution of concentrated sulphuric acid (7 ml) in water (40 ml) . After stirring for fifteen minutes the solution was heated to 70°C and the distillate was collected in a U-tube cooled in a dry ice-acetone bath.

Yield 42%; \textsuperscript{2}H\textsubscript{1} = 98%, \textsuperscript{2}H\textsubscript{0} = 2%; b.p. 21–23°C/760 mm Hg, (Lit\textsuperscript{280} 23°C/760 mm Hg); N.M.R (CDCl\textsubscript{3}) : \delta 2.15 (s).
(ii) (Ethan-\(^2\)H\(_1\))aldoxime

Prepared from ethan-\(^2\)H\(_1\)-al using the procedure outlined previously for aliphatic aldoximes.

Yield 75\%; \(^2\)H\(_1\) = 98\%, \(^2\)H\(_0\) = 2\%; b.p. 110–114°C/760 mm Hg,
(Lit.\(^{271}\) 115°C/760 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta\) 1.85, 3H(s); 9.8, 1H(s).

2.6.2 1,1,1-\(^2\)H\(_3\)-heptan-4-one oxime

(i) 2,2,2-\(^2\)H\(_3\)-Benzyl acetate

Prepared from \(^2\)H\(_4\)-acetic acid and benzyl alcohol.

Yield 80\%; \(^2\)H\(_3\) = 98\%, \(^2\)H\(_2\) = 2\%; b.p. 98–100°C/17 mm Hg,
(Lit.\(^{281}\) 213.5°C/756 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta\) 5.1, 2H(s); 7.4, 5H(s).

(ii) 2,2,2-\(^2\)H\(_3\)-ethanol

Prepared from the reduction of 2,2,2-\(^2\)H\(_3\)-benzyl acetate using a modified procedure based on that of Friedman and Jurewicz\(^{282}\).

Lithium aluminium hydride (35 mmol, 1.39 g) was added portionwise, over 1 hr, to a solution of 2,2,2-\(^2\)H\(_3\)-benzyl acetate (65 mmol, 10 g) in anhydrous diglyme (100 ml) cooled in an ice salt bath, and then heated to 80°C for 2 hours. After cooling to 25°C, 2-butoxyethanol (195 mmol, 23 g) was added, the temperature was raised to 140°C, upon which 2,2,2-\(^2\)H\(_3\)-ethanol distilled from the reaction mixture into a flask cooled in an ice bath. Fractional distillation of the distillate gave pure 2,2,2-\(^2\)H\(_3\)-ethanol.

Yield 75\%; \(^2\)H\(_3\) = 98\%, \(^2\)H\(_2\) = 2\%; b.p. 74–77°C/760 mm Hg, (Lit.\(^{282}\) 77–78°C/760 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta\) 1.8, 2H(s); 3.7, 1H(s).

(iii) 2,2,2-\(^2\)H\(_3\)-ethyl iodide

Prepared from 2,2,2-\(^2\)H\(_3\)-ethanol using the procedure of Vogel\(^{283}\).

Yield 68\%; \(^2\)H\(_3\) = 98\%, \(^2\)H\(_2\) = 2\%; b.p. 68–71°C/760 mm Hg, (Lit.\(^{283}\) 72–73°C/760 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta\) 3.2 (s).
(iv) Ethyl 2(2,2,2-^H^-ethyl) 3-oxohexanoate

Prepared from the modified procedure based on that of Renfrow. Ethyl 3-oxohexanoate (30 mmol, 4.74 g) was added dropwise to a suspension of sodium hydride (33 mmol, 80% in oil, 1.0 g) in tetrahydrofuran (30 ml). After stirring for fifteen minutes, 2,2,2-^H^-ethyl iodide (30 mmol, 3.7 g) was added and the mixture was heated under reflux for three hours. After cooling to room temperature, aqueous hydrochloric acid (10%, 30 ml) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3×20 ml). The combined organic extracts were washed with aqueous sodium chloride (saturated, 25 ml) and dried (Na$_2$SO$_4$). Removal of the solvent followed by distillation gave ethyl 2(2,2,2-^H^-ethyl) 3-oxo-hexanoate.

Yield 66%; $^2$H$_3$ = 98%, $^2$H$_2$ = 2%; b.p. 28–31°C/0.1 mm Hg, (Lit. 104–107°C/15 mm Hg); N.M.R (CDCl$_3$): $^6$ 1.0, 3H(t); 1.5, 3H(t); 1.8, 2H(d); 1.95, 2H(m); 3.35, 1H(t); 4.2, 2H(q).

(v) 1,1,1-^H^-heptan-4-one

Prepared from the modified procedure based on that of Renfrow. Ethyl 2(2,2,2-^H^-ethyl) 3-oxohexanoate (12 mmol, 2.66 g) and aqueous sodium hydroxide (10%, 25 ml) was heated under reflux for eight hours, cooled to 25°C. Following extraction with diethyl ether (2×15 ml), the combined organic extracts were washed with aqueous sodium chloride (saturated, 15 ml) and dried (Na$_2$SO$_4$). Removal of the solvent followed by distillation gave 1,1,1-^H^-heptan-4-one.

Yield 80%; $^2$H$_3$ = 98%, $^2$H$_2$ = 2%; b.p. 142–144°C/760 mm Hg, (Lit. 144–145°C/760 mm Hg); N.M.R (CDCl$_3$): $^6$ 0.9, 3H(t); 1.5, 4H(unresolved multiplet); 2.4, 4H(t).
(vi) 1,1,1-$^2$H$_3$-heptan-4-one oxime

Prepared from 1,1,1-$^2$H$_3$-heptan-4-one using the general procedure for preparation of ketoximes.

Yield 86%; $^2$H$_3$ = 98%, $^2$H$_2$ = 2%; b.p. 70–76°C/15 mm Hg, (Lit.\textsuperscript{281} 194.5–195°C/760 mm Hg); N.M.R (CDCl$_3$): δ 0.95, 3H(t); 1.6-4H(unresolved multiplet); 2.25, 2H(t); 2.45, 2H(t); 9.4, 1H(s).

2.6.3 4,4,4-$^2$H$_3$-Butan-2-ketoxime

(i) Ethyl 2($^2$H$_3$-methyl) 3-oxobutanoate

Prepared from ethyl 3-oxobutanoate and $^2$H$_3$-methyl iodide using the procedure outlined for compound 2.6.2(iv).

Yield 74%; $^2$H$_3$ = 99%, $^2$H$_2$ = 1%; b.p. 76–80°C/15 mm Hg, (Lit.\textsuperscript{287} 75.5–76.5°C/12 mm Hg); N.M.R (CDCl$_3$): δ 1.2, 3H(t); 2.3, 3H(s); 3.5, 1H(s); 4.2, 2H(q).

(ii) 4,4,4-$^2$H$_3$-butan-2-one

Ethyl 2($^2$H$_3$-methyl) 3 oxobutanoate(6 mmol, 0.9g) was heated under reflux in sodium hydroxide (10%, 5ml) for 6 hours, cooled to 25°C, saturated with sodium chloride, the upper layer separated, dried (Mg$_2$SO$_4$), and distillation gave 4,4,4-$^2$H$_3$-butan-2-one.

Yield 68%; $^2$H$_3$ = 99%, $^2$H$_2$ = 1%; b.p. 77–80°C/760 mm Hg, (Lit.\textsuperscript{288} 79.6°C/760 mm Hg); N.M.R (CDCl$_3$): δ 1.4, 2H(s); 2.2, 3H(s).

(iii) 4,4,4-$^2$H$_3$-butan-2-ketoxime

Prepared from 4,4,4-$^2$H$_3$-butan-2-one using the general procedure for the preparation of ketoximes.

Yield 75%; $^2$H$_3$ = 99%, $^2$H$_2$ = 1%; b.p. 40–44°C/15 mm Hg, (Lit.\textsuperscript{281} 151.5°C/760 mm Hg); N.M.R (CDCl$_3$): δ 1.2, 2H(s); 1.9, 3H(s); 9.3, 1H(s).
2.6.4 4 Phenylbutan-2-one oxime

(i) Ethyl 2(phenylmethyl)-3-oxobutanoate

Ethyl 2(phenylmethyl)-3-oxobutanoate was prepared from ethyl 3 oxobutanoate and benzyl chloride using the procedure outlined for compound 2.6.2(iv).

Yield 76%; b.p. 53–56°C/0.15 mm Hg, (Lit.\textsuperscript{28} 110–112°C /2 mm Hg); N.M.R (CDCl\textsubscript{3}) : \(\delta 1.2, 3H(t); 2.1, 3H(s); 3.1, 2H(d); 3.5, 1H(t); 4.1, 2H(q); 7.15, 5H(s)\).

(ii) 4 Phenylbutan-2-one

Ethyl 2(Phenylmethyl) 3-oxobutanoate (25 mmol, 5.77g) was hydrolysed with aqueous sodium hydroxide (10%, 25 ml) using the procedure outlined for compound 2.6.2(v).

Yield 86%; b.p. 114–116°C/15 mm Hg, (Lit.\textsuperscript{29} 235 °C/60 mm Hg); N.M.R (CDCl\textsubscript{3}) : \(\delta 2.0, 3H(s); 2.2, 2H(t); 2.7, 2H(t); 7.2, 5H(s)\).

(iii) 4 Phenylbutan-2-one oxime

Prepared from 4 phenylbutan-2-one using the general procedure for ketoximes.

Yield 72%; m.p. 82–85°C, (Lit.\textsuperscript{30} 87°C); N.M.R (CDCl\textsubscript{3}) : \(\delta 2.2, 3H(s); 2.4, 2H(t); 2.7, 2H(t); 7.2, 5H(s); 10.5, 1H(s)\).

2.6.5 5 Phenylpentan-2-one oxime

(i) Ethyl 2(2-Phenethyl)-3-oxobutanoate

Prepared from ethyl 3-oxobutanoate and 2-phenethyl bromide using the procedure outlined for compound 2.6.2(iv).

Yield 78%; b.p. 70–72°C/0.08 mm Hg, (Lit.\textsuperscript{31} 174–176°C/18 mm Hg); N.M.R (CDCl\textsubscript{3}) : \(\delta 1.3, 3H(t); 1.9, 2H(m); 2.2, 3H(s); 2.7, 2H(t); 3.3, 1H(t); 4.2, 2H(q); 7.2 5H(s)\).
(ii) 5 Phenylpentan-2-one
Prepared from Ethyl 2(2-phenethyl)-3-oxobutanoate using the procedure outlined for compound 2.6.2(v).
Yield 76%; b.p. 132–134°C/17 mm Hg, (Lit.\textsuperscript{292} 128–130°C/15 mm Hg);
N.M.R (CDCl\textsubscript{3}) : δ 1.7, 2H(t); 1.8, 2H(m); 2.0, 3H(s); 2.6, 2H(t); 7.15, 5H(s).

(iii) 5 Phenylpentan-2-one oxime
Prepared using the general procedure for ketoximes.
Yield 68%; b.p. 91-94 °C/0.15 mm Hg.
Found : C, 74.67. H, 8.34% (M\textsuperscript{+} 177.11539); C\textsubscript{11}H\textsubscript{15}NO requires C, 74.54. H, 8.52. (M\textsuperscript{+} 177.11541).
N.M.R (CDCl\textsubscript{3}) :
\textsuperscript{1}H (300 Mhz) δ 1.83, 2H(m); 1.86, 3H(s); 2.22, 2H(t); 2.6, 2H(t); 7.14-.28 5H(m); 9.39, 1H(s).\textsuperscript{13}C (300 Mhz) δ 13.40q, 19.68t, 27.83t, 35.24t, 125.78d, 128.25d, 128.36d, 141.73s, 158.45s.

