Separation Science and Technology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713708471

Gas Chromatography: A New Industrial Process of Separation. Application to Essential Oils

R. Bonmati[a]; G. Chapelet-letourneux[b]; G. Guiochon[c]
[a] ELF PETROLEUM CORPORATION, NEW YORK, NEW YORK, USA [b] PRODUCTION SCALE GAS CHROMATOGRAPHY, ST SYMPHORIEN D'OZON, FRANCE [c] LABORATORY OF ANALYTICAL PHYSICAL CHEMISTRY, ECOLE POLYTECHNIQUE, PALAISEAU-CEDEX, FRANCE

To cite this Article Bonmati, R. , Chapelet-letourneux, G. and Guiochon, G.(1984) 'Gas Chromatography: A New Industrial Process of Separation. Application to Essential Oils', Separation Science and Technology, 19: 2, 113 — 155
To link to this Article: DOI: 10.1080/01496398408060651
URL: http://dx.doi.org/10.1080/01496398408060651

SEPARATION SCIENCE AND TECHNOLOGY, 19(2 & 3), pp. 113-155, 1984

Gas Chromatography: A New Industrial Process of Separation. Application to Essential Oils

R. BONMATI

ELF PETROLEUM CORPORATION, USA
NEW YORK, NEW YORK 10019

G. CHAPELET-LETOURNEUX

PRODUCTION SCALE GAS CHROMATOGRAPHY
ELF FRANCE, BP 22
69360 ST SYMPHORIEN D'OZON, FRANCE

G. GUIOCHON

LABORATORY OF ANALYTICAL PHYSICAL CHEMISTRY
ECOLE POLYTECHNIQUE
91128 PALAISEAU-CEDEX, FRANCE

INTRODUCTION

Originally, chromatography was designed as a preparative technique for biological organic chemistry (*1*). Liquid chromatography was the preferred method, and people used a vertical column filled with silica or alumina through which a carrier liquid was percolated. The output liquid or eluent was collected in many different fractions which were then analyzed, concentrated, and used as needed. The weight of the vertical column of liquid was the only driving force which drastically limited the separation power and the productivity of the technique (*2*)

Around 1952, James and Martin conceived the idea of using a gas as the carrier fluid, and gas–liquid chromatography came into being as a powerful analytical tool (*3*). In this technique a gas flow percolates through a column packed with an inert, porous support (usually a diatomaceous product) impregnated with some suitable nonvolatile liquid. Carried by the gas, the

 0149-6395/84/1902-0113$3.50/0

components of the mixture are eluted in the order of increasing equilibrium constant of dissolution in the stationary liquid. Gas chromatography underwent an extremely rapid and considerable growth because of its inherent advantages of precision, speed, and convenience, and because it was the answer to the most pressing industrial need of the petroleum and chemical industries at the time: quality control.

Right from the beginning, the possibility of using gas chromatography as a process for the total separation, on an industrial scale, of the individual components of mixtures was recognized (*4*). The use of large diameter columns and the condensation of the separated bands at the column outlet were soon attempted. In spite of the apparent simplicity of this concept, the results of efforts in this direction by numerous researchers were disappointing because serious theoretical and practical problems were overlooked (*5*).

What happened was this: On the one hand, the resolution ability of columns packed by conventional techniques decreased with increasing diameter (*6*). The results of these experiments were taken as a natural happening, and no or little effort was made to understand the reasons for this phenomenon. On the other hand, no valid theory of chromatography at finite concentration was available to permit process optimization. Furthermore, various practical difficulties were encountered, due mainly to the discontinuity of operation since the charge injections and the condensation of the separated vapors have to be sequential. Accordingly, the corresponding units (vaporizer and traps) work in a transitory state, not in a steady state as do most comparable units in the chemical industry. Finally, the research was carried out mostly by analytical chemists whose misconceptions of chemical engineering led to troubles.

These problems and the disappointing results of the initial test runs have delayed the practical development of the process for uses other than in the laboratory, at gram-level production for research purposes, or for applications where the cost of the product is negligible compared to the overall cost of the project.

Eight years of research work by a task force of chemical engineers and chromatography specialists has enabled us to master the problems encountered in trying to apply gas chromatography to industrial separations, and to arrive at the following improvements:

(a) A better knowledge has been gained about the design and packing of chromatographic columns. A study of column packing techniques has shown that resolution capability need not decline with column diameter to any significant degree. Experimental studies involving the packing of a large number of columns of between 4 and 40 cm in diameter confirm this finding.

(b) Accurate theoretical models of the chromatographic process at finite concentration are now available (*7–9*). These make possible computer simulation and permit the optimization of the separation process and its design and operating parameters (*10, 11*).

(c) All major technological problems have been solved, especially the optimization of the feedstock vaporizer and the traps under thermal transient state conditions (*12*).

(d) We understand the limits of practical uses of chromatography as compared to normal and extractive distillation (*12*). The former is better suited for the separation of closely related compounds where distillation is not practical and of prohibitive cost. Furthermore, gas chromatography permits the extraction of one or several compounds from a complex mixture without separating the other components.

Two chromatographic units with columns of 125 mm (5 in.) in diameter have now been in use for several years. They function well with excellent reliability, easy clean-up after a batch is finished, and fast restart with new operation conditions for another batch. Depending on the nature of the feedstock and the character of the separation to be carried out, their production capacity varies from 2 to 15 tons/year.

A number of columns of larger diameters (300 and 400 mm) have been tested successfully, and an industrial unit whose yearly capacity ranges between 20 to 150 tons/year is now in operation in Jacksonville, Florida.

The operating principles and the basic characteristics of such units which distinguish them from previous process concepts and from other methods of physical separation will be described briefly. The most important theoretical results obtained in our work will be given, as well as some principles of optimization which can be derived therefrom.

Finally, we present a few examples of successful separations to illustrate the technical possibilities and the economic aspects of the process.

I. PRINCIPLE OF A CHROMATOGRAPHIC SEPARATION UNIT

An industrial chromatographic process unit is basically different in its design and operation from an analytical apparatus because its purpose is the production of pure compounds and not the collection of data. In analytical application, the components of the mixture analyzed are identified from the elution time of the corresponding peak on the detector signal and they are quantitized from the peak area. The separated compounds are discarded; only the information content of the detector signal is important. To optimize the amount of information collected from such a signal, one needs to inject

small samples so the partition process and the detector both perform linearly, and total separation of the peaks of all compounds of interest is achieved.

In preparative chromatography the detector signal is used merely to control the performance of the unit. Interference between the bands of two compounds is not important as long as the production has been maximized and the amount of mixture to be recycled, obtained by separate trapping of the interference zone, is moderate. The concept of the industrial process of chromatography, on the other hand, is similar to that of a small-scale laboratory apparatus because of the identity of the process principle as shown in Fig. 1.

Purified carrier gas from the recycling unit is heated at column temperature and percolates the column at a carefully controlled flow rate. During injection periods the liquid feedstock is pumped to the vaporizer-injector subunit 3 from which an homogeneous vapor mixture flows to the chromatographic column 4 where separation takes place. Although the feedstock is injected to the unit in pulses typically a few tenths of seconds every few minutes, the vaporizer-injector functions in such a way that the feed rate to the column and the concentration of the feedstock in the vapor mixture are maintained constant during the injection time and the pulses have very steep boundaries. The feed rate (usually 1 to 5 g/s for units of 2,000 to 15,000 kg annual capacity) and the duration of the injection (10 to 30 s or sometimes longer) depend on the nature of the specific separation.

In the column the separation of the various constituents of the feedstock occurs as follows: each component carried along by the gas, which percolates through the column, moves at a different velocity according to its solubility in the stationary liquid phase which impregnates the support that constitutes the column packing. An appropriate choice of liquid phase assures the separation of the different components of the mixture depending on their vapor pressure, molecular volume, polarity, etc. This separation mechanism is identical to that realized in analytical gas-liquid chromatography, although the concentration of the vapors in the carrier gas is now large and the solubility isotherm can no longer be considered as linear. Hence the peaks have band shapes characteristic of overloaded columns and are not symmetrical. Adsorption on the support may be considered as less important than in analytical GC, as long as it is physical adsorption, but the support should be chemically inert and specially treated to prevent any catalytic effect on either the stationary phase or the components of the feedstock because the presence of small amounts of products of a catalytic reaction in the purified products of the unit could have catastrophic consequences. The volume of liquid coating is smaller than about half the internal porosity of this support in order to prevent excessive swelling of the solution when a large

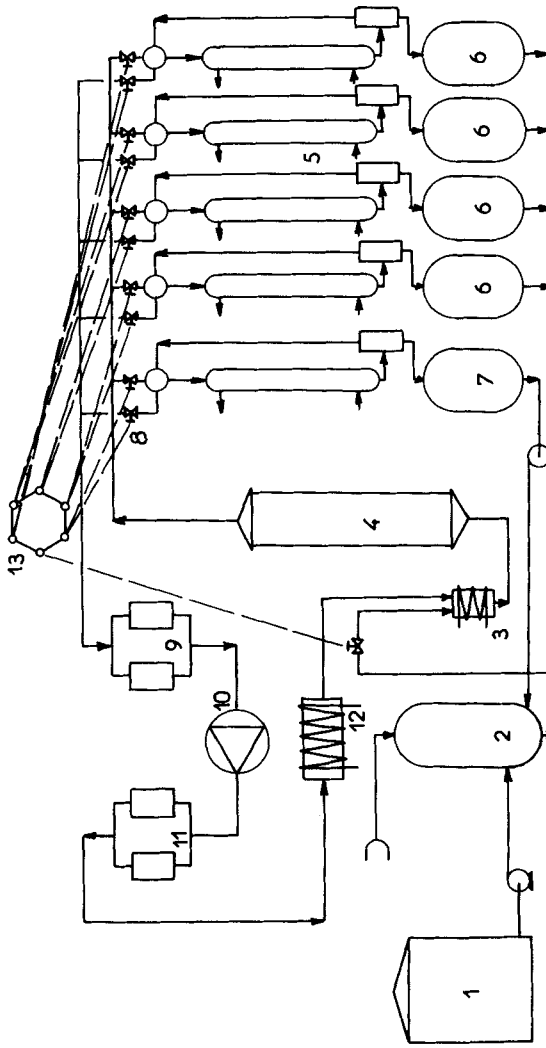

FIG. 1. Basic flow diagram of the chromatographic process: (1) Feed storage, (2) Feed vaporizer, (3) Injector, (4) Chromatographic column, (5) Condensers, (6) Product collection, (7) Recycle products, (8) Valves, (9) Carrier gas cleaner, (10) Compressor, (11) Desoxygenation of carrier gas, (12) Carrier gas preheater, (13) Electronic programmer.

solute zone passes and sweating of this solution out of the particules, which may result in the eventual destruction of the column (*11*).

At the column outlet the different fractions produced are sent to individual traps, 5, where they condense and are stored, 6. Depending on the product, either cooling water or a refrigerated fluid is used to remove the condensation heat. Incomplete condensation due to either excessive vapor pressure or the formation of fog, which might cause loss of products, is avoided through careful study of this heat exchanger-condenser. Typical condensation yields exceed 98.5% for our industrial units. Intermediate zones containing mixtures of compounds are collected in a separate trap, 7, and recycled to the feedstock, 2.

The process is, obviously, cyclic. The frequency of injections and of collection of the individual product fractions is determined by the width of the elution band at the column outlet. All the necessary operating functions to be carried out sequentially, namely the injection of the feedstock and the opening and closing of the product receivers through the high temperature valves 8, are controlled by an electronic programmer functioning on cycle times, 13.

