

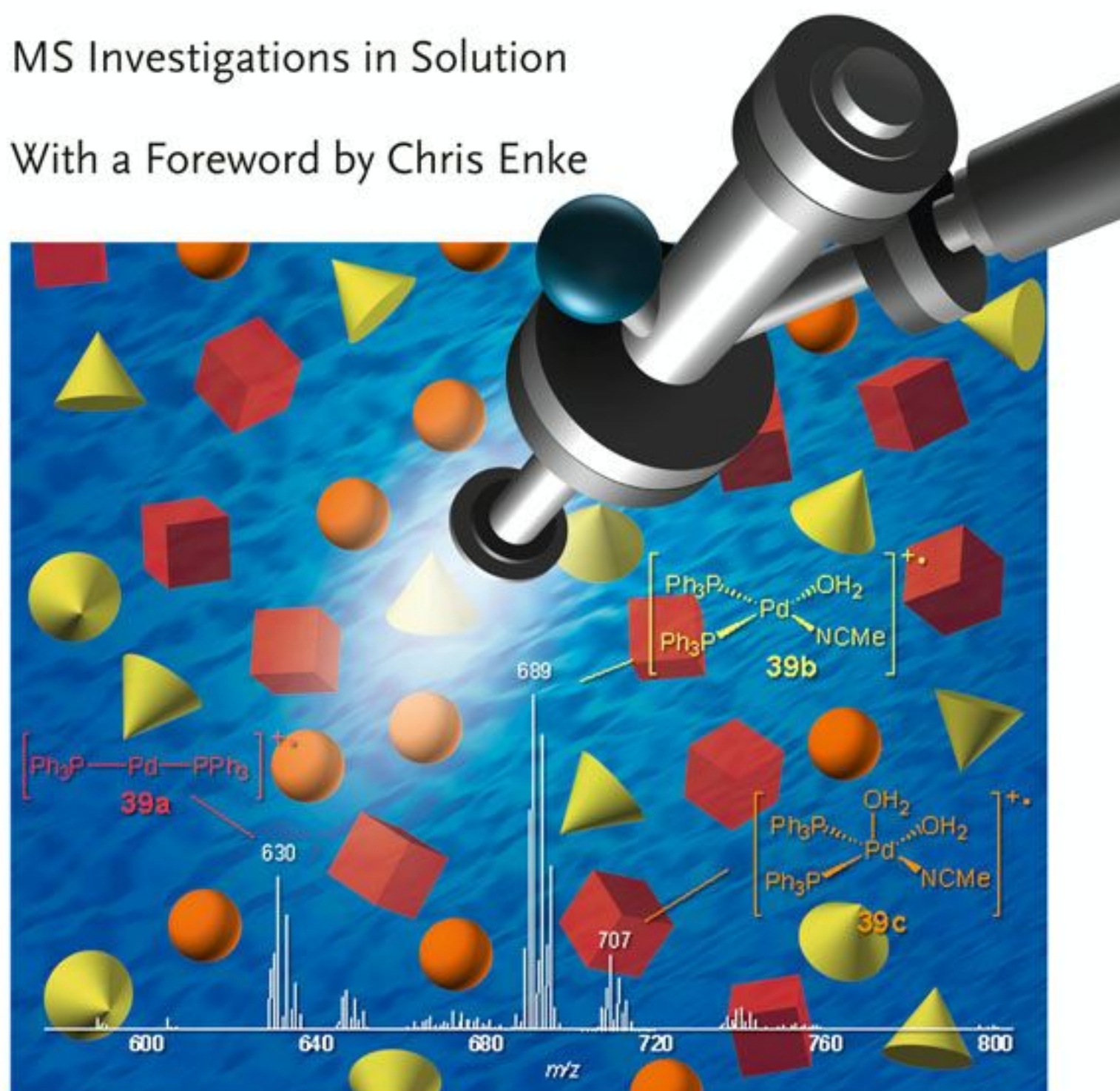
Edited by Leonardo S. Santos

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Reactive Intermediates

MS Investigations in Solution

With a Foreword by Chris Enke



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*To Gisa, Guilherme and Larissa
whose patience and love enable them
to hold out the hours of homework
and the moments of my absence*