2.6.6 6 Phenylhexan-2-one oxime
(i) Ethyl 2(3-phenylpropyl)-3-oxobutanoate
Prepared from ethyl-3-oxobutanoate and 3-phenylpropyl bromide using the using the procedure outlined for compound 2.6.2(iv).
Yield 73%; b.p. 68–71°C/0.1 mm Hg, (Lit.\textsuperscript{293} 160–165°C/12 mm Hg);
N.M.R (CDCl\textsubscript{3}) : δ 1.3, 2H(t); 1.9, 2H(t); 2.2, 3H(s); 2.4, 4H(unresolved multiplet), 2.7, 2H(t); 4.3, 2H(q); 7.3, 5H(s).

(ii) 6 Phenylhexan-2-one
Prepared from Ethyl 2(3-phenylpropyl)-3-oxobutanoate using the procedure outlined for compound 2.6.2(v).
Yield 75%; b.p. 70–73°C/15 mm Hg, (Lit.\textsuperscript{294} 137°C/8 mm Hg);
N.M.R (CDCl\textsubscript{3}) : δ 1.6, 2H(t); 1.75, 3H(s); 2.2, 4H(multiplet); 2.5, 2H(t); 7.35, 5H(s).
(iii) 6 Phenylhexan-2-one oxime
Prepared using the general procedure for ketoximes.
Yield 72%; b.p. 140–42°C/15 mm Hg; M⁺⁺ (found) = 191.13106, C₁₂H₁₇NO requires 191.13104; N.M.R (CDCl₃) : δ 1.7, 2H(t); 1.9, 3H(s); 2.3, 2H(t); 2.6, 4H (unresolved multiplet); 7.35, 5H(s); 9.8, 1H(s).

2.6.7 5,5-²H₂-5-Phenylpentan-2-one oxime
(i) Methyl-2,2-²H₂-phenyl acetate
A mixture of methyl phenyl acetate (27 mmol, 4.0g), ²H₁-methanol (270 mmol, 9.0g) and sodium (50 mg) was heated under reflux for 24 hours. After cooling to 25°C, deuterium oxide (2 ml) was added, the aqueous solution was extracted with diethyl ether (2x10 ml) and the combined organic extracts were dried (Na₂SO₄). Removal of the solvent followed by distillation gave methyl-2,2-²H₂-phenyl acetate.
Yield 85%; ²H₂ = 98%, ²H₁ = 2%; b.p. 94–97°C/16 mm Hg, (Lit.²⁵² 228°C/753 mm Hg); N.M.R (CDCl₃) : δ 3.67, 3H(s); 7.27, 5H(s).

(ii) 2-Phenyl-2,2-²H₂-ethanol
Methyl-2,2-²H₂-phenyl acetate was reduced with lithium aluminium hydride using the procedure of Saunders et al.²⁹⁵ to yield 2-phenyl-2,2-²H₂-ethanol.
Yield 66%; ²H₂ = 98%, ²H₁ = 2%; b.p. 51–53°C/0.8 mm Hg, (Lit.²⁹⁵ 102–103°C/15 mm Hg); N.M.R (CDCl₃) : δ 3.8, 2H(s); 7.28, 5H(s).

(iv) 2-Phenyl-2,2-²H₂-ethyl bromide
2-Phenyl-2,2-²H₂-ethanol (11 mmol, 1.4g) was added dropwise to phosphoros tribromide (5 mmol, 1.36g) and the mixture was heated at 100 °C for one hour. The solution was poured into ice/water (10 ml), the layers separated, the aqueous layer extracted with dichloromethane (3x10 ml), the organic layers were washed with aqueous sodium hydroxide (10%, 10 ml) and dried
(Na₂SO₄). Removal of the solvent followed by distillation gave 2-phenyl-2,2-
²H₂-ethyl bromide.

Yield 72%; ²H₂ = 98%, ²H₁ = 2%; b.p. 41–43°C/0.3 mm Hg,
(Lit.²⁹⁵ 94°C/15 mm Hg); N.M.R (CDCl₃): δ 3.7, 2H(s); 7.3, 5H(s).

(iv) Ethyl 2-(2-phenyl-2,2-²H₂-ethyl)-3-oxobutanoate

Prepared from 2-phenyl-2,2-²H₂-ethyl bromide and ethyl 3-oxobutanoate using
the procedure outlined for compound 1.6.2(iv).

Yield 65%; ²H₂ = 98%, ²H₁ = 2%; b.p. 70–76°C/0.1 mm Hg,
Lit.²⁹¹ = 174–176°C/18 mm Hg; N.M.R (CDCl₃): δ 1.3, 3H(t); 1.9, 2H(d); 2.2,
3H(s); 3.3, 1H(t); 4.2, 2H(q); 7.2, 5H(s).

(v) 5,5-²H₂-5-Phenylpentan-2-one

Prepared from Ethyl 2-(3-Phenyl-2,2-²H₂-ethyl)-3-oxobutanoate using the
procedure outlined for compound 2.6.2(v).

Yield 68%; ²H₂ = 98%, ²H₁ = 2%; b.p. 52–55°C/0.1 mm Hg, (Lit.²⁹² 128–
130°C/15 mm Hg); N.M.R (CDCl₃): δ 1.75, 2H(t); 1.8, 2H(t); 2.1, 3H(s); 7.2, 5H(s).

(vi) 5,5-²H₂-5 Phenylpentan-2-one oxime

Prepared using the general procedure for ketoximes (2.2).

Yield 74%; ²H₂ = 98%, ²H₁ = 2%; b.p. 85–91°C/0.1 mm Hg;
N.M.R (CDCl₃): δ 1.85, 3H(s); 2.0, 2H(t); 2.1, 2H(t); 7.2, 5H(s).

2.6.8 Syn-Phenyl (²H₁-methan)aldoxime

(i) Phenyl (²H₂-methan)ol

Ethyl benzoate was reduced with lithium aluminium deuteride using the
procedure of Saunders et al.²⁹⁵ to yield phenyl (²H₂-methan)ol.

Yield 68%; ²H₂ = 98%, ²H₁ = 2%; b.p. 81–83°C/16 mm Hg, (Lit.²⁹⁶ 76–77°C/14
mm Hg); N.M.R (CDCl₃): δ 3.5, 1H(s); 7.25, 5H(s).
(ii) Phenyl \(2\text{H}_1\)-methanal

Phenyl \(2\text{H}_1\)-methanal was prepared from phenyl \(2\text{H}_2\)-methanol using the procedure of Ratcliffe and Rodehorst\(^{297}\).

Yield 57%; \(2\text{H}_1 = 98\%\), \(2\text{H}_0 = 2\%\); b.p. 70–72°C/16 mm Hg, (Lit.\(^{298}\) 179°C/751 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta 7.4\) (s).

(iii) Syn Phenyl \(2\text{H}_1\)-methanaldehyde

Prepared from phenyl \(2\text{H}_1\)-methanal using the procedure of Yogel\(^{272}\).

Yield 66%; \(2\text{H}_1 = 98\%\), \(2\text{H}_0 = 2\%\); b.p. 70–72°C/17 mm Hg, (Lit.\(^{272}\) 122–124 °C/12 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta 7.4\), 5H(s); 9.2, 1H(s).

2.6.9 Syn \(2,4,6\text{H}_3\)-Phenyl \(2\text{H}_1\)-methanaldehyde

(i) \(2,4,6\text{H}_5\)-Aniline

Prepared from the exchange reaction of aniline and deuterium oxide using the procedure of Best and Wilson\(^{279}\). \(2\text{H}_3 = 98\%\), \(2\text{H}_2 = 2\%\).

(ii) \(2,4,6\text{H}_3\)-Bromobenzene

Prepared from \(2,4,6\text{H}_5\)-aniline using the procedure of Vogel\(^{300}\).

Yield 58%; \(2\text{H}_3 = 98\%\), \(2\text{H}_2 = 2\%\); b.p. 153–155°C/760 mm Hg, (Lit.\(^{301}\) 155–156°C/760 mm Hg); N.M.R (CDCl\(_3\)) : \(\delta 7.5\), 2H(s).

(iii) \(2,4,6\text{H}_3\)-Benzoic acid

Prepared from \(2,4,6\text{H}_3\)-bromobenzene using the procedure of Vogel\(^{302}\).

Yield 62%; \(2\text{H}_3 = 98\%\), \(2\text{H}_2 = 2\%\); m.p. 120–121°C, (Lit.\(^{302}\) 121°C); N.M.R (CDCl\(_3\)) : \(\delta 7.25\), 2H(s); 8.9, 1H(s).
(iii) Methyl 2.4.6-²H₃-benzoate
Prepared from 2,4,6-²H₃-benzoic acid using the procedure of Vogel³⁰³.
Yield 68%; ²H₃ = 98%, ²H₂ = 2%; b.p. 72–75°C / 14 mm Hg, (Lit.³⁰³ 198–
200°C/760 mm Hg); N.M.R : δ 3.9, 3H(s); 7.45, 2H(s).

(iv) 2.4.6-²H₃-Phenyl (²H₂-methan)ol
Prepared from methyl 2,4,6-²H₃-benzoate using the procedure of Nystrom and
Brown³⁰⁴.
Yield 81%; ²H₅ = 98%, ²H₄ = 2%; N.M.R : δ 2.8, 1H(s); 7.5, 2H(s).

(v) 2.4.6 Phenyl (²H₁-methan)al
Prepared from 2,4,6-²H₃-phenyl(²H₂-methan)ol using the procedure of Ratcliffe
and Rodehurst²⁹⁷.
Yield 73%; ²H₄ = 98%, ²H₃ = 2%; b.p. 68–73°C/15 mm Hg, (Lit.²⁹⁸ 179°C /751
mm Hg); N.M.R : δ 7.55 (s).

(vi) Syn 2.4.6-²H₃-Phenyl (²H₁-methan)aldehyde
Prepared from 2,4,6-²H₃-phenyl(²H₁-methan)al using the procedure of
Vogel²⁷².
Yield 62%; ²H₄ = 98%, ²H₃ = 2%; b.p. 124–126°C/15 mm Hg, (Lit.²⁷² 122–
124°C/12 mm Hg). N.M.R : δ 7.4, 2H(s); 9.5, 2(s).
8.3 Synthetic Procedures used for Chapter 3

3.1 General Preparation of Semicarbazones
Semicarbazones derived from ethanal, propanal, butanal, benzaldehyde, propan-2-one, butan-2-one, pentan-3-one, heptan-4-one and acetophenone are known compounds and were prepared using the routine procedure of Voge.

3.2 Preparation of Deuterium labelled semicarbazones
N,N,3-2H3-ethanal semicarbazone was produced by stirring the unlabelled ethanal semicarbazone in deuterium oxide for 2 hours (2H3 = 90%).

1,1,1,3,3,3-2H6-Propan-2-one semicarbazone was prepared from 2H6-propan-2-one using the standard procedure.

3.3 N,N Dimethylsemicarbazones

3.3.1 N,N Dimethylhydrazine carboxamide
Prepared from hydrazine hydrate and N,N-dimethylcarbamoyl chloride using the procedure of Voge. Yield 76%, m.p. 81–83°C, (Lit. 83°C).

3.3.2 2-(1-Methylene)-N,N-dimethylhydrazine carboxamide
A mixture of propan-2-one (68 mmol, 4g) and N,N-dimethylhydrazine carboxamide (70 mmol, 7.21g) was heated under reflux for 6 hrs. After cooling to 25°C, the mixture was extracted with diethyl ether (3x20 ml) and the combined organic extracts were dried (Mg2SO4). Removal of solvent followed by recrystallisation from aqueous ethanol gave colourless crystals of 2-(1-Methylene)-N,N-dimethylhydrazine carboxamide.

