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The role of mass spectrometric methods in ionic reaction mechanistic studies

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Abstract

The role of various mass spectrometric methods, including electron ionization, collisional activation, metastable peak shapes, analysis of neutrals from ionic unimolecular dissociations, field ionization kinetics, drift cell, and Fourier transform ion cyclotron resonance spectrometry, in ionic reaction mechanistic studies is described. This is illustrated by selected examples of research performed in the author's group over the last three decades. They comprise inter alia intramolecular acid–base, anchimeric assistance, nucleophilic attack, isomerization, cycloaddition, S_N2, and hydride ion transfer reactions. (Int J Mass Spectrom 200 (2000) 27–42) © 2000 Elsevier Science B.V.

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1. Introduction

It is a great honour and pleasure to contribute an invited article to this journal on the occasion of publication of its 200th volume. During the time span from the foundation of the journal in 1968 until present tremendous and revolutionary developments in mass spectrometry have taken place. They have had and continue to have an enormous impact on the research and applications which can be performed in a very wide sense by use of mass spectrometry. Essential in the past and for the long-term future of mass spectrometry has been and will be the interplay between fundamental research, instrumental/methodological developments and applied research. This can be concluded from the huge amount of articles published over the last four decades in the field of mass spectrometry.

In the present article an attempt is made to give a personal view on the significance and role played by the various mass spectrometric methods, developed over the years, in ionic reaction mechanistic studies. The article is not intended to be exhaustive on this subject and most of the illustrative examples of research presented will be from the author's laboratory.

From the outset it should be noted that the method of stable isotopic labeling is indispensable in reaction mechanistic studies notwithstanding the power of the developed mass spectrometric/physical methods. Application of these methods together with theoretical calculations in concert has proven to be most advantageous and successful in mechanistic studies of unimolecular and bimolecular reactions of gas-phase ions. That is, in many cases it is possible nowadays to

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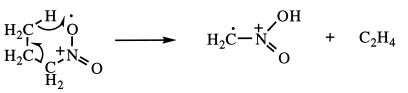
determine the energetics and kinetics of the reacting systems fairly quantitatively together with the structures associated with the initial, transition and final states, thus providing a reasonably comprehensive picture of the reaction mechanisms involved.

2. Electron ionization

The method of electron ionization, formerly termed electron impact, has been most widely used for many years in chemical research and analysis by use of mass spectrometry [1,2]. Many classes of organic compounds have been studied in the sixties with regard to their electron ionization induced fragmentations [3]. The latter were discussed in terms of the mechanistic language of the organic chemist at that time. However, the term "rationalization" was preferred over the term "mechanism" to express that the evidence was by no means rigorous notwithstanding the increased application of stable isotopic labeling [3]. Major problems were that the structures of the generated fragment ions were actually not known and that deuterium labeling revealed for a substantial number of compounds the occurrence of hydrogen scrambling prior to or during fragmentation of the corresponding molecular ions. Nevertheless, combined application of high resolution mass spectrometry [1], stable isotopic labeling [3], and the acceleration voltage scan technique to sensitively detect metastable ion transitions [4] enabled to reveal for many cases the mechanistic pathways in going from the molecular ions to their fragment ions. The following example may illustrate this.

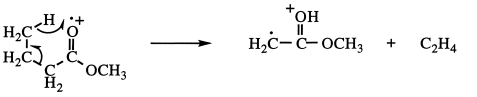
The molecular ion of 1-nitropropane has been shown to eliminate ethylene via the well-known McLafferty rearrangement [5] to give the aci form of nitromethane [6], which is comparable to the enol form of α-hydrogen containing aldehydes and ketones, as visualized in Scheme 1.



1, m/z 89 **2**, m/z 61

Scheme 1.

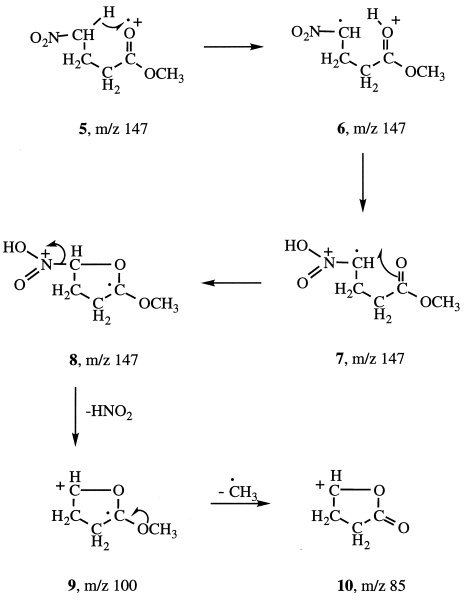
Such rearrangement for the molecular ion of methyl *n*-butyrate leads to formation of the very abundant enol ion of methyl acetate [3], as shown in Scheme 2.



3, m/z 102 **4**, m/z 74

Scheme 2.

However, in the electron ionization spectrum of the methyl ester of 3-nitrobutyric acid, where the nitro group and carbomethoxy group are present together in one molecule, the peaks due to the ions **2** and **4** are vanishingly small or even absent [7]. Very interesting is that the molecular ion of this molecule eliminates nitrous acid, which is exceptional for primary nitro compounds showing NO_2 loss. This loss of nitrous acid is hardly or not at all observed for methyl esters of nitrocarboxylic acids, where the nitro group and carbomethoxy group are separated by either less or more than three methylene groups. Moreover, deuterium labeling has shown that the nitrous acid, eliminated from the molecular ion of the methyl ester of 3-nitrobutyric acid, contains the hydrogen atom of the 3-position [7]. Such elimination of nitrous acid cannot be due to a direct ionization of the methyl ester of 3-nitrobutyric acid in its acinitro form because it should have been observed then also for the methyl esters of nitrocarboxylic acids with less or more than three methylene groups. Yet, the specificity of the reaction under discussion and its occurrence, provided that three methylene groups separate the nitro and carbomethoxy groups, suggest as initial reaction step a 1,5-hydrogen shift of the hydrogen atom from the 3-position to the carbonyl group of the ester function like in a McLafferty rearrangement and shown in Scheme 3 by the sequence **5** → **6**. In ion **6**, where the nitro group stabilizes the adjacent carbon radical position and the ester function is protonated, an acid–base reaction can now take place between these groups to give the acinitro form of the methyl ester of 3-nitrobutyric acid, see sequence **6** → **7** in Scheme 3.



