International Journal of Mass Spectrometry 200 (2000) 243–251

Development of chemical ionization mass spectrometry

Burnaby Munson

Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716-2522, USA

Received 25 May 2000; accepted 14 August 2000

Keywords: Ion-molecule reactions; Chemical ionization; Positive ions

---

Chemical ionization mass spectrometry (CIMS) is an analytical application of ion/molecule reactions. This analytical technique is a direct result of studies of ion/molecule reactions over the years at increasing pressures in the reaction chambers of mass spectrometers. Ion/molecule reactions were observed early in the development of mass spectrometry, to some extent as curiosities or nuisances [1–3]. Modern ion/molecule research, however, is continuous from experiments in the 1950s: the work of Tal'roze in the Soviet Union, Stevenson and Schissler at Shell Development Co. in the USA, and Field, Franklin, and Lampe at Humble Oil and Refining Co (ESSO Research and Engineering Co.) in the USA [4–6].

The ion/molecule reactions observed in these early experiments were fast, with bimolecular rate constants of the order of 1×10^{-9} cm^3/molecule s ($\approx 6 \times 10^{+11}$ L/mol s). However, the pressures and reaction times were low ($\approx 10^{-3}$ mm Hg or ≈ 0.13 Pa and ≈ 1 μs); so the reactions gave only small conversions to products. In experiments with mixtures, the primary ions from each gaseous component reacted with each gaseous component; consequently, the distributions of ionic products were generally complex and often difficult to interpret. Roughly equal amounts of both reactants were required to observe ion/molecule reactions.

There were no obvious analytical applications of these studies. However, analytical applications of ion/molecule reactions were shown about this time. The most important piece of information that a mass spectrum can provide is the molecular weight of the compound. The electron ionization (EI) mass spectra of many compounds do not contain abundant, or even detectable, $M^{+\cdot}$ ions. Some polar compounds for which the EI mass spectra contained no $M^{+\cdot}$ ions formed MH^+ ions when significantly larger samples than usual were introduced into standard electron ionization sources [7,8]. The appearance of these pressure or sample size dependent MH^+ ions could confirm the molecular weights of the compounds.

The ion/molecule reaction studies in the 1950s were done with slightly modified electron ionization mass spectrometers that operated with ion sources at high voltage and had relative small diffusion pumps. Analytical electron ionization mass spectrometers at this time detected only positive ions; consequently, all of the initial ion/molecule work (and hence the initial chemical ionization studies) was done with positive ions. The low pumping capacities of the instruments and the lack of separate diffusion pumps on the ionization and analyzer regions of the mass spectrometers led to instrumental problems as the source pressures were increased. If the pressure in the source was increased sufficiently for extensive ion/molecule reactions then collisional broadening of peaks and significant collisional losses of ions occurred because of the (relatively) high pressures in the analyzer. In

PII S1387-3806(00)00301-8

addition, the pressures became high enough that electrical discharges were often observed between the high voltage source and the nearest ground.

Large pumping capacity and separate diffusion pumps on both the source region and analyzer (as well as a "tight" source) are required to allow operation of mass spectrometers at pressures of ≈0.1–1 mm Hg (100–1000 μ in the terminology of that day or ≈13–133 Pa these days). One such instrument was built at the Humble (ESSO) Research Laboratories in Baytown, Texas, moved to the ESSO laboratories in Linden, NJ, and then moved to the Rockefeller University in New York [9]. This instrument was periodically modified and used until 1989.

New information on ion/molecule reactions was obtained with each increase in source pressure of a factor of ≈10. At low pressures, ≈0.002–0.020 Torr, one could see products of fast bimolecular ion/molecule reactions, but no significant loss of reactant ions. Because the average number of collisions between the ions and the molecules was very small, any reaction that was observed necessarily occurred with high efficiency and had no activation energy [1–3]. These experiments led to the major commandment of ion/molecule chemistry: thy reactions shall not be endothermic.

In the next sets of experiments at pressures up to ≈0.20 Torr, one could observe the disappearance of reactant ions as well as the formation of their product ions and species balance helped to determine the reactant/product sequences. In addition, one could observe the formation of ions produced by consecutive bimolecular reactions (kinetically, third order). Generally, though, there were no decreases in the relative abundances of the second order product ions [10,11]. However, at even higher pressures of 1–2 Torr, consecutive reactions, with low levels of impurities as well as with sample molecules, became the dominant processes. Reactions of second order product ions and products of higher kinetic order ion/molecule reactions were easily observed [12–14]. An ion whose concentration increased and then decreased with increasing pressure was created and removed by ion/molecule reactions.

