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Renaissance of gas chromatography–time-of-flight mass spectrometry

Meeting the challenge of capillary columns with a beam deflection instrument and time array detection

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ABSTRACT

This report describes the use of a unique beam deflection time-of-flight mass spectrometer to address some of the demands made on mass spectrometry by new developments in high-resolution capillary column gas chromatography. An integrating transient recorder is used in combination with this beam deflection time-of-flight instrument to apply the concept of time array detection in capturing all of the mass spectral information available from the ion source, thereby greatly enhancing the signal-to-noise ratio quality of the mass spectral data. The applicability of the time array detection approach to gas chromatography–mass spectrometry is demonstrated in the context of an analysis of the standard Grob mixture for assessing performance of capillary column chromatography. During analysis of the Grob mixture by gas chromatography–mass spectrometry, mass spectra were recorded at a rate of 20 scan files per second. The data indicate that this rate of mass spectral scan file generation is adequate to provide a suitable data base for reconstruction of the chromatographic profile. In addition, the effective scan rate is high enough that there is no distortion in the relative peak intensities throughout the individual mass spectra of components regardless of the relatively high dynamic changes in partial pressure of the analyte as reflected by the sharp peaks in the chromatographic profile. The experimental results indicate that the beam deflection time-of-flight mass spectrometer can provide mass spectra at a scan file generation rate much higher than that possible with the conventional quadrupole or magnetic sector mass spectrometer, but at comparable detection limits.

INTRODUCTION

Gas chromatography (GC)–mass spectrometry (MS) is a powerful technique because it combines a separation technique with an identification technique. The separation power of modern high-performance gas–liquid chromatography helps

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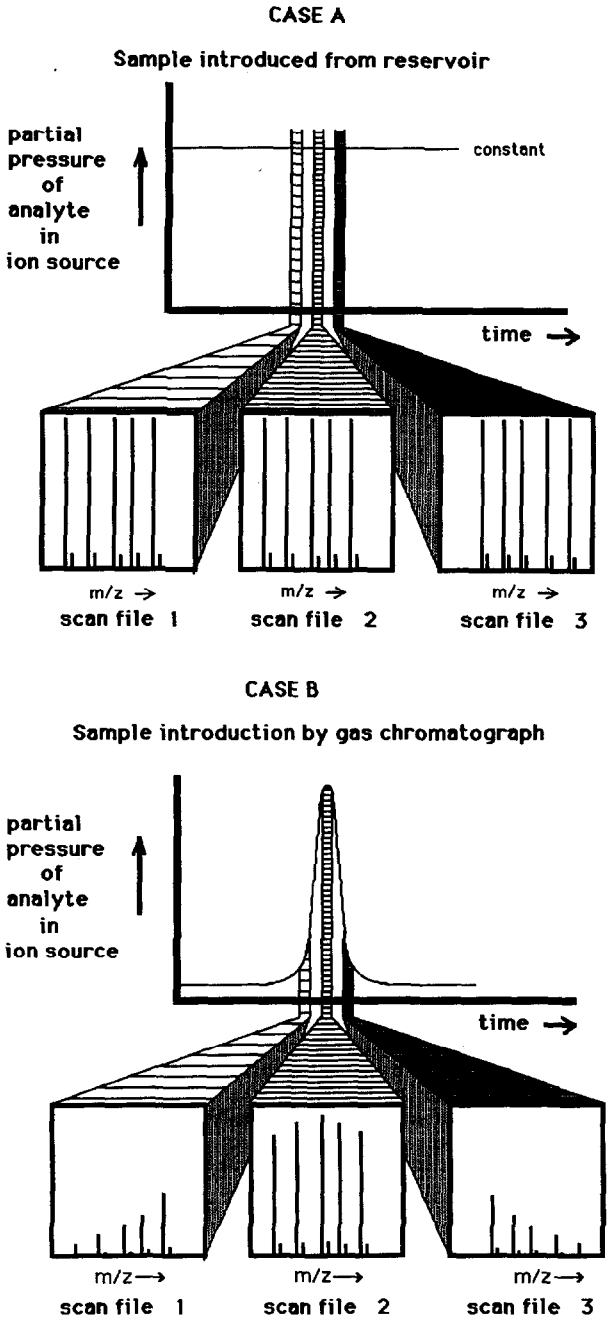

Fig. 1. Graphical illustration of the influence of analyte partial pressure in the ion source of a mass spectrometer on the resulting bar graph mass spectra. Case A: When analyte partial pressure is constant, spectra in scans 1, 2 and 3 are identical in the relative intensities of the peaks representing this hypothetical compound. Case B: When the partial pressure of the hypothetical compound changes in the ion source during scans 1, 2 and 3, the spectra are skewed as described in the text.

