1
State of the Art in the LC/MS

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1.1
Introduction

The dramatically increased demands on the qualitative and quantitative analysis of more complex samples are a huge challenge for modern instrumental analysis. For complex organic samples (e.g., body fluids, natural products or environmental samples), only chromatographic or electrophoretic separations followed by mass spectrometric detection meet these requirements. However, at the moment a tendency can be observed, in which a complex sample preparation and preseparation is replaced by high-resolution mass spectrometer with atmospheric pressure ion sources. However, numerous ion–molecule reactions in the ion source – especially in complex samples due to incomplete separation – are possible because the ionization in typical atmospheric pressure ion sources is nonspecific [1]. Thus, this approach often leads to ion suppression and artifact formation in the ion source, particularly in electrospray ionization (ESI) [2].

Nevertheless, sources such as ASAP (atmospheric pressure solids analysis probe), DART (direct analysis in real time), and DESI (desorption electrospray ionization) can often be successfully used. In ASAP, a hot nitrogen flow from an ESI or APCI (atmospheric pressure chemical ionization) source is used as a source of energy for evaporation and the only change to an APCI source is the installation of an insertion option to place the sample in the hot gas stream within the ion source [3]. This ion source allows a rapid analysis of volatile and semivolatile compounds and, for example, was used to analyze biological tissue [3], polymer additives [3], fungi and cells [4], and steroids, [3, 5]. ASAP has much in common with DART [6] and DESI [7]. The DART ion source produces a gas stream containing long-lived electronically excited atoms that can interact with the sample and, thus, desorption and subsequent ionization of the sample by Penning ionization [8] or proton transfer from protonated water clusters [6] is realized. The DART source is used for the direct analysis of solid and liquid samples. A great advantage of this source is the possibility to analyze compounds on surfaces such as illegal substances on dollar bills or fungicides on wheat [9]. Unlike ASAP and DART, the great advantage of DESI is that the volatility of the analyte is not a

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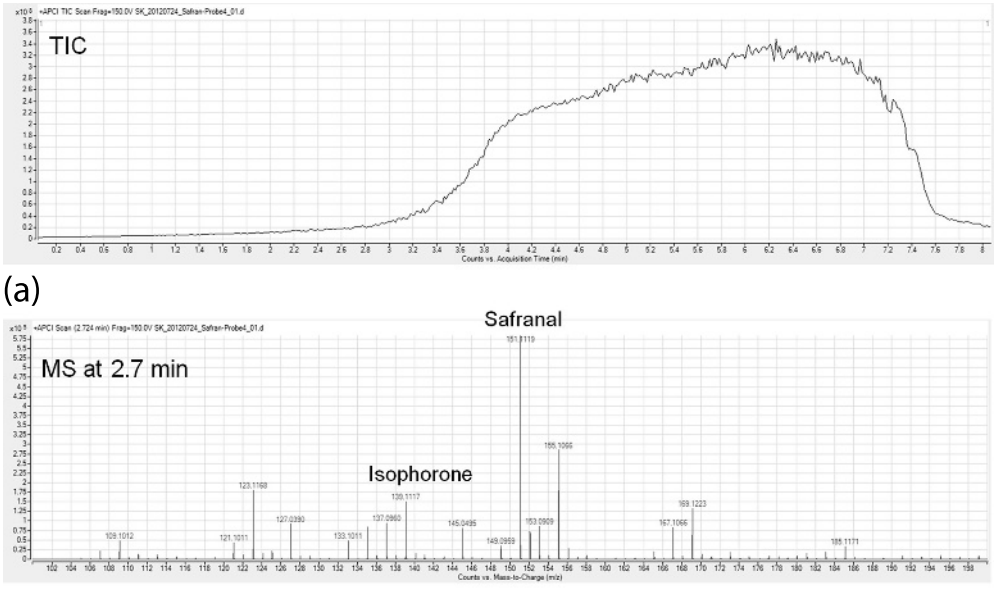

Figure 1.1 Analysis of saffron using direct-inlet probe-APCI with high-resolution QTOF-MS. (a) TIC of the toal analysis. (b) mass spectrum at the time of 2.7 min.

