FOUR DECADES OF JOY IN MASS SPECTROMETRY

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*Tremendous developments in mass spectrometry have taken place in the last 40 years. This holds for both the science and the instrumental revolutions in this field. In chemistry the research was heavily focused on organic molecules that upon electron ionization fragmented via complex mechanistic pathways as shown by isotopic labeling experiments. These studies, including ion structure determinations, were performed with use of double focusing mass spectrometers of both conventional and reversed geometry, and equipped with various types of metastable ion scanning and collision-induced dissociation techniques developed by physical and analytical chemists. Time-resolved mass spectrometry by use of the field ionization kinetics method, developed by physical chemists, was another powerful way to unravel details of unimolecular gas phase ion dissociations. Then the development of new ionization methods, such as desorption chemical ionization, field desorption, and fast atom bombardment permitted not only to analyze unvolatile, thermally labile and higher molecular weight compounds, but also to study their chemical behavior in the gas phase, initially with use of double focusing instruments and later on with multisector and hybrid mass spectrometers. These ionization methods also enabled to study organometallic compounds and increasingly the field of medium-sized to large biomolecules, the latter being exploded in the last decade by the development of electrospray- and matrix-assisted laser desorption ionization/time-of-flight mass spectrometry. Another area of research concerned the bimolecular chemistry of organic ions with organic molecules in the gas phase. Initially this was performed with use of among others drift-cell ion cyclotron resonance spectroscopy, that later on was replaced by the developed method of ion trapping and Fourier transform ion cyclotron resonance. Combination of the latter with the afore-mentioned ionization methods has shifted also in this case the research on organic molecules to organometallic/inorganic systems, and predominantly to biomolecules in the last decade. This invited review will describe the research efforts made by the author's group over the last 40 years together with some personal experiences during his career.
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I. INTRODUCTION

This review presents an invited historical account of my scientific and personal experiences during my career of 40 years in mass spectrometry. The foundation of my career was laid at the University of Amsterdam, The Netherlands. Initially I had planned to obtain my master's degree with Professor G.J. Hoijtink in Physical Chemistry who had moved from the Vrije Universiteit in Amsterdam to the University of Amsterdam in 1960 and who gave very exciting lectures about chemical bonding and the underlying theory. During these lectures Professor Hoijtink emphasized that theory was important, but that one never should forget experiments to check the theory. A difficulty, however, was that compounds required for the experiments were frequently not available. I then decided to obtain my master's degree with Professor Th.J. de Boer in Physical Organic Chemistry to overcome this difficulty by becoming able to synthesize compounds when required for the experiments. My specific request to Professor de Boer was a project that would be a combination of theory and experiment. This resulted in a mass spectrometric project aimed at providing evidence for the occurrence of the McLafferty rearrangement for 1-nitropropane upon electron ionization which at that time, that is 1963, was already known for aliphatic aldehydes, ketones, acids, and esters (McLafferty, 1956, 1959; Gilpin & McLafferty, 1957).

II. THE YEARS OF MASTER'S DEGREE AND Ph.D. DEGREE RESEARCH

In the master's degree research on 1-nitropropane (see Section I) it was found from site-specific deuterium labeling of this

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compound and using a single focusing A.E.I. MS2H magnetic sector mass spectrometer (Associated Electrical Industries Ltd, Manchester, UK) that it indeed eliminated upon 70 eV electron ionization ethene *via* the McLafferty rearrangement, that is, through rearrangement of one of the terminal methyl or γ-hydrogens to one of the oxygen atoms of the nitro group and cleavage of the C(α)–C(β) bond. It was also observed that this molecule eliminated a hydroxyl radical containing exclusively a γ-hydrogen atom. These observations together led to a reaction scheme in which the ethene elimination occurred after the γ-hydrogen rearrangement (Nibbering, de Boer, & Hofman, 1965) (see Scheme 1 below) that in a discussion at the fourth triennial International Mass Spectrometry Conference in 1967 at Berlin, Germany, was put forward as another example of a stepwise McLafferty rearrangement (Nibbering, 2004). It should be noted that many years later 1-nitropropane has been reinvestigated with use of a much more sensitive instrument, especially with regard to the $(M-OH^\gamma)^+$ ion that initially is a biradical in which as first step a 1,2-H shift from the α-carbon to nitrogen occurs prior to further rearrangement and fragmentation (Hindawi et al., 1986).

Following my master's degree, I then started my Ph.D. study under the supervision of Professor Th. J. de Boer in April 1964 on the mass spectral behavior of aralkyl compounds with a functional group in the side-chain, such as OH, halogen, NO_2. To this end extensive site-specific deuterium labeling was applied and use was made of both the A.E.I. MS2H instrument mentioned before and a new A.E.I. MS9 double focusing mass spectrometer with Nier–Johnson geometry, which after its installation was quickly upgraded to an A.E.I. MS902 instrument (Associated

Electrical Industries Ltd, Manchester, UK). Moreover, this instrument was then also equipped soon with an in-house made high voltage scan unit and later on in 1975 with an in-house made β-slit to determine the metastable precursor ions of a particular mass selected ion and to measure metastable peak shapes, respectively. For the former the console of the A.E.I. MS902 mass spectrometer was equipped with a knob named "Jennings scan" after Professor K.R. Jennings who had developed the wide-range high voltage scan by decoupling the accelerating voltage and the electric sector potential (Jennings, 1965, 1967), their ratio being variable by ±1.3% only on the standard A.E.I. MS9 instrument (Barber & Elliott, 1964). The high voltage was scanned from 4 to 8 kV and associated with it a mechanical disk with a sharp cam activated after each turn, that is, 10% increase of the high voltage, a switch to give a mark on the UV recorder paper. In this way the masses of the metastable precursor ions could be calculated easy which was essential and very helpful to unravel the unimolecular gas-phase ion chemistry of the compounds studied. Some highlights of the Ph.D. research were the observed-specific H/D exchange between the hydrogen atoms of the methylene group of position 1 and the *ortho*-hydrogen atoms in the molecular ions of 1-bromo-3-phenylpropane prior to the loss of ethene (Nibbering & de Boer, 1968a), the specific H/D exchange between the hydroxyl hydrogen, the hydrogen atoms of the methylene group of position 3, and the *ortho* hydrogens in the molecular ions of 3-phenyl-1-propanol prior to the loss of a molecule of water (Nibbering & de Boer, 1968b), the H/D exchange of the hydroxyl hydrogen and the aromatic ring hydrogens in the metastably decomposing molecular ions of 2-phenylethanol-1 prior to the loss of vinyl alcohol (Nibbering & de Boer, 1968c) and the successive loss of nitric oxide, ethylene, and carbon monoxide from the molecular ions of 3-phenyl-1-nitropropane (Nibbering & de Boer, 1970). The first-mentioned observation was considered to be evidence for the stepwise character of the McLafferty rearrangement as discussed at the triennial International Mass Spectrometry Conference in Berlin, Germany in 1967 (Nibbering, 2004), whereas the structure of the resulting $(M-C_2H_4)^{\bullet+}$ ion was shown many years later to be that of benzyl bromide (Yamaoka, Fokkens, & Nibbering, 1999). The third-mentioned observation on the H/D exchange was proposed to involve a σ-bonded protonated aromatic ring intermediate in which the proton walked along the ring *via* 1,2-shifts as was suggested earlier for the molecular ion of cycloheptatriene (Meyer & Harrison, 1964) and later on has been studied as a very broad and detailed research topic (Kuck, 1990, 2005b). The last-mentioned observation was initially rationalized as being due to an attack of one of the oxygen atoms of the nitro group upon one of the *ortho* positions of the phenyl ring, but was later shown to be the result of an initial benzylic hydrogen atom abstraction by one of the oxygen atoms of the nitro group, followed by hydroxyl migration to the benzylic carbon center and subsequent elimination of nitric oxide, ethene, and carbon monoxide that contained exclusively the benzylic carbon atom according to the ^{13}C labeling applied (Molenaar-Langeveld & Nibbering, 1974a). See Scheme 2.

For the course of my career it should be mentioned that in the midst of my Ph.D. study Dr. H.J. Hofman, at that time the leader of the mass spectrometry group of the Laboratory of Organic Chemistry, left the University of Amsterdam and joined the
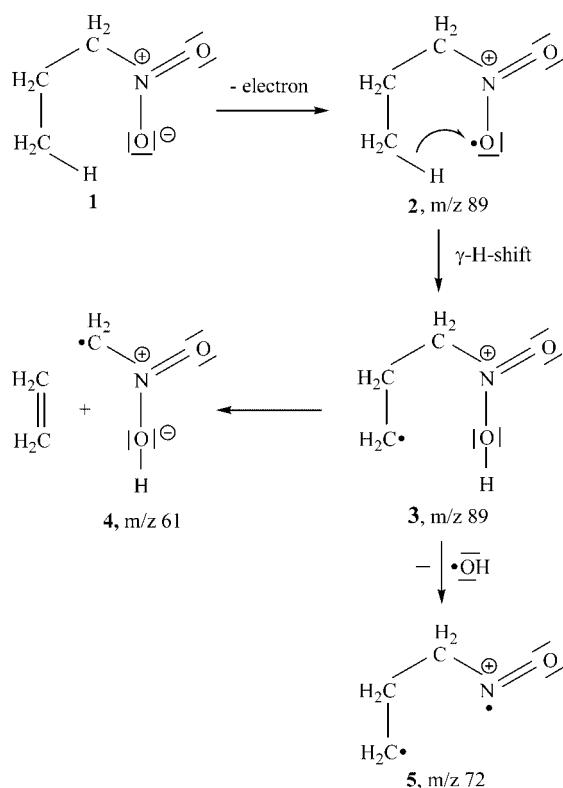
SCHEME 1.
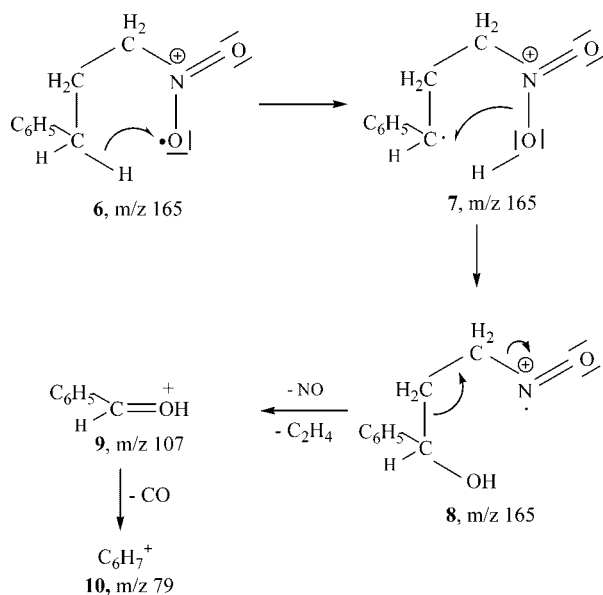
SCHEME 2.

research laboratory of Unilever in Vlaardingen, The Netherlands. Although I had planned to move to industry after my Ph.D. study (I had had already interviews with officers of the Royal Shell Laboratory in Amsterdam and the Philips Physics Laboratory in Eindhoven, The Netherlands), the permanent staff members Dr. I.P. Dirkx, in charge of the UV group, and Dr. P.J. van der Haak, leader of the whole spectroscopy group, convinced me to apply for the vacant position. Following an interview with Professors Th.J. de Boer and H.O. Huisman (Synthetic Organic Chemistry), who alternately were director and adjunct director of the Laboratory of Organic Chemistry, I occupied the vacant position and became in charge of the mass spectrometry group. This enabled me to build up a research group in mass spectrometry, where in a natural way three aspects received attention, that are fundamental research, instrumental and methodological developments and applications. The first cooperative study with another laboratory was on aluminum isopropoxide that was brought in by the Laboratory of Inorganic Chemistry of the University of Amsterdam. The question was to determine the kind of polymers of aluminum isopropoxide in the vapor phase that as a solid was introduced with a direct insertion probe into the mass spectrometer. Largely tetramer species were observed with possible minor quantities of dimer and trimer species also present. The molecular ion of the tetramer eliminated an isopropoxy radical or successively a methyl radical and acetaldehyde, followed by the loss of a di-isopropyl ether, while further fragmentation involved the loss of propene, di-isopropyl ether, and/or aluminum oxide isopropoxide as indicated by the presence of metastable peaks and the applied deuterium labeling (Fieggen, Gerding, & Nibbering, 1968).

III. THE EARLY YEARS AFTER THE Ph.D. STUDY

After having received my Ph.D. degree on October 2, 1968 and in that year subsequently being awarded the Shell Research

Chemistry Prize, the year of 1969 was very exciting. The mentioned prize enabled me to cross for the first time the Atlantic Ocean, and to make a lecture tour and visit organic chemists and mass spectrometrists throughout the United States and one in Canada. Successively, I visited the scientists F.H. Field (Chemical Ionization) and G. Wanless (Field Ionization) at the Esso Research and Engineering Company, Linden, New Jersey (there was also the home-built chemical ionization mass spectrometer with which F.H. Field and B. Munson performed their pioneering work on chemical ionization); E.R. Thornton (organic chemist, known for his work on the location of transition states of condensed phase reactions and isotope effects, who had the first commercial Hitachi RMH2 high-resolution double focusing mass spectrometer with the ion beam in the horizontal plane) at Philadelphia, Pennsylvania; M.M. Bursey (he possessed one of the early marketed Varian Associates drift cell ion cyclotron resonance mass spectrometers) at Chapel Hill, North Carolina; R.W. Kiser (at the time of the visit he was developing a combination of a fast electric sector scan and a slow magnetic scan for detecting and recording of metastable ion transitions in double focusing mass spectrometers) at Lexington, Kentucky; W.H. Pirkle (organic chemist whose research was on electron ionization-induced fragmentation and photochemistry of organic compounds, and NMR of organic compounds in optically active solvents) at Urbana, Illinois; S. Meyerson (very well-known for his tropylium ion and work on aromatic hydrocarbon ions) at the Research and Development Department of the American Oil Company at Whiting, Indiana; T.H. Kinstle (organic chemist whose research was on charge localization and phenyl group migrations in molecular ions of tropones, nitro, chloro-substituted diphenyl ethers, styryl sulfoxides, and sulfones); and H. Svec (he was developing an instrument where positive and negative ions were extracted from the ion source in opposite directions followed by acceleration and mass analysis) at Ames, Iowa; P. Brown (organic chemist whose research was on alkyl/aryl migration aptitudes in molecular ions of carbonates and Hammett σ-substituent relationships in mass spectrometry and who was a keen fast car driver like the author with motorbikes) at Phoenix, Arizona; S. Winstein (very well-known organic chemist at UCLA, who had visited and lectured before in Amsterdam with whom on that occasion I had had very lively discussions about the homotropylium ion) in Los Angeles, California; C. Djerassi (organic chemist at Stanford University, very well-known for his work on steroids and his books (together with his co-authors H. Budzikiewicz and D.H. Williams) on the structure elucidation of natural products (alkaloids, steroids, terpenoids, sugars) by mass spectrometry, the interpretation of mass spectra of organic compounds and mass spectrometry of organic compounds. I still remember very well that before my lecture three mass spectra of isomers were handed out to all students present with the information that the elemental composition was $C_9H_{18}O$ and with the request to report within 2 weeks on the structures of the isomers and how these were derived from the spectra including the time to arrive at them. I also asked for these spectra and the structures of the isomers could be derived from them in a ½ hr as being ketones while in total 1936 (!) different aliphatic isomers were possible for the elemental composition given (Duffield et al., 1969). On that occasion I also visited R.E. Finnigan who together with Dr. T.Z. Chu was developing their company in

quadrupole mass spectrometers on the campus of the Stanford University) in Palo Alto, California; A.L. Burlingame (he was very busy all the time during my visit to his Space Sciences Laboratory because of the first and very soon scheduled manned lunar landing flight with the Apollo 11 vehicle to among others collect soil and rock samples of the Moon) in Berkeley, California; P. Wadsworth (senior scientist and head of the analytical division of the Shell Research Laboratory) in Emeryville, California; F.W. McLafferty (very well-known for the mass spectrometric rearrangement named after him and for his books on mass spectral correlations, mass spectrometry of organic ions, and interpretation of mass spectra) at the Cornell University in Ithaca, New York, and finally A.G. Harrison (very well-known for his ionization and appearance energy measurements and associated chemistry, in particular of aromatic hydrocarbon ions) in Toronto, Canada.

It may be clear to the reader that the trip to the United States was not only a very enjoyable, but also a very stimulating experience for me being very impressed by the potential of ion cyclotron resonance to study ion structures and their associated chemistry by use of ion/molecule reactions. After my return in the Laboratory of Organic Chemistry I thus took as soon as possible action to obtain a grant from the chemistry division of the Netherlands Organization for Pure Research (SON/ZWO) to purchase a Varian ion cyclotron resonance (ICR) mass spectrometer. This grant was awarded in 1970 and after the purchase of a Varian V-5903 ICR spectrometer and its time-consuming installation because of a terrible electrical pollution in the laboratory, real experiments could be performed in the beginning of 1972 (see Section IV).

The second important event in 1969 was the acquisition of funds provided by the laboratories for Organic Chemistry (25%) and Analytical Chemistry (25%), the remaining (50%) coming from a special funding by the University of Amsterdam, to purchase a new double focusing mass spectrometer with data system. The idea was to perform among others research in the field of GC/MS in cooperation with Professor J.F.K. Huber of the Laboratory for Analytical Chemistry, who was a well-recognized scientist in the field of separation techniques. Various mass spectrometry companies were visited and eventually it was decided to purchase a Varian Mat 711 double focusing mass spectrometer with Mattauch–Herzog geometry and coupled to a Varian 620i data system (MAT GmbH, Bremen, Germany). Its price was such that still some money was available and upon a question to me during the visit to the MAT GmbH factory in Bremen, Germany, what I wanted to have further, my reply was a field ionization source. This was based upon the inspiring work of Professor H.D. Beckey of the University of Bonn, Germany, who had published on fast metastable ions (Beckey, 1961) showing that skeletal rearrangements and hydrogen randomization, frequently occurring upon electron ionization (Kuck, 2002) and complicating structure elucidation of compounds, were much suppressed upon field ionization. The field ionization source was delivered in 1974 and since then it was possible to perform research using field ionization kinetics (Derrick, Falick, & Burlingame, 1972) and field desorption (Beckey, 1969) in my group (see Section VI). It is worth to note that the installation of the Varian MAT 711 instrument in the Laboratory for Organic Chemistry in 1970 encountered a very serious difficulty in the

sense that the ion beam was very unstable. After months it was found out that this was due to the tram system in Amsterdam running on D.C. (like in Sao Paulo, Brazil) which gave rise to magnetic field variations up to 80 m Gauss perpendicular to the horizontal plane of the ion beam flight path and not noticed in the A.E.I. MS902 instrument (see above) having the ion beam flight path in the vertical plane. The MAT GmbH company then simulated the D.C. of the Amsterdam tram system by a closed D.C. electrical circuit in the gutter of the company building and came up with the solution to position a coil of 740 m copper wire in a square wooden frame above the instrument with a sensor at the ceiling of the room which triggered a D.C. current through the coil to compensate for the magnetic field variations mentioned. This was an excellent solution and a static mass resolving power of more than 90,000 (10% valley definition) in the electron ionization mode was obtained with the Varian MAT 711 instrument.

Meanwhile the research continued, which initially was heavily focused on ion structures and mechanisms of unimolecular ion dissociations. Because of the fascinating and well-established tropylium ion structure (Rylander, Meyerson, & Grubb, 1957; Kuck, 2005a) particular attention was paid to provide solid evidence for the existence of heteroatom containing tropylium ions, such as the azatropylium ion (Neeter, Nibbering, & de Boer, 1970) and substituent carrying tropylium ions, such as the cyanotropylium ion already studied before during my Ph.D. study (Nibbering & de Boer, 1968d). In these earlier studies only deuterium labeling was applied because of the relatively high prices for starting materials containing other stable isotopes, such as ^{13}C, ^{15}N, and ^{18}O and required to synthesize the correspondingly labeled molecules. Applying this labeling of molecules in addition to deuterium labeling showed that the mechanisms of ion dissociations were much different from expected within the available knowledge. Thus, ^{13}C- and ^{15}N-labeling of the side-chain cyano group of o-, m-, and p-cyanobenzyl cyanides, which were chosen because upon ring expansion of their molecular ions to a substituted cycloheptatriene structure the ring and side-chain cyano groups would become equivalent assuming rapid 1,2-hydrogen shifts along the ring, showed that the cyano groups were not equivalent in the hydrogen cyanide elimination (Molenaar-Langeveld, Nibbering, & de Boer, 1971). That study indicated that even in the hydrogen cyanide elimination the cyano group did not contain to some extent the original cyano group carbon atom, which was confirmed by the hydrogen cyanide elimination from the metastably decomposing molecular ions of benzyl cyanide. The latter eliminated molecule contained for 78% the original cyano carbon atom, whereas the remaining 22% contained the benzylic carbon atom. These observations were rationalized by hydrogen and phenyl ring shifts over the side-chain carbon atoms prior to the loss of hydrogen cyanide (Molenaar-Langeveld, Nibbering, & de Boer, 1971). These results prompted to study also other molecules, which had been suggested to generate ring-substituted tropylium ions, such as the dihydroxytropylium ion from the molecular ion of m-hydroxybenzylalcohol by loss of a hydrogen atom (Shannon, 1962). The formation of a dihydroxytropylium ion was excluded by specific deuterium and ^{18}O-labeling of m-hydroxybenzylalcohol which showed that the hydroxyl groups had not become equivalent prior to or during fragmentation. That is, the $[M–H]^+$ ion

eliminated a molecule of carbon monoxide that contained exclusively the benzylic oxygen atom (Molenaar-Langeveld & Nibbering, 1972). Another interesting observation in this study was that the molecular ion eliminated a molecule of water that contained exclusively the benzylic oxygen atom, whereas that lost from the [M–H]$^+$ ion exclusively contained the phenolic oxygen atom. In both reaction channels the hydrogen atoms in the eliminated molecule of water originated from the hydroxyl groups. These observations were rationalized as summarized in Scheme 3, where in the molecular ion the acidic phenolic proton *via* a transient π-complex (to avoid exchange of the phenolic proton with the aromatic ring hydrogen atoms) was transferred to the basic benzylic hydroxyl group followed by loss of a molecule of water thus containing the benzylic oxygen atom. In the [M–H]$^+$ ion, however, the generated protonated aldehyde group now acted as acid to transfer its proton *via* a transient π-complex to the basic phenolic hydroxyl group with subsequent elimination of a water molecule thus containing the phenolic oxygen atom to give the formyl-substituted phenyl cation (Molenaar-Langeveld &

Nibbering, 1972). In a similar way it was shown by deuterium labeling that the metastably decomposing [M–H]$^+$ ions of *p*-aminotoluene and benzylamine behaved quite differently excluding that they both had rearranged to an aminotropylium ion. The former ions eliminated HCN (or HNC) that retained the amino hydrogen like that lost from ionized aniline, while the latter ions lost HCN containing exclusively the benzylic hydrogen (Bruins, Nibbering, & de Boer, 1972).

As a logical consequence, also substituted cycloheptatriene compounds were studied, where ^{13}C-labeling showed that in their molecular ions ring contraction to a six-membered ring took place as noted in the methyl loss from the molecular ion of 7-methylcycloheptatriene (Venema, Nibbering, & de Boer, 1971) and 7-cyanocycloheptatriene, where a ring carbon atom was found to participate in the HCN (or HNC) elimination (Venema, Nibbering, & de Boer, 1972).

Another interesting ion structure, that is the phenylated cyclopropane ion, resembling an ion/molecule complex and proposed earlier (Grubb & Meyerson, 1963), motivated my group to show whether an analogous pyridylated cyclopropane ion would exist. Deuterium and ^{13}C-labeling however showed that such ion was generated from neither the [M–CH$_3$]$^+$ ion of 4-*t*-butylpyridine nor from the [M–CH$_3$]$^+$ ion of re-investigated *t*-butylbenzene. Instead, the results obtained were explicable by 1,2-hydrogen-, 1,2-pyridyl- or 1,2-phenyl-, and 1,2-methyl shifts over the side-chain carbon atoms (Neeter & Nibbering, 1973). From this and earlier studies in my group it became increasingly clear that hydrogen randomization and skeletal rearrangements in organic ions occurred as independent processes.

Three other studies should be mentioned before going on to the next section. The first concerns the *ortho*-attack of side-chain functional groups on aromatic rings, such as in the molecular ion of methyl cinnamate where as one of the first examples it was shown on the basis of deuterium labeling that the carbonyl oxygen formed a bond with the *ortho*-carbon atom leading to loss of the *ortho*-hydrogen atom (Ronayne, Williams, & Bowie, 1966). Evidence for a similar attack in the molecular ion of 3-phenyl propionate was put forward on the basis of ^{18}O-labeling of the carbonyl group which showed that in the successive elimination of C$_2$H$_5^\bullet$, C$_2$H$_2$O, and CO the ^{18}O-label was lost exclusively in the last step (Kadentsev et al., 1968).

This explanation would mean that the eliminated CO molecule contained one of the *ortho*-carbon atoms that was not the case as shown by ^{13}C-labeling indicating that the eliminated CO molecule contained exclusively the benzylic carbon atom instead (Resink, Venema, & Nibbering, 1974).

The mechanistic rationalization of the reaction sequence of C$_2$H$_5^\bullet$, C$_2$H$_2$O, and CO loss is pictured in Scheme 4, which starts with abstraction of a benzylic proton by the carbonyl oxygen in an acid-base reaction (this is preferred over a benzylic hydrogen abstraction by the radical cation located on the carbonyl oxygen in the original publication as the local ionization energy of the phenyl ring will be lower than that of the ester group. Yet, it leads to the same intermediate). Subsequent attack of the generated benzylic radical on the protonated carbonyl group results easily in the successive loss of C$_2$H$_5^\bullet$, C$_2$H$_2$O, and CO in agreement with the ^{13}C- and also D-labeling applied (Resink, Venema, & Nibbering, 1974). The second study concerns the hydrogen exchange in the molecular ions of
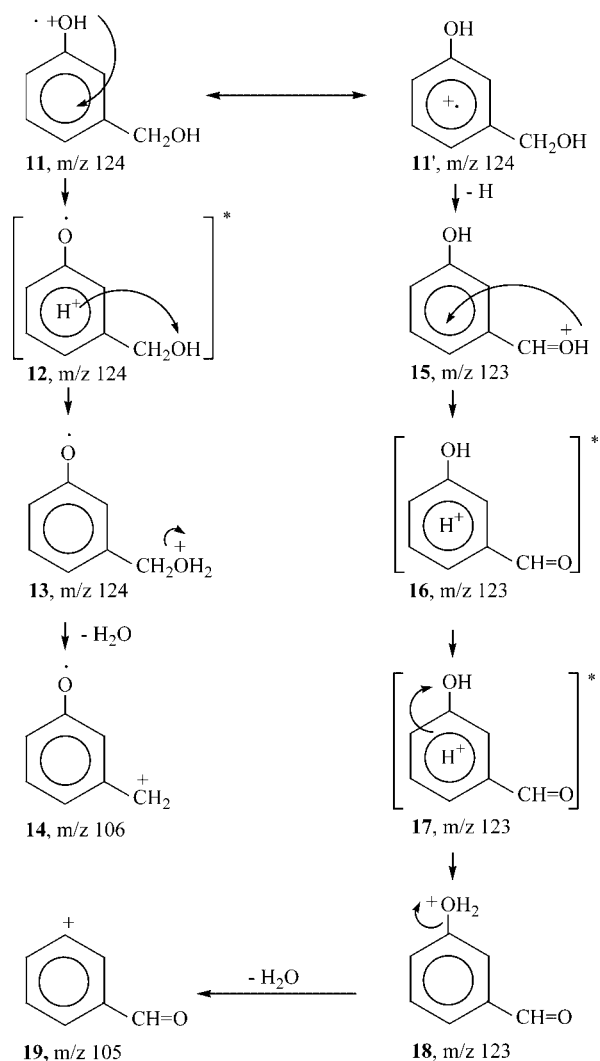

SCHEME 3.
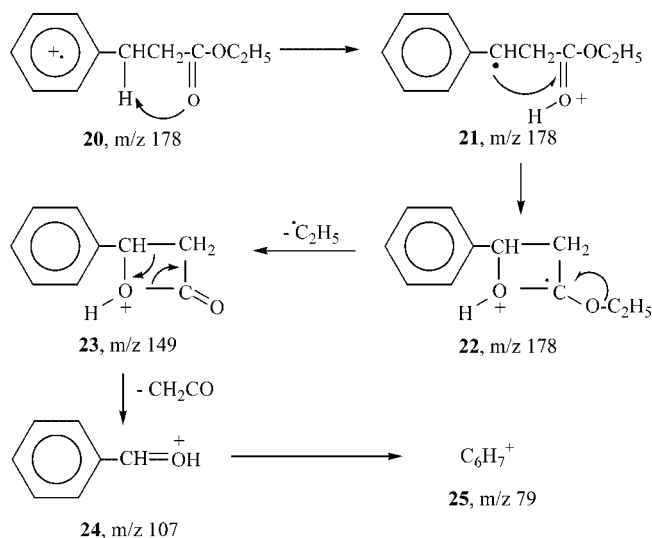
SCHEME 4.

isonicotinic and nicotinic acid. The former eliminated a hydroxyl radical and water after an exchange between the hydroxyl hydrogen and its *ortho* hydrogens. This exchange increased at longer ion lifetimes and correspondingly suffered from larger isotope effects, while it very notably decreased at higher ion internal energies. However, in the molecular ions of nicotinic acid the hydrogen exchange occurred for ~95% between the hydroxyl hydrogen and only the α-hydrogen of the pyridine ring prior to the loss of a hydroxyl radical and water (Neeter & Nibbering, 1971).

The third study concerns 2-phenoxyethyl chloride/bromide that were chosen to investigate the influence of the oxygen atom on the possible H/D exchange between the hydrogen atoms of the methylene group of position 1 and the *ortho*-hydrogen atoms in their molecular ions as found for 3-phenyl-1-bromopropane (*vide supra*). Such an exchange or any other H/D exchange was not observed, but a positional interchange of the phenyl group and the chlorine/bromine atom was found instead as indicated by the great similarity of the spectra of the 1,1- and 2,2-dideuterated analogs, in particular by the presence of peaks at both m/z 107 ($C_6H_5OCH_2$) and m/z 109 ($C_6H_5OCD_2$) (Theissling, Nibbering, & de Boer, 1971). Having excluded that this positional interchange was due to a thermal process, three possible intermediate structures were considered to account for it:
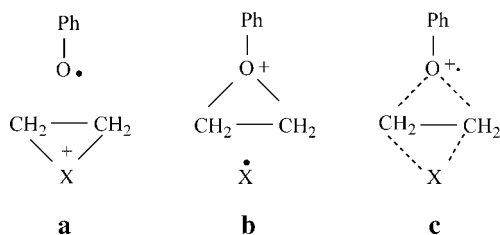
Intermediate **a** should be favored by radical-stabilizing substituents, but such effects were not observed so that this

intermediate was rejected. Intermediate **b** would facilitate the loss of a halogen radical, but this process was hardly observed so that this intermediate was also discarded. Intermediate **c** was therefore preferred (Theissling, Nibbering, & de Boer, 1971). Later on the 2-phenoxyethyl chloride/bromide has been studied further by use of a variety of methods as will be discussed in Sections V and VI below.