Scheme 3.

Following ring closure of ion **7**, a successive elimination of nitrous acid and the original ester methyl group, shown by deuterium labeling, can occur as visualized by the sequence **7** → **8** → **9** → **10** in Scheme 3 [7].

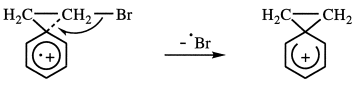
The following mechanistically important conclusions can be drawn from the described research results. (1) The McLafferty rearrangement proceeds in a stepwise fashion. This was shown before in the ethylene loss from the molecular ion of butyric acid [8,9] and strongly supported by the loss of $OH^{\cdot}$ from the molecular ion of 1-nitropropane, containing exclusively one of the terminal methyl hydrogens [6], and the specific hydrogen atom exchange between position 1 and the ortho-positions in the molecular ion of 3-phenyl-1-bromopropane prior to ethylene loss [10]. (2) Following the initial step of the McLafferty rearrangement an intramolecular acid–base reaction takes place, effecting the tautomerization of the nitro group to its aci form. Such tautomerization is similar to the enolization of α-hydrogen containing aldehydes and ketones in the condensed phase by bimolecular acid-base reactions, thus avoiding the barrier for a direct 1,3-hydrogen shift which is expected to be high, based on the rules for orbital symmetry conservation [11]. It should be noted that in the condensed phase the species with acinitro and enol structures are usually transient intermediates playing among others a role in the hydrogen/deuterium exchange of the α-hydrogens with deuterated reagents [12].

3. Collisional activation

As noted in Sec. 2, for mechanistic studies it is essential to know the structures of the fragment ions, generated via unimolecular dissociations, and of the product ions, generated via ion/molecule reactions as, for example, in chemical ionization and Fourier transform ion cyclotron resonance mass spectrometry. At the end of the 1960s inspiring results of high kinetic energy collision-induced dissociation of aromatic ions [13] and isomeric $C_2H_5O^+$ ions [14] were reported. They showed that such dissociations could be used very well to characterize ion structures in terms of the connectivity of their atoms. Especially the development of reverse geometry double focusing mass spectrometry in the early beginning of the seventies [15], in which the magnetic sector preceded the electric sector, gave an enormous impulse to develop and apply the method of collisional activation [16,17] in the determination and characterization of stable, long-lived ion structures.

A huge number of publications on this topic appeared which have been summarized in several chapters of a book [18] and an extensive review [19]. Nowadays collisional activation, also termed collision-induced dissociation, is a standard method in mechanistic studies to determine and characterize ion structures. A notable example of one of the earlier collisional activation studies has been the structure determination of the $(M–Br)^+$ ion from 2-phenyl-1-bromoethane [20]. This abundant ion was proposed earlier [21] to be formed by phenyl participation in the $Br^{\cdot}$ loss from the molecular ion **11** to give the phenonium ion **12** according to Scheme 4.

The phenonium ion **12** and its open form, the 2-phenylethyl cation, as reaction intermediates have for many years given rise to a very lively debate among organic chemists working in the condensed

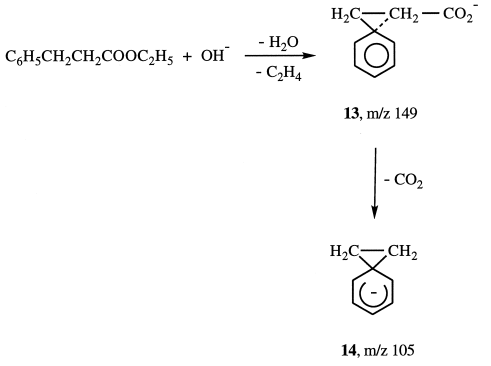


11, m/z 184, 186 **12**, m/z 105

Scheme 4.

phase [22]. By recording the collisional activation spectra of the $(M–Br)^+$ ions from 2-phenyl-1-bromoethane, dideuterated in either the 1- or 2-position, at an electron energy of ~11 eV, it was shown that the spectra were identical and that the $(M–Br)^+$ ions lost CH_2 and CD_2 in equal abundance [20]. These observations are consistent with the structure of ion **12** in Scheme 4, but could also be in line with the open structure of the 2-phenylethyl cation in which, via the phenonium ion **12**, the phenyl ring could be equilibrated over the positions 1 and 2 [22]. However, the calculated STO-3G energies for the different possible forms of the open 2-phenylethyl cation structure were known to be 1.5–2 eV higher than that for the phenonium ion **12** [23], thus providing strong support, if not evidence, for the latter structure in the collisional activation study [20].

It is interesting to note that many years later the negative counterpart of the phenonium ion **12** has been generated in a chemical ionization source by reaction of OH^- with the ethyl ester of 3-phenylpropanoic acid [24]. Following the OH^- induced elimination of ethylene, phenyl participation in the loss of carbon dioxide leads to the negative ion under discussion, see sequence **13** → **14** in Scheme 5.



13, m/z 149

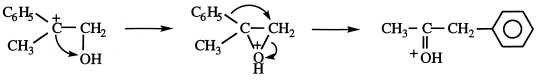
14, m/z 105

Scheme 5.

Collisional activation together with use of reference ions and a series of other experiments has provided strong support for the structure of ion **14** [24].

Another early collisional activation study concerns the structure of the ion generated from the molecular ion of 2-methyl-2-phenylpropane-1,3-diol by loss of a hydroxymethyl radical [25]. The formation of this ion has been suggested to lead eventually to the structure of oxygen protonated phenylacetone on the basis of deuterium labeling experiments and its metastable decompositions, as visualized in Scheme 6 [26].

The nucleophilic attack of the OH group on the benzylic carbenium ion centre in the initially generated ion **15** and the subsequent ring opening and 1,2-phenyl shift to the incipient carbenium ion centre of ion **16** to give ion **17** are well-known reaction steps in both gas phase ion chemistry [26] and the condensed phase [22]. However, it still had to be proven that the nondecomposing ion **17** had the oxygen protonated phenylacetone structure. This was indeed confirmed by the collisional activation spectrum of **17** being identical wit that of the $(M–CH_3)^+$ ion from 1-phenyl-2-methylpropan-2-ol as reference ion [25].