prerequisite for a successful analysis (same as in the classic ESI). DESI is most sensitive for polar and basic compounds and less sensitive for analytes with a low polarity [10]. These useful ion sources have a common drawback. All or almost all substances in the sample are present at the same time in the gas phase during the ionization in the ion source. The analysis of complex samples can therefore lead to ion suppression and artifact formation in the atmospheric pressure ion source due to ion–molecule reactions on the way to the MS inlet. For this reason, some ASAP applications are described in the literature with increasing temperature of the nitrogen gas [5, 11, 12]. DART analyzes with different helium temperatures [13] or with a helium temperature gradient [14] have been described in order to achieve a partial separation of the sample due to the different vapor pressures of the analyte. Related with DART and ASAP, the direct inlet sample APCI (DIP-APCI) from Scientific Instruments Manufacturer GmbH (SIM) was described 2012, which uses a temperature-push rod for direct intake of solid and liquid samples with subsequent chemical ionization at atmospheric pressure [15]. Figure 1.1 shows a DIP-APCI analysis of a saffron sample (solid, spice) without sample preparation with the saffron-specific biomarkers isophorone and safranal. As a detector, an Agilent Technologies 6538 UHD Accurate-Mass Q-TOF was used. The total ion chromatogramm (TIC) of the total analysis and the mass spectrum at the time of 2.7 min are shown in Figure 1.1a,b, respectively. The analysis was started at 40 °C and heated the sample at 1 K/s to a final temperature of 400 °C.

These ion sources may be useful and time saving but for the quantitative and qualitative analysis of complex samples a chromatographic or electrophoretic preseparation makes sense. In addition to the reduction of matrix effects, the comparison of the retention times also allows an analysis of isomers.

1.2 Ionization Methods at Atmospheric Pressure

In the last 10 years, several new ionization methods for atmospheric pressure (AP) mass spectrometers have been developed. Some of these are only available in some working groups. Therefore, only four commercially available ion sources will be presented in detail here.

The most common atmospheric pressure ionization (API) is electrospray ionisation (ESI), followed by APCI and APPI (atmospheric pressure photoionization). A significantly lower significance shows the APLI (atmospheric pressure laser ionization). However, this ion source is well suited for the analysis of aromatic compounds and, for example, the gold standard for PAH (polyaromatic hydrocarbons) analysis. This ranking reflects more or less the chemical properties of the analytes, which are determined with API MS: Most analytes from the pharmaceutical and life sciences are polar or even ionic and, thus, are efficiently ionized by ESI (Figure 1.2). However, there is also a considerable interest in API techniques for efficient ionization of less or nonpolar compounds. For the ionization of such substances ESI is less suitable.

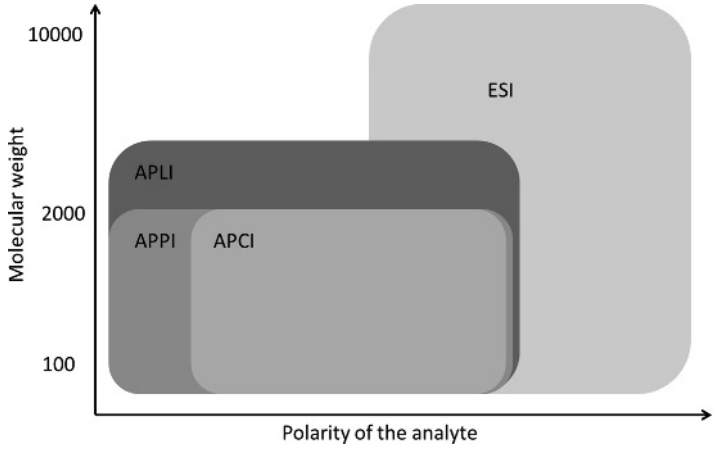

Figure 1.2 Polarity range of analytes for ionization with various atmospheric pressure ionization (API) techniques. Note: The extended mass range of APLI against APPI and APCI results from the ionization of nonpolar aromatic analytes in an electrospray Reproduced with kind permission of O. J. Schmitz, T. Benter, Advances in LC-MS Instrumentation: Atmospheric pressure laser ionization, Journal of Chomatography Libary, Vol 72 (2007), Chapter 6, Pages 89-113.