IV. THE YEARS OF DRIFT-CELL ION CYCLOTRON RESONANCE MASS SPECTROMETRY

A. Positive Ion/Molecule Reactions

The first experiment with use of the drift-cell ion cyclotron resonance (ICR) mass spectrometer following its installation (see Section III and for description of the method Baldeschwieler, 1968; Beauchamp, 1971) was to establish whether the ethene loss from the molecular ion of phenyl ethyl ether occurred *via* a 1,5-hydrogen shift from the methyl group to one of the *ortho*-carbon atoms of the phenyl ring or *via* a 1,3-hydrogen shift from the methyl group to the oxygen atom. The former would lead to the formation of a 2,4-cyclohexadienone ion, the latter to that of a phenol ion. This could be distinguished by deuterium labeling of the methyl group of phenyl ethyl ether and then probing whether the $[M - C_2H_2D_2]^{\bullet+}$ ion did transfer a proton and deuteron or only a deuteron to a suitable base. It was found that the $[M - C_2H_2D_2]^{\bullet+}$ ion transferred a deuteron for more than 95% to the base 4-*t*-butylpyridine, so that obviously a phenol ion was formed (Nibbering, 1973), the results being summarized in Scheme 5.

Soon after publication of this study, an article appeared showing that at least part of the 2,4-cyclohexadienone ions, generated from bicyclo-[2,2,2]oct-2-en-5,7-dione, isomerized to the phenol structure on the ICR time scale (Tomer & Djerassi, 1973). The strategy of proton versus deuteron transfer was later on applied to the $C_6H_6O^{\bullet+}$ ions generated from 2-phenoxyethyl halides (F, Cl, Br, I), part of their unimolecular ion dissociations having been discussed already in the previous section. From a detailed analysis of the results obtained that included not only side-chain, but also fully deuterated phenyl ring compounds (the
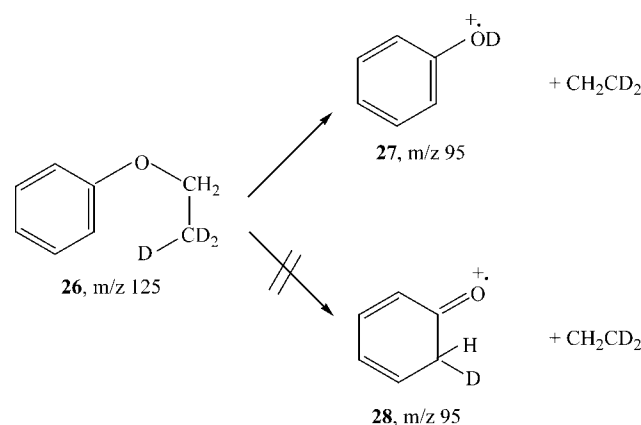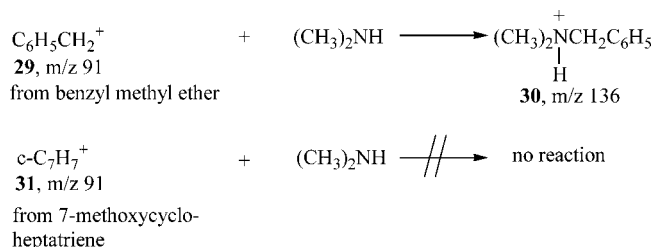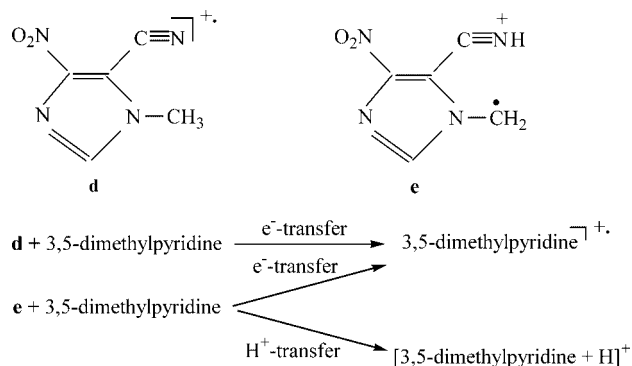

SCHEME 5.

molecular ion of 2-phenoxyethyl fluoride did not suffer from the positional interchange observed for the chloride and bromide analogs as mentioned in the previous section) it was concluded that not only phenol ions, but also 2,4-cyclohexadienone ions increasingly were formed in the order F < Cl < Br (Theissling & Nibbering, 1978). The formation of the latter ions was confirmed by use of other methods as will be mentioned in Section V.

Another early study to distinguish isomeric ion structures concerned the molecular ion of 1-methyl-4-nitro-imidazole-5-carbonitrile (**d**) and the $(M - H_2O)^{•+}$ fragment ion from 1-methyl-4-nitro-imidazole-5-carboxamide (**e**). That study, performed in cooperation with Dr. J. Memel from the North East London Polytechnic in London, England, required the use of a direct insertion probe and because of the relatively unstable pressure of the compounds in the source of the three-section ICR drift-cell (ion source-ion analyzer-ion collector), it took nearly a month of frequently repeated double-resonance experiments to establish that ion **d** reacted only by charge transfer, while ion **e** was found to react by both proton transfer and charge transfer with 3,5-dimethylpyridine as summarized in Scheme 6 (Memel & Nibbering, 1973). Note that ion **e** is a distonic ion, a naming that has been introduced many years later (Yates, Bouma, & Radom, 1984).

Another interesting ion structure discrimination on the basis of ion/molecule reactions in ICR was that between the benzyl and tropylium ion. The benzyl cation generated from benzyl methyl ether turned out to be reactive towards dimethylamine (Bruins & Nibbering, 1974a), but the tropylium ion generated from 7-methoxycycloheptatriene was not (Venema & Nibbering, 1974a) as summarized in Scheme 7. Benzyl and tropylium ions were at that time also distinguished from each other by use of collisional activation (McLaffert & Winkler, 1974) and photodissociation (Dunbar, 1975).

Other ion structure characterization studies concerned the long-lived molecular ion of proprionitrile that was investigated in cooperation with Dr. S. Meyerson of the Standard Oil Company in Naperville, Illinois (Theissling, Nibbering, & Meyerson, 1976), the long-lived protonated benzene in which by 1,2-shifts of the proton along the ring a complete hydrogen randomization occurred (Bruins & Nibbering, 1976a), the 1-methoxycyclopropyl- and its isomeric 2-methoxyallyl cation, and the $[M–methyl]^+$ and $[M - ethylene]^{+•}$ ions from ionized methyl isobutyrate.

SCHEME 6.

$C_6H_5CH_2^+$ + $(CH_3)_2NH \longrightarrow (CH_3)_2\overset{+}{N}CH_2C_6H_5$
29, m/z 91
from benzyl methyl ether
$\overset{|}{H}$
30, m/z 136

$c\text{-}C_7H_7^+$ + $(CH_3)_2NH \not\longrightarrow$ no reaction
31, m/z 91
from 7-methoxycyclo-heptatriene

SCHEME 7.

With regard to the long-lived protonated benzene, its intermolecular exchange with benzene has been studied afterwards in cooperation with Professor D. Kuck of the University of Bielefeld, Germany, by use of deuterium labeling and Fourier transform ion cyclotron resonance. This exchange turned out to be very slow and occurred not only in successively formed encounter complexes, but also within the firstly generated collision complex (Kuck et al., 1985) whereas the intramolecular exchange in protonated α,ω-diarylalkanes had been found to be very fast (Kuck, Bäther, & Grützmacher, 1979; Kuck, 1990, 2002, 2005b). The mentioned 1-methoxycyclopropyl cation was generated by electron ionization of 1-bromo-1-methoxy-cyclo-propane and did transfer either a methyl cation from the original methoxy group or a proton from the ring to the bases of ammonia, methylamine, dimethylamine, and trimethylamine as shown by deuterium labeling experiments. These reactions were not observed for the isomeric 2-methoxyallyl cation, that was generated from its corresponding bromide by electron ionization (Van Tilborg, van Doorn, & Nibbering, 1979). Later on collision-induced dissociation experiments, performed in cooperation with Professor H. Schwarz of the Technical University in Berlin, Germany, on the $[M–Br]^+$ ion from 1-bromo-1-methoxycyclo-propane confirmed that its structure was different from the isomeric 2-methoxyallyl cation, but that it was not generated in major quantities in the ion population predominantly consisting of 1-methoxyallyl cations (Ciommer et al., 1982). With regard to the elimination of a methyl radical and a molecule of ethylene from ionized methyl isobutyrate, their mechanistic pathways were investigated in a joint effort of five different labs by use of ion cyclotron resonance in combination with field ionization kinetics, collisional activation, ^{13}C- and deuterium labeling, and isotope effects. The loss of the methyl radical was preceded by a slow hidden hydrogen transfer from one of the β-methyl groups to the carbonyl oxygen and led to the formation of protonated methyl acrylate. The elimination of ethylene took place by three distinct multistep pathways, involving hydrogen migrations and skeletal rearrangements, and all leading to the formation of the ionized enol of methyl acetate (Hemberger et al., 1980). In addition to these ion structure studies, relative gas-phase basicities of some (un)substituted piperidines and 1-aza-adamantanes were determined in view of possible through bond and through-space effects (Theissling & Nibbering, 1974) and of mercaptopyridines with the aim to obtain a quantitative insight into their tautomeric equilibria (Theissling et al., 1977). The results of the former study were interpreted as arising from through-space effects, while the latter study in cooperation with Professor A.R. Katritzky presently being at the University of

Florida in Gainesville, Florida showed that the 2- and 4-mercaptopyridines were significantly more stable in the gas phase than their corresponding pyridthione tautomers.

Meanwhile the research had shifted to studying also organic ion/molecule reactions in the absence of solvent molecules and/or counter ions. Some of these studies were inspired by functional group interactions occurring in unimolecularly decomposing ions (see Section V below), others by organic reactions in the condensed phase. An example of the former is the amide bond formation through benzoylation of primary-, secondary-, and tertiary amines by reaction of either the benzoyl cation with neutral amines or benzaldehyde with protonated amines to give the corresponding protonated amides by association or elimination of a hydrogen molecule, respectively (Bruins & Nibbering, 1975). Examples of the latter are the formation of a six-membered ring by a $[2+4]$ cycloaddition and a five-membered ring by a $[2+3]$ cycloaddition, where the numbering refers to the number of atoms involved in the ring formation. The $[2+4]$ cycloaddition was achieved by a Diels–Alder type reaction of ionized 1,3-butadiene with vinyl ethyl (methyl) ether, a study that was performed in cooperation with Professor K.R. Jennings of the University of Warwick in Coventry, England (van Doorn et al., 1978). This result was confirmed by an independent study which showed that the cycloaddition occurred in a stepwise fashion, that is, at a higher pressure than in ICR the open-chain intermediate could be intercepted by collisional stabilization (Groenewold & Gross, 1984). $[2+3]$ cycloaddition was shown to occur in reactions between suitably substituted allyl cations and olefins. Notably the reaction of the 2-methoxyallyl cation with 1,2-dimethoxyethene yielded a product ion by elimination of two molecules of methanol from the collision complex. These eliminated methanol molecules were shown by deuterium labeling to contain the original methoxy groups of 1,2-dimethoxyethene, while the two hydrogens were provided by each of the methylene groups of the 2-methoxyallyl cation as expected for the five-membered ring formation (Van Tilborg, van Doorn, & Nibbering, 1980).

The $[2+4]$- and $[2+3]$-cycloadditions discussed have been summarized in Scheme 8, where for simplicity reasons they have been pictured as one-step reactions.

B. Negative Ion/Molecule Reactions

Another new field of research on the generation and bimolecular chemistry of negative ions in the gas phase was started in 1976. For that purpose a four-section ICR drift-cell was constructed in-house where the second section was the reaction section, while the first-, third-, and fourth section were the traditional ion source, ion analyzer, and ion collector sections, respectively. An invited review on the results from negative ion research by use of drift-cell ICR in my group has been published (Nibbering, 1981).

Early negative ion studies concerned the reaction of $O^{\bullet-}$ with a variety of organic molecules. This reactant ion, generated from N_2O by dissociative low-energy electron capture (Chantry, 1969) was known to formally abstract in most cases $H_2^{\bullet+}$ from a single carbon atom if not aromatic, a notable example being ethene (Goode & Jennings, 1974). This abstraction occurs in a stepwise fashion, that is, in most cases it starts with a hydrogen
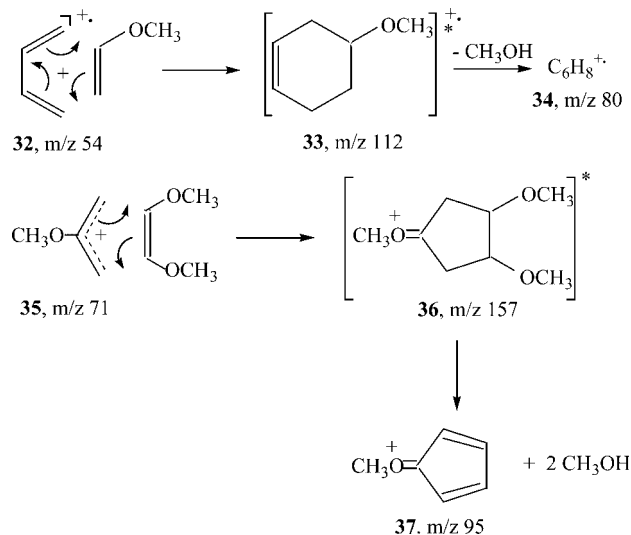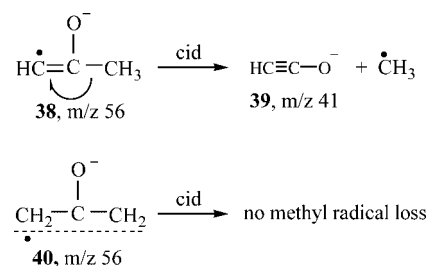

SCHEME 8.

atom abstraction to give OH^- that within the correspondingly formed collision complex reacts further by proton abstraction to give the final product ion (Nibbering, 1981; Lee & Grabowski, 1992). Indeed, the formal $H_2^{\bullet+}$ abstraction was found in the reaction of $O^{\bullet-}$ with propyne, but deuterium labeling showed that not only a 3,3-$H_2^{\bullet+}$ abstraction, but also a 3,1-$H_2^{\bullet+}$ abstraction occurred (Dawson, Kaandorp, & Nibbering, 1977). The product ion $HCC{\equiv}CH^{\bullet-}$ from the former reaction was reactive towards methyl formate, but the ion $^{\bullet}CH_2C{\equiv}C^-$ from the latter was not. In a similar way it was shown by deuterium labeling that $O^{\bullet-}$ reacted with acetone by both 1,1-$H_2^{\bullet+}$ and 1,3-$H_2^{\bullet+}$ abstraction, again leading to different ion structures (Dawson, Noest, & Nibbering, 1979b). The product ion from the former reaction did eliminate a methyl radical upon collision-induced dissociation, while that from the latter reaction showed no fragmentation as summarized in Scheme 9.

Another interesting reaction of a radical anion was that of the archetype ion $CH_2C^{\bullet-}$ with N_2O. ^{15}N-labeling showed that this ion attacked the terminal nitrogen atom of N_2O to give under expulsion of NO the cyanomethyl anion (Dawson & Nibbering, 1978), see Scheme 10.

A similar attack on N_2O was found for the allyl anion, where the collision complex eliminated a molecule of water to give the 1-diazoallyl anion as shown by deuterium labeling (Dawson,

SCHEME 9.

SCHEME 10.

Noest, & Nibbering, 1979a) and in line with an earlier suggestion (Bierbaum, DePuy, & Shapiro, 1977). That study (Dawson, Noest, & Nibbering, 1979a) proved in this way that an intramolecular H/D exchange in the allyl anion was absent, a result that was used to find out how the allyl anion would react with tetrafluoroethene in view of possible cycloadditions. On the basis of the applied deuterium labeling it could be concluded that 65% of the allyl anions reacted by a linear addition, 20% by a [2 + 2] cycloaddition, and only 15% by a [2 + 3] cycloaddition (Nibbering, 1979a), see Scheme 11.

It was then decided to substitute the allyl anion with a cyano group in the 2-position as this group would stabilize the negative charge in the [2 + 3] cycloaddition complex with tetrafluoroethene and thus drive the reaction (Dawson & Nibbering, 1980). However, the synthesis of a suitable precursor to generate the specifically deuterated 2-cyanoallyl anion was unsuccessful. The

linear addition:

[2+2]-cycloaddition:

[2+3]-cycloaddition:

SCHEME 11.

SCHEME 12.

isomeric, but distinct 1-cyanocyclopropyl anion, for the generation of which suitably deuterium labeled precursors were available, did react with tetrafluoroethene by elimination of two HF molecules, although to a minor extent. The dominant reaction was the expulsion of ethene for which the mechanism in Scheme 12 has been presented (Dawson & Nibbering, 1980).

Three other studies should be mentioned before going on to the next section. The first concerns the reactions of various anions with aliphatic nitrites (Noest & Nibbering, 1980a,b). Four reaction channels were found and the competition between them depended on the nature of both the anion and the aliphatic nitrite. The routes associated with these channels were an S_N2, an E_2, an $E_{CO}2$, and an addition-elimination mechanism. The first two lead to the formation of the NO_2^- ion, the third to NO^- and/or solvated NO^- depending on the exothermicity of the reaction and the fourth to a product ion in which the original anion becomes bonded to the nitrogen atom, as summarized/exemplified in the overall Scheme 13.

These results were confirmed by an independent flowing afterglow and selected ion flow tube study which showed an additional reaction channel at the much higher pressure used than in ICR (King et al., 1981), but also observed when the ICR was operated at a higher pressure than usual (Klass & Bowie, 1980). The additional reaction channel is given in Scheme 14, showing that following the addition-elimination reaction of the acetone enolate anion with neopentyl nitrite, the displaced neopentyloxy anion can react further within the ion/molecule complex by a subsequent addition-elimination reaction to form the nitrosomethyl anion in competition with a proton abstraction reaction, such as given in the bottom of Scheme 13.

The second study concerns the reaction of the OH^- ion with methyl phenyl ether. This reaction was assumed to proceed purely through an S_N2 mechanism to yield the phenoxide ion (Olmstead & Brauman, 1977). This is indeed the major reaction channel, but ^{18}O-labeling showed that approximately 15% of the OH^- ions attack the phenyl ring at the ipso position, displacing via a nucleophilic aromatic substitution reaction (S_NAr reaction) the methoxy group that as methoxide subsequently abstracts the phenolic proton from the generated phenol species to give the

SCHEME 13.

phenoxide ion (Kleingeld & Nibbering, 1980). This type of reaction has been studied later on very extensively (see Section VII below). The third study concerns the H/D-exchange of all hydrogen atoms of the [M–H]$^-$ ions of 2,2-dimethylpropional-dehyde and 2-methyl-2-nitrosopropane in the presence of D$_2$O (Noest & Nibbering, 1980c). This was an unexpected result because it implies the formation of a primary carbanion known to be unstable with respect to electron detachment apart from a very few exceptions. Two suggestions were made to account for the stability of the primary carbanion. One was the interaction of the dipole of the aldehyde or nitroso group with the negative charge of the sp^3-orbital of the primary carbon atom (structure **f** below), the other was homoconjugation by rehybridization of the sp^3 orbital to a p-orbital, so as to overlap with the π-system of the aldehyde or nitroso group (structure **g** below). The latter structure could lead to ring closure to form a 2,2-dimethylcyclopropoxide
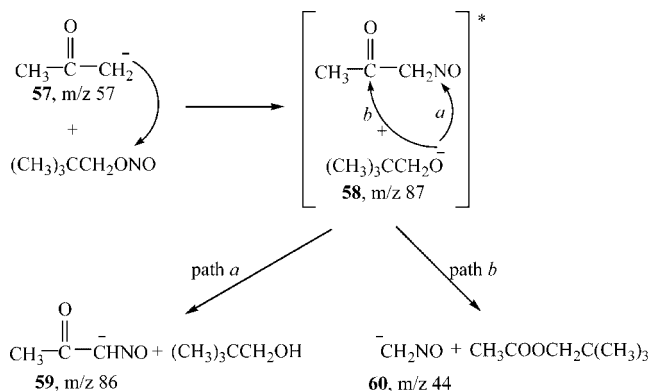
SCHEME 14.

ion which would imply that the [M-H]$^-$ ion of 2,2-dimethylcy-clopropanol could also undergo ring opening and show H/D exchange in the presence of D$_2$O as was observed indeed (Nibbering, 1981).

In a more advanced FTICR study later on, the interconversion between the ring-opened and ring-closed ion structures discussed has been confirmed which by protonation/deprotonation steps in the ion/molecule complexes with water eventually are converted into the enolate anion of 3-methylbutanal (Peerboom, Ingemann, & Nibbering, 1985). With regard to primary carbanions in the gas phase, it is interesting to note that a decade later the [M-H]$^-$ ion of neopentane, generated by collision-induced CO$_2$ and CH$_2$O elimination from the 3,3-dimethylbutyrate and 3,3-dimethylbutoxide ions, respectively, has been reported as a stable ion in the gas phase (Graul & Squires, 1990).
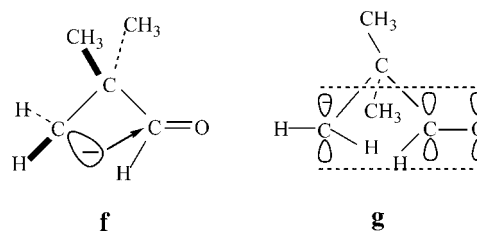
V. THE YEARS OF DOUBLE FOCUSING SECTOR MASS SPECTROMETRY UNTIL 1983

The research described in Section III was continued with use of not only the A.E.I. MS 902 instrument, but also the Varian MAT 711 mass spectrometer that became operational in the course of 1971, both instruments being used also for analyses of samples of the Laboratory of Organic Chemistry and other laboratories of the Department of Chemistry of the University of Amsterdam. In the period, covered in this section, the new field of research of field ionization kinetics and field desorption was started in my group and was performed with use of the Varian MAT 711 instrument, but that will be described in the separate Section VI. In this section the course of the research will be covered as it developed along with new methods in double focusing sector mass spectrometry. Of course, stable isotopic labeling remained a very powerful tool as shown by the following examples. With the knowledge that upon electron ionization ethene was eliminated *via* the McLafferty rearrangement from the molecular ions of 1-nitropropane (Nibbering, de Boer, & Hofman, 1965) and methyl butyrate (Budzikiewicz, Djerassi, & Williams, 1967), the methyl ester of γ-nitrobutyric acid was selected to study the competition between the two of such possible rearrangements in its molecular ion. Surprisingly, the peaks at *m/z* 61 and 74 in the electron ionization mass spectrum that would arise from a McLafferty rearrangement involving the nitro and ester group, respectively, were extremely small or even absent. The unusual loss of HNO$_2$ was observed instead and extensive deuterium labeling showed that this molecule contained a γ-hydrogen atom, so that the loss of HNO$_2$ was a formal 1,1-elimination. Taking all the results together from that particular study (Molenaar-Langeveld & Nibbering, 1974b; Nibbering, 2004) this elimination could

readily be explained by a McLafferty rearrangement of one of the γ-hydrogen atoms to the ester group that subsequently in an acid-base reaction protonated the nitro group which was followed by bond formation between the γ-carbon and the carbonyl oxygen prior to the loss of HNO_2. Two important conclusions can be drawn from this study, which are (i) the McLafferty rearrangement is a stepwise process and (ii) the nitro form is converted into its aci-form with the help of the ester group which acts like an intramolecular catalyst.

The concept of charge localization (or better charge/radical localization) in molecular ions, already extensively and with success applied in the mid 60s (Budzikiewicz, Djerassi, & Williams, 1967) to rationalize mechanistically their unimolecular dissociations, was another topic that was tested by extensive stable isotopic labeling experiments. For that purpose the molecule of 1,4-dibenzyloxybutane was selected because of an earlier study of benzyloxyalkyl-substituted purine and pyrimidine nucleoside analogs in which the application of charge localization implied a mechanistically interesting and intramolecular migration of a benzyl group (Grose, Eggelte, & Nibbering, 1971). Its molecular ion generated not only the well-known ion with m/z 91 by benzylic bond cleavage, but also showed the loss of a neutral benzyl radical. On the basis of D- and ^{18}O-labeling and kinetic isotope effects the mechanism for this reaction was proposed as depicted in Scheme 15 (Bruins & Nibbering, 1974b).

It starts with abstraction of a benzylic proton by the opposite ether oxygen in an acid-base reaction (this is preferred over a benzylic hydrogen abstraction by the radical cation located on the ether oxygen in the original publication as the local ionization energy of the phenyl ring will be lower than that of the ether group. Yet, it leads to the same intermediate). The remaining neutral ether oxygen atom then picks up the benzyl cation from the protonated ether function in an intramolecular type of S_N2 reaction (S_Ni reaction) followed by a homolytic cleavage reaction

that leads to the loss of the benzyl radical. The resulting [M–91]+ ion is the precursor of three secondary ions which are (i) protonated tetrahydrofuran by loss of benzaldehyde, (ii) protonated benzaldehyde, containing the elements of the original benzyloxy group, and (iii) the [M–H]+-ion of tetrahydrofuran by loss of benzyl alcohol, containing the original benzyl group, the opposite ether oxygen atom, and one of its adjacent methylene hydrogen atoms. This study showed clearly the effects of functional group interactions and initiated research on α-benzylamino-ω-benzyloxyalkanes where similar dissociation channels of the molecular ions were observed, all of them mechanistically being rationalized with charge/radical localization at the amine nitrogen atom (Bruins & Nibbering, 1976b). It also induced the amide bond formation via an ion/molecule reaction as mentioned in Section IV. Concerning charge localization, the research on the amino acid methionine should be mentioned. Its electron ionization-induced fragmentation had been studied before which was rationalized in terms of charge localization, in particular the successive loss of the carboxyl radical and vinylamine from the molecular ion to give the $CH_3SCH_2^+$ ion (Svec & Junk, 1967). However, this was seriously criticized in a later study on the basis of elemental compositions of ions measured by a high-resolution scan of the mass spectrum that was processed by a data system (Bentley, Johnstone, & Mellon, 1971). It was then decided to perform accurate mass measurements of the ions from m/z 40 to the molecular ion by manually peak matching at a minimum static mass resolving power of 20,000 (10% valley definition) using the Varian MAT 711 instrument and to record all metastable transitions with use of both this instrument and the A.E.I. MS902 mass spectrometer. Many nominal masses appeared to be multiplets rather than singlets, which were suggested by the high-resolution scan, and the observed metastable transitions confirmed the earlier suggested successive elimination of the carboxyl radical and vinylamine from the molecular ion in addition to many other dissociation routes (van den Heuvel & Nibbering, 1975).

However, two instrumental developments had occurred that were of paramount importance for ion mechanistic dissociation and ion structure studies. The first was collision-induced dissociation of high kinetic energy aromatic ions achieved by loosening the bolts of the energy analyzer of an A.E.I. MS9 mass spectrometer so that air could leak in (Jennings, 1968). The results were reproduced in my group on the available A.E.I. MS902 instrument during the cycloheptatriene studies (see Section III) but were considered to be too risky to continue as that instrument had to be used heavily for analytical service of the department of chemistry. The method of collision-induced dissociation, also called collisional activation, has turned out to be a powerful method to determine the structures of long-lived ions (Haddon & McLafferty, 1968; McLafferty et al., 1973). The second was the development of reversed geometry double focusing mass spectrometry in which the magnetic sector preceded the electrostatic analyzer enabling to study the ion chemistry and structure of mass selected ions by spontaneous and collision-induced dissociations (Beynon, Caprioli, & Ast, 1971; Cooks et al., 1973). In 1973, I submitted an extensive research proposal to the chemistry division of the Netherlands Organization for Pure Research (SON/ZWO) to obtain a grant for the purchase of a reversed geometry double focusing mass spectrometer, but
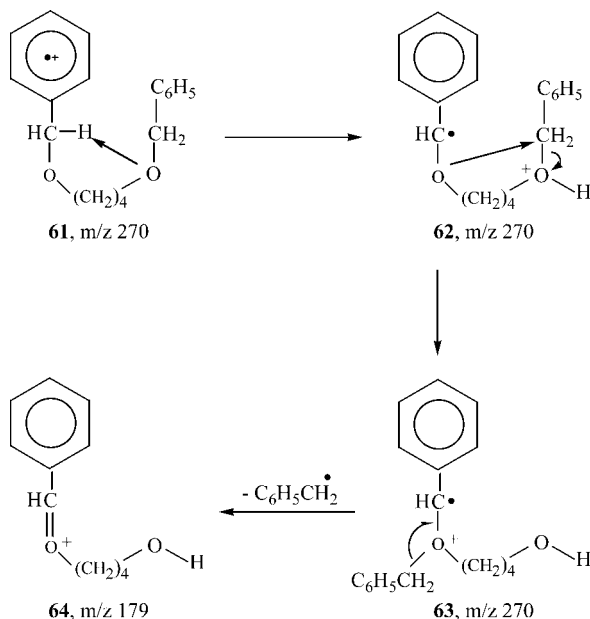
SCHEME 15.

received the reply with the recommendation to perform first experiments on such instrument were available. The choice was then to spend a few months as visiting scientist on the basis of a Netherlands Organization for Pure Research (ZWO) traveling grant and with permission of Professor H.O. Huisman, the Director of the Laboratory of Organic Chemistry, in the laboratory of Professor F.W. McLafferty at the Cornell University in Ithaca, New York, who had modified his Hitachi RMU-7 double focusing mass spectrometer to a reversed geometry instrument. This visit took place in 1974 and was a very enjoyable and scientifically a very rewarding experience. Together with Dr. Takao Nishishita from Japan and Dr. Chris van de Sande from Belgium (we were called the three musketeers) three publications eventually appeared, two on $C_8H_9^+$ ions (Nibbering et al., 1974a; Köppel et al., 1977), and one on the $C_9H_{11}O^+$ ion from 2-methyl-2-phenylpropane-1,3-diol (Nibbering et al., 1974b). Among the different $C_8H_9^+$ ion structures, the evidence presented for the existence of the long-lived phenonium ion on the basis of the collisional activation spectra of the [M–Br]$^+$ ions from site-specifically stable isotope labeled 2-phenylethyl bromides was very exciting as this species had given rise to a lively and controversial debate among organic chemists (Lowry and Richardson, 1976). Many years later my group has provided evidence that also the negative counterpart of the phenonium ion is a stable ion in the gas phase (Maas, van Veelen, & Nibbering, 1989).