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Foreword

Mass spectrometry could be described, without implying any criticism, as an example of work in progress. Each time it appears to be approaching 'maturity,' another breakthrough occurs to expand its usefulness in new areas of science. As this volume clearly demonstrates, that process is still going on. In the early twentieth century, mass spectrometry was principally a tool for physicists to study particles and petroleum chemists to characterize petroleum mixtures. Wider use by chemists began with the ability to obtain structural information from the spectra of pure organic molecules. The analytical application of mass spectrometry truly came of age with its use as a detector for gas chromatography. Indeed, up to the present, advances in chromatography and mass spectrometry have leapfrogged each other, combining to create analytical tools that have steadily advanced in selectivity and detection limit for over two decades. The power of these tools is such that they have found critical applications in virtually every area of science, engineering, and medicine.

From the standpoint of mass spectrometric instrumentation, the story of this evolution has taken place on four fronts:

- (1) Methods of separating ions of different atomic or molecular masses
- (2) Methods of obtaining more chemical information by tandem mass spectrometry
- (3) Methods of ionizing analyte molecules
- (4) Methods that improve sensitivity and throughput.

Spectacular advances in all four of these areas have facilitated the remarkable expansion of mass spectrometry in diverse areas, including the subject of this volume. Sometimes new applications are introduced by mass spectrometrists recognizing an area of opportunity and sometimes by researchers in that area who have the temerity and opportunity to try a new technique. In any case, mass spectrometry has become a central tool in scientific investigation, and facilities for its use have become a critical part of virtually all scientific research organizations.

Mass Analyzers

Most analytical methods use a bulk property to distinguish, separate, or identify an analyte. Properties such as chemical reactivity, chromatographic retention time, and optical absorbance or emission reveal information about an aggregate of analyte molecules, giving a collective response value. A remarkable thing about a mass spectrum, and one of the unique attributes of mass spectrometry, is that the analyte molecules or atoms are separated by mass, and the detector records the mass of each individual analyte molecule. The isotopic composition of the analyte is revealed as are mass shifts due to modifications of very large molecules, even when only a fraction of them have been modified.

To perform a separation of sample molecules or atoms according to their individual masses, all mass spectrometers rely on the fact that the trajectory of a charged particle in the presence of electric and magnetic fields is mass-dependent, or, more exactly, dependent on the mass-to-charge ratio (m/z) of the particle. To avoid distortion of the differentiating trajectory by collisions with molecules, this separation must be carried out in a vacuum, though, as we shall see, sometimes such collisions can be used to advantage.

Chapter 1 in this volume reviews the historical development of mass spectrometers in some detail. I will here introduce the general concepts of mass separation in the context of some seminal developments in the instrumentation. Ions accelerated to a nearly constant kinetic energy ($1/2 mv^2$) will, in a region with uniform magnetic field, have a curved trajectory dependent on the ion momentum. Magnetic sector mass spectrometers, based on this principle, held a dominant position for many years. The addition of an electric sector greatly improved the mass resolution, and these 'double-focusing' mass spectrometers were the gold standard into the 1990s. Obtaining mass resolutions in the tens of thousands enabled the development of 'exact mass' determination, whereby the amount of the mass defect in the elements could be used to determine the chemical formula of an analyte based on the measurement of the ion m/z to within some few parts per million. The champion, however, for mass resolution has been the Fourier transform ion cyclotron resonance (FTICR) mass spectrometer introduced by Marshall and Comisarow in 1974. Ions in a very high magnetic field move in a circle on a plane orthogonal to the magnetic field flux. The frequency of their rotation is a function of their m/z value. A batch of ions is excited to rotation and the resulting signal is analyzed by Fourier Transform to obtain the frequencies and thus the m/z 's of the ions in the batch. Mass accuracies in small fractions of parts per million have been achieved.

