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# A REVIEW OF HYPHENATED CHROMATOGRAPHIC INSTRUMENTATION

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# A REVIEW OF HYPHENATED CHROMATOGRAPHIC INSTRUMENTATION

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## ABSTRACT

Samples presented for chemical analysis are invariably mixtures, often very complex mixtures. This has led to the widespread acceptance and application of what have become called hyphenated chromatographic techniques. These techniques are combinations of chromatographic instrumentation with some (usually) spectroscopic technique. In this review, we treat the most important and useful of these combinations. The basic instrumental features of each method are described, and possible applications are discussed. The relative capabilities of each technique are weighed, and tradeoffs are discussed. In closing, a list of suggested further reading is provided.





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## INTRODUCTION

When we deal with instrumental analytical methods, we are almost invariably dealing with samples which are presented as mixtures. These mixtures may be very simple, such as one solute (or sample) dissolved in a single solvent of the analyst's choice, or quite complex, such as a potential hazardous waste sample, over which we have no control or prior knowledge. For this reason, the coupling of analytical separation techniques (primarily gas, liquid and supercritical fluid chromatography) with other analytical methods such as spectroscopic techniques has been a great success. The resulting combined instrumental methods have been called hyphenated chromatographic techniques. The most important hyphenated methods are gas chromatography–mass spectrometry (**GC-MS**), liquid chromatography–mass spectrometry (**LC-MS**), gas chromatography–Fourier transform infrared spectrophotometry (**GC-FTIR**), gas chromatography–atomic emission spectroscopy (GC-AES), supercritical fluid chromatography–mass spectrometry (**SFC-MS**), and supercritical fluid chromatography–Fourier transform infrared spectroscopy (**SFC-FTIR**). There are also the double hyphenated techniques such as gas chromatography–Fourier transform infrared spectroscopy–mass spectrometry (**GC-FTIR-MS**). The most important and most widely used of these hyphenated methods is GC-MS, which will be given the most extensive discussion in this article.

Only very brief discussion of each of the individual techniques will be given here, since these topics are covered in detail elsewhere. In this article, only the specific issues and consequences pertaining to the "marriage" of the chromatographic instrumentation with the other techniques will be emphasized. For the more important hyphenated techniques, the operation of the unit as a whole will be described in more detail.

## GAS CHROMATOGRAPHY–MASS SPECTROMETRY

The routine use of a mass spectrometer as a detector for gas chromatography began the trend toward hyphenated techniques in the mid-1960s. This combination of two major instrumental analysis methods provides one of the most powerful analytical techniques available, clearly more than the sum of the individual parts. Indeed, if the quantity and quality of the resulting information is considered, then one must concede that the combination provides an exponential

increase in useful information. This is because mass spectrometry is the single most useful tool for organic structure elucidation, relative molecular mass determination, and compound identification. It is also a very sensitive trace analysis technique, a topic that will be treated in more detail later in this article. GC-MS couples the high quality molecular information and the high sensitivity of mass spectrometry with the ability of modern capillary column gas chromatography to resolve complex mixtures (containing upwards of 300 components). A typical 1 h long GC-MS analysis can provide 10,000 usable data points for the scientist to analyze.

Originally, users with high-resolution mainframe mass spectrometers interfaced gas chromatographs to the direct insertion ports of their mass spectrometers. The great technological success of the combination is what in fact led to the development of the bench-top mass spectrometers, specifically as detectors for gas chromatography.



Among the few technical disadvantages of the mass spectrometer are (1) it is destructive to the sample, and (2) it is sensitive to differences in homologues, but it is not usually sensitive to differences in various levels of isomerization. A more detailed discussion of these disadvantages is presented in the section on gas chromatography-Fourier transform infrared spectrometry.

It is difficult to consider the mass spectrometer (or mass selective detector, MSD, a term that will often be used when considering GC-MS systems) in the same vein as other gas chromatographic detectors such as the thermal conductivity or flame ionization detectors. The cost and complexity of the combination requires the consideration of the GC-MS instrument as a system unto itself. A schematic diagram of such a system is provided in Figure 1.

The mass spectrometer consists of a vacuum chamber that is pumped to a level of $1.3\times10^{-3}$ to $1.3\times10^{-4}$ Pa ($10^{-5}$ to $10^{-6}$ torr). This can be accomplished using a turbomolecular pump or a diffusion pump, both of which must be backed by a mechanical rough pump which produces a vacuum of at least 0.13 Pa ($10^{-3}$ torr). In general, the greater the pumping capacity (or rate), the better is the performance of the mass spectrometer.

Inside the vacuum chamber are the ion source, the mass filter, and the electron multiplier detector. The ion source usually consists of an "electron gun" filament which ionizes the sample eluting from the chromatograph. The molecular or parent radical ion, $\mathbf{M}^{\cdot+}$, is produced by the following mechanism:

$$\mathbf{M} + \mathbf{e}^- \rightarrow \mathbf{M}^{\cdot+} + \mathbf{2e}^- . \qquad \textbf{(1)}$$

Collisions involving higher energy interactions produce smaller fragments of the parent molecule. Actually, only a small fraction of the sample is ionized. Most of the sample leaving the column will be pumped away without ever encountering an electron from the source. Some instruments allow the use of chemical ionization

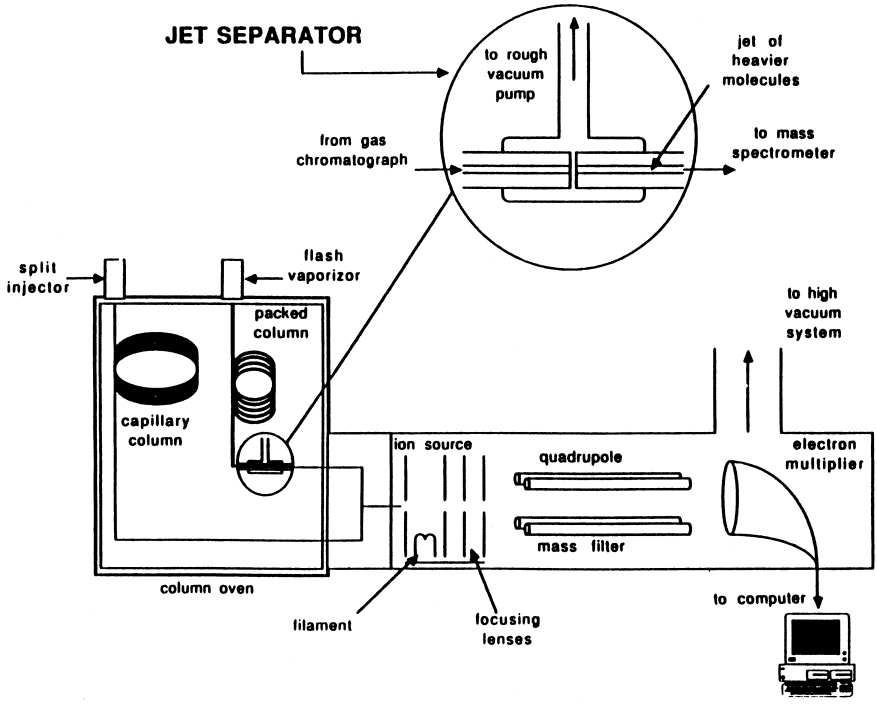


***Figure 1.*** A schematic diagram of a typical gas chromatography–mass spectrometry system, showing a direct interface for a capillary column, and a molecular jet separator for a packed column.



reagent gases as an alternative to electron impact ionization. The ion source also contains a series of electronic lenses which accelerate and focus the (usually) positive ions which are formed by the collision process. The beam of ions is passed to the mass filter, which is most often of the quadrupolar or ion trap type. The electron multiplier amplifies the electron current signal, and a computer system is required to process this signal into the familiar mass histogram (intensity against m/e) format. Usually, a composite format is presented in the form of a total ion chromatogram. This is a display of peaks presented in the format of total intensity (of a user-selected range of m/e) plotted against time, just as the output from any GC detector.