15, m/z 135 **16**, m/z 135 **17**, m/z 135

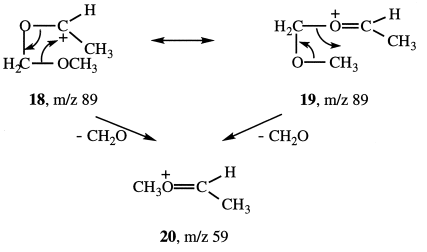
Scheme 6.

4. Metastable peak shapes

The underlying theory of metastable ions has developed tremendously since an explanation was given for the occurrence of small diffuse peaks, renamed into metastable peaks, at non-integral masses in the mass spectra of simple hydrocarbons in 1946 [27]. These metastable peaks can have a large variety of shapes which are related to the amount of kinetic or translational energy released during dissociation of metastable ions [28–30]. This translational energy release can provide much information about the tran-

sition state and dynamics of the metastable ion decomposition [31], in particular because of the accurate translational energy release distribution which can be obtained from the metastable peak shape [32]. It will be obvious that metastable ion dissociation and the associated kinetic energy release are essential for ionic reaction mechanistic studies. The following two examples may illustrate this.

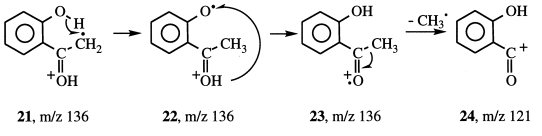
The $(M–methyl)^+$ ion from methoxymethyl isopropyl ether eliminates formaldehyde. On the basis of specific ^{18}O and deuterium labeling two reaction pathways have been uncovered for this elimination as summarized in Scheme 7 [33].



Scheme 7.

The sequence **18** → **20** corresponds with a methoxy group migration, induced by a nucleophilic attack of this group on the carbenium ion centre in ion **18**. The sequence **19** → **20** is a methyl migration reaction, which later has been suggested to proceed by means of a methyl cation bonded complex of formaldehyde and acetaldehyde [34] rather than via the four-centre mechanism depicted in ion **19**. The interesting issue of Scheme 7 is the existence of two competitive reaction channels which from the same reactant ion lead to the same product ion via different transition states. The channel **18** → **20** is expected to require a higher activation energy than channel **19** → **20** because in the former reaction one of the two C–O bonds cleaved has a considerable double bond character. This is indeed confirmed by the larger kinetic energy release observed for channel **18** → **20** than for **19** → **20** [33].

Another application of the use of kinetic energy release in combination with deuterium labeling concerns the elimination of a methyl radical from the $(M–C_2H_4)^{\cdot+}$ ion of *o*-hydroxybutyrophenone [35]. The elimination of ethylene proceeds via the well-known McLafferty rearrangement [5] to give the enolic radical cation of *o*-hydroxyacetophenone. Usually enol radical cations are more stable species in the gas phase than their corresponding tautomeric keto radical cations [36], from which they are separated by a relatively high barrier as the direct 1,3-hydrogen shift for tautomerization is a symmetry forbidden process within the Woodward-Hoffman rules [11]. Nevertheless, the $(M–C_2H_4)^{\cdot+}$ ion of *o*-hydroxybutyrophenone eliminates metastably a methyl radical containing for about 90% the hydrogen atoms from the original hydroxy group and methylene group adjacent to the carbonyl group, the remaining 10% originating from the terminal methyl group [35]. Most noteworthy is that this methyl elimination occurs with a relatively small kinetic energy release, being similar to that for the methyl loss from the molecular ion of *o*-hydroxyacetophenone and in sharp contrast with the large kinetic energy release for methyl loss from the $(M–C_2H_4)^{\cdot+}$ ion of *p*-hydroxybutyrophenone [35]. All the observations taken together have led to the mechanistic scheme for the methyl elimination from the $(M–C_2H_4)^{\cdot+}$ ion of *o*-hydroxybutyrophenone as given in Scheme 8.



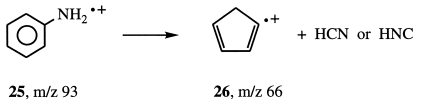
Scheme 8.

As may be noted from Scheme 8, the enolic radical cation **21** rearranges to the tautomeric keto radical cation **23** by way of two successive 1,5-hydrogen shifts prior to methyl elimination. These 1,5-hydrogen shifts circumvent the high barrier for a direct 1,3-hydrogen shift referred to above, while the tautomerization in this case can be regarded as being intramolecularly catalyzed by the *o*-hydroxy group [35].

5. Analysis of neutrals from ionic unimolecular dissociations

Usually there is no doubt about the structure of the neutral fragment which is generated in a metastable ion decomposition and which frequently is a small molecule. However, there are exceptions to this rule as will be exemplified in the following. A method developed in the beginning of the 1980s to determine the structure of the eliminated neutral fragment is based upon the fact that fast moving neutral species can be ionised by collision with suitable target gases [37]. In practice, the fast moving fragment ions generated in mass selected metastable ion dissociations are deflected by an electrode, whereas the fast moving eliminated neutrals are collided with a target gas in a collision cell leading to their ionization and dissociation. The ions generated in this way are subsequently recorded to give the mass spectrum of the neutral fragment which can be used for the purpose of characterization and identification.

This approach has been applied to determine the structure of the neutral with 27 Da which is eliminated from the molecular ion of aniline and which could be either HCN or HNC, Scheme 9.

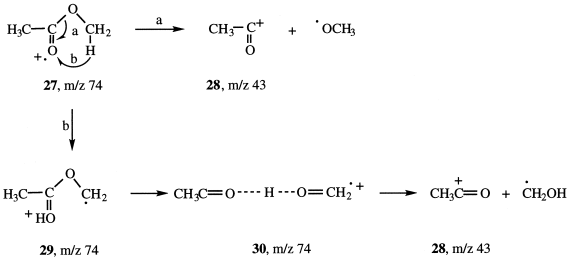


25, m/z 93 **26**, m/z 66

Scheme 9.