make available at least partially purified mixture components for analysis by mass spectrometry for identification purposes. Paradoxically, the dynamic nature of sample concentrations at the outlet of a gas chromatograph, especially in capillary column chromatography, tends to violate one of the cardinal rules in MS [1]. That is, it is important for the partial pressure of the analyte in the ionization chamber to remain constant during the time interval in which the mass spectrometer is scanned to acquire a mass spectrum; this condition ensures that the relative peak intensities represented in the mass spectrum are related to structural features of the molecule, and not distorted due to changes in partial pressure of the analyte during acquisition of that mass spectrum.

The influence of a dynamic partial pressure of an analyte in a mass spectrometer's ion source on the appearance of the acquired mass spectra is illustrated in Fig. 1. Case A in Fig. 1 represents the acquisition of three mass spectra of a hypothetical analyte maintained at constant pressure in the ion source. Case B in Fig. 1 represents analysis of the same hypothetical analyte when introduced to the mass spectrometer ion source via a gas chromatograph. The partial pressure of analyte in the ion source of the mass spectrometer rises and then falls as the analyte emerges from the gas chromatographic column. Scans 1 and 3 were acquired as the analyte concentration (partial pressure) was changing most rapidly in the ion source during mass spectral acquisition, and these mass spectra show a distortion or skewing of relative peak intensities. The relative peak intensities in each mass spectrum are indicative of the partial pressure of the analyte in the ion source, as well as the inherent fragmentation pattern of the compound. This situation complicates mass spectral interpretation, and limits compound identification based on mass spectral matching approaches.

Problems in capilary GC–MS

Problem 1: The acquisition of true mass spectra. The very definition of a gas chromatogram is, in fact, the temporal profile of partial pressures of analytes as they emerge from the chromatographic column. Improvements in the resolving power of capillary columns during the last decade, as reflected by the very sharp peaks (2–3 s in duration) in the chromatograms [2,3], have placed severe demands on the mass spectrometer to scan quickly enough to avoid distorting the mass spectra without sacrificing other important mass spectral features such as resolving power and the signal-to-noise ratio associated with the data. This problem is exacerbated during the common occurrence of poorly resolved components; in this case, the ion source may contain the vapor of one component or the other for only a few milliseconds, and it is imperative to capture an undistorted "pure" spectrum during this brief interval. An assessment [4] of the capacity for various mass analyzers to scan rapidly during analyses by GC–MS indicates that present demands for high scan rates (approaching ten scans per second over the mass range 50 to 500 daltons) made by high-resolution GC has forced many of the common mass analyzers to their very limit of performance as established by the physics underlying their operating principles. On the other hand, the time-of-flight mass spectrometer, by virtue of its rapid cycle time, has the capacity for generating complete mass spectra at a rate even higher than that presently demanded by GC–MS instruments that utilize the most efficient high-resolution GC capillary columns.

Problem 2: The satisfactory reconstruction of the chromatographic profile from mass spectral data. The problem resulting from the great disparity between the rate of change in sample partial pressure in capillary GC and the data acquisition rate of complete mass spectra is illustrated in Fig. 2. In each of the three panels in Fig. 2, the true chromatographic profile is illustrated by the dashed line; the solid line in each of the three panels is an attempt to reconstruct the chromatographic profile from data points available from a data base consisting of consecutively-recorded mass spectra. Each point represents the reconstructed total ion current (TIC) obtained by summing the measured intensities of all of the mass spectral peaks in one mass spectrum. In panels A and B, the rate of data acquisition yielded one scan file per second; thus, in these two panels there is available only one TIC point per second for purposes of reconstructing the chromatographic profile. The only difference between panels A and B is the synchrony between the repetitive scanning of the mass spectrometer and initialization of the chromatographic process. As can be seen in panels A and B, such utilization of mass spectral data for reconstruction of the true chromatographic profile is severely limited. However, as shown in panel C, if three points per second are available (due to scanning the mass spectrometer three times per second) from which to reconstruct the chromatographic profile as indicated by the solid line in panel C, the true chromatographic profile is more correctly described.