Two other important events during my stay at Cornell in 1974 should be mentioned. It enabled me to attend the 22nd ASMS Conference in Philadelphia, Pennsylvania, where I (i) met for the first time Professor M.L. Gross (then at the University of Nebraska at Lincoln, Nebraska and presently at the Washington University in St. Louis, Missouri) who became a personal friend and with whom I have published over many years joint articles and where I (ii) attended the lecture of Professor M.B. Comisarow of the University of British Columbia, Vancouver, Canada who reported on the first Fourier transform ion cyclotron resonance (FTICR) experiments performed in December 1973 together with Professor A.G. Marshall (Comisarow & Marshall, 1974). That lecture was very inspiring for the development of FTICR in my group (see Section VIII below). Upon return to The Netherlands it soon turned out that Professor G. Dijkstra of the University of Utrecht, The Netherlands, concealedly had managed to raise funds to purchase the first ZAB-2HF reversed geometry mass spectrometer (VG Micromass, Altrincham, UK). SON/ZWO has made attempts to obtain measurement time for me on this instrument, but unfortunately without success. Many experiments, for which reversed geometry double focusing mass spectrometry was useful, have therefore been carried out with the help of colleagues outside The Netherlands. The following examples will illustrate this. Thus, in cooperation with scientists of the Varian MAT company in Bremen, Germany, application of the initially named 'direct analysis of daughter ions' (DADI) technique, but soon renamed as the 'mass analyzed ion kinetic energy' (MIKE) technique (Beynon et al., 1973), to the molecular and [M–H]$^+$- ions of the isomeric o- and p-xylenes, and 7-methylcycloheptatriene showed that the corresponding spectra were very similar including the abundances of the non-decomposing ions and therefore pointing strongly to common ion structures (Venema et al., 1975). This result was in full agreement with an earlier ^{13}C-labeling study of 7-methylcyclo-heptatriene that had shown ring contraction of its molecular ion to a six-membered ring (Venema, Nibbering, & de Boer, 1971). In cooperation with Professor J.H. Beynon and colleagues and with use of the MIKE mass spectrometer at the Purdue University, West Lafayette, Indiana it was shown by application of ^{13}C-labeling that the CH^+ loss from the metastably decomposing doubly charged molecular ion of malononitrile involved the methylene and nitrile carbon atoms in the statistical probability ratio, suggesting that it fragmented through a bipyrimidal intermediate (Beynon et al., 1975). This mass spectrometer was also used in cooperation with Professor R.G. Cooks for kinetic energy release measurements in a D- and ^{18}O-labeling study of the formaldehyde loss from the [M–methyl]$^+$ ion of methoxymethyl isopropyl ether, a system that had been selected in my group to find out whether this loss occurred via a methyl or methoxyl migration. At an electron energy of 70 and 15 eV the formaldehyde elimination from ions decomposing in the ion source occurred via approximately 90% methoxyl and 10% methyl migration that was more than opposite for the metastably decomposing ions that virtually exclusively (>99%) lost formaldehyde by methyl migration. It was concluded that the methoxyl migration channel has the higher activation energy and the higher frequency factor, but very interesting is the unusual situation that both this channel and the methyl migration channel start from the same reactants leading to the same products (Schoemaker, Nibbering, & Cooks, 1975). The higher activation energy for the methoxyl migration channel has been confirmed afterwards by a drift-cell ICR study in which the lower energy demanding methyl migration has been suggested to proceed via a methyl cation bonded complex of formaldehyde and acetaldehyde on the basis of ^{18}O-labeling (van Doorn & Nibbering, 1978; Nibbering, 1979b). In cooperation with Professor K. Levsen and with use of the reversed geometry mass spectrometer at the University of Bonn, Germany, it was shown that the long-lived $C_6H_6O^{•+}$ ions generated from the molecular ions of 2-phenoxyethyl halides were indeed a mixture of phenol and 2,4-cyclohexadienone ions (Borchers et al., 1977) as suggested earlier by drift-cell ICR experiments (see Section IV). Subsequently and in cooperation with Professor M.L Gross it was found that the kinetic energy release measured for the CO loss from the metastably decomposing molecular ion of phenol was significantly larger than from the 2,4-cyclohexadienone ion, but that it decreased as a function of the phenol ion lifetime (for studying relatively longer-lived phenol ions the accelerating voltage was decreased) so much so that it approached the value for the CO loss from the metastably decomposing 2,4-cyclohexadienone ion (Russell, Gross, & Nibbering, 1978). This observation was then used as a tool to study the metastably decomposing $C_6H_6O^{•+}$ ions from the molecular ions of 2-phenoxyethyl halides which behaved like the phenol ions. This led to the conclusion that—taking into account the deuterium labeling results—the 1,5-hydrogen shift to one of the ortho-positions of the phenyl ring in the halides molecular ions was successively followed by transfer of one of the hydrogen atoms of the generated ring methylene group to the oxygen atom possibly with assistance of the halogen atom and cleavage of the C–O bond to give the phenol ions (Russell et al., 1979a). For the assistance of the halogen atom in the hydrogen transfer a previous

study was invoked on the enol-keto isomerization of the $[M - C_2H_4]^{\bullet+}$ ion from *o*-hydroxybutyrophenone which was possible by virtue of the hydroxyl group in the *ortho*-position acting like a catalyst (Molenaar-Langeveld et al., 1978). Of course, the study of the metastably decomposing $C_6H_6O^{\bullet+}$ ions from the molecular ions of 2-phenoxyethyl halides (Russell et al., 1979a) could not fully eliminate the presence of some fraction of long-lived 2,4-cyclohexadienone ions, the latter species being confirmed later on by a photodissociation study of the $C_6H_6O^{\bullet+}$ ions from 2-phenoxyethyl chloride in which also the $C_6H_6O^{\bullet+}$ ions from phenol, 2,4-cyclohexadienone, and phenyl ethyl ether were investigated (van Velzen et al., 1982). That study and many subsequent photodissociation experiments during my career took place always in cooperation with Dr. W.J. van der Hart of the University of Leiden in The Netherlands. It is now appropriate to mention another important development around that time, which is the concept of ion/molecule complexes suggested to occur as intermediates during unimolecular dissociations of ions, in particular metastably decomposing ions. It started with the observation that the metastable ions $[CH_2O=CH_2CH_2CH_3]^+$ and $[CH_2O=C(CH_3)_2]^+$ behaved the same in dissociation channels and kinetic energy release for which as explanation the intermediacy of a proton bonded complex of formaldehyde and propene was proposed (Bowen, Stapleton, & Williams, 1978). Then it was reported that in the metastably decomposing molecular ion of 3,20-diaminopregnane a hydrogen from the amino group at C(20) was transferred to the amino group at C(3) as shown by deuterium labeling which distance could not be bridged by a direct hydrogen transfer over the rigid steroid skeleton, but had to involve an intermediate ion/molecule complex (Longevialle & Botter, 1980). Practically at the same time the formation of phenol ions from ionized phenyl alkyl ethers was interpreted as proceeding through an alkyl ion/ phenoxy radical complex (Morton, 1980). Since then the concept of ion/molecule complexes as intermediates in unimolecular ion dissociations has received an extensive research interest and has been widely accepted by the gas-phase ion chemistry community as reflected by several reviews on this topic (Morton, 1982; McAdoo, 1988; Bowen, 1991a,b; Longevialle, 1992; McAdoo & Morton, 1993) including publications on the criteria and theoretical aspects of ion/molecule complexes as intermediates (Morton, 1992, 2005). Nevertheless, 10 years later a study of the dissociation dynamics of the phenyl ethyl ether radical cations by photoelectron photoion coincidence arrived at the conclusion that it was unlikely that the phenol ion was generated from it by the intermediacy of an ion/radical complex (Riley & Baer, 1991), but this was promptly refuted by another study showing on the basis of deuterium labeling, appearance energy and kinetic energy release measurements that the transition state of metastably decomposing phenyl ethyl ether radical cations was best represented as a proton bonded complex of the phenoxy radical and ethene (Harnish & Holmes, 1991). Also the phenol ion formation from the 2-phenoxyethyl halides discussed above can be readily explained by the intermediacy of ion/radical complexes (Nguyen, Cheng, & Morton, 1992), but the 2,4-cyclohexadienone ion formation rationally must involve a 1,5-hydrogen shift in their covalently bonded molecular ion structure. The latter conclusion has been reinforced in my group many years later for part of the decomposing molecular ions of

some 3- and 4-substituted aryl *n*-propyl ethers, in particular the 3-methoxy-substituted aryl *n*-propyl ether, where the substituted 2,4-cyclohexadienone ions were formed with a reversible 1,5-hydrogen shift (Matimba, Ingemann, & Nibbering, 1996). Such a reversible 1,5-hydrogen shift was also observed for the decomposing molecular ions of alkyl phenyl thioethers, but here the formation of the 2,4-cyclohexadienthione ions was not found (Van Amsterdam, Ingemann, & Nibbering, 1995). It should further be mentioned at this point that a decade ago photoionization experiments with an extended series of deuterium labeled phenyl *n*-propyl ethers have led to a mechanistic picture in which not only an *i*-propyl cation/phenoxy radical complex is involved, but also complexes containing corner-protonated cyclopropane and where the loss of propene by a conventional 1,5-H shift from the 2-position of the *n*-propyl group to the remaining part of the decomposing ion takes place (Traeger & Morton, 1996). Finally, the formation of ion/neutral complexes in dissociation reactions of ionized propoxypyridines has been shown to be isomer dependent (Molenaar-Langeveld et al., 2000). From all these studies it is clear that it depends on the critical energies to form an ion/molecule complex or to rearrange the conventional and covalent ion structure *via* a 1,5-hydrogen shift to another covalent, but distonic ion structure (Hammerum, 1988) and further barriers in the potential energy surface whether the unimolecular dissociation of an ion will take place *via* an ion/ molecule complex or a covalently bonded structure. Anyhow, the borderline between unimolecular and bimolecular gas-phase ion chemistry has become very thin over the last 25 years.

Before closing this section, a few other studies performed in the covered time period should be mentioned. One of them concerns the electron ionization induced loss of hydrogen cyanide from 2-, 3-, and 4-cyanopyridines that were selected to find out by specific [13]C- and ^{15}N-labeling of the pyridine ring and cyano groups whether Dewar and ring-opened structures of their molecular ions were involved, a timely topic at that time in the mass spectral behavior of benzene and pyridine (Molenaar-Langeveld et al., 1979). This study was carried out in cooperation with Professors K.R. Jennings of the University of Warwick in Coventry, England and J.H. Beynon of the University College of Swansea in Swansea, Wales. The results obtained indeed supported Dewar structures, accounting for the observed equilibrated positional interchange of the ring carbon atoms, and ring-opening and ring-closing closure reactions, accounting for the equivalence of the pyridine ring and cyano group nitrogen atoms in the hydrogen cyanide loss, which was further confirmed by the behavior of the open-chain and [13]C- labeled 1,4-dicyanobuta-1,3-diene compound. The other was the study of the abundant loss of a molecule of water from the molecular ion of the tricyclic ketone *cis*-2,3-trimethylene-1-tetralone due to an intramolecular reduction of the carbonyl group for which mechanistic details were elucidated by deuterium labeling (Zwinselman, van den Heuvel, & Nibbering, 1980).

VI. FIELD IONIZATION KINETICS AND FIELD DESORPTION MASS SPECTROMETRY

As mentioned already in Section III, research in field ionization and field desorption mass spectrometry was started in my group

in 1974 upon delivery of the combined electron ionization/field ionization/field desorption source for the Varian MAT 711 double focusing mass spectrometer. Most of this research has been performed with use of this instrument, but later on also the ZAB-2HF reversed geometry mass spectrometer (VG Micromass, Altrincham, UK) which became operational in 1983 (see Section VIII) has been used for it. In this section the whole period of this research will be covered, but for clarity reasons the presentation will be given in two sections, that is, the first on field ionization kinetics and the second on field desorption mass spectrometry.

A. Field Ionization Kinetics

This method has been developed around the 1970s (Chait & Kitson, 1970; Schulze & Richter, 1971; Derrick, Falick, & Burlingame, 1972) following the original work on fast metastable ions in field ionization mass spectrometry (Beckey, 1961). The principles of field ionization kinetics and its applications to mechanistic studies of unimolecularly decomposing ions have been described in a number of reviews that include the research performed in my group (Nibbering, 1984a, 1991, 2000, 2005a). A selection of examples will be presented below. The field ionization kinetics method allows studying 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 behavior 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. In combination with stable isotopic labeling the method is therefore very powerful to uncover mechanistic details in comparison with electron ionization where the residence time of the ions of approximately 1 μsec in the ion source results in an integrated view of the reactions, including frequently occurring hydrogen and skeletal rearrangements, that have taken place following the ionization event.

1. Positive Ions

After having developed in-house software to acquire and process field ionization kinetics data from the Varian MAT 711 double focusing mass spectrometer by computer (van der Greef et al., 1977) the first compound that was studied was 2-phenoxyethyl chloride. Its molecular ion suffered from an equilibrated positional interchange of the phenoxy group and the halogen atom prior to decomposition as discussed in Section III. Although in that study (Theissling, Nibbering, & de Boer, 1971), it was carefully checked that this positional interchange was not due to a thermal process in the neutral molecule, field ionization kinetics experiments showed definitely that the interchange occurred in the molecular ion (Van der Greef, Theissling, & Nibbering, 1978). Subsequently, 3-phenylpropanal was studied because under electron ionization conditions an extensive hydrogen randomization and even an *ortho* attack by the carbonyl oxygen, albeit to a minor extent, in its molecular ion had been found previously by deuterium labeling (Venema, Nibbering, & de Boer, 1970) and ^{13}C-labeling (Venema & Nibbering, 1974b),

respectively. The field ionization kinetics measurements in combination with deuterium labeling of this molecule and field ionization spectra of its isomer 3-phenyl-2-propen-1-ol together with kinetic energy release measurements (performed at the University of Ottawa, Canada) led to the following conclusions. At short lifetimes ($\leq 10^{-10.2}$ sec) the molecular ion of 3-phenylpropanal eliminates C_3H_4O (as $CO + C_2H_4$) and C_2H_2O by transfer of the aldehydic hydrogen to the ring, while these processes at longer ion lifetimes (up to two $10^{-9.6}$ sec) are accompanied by two distinct hydrogen exchange mechanisms, that is (i) interchange between the aldehydic and benzylic hydrogens and (ii) interchange between the aldehydic and *ortho* hydrogens. At longer ion lifetimes a third hydrogen exchange mechanism occurs, that is, between the hydrogens of position 2 and the phenyl ring, while part of the molecular ions of the 3-phenyl-2-propen-1-ol rapidly isomerize to the structure of 3-phenylpropanal (Wolkoff, van der Greef, & Nibbering, 1978). In a similar way the elimination of a water molecule from the molecular ion of 3-phenylpropanol has been investigated where previously it had been found from an electron ionization study that this reaction in the metastable timeframe occurred after a complete exchange between the hydroxyl hydrogen, the hydrogen atoms of the methylene group of position 3, and the *ortho* hydrogens (see Section II). Field ionization kinetics measurements showed that the molecular ions with lifetimes as short as 10^{-11} sec lost a molecule of water *via* a specific 1,3-elimination, while at longer ion lifetimes first a complete exchange between the hydroxyl hydrogen and the methylene hydrogen atoms of position 3 and then also involving the *ortho* hydrogens accompanied this reaction (Van der Greef & Nibbering, 1979a). The structure of the formed $[M - H_2O]^{+\bullet}$ ions has been probed a few years later by collisional activation and charge stripping experiments, but that was indistinguishable from those of cyclopropylbenzene and/or allylbenzene under the applied conditions (Lay et al., 1983). Another field ionization kinetics study concerned the formation of the ions with m/z 33 from the molecular ion of isobutyl alcohol (Tajima, van der Greef, & Nibbering, 1978). Deuterium labeling showed that the molecular ions with lifetimes of 10^{-11} sec generated these ions *via* a 1,4-hydrogen shift from one of the methyl groups to oxygen, followed by a 1,2-elimination of protonated methanol with a hydrogen from the other methyl group. At longer molecular ion lifetimes, that is, after $\sim 4 \times 10^{-10}$ sec, this reaction occurs following a complete exchange between the hydroxyl hydrogen and the hydrogens from both methyl groups. In the metastable time window at molecular ion lifetimes of 10^{-6}–10^{-5} sec, also the methylene hydrogens participate in the exchange process, albeit to a minor extent. The latter exchange was explained in terms of covalently bonded ion structures like the exchanges at much shorter ion lifetimes (Tajima, van der Greef, & Nibbering, 1978). Later on the formation of the protonated methanol ions from isobutyl alcohol at molecular ion lifetimes of 10^{-6}–10^{-5} sec was rationalized in terms of intermediate ion/molecule complexes that first were suggested to consist of methanol and propene (Bowen & Williams, 1981), but afterwards of the distonic ion of methanol and propene (Hammerum & Derrick, 1986; Bowen, 1991a). That hydrogen atoms can migrate very fast over a carbon skeleton was shown in cooperation with Professor M.L. Gross by a deuterium labeling study of 1,3-butadiene where

from the loss of a methyl radical from its molecular ion it was found that the hydrogen randomization was complete at molecular ion lifetimes of $\sim 10^{-11}$ sec (Russell et al., 1979b). This methyl radical contained more than 85% of the terminal carbon atoms at molecular ion lifetimes of $\sim 10^{-11}$ sec as shown by ^{13}C labeling, but at longer ion lifetimes the inner carbon atoms also participated increasingly, though slowly, in this methyl loss which became almost random at 10^{-5} sec. These observations have been explained by invoking the formation of a methylcyclopropene ion in a rate determining step at short ion lifetimes 10^{-11}–10^{-9} sec, that at longer ion lifetimes equilibrates with 1,3-butadiene by ring opening and ring closure reactions. Another study in cooperation with Professor D.J. McAdoo of the University of Texas Medical Center in Galveston, Texas, that showed extensive hydrogen and carbon skeletal rearrangements at increasing molecular ion lifetimes, concerned *n*-butanoic acid. Its molecular ion eliminates the original terminal methyl group and ethylene, containing the carbon and hydrogen atoms of positions 3 and 4, at lifetimes $<10^{-9}$ sec, but at longer times all the alkyl carbon atoms and all hydrogens participate in these reactions as shown by the extensive ^{13}C- and deuterium labeling applied (Zwinselman et al., 1983a; McAdoo et al., 1985). The methyl elimination is initiated by a 1,4-H shift from the 3-position to the carbonyl oxygen, followed by a 1,2-shift of the protonated carboxyl group from the 2-position to the 3-position after which the methyl group can be eliminated to give protonated acrylic acid. Yet, a more refined mechanistic picture in combination with high-level theoretical calculations has been presented afterwards (Hudson & McAdoo, 2001; Loos, Schröder, & Schwarz, 2005). Surprisingly, 2-ethylbutanoic acid which in cooperation with Professor J.H. Bowie of the University of Adelaide, Australia, was selected for a study to find out whether the radical site, generated at the C-4 atom after a 1,5-H shift to the carbonyl oxygen, would lead to hydrogen exchange between the C-4 and C'-4 positions in its molecular ion, behaved very differently. Extensive ^{13}C and deuterium labeling in both methyl groups showed that the ethene and ethyl eliminations occurred without any detectable exchange between the hydrogen or carbon atoms of the two original ethyl groups over the whole range of studied ion lifetimes and that on the basis of collision-induced dissociation experiments the structure of the $[M-ethyl]^{+\bullet}$ ions was for 95% carbonyl protonated crotonic acid (Kluft et al., 1998). These observations led to the conclusions that the ethene elimination occurred faster after the 1,5-H shift from C-4 (or C'-4) to the carbonyl oxygen than the time required for the possible hydrogen exchange and that the ethyl elimination took place after a 1,4-H shift from position C-3 (or C'-3) to the carbonyl oxygen by a fast and simple cleavage of the C-2–C'-3 (or C-3) bond. The latter reaction is presented in Scheme 16.
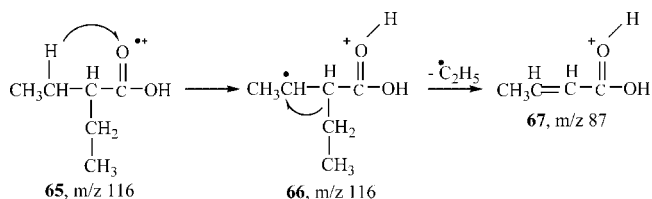
Another molecule that has been studied in detail was methoxycyclohexane, which was chosen with the aim to find out whether its molecular ion eliminates methanol in a stereospecific way as was found earlier for the loss of cyclohexanol (Derrick, Holmes, & Morgan, 1975). It was observed that the major part of methanol is lost at molecular ion lifetimes $\leq 10^{-10.1}$ sec *via* a 1,4-elimination, $\sim 19\%$ of this channel being a stereospecific *cis*-elimination and the remaining 81% being only site-specific (Molenaar-Langeveld & Nibbering, 1986). This pointed at a ring opening of the major part of the molecular ions by rupture of the C(1)–(C-2) bond which was in sharp contrast with the highly stereospecific ($>90\%$) *cis*-1,4-elimination of water from the obviously ring-closed structure of ionized cyclohexanol (Derrick, Holmes, & Morgan, 1975). Another interesting observation for methoxycyclohexane was the sudden increase of a non-stereospecific 1,3-elimination of methanol between 10^{-10} and 10^{-9} sec at the expense of the 1,4-elimination for which on the basis of energetic arguments the key intermediates of ionized 1-methoxyhexene-1 and 6-methoxy-hexene-1 have been proposed, respectively (Molenaar-Langeveld & Nibbering, 1986). The latter ionized molecule was shown by ^{13}C and deuterium labeling to rearrange for the major part to methoxycyclohexane that after ring contraction to ionized 2-methyl-1-methoxycyclopentane lost an ethyl radical (Molenaar-Langeveld, Fokkens, & Nibbering, 1988). In an earlier study also the formation of 3-methoxyhexene-1 from ionized methoxycyclohexane had been found at ion lifetimes of 10^{-10} sec that is responsible for the elimination of a propyl radical, being quite different from the textbook propyl loss found at $<10^{-10}$ sec (Molenaar-Langeveld & Nibbering, 1983), which proceeds *via* successive cleavage of the C(1)–C(2) bond, 1,5-H shift from C(6) to C(2), and rupture of the C(4)–C(5) bond (Budzikiewicz, Djerassi, & Williams, 1967). Two other studies should be mentioned that were performed with use of the Varian MAT 711 instrument before presenting some field ionization kinetics results obtained with use of the VG Micromass ZAB-2HF double focusing reversed geometry mass spectrometer. The first is the loss of hydrogen cyanide from the molecular ion of pyridine where it was found from ^{13}C labeling in the 2-position that HCN and H^{13}CN were lost in a 1:1 ratio up to molecular ion lifetimes of $10^{-10.2}$ sec, whereas the hydrogens already start to lose their positional identity at 10^{-12} sec showing that the hydrogens can move along an unrearranged pyridine ring skeleton (Kluft & Nibbering, 1986). The second is a cooperative study with Professor R. Herzschuh of the Karl Marx University in Leipzig, Germany, on the elimination of cyclopentene from the ionized endo isomer of 8,9-disubstituted tricyclo [5.2.1.0^{2,6}] decenes that is not observed for the exo isomer. This reaction requires migration of the hydrogen atoms of carbon positions 8 and 9 to the double bond carbon positions 3 and 4, and is then followed by elimination of cyclopentene *via* a retro-Diels–Alder reaction as summarized in Scheme 17.

Such a double hydrogen atom transfer for neutral systems is known as a suprafacial dyotropic hydrogen transfer and thermally allowed $[\sigma^2 s + \sigma^2 s + \pi^2 s]$ pericyclic reaction (Woodward & Hoffmann, 1970). The question to be addressed was whether the two hydrogen atoms in the molecular ions were migrating in a concerted or stepwise fashion. From the field ionization kinetics experiments strong support was obtained that the hydrogen atoms were migrating in a concerted way to the double bond (Kluft
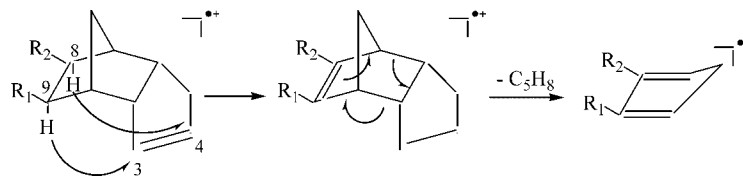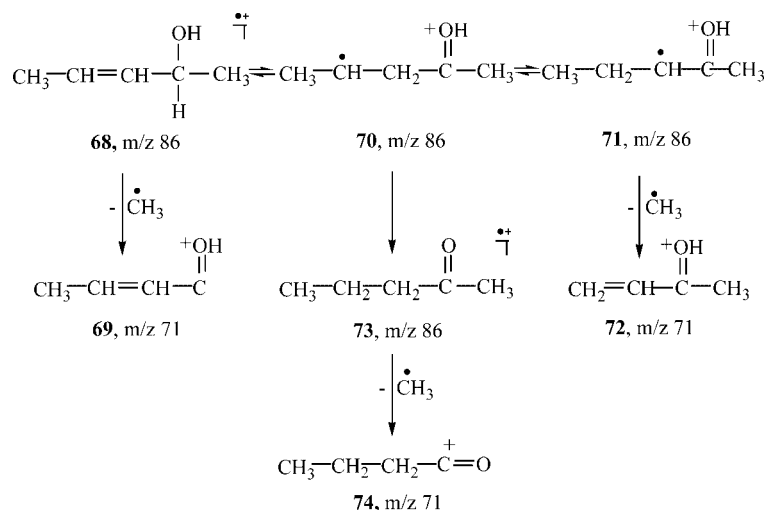

SCHEME 16.

SCHEME 17.

et al., 1986), a conclusion that later on was supported further by a computational study (Nibbering & van der Hart, 2002). In 1987 the VG Micromass ZAB-2HF double focusing reversed geometry mass spectrometer started to be used for field ionization kinetic experiments after having taken the necessary steps to couple it to the Varian Spectro System 100 data system of the Varian MAT 711 instrument for recording on-line, storing and processing the data. This instrument enabled to measure more accurately the position of a maximum or even to observe different maxima in normalized rate curves because of the high kinetic energy resolving power of its electric sector ($\sim$15,000) that consequently resulted in more accurate lifetime measurements. The first was shown by a study of the carbenium ion formation from isomeric butyl chlorides and bromides by halogen atom loss where the maximum rate was found to shift to longer lifetimes in the order t-butyl $<$ s-butyl $<$ i-butyl $<$ n-butyl in line with the stability order of the corresponding ions (Kluft & Nibbering, 1989). The second was shown in the same study for the loss of a bromine atom from ionized i-butyl and n-butyl bromide, where a second maximum in the normalized rate curves was observed at a longer molecular ion lifetime. This was interpreted as being due a 1,2-hydride shift-assisted C-Br cleavage, giving the t-butyl and s-butyl cations, respectively. It should be noted that such suggested pseudo direct bond cleavage mechanism had been proposed also in photoionization (Traeger, 1980) and photoelectron-photoion coincidence (Rosenstock et al., 1982; Oliveira et al., 1988) studies.

The observation of different maxima in the normalized rate curves also prompted to have a closer look at the methyl loss from ionized 3-penten-2-ol. From a previous deuterium labeling study three channels for this reaction had been found (Zwinselman et al., 1981a) that have been summarized in Scheme 18.

At ion lifetimes $<10^{-10.5}$ sec the methyl group from position 1 was lost leading to the formation of protonated crotonaldehyde, at lifetimes between $10^{-10.5}$ and 10^{-9} sec the methyl group of position 5 was eliminated which was suggested to give protonated methyl vinyl ketone, while at longer ion lifetimes again the methyl group of position 1 was expelled which was proposed to yield the butyryl cation. The normalized rate curve for methyl loss indeed showed two maxima, one at $10^{-10.5}$ sec corresponding with methyl loss from position 1 according to the applied deuterium labeling and another at $10^{-10.1}$ sec. Collision-induced dissociation experiments were then performed on the [M–methyl]$^+$ ions generated at $10^{-10.5}$ and at $10^{-10.1}$ sec, and the resulting time-resolved MS/MS spectra indeed matched with those of the protonated crotonaldehyde and methyl vinyl ketone reference species, respectively, as shown in Figure 1 (Zappey, Ingemann, & Nibbering, 1991a).

Sometimes the intensities of the fragment ion signals were too low to perform field ionization kinetics experiments. To overcome this problem, an infrared laser was used to vibrationally excite by multiphoton absorption the molecules in the region between the emitter and counter electrode of the field ionization source with a notable effect on the aimed fragmentation of the for that purpose studied molecule of diethyl ether (Aben & Nibbering, 1995). Unfortunately, this has not been further exploited.
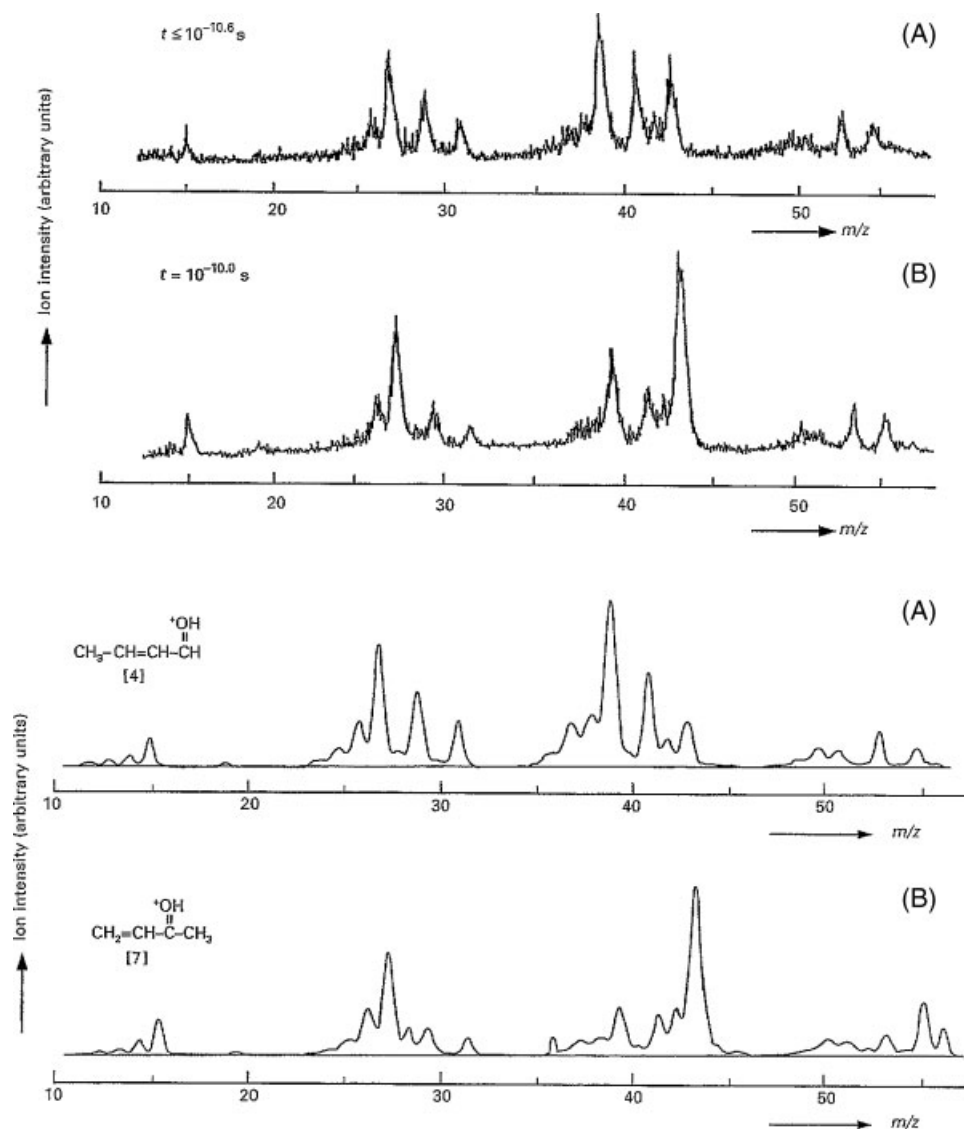

SCHEME 18.