Helium, or better still, hydrogen, is used as the carrier gas. For reasons of economy due to the very large flow rate of the carrier gas inside the unit, this gas is recycled. Taken at the outlet from the product receivers, it flows through an activated charcoal bed, 9, where traces of noncondensed product vapors are removed, and it is returned at the desired pressure to the vaporizer-injector by a group of compressors, 10, through a desoxygenation column, 11, and a heater, 12, which brings it to column temperature. Two adsorber vessels are provided for alternate service. It is of major importance for long column life at moderate or high temperatures to keep the oxygen concentration of the carrier gas low. Thus, for example, the feedstock has to be stripped of dissolved air by bubbling an inert gas through the storage tank, 1.

In the case of operation at reduced pressure, an additional compressor maintains the receivers at the desired pressure.

II. PROCESS CHARACTERISTICS

The process of gas–liquid chromatography, as described above, has a certain number of features which give it an unusual position among known processes for separating individual compounds.

We shall describe here the most important of these features which are the large efficiency and the high degree of selectivity of the columns, and the simplicity of control of the units and their flexibility.

Column Efficiency

The most essential part of the unit is the column. The simple idea of increasing the column diameter to increase the throughput proved to be impractical in earlier works because of the great difficulty encountered in achieving a homogeneous column packing which would be free of voids, short-circuit passages, or regions of high or low permeability due to fluctuations of the packing density. This particular problem grows with increasing column diameter. It results in low column efficiency, an efficiency which decreases with increasing column diameter, because solute zones are carried down the column faster in the parts of the column where the permeability is larger whereas the radial equilibrium proceeds only by diffusion so the time needed to achieve equilibrium across the column increases with the square of its diameter, while the size of regions of the column where high or low packing density fluctuations occur also increases with column diameter. This phenomenon has baffled chromatographers for years (6, 13).

To characterize the column efficiency, we commonly use the number N of theoretical plates and the height equivalent to a theoretical plate (HETP), which is the ratio of column length L to N ($H = L/N$). Within some limits H characterizes a column and its operating conditions (gas flow rate, sample size). As the signal obtained for the injection of a small narrow plug of a pure compound is most often very nearly a Gaussian curve, the conventional definition of N is $N = (t_R/\sigma)^2$, where t_R is the retention time of the plug and σ is its standard deviation. To achieve a certain degree of separation between the eluted bands of two compounds, one needs a column characterized by a certain number of theoretical plates, N. The shorter the column, the faster the analysis and the larger the production, hence the interest of achieving the preparation of columns with small H values.

To overcome the decrease in column efficiency at large diameters, the idea of using an alternative procedure to secure good mixing of the gas stream was suggested. In this context, ABCOR proposed and patented the idea of using a baffled column (*14, 15*). Experience proved that good mixing was even more difficult to achieve that way and that design and construction of the baffles were very tricky. Baffled columns were better than poorly packed columns, but far less good than conventional packed columns used in analytical gas chromatography (*16*).

As no theoretical consideration could explain the decrease of column efficiency with increasing diameter (*17*), we preferred to search for a method to achieve a homogeneous column packing. A systematic analysis of the influence of the parameters of vibration and shock on the packing quality was

made by using appropriate means of characterizing and measuring the packing heterogeneity (texture analysis).

The result of this study was the development of a proprietary packing technique which permits a considerable improvement of column efficiency at large diameters, as shown in Fig. 2 where the variation with the carrier gas flow velocity of the HETP values of columns of 125 mm diameter packed with various methods is plotted. As usual, these plots have an hyperbolic shape with a minimum value (*18–20*). Another characteristic feature is that usually the lower the minimum plate height, the larger the velocity at which it occurs. Thus an increase in column performance permits the use of a shorter column at a faster flow velocity to achieve a given separation, and the production is considerably enhanced (*11*).

Thus, Curve 3 in Fig. 2 indicates that it is possible to achieve HETP values in the order of 0.95 to 1.25 mm, corresponding to between 800 and 1050 theoretical plates per meter of column length, for columns of between 12 and 40 cm in diameter.

Analytical columns packed with the same stationary phase have between 1300 and 1500 plates per meter. We are of the opinion, however, that a significant part of this loss is not due to inhomogeneous column packing but to end effects. The effect of the flow pattern at both ends has to be minimized if higher efficiency is to be reached, which has not yet occurred in practice.

Theory indicates that under the conditions achieved with our packing technique the column efficiency (HETP) no longer is a function of the column diameter but solely of the particle size of the packing particles. This is illustrated by Curves 3–5 in Fig. 2. Approximately the same separation efficiency was observed over a wide range of gas flow velocities for column diameters of 125 to 400 mm during our tests. The size of the packing particles remained unchanged.

Figure 2 also shows that the column can be operated at large carrier gas velocities without a significant loss of separation efficiency. Thus, a marked increase of production capacity is possible. This is one of the interesting results of column performance improvements.

The large diameter columns (30 and 40 cm i.d.) described in Fig. 2 were packed by using equipment designed to pack the 12.5 i.d. columns of the pilot plant. This equipment, which was slightly underdesigned for these large columns (a 40-cm i.d. 1.50 m long column contains 100 kg of stationary phase; a 12.5-cm i.d. 1.50 m long column contains only 10 kg), was replaced by a bigger one to prepare the column for use in an industrial unit (*21*). The maximum efficiency was 1600 plates; operation of the column at a 17-cm/s outlet velocity still gives more than 1200 plates. The production of a compound of given purity per unit surface area of column cross section is

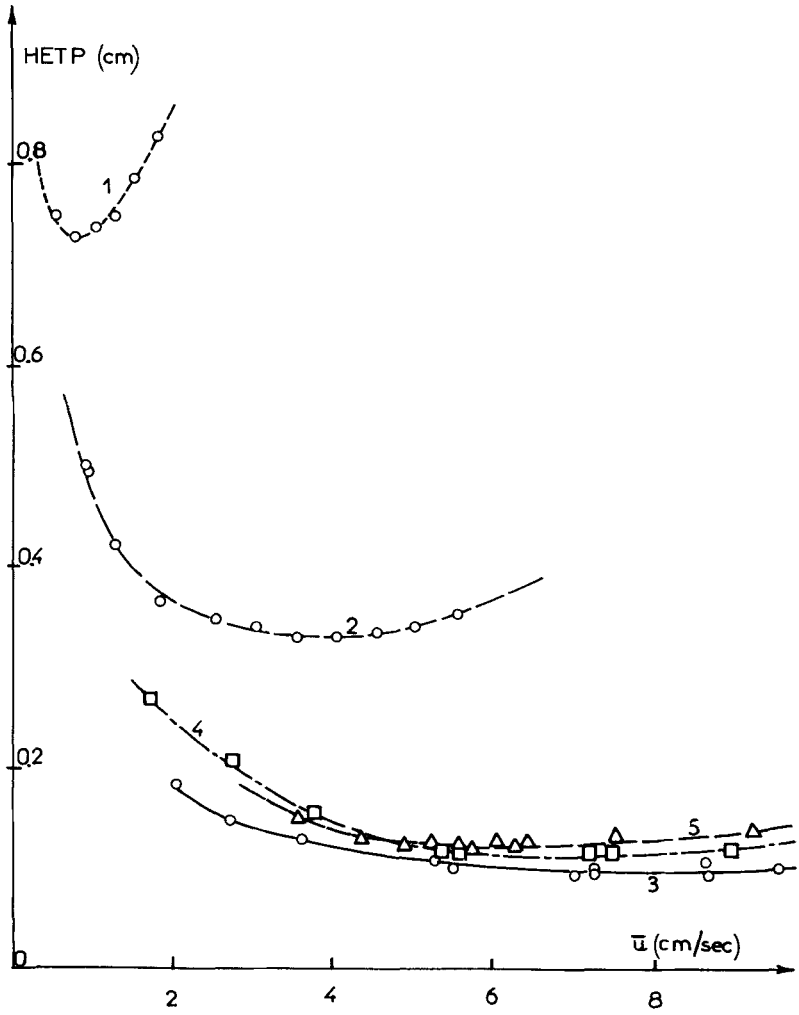

FIG. 2. Separation efficiency of large diameter columns. Packing technique: (1) Simple gravity filling, (2) Strong vibrations during packing, (3 to 5) Vibrations and shocks of controlled intensity during packing. Column diameter: (1 to 3) 125 mm i.d., (4) 300 mm i.d., (5) 400 mm i.d. Column length: (1, 2) 3.0 m, (3–5) 1.50 m. Packing material: Chromosorb PNAW, 60–80 mesh, coated with 20% (w/w) squalane. Solute: Isoprene. Temperature: (1, 2) 35°C, (3 to 5) 40°C.

better for a large diameter column than for a laboratory-scale one (cf. Fig. 3), which confirms the good efficiency of the packing.

The high column efficiency which results from fast mass-transfer in the column is associated with a large optimum velocity, so the same separation characterized by a specific number of plates can now be achieved with a shorter column operated at a higher flow rate; production is increased on both counts.

Table 1 gives evidence of the improvement in separation efficiency resulting from the use of chromatographic columns prepared in accordance with the ELF/SRTI packing technique as compared with a baffled column (*21*). The separation of α/β-pinene was chosen for this presentation in spite of its lack of practical interest because this mixture is the only one, to our knowledge, for which sufficient test data have been published to permit comparison.

Table 1 shows that the processing capacity, at similar product purity, is greatly increased when using a column prepared in accordance with ELF/SRTI packing technique. Also, the larger efficiency permits the use of a

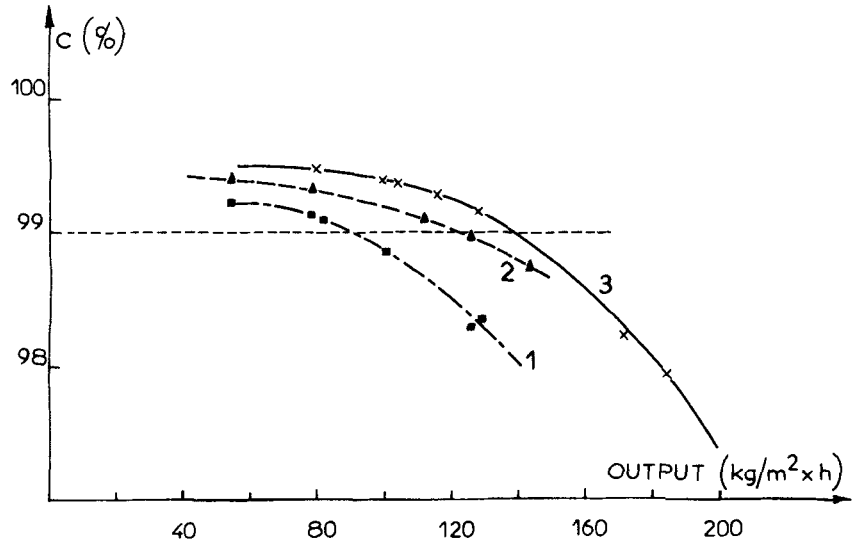

FIG. 3. Scaling up of the production of large-scale preparative chromatographic units. Plot of the purity of the linalol produced (C) as a function of the output (production per unit surface area and time). In all cases the carrier gas velocity is 15 cm/s, the column temperature is 180°C. Laboratory scale unit: Column length 2 m, diameter 4 cm, carrier gas flow rate 0.6 m^3/h. Pilot plant unit: Column length 1.5 m, diameter 12.5 cm, carrier gas flow rate 6 m^3/h. Industrial unit: Column length 1.5 m, diameter 40 cm, carrier gas flow rate 66 m^3/h.