Problem 3: Limitations of "scanning" mass analyzers. Another major problem in GC–MS is the sacrifice of considerable ion counting statistical information when the technique of scanning of the mass spectrometer is used. As in most spectroscopic

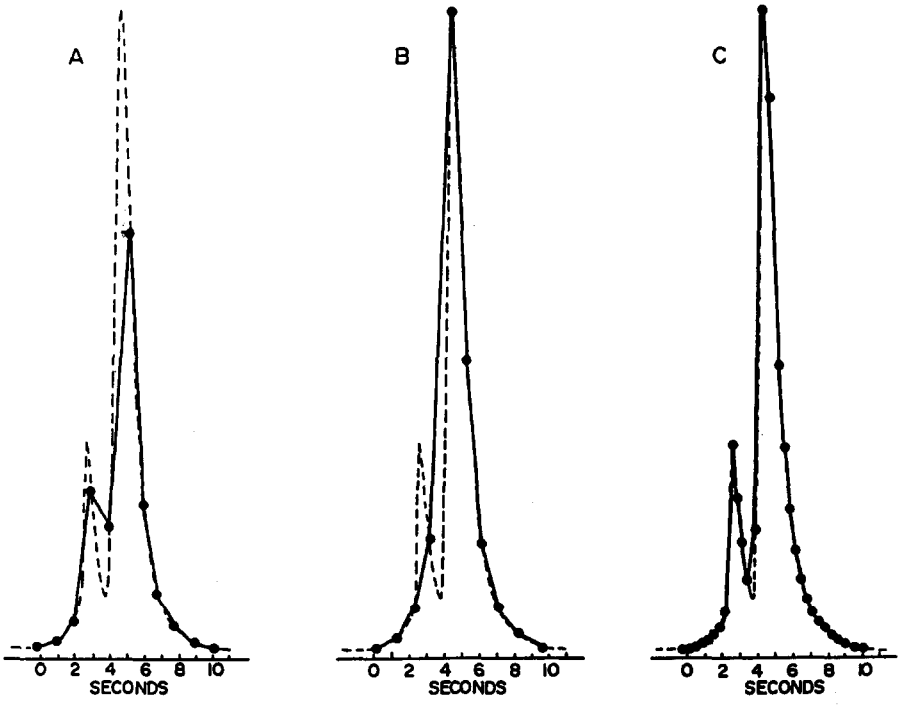

Fig. 2. Comparison of the true chromatographic profile (---) and attempts to reconstruct the chromatographic profile (—) from 10 data points for cases A and B, and 30 data points for case C, as described in the text (adapted from ref. 4 with permission of the American Chemical Society).

instruments which use the exclusive process of scanning, considerable information is lost as some parameter is varied to allow resolution elements of the mass spectrum to consecutively pass across the detector slits. Sweeley *et al.* [5], Hammar *et al.* [6] and other pioneers as reviewed by Falkner [7] solved this problem with selected-ion monitoring (SIM) which dedicates the instrument to monitoring ion current at only a selected resolution element (m/z value). Whereas the excellent sensitivity of SIM (femtomoles) is achieved by integrating all of the ion current from the ion source at a particular resolution element or m/z value of the mass spectrum, such good sensitivity could be achieved, in principle, while acquiring complete mass spectra if it were possible to integrate all ion current at all resolution elements or all m/z values across the mass spectrum all of the time. Such a process is possible only through array detection which measures all ion currents over a range of m/z values simultaneously. It would be desirable to acquire the complete mass spectrum in consecutive scans at the same high sensitivity otherwise available only by selected-ion monitoring. The key features of repetitive scanning and its advantages and disadvantages are presented in Fig. 3 in parallel with the key features of SIM together with its advantages and disadvantages.

A solution

As indicated in the conclusion of Fig. 3, the beneficial aspects of repetitive acquisition of mass spectra in the generation of a complete data field for a GC–MS

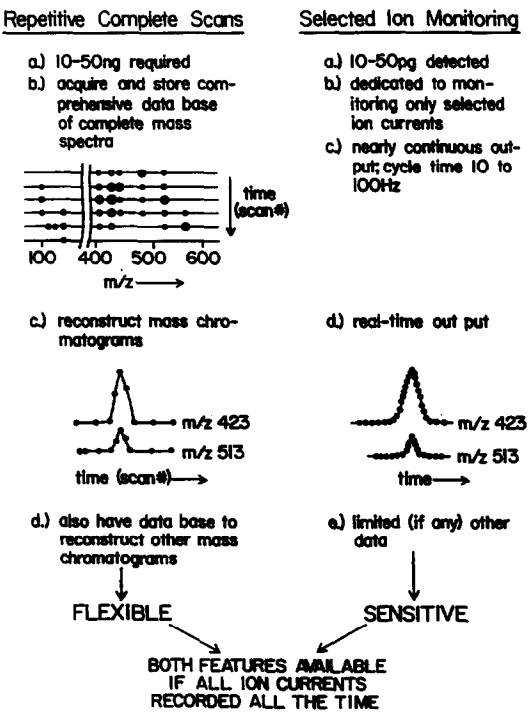

Fig. 3. Summary of operational features and mutually exclusive advantages of the technique of repetitive scanning and selected ion monitoring (reprinted from ref. 1 with permission from Raven Press).

