CRC

HANDBOOK of MASS SPECTRA of DRUGS

Irving Sunshine

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CRC Handbook of Mass Spectra of Drugs

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Handbook of Spectrophotometric Data of Drugs
Irving Sunshine, Editor

PREFACE

"The old order changeth, yielding place to the new". This truism is attested to by the flood of scientific data on drugs which has been published in the last few years. This plethora should be at the fingertips of scientists so that they can find and use it easily. Thus, two Volumes have been compiled to complement the chromatographic data accumulated in the CRC Handbook Series in Clinical Laboratory Science, Section B: Toxicology. One of these Volumes concerns itself with spectrophotometry and the other with mass spectrometry. In each of these Volumes, a presentation of the particular aspect precedes the tabulation of the assembled data. These data are permuted in several ways so that the analyst may find the particular datum he needs in its sequential arrangement. Using this format may be redundant, but this was done with the user's best interest in mind. His ability to search for the information he requires must be facilitated so that these volumes truly become "desk side" references.

Compiling and collating the various tabulations is a tedious, painstaking, laborious process which can never be complete. There are few comprehensive sources from which one can abstract the desired information. The number of products with which one is concerned in Analytical Toxicology keeps growing, thanks to the ingenuity of medicinal and pharmaceutical chemists. This growth precludes the inclusion of all substances in the tables. Also, data on many older preparations are not included simply because it is very difficult to get all the desired information from original sources. While many laboratories have been most generous in this cooperative effort, a significant number could not find the necessary time and personnel to provide requested facts.

As the compilations such as those included in these volumes demonstrate their value, successive efforts will enlarge and improve them. In the coming age of computer technology, the black box may replace these books. Until that happens, I trust the user will find these volumes helpful. Input is also helpful, so an open invitation is extended to each user of these volumes to submit corrections, complaints, and additional data.

Obviously, all this could not be achieved by one person working alone. To the many scientists who contributed their little bits to these volumes go my and your profuse thanks. Without their help these volumes would never evolve.

Irving Sunshine
Cleveland, 1980

THE EDITOR

Dr. Irving Sunshine is Chief Toxicologist at the Cuyahoga County (Cleveland), Ohio Coroner's Office, Professor of Toxicology in the Department of Pathology and Professor of Clinical Pharmacology in the Department of Medicine at the School of Medicine, Case Western Reserve University; Chief Toxicologist for the University Hospitals in Cleveland, Ohio; Director of the Cleveland Poison Information Center; and Editor-In-Chief for Biosciences for CRC Press, Inc. He is a Diplomate of both the American Board of Clinical Chemistry and The American Board of Forensic Toxicology and is on the Board of Directors of both these organizations.

Born in New York City, he obtained all his formal education in various Colleges of New York University, earning the B.Sc., M.A., and Ph.D. degrees. While earning his Ph.D., he taught chemistry in various colleges in the New York area and during the war, he worked during the "grave yard" shift on a pilot plant for the separation of uranium isotopes as a part of "The Manhattan Project". His development in toxicology was encouraged by two memorable mentors, Dr. Alexander O. Gettler and Dr. Bernard Brodie.

Prior to moving "west" to Cleveland, Ohio, where he has been since 1951, he served as the Toxicologist for the City of Kingston (N.Y.) Laboratory and for Ulster County. Since coming to Cleveland he has developed many interests which resulted in the publication of over 100 papers and several monographs. He is also a member of the Boards of Editors of many of the major toxicology journals.

His educational activities extend beyond the local college campuses. In the course of years he has organized and participated in numerous toxicology workshops which were held in many centers throughout the United States. As a member of the Education Committee of the American Association for Clinical Chemistry, he has been responsible for the National Tour Speaker Program, the Local Section Guest Lecturer Program, and the Visiting Lecturer Program. In recognition of his achievements in clinical chemistry, Dr. Sunshine was presented with the Association's "Ames Award" in 1973. Further recognition was accorded Dr. Sunshine by the Italian Society of Forensic Toxicologists which voted to make him an Honorary Member of that group. In 1978, The International Exchange of Scholars awarded him a Fulbright Visiting Professorship to the Free University of Brussels.