Yield = 68%; m.p. 80–82°C. This compound is unstable on exposure to the
Experimental

atmosphere and microanalytical data were not obtained.

N.M.R (CDCl₃): δ 1.87, 3H(s); 2.03, 3H(s); 3.03, 6H(s). M⁺⁺ (found) 143.1052; C₆H₁₃N₃O requires 143.1040.

3.3.3 2-(1-Phenylethylidene)-N,N-dimethylhydrazine carboxamide

Prepared from acetophenone using the procedure outlined for compound 3.3.2 and recrystallised from aqueous ethanol.

Yield 54%; m.p. 124–126°C. This compound is unstable on exposure to the atmosphere and microanalytical data were not obtained.

N.M.R (CDCl₃): δ 2.04, 3H(s); 3.03 6H(s), 7.5, 5H(s). M⁺⁺ found 205.1213; C₁₁H₁₅N₃O requires 205.1215.

3.4 General Preparation of hydrazones

Hydrazones derived from propan-2-one₃₀⁸, butan-2-one₃₀⁸, pentan-3-one₃₀⁸, hexan-2-one₃₀⁸, hexan-3-one₃₀⁸, and butyrophenone₃₀⁸ were prepared from the appropriate ketone and hydrazine hydrate using the procedure of Karabatsos and Osborne₃₀⁸.

3.5. General preparation of methyl and dimethylhydrazones

Methyl or unsym dimethylhydrazine (35mmol) and the aldehyde/ketone (30mmol) were heated under reflux for 4 hrs. After cooling to 25°C, the solution was extracted with diethyl ether (3x15 ml) and the combined organic extracts were dried (Mg₂SO₄). Removal of the solvent gave crude hydrazones which were purified by distillation in vacuo. (Yields 50–85%).

Methylhydrazones of ethanal₃₀⁹, propanal₃¹⁰, butanal₃¹⁰, pentanal₃¹⁰, benzaldehyde₃¹¹, propan-2-one₃¹₂, butan-2-one₃¹⁰, 3-methylbutan-2-one₃¹⁰, pentan-2-one₃¹⁰, pentan-3-one₃¹⁰, 4-methylpentan-3-one₃¹⁰, heptan-4-one₃¹⁰, hexan-2-one₃¹⁰, nonan-2-one₃¹⁰ and acetophenone₃¹⁰ are known compounds.
3.6. Preparation of labelled hydrazones

3.6.1 $^{2}\text{H}_6$-Propan-2-one hydrazones

A mixture of $^{2}\text{H}_6$-propan-2-one (20mmol, 1.249g), the appropriate hydrazine (20mmol) and 4Å molecular sieves (0.3g) was heated under reflux for 6 hrs. After cooling to 25°C, the mixture was extracted with diethyl ether and the combined organic extracts were dried ($\text{Mg}_2\text{SO}_4$) and distilled to yield the required $^{2}\text{H}_6$-Propan-2-one hydrazone. (Yields 75 – 80%).

$^{2}\text{H}_6$-Propan-2-one hydrazone b.p. 123–125°C; $^{2}\text{H}_6 = 90\%$; $^{2}\text{H}_5 = 8\%$; $^{2}\text{H}_4 = 2\%$. $^{2}\text{H}_6$-propan-2-one methyl hydrazone b.p. 116–118°C; $^{2}\text{H}_6 = 90\%$; $^{2}\text{H}_5 = 8\%$; $^{2}\text{H}_4 = 2\%$. $^{2}\text{H}_6$-Propan-2-one dimethyl hydrazone b.p. 92–94°C; $^{2}\text{H}_6 = 90\%$; $^{2}\text{H}_5 = 8\%$; $^{2}\text{H}_4 = 2\%$.

3.6.2 $^{2,2,4,4}$-$^{2}\text{H}_4$-Pentan-3-one hydrazones

Prepared from $^{2,2,4,4}$-$^{2}\text{H}_4$-pentan-3-one and methyl or dimethyl hydrazine using the procedure outlined for compounds 3.6.1.

$^{2,2,4,4}$-$^{2}\text{H}_4$-Pentan-3-one methylhydrazone b.p. 138–140°C; $^{2}\text{H}_4 = 95\%$; $^{2}\text{H}_5 = 3\%$; $^{2}\text{H}_4 = 2\%$. $^{2,2,4,4}$-$^{2}\text{H}_4$-Pentan-3-one dimethylhydrazone b.p. 150–152°C; $^{2}\text{H}_4 = 95\%$; $^{2}\text{H}_5 = 3\%$; $^{2}\text{H}_4 = 2\%$. Dimethylhydrazones of ethanal, propanal, butanal, pentanal, benzaldehyde, propan-2-one, butan-2-one, 3-methylbutan-2-one, pentan-2-one, pentan-3-one, 4-methylpentan-3-one, heptan-4-one, hexan-2-one, nonan-2-one and acetophenone are known compounds.
3.6.3 1,1,1-2H₃-Ethanal hydrazones
Prepared from 1,1,1-2H₃-ethanal and methyl or dimethyl hydrazine using the procedure outlined for compounds 3.6.1.

1,1,1-2H₃-Ethanal methylhydrazone\(^309\) b.p. 80–82°C; \(^2\)H₃ = 97%; \(^2\)H₂ = 3%.
1,1,1-2H₃-Ethanal dimethylhydrazone\(^313\) b.p. 90–93°C; \(^2\)H₃ = 95%; \(^2\)H₂ = 3%.

3.6.4 2-2H₁-Ethanal hydrazones
Prepared from 2-2H₁-ethanal and methyl or dimethylhydrazine using the procedure outlined for compounds 3.6.1.

2-2H₁-Ethanal methylhydrazone\(^309\) b.p. 79–82°C; \(^2\)H₁ = 99%; \(^2\)H₂ = 1%.
2-2H₁-Ethanal dimethylhydrazone\(^313\) b.p. 90–92°C; \(^2\)H₁ = 99%; \(^2\)H₂ = 1%.

3.6.5 1,1,1-2H₃-Pentan-3-one methylhydrazone
(i) Ethyl 3-oxopentanoate
Prepared from 3-oxobutanoate using the procedure of Weiler\(^320\).
Yield 80%. b.p. 75–77°C/20 mm Hg, (Lit.\(^320\) 70–71°C/14 mm Hg);
N.M.R (CDCl₃) : \(\delta\) 1.3, 3H(t); 1.4, 3H(t); 2.2, 2H(q); 3.5, 2H(s); 4.22, 2H(q).

(ii) Ethyl 2(1,1,1-2H₃-methyl) 3-oxopentanoate
Prepared from ethyl 3-oxopentanoate and \(^2\)H₃-iodomethane using the procedure outlined for compound 2.6.2(iii).
Yield 72%; \(^2\)H₃ = 99%, \(^2\)H₂ = 1%; b.p. 87–89°C/16 mm Hg, (Lit.\(^321\) 199°C/760 mm Hg);
N.M.R (CDCl₃) : \(\delta\) 1.3, 3H(t); 1.4, 3H(t); 2.1, 2H(q); 3.35, 1H(s); 4.2, 2H(q).

(iii) 1,1,1-2H₃-Pentan-3-one
Ethyl 2(1,1,1-2H₃-methyl) 3-oxopentanoate was hydrolysed in aqueous sodium hydroxide (10%) using the procedure outlined for compound 2.6.2(iv).
Yield 60%; \(^2\)H₃ = 99%, \(^2\)H₂ = 1%; b.p.100–102°C/760 mm Hg, (Lit.\(^322\) 102°C/760 mm Hg);
N.M.R (CDCl₃) : \(\delta\) 1.1, 3H(t); 2.4, 2H(q); 2.4 2H (br s).
Experimental

(iv) 1,1,1-2H₃-Pentan-3-one methylhydrazone

Formed from 1,1,1-2H₃-Pentan-3-one with methylhydrazine using the general procedure (3.5).

Yield 73%; ²H₃ = 99%, ²H₂ = 1%; b.p. 138–140°C/760 mm Hg;
N.M.R (CDCl₃) : δ 1.4, 3H(t); 2.02, 2H(q); 2.1, 2H(bs); 2.34, 3H(s)

3.6.6 1,1,1-2H₃-Pentan-3-one dimethylhydrazone

Prepared by lithiation of butan-2-one dimethylhydrazone followed by reaction with ²H₃-iodomethane using the procedure of Ludwig²²³.

Yield 78%; ²H₃ = 99%, ²H₁ = 1%; b.p. 150–152°C/760 mm Hg;
N.M.R (CDCl₃) : δ 1.2, 3H(t); 2.02, 2H(bs); 2.35, 2H(q); 2.4, 6H(s).

8.4 Synthetic Procedures used for Chapter 4

4.1 Preparation of α oximino ketones [R¹COC(=NOH)R²]

The following α oximino ketones are known compounds and were prepared by the general procedure of Ferris²²⁴.

R¹ = R² = Me²²⁵; R¹ = Me, R² = Et²²⁶; R¹ = Me, R² = Pr²²⁷; R¹ = Me, R² = iso Pr²²⁸; R¹ = Me, R² = Bu²²⁹; R¹ = Me, R² = iso Bu²³⁰; R¹ = Me, R² = COMe²³¹; R¹ = Me, R² = Ph²³²; R¹ = Et, R² = Me²³³; R¹ = Pr, R² = Et²³⁴; R¹ = Ph, R² = Me²³⁵.

4.2 Preparation of β-oxo aldoximes [R¹COC(=NOH)H]

The following β-oxo aldoximes are known compounds and were prepared by the general procedure of Sharp and Spring²³³.

R¹ = Me²³⁹, Pr²⁴⁰, iso Pr²⁴⁰, tert Bu²⁴⁰, Ph²⁴¹.
4.3 4 Methylhexan-2,3-dione ketoxime [MeCOC(=NOH)sec Bu]

Prepared from 4-methylhexan-2-one using the general procedure\textsuperscript{324}. Yield 40%; b.p. 54–56°C/0.2 mm Hg. The compound is unstable on exposure to the atmosphere and microanalytical data were not obtained.

\[ M^{+*} \text{ (found)} = 143.0939, \text{C}_7\text{H}_{13}\text{NO}_2 \text{ requires 143.0946.}\]

\[ {^1}\text{H N.M.R (60 Mhz, CDCl}_3\text{)} : \delta 1.0-1.3, 6\text{H(m); 1.4-2.1, 3\text{H(m); 2.33, 3\text{H(s).}}\]

\[ {^{13}}\text{C N.M.R (300 Mhz, CDCl}_3\text{)} : \delta 12.35 (\text{CH}_3), 16.18 (\text{CH}_3), 19.25 (\text{CH}_3), 25.76 (\text{CH}_2), 44.75 (\text{CH}), 149.53 (\text{C=N}), 162.27 (\text{C=O}).\]

4.4 Preparation of labelled compounds

\[ 2\text{H}_5\text{-Phenylpropan-1,2-dione-2-oxime, [C}_6\text{D}_5\text{COC(=NOH)Me}, \]

\[ 1(2\text{H}_5\text{-Phenyl)-2 phenylethanedione-2-oxime, [C}_6\text{D}_5\text{COC(=NOH)Ph}, \text{ and} \]

\[ 1(2,4,6-2\text{H}_3\text{-Phenyl)-2-phenylethanedione-2-oxime, [C}_6\text{D}_3\text{H}_2\text{COC(=NOH)Me]} \]

were available from a previous study\textsuperscript{200}.