1.2.1 Overview of API Methods

Ionization methods that operate at atmospheric pressure, such as atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI), have greatly expanded the scope of mass spectrometry [17–20]. These API techniques allow an easy coupling of chromatographic separation systems, such as liquid chromatography (LC), to a mass spectrometer.

There is a fundamental difference between APCI and ESI ionization mechanism. In APCI, ionization of the analyte takes place in the gas phase after evaporation of the solvent. In ESI, the ionization takes place already in the liquid phase. In the ESI process, protonated or deprotonated molecular ions are usually formed from highly polar analytes. Fragmentation is rarely observed. However, for the ionization of less polar substances, APCI is preferably used. APCI is based on the reaction of analytes with primary ions, which are generated by corona discharge. But the ionization of nonpolar analytes is very low with both techniques.

For these classes of substances other methods have been developed, such as the coupling of ESI with an electrochemical cell [21–32], the "coordination ion-spray" [32–47] or the "dissociative electron-capture ionization" [38–42]. The atmospheric pressure photoionization (APPI) or the dopant-assisted (DA) APPI presented by Syage *et al.* [43, 44] and Robb *et al.* [45, 46], respectively, are relatively new methods for photoionization (PI) of nonpolar substances by means of vacuum ultraviolet (VUV) radiation. Both techniques are based on photoionization, which is also used in ion mobility mass spectrometry [47–50] and in the photo ionization detector (PID) [51–53].

1.2.2 ESI

In the past, one of the main problems of mass spectrometric analysis of proteins or other macromolecules was that their mass was outside the mass range of most mass spectrometers. For the analysis of larger molecules, such as proteins a hydrolysis and the analysis of the resulting peptide mixture had to be carried out. With ESI it is now possible to ionize large biomolecules without prior hydrolysis and analyze them by MS.

Based on previous works from Zeleny [54], Wilson and Taylor [55, 56], Dole *et al.* produced high molecular weight polystyrene ions in the gas phase from a benzene/acetone mixture of the polymer by electrospray [57]. This ionization method was finally established through the work of Fenn in 1984 [58], who was awarded the Nobel Prize for Chemistry in 2002.

In order to describe the whole process of ion formation in ESI, a subdivision of processes into three sections makes sense:

- Formation of charged droplets
- Reduction of the droplet
- Formation of gaseous ions.

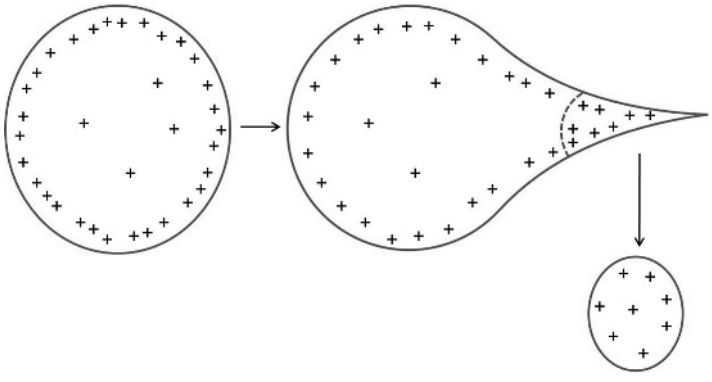

Figure 1.3 Reduction of the droplet size.

To generate positive ions a voltage of 2–3 kV between the narrow capillary tip (10^{-4} m outer diameter) and the MS input (counter electrode) is applied. In the exiting eluate from the capillary, charge separation occurs. Cations are enriched at the surface of the liquid and moved to the counter electrode. Anions migrate to the positively charged capillary, where they are discharged or oxidized. The accumulation of positive charge on the liquid surface is the cause of the formation of a liquid coned, as the cations are drawn to the negative pole, the cathode. This so-called Taylor cone resulted from the electric field and the surface tension of the solution. With certain distance from the capillary, there is a growing destabilization and a stable spray of drops with an excess of positive charges will emitted.

The size of the droplets formed is dependent on the

- Flow rate of the mobile phase and the auxiliary gas
- Surface tension
- Viscosity
- Applied voltage and
- Concentration of the electrolyte.

These drops lose solvent molecules by evaporation and at the Raleigh limit (electrostatic repulsion of the surface charges > surface tension) much smaller droplets (so-called microdroplets) are emitted (Figure 1.3). This occurs due to elastic surface vibrations of the drops which lead to formation of Taylor cone-like structures.