He is also a "has been." He has been President of The American Association of Poison Control Centers, Chairman of the National Council for Poison Control Week, Chairman of the Toxicology Section of The Academy of Forensic Sciences, and Chairman of the Cleveland Section of The American Association for Clinical Chemists, as well as a former member of the Association's Board of Directors.

ASSISTANT EDITOR

Dr. Michael Caplis is Director of Biochemistry and Toxicology at St. Mary's Medical Center, Gary, Indiana, Consultant Toxicologist, Northwest Indiana, Region I, and Adjunct Professor, Indiana School of Medicine — Indiana University Northwest. He is a Diplomate on the American Board of Forensic Toxicology and a Fellow of the American Academy of Forensic Science, American Academy of Clinical Toxicology, National Academy of Clinical Biochemistry.

Born in Ypsilanti, Michigan, he obtained a formal education in chemistry, biology, and biochemistry. He earned a Bachelor of Science degree in chemistry at Eastern Michigan University and a Masters of Science and Ph.D. degrees in biochemistry at Purdue University. While attending college, he taught math, chemistry, and physics at the high school level and worked as an analytical biochemist for the Indiana State Chemist, Purdue University. He has taught biochemistry, toxicology, and forensic toxicology at the university level.

Since coming to Gary in 1969, he has developed a specialized clinical biochemistry laboratory at St. Mary's Medical Center and, through cooperative funding at the federal, state, and local level, a regional Toxicology Center for Northwest Indiana. His interests have resulted in numerous publications in both the clinical and toxicology fields.

He is a member of the American Academy of Clinical Toxicology, American Academy of Forensic Science, National Academy of Clinical Biochemists, American Association for the Advancement of Science, American Association of Clinical Chemists, American Chemical Society, Association of Official Analytical Chemists, Midwest Association of Forensic Scientists, and American Association of Crime Laboratory Directors.

ASSOCIATE EDITORS

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MASS SPECTROMETRY

Rodger L. Foltz

Within the past few years mass spectrometry has become an important analytical tool in many of the larger toxicology laboratories. Its popularity is destined to increase rapidly as toxicologists become more familiar with its capabilities, since mass spectrometry combines sensitivity and specificity to a degree unmatched by other analytical techniques. These features are particularly valuable in toxicological analyses where the toxicant is usually a trace component in a complex biological matrix.

Mass spectrometry is currently limited by the requirement that the compound be capable of volatilization at temperatures below its decomposition point. Several new techniques of ionization show promise of eliminating this restriction, but their widespread application is at least several years in the future. In practice, the volatility requirement is only a minor limitation to toxicologists since most organic toxicants do have adequate volatility, or they can be converted to volatile compounds by derivatization or other chemical manipulations. A more vexing limitation to wider use of mass spectrometry is the high cost of purchasing and maintaining a mass spectrometer system. Unfortunately, the cost problem appears to be worsening. New mass spectrometry capabilities and techniques are being developed at an awesome rate, and often the new developments require additional instrumentation, such as new ionizers, inlets, and computer hardware. Although a basic mass spectrometer system can be purchased for under $30,000, the lure of expanded capabilities and throughput achievable by inclusion of a computer and other options is often irresistible. As a result, laboratories wanting to stay competitive will find themselves spending upwards from $100,000 for a new mass spectrometer system. In order to justify costs of this magnitude, it is important that the mass spectrometer be operated efficiently and with as high a throughput of samples as possible. This can only be accomplished if the persons involved in operating the facility are knowledgeable and dedicated spectroscopists, willing and able to participate in the preparation of samples, the operation and maintenance of the instruments, and interpretation of the data. Furthermore, it is important to recognize the types of analyses for which mass spectrometry is best suited. Mass spectrometry is appropriately used when no other analytical methods possessing adequate sensitivity and specificity are available. In this regard, mass spectrometry, particularly in combination with gas chromatography (GC-MS) and isotope-labeled internal standards, can form the basis of a definitive quantitative assay which can be used to validate other assays. GC-MS suffers some disadvantages: sample throughput is relatively slow and the system is difficult to fully automate. Consequently, one should always consider whether a particular assay can be done adequately by a cheaper and faster method.