The initial CIMS experiments took advantage of the relatively simple distribution of product ions at high pressures of methane and the enhanced sensitivity toward impurities because of the large number of collisions between ions and molecules [15]. The sensitivity of ionic distributions in gases to trace levels of impurities was shown many years ago in drift velocity experiments [16].

The dominant ion/molecule reactions in methane were established in the 1950s. [4–6]

$$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3 \tag{1}$$

$$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2 \tag{2}$$

The nonreactivity of both CH_5^+ and $C_2H_5^+$ with methane was established by experiments at pressures as high as 2 Torr in which the relative abundances of CH_5^+ and $C_2H_5^+$ increased to constant values [12]. The experimental results for the distribution of ions in high pressures of CH_4 were dishearteningly irreproducible for a few months, particularly the relative abundance of unexpected (and undesired) ions at *m/z* 19. Extensive purification of the methane and of the inlet system was needed to establish the lack of reactivity of CH_5^+ and $C_2H_5^+$ with methane. The ions at *m/z* 19 resulted from fast ion/molecule reactions with highly variable, but very low, levels of water desorbed from the inlet system. This lack of reaction of CH_5^+ and $C_2H_5^+$ was unequivocally established later by more traditional kinetic studies: time dependent experiments by using Fourier transform ion cyclotron resonance mass spectrometry (FTICR MS) at very low pressures and long times [17]

$$CH_5^+ + CH_4 \rightarrow \text{no products} \tag{3}$$

$$C_2H_5^+ + CH_4 \rightarrow \text{no products} \tag{4}$$

After it was shown that the two major product ions of ion/molecule reactions with methane did not react with methane, experiments were tried on mixtures of methane with small concentrations of other compounds to study the ion chemistry of CH_5^+ and $C_2H_5^+$. Studies were made on mixtures of constant composition (<1% of the additive) at increasing pressures. A maximum in the relative abundance of CH_5^+ (or $C_2H_5^+$) with increasing pressure clearly indicated the reaction of the ion with the additive. The products of ion/molecule reactions of these ions with simple molecules were obvious and became the dominant ionic species at high pressures. CH_5^+ reacted rapidly with almost every compound. Similar observations were made subsequently in FTICR MS experiments [17]. The CH_5^+ ion at *m/z* 17 in methane reacted predominantly as a strong Bronsted acid by proton transfer or dissociative proton transfer and the $C_2H_5^+$ ion at *m/z* 29 reacted as a weaker Bronsted acid by proton transfer and as a Lewis acid by hydride transfer [14,17–19].

Experiments were done with mixtures of methane containing small amounts of isomeric hexanes. (The isomers were readily available in high purity and the research was being done in the laboratories of an oil company.) A comparison of the product ion distribution of a mixture of methane with a small amount of *n*-hexane and of a similar mixture of methane with 2,2-dimethylbutane showed abundant $(M - H)^+$ ions for each compound and relatively simple but different distributions of lower molecular weight alkyl ions. From the $(M - H)^+$ ions of the two hexanes, one could determine the molecular weights of the compounds and from the differences in relative abundances of fragment ions, one could differentiate between the two isomers.

Chemical ionization mass spectrometry, the production of ions characteristic of a sample by ion/molecule reactions began with these experiments [20,15]. One set of early experiments (never published) involved the use of $i\text{-}C_4H_{10}$ for the analysis of mixtures of alkylcycloparaffins. We expected that the *t*-butyl ion from *i*-butane would give $[M - H]^+$ ions by hydride abstraction of the tertiary hydrogens in these compounds. Consequently, we expected to (and did) see $(M - H)^+$ ions to estimate the carbon number distribution of compounds in the mixture. These analyses involved the use of an unproven technique for the analysis of a complex mixture of generally unknown compounds, but the unproven technique of CIMS worked to provide more information about the molecular weight distributions in these mixtures than was available by any other means at the time.

The general mechanism of CH_4 CIMS was quickly established: predominantly proton transfer from CH_5^+ to specific sites in the molecules followed by rapid decompositions (both cleavages and rearrangements) with the loss of simple stable molecules. The initial hope (just a hope, not a reasoned expectation) that the only reactions would be cleavage reactions at the site of protonation vanished with the prominent rearrangement decompositions of the MH^+ ions of esters. The $C_2H_5^+$ ions reacted by both proton and hydride transfer to give MH^+ and $(M - H)^+$ ions for molecular weight determination. In addition, adduct formation to give small amounts of $[M + C_2H_5]^+$ and $[M + C_3H_5]^+$ ions was also observed with unsaturated compounds. These adduct ions provide additional confirmation of the molecular weight of the compound and an indication of unsaturation somewhere in the molecule [15,21–24]. Adduct formation by ethyl, *t*-butyl, ammonium, and other ions is strongly dependent on the temperature and pressure of the reagent gas, as well as molecular structure. Consequently, the use of adduct ions has not been extensively used as a tool for structural characterization.

