Introduction

1

Learning Objectives

- The relevance of mass spectrometry
- Mass spectrometry – Basic concepts
- How mass spectra are displayed and communicated
- The performance features of mass spectrometry
- Basic terminology and conventions in data presentation
- Aims and scope and general organization of this textbook

1.1 Mass Spectrometry: Versatile and Indispensable

Mass spectrometry (MS) is an indispensable analytical tool in chemistry, biochemistry, pharmacy, medicine, and many related fields of science. No student, researcher or practitioner in these disciplines can really get by without a substantial knowledge of mass spectrometry.

Structure elucidation of unknown substances, environmental and forensic analytes, quality control of drugs, foods, and polymers – all rely to a great extent on mass spectrometry [1–7]. Mass spectrometry is employed to analyze combinatorial libraries [8], sequence biomolecules [9], and to explore metabolism in single cells [10, 11]. Today, "mass spectrometry is interwoven with biology to an extent that basic considerations of proteomics research are dealt with in a MS journal" [12]. Crude oils, derived products, and other highly complex mixtures, like dissolved organic matter (DOM), are analyzed by ultrahigh-resolution mass spectrometry [13–15]. Miniaturized mass spectrometers [16] contribute to our safety or can be employed in space missions [17, 18]. There are even some potential uses of mass spectrometry in homes and gardening [19].

J.H. Gross, *Mass Spectrometry*, DOI 10.1007/978-3-319-54398-7_1

Table 1.1 Fields of application of mass spectrometry

Key application and field of application	Explanation
Elemental and isotopic analysis Physics Radiochemistry Geochemistry	Elemental identification and isotopic abundance measurement of both short-lived and stable species in physics and radiochemistry (nuclear waste), in geochemistry and more recently in the life sciences.
Organic and bio-organic analysis Organic chemistry Polymer chemistry Biochemistry and medicine	Identification and structural characterization of molecules from small to very large as provided either by chemistry, physiological processes, or polymer chemistry.
Structure elucidation Organic chemistry Polymer chemistry Biochemistry and medicine	Mass spectrometric experiments can be arranged consecutively to study mass-selected ions in tandem mass spectrometry (MS/MS or MS^2). Eventually products are subjected to a third level (MS^3) and so forth (MS^n).
Characterization of ionic species and chemical reactions Physical chemistry Thermochemistry	Tandem MS provides an elegant means for the study of unimolecular or bimolecular reactions of gas phase ions and for the determination of ion energetics.
Coupling to separation techniques Quality control Environmental analysis Complex mixture analysis Forensics Petroleum chemistry Food chemistry	MS can be coupled to separation methods such as gas chromatography (GC) and liquid chromatography (LC). In 'hyphenation', i.e., as GC-MS or LC-MS, MS delivers high selectivity and low detection limits for the analysis of trace compounds in complicated matrices or the deconvolution of complex mixtures.
Mass spectral imaging Biomedical studies Pharmaceutical developments Material sciences	Mass spectra can be obtained from micrometer-sized areas on surfaces, translating the lateral distribution of compounds on surfaces (microelectronics, slices of tissue) into images, which in turn can be correlated to optical images.
Miniaturization Field portable MS Space missions Military applications	Mass spectrometers can be very small. Portable instruments allow for environmental on-site analysis, detection systems for explosives and warfare chemicals, and last but not least for many space missions.

Whatever the analytical interest may be: mass spectrometry aims to identify a compound from the molecular or atomic mass(es) of its constituents. The information delivered by mass alone can be sufficient for the identification of elements and the determination of the molecular formula of an analyte. The relative abundance of isotopologs helps to decide which elements contribute to such a formula and to estimate the number of atoms of a contributing element. Under the conditions of certain mass spectrometric experiments, fragmentation of ions can deliver information on ionic structure. Thus, MS elucidates the connectivity of atoms within smaller molecules, identifies functional groups, determines the (average) number and eventually the sequence of constituents of macromolecules, and in some cases even yields their three-dimensional structure (Table 1.1).

1.2 Historical Sketch

1.2.1 The First Mass Spectra

The first instrument to separate ions by mass-to-charge ratio was constructed by Joseph John Thomson (Nobel Prize in physics in 1906 for the discovery of the electron) in his attempt to understand electric discharges in gases and to analyze the charged gas phase species involved. His work [20–23] led to the discovery of atoms, isotopes, and thus to his recognition as the father of mass spectrometry (Fig. 1.1). While Thomson's original book from 1913 is hard to come by, there is a reprint by the *American Society for Mass Spectrometry* (ASMS) that is readily available.

Particularly due to Francis William Aston's work in the following decade, the new revolutionary technique soon provided means for the atomic characterization of numerous elements [24–28] for which Aston was awarded the Nobel Prize in chemistry in 1922 [29, 30]. Further Nobel Prizes related to MS are tabulated in the Appendix.

1.2.2 Thomson's Parabola Spectrograph

Thomson's apparatus, the parabola spectrograph, employs parallel magnetic and electric fields to achieve a deflection of ionic species depending on charge sign, charge, and mass. Ions exiting the ion source are passed through a collimator to create a roughly parallel beam that is then sent into the analyzer (Fig. 1.2) [23, 31]. The electric field of a planar capacitor deflects ions vertically either upward (cations in this illustration) or downward (anions) depending on their

Fig. 1.1 The Thomson Medal in honor of Joseph John Thomson, generally regarded as the father of mass spectrometry, is awarded by the *International Mass Spectrometry Foundation* (IMSS) to outstanding scientists in the field of mass spectrometry

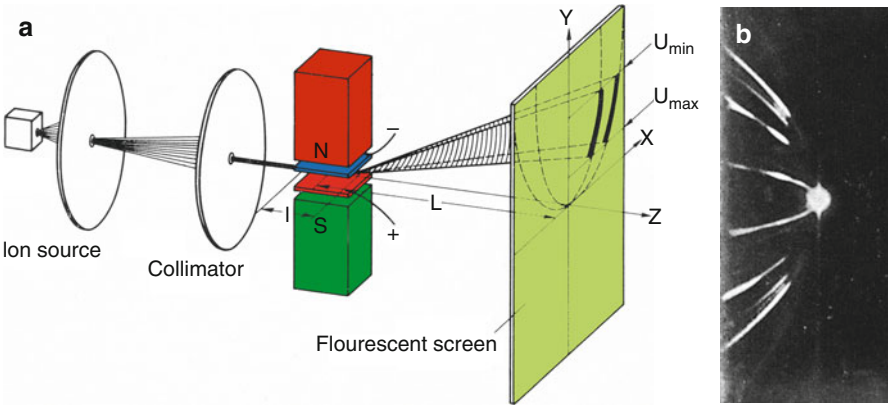

Fig. 1.2 Parabola spectrograph as constructed by J. J. Thomson. (**a**) Schematic, (**b**) photograph of the light emission from the fluorescent screen as obtained with this instrument (shown rotated by 90° with respect to the schematic) (Adapted from Ref. [31] with kind permission of Curt Brunnée)

charge sign. As fast ions will be deflected by a smaller angle than slower ones, the angle of *y*-deflection is a measure of ion kinetic energy. The magnetic field bends the beam horizontally in a way that depends on the mass-to-charge ratio and, again, charge sign. Heavier ions stay closer to the axis while lighter ones are pushed further out. Overall, this results in light emission on the fluorescent screen along parabolic branches, one branch per ion species that allow reading the ion momentum from the *x*-axis and kinetic energy from the *y*-axis. Thus, this apparently simple device simultaneously delivers a wealth of information. (Details on how magnetic and electric fields effect ion separation will be dealt with in Sect. 4.3.)