analysis can be combined with the high sensitivity of SIM only if array detection is used to record the mass spectrum. The approach of using array detectors in mass spectrometry was pioneered by Giffen *et al.* [8] at the Jet Propulsion Laboratory in the 1970s. This resulted in the development of a device called an electro-optical ion detector which was evaluated subsequently in GC–MS by Hedfjall and Ryhage [9]. The technique of Fourier transform (FT) MS also provides array detection in that all ions present in the device are detected simultaneously [10], although the application of this instrument in GC–MS has not been extensively pursued to date. While FT-MS can obtain an impressive number of mass spectra per second, there are acquisition rate/resolution trade-offs. To avoid problems with limited dynamic range and other potential mechanical difficulties with these and other approaches to array detection, the research effort in the Michigan State University (MSU) Mass Spectrometry Facility has pursued developments in time-of-flight MS to conduct array detection in time.

Time-of-flight (TOF) MS, because of its pulsed nature and the very short time required for producing any given transient mass spectrum, *i.e.*, an ion sampling time ranging from 3 to 100 μs, makes this technique an ideal method for sampling rapidly changing partial pressures of analytes in the ion source. As explained in early reports on this work [4,11], time array detection is achieved in TOF-MS by digitizing the output from the detector such that all information in all resolution elements of the transient time-of-flight mass spectrum are collected following each extraction pulse from the ion source. For this purpose, an integrating transient recorder (ITR) has been designed and implemented, as described elsewhere [12]. Briefly the ITR digitizes the ion detector output at 200 MHz, is capable of producing up to 50 complete mass spectra per second, and can sustain high data collection rates continuously for up to one hour without loss of data. Another major requirement for proper utilization of time array detection is the necessity of providing optimum ion focus for ions of all m/z values from each ion packet so that each of the 5000–10 000 transient mass spectra reaching the detector per second have properly resolved mass spectral peaks. Conventional techniques in TOF-MS such as time-lag focusing are mass-dependent and are not generally useful in conjunction with time array detection, although we have obtained preliminary results [13] using time array detection with mass collection over narrow mass ranges which fall within the limits of acceptable focus by a fixed value of the time-lag parameter. The MSU group also has pursued techniques of beam deflection TOF-MS for purposes of achieving mass-independent ion focus and for improving the resolving power, in general, of TOF-MS by eliminating the aberration in resolution caused by the "turn around time" problem [14]. The technical details of a most recent version of a beam deflection TOF-MS system will be described elsewhere [15]. This report provides a preliminary assessment of the beam deflection TOF-MS system developed at MSU with time array detection for purposes of gathering complete mass spectra from a standard test mixture introduced via capillary column GC.

EXPERIMENTAL

Preliminary results from the GC–TOF-MS system based on beam deflection as represented schematically in Fig. 4 are presented here. In brief, the gas chromatograph used is a Hitachi 663-30, fitted with an 18 m (DB-1, 0.18 mm I.D.) capillary column; the test sample described herein is the Grob mixture (Supelco catalog No.

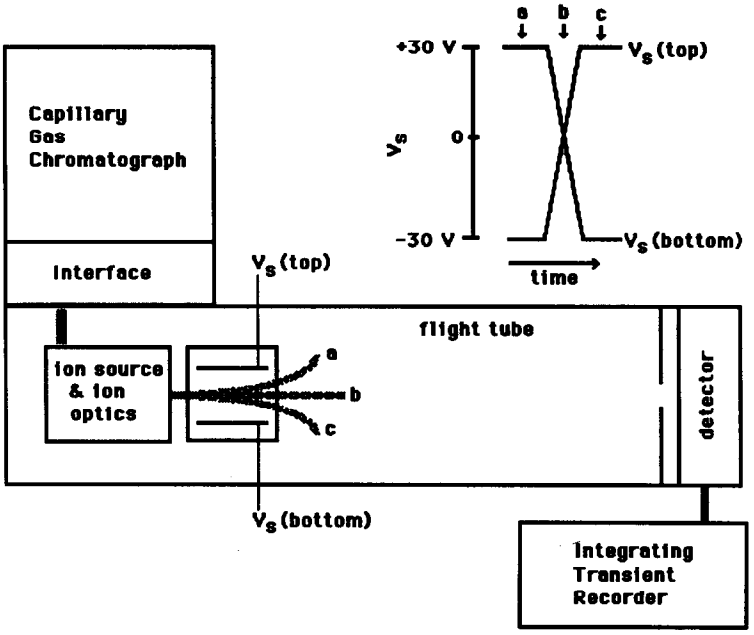

Fig. 4. Schematic diagram of the beam deflection TOF-MS system showing the gas chromatograph, continuous ion source, beam deflection assembly, CEMA detector, and ITR.