A major impetus to the use of CIMS as an analytical technique was given by a series of papers by Fales and co-workers on the CI mass spectra of complex molecules [25–28]. These articles showed CH_4 CI mass spectra that contained more abundant high mass ions than EI spectra of the same compounds and generally fewer fragment ions. The authors gave examples of CH_4 CI mass spectra that provided easier identification of functional groups in multifunctional compounds than the corresponding EI mass spectra. A phrase such as “The CI mass spectrum of XVI (ephedrine) could stand alone as a complete structure proof.” might have convinced others to try the technique [26]. The development of a commercially available source, as a modification to existing instruments, that could provide both EI and CI mass spectra greatly helped the spread of CIMS [29]. In the late 1970s and early 1980s commercial mass spectrometers with both EI and CI capabilities became readily available and many research groups began to use CIMS in mass spectrometric analyses.

It was recognized very early in the development of CIMS that using a weaker acid than CH_5^+ or $C_2H_5^+$

would give simpler CI mass spectra than those obtained with CH_4 as the reagent gas, and generally much simpler than the standard EI mass spectra. Obtaining simplified spectra for quantification or confirmation of the identity of a compound known (or expected) to be in complex mixtures is perhaps the most common use of CIMS. The dominant reactant ion in high pressures of i-C_4H_{10} is t-$C_4H_9^+$ at *m/z* 57. This ion is a weaker Bronsted acid than CH_5^+ or $C_2H_5^+$ and also a weaker Lewis acid than $C_2H_5^+$; consequently i-C_4H_{10} CI mass spectra contain fewer fragment ions than CH_4 CI spectra. The i-C_4H_{10} CI mass spectra of 41 common drugs of abuse contain MH^+ ions at different masses as the base peaks. Consequently, the drugs could be tentatively identified from a probe sample of a gastric extract [28]. Similarly, the rearrangement decomposition ions in the i-C_4H_{10} CI mass spectra of esters,

$$R_1COOR_2 + t\text{-}C_4H_9^+ \rightarrow R_1COOH_2^+ + (R_2\text{–}H),$$

allowed easy identification of the acids of sterol esters from probe samples of complex mixtures; whereas the EI mass spectrum of a single compound could easily hide many impurities [30].

If the i-C_4H_{10} CI mass spectra of the compounds contained no fragment ions and there was no other information about the class of compound involved, identification of the compounds could be achieved by comparisons of collisionally induced decomposition (CID) spectra of the MH^+ ions with reference spectra. Consequently, the combination of selective CIMS to give MH^+ ions and the molecular weight of each compound and CID for fragmentation has been used for identification of compounds in complex mixtures without separation or pretreatment [31].

The simplified spectra obtained from i-C_4H_{10} chemical ionization were used early in the development of CIMS for quantitative analyses of complex mixtures. If the CI spectra of the compounds, frequently i-C_4H_{10} CI spectra, contain no fragment ions, the likelihood of interferences is greatly reduced, and the need of extensive pretreatment or chromatographic separation is eliminated or greatly reduced. Early examples used stable isotopes as internal standards for drugs and their metabolites and reported good precision and accuracy for samples analyzed from standard probe introduction [32]. Other experiments were done utilizing the selective ionization of CIMS (again, i-C_4H_{10} CI) for quantification of complex mixtures by recording the ion currents for each compound as the entire sample was evaporated from a probe [33]. Internal standards and careful control of the experimental conditions are necessary for reliable analyses.

Other CI reagent gases have been used for selective detection and quantification of compounds in complex matrices. Methane/ammonia mixtures give NH_4^+ as the dominant reagent ion that will react only with basic or polar materials to give MH^+ or MNH_4^+ ions and virtually no fragmentation. CIMS, itself, resulted from observations of the effects of impurities on the ionic distribution in methane: useful results from incidental observations. The use of methane/ammonia mixtures came from similar observations. Changing from one CI reagent gas to another is often not complete in short times because of retention of some of the first reagent gas in the inlet lines of the introduction system. (The current inlet systems are much more efficient about this change than the early, often homemade, inlet systems but are not perfect.) Consequently, when one changes reagent gases, one should start with the highest energy reagent gas system and work to lowest energy reagent to avoid contamination of the reagent ion spectra.

It was noted that methane CI spectra obtained shortly after ammonia CI spectra often contained $[M + 18]^+$ ions [34]. These $[M + NH_4]^+$ions came from the relatively abundant $NH_4{}^+$ ions in the reagent gas spectrum produced from reactions with trace amounts of NH_3 in the introduction system. The $[M + NH_4]^+$ions were helpful in identifying the molecular weights of polar, but slightly basic, compounds. These observations serve to remind that one should always check the CI reagent ions during experiments: they are not always what they should be.