From the spectrum, showing the large peak at *m/z* 12 due to $C^{\cdot+}$ and a smaller peak at *m/z* 15 due to $NH^{\cdot+}$, it could be easily concluded that the neutral species was HNC [38]. In a similar way it has been shown that the molecular ion of pyridine eliminates HCN, its spectrum showing the largest peak at *m/z* 13 due to HC^+ and a considerable peak at *m/z* 12 due to $C^{\cdot+}$ [38].

Another very interesting example is the loss of the neutral with 31 Da from metastably decomposing methyl acetate molecular ions. This species is expected to be the methoxy radical, $CH_3O^{\cdot}$, which is true but not exclusive, because the neutral is also lost as



27, m/z 74 **28**, m/z 43

29, m/z 74 **30**, m/z 74 **28**, m/z 43

Scheme 10.

the hydroxymethyl radical, $^{\cdot}CH_2OH$ [37,39], in a ratio of ~4:1, respectively [40]. The corresponding scheme, supported by high-level ab initio calculations [41], is summarized in Scheme 10.

The key intermediate in the $^{\cdot}CH_2OH$ loss channel is the hydrogen bridged radical cation **30** in Scheme 10.

It should be noted that hydrogen bridged radical cations nowadays have become well-accepted intermediates [42] receiving much computational interest [43].

6. Field ionization kinetics

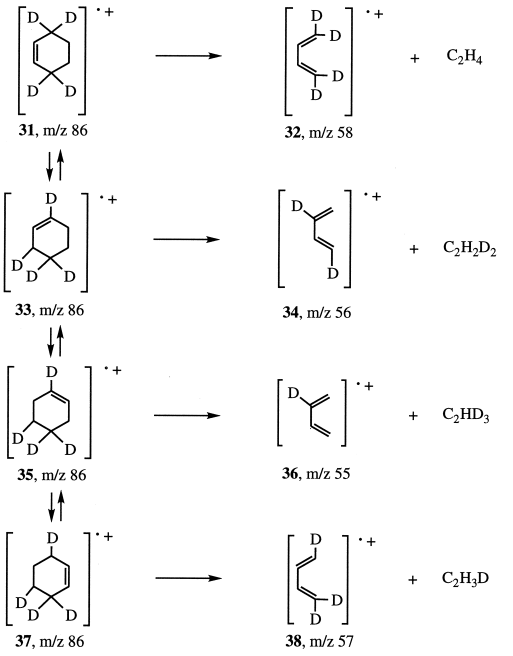
The previous sections have described methods which in combination with stable isotopic labeling and theoretical calculations allow to obtain detailed structural information on the reactant ions and their ionic and neutral dissociation products in addition to the associated transition states.

In this way a relatively good picture can be obtained of the reaction mechanism of a unimolecular ionic dissociation. However, the methods described apply to ions which on the time scale of the mass spectrometer are either long lived (>10 μs) or metastable (between 1 and 10 μs). These lifetimes and the residence time of the ions for about 1 μs in an electron ionization ion source are very long compared to the vibrational periods of chemical bonds of 0.01–0.1 ps and the ionization event itself occurring within 0.1 fs. Within the residence time of about 1 μs in the ion source, extensive hydrogen and skeletal rearrangements can take place in the ions which consequently are integrated to give eventually the electron ioniza-

tion mass spectrum. It will be clear that such an integrated view may readily obscure mechanistic details of the ionic dissociations. In such cases a time-resolved view of the ionic dissociations can be very helpful and enlightening, which at least for decomposing molecular ions can be obtained by use of the method of field ionization kinetics. This method has been developed in the beginning of the 1970s [44,45] following the original work on fast metastable ions in field ionization mass spectrometry [46]. The principles of field ionized kinetics and its application to mechanistic studies have been described in a number of reviews [47–49]. In brief, the method allows to study in a continuous and time-resolved way the unimolecular dissociations of molecular ions with lifetimes from picosecond to nanosecond following ionization, while information on the dissociation behaviour at longer lifetimes in the order of microsecond can be obtained from the metastable ion fragmentations in the field free regions of the sector instruments used.

The strength of the field ionization kinetics method in mechanistic ion dissociation studies is shown to full advantage when it is used in combination with stable isotopic labeling. A few examples, presented below, may illustrate this.

The first example concerns the elimination of ethylene from the molecular ion of cyclohexene which can be considered to proceed by means of a retro-Diels-Alder reaction by analogy with the well-known Diels-Alder reaction in organic chemistry [22]. If specifically deuterated cyclohexenes are subjected to electron ionization, then a practically statistical distribution of hydrogen and deuterium atoms over the carbon skeleton prior to or during the elimination of ethylene is observed [45]. This is a well-known phenomenon for both linear and cyclic alkenes where the double bond shifts readily upon electron ionization. At shorter molecular ion lifetimes, as can be studied by field ionization kinetics, hydrogen rearrangements leading to these double bond shifts are largely suppressed [50]. Thus, the molecular ion of cyclohexene-3,3,6,6-d_4 with a lifetime of 10 ps eliminates for more than 50% C_2H_4 to give the ion *m/z* 58 [45] as expected for the retro-Diels-Alder



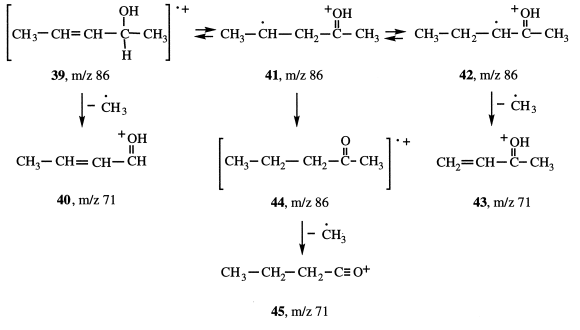
Scheme 11.

reaction in Scheme 11, sequence **31** → **32**. At longer lifetimes a rapid increase of the loss of the deuterated ethylene molecules is observed until at ns a statistical distribution of the H and D atoms has occurred prior to decomposition. The interesting observation, however, is that the maximum rates of the variously labeled ethylene eliminations occur at different times, the order with increasing lifetimes being C_2H_4 < $C_2H_2D_2$ < C_2HD_3 < C_2H_3D [45]. This has been rationalized by invoking 1,3-allylic H/D shifts in the molecular ions prior to the retro-Diels-Alder reaction, given in Scheme 11.