Of the many books on mass spectrometry, those authored by Beynon et al.,[1] Biemann,[2] McLafferty,[3] and Budzikiewicz et al.[4] and edited by Waller[5] have proven most useful. Mass spectrometry research results are published in a wide variety of journals. Fortunately, excellent reviews of the field appear at regular intervals.[6,7] Currently there are three English-language journals devoted exclusively to publishing research involving mass spectrometry: (1) *Biomedical Mass Spectrometry,*[8] (2) *Organic Mass Spectrometry,*[9] and (3) the *Journal of Mass Spectrometry and Ion Physics.*[10] Of these, the first is most likely to be used extensively in a toxicology laboratory, as it is highly applications oriented, while papers appearing in the second and third tend to be concerned with fundamental processes occurring in mass spectrometry. The *Mass Spectrometry Bulletin*[11] is the most current and comprehensive guide to the mass spectrometry literature. This monthly publication lists the titles, key subject terms, and

references for articles containing mass spectrometry data appearing in over 250 journals. Each issue contains indexes based on subject, author, compound classification, and elements. Also, an Elemental Composition Index is published annually.

Basic Components of a Mass Spectrometer

The basic processes in any mass spectrometer include introduction and volatilization of the sample, ionization of the sample molecules, separation of the resulting ions according to their masses, and measurement of the ion current at each mass. Numerous books[1-5,12-15] and review articles[16-20] contain detailed descriptions of the different methods and types of instrumentation that have been used to accomplish each of these processes. This discussion will be limited to those instrumental methods which are particularly useful to toxicology laboratories.

Sample Ionizer

A mass spectrum is most often represented by a bar graph in which the height of each bar or line represents the relative intensity of ion current at a particular mass (Figure 1). Actually the units of the abscissa are mass to charge rations (M/e); however, the charge is normally one and, therefore, the ratio is often loosely referred to as mass. The appearance of a mass spectrum is determined primarily by the structure of the sample molecules and the ionization process employed. Electron impact (EI) is the most widely used method of ionization for organic molecules. In this method, sample molecules in the gas phase are

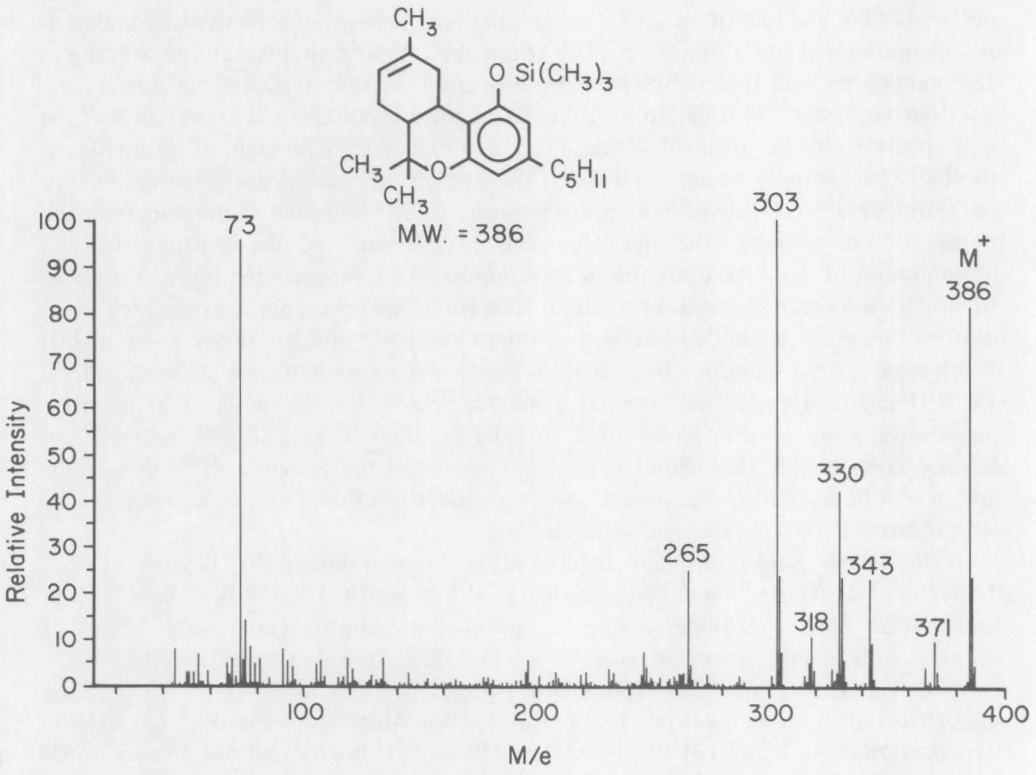

FIGURE 1. A representative mass spectrum in which the line heights represent the relative ion current intensities at each M/e value (mass to charge ratio). The compound represented corresponds to the trimethylsilyl derivative of Δ^8-tetracannabinol.