A most critical part of the GC-MS system is the interface between the gas chromatograph (which operates at slightly above atmospheric pressure) and the mass spectrometer (which operates under high vacuum). The magnitude of this difference in pressure is $10^8$-fold or more. Thus, accomplishing the transition

without degrading the chromatography or the mass spectrometry can be difficult. Moreover, one cannot allow the interface itself to become a cause of sample ionization or thermal decomposition. All sample ionization must occur only in the ion source of the mass spectrometer.

## The Direct Interface

Whenever possible, the **direct interface** is the most desirable because of its simplicity. The direct interface is simply a length of capillary tubing that transfers sample and carrier directly into the source. Usually, this is simply the last 10–20 cm of the chromatographic column held in the entry port fitting by a gland or ferrule (usually made from graphite, polyimide or graphite-filled polyimide). The carrier gas, which is usually helium or another gas having a low relative molecular mass, is swept out of the source by the vacuum system much faster than the sample. This leaves the volume element of the source relatively rich in sample. The direct interface approach can be used when the column exit flow rates are between 0.5 and 2 mL/min, thus it is usually limited to smaller (0.25–0.32 mm inside diameter) open tubular (or capillary) columns. The use of the direct interface with larger diameter capillary columns may require the use of a restrictor after the column. The restrictor is simply a length of uncoated fused silica capillary tubing that connects to the column exit and carries the column effluent into the mass spectrometer.

The many advantages of the direct interface include the minimization of dead volume, the absence of unswept volume, and no loss of sample. The interface containing the capillary is usually heated to between 250 and 270 °C. This facilitates sealing the capillary to the mass spectrometer entry fitting, and also prevents adsorption or condensation of sample components at the end of the column. When subambient column temperatures are used, the entry fitting must be insulated (usually with glass wool) so that it is not chilled. The direct interface can be used with any chromatographic carrier gas, although helium is the most common carrier that is used in the United States.

While the direct interface is usually the most reliable, there are a number of important disadvantages. The final few centimeters of the column are exposed to vacuum. Thus, a negative pressure will exist in some small portion of the column. This can sometimes degrade the chromatographic results, although with small diameter capillary columns this is usually not a problem. This effect is especially pronounced in the relatively rare cases in which hydrogen is used as the carrier gas. With hydrogen, as much as 1 m of the end of the column can be under a negative pressure.

Because the column is connected directly to the source, it is impossible to change the column without venting the mass spectrometer. The resulting

vent/pump-down cycle usually takes four hours to complete (actually, a spectrum can be measured in 30 minutes or so, but a longer pump-down time is needed to sufficiently reduce the contaminant background to allow the measurement of high quality spectra). Also, there is always the possibility of source contamination when the mass spectrometer is vented. Moreover, it is impossible to isolate the mass spectrometer from the chromatograph when the column is connected. This can make troubleshooting of the mass spectrometer problematic.

Another difficulty is the lack of explicit flow rate and exit pressure information for a column that is directly interfaced to a mass spectrometer. The column carrier gas flow rate and exit pressure are often needed for efficiency or retention parameter calculations. The final section of the column that is in the heated interface will become embrittled over time. It is therefore not unusual for the column to break inside the source when columns are changed. This situation is manifest as a dramatic decrease in observed ion intensity (both from sample and background noise). Breakage of the direct interface capillary section necessitates a complete source cleaning.

When a packed column or a large bore open tubular column is used with a mass spectrometer, a different, more complex interface is needed. This is because of the relatively high flow rates (5–40 mL/min) used with these columns. A typical bench-top mass spectrometer vacuum system cannot pump away such a large volume. The interfaces for high-flow applications include the molecular jet separator interface, the effusion interface, the semipermeable membrane interface, and the varieties of the split interface.



## The Molecular Jet Separator

A **molecular jet separator**, shown in the inset of Figure 1, is a glass envelope containing transfer lines that terminate in two collinear orifices. The two orifices are separated by approximately 0.5 mm. One line carries sample from the chromatographic column and the other carries sample to the mass spectrometer. The inside of the glass envelope is maintained at rough vacuum with a mechanical pump. As the column effluent expands out of the entry orifice, most of the (relatively light) carrier gas and, inevitably, some sample is drawn off into the low vacuum region. A significant fraction of the sample molecules will continue on a linear path and enter the orifice leading to the mass spectrometer. Heavier molecules of sample are less likely to be diverted from the linear flow path to the rough vacuum because of their greater momentum. These molecules will remain roughly focused at the center of the jet and are drawn into the ion source of the mass spectrometer by the high vacuum.

The use of a jet separator results in some degradation of performance of the overall GC-MS system. The major manifestations of this degradation are lower

sensitivity and resolution. Because of this, it is important to tune the column flow rate for the particular jet separator that is being used. The analysis of lighter molecules is difficult with the jet separator, since most will be lost to rough vacuum with the carrier gas. Jet separators are delicate devices, and must be handled carefully. During use, they should be heated uniformly, without the development of hot or cold spots, or an implosion can result. Moreover, they can introduce unfavorable adsorption and chemical reaction sites into the chromatographic system. Only helium or hydrogen are practical chromatographic carrier gases when the molecular jet separator is used as the interface.

## The Effusion Interface

The **effusion interface** is similar in mechanism to the molecular jet separator in that separation of the carrier gas from the sample is done on the basis of mass difference. It is used only when helium or hydrogen is used as the chromatographic carrier gas. This device consists of a porous glass tube (often called a frit) that is enclosed in a glass envelope that is maintained at rough vacuum. Helium (or hydrogen) will preferentially pass through the frit, leaving the heavier sample species inside the tube. These heavier sample species will be carried into the source by a length of uncoated fused silica capillary tubing.

There are many disadvantages associated with the use of this device. Low relative molecular mass sample molecules can be lost through the frit. The interface itself is relatively large in volume, and will always cause chromatographic peak broadening, and often this distortion will be severe. Because of its size, the device has a relatively large surface area upon which adsorption and chemical reactions can occur.

## The Membrane Interface

The **membrane interface**, invented in 1969, is a device that separates the chromatographic effluent from the mass spectrometer vacuum chamber with a polymer membrane made from some suitable material such as a silicone. The flow from the column is directed at the surface of the membrane, where organic sample molecules dissolve in, and then permeate through the membrane. These species re-emerge from the membrane in the ion source of the mass spectrometer. Unlike the molecular jet separator and the effusion interface, vacuum is not applied to the chromatographic effluent; the effluent remains at atmospheric pressure upon leaving the column, thus allowing the column to be changed without venting the mass spectrometer. This interface has the advantage of a very high enrichment, since only a tiny fraction of carrier gas will penetrate the membrane. It

can be used with any inorganic carrier gas. Another advantage and application of this interface is in the safe analysis of corrosive species. If there is the potential of acid gas formation or transport through the column, the semipermeable membrane interface will provide very effective protection to the mass spectrometer ion source.

The performance of this interface is dependent on the solubility and diffusivity (that is, the sorption) of sample species in the membrane polymer. It is very selective toward organic compounds, and is very effective at discriminating against moisture that may be present in samples. This aspect of the interface is very attractive for the analysis of fermentation broths, and for environmental samples of gas and liquids that may be rich in water. In these instances, hydrophobic polymers are chosen as the interface material. Applications must be chosen with care, however, since the mass transport of high relative molecular mass, polar compounds is much lower than that of other organic species.