1.2.3 Milestones

Thomson and Aston only marked the beginnings of what expanded into more than a century of exciting developments in mass spectrometry, the major milestones of which were recently compiled [32]. From the 1950s to the present, mass spectrometry has made major strides and innovations are still being made at an enormous pace [29, 30, 33, 34].

The pioneering mass spectrometrist worked with home-built rather than commercial instruments. These machines, typically magnetic sector instruments using electron ionization, delivered a few mass spectra per day, providing that the device was delicately handled. Intimate knowledge of such an instrument and interpretation skills of the according EI spectra would provide the mass spectrometrist with a previously unknown wealth of insight into structural details [35–40]. The life sciences, in particular, have provided a great impetus for new developments that expand the mass range to higher molecular weights and increasingly fragile molecules. Environmental and pharmaceutical research has been a driving force

in reaching even lower limits of detection. Current research is aimed at methods of ion sampling, ion generation, and subsequent ion transfer into mass analyzers for superior performance.

Nowadays, the output of mass spectra has reached an unprecedented level. Highly automated systems produce thousands of spectra per day when running a routine application where samples of the very same type are to be treated by an analytical protocol that has been carefully elaborated by an expert beforehand. A large number of ionization methods and types of mass analyzers has been developed and combined in various ways. Thus, people sometimes feel overwhelmed by the mere task of selecting one out of about a dozen of promising techniques available for their particular sample. It is precisely this diversity that makes a basic understanding of the concepts and tools of mass spectrometry more important than ever. On the other extreme, there are mass spectrometry laboratories specialized on employing only one particular method – preferably matrix-assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI). In contrast to some 50 years ago, the instrumentation is now concealed in a sort of "black box", more appealingly designed to resemble an espresso machine. So let us take a look inside!

1.3 Aims and Scope of This Textbook

This book is tailored to be your guide to mass spectrometry – from the first steps to your daily work in research. Starting from the very principles of gas phase ion chemistry and isotopic properties, it leads you through the design of mass analyzers, mass spectral interpretation, and applied ionization methods. The book closes with chapters on chromatography-mass spectrometry coupling and one on inorganic mass spectrometry. In total, it comprises fifteen chapters that can be read independently from each other. However, for the novice it is recommended to work through from start to finish, occasionally skipping over more advanced sections (Table 1.2). Now in its 3rd edition, "Mass Spectrometry – A Textbook" continues to be your companion from undergraduate to graduate studies in chemistry, biochemistry, and other natural sciences, and aims to hold its value when serving as a hands-on reference in the course of professional life.

Step by step, you will understand how mass spectrometry works and what it can do as a powerful tool in your hands – equally well for analytical applications as for basic research. An improved layout and additional high-quality figures, about one third of them now in color, will make is easier and quicker to acquire the new knowledge. Many tables and flow charts have been added, compiling facts and comparing topics. Interrelationships are pointed to where appropriate. The correctness of scientific content has been examined by leading experts. Each chapter begins with a set of Learning Objectives and now also closes with a brief Summary followed by an elaborate list of references, emphasizing tutorial and review articles, book chapters, and monographs in the respective fields. Titles are included with all citations to help with the evaluation of useful further reading [41] and *digital object*

Table 1.2 Chapters of this book: overview for orientation

No.	Chapter title	Comment
1	Introduction	Getting ready, getting started
2	Principles of Ionization and Ion Dissociation	Tools of the trade. Basics needed for the understanding of any of the subsequent chapters
3	Isotopic Composition and Accurate Mass	
4	Instrumentation	
5	Practical Aspects of Electron Ionization	Electron ionization: the classical key to organic MS and indispensable part of every introductory course
6	Fragmentation of Organic Ions and Interpretation of EI Mass Spectra	
7	Chemical Ionization	Traditional, nonetheless still highly relevant soft ionization methods
8	Field Ionization and Field Desorption	
9	Tandem Mass Spectrometry	Fully controlled dissociation of mass-selected ions for many interesting purposes
10	Fast Atom Bombardment	More soft ionization methods. The latter two represent today's most relevant techniques in MS
11	Matrix-Assisted Laser Desorption/ Ionization	
12	Electrospray Ionization	
13	Ambient Desorption/Ionization	Exciting rather new field based on advances in atmospheric pressure ionization methods
14	Hyphenated Methods	Coupling of separation techniques to MS
15	Inorganic Mass Spectrometry	There is even more: a glimpse beyond the horizon of organic and biomedical MS

identifiers (DOIs) have been added to facilitate retrieval of the articles. References for general further reading on mass spectrometry are compiled at the end of this Introduction.

The coverage of this book is basically restricted to what is called "organic mass spectrometry" in a broad sense. It includes the ionization methods and mass analyzers currently in use, and in addition to classical organic compounds it covers applications to bio-organic samples such as peptides and oligonucleotides. Of course, transition metal complexes, synthetic polymers, and fullerenes are discussed as well as environmental or forensic applications. Elemental analysis, the classical field of inorganic mass spectrometry has been added to get a taste of mass spectrometry beyond molecular species.

Exercises

Many elaborate examples are included in this textbook, while conventional "problems and solutions" sections are omitted. Exercises complementing each chapter are available for free on the textbook's dedicated website at http://www.ms-textbook.com.

1.3.1 Facets of Mass Spectrometry

There is no single "golden rule" in approaching the wide field of mass spectrometry. In any case, it is necessary to learn about the ways of sample introduction, generation of ions, their mass analysis, and their detection as well as about data recording and presentation of mass spectra – and what's more is the art of interpreting mass spectra. All these aspects are correlated to each other in many ways and in their entirety contribute to what is referred to as mass spectrometry (Fig. 1.3). In other words, mass spectrometry is multi-facet rather than to be viewed from a single perspective. Like a view onto a globe does not reveal the complete surface of our planet, but roughly just one continent at a time, mass spectrometry needs to be explored from various vantage points [42].