FIGURE 1. The **upper panels A** and **B** show the collision-induced MS/MS spectra of the (M-methyl)$^+$ ions, generated upon field ionization from the molecular ion of pent-3-en-2-ol at molecular ion lifetimes of $\leq 10^{-10.6}$ and $10^{-10.0}$ sec, respectively. The **lower panels A** and **B** show the reference collision-induced dissociation MS/MS spectra of protonated crotonaldehyde and protonated methyl vinyl ketone, respectively. Reprinted from Zappey, Ingemann, and Nibbering (1991a) with permission from John Wiley & Sons Ltd., Copyright 1991.

Before closing this section, the comparative study of field ionization kinetics and angle-resolved mass spectrometry in cooperation with Professor R.G. Cooks should be mentioned. It showed that the latter can give the same type of information on unimolecular ion dissociations as the former. In the angle-resolved mass spectrometry experiments the dissociations of high kinetic energy mass selected ions are studied as a function of the laboratory scattering angle, which is related to the internal energy deposition upon collision and hence ion lifetimes (Laramee, Carmody, & Cooks, 1979; Hubik et al., 1980). An excellent agreement between the two methods was observed for the molecules studied, which were 3-methyl-3-buten-2-ol, 3-penten-2-ol, and cyclohexene (Burinsky et al., 1981). Of course,

such an agreement is obtained if the high kinetic energy mass selected ions have not rearranged to another structure during their flight from the ion source to the collision region.

2. Negative Ions

Two studies concerned negative ion field ionization, that is, tunneling of an electron from the emitter to a nearby molecule in the gas phase. This topic had received inspiration from the drift-cell ion cyclotron resonance research on negative ions in my group (see Section IV) and from two publications, which had reported that molecular anions could be desorbed from a

multi-point field surface at a field strength below that of field emission of electrons (Anbar & St. John, 1975a,b). The emission of electrons from the emitter was also observed in my group, but were initially minimized as much as possible by increasing the distance between the emitter and the counter electrode, which enabled to obtain very abundant molecular anions of tetra-cyanoethylene and perform field ionization kinetics experiments on negative ions from *m*-nitrobenzoic acid (van der Greef & Nibbering, 1979b). In a subsequent publication and in coopera-tion with Professor F.W. Röllgen of the University of Bonn, Germany it was shown that molecular anions from not only tetracyanoethylene, but also multiply halogen/cyano-substituted *p*-benzochinones and dodecacarbonyl-tetracobalt could be generated by a field ionization process at field strengths below the onset field strength for field electron emission (Mes et al., 1980). In that publication it was also theoretically discussed that the electron affinity of the molecule should be larger than half of the work function of the emitter surface to avoid electron detachment of the initially generated molecular anion and thus to generate sufficiently stable molecular anions. Anyhow, this work has led to the development of negative ion field desorption in close and already at that time existing cooperation with the University of Bonn, as will be presented in the Subsection *B2*.

B. Field Desorption

1. Positive Ions

As mentioned in the beginning of this section, the use of field desorption in my group started in 1974. Initially the desorption of ions from compounds deposited on the activated 10 μm diameter tungsten wire emitter was performed by manually controlled heating, but this led to a very frequent breaking of the emitter. It was therefore decided to build in-house an ion emission control unit as had been used in a joint study of *N*-substituted propane and butane sultams with Professor H.-R. Schulten of the University of Bonn, Germany (Schulten & Nibbering, 1977) and an emitter activation unit. A schematic representation of the in-house built emission control unit is given in Figure 2.

It consists of a feedback system in which the total ion current is measured on the cathode (I_m) and compared with a preset value (I_s). The outcome of the comparison will result in an increase of the emitter current if $I_m < I_s$ or in a decrease $I_s < I_m$ (rise and fall mode). The system can also be set to respond only if $I_m < I_s$ (rise only mode). In the rise and fall mode a stable ion emission current can be obtained which can last for minutes as shown in Figure 3 for field desorbed cortisol (van der Greef & Nibbering, 1977) or even hours depending on the amount of sample deposited on the emitter or the preset value of ion emission.

The rise only mode was used for field desorption kinetics experiments (van der Greef & Nibbering, 1977) and has been applied in an extensive low- and high-resolution field desorption study of the fragmentation of deuterium labeled analogs of the α-amino acid methionine (van der Greef et al., 1978). With use of the emission control unit numerous positive ion field desorption analyses of compounds were successfully performed for not only the department of chemistry and other departments of the University of Amsterdam, but also chemistry department and
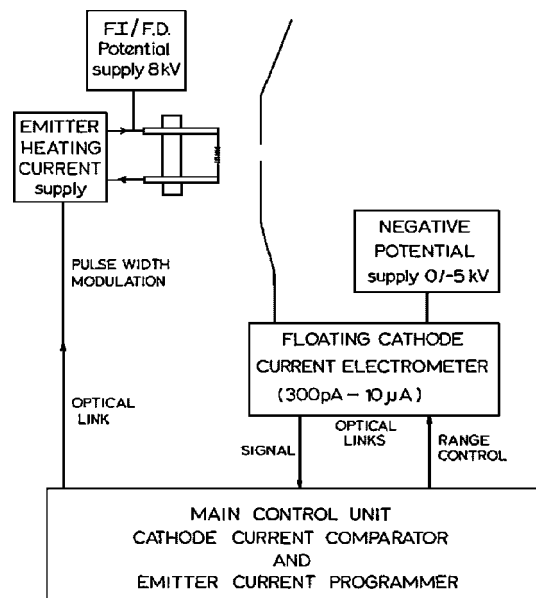
FIGURE 2. Schematic representation of emission-controlled field desorption mass spectrometry.

sometimes medical faculties of other Dutch universities and the National Cancer Institute in Amsterdam, The Netherlands. The compounds included a large variety of thermally labile or unvolatile organic compounds, such as the potassium salt of
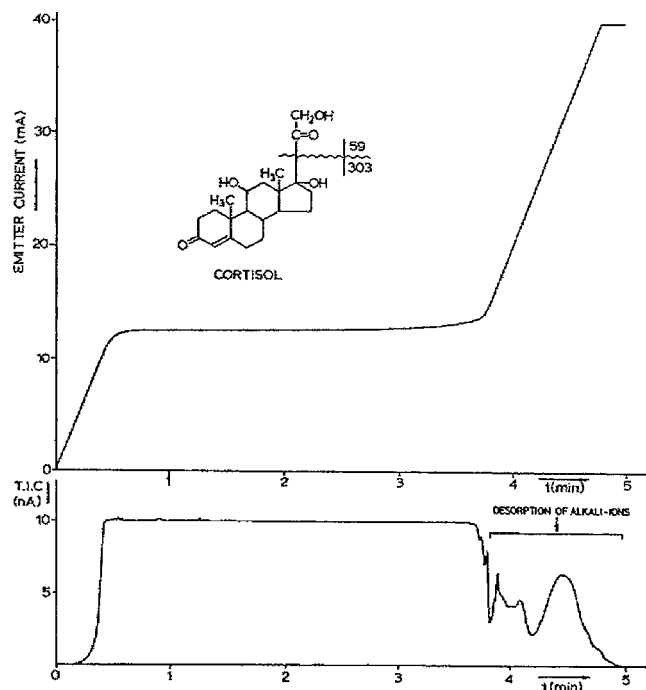
FIGURE 3. Thermogram (upper part) and total ion current versus time plot (lower part) of an emission-controlled field desorption experiment with cortisol. Reprinted from van der Greef and Nibbering (1977) with permission of Elsevier Scientific Publishing Company, Amsterdam, Copyright 1977.

perylene sulfonic acid, synthetic disulfides, cystine, numerous organometallic compounds, nucleosides, nucleotides, glycosides isolated from plants, peptides up to 2,000 Daltons, the copper complex of the glycopeptide bleomycin, methotrexate and metabolites, the carcinogenic 2′,3-dimethyl-4-hydroxyamino diphenyl, etc.

Sometimes the analyses performed and the mass spectrometric results obtained led to joint publications, such as on a series of various metal carbonyl 1,4-diazabutadiene compounds (Staal et al., 1981), on the identification of a compound isolated from the urine of a neonate with respiratory insufficiency and convulsions, which was shown to be a mixed disulfide of 2-mercaptoethane sulfonate and cysteine (Duran et al., 1981), and on the identification of 2-acylindole alkaloids from leaves of *Pterotaberna inconspicua* (Bakana et al., 1984). Later on comparative studies were performed with the ionization method of fast atom bombardment, such as for the loss of ammonia from protonated arginine. By varying the current through the emitter, field desorption spectra could be obtained exhibiting either only the signal of the protonated molecule or also the signal resulting from loss of ammonia, that according to ^{15}N-labeling contained exclusively one of the nitrogen atoms of the guanidyl group (Zwinselman et al., 1983b). The same observation was made for the metastably decomposing ions of ^{15}N-labeled protonated arginine generated by fast atom bombardment, but part of the ions decomposing in the ion source seemed to behave differently. Anyhow, field desorption gave much less fragmentation than fast atom bombardment. The same was true in such comparative study of the geometrically isomeric maleic and fumaric acids, and their methyl homologs and of the isomeric phthalic acids (Dallinga et al., 1984). No fragmentation was observed under the measuring conditions of field desorption, whereas an abundant fragmentation took place upon fast atom bombardment. The $[M + H]^+$ ions of the geometric Z-isomers showed only loss of water to a significant extent, whereas those of the E-isomers additionally fragmented by either successive loss of water and carbon monoxide or elimination of carbon dioxide. Similarly, phthalic acid suffered from less fragmentation than its isomeric iso- and terephthalic acid.

In field desorption multiple protonation or cationization can occur with appropriate molecules, as has been reported for some sodium cationized polysaccharides where $[M + nNa]^{n+}$ signals were observed with $n = 1, 2,$ and 3 (Linscheid et al., 1981). Many years later it has been possible in my group to multiply cationize polyethylene glycols 3400 and 4600 with up to seven alkali cations using in that case a JEOL JMS SX/SX 102A (JEOL, Akishima, Tokyo, Japan) four-sector mass spectrometer (Guo et al., 1999). This instrument, having an excellent performance, was equipped with electron-, chemical-, field-, field desorption-, and fast atom bombardment ionization sources and could be coupled with GC or HPLC. It was obtained 1 year after the 12th International Mass Spectrometry Conference held in 1991 at Amsterdam, that the author had presided and had organized together with a very pleasant local organizing committee. The acquisition of this instrument was funded jointly by the chemistry division of the Netherlands Organization for Scientific Research (SON/NWO) and the University of Amsterdam as a replacement of the Varian MAT 711 instrument purchased in 1969 (see Section III).

2. Negative Ions

It is now appropriate to present the subject of negative ion field desorption as announced at the end of the Subsection *A2*. Following the successful generation of negative ions in the gas phase by field ionization (Mes et al., 1980), the next step was to desorb negative ions from the emitter below the threshold of field electron emission. To this end smooth wire cathodes were used on which the sample mixed with an aqueous solution of poly-ethylene oxide in a 1:1 ratio was deposited, while the potential difference and the distance between the cathode and the slotted anode were decreased and increased, respectively, with respect to the values used in positive ion field desorption. In this way negative ion field desorption mass spectra were obtained for various organic and inorganic compounds, including arginine, sucrose, the tripeptide LeuGlyGly, the sodium salt of 2-naphthalene-sulfonic acid, and inorganic salts (Ott et al., 1980). In some cases LiCl was added to the mixture of sample and polyethylene oxide, resulting in $[M + Cl]^+$ ion formation, such as for chloramphenicol, 20-hydroxycholesterol, and sucrose. The method was further exploited to show the successful analysis of organic salts from aromatic compounds (Ott et al., 1981a), of sugars, sulphonic, and fatty acids either clustered with Cl^- (sugars) or their anions (acids) (Zwinselman et al., 1981b), of volatile molecules, such as formic and acetic acid, by donating them from the gas phase onto a negatively charged Cl^- or NO_3^- ion donating surface (Ott et al., 1981b), of anionic surfactants (Dähling et al., 1982) and of the detection of the fluoroborate anion in water at ppb levels in view of a possible contamination of a water well with sodium tetrafluoroborate (van der Greef et al., 1982a). For non-acidic compounds such as saccharides and nucleosides, it was shown that their $[M-H]^-$ ions were generated by ion/molecule reactions in the space charge region of the negatively charged sample layer (Dähling et al., 1983).

Frequently both positive and negative ion field desorption was applied for sample analysis, an interesting example of an organometallic complex having a Mn–Co bond being presented in Figure 4. The upper panel shows the molecular ion and the Mn-containing fragment ion in the positive ion field desorption mode, while the lower panel shows the Co-containing fragment ion in the negative ion field desorption mode.

During the years of my career I have experienced field desorption mass spectrometry as an elegant and powerful method in the performed analytical work on a large variety of thermally labile and stable unvolatile, apolar and polar organic and organometallic compounds, and on molecules from biochemical/biomedical/biological and environmental sources.

It has the advantage that (i) any type of solvent can be used, (ii) not much sample amount is required, (iii) it is not polluting the ion source, and (iv) it leads to very limited or no fragmentation at all. Of course, the method has also some limitations that (i) the emitters are fragile, (ii) the presence of much salt gives problems in obtaining stable ion emission currents, and (iii) it is applicable to small- and medium-sized molecules in comparison with the presently and very frequently applied ionization methods of electrospray- and matrix-assisted laser desorption ionization. It is for me very gratifying to note that very recently the new and very promising method of liquid injection field desorption ionization has been developed where sample solutions are directly delivered
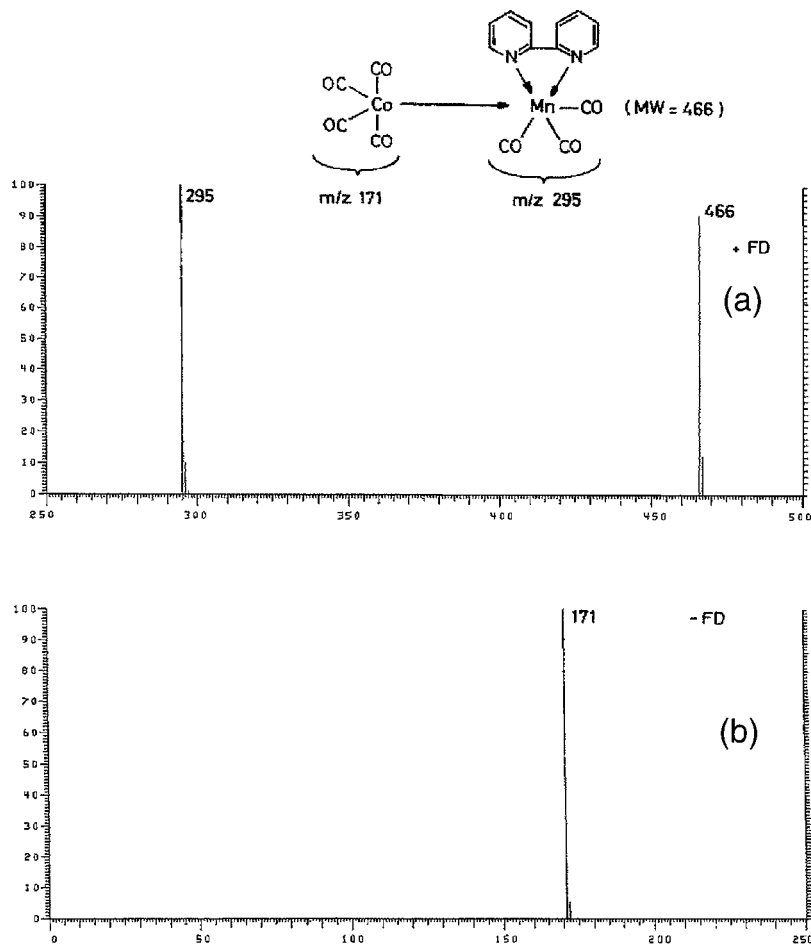
FIGURE 4. Positive ion (**a**) and negative ion (**b**) field desorption mass spectra of a manganese-cobalt complex.

to the emitter in the ion source *via* a capillary dipped in the sample vial without breaking the vacuum (Linden, 2004).

VII. THE YEARS OF FOURIER TRANSFORM ION CYCLOTRON RESONANCE MASS SPECTROMETRY

Research in this area of mass spectrometry has been performed with use of two instruments, which are an in-house constructed instrument and later on a commercial Bruker spectrometer.

The results obtained will be presented in two sections, that is, in the order of the instruments given, respectively.

A. The Home-Built Fourier Transform Ion Cyclotron Resonance Mass Spectrometer

1. Design and Construction

As mentioned in Section V, my attendance of the 22nd ASMS Conference in Philadelphia, Pennsylvania, in 1974 was very inspiring to develop Fourier transform ion cyclotron resonance

(FTICR; see for a simple description of the method Nibbering, 1981) in my group. Upon return in the laboratory I checked with and asked the technical staff whether a broad band FTICR instrument could be constructed on the basis of the existing electronics and computer technology. The answer was no, but the question was repeated regularly because from temporary students of an electrotechnical high school in my group it could be noticed that the developments in electronics and computer technology were very fast. At the end of 1978 the answer of Dr. J.H.J. Dawson, a wizard in electronics and a postdoctoral fellow in my group, was that it might be possible to construct a broad band FTICR instrument. This project was started on April 1, 1979 after a visitor's grant from the Netherlands Organization for Pure Research (ZWO) was arranged for Dr. Dawson. He developed the required electronic and mechanical hardware (cubic inch cell), while Dr. A.J. Noest, at that time a Ph.D. student in my group and with assistance of Dr. C.W.F. Kort, a permanent staff member in the author's laboratory, developed the software for communication between the operator and instrument, and between the instrument and computer, which was a MINC 11 DEC computer with a 32 K memory and two floppy disk units. Although there was a debate in my group whether the instrument should be hardware controlled or software controlled, the choice

at that time was for the former because it was considered to be essential to accumulate the transient signals exactly reproducibly in time, so as to obtain after Fourier transformation well-defined peaks with a good signal-to-ratio. Highlights of the hardware developments were the in-house built frequency synthesizer that could run from 0 to 3 MHz in 61 Hz steps with a scan rate from 0 to 4.10^{+9} Hz and with the possibility to shift the phase by $180°$ at a particular frequency during the scan (Dawson, 1982). In the latter case a notch is created at the frequency with $180°$ phase shift in the pulse of a fast frequency sweep that later has been formulated mathematically (Noest & Kort, 1983) and practically has been used frequently in my group to isolate ions with a particular m/z value for ion/molecule reaction studies. A highlight in the software development was the multiplying of the transient time domain signal by a weight function to reduce peak height errors in the FTICR spectra (Noest & Kort, 1982) that later on has been improved further by including the decay times of the individual ion transient signals being different especially for very different m/z values (De Koning et al., 1989) and obviously is very important for quantitative ion/molecule reaction studies. In November 1979 the decision had to be made in the project whether it should be possible to return physically to the existing situation of the drift-cell ion cyclotron resonance spectrometer, if the project would fail. Because of this uncertainty the existing vacuum system was incorporated in the planned work that did not interfere at all with the ongoing research using the drift-cell ion cyclotron resonance spectrometer being described already in Section IV. Then in March 1980 the existing Varian V-5903 ICR spectrometer was converted into the home-built FTICR spectrometer in 3 weeks time and the first FTICR spectrum was obtained on April 2, 1980. This instrument has been in use for ion/molecule reaction studies until the end of my career in 2001 at the University of Amsterdam. Much of the performed research with use of this instrument in my group has been summarized in a number of invited reviews (Nibbering, 1984b, 1986a,b, 1988, 1990, 1994) in between a series of more general reviews on FTICR that have appeared (Johlman, White, & Wilkins, 1983; Nibbering, 1985a,b, 1992; Laude et al., 1986; Wilkins et al., 1989; Köster et al., 1992; Marshall, Hendrickson, & Jackson, 1998; Marshall, 2000, 2003).

## 2. S_N2, Hydride Ion, S_NAr, H/D Exchange, and $B_{AC}2$ Reactions

One of the first results was on the formation of protonated dimethyl ether by reaction of protonated methanol with methanol. That reaction had been studied before in a drift-cell ICR spectrometer and was proposed to proceed *via* a four-center mechanism in which the proton from protonated methanol exchanged with the methyl from neutral methanol in forming the protonated dimethyl ether product ion by expulsion of water (Henis, 1968). The product ion would thus contain the oxygen atom of protonated methanol, while in my group an S_N2 mechanism was considered to be much more plausible, that is, a back-side attack of neutral methanol on the carbon of protonated methanol under expulsion of water, so that the product ion would contain the oxygen atom of the neutral methanol as visualized in Scheme 19.
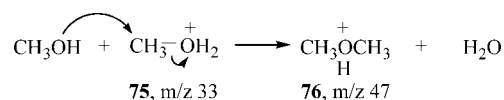

SCHEME 19.

To provide experimental support for this mechanism the idea was to take methanol containing the natural abundant oxygen isotopes, ionize it, eject *all* ions from the FTICR cell by application of appropriate radio frequency pulses with the exception of $CH_3{}^{18}OH_2^+$ which then is in a bath gas of 99.8% $CH_3{}^{16}OH$. Then let the reaction go and eject continuously $CH_3{}^{16}OH_2^+$, formed during the reaction by the facile proton transfer from $CH_3{}^{18}OH_2^+$ to $CH_3{}^{16}OH$, from the FTICR cell with the result that protonated dimethyl ether containing the ^{16}O label was indeed the major ($\sim75\%$) product ion under the applied experimental conditions (Kleingeld & Nibbering, 1982a). This result has led to a lively debate and a number of both experimental and theoretical studies afterwards that have confirmed the S_N2 mechanism, but also have uncovered details of the competing proton transfer channel (Dang & Bierbaum, 1992; Bouchoux & Choret, 1997). Another early project, that was undertaken because of a previous hydride ion transfer study between methoxide and formaldehyde (Ingemann, Kleingeld, & Nibbering, 1982), concerns the reaction of the hydroxide ion with formaldehyde that led to the observation of a peak at m/z 19 in the FTICR spectrum. The frequency of the corresponding FTICR 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 which showed that its formation involved a successive proton abstraction and hydride transfer in the encounter complex followed by elimination of carbon monoxide to give the hydride solvated water molecule as pictured in Scheme 20.

The article on this result (Kleingeld & Nibbering, 1983a) was received for publication on July 30, 1982 prior to the NATO Advanced Study Institute on Chemistry of Ions in the Gas Phase meeting in Vimeiro, Portugal, September 6–17, 1982 where it was presented by me together with other studies from my group in a plenary lecture (Ingemann, Kleingeld, & Nibbering, 1984). At that meeting it was found out that independently H_3O^- had been observed as a product from collision between $OH^- \cdot H_2O$ and H_2 in a longitudinal double mass spectrometer as described in an abstract, published in February, 1982 (Paulson & Henchman, 1982) and also presented at the Vimeiro meeting (Paulson & Henchman, 1984). Later on the H_3O^- ion has been generated also in the chemical ionization source of a VG Micromass ZAB-2HF
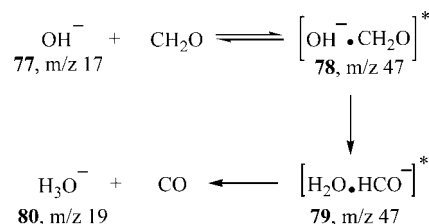
SCHEME 20.

reversed geometry double focusing mass spectrometer where it was subjected after acceleration to a kinetic energy of 8 keV to collision-induced dissociation and charge reversal (de Lange & Nibbering, 1987). In the former experiment exclusively OH⁻ was formed by elimination of molecular hydrogen for which large isotope effects were observed upon deuterium labeling. In the latter experiment much more abundant $H_2^{+\bullet}$ and H_3^+ ions were formed than upon collision-induced dissociation of directly generated and accelerated H_3O^+ ions. The H_3O^- ion has received very much interest afterwards in theoretical, photoelectron spectroscopic, kinetic, and thermochemical studies as summarized in an excellent article that among others reported the hydride-water bond energy to be 60 ± 4 kJ/mol (Miller et al., 1994). In addition to the discussed long-lived H_3O^- ions, such ions are also short-lived intermediates in the H/D exchange between OH⁻ (or OD⁻) and D_2 (or H_2), which was also reported at NATO Advanced Study Institute on Chemistry of Ions in the Gas Phase meeting in Vimeiro, Portugal, September 6–17, 1982 (DePuy, 1984) followed by subsequent publications (Grabowski, DePuy, & Bierbaum, 1983; Troutman Lee & Farrar, 2000). It should be noted that the water solvated hydroxide ion $OH^- \cdot H_2O$, that could be made later on in the low-pressure FTICR cell, also reacts with formaldehyde but now leading to the long-lived tetrahedral intermediate **h** by nucleophilic attack of OH⁻ on the carbonyl carbon of formaldehyde and showing the dramatic effect of solvation on the course of the reaction (van der Wel & Nibbering, 1988b).

$$
\begin{array}{c}
\text{O}^- \\
| \\
\text{H} - \text{C} - \text{H} \\
| \\
\text{OH}
\end{array}
$$

h, m/z 47
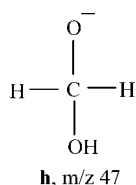
After the successful generation of the H_3O^- ion, a year later also the long-lived NH_4^- ion was generated by my group by first abstracting in an exothermic reaction a proton from formaldehyde by NH_2^- to give HCO^- which subsequently reacted by hydride transfer to an ammonia molecule under expulsion of carbon monoxide to give the hydride solvated ammonia molecule (Kleingeld et al., 1983). This species, which had been one of the negative ion clusters in theoretical calculations of solvation energies as presented also at the Vimeiro meeting (Squires, 1984), has been studied afterwards by negative ion photoelectron spectroscopy (Coe et al., 1985) and has also received much interest in theoretical studies (Ortiz, 1987; Gutowski et al., 1988). Again a year later during a study of the reactions of $O^{\bullet-}$ with methylamine, ethylamine, and dimethylamine a peak was noted at m/z 18 with an intensity higher than could be accounted for by natural isotopes of lower mass ions. This peak shifted to m/z 20 when $^{18}O^{\bullet-}$ was used as reactant ion and to m/z 19 when trideuteromethyl-amine was used as the substrate. Accurate mass measurements of these ions were in agreement with the elemental compositions of H_2O, $H_2^{18}O$, and HDO, respectively, so that the authors were forced to assume that $H_2O^{\bullet-}$ ion can exist as a stable species in the gas phase (De Koning & Nibbering, 1984). In reaction with formaldehyde it gave OH⁻ as the only observed

product suggesting that this ion could best be described as a hydroxide ion to which a hydrogen atom is attached.

Another early study with use of the home-built FTICR instrument was on nucleophilic aromatic substitution in the gas phase that took place in cooperation with Professor C.H. DePuy of the University of Colorado in Boulder, Colorado, where in 1980 I had given upon invitation a 2 weeks summer course on unimolecular and bimolecular gas phase ion chemistry research which I still remember with extremely great pleasure! In that study a great variety of nucleophiles was allowed to react with pentafluoroanisole from which three competitive reaction channels were found being summarized in Scheme 21 (Ingemann et al., 1982).

The minor channel was the ipso substitution on the carbon atom bearing the methoxy group as found earlier for methyl phenyl ether itself (see Section IV). The intermediate channel was the S_N2 subsitution reaction, while the most dominant channel was the S_NAr reaction where a fluoride ion was displaced leading to an F⁻ ion/molecule complex (see Scheme 22). This complex then reacted further by proton transfer, S_N2 and E_2 reactions depending on the nature of the originally attacking nucleophile and showed that the associated potential energy surface could contain various wells.

This work has been extended later on to the isomeric 2-, 3-, and 4-fluoroanisole, where an additional channel was found, that is, proton abstraction from the aromatic ring by the nucleophile (Ingemann & Nibbering, 1983). The resulting deprotonated species exchange all their aromatic hydrogens with deuterium in the presence of D_2O, while those from 2- and 4-fluoroanisole also exchange their methyl hydrogens *via* an intramolecularly generated primary carbanion, that is, through proton abstraction from the methyl group by a deprotonated *ortho* position of the aromatic ring. Similar exchanges were observed prior to the formation of phenoxide from anisole itself by S_N2 substitution with OH⁻ (Kleingeld & Nibbering, 1983b). A subsequent study of ethyl, *n*- and *i*-propyl pentafluorophenyl ethers has allowed to
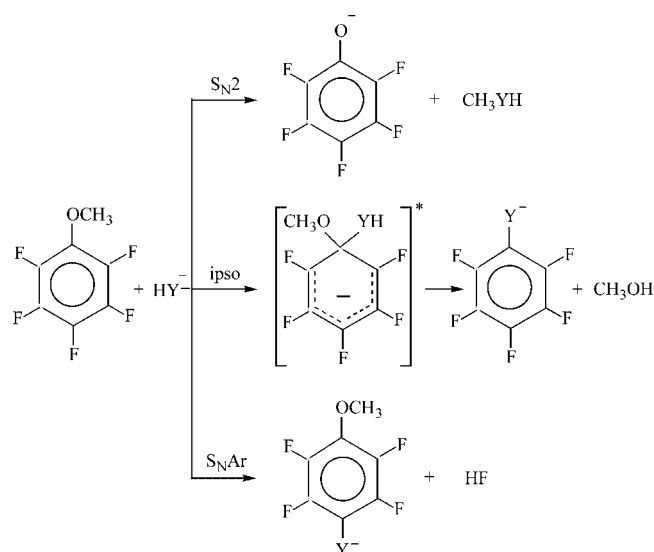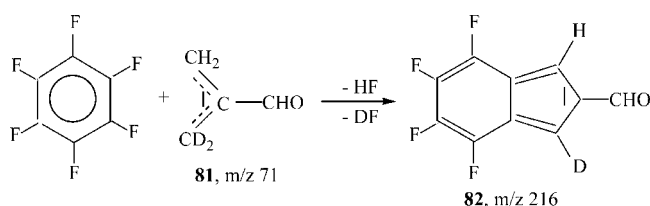

SCHEME 21.
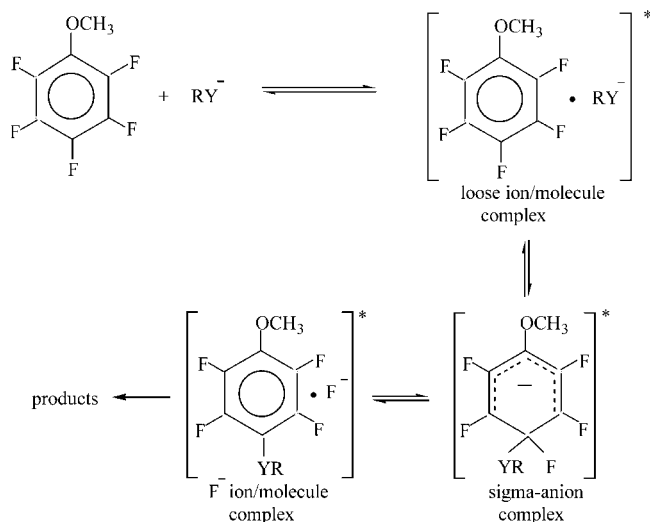
SCHEME 22.

obtain insight in the competition between the different E_2 channels which are possible in the F^- ion/molecule complexes generated in the S_NAr reaction (Ingemann & Nibbering, 1984a). An interesting reaction of the 2-formyl allyl anion with pentafluoroanisole and also hexafluorobenzene was a cycloaddition as supported by specific deuterium labeling as visualized for the latter substrate in Scheme 23 (Kleingeld & Nibbering, 1984a).

