

## MILESTONE 13

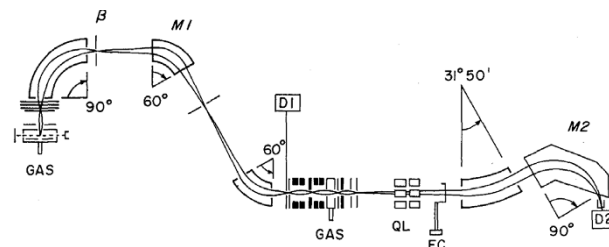
## Forming fragments

The 1960s were a productive time for the pioneers of mass spectrometry. New methods of ionizing molecules were under development, and technical advancements in the preceding decade had improved the accuracy of mass spectrometers. Yet, although the technique could identify the mass-to-charge ratios and relative abundances of ionized molecules, it could not provide any information about the relative arrangement of atoms within them.

In 1966, Jean Futrell and C.D. Miller reported a mass spectrometer design that would ultimately lead to the analysis of ions by means of collision-induced dissociation tandem mass spectrometry. That was not, however, their aim at the time. Instead, Futrell and Miller wanted to study the interaction of charged ions with neutral molecules. To do this, they developed a setup that used a spectrometer as an ion gun to direct the ion into a collision chamber containing a neutral gas; the effects of the interactions between the ion and the gas could then be detected using a second spectrometer. This arrangement—two spectrometers separated by a collision chamber—became the standard for collision-induced dissociation tandem mass spectrometry (MS/MS).

Despite the innovative nature of their setup, Futrell and Miller did not use it to determine any new structural information about the parent ion. This would require another breakthrough later in the same year, when T.W. Shannon and Fred McLafferty showed that ions with the chemical formula  $C_2H_5O^+$  can be classified into different groups on the basis of the spectra that arise from the decomposition of a 'metastable peak'. This type of peak represents ions with lifetimes that are shorter than the time required for them to travel between the ionization source and the

A schematic of the tandem mass spectrometer developed by Futrell and Miller. Reprinted with permission from Futrell, J.H. & Miller, C.D., Tandem mass spectrometer for study of ion-molecule reactions, *Rev. Sci. Instrum.* **37**, 1521 (1966).



detector. The decomposition of different structural isomers of  $C_2H_5O^+$  ions produces characteristic fragmentation patterns; therefore, these patterns provide structural information about the metastable parent ion. This approach—selecting a specific ion from the mixture formed and then analyzing the spectra that are generated through fragmentation—is the basic premise of MS/MS. However, Shannon and McLafferty relied on the parent ion generating a metastable peak that would decompose quickly inside the mass spectrometer—which is rarely the case.

Keith Jennings ablated the need for a metastable peak in 1968. Although he used a setup that differed from Futrell's and Miller's, it relied on a similar concept: colliding stable molecular ions with a gas introduced into the spectrometer. He showed that it was possible to record a 'collision-induced mass spectrum', in which a collision produces ions that are fragments of the parent ion, which can then be detected. This meant that a metastable peak was no longer necessary. Furthermore, the decomposition of an ion that gives rise to a metastable peak is highly dependent on the parent ion's internal energy. In contrast, collision-induced dissociations give rise to spectra that are independent of the energy of the parent ion, thereby simplifying its identification.

Collectively, these papers showed that a mass spectrometer could be used to select a species of ion, collide it with a neutral molecule to break it into fragments and then analyze it in a second mass spectrometer. Crucially, the work also showed that the fragment ions could be used to infer information about the structure of the parent ion—information not available from the parent ion's spectra. These concepts enabled the development of collision-induced dissociation, and the alternative fragmentation methods that subsequently followed, into powerful, highly sensitive techniques for detecting analytes and determining their molecular structure.

Russell Johnson, Associate Editor, Nature Chemistry

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