Though mass analysis based on ion flight time was an early innovation, the lack of good high-speed electronics and its poor mass resolution prevented its wide adoption. What did bring mass spectrometry into the main stream of chemical analysis was the development of the quadrupole mass spectrometer. This simple device provided unit resolution mass spectra in a relatively compact, low-cost format. The partnership of the quadrupole mass analyzer with gas chromatography resulted in a powerful analytical tool that continues to see wide use in a variety

of areas. Wolfgang Paul, who invented the familiar quadrupole with four rods and an RF generator, also developed a circular variation called the ion trap, composed of a ring electrode and two end cap electrodes. The conversion of the ion trap into a mass spectrometer involved Stafford's invention of the means of scanning the stored ions out of the trap in order of their m/z values after first reducing their kinetic energies by the introduction of helium gas at low pressure to act as a cooling collision partner.

Meanwhile, three developments brought time-of-flight mass spectrometry back into contention. The first was the high-speed signal analysis available with solid-state electronics, and the second was the ion mirror introduced by Mamyrin, which improved the mass resolution by focusing ions that had been spatially dispersed at the time of ion acceleration along the flight tube. In 1989, Dawson and Gilhaus reduced the initial ion kinetic energy dispersion by forming a low-energy beam of ions from the source so that their main kinetic energy was along the axis of the beam. A section of the beam was then accelerated orthogonally to the beam axis for the measurement of flight time. Time-of-flight instruments that combine the ion mirror with orthogonal acceleration have achieved resolutions in the tens of thousands – sufficient for exact mass measurements.

An important distinction among methods of mass analysis is whether they operate in continuous or batch mode. In the continuous mode, ions are continuously being generated, sorted, and detected. Magnetic sector and most linear quadrupole mass analyzers are in the continuous category. If a single detector is used with a continuous method, the mass analyzer is acting as a mass filter, passing only a narrow range of m/z values at each time. To obtain a mass spectrum, the mass filter is scanned across the range of m/z values of interest. At any time, ions outside the immediate range are lost. Batch instruments, on the other hand, perform their mass analysis on sets or batches of ions. Ions from continuous ion sources must therefore be 'bunched' for batch analysis. On the other hand, discontinuous methods of ion generation are well matched to batch instruments. Time-of-flight, FTICR, and ion trap instruments are of the batch type. A mass spectrum is generated from each batch analysis, so that all ions over a wide m/z range in each batch are detected. Among batch instruments, the time required to analyze each batch sets the maximum spectral generation rate. Time-of-flight instruments can generate thousands of spectra per second, while ion trap instruments begin to lose resolution at spectral generation rates above a few per second. Higher spectral generation rates are, of course, useful when following the output of a fast chromatographic separation or the rate of a rapid reaction.

Progress in mass analyzer instrumentation continues on two fronts, evolutionary and revolutionary. Instruments of the classic types discussed above are improving in efficiency, simplicity, portability, and user friendliness with every 'new model' cycle. Revolutionary changes have included Makarov's orbitrap mass analyzer which achieves near FTICR resolutions using only RF fields in a unique design. The linear quadrupole has now been implemented as a linear ion trap by Welling where ions can be bunched, cooled, fragmented, or reacted with background gas, prior to or between stages of mass analysis.

Mixture Composition and Molecular Structure by Mass Spectrometry

Arguably one of the most significant advances in adding analytical power to mass spectrometry was the development of tandem mass spectrometry, or the application of two or more sequential stages of mass analysis. Obviously, no new information is obtained by repeating a mass analysis unless some reaction which changes the analyte ion's mass or charge occurs between the stages of mass analysis. Knowing the m/z of the ion prior to the reaction (the precursor ion) and then knowing the m/z 's of the product ions can give important clues to the structure of the precursor ions as well as the process by which the product ions are formed. This possibility was first noticed by the observation of metastable ions that fragmented between the electric and magnetic sectors of a double-focusing mass spectrometer. Such fragmentations caused spurious peaks in the mass spectrum. Once their origin was explained, the phenomenon was used to study the ion fragmentation process. However, the intentional production and mass analysis of fragment ions for analytical applications began in 1976 with Cooks, who used a magnetic sector to select the precursor ion m/z , intentional collision with neutral gas target molecules to induce ion fragmentation, and an electric sector to sort out the product ions. In these sector-based tandem instruments, the mass resolution of the electric sector was low. Very high collision energies were required to achieve even relatively poor fragmentation efficiencies. Therefore, it was a surprise to many when, in 1978, Yost, Morrison, and I discovered high ion fragmentation efficiencies at low collision energies in a linear, non-mass-selective quadrupole. Our goal had been to obtain fragmentation between two quadrupole mass spectrometers for analysis by separation and identification. The triple-quadrupole, as it became known, brought tandem mass spectrometry (now called MS/MS) into the mainstream of analytical instruments because of its simplicity, high fragmentation efficiency, and unit mass resolution for both precursor selection and product analysis. In current nomenclature, this is now called a QqQ instrument, where the lower case q represents the linear quadrupole collision cell.