TABLE 1
Separation of α/β-Pinenes. Comparison of performances

Principal features	Previous test results (*21*)		Chromatographic process ELF-SRTI	
Column:				
Internal diameter (cm)	10	30.5	12.5	40
Length (m)	2.7	2.7	1.5	1.5
Internal arrangement	With baffles		No baffles	
Minimum plate height (mm)	4		1.1	
Plate number at operating velocity	450		750	
Programming of trap valves	From peak deflection		By timer at preset delay after injection	
Carrier gas:				
Nature	Helium	Helium	Helium	Hydrogen
Average flow velocity (cm/s)	9.2	—	9.5–10	13
Temperature (°C):	160	160	160	160
Cycle time (s)	80	—	80	60
Purity of α- and β-pinene obtained (wt%)	98.6 (α), 98.5 (β)		99.1 (α), 98.8 (β)	
Throughput (feed) rate (kg/d)	19	160	40	540

larger injection time at each cycle, hence the introduction of a larger sample.

Selectivity

The gas–liquid chromatographic process is characterized by the efficiency of the separation and its great selectivity which is achieved by the selection of a suitable stationary phase. A choice of efficient, stable liquids is available.

Special efforts have been made to prepare stationary phases stable at high temperatures. They have resulted in the development of a nonpolar liquid phase which can be used up to 280°C with column lifetimes exceeding 2 years (*22*) and of several polar phases.

The process permits the selective extraction of one or several impurities from a feedstock of complex composition in one single operation without complete separation, even if the impurities occur at very low concentrations (of the order of ppm). The charge remains unchanged; it does not undergo deterioration. The residence time in the chromatographic column is only a few minutes. The packing is an excellent scavenger of free radicals, so compounds that cannot be distilled can be chromatographed. In fractional

distillation, when the separation requirements become severe, a similar operation might require the use of two and possibly more fractionating columns. The performance of chromatographic separation is illustrated by numerous examples described earlier or in Section IV below.

Simplicity of Operations: Automation

An industrial process, in order to be efficient, must be operated simply and automatically. Most of the solutions proposed previously involved sophisticated systems of automatization which required service signals generally obtained from the inflection points of individual peaks or made use of the times at which the detector signal reached a given preset value. An additional logic was needed to determine whether the signal was actually increasing or decreasing.

Our experience demonstrated the inadequacy of this solution for preparative gas chromatography, because the main bands are often incompletely resolved or not resolved at all. We therefore chose a more rudimentary but more dependable solution which calls for a programmed electronic control on cycle times for the injection and sequential receiver opening steps.

This system is practical only if the retention times are reproducible. Fluctuations or drifts, even at a slow rate, play havoc with the proper functioning of the scheme. Therefore, carrier gas flow rate and column temperature must be controlled carefully, with tight specifications.

With the process described, fluctuations of retention times are kept below 0.1%, which is quite satisfactory in most cases. Since the deviation during 24 h is less than 0.1%, continuous operation can be achieved even without supervision during night hours. Safety devices could place the unit on standby in case one operating parameter did not meet specifications. The actual signal corresponding to the current injection is displayed on a screen together with a reference chromatogram kept in memory and obtained after the last adjustment of the unit parameters. A third curve shows the difference between the actual chromatogram and the reference, which makes it easy to see whether the unit is operating within its specification. In practice, only minor fluctuations of the amount of injected material are seen. Another control is provided by automatic GC analysis of the product trapped during each cycle.

When constancy of the retention times is assured, the principal advantages of operating on a time cycle base are:

The opening and closing of a product receiver can occur on the same side (positive or negative slope) of a band. This is impossible for other control schemes based on detector signals obtained at a column outlet because it

needs either a change in slope sign between opening and closing or a sophisticated logic system. It is therefore possible to separate different fractions easily at the beginning, the center, and/or the end of a band and to obtain pure products from unresolved bands. This feature is especially useful when deformed peaks occur as a consequence of the important feedstock loads necessary when maximum production capacity is wanted. In turn, this feature permits the easy operation of overloaded columns for large production.

The system performs well under all conditions of band resolution—good, bad, or none.

The system permits injection periods that are shorter than the retention time of the last component of the feedstock. This is of specific advantage when there are no impurities in the mixture which have retention times much longer or shorter than the main bands or when these impurities can be collected together.

The elimination of impurities can be carried out even if these components are undetected or if their corresponding peaks are insignificant; all that is needed is knowledge of their retention times. This also permits the use of a relatively insensitive but simple and highly reliable thermal conductivity detector, as its signal must only monitor the major peaks and control the unit.

A deviation or minor drift of the base line will not disturb the control system.

Finally, this process permits the commutation of columns in the course of a separation, which is the only way available in preparative chromatography to reduce the elution time of markedly retained compounds. In the case of mixtures containing compounds of very different retention characteristics, it is often more economical to use a two-step procedure, the first one being either distillation or chromatography on a short column at high temperature.

Flexibility

This process can be applied to any new problem of separation of volatile products with a minimum of previous measurements, particularly when the new feedstock to be processed has been analyzed by gas chromatography. The only warning regards the possible existence in the feedstock of low concentrations of harmful components with very long retention times, which often go undetected in normal analysis. They will not be separated by the chromatographic unit but will be found in the end products.

Such flexibility is made possible by the use of the results of our theoretical studies, whose principal results are briefly described in the following section. This characteristic of our process is of special importance for separations carried out on a small scale, where the study and work preparation required for other processes would involve expenses out of proportion with the economics of the contemplated separations.

Furthermore, experience has shown that with a very small number of columns ready for operation, most new separation problems can be solved promptly.

The liquid hold-up of the column is extremely low. Thus, the start-up of the unit is very rapid and the process losses are small. It should be noted that warming of the column is done by the carrier gas itself and that the entire batch of feedstock can be separated. By contrast, in distillation a portion of the feed is lost during start-up and cannot be recovered later.

III. THE MODEL OF INFINITE CONCENTRATION CHROMATOGRAPHY

The conventional, simplifying assumptions of linear chromatography serve as an excellent theoretical model of analytical chromatography. They allow the formation of a satisfactory description of the elution of individual bands of solute at small, i.e., quasi-zero, concentrations and permit the calculation of retention times or volumes based on thermodynamic equilibrium data for gas–solid or gas–liquid systems and of the profiles of the solute bands from kinetic data which are less simple to handle in practice. This theory is detailed in gas chromatography textbooks (*18–20*). However, it does not hold when the mobile phase concentration of the products analyzed is large.

Since in production scale gas–liquid chromatography the injection of the largest possible quantity of material is desired, a different theoretical model must be created to account for the observed facts and to permit the optimization of experimental conditions. Following the pioneering work of De Vault (*23*), which dealt with the simpler case of liquid chromatography, this problem has been studied and discussed by many researchers (*24, 25*).

It turns out that the theory of chromatography is more complicated when the mobile phase is a gas than when it is a liquid because the compressibility of gases causes a variation of velocity of the mobile phase in the column since the mass flow rate is constant along the column and makes the pressure profile a nonlinear function of column length. Furthermore, many of the physical properties of gases are a function of the pressure.

It is not surprising, therefore, that only recently has a general theory been formulated which permits a quantitative prediction of band shapes in both gas–liquid and gas–solid chromatography when test samples are injected in large quantity (*7–9*). It is not surprising that the general theory does not lead to analytical equations for the peak profiles but to methods of calculation usable only on computers (*10, 25*).

An excellent study of the general theory of chromatography was made by Helfferich and Klein (*26*), but the elegant mathematical methods used by them for solving the equations cannot be applied when complex isotherms are encountered. For this reason, a more complex and less elegant method must be used (*25*).

We shall briefly describe the phenomena which are responsible for the change of position and shape of the peaks at large concentrations, and then explain the method proposed for calculating their profiles. Finally, we shall present the principles of optimization which can be derived from this theoretical approach.

Effects Resulting from the Finite Concentration of Vapors in the Gas Phase

These effects are numerous. Some are more important than others. A complete theory should account for all of them. However, this would seem overambitious under present conditions and is not necessary for the solution of any practical problems. Consideration of some of these effects will thus be excluded. The two major phenomena which do have to be accounted for are the effects of sorption and of a nonlinear isotherm. Other important phenomena are the thermal effect, the effect of viscosity, the effects of diffusion and kinetics of mass transfer which are solely responsible for peak broadening in analytical chromatography and still play an important role at finite concentration, and finally the effect of nonideality of the gas phase.

The Sorption Effect

The volume occupied in the vapor phase by 1 mol of a substance is several hundred times larger than the same amount of substance in the liquid phase. When a given mass of vapor condenses, considerable contraction occurs (see Fig. 4).

In gas chromatography the carrier gas flow-rate at the column inlet is controlled and kept constant at all times, including the injection period. Inside a band, the vapor of the compound or mixture adds to the carrier gas.

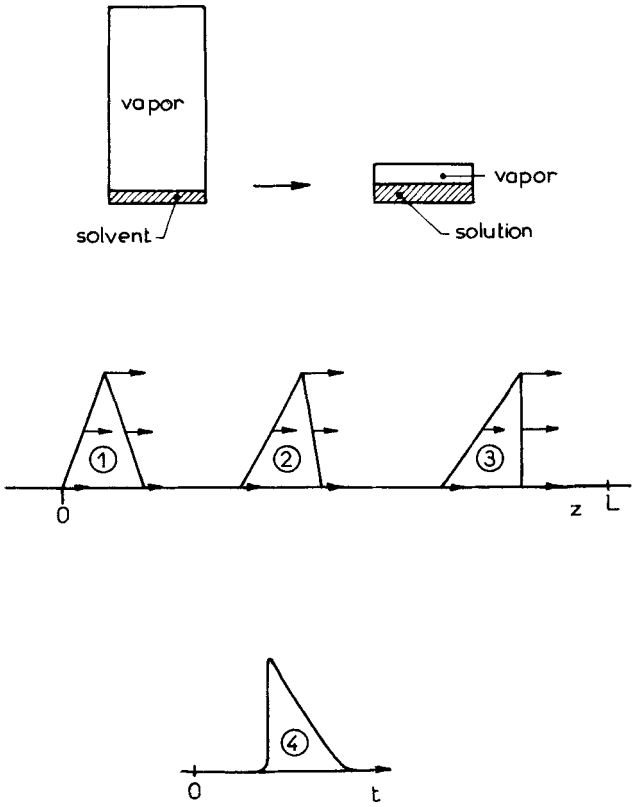

FIG. 4. The sorption effect. *Upper part:* Volumetric changes of solution and gas phase upon reaching dissolution equilibrium under constant pressure. Left, vapor + solvent, before equilibrium; right, vapor + solution at equilibrium. *Lower part:* Effect on band migration. The possibility of relating speed to concentration is based on certain characteristics of the mathematical equations developed by De Vault (*23*) and Jacob (*25*). In the case of a pure or predominant sorption effect, a stable discontinuity develops on the front (downstream) end of the band. (1) Hypothetical, symmetrical, concentration profile at column inlet; (2) intermediate profile; (3) steady-state profile (1, 2, 3 are concentration profiles inside the column); (4) elution profile at column outlet, i.e., concentration vs time profile.

Since the pressure has to decrease monotonously from column inlet to outlet and since in such a porous media as a chromatographic column there cannot be a pressure discontinuity, the velocity of the gas phase will be greater inside the peak where there is a mixture of carrier gas and product vapor than before and after the peak where there is only pure carrier gas. The gas phase velocity inside the peak will thus increase with increasing vapor concentration and be a maximum at the maximum concentration.

Hence, the part of the solute band where the concentration is large will move at a faster rate than the part where the concentration is lower; the zone of maximum concentration will try to reach the band front, which obviously it cannot overtake. An asymmetrical peak is formed with a steep front (which in an extreme case might be vertical) and a diffused, irregularly shaped tail end (see Fig. 4).