As can be seen from this reaction, the formation of the ions **32** (*m/z* 58), **34** (*m/z* 56), **36** (*m/z* 55), and **38** (*m/z* 57) requires 0, 1, 2, and 3 allylic 1,3-H/D shifts, respectively, which just corresponds to the shift of the maximum rate of the corresponding ethylene eliminations to longer lifetimes.

The second example refers to the loss of methyl from the molecular ion of 3-penten-2-ol. Deuterium labeling has shown that upon 70 eV electron ionization only ~40% of this methyl loss originates from position 1 [51]. This is surprising, because the methyl

group of position 1 is in the α-position with respect to the hydroxy group and allylic to the double bond, therefore being expected to be eliminated predominantly. A combined field ionization kinetics and deuterium labeling study has revealed three pathways for the loss of methyl from the molecular ion of 3-penten-2-ol [52]. At short ion lifetimes, that is less than 100 ps, predominantly the methyl group of position 1 is lost. At medium ion lifetimes, that is between 100 ps and 1 ns, the elimination of the methyl group of position 5 is the major dissociation channel. At longer ion lifetimes, that is more than 1 ns, the loss of the methyl group of position 1 becomes again increasingly important. These observations have been rationalized mechanistically in Scheme 12.



Scheme 12.

Route **39** → **40** is operative at ion lifetimes less than 100 ps and is suggested to lead to oxygen protonated crotonaldehyde, route **39** → **41** → **42** → **43** is dominating at ion lifetimes between 100 ps and 1 ns and is suggested to lead to oxygen protonated methyl vinyl ketone, while route **39** → **41** → **44** → **45** is coming up at longer ion lifetimes and is suggested to produce the butyryl cation [52]. It has been possible to obtain collision activation spectra of the ions **40** and **43**, generated at molecular ion lifetimes less than 100 ps and 1 ns after ionization, respectively [53]. These time-resolved collisional activation spectra have appeared to match well the distinct collisional activation spectra of the independently made and noninterconverting reference ions of protonated crotonaldehyde and methyl vinyl ketone, respectively.

It will be clear that field ionization kinetics is a very valuable tool in ionic reaction mechanistic studies. This is further corroborated by the fact that with use of this method evidence has been obtained that hydrogen and skeletal rearrangements of an unsaturated hydrocarbon radical cation, like 1,3-butadiene, are independently occurring processes [54].

7. Ion cyclotron resonance spectrometry

Ion cyclotron resonance spectrometry, based on the principle of cyclotron motion of ions during acceleration in a magnetic field [55], is a method for studying gas-phase ion/molecule reactions. It developed rapidly since the first instrument was built by Varian Associates in Palo Alto, CA, USA in the mid 1960s and subsequently was marketed as the Syrotron. The principle of ion cyclotron resonance spectrometry and its applications in the field of gas-phase ion/molecule chemistry have been described in a number of reviews [56–59] and in a book, its time of appearance covering the topic in a very broad sense [60]. Most of the experiments have been performed with use of the so-called drift cell ion cyclotron resonance method [60], although elongated rectangular- [61] and circular- or donut-shaped trapped-ion cells [58] have been designed and applied already in the early seventies, which later on have become standardly used in Fourier transform ion cyclotron resonance (see Sec. 8).

In brief, the commonly used drift cell consists of three sections as shown in Fig. 1 and is contained in

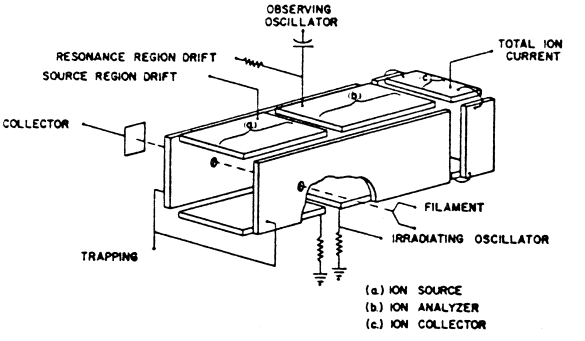


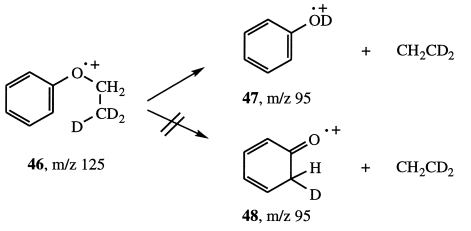
Fig. 1. Schematic diagram of the ion cyclotron resonance drift cell. (a) Ion source; (b) ion analyzer; and (c) ion collector (reprinted from [58]).

a vacuum chamber which is situated between the pole faces of an electromagnet.

Ions are generated in the ion source region and drift by application of small static voltages across the top and bottom plates of the cell in a cycloidal manner from the source region into the analyzer region. Small trapping voltages are applied to the side plates in both the source and analyzer regions to prevent escape of ions from the cell. Ions are detected by power absorption from a marginal oscillator applied to the analyser region and a mass spectrum is obtained by scanning the magnetic field at fixed frequency. The total ion current is measured by an electrometer connected to the collector region trapping plates, on which the trapping potential is removed to allow ions to reach the plates. Operating pressures are in the order of 10^{-4} Pa and ion path lengths of 10–100 m can be achieved; these make ion/molecule reactions occur [56–60]. The relationships between reactant ions and their corresponding product ions can be established by use of the double-resonance method [62]. It is based on the general observation that the rate constant for an ion/molecule reaction is a function of the translational energy of the reactant ion. Thus, if the translational energy of the reactant ions is increased by a second irradiating oscillator tuned to the resonance frequency of the reactant ions and applied either to the source or analyzer region of the cell, then a substantial change can occur in the amounts of product ions formed. This change can be an increase of product ions, which is usually observed for charge transfer reactions, whereas a decrease of product ions is observed for exothermic ion/molecule reactions [63]. In this way the double-resonance method can provide in a direct way important information on the thermochemistry of ion/molecule reactions.