At the end of such protuberances small droplets are formed, which have a significantly smaller mass/charge ratio than the "mother drop". Because of the unequal decomposition the ratio of surface charge to the number of paired ions in the droplet increases dramatically per cycle of droplet formation and evaporation up to the Raleigh limit in comparison with the "mother drops". Thus, only highly charged microdroplets are responsible for the successful formation of ions.

For the ESI process, the formation of multiply charged ions for large analyte molecules is characteristic. Therefore, a series of ion signals for, for example, pep-

tides and proteins can be observed, which differ to each other by one charge (usually an addition of a proton in positive mode or subtraction of a proton in negative mode).

For the formation of the gaseous analyte two mechanisms are discussed at the moment. The charged residue mechanism (CRM) proposed by Cole [59] and Kebarle and Peschke [60] and the ion evaporation mechanism (IEM) postulated by Thomason and Iribarne [61]. In CRM, the droplets are reduced as long as only one analyte in the microdroplets is present, then one or more charges are added to the analyte. In IEM, the droplets are reduced to a so-called critical radius ($r < 10$ nm) and then charged analyte ions are emitted from these drops [62]. It is essential for the process that enough charge carriers are provided in the eluate. This can be realized by the addition of, for example, ammionium formiate to the eluent or eluate. Without this addition, ESI is also possible with an eluate of acetonitrile/water (but not with MeOH/water), but a more stable and more reproducible electrospray with a higher ion yield is only formed by adding charge carriers before or after HPLC separation.

1.2.3 APCI

This ionization method was developed by Horning in 1974 [63]. The eluate is introduced through an evaporator (400–600 °C) into the ion source. Despite the high temperature of the evaporator, a decomposition of the sample is only rarely observed because the energy is used for the evaporation of the solvent, and the sample is not normally heated above 80 to 100 °C [64]. In the exit area of the gas flow (eluate and analyte), a metal needle (corona) is mounted to which a high voltage is applied. When the solvent molecules reach the field of high voltage, a reaction plasma is formed on the principle of chemical ionization. If the energy difference between the analyte and reactant ions is large enough, the analytes are ionized, for example, by proton transfer or adduct formation in the gas phase.

For the emission of electrons in APCI a corona discharge is used instead the filament in GC/MS (CI) because of the rapid fusing of the filament at atmospheric pressure. In APCI, with nitrogen as sheath and nebulizer gas and atmospheric water vapor (is also available in 5.0 nitrogen sufficient quantity), $N_2^{+\bullet}$ and $N_4^{+\bullet}$ ions are primarily formed by electron ionization. These ions collide with the vaporized solvent molecules and form secondary reactant gas ions, such as H_3O^+ and $(H_2O)nH^+$ (Figure 1.4).

$$N_2 + e^- \rightarrow N_2^{+\cdot} + 2e^-$$
$$N_2^{+\cdot} + 2N_2 \rightarrow N_4^{+\cdot} + N_2$$
$$N_4^{+\cdot} + H_2O \rightarrow H_2O^{+\cdot} + 2N_2$$
$$H_2O^{+\cdot} + H_2O \rightarrow H_3O^+ + OH^{\cdot}$$

$$H_3O^+ + n\,H_2O \rightarrow H_3O^+ \cdot (H_2O)_n$$

Figure 1.4 Reaction mechanism in APCI.

The most common secondary cluster ion is $(H_2O)_2H^+$, together with significant amounts of $(H_2O)_3H^+$ and H_3O^+. These charged water clusters collide with the analyte molecules, resulting in the formation of analyte ions:

$$H_3O + M \rightarrow [M + H]^+ + H_2O \tag{1.1}$$

The high collision frequency results in a high ionization efficiency of the analytes and adduct ions with little fragmentation. In the negative mode, the electrons that are emitted during the corona discharge form together with large amounts of N_2 and the presence of water molecules OH^- ions. Due to the fact that the gas phase acidity of H_2O is very low, OH^- ions in the gas phase form by proton transfer reaction with the analyte H_2O and $[MH]^-$ (M = analyte) [64]. The problem with APCI is the simultaneous formation of different adduct ions. Depending on eluent composition and matrix components, it is possible that Na^+ and NH_4^+ adducts are formed in addition to protonated analyte molecules, making the data evaluation more difficult.

