MASS SPECTROMETRY

Instrumentation, Interpretation, and Applications

Edited by

Rolf Ekman
Jerzy Silberring
Ann Westman-Brinkmalm
Agnieszka Kraj

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MASS SPECTROMETRY

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FOREWORD

Over the last two decades mass spectrometry has become one of the central techniques in analytical chemistry, and the analysis of biological (macro)molecules in particular. Its importance is now comparable to that of the more traditional electrophoresis and liquid separations techniques, and it is often used in conjunction with them as so-called "hyphenated" techniques, such as LC-MS.

This development was originally triggered by the discovery of novel techniques to generate stable ions of the molecules of interest and the development of associated ion sources. Such a technique has to meet two basic requirements: first the molecules, usually existing in the liquid or solid condensed state, have to be transferred into the gas phase and eventually into the vacuum of a mass analyzer; second, the neutral molecules have to acquire one or several charges to be separated and detectable in the mass analyzer. Both steps had traditionally been prone to internal excitation of the molecules leading to fragmentation and loss of analytical information. The two techniques that evolved as the frontrunners and nowadays dominate mass spectrometry are electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI). Even though these two techniques solve the problem of transfer from the condensed to gas phase as well as the ionization in very different ways and were developed completely independently, their breakthrough happened concurrently in 1988. This concurrent development was, most probably, not a shear coincidence. The basics of the macromolecular structure and function of biological systems, the role of DNA and proteins in particular, had evolved over the three decades before and it had become apparent at least to a small group of scientists that to unravel the details of their structure required a leap in the development of more sensitive and more specific analytical techniques. Mass spectrometry held at least the promise for such a leap, even though most of the "experts" thought it impossible. This might suggest that in science, as in other fields of human development it holds that, "where is a need, there is a way." It is also important to realize in this context, that both ESI and MALDI make use of principles developed in the years before, such as field desorption and desorption by particle beams, as well as chemical ionization in the gas phase.

The novel ionization mechanisms have early on induced the revival of some mass analyzer principles such as the (axial ion extraction) time-of-flight (TOF) instruments, which had been written off as having too low a performance earlier. More recently a whole plethora of new mass spectrometers have been marketed, combining both ESI and MALDI with high performance spectrometers such as the orthogonal extraction TOFs, Fourier transform ion cyclotron (FT-ICR) and orbitrap instruments. These developments have been largely introduced by the instrument manufacturers. The parallel development of high speed digital signal processing, data analysis, and data banking has also played a major role in the development of the field.

Mass spectrometry has meanwhile become an important part of academic education in analytical chemistry. It can be found in the curricula of most undergraduate as well as graduate courses in the field. The publication of this dedicated textbook is, therefore, a timely undertaking and the editors and authors are to be complimented for the effort to put the book together.

How much detail does a student need to know and how much detail should a textbook then contain? This is an almost unsolvable problem because of the diversity of students and their analytical needs. The majority of students will eventually move on into special fields in (bio)chemistry, molecular or systems biology or polymer chemistry. For them mass spectrometry will "only" be one of the commodities to help them solve their problems, which are defined by their field of activity, not the analytical technique. How much of the basics in mass spectrometry will they need to know? Again, this depends on the problem at hand. For many a routine application of commercial instruments and the manufacturers' manuals will suffice. However, if the problem is not routine the analytical technique cannot be either. Mass spectrometry is and, most probably, will remain a rather complex technique. To fully exploit its tremendous potential, but, equally important, to avoid its many pitfalls, a deeper understanding of the mechanisms and the technology will be mandatory. This book will, hopefully, help students to lay the basis for this expertise and, once the need arises, allow them to go back to the more specialized literature at a later time. It is in this sense that I hope this book will be a real help to many of them.

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PART I

INSTRUMENTATION

INTRODUCTION

The first part of this book is dedicated to a discussion of mass spectrometry (MS) instrumentation. We start with a list of basic definitions and explanations (Chapter 1). Chapter 2 is devoted to the mass spectrometer and its building blocks. In this chapter we describe in relative detail the most common ion sources, mass analyzers, and detectors. Some of the techniques are not extensively used today, but they are often cited in the MS literature, and are important contributions to the history of MS instrumentation. In Chapter 3 we describe both different fragmentation methods and several typical tandem MS analyzer configurations. Chapter 4 is somewhat of an outsider. Separation methods is certainly too vast a topic to do full justice in less than twenty pages. However, some separation methods are used in such close alliance with MS that the two techniques are always referred to as one combined analytical tool, for example, GC-MS and LC-MS. In effect, it is almost impossible to study the MS literature without coming across at least one separation method. Our main goal with Chapter 4 is, therefore, to facilitate an introduction to the MS literature for the reader by providing a short summary of the basic principles of some of the most common separation methods that have been used in conjunction with mass spectrometry.