Ion cyclotron resonance spectrometry has shown to be very suited for studying near thermal ion/molecule reactions and has provided many thermochemical data and much information about ion structures and ion/molecule reaction mechanisms [56–60].

The author entered this field in the beginning of the seventies after an exciting and inspiring lecture tour through the United States, where he had seen the ion cyclotron resonance spectrometer in the laboratory of Professor Maurice M. Bursey at the University of North Carolina in Chapel Hill. Many results have been obtained by the author's research group over almost a decade which have been published in a couple of reviews [64,65]. The first performed experiments concerned the loss of ethylene from the molecular ion of phenyl ethyl ether [66]. This reaction could proceed by means of transfer of one of the methyl hydrogens to either the oxygen atom or the ortho position of the phenyl ring. This question has been addressed by investigating the bimolecular chemistry of the $(M–C_2H_2D_2)^{\cdot+}$ ion from phenyl ethyl ether, deuterated in the methyl group. Transfer to oxygen would lead to the molecular ion of phenol-O-d_1, whereas transfer to one of the ortho-positions of the phenyl ring would result in the formation of the radical cation of the tautomeric cyclohexadienone species, containing a CHD group, see the sequences **46** → **47** and **46** → **48** in Scheme 13, respectively.

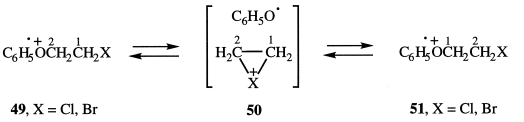


Scheme 13.

The $(M\text{-}C_2H_2D_2)^{\cdot+}$ ion appeared to transfer a deuteron, but not a proton to the base of 3,5-dimethyl pyridine, thus excluding the sequence **46** → **48** in Scheme 13 and proving that the methyl hydrogen is transferred to oxygen to give the molecular ion of phenol [66]. This approach has been applied to elucidate the mechanism(s) of $C_6H_6O^{\cdot+}$ formation from the molecular ions of 2-phenoxyethyl halides. It should be noted that these molecular ions, if generated by electron ionization, eliminate a halomethyl radical following an almost fully equilibrated positional interchange of the phenoxy group and the halogen atom X over the side-chain carbon atoms when X = Cl or Br [67]. This positional interchange is dependent on the molecular ion lifetime as shown by field ionization

kinetic experiments [68], but is not accompanied by any hydrogen atom exchange between the side-chain and the aromatic ring [67,68]. However, the $C_6D_5HO^{\cdot+}$ ions, generated from the molecular ions of ring-d_5 labeled 2-phenoxyethyl chloride and bromide do transfer in an ion/molecule reaction a deuteron in addition to a proton to 4-*t*-butylpyridine [69]. These observations have been taken as evidence that at least part of the $C_6H_6O^{\cdot+}$ ions from 2-phenoxyethyl chloride and bromide have the ionized cyclohexadienone structure (cf. ion **48** in Scheme 13), which is generated by a 1,5 H-shift in the molecular ions to one of the ortho positions of the phenyl ring under expulsion of vinyl chloride and bromide, respectively. In a similar way experimental evidence has been provided to show that both phenol and cyclohexadienone radical cations are generated from the molecular ions of 2-phenoxyethyl fluoride in which no positional interchange of the phenoxy group and the fluorine atom is occurring prior to decomposition [69]. Conformational effects in the molecular ions of the 2-phenoxyethyl halides have been considered to explain the radical cation formation of both phenol and cyclohexadienone [70] being such different with respect to the exclusive ionized phenol formation from the molecular ion of phenyl ethyl ether [66]. At any rate, a subsequent photodissociation study has confirmed that the $C_6H_6O^{\cdot+}$ ion from phenyl ethyl ether has the phenol structure and that the $C_6H_6O^{\cdot+}$ ion from 2-phenoxyethyl chloride is generated in both the phenol and its tautomeric cyclohexadienone structure [71].

The relatively complex behaviour of the ionized 2-phenoxyethyl halides is due to their rearrangements, especially at a low internal energy content, which lead to the formation of ion/molecule complexes prior to decomposition. Such ion/molecule complex-mediated reactions have become well-accepted since inspiring publications on this concept have appeared in the early eighties [72–75]. Thus, the positional interchange of the phenoxy group and the halogen atom in the molecular ions of 2-phenoxyethyl chloride or bromide occurs within this view by means of an ion/molecule complex, consisting of a phenoxy radical and a cyclic ethylene chloronium or bromonium

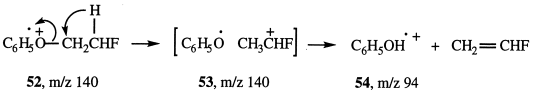


Scheme 14.

ion, respectively; see complex **50** in Scheme 14. Nucleophilic attack of the phenoxy radical in complex **50** on the methylene carbon atoms of the cyclic ethylene halonium ion with concomitant ring opening would then regenerate the 2-phenoxyethyl halide ions **49** and **51**.

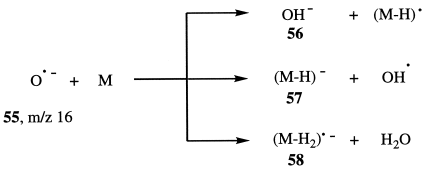
The complex **50** had been suggested before [67] to account for the observed positional interchange, but at that time was not preferred because of aromatic ring substituent effects on this interchange. However, it is unlikely that complex **50** leads to the formation of the $C_6H_6O^{\cdot+}$ ions because the cyclic ethylene chloronium and bromonium ions have been shown to be halogenyl cation donors, but not proton donors [76].

A recent supersonic jet/REMPI spectroscopic study of 2-phenoxyethyl fluoride [77] has indicated that in addition to the above described 1,3 and 1,5 H shifts to oxygen and the ortho position of the phenyl ring, respectively, ion/molecule complexes consisting of a phenoxy radical and a bridged fluoronium ion or a fluoroethyl cation are involved in the ionized phenol formation. The latter, visualized in Scheme 15, can explain indeed some of the earlier observations made [69].



Scheme 15.