4-7304). The GC–MS interface is a heated block design from JEOL. The time-of-flight mass spectrometer is a highly modified Bendix 12-101 instrument. The source and source housing from a double-focusing mass spectrometer, a DuPont 21-491, is used to provide a continuous, narrow, focussed beam of ions produced by electron or chemical ionization. Ions formed in the source are accelerated to a kinetic energy of approximately 3000 eV. Ion packets are formed by beam deflection [14]. To obtain a rapidly changing electric field in the beam deflector for good mass spectral resolution, dynamic voltages ("pulses") of equal magnitude, but of opposite sign (designated as V_s in Fig. 4), are applied to each deflection plate yielding temporally narrow ion packets. The time-dependent voltages used are generated from pulsing circuitry that was developed in-house. Typically, the voltages V_s applied are modulated between $+30$ V and -30 V. The circuitry provides a rise time of <10 ns and a fall time of <20 ns. Ion packets traverse a 2.0-m flight tube, and transient mass spectra are generated at a rate of 5000 s^{-1}. This beam deflection TOF-MS system provides better than unit resolution for all ions in the m/z 2–1000 range, with all ions in optimal focus for each ion packet. A resolving power of >1400 has been demonstrated for this instrument [15].

An in-house designed and built integrating transient recorder [12] was used to continuously collect full mass range, mass spectra throughout the entire duration of the GC–MS run (20 min). Data collection with the ITR is accomplished by a 200 MHz flash analog-to-digital converter. The digitized data are passed to 16 high speed ECL (emitter coupled logic) summer cards where 5 to 5000 transients are summed to form a mass spectral scan file. If 5000 transients are produced each second by the

TOF-MS system, summation of 5 to 5000 transients corresponds to mass spectral generation rates of 1000 scan files per second to 1 scan file per second, respectively. The integrated scan files are passed across a VME bus to three Motorola 68020 parallel processors whereby time/mass calibration, and/or conversion to reconstructed mass chromatograms and/or real-time conversion to mass, intensity pairs occurs. Finally, the processed scan files are written to a 300 Mbyte Priam disk drive (typical scan file sizes = 500–2000 bytes).

RESULTS AND DISCUSSION

The principal goals of this paper are to demonstrate that beam deflection TOF-MS is capable of producing good quality mass spectra and that these mass spectra are well focussed and resolved over the complete mass range so that time array detection can be implemented by means of an ITR. The importance of acquiring complete mass spectra at a rate of 20 scan files per second in deconvoluting unresolved chromatographic components is illustrated in the analysis of a capillary column test mixture. As described elsewhere, the ITR is capable of generating up to 1000 complete summed spectra per second [4,11,12]. This scan file generation rate would provide 1000 data points per second from which a chromatographic profile could be reconstructed from a data base of consecutively-recorded mass spectra. However, such a high frequency of scan file generation is not necessary to reconstruct the profiles available from most high-resolution gas chromatographs at this time. In the preliminary assessment of time array detection described here, a scan file generation rate of 20 scan files per second has been found adequate to provide 20 data points per second from which to reconstruct chromatographic profiles having peak widths on the order of two seconds.

Representation of the chromatographic profile

Fig. 5 shows the reconstructed total ion current (RTIC) chromatogram of a standard test mixture [16] analyzed using GC–beam deflection TOF-MS–ITR, repre-