1.2.4 APPI

APPI is suitable for the ionization of nonpolar analytes, in which the photoionization of molecule M leads to the formation of a radical cation $M^{\bullet+}$. If the ionization potentials (IPs) of all other matrix elements are greater than the photon energy, then the ionization process is specific for the analyte. However, in the APPI different processes can very strongly influence the detection of $M^{\bullet+}$:

1. In the presence of solvent molecules and/or other existing components in large excess, ion–molecule reactions can proceed.
2. VUV photons are efficiently absorbed from the gas phase matrix.

Thus, for example, in the presence of acetonitrile (a commoonly used mobile phase in HPLC) mainly $[M + H^+]$ is formed even though the IP of acetonitrile is more than 2.2 eV higher as the photon energy [65]. In general, in the case of polar compounds, which are dissolved in CH_3CN/H_2O, the formation of $[M + H]^+$ is usually observed, while nonpolar compounds such as naphthalene, usually form $M^{\bullet+}$ [66]. A detailed mechanism for the formation of $[M + H]^+$ was proposed by Klee *et al.* [67]. In APPI, the ion yield is reduced due to the limited VUV photon flux, and the interactions with solvent molecules. Therefore, the dopant-assisted atmospheric pressure photo ionization (DA-APPI) was introduced as a new ionization method from Bruins *et al.* [66].

The total number of ions which are formed by the VUV radiation is significantly increased by the addition of a directly ionizing component (dopant). If the dopant is selected such that the resulting dopant ions have a relatively high recombination energy or low proton affinity, then the dopant ion can ionize the analytes by charge exchange or proton transfer. In addition to acetone and toluene, anisole was also found to be a very effective dopant in APPI [68]. By adding a dopant the sensitivity can be increased, but the possible adduct formations often lead

to significantly more complicated APPI mass spectra [45, 66, 68]. Recent studies suggest that the direct proton transfer from the initially formed dopant ions plays only a very minor role, and the ionization process is dominated by a very complex, thermodynamically controlled cluster chemistry.

1.2.5 APLI

Atmospheric pressure laser ionization (APLI) was developed in 2005 [69]. It is a soft ionization method with easy-to-interpret spectra for nonpolar aromatic substances and only minor tendency for fragmentation of the analytes. APLI is based on the resonance-enhanced multiphoton ionization (REMPI), however, at atmospheric pressure.

The REMPI method allows the sensitive and selective ionization of numerous compounds. Here, for example, the following approach is used:

$$M + mhv \rightarrow M^* \tag{1.2}$$

$$M^* + nhv \rightarrow M^{\bullet +} + e^- \tag{1.3}$$

Reactions (1.1) and (1.2) represent a classical $(m + n)$ resonance-enhanced multiphoton ionization (REMPI) process, which $n = m = 1$ is often very beneficial used for the ionization of polyaromatic hydrocarbons (PAH). Because the absorption bands of PAHs are relatively broad at room temperature and PAHs have high molecular absorption coefficient in the near ultraviolet and a relatively long lifetime of the S1 and S2 states, a fixed frequency laser, for example the 248 nm line of a KrF excimer laser, can be used. Under these conditions, an almost selective ionization of aromatic hydrocarbons can be achieved.

A great advantage of APLI in comparison to APPI is that neither oxygen nor nitrogen and the solvents typically used in the HPLC (for example, water, methanol, acetonitrile) have appreciable absorption cross sections in the used wavelength range. An attenuation of the photon density within the ion source, that is, a significant coupling of electronic energy into the matrix, as observed in the APPI, does not take place in APLI. The APLI is very sensitive in the determination of PAHs and, therefore, represents a valuable alternative to APCI and APPI, but APLI is not only restricted to the analysis of such simple aromatic compounds. More complex oligomeric or polymeric structures, and organometallic compounds can also be analyzed [70]. It is also possible to analyze nonaromatic compounds after derivatization of their functional group with so-called ionization markers, in analogy to fluorescence derivatization [71]. With this technique you can benefit from the selectivity of the ionization (only aromatic systems) and the outstanding sensitivity of the method. In addition, a parallel ionization of sample components with ESI or APCI together with APLI was realized [72–74] to analyze polar (ESI) or nonaromatic medium polar (APCI) together with aromatic (APLI) compounds.