## Split Interfaces

The final interfaces we will consider are the **direct split** and the **open split**. The direct split interface is simply a "T" connection that vents the bulk of the effluent of a chromatographic column to the atmosphere (at atmospheric pressure). This device is often constructed from platinum. Only a small quantity of carrier gas and sample are allowed to enter the ion source of the mass spectrometer. The transfer is done with a length of tubing equipped with a restrictor, or a length of tubing of sufficiently small diameter to prevent overloading the mass spectrometer vacuum system. This interface is simple to construct and operate, but it suffers from many problems. Temperature programming of the column can significantly change the carrier gas flow rate at the split because of the temperature dependence of the carrier gas viscosity. This makes the operation of the interface quantitatively irreproducible. Also, since most of the sample is lost through the split vent, poor sensitivity can be a problem.

The **open split** interface consists of a transfer line that terminates in a restrictor, with a surrounding glass tube that carries a stream of flowing helium. The chromatographic column is placed directly against the restrictor end of the transfer line. Sample and carrier eluting from the chromatographic column impinge upon the restrictor, and most of the column carrier gas is swept away by the helium in the surrounding tube. Heavier sample molecules preferentially enter the restrictor and are carried to the ion source of the mass spectrometer. This is a very popular interface, even for use with small diameter capillary columns that are amenable to the direct interface approach. The advantages include the ability to change columns without venting the mass spectrometer, and controllable hydrodynamics at the chromatographic column exit. The chromatographic performance obtained with this interface is not as good as the direct interface, however.

## GC-MS Operation

The mass spectrometer detector can be used in one of two modes: the mass scanning mode or the selected ion-monitoring mode. When operating in scan mode, the mass spectrometer will record complete mass spectra over the molecular mass range selected by the operator. It is usual to keep the molecular mass range which is scanned as small as possible without sacrificing needed information, since a finite time is require to sweep the spectrum. This means that if a large relative molecular mass range is scanned, there will be relatively fewer spectra obtained per second than if a smaller range is scanned. The typical sensitivity of the mass spectrometer operated in scanning mode is 10 ng/mL.

In the selected ion-monitoring mode, the user selects one or more ion masses of interest, and the signal levels for only these ion masses are recorded. Selected ion monitoring is used primarily for high sensitivity quantitative analysis. Instead of scanning over hundreds of molecular mass units, a continuous intensity (ion abundance) measurement is made only for the selected masses. This is done by having the instrument rapidly jump from one selected mass to another. When the mass spectrometer is used in this fashion, the sensitivity approaches that of the electron capture detector that is used for the detection of highly halogenated compounds (10 pg/mL). When operated in either scan mode or selected ion-monitoring mode, the mass spectrometer will exhibit a linear dynamic range of $10^5$ for use as a quantitative chromatographic detector.

The mass spectrometer is one of the most expensive detectors available for the gas chromatograph. A high capability unit can easily cost three or four times more than the gas chromatograph itself. The mass spectrometer is relatively complex and requires some degree of training in order to be used effectively. Another consideration in the operation of a mass spectrometer is maintenance, which, relative to other GC detectors, is hardly routine. Pumping system service, source cleaning, filament replacement, and electron multiplier replacement must be performed periodically. This usually requires extreme care, very clean conditions, and a very steady hand.

As shown in Figure 1, the output from the mass spectrometer is fed into a data collection system that consists of a computer or work station that is driven with special control and peak-processing software. A strip chart recorder or chromatographic integrator is not a viable data collection device for a GC-MS system because of the sheer volume of data that results from a single measurement. The raw chromatographic data are presented as a total ion chromatogram. This is a recording of total signal (from all ions masses measured) as a function of time. The individual mass spectra are area slices of each chromatographic peak and of the baseline.

The programs that are used for data analysis are quite sophisticated, and allow deconvolution and manipulation of very complex total ion chromatograms.

Each chromatographic peak can be examined for the mass spectra of the constituent substance(s). The computer allows manipulation of spectra, such as the addition, subtraction, and averaging of spectra, scale changes and magnification, and the searching of measured spectra against libraries. These tasks are done automatically with search-and-match software. These programs retrieve possible matching spectra, and then assign quality factors to the list of potential matches. Spectral libraries can be built up by the user or purchased from the manufacturer and other sources. NIST has developed a 110,000 compound library (containing more than 130,000 spectra) starting with a database developed jointly by the U.S. Environmental Protection Agency (EPA) and the U.S. National Institutes of Health (NIH).

Mass spectral library searches require a good deal of technical skill to critically interpret, however, because their complexity will often lead to erroneous "hits". It has been estimated that in only 75 percent of GC-MS analyses is the correct identification assigned to the highest quality match. It is therefore up to the user to recognize and compensate for search difficulties.

The relationship between the chromatographic peak area and sample quantity or concentration is obtained by the calibration method, as with other chromatographic detectors. The computer provides the integration of the total ion chromatogram. The computer is also necessary to control the mass spectrometer. This includes the multitask operation of continuous diagnostics and performance parameter control, and the lens tuning that must be done frequently.

It is possible to achieve a high degree of connectivity between GC-MS instrumentation and other instrumentation and computers using laboratory information management systems (LIMS).



## GAS CHROMATOGRAPHY–ISOTOPE RATIO MASS SPECTROMETRY

An important variation of the GC-MS technique is gas chromatography–combustion interface isotope ratio mass spectrometry (GC-CIIRMS). This is the coupling of high resolution GC with a mass spectrometric technique that measures the isotopic abundance ratio of key atoms in a sample with that of a standard. This generates a very precise quantitative measure that is a very useful guide to sample identity. As an example of the precision of the technique, we can consider the isotopes of carbon: the isotopic ratio of $^{13}C/^{12}C$ can be measured with a precision of $10^{-5}$ atom percent. GC-CIIRMS methods are not used nearly as much as GC-MS techniques, despite the fact that isotope ratio mass spectrometry was on of the earliest analytical applications of mass spectrometry.

To use GC-CIIRMS, each separated band must be converted to a simple gas such as hydrogen, carbon dioxide, sulfur dioxide or nitrogen upon leaving the col-

umn. Usually, samples are converted to yield a stream of carbon dioxide or nitrogen, with oxidation to carbon dioxide being the most common reaction path. The interface for conversion to carbon dioxide consists of a combustion furnace containing a bed of either copper oxide and platinum (maintained at 820°C), or a bed of copper oxide, nickel oxide and platinum (maintained at 940°C). The interface for nitrogen conversion simply adds a reduction zone consisting of copper wires (heated to 600°C) following the combustion zone in the furnace.

Solvent peaks are prevented from entering the furnace using a valve bypass system. This prevents overloading and quenching sites in the furnace bed. Ultrahigh purity helium (99.999+ percent purity) is required for the GC carrier gas. Since water is also produced as a by-product of the combustion process, a Nafion membrane is used downstream from the furnace as a trap module. Since Nafion is permeable to water, but not to carbon dioxide, water will pass out of the trap, leaving the stream enriched with carbon dioxide. An open split follows the membrane module, to regulate the pressure and flow rate of the stream entering the mass spectrometer.



The dry gas stream, in helium, is then carried into the mass spectrometer, where the isotopic ratio measurement is made relative to a suitable standard, which is introduced separately. For the $^{13}C/^{12}C$ ratio, the standard has been the carbon from the calcium carbonate of the PeeDee formation in South Carolina in the United States (PeeDee belemnite). Although the GC-ICCRMS method produces very high precision ratio information, there are a number of important constraints and difficulties that must be accommodated. Relatively large samples are required for GC-CIIRMS, relative to GC-MS. For $^{13}C/^{13}C$ measurements, 0.1 to 1 nmol samples are required, while for $^{15}N/^{14}N$, 5 to 10 nmol samples are needed. The entire system must be thoroughly leak tested to ensure that no fugitive signals are produced from external or environmental sources. The resolution of the gas chromatograph must be optimized, and often different analytical protocols are required than are required for GC-MS; they are often not interchangeable. The run times are usually longer for GC-CIIRMS, since temperature programs must be established to optimize resolution.

