Mass Spectrometry in the Health and Life Sciences

Edited by
A. L. Burlingame and Neal Castagnoli, Jr.

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mass spectrometry in the health and life sciences

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edited by
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PREFACE

Several of the authors of this volume discuss the importance of conventional techniques of computerized mass spectrometry and certain tandem instrument systems such as gas chromatography/mass spectrometry and quadrupole MS/MS. Such instruments are well established and routinely used in chemical, pharmaceutical, environmental and some biochemical and clinical chemistry laboratories. These methods are well suited to carrying out sensitive and specific qualitative and quantitative analyses of substances which are both volatile per se and also polar, if they are stable to chemical derivatization using procedures such as permethylation and persilylation. A number of authors have discussed column and chromatographic isolation methodology, derivatization procedures, and the uses of stable isotopes in connection with the preparation of biological samples for GC/MS and selected ion monitoring analyses. These methods are well established for studies of complex mixtures, such as those of steroids, bile acids, drugs, organic acids, etc., occurring in physiological fluids and tissues, etc., and are of indispensable utility in the elucidation of metabolic pathways, studies of bioavailability (pharmacokinetics) and clinical diagnosis of genetic diseases.

However, similar utility of these mass spectrometric methods are less well entrenched in biochemistry, biological chemistry or clinical research laboratories since most biological substances are usually highly polar, chemically and thermally labile molecules which span the complete range of molecular weights. A significant fraction of substances in the low molecular weight category is routinely accessible to these well established mass spectrometric methods already mentioned (< 1,000 to 1,500 daltons). The development of methodology to deal with intermediate size range is presently undergoing dramatic development as discussed in this volume (< 25,000 daltons). The high mass region is presently only accessible through specific enzymic digestions or chemical degradation of macromolecules to obtain mixtures of substances which are tractable using the established and new techniques in the low to intermediate molecular size ranges, respectively. While the molecular size that was

tractable for study by mass spectrometry was virtually static for several decades, it is now clear that the upper limit of the intermediate mass range (increased already a solid factor of ten in the last five years) will continue to climb as the imagination and ingenuity of these scientists and engineers is brought into practice in new instrumental designs and hardware.

The developing accessibility of this intermediate mass range is a direct result of the recent discoveries of completely new methods for ionization and ejection of labile biological molecules into mass spectrometers, such as field desorption, ^{252}Cf fission fragment desorption and energetic atom or ion sputtering from solid and viscous liquid matrices. These so-called soft ionization methods have triggered the revolution in mass spectrometric methodology and new high mass instrumentation presently under way and have begun to deal with a greatly expanded scope of molecular classes and sizes of substances which are of direct importance to the mainstream of biological and physiological chemical science. For example, questions of the detailed interactions of small molecules, endogenous or exogenous, with macromolecules such as ligands and their receptors; or how covalent modifications of macromolecules modulate structure, topology and physiological function are beginning to yield to the new soft ionization and higher mass methods. Similarly, the structural characterization of recombinant proteins expressed in different cell types or the nature of cellular recognition or communication determinants are being studied as well as antigen-antibody epitopes in immunochemistry. In the field of metabolism, involving relatively low molecular weight drugs or endogenous substances, similar successes have occurred in characterization of their intact, polar conjugates. These varied types of conjugates or adducts are produced through metabolic activation of the parent compound to electrophilic intermediates which react with glutathione and other cellular nucleophilic sites including those on macromolecules. In addition enzymically catalyzed conjugates occur such as with glucuronic acid, sulfate, phosphate, taurine, etc. In addition, intact quaternary ammonium or phosphonium salts may now be studied. In truth, there are almost innumerable other examples of previously intractable biological substances which may now be analyzed as indicated in the contents of this volume.

The importance of these new methods in obtaining molecular weights, in determining the nature of microheterogeneity and in sequencing proteins, covalently modified proteins, carbohydrates, and other hetero-bio-oligomers has already become widely recognized in these past five years of rapid development of FAB

and LSIMS. This almost explosive growth is a result of both the large scale expansion of new mass spectrometric techniques into previously intractable biomedical structural problems, and equally important, a result of the relative ease of usage of the new sputtering type of ion sources using viscous liquid matrices.

However, the ionization/ejection of bio-oligomers for example from viscous solutions by energetic particle bombardment has two inherent technical problems at this stage of development of the methodology, both of which will be solved in principle by new types of high performance MS/MS instrumentation. These present problems of FAB/LSIMS methods are that: 1) the secondary ion mass spectra consist of a mixture of ionic species - those from the sample and those from the variety of viscous matrices - the latter adding a serious "chemical noise" contribution to the former; 2) in this ionization/ejection process, the amount of deposition of internal energy (vibrational/rotational) necessary to create the structurally meaningful fragmentation pattern (mass spectrum) appears to be relatively limited - so that the intact molecular ions of the high mass substances are often, unnecessarily, relatively abundant with respect to the fragment ions which comprise the rest of the mass spectrum. Of course, this fact is both an advantage and disadvantage depending upon the kind of experimental information being sought. It will be, of course, an inherent advantage for generation of the most intense possible mass selected "parent ion" beam for using tandem MS/MS methodology. This feature will permit one to obtain the optimized signal-to-chemical-noise "daughter ion" fragmentation pattern, or the collision-induced daughter ion spectrum, while simultaneously eliminating the matrix ions, adduct ions, chemical-noise, and indeed other components in the mixture in question. In the design of new MS/MS instruments to solve these problems and meet these challenges, several overall system performance characteristics will have to be taken into account, such as high sensitivity, mass resolution, high mass range and efficient collision cells.

In addition, the invention of new techniques such as Thermospray for tandem high performance liquid chromatography/mass spectrometry systems holds considerable promise for studies of mixtures of labile biological substances, even at higher mass.

The modus vivendi for this highly successful symposium was to provide the first opportunity for a major segment of the leading world authorities to present their perspectives on research advances and problems in soft ionization biological mass spectrometry and discuss their achievements and goals within the

common framework of innovative techniques and the future potentialities of advanced types of new instrumentation. In a conceptual sense, the germ for such a symposium with a biological and biomedical theme was planted during the small symposium held by Howard Morris at Imperial College in London in July 1980(1). This present multi-authored work provides the first up-to-date, authoritative overview of the scientific achievements, instrumental advances and future potentialities which will continue to be brought to bear at an increasing pace on research in the health and life sciences at the common molecular denominator. It will provide a ready reference to the practioner, student and biomedical scientist or clinician alike for this whole field for some time to come. This volume also contains the discussions following each invited plenary and keynote lecture which provides the reader with a sense of the major issues, problems and future expectations in this rapidly emerging symbiosis between biology, medicine and advanced mass spectrometry.

The success of the symposium and production of this important unifying volume is due to the Organizing Committee, their ability to secure the necessary financial support, their selection of the plenary and keynote scientists and the enthusiastic appreciation of all the scientific participants.

Special recognition and hearty thanks are due to Neal Castagnoli, Jr. as Chairman of the Organizing Committee and the Symposium itself as well as Co-Editor of this volume, and to Marilyn F. Schwartz for her impeccable planning, coordination and management of a model symposium and impressive social agenda. The editors also wish to acknowledge the professional contributions of Sharon Garrett in producing the publication copy.

A. L. Burlingame
San Francisco, May 1985

(1) H.R. Morris, Ed., Soft Ionization Biological Mass Spectrometry, Heyden, London, 1985.

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