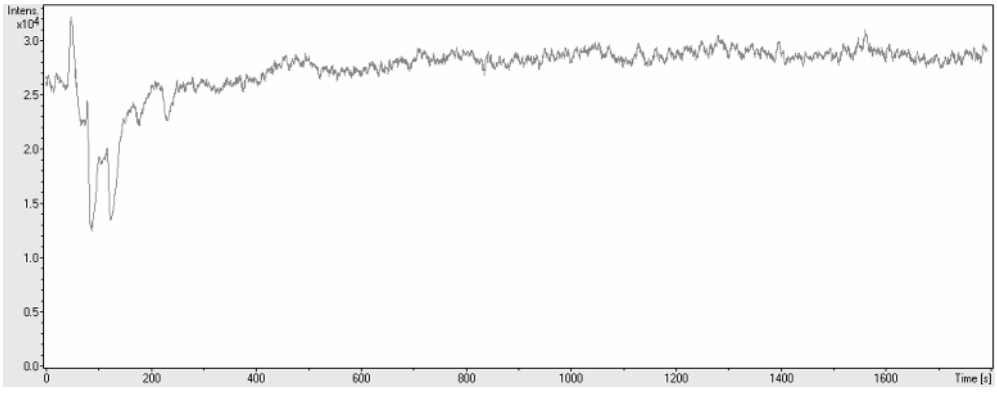

Figure 1.5 Ion suppression in APCI-MS of PAH in urine.

1.2.6 Determination of Ion Suppression

In many mass spectrometric analyses of complex samples, ion suppression leads to a more difficult quantitative determination and time-consuming sample preparation is often required. It should therefore be studied more in advance whether there is a signal-reducing influence of the matrix.

For the investigation of ion suppression, the sample solution (without analyte) is injected in the HPLC and a solution with the analyte (stable-isotopic labeled analyte, if no sample solution without analyte is available) is mixed behind the separation column via a T-piece to the eluate and the mass trace of the analyte (or stable-isotopic labeled analyte) is analyzed during the total analysis time. After the column, the separated matrix ingredients are mixed with the analyte in the T-piece and are transported into the ion source. The change in intensity of the analyte mass trace before and after the injection of the matrix provides information about a possibly occurring ion suppression.

Figure 1.5 shows the determination of ion suppression of a PAH analysis in urine with APCI-QTOF. During the analysis time between 80 and 400 s, the mass trace is considerably diminished and reached the normal level after about 450 s. This means that disturbing matrix components in the urine left the column between 80 and 400 s, which leads to ion suppression.

1.2.7 Best Ionization for Each Question

On the basis of Figure 1.2, the method which allows the most effective ionization for the analyte of interest can roughly be estimated. Depending on the polarity of the analyte, the ionization should be done with ESI (polar analytes), APCI (moderately polar analytes), APPI (nonpolar analytes), or with APLI (aromatics). However, the matrix plays an important role in making this decision. For com-

plex samples, ion suppression with electrospray ionization is more likely and more pronounced than for the other ionization methods discussed here. The ion beam line plays also an important role in the inlet region of the mass spectrometer. ESI ion sources with a Z-spray inlet show often less ion suppression than normal ESI ion sources. Also, the eluate flow must be adapted to the ion source. For example, slightly higher fluxes than with ESI sources can often be used in APCI sources. Although equipment manufacturers promise other flow rates, it is useful to operate ESI sources with fluxes below 300 µl/min and APCI, APPI, and APLI sources with fluxes below 500 µl/min with regard to spray stability, reproducibility, and ion suppression. Of course, based on the application even larger flows can be used, but often problems such as ion suppression or spray instability are observed.

1.3 Mass Analyzer

The most frequent mass spectrometers, which are routinely coupled to the LC:

- Quadrupole
- TripleQuad
- IonTrap
- TOF
- Orbitrap.

With regard to sensitivity and ratio of price and performance (including maintenance), a quadrupole MS is a very good purchase. With single ion mode (SIM), a very good sensitivity can be achieved and a fast quadrupole (from about 25–50 Hz) allows coupling with a fast UHPLC separation.