4.4.1 1,1,1-2\text{H}_3\text{-Butan-2,3-dione-3-oxime}

(i) 1,1,1,3,3-2\text{H}_5\text{-Butan-2-one}

A mixture of butan-2-one (5g) and deuterium oxide(10ml) [containing sodium (30mg)] was heated under reflux for 24 hrs, cooled to 25°C, and saturated with sodium chloride. The upper layer was separated and the exchange procedure was repeated to give 1,1,1,3,3-2\text{H}_5\text{-butan-2-one.}

Yield 70%; \( 2\text{H}_5 = 95\%, \text{ 2H}_4 = 3\%, \text{ 2H}_3 = 2\%; \text{ b.p. 78–79°C/760 mm Hg, (Lit.}\textsuperscript{288} = 76.6°C/760 mm Hg); \text{ N.M.R (CDCl}_3\text{)} : \delta 1.1 \text{ (broad singlet).}\]

(ii) 1,1,1-2\text{H}_3\text{-Butan-2,3-dione-3-oxime}

Prepared from 1,1,1,3,3-2\text{H}_5\text{-butan-2-one using the general procedure}\textsuperscript{234}.

Yield 65%; \( 2\text{H}_3 = 90\%, \text{ 2H}_2 = 10\%; \text{ m.p. 70–72°C, (Lit.}\textsuperscript{326} 76.5°C); \text{ N.M.R (CDCl}_3\text{)} : \delta 1.9 \text{ (s).}\]
4.4.2 1,1,1-2H3-Pentan-2,3-dione-3-oxime
Prepared from pentan-2-one using the procedure outlined for compound 4.4.1.
Yield 68%; 2H3 = 90%, 2H2 = 10%; m.p. 52–55°C, (Lit.326 53–55°C);
N.M.R (CDCl3) : δ 1.2, 3H(t); 1.9, 2H(q).

4.4.3 3,3,3-2H3-1-Phenylpropan-1,2-dione-2-oxime
Prepared from 1-phenylpropan-2-one using the procedure outlined for compound 4.4.1.
Yield 72%; 2H3 = 90%, 2H2 = 10%; m.p. 163–164°C, (Lit.334 164–5°C);
N.M.R (CDCl3) : δ 7.5, 3H(m); 8.0, 2H(m).

4.4.4 4,4-2H2-Pentan-2,3-dione-3-oxime
(i) 1,1-2H2-Ethanol
Prepared from the reduction of benzyl acetate with lithium aluminium deuteride using the procedure outlined for compound 2.6.2(i).
Yield 76%; 2H2 = 98%, 2H1 = 2%; b.p. 75–77°C/760 mm Hg, (Lit.282 77–78 °C/760 mm Hg); N.M.R (CDCl3) : δ 1.22, 3H(s); 2.6, 1H(s).

(ii) 1,1-2H2-Ethyl iodide
Prepared from 1,1-2H2-ethanol using the procedure of Vogel283.
Yield 69%; 2H2 = 98%, 2H1 = 2%; b.p.69–71°C/760 mm Hg, (Lit.283 72–73°C/760 mm Hg); N.M.R (CDCl3) : δ 1.8 (s).

(iii) Ethyl 2(1,1-2H2-ethyl) 3-oxobutanoate
Prepared from ethyl 3-oxobutanoate and 2H3-methyl iodide using the procedure outlined for compound 2.6.2(iv).
Yield 68%; 2H2 = 98%, 2H1 = 2%; b.p. 94–96°C/16mm Hg, (Lit.336 198°C/760 mm Hg); N.M.R (CDCl3) : δ 1.13, 3H(s); 2.23, 3H(s); 3.36, 1H(s); 4.23, 2H(q).
(iv) **4.4-\textsuperscript{2}H\textsubscript{2}-Pentan-2-one**

Ethyl 2(1,1-\textsuperscript{2}H\textsubscript{2}-ethyl) 3-oxobutanoate was hydrolysed with aqueous sodium hydroxide (10%) using the procedure outlined for compound 2.6.2(iv).

Yield 63%; \( ^2\text{H}_2 = 98\% \), \( ^2\text{H}_1 = 2\% \); b.p. 99–103°C/760 mm Hg, Lit.\textsuperscript{337} b.p. 102°C/760 mm Hg); N.M.R (CDCl\textsubscript{3}): \( \delta 0.9, 3\text{H}(s); 2.2, 3\text{H}(s); 3.4, 2\text{H}(s) \).

(v) **4.4-\textsuperscript{2}H\textsubscript{2}-Pentan-2,3-dione-3-oxime**

Prepared from 4,4-\textsuperscript{2}H\textsubscript{2}-pentan-2-one using the general procedure\textsuperscript{324}.

Yield 65%; \( ^2\text{H}_2 = 98\% \), \( ^2\text{H}_1 = 2\% \); m.p. 52–55°C, (Lit.\textsuperscript{309} 53–55°C); N.M.R (CDCl\textsubscript{3}): \( \delta 1.0, 3\text{H}(s); 2.36, 3\text{H}(s) \).

4.4.5 **5,5,5-\textsuperscript{2}H\textsubscript{3}-Pentan-2,3-dione-3-oxime**

(i) **2,2,2-\textsuperscript{2}H\textsubscript{3}-Ethyl iodide**

Previously prepared from 2,2,2-\textsuperscript{2}H\textsubscript{3}-ethanol using the procedure outlined for compound 2.6.2(iii).

(ii) **Ethyl 2(2,2,2-\textsuperscript{2}H\textsubscript{3}-ethyl) 3-oxobutanoate**

Prepared from ethyl 3-oxobutanoate and 2,2,2-\textsuperscript{2}H\textsubscript{3}-ethyl iodide using the procedure outlined for compound 2.6.2(iv).

Yield 71%; \( ^2\text{H}_3 = 98\% \), \( ^2\text{H}_2 = 2\% \); b.p. 98–100°C/20 mm Hg, (Lit.\textsuperscript{309} 198°C/760 mm Hg); N.M.R (CDCl\textsubscript{3}): \( \delta 1.5, 2\text{H}(bd); 2.23, 3\text{H}(s); 3.36, 1\text{H}(t); 4.23, 2\text{H}(q) \).

(iii) **5,5,5-\textsuperscript{2}H\textsubscript{3}-Pentan-2-one**

Ethyl 2(2,2,2-\textsuperscript{2}H\textsubscript{3}-ethyl) 3-oxobutanoate was hydrolysed in aqueous sodium hydroxide (10%) using the procedure outlined for compound 2.6.2(iv).

Yield 68%; \( ^2\text{H}_3 = 98\% \), \( ^2\text{H}_2 = 2\% \); b.p. 100–102°C/760 mm Hg, (Lit.\textsuperscript{309} 102°C/760 mm Hg); N.M.R (CDCl\textsubscript{3}): \( \delta 1.26, 2\text{H}(t); 2.2, 3\text{H}(s); 2.4 2\text{H}(t) \).
(iv) 5,5,5-\textsuperscript{2}H\textsubscript{2}-Pentan-2,3-dione oxime
Prepared from 5,5,5-\textsuperscript{2}H\textsubscript{2}-pentan-2-one using the standard procedure\textsuperscript{324}.
Yield 74\%; \textsuperscript{2}H\textsubscript{3} = 98\%, \textsuperscript{2}H\textsubscript{2} = 2\%; m.p. 49–52°C, (Lit.\textsuperscript{326} 53–55°C); N.M.R (CDCl\textsubscript{3}) : δ 2.36, 3H(s); 2.65, 2H(s).

4.5 General preparation of α-(O-methyl)oximino ketones
The following aldoxime methyl ethers [RCOC(=NOMe)H] were prepared by reported procedures: \( R = \text{Me}\textsuperscript{340} \) and \( R = \text{Ph}\textsuperscript{341} \).
The following α oximino ketone O-methyl ethers \([R^1\text{COC}(=\text{NOMe})R^2]\) are known, and were prepared by the general procedure outlined below:
\( R^1 = R^2 = \text{Me}\textsuperscript{341}; \quad R^1 = \text{Me}, R^2 = \text{Et}\textsuperscript{342}; \quad R^1 = \text{Et}, R^2 = \text{Me}\textsuperscript{343} \).

General Procedure
The α-oximino ketone (30mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise, under nitrogen, to sodium hydride (33 mmol, 80\% in oil, 0.92g) in tetrahydrofuran (20 ml). After stirring for fifteen minutes, iodomethane (35 mmol, 5g) was added and the mixture was heated under reflux for 2 hrs. After cooling to 25°C, aqueous hydrochloric acid (20\%, 15 ml) was added, and the mixture was extracted with diethyl ether (3x20 ml). The combined organic extract was washed with aqueous sodium chloride (saturated, 25 ml) and dried (\( \text{Na}_2\text{SO}_4 \)). Removal of the solvent followed by distillation in vacuo gave the appropriate α-(O-methyl) oximino ketone, (Yields 50–80\%).

4.6 Preparation of unknown α-(O-methyl)oximino ketones

4.6.1 1-Phenylpropan-1,2-dione-1(methyl oxime) [MeCOC(=NOMe)Ph]
Prepared from 1-phenylpropan-1,2-dione-1-oxime using the general procedure described above.
Yield 67%; b.p. 68–70°C/0.1 mm Hg.
Found: C, 67.8; H, 6.25; N, 7.9% (M⁻² = 177.0797); C₁₀H₁₁NO₂ requires
C, 67.8; H, 6.3; N, 7.8% (M⁻² = 177.0790).
N.M.R (CDCl₃) : δ 2.5, 3H(s); 4.06, 3H(s); 7.4 5H(s).

4.6.1 1-Phenylpropan-1,2-dione-2(methyl oxime) [PhCOC(=NOMe)Me]
Prepared from 1-phenylpropan-1,2-dione-2-oxime using the general procedure
described above (4.5).
Yield 62%; b.p. 52–54°C/0.04 mm Hg.
Found: C, 68.0; H, 6.1; N, 7.9% (M⁻² = 177.0796); C₁₀H₁₁NO₂ requires
C, 67.8; H, 6.3; N, 7.8% (M⁻² = 177.0790).
N.M.R (CDCl₃) : δ 2.16, 3H(s); 4.06, 3H(s); 7.5, 3H(m); 8.0, 2H(m).

4.7 Preparation of labelled α-(O-methyl)oximino ketones

4.7.1 1,1,1-²H₃-Butane-2,3-dione-3(methyl)oxime
Prepared from 1,1,1-²H₃-butane-2,3-dione oxime using the general procedure
described above (4.5).
Yield 75%; ²H₃ = 90%, ²H₂ = 10%; b.p. 44–46°C/29 mm Hg, (Lit.343 126–
127°C); N.M.R (CDCl₃) : δ 1.93, 3H(s); 4.1, 3H(s).

4.7.2 4,4,4-²H₃-Butane-2,3-dione-3(methyl)oxime
(i) 4,4,4-²H₃-Butane-2,3-dione-3-oxime
Prepared from 4,4,4-²H₃-butane-2-one [compound 2.6.3(ii)] using the general
procedure of Ferris324.
Yield 70%; ²H₃ = 98%, ²H₂ = 2%; m.p. 72–76°C, (Lit.325 76.5°C);
N.M.R (CDCl₃) : δ 2.35 (s).
(ii) 4.4,4-^H3-Butane-2,3-dione-3(methyl)oxime
Prepared from 4,4,4-^H3-butane-2,3-dione-3-oxime using the general procedure described above (4.5).
Yield 78%; $^2$H$_3$ = 98%, $^2$H$_2$ = 2%; b.p. 44–46°C/29 mm Hg, (Lit.$^{343}$ 126–127°C); N.M.R (CDCl$_3$) : δ 2.1, 2H(s); 2.35, 3H(s).