Mass Spectrometry. Edited by Ekman, Silberring, Westman-Brinkmalm, and Kraj

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DEFINITIONS AND EXPLANATIONS

Ann Westman-Brinkmalm and Gunnar Brinkmalm

The objective of this chapter is to provide the reader with definitions or brief explanations of some key terms used in mass spectrometry (MS). As in many other scientific fields there exist in the MS community (sometimes heated) debates over what terms and definitions are correct and what the everyday MS terminology really stands for. Maybe this is an inevitable phenomenon in any multidisciplined, highly active, and fast evolving branch of science. However, in this chapter we will try to keep out of harms way by providing the reader mainly with definitions based on suggestions by the current IUPAC project "Standard Definitions of Terms Relating to Mass Spectrometry" [1], see also "Mass Spectrometry Terms and Definitions Project Page" [2]. This project is currently in its final stage and will be officially published in the near future. However, in some cases we could not refrain from adding some contrary opinions. See also Chapters 5 and 6 for more detailed explanations of some of the basic concepts of MS. When studying the different chapters in this book the reader will notice that all authors (including ourselves) have not adhered strictly to the list of recommended definitions found in this chapter. This is a realistic reflection of the MS literature in general and the reader should not allow herself or himself to be too confused or discouraged. Our general advice is, "when in Rome, do as the Romans do." However, to aid the reader, the editors have when possible provided alternative or additional terms in concordance with the IUPAC definitions.

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Accurate Mass An experimentally determined mass of an ion that is used to determine an elemental formula. For ions containing combinations of the elements C, H, N, O, P, S, and the halogens, with mass less than 200 Da, a measurement with 5 ppm uncertainty is sufficient to uniquely determine the elemental composition. See also related entries on: *average mass; dalton; molar mass; monoisotopic mass; nominal mass; unified atomic mass unit.*

Atomic Mass Unit See *unified atomic mass unit.*

Average Mass The mass of an ion, atom, or molecule calculated using the masses of all isotopes of each element weighted for their natural isotopic abundance. See also related entries on: *accurate mass; dalton; molar mass; monoisotopic mass; nominal mass; unified atomic mass unit.*

Dalton (Da) A non-SI unit of mass (symbol Da) that is equal to the unified atomic mass unit. See also related entries on: *accurate mass; average mass; molar mass; molecular weight; monoisotopic mass; nominal mass; unified atomic mass unit.*

Daughter Ion See *product ion.*

Dimeric Ion An ion formed by ionization of a dimer or by the association of an ion with its neutral counterpart such as $[M_2]^{+\bullet}$ or $[M\text{-}H\text{-}M]^{+}$.

Electron Volt (eV) A non-SI unit of energy defined as the energy acquired by a particle containing one unit of charge through a potential difference of one volt, $1\ \text{eV} \approx 1.6 \cdot 10^{-19}$ J.

Extracted Ion Chromatogram A chromatogram created by plotting the intensity of the signal observed at a chosen m/z value or series of values in a series of mass spectra recorded as a function of retention time. See also related entry on: *total ion current chromatogram.*

Field Free Region Any region of a mass spectrometer where the ions are not dispersed by a magnetic or electric field.

Fragment Ion See *product ion.*

Ionization Efficiency Ratio of the number of ions formed to the number of atoms or molecules consumed in the ion source.

Isotope Dilution Mass Spectrometry (IDMS) A quantitative mass spectrometry technique in which an isotopically enriched compound is used as an internal standard. See Chapter 14 for a more detailed explanation.

Isotope Ratio Mass Spectrometry (IRMS) The measurement of the relative quantity of the different isotopes of an element in a material using a mass spectrometer.

m/z The three-character symbol m/z is used to denote the dimensionless quantity formed by dividing the mass of an ion in unified atomic mass units by its charge number (regardless of sign). The symbol is written in italicized lower case letters with no spaces. Note 1: The term mass-to-charge ratio is deprecated. Mass-to-charge ratio has been used for the abscissa of a mass spectrum, although the quantity measured is not the quotient of the ion's mass to its electric charge. The three-character symbol m/z is recommended for the dimensionless quantity that is the

independent variable in a mass spectrum. Note 2: The proposed unit thomson (Th) is deprecated [1].