passed through a beam of electrons. A small fraction of the molecules is ionized by electron bombardment. Typically, electron beams with energies of about 70 eV are used. Since the ionization potentials of organic compounds lie between 8 and 12 eV, the excess energy usually causes extensive fragmentation to lower mass ions. The resulting pattern of ion currents vs. M/e is reproducible and characteristic for each organic molecule. Even though both positive and negative ions are formed, the former predominate and constitute the normal EI mass spectrum. EI mass spectra are often complex and potentially contain considerable structural information. However, our ability to extract this information is severely restricted by our limited understanding of the fundamental processes that govern how a molecular ion fragments. Interpretation of EI mass spectra is still based primarily on a collection of empirical observations relating structural features to specific fragmentation processes.[1-4]

Chemical ionization (CI) is an alternative method of generating gas-phase organic ions which is rapidly gaining in popularity.[21-23] In this technique, a reagent gas is introduced into the ion source to give a pressure of about 1 torr. Some of the reagent gas molecules are ionized by electron impact, and they subsequently cause ionization of the sample molecules by means of ion-molecule reactions. These reactions include proton transfer, hydride abstraction, ion attachment, and charge transfer, all of which are relatively low energy processes. As a consequence, CI mass spectra typically show intense peaks in the molecular ion region and relatively little fragmentation. The ability to clearly indicate the molecular weight of a compound is the most notable feature of CI mass spectra. However, the technique offers other useful features. Different reagent gases can be used, each generating a different spectrum.[24,25] Methane was the first reagent gas to be used and still is the most popular.[26] Methane CI mass spectra often show a moderate amount of fragmentation, but the fragment ions can be easily identified and often provide useful structural information. Isobutane[27] and ammonia[28] are "milder" reagent gases which typically generate CI mass spectra containing little or no fragmentation. When aprotic gases such as argon[29] and helium[30,31] are used as reagent gas, the sample molecules are ionized primarily by charge exchange and the resulting spectra are very similar to conventional EI mass spectra. Nitric oxide[32,33] is a reagent gas which has also been shown to be useful for certain classes of organic compounds.

Until recently, only the positive ions generated by chemical ionization were recorded. However, it has been shown that negative ions can also be generated in high abundance and that the resulting negative ion CI mass spectra contain additional, useful, structural information.[34,35] What is more, a commercial GC-MS system has been modified to permit simultaneous acquisition of both negative and positive CI mass spectra.[36]

A CI ion source is sufficiently similar in design to an EI ion source that it is possible to build a single instrument capable of performing well in either mode of ionization. In view of the complementary nature of CI and EI ionization, it is likely that in the near future all new organic mass spectrometers will have both capabilities.

Other ionization methods such as field ionization,[37] field desorption,[38] atmospheric pressure ionization,[39] and californium-252 plasma desorption ionization[40] have exciting potential for special applications but do not currently have general applicability in toxicology laboratories.

Mass Analyzer

The vast majority of mass spectrometers presently in use achieve mass analysis by either magnetic deflection or a quadrupole mass filter. Each type of analyzer has its advantages. Magnetic instruments have a higher mass range and generally are capable of greater resolution. Metastable ion peaks can be observed on magnetic instruments but are not detected with quadrupole mass spectrometers. Metastable ions are those which undergo fragmentation between the ion source and the ion detector.[41] The ability to

detect the products of metastable ion decompositions is very useful in the study of fragmentation mechanisms. Quadrupole mass spectrometers tend to be lower priced, are capable of very rapid scans, and are better suited to operation under computer control.