## HIGH PERFORMANCE LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY

The combination of high performance liquid chromatography with mass spectrometry (HPLC-MS) results in a very powerful method for the analysis of heavy compounds (up to and sometimes exceeding a relative molecular mass of 100,000). It was developed because GC-MS can only be used for the analysis of between 15 and 20 percent of all known organic compounds, as a result of physical property considerations (normal boiling temperatures, vapor pressures, melt-

ing point temperatures, etc.). The HPLC-MS combination is a significantly more complex, expensive and large instrument than any standard GC-MS. Very rarely can an HPLC-MS system be considered a bench-top device. Moreover, there are numerous varieties of ionization methods and sources to choose from, which can be combined with equally numerous varieties of mass analyzers. This multiplicity of combinations makes each HPLC-MS system almost a unique, one of a kind instrument suited for particular classes of analyses. The eluent in HPLC is very different from that in GC, since it is a liquid that usually has a relatively high concentration of water. The analytes are often heavy, polar compounds. These are significant complications in the design of effective interfaces.

## Ionization Processes



The electron impact process that is commonly used in the mass spectrometry of more volatile compounds (and in GC-MS instrumentation) is usually inadequate for the very high relative molecular mass, polar, thermally labile compounds that are traditionally the province of HPLC separation. For electron impact ionization to be effective, a volatile compound must be introduced into the ion source, at whatever pressure the source is operating. It is therefore not appropriate to speak of an interface between HPLC and MS in the same vein as with GC and MS. The interface and the ion source must be treated as a unit (that is, an ionization interface), not merely as a transition region as it is with GC-MS. The analysis of heavy polar materials by mass spectrometry usually involves ionization by one of the desorption ionization methods, in which nonvolatile, thermally labile compounds are desorbed directly from a solution or a surface.

The most common ionization interfaces used for HPLC-MS are the atmospheric pressure (or near atmospheric pressure) approaches of electrospray, ion-spray and thermospray. Other, less common ionization interfaces include $^{252}Cf$ plasma desorption, field desorption, fast atom bombardment, laser desorption, matrix assisted laser desorption, and liquid secondary-ion desorption. While the latter methods have been used with HPLC with varying degrees of success, their application is usually confined to very specialized applications. Much older interfaces, such as the moving belt interface, are rarely applied in modern instruments, and will not be discussed here.

Electrospray, thermospray and ion-spray ionization interfaces produce charged droplets of liquid from which ions are desorbed. It is essential to form small droplets of uniform size, a process that involves the disruption of the bulk liquid surface with some type of energy input. The droplet size and distribution depends not only on the method used for their production, but also on the HPLC solvent flow rate and composition.

Although the electrospray, ion spray and thermospray processes themselves result in the production of ions, an auxiliary electron impact capability, in the form

of an electron gun under high vacuum conditions, is sometimes added to these ionization interfaces if the number of ions generated by the primary ionization method is not adequate. The use of one of the ionization interfaces with the addition of electron impact ionization is termed filament-on operation (referring to the filament in the electron gun of the source).

## Electrospray Ionization Interfaces

**Electrospray ionization interfaces** gained popularity in the 1990s, and have been largely responsible for the increasing popularity of HPLC-MS. A schematic diagram of such an interface is shown in Figure 2a. A liquid spray (of several μL/min) formed from the pressurized effluent of the column is subjected to a high voltage gradient (approximately 5 kV) to produce ionization. The charged droplets formed in electrospray are very small (approximately 10 μm average diameter), and the distribution is very uniform (between 1 μm to 20 μm). The charged ions that are produced by the electric stress are then accelerated by electrostatic lenses through a countercurrent of nitrogen gas that carries off most of the uncharged species and solvent molecules. The ions then enter a differentially pumped molecular beam skimmer, and are then carried into the mass analyzer. It is in the skimmer region that the auxiliary electron impact source is placed (if it is needed).

Electrospray ionization interfaces produce relatively mild ionization conditions, and as a consequence, the spectra are fairly simple. Usually, for simple molecules, $[M + H]^+$ and $[M - H]^-$ ions are produced (where M is the relative molecular mass of the parent molecule), even for thermally labile species. Multiply charged ions are also usually produced, however, only molecules capable of sustaining multiple charges will exhibit this phenomenon. This includes biological molecules such as proteins, peptides, polypeptides, and nucleic acids. The pro-



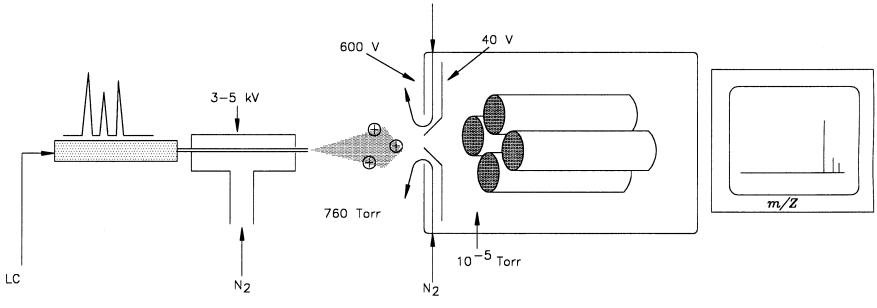


***Figure 2a.*** A schematic diagram of an electrospray ionization interface for HPLC-MS.

duction of multiply-charged ions is advantageous, since these ions allow the analysis (in standard instruments) of species having relative molecular masses above 100,000. [Recall that the x-axis of the mass histogram is in units of m/e, thus producing multiply-charged ions effectively doubles the mass range.] The sensitivity is very good (in the picomole range), but this is sample dependent. A mass accuracy of 0.01 percent is common, and the absence of numerous noise peaks enhances sensitivity and reliability. There are limits on the practical electrical conductivity levels of the mobile phases that must be observed, however. Moreover, the low solvent flow rate required for electrospray will often pose difficulties in analyses, although some units are now capable of handling a flow rate of 0.5 mL/min. Typical HPLC solvent delivery systems cannot produce effective gradients at such low flow rates, and therefore sometimes the chromatography suffers. The method is therefore best applied with packed microcolumns that have a 1 mm inside diameter.



## Ion Spray Ionization Interfaces

The **ion spray ionization interface**, shown schematically in Figure 2b, is closely related to electrospray, the main difference being the addition of pneumatic nebulization of the spray to assist in solvent evaporation. This is usually a pressurized organic sheath liquid that surrounds the column effluent spray, to reduce surface tension and to enhance the evaporation. It is therefore unnecessary to have an organic component in the mobile phase, thus the solubility of polar molecules is enhanced. This interface usually operates with a column flow of 40–50 μL/min (that is, the typical effluent from a 1 mm I.D. HPLC column). The spectral characteristics of this interface are very similar to the electrospray interface.