1.4 What Is Mass Spectrometry?

Now, what is mass spectrometry? Well in any case, mass spectrometry is special in many ways. Up front, most *mass spectrometrists* do not fathom to be addressed as *mass spectroscopists*.

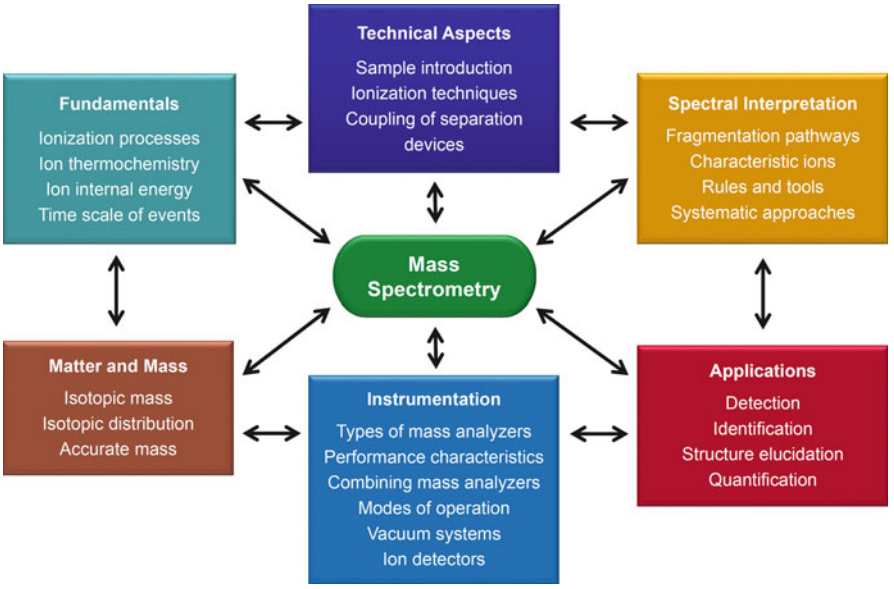

Fig. 1.3 The many facets of mass spectrometry. Each aspect is closely related to the others in various ways. Their assemblage yields an impression of the dimensions of MS

Zeroth law of mass spectrometry
"First of all, never make the mistake of calling it 'mass spectroscopy'. Spectroscopy involves the absorption of electromagnetic radiation, and mass spectrometry is different, as we will see. The mass spectrometrists sometimes get upset if you confuse this issue" [43].

Indeed, there is almost no book using the term *mass spectroscopy* and all scientific journals in the field bear *mass spectrometry* in their titles. You will find such highlighted rules, hints, notes, and definitions throughout the book. This more amusing one – we might call it the "zeroth law of mass spectrometry" – has been taken from a standard organic chemistry textbook. The same author completes his chapter on mass spectrometry with the conclusion that "despite occasional mysteries, mass spectrometry is still highly useful" [43].

Historical remark
Another explanation for this terminology originates from the historical development of our instrumentation [29]. The device employed by Thomson for the first mass-separating experiments was a type of *spectroscope* showing blurred signals on a fluorescent screen [44]. Dempster constructed an instrument with a deflecting magnetic field angled at 180°. In order to detect different masses, it could either be equipped with a photographic plate – a so-called *mass spectrograph* – or it could have a variable magnetic field to detect different masses by focusing them successively onto an electric point detector [45]. Later, the term *mass spectrometer* was coined for the latter type of instruments using a *scanning* magnetic field [46].

1.4.1 Basic Principle of Mass Spectrometry

"The basic principle of *mass spectrometry* (MS) is to generate ions from either inorganic or organic compounds by any suitable method, to separate these ions by their *mass-to-charge ratio* (m/z) and to detect them qualitatively and quantitatively by their respective m/z and abundance. The analyte may be ionized thermally, by electric fields or by impacting energetic electrons, ions or photons. The ... ions can be single ionized atoms, clusters, molecules or their fragments or associates. Ion separation is effected by static or dynamic electric or magnetic fields." Although this definition of mass spectrometry dates back to 1968 when organic mass spectrometry was in its infancy [47], it is still valid. However, some additions should be made. First, ionization of a sample can be effected not only by electrons, but also by (atomic) ions or photons, energetic neutral atoms, electronically excited atoms, massive cluster ions, and even electrostatically charged microdroplets can also be used to effect. Second, as demonstrated with great success by the time-of-flight

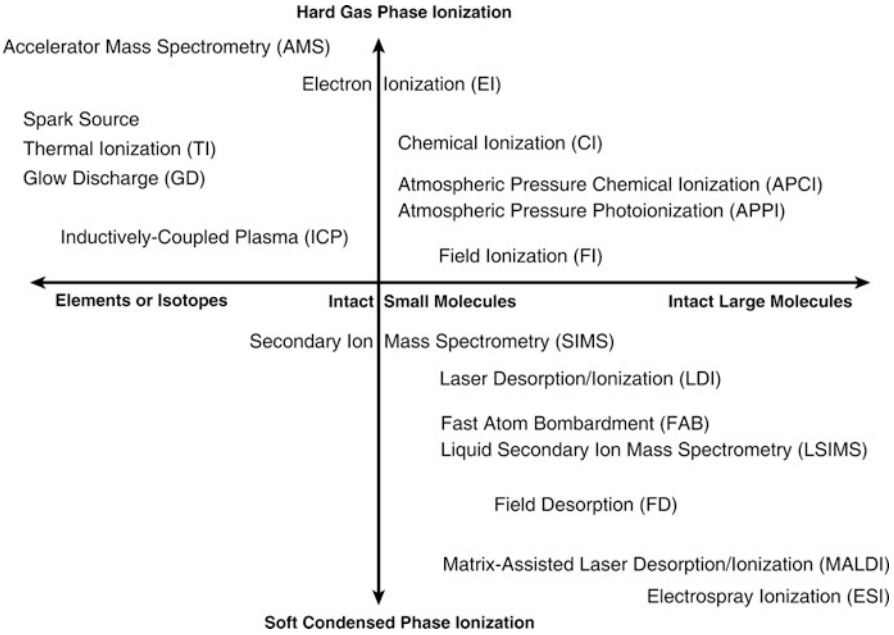

Fig. 1.4 Mass spectrometric techniques for different needs arranged by main fields of application and estimated relative hardness or softness (Reproduced from Ref. [42] by permission. © Wiley-VCH, Weinheim, 2009)

analyzer, ion separation by m/z can also be effected in field-free regions, provided the ions possess a well-defined kinetic energy at the entrance of the flight path.