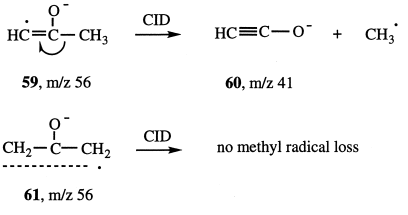
Ion cyclotron resonance spectrometry has also been applied successfully to study negative ion/molecule reactions in the gas phase [64,65]. A few selected examples may illustrate this. A negative ion, which shows interesting chemistry with organic substrates, is the radical anion of the oxygen atom, $O^{\cdot-}$, generated from N_2O by a low energy electron dissociative resonance capture process [78]. This ion can



Scheme 16.

react with a molecule M as a radical to abstract a hydrogen atom and as a base to abstract a proton to give OH^- and $(M–H)^-$, respectively, see Scheme 16. Interestingly, the abstraction of a hydrogen atom and a proton can also occur in a single collision event to give $(M–H_2)^{\bullet -}$ as shown in Scheme 16 as well.

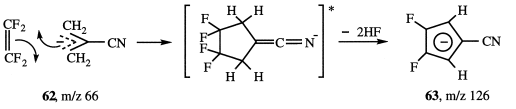
In most cases studied in the seventies the formal abstraction of $H_2^{\bullet +}$ to give the ion **58** had been shown to occur from the same carbon atom [79,80]. However, examples were soon found in which in the formal $H_2^{\bullet +}$ abstraction the hydrogens also turned out to originate from different positions. Notably are the 1,3- and 3,3-$H_2^{\bullet +}$ abstraction from propyne [81] and the 1,1- and 1,3-$H_2^{\bullet +}$ abstraction from acetone [82] as shown by deuterium labeling. The latter abstractions have been supported further by translational excitation of the corresponding product ions, so as to collisionally induce dissociation in the drift cell of the ion cyclotron resonance spectrometer. The product ion resulting from 1,1-$H_2^{\bullet +}$ abstraction dissociates by methyl radical loss, which is not observed for the product ion resulting from 1,3-$H_2^{\bullet +}$ abstraction [82] as summarized in Scheme 17.



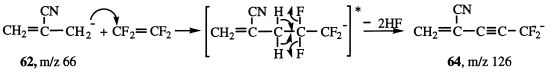
Scheme 17.

The very rich chemistry associated with the reactions of $O^{\bullet -}$ with organic molecules has been described in a number of recent reviews [83,84].

A last example concerns the reactions of the isomeric 2-cyanoallyl- and 1-cyanocyclopropyl anions with tetrafluoroethylene [85]. The former anion reacts with C_2F_4 by expulsion of two HF molecules by either a 2 + 3 (atom) cycloaddition or a simple "end-on" addition as shown in Schemes 18 and 19,



Scheme 18.

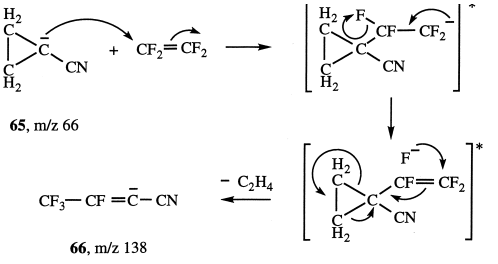


Scheme 19.

respectively.

In sharp contrast, the 1-cyanocyclopropyl anion reacts with tetrafluoroethylene by expulsion of ethylene! The mechanism proposed for this unexpected reaction has been visualized in Scheme 20 [85].

The key intermediate in Scheme 20 is the formation of a F^- solvated ion. Such formation of solvated ions from covalently bonded ion structures is nowadays (on the basis of a large amount of experimental work) a well-accepted concept to explain their dissociation behaviour [86].



Scheme 20.

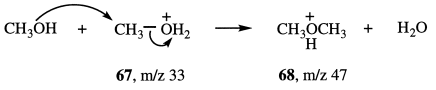
8. Fourier transform ion cyclotron resonance mass spectrometry

Following the successful application of drift cell ion cyclotron resonance spectrometry to gas-phase ion/molecule chemistry, as described in the previous

section, and the successful design and use of a simple trapped ion analyzer cell [87], a very important publication on Fourier transform ion cyclotron resonance (FTICR) by M.B. Comisarow and A.G. Marshall appeared in 1974 [88]. They were able to obtain the Fourier transformed signal for the molecular ion of methane. The author was in the privileged position to have attended the lectures on this FTICR development by Professor Mel Comisarow at the 22th ASMS Conference, held at Philadelphia in 1974, and by Professor Alan Marshall, presented at the Cornell University in Ithaca, New York, during the author's stay in 1974 in the laboratory of Professor Fred W. McLafferty. Inspired by these lectures and because of rapid developments in microelectronics and computer technology, it eventually became possible to design and build a broadband FTICR spectrometer in the author's laboratory, which came into operation on the 2nd of April, 1980 [65,89,90,91].

Many reviews on the theoretical and methodological aspects of FTICR have appeared [92–94] in addition to its application to gas-phase ion/molecule chemistry [65,95–98]. The basic principles of FTICR have been described extensively in these reviews and will therefore not be repeated here. Some selected examples of chemical research performed in the author's group with use of the elegant method of FTICR over the last two decades, will be presented below.

The first concerns the mechanism of the reaction between protonated methanol and methanol. This reaction leads to the formation of protonated dimethyl ether via expulsion of a molecule of water. The mechanism is expected to be an S_N2 reaction, which is well known in organic chemistry and which in this particular case would mean that the eliminated molecule of water contains the oxygen atom of the protonated methanol as visualized in Scheme 21:

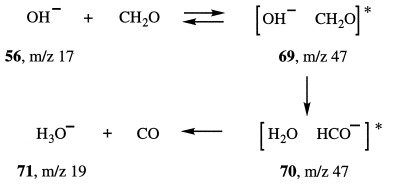


Scheme 21.