Methane/ammonia mixtures are particularly useful for the analysis of complex mixtures of polar compounds. Many of the common organic polymer additives are high molecular weight and polar, with very simple CH_4/NH_3 spectra: MH^+ and/or MNH_4^+. The CH_4/NH_3 reagent gas system does not detect hydrocarbons. Consequently, one can evaporate and detect additives from polymer samples at high temperatures without interference from hydrocarbons. The organic polymer additives were quantified by heating small amounts of polymer from a probe into the mass spectrometer without an extraction or separation step. Calibration curves for each compound were required [35]. A complex mixture of ethoxylated alcohols, $C_nH_{2n+1}(OCH_2CH_2)_xOH$, was analyzed by evaporation of the sample from a probe. The CH_4/NH_3 spectra of these compounds contained only MNH_4^+ ions that did not interfere with each other for different values of n or x and semiquantitative results could be obtained from the integrated areas for each oligomer [36]. A major problem with the quantitative analyses of all complex mixtures is the necessity of having calibration factors for every compound.

Early experiments with NH_3 and ND_3 developed another area of major importance in CIMS: the determination of exchangeable hydrogens in compounds [37]. The ability to count exchangeable hydrogens also allows the identification of some isomers. Primary, secondary, and tertiary amines were differentiated by a comparison of their NH_3 and ND_3 CI mass spectra. As an example, the NH_3 CI spectrum of 2,6-dimethylaniline contains $C_8H_9NH_3^+$ and $C_8H_9NH_2 \cdot NH_4^+$ ions at *m/z* 122 and 139 and the NH_3 CI spectrum of the isomeric *N*-ethylaniline contains $C_6H_5NH_2C_2H_5^+$ and $C_6H_5NHC_2H_5 \cdot NH_4^+$ ions at the same masses. The relative abundances of MH^+ and MNH_4^+ ions were too sensitive to experimental conditions to be reliable measures for isomer differentiation. The ND_3 CI spectra of these isomers, however, are different because the labile hydrogens on the N atoms are exchanged. Consequently, the ND_3 CI spectrum of 2,6-dimethylaniline contains $C_8H_9ND_3^+$ and $C_8H_9ND_2.ND_4^+$ ions at *m/z* 125 and 145 and the ND_3 CI spectrum of *N*-ethylaniline contains $C_6H_5ND_2C_2H_5^+$ and $C_6H_5NDC_2H_5 \cdot ND_4^+$ ions at *m/z* 124 and 144 [37]. Other exchange reactions (using D_2O or CH_3OD) have been used for the identification of isomers in complex mixtures of oxygenated compounds by gas chromatography/chemical ionization mass spectrometry (GC/CIMS) [38].

There has always been a significant interplay between applications and fundamentals in CIMS. Exchange reactions (or the lack thereof) have been used to deduce the sites of protonation of gas phase species. The ND_3 CI spectra of *o*- and *p*-phenylenediamine show exchange of the four amine hydrogens, and, consequently, the MH^+ ions are N protonated. The ND_3 CI spectrum of the *m*-isomer shows exchange of some of the ring hydrogens as well, and the MH^+ ions must be at least partially ring protonated [39]. Gas phase H/D exchange reactions with complex molecules continue to be important tools in structure elucidation or confirmation as indicated by work with ND_3 exchange of ions produced by electrospray ionization in the nebulizer or curtain region in an atmospheric pressure ionization (API) mass spectrometer [40].

In the original work on CIMS (and in the patent), the analytical reactions involved proton transfer, hydride transfer, or adduct formation. Subsequently, the use of any ion/molecule reaction for analysis was considered part of CIMS. Charge exchange (or electron transfer) is now also considered as chemical ionization. The same fundamental postulate applies to charge exchange as to proton or hydride transfer. If the reaction is exothermic, it is likely to be fast; if it is endothermic, it is likely to be slow.

For charge exchange, the selectivity is based on the ionization energy of the reagent gas and of the sample. If the IE of the reagent gas is greater than the ionization energy of the sample, then the charge transfer reaction should occur,

$$R^{+\cdot} + S \rightarrow S^{+\cdot} + R$$

One obvious difference in ionization energies that can be estimated is the difference between saturated and unsaturated compounds. The ionization energies of unsaturated compounds are consistently lower than the ionization energies of analogous saturated compounds [41]. Low energy charge exchange reagents (low ionization energy) are, then, selective reagents for unsaturated compounds.