Most of the major differences in performance capabilities between magnetic and quadrupole instruments have been largely overcome by design improvements. The early quadrupole analyzers were limited to ion masses below about 500, whereas the newer instruments are capable of detecting ions up to M/e 1000 to 1200. The less stringent vacuum requirements of the quadrupole analyzer and the absence of high accelerating voltages made it easier to adapt quadrupole instruments to chemical ionization. However, manufacturers of magnetic instruments have now re-engineered their products so that they can also offer CI capability. Magnetic instruments tend to have a better inherent sensitivity (particularly at high mass), but computer control of quadrupole analyzers permits optimization of the scan parameters to the point where comparable sensitivities can be achieved.

Ion Current Detector

The electron multiplier is almost universally used as the primary ion current detector in organic mass spectrometers. This device converts the impinging ions to electrons and amplifies the electrical current by as much as 10^7. The output of the electron multiplier is further amplified and passed to a high-speed recorder or a digital data system. The overall gain of this system can be sufficient to observe single ions reaching the detector. Other types of detectors, such as photographic plates,[42] are useful for special applications.

Sample Inlets

Sample inlets provide a means of volatizing the sample and introducing it into the ion source of the mass spectrometer. The type of inlet that should be used depends on the volatility and stability of the sample, as well as the amount of material available and its state of purity. Every mass spectrometer used for analysis of organic materials should have at least three separate inlets: (1) a direct insertion probe, (2) a controlled leak inlet, and (3) a gas chromatographic inlet.

Direct Insertion Probe

Solids and high-boiling liquids can be introduced into the mass spectrometer by means of a "direct insertion probe." The sample is placed in a small glass capillary which is seated in a cavity at the end of a heatable probe. The probe is then introduced via a vacuum lock into the ion source, where it is heated to a temperature sufficient to give a vapor pressure of about 10^{-6} torr. The entire operation is simple and rapid (<5 min); therefore, it is usually the inlet used if the sample is relatively pure. It is also the preferred inlet if the sample material is thermally unstable or has insufficient volatility to be introduced via the gas chromatographic inlet. It is an efficient method of sample introduction with respect to sample utilization. Mass spectra can be obtained on quantities as small as 0.1 μg. However, when working with such small sample quantities, contaminants can be a problem. If the sample and the contaminants have different vapor pressures, some fractionation can be achieved by slow, controlled heating of the probe. Nevertheless, it is highly desirable to minimize contaminants by keeping the sample probe and glass capillaries scrupulously clean. Since the latter are difficult to clean, many laboratories simply use readily available melting point capillary tubes which can be easily cut to the desired length and discarded after use.

An alternative to placing the sample inside the glass capillary is to evaporate a solution of the sample on the outside of the capillary tube or a glass rod of similar dimensions. This technique has several advantages. First, the deposited film tends to evaporate more uniformly when heated than do crystals placed inside the capillary. Second, it is less

likely that too much sample will be used, since the amount is limited by the quantity of residue which will adhere to the outside of the capillary. Finally, it has been reported[43] that certain compounds which are difficult to volatilize may give usable spectra if they are deposited on the outside of the capillary and introduced directly into the ion chamber of a chemical ionization ion source.

The direct probe technique is often used to obtain mass spectra of compounds isolated by paper or thin-layer chromatography (TLC). Some success has been achieved by scraping the portion of the TLC adsorbent containing the material of interest directly into the glass capillary tube.[44] However, the presence of the solid adsorbent tends to lower the volatility of the sample and can catalyze decomposition when the probe is heated in the mass spectrometer. Consequently, it is usually preferable to elute the sample from the TLC adsorbent, concentrate the eluent, and then deposit it on or in the glass capillary sample holder.

Mass spectra obtained on samples isolated by TLC inevitably show the presence of contaminants, often in such high concentration that the ions due to the sample are masked by the more abundant contaminant ions. This is particularly likely when the material of interest is located on the TLC plate by a selective method of visualization, such as UV absorption, fluorescence, or radioactivity. Consequently, before submitting a TLC-isolated sample for mass spectral analysis, it is often helpful to subject a duplicate plate to a general visualization process, such as exposure to iodine vapor or acid-charring, in order to determine if the TLC spot of interest is free of other organic materials.