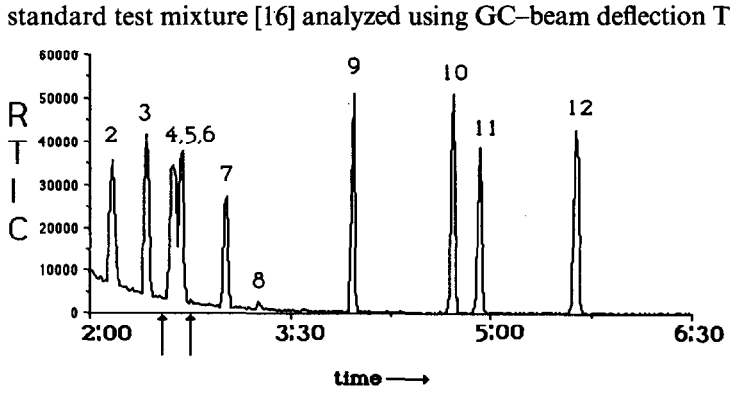

Fig. 5. Reconstructed TIC chromatogram (RTIC) of standard Grob test mixture as separated on a 20 m × 0.18 mm I.D. column containing DB-1, 0–0.4 μm film thickness at a flow-rate of 1.5 ml/min with a temperature program of 20°C/min from 120 to 200°C. Components (approx. 50 ng each) in the mixture: 1 = 2,3-butanediol; 2 = decane; 3 = 1-octanol; 4 = nonanal; 5 = 2,6-dimethylphenol; 6 = undecane; 7 = 2,6-dimethylaniline; 8 = 2-ethylhexanoic acid; 9 = C_{10} acid methyl ester; 10 = C_{11} acid methyl ester; 11 = dicyclohexylamine; 12 = C_{12} acid methyl ester. Time in min:s.

senting approximately 50 ng of each component. A scan file generation rate of one scan file per second offers one TIC point per second to reconstruct the chromatographic profile. Generation of one TIC point per second is typical of most available GC–MS instruments (*e.g.*, quadrupoles and magnetic sector instruments) in use today.

Several questions must be addressed concerning the results in Fig. 5. Does the RTIC, reconstructed from the one-scan-file-per-second data base, adequately represent the chromatography? Also, it was known that the mixture contained 12 components, but only 10 peaks are shown in the RTIC. The portion of the chromatogram containing the solvent peak and 2,3-butanediol is not shown here (Fig. 5), so there should be 11 components represented by the RTIC. To answer these questions, another aliquot of the test mixture was analyzed by GC–beam deflection TOF-MS–ITR, summing every 250 transient mass spectra, thereby generating 20 scan files per second. The RTIC chromatogram, resulting from the 20-scan-files-per-second data base at approximately 2.5 min into the run, is shown in Fig. 6b; for comparison, the corresponding segment of the RTIC in Fig. 5 (between the vertical arrows), obtained from the one-scan-file-per-second data base is reproduced as Fig. 6a. There are two obvious advantages to the greater scan file generation rate that can be seen upon comparing Fig. 6a and b. Because the 20-scan-files-per-second data base offers 20 points per second to reconstruct the waveform (Fig. 6b), the chromatographic profile is more accurately represented in terms of peak shapes, relative heights, and relative

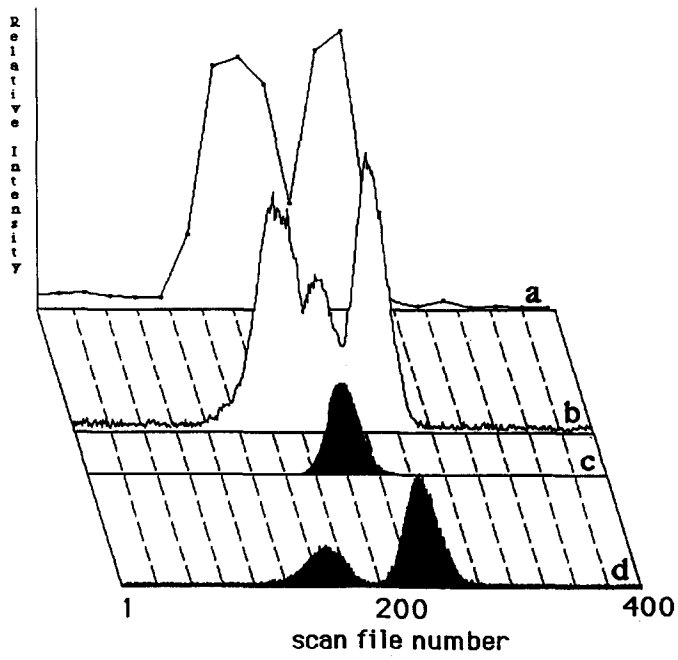

Fig. 6. (a–d) Data over a region of the chromatogram representing coeluting components. (a) RTIC obtained from spectra collected at 1 scan file/s; it only shows evidence for two components. (b) RTIC obtained from spectra collected at 20 scan files/s; it shows evidence for three components. (c) Mass chromatogram at m/z 122 representing the molecular ion of 2,6-dimethylphenol. (d) Mass chromatogram at m/z 57 representing an alkyl cation, a characteristic ion of both nonanal and undecane.

areas. This feature of the data provides better quantification of the components in the mixture. The other advantage is that the RTIC generated from higher scan file generation rates more accurately represents the true chromatographic profile. It is obvious from the RTIC presented in Fig. 6b that this region of the chromatogram contains three components.