The large variety of ionization techniques and their key applications can be roughly classified by their relative hardness or softness and (molecular) mass of suitable analytes (Fig. 1.4).

1.4.2 Mass Spectrometer

Obviously, almost any technique to achieve the goals of ionization, separation and detection of ions in the gas phase can be applied – and actually has been applied – in mass spectrometry. Fortunately, there is a simple basic scheme that all mass spectrometers follow. A mass spectrometer consists of an *ion source*, a *mass analyzer*, and a *detector* which are operated under high vacuum conditions. A closer look at the front end of such a device might separate the steps of *sample introduction*, *evaporation*, and successive *ionization* or *desorption/ionization*, respectively, but it is not always trivial to identify each of these steps as clearly separated from each other. Since the 1990s, mass spectrometers are operated under total data system control. The latter is also highly important for data acquisition, customization of spectral plots, and in-depth data analysis (Fig. 1.5).

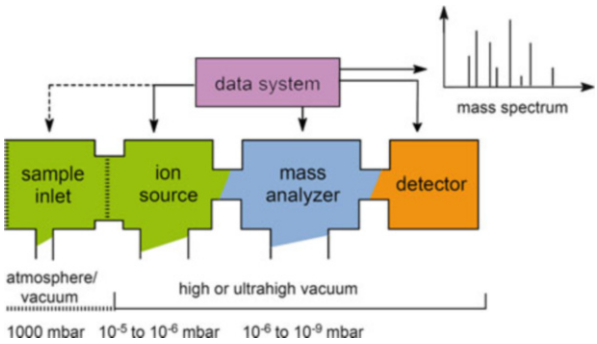

Fig. 1.5 General layout of mass spectrometers. Several types of sample inlets can be attached to the ion source housing. Transfer of the sample from atmospheric pressure into the high vacuum of the ion source and mass analyzer is accomplished by use of a vacuum lock (Sect. 5.2) or other types of interfaces (Sect. 12.2)

The *consumption of analyte* by its examination in the mass spectrometer is an aspect deserving our attention: Whereas other spectroscopic methods such as nuclear magnetic resonance (NMR), infrared (IR) or Raman spectroscopy do allow for sample recovery, mass spectrometry is destructive, i.e., it consumes the analyte. This is apparent from the process of ionization and translational motion through the mass analyzer to the detector during analysis. Although some sample is consumed, it may still be regarded as practically nondestructive, however, because the amount of analyte needed is in the low microgram range or even by several orders of magnitude below. In turn, the extremely low sample consumption of mass spectrometry makes it the method of choice when most other analytical techniques fail because they are not able to yield analytical information from nanogram amounts of sample.

1.4.3 Mass Scale

Plotting mass spectra on a physical scale of mass per electric charge (kg C^{-1}) would be very inconvenient to use. Thus, mass spectrometrists have adopted the use of a scale of atomic mass per number of elementary charges and termed it *mass-to-charge ratio*, m/z, (read "m over z" and write m/z) [48]. There is only one correct writing convention: the location of a peak on the abscissa is to be reported as "at m/z x".

Unfortunately, m/z is a rather artificial construct, as it has not received the status of a physical unit. Instead, m/z is dimensionless by definition. It may be understood as the ratio of the numerical value of ionic mass on the atomic mass scale and the number of elementary charges of the respective ion. The number of elementary charges is often, but by far not necessarily, equal to one. As long as only singly charged ions are observed ($z = 1$) the m/z scale directly reflects the atomic mass scale. However, there can be conditions where doubly, triply, or even highly charged ions are being created from the analyte depending on the ionization method employed.

Thomson versus *m/z*
Some mass spectrometrists use the unit *thomson* [Th] (to honor J. J. Thomson) instead of the dimensionless quantity *m*/*z*. Although the thomson is accepted (or tolerated), it is not an SI unit. The Thomson is equivalent to *m*/*z* in that there is no conversion factor between these units.

The distance between peaks on that axis has the meaning of a neutral loss from the ion at higher *m*/*z* to produce the fragment ion at lower *m*/*z*. Therefore, the amount of this neutral loss is given as "*x* u", where the symbol u stands for *unified atomic mass*. It is important to notice that the mass of the neutral is only reflected by the difference between the corresponding *m*/*z* values, i.e., $\Delta(m/z)$. This is because the mass spectrometer detects only charged species, i.e., the charge-retaining group of a fragmenting ion. Since 1961 the *unified atomic mass* [u] has been defined as $^{1}/_{12}$ of the mass of one single atom of the nuclide ^{12}C, which, by convention, has been set to precisely 12 u (Sect. 3.1).

Dalton versus u
Mass spectrometrists working in the biomedical field tend to use the *dalton* [Da] (to honor J. Dalton) instead of the *unified atomic mass* [u]. The dalton also is not an SI unit. The dalton is equivalent to unified atomic mass in that there is no conversion factor between these units.

1.4.4 Mass Spectrum

A *mass spectrum* is the two-dimensional representation of signal intensity (ordinate) versus *m*/*z* (abscissa). The position of a *peak*, as signals are usually called, reflects the *m*/*z* of an ion that has been created from the analyte within the ion source. The *intensity* of this peak correlates to the *abundance* of that ion.

Sometimes but not necessarily, the peak at highest *m*/*z* results from the detection of the intact ionized molecule, the *molecular ion*, $M^{+\bullet}$. The *molecular ion peak* is usually accompanied by several peaks at lower *m*/*z* caused by fragmentation of the molecular ion to yield *fragment ions*. Consequently, the respective peaks in the mass spectrum may be referred to as *fragment ion peaks*.

The most intense peak of a mass spectrum is called *base peak*. In most representations of mass spectral data the intensity of the base peak is normalized to 100% *relative intensity*. This largely helps to make mass spectra more easily comparable. The normalization can be done because the relative intensities are basically independent from the absolute ion abundances registered by the detector.

Our first mass spectrum In the electron ionization mass spectrum of a particular hydrocarbon, the molecular ion peak and the base peak of the spectrum happen to correspond to the same ionic species at *m*/*z* 16 (Fig. 1.6). The fragment ion peaks at *m*/*z* 12–15 are spaced at $\Delta(m/z) = 1$. Obviously, the molecular ion, $M^{+\bullet}$, fragments by loss of $H^{\bullet}$ which is the only possibility to explain the peak at *m*/*z* 15 by loss of a neutral of 1 u mass. Accordingly, the peaks at lower *m*/*z* might arise from loss of an H_2 molecule (2 u) and so forth. It is rather obvious that this spectrum corresponds to methane, CH_4, showing its molecular ion peak at *m*/*z* 16 because the atomic mass of carbon is 12 u and that of hydrogen is 1 u, and therefore 12 u + 4 × 1 u = 16 u. Removal of one electron from a 16 u neutral yields a singly-charged radical ion that is detected at *m*/*z* 16 by the mass spectrometer. Of course, most mass spectra are not that simple, but this is how it works.