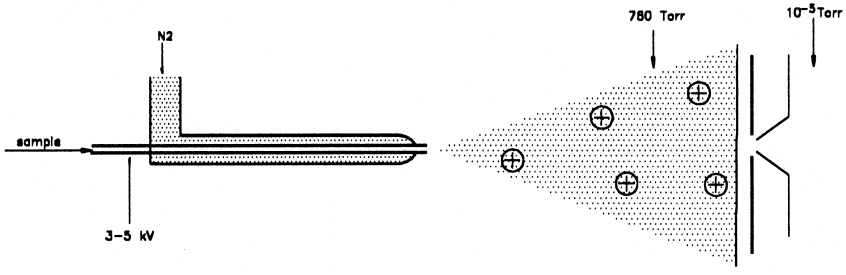


***Figure 2b.*** A schematic diagram of an ion spray ionization interface for HPLC-MS.

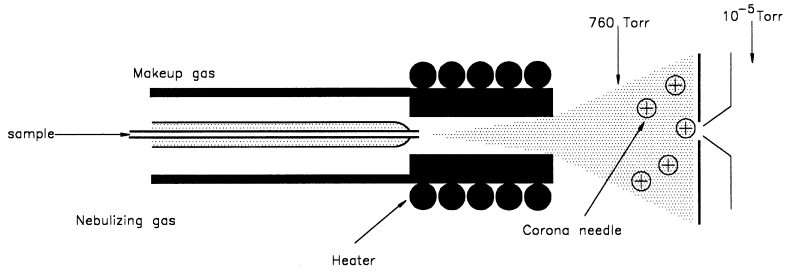


***Figure 2c.*** A schematic diagram of a thermospray ionization interface for HPLC-MS.

## Thermospray Ionization Interfaces

The **thermospray ionization interface,** shown schematically in Figure 2c, uses both heat and the supersonic jet expansion process to remove the HPLC solvent. The spray is dispensed into a region of rough vacuum, and as the jet expands, the solution droplets become smaller until evaporation occurs. It is estimated that thermospray produces approximately 90 percent vapor and 10 percent droplets. The vapor is swept away and is vented. The droplets range in size from 5 to 200 μm, and it is from these droplets that ion desorption occurs. The probe temperature must be controlled automatically to compensate for changes in mobile phase composition and velocity. The technique is usually used with ammonium acetate (a relatively volatile buffer salt) in the mobile phase to precharge the molecules in the solution. The resulting ions are then accelerated into the mass analyzer. The need for rough vacuum in the interface has a favorable consequence: it allows the application of relatively high flow rates (up to 2 mL/min) from the column into the interface. Although the thermospray method usually produces sufficient ionization, auxiliary electron impact or discharge ionization capability is usually a necessary accessory for cases where filament-off operation produces an insufficient number of ions.

Thermospray ionization is very useful in the analysis of highly functionalized polar solutes that require high water concentrations in the mobile phase. The spectra are very simple, with $(M + H)^+$ and $(M - H)^-$ ions being predominantly produced, with the protonated form favored. Ion-molecule reactions will also commonly form the $[M + NH_4]^+$ quasimolecular cluster ions, due to the presence of the ammonium acetate buffer. Molecule–anion adducts are also formed. Because of the spectral simplicity, the specificity of the spectra can be unfavorable. This approach must therefore often be further combined with tandem MS-MS instrumentation, to further fragment the daughter ions produced by the mild thermospray ionization. Because of the predominance of singly-charged ions result-

ing from thermospray ionization, larger molecules (having relative molecular masses in excess of 10,000) cannot be analyzed by this method, since this is outside the range of commercial quadrupole mass analyzers.

## SUPERCRITICAL FLUID CHROMATOGRAPHY–MASS SPECTROMETRY

Supercritical fluid chromatography (SFC) is a chromatographic technique in which the mobile phase is a fluid that is above its critical point. The most common fluid that is used as a mobile phase in SFC is carbon dioxide, although mixtures with organic modifiers are also commonly used. Both capillary columns and packed columns have been used in SFC, although the vast majority of work has been done with cross-linked polymeric stationary phases in capillary columns.



Interfacing a mass spectrometer with supercritical fluid chromatography has been a challenging task, one that achieved practical results only in the mid-1980s. The problem is very similar to the introduction of a liquid sample (from high performance liquid chromatography, for example). A large volume of carbon dioxide (the solvent) elutes from a SFC column. This solvent stream must be removed from the source. For this reason, a modification of the thermospray interface used with HPLC must be employed. This interface usually consists of a transfer line region and a restrictor region. The transfer line is a length of uncoated (and sometimes deactivated) fused silica capillary tubing (typically with an inside diameter of 25 μm). The coated chromatographic column is connected to this line with a zero-dead volume fitting. The other end of the transfer line is flame-tapered to form a restrictor with an inside diameter of between 3–5 μm, for a length of 1–3 cm. The fused silica transfer line and restrictor are contained in a stainless steel tube that is resistively heated. Often, a dual-zone temperature controller is used, one for the transfer line section and a separate one for the restrictor region. The opening of the restrictor is positioned in the source of the mass spectrometer, similar to the way that the direct interface in GC-MS terminates in the source.

The vacuum system on a mass spectrometer used for SFC-MS must be of a higher volume capacity than that typically used for GC-MS. Such vacuum systems are not found on bench top mass spectrometers, but rather on stand-alone units that accommodate a direct insertion probe in addition to gas chromatographic column interfaces. The thermospray interface from the SFC is most conveniently placed into one of the direct insertion probe positions.

The operation of the SFC-MS interface is much more complex than the operation of any of the GC interfaces. Since SFC itself is a niche technique, SFC-MS is applied only for carefully chosen specific applications. At this time, there are no commercial, off-the-shelf units available. There are manufacturers that will build such units on a per-order basis, however.

## GAS CHROMATOGRAPHY–FOURIER TRANSFORM INFRARED SPECTROPHOTOMETRY

While the mass spectrometer is one of the richest sources of information about chemical compounds, there are some deficiencies that result from the physical principle (molecular fragmentation) upon which the technique is based. Mass spectrometry will provide the relative molecular mass of the parent species and of important radical-ion fragments, but if the molecule is small or too simple to have a useful fragmentation pattern, there is little information in the spectrum. A mass spectrometer would have difficulty providing conclusive spectroscopic distinction between carbon dioxide and propane, for example. This is an important example problem, especially in the natural gas industry.

Similar situations arise in the analysis of light halocarbons used in the refrigeration industry. Here the problem of little or no fragmentation is often exacerbated by the absence of an identifiable parent ion.

Mass spectrometry also falls short in providing conclusive identification among cis- and trans- isomers. For example, the mass spectra of cis- and trans-1,2-dichloroethene are virtually identical, with differences arising only in the ion abundances. Ion abundances are an insufficient basis for identification between the two compounds. Unsaturated ring structure isomers are another problem. These are ring compounds that differ from one another only in the location of points of unsaturation on the ring. Examples of these types of compounds include 1,3-cyclohexadiene and 1,4-cyclohexadiene. The locations of ring junctions in isomeric polynuclear aromatic hydrocarbons (a very important class of priority pollutant compounds) cannot be ascertained by mass spectrometry. Examples of these compounds would be anthracene and phenanthrene.

Discerning the substitution pattern of aromatic compounds (ortho-, meta- and para-) is also not possible with mass spectrometry alone. Thus, the mass spectra of the xylenes are very similar. It is also difficult to differentiate between primary alcohols and unsaturated compounds. For example, primary alcohols, the corresponding cycloalkane, olefin and alkyl-substituted cyclopropanes give very similar mass spectra.

Another potential instrumental difficulty arises in the analysis of aqueous solutions on appropriate chromatographic columns. Large quantities of water pose difficulties for the ion sources of most small mass spectrometers. This is an important area of application, especially in biotechnology and for various chemical analyses that are based on aqueous complexant reagents such as EDTA.

In each of the above cases, the additional information of a vapor phase infrared spectrum can remove a great deal of the ambiguity in identification of eluted peaks from a chromatographic column, hence the desire to directly couple infrared capability with the gas chromatograph. It is perhaps more correct to say that the hyphenated technique is gas chromatography–Fourier transform infrared spectrome-

try (GC-FTIR). This is because the instrumentation of dispersive infrared spectrometry is unsuited for use as a chromatographic detector since of the time required to record a complete spectrum is far to long. There are 2 approaches to the interface of a FTIR to a gas chromatograph: the light-pipe flow-through interface, and the family of trapping or deposition interfaces. Both of these approaches are used to record transmission infrared spectra. The most common approach that is applied to commercial instrumentation is the light-pipe flow-through cell.