Unlike gas chromatography, such deformation of the peak does not occur in liquid chromatography because, in this last case, the difference is very small between the partial molar volumes of the solute in the stationary and moving phases, the mobile phase is not compressible, and when the solute dissolves in the stationary phase at peak front, there is practially no change in local velocity.

The sorption effect is frequent in gas chromatography, even in analytical conditions, for compounds which are weakly retained in the column; for example, the solvent peak in the analysis of dilute solutions.

Effect of the Isotherm

At large concentrations the solubility of adsorption isotherms are no longer linear. The isotherms are the curves representing the variation of composition of the liquid phase in equilibrium with the increasing partial pressures of the solute in the gas phase at constant temperature. The classical diagram of Raoult shows such an isotherm in the conventional way; from it are defined the activity coefficients which in the case of real solutions vary with the composition (see Fig. 5A). To correctly describe the situation in gas–liquid chromatography, it is necessary, however, to use a diagram that is similar to the one in use for adsorption isotherms. The total amount of solvent available to make solutions is constant in a chromatographic column, and we need to know the amount of solute dissolved in a given quantity of liquid phase as a function of the vapor pressure (see Fig. 5B). It can be demonstrated that in gas–liquid chromatography this isotherm is always convex toward the pressure axis, while concave isotherms can occur only in gas–solid chromatography, and even there they are rather infrequent (*9*).

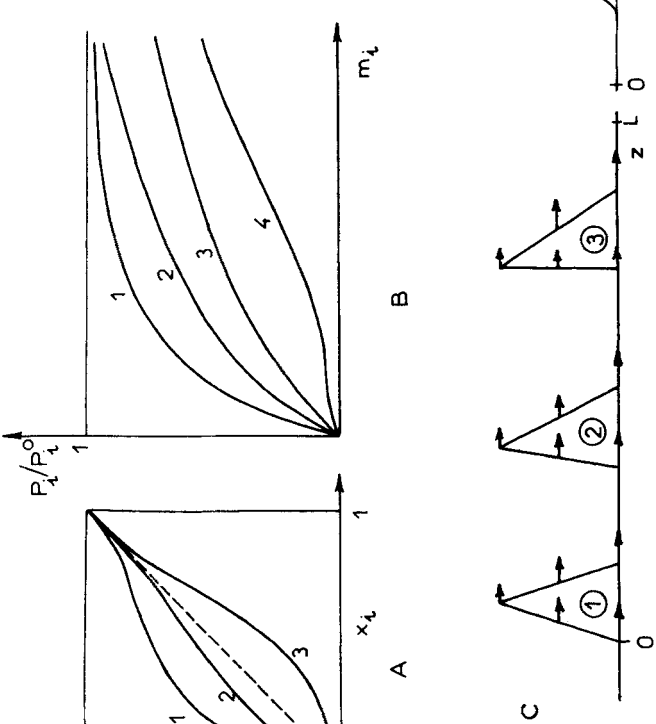

FIG. 5. The isotherm effect. *Upper part:* (A) Raoult diagram, vapor–solution equilibrium; (B) vapor–solution equilibrium with a given, constant mass of solvent (vapor pressure vs mass of solute in solution). Curve 4 corresponds to an unusual case of gas–solid isotherm. *Lower part:* (C) Effect on band migration (cf. Fig. 4 and text). (1) Symmetrical injection profile (2) intermediate profile, (3) steady-state profile, (4) elution profile.

As a result, in gas–liquid chromatography the solubility of a vapor in the liquid phase always increases with its partial pressure. Thus, the partition coefficient, and hence the retention, increases with increasing concentration. The regions of the solute band where this concentration is larger will move slower than those where the concentration is smaller (cf. Fig. 5C). The resulting deformation of the peak occurs in the direction opposite to the one caused by the sorption effect (compare Figs. 4 and 5).

Conflicting Effects of Sorption and Isotherm

These two effects always oppose each other in gas–liquid chromatography and frequently also in gas–solid chromatography. The isotherm effect will prevail at low temperatures when solubility is large and partial pressures, which are lower than the saturation vapor pressure, are insufficient to cause an important sorption effect. By contrast, the sorption effect will predominate at high temperatures when the partial pressure is large but the concentration in solution is relatively small and the isotherm effect is moderate or nonexistent.

Valentin et al. (*12*) demonstrated that the changeover occurs in a narrow temperature range near the boiling temperature of the component under a pressure equal to the average column pressure which, in general, is above atmospheric pressure but sometimes will be kept below this level by operating the column at an outlet pressure below atmospheric pressure. In a narrow intermediary range the bands of solute obtained from large samples remain narrow and symmetrical even at very large concentrations, which favors high productivity. Consequently, theory supplies us with well-defined conditions to optimize column temperature and inlet and outlet pressures (*12*).

Effect Viscosity

The viscosity of organic vapors is, generally, much below that of usual carrier gases, except for hydrogen. The use of this last gas renders the effect of viscosity negligible. Otherwise, a change of viscosity can markedly affect the solute band. As indicated under the heading "The Sorption Effect," however, flow velocity is larger inside the peak, which partly compensates for the decrease in viscosity of the mixture and reduces the change in the pressure profile. Since the band occupies only a rather narrow zone in the column, the overall effect is small and can be neglected. This is also in agreement with the observation that the pressure profile does not vary during the time of elution of a band of large concentration (*27*).

Nonideal Behavior of the Gas Phase

Molecular interactions in the gas phase cause a deviation from the ideal gas laws: the density of the gas phase is larger and the pressure is lower than the values derived from the ideal gas law. This nonideal behavior increases with increasing pressure, especially in the case of vapors far below their critical temperature. A change of the apparent equilibrium constants may result, the effects of which may combine with those of a nonlinear isotherm.

The two effects must, however, be separated from each other in the calculation because the pressure in the column varies over its length. This effect is negligible when hydrogen or helium is used as the carrier gas. This could be important with steam or carbon dioxide which are sometimes used because of the ease with which they can be condensed and separated from the products of the separation.

Thermal Effect

The elution of a chromatographic band gives rise to a thermal profile which is a function of the concentration profile of this band. When the vapors dissolve in the stationary phase at the front of the peak, they release heat, but at the tail of the peak the vaporization of the solute requires a heat supply. There is no exact compensating effect because in the meantime the heat released at the front of the peak dissipates in axial and radial directions. Therefore, neither isothermic nor adiabatic conditions can prevail.

The temperature profile reacts with the concentration profile and causes it to widen for the following reason. The higher the temperature, the smaller the equilibrium constant, so the front of the peak, which is heated by the temperature effect, tends to move at a faster rate, while the tail of the peak, which is at a lower temperature, will move at a smaller velocity than the zone center. However, in the presence of hydrogen or helium, because of the high specific heat and the large heat conductivity of these carrier gases, the widening effect is small enough to be neglected.

Resistance to Mass Transfer and Diffusion

The kinetics of mass transfer by radial and axial diffusions has been studied extensively for analytical chromatography. Although an exact quantitative description of these phenomena is hardly possible, they are, nevertheless, well understood (*28*). The practical difficulty is in the

determination of the numerical values of the coefficients which have to be used. They are difficult to measure when the concentration of the solute is very small; at present they are nearly impossible to estimate correctly when the concentration attains finite values (*17*).

Therefore, an empirical approach must be used. It is derived from the coefficients of the equation which yields the height equivalent of a theoretical plate (HETP) as a function of the velocity of the carrier gas in the column (cf. Fig. 2). As a first approximation, we assume that these coefficients remain unchanged at large concentrations. This seems justified in the light of the experimental results obtained.

At any rate, although resistance to mass transfer is the only source of band broadening in analytical chromatography, in preparative chromatography it is of second order, much less important than the effects of sorption and isotherm (*7–12*, *25*, *29*).

Equations of Mass Balance

An exact solution to the problem of propagation of bands of finite concentration can be obtained by applying the general principles of chemical engineering (*7*) which call for the following steps:

Derivation of a system of partial differential equations obtained by writing the mass balances for each component of the sample and for the carrier gas.
Writing equations which give the flow velocity in the column and the kinetics of mass transfer.
Definining the boundary conditions of the system.
Solving the mathematical problem.

Several groups have followed this approach (*7–9*, *24*, *25*). It is generally assumed that the gas phase follows the behavior of an ideal gas, that the thermal effect can be neglected, and that the pressure profile remains stationary. All these constitute a group of valid assumptions. Unfortunately, even with these simplifications the general system of mass-balance equations described above, which takes into account the effects of sorption, isotherm, and resistance to mass-transfer, cannot be solved analytically or numerically, and thus cannot be applied. Further simplifications must be introduced (*25*). This is where our approach parts from the work of others (*24*).

Most authors assume a constant carrier gas velocity. This amounts to neglecting the sorption effect, and therefore is incorrect from the beginning. Others consider the effect of finite concentration to be a mere perturbation of

the classical models of analytical chromatography at zero concentration or of linear chromatography. Unfortunately, this precludes a correct account for the effects of isotherm and of sorption, and cannot give a reasonable picture of the band shape in industrial chromatography.

As long as one does not realize the fact that the effect of the kinetic phenomena in mass-balance equations is of second order while those of sorption and isotherm are first order, no useful theoretical results can be obtained. The reason why that basic fact has been ignored for so long is that the terms which account for sorption and isotherm effects, although first order, become zero at small concentrations, which is the case in analytical chromatography, while the second-order terms tend toward a finite limit. This is why the former approach was basically wrong, and also why the temptation to account for the finite concentration effect by a perturbation approach was so strong.

Jacob and Valentin (*7–10*, *25*) derived a new theory which, as a first approximation, neglects the second-order terms. Subsequently, a new version was elaborated which accounts for them through the use of an empirical overall diffusion coefficient in the numerical calculations (*10*, *12*). This method is actually a rigorous theory of ideal, nonlinear chromatography which allows convenient discussion of the equations of mass-balance and a description of the effects specific to large concentrations which cause broadening and asymmetric deformation of the peaks.

One of the essential principles of this theory (which will not be discussed here in detail) is the demonstration that stable discontinuities of concentration can exist in a chromatographic profile and will propagate steadily if some conditions are fulfilled. The conditions of stability and propagation of these discontinuities can be defined by means of this theory (*8*, *25*). It should be emphasized that no other approach to the theory of chromatography at finite concentrations can explain this experimental result which is illustrated by Fig. 5 and by most published chromatograms of preparative applications (*11*, *20*, *30*).

Existence and Stability of Discontinuities of Concentration

Helfferich (*26*) recognized the existence of discontinuities but did not employ them in his models. Earlier, De Vault (*23*) reported their occurrence. The importance of this phenomenon was recognized by Jacob (*25*) who found that the discontinuities were one of the essential elements of the general theory of nonlinear chromatography.

The system of partial differential equations to which the mass-balance equations lead is, for the mathematician, a quasi-linear system if we assume

that axial diffusion and mass-transfer resistances can be neglected. One of its essential points is to accept the propagation of stable discontinuities of concentration as a possible solution.

This phenomenon can be compared, from the mathematical point of view, to the propagation of shock waves in acoustics or to the bursting of waves on the seashore (*8*). An acoustical shock wave is a discontinuity of pressure which proceeds at a speed slightly faster than the speed of sound at ambiant temperature. The localized compression which accompanies it heats the gas in such a way that the waves which propagate more rapidly than the shock penetrate into a cold gas where their velocity is smaller than that of the shock. On the other hand, those waves which tend to propagate more slowly move into a warm area and their speed then exceeds that of the shock. These contrasting effects assure the stability of the shock until eventually too much of its energy is used heating the gas where it propagates and it collapses.