1.4.5 Statistical Nature of Mass Spectra

It is important to be aware that a single molecule can only yield one ion of one *m*/*z* value. This ion may either reflect the intact molecule or any of its fragment ions. Statistics on thousands of ion formations and dissociations are needed to generate a useful mass spectrum exhibiting signals at different *m*/*z* where each of them can be assigned a relevant relative intensity. To understand this, simply imagine a single methane molecule that gets ionized and detected as a molecular ion: this would lead to a spectrum showing a single line at *m*/*z* 16, the intensity of which would have no meaning beyond 'yes' and 'no' (Fig. 1.7a). Alternatively, the molecular ion might fragment to yield a single CH_3^+ ion at *m*/*z* 15; again, the spectrum would show only one line. In fact, such a spectrum could not tell us whether the peak is caused by a molecular or a fragment ion. Eight ions might lead to a spectrum where each ion corresponds to 33.3% relative intensity (as in Fig. 1.7c) even though other distributions would be possible. Eleven ions could scale the intensity in 20%

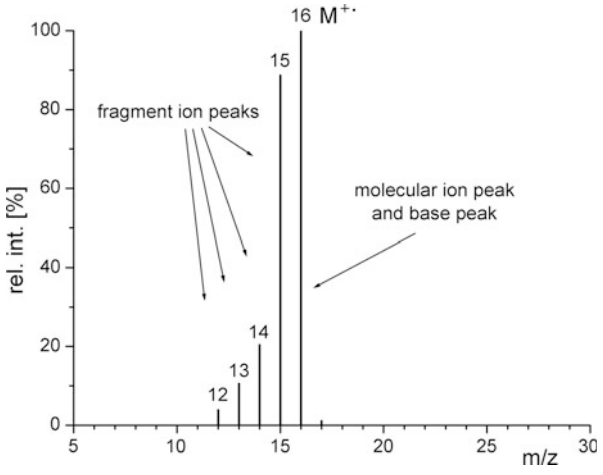

Fig. 1.6 Electron ionization mass spectrum of a low-mass hydrocarbon (Adapted with permission. © National Institute of Standards and Technology, NIST, 2002)

steps, while 23 ions could lead to a spectrum with 10% steps. It is evident that a spectrum with intensity levels as accurate as 0.1% has to be based on thousands of ions (Fig. 1.7f).

Attomole sensitivity? Sometimes, instruments are advertised to offer attomol sensitivity. Is this possible at all? The amount of 1 amol $= 10^{-18}$ mol still corresponds to $6.022 \times 10^{23} \times 10^{-18} = 6.022 \times 10^{5}$ molecules. Assuming 10% of the sample could be ionized and 10% of this fraction would be detected, the resulting spectrum would still be based on 1% of the sample molecules, i.e., 6000 ions. Obviously, attomole sensitivity touches on the limit of what is required to deliver a useful spectrum.

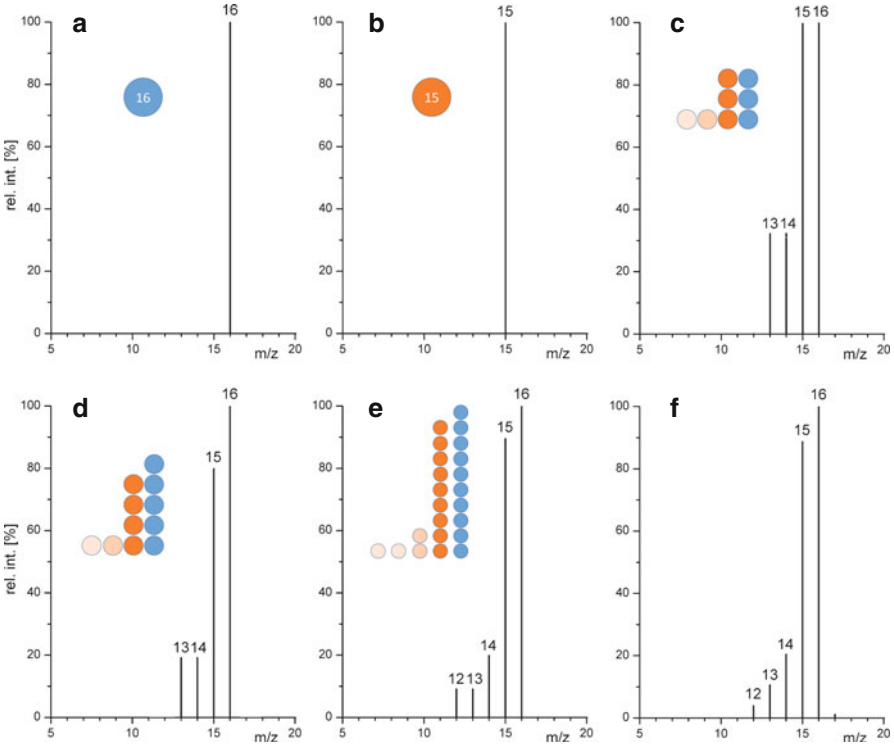

Fig. 1.7 Statistical nature of mass spectra and the appearance of methane spectra based on very low numbers of ions. (**a**) and (**b**) by one ion, (**c**) by eight ions, (**d**) by eleven ions, (**e**) by 23 ions, and (**f**) by thousands. The isotope peak of 1.1% relative intensity at *m*/*z* 17 is only visible and meaningful in the case of (**f**)

Avoid overload
There is also an upper limit for the number of ions and neutrals per volume inside the ion source from the point of which the appearance of spectra will significantly change due to ion–molecule reactions (Sect. 7.2).

1.4.6 Bars, Profiles, and Lists

The above spectra are represented as a *bar graph* or *histogram*. Such *data reduction* is common in mass spectrometry and useful as long as peaks are well resolved. The intensities of the peaks can be obtained either from measured peak heights or more correctly from peak areas. The position, i.e., the *m*/*z* ratio, of the signal is determined from its centroid. Noise below some user-defined cut level is usually subtracted from the bar graph spectrum. If peak shape and peak width become important, e.g., in case of high-mass analytes or high-resolution measurements, spectra should be represented as *profile data* as initially acquired by the mass spectrometer. *Tabular listings* of mass spectra are used to report mass and intensity data more accurately (Fig. 1.8).

Accurate intensity data is important for the analysis of isotope patterns. Also, accurate mass data can be used to derive the elemental composition of ions (Sect. 3.5).