## The Light-Pipe Interface

A schematic diagram of the essential components of a FTIR instrument interfaced to a gas chromatograph with a **light-pipe** is shown in Figure 3. The light-



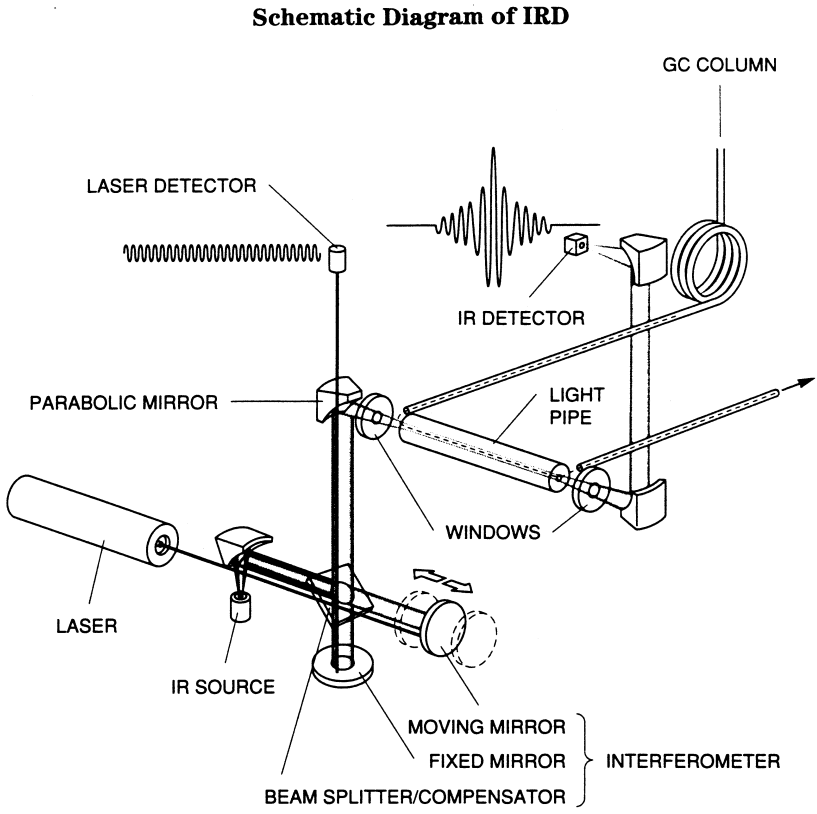


***Figure 3.*** A schematic diagram of a gas chromatography–Fourier transform infrared spectrometer system based on a light-pipe interface (courtesy of Bio-Rad Corporation).

pipe is a gold-coated quartz, glass or stainless steel tube approximately 120 mm long, with a 1 mm hole running through its length. The ends of the light-pipe are terminated with potassium chloride windows, although for applications involving aqueous solutions, zinc selenide windows are available. The gold coating inside the cavity is needed to provide a high reflectivity for IR radiation, and to provide a chemically inert surface. The pipe volume, which is usually between 90 and 120 μL, is an important operational parameter of this interface, but the individual parameters of pipe length and diameter require separate attention and specification to optimize the interface for a given column inside diameter.

The light-pipe diameter is matched to the cavity in the infrared radiation source, and it is made sufficiently small not to cause serious degradation in the chromatographic zone separation. The solid angle of the IR beam that emerges from the light-pipe is much smaller than that of the input beam. This is because of reflection losses and vignetting inside the pipe, factors that become more severe as the pipe diameter is decreased. As one can infer from the Beer-Lambert Law, the response of an IR spectrometer will depend on the number of absorbing species in the beam. The pipe length at any given diameter is therefore an important parameter. To maintain chromatographic resolution while providing reasonable absorption, the volume of the pipe should be designed to contain approximately 25 percent of a typical eluting (Gaussian-like) peak that has a full-width-at-half-height of 110 μL.

The pipe is held inside of a fitting that accommodates two high-temperature transfer lines, one that carries sample in, and one that carries sample out. Usually, the line that carries the chromatographic effluent from the light-pipe is routed back into the chromatographic oven so that it may be connected to other detectors such as a flame ionization detector. The light-pipe itself is usually maintained at 250°C, but for special applications, it is possible to increase the temperature to 320°C for short periods of time. The high operating temperature keeps the pipe clean for long periods of operation. Because window materials have a relatively low thermal conductivity, the windows can be a weak point in the light-pipe design when the pipe is operated at high temperatures. For this reason, the temperature of the interface must be uniform, and not subject to abrupt changes. Also, at higher temperatures, the pipe itself can become an infrared radiator and saturate the signal level of the detector. The light-pipe normally operates at atmospheric pressure or slightly above.

For compounds that absorb infrared radiation strongly (that is, those group frequencies that are listed as "strong" in standard correlation charts), the FTIR detector based on a light-pipe interface can provide a sensitivity of 5 ng/μL when all conditions are optimized. This is 1–2 orders of magnitude lower than the sensitivity of a typical mass spectrometer that can be interfaced to a gas chromatograph. It must be understood that the ultimate obtainable sensitivity is the result of the manipulation of many codependent physical and instrumental variables. These include the efficiency of the sample transfer process, the chromatographic peak

width, the alignment and focus of the infrared beam, and the condition and range of the infrared detector, in addition to the extinction coefficients (or absorptivity) of the compound being measured.

## The Deposition Interface

The other major type of interface that is commercially produced is the **trapping or deposition interface**. Because these devices operate at low temperatures, they are sometimes called the **cryotrapping** or **cryogenic interfaces,** and one will sometimes see it described as the **buffer memory** technique. These devices operate by depositing the chromatographic effluent onto a moving plate of a material that is transparent to infrared radiation (usually zinc selenide). The plate is cooled to liquid nitrogen temperature with a braided copper cold finger. A computer-controlled moveable stage sweeps the plate in the x-y plane such that the chromatographic effluent is deposited as a continuous line of spots, each having a width of approximately 100 μm. The stage movement is controlled to provide a spot thickness appropriate for good spectral measurement and quantitation, without sacrificing chromatographic resolution.



Typically, chromatographic elution bands that are separated by 2 sec can be deposited as separate spots, a displacement that is adequate for most mixtures. After sample components are deposited, the moving stage brings the line of sample into the infrared beam, which is focused with the standard Schwartzchild optics that are used in IR microscopes. The interferometer processes spectra measured from the plate in the same way as with the light-pipe interface, with detection provided by a standard mercury-cadmium-telluride (MCT) cell. This cell is cooled to liquid nitrogen temperature with a small Dewar flask containing enough cryogen for approximately 18 hrs. of continuous operation. The cold plate and moving stage operate in a vacuum chamber maintained at approximately $10^{-5}$ torr. This is needed to prevent the deposition of atmospheric contaminants.

This type of interface is more suited to trace analysis work than is the light-pipe. Under ideal conditions, strongly absorbing species can be detected at a level of 50 pg/μL. This is close to the sensitivity obtainable with the mass spectrometer. Similar to the earlier line of discussion, this figure is for a system that has been optimized for high sensitivity. The factors that will affect sensitivity of the deposition approach include those discussed above for the light-pipe approach, but will also include the speed and efficiency of the deposition process.

## Matrix Isolation Deposition

A variation of the deposition method is the matrix isolation trapping interface. In this technique, the sample spots are deposited on a gold-plated copper disk

that is cooled to between 11 and 12 K using a closed cycle helium refrigerator. The chromatographic carrier gas used for this method consists of 98 percent helium, with the balance being argon. The argon will solidify to form the isolation matrix at the deposition temperature, while the helium will be swept away by the vacuum. The chromatographic effluent is typically deposited as a 0.3 mm band, and reflection-absorption infrared spectra are recorded. Matrix isolation is useful for simplifying infrared spectra by eliminating or reducing intermolecular interactions. Matrix isolated spectra contain fewer absorption bands than either non-isolated condensed phase spectra or vapor phase spectra. This makes comparison with library spectra difficult, however, since very few matrix-specific, isolated spectra are available in databases. Since the peaks are deposited in a small and highly focused line, the sensitivity and selectivity is higher than with conventional deposition. It is considerably more costly, however.