4.7.3 Butane-2,3-dione-3(2^H3-methyl)oxime
Butane-2,3-dione-3-oxime was converted to the $^2$H$_3$-methyl ether using $^2$H$_3$-iodomethane by the general procedure described above (4.5).
Yield 64%; $^2$H$_3$ = 99%, $^2$H$_2$ = 1%; b.p. 44–46°C/29 mm Hg, (Lit.$^{343}$ 126–127°C); N.M.R (CDCl$_3$) : δ 2.36, 3H(s); 2.6, 3H(s).

4.7.4 1-^H1-2 Phenyl-2-oxoethanal (methyl)oxime [PhCOC(=NOMe)D]
(i) 1-^H1-2 Phenyl-2-oxoethanal'doxime [PhCOC(=NOH)D]
Prepared by a reported route$^{346}$, except that D$_2$O was used as solvent (in place of H$_2$O).
Yield 45%; $^2$H$_1$ = 95%, $^2$H$_2$ = 2% ;
N.M.R (CDCl$_3$) : δ 8.25, 5H(m).

(ii) 1-^H1-2 Phenyl-2-oxoethanal (methyl)oxime
The aldoxime was converted to the methyl ether using the general procedure (4.5).
Yield 64%; $^2$H$_1$ = 95%, $^2$H$_0$ = 5%; N.M.R (CDCl$_3$) : δ 4.06, 3H(s); 8.2, 5H(m).
8.5 Synthetic Procedures used for Chapter 5

5.1 Preparation of Hydroxamic Acids

The following aliphatic hydroxamic acids \([R_1\text{CONHOH}]\) were prepared from the ethyl ester of the appropriate carboxylic acid and hydroxylamine solution using the procedure of Fishbein, Daly and Streeter\(^{347}\).

\[ R_1 = \text{Me}^{347}, \text{Et}^{347}, \text{Pr}^{347}, \text{iso Pr}^{347}. \]

Benzohydroxamic acid \((R_1 = \text{Ph})\) was prepared from the standard procedure of Hauser and Renfrow\(^{348}\).

5.2 Preparation of O-Alkylhydroxamic acids

The following O-alkylhydroxamic acids \([R_1\text{CONHOR}_2]\) were prepared using the procedure of Pickart and Jencks\(^{349}\).

\[ R_1 = R_2 = \text{Me}^{349}; \quad R_1 = \text{Me}, R_2 = \text{Et}^{349}; \quad R_1 = \text{Pr}, R_2 = \text{Me}^{349}. \]

5.3 Preparation of Hydrazides

The following aliphatic hydrazides \([R_1\text{CONHNH}_2]\) were prepared from the ethyl ester of the appropriate carboxylic acid and hydrazine hydrate using the procedure of Horner and Fernekess\(^{350}\).

\[ R_1 = \text{Me}^{350}, \text{Et}^{350}, \text{Pr}^{350}, \text{Ph}^{350}, \text{PhCH}_2^{350}. \]

5.4 Preparation of N,N-dimethylhydrazides

The following aliphatic N,N-dimethylhydrazides \([R_1\text{CONHNMe}_2]\) were prepared from the ethyl ester of the appropriate carboxylic acid and dimethyl hydrazine using the procedure of Hinman\(^{351}\).

\[ R_1 = \text{Me}^{351}, \text{Et}^{351}, \text{Pr}^{351}, \text{Ph}^{351}. \]
5.5 Preparation of labelled hydroxamic acids and hydrazides

5.5.1 2,2,2-²H₃-Ethyl acetate

(i) 2,2,2-²H₃-Sodium acetate

²H₄-Acetic acid was titrated with sodium hydroxide, the solvent was removed and the 2,2,2-²H₃-sodium acetate was dried over P₂O₅ in a dessicator for 24 hrs.

Yield = 98%. ²H₃ = 99%, ²H₂ = 1%.

(ii) 2,2,2-²H₃-ethyl acetate

Prepared from 2,2,2-²H₃-sodium acetate and triethyl phosphate using the procedure of Ropp.³⁵²

Yield 65%; ²H₃ = 99%, ²H₁ = 1%; b.p. 75–77°C/760 mm Hg, (Lit.³⁰⁹ 77.1°C/760 mm Hg).

5.5.2 2,2,2-²H₃-Acetohydroxamic acid

Prepared from 2,2,2-²H₃-ethyl acetate using the general procedure of Fishbein, Daly and Streeter.³⁴⁷

Yield 54%; ²H₃ = 98%, ²H₂ = 2%; m.p. 88–91°C, (Lit.³⁴⁷ 89–91°C).

5.5.3 2,2,2-²H₃-Acetoxydrazide

Prepared from 2,2,2-²H₃-ethyl acetate using the general procedure of Horner and Fernekess.³⁵⁰

Yield 61%; ²H₃ = 98%, ²H₂ = 2%; b.p. 105–107°C/25 mm Hg, m.p. 20–25°C, (Lit.³⁰⁹ 53°C/0.2 mm Hg).
8.6 Synthetic Procedures used for Chapter 6

8.6.1 Preparation of Amidoximes
N-Hydroxyethanimidamide, N-hydroxypropanimidamide, N-hydroxybutanimidamide, N-hydroxybenzenecarboximidamide, N-hydroxy-4-methylbenzenecarboximidamide, N-hydroxy-4-methylbenzenecarboximidamide, N-hydroxy-N'-propylbenzenecarboximidamide, N-hydroxy-N',N'-dimethyl-benzenecarboximidamide, N-hydroxy-N',N'-diethylbenzenecarboximidamide, N-hydroxy-N',N'-dimethyl-benzenecarboximidamide, N-hydroxy-N',N'-dimethyl-benzenecarboximidamide, N-methoxybenzenecarboximidamide, N-methoxy-N',N'-dimethylbenzenecarboximidamide, and N-trimethylsiloxybenzenecarboximidamide are known compounds and were prepared by standard routes.

8.6.2 Preparation of Deuterium labelled Amidoximes
N-Hydroxyethanimidamide or N-hydroxybenzenecarboximidamide (0.5g) was stirred in deuterium oxide (5 ml) for one hour at 25°C. The solvent was removed to yield N-(2H1-Hydroxy)ethanim(2H2-amide) or N-(2H1-Hydroxy)benzenecarboximid(2H2-amide). 2H3 = 95%, 2H2 = 5%.

8.6.3 N-hydroxybenzenecarboximid(−15N1-amide)
N-hydroxybenzeneimidoyl chloride was prepared using the procedure of Wiley and Wakefield. The crude N-hydroxybenzeneimidoyl chloride (2.0g) was added to a solution of 15N-ammonia (Aldrich Chem. Co., 15N1 = 98%) in methanol (50 ml) and the solution stirred at -78°C for 12 hrs. The solvent was evaporated, water (10 ml) was added and the solution was extracted with ether (3x15 mls) and dried (Na2SO4). Removal of the solvent followed by distillation in vacuo gave N-hydroxybenzenecarboximid(−15N1-amide). Yield 45%. 15N1 = 98%; m.p. 76–80°C, (Lit. 78–80°C).
8.6.4 N-Methoxyethanimidamide

N-Methoxyethanimidamide was prepared using the procedure of Johnson and Cornell.\textsuperscript{362}

The crude residue was purified by rapid filtration through a silica column with dichloromethane, ethyl acetate and ethanol as eluants.

Yield 70\%: b.p. 40-41°C/0.5mm Hg.

M\(^+\) 88.0637; C\(_3\)H\(_8\)N\(_2\)O requires M\(^+\) 88.0633.

N.M.R (CDCl\(_3\)):

\(^1\)H (300 Mhz) \(\delta\) 1.85, 3H(s); 3.77, 3H(s); 4.53, 2H(s).

\(^13\)C (300 Mhz) \(\delta\) 16.96 CH\(_3\), 60.76 CH\(_3\), 150.24 C=N.

8.6 Synthetic Procedures used for Chapter 7

Isothiazole, thiazole, oxazole, isoxazole, pyrazole, imidazole, 4-methylthiazole, 5-methylthiazole, 1-methylimidazole, 2-methylimidazole, 4(5)-methylimidazole were purchased from Aldrich Chemical Co.

3-Methylisothiazole, 4-methylisothiazole, 5-methylisothiazole, 3-isothiazole carboxylic acid, 4-isothiazolecarboxylic acid and 5-isothiazolecarboxylic acid were kindly provided by Prof. J.H. Bowie.

2-Methylthiazole was prepared using the procedure of Kurkij and Brown.\textsuperscript{366}
8.7.1 Preparation of deuterium labelled heterocyclic compounds

2-$^2$H$_1$-thiazole, 2-$^2$H$_1$-4-methylthiazole and 2-$^2$H$_1$-5-methylthiazole were prepared by the following procedure.

$n$-Butyl lithium (11 mmol) was added to the appropriate heterocycle (10 mmol) in anhydrous tetrahydrofuran (5 ml) at $-78^\circ$C. After stirring for 5 minutes, deuterium oxide (4 ml) was added and the solution was allowed to warm to room temperature. After extraction with diethyl ether, the organic extracts were washed with sodium chloride (saturated, 15 ml) and dried (Mg$_2$SO$_4$). Removal of the solvent gave the appropriate deuterium labelled heterocycle.
References

References

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Publications


Gas-phase Rearrangements of Deprotonated Ketoximes, Ketoxime Ethers, and Aldoximes. A Negative-ion Beckmann Rearrangement

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Roger N. Hayes
Department of Chemistry, University of Nebraska, Lincoln, Nebraska, 68588-0362, USA

Evidence is presented which indicates that the pronounced loss of water from deprotonated ketoximes involves specific proton transfer followed by a negative-ion Beckmann rearrangement. For example, Me₂C=NO⁻ → CH₃(Me)C=NOH → [(CH₃=CHMe)⁻OH] → CH₃C=NCH₂⁺ + H₂O. Deprotonated ketoximes, e.g. MeCH=NO⁻, fragment in this way, but also undergo the competing process MeCH⁺=NO⁻ → MeC=NOH → [MeCN]⁻ + OH⁻ → CH₃CN + H₂O. Other rearrangements occur when proton transfer to oxygen does not occur, e.g. Ph₂C=NO⁻ → Ph²⁺ + PhCN.

We have recently reported a number of simple ‘rules’ for fragmentations of even-electron negative ions including enolates, C₂N⁻ and O₂⁻ species. Most fragmentations involve loss of a neutral molecule, and many such reactions are initiated from the charged centre through ion complexes [e.g. equation (1), R¹ = H, alkyl or aryl]. When such reactions are either unfavourable or not possible, one of two events generally occurs, viz. (i) proton transfer to the original charged centre produces a new anion which may fragment [e.g. carbonyl species, equations (2) and (3)] or (ii) some type of internal (skeletal) rearrangement occurs [e.g. sigmatropic 1,2 and Smiles 1 (equation (4)) rearrangements].

Deprotonated ketoximes (R¹=CH₂C=NO⁻) (R¹ and R² = H, alkyl or aryl), are somewhat akin to carbonyl species [see equations (2) and (3)], since it is unlikely that fragmentation can be directly effected through O⁻. Either proton transfer to oxygen, or some internal rearrangement would be expected to precede fragmentation. Proton transfer [see equation (5)] could be facile since the acidities at the two centres should differ only by some 30 kJ mol⁻¹. For example, the gas phase ΔH°₈⁻ values for MeC=NOH₄ and (CH₃)₂C=NOMe₄ are 1 332 and 1 561 kJ mol⁻¹ respectively.