The occurrence of reactions within the primary generated product ion/molecule complexes is not limited to the aromatic molecules discussed. For example, following the S_N2 substitution reaction of the chloromethyl anion with methyl chloride the resulting chloride/ethyl chloride complex reacts further by E2 elimination (Bickelhaupt et al., 1992). Another study that was performed in cooperation with Professor C.H. DePuy and with Professor R.T. McIver Jr. of the University of California at Irvine, California was the debated phenoxide formation from reaction between nucleophiles and phenyl acetate. In principle three mechanisms could account for it, that is, an S_N2, a $B_{AC}2$ (displacement *via* nucleophilic attack on the carbonyl carbon), and an E_2 (*via* proton abstraction from the methyl group) mechanism, but it was shown that only the S_N2 mechanism was operative with the nucleophiles OH^-, CH_3O^-, $CH_3COCH_2^-$, and methanol solvated CH_3O^- (Kleingeld et al., 1982). However, for phenyl trifluoroacetate the OH^- ion was found to react *via* both the S_N2 and the $B_{AC}2$ mechanism in the ratio of 1 to 3, the former now being less attractive because of the repulsion between the

approaching OH^- ion and the fluorine atoms of the trifluoromethyl group (Kleingeld & Nibbering, 1982b). Almost 10 years later and in cooperation with Professor J.M. Riveros of the University of Sao Paulo in Brazil the reaction of F^- with phenyl acetate and ring-substituted analogs has been studied which yielded as main products not only (substituted) phenoxide, but also HF solvated (substituted) phenoxide ions (Riveros, Ingemann, & Nibbering, 1991a). The abundance of the former ions was found to increase significantly upon increase of the translational energy of the F^- ion.

3. Distonic Radical Cations and Anions, Carbene Radical Anions, and Dipole Stabilized Carbanions

In the beginning of the 80s distonic ions were becoming very popular (Bouma, Nobes, & Radom, 1982; Bouma, McLeod, & Radom, 1982; Holmes et al., 1982; Yates, Bouma, & Radom, 1984). In cooperation with Professor H. Schwarz it was shown that such species could also be distinguished from their conventional isomers by use of ion/molecule reactions. That is, the distonic ions $CH_2XCH_3^{+\bullet}$ ($X = Cl$, Br) reacted with NO by $CH_2^{+\bullet}$ transfer to give CH_2NO^+ and with CH_3CN by methyl cation transfer to give $CH_3CNCH_3^+$, whereas the conventional isomeric ions reacted with NO by electron transfer to give NO^+ and with CH_3CN by proton transfer to give CH_3CNH^+ (Weiske et al., 1984). Such a distinction between a distonic and conventional ion structure by use of ion/molecule reactions had been reported earlier in 1973 by my group before the term "distonic ion" was introduced (see Section IV). In addition to the distinction of distonic ions by ion/molecule reactions and studies of their bimolecular gas-phase ion chemistry (Stirk, Kiminkinen, & Kenttämaa, 1992; Kenttämaa, 2005) these species were also generated *via* ion/molecule reactions. An interesting example was the synthesis of the distonic ion of methylamine by reaction of the radical cation of ketene with ammonia, a study that was also performed in cooperation with Professor H. Schwarz (Drewello et al., 1987a). That substitution reaction was relatively facile notwithstanding that a direct nucleophilic attack on a radical cation would be a "forbidden" process (Pross, 1986). Methylene radical cation transfer from ionized oxirane to dimethyl sulfide generated the α-sulfur distonic ion $^\bullet CH_2S^+(CH_3)_2$ (van Amsterdam et al., 1993a), its reactions with alkenes having been studied afterwards (van Amsterdam et al., 1993b). Distonic radical anions have also been generated, such as the $^\bullet CH_2-S-^-CH-CN$ and $^\bullet CH_2CO_2^-$ ions by reaction of $O^{\bullet-}$ with methylthioacetonitrile (Born, Ingemann, & Nibbering, 1995) and β-propriolactone/β-butyrolactone (Born et al., 1998), respectively. The bimolecular reactivity of the former ion has been compared with that of its isomeric carbene radical anion, $CH_3SC^{\bullet-}CN$, by reaction with dimethyldisulfide (Kauw et al., 1996). The carbene radical anion reacts by loss of a thiomethyl radical from the collision complex, while the isomeric distonic radical anion reacts by an additional loss of methanethiol from the encounter complex. Negative distonic ions have been reviewed not long ago (Nibbering, 2003). Concerning carbene radical anions, it is interesting to note that the reactivity of mono-halogen carbene radical anions has been compared with that of their corresponding carbanions (Born,

81, m/z 71   **82**, m/z 216

SCHEME 23.

Ingemann, & Nibbering, 1996b). The former have been found to react less efficiently than the latter in the S_N2 substitution reaction with methyl halide, methyl trifluoroacetate, and dimethyl carbonate.

Another study in cooperation with Professor C.H. DePuy concerns the reactions of anions with methyl formate and *N,N*-dimethylformamide (DePuy et al., 1985). Various reaction channels were found to be operative for methyl formate, such as carbonyl addition and displacement on the methyl group. Important for this substrate was also the proton abstraction channel, not only from the formyl position known as the Riveros reaction (Riveros, 1974, 2005), but also from the methyl group leading to a dipole stabilized carbanion. Such proton abstractions were also observed for *N,N*-dimethylformamide, where the dipole stabilized carbanion together with that from methyl formate was subjected to a further investigation (Ingemann & Nibbering, 1985a). Then the interesting observation was made that the [M–H]⁻ ion of $DCON(CH_3)_2$ exchanged two of its hydrogens rapidly with ND_3 while the exchange of a third hydrogen was very slow and minor as shown in Figure 5.

The explanation of this observation is given in Scheme 24, where the deprotonated methyl group in *anti*-position with respect to the carbonyl group exchanges its hydrogen atoms, but not the methyl group in the *syn*-position with respect to the carbonyl group because of the large rotation barrier for rotation around the C–N bond (Ross & True, 1984) and the significant difference in acidity calculated for the *anti*- and *syn*-methyl group (Rondan et al., 1981).

Similar observations have been made for the two methyl groups of *N,N*-dimethyl-*N*-nitrosamine with CD_3OD as exchange reagent, but not for those of *N,N*-dimethylthioformamide which have been found to be close in acidity (Ingemann & Nibbering, 1985b).

4. Acidity, Proton Affinity, and Heat of Formation Measurements

Quantitative acidity measurements have been performed for phenyl methyl thioether, where the methyl group is the most acidic site and dimethyl sulfide (Ingemann & Nibbering, 1984b), and for trimethyl phosphine and the methyl halides (Ingemann & Nibbering, 1985c). These studies were performed to obtain insight into the extent of the stabilizing effect of the heteroatoms on the primary carbanions formed and for the methyl halides it was found that the acidity increased in going from F to I. The latter was in line with the existing theory that the acidity increases if the heteroatom is more polarizable because that would increasingly stabilize the primary carbanion. However, recent theoretical calculations have indicated that for the latter the opposite is true, that is, the primary carbanion is better stabilized in going from I to F and that the higher acidity of CH_3X in going from F to I is due to a larger decrease of the C–X bond strength in the neutral than in the anion (Bickelhaupt, Hermann, & Boche, 2006). Other quantitative acidity measurements have concerned 1,3-butadiene at its 2-position (De Visser et al., 1995), fluorobenzene at its *ortho* position and 1,4-difluorobenzene (Matimba, Ingemann, & Nibbering, 1993) and in cooperation with Professor M. Schlosser of the University of Lausanne, Switzerland, polyfluorinated benzenes (Büker et al., 1997), *bis*- and oligo(trifluoromethyl)-benzenes (Schlosser et al., 1998) and polychlorinated benzenes (Schlosser et al., 2001). The experimentally obtained acidity values for the various polyfluorinated and polychlorinated benzenes have been compared with those calculated at various level of theory, where an excellent agreement was found upon use of the B3LYP/aug-cc-p-VTZ//B3LYP/cc-pVTZ method (Hyla-Kryspin et al., 2005). Acidities have also been determined by measuring the proton affinity of
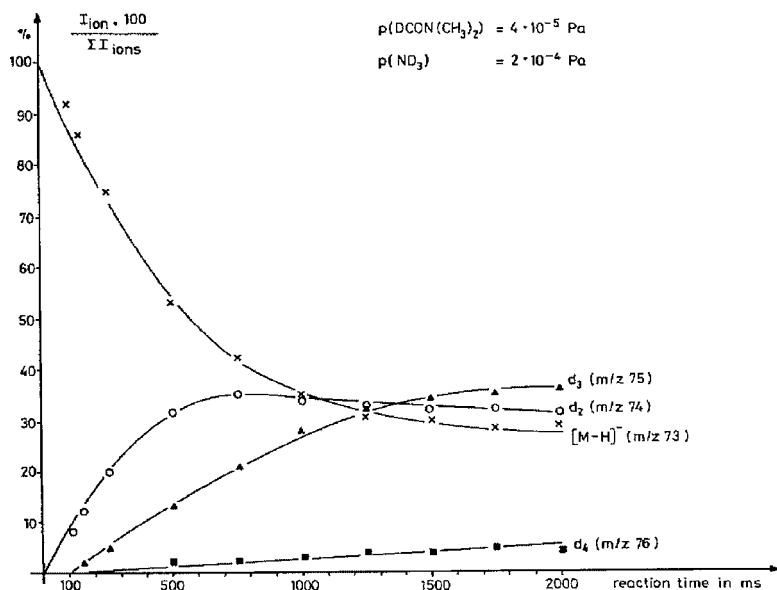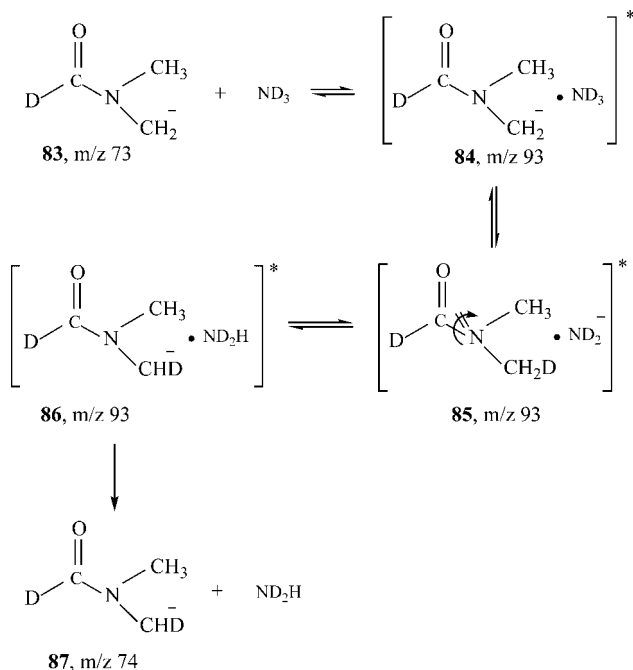
FIGURE 5. The hydrogen-deuterium exchange reaction between the (M–H)⁻ ions from $DCON(CH_3)_2$ and ND_3 as a function of reaction time. Reprinted from Ingemann and Nibbering (1985a) with permission from the American Chemical Society, Copyright 1985.

SCHEME 24.

anions through proton abstraction from reference acids known as the bracketing method (Bartmess, 2003). In the case of radical anions which in many cases can be generated *via* a formal $H_2^{+\bullet}$ abstraction by $O^{-\bullet}$ from many organic molecules (Lee & Grabowski, 1992; Born, Ingemann, & Nibbering, 1997) the acidities of radicals can be determined in this way. This showed that very frequently the radical was more acidic than its parent molecule, such as the phenyl radical and its mono-substituted F-, Cl-, and CN-analogs (Matimba et al., 1991), the nitrogen radical of hydrazobenzene (Ingemann, Fokkens, & Nibbering, 1991), the isocyanomethyl radical (Matimba et al., 1992), the halomethyl radicals (Born, Ingemann, & Nibbering, 1994), and the cubyl radical (Staneke et al., 1994), the latter study in cooperation with Professor S. Kass of the University of Minnesota in Minneapolis, Minnesota. Generally the higher acidity of the radicals, denoted by $\Delta H^o_{acid}(H–A^\bullet)$, with respect to their parent molecules H_2A is due to a higher electron affinity of the corresponding neutral A species, denoted by EA(A) than of the $H–A^\bullet$ radicals, although sometimes it can be accounted for by a lower homolytic bond dissociation energy of the $H–A^\bullet$ bond of the radical, denoted by $BDE(H–A^\bullet)$, than of the parent molecule, as may be clear from the following equation:

$$\Delta H^o_{acid}(H–A^\bullet) = BDE(H–A^\bullet) - EA(A) + IE(H^\bullet)$$

in which $IE(H^\bullet)$ is the ionization energy of the hydrogen atom.

Proton affinity (PA) measurements by the bracketing method and in cooperation with Professor J. F. Liebman of the University of Maryland in Baltimore, Maryland have also been used to determine the heats of formation (ΔH^o_f) of neutral imines (Peerboom et al., 1990), by using the known ΔH^o_f values of immonium ions and application of the following equation:

$$\Delta H^o_f(R_1R_2C=NH) = PA - \Delta H^o_f(H^+) + \Delta H^o_f(R_1R_2C=NH_2^+)$$

The bracketing method has been applied as well to determine the acidity change of ions excited by visible laser light with respect to unexcited ions. To this end it had first to be established that the ions of interest require the absorption of two photons of the used laser light for dissociation so that it is certain that also ions are formed which are excited by the absorption of one photon and can react by proton transfer in an ion/molecule reaction (Van Amerom, van der Hart, & Nibbering, 1999). Then by carefully designed sequences of pulses, the ions of interest after their isolation in the FTICR cell were allowed to react with reference bases with the laser light on and off in two successive experimental cycles from which difference spectra were obtained by subtracting the corresponding Fourier transformed signals. In this way it has been found that indene radical cations excited by laser light of 514.5 nm can transfer a proton to a base where the reaction in the ground state of the reaction partners is endothermic up to a maximum of 48 kJ/mol (van Amerom et al., 2000). In a similar way protonated naphthalene, excited by laser light of 488 nm, has been observed to be capable to transfer its proton to a base where the reaction in the ground state of the reaction partners is endothermic up to a maximum of 60 kJ/mol (van Amerom et al., 2001).

Another method that has been used to determine proton affinities is the desilylation method developed by Professor C.H. DePuy and used in flowing afterglow-selected ion flow tube (FA-SIFT) studies (DePuy, Bierbaum, & Damrauer, 1984; DePuy et al., 1989). It is based upon the decomposition of a penta-coordinate siliconate anion, generated by reaction of hydroxide with an alkyltrimethylsilane, into the ions $(CH_3)_2RSiO^-$ and $(CH_3)_3SiO^-$ by elimination of methane and alkane, respectively. The ratio of the abundances of the $(CH_3)_2RSiO^-$ and $(CH_3)_3SiO^-$ ions then reflect the acidity difference between methane and the alkane RH. The proton affinities measured for alkyl and cycloalkyl anions in my group by use of the desilylation method and the home-built FT-ICR instrument agreed very well with those obtained by use of the FA-SIFT method (Peerboom et al., 1992) and have been extended to cycloalkyl anions with various adjacent π-accepting substituents, the results being analyzed in terms of polarizability, field/inductive, and resonance effects (Peerboom, de Koning, & Nibbering, 1994).

Other neutral molecules for which the heats of formation have been determined are benzene (Riveros, Ingemann, & Nibbering, 1991b), mono-halogen-substituted carbenes (Born, Ingemann, & Nibbering, 1994), di-halogen-substituted carbenes (Born, Ingemann, & Nibbering, 2000), and formyl/thioformyl cyanide (Born, Ingemann, & Nibbering, 1996a). In the latter study that was undertaken because of the earlier reported methyl radical loss from deprotonated methoxyacetonitrile to give the radical anion of formyl cyanide (Dawson & Nibbering, 1980) also use was made of a Bruker Spectrospin CMS 47 X instrument to determine the required bond dissociation energy for this methyl loss by threshold collision-induced dissociation. This instrument (see Subsection *B1* below) was also additionally or exclusively used in the two earlier-mentioned studies on the imine heats of formation (Peerboom et al., 1990) and the acidity of the nitrogen radical of hydrazobenzene (Ingemann, Fokkens, & Nibbering, 1991) for reasons of interference of neutrals and low volatility, respectively. However, before describing the research performed with use of this instrument (see next

subsection), the investigations by use of the home-built FTICR mass spectrometer will be continued.

5. Carbonyl Addition-Elimination Reactions

Carbonyl containing compounds, such as aldehydes, esters, and anhydrides were studied in my group because of the variety of reactions that are possible with nucleophiles, such as proton abstraction, S_N2 substitution, and addition elimination. An interesting question was whether in the addition elimination a tetrahedral intermediate, that is a species in a potential energy minimum, is formed. This is indeed the case as shown by ^{18}O-labeling experiments for the OH^- adduct of benzaldehyde (Kleingeld & Nibbering, 1984b) and formaldehyde (van der Wel & Nibbering, 1988b, vide supra), by the reversible addition of $CH_3{}^{18}O^-$ to methyl benzoate and dimethyl carbonate giving the unlabeled methoxide ion (van der Wel & Nibbering, 1988a) and indirectly by the reaction of $DCOOH^{-\bullet}$ with unlabeled methyl formate to give almost exclusively the $DCOO^-$ product ion (van der Wel & Nibbering, 1986). For the latter reaction the mechanism has been proposed as given in Scheme 25, where the first addition of the reactant ion to the carbonyl group of methyl formate is followed by an intramolecular addition to the original reactant ion carbonyl group forming a five-membered ring as precursor of the final product ion.

Rate constant measurements for reactions of various nucleophiles with 1-pivaloyl-1,2,4-triazole, which were performed in cooperation with Professor J.B.F.N. Engberts of the University of Groningen in The Netherlands, could also be explained with the occurrence of a tetrahedral intermediate, but those with pivaloyl chloride and S-methyl thiopivaloate were more in line with a tetrahedral transition state structure (van der Wel et al., 1988). In a cooperative study with Professor M.M. Kayser of the University of New Brunswick, Canada on the BH_4^- reduction of some 2-substituted maleic anhydrides it was found that in the case of methylmaleic anhydride preferentially the carbonyl group neighboring the methyl substituent was reduced in addition to a non-preferential hydride ion transfer to the carbon
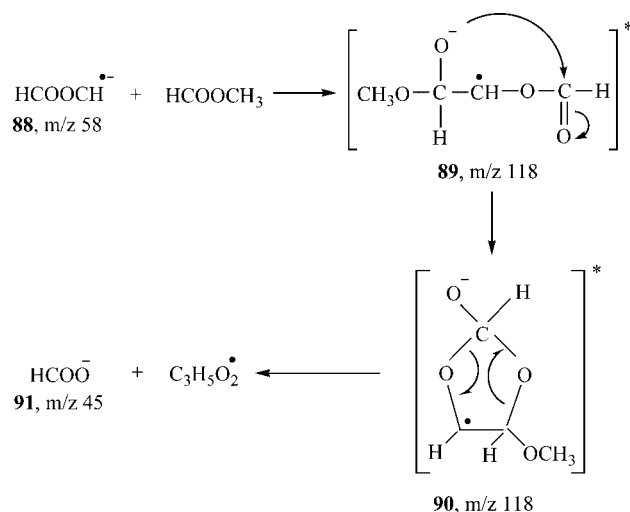
atoms of the double bond. For ethoxymaleic anhydride, however, the hydride ion was transferred to the ethoxy group carrying carbon atom, while in phenylmaleic anhydride it was transferred to the phenyl ring. All these observations were in agreement with ab initio calculations indicating that the hydride ion transfer from BH_4^- to the molecules studied take place under orbital control rather than under control of long-range ion-induced dipole interactions between the reactants (Van der Wel, Nibbering, & Kayser, 1988).

6. Base-Induced Elimination Reactions

Much research has also been focused on base-induced elimination reactions. One of the first was the reaction of hydroxide with diethyl ether giving both ethoxide and water solvated ethoxide ions. Deuterium labeling showed that the kinetic isotope effects for the two channels were quite different after having excluded by ^{18}O-labeling experiments that these ions were formed by an S_N2 mechanism. From the deuterium labeling also notable leaving group effects were found. With the amide bases $C_2H_5NH^-$, CH_3NH^-, and NH_2^- only unsolvated ethoxide ions were formed where the kinetic isotope effect increased with increase of the PA of the base (De Koning & Nibbering, 1987). The latter was interpreted in terms of a variable E2 transition-state structure that shifts to the carbanion or E1cb region of the E2 spectrum with increasing base strength. In the reaction with hydroxide the mechanism for the unsolvated ethoxide formation was proposed to be an anti-elimination proceeding via an anti-periplanar transition state, while the mechanism for the water solvated ethoxide formation was suggested to be a syn-elimination where the hydroxide and the leaving ethoxy group interact with each other. In the same study also the base-induced elimination reactions of cis- and trans-1-tert-butyl-4-methoxycyclohexane have been investigated. Both systems react with hydroxide to give unsolvated and water solvated methoxide ions. The behavior of the cis substrate resembled that of diethyl ether, but for the trans substrate a significantly larger leaving group effect was observed that would indicate a drastic shift of the transition state toward the carbenium ion or E1 region of the E2 spectrum. This work was followed up by a study of the base-induced elimination reactions of diethyl sulfide (Van Berkel, de Koning, & Nibbering, 1987). It was then found that the amide bases $(CH_3)_2NH^-$, $C_2H_5NH^-$, and NH_2^- preferentially react via an α', β elimination, that is α' proton abstraction from the sulfide followed by an intramolecular syn elimination to generate the ethyl thiolate anion. For the reaction with hydroxide and methoxide an E2 elimination has been found to give the unsolvated ethyl thiolate anion. In the case of hydroxide this elimination is preceded by a rapid exchange of the hydroxide hydrogen with the α-hydrogens of the sulfide in the encounter complex. For the nearly thermoneutral reaction with F^-, it has been concluded from kinetic isotope and leaving group effects that two mechanisms are operative. One is an E2C mechanism involving a two-side attack of F^- on the β-hydrogen and α-carbon of the sulfide yielding the unsolvated ethyl thiolate anion. The other is a syn-elimination involving a two-side attack of F^- on the β-hydrogen and the leaving group, generating the HF solvated ethyl thiolate anion. Extension to base-induced elimination of

SCHEME 25.

cyclic thioethers revealed that three reaction channels were operative, that is (i) E2 elimination, (ii) α′ proton abstraction followed by α′, β-elimination, and (iii) S_N2 subsitution (De Koning & Nibbering, 1988). In that study it was also found that the gas-phase acidity diminished if the cyclic thioethers became more strained. The work on the open chain and cyclic sulfides has been incorporated in an invited and general review on the mass spectra of sulfur compounds (Nibbering, Ingemann, & de Koning, 1993). Another cyclic system that was studied was tetrahydrofuran. This reacted with hydroxide *via* a 1,2-elimination to give but-3-ene-1-oxide ions, part of them decomposing by elimination of molecular hydrogen or formaldehyde, and yielding the buta-1,3-diene-1-oxide or allyl anions, respectively (Bickelhaupt, de Koning, & Nibbering, 1993a). In collisions with water the but-3-ene-1-oxide ions reacted further by proton abstraction giving a complex that *via* a reversible hydroxide-induced E1cb process led to an efficient formation of water solvated hydroxide by elimination of 1,3-butadiene. In addition to the discussed base-induced 1,2-eliminations forming a carbon-carbon double bond, also a base-induced 1,2-elimination of *N,O*-dimethylhydroxylamine has been studied that leads to formation of a carbon-nitrogen double bond (Bickelhaupt, de Koning, & Nibbering, 1993b). That 1,2-elimination did not occur for *O*-methylhydroxylamine that reacted with the base by proton transfer and substitution on the nitrogen *via* an S_N1-like transition state, but not on the carbon *via* an S_N2 reaction. Also base-induced 1,4-elimination reactions have been studied for the allylic ethers CH_3-CH=CH-CH_2-OEt (or Me) and CH_2=CH-CH_2-OEt in combination with density-functional theory (DFT) calculations (Bickelhaupt et al., 1995). Both experiment and theory have shown an E1 cb mechanism for the 1,4-elimination that is a very facile process and effectively competes with simple proton transfer, 1,2-elimination, vinylic 1,2-elimination, aliphatic (S_N2), and allylic (S_N2') substitution. In that study it has also been shown that the E1cb mechanism can be associated with a single-, double-, and triple-well potential energy surface. The base-induced 1,4-elimination has been reviewed recently (Bickelhaupt, 2001). DFT calculations have also been performed for the F^--induced 1,2-elimination of ethyl fluoride (Bickelhaupt et al., 1993) and for this system where F^- is solvated by nHF molecules ($n = 0-4$) (Bickelhaupt, Baerends, & Nibbering, 1996) to obtain a qualitative understanding of the effect of solvation on E2 and S_N2 reactions. These calculations have shown that solvation increases the activation energies of these reactions because the reactants are more strongly solvated than the transition states, but the S_N2 transition state is stabilized much more and becomes lower in energy than the *anti*-E2 transition state. Furthermore, the *anti*-E2 transition state is calculated to be lower in energy than the *syn*-E2 transition state both for the unsolvated and solvated F^- base.

Gas-phase base-induced elimination in which the base is a neutral species and the substrate is a positive ion has also been studied in cooperation with Professor M. Speranza of the University of Rome, Italy. In particular various aliphatic amines were brought into reaction with undeuterated and deuterated diethylmethyloxonium ions (Occhiucci et al., 1989). Both E2 elimination and S_N2 substitution were observed, the efficiency of the former being enhanced upon increasing the base strength of the amine. However, upon translational excitation of the

diethylmethyloxonium ions other mechanisms become operative, which in the encounter complexes are initiated by an initial one-electron transfer from the amine base to the oxonium ion. Such an initial electron transfer in an encounter complex has also been suggested for the nucleophilic addition of the thioformaldehyde radical anion to the carbonyl group of phenyl trifluoroacetate (Staneke, Ingemann, & Nibbering, 1996).

7. Ambient Anions

Ambident species having two different reaction sites are well known in organic chemistry (Klopman, 1974). Enolate anions are such species that in reactions with pentafluoroanisole (Ingemann et al., 1982) and hexafluoropropene (Brickhouse & Squires, 1989) had been found to react at both the oxygen and carbon center. From the systematic study with hexafluoropropene it was suggested that reaction at the oxygen center would be favored if the difference in heats of formation of the keto and enol forms of the neutral carbonyl compounds would be <60 kJ/mol (Brickhouse & Squires, 1989). However, various enolate anions violated this criterion and some of them were observed in my group to react in an opposite way with regard to O/C site addition to the substrates hexafluorobenzene and hexafluoropropene (Freriks, de Koning, & Nibbering, 1991). This indicated that the reaction selectivity of the enolate anion was not determined by its intrinsic property alone, but also by the nature of the attacked substrate. Yet, a correlation was found between the reaction selectivity and the electron detachment threshold energy, that is, the energy of the HOMO, of the enolate anions.

For example, enolate anions with HOMO energies below -1.90 eV react with hexafluoropropene predominantly *via* the carbon center, those above -1.70 eV *via* the oxygen center, while those around -1.80 eV react *via* both centers. Subsequently DFT calculations of the MO energy levels of hexafluoropropene and hexafluorobenzene showed that their LUMO energies are -4.53 and -4.83 eV, respectively, indicating that the latter are between the HOMO and HOMO-1 of the enolate anions. In the HOMO of enolate anions the relative orbital coefficient is largest on carbon, while in the HOMO-1 this is largest on oxygen. With this knowledge the observations could be rationalized, that is, if the HOMO energy of the enolate anion is closest to the LUMO of the substrate, then reaction at the carbon center will prevail. Reaction at the oxygen center will dominate, however, if the HOMO-1 energy of the enolate anion is closest to the LUMO of the substrate. In other words, the competition between reaction at the carbon and oxygen center of the enolate anion is controlled by specific frontier orbital interactions of the reactants rather than by the charge distribution in the enolate anion alone (Freriks, de Koning, & Nibbering, 1991). Monohydrated enolate anions showed a similar ambident reactivity towards hexafluoropropene and hexafluorobenzene where the conclusion was that the water molecule evaporated from the encounter complex prior to reaction (Freriks, de Koning, & Nibbering, 1992a). Further support for specific frontier orbital interactions of the reactants was obtained from the ambident reactivity pattern of cyclic enolate anions where the variation of the O/C site reaction selectivity with ring size correlated very well with the variation of the corresponding electron detachment threshold energy (Freriks, de Koning, & Nibbering, 1992b).

This work has been extended to *N*-deprotonated amides (Freriks, de Koning, & Nibbering, 1992c) and thio-enolate anions (Freriks, de Koning, & Nibbering, 1993) where the preferred reaction at the nitrogen- and sulfur center, respectively, with unsaturated perfluorocarbon compounds has been discussed in terms of specific frontier orbital interactions of the reactants. However, oximate anions reacted exclusively at their oxygen center for which electrostatic interactions between the reactants were held responsible (Freriks, de Koning, & Nibbering, 1993). It should be noted that the discussed specific frontier orbital interactions between reactants had been concluded before for the hydride ion transfer from the BH_4^- ion to 2-substituted maleic anhydrides (*vide supra*, Subsection 5; Van der Wel, Nibbering, & Kayser, 1988).