Based on quadrupole MS, a further development represents the triple quadrupole mass spectrometer, which play an increasingly important role, especially in the target analysis in complex samples. The sample preparation is minimized, a preliminary separation is often omitted and the potentials of the first and third quadrupole are adjusted so that only a certain mass is allowed to pass these quadrupoles. In the first quadrupole, the ion of the target analyte and in the third quadrupole a characteristic ion fragment, which is induced by collisions with argon in the second quadrupole (actually a fragmentation cell) is passed through. Due to the analysis of the fragment ion, the chemical noise (matrix) is greatly reduced and the triple quadrupole mass spectrometers are one of the most sensitive and selective mass spectrometers. Detection limits in zeptomoles area (amount of substance on the separation column) have been realized for some analytes.

Similar to a quadrupole, an ion trap is constructed. However, the ions are collected in the trap, and then, either a mass scan or single to multiple fragmentation of the target analyte can be performed. Modern ion trap MS systems are characterized by a very good linearity and sensitivity and a fast data acquisition (e.g., 20 Hz) and, thus, can even be coupled with UHPLC. They are particularly suitable for structure determination of biomolecules (e.g., carbohydrates, peptides).

For more as 20 years, the use of time-of-flight (TOF) mass spectrometers is increasing, which is related to the orthogonal ion beam guiding in the device. The orthogonal ion beam has made it possible to couple even continuous ion sources, such as ESI and APCI, without loss of resolution to a TOF-MS. Recently, the resolution was steadily improved through the introduction of repeller electrodes, ion funnels, and more powerful electronics etc., so that now several manufacturers offer TOF-MS systems with resolutions up to 50 000 while realizing data acquisition rates of 20 Hz or more. Thus, these devices are ideally suitable for the coupling of fast separation techniques such as UHPLC and can also provide assistance in the identification of unknown sample components due to the high resolution and mass accuracy (< 1 ppm).

One of the latest mass analyzer is the LTQ Orbitrap mass spectrometer (LTQ = linear trap quadrupole). In this, the commercial LTQ is coupled with an ion trap, developed by Makarov [75, 76]. Due to the resolving power (between 70 000 and 800 000) and the high mass accuracy (1–3 ppm), Orbitrap mass analyzers for example be used for identification of peptides in protein analysis or for metabolomic studies. In addition, the selectivity of MS/MS experiments can be greatly improved. However, the coupling is not useful with UHPLC for rapid chromatographic preseparation, as the data acquisition rate is too low for a reproducible integration of the narrow signals produced with UHPLC.

In addition to some other mass spectrometers, FT-ICRMS devices are also used. The latter, in addition to very high acquisition and operating costs (e.g., helium), has the disadvantage of low data acquisition rate (same problem as with the Orbitrap), so the coupling with a fast analysis, such as UHPLC cannot be realized. However, they are unbeaten in resolution (> 800 000) and an extremely useful tool in metabolomic research.

1.4 Future Developments

The trend in mass spectrometry is currently clearly toward higher resolution and faster data acquisition.

Probably in future resolution of about 100 000 and data rates of 20–40 Hz can be achieved with TOF-MS. With Orbitrap-MS, it is assumed that resolutions of more than 500 000 will be possible by more precise production of the cell and electronic. This could then by shortening the scanning speed, which is accompanied by a loss of resolution, allow a fast preseparation with UHPLC.

In the area of nontarget analysis, the combination of ion mobility spectrometry (IMS) with a high resolution QTOF-MS presents a powerful analysis platform. Two commercial systems with different varieties of ion mobility methods – the drift time ion mobility spectrometry (DTIM) from Agilent 6560 and the traveling wave ion mobility spectrometry (TWIMS) from Waters (Vion IMS QTOF) – are currently available. Due to the structure-dependent drift time in the drift tube of the IMS, isobaric substances can be separated from each other. Figure 1.6 shows