One application of selective detection and quantification by charge exchange that can be predicted from known properties of molecules is in the analysis of aromatic and unsaturated hydrocarbons in petroleum mixtures. The ionization energy of chlorobenzene (IE = 9.04 eV) is higher than the ionization energies of toluene and all higher alkylbenzenes and lower than those of the alkanes and cycloalkanes. The $C_6H_5Cl^{+\cdot}$ ion is, fortunately, the dominant ion in the low pressure EI and "high pressure" CI spectra of chlorobenzene. In addition, $C_6H_5Cl^{+\cdot}$ reacts rapidly with the alkylbenzenes and alkylnaphthalenes to give only molecular ions. Complex mixtures of fuels were analyzed for aromatic content (by carbon number, not isomers, of course) using chlorobenzene CI, without chromatographic separation [42].

Benzene (IE = 9.25 eV) has also been used as a selective charge exchange reagent for the identification and quantification of unsaturated compounds in GC/CIMS studies [43,44]. The benzene molecular ion, $C_6H_6^{+\cdot}$, is the dominant ion in the EI and high pressure CI mass spectra of benzene. The $C_6H_6^{+\cdot}$ ion reacts rapidly by charge transfer with aromatic hydrocarbons with virtually no fragmentation and gives no product ions from reactions with alkanes. One can also differentiate between methyl esters of saturated and unsaturated fatty acids with GC/CIMS using benzene charge exchange [43].

For these and other quantitative analyses, one needs sensitivity factors for the compounds being analyzed. The molar sensitivities in CIMS should be closely related to, if not proportional to, the rate constants for the ion/molecule reactions. The relative molar sensitivities for benzene charge exchange with alkylbenzenes (C_8–C_{12}) were essentially independent of structure and molecular weight [44]. The simple Langevin model predicts only a very small increase in rate constant for charge exchange between $C_6H_6^{+\cdot}$ and alkylbenzenes with increasing molecular weight of the alkylbenzenes for this range of compounds and no variation for the different isomers.

Aromatic hydrocarbons have been analyzed in petroleum mixtures for many years, using low energy electron ionization. However, the relative molar sensitivity (RMS) for an alkylbenzene obtained with low energy electrons is sensitive to the exact electron energy used in the experiments and very sensitive to the structure of the isomer: RMS(tetramethylbenzene)/RMS(*n*-butylbenzene) ≈ 4 [45]. The lack of variation in sensitivity with substitution pattern is potentially a major advantage for charge exchange CI compared with low electron energy ionization.

Several different CI reagent gases have been tried in positive ion CIMS, at least for a few examples [46]. However, the use of selective reagents in CIMS for functional group analysis, for identification of different classes of compounds, or for isomer differentiation has not been widely used. One difficulty in working with "unusual" CI reagents is that the spectrum of the reagent gas is generally not a simple one species spectrum. The major reagent ion in the spectrum of benzene at high pressures is $C_6H_6^{+\cdot}$, but there is a significant abundance of $C_6H_7^+$ ions [44]. Consequently, both charge exchange and proton transfer reactions can occur and sample ions, as MH^+ but not $M^{+\cdot}$ ions, are observed in the benzene charge exchange spectra of methyl esters of saturated fatty acids. Therefore, a benzene GC/CIMS trace, as total sample ionization versus time, for a mixture of methyl esters of saturated and unsaturated fatty acids does not show the desired clean distinction of sample ions with the unsaturated esters and no sample ions with the saturated esters.

In addition, it has been our experience that the heavier reagent gases, (even benzene or tetramethylsilane) cause a decrease in ion intensity over time, make extended use somewhat problematical, and require more frequent cleaning of the source assembly. These problems are likely the results of deposits of decomposition products on the insulators and/or plates in the ion source assembly. Using mixtures with He rather than the pure reagent gas increases the sensitivity of the analysis and reduces the contamination problems and frequency of cleaning of the source assembly.

The recent accessibility of ion traps has the potential for greatly increasing the use of selective detection in CIMS because one can separate and use a single reactant ion to achieve the desired selectivity and contamination by the reagent gas should be less [47]. The analytical use of ion/molecule reactions as an extension of chemical ionization has developed as the instrumentation developed and includes reactions of ions produced by many methods in ion traps and ion cyclotron resonance instruments [48,49].

Another area that has not developed extensively is the use of chiral CI reagents since the first reports of differences in abundances of protonated dimers of *d*- and *l*-tartrates [50]. There have been occasional efforts in this area over the years, but with little obvious success or general applicability [46]. There have been occasional experiments in this area in recent years [51].

Since the spectra in CIMS are produced by fast ion/molecule reactions with the samples, it is always possible that sample ion/sample molecule reactions can occur in the source as well as reactions of reagent ions with sample molecules. As long as the extent of conversion of sample ions to product ions is small, sample ion/sample molecule reactions will be small compared with direct reactant ion/sample molecule reactions. However, in most experiments there is neither determination of the extent of conversion of reactant ions to product ions nor any real measurement of reagent gas or sample pressure. Many of the current data systems report average spectra from GC/CIMS experiments, usually taken at the tops of chromatographic peaks; consequently, no variation in spectra with sample size would be noted. For the usual purpose of identifying the compounds, however, the mechanism of formation of the sample ions is not essential: MH^+ ions formed by any means give the same molecular weights of the compounds.