Comment: Here the authors feel obliged to state that a mass analyzer *does* separate gas-phase ions according to their mass-to-charge ratio (m/q, see formulas below) and neither mass nor charge are dimensionless quantities. z, being the number of charges, is dimensionless, leading to the fact that the unit for m/z is u or Da. The SI unit for m/q is kilogram/coulomb (kg/C), but is not practical because of the actual numbers involved. Alternative units for m/q would be atomic units. Historically u/e has been used, where e equals the elementary charge. Unfortunately e is constant (the value of the charge of the proton and electron), not a unit—there is presently no accepted atomic unit for charge. Therefore such a unit has been suggested—millikan (Mi). A unit for m/q has also been suggested—thomson (Th), where Th = u/Mi or Da/Mi, all being atomic units. All this can seem like nit-picking, but it is very impractical not to have an accepted unit for the very thing we measure in mass spectrometry.

Time-of-flight	$t_{TOF} = \frac{L}{v} = L\sqrt{\frac{m}{2qU_a}}$
Magnetic sector	$\frac{m}{q} = \frac{B^2r^2}{2U_a}$
FTICR	$f_c = \frac{qB}{2\pi \cdot m}$

Mass See entries on: *accurate mass; average mass; dalton; molar mass; molecular weight; monoisotopic mass; nominal mass; unified atomic mass unit.*

Mass Accuracy Difference between measured and actual mass [3]. Can be expressed either in absolute or relative terms.

Mass Calibration (time-of-flight) A means of determining m/z values from their times of detection relative to initiation of acquisition of a mass spectrum. Most commonly this is accomplished using a computer-based data system and a calibration file obtained from a mass spectrum of a compound that produces ions whose m/z values are known.

Mass Defect Difference between exact and nominal mass [3].

"Mass" Limit The m/z value above or below which ions cannot be detected in a mass spectrometer.

Mass Number The sum of the protons and neutrons in an atom, molecule, or ion.

Mass Peak Width ($\Delta m_{50\%}$) The full width of a mass spectral peak at half-maximum peak height [3].

Mass Precision Root-mean-square (RMS) deviation in a large number of repeated measurements [3].

Mass Range The range of m/z over which a mass spectrometer can detect ions or is operated to record a mass spectrum.

Mass Resolution The smallest mass difference Δm (Δm in Da or $\Delta m/m$ in, e.g., ppm) between two equal magnitude peaks such that the valley between them is a specified fraction of the peak height [3].

Ten Percent Valley Definition

Let two peaks of equal height in a mass spectrum at masses m and m, Δm, be separated by a valley which at its lowest point is just 10% of the height of either peak. For similar peaks at a mass exceeding m, let the height of the valley at its lowest point be more (by any amount) than 10% of either peak. Then the "resolution" (10% valley definition) is $m/\Delta m$. The ratio $m/\Delta m$ should be given for a number of values of m [4].

Comment: This is a typical example of the confusion regarding the definition of the term resolution. Here resolution is used instead of the more appropriate phrase mass resolving power (which is the inverse of resolution).

Peak Width Definition

For a single peak made up of singly charged ions at mass m in a mass spectrum, the "resolution" may be expressed as $m/\Delta m$, where Δm is the width of the peak at a height that is a specified fraction of the maximum peak height. It is recommended that one of three values 50%, 5%, or 0.5% should always be used. (Note that for an isolated symmetrical peak recorded with a system that is linear in the range between 5% and 10% levels of the peak, the 5% peak width definition is equivalent to the 10% valley definition). A common standard is the definition of resolution based upon Δm being the full width of the peak at half its maximum (FWHM) height [4]. See Fig. 1.1 and also Chapter 5.

Comment: See comment for *Ten percent valley definition* above.

Mass Resolving Power ($m/\Delta m$) In a mass spectrum, the observed mass divided by the difference between two masses that can be separated, $m/\Delta m$. The method by which Δm was obtained and the mass at which the measurement was made should be reported.

Mass Spectrometer An instrument that measures the m/z values and relative abundances of ions. See also discussion in entry m/z.

Mass Spectrometry Branch of science that deals with all aspects of mass spectrometers and the results obtained with these instruments.