In the wake of the introduction of the triple-quadrupole instrument, both mixture analysis and structure determination applications of MS/MS were pursued simultaneously. For mixture analysis, it was desirable to use 'soft' ionization so that each analyte in the mixture represented only one m/z value. When this value was selected with the first mass analyzer and fragmented, its product m/z pattern could be mined for identification information much as a primary mass spectrum had been previously. Clearly this could be done for each component of the mixture in turn. At first, this appeared to allow the first mass analyzer to take the place of prior chromatographic separation, but it quickly became clear that MS/MS was an even more powerful chromatographic detector than MS, providing greater selectivity and more information for identification. Investigators were intrigued by this new concept. If MS/MS was good, would MS/MS/MS be better? Pentaquadrupole (QqQqQ), dual double-focusing (BEqBE), and many other configurations were constructed during this phase of tandem MS exploration. Another aspect explored was the scan modes other than the one that produces the product spectrum. Scanning the first

mass analyzer produces a spectrum of all the precursor m/z s that can produce the product m/z to which the second mass analyzer is set. This is called a precursor scan and is useful for the identification of all species in the sample which produce a particular ionic fragment. Scanning both mass analyzers with the second lagging behind the first by a constant m/z gives a spectrum of all the precursor ions that produce a neutral fragment of the set mass difference. The precursor and neutral loss scans are powerful analytical tools as was well demonstrated at the time. As we shall see, later tandem instrument designs produce product ion scans more efficiently than the QqQ instruments. Precursor and neutral loss scan information is available, but only with additional experiment time and extra data processing. As a result, these alternative scans are now too often overlooked. They could be especially useful in the study of gas phase reactions occurring in the collision chambers of tandem instruments.

If chromatographic sample introduction is used with soft ionization and MS/MS, the precursor mass spectrometer must be tuned to pass the precursor ion for the eluting analyte. If the peak contains just one component, the chromatography and the precursor mass analyzer are redundant. This can be alleviated by using collisional fragmentation before the first mass analyzer to obtain structural information for each eluant or by choosing a characteristic fragment ion to increase selectivity. If the chromatogram is relatively crowded with peaks, it is very likely that the peak is not just a single component, but rather contains a number of minor components. These can be discovered and analyzed using the first mass analyzer to exclude the major component.

A normal mass spectrum using a hard ionization source already contains many fragment ion m/z values. In fact, it may not contain the molecular ion at all. MS/MS can be used to further fragment each of the primary fragments to further characterize the molecule, fragment by fragment and also to determine which fragments arise from which larger fragments. If the product analyzer has exact mass capabilities, this method of structural analysis is all the more powerful.

Methods of Ion Formation

We know that ionization methods are either hard, producing fragments of the ionized molecules, or soft, producing principally positively charged ions by the addition of a proton or other cation, or negatively charged ions by the abstraction of a proton or the addition of an anion to the analyte molecule. They are also categorized by being vacuum or atmospheric. Vacuum techniques work well with volatile components, as with the electron impact ionization sources used with gas chromatographic or membrane inlet systems. Ionization can be from the electron impact directly (EI, a hard ionization technique) or from reaction with a reagent ion such as CH_5^+ that was created by electron impact with a reagent gas molecule (chemical ionization, a soft ionization technique). A nonvolatile sample subjected to heating generally decomposes rather than evaporates unless the heating is performed very rapidly. In general, the more rapid the heating, the less decomposi-