## GC-FTIR Operation

The operation of the interferometer used for chromatographic detection is similar to that of standard bench top IR units. The speed of the interferometer system allows infrared spectra to be obtained "on the fly" at the rate of approximately 12 spectra or scans per second. The moving mirror path length needs to be only 1.3 mm to provide a spectral resolution of 8 $cm^{-1}$. Spectra are provided from 4000 to 600 $cm^{-1}$ when standard potassium chloride optics are used in the device. The infrared radiation detector employed with the interferometer is usually the MCT cell.

The information from a GC-FTIR system can be presented and manipulated in a number of ways. The initial chromatogram that is presented is a total response chromatogram that contains absorption information covering the entire mid-infrared region. The total response chromatogram is analogous to the total ion chromatogram presented by the GC-MS instrument. Construction of this chromatogram is a simple computational task, since all wavelengths are measured simultaneously by the interferometer. When used for quantitative analysis, the total response chromatogram will provide a linear dynamic range of $10^3$. It is also possible to generate single wavenumber chromatograms, selecting strong functional group responses that are germane to a particular analysis. These chromatograms are also called functional group chromatograms. The chromatograms can be viewed in real time, or reconstructed after a chromatographic analysis.

It is important to remember that the infrared spectra presented by GC-FTIR are vapor phase spectra, and will differ markedly from spectra measured in the condensed phase. The differences will be most pronounced for small molecules and for molecules that are capable of a high degree of intermolecular interactions such as hydrogen bonding. Bands that arise from hydrogen bonding species, such

as the -OH bands centered at approximately 3500 $cm^{-1}$, may be very weak or absent in vapor phase spectra. Species without hydrogen bonding will show differences because of the absence of the reaction field that is present in the higher density of the condensed phase. An example is the strong carbonyl (C=O) stretching band, which will shift to higher wavenumbers than those obtained when the spectra are measured in solution. Vapor phase spectra usually show less fine structure and band splitting than corresponding condensed phase spectra. These differences must be borne in mind when interpreting the results from GC-FTIR analyses. One important advantage of vapor phase spectra is the absence of the sloping baseline that is often present in condensed phase spectra.

The infrared spectra measured for the chromatographic peaks can be interpreted for functionality by the analyst, or compared with high quality library spectra with a search and match routine. This is a very valuable technique, although the infrared spectra libraries that are available are not as extensive as those available for mass spectra. Current libraries contain approximately 10,000 spectra, a number that seems small when compared to the number of mass spectra available in databases. One must remember that the Gaussian/Lorentzian bands of infrared spectroscopy are much more difficult to deal with than the two parameter data presentation (ion current intensity against ion mass/charge) of mass spectrometry. The most common method applied in the search and match routines is the normalization of all peak absorbances to the absorbance of the most intense peak. The comparison is then made against the library spectra that have been similarly normalized. This approach works very well for vapor phase spectra, because of the absence of the sloping baseline mentioned earlier.



When a library search of IR spectra presents a series of possible matches (along with the match quality factors), they are always compounds that are at least related to the unknown and to one another. This is not usually the case with the matches obtained from the search of mass spectral databases. When the infrared spectrum of the unknown is in fact in the IR library, it will be retrieved as the most likely match 95 percent of the time. This is in contrast with the 75 percent figure for mass spectral database searches.

## SUPERCRITICAL FLUID CHROMATOGRAPHY–FOURIER TRANSFORM INFRARED SPECTROSCOPY

The motivations for wanting to interface infrared spectrometric instrumentation with supercritical fluid chromatography (SFC-FTIR) are similar to those discussed for GC-FTIR. The technical problems are somewhat different due to the mobile phase that is usually employed (carbon dioxide with organic modifiers) and the operational conditions of SFC.

Carbon dioxide shows two strong absorptions in the mid-infrared region. There is an asymmetric stretching band that is wide and intense, centered around

2350 $cm^{-1}$, and another wide, intense band between 3650 and 3584 $cm^{-1}$. The remainder of the spectrum is relatively free from other absorbances at low pressures. As the pressure of the fluid is increased, however, Fermi resonance bands arise between 1200 and 1400 $cm^{-1}$. The addition of organic modifiers to carbon dioxide further complicates the spectrum. These spectral aspects of the carrier fluid make the light-pipe approach unfavorable in SFC-FTIR, although xenon, which is totally transparent in the infrared, is sometimes used as a solvent. The high cost of xenon and its poor solvation properties prohibits the widespread use of this fluid, however. Some applications of the light-pipe in SFC-IR have been reported, but they involve very short path length pipes (typically having a volume of 0.8–1.4 μL) that provide marginal sensitivity.

The deposition interface method is most commonly applied to SFC-FTIR. The supercritical fluid is easily volatilized at the capillary column exit, and sample can be collected either on a potassium bromide or zinc selenide plate (as with GC-FTIR) or on potassium chloride powder, for diffuse reflectance measurements. To collect sample, the moving plate or powder bed is positioned after the restrictor exit of the chromatographic column. Since there is no interference from the mobile phase using these deposition techniques, it is possible to obtain usable spectra with nanogram quantity samples.



## GAS CHROMATOGRAPHY–FOURIER TRANSFORM INFRARED SPECTROSCOPY–MASS SPECTROMETRY

Since the information that is provided by infrared spectroscopy and mass spectrometry can be complementary in many qualitative analysis circumstances, development of the triple-hyphenated technique of gas chromatography–Fourier transform infrared spectroscopy–mass spectrometry (GC-FTIR-MS) was inevitable. There are two approaches to GC-FTIR-MS: the parallel configuration, in which the chromatographic column effluent stream is split and directed into the FTIR and MS separately, and the series configuration, in which the effluent passes first through the light-pipe of the FTIR, and is then directed into the source of the MS.

The parallel configuration is shown schematically in Figure 4a. The column exit is connected to a splitter consisting of fused silica capillary tubing of different internal diameters. The split ratio is usually 10:1, with the bulk of the flow diverted into the light-pipe. The retention times of the MS total ion chromatogram will lead those of the FTIR total response chromatogram by 1 to 2 sec, but otherwise the two chromatograms are very similar. This approach produces minimal chromatographic peak broadening, and although the splitter is a fragile device, the approach has proven to be reliable.

The series configuration is shown schematically in Figure 4b. All of the chromatographic column effluent will flow into the light-pipe before flowing into

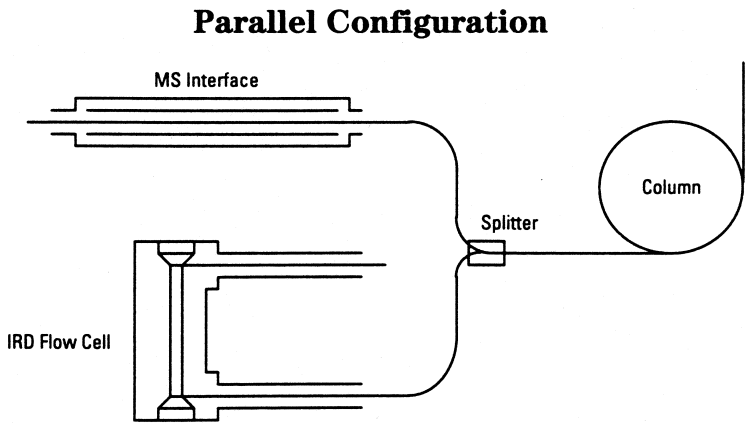


*Figure 4a.* A schematic diagram of a parallel configured gas chromatography–Fourier transform infrared spectroscopy–mass spectroscopy system (courtesy of Bio-Rad Corporation).