This paper reports the basic fragmentations of deprotonated ketoximes, ketoxime ethers and aldoximes, and provides evidence in favour of a number of rearrangement reactions including the negative-ion Beckmann rearrangement.

Results and Discussion
Collision-induced Dissociations of Deprotonated Alkyl Ketoximes.—Alkyl ketoxime spectra are listed in Table 1 or recorded in Figures 1–3. Deprotonation was effected by NH₃ under these conditions, R₂C=NOH systems yield M – D⁺ and M – H⁺ ions in the approximate ratio 4:5:1. This is the expected result since although the OH position is the more acidic, OH and –CHC=N– differ in acidity by only some 30 kJ mol⁻¹. Labelling experiments are crucial for this study, and exchange reactions must be carried out with care because of the similarities in acidity at the two described positions. Full details are provided in the Experimental section.

The oxime of acetone is prototypical in this series; its decompositions are shown in Figures 1 and 2. Major fragmentations shown in Figure 1 are the loss of H⁺, the losses of H₂O and CH₃ and the formation of HO⁻. Less abundant peaks are observed for the loss of HON⁻ and the formation of CNO⁻, CH₃CN, NO⁻, and CN⁻. The characteristic decomposition of virtually all oximes is loss of water; for the majority of alkyl ketoximes this process gives the base peak of the spectrum (Table 1). Loss of water is not a usual feature in negative ion spectra of systems containing O⁻ functionality, but is sometimes pronounced when such a loss gives a stabilized anion (e.g. formation of conjugated benzyl anions). The spectrum of the M – H⁺ ion from Me₂C=NOH is shown in Figure 2; this species loses H₂O and HOD in the ratio 6:5:1. Thus, the loss of water follows rapid interconversion of (1) and (2) (Scheme 1); in this case the data may be interpreted in terms of random loss of water together with a small isotope effect (H/D = 1.3) in favour of H₂O rather than HOD loss.

We suggest that the loss of water occurs from (2) (Scheme 1) by a negative-ion Beckmann rearrangement, with methyl-anion migration proceeding to N to form ion complex (3). This species is the precursor of three of the fragmentations observed in Figure 1 (also Figure 2); viz. the formation of HO⁻ by direct displacement [equation (6)], the elimination of water [equation (9)] together with the production of deprotonated acetonitrile by the S₆w reaction shown in equation (10). The competitive loss of methane can be rationalised by a similar process; here, methyl anion migration from (2) forms a transient species (4) in which the methyl anion may deprotonate the acidic hydrogen attached to O as shown in equation (11). The final major fragmentation is loss of H⁺. Loss of a radical to form a stabilized ion radical is a common fragmentation of even-electron anions, in this case loss of a hydrogen atom from either (1) or (2) will form the products shown in equation (6) and (7). Of the minor fragmentations, loss of NO⁻ may occur through (2) to form...
Table 1. Collisional activation mass spectra of deprotonated alkyl ketoximes.*

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<th>Formation</th>
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<td>Me$_2$CNOH $-$ H$^+$</td>
</tr>
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</tr>
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<td>Me$_2$CNOH $-$ H$^+$</td>
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</tr>
</tbody>
</table>

* Numbers listed in the table refer to relative abundances of peaks with reference to base peak (100%) of that spectrum.

* Loss of MeOH yields CH$_3$CN. * Not resolved. $^*$ CNO$^-$ and CD$_2$CN = 42 amu. The ion Pr$_2$CNOH $-$ H$^+$ loses H$_2$O and HOD in the approximate ratio 2:1 (weak spectrum).
...and NO\(^-\) could be formed from (I). The mechanisms of the processes forming CN\(^-\) and CNO\(^-\) are not known.

The classical Beckmann rearrangement\(^{11}\) in the condensed phase is an acid-catalysed reaction: protonation of oxygen aids the reaction by elimination of H\(_2\)O, a good leaving group.\(^{13}\) The group which migrates to N is often that \textit{trans} to hydroxyl, but isomerisation occurring prior to migration is also known.\(^{11}\) Beckmann rearrangements of molecular radical cations have not been reported, but such reactions do occur for protonated oximes in the gas phase.\(^{14}\)

In the case of the negative-ion Beckmann rearrangement, elimination of H\(_2\)O from intermediate (2) (Scheme 1) should yield CH\(_3\)C=NC\(_2\)H\(_3\); \(m/z\) 54 in Figure 1; see also equation (9). The collisional activation and charge reversal (positive ion)\(^{15}\) mass spectra (MS/MS/MS) of \(m/z\) 54 are recorded in Table 2. The spectra are consistent with structure CH\(_3\)C=NC\(_2\)H\(_3\), i.e. both CA and CR spectra show pronounced loss of CH\(_3\) (Table 2). In the case of an unsymmetrical oxime, \(m/z\) migration would not be expected since isomerisation of the double bond should occur [see (1), Scheme 1]. Thus the simplest example, deprotonated butan-2-one ketoxime, should give two Beckmann rearrangements: ethyl and methyl anion migration should yield (5) and (6) respectively, and internal deprotonation in these intermediates should occur as shown in equations (12), (14), and (15). Since Me(CD\(_3\)CH\(_2\))\(_2\)CNO\(^-\) loses H\(_2\)O exclusively (Table 1), process (14) does not occur. This is in accord with the greater acidity of the protons...
3.0, indicates that the rate determining step involves either loss or transfer of a terminal hydrogen. We suggest the mechanism shown in equation (17), a mechanism consistent with the previously cited examples.²,¹⁶

**Ketoxime Alkyl Ethers.**—If our proposal for a negative-ion Beckmann rearrangement of oximes is correct (see Scheme 1), then deprotonated ketoxime methyl ethers \( \text{CH}_2\text{C}=(\text{Me})\text{NO}^- \) should form \( \text{MeO}^- \) and eliminate \( \text{MeOH} \) by a Beckmann mechanism. The collisional activation spectra of related ketoxime alkyl ethers are listed in Table 3. The spectra are simple, and are dominated by the expected losses; these are rationalised for the methyl ether of acetone ketoxime by the Beckmann process shown in equations (18) and (19).

The product ion of equation (19), \( \text{CH}_2\text{C}=(\text{NCH}_2) (m/e 54) \), should be the same as that formed by the analogous reaction of deprotonated acetone ketoxime [equation (9), Scheme 1]. The collisional activation and charge reversal spectra (MS/MS/MS)
Table 3. Collisional activation mass spectra of deprotonated ketoether ethers.

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<tr>
<td>CH2(Me)=C=NOE</td>
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<td>15</td>
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<td>99</td>
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* Numbers listed in Table 3 refer to relative abundances of peaks with reference to the base peak (100%) of that spectrum.

Table 4. Collisional activation mass spectra of deprotonated aryl ketoximes.

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<th>Et</th>
<th>NOH'</th>
<th>C6H5</th>
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<td>Ph(Me)CH2CH2CNOH − H*</td>
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<td>35</td>
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<tr>
<td>Ph(Me)CH2CH2CNOH − D*</td>
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<td></td>
<td>35</td>
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<td></td>
<td>PhOH</td>
</tr>
</tbody>
</table>

* Numbers listed in Table 4 refer to relative abundances of peaks with reference to the base peak (100%) of that spectrum.

* There is also a loss of NO2' (13%).

Figure 4. Collisional activation mass spectrum of [PhCD3CH2CH2C(Me)]=NOH − H*]−.

Table 4 of these two ions are compared in Table 2. The spectra are identical.

CH3(Me)=C=NOMe −→ [(CH3=C=NMe)MeO]−
MeO− + CH2=C=NNMe (18) CH2=C=NNCH3 + MeOH (19)

Aryl ketoximes. —Spectra are listed in Table 4, and a particular example is illustrated in Figure 4. Alkyl aryl ketoximes behave normally; for example, deprotonated acetophenone ketoxime eliminates water as shown in equation (20) (Scheme 3). The spectrum of deprotonated Me(PhCH2CH2C=NOH) is particularly interesting since it emphasises the readiness of methylene proton transfer reactions which may occur in such systems. The fragmentations are best illustrated by the spectra of the labelled ions shown in Figure 4 and Table 4. In these cases the Beckmann rearrangement is completely suppressed by more energetically favourable fragmentations. For example, proton transfer from the benzyllic position to OH− yields (7) which decomposes as shown in equation (21). Alternatively, proton transfer to O− gives (8) which fragments to produce PhCH2− [equation (22)] and to eliminate toluene [equation (23)].

Finally, deprotonated benzophenone cannot undergo the negative-ion Beckmann rearrangement. Instead, a phenyl group migrates to oxygen with the ultimate formation of PhO− [equation (24)]. The alternative elimination of phenol is minor in comparison because PhO− is not a strong enough base to effectively deprotonate benzotroline (see Table 4; also ΔH°red PhOH = 1 461 kJ mol−1).17 In addition, benzene is eliminated by the process shown in equation (25) (in this case C6H5 is a strong enough base to deprotonate PhCNO − ΔH°red C6H5 = 1 677 kJ mol−1).18

* An alternative mechanism could involve a Smiles intermediate. Even if this were so, the reaction would then proceed through the ion complex [PhO−(PhCNO)].
Aldoximes.—We have left the discussion of aldoximes until last, since they have the most complex fragmentations of all oximes studied. This result was not unexpected since the conventional Beckmann rearrangement is known to be sluggish with aldoximes; hydrogen only migrates under special catalytic conditions. The clue to the complexity of the spectra is demonstrated by the HO⁻ peak profiles shown in Figure 5. The HO⁻ peak from deprotonated acetone ketaloxime is Gaussian with no fine structure, suggestive of formation by a single mechanism (see also Figure 1 and Scheme 1). The corresponding peak from acetaldehyde aldoxime is composite, with a sharp peak superimposed on a dished-shaped peak. This is indicative of two modes of formation of HO⁻ in this case. Most significant is the dished-shaped peak from PhCH₃NO⁻, an ion which cannot undergo a negative-ion Beckmann rearrangement of the type shown in Scheme 1. The spectra of selected aldoximes are listed in Table 5, and it is most convenient to start with PhCH₃NO⁻. The first observation is that Z and E isomers have identical spectra, the second that the major fragmentation involves statistical (random) loss of H⁺ from the phenyl ring. But the characteristic fragmentations are the formation of HO⁻ and the loss of H₂O. Labelling studies (Table 5) show that the formation of HO⁻ specifically involves the methylene hydrogen, and that the loss of this hydrogen together with statistical loss of a ring hydrogen constitutes the H₂O loss. These processes are summarised in
Table 5. Collisional activation mass spectra of deprotonated aldoximes.

<table>
<thead>
<tr>
<th>Parent ion</th>
<th>Loss</th>
<th>CH₂D</th>
<th>CD₃H</th>
<th>H₂O</th>
<th>HOD</th>
<th>D₂O</th>
<th>Et⁺ (H₂O + CH₄)</th>
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<tr>
<td>MeCH-NOD – D⁺</td>
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<td>23*</td>
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</tr>
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<td></td>
<td>32*</td>
<td>60</td>
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<td></td>
</tr>
<tr>
<td>MeCD-NOH – H⁺</td>
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<td>20*</td>
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<td></td>
<td>20*</td>
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<td>4</td>
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<tr>
<td>syn PhCH-NOD – D⁺</td>
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</table>

0 CD-NOH – H⁺ 100 53 12 18

Formation

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<td>0.2</td>
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</tr>
</tbody>
</table>

0 CD-NOH – H⁻ 2 0.5 0.5

Numbers listed in Table 5 refer to relative abundances of peaks with reference to the base peak (100%) of that spectrum.