There have been a few cases in which large differences in CI mass spectra were noted across chromatographic peaks in GC/CIMS experiments. These observations are clear indications of sample ion/sample molecule reactions and have been verified by ICR experiments. Tetramethylsilane CI spectra of alcohols and ethers are particularly sensitive to sample size because the trimethylsilyl adduct ions, $(M + 73)^+$, that identify the molecular weights of the compounds are formed by a two-step process [52,53]

$$(CH_3)_3Si^+ + C_nH_{2n+1}OH \rightarrow (CH_3)_3SiOH_2^+ + C_nH_{2n}$$

$$(CH_3)_3SiOH_2^+ + C_nH_{2n+1}OH \rightarrow (CH_3)_3SiOH^+C_nH_{2n+1} + H_2O$$

The $(M + 73)^+$ ions are much more abundant at the top of a chromatographic peak than on the sides. There are significant differences in rate constants for the reaction of $(CH_3)_3SiOH_2{}^+$ with some isomeric alcohols; and primary, secondary, and tertiary alcohols could be distinguished from variations in their spectra across chromatographic peaks at relatively small extents of conversion, up to ≈15%, that is, with analytical size samples. Experiments with C_6D_6 as the CI reagent showed variable abundances of $M^{+\cdot}$, MH^+, and MD^+ ions across the chromatographic peaks for some very basic compounds, like substituted pyridines [54]. The MH^+ ions resulted from the two-step sequence involving sample ion/sample molecule reactions.

$$C_6D_6^{+\cdot} + M \rightarrow M^{+\cdot} + C_6D_6$$

$$M^{+\cdot} + M \rightarrow MH^+$$

Recent (unpublished) experiments in our laboratory with polyethylene glycols and their mono- and dimethyl ethers show extensive sample ion/sample molecule reactions in the CH_4 CI mass spectra. Sample ion/sample molecule reactions may be relatively common in routine CI mass spectra.

API or atmospheric pressure chemical ionization (APCI) was developed in the 1970s as an outgrowth of experiments in plasma chromatography and has become a routinely used technique in analytical mass spectrometry [55,56]. In the original experiments, ionization was done with a ^{63}Ni radiation source at atmospheric pressure and the ions were sampled through a pinhole (≈25 μm) into the mass analyzer. High purity N_2 was the carrier gas, but traces of water in the inlet system led to $H_3O^+(H_2O)_n$ ions as the reagent ions. Consequently, MH^+ ions were generally observed for the samples.

By using ultrahigh purity N_2 and extensive bakeout of the entire system, one can observe $N_4^{+\cdot}$ ions as the dominant reactant ions in the reagent gas, but these are not practical operating conditions. Traces of solvents used for injection of samples into the gas chromatograph often persist for some time after injection and produce other reactant ions that then react with the samples. One can study the change in abundance of reactant ions with time or concentration of added reagent.

The early experiments showed that APCI is extremely sensitive for the detection of basic compounds (or compounds with low ionization energies). Sample ions in API (or APCI) are formed from weakly acidic ions (solvated protons) and collisional stabilization occurs for any excited $MH^{+}*$ ions at the high pressures. Consequently, the spectra generally contain only MH^{+} ions (and occasionally solvated ions). Because the reaction times are longer, there is a greater conversion of sample molecules to sample ions than under lower pressure CI conditions; hence, there is a very high sensitivity for API for very basic compounds. The technique, however, is not sensitive to (or will not detect) many nonbasic compounds. Most of the applications of APCI in GC/MS studies, consequently, involve higher molecular weight, polar, and basic samples [57]. The sensitivity for different compounds in APCI increases with increasing gas phase basicity of the compound to an essentially constant value for very basic N-containing compounds [58]. This variation is consistent with the idea that exothermic proton transfer reactions are rapid, with similar rate constants, and endothermic reactions are slow. Because there are several reactant ions (with different acid strengths), there is a relatively continuous variation in sensitivity of the samples with their basicities.

The first use of API (APCI) was with GC/MS systems, but the application to liquid chromatography/mass spectrometry (LC/MS) systems was obvious and rapidly developed [59,60]. Liquid chromatography with an APCI source is now a routine technique in the pharmaceutical industry, particularly for quantitation. LC/MS/MS is often used to increase the sensitivity and specificity of the procedures [61].