Controlled Leak Inlet

Gases and volatile liquids can be introduced into the mass spectrometer by means of a reservoir connected to the ion source via a controlled leak. This type of inlet is normally used for introducing a reference material for mass calibration and tune-up of the instrument. It can also be used for introducing CI reagent gases or when a relatively steady sample flow rate into the ion source is required. The amount of sample needed depends on the size of the reservoir and the conductance of the leak. However, in general, this type of inlet is not used if less than about 1 mg of sample is available.

Gas Chromatographic Inlet

The development of techniques for coupling the gas chromatograph to the mass spectrometer has done more to expand the usage of mass spectrometry than any other single development. Whether one views the gas chromatograph as an inlet for the mass spectrometer or the mass spectrometer as a detector for the gas chromatograph depends on one's personal perspective and bias. The important fact is that the combination of the two instruments constitutes an analytical system of unprecedented capabilities. In most respects, the gas chromatograph and the mass spectrometer complement each other and are compatible. Both are gas phase, microanalytical techniques. Gas chromatography is capable of higher separation efficiency than any other current technique, while the mass spectrometer offers detailed structural information and, when corresponding reference spectra are available, can provide conclusive identification of analytes.

The major point of incompatibility between the GC and the MS is the pressure within the active elements of each system. The GC column is normally operated at above atmospheric pressure, while the mass analyzer of the MS must be maintained below 10^{-5} torr. Numerous splitters, separators, and other devices have been developed for overcoming this incompatibility.[45–47] In spite of the progress that has been made in the design of GC-MS interfaces, the link between the two remains a critical stage in the combined operation and a likely source of problems. As a general rule, the connection between the GC and MS should be kept as simple and direct as possible. In line with this principle, there is a current trend toward direct coupling of the GC and MS without

separators or splitters. This poses no major problem in the case of capillary column chromatography where the carrier gas flow rate is only 1 to 2 ml/min. It is also commonly done when chemical ionization is used. In this case, the carrier gas (methane) can be used as the CI reagent gas. For the combination of packed columns and electron impact ionization, some type of separator is still normally used. The glass jet separator appears to be preferable for biological samples because it shows the least tendency to cause loss of sample due to decomposition or adsorption. Its major fault is its propensity to become clogged, necessitating instrument shut-down and cleaning.

GC-MS analysis is often more dependent on the proper performance of the gas chromatograph than that of the mass spectrometer. Consequently, before initiating a new GC-MS analysis, it is generally advantageous to check out and optimize the GC conditions on a separate GC unit equipped with a flame ionization detector (FID). The results of this preliminary work will facilitate setting up the mass spectrometer's scan and amplification parameters in order to obtain the best quality mass spectra and make the most efficient use of the GC-MS system. Furthermore, a comparison of the FID chromatogram and the total ion current (TIC) chromatogram provides a valuable assessment of the performance of the two systems. If, for example, the peaks in the TIC chromatogram show more tailing than those in the FID chromatogram, it is likely that there is a problem in the interface, such as cold spots or unswept dead volumes.

The amount of sample required for analysis by GC-MS depends on many factors. As a general guide, most modern GC-MS systems should be able to routinely generate good quality spectra on 10 to 100 ng of compound injected into the gas chromatograph. However, instrument capabilities are being continually improved so that some are now able to generate complete mass spectra on considerably smaller quantities ($\sim$ 100 pg). When operated in the selected-ion-monitoring mode, a GC-MS system should be capable of detecting subnanogram quantities of most gas chromatographable compounds.

The selection of gas chromatographic columns is discussed in the chapter on gas chromatography. For GC-MS work it is particularly important to use thermally stable liquid phases. Because of the sensitivity of the mass spectrometer, column bleed is often the primary barrier to lower detection limits. Fortunately, liquid phases are readily available which have excellent thermal stability and cover a wide range of polarities, so that there is little justification for using high-bleed liquid phases such as polyethylene glycols, hydrocarbons, and polyesters.

Packed columns are currently those most widely used because of their capacity, versatility, and general availability. However, glass capillary columns offer attractive advantages: better resolution, lower sample losses due to adsorption and surface-catalyzed decomposition, and elimination of the need for a separator. Glass capillary GC technology has advanced more rapidly in Europe than in North America. Nevertheless, wider recognition in this country of the advantages of a glass capillary column seems inevitable.