Loss of CH₃ gives CNO⁻. Loss of CH₂D or CD₃H (as appropriate) gives CNO⁻. D₂O and CD₃H = 20 amu. This spectrum also shows a peak at m/z 66 (35%) corresponding to (H₂O + H₂). This spectrum shows the following peaks in this region — m/z 69 (35%, H₂O, 68 (20%, HOD), 67 (17%, (H₂O + H₂)) and 66 (19%, (H₂O + H₂) and/or (H₂O + HD)). In this case the peak at m/z 52 corresponds to — (H₂O + CH₂D) and/or (H₂O + CH₃D). Also peaks at m/z 67 (25%, (H₂O + H₂)) and 66 (12%, (H₂O + HD)). Peaks in this region are m/z 53 (27%, (H₂O + CH₂D)) and 52 (41%, (H₂O + CH₃D)).

Equations (26) and (27) (Scheme 4), and it is process (26) which gives rise to the dihydrogenated peak shown in Figure 5(c). There is no formation of PhO⁻ noted in this spectrum [cf equation (24), Scheme 3], hence in this reaction the migratory aptitude of H is greater than phenyl.

The two alkyloximes and their labelled derivatives show many features in common with the ketoximes discussed earlier. But they are different in several respects, and these differences are discussed for acetaldehyde aldoxime, since its characteristic fragmentations are similar to those of Table 5 of the butyraldehyde derivative. There are two mechanisms for both the formation of HO⁻ and the loss of H₂O. The first is the Beckmann rearrangement involving hydrogen transfer to nitrogen [equations (28) and (29)]. Formation of HO⁻ by the Beckmann process produces the sharp central component of Figure 5(d) [cf Figure 5(a)]. The second process is analogous to that shown in equations (26) and (27), viz., methylene transfer to oxygen [equations (30) and (31)], with the formation of HO⁻ by this route producing the dihydrogenated component of Figure 5(b) [cf Figure 5(c)]. Finally, the ions CNO⁻ and CH₂⁻ are pronounced in this spectrum; we suggest formation as shown in equations (32) and (33).

Conclusions

The compounds used in this study were chosen because deprotonation should yield a charged species which should not be able to fragment directly. This expectation is realised: elimination of neutral molecules from deprotonated oximes follow either proton transfer and/or skeletal rearrangement. The characteristic fragmentation involves a Beckmann type rearrangement, however other rearrangements involving migration of substituents to the O⁻ centre are also noted.

Experimental

Collisional activation mass spectra (MS/MS) were recorded using a Vacuum Generators ZAB 2HF mass spectrometer operating in the negative chemical-ionisation mode. All gasses were fully open to obtain maximum sensitivity and to minimize energy resolution effects. The chemical ionization slits were used in the ion source, ionizing energy 70 eV (tungsten filament); ion source temperature 180 °C, accelerating voltage 7 kV. Deprotonation of all neutral was effected by H₂N⁺ from NH₃. The indicated source pressure of NH₃ was 1 x 10⁻³ Torr. The substrate pressure (liquids introduced through the septum inlet at 150 °C; solids through the direct probe with no heating) was typically 5 x 10⁻² Torr. The estimated total pressure in the ion source is 10⁻¹ Torr. The pressure of helium in

* 1 Torr = 133,322 Pa.
the second collision cell was $2 \times 10^{-7}$ Torr measured by an ion gauge situated between the electric sector and the second collision cell. This produced a decrease in the main beam signal of ca. 10%, and corresponds to essentially single collision conditions.

Consecutive collision induced dissociation spectra (MS/MS/MS) and charge reversal MS/MS/MS spectra were measured with a Kratos MS 50 TA instrument previously described. Neutral substrates were deprotonated by MeO- from MeONO to a Kratos Mark IV chemical ionization source ion source temperature 100 °C, electron energy 280 eV, emission current 500 μA and accelerating voltage 8 kV. Samples were introduced through an all glass heated inlet system at 100 °C. The indicated source pressure of substrate was $2 \times 10^{-5}$ and of methyl nitrite $1 \times 10^{-4}$ giving an estimated source pressure of ca. 10 Torr. The indicated pressure of helium in the collision cells was $2 \times 10^{-4}$ Torr giving a decrease in the main beam signal of 30%.

Oximes derived from acetaldehyde, propanal, butanal, acetone, butan-2-one, pentan-2-one, 2-methylbutan-3-one, hexan-2-one, 3-methylpentan-2-one, 2,2-dimethylbutan-3-one, pentan-3-one, hexan-3-one, heptan-4-one, 2,4-dimethylpentan-3-one, acetoephone, butyrophenone, and benzyl phenyl ketone are known compounds, and were prepared by standard method. Z- and E-Benzaldoximes were prepared by the method of Vogel.

5-Phenylpentan-2-ketoxyne was prepared from 5-phenylpentan-2-one by the standard method. Yield, 78% b.p. 91-94 °C/0.15 mmHg. (Found: C, 74.55; H, 8.35% C6H13NO requires C, 74.55; H, 8.5%).

The Oximes.—O Deuterium Exchange. The following compounds were prepared by the general procedure outlined below:

- 2,2,2-[H3]ethanal-dioxide-O-[H3].
- 2,2,2,2'-propan-2-ketoxyne-O-[H3].
- 1,1,1,3,3-[H3]-butan-2-ketoxyne-O-[H3].
- 1,1,1,3,3-[H3]-butan-2-ketoxyne-O-[H3].
- 2,2,4,4,4-[H3]-2,2-dimethylbutan-3-ketoxyne-O-[H3].
- 1,1,1,3,3-[H3]-methyl phenyl ketoxime-O-[H3].
- and syn- and anti-benzaldoximes-O-[H3].

A mixture of the appropriate aldehyde/ketone (10 g), deuterium oxide (7.5 cm3) and sodium (10 mg), was heated under reflux for 4 h under an atmosphere of nitrogen. Hydroxylamine hydrochloride (1.2 mol equiv.) and sodium hydroxide (1.2 mol equiv.) were added and the mixture heated under reflux for 1 h. On cooling, sodium chloride (2 g) was added, the mixture extracted with diethyl ether (2 x 10 cm3) the ethereal solution dried (Na2SO4) and the solvent removed to yield the labelled oxime. This procedure gave better than 90% incorporation of the appropriate number of deuterium atoms.

O-Deuteriated oximes. The O-deuteriated oximes of ethanal-dioxide, butan-2-ketoxyne, heptan-4-ketoxyne and 5-phenylpentan-2-one were made in the following way.

The oxime (0.3 cm3) and deuterium oxide (1 cm3) were shaken together at 60 °C. Samples of the oxime (the upper layer) were pipetted off every 30 s, inserted into the septum inlet of the mass spectrometer, and the deuterium incorporation determined by positive-ion mass spectrometry. Generally, incorporation was ca. 10% 2H2O, 90% 2H1 at 3 min, and 90% 2H2, 10% 2H1 at 4 min (100% 2H2 could not be achieved). The time required to achieve an incorporation 90% 2H2, 90% 2H1 was determined, the mass spectrometer switched to the negative-ion mode, the labelling experiment repeated under identical conditions, the 10% 2H2, 90% 2H1 sample inserted into the septum inlet of the mass spectrometer, and the D2O/CA/NICl spectrum recorded (by fast scan) within 30 s of insertion of the sample.

1-[H2]Ethanal-dioxide was prepared from 1-[H2]butyraldehyde by the method of Leitch. Yield, 42%, [H2] = 98% syn-Phenyl([H2]methan)dioxide-3 was oxidized to phenyl([H2]methan)dioxide, which was converted into the oxime by the standard method (overall yield from PhCD(OH), 22%, = 98%).

The labelled compounds were analyzed by the method of Vogel.
2,4.6-[2H]phenyl[1H]methyl)nalanil (73% yield),24 and finally syn-(2,4.6-[2H2]phenyl)[1H]methyl)aldehyde (62% yield, \( \frac{2H}{H} = 96\% \)).

4,4,4-[2H]Butan-2-ketoxime. The reaction 40 of ethyl 3-oxobutanate with \([2H]_{3}\)methyl iodide gave ethyl 2-(\([2H]_{3}\)methyl)-3-oxobutanate (74% yield), which on hydrolysis/carboxylation 40 gave 4,4,4-[2H]butan-2-one (66% yield) which was converted into the oxime by the standard method (75% yield; \( \frac{2H}{H} = 99\% \)).

1,1-[2H]Heptan-4-ketoxime. This was prepared as for 4,4,4-[2H]butan-2-ketoxime (above), except that the starring materials are ethyl 3-oxobutanate and 2,2-[2H]ethyl iodide.

Overall yield 40% \( \frac{2H}{H} = 98\% \).

5,5-[2H]5-Phenylpentan-2-ketoxime. Methyl phenylacetate when treated 41 with methanol \( O\)-[2H]sodium gives methyl 2,2-[2H]phenylacetate (1H \( \approx 98\% \)), which upon reduction 43 with lithium aluminium hydride yields 2-phenyl-2,2-[2H]ethanol (66% yield), which in turn may be converted into 2-phenyl-2,2-[2H]ethyl bromide (72% yield),42 ethyl 2(2-phenyl-2,2-[2H]ethyl)-3-oxobutanate (65% yield),43 5,5-[2H]5-phenylpentan-2-one (68% yield),43 and finally 5,5-[2H]5-phenylpentan-2-ketoxime (87% yield, \( \frac{2H}{H} = 98\% \)).

Acknowledgements

We thank the Australian Research Council for the financial support of this project.

References

36 Ref. 31, p. 602.
37 Ref. 31, p. 756.
38 Ref. 31, p. 781.

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G.W. Adams and J.H. Bowie (1990) Do deprotonated semicarbazones undergo the negative-ion Beckmann rearrangement in the gas phase? 
*Rapid Communications in Mass Spectrometry, v. 4(8), pp. 275–276, August 1990*

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

[http://dx.doi.org/10.1002/rcm.1290040802](http://dx.doi.org/10.1002/rcm.1290040802)
Deprotonated hydroxyamic acids and cognate systems undergo a number of rearrangement processes upon collisional activation. It is proposed that ions RCONH undergo the Lossen rearrangement to form \( [(\text{OCN})\text{HO}]^- \), and that this reactive intermediate may decompose to form the ionic products \( \text{HO}^+ \), [(R – H)] NCO\(^-\), NCO\(^-\) and RNH\(^-\). Alternatively, hydrogen transfer yields RCONHO\(^-\) which may undergo a three-centre reaction to produce RCO\(^-\)NH; this species may decompose to yield both RCO\(^-\) and [(R – H)CO]\(^+\)\(^+.\) Fragmentation processes have been investigated by both deuterium labelling and product ion studies.

Deprotonated organic molecules, under conditions of collisional activation, undergo characteristic decomposition in the gas phase. A set of general ‘rules’ for such fragmentations has been proposed. The charged site is normally involved in fragmentation, and when simple radical or neutral loss is either improbable or energetically unfavourable, skeletal rearrangement of the ion often precedes decomposition. A number of intramolecular rearrangements of even-electron anions have been reported recently; often such reactions have analogies with base catalysed reactions which occur in solution. Some examples include the Wittig, oxy Cope, Claisen, Smiles and Beckmann rearrangements.