1.5 Ion Chromatograms

Gas chromatography (GC) and liquid chromatography (LC) result in the separation and subsequent elution of the components of a mixture from the chromatographic column at individual *retention times*. When a mass spectrometer is employed as the

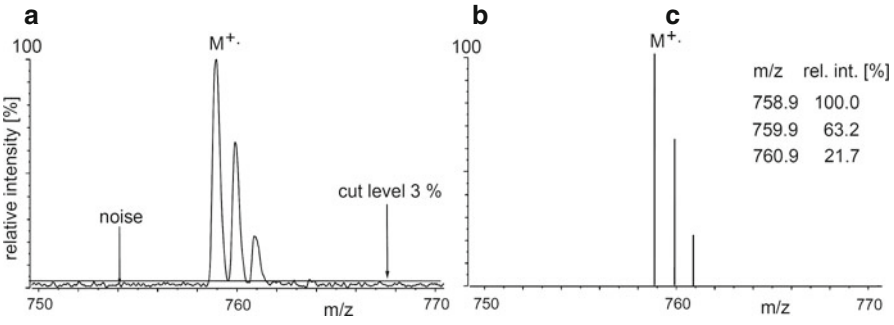

Fig. 1.8 Tetrapentacontane, $C_{54}H_{110}$: Three representations of the molecular ion signal in the field desorption mass spectrum (Sect. 8.6) (**a**) profile spectrum, (**b**) bar graph representation, and (**c**) tabular listing

chromatographic detector (GC-MS and LC-MS, Sects. 5.4 and 5.5; Chap. 14) its output must somehow represent the chromatogram that would otherwise have been obtained with "classic" chromatographic detectors (FID, TCD, UV). The chromatogram as produced by the mass spectrometer is composed of a large *set of consecutively acquired mass spectra*, each providing mass spectral data of the eluting species. Thus, the components can be identified one after the other by their individual mass spectra. Because mass spectral chromatograms represent ionic abundances as a function of retention time, these are termed *ion chromatograms*.

The *total ion current* (TIC) can either be measured by a *hardware TIC monitor* before mass analysis (nA to μA range), or its equivalent can be *reconstructed* or *extracted* after mass analysis [49]. Both adjectives, reconstructed and extracted, serve to illustrate that the chromatogram has been obtained post-acquisition from a set of spectra by a computational process that selects user-defined signals to build the trace.

True TIC
Modern instruments do not anymore support hardware TIC measurements, but until the 1970s, there used to be a hardware TIC monitor on the electronics panel. The TIC was obtained by measuring the ion current caused by those ions hitting the ion source exit plate instead of passing through its slit.

Thus, the TIC represents a measure of the overall intensity of ion production or of mass spectral output as a function of time, respectively. The TIC obtained by means of *data reduction* [50], i.e., by summation of peak intensities of each mass spectrum as successively acquired during analysis, is termed *total ion chromatogram* (TIC). For this purpose, the sums of all ion intensities belonging to each of the spectra is plotted as a function of time or scan number, respectively.

The term *total ion current chromatogram* (TICC) refers to a chromatogram obtained by plotting the total ion current detected in each of a series of mass spectra recorded as a function of retention times of the chromatographically separated components of a mixture (which essentially is implicated by: TIC). Sometimes we find combinations such as *reconstructed total ion current* (RTIC) or *reconstructed total ion current chromatogram* (RTICC, Table 1.3).

The term *reconstructed ion chromatogram* (RIC) was and still is used by many to describe the intensity of a given m/z or m/z range plotted as a function of time or scan number. Recently, the term *extracted ion chromatogram* (EIC) has been used to describe a chromatogram created by plotting the intensity of the signal observed at a chosen m/z value or set of values in a series of mass spectra recorded as a function of retention time. Plotting RICs or EICs is especially useful to identify a target compound of known m/z from complex GC-MS or LC-MS data. In other words, the RIC allows to retrieve the retention time of the target compound. RICs can also be used to uncover the relationship of certain m/z values to different mass spectra obtained from the measurement of a single (impure) sample. Thus, RICs

Table 1.3 Ion chromatograms

Acronym	Full name	Explanation
TIC	Total ion chromatogram	Sum of all signal intensities per spectrum vs. retention time. TIC is recommended.
TICC	Total ion current chromatogram	
RTIC	Reconstructed total ion chromatogram	
RTICC	Reconstructed total ion current chromatogram	
RIC	Reconstructed ion chromatogram	Signal intensity at selected *m*/*z* vs. retention time. Both are in use.
EIC	Extracted ion chromatogram	
BPC	Base peak chromatogram	Base peak intensity of each spectrum plotted vs. retention time.

(EICs) often reveal valuable information on impurities accompanying the main product, e.g., remaining solvents, plasticizers, vacuum grease, or synthetic by-products (Sect. 5.2 and Appendix A.9).

Finally, the *base peak chromatogram* (BPC) is a chromatogram obtained by plotting the intensity of the base peak detected in each of a series of mass spectra recorded as a function of retention time. BPCs can be useful to enhance the visibility of compound peaks in a complex chromatogram, especially when soft ionization methods are employed that cause most of the ion current to occur in one ionic species.

Ion chromatograms Polycyclic and nitro musks are frequently used as fragrances in cosmetic products. A GC-MC procedure for their identification and quantitation employs the characteristic RICs (EICs) of tonalide (AHTN), $C_{18}H_{26}O^{+\bullet}$, *m*/*z* 258, and xylene musk (MX), $C_{12}H_{15}N_3O_6^{+\bullet}$, *m*/*z* 297 [51]. Although eluting simultaneously (peak **3** in Fig. 1.9), EICs allow to separate both components by choosing characteristic *m*/*z* values, e.g., of the respective molecular ions or abundant fragment ions. The concentration of the solution injected was in the order of 1 µg ml^{-1} per component.

A certain degree of fractionation is also observed during evaporation of mixtures from a *direct insertion probe* (DIP), although the separation by far cannot be compared to that of chromatographic systems. Nonetheless, plotting the TIC or a RIC yields an overview of the temporal distribution of component spectra across a measurement using a DIP (Sect. 5.2).

