Mass spectrometry across the sciences

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Mass is a fundamental yet easily understood characteristic of a chemical species. For many analytical problems, mass is also highly specific. J. J. Thomson's 1912 mass spectrum of neon showed isotopes of masses 20 and 22 in a 10:1 ratio, explaining its apparently anomalous atomic weight of 20.2 (1). Mass spectrometry (MS) then became important for such fundamental data of elements and for isotopic analysis, such as $^{235}U/^{238}U$ in the nuclear weapons program. Also critical in World War II, MS replaced laborious analytical distillations of light hydrocarbon gases, such as butadiene feedstocks for the synthetic rubber program. Gaseous ions are required for mass separation; ionization of a molecule such as butane, C_4H_{10}, causes bond dissociation into many fragments (CH_3, C_2H_5, C_3H_7, etc.), so that their masses and relative abundances provide multiple characteristics for both specificity and quantitation (2). Furthermore, ion detectors give unusual sensitivity and recording speed. Complex mixture analysis became routine by coupling MS online to gas and liquid chromatography, with computer automation providing far more information far faster. Additional molecular specificity became possible with "MS/MS," in which additional mass spectra are obtained from the molecule's fragment ions or from the individual molecular ions of a mixture mass spectrum (3).

In the last two decades, these molecular MS capabilities have been dramatically extended by the development of methods such as laser desorption (4) and electrospray ionization (ESI) (5) to ionize and introduce nonvolatile molecules into the mass spectrometer. It became possible to obtain mass spectra of proteins, DNA/RNA, carbohydrates, lipids, polymers, etc., with their increased data complexity offset by dramatic instrument improvements in resolving power and mass accuracy. This has led to diverse MS methodology for research and analysis, with unique capabilities of specificity, sensitivity, speed, sampling, and automated computer data acquisition/reduction.

This special issue attempts to illustrate the breadth and uniqueness of applications of molecular MS to a variety of scientific fields with current examples. The specificity of MS is shown dramatically by the characterization of petroleum, a notoriously complex mixture (6). Although valued for its ≈90% hydrocarbon content, its compounds containing the elements N, O, and S are a serious problem for poisoned catalysts, corrosion, pollution, etc. High resolving-power (>400,000) MS has identified >60,000 isotopic compositions $^{12}C_c^{1}H_h^{14}N_n^{16}O_o^{32}S_s$ based on the packing-fraction differences (variation from unit mass) of these five isotopes. Using the high sensitivity of MS, unexpected hydrocarbons have been reported in extraterrestrial samples (7). However, a new two-step laser technique applicable to captured 81P/Wild 2 cometary particles shows that impact heating can produce artifactual organic compounds along particle capture tracks in aerogel. Application of this technique to other carbonaceous samples suggests that the unexpected fullerenes found recently can be artifacts of laser heating.

Details of the transition from condensed phase to gas phase can be inferred from gaseous clusters by observing the change in their MS spectra with increase in the number of their monomer or solvent units; a sufficiently high number of units can simulate bulk properties (8). The hydrated electron, a powerful reductant basic to fields from radiation chemistry to biology, is studied in electrosprayed clusters of multivalent metal ions with an increasing number of H_2O molecules; the electron capture energy can be measured by the extent of H_2O loss. Some metal ions in H_2O clusters suffer charge reduction, whereas others show different types of electron and ion solvation. Bulk W_nO_{3n} catalyzes the oxidation of propene to propene oxide and CO to CO_2 (9). In this reaction, gaseous $W_nO_{3n}^+$ species of selected n values exhibit enhanced activity and selectivity, indicating a radical oxygen center (W-O•) mechanism. Related MS studies investigate gaseous ion reactions to activate methane for conversion to more useful products such as methanol (10). Reaction mechanisms inferred from $C(H,D)_4$ isotope effects differ widely with variation of transition metal reactants and their ligands, suggesting strategies for the further improvement of technical processes.

Recent MS techniques directly image biomedically-important molecules in tissue samples, illustrating the complementarity of ESI and laser desorption for transferring a wide variety of molecules into the mass spectrometer. A solvent electrosprayed onto an object in open air can desorb molecules directly for MS, such as insecticides on fruit or drugs on currency (11). For a tissue sample, this can provide the spatial distribution of a specific drug or metabolite. Matrix-assisted laser desorption/ionization (MALDI) is used to map specific proteins in brain tissue and human breast carcinoma, with four truncated forms of the β-amyloid protein also found directly in Alzheimer's plaques (12). MALDI MS imaging has been applied to human biopsies in collaboration with pathologists in studies aimed at developing improved diagnoses and treatment efficacy assessments, vital issues in the growing area of personalized medicine.

Such analysis and characterization of peptides and proteins ("proteomics") (13) has been the fastest expanding area, by far, that has resulted from methods for introducing nonvolatiles into the mass spectrometer (4, 5). A critical review of advancing MS capabilities for large-scale analyses of the protein complement of cells, tissues, and body fluids comes from two leading research laboratories. A strong case is made that MS proteomics has now reached a new level of accuracy and efficiency using far more sophisticated instrumentation with online liquid chromatographic separation of complex mixtures, subsecond spectral measurement of unusual mass accuracy (parts per million) and resolving power ($>10^5$), and efficient computer automation for reduction and interpretation of the results.

Protein characterization by ESI/MS has been extended even to megadalton protein complexes (14). Despite its size and 13 subunits, ESI of the 800-kDa eukaryotic translation factor eIF3 yields intact molecular ions. Mass spectra of its dissociation products show that it contains three relatively stable modules, whose interactions are defined by 27 subcomplexes. For many other proteins, however, the native solution conformation is not retained in the gas phase (15). A variety of recent evidence shows that folding, unfolding, and refolding of

Author contributions: F.W.M. analyzed data and wrote the paper.

The author declares no conflict of interest.

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protein tertiary structure can occur in the 10^{-12} to 10^{2} s after electrospray introduction into the mass spectrometer. Where experimentally desirable, control of specific steps can make possible either retention or appropriate modification of conformation during introduction into the mass spectrometer.

This sampling represents only a tiny fraction of the mass spectrometers in daily use worldwide for identification and analysis of a wide range of molecules, including flavors, natural products, pollutants, drugs, metabolites, and those in chemical process streams. MS specificity is ideal for efficiently probing the molecular complexity found in many fields including agriculture, atmospheric chemistry, biomedicine, food, forensics, geochemistry, and so forth. Hopefully, the illustrations here will suggest further novel applications in other scientific fields represented by the uniquely broad readership of PNAS.

ACKNOWLEDGMENTS. The authors of references 6–15 offered helpful suggestions. Generous financial support was supplied by the National Institute of General Medicine, the National Institutes of Health, Grant GM16609.

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