Many compounds can be more effectively analyzed by GC-MS after chemical conversion to a derivative. Derivatization is used to increase a compound's volatility or its thermal stability, to improve its GC behavior by substituting lipophilic groups for "active" hydrogens, or to advantageously alter the compound's mass spectrum. For example, the latter two benefits are realized when amphetamine is converted to its trifluoroacetamide (TFA) derivative. Figure 2 compares the EI mass spectra of the drug and its derivative. The most intense peaks in the EI mass spectrum of methamphetamine occur at low mass (M/e = 44, 91, 65), where interference from other compounds is likely. In contrast, the mass spectrum of the TFA derivative shows a base peak at M/e 140, a mass which is more useful for detection in that it is less likely to be masked by ions from other compounds. A recent review[48] contains a detailed discussion of the advantages and potential pitfalls in chemical derivatization and a systematic survey of the many derivatizing agents and techniques in use.

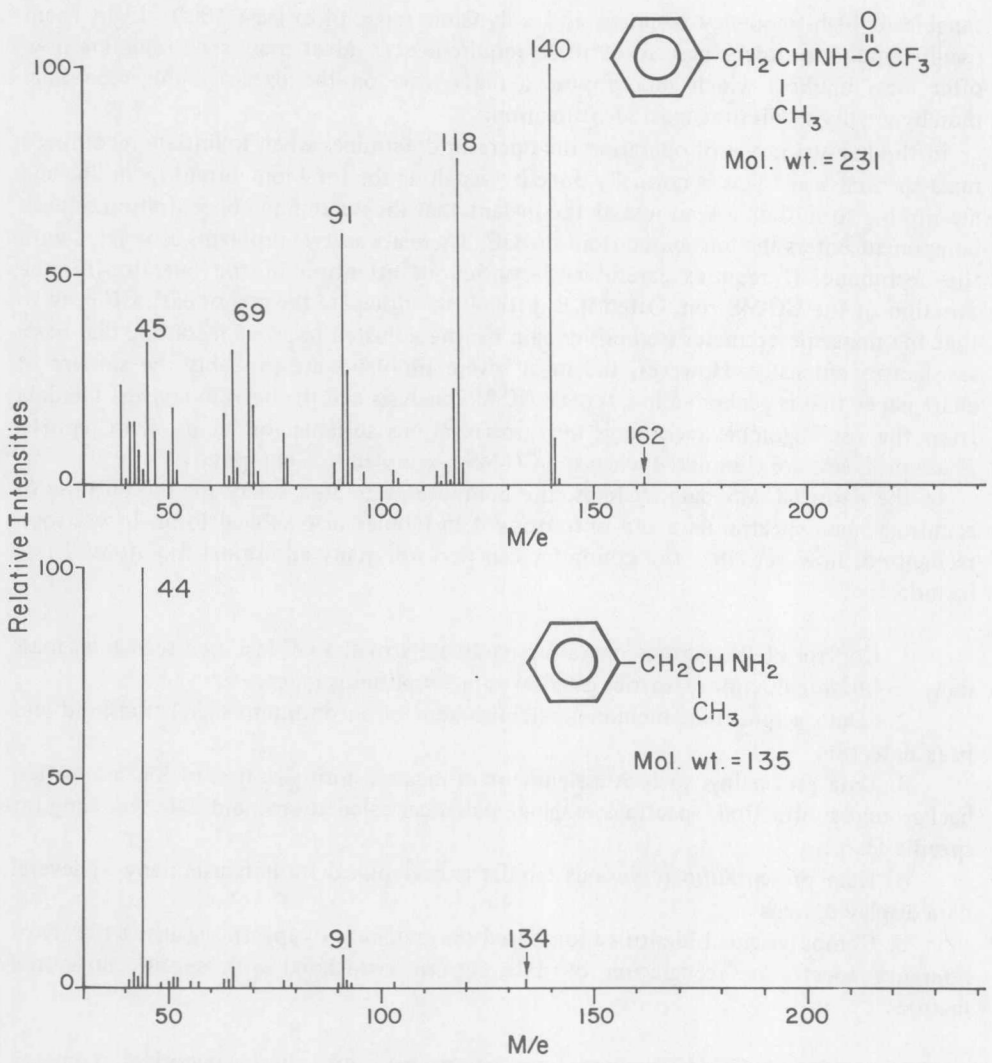

FIGURE 2. Comparison of the EI mass spectra of amphetamine (bottom) and amphetamine trifluoroacetamide (top).