The conditions of stability of the discontinuities of concentration are mathematically similar (*8*). In the case of a rectangular profile of the zone that is injected into the column, discontinuities will exist from the beginning. They can be stable or unstable. When the injection profile is continuous, a discontinuity will usually appear when an inflection tangent becomes vertical as a consequence of the progressive deformation of the profile under the effect of sorption or isotherm which causes the velocity to increase or decrease with increasing concentration. The discontinuity will then expand at the expense of the continuous parts of the profile. Eventually, however, the discontinuity will disappear if the column is long enough because, during any chromatographic phenomenon, there is a constant dilution which causes the conditions of linear chromatography to prevail at the end and the signal finally assumes a Gaussian profile.

The study of chromatograms from preparative chromatography demonstrates that the occurrence of discontinuities is a reality and not only a theory or a mathematical artefact. Discontinuities do exist, or at the very least depict a real situation as long as the band is inside the column. Naturally, a true discontinuity shows a sharp change in concentration, and therefore results in the occurrence of an infinite concentration gradient and an infinite diffusion speed which renders the outlines of the true profile somewhat blunt when recorded, due to the diffusion effect in the detector and the void volumes of connection tubings.

The stability of discontinuities can be studied with the help of a special diagram (see Fig. 6) which shows the molar fraction of solute in the gas phase upstream of the shock on the abscissa, and the molar fraction in the column downstream of the shock on the ordinate. Any possible concentration shock can be represented by a point on the diagram, which is its image. Accordingly, the image of a shock on the front or the tail part of a peak is

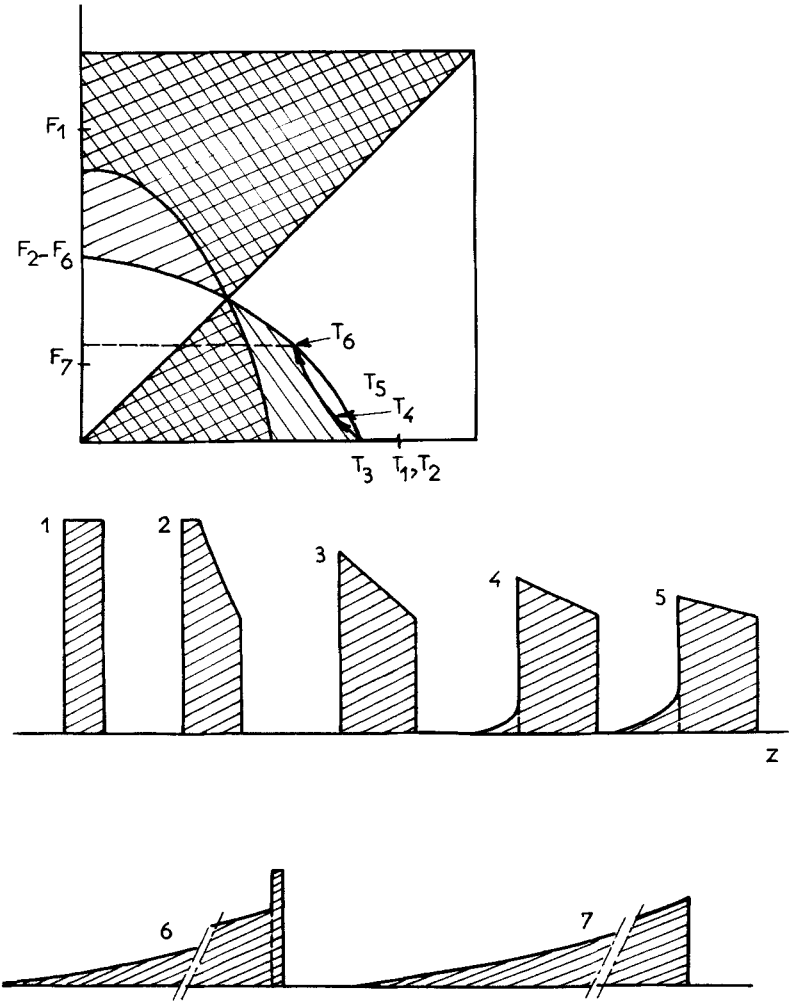

FIG. 6. Propagation through the column of a rectangular injection. This is an example of the variation of the profile of a large concentration signal in the case of a complex stability diagram of the discontinuities or concentration shocks. *Upper part:* Stability diagram. *Profiles:* (1) Injection band, (2–7) band during its propagation downstream of the column (for explanation, see text).

above or below the bisector of the axes. The conditions of stability are represented by curves, inside which can be found the images of stable discontinuities (*8*). Shocks whose images are outside these curves are unstable and, if forced to appear (at injection, for example), collapse immediately.

Propagation of the Solute Bands

As an example, we describe the migration of a solute band of rectangular profile in conditions where the stability diagram is the one shown in Fig. 6. This description is based on the general results of a published previously theoretical study of the model (*9*).

At injection, Profile 1 in Fig. 6 shows two shocks—one on each side. The stability diagram shows that the rear shock (Image T_1) is stable but not the front shock (Image F_1). Only a shock whose image has the same height as the coordinate of F_2 on Fig. 6 can be stable on the peak front. Consequently, the profile changes and widens rapidly. A continuous profile appears at the top of the peak, above the frontal shock (cf. Fig. 2, Profiles 2 and 3).

The front and rear shocks propagate at constant but different velocities, and their distance increases progressively. The horizontal plateau disappears and a continuous profile is formed (Fig. 6-3). While the front shock height remains stable, the rear shock starts to decline with its image moving toward the origin. When the image reaches the point T_3 on the diagram, the discontinuity at the peak rear becomes partially stable. Its trajectory follows Curve T_{3-6} which is derived from isotherm equations and experimental conditions. A tail with a continuous profile starts to appear below and after the rear shock, which decreases progressively while the front shock remains stable (Profiles 4 and 5).

Curve T_{3-6} encounters the border of the zone of stability at T_6, where the rear shock becomes stable again. Its speed then increases and it becomes faster than the front shock, which causes the two shocks to approach each other. They end up meeting (Profile 6), the rear shock disappears, and the profile keeps only a front shock (Profile 7), the image of which slowly moves from F_6 down toward the origin, where it eventually disappears if the column is long enough. The profile is now totally continuous.

It should be noted that Profiles 1 to 7 in Fig. 6 represent variations of concentration as a function of the abscissa along the column at a given time, whereas classical chromatograms describe the variation of concentration at the column outlet as a function of time. To relate concentration profiles along the column to time-based chromatograms, it should be kept in mind that the

part of the profile which is furthest down the column is the one which exists first.

These results are in qualitative agreement with numerous experiments. For example, the diagram in Fig. 7 shows the chromatograms obtained by analyzing benzene on graphitized carbon black and features some resemblance with the profiles in Fig. 6. Thus, the theoretical results constitute a good representation of reality, because this is the only approach which explains the occurrence and collapse of sharp concentration changes on chromatographic profiles.

Application

The theoretical studies described above permit the preparation of programs which, for a given injection profile, allow the calculation of the elution profile of a pure substance or that of a mixture of two or more compounds.

As an example, the diagrams on Fig. 8 show the separation of two components in a case where the isotherm effect prevails. The appearance of two shocks is observed. The first one appears between the mixture of carrier gas and vapor B and the ternary mixture of carrier gas and unresolved vapors A and B in the middle of the compound band. The second one appears between the mixture of carrier gas and vapor B and the pure carrier gas, at the rear of the compound band.

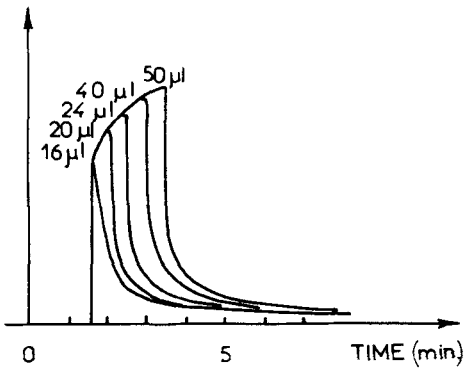

FIG. 7. Chromatograms obtained with increasing amounts of benzene injected on a graphitized carbon black column (4 mm i.d.), temperature 30°C, 50 µL on a 4-mm i.d. column is equivalent to 0.5 L or 0.44 kg of benzene on a 40 cm i.d. column. As with most adsorbents, graphitized carbon black is heavily overloaded with a relatively small amount of sample and cannot be used economically in industrial preparative applications except for very specific separations.

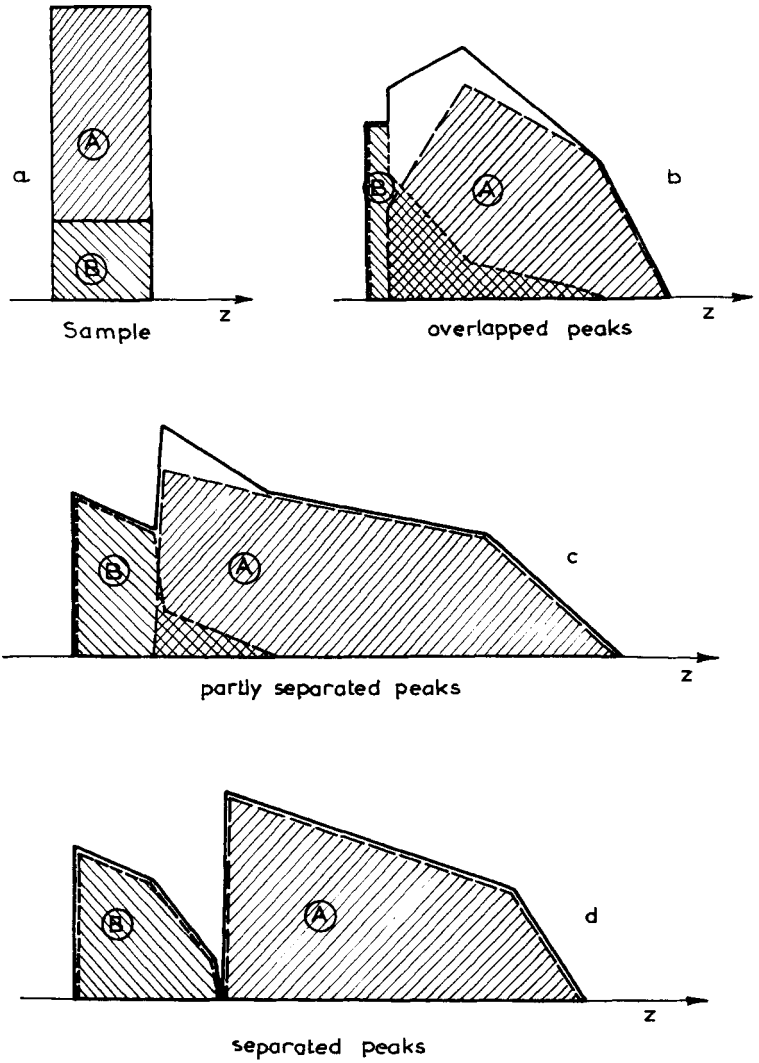

FIG. 8. Results of a computer simulation of the chromatographic separation of a 2-component mixture with rectangular injection. Profiles a to d illustrate different stages from injection (a) to complete separation (d). The dotted lines and hatched areas correspond to the profiles of Components 1 and 2; the solid line to the profile recorded by a nonspecific detector. These profiles are for bands inside the column. The conventional chromatogram is recorded at the column exit. The downstream end of the band is, of course, eluted first.

The resulting profile is representative of classical profiles from preparative chromatography as shown in Fig. 9. It illustrates the fundamental phenomenon that at high concentrations the separation between two bands is well advanced before it becomes visible on the chromatogram. It looks like the second compound were pushing the first one, which in fact is not true at all. In this manner, substantial production can be obtained by recycling a moderate fraction of the mixture when the profiles show only the vague beginning of a valley.