It will be obvious that for experimental evidence of Scheme 21 the neutral methanol should be labelled differently from the protonated methanol with regard to the oxygen atom. This has been achieved by use of natural methanol containing 99.8% $CH_3{}^{16}OH$ and 0.2% $CH_3{}^{18}OH$. Following electron ionization of natural methanol and the generation of protonated methanol species by ion/molecule reactions, ejection of all ions from the FTICR cell with the exception of $CH_3{}^{18}OH_2^+$ and continuous ejection of through proton transfer regenerated $CH_3{}^{16}OH_2^+$ and $^{13}CH_3{}^{16}OH_2^+$ provide the required reacting system, that is 99.8% $CH_3{}^{16}OH$ reacting with pure $CH_3{}^{18}OH_2^+$ [99]. The experimental result obtained is that protonated ^{16}O-labeled and ^{18}O-labeled dimethyl ether are formed in a 3:1 ratio, proving that the major part of the reactions proceed via the backside S_N2 displacement Scheme 21 [99]. Such displacement is suggested also for the minor part of the reactions following a proton transfer from $CH_3{}^{18}OH_2^+$ to $CH_3{}^{16}OH$ in the corresponding collision complex [100]. Although this S_N2 reaction has been questioned in view of the fact that the proton-bound structure of the dimer of methanol is most stable [101], it should be recognized that in the experiment described above only that part of the phase space is sampled which leads to the products of protonated dimethyl ether and a molecule of water [99]. Afterwards the S_N2 mechanism has been supported fully by theoretical calculations [102–104] and confirmed experimentally by an extensive flowing afterglow-triple quadrupole study [105].

Another example is the very interesting observation made in the beginning of the eighties that the hydroxide ion reacts with formaldehyde to give a product ion with *m/z* 19 [106]. With the FTICR instrument used, the corresponding signal was very close to that of the radio-station Scheveningen in The Netherlands, but was proven to be due to H_3O^- by deuterium and ^{18}O-labeling experiments [106]. The latter showed that the H_3O^- ion exclusively contained the oxygen atom of the hydroxide ion. Moreover, the H_2DO^- ion generated by reaction of OD^- with CH_2O transfers a hydride, but not a deuteride, to formaldehyde being consistent with the behaviour of the HD_2O^- ion generated by reaction of OH^- with

CD_2O, which transfers a deuteride, but not a hydride, to formaldehyde. All these observations lead to the picture of the H_3O^- ion as being a hydride ion solvated by water, formed as shown in Scheme 22:

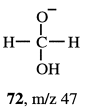


Scheme 22.

Upon formation of the complex **69**, the solvation energy allows a proton transfer from the formaldehyde molecule to OH^- to give the complex **70**. However, complex **70** so generated cannot separate because water is more acidic than formaldehyde. Instead, an exothermic channel is available for complex **70** in which hydride transfer from the formyl anion to the water molecule occurs, leading to H_3O^- and carbon monoxide (Scheme 22) [106]. The last step is fully in line with the hydride affinity of water, being twice as large as that of carbon monoxide [107].

It should be noted that H_3O^- has been prepared independently in an ion-beam experiment [108] and that both photoelectron spectroscopy [109] and theoretical calculations [110–112] have confirmed that it is a hydride solvated water molecule.

Later on it has been possible to prepare water solvated hydroxide ions in the FTICR cell which react with formaldehyde to give the long-lived [HO^- + CH_2O] adduct ions [113]. CID experiments on the isotopically labeled [$D^{18}O^-$ + CD_2O] adduct ions showed the formation of DO^- and $D^{18}O^-$ ions in the ratio of 40:60, respectively. These results together with the reactivity of the [HO^- + CH_2O] adduct ions in ion/molecule reactions have proven the existence of the tetrahedral intermediate **72** (Scheme 23), formed by nucleophilic attack of OH^- on the carbonyl carbon of formaldehyde which is well-known to occur in the condensed phase [113].



72, m/z 47

Scheme 23.

The described results also show the enormous influence, which a single solvent molecule can have on the course of a gas-phase ion/molecule reaction.

Soon after the successful generation of H_3O^- it has been possible to prepare also NH_4^- in the gas phase [114]. In that case free HCO^- has been produced by reaction of NH_2^- with formaldehyde, which in a subsequent ion/molecule reaction with ammonia yields the NH_4^- ion. Like the H_3O^- ion, the NH_4^- ion is best described as a hydride ion solvated by an ammonia molecule [114]. Such description has been confirmed later on by photoelectron spectroscopy [115] and theoretical calculations [110,111,116,117].

A very large variety of ion/molecule reactions has been studied afterwards, which has shown that the associated potential energy surfaces can be very complicated. For example, nucleophiles react with methyl pentafluorophenyl ether by aromatic ring substitution releasing a fluoride anion which subsequently reacts further with the newly generated aromatic molecule by S_N2 or E2 reactions [118,119]. For more of such examples the reader is referred to a number of reviews [65,95–98,120].

Other recent FTICR studies, which should be mentioned here, are the ion/molecule chemistry of distonic ions [121–123] and solvated distonic ions [124,125] and the metal ion catalysed coupling reactions between methane and ammonia [126] and other small nucleophiles [127] as well as the metal ion catalysed oxidation of methane [128], ethylene [129,130] and benzene [131].

9. Final remarks

In addition to the methods used by the author's group as described above, various other methods have been applied successfully over the last three decades in gas-phase ionic reaction mechanistic studies. These are the electron bombardment flow reactor method enabling analysis of the neutral products from unimolecular ion dissociations [132,133], photodissociation

[134,135], radiolysis [136,137], and flowing afterglow [138,139]. All these methods have provided a wealth of reaction mechanistic details of gas-phase unimecular and bimolecular ionic reactions in addition to associated kinetic and thermodynamic data.

At the beginning of the author's career gas-phase ion chemistry was regarded by many of his colleague chemists as being high energy chemistry with no relationship to organic chemistry in the condensed phase. It is gratifying for him to note that gas-phase ion chemistry studies performed by many mass spectrometry groups including the author's group over the last three decades have shown that mechanistically ionic reactions in the gas phase are closely related and in many cases even similar to those in the condensed phase. The challenge for the forthcoming years will be not only to advance gas-phase ion chemistry in balance with newer methods of ion generation, but also to exploit the obtained knowledge in mass spectrometric studies of larger systems, such as supramolecular assemblies and synthetic or natural (bio)polymers.

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