Chester and Cram [17] have investigated the relationship between the number of data points required to represent the profile of a given chromatographic peak and the characteristic features of that peak shape as described by σ, where σ^2 is the variance that can be related to the mathematical function describing the profile. It has been previously estimated that 10 data points (scan files) per standard deviation unit are necessary to obtain an accurate representation of the chromatographic peak height, area, and position assuming a Gaussian peak [18]. The minimum number of data points which can accurately represent this profile is 10 scan files per second. Most scanning mass analyzers would not be able to represent the chromatography in this situation due to their scan file generation rate limitations.

The high scan file generation rates allow the presence of three components to be recognized in this unresolved region of the reconstructed chromatogram in Fig. 6b. Can the three components be identified from the mass spectral data base even though the components are coeluting? Because the components in the test mixture are known, as well as the type of column used for analysis, we were able to determine which components were expected to be in this region of the chromatogram. One of the expected components is 2,6-dimethylphenol. Instead of searching through the 200 scan files which contain mass spectral data for a match of the data to a library mass spectrum of this compound, we can display the mass chromatogram of one of the dominant ions in the mass spectrum of 2,6-dimethylphenol. A mass chromatogram is a graphic display of the peak intensity at a specified mass-to-charge value *versus* scan file number [19]. The library mass spectrum of 2,6-dimethylphenol indicates that the molecular ion is represented by the base peak at m/z 122. Fig. 6c is the mass chromatogram of m/z 122 and identifies the middle component as 2,6-dimethylphenol. Another component expected to be in this region of the RTIC is undecane; the alkyl cation $C_4H_9^+$, m/z 57, was selected as a designate ion for this hydrocarbon. The mass chromatogram at m/z 57 displayed in Fig. 6d shows that the mass spectra of both of the other two components contain this alkyl cation. The mass chromatograms at m/z 57 and 122 (Fig. 6d and c, respectively) provide information on the chromatographic peak shapes of the three components. By choosing a scan file which does not contain both m/z 122 and m/z 57, one can obtain a pure mass spectrum for each of the three components represented here. A visual inspection of the mass chromatogram represented in Fig. 6d shows a region (scan files 190–200) where the ion current at m/z 57 is minimal. Because the mass spectra of the other two components have an intense peak at m/z 57, this is a region of the data base that should provide a reasonably pure mass spectrum of the middle component. The mass spectrum contained in scan file 192 is shown in Fig. 7a. A similar procedure was used to obtain pure mass spectra of the other two components by choosing scan files which do not contain ion current at m/z 122. Ion current at m/z 122 is observed in scan files 160–232. Fig. 7b shows the mass spectrum in scan file 159 which is identical with the library spectrum of nonanal. Fig. 7c shows the mass spectrum in scan file 240 which is identical with that of undecane.