There is the entire area of negative ion chemical ionization mass spectrometry that is worthy of a separate discussion, but that discussion will be left to others who were involved in its development.

CIMS is now routinely used in analytical mass spectrometry in many industries. It is no longer an academic curiosity or a technique known only to specialists. The technique is sufficiently well known that it is often not specified in the abstracts of papers when it is used for identification or quantification. Unfortunately, this familiarity sometimes leads to the omission of important details about instrumental parameters, sometimes even the reagent. Many commercial instruments have CI, as well as EI, capabilities. CIMS has begun to make its way into the undergraduate curriculum, at least as far as textbooks are concerned as an accepted technique, along with EIMS [62,63]. For a thorough review of fundamentals and applications of CIMS, the classic (and essentially only) reference is Harrison’s monograph [64].

CIMS represents the development of a useful analytical technique from observations of the effects of unwanted (and initially unsuspected) impurities on ion/molecule reactions of unusual ions. Although CIMS was not an accidental discovery, it was certainly a serendipitous one. Its growth over the years has been the result of continual interplay between applications toward specific problems and fundamental studies of ion/molecule reactions. Like Frank Field, with whom I had the pleasure of working as a collaborator for a few years and as a professional colleague for many years, I take pleasure in beginning and helping develop such a useful technique [20].

References

[1] Sir J.J. Thomson, Rays of Positive Electricity and Their Applications to Chemical Analysis, Longmans, London, 1913.

[2] T.R. Hogness, E.G. Lunn, Phys. Rev. 26 (1925) 44.

[3] F.W. Aston, Mass Spectra and Isotopes, Longmans, London, 1933.

[4] V.L. Tal’roze, A.K. Ljubimova, J. Mass Spectrom. 33 (1998) 502 (translated from Doklady Akad. Nauk. S. S. S. R. 86 (1952) 909).

[5] D.P. Stevenson, D.O. Schissler, J. Chem. Phys. 23 (1955) 1353.