From profiles determined using the method described above, it is easy to calculate productivity and yield. Such calculations can easily be repeated for different values of the parameters. In this way, the effect of column length, carrier gas velocity, injection profile, etc. can be studied and operating conditions chosen to achieve maximum productivity (*10*, *12*) or minimum production cost.

Optimization

From the theory of chromatography at finite concentration, its application through simulation calculations, or from other applications of the basic principles of physical chemistry, we can derive guidelines for the rapid optimization of a preparative separation by GC. The following findings are among the principal results of our studies:

The use of hydrogen as the carrier gas leads to the largest productivity, the optimum efficiency being achieved at a very large carrier gas velocity (*12*). This is because diffusion coefficients are largest and mass transfers are fastest with hydrogen.

When the charge contains a number of different compounds, it is preferable to select a multistage scheme. A rapid first separation on a short column permits the collection of fractions which, subsequently, are processed on a longer column. The elimination of heavy constituents from the mixture which is used in the final separation step drastically reduces the processing time (*11*).

There is an optimal column length which is relatively short—of the order of 1 to 3 m (*10*).

Relatively large amounts of feedstock can be injected and good productivity maintained until practically no visible separation occurs. Of course, the injection of considerable quantities of feedstock should be carried out with long injection times so the maximum concentration is not too large (*11*). There is a maximum injection speed beyond which the column will not function satisfactorily because the pores of the support become filled by

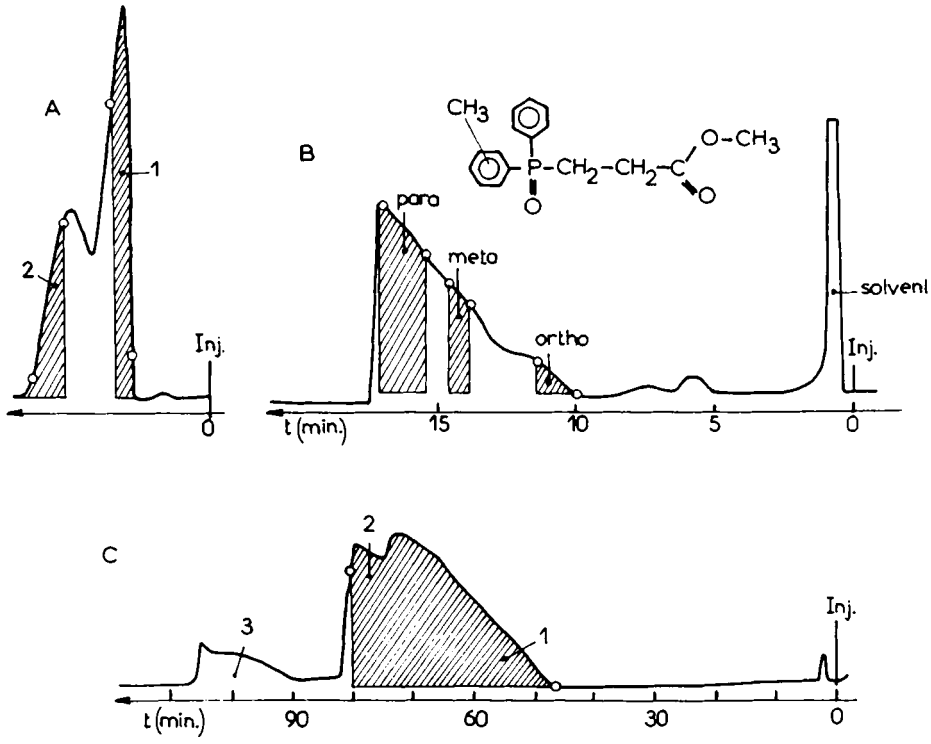

FIG. 9. Examples of peak profiles obtained in gas–liquid chromatography at large concentrations. *A. Sorption effect dominant:* Separation of *trans-* (1) and *cis-* (2) pentadiene-1,3. Column: 4 cm long, 4 cm i.d., chromosorb P, 60/80 mesh, coated with 20% squalane, 35°C, helium carrier gas 31/min. Cycle time 20 min. Feed rate: 4 mL/cycle. *B. Isotherm effect dominant:* Separation of the geometrical isomers of a phosphinic acid methyl ester. Column: 4 cm i.d., 3 m long, chromosorb G, NAW coated with 4% of ELF-SRTI nonpolar phase. Hydrogen carrier gas. Cycle time 12 min. Feed rate 0.5 g/cycle. *C. Isotherm effect dominant:* Separation of the isomers of 2,4-diphenyl pentane obtained from synthesis: *meso* (1), *d* + *l* (2), 2,4,6-triphenyl heptane isomers (3). Column: 2 cm i.d., 3 m long, chromosorb G coated with 1% SE30, temperature 150°C. Helium carrier gas, 1 L/min.

the solution, the stationary phase solution oozes out and is carried downstream by the carrier gas, and the column is ruined.

Accordingly, the coating ratio of the packing should not be too large (10 to 20% maximum, w/w).

The optimum operating temperature is approximately the boiling point of the most important compound to be separated (*9*). This is the condition needed to stabilize the front and the rear shocks simultaneously (effects of sorption and of isotherm, respectively). This optimal temperature changes rapidly with the mean column pressure, which in turn can be adjusted by a proper choice of the outlet pressure.

The maximum amount of feedstock that can be injected, and with it the productivity, increases with increasing temperature. But temperature is limited by the need to assure adequate retention (k' of the order of 2 to 5) for the sake of good separation. The coating ratio of support by the stationary phase cannot exceed 15 to 20%, otherwise the column is too easily flooded (*8*).

The optimum coating ratio results from a compromise which prevents column flooding, prevents thermal degradation of the stationary phase, satisfies the need for sufficient retention at high temperature, and employs the maximum sample size to permit adequate resolution between the compounds for separation.

When the liquid phase or the product must not be exposed to high temperature, a reduction of the optimal temperature can be achieved by lowering the column outlet pressure (cf. Figs. 10 and 11, Ref. *12*). The productivity will decrease but to a much lesser degree than if operation is at the same temperature under atmospheric pressure.

EXPERIENCE RECORD

Field of Application

Gas–liquid chromatography is competitive with other physical processes of separation, such as fractional distillation under atmospheric pressure or vacuum, or extractive distillation, in the case of difficult separations and for specific applications.

When separation is relatively easy (with a relative volatility above 1.2), the productivity of gas–liquid chromatography is lower than that of distillation. By contrast, when separation becomes difficult (i.e., with relative volatilities smaller than 1.1), the reflux requirement of fractionating columns

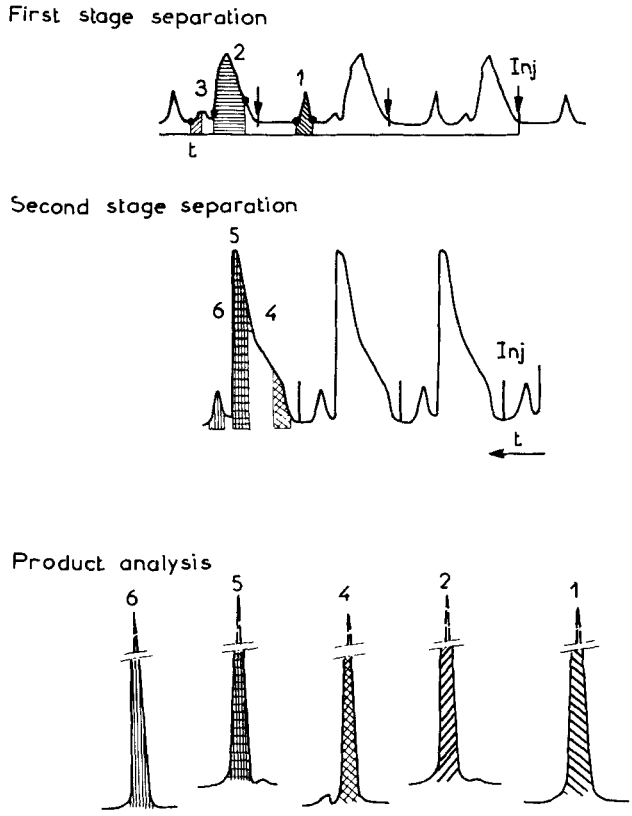

FIG. 10. Separation of the methyl esters derived from soya oil. *Upper diagram:* First stage. Separation of methyl palmitate (1), methyl stearate (3), and nonsaturated, C_{16} methyl esters (2). The three hatched peaks correspond to the first injection. Column: 4 cm i.d., 3 m long, Chromosorb G coated with 4% nonpolar phase, temperature 235°C. Absolute pressures: inlet 1240 torr, outlet 20 torr. Hydrogen carrier gas. Cycle time 18 min, feed rate 0.60 g/cycle. *Middle diagram:* Second stage. Separation of methyl oleate (4), linoleate (5), and linolenate (6). Same column size, Chromosorb G coated with 4% polar phase, temperature 200°C. Hydrogen carrier gas, cycle time 13.3 min, feed rate 0.60 g/cycle. *Lower diagram:* Analytical chromatograms of the five individual products, all 99+% purity.

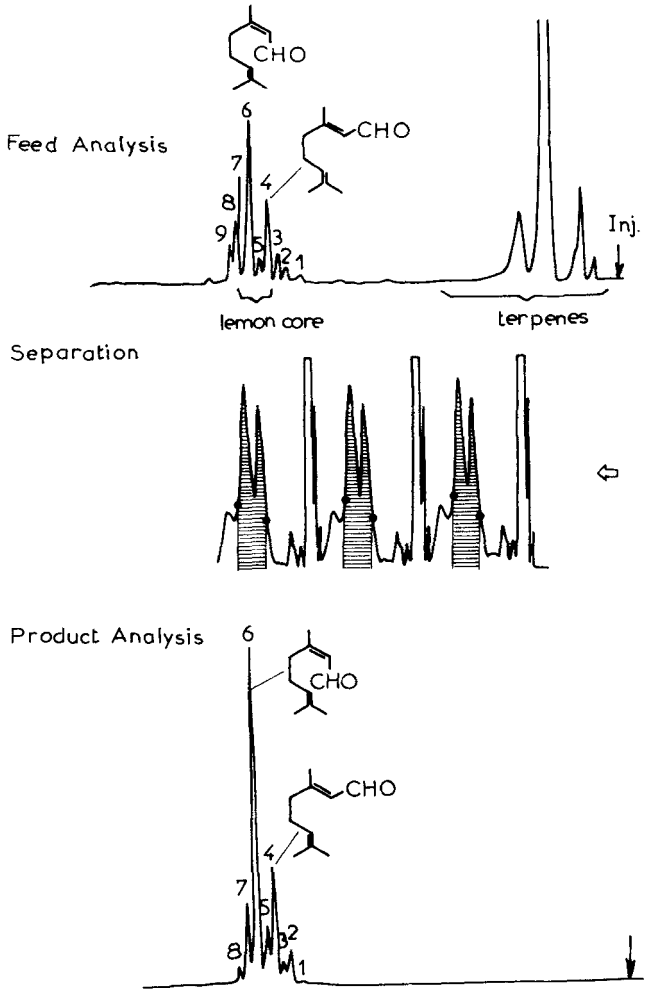

FIG. 11. Deterpenation of lemongrass oil "5X." *Upper diagram:* Analysis of feedstock showing terpenes and "lemon core." *Middle diagram:* Preparative chromatography. Column 40 mm i.d., 0.5 m long, Chromosorb coated with 20% ELF-SRTI polar stationary phase, temperature 150°C. Inlet pressure: atmospheric. *Lower diagram:* Analysis of product; lemon core soluble in 2 to 3 parts of 70% EtOH. Same conditions as for feedstock. Although carried out at 150°C, gas chromatographic separation gives a pure product of better taste than distillation at 70°C because of a much shorter residence time.

increases quite rapidly and becomes prohibitive. Chromatographic processes are most useful for difficult or impractical separations; i.e., for separating closely related isomers, for processing azeotrope or pseudoazeotropic mixtures, or for blends exhibiting "pinched" vapor–liquid equilibria. Examples of problems already successfully studied are given in Table 2.