Other Types of Inlets

Many additional types of inlets have been developed to solve specific sampling problems. Those which are likely to be of greatest interest to a toxicology laboratory include devices for direct sampling of gases at atmospheric pressure[49,50] and for adsorption and concentration of organic vapors prior to introduction into the GC-MS.[51] In view of the remarkably successful mating of the gas chromatograph and the mass spectrometer, it is not surprising that there is also tremendous interest in methods for the direct coupling of a liquid chromatograph (LC) to a mass spectrometer. Several approaches to developing LC-MS interfaces have been tried with some success.[52] However, so far all of the methods are limited in the types of solvents that can be handled and are restricted to the analysis of compounds which can be volatilized without decomposition.

Data Handling and Computerization

In the absence of a data system a GC-MS must have two separate recorders, one to record the total ion current signal and another to record mass spectra. The latter must be

capable of high-frequency response and a dynamic range of at least 1000. Light beam oscillographic recorders best meet these requirements. Most mass spectrometers now offer mass markers which superimpose a mass scale on the oscillographic recording, thereby greatly facilitating mass identification.

In the manual mode of operation the operator determines when to initiate recording a mass spectral scan. This is normally done by watching the total ion current recording and attempting to initiate a scan just at the instant that the maximum concentration of each component enters the ion source from the GC. There are several problems associated with this technique. It requires careful and continuous attention of the operator for the duration of the GC-MS run. Often it is difficult to anticipate the size of each GC peak so that the mass spectrometer's amplifier gain can be adjusted to give a recording that has a satisfactory intensity. However, the most severe problems are probably the amount of chart paper that is generated in a typical GC-MS analysis and the need to convert the data from the oscillographic recordings into presentations suitable for inclusion in reports. These problems are eliminated when the GC-MS is coupled to a computer.

In the early GC-MS data systems, the computer was used solely for the purpose of acquiring mass spectral data and outputting it in tabular or graphical form. It was soon recognized, however, that the computer can perform many additional functions. These include:

1. Control of the various operating parameters of the GC-MS, i.e., scan rate, mass range, column temperature, carrier gas flow rate, amplifier gain, etc.
2. Data acquisition, including establishment of an optimum signal threshold and peak detection
3. Data processing, such as assignment of masses, normalization of ion intensities, background subtraction, spectra averaging, statistical calculations, and data searching for specific features
4. Data presentation in various tabular and graphical formats using any of several data display devices
5. Computer-aided identification based on matching of spectra against a library of reference spectra or recognition of data patterns associated with specific structural features

Computer-based GC-MS analyses can be grouped into two categories: repetitive scanning or selected ion monitoring. In the former the mass analyzer repetitively scans over the mass range of interest. Scan times are normally 2 to 4 sec so that in a GC-MS analysis consuming 30 min, 400 or more spectra will be entered into the computer. Upon completion of the run, the computer reconstructs a total ionization chromatogram (TIC) by plotting the summation of the ion intensities for each scan vs. scan number. The resulting plot can be displayed on a video screen or drawn by a digital plotter. It should be similar in appearance to a normal gas chromatogram of the same sample. The primary use of the total ionization chromatogram is to indicate which scans contain mass spectral data corresponding to each component of interest. For example, Figure 3 shows the total ionization chromatogram from a GC-MS analysis of an extract of the urine from an emergency room patient intoxicated with an overdose of a drug. Figure 4 is the computer plot of the methane CI mass spectrum (No. 180) corresponding to the major peak in the TIC. The protonated-molecule ion (MH^+) was easily identified in this spectrum on the basis of the very typical intensity pattern for the $M-H^+$, MH^+, $MC_2H_5^+$, and $MC_3H_5^+$ ions. Further interpretation of the spectrum led to the conclusion that it corresponded to the tricyclic antidepressant drug, amitriptyline. In the same manner, spectra numbers 190, 226, and 243 were plotted, examined, and identified as due to the three major metabolites of amitriptyline.