[6] F.H. Field, J.L. Franklin, F.W. Lampe, J. Am. Chem. Soc. 79 (1957) 2419.
[7] F.W. McLafferty, Anal. Chem. 29 (1957) 1782.
[8] J.H. Beynon, Mass Spectrometry and its Applications to Organic Chemistry, Elsevier, London, 1960, p. 275.
[9] F.H. Field, J. Am. Chem. Soc. 83 (1961) 1523.
[10] S. Wexler, N. Jesse, J. Am. Chem. Soc. 84 (1962) 3425.
[11] F.H. Field, J.L. Franklin, M.S.B. Munson, J. Am. Chem. Soc. 85 (1963) 3575.
[12] F.H. Field, M.S.B. Munson, J. Am. Chem. Soc. 87 (1965) 3289.
[13] T.W. Martin, R.E. Rummel, C.E. Melton, Science 138 (1962) 77.
[14] M.S.B. Munson, J. Am. Chem. Soc. 87 (1965) 4242.
[15] M.S.B. Munson, F.H. Field, J. Am. Chem. Soc. 88 (1966) 2621.
[16] L.B. Loeb, Fundamental Processes of Electrical Discharges in Gases, Wiley, New York, 1939, Chap. 2.
[17] S. Ghaderi, P.S. Kulkarni, E.B. Ledford Jr., C.L. Wilkins, M.L. Gross, Anal.Chem. 53 (1981) 428.
[18] M.S.B. Munson, F.H. Field, J. Am. Chem. Soc. 87 (1965) 3294.
[19] R.P. Clow, J.H. Futrell, J. Am. Chem. Soc. 94 (1972) 3748.
[20] F.H. Field, J. Am. Soc. Mass. Spectrom. 1 (1990) 270.
[21] M.S.B. Munson, F.H. Field, J. Am. Chem. Soc. 88 (1966) 4337.
[22] F.H. Field, M.S.B. Munson, D.A. Becker, Adv. Chem. Ser., Am. Chem. Soc. 58 (1966) 167.
[23] M.S.B. Munson, F.H. Field, J. Am. Chem. Soc. 89 (1967) 1047.
[24] F.H. Field, M.S.B. Munson, J. Am. Chem. Soc. 89 (1967) 4272.
[25] H.M. Fales, G.W.A. Milne, M.L. Vestal, J. Am. Chem. Soc. 91 (1969) 3862.
[26] H.M. Fales, H.A. Lloyd, G.W.A. Milne, J. Am. Chem. Soc. 92 (1970) 1590.
[27] H.M. Fales, G.W.A. Milne, T. Axenrod, Anal. Chem. 42 (1970) 1432.
[28] G.W.A. Milne, H.M. Fales, T. Axenrod, Anal. Chem. 43 (1971) 1815.
[29] D. Beggs, M.L. Vestal, H.M. Fales, G.W.A. Milne, Rev. Sci. Instrum. 42 (1971) 1578.
[30] T. Murata, S. Takahashi, T. Takeda, Anal. Chem. 47 (1975) 577.
[31] D.V. Davis, R.G. Cooks, J. Agric. Food Chem. 30 (1982) 495.
[32] W.A. Garland, W.F. Trager, S.D. Nelson, Biomed. Mass Spectrom. 1 (1979) 124.
[33] R.J. Weinkam, H. Lin, Anal. Chem. 51 (1979) 972.
[34] D.E. Smith, J.S. Smith, D. Jerolamon, A.F. Weston, D. Richton, E.J. Brozowski, Proceedings of the 26th ASMS Conference on Mass Spectrometry, St Louis, MO, 1978.
[35] P. Rudewicz, B. Munson, Anal. Chem. 58 (1986) 358.
[36] P. Rudewicz, B. Munson, Anal. Chem. 54 (1986) 674.
[37] D.F. Hunt, C.N. McEwen, R.A. Upham, Tetrahedron Lett. 47 (1971) 4539.
[38] M.V. Buchanan, Anal. Chem. 56 (1984) 546.
[39] D.F. Hunt, S.K. Sethi, J. Am. Chem. Soc. 102 (1980) 6953.
[40] M.M. Hemling, J.J. Conboy, M.F. Bean, M. Mentzner, S.A. Carr, J. Am. Soc. Mass Spectrom. 5 (1994) 434.
[41] S.G. Lias, in NIST Chemistry WebBook, NIST Standard Reference Database No. 69, W.G. Mallard, P.J. Linstrom (Eds.), NIST Gaithersburg, MD, 1999 (http:webbook.nist.gov).
[42] L.W. Sieck, Anal. Chem. 55 (1983) 38.
[43] S.C. Subba Rao, C. Fenselau, Anal. Chem. 50 (1978) 511.
[44] C. Allgood, Y.C. Ma, B. Munson, Anal. Chem. 63 (1991) 721.
[45] G.F. Crable, G.L. Kearns, M.S. Norris, Anal. Chem. 32 (1960) 13.
[46] M. Vairamani, U.A. Mizra, R. Srinivas, Mass Spectrom. Rev. 9 (1990) 235.
[47] E.S. Eichmann, J.S. Brodbelt, J. Am. Soc. Mass Spectrom. 4 (1993) 97.
[48] J.S. Brodbelt, Mass. Spectrom. Rev. 16 (1997) 91.
[49] M.K. Green, C.B. Lebrilla, Mass Spectrom. Rev. 16 (1997) 53.
[50] H.M. Fales, G.J. Wright, J. Am. Chem. Soc. 99 (1977) 2339.
[51] E.N. Nicolaev, D.V. Denisov, M.I. Nicolaeva, V.S. Rakov, J.H. Futrell, Proceedings of the 46th ASMS Conference, May, 1998, p. 446.
[52] R. Orlando, F. Strobel, D.P. Ridge, B. Munson, Org. Mass Spectrom. 22 (1987) 597.
[53] R. Orlando, D.P. Ridge, B. Munson, Org. Mass Spectrom. 23 (1988) 527.
[54] C. Allgod, Y. Lin, Y.C. Ma, B. Munson, Org. Mass Spectrom. 25 (1990) 497.
[55] E.C. Horning, M.G. Horning, D.I. Carroll, I. Dzidic, R.N. Stillwell, Anal. Chem. 45 (1973) 936.
[56] D.I. Carroll, I. Dzidic, E.C. Horning, R.N. Stillwell, Appl. Spectrosc. Rev. 17 (1981) 337.
[57] R.K. Mitchum, W.A. Korfmacher, Anal. Chem. 55 (1983) 1485A.
[58] J. Sunner, G. Nicol, P. Kebarle, Anal. Chem. 60 (1986) 1300.
[59] A.P. Bruins, Trends Anal. Chem. 13 (1994) 37.
[60] A.P. Bruins, Trends Anal. Chem. 13 (1994) 81.
[61] J.D. Gilbert, T.V. Olah, D.A. McLoughlin, in Biochemical and Biotechnological Applications of Electrospray Ionization Mass Spectrometry, A.P. Snyder (Ed.), American Chemical Society., Washington, DC, 1995, Chap. 17.
[62] J.B. Lambert, H.F. Shurvell, D. Lightner, R.G. Cooks, Introduction to Organic Spectroscopy, Macmillan, New York, 1987.
[63] D. A. Skoog, J.J. Leary, Principles of Instrumental Analysis, 4th ed., Saunders, New York, 1992.
[64] A.G. Harrison, Chemical Ionization Mass Spectrometry, 2nd ed., CRC Press, Boca Raton, FL, 1992.