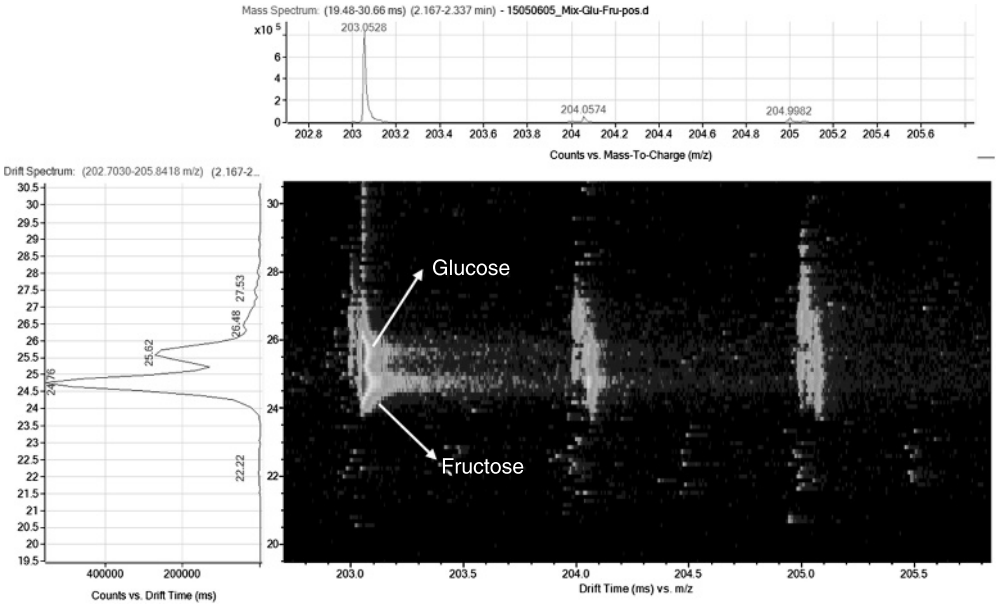

Figure 1.6 Analysis of a mixture of glucose and fructose with IM-qTOF-MS.

the separation of two isobaric substances, glucose and fructose, in the IM-QTOF-MS system (Agilent 6560) by their different drift time (in ms) in the 80 cm long drift tube of the system. Particularly noteworthy is that the collision cross section (CCS) of substances can directly (the Agilent system) or indirectly (through comparison with a standard, the Waters system) be determined with the help of the drift time. With a database of CCS values and precise mass, a fast and reliable identification of the signals can then be carried out for a nontarget analysis.

Another focus in future developments will be the optimization of ion sources with respect to ion generation and ion transport at different flows which are used in nano- and micro-HPLC, LC × LC and supercritical fluid chromatography (SFC) to increase the sensitivity.

1.5 What Should You Look for When Buying a Mass Spectrometer?

In addition to the available budget, in my opinion the following points playing a central role for a buying decision:

- Should a target analysis or comprehensive analysis of the sample be carried out
- Needed sensitivity
- Software
- Sample throughput
- MS analysis with or without preseparation process.

If only target analyzes are planned (e.g., analysis of known impurities in a product or pesticide analysis), a quadrupole or triple quadrupole-MS would be the best choice. With these devices a very sensitive analysis will be guaranteed and also a quick preseparation (e.g., UHPLC) is now possible for many devices.

If nontarget analysis should be realized, high-resolution mass spectrometer like QTOF or Orbitrap would facilitate the analysis considerably. Due to the additional separation dimension and the determination of CCS values, the new MS systems with an upstream ion mobility spectrometer are certainly an interesting alternative. Even if a high sample throughput is still necessary, the QTOF would have precedence over the slow Orbitrap in high resolution mode. However, regarding the resolution, Orbitrap is the more powerful system compared with QTOF. The sensitivity of qTOF is about a factor 10 lower than that of a triplequad, but detection limits in the lower ppb range are quite possible.

Perhaps, due to a high number of samples, no preseparation will be done. But then it should be ensured that suitable so-called ambient desorption ionization techniques, for example, DESI, DART, ASAP, DIP-APCI, can be coupled to the MS.

Finally, there are large differences in the respective MS software. Here, the user should determine the strengths and weaknesses of the various software systems.

In addition to the price of the system, the operating costs should also be considered. Besides a high nitrogen consumption, the mass spectrometer should be serviced annually. Depending on the effort and manufacturer, maintenance alone leads to an annual cost of 5000–20 000 euros.

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