MS/MS The acquisition and study of the spectra of the electrically charged products or precursors of m/z selected ion or ions, or of precursor ions of a selected neutral mass loss. Also termed tandem mass spectrometry.

Comment: There are two different opinions of what MS/MS is an abbreviation of. One is mass spectrometry/mass spectrometry [1]. The other is mass selection/mass separation.

Mass Spectrum A plot of the detected intensities of ions as a function of their m/z values. See discussion in entry m/z.

Mass-to-Charge Ratio or Mass/Charge See discussion in entry m/z.

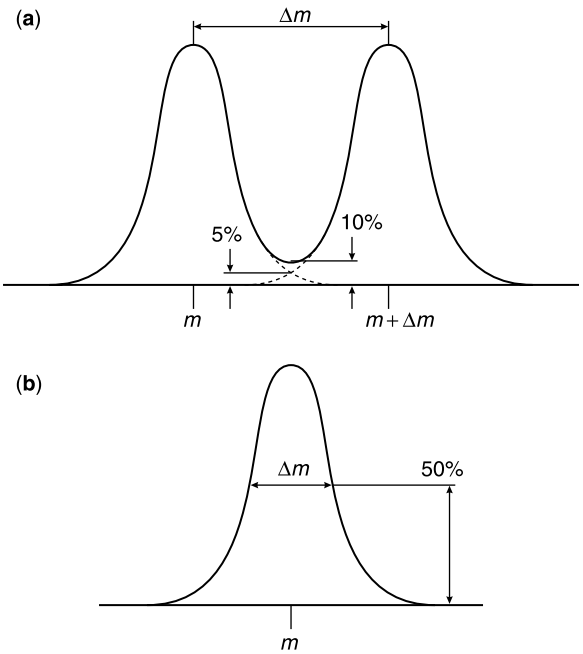

Figure 1.1. The two different ways of establishing mass resolution or mass resolving power. (a) The 10% valley definition. The peak separation Δm is defined as the distance between the centers of two peaks of equal height when the valley bottom between them is 10% of their height. If the peaks are symmetric this will also in theory correspond to the peak width at 5% peak height. This is a true peak separation definition but is usually problematic to establish because of the difficulty of finding two peaks of equal height properly separated in a mass spectrum. (b) The full width at half-maximum (FWHM) definition. Here the peak width Δm is determined at 50% of the peak height. This number is easy to obtain since just a clearly separated peak is required, but it is instead not directly addressing peak separation capability. For Gaussian peak shapes the FWHM definition will yield a mass resolving power number roughly twice that of the 10% valley definition.

Metastable Ion An ion that is formed with internal energy higher than the threshold for dissociation but with a lifetime long enough to allow it to exit the ion source and enter the mass spectrometer where it dissociates before detection.

Molar Mass Mass of one mole ($\approx 6 \cdot 10^{23}$ atoms or molecules) of a compound. Note: The use of the term molecular weight is urged against because "weight" is the gravitational force on an object, which varies with geographical location. Historically the term has been used to denote the molar mass calculated using isotope-averaged atomic masses for the constituent elements.

Molecular Ion An ion formed by the removal of one or more electrons to form a positive ion or the addition of one or more electrons to form a negative ion.

Molecular Weight See *molar mass.*

Monoisotopic Mass Exact mass of an ion or molecule calculated using the mass of the most abundant isotope of each element [1]. This recommendation refers to a somewhat unfortunate statement by Yergey et al. [5], who have contributed with an otherwise enlightening paper on the subject. In the paper, only elements for which their most abundant isotopes are also their lightest, are considered. The practical problem arises when this is not the case (e.g., for Fe or B). Here the authors instead prefer the definition "the mass of an ion or molecule calculated using the mass of the lightest isotope of each element." For molecules containing the most common elements, such as C, H, N, O, S where the lightest isotope also is the most abundant the two suggested definitions give the same end result, but this is not the case for B, Fe, and many other elements. Cytochrome c includes one Fe; with the definition that the monoisotopic peak is the one containing only the most abundant isotopes of the elements, the result is that one of the isobars of the second isotopic peak would be the monoisotopic. The second isotopic peak also includes the isobars of one ^{2}H, or one ^{13}C, or one ^{15}N, or one ^{17}O, or one ^{33}S, in sum there are six isobars of which only one is the true monoisotopic peak. With the "lightest isotope" definition, the first isotopic peak does not have isobars and is therefore well defined.