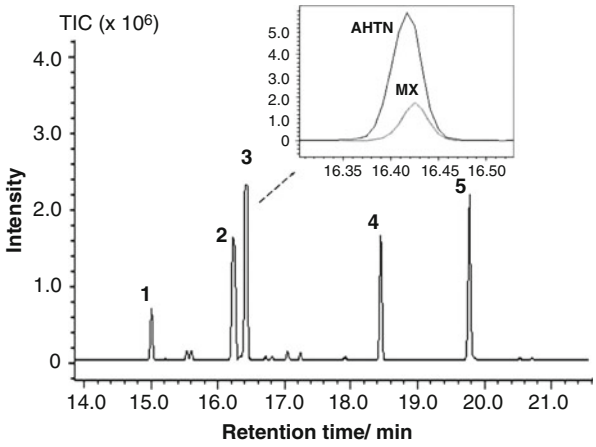

Fig. 1.9 Typical GC-MS chromatogram, i.e., TIC (TICC) in full scan mode for synthetic musks and some standards. However, the elution of two components occurs almost simultaneously and leads to superimposed peaks. The inset shows the characteristic RICs (EICs) of tonalide (AHTN), $C_{18}H_{26}O^{+\bullet}$, *m/z* 258, and xylene musk (MX), $C_{12}H_{15}N_3O_6^{+\bullet}$, *m/z* 297 (Reproduced from Ref. [51] with permission. © The Japan Society for Analytical Chemistry, 2009)

1.6 Performance of Mass Spectrometers

1.6.1 Sensitivity

The term *sensitivity* specifies the overall response of any analytical system for a certain analyte when operated under well-defined conditions. The *sensitivity* is defined as the slope of a plot of analyte amount vs. signal strength. In mass spectrometry, sensitivity is reported as electric charge of a specified ion species reaching the detector per mass of analyte used. The sensitivity is given in units of C μg^{-1} for solids [49]; for gaseous analytes, it can be specified as the ratio of ion current to analyte partial pressure in units of A Pa^{-1} [50].

According to the above definition, sensitivity does not only depend on the ionization efficiency of EI or any other ionization method. Also relevant are the extraction of ions from the ion source, the mass range acquired during the experiment, and the transmission of the mass analyzer. Therefore, the complete experimental conditions have to be stated with sensitivity data.

Calculating sensitivity Magnetic sector instruments are specified to have a sensitivity of about 4×10^{-7} C μg^{-1} for the molecular ion of methylstearate, *m/z* 298, at $R = 1000$ in 70 eV EI mode. One microgram of methylstearate is equivalent to 3.4×10^{-9} mol or 2.0×10^{15} molecules. The charge of 4×10^{-7} C corresponds to 2.5×10^{12} electron charges of 1.6×10^{-19} C each. Vice versa, in dividing the

number of molecules per microgram by the number of charges at the detector we may conclude that only one out of 800 molecules is finally detected.

1.6.2 Limit of Detection

The *limit of detection* (LOD), also termed *detection limit*, is almost self-explanatory, yet it is often confused with sensitivity. The limit of detection defines the smallest flow or the lowest amount of analyte necessary to obtain a signal that can be discerned from the background noise. The detection limit is valid for one well-specified analyte upon treatment according to a particular analytical protocol [49, 50, 52].

Of course, the sensitivity of an instrumental setup is of key importance to low detection limits; nevertheless, the detection limit is a clearly different quantity. The detection limit may either be stated as a relative measure in trace analysis, e.g., 1 ppb of dioxin in waste oil samples (equivalent to 1 μg kg^{-1} of sample), or as an absolute measure, e.g., 1 femtomol of substance P in MALDI-MS.

1.6.3 Signal-to-Noise Ratio

The *signal-to-noise ratio* (S/N) describes the uncertainty of an intensity measurement and provides a quantitative measure of a signal's quality by quantifying the ratio of the intensity of a signal relative to noise.

Noise results from the electronics of an instrument, and thus noise is not only present *between* the signals but also *on* the signals. Consequently, intensity measurements are influenced by noise. Real and very numerous background signals of various origin, e.g., matrix compounds as employed in fast atom bombardment (FAB) or matrix-assisted laser desorption/ionization (MALDI), column bleed in gas chromatography (GC), and other impurities can appear to be electronic noise, so-called "chemical" noise. In the strict sense, this should be distinct from electronic noise and should be reported as *signal-to-background ratio* (S/B) [52]. In practice, this can be difficult to do.

Electronic noise is statistical in nature, and therefore can be reduced by elongated data acquisition and subsequent summing or averaging of the spectra, respectively. Accordingly, an intensive peak has a better S/N than a low-intensity peak within the same spectrum.

The reduction of noise is proportional to the square root of acquisition time or number of single spectra that are averaged [53], e.g., the noise is reduced by a factor of 3.16 by averaging 10 spectra or by a factor of 10 by averaging 100 spectra, respectively.

How much noise? Signals are regarded to be clearly visible at $S/N \geq 10$, a value often stated in the context of detection limits. A mass spectrometer in good condition yields $S/N > 10^4$, which means in turn that even isotopic peaks of low

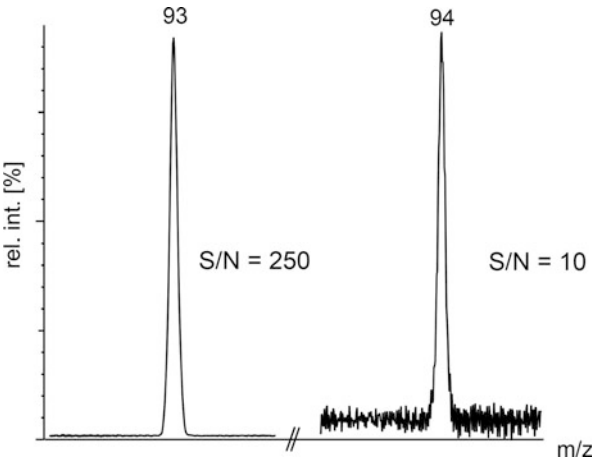

Fig. 1.10 Signal-to-noise ratio. Among the signals due to the toluene molecular ion, the first isotopic peak at *m/z* 93 has S/N = 250, while the second isotopic peak at *m/z* 94 has S/N = 10

relative intensity can be reliably measured, provided there is no interference with background signals. Among the signals from the toluene molecular ion in the below figure, the first isotopic peak resulting from $[^{13}C^{12}C_6H_8]^{+\bullet}$ at *m/z* 93, still had S/N = 250 while the second isotopic peak resulting from $[^{13}C_2{}^{12}C_5H_8]^{+\bullet}$ at *m/z* 94 just had S/N = 10 (Fig. 1.10). The theoretical ratio of intensities of the peaks at *m/z* 92 : 93 : 94 is given by 100 : 7.7 : 0.3, i.e., the ratio of intensities directly reflects the S/N ratio. Pursuing this consideration, we may expect the peak at *m/z* 92 that corresponds to $[^{12}C_7H_8]^{+\bullet}$ to have had S/N = 3250. In practice, S/N $\geq$ 1000 means that noise is essentially invisible in the spectral plot.