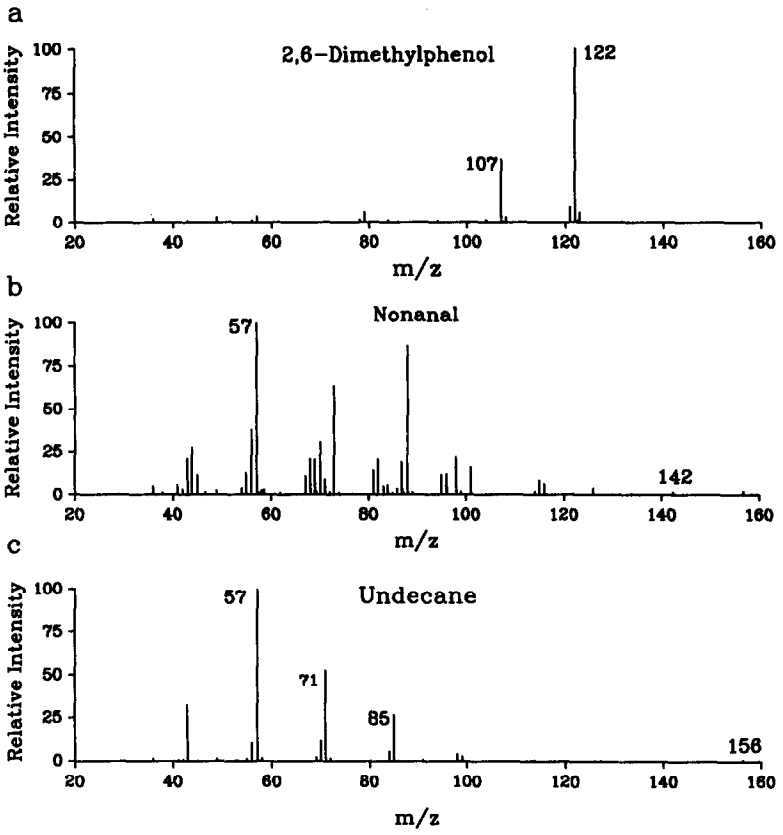

Fig. 7. Mass spectra selected from the several hundred scan files collected at 20 scan files/s as represented in Figs. 5 and 6. (a) Mass spectrum of 2,6-dimethylphenol obtained from scan file 192. (b) Mass spectrum of nonanal obtained from scan file 159. (c) Mass spectrum of undecane obtained from scan file 240. These spectra represent components 5, 4 and 6 in Fig. 5.

Limits of detection

The detection limit of the GC–beam deflection TOF-MS–ITR at 20 scan files per second was compared to that of the JEOL JMS-AX505H MS system which is a commercially available double-focusing sector instrument routinely used for GC–MS analyses. The fastest scan rate available with the JEOL instrument is 0.9 s per decade (*e.g.*, *m/z* 50-500) which generates 1.1 scan files per second.

Complete mass spectra were collected during the analysis of the standard test mixture at various concentrations at the scan file generation rate described above for each mass spectrometer. Mass chromatograms were reconstructed from the corresponding data bases. The area of the peak in the mass chromatogram at *m/z* 122 (corresponding to the base peak in the mass spectrum of 2,6-dimethylphenol) was plotted *versus* the amount of analyte injected. The limit of detection was calculated using the method of regression analysis [20] on each data set. The *y*-intercept of each regression line was used as an estimate of the blank signal, y_b. The signal, $y = y_b + 3s_b$, determines the limit of detection. The limit of detection calculated for both the

JEOL instrument and the GC–beam deflection TOF-MS–ITR system was 0.6 ± 0.2 ng of 2,6-dimethylphenol.

Quality of mass spectra

An important feature of the data obtained with GC–beam deflection TOF-MS–ITR is the absence of mass spectral skew, due to the high sampling rate (5000 s^{-1}) of the continuous ion beam. Thus, the mass spectra of individual components obtained at different scan file generation rates are identical, each having the same relative peak intensities throughout the mass range. This feature of the data would have allowed identification of the three components by use of available mass spectral deconvolution routines [21] to distinguish the coeluting components based on their characteristic contributions to peak intensities among the adjacent scan files.

CONCLUSIONS

We have shown that the GC–beam deflection TOF-MS–ITR combination is capable of providing good-quality GC–MS data. The GC–beam deflection TOF-MS–ITR system can generate data files at a rate greater than those commonly available from quadrupole and magnetic sector instruments. The importance of the high scan file generation rate was illustrated by comparison of reconstructed total ion current chromatograms from data bases collected at 20 scan files per second and at one scan file per second, the latter being representative of the performance of most magnetic or quadrupole instruments (even though, in principle, these instruments can generate data at higher rates, but at the expense of performance and data quality). Here we have shown an example where one scan file per second is insufficient to reproduce the chromatographic profile; in this case, we reanalyzed the mixture by GC–MS generating 20 scan files per second. Each mass spectral transient is free of any skewing due to the changing partial pressure of the analyte in the ion source, thus the summed spectra are free of the types of skew that would be imposed by other scanning instruments.

This report describes one approach by which the MSU research group is attempting to respond to the fact that developments (*e.g.*, scan speeds) in MS have not progressed in a timely fashion commensurate with improvements in GC resolving power. Chromatograms are now being reported with peak widths on the order of tens of milliseconds [2]; further improvements in GC could make contemporary MS of little use as a GC detector. While these preliminary results with the GC–beam deflection TOF-MS–ITR system are not competitive from the standpoint of sensitivity (because the source is designed for a magnetic sector instrument), they do illustrate that developments in TOF-MS and its use with the ITR provide a mass spectrometer that can "keep up" with the demands imposed by high-resolution GC on MS. These developments provide the basis for sustaining the use of MS as a GC detector, the data from which can be used to both adequately represent the chromatography and identify eluting components of complex mixtures.

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