In such situations the chromatographic process is useful for the separation, at atmospheric or under greatly reduced pressure, of mixtures of polar or apolar components in the boiling range of 0 to 300°C. Separation under satisfactory economic conditions of high boiling feedstocks has become possible thanks to the recent development of stable and selective liquid phase materials of a polar and nonpolar nature, suitable for working at temperatures in the range of 200 to 300°C.

In addition, the residence time of compounds in the unit is much smaller than in atmospheric or vacuum distillation (no reflux). Thermally unstable labile compounds can thus be purified with a corresponding reduction in the possibility of degradation. A new and original method of passivation of active surface sites has been developed for the support. This permits the processing of substances which are sensitive to isomerization or polymerization reactions. This method has proven most suitable for the treatment of terpene derivatives, as shown by our typical test that a column is satisfactory only if linalyl acetate is eluted without trace of decomposition products. It has the additional advantage of preventing molecular rearrangements caused by the

TABLE 2
Separation Problems Solved by Preparative Gas Chromatography

Pair of compounds separated	Nature of the problem
trans-Anethole, *cis*-anethole	Boiling points at 2.3 cmHg: 81–81.5 and 79–79.5°C
Humulene, caryophyllene-β	Boiling points at 10 mmHg: 118–119°C and 120°C
Trifluoromethylbromobenzene-1,3 and -1,4	Boiling points at 76 cmHg: 154°C (1,3) and 155°C (1,4)
Bromothiophene 1 and 2	Boiling points at 76 cmHg: 150.5°C (1) and 158.5°C (2)
Geraniol, nerol	Boiling points at 76 cmHg: 227–228 and 229–230°C
Benzaldehyde in benzyl alcohol	Concentration of aldehyde in feedstock ~0.1% concentration in end product < 100 ppm
Benzene, *n*-heptane	Azeotropic mixture
Caryophyllene, anethole	Azeotropic mixture
cis- and *trans*-1,3-pentadiene	Extraction from a C_5 cut of a petroleum refinery where they account for ~12% of the cut
Lemon 5X deterpenation	Extraction from the lemon essential oil of terpene hydrocarbons which are poorly soluble in water. Separation at 150°C without any change in flavor

presence of sodium ions resulting from the use of conventional methods of passivation.

If, despite the inactivity of the support and the short residence time, some products have to be processed at low temperatures, a partial compensation for the loss of productivity can be achieved by functioning under low pressure (*12*).

The physical characteristics of the chromatographic process permit purifications that until now were considered as technically impossible or economically unjustifiable. In this field of application it can successfully compete with chemical purification methods. Problems involved in the physical separation of certain isomers (for instance, positional isomers) frequently lead, in the initial steps of an organic synthesis, to carrying out reactions on mixtures and keeping unwanted or detrimental by-products and their compounds for a later stage of synthesis better suited for physical separation, or, alternatively, resorting to the preparation of intermediate substances easier to separate, for instance, by fractional crystallization.

Finally, chromatography is ideal for extracting one component from a complex mixtures without requiring complete separation, whether this component is particularly valuable or undesirable.

Examples of Separation

The successful development of such a process in the laboratory, the pilot unit, and finally at the level of a demonstration industrial unit calls for testing and processing a large variety of organic products, both natural and synthetic. Table 3 gives the characteristics of the various units used for preparative applications, excluding those which were built to study column packing technology or the principles of the process.

Table 4 gives a list of products which were successfully processed in connection with this development. Fragrances and aromatic compounds

TABLE 3
Technical Characteristics of the Units Used for Preparative Applications

Column diameter (cm)	Average production		Flow rate (m^3/h)	Number of units in operation
	kg/h	ton/year		
4	0.12	1	0–1	>20
12.5	1.25	10	1–10	2
40	12.5	100	60	1
60	28	225	135	Under study

have been used most frequently until now, but more and more work is being carried out on pharmaceutical intermediates and end products.

The examples described in Table 5 and Figs. 9 to 11 demonstrate various possibilities of the technique. It should be emphasized that most of these applications, especially the earlier ones, were not optimized for production purposes because it is rarely economical to optimize a laboratory separation. The results described in Table 3 nevertheless show what can be achieved on an automatic laboratory unit (THN 102) with columns of 20 and 40 mm i.d. that are operated without special attention. Most of these columns had a lifetime of several years. A French company uses such equipment and a 40-mm i.d. column to prepare a ton a year of a valuable intermediate, changing the column every second year.

Of the many separations carried out with a 12.5-cm i.d. column on the demonstration unit, most have to be kept confidential. The five examples of industrial separation shown in Table 6 are indicative of the productivity of

TABLE 4
List of Products Studied

Alcanes:	Terpene and terpene derivatives:	Other compounds:
Normal alcanes from C_5 to C_{32}	Alpha- and beta-pinenes	Methyl esters of fatty acids:
Normal paraffins	Myrcene	oleic, linoleic,
Iso-paraffins	Camphene	linolenic, stearic,
Cyclo-paraffins	Limonene	palmitic
	Humulene	
	Caryophyllene	
	(azeotrope with	Thiophenes:
Alcenes and alcynes:	anethole)	-, 2-bromo
	Alpha and beta	-, 3-bromo
Normal olefins	cedrenes	-, 2-methyl
Iso-olefins		-, 3-methyl
Cyclo-olefins	Nerol	
Di-olefins: isoprene,	Geraniol	Thenylamine
cis/trans pentadiene,	Citronellol	Chloropyridines
vinylacetylene	Farnesols (*cis-trans, trans-trans*)	Phosphines
		Indoles
Aromatic compounds:	Eugenol	
benzene	Citrala a and b	Essential oils:
alkyl-benzenes	Citronellal	Ylang ylang
m/p-bromo, fluoromethyl	Methyl-ionones	Virginia pine oil
benzene	(α,β,γ, iso, *n*)	Clove oil
benzyl alcohol/		Fennel oil
benzaldehydes		Lemongrass oil
2,4-phenyl pentane		Orange oil
(*meso/d,l*)		Lemon oil
anethole (*cis-trans*)		

TABLE
Separations Achieved c

Feedstock	1st stage operation				
	Column				
	Length (m)	Diameter (cm)	Temperature (°C)	Phase[a]	Feed rate (g/h)
n-Perfluoroheptane + iso-C_7F_{16}	9	1	40	QFI	0.6
cis- and *trans*-Pentadiene-1,3	4	4	35	Squalane	12
Isopentane	4	4	35	Squalane	14
Hexane	2	4	66	Squalane	7.5
Cyclododecane	3.8	4	200	SE 30	2.5
2,4-Diphenylpentane *d,l* + *meso*	6	2	150	SE 30	0.3C
Vanilla extract	2	4	230	SE 30	36
Soya oil	3	4	235	NP	2.0
Farnesol	3	4	180	P	?
Terpentine	1.5	4	175	Carbowax 20M	23
Clove essential oil	3	4	170	Carbowax 20M	22
Virginia pine wood oil	3	4	150 (180)	Carbowax 20M	1.5(6)
Orange essential oil	2	4	180	Carbowax 20M	47
$CH_3-\phi-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|\|}}{P}}-CH_2-CH_2-CO-OCH_3$	3	4		NP	2.5
Clove essential oil	3	4	220	P	30
Fennel oil	1	4	120	FFAP	6
Lemon grass oil	0.5	4	150	P	
Bromothiophene	2	4	150	Carbowax 20M	160
Isobutyl acetate	3	4	110	Carbowax 20M	15
Propylene sulfide (methyl thiacyclopropane)	3	4	80	Carbowax 20M	11

[a]NP = Elf proprietary nonpolar phase, P = Elf proprietary polar phase.

2nd stage operation					
Column					
Length (m)	Diameter (cm)	Temperature (°C)	Phase	Feed rate (g/h)	Final products and % purity
		None[b]			n-C_7F_{16} > 99.2%
		None			*cis*-Pentadiene: 99.2%, *trans*-pentadiene: 99.8%
		None			Isopentane: 99.96%; pentane: 380 ppm; butane: 3 ppm; isobutane: 2 ppm
		None			*n*-Hexane: 99.91%; 3Me-pentane: 760 ppm; Me cyclopentane; 55 ppm
		None			Cyclododecane: 99.9%. The product condensates as a solid in the trap
6	2	150	SE30	0.30	Each isomer > 99%
		None			*o*-Vanillin 97%: 20 g/h; *o*-Vanillin 95%: 26.5 g/h *o*-ethyl vanillin, guaiacol < 1% each
3	4	200	P	2.7	Methyl oleate, linoleate, linolenate, each > 99%
		None			*trans-trans* and *trans-cis:* each > 99%
4	4	135	DEGS	4.5	Longifolene, β-caryophyllene, humulene, α-terpineol: 92–95% each
		None			Humulene: 98.5%; β-caryophyllene: 99.4%
		None			cedrene: 97.5%; thuyopsene: 95%
4	4	170	Carbowax, 20M	40	Limonene: 99.9%
		None			*o,m,p*-Isomers: each > 95%
		None			Eugenol: 99.9%
		None			*trans*-Anethole: 99.8%
		None			Lemon core, soluble in 2–3 parts of 70% ethanol (extraction of low solubility terpenes)
		None			Bromo-3-thiophene: > 99%
		None			Isobutyl acetate: 99.95%
		None			Methyl thiacyclopropane: 99.9%

[b] "None" means no second stage operation.

TABLE 6
Examples of Chromatographic Separations Carried Out on the Demonstration Unit ($\phi = 12.5$ cm)

	Concentration		Operating conditions	Production, kg/h (tons/year)[a]	Observations
	Feedstock (%)	Product (%)			
Case 1:					
Pentane	99.3	99.995	Carrier gas: helium	1.5	The maximum purity was desirable
Isopentane			Temperature: 225°C	(12)	
			Outlet pressure atmospheric		
Case 2:					
Benzyl alcohol	99.5	99.6	Carrier gas: hydrogen	1	Example of selective removal of an impurity. Short contact time (under reduced pressure) and the passification of the support prevents the degradation of the alcohol to the aldehyde
Benzyl aldehyde	0.1	<0.01	Temperature: 150°C	(8)	
Other compounds	0.4		Outlet pressure: 50 torr		
			Passified support		
Case 3:					
α-Pinene	70	99 2	Carrier gas: hydrogen	2.5	Example of the simultaneous purification of two products
β-pinene	30	1 98	Temperature: 160°C	(20)	
			Outlet pressure atmospheric		
Case 4:					
Clove essential oil			Carrier gas: helium	0.4	Recovery of a purified product from a natural essential oil. The quality of the product is unimpaired in spite of the rather severe processing conditions (220°C).
Eugenol	75	99.8	Temperature: 220°C	(3.2)	
			Outlet pressure atmospheric		
Case 5:					
Bromo-3-thiophene	91.6	99.0	Carrier gas: hydrogen	1.25	Purification of close boiling isomers
Bromo-2-thiophene	4.6	1.0	Temperature: 150°C	(10)	
Other compounds	3.8	<0.05	Outlet pressure atmospheric		

[a] Assuming the unit operates 8000 h/year (1 month downtime).

the process. The throughput flow rates shown correspond to annual inputs ranging from about 3 to 20 tons while the product yields vary from 75 to 100% depending on the difficulty of the separation problem, the degree of purity required for the end product, and the economics. In most cases the losses are a few percent, retrieved in the charcoal trap and usually not recovered. The remaining part of the feedstock trapped in receiver 7 can be recycled.