8. Organometallic Anions

A few studies of organometallic compounds will be presented which had to be volatile for introduction into the home-built FTICR mass spectrometer. One of the first was the reaction of nucleophiles with the dimer of trimethylaluminum, $(Me_3Al)_2$. With the nucleophiles $Nu^- = C_6H_5^-$, $CH_2=CH-CH_2^-$, $C_2H_5O^-$, CH_2CN^-, CN^-, and CH_3S^- predominantly the product ions Me_3AlNu^- were formed, while in reaction with CH_3O^- a hydride ion transfer took place to generate the Me_3AlH^- ion (Van den Berg, Ingemann, & Nibbering, 1992a). The latter anion did not transfer a hydride ion to simple carbonyl compounds with the exception of hexafluoroacetone where only traces of the $(CF_3)_2CHO^-$ ion could be detected. Instead, the Me_3AlH^- ion reacted with the dimer of trimethylaluminum to give the hydride ion bonded dimer species $Me_3Al-H-AlMe_3^-$. Reactions of negative ions with (η^5-cyclopentadienyl)-dicarbonylcobalt(I) showed proton transfer and nucleophilic attack as two main reactions (Van den Berg, Ingemann, & Nibbering, 1992b). The nucleophilic attack led to the elimination of one or two CO molecules from the collision complex and was proposed to take place both at one of the CO ligands and at the metal center. With the $O^{\bullet-}$ radical anion as nucleophile a competitive attack upon one of the CO ligands and the cyclopentadienyl ligand was observed. Such a competitive attack in addition to attack upon the metal center was also observed for reaction of $O^{\bullet-}$ with (η^5-cyclopentadienyl)-tricarbonylmanganese(I) and (η^5-methylcyclopentadienyl)tri-carbonylmanganese(I), in which study both ^{18}O- and deuterium labeling was applied (Van den Berg, Ingemann, & Nibbering, 1994). The main attack was upon a CO ligand leading to the elimination of three CO molecules from the collision complex. The resulting $C_5H_5MnO^-$ ions from (η^5-cyclopent-adienyl)tricarbonyl-manganese(I) were suggested to have the (cyclopentadienone)MnH$^-$ structure, while the $C_6H_7MnO^-$ ions from (η^5-methylcyclopentadienyl)tricarbo-nylmanganese(I) were proposed to have both the (methyl-cyclopentadienone)MnH$^-$ and the (fulvene)Mn(OH)$^-$ structure on the basis of ion/molecule reactions with a variety of substrates, including nitrous oxide, sulfur dioxide, and water.

9. The Structure of Ionized 1,5-Hexadiyne

An interesting application of the notch ejection technique, described in Subsection *1* above, was in a study of the structure of the radical cation of 1,5-hexadiyne that was performed in cooperation with Dr. W.J. van der Hart. Photodissociation of its $C_6H_6^{\bullet+}$ ion could not be applied in this case because of the interference of the natural ^{13}C isotope containing ion $^{13}C_1$ $^{12}C_5H_5^+$. However, the latter ion was more reactive. Thus, first a notch ejection pulse was applied to isolate the ions with the nominal mass of m/z 78. Then after a delay time, during which the $^{13}C_1$ $^{12}C_5H_5^+$ ions had reacted away, a second notch ejection was applied to isolate the remaining $C_6H_6^{\bullet+}$ ions. These ions behaved in ion/molecule reactions with neutral 1,5-hexadiyne and 2-propyl iodide like the molecular ion of benzene, so that the conclusion was drawn that they had the benzene structure (van der Hart et al., 1986). However, ionized 1,5-hexadiyne has a heat of formation above the lowest fragmentation threshold leading to ions having the phenyl ion structure, while the barrier for isomerization to the benzene structure is negligibly small (Lifshitz & Ohmichi, 1989). Thus, in principle these ions could not survive with respect to fragmentation on the basis of the energetics. This problem was solved in a cooperative study with Professor R.C. Dunbar of the Case Western Reserve University in Cleveland, Ohio, showing that the isomerized 1,5-hexadiyne ions did survive by IR radiative emission (van de Guchte et al., 1993).

B. The Bruker Fourier Transform Ion Cyclotron Resonance Mass Spectrometer

1. Instrumental/Methodology Developments

A Bruker Spectrospin CMS 47 X instrument with a super-conducting magnet of 4.7 T (Spectrospin AG, Fällanden, Switzerland) was acquired in 1986, equipped with an external ion source in 1988 and upgraded to a Bruker Apex™ 47 e FTICR (Bruker Daltonics, Billerica, MA) mass spectrometer in 1996.

Before presenting the chemical research performed with use of this instrument, first instrumental/methodology developments by my group will be described that were undertaken to optimize the operational procedures as much as possible. The high mass resolving power of the FTICR method was already known and had been shown to be $>1 \times 10^8$ for the m/z 18 signal of $H_2O^{\bullet+}$ (Allemann, Kellerhals, & Wanczek, 1983) and $>2 \times 10^8$ for the m/z 40 signal of $Ar^{+\bullet}$ (Wanczek et al., 1987) as measured from their full width at half height. However, it was of interest to know how high the so-called front-end resolution of primary ion selection could be prior to collision-induced dissociation experiments which for a multisector, in particular a triple analyzer instrument, had been shown to be as high as 10^5 (Gross et al., 1982). With use of a carefully designed sequence of ion ejection pulses it was shown that the molecular ions of cyclopropylbenzene and di-*n*-propylsulfide, having the same nominal mass m/z 118, could be selectively isolated in the FTICR cell (De Koning et al., 1987). This corresponded to a front-end resolution of primary ion selection in excess of 35,000 at m/z 118. In subsequent collision-induced dissociation experiments on each of the mass-selected molecular ions a back-end resolution of 205,000–475,000 was obtained for the product ions over the mass range m/z 61–117, while the accuracy of mass measurements on these product ions was shown to be better than 1 ppm. It

should be noted that a little bit later a front-end resolution of primary ion selection in excess of 20,000 at m/z 92 of the $^{12}C_7H_8^{+\bullet}$ and $^{13}C_1$ $^{12}C_6H_7^+$ toluene ions was reported as achieved by application of a stored waveform inverse Fourier transform (SWIFT) excitation field (Chen & Marshall, 1987). Another experiment in my group was the optimization of a narrow band signal by application of a computer-controlled simplex optimization on the basis of mass spectrum resolution, line shape, and signal-to-noise ratio. In this way a resolution of 1.6×10^6 in the absorption mode was obtained for the m/z 1066 signal from a *tris*(perfluorononyl)-*s*-triazine fragment (Elling et al., 1989). For quantitative ion/molecule reaction studies it is essential that care is taken that the kinetic energy of the ions is practically thermal to obtain reliable thermochemical data. One of the problems in isolating the ions of interest in the FTICR cell by on-resonance ejection of unwanted ions is that the latter can cause off-resonance excitation of the ions to be isolated as known from theory (Hanson, Castro, & Russell, 1989). This off-resonance excitation was shown for the phenyl ions of benzene upon on-resonance excitation and ejection of the molecular ions of benzene from the FTICR cell, leading to an alternating excitation and de-excitation of the effective cyclotron motion of the former ions with a periodicity equal to $2\pi(\omega_o - \omega_{eff})$, where ω_o is the frequency of the excitation field applied to eject the molecular ions of benzene and ω_{eff} is the effective cyclotron frequency of the phenyl ions (Heck et al., 1991). On this basis the net translational energy of the phenyl ions due to off-resonance excitation could be minimized by setting the duration of the excitation field equal to $k2\pi(\omega_o - \omega_{eff})$, where k is an integer so that the selected phenyl ions have experienced a number of full off-resonance excitation/de-excitation periods at the end of the benzene molecular ions ejection event. This procedure permitted to isolate selectively $C_6H_5D^{+\bullet}$ ions in th FTICR cell from a mixture of the nominal m/z 79 $C_6H_5D^{+\bullet}$ and $C_6H_3D_2^+$ ions in an abundance ratio of 1:10, showing a front-end resolution of primary ion selection at m/z 79 of ~48,000. This method has been applied from then on in my group to mass-specifically select ions for ion/molecule reaction studies. Around the same time off-resonance excitation has been shown to be a useful method to dissociate ions by collisional activation and has become known as the sustained off-resonance irradiation (SORI) method (Gauthier, Trautman, & Jacobson, 1991). With the updating of the Bruker Spectrospin CMS 47 X instrument to a Bruker Apex^{TM} 47 e FTICR mass spectrometer in 1996 (*vide supra*) a new data system and new software together with a 6-cm diameter cyclindrical infinity cell were installed. This prompted my group to optimize again the operational procedures that led to the development of the correlated harmonic excitation fields (CHEF) method (De Koning et al., 1997). Its principle is similar to that described above (Heck et al., 1991), but has been extended to eject not only ions with a particular mass by a correlated single excitation field, but also ions with a range of different masses by a correlated swept-frequency excitation field to avoid off-resonance excitation of the ions to be isolated. Using this method it has been possible to isolate $C_6H_2D_3^+$ ions by ejection of ions within the bandwidth from m/z 77 to 83, including $C_6H_4D_2^{+\bullet}$ ions, corresponding to a front-end resolution of primary ion selection at m/z 80 of ~48,000 (De Koning et al., 1997). In the same publication it was shown that the molecular ion of hexanal,

known to be very labile with respect to the loss of a water molecule, could be isolated successfully in the FTICR cell with use of the CHEF method.

2. Organometallic Anions

Ongoing and new chemical projects were continued and initiated, respectively, with use of the Bruker FTICR instrument that enabled to work with unvolatile compounds and to generate ions of interest by collision-induced dissociation which could be thermalized by non-reactive collisions with a gas admitted into the FTICR cell by pulsed valve addition prior to ion/molecule reaction studies.

Thus, with regard to the research on the chemistry of organometallic species, described in Section *A8*, reactions of the metal carbonyl anions $M(CO)_n$, where M = Cr, Mn, and Fe and $n = 1–3$, with *n*-heptane, water, and methanol did not show the aimed correlation between their number of valence electrons and their reactivity (Van den Berg, Ingemann, & Nibbering, 1993). An extensive ^{13}C-, D-, and ^{18}O-labeling study of the reactivity of the $Fe(CO)_2^-$ ion towards methanol showed three primary product ion channels being (i) decarbonylation, (ii) dehydrogenation, and (iii) *bis*-dehydrogenation, the latter leading to formation of the $Fe(CO)_3^-$ ion (van den Berg et al., 1993). Reactions of the metal carbonyl anions $M(CO)_n^-$, where M = Cr, Mn, Fe, Co, and $n = 0–3$ and $M = Co(CO)_nNO^-$ and $n = 0–2$, with methyl formate and its ^{13}C- and D-labeled analogs revealed that the metal center of the dicarbonyl and tricarbonyl anions initially inserted into the bonds adjacent to the carbonyl function to give five- or six-coordinate intermediates, respectively (van den Berg et al., 1994a). In this way the $Fe(CO)_3^-$ ion appeared to exchange eventually all its CO ligands for ^{13}CO in successive reactions with $H^{13}COOCH_3$! Then, most of the metal carbonyl anions $M(CO)_n^-$, where M = Cr, $n = 2–5$; M = Mn, $n = 1–5$; M = Fe, $n = 1–4$, were observed to react with nitrous oxide by oxygen atom transfer to yield oxo-metal anions and oxo-metal carbonyl anions, while with dioxygen mainly oxo-metal anions were generated (van den Berg et al., 1994b). A general review on the gas-phase bimolecular chemistry of metal carbonyl anions has appeared recently (Nibbering, 2005b). Finally, the reactions of the MnO_2^- and MnO_3^- ions with a series of C_1-C_4 aliphatic alcohols and with mono- and pentafluoro-aromatic compounds have been studied. The MnO_2^- ion did oxidize primary (with the exception of methanol) and secondary alcohols but not *t*-butanol, while the MnO_3^-/alcohol reactions were more complex leading to a variety of product anions (Fokkens, Gregor, & Nibbering, 1991). Electron transfer, proton abstraction, and displacement of fluorine by these oxometallate anions were identified as the principal reaction channels with mono- and pentafluoro-aromatic compounds (Fokkens, Gregor, & Nibbering, 1992). A large number of the described studies with metal containing anions on the Bruker instrument were performed in cooperation with Professor I.K. Gregor of the University of New South Wales in Sydney, Australia.

3. Hypervalent Ions

Some research has been performed on protonated methane and ethane. The former is the prototype of a hypercoordinated

carbocation, which was discovered by mass spectrometry as early as 1952 (Tal'roze & Lyubimova, 1952) and applied in the early development of chemical ionization mass spectrometry (Munson & Field, 1966). For the discussion below it is important to note that proton transfer from ionized methane to neutral methane is the dominant reaction channel in forming protonated methane (Henchman et al., 1989), while its most stable structure had been calculated to have the C_s symmetry with two equivalent hydrogens in the three-center two-electron bond and the three remaining hydrogens being approximately equivalent (Komornicki & Dixon, 1987). In addition, the activation energy for the intramolecular exchange between the two hydrogens in the three-center two-electron bond and the three remaining hydrogens had been calculated to be between 4 and 67 kJ/mol, assuming that the exchange process proceeds *via* a transition state of C_{2v} or D_{3h} symmetry (Hirao & Yamabe, 1984). An experiment was then set up to generate CH_4D^+ and CD_4H^+ ions from a 1:1 mixture of CH_4 and CD_4 in the external ion source, using an electron energy close to the ionization threshold energy of methane and a pressure such that the average number of primary collisions between ionized methane and neutral methane was as low as possible. Subsequently the ions were transferred to the FTICR cell and following careful isolation were allowed to transfer a proton/deuteron to ammonia which was chosen because of its much higher proton affinity thus minimizing intermolecular H/D exchange in the short-lived encounter complex. It was then observed that the CH_4D^+ and CD_4H^+ ions transferred a proton and deuteron with equal probability to ammonia *if* the average number of collisions was very low and that this proton and deuteron transfer rapidly became statistical upon a slight increase of the average number of collisions (Heck, de Koning, & Nibbering, 1991a). The conclusion was therefore drawn that the chemical behavior of protonated methane was compatible with the C_s symmetry structure and that the intramolecular exchange between the two hydrogens in the three-center two-electron bond and the three remaining hydrogens was a very fast process that already could be induced by weak interactions with the chemical ionization gas. In a subsequent publication it was shown that translationally activated protonated methane indeed transferred a methyl cation to argon, krypton, and xenon to form the corresponding methyl cationized noble gas atoms being in line with its C_s symmetry structure (Heck, de Koning, & Nibbering, 1992a). This C_s symmetry structure has been stated to be best pictured as a "CH_3 tripod" with an "H_2 moiety" attached to the carbon (Marx & Parrinello, 1999). It is interesting to note that a complex high-resolution infrared spectrum of CH_5^+ has been reported (White, Tang, & Oka, 1999).

By proton transfer from suitable proton donors to ethane and methyl cation transfer from suitable methyl cation donors to methane, it has been possible to generate long-lived protonated ethane in the FTICR cell (Heck, de Koning, & Nibbering, 1992b). From deuterium labeling it has been found that the intramolecular randomization of hydrogens in the $C_2H_7^+$ ion is a very fast process. Unimolecularly it eliminates a hydrogen molecule for which large isotope effects were observed, while bimolecularly it can react as a proton or methyl cation donor.

Cyclic ethylenehalonium ions are chemically interesting species and are intermediates in the halogenation of olefins, where especially the bromonium ion has received much attention

both in solution and in the gas phase (Holman, 2005). In my group experiments have been performed to generate these ions, study their bimolecular chemistry and distinguish them from their isomeric α-ethyl cations. The $[M–Cl]^+$ and $[M–Br]^+$ ions, generated by loss of a chlorine and bromine atom from the molecular ions of 1,2-dichloro- and 1,2-dibromoethane, respectively, did not show H/D exchange with D_2O, but did transfer Cl^+ and Br^+ to alkenes and vinyl ethers (Heck, de Koning, & Nibbering, 1993a). This behavior is in line with the halonium ion structure and differs from that of the isomeric α-ethyl cations, which underwent H/D exchange with D_2O, but did not transfer Cl^+ or Br^+ to alkenes and vinyl ethers. In that study no evidence was obtained for the formation of a fluoronium ion by loss of a bromine atom from the molecular ion of 1-bromo-2-fluoroethane, where the ion behaved as an α-fluoroethyl cation showing H/D exchange with D_2O. In an accompanying study on the loss of water from protonated β-haloethanols it was found that α-fluoroethyl cations were formed from β-fluoroethanol, a mixture of α-chloroethyl and chloronium ions was generated from β-chloroethanol and that only bromonium ions resulted from β-bromooethanol (Heck, de Koning, & Nibbering, 1993b). Afterwards a four-membered trimethylenebromonium ion in addition to a propylenebromonium ion were suggested to be formed by loss of a bromine atom from the molecular ion of 1,3-dibromopropane on the basis of a predominant adduct formation with methylamine and in particular with trimethylamine, which was not observed for the isomeric $C_3H_6Br^+$ ions from 1,2- and 2,2-dibromopropane (Heck & Nibbering, 1995).

4. 2-Center, 3-Electron Bonded Species

Relative much research efforts have been put into the chemistry of 2-center, three-electron (2c,3e) bonded species. One of the first studies in cooperation with Professor H. Schwarz and with Professor K.-D. Asmus of the Hahn-Meitner Institute in Berlin, Germany, was the formation of the (2c,3e) bonded species of di-isopropyl sulfide directly inside the FTICR cell which was shown to have a strong sulfur–sulfur bond (Drewello et al., 1987b). Then an interesting publication appeared which showed that radical cation dimers could be generated from ionized noble gas dimers by successive exchange with molecules of interest by use of a selected ion flow tube flowing afterglow instrument (Smith & Adams, 1989). Subsequently this method was adapted for use with the Bruker FTICR instrument where ionized argon, krypton, and xenon noble gas dimers were successively generated in the external ion source, transferred to the low pressure FTICR cell and exchanged with molecules to give the radical cation dimers of water, hydrochloric acid, ethane, cyanogens, and acetonitrile (Heck et al., 1990). Afterwards quantitative studies of the dimer radical cations of water, dialkyl sulfides, and methyl chloride were performed. The dimer radical cation of water was shown to react as an electron acceptor, a proton donor, and a reagent that can exchange an $OH^•$ moiety, while the adiabatic ionization energy of its neutral counterpart was determined to be 10.81–10.90 eV (De Visser, de Koning, & Nibbering, 1995).

The bond dissociation energies of the radical cation dimers of diethyl-, di-*n*-propyl-, and di-*n*-butyl sulfide were measured by use of translational energy-resolved collision-induced dissocia-

tion to be 1.19, 1.01, and 0.92 eV, respectively, showing a weakening of the (2c,3e) S–S bond and decrease of its associated σ/σ^* orbital energy splitting with larger and consequently enhanced electron donating alkyl groups (De Visser, de Koning, & Nibbering, 1996). This work has been extended to study ligand exchange equilibria between radical cation dimers of dialkyl sulfides and neutral disulfides where from the measured free energy changes and calculated entropies of reaction the bond dissociation enthalpies of dialkyl sulfide dimer radical cations have been derived (De Visser et al., 1998). The values obtained for the disulfides by translational energy-resolved collision-induced dissociation (*vide supra*) agreed within experimental error very well with the new values from the ligand exchange equilibria. DFT and *ab initio* calculations at various levels of theory for the model system of the radical cation dimer of hydrogen sulfide have shown that its sulfur–sulfur bond is nearly 60% provided by the (2c,3e) bond between the unpaired sulfur $3p_x$ electron on $H_2S^{+\bullet}$ and the sulfur $3p_x$ lone pair on H_2S, while more than 40% originates from electrostatic attraction (Bickelhaupt et al., 1998). In the consecutive exchange reaction of the xenon dimer radical cation with methyl chloride two different stable dimer radical cations of methyl chloride appeared to be formed. One was the (2c,3e) bonded species $CH_3Cl \therefore ClCH_3^{\bullet+}$ and the other the methyl chloride chloronium ylid ion $CH_3Cl \cdot H \cdot ClCH_2^{\bullet+}$. The former was observed to react as an electron acceptor and as a proton donor and its (2c,3e) Cl–Cl bond energy was measured to be 109 kJ/mol, being in excellent agreement with the value of 105.4 kJ/mol calculated at the *ab initio* MP2/6-311G(d,p) level of theory. The latter only reacted as an electron acceptor and its bond energy with respect to protonated methyl chloride and chloromethyl radical as products was determined to be 76 kJ/mol, while a value of 62.8 kJ/mol was calculated at the *ab initio* MP2/6-311G(d,p) level of theory. It was concluded that the $CH_3ClClCH_3^{\bullet+}$ species was the intermediate in the electron transfer reaction and the $CH_3Cl \cdot H \cdot ClCH_2^{\bullet+}$ ion in the proton transfer reaction between the radical cation of methyl chloride and neutral methyl chloride. Finally, the formation of the $CH_3Cl \cdot H \cdot ClCH_2^{\bullet+}$ ion was proposed to occur in the dimer radical cation where the neutral methyl chloride may "drag" the C-H hydrogen of the ionized methyl chloride across the C–Cl bond to give the methyl chloride solvated $HClCH_2^{\bullet+}$ distonic ion (De Visser, de Koning, & Nibbering, 1998). Such a mechanism had been proposed before for the interconversion of $CH_3OH^{\bullet+}$ into $^\bullet CH_3OH_2^+$, assisted by an associated molecule of water (Gauld et al., 1996).

5. Highly Charged Noble Gas Ions

Another interesting project was the ion/molecule chemistry of highly charged noble gas ions in the FTICR cell. Its origin goes back to the early spring of 1988 when I gave an invited lecture at the University of Uppsala in Sweden, where I met Professor I. Bergström, the former Director of the Manne Siegbahn Institute in Stockholm, Sweden. The day after the lecture Professor Bergström was my host in Stockholm and showed me his very interesting laboratory where among others research on highly charged noble gas ions, such as Ar^{18+}, was going on. He asked then me about the possible application of highly charged noble

gas ions in chemical research which following further discussions eventually resulted in a project on highly charged particles in traps funded by the EC Science Organization in Brussels, Belgium with the participating groups of Professor Bergström as leader of the project, Professor H.-J. Kluge of the Physics Department of the Johannes Gutenberg University in Mainz and GSI in Darmstadt, Germany and me. With extremely great pleasure I remember the very interesting and enjoyable group meetings, such as held in the little village Hunspach in the Alsace, France, where my suggestion of the nickname "SMILE-TRAP" as abbreviation for the Stockholm–Mainz Ion LEvitation TRAP was adopted (Bergström, 1995) and the Nobel Symposium 91 on trapped charged particles and related fundamental physics, held in Lysekil, Sweden, August 19–26, 1994. In principle Xe^{10+} ions could be observed with the Bruker instrument having a 4.7 T superconducting magnet, but the in-house construction of the required high kinetic energy electron gun failed in the sense, that the stray magnetic field hampered to fire the electrons into the FTICR cell. Then it was decided to generate high kinetic energy electrons directly in the cell, but application of 1 kV potential difference to accelerate them blew up some electronic units. So, in the end 350 eV electrons could be made that allowed the generation of Xe ions with a charge up to 5+, although their abundance was too low for further experiments. First attempts were made to let the multiply charged ions react with organic molecules, such as benzene or methyl iodide, but the results were not exciting. However, then the interesting observation was made that, following the isolation of $^{132}Xe^{4+}$ ions from ionized natural xenon gas in the cell, after a reaction time of 1 sec all the natural isotope peaks of doubly charged xenon ions appeared in the FTICR spectrum, while only $^{132}Xe^{3+}$ ions were observed. The latter were shown by ion ejection experiments not to be responsible for the formation of the natural isotope doubly charged xenon ions, so that the conclusion was drawn that part of the $^{132}Xe^{4+}$ ions reacted with xenon by a double electron transfer in a single collision event (Von Köding, Pinkse, & Nibbering, 1993). Rate coefficients for this double electron transfer were not measured because the authors did not know how to cool the $^{132}Xe^{4+}$ ions to thermal energies by collisions with an inert (!) bath gas although it was suggested by the colleagues in the EC Science funded project to use protons for that purpose. Fortunately also a double electron transfer between doubly charged xenon ions and neutral xenon atoms was observed. Cooling of the doubly charged xenon ions was then possible with He as bath gas and rate coefficient measurements showed that the double electron transfer was more efficient than the single electron transfer (Von Köding, Pinkse, & Nibbering, 1995).

This work has been extended to reactions of doubly charged krypton ions with neutral krypton atoms and doubly charged argon ions with neutral argon atoms where rate coefficient measurements showed that the double electron transfer is even more favored in comparison with the xenon system (Von Köding & Nibbering, 1999). It should be noted that in an earlier drift tube study the double electron transfer was also observed to be more efficient than the single electron transfer in the reaction of doubly charged krypton or xenon ions with neutral krypton or xenon atoms, respectively (Okuno, Koizumi, & Kaneko, 1978).

6. Protonated Alkyl Dipeptides

Approaching the end of this section, the research performed on the protonated alkyl dipeptides GlyGly, GlyAla, GlyVal, AlaGly, AlaAla, AlaVal, ValGly, and ValVal will be presented. These systems were chosen to obtain insight in the underlying factors that determine their H/D exchange behavior with deuterated reagents. In H/D exchange experiments with D_2O and CD_3OD all their labile hydrogens were exchanged, but the efficiency of exchange decreased in the *N*-terminal amino acid order Gly > Ala > Val and three hydrogens were found to exchange relatively fast. The same was observed for the protonated model compound *N*-ethylglycylamide, but not for the protonated model compounds ethylamine and 5-aminovaleric acid which do not exchange at all. The fourth hydrogen of the protonated alkyl dipeptides exchanged increasingly faster in the *C*-terminal amino acid order Gly < Ala < Val and was also observed for protonated *N*-ethylglycylamide.

The fifth hydrogen of the protonated alkyl dipeptides exchanged relatively slow and was of minor importance. From these observations the following conclusions were drawn: (i) in the long-lived protonated dipeptides the exchangeable hydrogens are not mobile; (ii) the D_2O and CD_3OD molecules are able to make the exchangeable hydrogens mobile because of multiple and relatively strong hydrogen bonding as indicated by the required presence of the peptide bond; (iii) the mobilization of the exchangeable hydrogens becomes easier with lower proton affinity of the *N*-terminal amino group and with increasing proton affinity of the peptide bond NH group. With these conclusions an ''onium'' ion mechanism was proposed for the H/D exchange in which multiply hydrogen bonded protonated alkyl dipeptide/ exchange reagent complexes are considered to be the key intermediates (Gur, de Koning, & Nibbering, 1995). That the proton affinity of the *N*-terminal amino group has a large effect on the H/D exchange behavior was shown afterwards for the isomeric protonated GlyPro and ProGly. The former did exchange with D_2O like the protonated alkyl dipeptides discussed above in sharp contrast with the latter that hardly exchanged because of the high proton affinity of the terminal *N*-proline (Sinnige, de Koning, & Nibbering, 2000). It should be noted that in an independent study of the H/D exchange of peptides the multiple hydrogen bonding with the exchange reagent and the proton affinity of the *N*-terminal amino group had been reported to play a crucial role (Gard et al., 1994). Furthermore, in a more elaborate experimental and computational study of Gly_nH^+ with $n = 1$–5, additional mechanisms to the ''onium'' ion mechanism for H/D exchange have been disclosed (Campbell et al., 1995; Beauchamp, 2003). Chiral effects in gas phase H/D exchange reactions of protonated alkyl dipeptides with (S)- and (R)-butan-2-ol appeared to be negligible (Gur, de Koning, & Nibbering, 1996). More successful were the reactions between protonated alkyldipeptides and acetonylacetone, which led to the formation of an association complex and a product ion by loss of a molecule of water. The latter was shown to be due to a coupling of the *N*-terminal nitrogen atom with one of the carbonyl carbons of the acetonylacetone and resulted by loss of the water molecule in an imine bond formation as supported by deuterium labeling. This product ion lost another molecule of water upon low energy collision-induced dissocia- tion to give an ion with a 2,5-dimethylpyrrole derived structure, its formation resembling the Paal–Knorr pyrrole synthesis from an α,δ-dicarbonyl compound and ammonia or a primary amine in the condensed phase (Gur, de Koning, & Nibbering, 1997). The research on the discussed protonated dialkylpeptides has been incorporated in a general gas-phase ion chemistry review Nibbering, 1998).

VIII. THE YEARS OF REVERSED GEOMETRY DOUBLE FOCUSING, HYBRID AND MULTISECTOR MASS SPECTROMETRY

As mentioned in Section V, an extensive research proposal submitted in 1973 to the chemistry division of the Netherlands Organization for Pure Research (SON/ZWO) to obtain a grant for the purchase of a reversed geometry double focusing mass spectrometer was not awarded. A strongly modified research proposal for the purchase of such an instrument was submitted again to the same granting body in December 1980 and was awarded in August 1982. Around that time Prof. J. Los, the Director of the FOM Institute for Atomic and Molecular Physics in Amsterdam, invited me to join his institute. However, in discussion and agreement with Prof. Los I could not accept his invitation in view of the recent SON/ZWO funding of the reversed geometry double focusing mass spectrometer project. Following visits to various mass spectrometry companies it was decided eventually to purchase a reversed geometry VG ZAB-2HF high field double focusing mass spectrometer together with ion sources for electron-, chemical-, field-, fast atom bombard- ment-, and field desorption ionization and coupled to a VG 11/ 250 data system (VG analytical Ltd, Manchester, UK) which was delivered and installed in the course of 1983.

The research performed with use of this instrument and its updated and modified versions and with use of a four-sector mass spectrometer, to be described below, will not include biomole- cules. They will be dealt with in the next Section IX. In addition, positive ions will be described first in the following section.