The Lossen rearrangement is one of the better known nitrogen anion rearrangements in the condensed phase. Hydroxamic acids (or their acyl derivatives) yield isocyanates when treated with base (eqn. (1)), or sometimes just on heating. If this reaction occurs in the gas phase, then ion–molecule complex I (eqn. (2)) should be formed initially. Such a complex should be easily identified by its fragmentation behaviour. This paper therefore reports the fragmentation behaviour of deprotonated hydroxyamic acids and cognate systems with a view to determining whether the Lossen rearrangement occurs in the gas phase.

\[
\text{RCONH}_2 + \text{H}_2\text{O} \rightarrow \text{RCONHO}^- + \text{H}_3\text{N}^+ \quad (1)
\]

\[
\text{[(R – N = C = O) H\(^+\)]}^- \quad (2)
\]

Results and Discussion

The collisional activation mass spectra (CA MS/MS) of a variety of deprotonated hydroxyamic acids and cognate systems are listed in Table 1 or illustrated in Figs. 1–3. The tandem mass spectra (MS/MS/MS) of certain product ions from selected spectra are recorded in Table 2. These spectra are mainly charge reversal (positive ion) mass spectra, but some CA MS/MS/MS data are also included.

Hydroxyamic acids should deprotonate preferentially on nitrogen: this can be seen from the following known \( \Delta H^\circ_{\text{acid}} \) values—MeCONH\(_2\) (1430 kJ mol\(^{-1}\)), \(^3\)PhCONH\(_2\) (1452.5 kJ mol\(^{-1}\)), \(^1\)C\(_2\)H\(_2\)CONMe\(_2\) (1569.5 kJ mol\(^{-1}\)) \(^1\) and NH\(_2\)OH (1629 kJ mol\(^{-1}\)). In accord with this prediction, CD\(_2\)CONHOH is deprotonated by NH\(_2\) to form only an (M – H)\(^+\) species.

The fragmentation of deprotonated hydroxyamic acids are complex: let us consider the spectra of MeCONHOH (Table 1) and CD\(_2\)COONHO (Fig. 1) as prototypical examples. The major fragmentations are explicable in terms of reactions directed by the nitrogen anion site. Loss of a hydrogen atom occurs by the two processes shown in eqns. (3) and (4) (Scheme 1); both form a stabilised radical anion. The only reactions which appear to occur following proton transfer from the methyl group to the nitrogen site are those forming H\(_2\)O (eqn. (5)) and MeCO\(^-\) (eqn. (6)). The structures of these product ions are confirmed by the data in Table 2. These are interesting reactions, because even though ‘NHOOH is a powerful base (\( \Delta H^\circ_{\text{acid}} \) CH\(_2\)CO and NF\(_2\)OH = 1526 ± 16 and 1670 ± 13 kJ mol\(^{-1}\), respectively), the electron affinity of ‘NHOOH is calculated to be −17 kJ mol\(^{-1}\), indicating that ‘NHOOH should be unstable with respect to its radical.†

The key question, however, is whether a gas phase Lossen rearrangement is operative, i.e. whether an incipient methyl
Table 1 Collisionsal activation mass spectra of deprotonated R′CONHR′(R′ = OH, OMe, NH₃, and NMe₃) species

<table>
<thead>
<tr>
<th>Neutro precursor (R′CONHR′)</th>
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<tr>
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* NH₃ and CH₃ are both 16 amu.

Fig. 2 Collisional activation mass spectrum of deprotonated PhCONOH

Anion rearranges to the nitrogen site. It seems that a transient methyl anion system is formed, since a major fragmentation is loss of methane with formation of OCN⁻ [eqn. (7)]. The structure of the production ion is confirmed by the data recorded in Table 2.

There is a number of fragments which require more deep seated rearrangement of the system. These fall into two major categories: (i) the formation of HO⁻ and NCO⁻ and the loss of H₂O, and (ii) the losses of NH and NH₂⁺. We suggest that the former set of reactions is best rationalised in terms of fragmentation through Lossen intermediate 2. Whether that intermediate is formed directly from MeCONOH or indirectly from MeCONOH⁻ is not known. We suggest that 2 may decompose directly to form HO⁻ [eqn. (8)], effect internal deprotonation [eqn. (9)] and undergo an internal S₈2 reaction [eqn. (10)]. The formation of NCO⁻ is a major process; the structure of this ion is confirmed by the data presented in Table 2.

The losses of NH and NH₂⁺ form MeCO₂⁻ and (CH₂CO₂)⁻, respectively. We suggest that these are formed following proton transfer/three-centre rearrangement as shown in eqns. (11) and (12). * Two possible reaction sequences shown in eqn. (12)

* A reviewer has suggested that MeCONHO⁻ [eqn. (11)] may also be formed directly by deprotonation of the neutral. This possibility cannot be excluded on available evidence, even though the O-H is the least acidic position in the neutral.
The table in Data Table 2 confirm the structure of the product radical anion but whether the decomposition of $\text{CH}_2\text{CO}_2\text{NH}_2$ is concerted [eqn. (12)], or stepwise (i.e. proceeding through 4c-5) is open to debate. In general terms, other deprotonated hydroxymalic acids fragment similarly. Several features require specific mention however; (i) when the alkyl substituent is $\geq$ Et, the intermediate analogous to 4(5) (Scheme 2) may also eliminate ammonia [See eqn. (13), Scheme 3], (ii) the standard reaction shown in eqn. (14) occurs when a propyl substituent is present (it has been shown previously that such reactions are two-step: loss of a terminal hydrogen atom is followed by elimination of ethene$^{23}$, and (iii) for a phenyl derivative, both Ph$^-$Teqn. (15), $E_a$ (Ph$^-$) $\approx 87$ kJ mol$^{-1}$]$^{23}$ and OCN$^-$ [cf. eqn. (6)] are formed, as are PhCO$_2$[cf. eqn. (11) and Table 2] and PhNH$^-$ (see Fig. 2, also Table 2). The structure of PhNH$^-$ is confirmed by comparison of its spectra (Table 2) with those of deprotonated anilines. The formation of PhNH$^-$ involves loss of CO$_2$; this reaction is likely to proceed via the intermediary of a Losan complex [see eqn. (16), and cf. eqns. (8)-(10)]. The deprotonated hydroxamic acid $O$-methyl ether shows reactions analogous to those described in eqns. (3) and (8)-(10) (Scheme 1).

**Scheme 1**

$\text{[MeCOCO}_2\text{N}^-\text{H}^-\text{]}$ $\rightarrow \text{CH}_2=\text{COCO}_2^-=\text{N}^-$ $\text{H}^-$ (13)

**Scheme 2**

$\text{P}_{\text{CO}}\text{N}^-\text{OH}$ $\rightarrow \text{C}_\text{H}_\text{N}^-\text{O}^-\text{H}^+$ (14)

**Scheme 3**

$\text{[PhNCO}_2\text{H}^-\text{]}$ $\rightarrow \text{PhNCO}_2^-\text{PhNH}^+$ $\text{CO}_2^-$ (16)

\[ \text{Lossen} \]

The reaction of hydrazides (RCONH$^-$N$_2$H) with nitrous acid in solution yields RCNO$^-$ via a Curtius rearrangement. Interestingly, the reaction between RCONH$^-$N$_2$H systems and strong base in solution does not lead to a Losan rearrangement; instead, hydrolysis is noted. What is the situation in the gas phase? The mass spectra of RCONH$^-$N$_2$H and cognate systems are listed in Table 1, and a specific example is illustrated in Fig. 3. The spectrum of CD$_3$CONH$^-$N$_2$H (Fig. 3) has fewer peaks than that of CD$_3$CONOH (Fig. 1). Fig. 3 shows losses of $H^+$, CD$_3$H and CD$_3$N$_2$H$^-$ [cf. eqns. (3), (7) and (10)], but there are no losses of $D^+$, $\text{NH}^+$, $\text{NH}_3$, $\text{N}_2\text{H}^+$ or $\text{NH}_2\text{NH}^+$ and no formation of NH$^-$. [cf. eqns. (4), (11), (9), (6) and (5)].
dimethylamino derivative (Table 1) exhibits similar behaviour. Two other pertinent observations are: (i) loss of NH$_3$ from CD$_3$CONHNH$_2$ yields (CD$_3$NCO)$^-$ (Table 2) not (CD$_3$CO)$^-$ (cf. eqn. (12)), and (ii) the spectrum of PhCONH$_2$ lacks the pronounced peak due to PhNH$_2$ which, if present, would support the operation of the Lossen rearrangement [cf. Fig. 2, also eqn. (16)]. We conclude that (i) three-centre rearrangements of the type shown in Scheme 2 do not occur in these systems, and (ii) with the possible exception of NCO$,^-$ there are no detectable product ions resulting from a Lossen anion/neutral complex [cf. 2, also eqns. (8) (10) and (16)].

The major fragmentations noted for MeCONNH$_2$ are summarised in Scheme 4. The processes resulting in losses of H$^+$ and CH$_4$ are shown in eqns. (17) and (18), respectively; the structure of the product ion of eqn. (18) is confirmed by the data listed in Table 2. We suggest that MeNCO$^-$ and NCO$^-$ (see data in Table 2) may be formed via Lossen radical/radical anion complex 6 [eqns. (19) and (20)].

In conclusion, deprotonated hydroxamic acids undergo several rearrangement reactions under conditions of collisional activation in the gas phase. One of these is suggested to be the classical Lossen rearrangement, and the second involves an unusual 1,2 oxygen rearrangement to the carboxyl site.

**Experimental**

Collisional activation mass spectra (MS/MS) were recorded using a Vacuum Generators ZAB 2HF mass spectrometer operating in the negative chemical-ionisation mode. All slits were fully opened to obtain maximum sensitivity and to minimise energy resolution effects. The chemical ionisation slit was used in the ion source, ionising energy 70 eV (tungsten filament), ion source temperature 180°C, accelerating voltage 7 kV.

Deprotonation of all neutrals was effected by H$_2$N$^+$ (from NH$_3$) at 133.323 Pa. The initial source pressure of NH$_3$ was 1 $\times$ 10$^{-2}$ Torr. The substrate pressure (liquids introduced through the septum inlet at 150°C; solids through the direct probe with no heating) was typically 5 $\times$ 10$^{-2}$ Torr. The estimated total pressure in the ion source is 10$^{-1}$ Torr. The pressure of helium in the second collision cell was 2 $\times$ 10$^{-2}$ Torr measured by an ion gauge situated between the electric sector and the second collision cell. This produced a decrease in the main beam signal of ca. 10%, and corresponds to essentially single collision conditions.

Consecutive collision induced dissociation spectra (MS/-MS/MS) and charge reversal MS/MSMS spectra were measured with a Kratos MS 50 TA instrument previously described. Neutral substrates were deprotonated by MeO$^-$ (from MeONO$_2$) in a Kratos Mark IV chemical ionisation source; ion source temperature 100°C, electron energy 280 eV, emission current 500 µA and accelerating voltage 8 kV. Samples were introduced through an all glass heated inlet system at 150°C. The indicated source pressure of substrate was 2 $\times$ 10$^{-5}$ Torr and of methyl nitrite 1 $\times$ 10$^{-6}$ Torr giving an estimated source pressure of ca. 10$^{-1}$ Torr. The indicated pressure of helium in the collision cells was 2 $\times$ 10$^{-4}$ Torr giving a decrease in the main beam signal of 30%.

All of the hydroxamic acid derivatives are known and were prepared by literature procedures, viz R$^1$CONHOR$^2$; R$^1$ = Me, Et, Pr, Ph, R$^2$ = H, $^5$H, $^3$H, and R$^1$ = Me, Et, Pr, Ph, PhCH$_3$; R$^1$ = H, $^5$H, and R$^2$ = H. All hydrazines are known, viz. R$^1$CONHNR$^2$$^2$. The two deuterium labelled compounds were prepared from CD$_3$CO$_2$Et by the standard procedures.$^{19,32}$

istinguishable from NH$_3$ by the standard procedures.$^{19,32}$

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*If NCO$^-$ is formed by a radical reaction in this case, then whether this reaction (9) is a radical or S$_2$ reaction is open to question.*

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**References**

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