1.7 Terminology – General Aspects

General consensus regarding terms, acronyms, and symbols is of paramount importance for adequate communication in mass spectrometry. The currently accepted terminology is chiefly governed by the following publications:

- 1991: Compilation by Price under the guidance of the *American Society for Mass Spectrometry* (ASMS) [54].
- 1995: Compilation by Todd representing the official recommendations of the *International Union of Pure and Applied Chemistry* (IUPAC) [55].
- 2006: Terminology reference book by Sparkman [52].
- 2013: Update of terms and definitions by IUPAC [56]; a project that started in 2005 [57] and went through several stages of comments and suggestions [58–60].

Still, terminology in MS is not perfectly uniform. IUPAC in its 1995 version, for example, stays in opposition to the vast majority of practitioners, journals, and books when talking about *mass spectroscopy*, while both, Price and Sparkman are

using *mass spectrometry*. IUPAC accepts terms such as *daughter ion* and *parent ion* as equivalent to *product ion* and *precursor ion*, respectively. Sparkman discourages the use of *daughter ion* and *parent ion* as these are archaic and gender-specific terms. None of these collections is fully comprehensive. Nevertheless, there is about 95% agreement between these guidelines to terminology in mass spectrometry and their overall coverage can be regarded as highly sufficient, making the application of any of these beneficial to oral and written communication.

Unfortunately, misleading and redundant terms are used throughout the literature, and thus, we need at least to understand their intention even if we are not going to use them actively. Terminology in this book avoids outdated or vague terms and special notes are given for clarification where ambiguities might arise.

Acronyms galore
Mass spectrometrists like to communicate their work using countless acronyms [61, 62], and thus there is no sense in trying to avoid them here. All acronyms are explained at first use in a chapter and are included in the subject index. For convenience, one hundred common MS acronyms are provided in the Appendix.

1.7.1 Basic Terminology in Describing Mass Spectra

One should be aware of some basic, but often misunderstood, terminology when describing mass spectra.

1. We may refer to a whatever-*type* (*mass*) *spectrum*, e.g., an *EI mass spectrum*. But, as MS means *mass spectrometry* as a method, the term *MS spectrum* is clearly incorrect.
2. Multi-stage MS (MS/MS equal to MS^2) refers to *tandem mass spectrometry*. Analogous to 1, it is correct to say *tandem mass spectra*, not *MS/MS spectra*.
3. Ions are detected *at* a certain *m*/*z* value. Correct phrasings are "the molecular ion at *m*/*z* 16" or "$M^{+\bullet}$, *m*/*z* 16" or "$CH_4^{+\bullet}$, *m*/*z* 16", for example.
4. Ranges in spectra or ranges set in operating a mass spectrometer are to be referred to in the form of "*m*/*z* 10–100" or "*m*/*z* 10 to *m*/*z* 100".
5. Mass spectrometers separate ions by mass-to-charge ratio, *m*/*z*. The abscissa of a mass spectrum is to be labelled only as "*m*/*z*". Any other labels like "mass", "*m*/*z* [Da]", or even worse "*m*/*z* [a.m.u]", are wrong.
6. Ions are correlated with peaks in a spectrum, not neutrals. Assigning an ion to a peak is already an act of interpretation.
7. Neutral losses (rarely called dark matter [52]) are exclusively recognized from the distance between peaks expressed in terms of the difference $\Delta(m/z)$. The mass of the corresponding neutral is then given in units of u.
8. A signal or peak is only the graphical representation of the mass spectrometer's detector output. It can just be observed, but not act by itself in any way.

Table 1.4 Symbols

Symbol	Meaning
•	Unpaired electron in radicals
+	Positive even-electron ions
–	Negative even-electron ions
+•	Positive radical ions
–•	Negative radical ions
	Arrow for transfer of an electron pair
	Single-barbed arrow for transfer of a single electron
	Indicates the position of a cleaved bond
	Fragmentation or reaction
	Occasionally for rearrangement fragmentation

9. Ions can act. Typically they fragment, dissociate, rearrange, react, isomerize.
10. It is advisable to use the common symbols compiled in Table 1.4, in particular, charge should precede the radical, as in +• or –•.

1.8 Units, Physical Quantities, and Physical Constants

The consistent use of units for physical quantities is a prerequisite in science, because it simplifies the comparison of physical quantities, e.g., temperature, pressure, or physical dimensions. Therefore, the *International System of Units* (SI) is used throughout the book. This system is based on seven units that can be combined to form any other unit needed. Nevertheless, mass spectrometers often have long lifetimes and 20-year-old instruments being scaled in inches and having pressure readings in Torr or psi may still be in use. In the Appendix of this book you will find tables that provide collections of SI units together with frequently needed conversion factors and a collection of physical constants and quantities.

1.9 Further Reading

This book provides extensive reference lists at the end of each chapter. Nonetheless, it may be useful to have the most relevant MS books compiled in one list.

First of all, there are some classical mass spectrometry books deserving our grateful attention [31, 63–73]. Then, some other introductory mass spectrometry books are to be mentioned [74–78]. Finally, various monographs covering MS in dedicated chapters are available; these are listed here in chronological order [30, 79–136].

1.10 Quintessence

Basic Principle
Mass spectrometry (MS) separates isolated ions in the gas phase by their mass-to-charge ratio. This is accomplished by means of electric and magnetic fields or combinations thereof. The fields may be constant in time, variable, or alternating, depending on the type of mass analyzer. Any sample needs thus to be transformed into the state of isolated gas-phase ions. There is a large variety of ionization techniques to perform this transition for almost any sample. The fact that the instrument's response relies on the detection of gaseous ions provides the basis for the outstanding low sample consumption of MS, generally in the nanogram to microgram range per sample. As sample consumption in MS is minimal, its potential applications are diverse and manifold.

Historical Development
Mass spectrometry was developed about a century ago. Initially applied to the characterization of elements and their isotopic composition, MS left the realms of physics in the 1940s to be applied for hydrocarbon analysis. From there, MS became a tool for compound characterization in organic chemistry and then expanded into biomedical and countless other natural sciences.

Applications of Mass Spectrometry
Mass spectrometry (MS) can be applied for the analysis of all classes of chemical compounds either elemental or molecular, pure or in complex mixtures. MS is thus widely applied not only in chemistry and the life science in the widest sense but also plays a significant role in pharmacology, geology, physics, and other sciences. MS is clearly interdisciplinary in itself and in regard to its different fields of application. It is the particular strength of MS to deliver analytical information from the tiniest amounts of a sample.

Important Terms and Concepts
The method is termed mass spectrometry (MS), the entire instrument is called a mass spectrometer. It consists of sample introduction system, ion source, mass analyzer, detector, and data system. A mass spectrum represents the output of a mass spectrometer. Mass spectra are plotted as (relative) signal intensity versus dimensionless mass-to-charge ratio, m/z. Alternatively, mass spectral data can be supplied in tabular form.

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