A. Positive Ions

1. Complex Skeletal Rearrangements

The previous observations in my group that the hydrogen cyanide lost from the molecular ions of aromatic nitriles did not contain exclusively the carbon atom of the original cyano group (see Section III) prompted to study this reaction from ionized benzonitrile as well. [15]N and specific ^{13}C labeling showed that ~50% of the molecular ions eliminated hydrogen cyanide in the ion source that contained the original cyano carbon, while the remaining percentage contained one of the phenyl ring carbons at random. This was even more dramatic for the metastably decomposing molecular ions where only 5%–7% of the expelled hydrogen cyanide molecules contained the original cyano carbon. These observations were explained by invoking a cycloaddition-cycloreversion process in the molecular ions leading to ionized 1-cyano-1,3-hexadien-5-yne as an intermedi- ate in the elimination of hydrogen cyanide (Molenaar-Langeveld,

Fokkens, & Nibbering, 1986). This behavior of benzonitrile was shocking because this molecule had served before as a model system in RRKM calculations where the hydrogen cyanide elimination was assumed to be a 1,2-elimination process (Chesnavich & Bowers, 1977). Afterwards a photodissociation study of the $C_6H_4^{\bullet+}$ fragment ions from benzonitrile showed that they had indeed a ring-opened structure (van der Hart et al., 1989). The work on benzonitrile induced to study also monosubstituted benzyl cyanides. The reason was that the identity of the cyano function had been shown earlier to be partly lost in the elimination of the elements of hydrogen cyanide from the molecular ions of benzyl cyanide, and *o-, m-,* and *p-*cyanobenzyl cyanides (see Section III), but not from the molecular ions of *o-* and *p-*methylbenzyl cyanide (Venema & Nibbering, 1974c). The question to be addressed therefore was to elucidate the nature and position of the substituent in the molecular ions of monosubstituted benzyl cyanides with respect to the hydrogen cyanide elimination. In combination with ^{13}C and deuterium labeling, it was shown that the electron withdrawing substituents F, Cl, or CF_3 led partly to the identity loss of the cyano group by skeletal rearrangements, but not the electron donating groups CH_3, HO, or CH_3O. For the latter two strong indications were obtained that the *m-* and *p-*substituent moved along the ring *via* a norcaradiene structure leading to the *o-*substituted isomer. This then lost in the case of the CH_3O substituent a C_2H_2N radical that contained the intact cyano function and a methylene group originating from the methoxy substituent and in the case of the HO substituent a {H,C,N,O] species that contained the carbon, nitrogen, and oxygen of the original cyano and hydroxyl group, respectively (Molenaar-Langeveld et al., 1992). It should be noted that the latter study was performed with use of the VG ZAB-2HF instrument after it was upgraded to a VG ZAB-HFqQ reverse-geometry double-focusing quadrupole hybrid mass spectrometer in 1989 (VG Analytical Ltd., Wythenshawe, Manchester, UK). At this point it is appropriate to present the background of this upgrading.

In the summer of 1987 I was invited by the chemistry division of the Netherlands Organization for Pure Research (SON/ZWO) to discuss with the colleagues in chemistry of the Utrecht University a possible move to that university. These discussions were very serious and a research plan with the associated infrastructure and instrumentation was set up until a newly appointed dean of the Faculty of Chemistry of the University of Amsterdam made clear that the faculty would not let me go by offering a research Institute of Mass Spectrometry. That offer was legalized officially by the Faculty of Chemistry of the University of Amsterdam in December 1987 and, after careful consideration of it with respect to the offer from the Utrecht University, accepted by me. This enabled me to realize the aforementioned instrumental upgrading, to appoint two full-time permanent scientific staff members (Dr. S. Ingemann and Dr. L.J. de Koning) and a 0.1 full-time chair of Physical Mass Spectrometry (Professor P.G. Kistemaker of the FOM Institute for Atomic and Molecular Physics in Amsterdam), while my chair was renamed from Organic into Chemical Mass Spectrometry as described in a short invited article together with the aims to be pursued by the Institute of Mass Spectrometry (Nibbering, 1993). In 1996 the staff was extended with a 0.1 full-time chair of

Industrial and Instrumental Mass Spectrometry (Professor F.H. Laukien of Bruker Daltonics, Billerica, MA).

Returning now again to the discussion of the research on cyano group containing molecules, extensive [13]C-, [15]N-, and deuterium labeling of cyanocyclohexane indicated that the carbons of positions 2 and 6 had become structurally indistinguishable from those of positions 3 and 5 prior to the loss of methyl and hydrogen cyanide from the molecular ion. This finding was suggested to be due to a rearrangement of the molecular ion to the key intermediate and symmetrical [2,2,1]-bicycloheptane-2-imine ion following migration of one of the hydrogens from position 4 to the nitrogen of the cyano group (Gremmen et al., 1997). Seemingly simpler systems that were studied were the molecular ions of cyanogen and isocyanogen. Their mass-analyzed ion kinetic energy spectra showed the formation of both CN^+ and $C_2^{+\bullet}$ notwithstanding the energy gap of 3.0 (cyanogen) and 3.5 eV (isocyanogen) between the two processes. This was explained by assuming that the higher energy demanding CN^+ formation took place from an isolated excited state of the molecular ions. The formation of $C_2^{+\bullet}$ had to occur from rearranged molecular ions for which C_2, bonded with one of its carbons to dinitrogen in a three-membered ring (cyanogen), and N_2, bonded with one of its nitrogens to C_2 in a three-membered-ring (isocyanogen) ion structures were proposed as intermediates on the basis of density functional theory calculations (Bickelhaupt et al., 1991).

Another interesting study that was performed in cooperation with Dr. A.M. Cardoso and Professor A.J. Ferrer-Correia of the University of Aveiro in Portugal concerned the formation of protonated methylamine from the molecular ions of 2-amino-1-phenylethanol-1 and its *p*-OH-substituted analog and of protonated dimethylamine from the *N*-methyl, *p*-OH-substituted analog. Based upon deuterium labeling results strong indications were obtained that the formation of these ions proceeded *via* the intermediacy of distonic methylamine or dimethylamine ion/*p*-hydroxybenzaldehyde molecule complexes, respectively (Cardoso et al., 1990). Within the same cooperation many years later the elimination of ammonia from the molecular ions of 1,4-diaminobutane and 1,5-diamino-pentane was studied using collision-induced dissociation and ion/molecule reactions, the latter being performed with use of the Bruker FTICR mass spectrometer mentioned in Subsection VII*B*. The motivation was that the $[M - NH_3]^{+\bullet}$ ion from 1,4-diaminobutane had been suggested to be the interesting ring-closed α-distonic ion of pyrrolidine (Mayerl & Hesse, 1976). However, the $[M - NH_3]^{+\bullet}$ ion from neither 1,4-diaminobutane nor 1,5-diaminopentane behaved like a distonic ion in reactions with dimethyl disulfide (Fernandes et al., 2002), known to be an excellent substrate to identify distonic ion structures by a unique $CH_3S^{\bullet}$ abstraction (Stirk, Kiminkinen, & Kenttämaa, 1992). Instead, on the basis of collision-induced dissociation experiments the ions were suggested to have an ionized enamine $CH_3(CH_2)n CH=CHNH_2^{+\bullet}$ structure ($n = 1,2$) being formed by simple cleavage of the C–N bond of a transient ring-closed α-distonic ion and subsequent hydrogen migration to the terminal carbon radical site (Fernandes et al., 2002).

It should be noted that in that study the product ion of ammonia loss from the even-electron protonated 1,5-diamino-pentane had the ring-closed structure of protonated piperidine.

Other electron ionization studies concerned the generation and characterization of the radical cation keto/enol tautomers of phenylketene (Shokhba et al., 1994), where the formation of the keto tautomer from ionized 7-phenylbicyclo[3.1.1]heptan-6-one by a complex rearrangement had been studied before (van den Heuvel et al., 1979), the HF loss from the $[M–CF_3]^+$ ion of $(CF_3)_2C(H)OH^{+\bullet}$ via two different and competing reaction channels (Yamaoka et al., 1997), the sulfur dioxide elimination from ionized 4-nitro- and 6-nitro-2,1-benzisothiazoline 2,2-dioxide derivatives (Danikiewicz et al., 1993), and the CO loss from the phenoxymethylene ions derived from phenoxyacetic acid and anisole (Molenaar-Langeveld, Ingemann, & Nibbering, 1993). The latter study owed its inception from the phenoxymethylene ions, generated from the molecular ions of 2-phenoxyethyl chloride and bromide (Theissling, Nibbering, & de Boer, 1971), which showed a composite metastable peak for the CO loss. The molecular ions of phenoxyacetic acid and anisole were selected as precursor ions to obtain insight into the mechanistic details of this reaction by a thorough ^{13}C and deuterium labeling study. The metastable phenoxymethylene ions from phenoxyacetic acid eliminated CO, which contained for ∼90% the carbon atom of position 1 of the phenyl ring. Based upon kinetic energy release measurements, thermochemical arguments and effects of substituents in the phenyl ring the broad component of the metastable peak was attributed to the loss of CO from a 2-methylphenoxy cation generated by rearrangement of the phenoxymethylene ion via a protonated benzo-oxocyclobutene species and cleavage of the $CH_2–O$ bond. The narrow component of the metastable peak was interpreted as being due to loss of CO from the acyclic and double bond conjugated acylium ion $CH_2=CH–CH=CH–CH=CH–C^+=O$, formed by cycloreversion of the protonated benzo-oxocyclobutene intermediate mentioned before. However, the metastable phenoxymethylene ions from anisole were observed to eliminate CO molecules, which contained for ∼45% the carbon of the methyl group, while the remaining part possessed the carbon atom of position 1 of the phenyl ring. Obviously this was due to a skeletal rearrangement of the molecular ions of anisole in such a way that the carbon atoms of the methyl group and position 1 of the phenyl ring were interchanged for which the mechanistic route in Scheme 26 has been proposed. This work together with other studies from my group has been incorporated also in an invited review (Nibbering, Ingemann, & de Koning, 1996).

With the available chemical ionization source it was also possible to investigate the effect of protonation of a functional group, such as the cyano group, by different reactant ions, that is at different reaction exothermicities, and at different pressures, which research was performed in cooperation with Professor H. Wincel from the Polish Academy of Sciences in Warsaw, Poland. In this way it was found that protonated acetonitrile could rearrange such that it formed not only the methyl cation from the original methyl group, but also a methyl cation that contained the cyano carbon as shown by ^{13}C and deuterium labeling experiments (Wincel, Fokkens, & Nibbering, 1989a). In that respect even a significant fraction of cyanomethyl cations has been observed to rearrange such that the two carbon atoms interchange their position presumably via three-membered ring structures, as concluded from ^{13}C labeling and behavior in ion/molecule reactions (Wincel, Fokkens, & Nibbering, 1990a). The
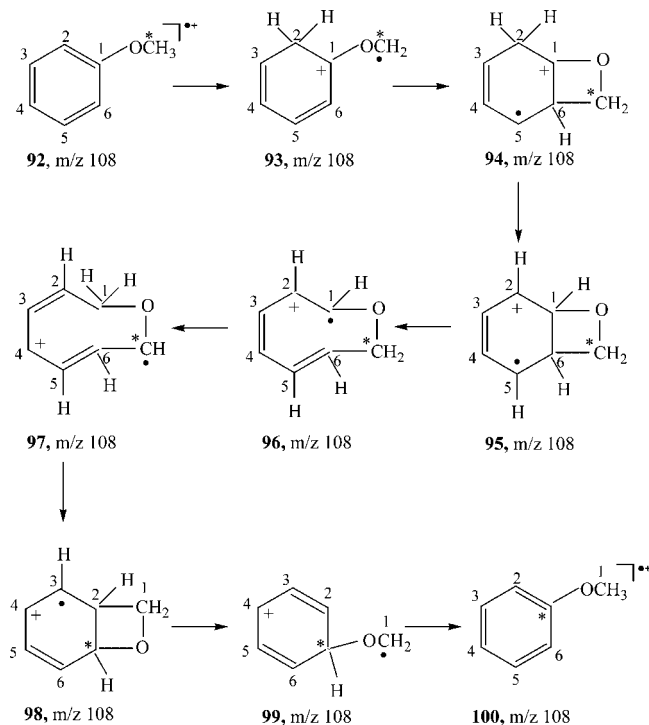
SCHEME 26.

isomeric and deuteronated n- and i-propyl cyanides did show an abundant $C_3H_6D^+$ ion formation upon metastable decomposition, which was explained by the initial formation of an isopropyl cation/CND complex. A successive proton and deuteron transfer between the partners in this complex and subsequent dissociation led to the products $C_3H_6D^+$ and HCN (Wincel, Fokkens, & Nibbering, 1991). Incidentally, the metastably decomposing radical cation of ethyl n-propyl thioether was also shown by ^{13}C and deuterium labeling to rearrange to a thioethyl radical/isopropyl cation complex prior to dissociation by methyl radical, propene, or allyl radical loss (Zappey, Ingemann, & Nibbering, 1991b). Methylation of acetonitrile was also studied where the resulting metastable ions appeared to decompose via two routes to give either protonated hydrogen cyanide or the ethyl cation. ^{13}C labeling showed that the former species retained the original cyano carbon for ∼90% that was not incorporated in the ethyl cation, while both species contained the hydrogens at random according to the applied deuterium labeling. These results were explained by 1,2-hydrogen shifts in the $CH_3CNCH_3^+$ ions to give the nitrogen protonated 3-aza-1,3-butadiene ion $H_2C=C(H)-N^+(H)=CH_2$ that via a successive ring closure to a four-membered ring and cycloreversion was converted into an ion/molecule complex consisting of protonated hydrogen cyanide and ethylene. This complex could then either break up directly or after a proton transfer to give protonated hydrogen cyanide or the ethyl cation, respectively (Wincel, Fokkens, & Nibbering, 1989b).

2. Site of Protonation of and Reactant Ion Attack Upon Polyfunctional Molecules

Another topic that has received research interest is the site of protonation of polyfunctional molecules. In the protonation of

benzonitrile and its site-specifically *ortho-*, *meta-*, or *para-*deuterated analogs by H_3^+, $CH_3OH_2^+$, and CH_3CNH^+ it has been found, that the proton attachment first occurs on the cyano group, from which the proton is transferred to the *ortho* position of the phenyl ring. Then after hydrogen exchange in the ring being far from complete as shown by the applied deuterium labeling, especially for the very exothermic protonation by H_3^+, a proton is transferred back to the cyano group prior to the loss of hydrogen cyanide (Wincel, Fokkens, & Nibbering, 1990b). In a similar way the site of protonation of phenyl *n*-propyl ether and ring methyl-substituted analogs by H_3O^+, $CH_3OH_2^+$, and CH_3CNH^+ was probed on the basis of propene loss and extensive deuterium labeling. The results obtained were interpreted to mean that protonation of phenyl *n*-propyl ether occurred preferentially at the oxygen atom, while a more balanced protonation at the oxygen atom and phenyl ring was inferred for the 4-methyl analog. A preference for ring protonation, however, was derived for the 3-methyl and 3,5-dimethyl-substituted analogs that became dominant for the 2,6-dimethyl- and 2,4,6-trimethylphenyl *n*-propyl ethers (Bogdanov et al., 1996). Protonation of fluorophenyl *n*-propyl ethers by H_3O^+, $CH_3OH_2^+$, and CH_3CNH^+ was found to be more important at oxygen for the 4-fluoro- and 2,6-difluoro-substituted analogs, while a significant fraction of ring protonation was inferred for the 3-fluoro-, 3,5-difluoro, and 2,4,6-trifluorophenyl *n*-propyl ethers (Bogdanov et al., 1998). In a cooperative study with Dr. A.M. Cardoso aralkylamines of the general formula $R^1R^2C_6H_3CHR^3$ $(CH_2)_nNR^4R^5$ with $R^1 = H$ or OH, $R^2 = H$, F, NO_2, OH or OCH_3, $R^3 = H$ or OH, R^4 and $R^5 = H$, and/or CH_3 and $n = 1–3$, were found to be preferentially deuteronated at the amino group by D_3O^+ and ND_4^+. The deuteron appeared to be transferred from the deuteronated amino group to the benzylic and *p*-hydroxyl groups, and to the aromatic ring where it exchanged with the ring hydrogens (Cardoso et al., 1998a). These aralkylamines were also studied with ions generated from dimethyl ether and trimethyl borate. The most abundant ion in the dimethyl ether plasma is the methoxymethyl cation that reacted mainly at the amino group, but also attacked the phenyl ring and the benzylic hydroxyl group, if present (Ramos et al., 2000a). Such attacks were also found for the dimethoxyborinium ion, $(CH_3O)_2B^+$, generated from trimethyl borate by electron ionization, but were more sensitive to the structure of the aralkylamines, that is, the amino group is an important, but not always the dominant site of initial reaction. In the case of 2-(4-nitro-phenyl)-ethylamine the site of attack was on one of the oxygens of the nitro group (Ramos et al., 2000b). Also the proton affinities of these aralkylamines were measured by use of the kinetic method (Cooks & Kruger, 1977; Zheng et al., 2003) and covered the range 900–962 kJ/mol (Cardoso et al., 1998b). Some of the aralkylamines were subjected to reactions with ions present in the nitromethane plasma. The most abundant NO^+ ions reacted *via* the channels of electron transfer and hydride abstraction, while proton transfer took place from the protonated nitromethane species. The immonium and $C_7H_7^+$ ions, generated by fragmentation of the formed radical cations of the aralkylamines, did lead to corresponding adduct ions with the neutral aralkylamines that for $C_7H_7^+$ were suggested to consist of a mixture of both covalently and non-covalently bonded species (Ramos et al., 2003). Protonation of methyl halides by use of deuterium

labeling showed that the proton was added on the halogen atoms F, Cl, and Br and that it had an increasingly stabilizing interaction with the carbon in the order of halogens given. In the case of iodomethane the interaction was such that the proton preferentially was bonded in a three-center two-electron bond with one of the methyl hydrogens (Heck, de Koning, & Nibbering, 1991b). Also the site of methylation of 1-phenyl-2-amino-propane by $(CH_3)_2F^+$, $(CH_3)_2Cl^+$, and $(CH_3)_3O^+$ was studied by collision-induced dissociation and neutralization-reionization experiments in combination with the Fourier transform ion cyclotron resonance method. It turned out that the $(CH_3)_2F^+$ ion transferred a methyl group to both the amino and the phenyl group with almost equal probability, while the $(CH_3)_2Cl^+$ ion predominantly and the $(CH_3)_3O^+$ ion almost exclusively methylated the amino group (Zappey et al., 1991). Incidentally, the dimethylhalonium $(CH_3)_2X^+$ ions with $X = F$, Cl, Br, and I were also studied by collision-induced dissociation and neutralization-reionization experiments. The former experiments showed methane elimination for the $(CH_3)_2F^+$ ion and in going from Cl to I an additional and increasingly competing loss of a methyl radical. The latter experiments resulted in the formation of $CH_3X^{+\bullet}$, CH_2X^+, and X^+ ions (Zappey et al., 1992). In cooperation with colleagues of the FOM Institute for Atomic and Molecular Physics in Amsterdam the neutralization of the isomeric ion structures of nitromethane, *aci*-nitromethane, and methyl nitrite by electron transfer from Cs or Na atoms was studied by recording the *neutral* fragment spectra and measuring the associated kinetic energy releases. These allowed distinction of the isomeric ion structures, but more importantly gave an insight into the dissociation dynamics of the electronically excited neutral species (Beijersbergen et al., 1992).

3. Ion/Molecule Reactions of the Methoxy Cation Following Charge Reversal of Methoxide

A project that has been for a long time on the list was to study the ion/molecule chemistry of the intriguing methoxy cation that was generated earlier as a stable species by charge reversal of the methoxide ion in high-energy collisions (Bursey et al., 1979) and was shown earlier to be ~ six times more efficient for CD_3O^- than for the unlabeled ion (Burgers & Holmes, 1984). This project was very suitable and challenging to show the capabilities of the VG ZAB-HFqQ reverse-geometry double-focusing quadrupole hybrid mass spectrometer to its full advantage as a complete laboratory on its own. First fully deuterated methoxide ions were generated in the chemical ionization source and following extraction and acceleration to 8 keV together with other anions selected with the magnet. Subsequenly two electrons were stripped off by collision with molecular oxygen to give the fully deuterated methoxy cations, which then successively were selected with the electric sector and decelerated to nearly thermal energies prior to injection into the RF-only quadrupole. Notwithstanding the reduction of the intensity of the original methoxide ion beam with a factor of ~10^5 following charge reversal, ion/molecule reactions between the methoxy cations and suitable substrates could be performed in the RF-only quadrupole from which the product ions were transferred to the final mass analyzing quadrupole for detection and ion abundance

measurements. In this way it was established that the methoxy cations reacted with methanethiol, propene, dimethyl ether and hardly with ethyl chloride by electron transfer, while the isomeric protonated formaldehyde reacted with these substrates by proton transfer (Zappey, Ingemann, & Nibbering, 1992).

4. Photodissociation by Crossing of a Decelerated Ion Beam With a Laser Beam

After the experiment described in the previous section, the deceleration lens system of the ZAB-HFqQ reverse-geometry double-focusing quadrupole hybrid mass spectrometer was in-house modified to cross the decelerated ion beam efficiently with a perpendicular pulsed excimer laser beam for photodissociation studies. With this set-up the isomeric radical cations of toluene, norbornadiene, and cycloheptatriene could be photodissociated with a very high efficiency and the corresponding mass spectra turned out to be essentially different (Aben et al., 1995). However, a problem with this set-up was the contribution of metastable ion decompositions to some of the signals. To avoid this contribution it was therefore decided to construct in-house an orthogonal time-of-flight section and to couple this to the double focusing part of the instrument at the end of the for that purpose newly designed deceleration lens system. The photodissociated ions resulting from the crossed mass-selected ion beam/laser beam interaction were then directly fired into the orthogonal time-of-flight section for detection and mass analysis. This project was successfully completed (Von Kóding, 2002), but then my career at the University of Amsterdam and the photodissociation research planned to be performed with use of this new instrumental set-up ended.

5. Applications

Before closing this part of the section, some application studies should be mentioned. They concerned the characterization of thiirenium ions of corresponding fluoroborate salts (Paradisi et al., 1987) and the characterization of N,N′-tetramethyl diazacoronands diiodides (Baranowska et al., 1989) by fast atom bombardment. Further, the applicability of the ionization methods of electron-, chemical-, field desorption-, fast atom bombardment-, thermospray-, and electrospray ionization for analysis of triphenyltin compounds, being widely introduced in the Dutch aquatic environment, was explored with use of not only the VG ZAB-HFqQ instrument, but also other mass spectrometers, such as the JEOL JMS SX/SX 102A four-sector mass spectrometer mentioned in Section VI (Miermans, Fokkens, & Nibbering, 1997). Field desorption appeared to be the most appropriate method to provide molecular weight information without fragmentation.

B. Negative Ions

In the mid 70s of the last century an interesting publication had appeared where high kinetic energy organic anions were converted into their positive counterparts by stripping off two electrons in one step by collisions with a neutral target gas,

known as charge inversion or charge reversal (Bowie & Blumenthal, 1975). This method was also applied in my group to the simple anions OH^-, $Cl_2^{-\bullet}$, CN^-, and C_2H^-, where it was observed by application of a voltage to the collision cell, that the stripping of two electrons occurred in two steps as well and that even a three-electron stripping was possible, either in one step or in a stepwise process of two- and one-electron stripping (De Lange & Nibbering, 1986). In a subsequent study the pressure dependence was studied of the charge reversal of the same anions with the exception of $Cl_2^{-\bullet}$ that enabled to develop a method for obtaining information about the number of collisions which had effected the charge reversal of the ions (De Lange & Nibbering, 1988). Then after a lively debate in the lab whether it would be possible to generate doubly charged negative ions by collision, carboxylate anions formed in the chemical ionization source from α,ω-dicarboxylic esters were subjected following acceleration to 8 keV and mass selection to collisions with helium. It was found that doubly charged negative ions were formed indeed by "ïon-pair" formation, if the charge carrying carboxylate groups were separated by more than two carbon atoms (Maas & Nibbering, 1989a). The next step was the development of a quantitative method for use with the VG ZAB-2HF instrument to assign the masses of ions involved in consecutive dissociations on the basis of the unique collision cell potential dependence of the kinetic energies of the granddaughter ions formed and to compare the method with that applied in three-sector instruments (Maas & Nibbering, 1989b). The developed method was then applied in a study of the collision-induced dissociation reactions of the monocarboxylate anions from the dimethyl and diethyl esters of glutaric acid and its 3,3-dimethyl analog in combination with deuterium labeling. Functional group interaction between the carboxylate anion and the ester group was found that led to anhydride formation, 1,5-hydrogen migration to the carboxylate anion, and to the uncharged ester group took place and charge remote fragmentations were observed. Interestingly, the mono-carboxylate anion of glutaric acid decomposed in two successive steps to give a methyl anion that contained the hydrogen atoms exclusively originating from positions 2 and 4 (Maas & Nibbering, 1990). The o-, m-, and p-methoxyphenyl anions, generated by negative chemical ionization from the corresponding ethyl methoxybenzoates, were shown by collision-induced dissociations to be distinct species. In addition to a minor loss of CH_2, the o-methoxyphenyl anions predominantly eliminated a molecule of formaldehyde showing that they had rearranged to the stable primary phenoxymethylene anions. The m- and p-methoxyphenyl anions lost for the major part a methyl radical being accompanied by a kinetic energy release that was significantly larger for the former anions (Visser, Maas, & Nibbering, 1990). The isomeric halophenyl anions $C_6H_4X^-$ (X = F, Cl, Br) have been studied by both collision-induced dissociation and charge reversal. The 2- and 3-fluorophenyl anions eliminated HF upon collision with molecular oxygen, but the 4-fluorophenyl anions did not show detectable amounts of fragment anions because of electron detachment. The latter was also the only process for the chlorophenyl anions, and the 3- and 4-bromophenyl anions, whereas the 2-bromophenyl anions did yield Br^-. The charge reversal spectra of the 2-, 3-, and 4-halophenyl anions from a given halobenzene turned out to be identical (Tomperi et al., 1993). In cooperation with Dr. A.M.

Cardoso the deprotonation of aralkylamines with the general formula $R^1C_6H_4CHR^2CH_2NR_2^3$ with $R^1 = H$, OH, F, or NO_2; $R^2 = H$ or OH; $R^3 = H$ or CH_3, by OH^- and OD^- was studied. Proton abstraction occurred from the benzylic position in the absence of a hydroxyl group in the aromatic ring, while from the hydroxyl group when present. The nitro compound formed only the molecular radical anion. The collision-induced dissociation spectra of the deprotonated molecules appeared to be strongly dependent on the structural features of the molecules (Cardoso et al., 1999). Finally, it should be noted that various rhenium compounds and activated Re_2O_7/Al_2O_3 catalysts were studied by use of negative ion fast atom bombardment. Analysis of the peaks in the obtained spectra indicated that on the surfaces of the catalysts Re_xO_y species are present with large numbers of x and y in addition to Re_2O_7 that could be precursors of active sites in the metathesis of olefins (Xiaoding et al., 1988).

IX. MISCELLANEOUS

In this section topics of research will be described that were not part of well-defined projects in my group and frequently were performed in cooperation with Ph.D. students and colleagues from other institutes or laboratories.

A. Stereochemistry

Stereochemistry has received over all the years much interest from gas phase ion chemists and has had several successes although it is an area of research where problems cannot be solved always easily by application of mass spectrometry (Splitter & Turecek, 1994).

However, a large difference was observed between the 70 eV electron ionization mass spectra of the *exo*- and *endo*-isomers of N-Ts-3-aza-7-carbethoxybicyclo[3.3.1]nonanes. The molecular ions of the former lost successively a molecule of ethanol and a tosyl radical (and *vice versa*), while the elimination of ethanol from the latter was totally absent, the expulsion of a tosyl radical being the major process. In both cases the tosyl radical loss was proposed to be anchimerically assisted by initially generated, but different radical sites in the molecular ions (Dekkers, Nibbering, & Speckamp, 1972). Another very interesting observation was made when the 70 eV electron ionization mass spectra of *endo*- and *exo*-2,3-*bis*-methoxycarbonylbicyclo[2.2.1]-heptane were recorded. The mass spectrum of the former had the base peak at m/z 146 and a peak at m/z 147 with a relative intensity of 7.7% which is close to the ^{13}C isotope contribution, while the latter had the base peak at m/z 145 and a peak at m/z 146 with a relative intensity of 11.5% which is a little bit higher than the ^{13}C isotope contribution. At first instance it was thought that a counting error had been made, because at that time the masses of the peaks were assigned manually from the UV chart recorded spectra. However, the one mass unit difference appeared to be real and was mechanistically rationalized as given in the Scheme 27 (A) and (B) (Eggelte & Nibbering, 1974). Panel (A) pictures the elimination of cyclopentadiene from the *endo* molecular ion to account for the formation of m/z 146, while the cyclopentadienyl
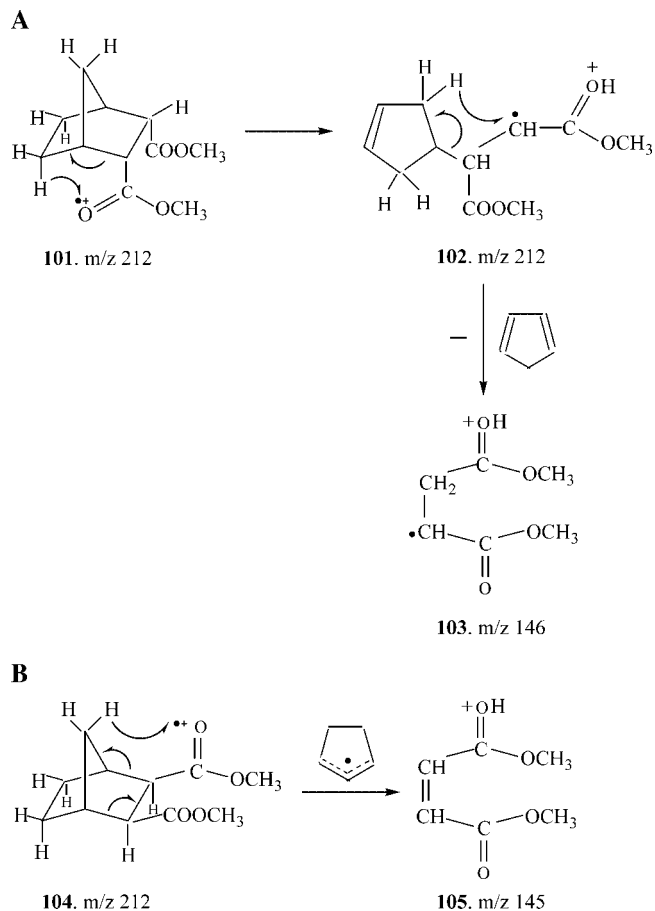
SCHEME 27.

radical loss from the *exo* molecular ion to give the ion m/z 145 is visualized in panel (B).

Large differences were also observed between the electron ionization mass spectra at both 70 and 15 eV of the geometrical *E*- and *Z*-isomers of α-ionone. The molecular ion of the *E*-isomer eliminated isobutene by a retro-Diels–Alder reaction, which was hardly observed for the *Z*-isomer that formed a bicyclic ion prior to or after a very favorable 1,5-hydrogen shift from the bis-allylic position before decomposition (Van Wageningen, Cerfontain, & Nibbering, 1974). Many years later and in cooperation with Professor A. Mandelbaum of the Technion-Israel Institute of Technology in Haifa, Israel, the conformation effect on the proton affinities of some stereoisomeric ethers were measured by use of the kinetic method in a triple quadrupole mass spectrometer and by equilibrium measurements using the Bruker Spectrospin CMS 47X Fourier transform ion cyclotron resonance instrument described in Subsection VIIB. The *cis*-isomer of 4-*t*-butylcyclohexyl methyl ether was found to have a ~0.4 kJ/mol higher proton affinity than the *trans*-isomer which for the *cis*-isomers of 4-phenylcyclohexyl methyl and ethyl ethers appeared to be 4 and 5 kJ/mol higher than for the corresponding *trans*-isomers, respectively (Denekamp et al., 1995). The latter result was explained by the internal hydrogen bond with the π-system of the phenyl ring.