Multiple Reaction Monitoring (MRM) See *selected reaction monitoring.*

Multiple-Stage Mass Spectrometry (MS^n) Multiple stages of precursor ion m/z selection followed by product ion detection for successive progeny ions.

Neutral Loss Loss of an uncharged species from an ion during either a rearrangement process or direct dissociation.

Nominal Mass Mass of an ion or molecule calculated using the mass of the most abundant isotope of each element rounded to the nearest integer value and equivalent to the sum of the mass numbers of all constituent atoms [1].

Example: The nominal mass of an ion is calculated by adding the integer masses of the lightest isotopes of all elements contributing to the molecule, for example, the nominal mass of H_2O is $(2 \cdot 1) + 16$ Da $= 18$ Da.

Comment: The same problem as for monoisotopic mass immediately arises for compounds containing elements such as Fe or B. See discussion in entry *monoisotopic mass*.

Peak A localized region of a visible ion signal in a mass spectrum. Although peaks are often associated with particular ions, the terms peak and ion should not be used interchangeably.

Peak Intensity The height or area of a peak in a mass spectrum.

A word of caution from the authors: The peak height and peak area are not interchangeable quantities. Consider for example how the height-to-area relationship depends on the resolving power of the mass analyzer or the response time of the detector.

Precursor Ion Ion that reacts to form particular product ions. The reaction can be unimolecular dissociation, ion/molecule reaction, isomerization, or change in charge state. The term parent ion is deprecated (but still very much in use).

Product Ion An ion formed as the product of a reaction involving a particular precursor ion. The reaction can be unimolecular dissociation to form fragment ions, an ion/molecule reaction, or simply involve a change in the number of charges. The terms fragment ion and daughter ion are deprecated (but still very much in use).

Progeny Ions Charged products of a series of consecutive reactions that includes product ions, first generation product ions, second generation product ions, etc.

Protonated Molecule An ion formed by interaction of a molecule with a proton, and represented by the symbol $[M+H]^+$. The term protonated molecular ion is deprecated; this would correspond to a species carrying two charges. The terms pseudo-molecular ion and quasi-molecular ion are deprecated; a specific term such as protonated molecule, or a chemical description such as $[M+Na]^+$, $[M-H]^-$, etc., should be used [1].

Selected Ion Monitoring (SIM) Operation of a mass spectrometer in which the abundances of one or several ions of specific m/z values are recorded rather than the entire mass spectrum.

Selected Reaction Monitoring (SRM) Data acquired from specific product ions corresponding to m/z selected precursor ions recorded via two or more stages of mass spectrometry. Selected reaction monitoring can be preformed as tandem mass spectrometry in time or tandem mass spectrometry in space. The term multiple reaction monitoring is deprecated [1].

Space-Charge Effect Result of mutual repulsion of particles of like charge that limits the current in a charged-particle beam or packet and causes some ion motion in addition to that caused by external fields.

Tandem Mass Spectrometry See MS/MS.

Thomson (Th) See discussion in entry m/z.

Torr Non-SI unit for pressure, 1 torr = 1 mmHg = 1.33322 mbar = 133.322 Pa.

Total Ion Current (TIC) Sum of all the separate ion currents carried by the different ions contributing to a mass spectrum.

Total Ion Current Chromatogram Chromatogram obtained by plotting the total ion current detected in each of a series of mass spectra recorded as a function of retention time. See related entry on *extracted ion chromatogram.*

Transmission The ratio of the number of ions leaving a region of a mass spectrometer to the number entering that region.

Unified Atomic Mass Unit (u) A non-SI unit of mass defined as one twelfth of the mass of one atom of ^{12}C in its ground state and $\approx 1.66 \times 10^{-27}$ kg. The term atomic mass unit (amu) is not recommended to use since it is ambiguous. It has been used to denote atomic masses measured relative to a single atom of ^{16}O, or to the isotope-averaged mass of an oxygen atom, or to a single atom of ^{12}C.