Finally, three examples of separations carried out on a large-scale industrial unit are given in Table 7. Figure 12 is a photograph of the unit. Production is between 50 and 100 tons per year. For more difficult separations it would be reduced. A longer column would then be more interesting to use (*10*). The present column is 1.50 m long.

V. ECONOMIC DATA FOR OPERATIONS AT THE 20 TO 150 TONS/YEAR CAPACITY

A review of the technical features of the chromatographic process would be incomplete without some indications concerning its cost of operation.

The examples are discussed in Table 7. They are the production of linalol, which is a good study case, and of thenylamine and trifluoromethylbromobenzene. Fractional distillation is ruled out because it would require a large number of theoretical plates and a high reflux ratio (for instance, 75 theoretical plates and a reflux ratio of 7.5:1 for thenylamine). In addition, a long residence time would cause significant product degradation and necessitate additional treatment.

In the case of thenylamine, the chromatographic technique permits the selective removal of an impurity in a one-step operation: a unit having a 400-mm i.d. 1.5 m long column could produce 50 metric tons/year of thenylamine of the desired specifications. Similarly, it could produce 60 metric tons/year of pure 1.3-trifluoromethylbromobenzene and 1.5 ton/year of the 1.4-isomer. Such a unit did achieve a production rate of 99.3% pure linalol, exceeding 12.5 kg/h in a test run.

Table 8 contains all the values necessary for the evaluation of the economics of the process in accordance with the prospective buyer's own requirements and assumptions for such calculations.

CONCLUSION

After the failures of the preceding decade, gas–liquid chromatography as an industrial purification process appears to have attained the stage of practical perfection.

TABLE 7
Examples of Chromatographic Separations Carried Out on an Industrial Unit ($\phi = 40$ cm)

Products	Concentrations (%)				Operating conditions
	Feedstock	Product	Reject	Recycle	
Linalol	95	99.3	61.6	95.2	Temperature: 180°C
Fenchol	4.4	0.2	37	4.8	Flow rate: 60 m^3/h
Other compounds	0.6	0.5	1.4	0.0	Carrier gas: H_2
					Outlet pressure: atmospheric
					Passified support
					Feedstock: 16.4 kg/h
					Product: 11.7 kg/h
Thenylamine	94.5	99.3	71.8	94.1	Carrier gas: H_2, outlet pressure
Light compounds	0.8	0.35	2.5	0.7	atmospheric
Heavy impurity	4.7	0.35	25.7	5.2	Feedstock: 7.6 kg/h
					Product: 6.1 kg/h
Trifluoromethylbromobenzene		(1)	(2)		Carrier gas: H_2, outlet pressure
Light impurities	4.0	0.6	8.1	1.4	1.4 atmospheric
1,3	91.0	98.9	1.9	22.2	92.2 Feedstock: 8.9 kg/h
1,4	5.0	0.5	90.0	36.4	6.4 Product 1: 7.4 kg/h.
					Product 2: 0.2 kg/h

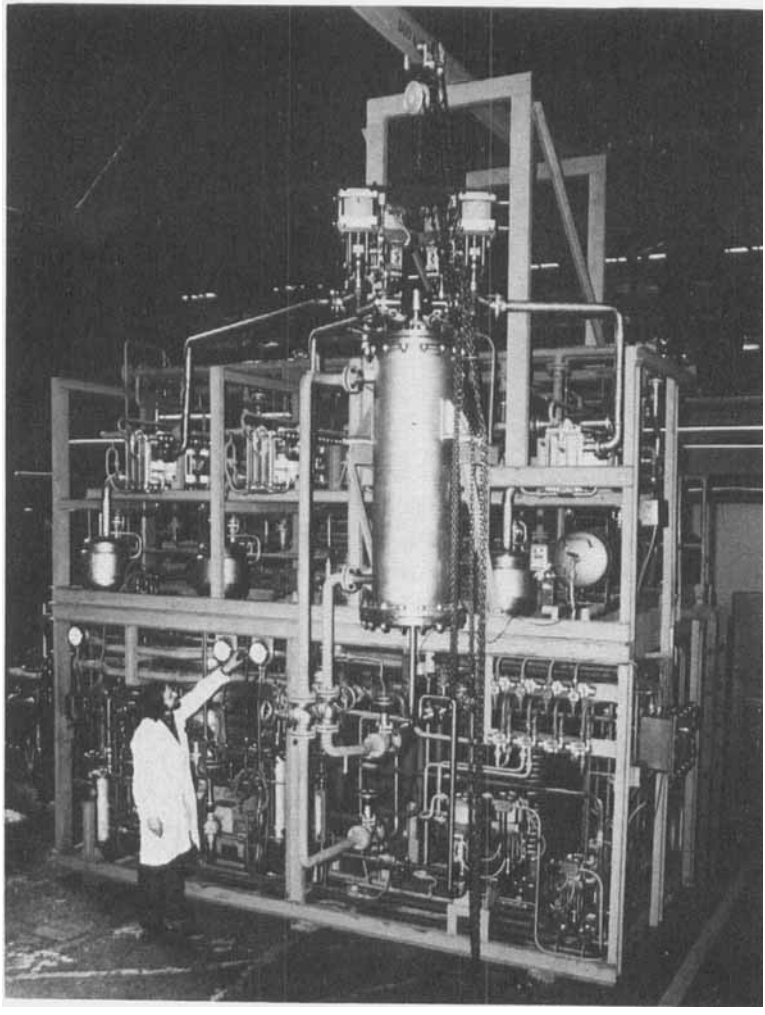

FIG. 12. Large-scale gas chromatographic unit. Column length 1.50 m, diameter 40 cm. The photography was taken before the thermal insulation is placed around the column and tubings. The column is in front of the unit overhanging from its top; the carrier gas exits at the top of the column through one of the four valves. It then goes to one of the four condensers (top row) and the condensates are collected in the corresponding cylindrical tanks. The feedstock tank is in the background of the unit, just behind the man.

TABLE 8
Economic Costs of Separation by Chromatography[a]

Utility consumption[b]	Linalol	Thenylamine	Trifluoromethyl-bromobenzene 1,3 and 1,4
Electrical energy (kWh)	1.3	2.6	2.2
Steam (3 atm, 180°C), kg	0.5	1.0	0.8
Cooling water (L)	170	300	220
Cold brine (−20°C) (calories)	—	—	0.2×10^6
Hydrogen lost, m^3, STP	0.04	0.09	0.05
Compressed air, m^3, STP	0.25	0.25	0.25
Operating manpower:			
Man per shift	1/3	1/3	1/3

[a] *Estimated unit cost:* Basic unit with recycling and purification of carrier gas. Erection and starting-up costs included (40 cm i.d., 1.5 m long column): $960,000.
[b] For 1 kg of feedstock.

Columns having an efficiency corresponding to about 1000 theoretical plates, 1.5 m length, and up to 400 mm i.d. are currently being built and operated with annual capacities ranging from 20 to 200 metric tons.

Experimental results are now supported by a sound theoretical framework that permits optimization. The control of operations has been perfected to such an extent that a demonstration unit with a 125-mm i.d. column is now operating at 5 to 15 tons/year capacity without night supervision. The field of application has been extended to include high boiling as well as thermal decomposition sensitive feedstocks.

The technique is sufficiently advanced to be used for the industrial preparation of pure compounds and the selective elimination of impurities. It is also in a position to compete in difficult cases with fractional distillation under vacuum, with extractive distillation, and with certain methods of chemical purification. Chromatography now stands among industrial processes which can be used for difficult purification operations. We anticipate that its application will lead to a reduction of processing costs in the production of specialty chemicals through simplification of processing steps, and possibly also to the production of new compounds.

REFERENCES

1. M. S. Tswett, *Tr. Protok. Varshav. Obshch. Estestvoispyt Otd. Biol.*, *14* (1903).
2. M. Martin, G. Blu, C. Eon, and G. Guiochon, *J. Chromatogr. Sci.*, *12*, 438 (1974).
3. A. T. James and A. J. P. Martin, *Biochem. J.*, *50*, 679 (1952).
4. E. Kovats and E. Heilbronner, *Chimia*, *10*, 288 (1956).
5. G. W. A. Rijnders, in *Advances in Chromatography* (J. C. Giddings and R. A. Keller, eds.), Dekker, New York, 1966, p. 215.

6. R. E. Pecsar, in *Preparative Chromatography* (A. Zlatkis and V. Pretorius, eds.), Wiley, New York, 1971, p. 73.
7. P. Valentin and G. Guiochon, *Sep. Sci.*, *10*, 245 (1975).
8. P. Valentin and G. Guiochon, *Ibid.*, *10*, 271 (1975).
9. P. Valentin and G. Guiochon, *Ibid.*, *10*, 289 (1975).
10. L. Jacob, P. Valentin, and G. Guiochon, *Chromatographia*, *4*, 6 (1971).
11. B. Roz, R. Bonmati, G. Hagenbach, P. Valentin, and G. Guiochon, *J. Chromatogr. Sci.*, *14*, 367 (1976).
12. P. Valentin, G. Hagenbach, B. Roz, and G. Guiochon, *Gas Chromatography 1972* (S. G. Perry, ed.), Applied Science Laboratory, London, 1973, p. 157.
13. M.D. Dixmier, B. Roz, and G. Guiochon, *Anal. Chim. Acta, 38,* 73 (1967).
14. R. F. Baddour, U.S. Patent 3,250,058 (May 10, 1966).
15. R. S. Timmins, L. Mir, and J. M. Ryan, *Chem. Eng.* (May 19, 1969).
16. K. P. Hupe, *Chromatographia*, *1*, 462 (1968).
17. J. C. Giddings, *J. Gas Chromatogr. 1*(1), 12 (1963); 1(4), 38 (1963).
18. A. B. Littlewood, *Gas Chromatography*, Academic Press, New York, 1970.
19. L. S. Ettre and A. Zlatkis, (eds.), *The Practice of Gas Chromatography*, Wiley-Interscience, New York, 1967.
20. R. A. Keller, and J. C. Giddings, in *Chromatography* (E. Heftmann, ed.), Reinhold, New York, 1975, p. 110.
21. J. M. Ryan and G. L. Dienes, *Drug Cosmet. Ind.*, p. 60 (October 1966).
22. M. Thizon, C. Eon, P. Valentin, and G. Guiochon, *Anal. Chem., 48*, 1861 (1976).
23. D. De Vault, *J. Am. Chem. Soc., 65*, 532 (1943).
24. V. Pretorius and V. De Clercq, in *Preparative Gas Chromatography* (V. Pretorius and A. Zlatkis, eds.), Wiley, New York, 1971.
25. L. Jacob and G. Guiochon, *Chromatogr. Rev., 14*, 77 (1971).
26. F. Helfferich and G. Klein, *Multicomponent Chromatography*, Dekker, New York, 1970.
27. R. P. W. Scott, *Anal. Chem., 36*, 1455 (1964).
28. J. C. Giddings, *Dynamics of Chromatography*, Dekker, New York, 1965.
29. L. D. Beljakowa, A. V. Kiselev, and N. B. Kovaleva, *Bull. Soc. Chim. Fr., 2967,* 285 (1967).
30. R. Bonmati and G. Guiochon, *Parfums, Cosmet. Aromes*, No. 11, 37 (1976).

Received by editor July 26, 1983