

MILESTONE 7

Breaking down problems

At its simplest, mass spectrometry gives information about the atomic or molecular weight of an element or compound. Initial applications of mass spectrometry focused on confirming the weight of a known compound or analyzing elemental samples. The next step was its use in determining molecular structures.

In the 1950s, there was a pressing need for such techniques. NMR spectroscopy was in its infancy, with commercial machines only beginning to emerge. Elemental analysis could confirm the composition of a sample, but it did not help with bond connectivity. Crystallography only worked for molecules that form single crystals.

It was in this climate that scientists began to use mass spectra as a means to reveal all, or part, of a molecule's structure. Some methods for small-molecule structure determination were straightforward; the simplest was to compare the molecule's spectrum with known reference spectra. By this time, laboratories at Dow Chemical, for example, had encoded reference spectra for thousands of compounds onto IBM punched cards. These could be compared rapidly with the significant peaks of an unknown sample, thus allowing automated matches to be made in many cases.

Even when reference spectra were not available, scientists learned how to extract increasingly greater amounts of information from spectral peaks, through a combination of empirical evidence and chemical intuition. Fred McLafferty, John Beynon and others examined many spectra, which led to a number of general observations. For example, they determined that when carbon-carbon double bonds are present, including in aromatic rings, cleavage occurs typically at the β -position. Molecules with carbonyls fragment at the position α to the double bond. Saturated rings fragment

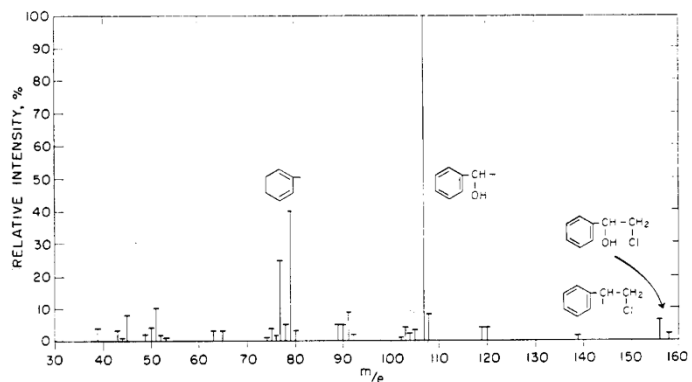
The mass spectrum of styrene chlorohydrin, as reported by McLafferty. Reprinted with permission from McLafferty, F.W., Mass spectrometric analysis broad applicability to chemical research, *Anal. Chem.* **28**, 306-316 (1956).

adjacent to the ring.

Applied together, these rules could distinguish

between closely related isomers. As an example, McLafferty examined styrene chlorohydrin, which has two possible isomers depending on the location of the hydroxyl and chlorine substituents. Employing the general rule that major bond breakage occurs β to a benzene ring, he could predict the main characteristics of the molecules' expected spectra: 2-chloro-2-phenylethanol should generate large peaks corresponding to $\text{PhCHCH}_2\text{OH}^+$ (loss of chloro) and PhCHCl^+ (loss of CH_2OH). 2-Chloro-1-phenylethanol, in contrast, should result in peaks for $\text{PhCHCH}_2\text{Cl}^+$ and PhCHOH^+ , also from β -bond cleavage. McLafferty observed the latter scenario and was able to assign the structural isomer confidently.

Mass spectra offer insight beyond structural assignments and have been employed to monitor gas-phase reactions of ions. Ionization techniques produce reactive gas-phase species within a mass spectrometer, and the products that arise from collisions can subsequently be monitored by the instrument's detector. F.H. Field, J.L. Franklin and F.W. Lampe were instrumental in developing this field, starting in the mid-1950s. They studied the secondary ions formed through gas-phase



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collisions, allowing reaction rates and rate constants to be estimated.

The structural information that could be deduced from mass spectra continued to increase. Carl Djerassi was instrumental in applying mass spectrometry analysis to natural products. In 1963, he and his co-workers performed a systematic study of fragmentation patterns in pentacyclic triterpenes, describing fragmentation behaviors and enabling unknown substances to be assigned to a particular subclass. Key ion fragments and the reactions that gave rise to them could be deduced. Even stereochemistry at carbon bridges could be determined—a powerful demonstration of how much these techniques had progressed, and foreshadowing their continued use today.

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ORIGINAL RESEARCH PAPERS McLafferty, F.W. Mass spectrometric analysis broad applicability to chemical research. *Anal. Chem.* **28**, 306-316 (1956) | Beynon, J.H. The use of the mass spectrometer for the identification of organic compounds. *Microchimica Acta* **44**, 437-453 (1956) | Field, F.H., Franklin, J.L. & Lampe, F.W. Reactions of gaseous ions. I. Methane and ethylene. *J. Am. Chem. Soc.* **79**, 2419-2429 (1957) | Budzikiewicz, H., Wilson, J.M. & Djerassi, C. Mass spectrometry in structural and stereochemical problems. XXXII. Pentacyclic triterpenes. *J. Am. Chem. Soc.* **85**, 3688-3699 (1963)