Abbreviations and Units

2-DGE	two-dimensional gel electrophoresis
a	atto, 10^{-18}
AC	alternating current
AMS	accelerator mass spectrometry
APCI	atmospheric pressure chemical ionization
API	atmospheric pressure ionization
AP-MALDI	atmospheric pressure matrix-assisted laser desorption/ionization
APPI	atmospheric pressure photoionization
ASAP	atmospheric-pressure solids analysis probe
BIRD	blackbody infrared radiative dissociation
c	centi, 10^{-2}
CAD	collision-activated dissociation
CE	capillary electrophoresis
CF	continuous flow
CF-FAB	continuous flow fast atom bombardment
CI	chemical ionization
CID	collision-induced dissociation
cw	continuous wave
CZE	capillary zone electrophoresis
Da	dalton
DAPCI	desorption atmospheric pressure chemical ionization
DART	direct analysis in real time
DC	direct current
DE	delayed extraction
DESI	desorption electrospray ionization
DIOS	desorption/ionization on silicon
DTIMS	drift tube ion mobility spectrometry
EC	electrochromatography
ECD	electron capture dissociation
EI	electron ionization
ELDI	electrospray-assisted laser desorption/ionization
EM	electron multiplier
ESI	electrospray ionization
ETD	electron transfer dissociation
eV	electron volt
f	femto, 10^{-15}
FAB	fast atom bombardment
FAIMS	field asymmetric waveform ion mobility spectrometry
FD	field desorption
FI	field ionization
FT	Fourier transform
FTICR	Fourier transform ion cyclotron resonance

FWHM	full width at half maximum
GC	gas chromatography
GD	glow discharge
GE	gel electrophoresis
GLC	gas-liquid chromatography
GPC	gel permeation chromatography
GSC	gas-solid chromatography
HIC	hydrophobic interaction chromatography
HPLC	high performance liquid chromatography
ICP	inductively coupled plasma
ICR	ion cyclotron resonance
IEC	ion-exchange chromatography
IEF	isoelectric focusing
IMS	ion mobility spectrometry
IR	infrared
IRMPD	infrared multiphoton dissociation
ITP	isotachophoresis
k	kilo, 10^3
LA	laser ablation
LC	liquid chromatography
LDI	laser desorption/ionization
LMIG	liquid metal ion gun
l-QIT	linear quadrupole ion trap
LSIMS	liquid secondary ion mass spectrometry
m	milli, 10^{-3}
m/z	mass-to-charge ratio
μ	micro, 10^{-6}
M	mega, 10^6
MALDESI	matrix-assisted laser desorption electrospray ionization
MALDI	matrix-assisted laser desorption/ionization
MCP	microchannel plate
MECA	multiple excitation collisional activation
MEKC	micellar electrokinetic chromatography
MIKES	mass-analyzed ion kinetic energy spectrometry
MPI	multiphoton ionization
MRM	multireaction monitoring
MS	mass spectrometry
MS/MS	mass selection/mass separation or mass spectrometry/mass spectrometry
MS^n	MS/MS of higher generations
n	nano, 10^{-9}
NSD	nozzle-skimmer dissociation
NPC	normal-phase chromatography
oa	orthogonal acceleration

p	pico, 10^{-12}
PD	plasma desorption; photodissociation
pI	isoelectric point
PI	photoionization
PLOT	porous layer open tubular
ppb	part per billion, 10^{-9}
ppm	part per million, 10^{-6}
ppt	part per trillion, 10^{-12}
PSD	post-source decay
q	quadrupole (or hexapole/octapole) used as collision chamber
Q	quadrupole, quadrupole filter
QIT	quadrupole ion trap (Paul trap)
QqQ	triple quadrupole
Qq-TOF	quadrupole–time-of-flight
REMPI	resonance-enhanced multiphoton ionization
RF	radio frequency, here used instead of AC (alternating current) to imply a high frequency
RI	resonance ionization
RPC	reversed-phase chromatography
RTOF	reflector time-of-flight
SDS	sodium dodecyl sulfate
SEC	size exclusion chromatography
SELDI	surface-enhanced laser desorption/ionization
SEM	scanning electron microscopy
SFC	supercritical fluid chromatography
SID	surface-induced dissociation
SIMS	secondary ion mass spectrometry
SNMS	secondary neutral mass spectrometry
SORI	sustained off-resonance irradiation
SRM	selected reaction monitoring
SS	spark source
SSD	solid state detector
STJ	superconducting tunnel junction
SWIFT	stored waveform inverse Fourier transform
TDC	time-to-digital converter
TI	thermal ionization
TOF	time-of-flight
TOF-TOF	tandem time-of-flight
TSI	thermospray ionization
UPLC	ultra performance liquid chromatography
UV	ultraviolet
VLE	very low-energy
WCOT	wall coated open tubular
z	zepto, 10^{-21}
ZE	zone electrophoresis