the mass spectrometer source. There is an open split located at the exit of the light-pipe to divert approximately 20 percent of the flow into the MS. The split ratio is determined by considering the MS pumping capacity and the total column flow rate. The retention times of the MS total ion chromatogram will lag those of the FTIR total response chromatogram by 5 to 6 sec. The peaks on the total ion chro-

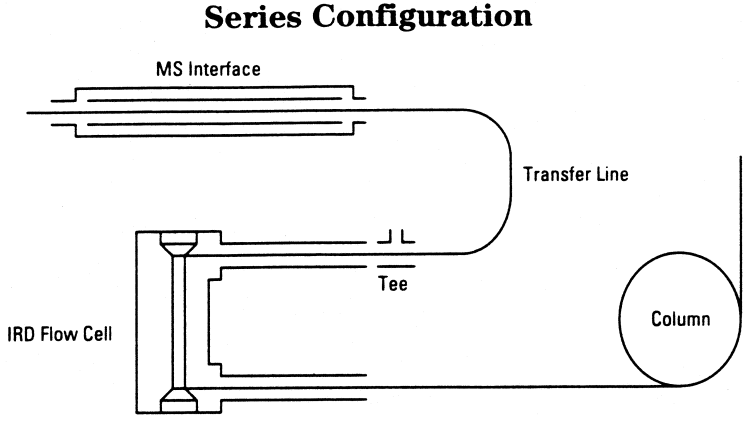


*Figure 4b.* A schematic diagram of a series configured gas chromatography–Fourier transform infrared spectroscopy–mass spectroscopy system (courtesy of Bio-Rad Corporation).

matogram will experience significant broadening, with matching peaks having widths that can be 1.5–2-fold those on the total response chromatogram.

## GAS CHROMATOGRAPHY–ATOMIC EMISSION SPECTROSCOPY

The combination of atomic emission spectroscopy (AES) with gas chromatography offers a very good element-specific survey analysis method that is helpful in the interpretation of subsequent analyses that may be performed with GC-MS and GC-FTIR.

Atomic emission is the release of energy (as light) after an atomic species has been excited or promoted to an energy level above the ground state by some applied stimulus such as thermal excitation. When the atomic spectra of molecules are desired, it is first necessary to break the molecule into the constituent atoms before excitation. The resulting atomic spectrum (presented as intensity plotted against wavelength) is a series of sharp lines that are element-specific. Thus, carbon emission produces a line at 193.1 nm, sulfur at 180.7 nm, and so on, for each element. When an atomic emission spectrometer is used to measure the carbon and hydrogen lines, it can serve as a universal detector for organic compounds.

A schematic diagram of a GC-AES system is provided in Figure 5. The chromatographic effluent emerges from the column exit and enters a discharge chamber. In this area, a plasma will break the separated components into the constituent atoms and raise them to their excited states. The light emitted when these excited state atoms decay back to the ground state passes through a window, where it is focused by a lens system into the spectrometer. The light emitted by the excited species in the plasma is collected by a mirror, which directs it to a rotating holographic grating. The grating separates the light spatially by wavelength, and a mirror focuses specified linewidths onto a moving photodiode array.

The excitation in AES is usually done by placing the sample in an intense heat source such as a flame, spark (AC), arc (AC or DC), or plasma. While atomic emission spectroscopy can be performed on samples presented as gases, liquids or solids, when AES instruments are interfaced to a gas chromatograph, the samples are maintained in the gas phase upon elution from the column; the interface is essentially a direct flow from the column exit. Microwave-induced plasma is a good practical excitation source for gaseous samples. The plasma is produced in a gaseous medium by a standing wave that is maintained inside of a resonant cavity. The plasma gas, which is usually helium but sometimes argon, is supplied to the discharge tube at between 20 and 100 mL/min. To produce a good chromatographic peak shape and to prevent the deposition of carbon particles inside the discharge tube, reagent or "scavenger" gases are also applied. These are usually hydrogen and oxygen. The relative flow rates of each reagent gas depends on the

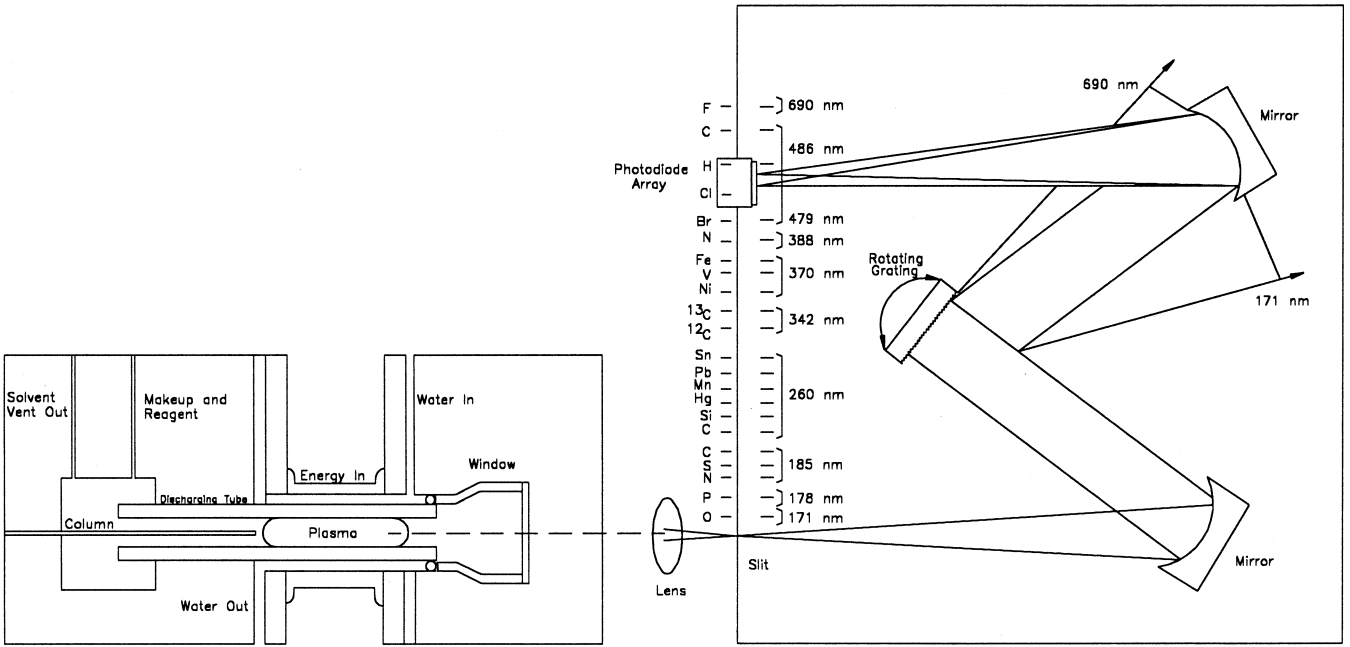


***Figure 5.*** A schematic diagram of a gas chromatography–atomic emission spectroscopy system (courtesy of Hewlett-Packard Corporation).

individual application. Despite the use of these reagent gases, one must usually replace the discharge tube frequently (every 6–8 weeks during periods of heavy usage).

The measurement will allow detection of eluted components at concentrations between 1 ng and 0.1 pg, depending on the element involved. The linear dynamic range of the AES as a GC detector is $10^3$.

The major applications of GC-AES include prescreening of samples for GC-MS and GC-FTIR analyses, and the generation of element-specific chromatograms. For prescreening purposes, one can measure, for example, a nitrogen elemental chromatogram; if no peaks are found, then one can eliminate all nitrogen-containing compounds that result from a GC-MS library search.

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