B. Curie-Point Pyrolysis

Studies using Curie-point pyrolysis were performed at the FOM-Institute for Atomic and Molecular Physics in Amsterdam, where this method had been developed (Meuzelaar et al., 1973). Both organic and biomolecules were subjected to this technique, but the latter will be described in Subsection J with the exception of methionine that had been studied earlier extensively by electron ionization (see Section V). This enabled to compare the mechanisms of dissociation upon Curie-point pyrolysis, where the products following low energy (13 eV) electron ionization were detected and analyzed by using a quadrupole mass spectrometer, with those upon electron ionization. The same peaks were observed in both the Curie-point pyrolysis mass spectrum, called a pyrogram, and in the electron ionization mass spectrum of methionine, although with different intensities. However, the applied deuterium labeling showed that the mechanisms of neutral and ion fragment formation were essentially different. For example, the neutral product with the mass of 116 Da was due to a 1,2-elimination of hydroxylamine from neutral methione, while the ion m/z 116 was generated by the successive loss of a molecule of water and a methyl radical from its molecular ion. Similarly, upon pyrolysis the product with the mass of 101 Da was generated by the successive loss of a molecule of water, carbon monoxide, and molecular hydrogen, while the molecular ion of methionine formed the ion m/z 101 in a one-step elimination of methanethiol (Posthumus & Nibbering, 1977a). Afterwards the results of this study have also been compared with those obtained from field desorption (see Subsection VIB) and fast atom bombardment, the latter showing predominantly loss of ammonia or water plus carbon monoxide from the protonated molecule (Van der Greef et al., 1982b). Essentially different fragmentation mechanisms upon pyrolysis were established as well for 4-phenylbutanoic acid on the basis of deuterium labeling. For example, upon pyrolysis water is expelled via a 1,2-elimination process and styrene is generated in one-step by a 1,5-hydrogen shift-induced loss of enolic acetic acid, while from the molecular ion the water loss occurs via a 1,4-elimination and the styrene ion formation via a two-step elimination of a molecule of water and of ketene (Posthumus, Nibbering, & Boerboom, 1976; Posthumus & Nibbering, 1977b).

Pyrolysis of the but-3-ynoic and buta-2,3-dienoic acids led in both cases to the formation of propyne by loss of carbon dioxide, while the elimination of carbon dioxide from the molecular ion of the former acid gave the allene ion and from that of the latter acid the propyne ion (Dallinga, Nibbering, & Boerboom, 1983). The structures of the product ions were in that case determined by collisional activation using a tandem mass spectrometer with simultaneous ion detection, designed and constructed by Dr. A.J.H. Boerboom in the FOM-Institute for Atomic and Molecular Physics in Amsterdam (Louter et al., 1980). The α,ω-dicarboxylic acids HOOC(CH$_2$)$_n$COOH ($n = 1$–6) generated upon pyrolysis mainly intramolecular anhydrides and cyclic ketones, but in some cases also products from intermolecular interactions, such as acetone for $n = 1$ and hydroxybenzoic acid for $n = 3$. The isomers of the unsaturated dicarboxylic acids HOOC(C$_2$H$_2$)COOH and HOOC(C$_3$H$_4$)-COOH showed in addition to structure-dependent dehydration reactions the loss of carbon dioxide following 1,5- and 1,4- hydrogen shifts from the carboxyl group to the double bond (Dallinga, Nibbering, & Boerboom, 1984).

C. Photoionization

Two photoionization studies were performed in cooperation with colleagues of the FOM-Institute for Atomic and Molecular Physics in Amsterdam. The first dealt with the effect of the ion source temperature on the photoionization mass spectra of n-hexane, 3-methylpentane, and ethanol. For that purpose a mathematical relationship was derived between the ion source temperature and the internal energy of the molecular ions that enabled the construction of thermal breakdown diagrams from which the lowest appearance energies could be obtained (Genuit & Nibbering, 1986). The latter were in very good agreement with literature photoionization data, indicating that the thermal energy was fully effective in the fragmentation reactions. The second concerned the time-of-flight photoionization mass spectra of linear, branched, and cyclic hexanes obtained with use of a single photon, which was generated by frequency tripling of the third harmonic of a Nd: YAG laser in a Xe cell. Also in that study the effect of temperature on the fragmentation was investigated and using the model from the previously mentioned study it was concluded for n-hexane that less than 50% of the difference between the photon energy and ionization energy was deposited in its molecular ion (Steenvoorden et al., 1991).

D. LC/MS

Only a few studies on aspects or applications of LC/MS have been performed, almost all of them in cooperation with colleagues from other labs. The first one was an invited survey on ionization methods with emphasis on LC/MS (Nibbering, 1982) prepared for the first of the three successive LC/MS meetings, held in Montreux, Switzerland in 1982, 1984, and 1986, that the author had co-organized with Professor R.W. Frei of the Vrije Universiteit in Amsterdam. The second and third were carried out in cooperation with Professor van der Greef of the University of Leiden in The Netherlands. The former study was on the generation of singly protonated water clusters and negatively charged water cluster ions from pure water injected via LC in a thermospray ion source operating in the discharge-on mode. The negatively charged water cluster ions consisted of two series of ions, that is, (H$_2$O)$_m$OH$^-$ (with m = 0- ∼ 40) and (H$_2$O)$_n^{-\bullet}$ (with $n = 11$–70), the latter being formed by associative electron capture (Tinke et al., 1991). The latter study was concerned with the mechanisms of repeller-induced effects in thermospray LC/MS that showed that three different processes were occurring. At lower repeller potentials the thermospray mass spectra of the eluent were determined by the proton affinities and the concentrations of the various solvent constituents, and by the stabilities of the formed cluster ions. At a higher repeller potential collision-induced dissociation of the background ions started to occur. At even higher repeller potentials endothermic proton transfer and solvent switching pathways were opened because of the high kinetic energy of the ions and cluster ions (Heeremans et al., 1991). The fourth study was performed in cooperation with Dr. T. Vree of the University of

Nijmegen and Professor R.A.A. Maes of the University of Utrecht in The Netherlands in which metabolites of methyl-prednisolone in the urine of patients were identified by use of LC/atmospheric pressure chemical ionization/ion trap mass spectrometry (Vree et al., 1999).

E. Drug Analysis

A few studies have dealt with the mass spectrometric analysis of drugs. Two of them were on tetrahydrocannabinol in cooperation with Dr. T. Vree. One was focused on the gas chromatographic behavior of various synthetic side-products of *cis-* and *trans-*tetrahydrocannabinols that were identified by use of mass spectrometry (Vree et al., 1973). The other was a mechanistic study on the elimination of C_5H_8 from the molecular ions of *trans-ortho-* and *trans-para-*1,2-tetrahydrocannabinol. This elimination occurs readily for the molecular ions of the corresponding 1,6-isomers by a retro-Diels–Alder reaction of the alicyclic ring, but for the *trans-ortho-* and *trans-para-*1,2-tetrahydrocannabinols the double bond must first shift from the 1,2-position to the 1,6-position. This took place to some extent, but it turned out that the occurrence of the retro-Diels–Alder reaction decreased dramatically upon methylation of the phenolic group. This observation indicated that the phenolic proton played an important role in the elimination of C_5H_8 from the molecular ions of *trans-ortho-* and *trans-para-*1,2-tetrahydrocannabinol for which transfer of the phenolic proton to the double bond in the 1,2-position was suggested (Vree & Nibbering, 1973). Many years later a fast atom bombardment study was undertaken to determine the structure of an orange-colored unstable product that was formed by oxidation of the non-steroidal anti-inflammatory drug diclofenac in the presence of myeloperoxidase and hydrogen peroxide. This product was shown to be dihydroxyazobenzene (Zuurbier et al., 1990). Around that time another long-standing structural problem was solved by use of NMR and mass spectrometry. It concerned β-philanthotoxin, a toxin from the insect paralyzing venom of the wasp *Philanthus triangulum*. Its electron ionization mass spectrum was a beautiful example for structural interpretation and together with other mass spectrometric measurements the toxin was shown to be a compound with an amide group and two amine functionalities, that is, $C_5H_{11}NHCO(CH_2)_4NH(CH_2)_3NH_2$ (Karst et al., 1990). More than 10 years after that study, a methodology was developed to create a drug library for the identification of toxicologically relevant drugs in plasma samples in which project each participant came from a different lab. The methodology was based upon collision-induced dissociation mass spectra of drugs, which were obtained by use of a single quadrupole instrument equipped with an atmospheric pressure-electrospray ionization source, following optimization of the so-called fragmenter voltage for each drug. The optimized fragmenter voltages were then applied by use of a variably ramped fragmenter voltage to acquire mass spectra for the library of drugs, which *via* HPLC were injected into the described quadrupole mass spectrometer. A search of significant peaks in the HPLC chromatogram of liquid-liquid extracted spiked blank serum and patient samples with a total of 40 different drugs was shown to result in a more than 95% positive identification by

application of the developed mass spectral library (Lips et al., 2001). Finally, in a cooperative study between four different labs it was shown that the frequently applied method of trimethylsilylation by a mixture of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide, ammonium iodide, and ethanethiol for steroid analysis by GC/MS can lead to artefacts when applied to silylate the steroids androsterone and etiocholanolone obtained from a urine matrix. The artefacts were identified as ethyl thio-containing products of the trimethylsilyl derivatives and gave a warning that such ethyl thio-incorporation may lead to misinterpretation in the search of formation of new metabolites (van de Kerkhof et al., 2002).

F. Supramolecular Assemblies

The background of research in supramolecular chemistry will be given first before presenting some of the results obtained in this field. In 1995 I had a discussion about matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) with my colleague Professor D.N. Reinhoudt of the University of Twente in Enschede, The Netherlands with whom I have a long-standing personal and professional friendship. We both agreed that this area of mass spectrometry, first developed at the end of the 80s (Karas et al., 1987; Karas & Hillenkamp, 1988; Tanaka et al., 1988), was needed as a useful and powerful extension to the arsenal of mass spectrometric methods available in the Institute of Mass Spectrometry of the University of Amsterdam. However, I had already planned to apply in that year for a grant from the chemistry division of the Netherlands Organization for Scientific Research (SON/NWO) to upgrade the Bruker FTICR instrument (see Subsection VII*B*). It was then agreed that Professor Reinhoudt would apply for a grant from the same organization to purchase a MALDI-TOF mass spectrometer that was awarded in 1995 for 70%, the remaining percentage of the grant to be provided by the University of Twente by so-called matching. This worked out successfully and with permission of the Board of Trustees of the University of Twente the ordered PerSeptive Biosystems Voyager-DE-RP-MALDI-TOF mass spectrometer (PerSeptive Biosystems, Inc., Framingham, MA) was delivered and installed in the Institute of Mass Spectrometry of the University of Amsterdam in 1996 with the gentleman's agreement that the instrument would be moved to the University of Twente when I would not be in charge anymore of the mentioned institute. With regard to the application of MALDI-TOF-MS in supramolecular chemistry, a very successful method to characterize non-charged multicomponent hydrogen bonded assemblies was to charge them in a non-destructive way with the soft Ag^+ ion which has a remarkably high affinity for a variety of aromatic and aliphatic π donors, cyano groups, crown ethers, or a combination thereof. In this way not only thermodynamically stable nine-component calix[4]arene-based assemblies with molecular weights of over 4,000 Da, but also thermodynamically less stable cyclic hexameric single-rosette assemblies, consisting of three molecules of melamine and three monosubstituted cyanurates, with molecular weights up to nearly 5000 Da and containing 18 hydrogen bonds could be characterized (Jolliffe et al., 1988). This work has been extended to the successful characterization of a

great variety of double-rosette assemblies (9 components, 36 hydrogen bonds) and even tetra-rosette assemblies (15 components, 72 hydrogen bonds), the latter having molecular weights up to ~8,500 Da (Timmerman et al., 2000). The Ag$^+$ labeling method was also applied to characterize dynamic libraries of hydrogen-bonded assemblies formed by mixing the individual components under thermodynamically controlled conditions (Crego Calama et al., 1998). Afterwards these dynamic assemblies could be converted by a suitable metathesis reaction quantitatively into covalent systems that without Ag$^+$ labeling could be easily analyzed by use of MALDI-TOF-MS (Cardullo et al., 2000). Finally, non-covalently bonded assemblies of metallodendrimers containing up to 12 porphyrins on the surface (Huck et al., 1998) and ''layer-block'' metallodendrimers containing hydrophobic shells of covalent dendritic wedges at the periphery with molecular weights of up to ~ 29,000 Da (van Maanen et al., 2001) were characterized successfully by application of MALDI-TOF-MS.

G. Fullerenes

A number of studies on substituted fullerenes have been performed in cooperation with Dr. D. Heymann of the Rice University in Houston in Texas and other labs. One of the first projects was to determine the number of Cl atoms in products obtained by exposing C_{60} or C_{70} in CS_2 or CCl_4/CS_2 solutions, saturated with chlorine, to ultraviolet irradiation. Different methods were applied together with negative ion MALDI-TOF-MS which showed the formation of $C_{60}Cl_n$ with $n = 7, 9, 11$ and $C_{70}Cl_7$. The other applied methods indicated a larger number of Cl atoms in the products which led to the conclusion that Cl-stripping occurred during laser evaporation even to completion as shown by the formation of the radical anions of C_{60} or C_{70} (Heymann et al., 1999). In the reaction of ozone with C_{60} in hydrocarbon solutions an unstable intermediate was detected and isolated. This was identified as a primary ozonide of C_{60} whose UV-vis absorption spectrum showed features consistent with a [6,6]-closed adduct. Its thermal dissociation into $C_{60}O$ and released O_2 in toluene solution required an activation energy of ~ 89 kJ/mol. The MALDI-TOF mass spectrum showed ions of $C_{60}O$ and C_{60} (Heymann et al., 2000). $C_{70}O$ in toluene gave upon exposure to light at room temperature undetermined products possibly because they were very insoluble in toluene, while after 140 days 21% of the original $C_{70}O$ remained (Heymann, Fokkens, & Nibbering, 1999).

In cooperation with Professor L.W. Jenneskens of the University of Utrecht, The Netherlands, the idea was to generate C_{60} directly in the source of the MALDI-TOF mass spectrometer using the laser light as the energy source for dehydrogenation of suitable organic precursor molecules. Initial experiments on a mixture of the $C_{60}H_{30}$ isomers tribenzo[l:l′:l″]benzo[1,2-e:3,4-e′:5,6-e″]triacephenanthrylene and tribenzo[l:l′:l″]benzo[1,2-e:3,4-e′:6,5-e″]triacephenanthrylene, which were formed in a ratio of 1:3 by the synthetic route applied, did show cyclodehydrogenation down to product ions with m/z 730–732 (Sarobe et al., 1999). However, only the former $C_{60}H_{30}$ isomer has the right carbon atom topology to form C_{60} by 15-fold consecutive intramolecular H_2 losses and accompanying ring closures, while

the latter isomer's carbon atom topology can only give eventually either a curved $C_{60}H_{12}$ or a flat $C_{60}H_{10}$ polyaromatic hydrocarbon by dehydrogenation. Afterwards it was possible to obtain pure tribenzo[l:l′:l″]benzo[1,2-e:3,4-e′:5,6-e″]triacephenanthrylene that indeed dehydrogenated fully to show the formation of $C_{60}^{\bullet+}$ ions in its MALDI-TOF mass spectrum, which was nearly identical to its post-source-decay MALDI-TOF spectrum (Gomez-Lor et al., 2002).

H. Polymers

In addition to the polymers of polyethylene glycols studied by multiple cationization in field desorption (see Section VI, Subsection $B1$), two publications have focused on the polymers of hyperbranched polyesteramides that were performed in cooperation with Dr. C.G. de Koster of DSM Research in Geleen, The Netherlands. The first concerned hyperbranched polyesteramides (DA_2), prepared from hexahydrophthalic anhydride (D) and di-isopropanolamine (A), which were characterized by use of MALDI-TOF, field desorption-, and electrospray ionization mass spectrometry. In the MALDI mass spectrum signals from the protonated molecules of D_nA_{n+1} and D_nA_n were almost absent, showing signals of the ions $[D_nA_{n+1}H-mH_2O]^+$ and $[D_nA_nH-mH_2O]^+$ with $m = 1,2$ instead. However, in the electrospray ionization mass spectra the signals from the protonated molecules D_nA_{n+1} and D_nA_n were frequently the base peaks in the cluster of signals of the $[D_nA_{n+1}H-mH_2O]^+$ and $[D_nA_nH-mH_2O]^+$ ions with $m = 1,2$, while the field desorption mass spectra resembled closely the electrospray ionization mass spectra. The conclusion was therefore that in source-decay took place of the protonated molecules of D_nA_{n+1} and D_nA_n in the MALDI-TOF mass spectrometer to give the ions $[D_nA_{n+1}H-mH_2O]^+$ and $[D_nA_nH-mH_2O]^+$ which can lead to an erroneous interpretation with regard to the chemical composition distribution and the end-group distribution of these polymers (Muscat et al., 2000). A comparison between the determination of the molecular mass of the hyperbranched polymer, prepared from 1,2-cyclohexanedicarboxylic anhydride and di-2-propanolamine, by size exclusion chromatography-differential viscometry and MALDI mass spectrometry as a function of elution volume showed a very good agreement (Gelade et al., 2001).

I. Fluorinated and Silicon-Containing Compounds

Many research projects have been performed during the last 10 years of my career in cooperation with Professor S. Tajima of the Gunma National College of Technology in Maebashi, Gunma, Japan, on a variety of simple organic molecules, in particular on fluorinated and silicon-containing compounds with use of his modified Hitachi RMU-7M reversed geometry instrument. Some examples will be presented below.

An interesting case was the loss of hydrogen fluoride from the $[M-CF_3]^+$ ion of 1,1,1,3,3,3-hexafluoro-2-propanol that exclusively contained the hydroxylic hydrogen. The metastable peak associated with this reaction was composite, where the broad and narrow component corresponded with kinetic energy releases of 690 and 8 meV, respectively. The former was

interpreted to be due to a 1,2-elimination of HF following migration of a fluoride from the trifluoromethyl group to the methine carbon and the latter to a heterolytic cleavage of the C–F bond after migration of the hydroxylic proton to one of the fluorine atoms of the trifluoromethyl group (Tajima et al., 1993). However, in a more elaborate study afterwards, in which also Professors H. Yamaoka of Osaka Women's University in Osaka and H. Yamataka of the Kyushu University in Fukuoka, Japan, participated, a more likely explanation for the broad component on the basis of *ab initio* calculations at the MP2/6-31G*//HF/6-31G* level of theory was put forward. The reaction started again with migration of a fluoride from the trifluoromethyl group to the methine carbon, but then the methine hydrogen migrated to the generated difluoro carbenium ion center to give protonated acetyl fluoride with a difluoromethyl group. Subsequently this ion rearranged in two steps to an HF-solvated difluoroacetyl cation from which HF was lost to generate the difluoroacetyl cation. The latter structure was confirmed by collision-induced dissociation experiments on the ions of the broad component of the metastable peak using the JEOL JMS SX/SX 102A four-sector mass spectrometer mentioned in Section VI (Yamaoka et al., 1997). In that study also the earlier proposed structure of the ions of the narrow component of the metastable peak was confirmed. In a study of ionized methyl and ethyl trifluoroacetates it was concluded that a large part of their metastably decomposing ions had the enol structure. Furthermore, their source generated and most abundant m/z 69 ions appeared to consist of both the trifluoromethyl cation and protonated carbon suboxide, the latter being formed by at least three and four different fragmentation routes from the methyl and ethyl esters, respectively (Tajima et al., 2002a). Heavily fluorinated diethyl ethers showed complex fragmentations upon electron ionization (Tajima et al., 2002b) while the metastable [M–methyl]$^+$ ions from 1,1,1-trifluoroisopropyl methyl ether decomposed *via* the four competitive channels of carbon monoxide, methyl fluoride, difluorocarbene, and methoxyfluorocarbene elimination (Tajima et al., 2003a).

With regard to silicon-containing compounds, the isomeric methoxytrimethylsilane and trimethylsilylmethanol behaved quite differently upon electron ionization. Their metastably decomposing ions both eliminate a methyl radical, for the former originating from the trimethylsilyl group. For the latter, however, first as key step a 1,2-trimethylsilyl group migration from carbon to oxygen occurs in the molecular ion which then eliminates a methyl radical containing the methylene carbon and the hydrogens from the methyl and methylene groups at random as shown by deuterium labeling (Sekiguchi et al., 1998). Interestingly, the isomeric methoxytrimethylsilane and trimethylsilylmethanol radical cations were also formed by ketene loss from the metastable ions of the methyl ester of trimethylsilylacetic acid. This ketene loss was suggested to involve ion-radical complexes, consisting of $(CH_3)_3Si^+/$ $^•CH_2CO-OCH_3$ and $(CH_3)_3Si^+/CH_2=C(OH)OCH_2^•$, respectively (Tajima et al., 2002c). Another compound that was studied was acetyltrimethylsilane. Its molecular ion eliminates a methyl radical giving two isomeric ions, that is $(CH_3)_2$ $SiOCH_3^+$ and $(CH_3)_3SiCO^+$, which in the metastable time window is occurring with an extensive hydrogen atom exchange according to the deuterium labeling applied. Both ions lose carbon monoxide, the former being accompanied by a methyl

migration and a large kinetic energy release, the latter by a small kinetic energy release (Tajima et al., 2003b). Finally, the silicon- and fluoro-containing molecule of 2,2,2-trifluoroethoxytrimethylsilane has been investigated. Its molecular ion eliminates a methyl radical from the trimethylsilyl group that is followed by migration of either F (major) or CF_3 (minor) to the silicon ion center prior to further decomposition (Tajima et al., 2003c).

J. Biomolecules

In addition to detailed studies on the amino acid methionine by use of various methods (see Sections V, VI, Subsection *B1*, and Subsection *B* above), the amino acid arginine (see Section VI section *B1*) and dipeptides (see Section VII Subsection *B6*) various other biomolecules have received research attention during my career. An early study in cooperation with Dr. A.J.H. Boerboom and Professor H.-R. Schulten was on nucleic acids that were subjected to Curie-point pyrolysis, the products being analyzed by both low mass resolution/low energy electron ionization and high mass resolution/field ionization mass spectrometry. Most of the peaks in the corresponding mass spectra originated from the carbohydrate moiety of the nucleic acid and DNA/RNA could be distinguished very easily by use of these key fragments, that is, the major ions for DNA were m/z 68, 70, 82, and 98 and for RNA m/z 84, 86, 98, and 114 reflecting the oxygen atom difference (Posthumus et al., 1974). A decade later Curie-point pyrolysis was applied to mycobacterial strains where the products following low energy electron ionization were analyzed and characterized by collisional activation using the tandem mass spectrometer with simultaneous ion detection mentioned above in Section B. The attention was focused especially on the ion m/z 59, because this was considered to be the key mass with the highest differentiation power for the six mycobacterium species that were studied. However, the latter unfortunately could not be distinguished in this way (Haverkamp et al., 1984).

In a cooperative fast atom bombardment and tandem mass spectrometry study with Professor M.L. Gross β-endorphins and adrenocorticotropic hormone (ACTH) peptides with molecular weights up to 2,000 Da were studied. These compounds were obtained as a gift from the Dutch pharmaceutical company Organon International in Oss, The Netherlands. The group of Professor M.L. Gross used a Kratos MS-50 triple sector (EBE) mass spectrometer and my group a VG Micromass ZAB-2HF double sector (BE) instrument. The metastable ion and collision-induced dissociation spectra from the two different instruments compared reasonably well. The fast atom bombardment spectra of the endorphins contained predominantly peaks due to the Y-series ions, while the metastable ion and collision-induced dissociation spectra showed abundant ions of both the B- and the Y-series. The metastable ion and collision-induced dissociation spectra of the ACTH peptides contained practically only peaks due to the Y-series ions that were less intense compared with those from the endorphins (Tomer et al., 1988). In cooperation with the Dutch pharmaceutical company mentioned the amino acid sequence of a synthetic neuropeptide, and its deuterium labeled analogs was verified by use of fast atom bombardment

and tandem mass spectrometry. The spectra showed predominantly peaks due to *N*-terminal sequence ions and some peaks due to *C*-terminal sequence ions and permitted to determine the amount and the position of deuterium incorporated in the peptide (Waghmare et al., 1989). Similarly, in cooperation with Professor J.H. van Boom of the University of Leiden in The Netherlands, four fully protected synthetic nucleopeptides were subjected to positive and negative ion fast atom bombardment and tandem mass spectrometry. This enabled not only to identify the main building blocks, but also to sequence their peptide part. The cleavage of the peptide-phosphate backbone occurred mainly *via* a 1,5-H shift from the side chain of the neighboring amino acid to the oxygen phosphate and the number of amino acids present in the peptide part was found to have influence on the location of sodium ion cationization (Waghmare et al., 1991). The same strategy was applied in a subsequent study to verify the position of the phosphate group in some cyclic and linear synthetic phosphopeptides. Based upon the occurrence/non-occurrence of loss of phosphoric acid from low abundant fragment ions, induced by low- and high-energy collisions, the position of the phosphate group could be determined unequivocally (Nijenhuis et al., 1993). High-resolution fast atom bombardment and tandem mass spectrometry were also used to sequence the heptapeptide-*p*-coumaric acid chromophore conjugate obtained after the combined pepsin/proteinase K digestion of the photoactive yellow protein from *Ectothiorhodospira halophila*. These experiments unambiguously showed that the *p*-coumaric acid molecule was bonded to Cys 69 *via* a thiol ester bond (Hoff et al., 1996).

An interesting observation was made in the chemical ionization spectra of a mixture of the amino acids glutamine and methionine, being protonated by reagent ions, such as H_3^+, CH_5^+, $CH_3NO_2H^+$. Product ions were formed with the masses of the protonated dipeptides Glu-Glu and Glu-Met, and the tripeptides Glu-Glu-Glu, Glu-Glu-Met and/or Glu-Met-Glu, and Glu-Met-Met, their amino acid sequences being derived from their metastable ion spectra obtained with use of the JEOL JMS SX/SX 102A four-sector mass spectrometer mentioned in Section VI. The mass-analyzed ion kinetic energy spectrum of the (Glu-Met)H^+ product ion was different from the authentic protonated dipeptide Met-Glu, but identical with that of the authentic protonated dipeptide γ-Glu-Met. Its formation was rationalized by attack of the amino group of methionine upon the carbonyl carbon of the protonated anhydride of glutamine formed by loss of water, resulting in ring opening and peptide bond formation (Wincel, Fokkens, & Nibbering, 2000a). This reaction resembles the amide bond formation by reaction of the benzoyl cation with neutral amines (Bruins & Nibbering, 1975), mentioned in Section IV. The protonation-induced loss of water from glutamine to form its anhydride could also be induced by reaction of NO^+ with glutamine, resulting in the formation of the corresponding NO^+ cationized anhydride. The latter species was also formed in the reaction of NO^+ with γ-Glu-Met by loss of methionine from the reaction complex (Wincel, Fokkens, & Nibbering, 2000b).

Finally, in a joint study between four labs the internal energy of the protonated peptide leucine enkephalin was increased by a well-defined amount *via* blackbody infrared radiation below the dissociation threshold using a Fourier transform ion cyclotron resonance mass spectrometer. Subsequently, the internal energy distribution was probed using on-resonance collisional activation to dissociate the ions in two different ways: (i) with variable kinetic energies at a constant initial ion temperature and (ii) with a constant kinetic energy at variable ion temperatures. From these experiments the conclusions were drawn that the internal energy of the ions could be manipulated in a controlled manner and that the effective conversion efficiency of the laboratory—frame kinetic energy to internal energy in collisions with argon was approximately $4.0 \pm 1.7\%$ (Guo et al., 2003).

X. EPILOGUE

This invited review, which covers ∼85% of the (co)-author's published work, has enabled me to look back with great pleasure and joy at the science that was done by my group in the field of mass spectrometry, at the many international and national cooperations with my colleagues, the many conferences for which I was invited as a speaker, the invited lecture tours through Poland in 1979, 1987, and 1999, Switzerland in 1979, Australia in 1983, the United States of America and Canada in 1984, Japan in 1992 and 1996, and Brazil in 1994, the longer stays at the Cornell University in Ithaca, New York in 1974, the University of Colorado in Boulder, Colorado in 1980, the University of Padova, Italy in 1988, the Technion-Israel Institute of Technology in Haifa, Israel in 1990, the Washington University in St. Louis, Missouri in 2001, and the University of Rome, Italy in 2002. I also remember with great pleasure the Sandbjerg meetings for young mass spectrometrists in Jylland, Denmark, organized by Professor S. Hammerum of the University of Copenhagen, Denmark in 1977, 1978, and 1989 and the joint group meetings with Professor H.-F. Grützmacher at the University of Bielefeld, Germany in 1990. I like to mention my Ph.D. students and students who have been successful in their academic careers who are Dr. A.P. Bruins, Associate Professor in the Department of Pharmacy of the University of Groningen, Dr. F.M. Bickelhaupt, Associate Professor of Theoretical Chemistry at the Vrije Universiteit in Amsterdam, Professor J. van der Greef, who occupies a part-time chair of Analytical Chemistry at the University of Leiden, Professor A.J.R. Heck, who occupies the chair of Biological Mass Spectrometry at the University of Utrecht, Professor H.E. Schoemaker, who has a part-time chair in Synthetic Organic Chemistry at the University of Amsterdam, Professor N.P.E. Vermeulen, who occupies the chair in Molecular Toxicology at the Vrije Universiteit in Amsterdam, all in The Netherlands and the late Professor A. Venema, who had a part-time chair in Analytical Chemistry at the University of Ghent in Belgium. I like to mention the visiting scientists Professor S. Tajima and Professor H. Yamaoka, who eventually obtained the chairs of Physical Chemistry at the Gunma National College of Technology in Maebashi, Gunma, Japan and Organic Chemistry at Osaka's Women University in Osaka, Japan, respectively.

The field has changed enormously in the last decade with an explosive expansion into the area of large biomolecules with research on their structure, function, and dynamical behavior (Kaltashov & Eyles, 2005). This has led to the development of new methods, such as electron capture dissociation of

multiply protonated peptides and proteins (Zubarev, Kelleher, & McLafferty, 1998; Zubarev, 2003). It is for me a very great pleasure to note that the mechanism of electron capture dissociation has been investigated recently in detail by high-level theoretical calculations (Uggerud, 2004; Syrstad & Turecek, 2005).

Unfortunately, my career ended at the University of Amsterdam in a very unpleasant way by a contraproductive reorganization of the department of chemistry because of the dramatic decrease of students in chemistry in which it was made clear to me that I had to abandon my work. Thus, after a 1-year sabbatical leave I went on an early retirement at October 1, 2001. However, my colleagues Professors S. Stolte of the Vrije Universiteit in Amsterdam and D.N. Reinhoudt of the University of Twente in Enschede, The Netherlands invited me to join then their universities as a guest professor which I accepted with great pleasure and which enabled me to finish my earlier commitments of the Presidency of the International Mass Spectrometry Society and the editorship of Volume 4 of the Elsevier Encyclopedia of Mass Spectrometry.

In summary, I have experienced my career as a fantastic and exciting trip through the world of mass spectrometry!

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