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Simple direct liquid introduction system usable as an interface for liquid chromatography–mass spectrometry on quadrupole and magnetic-sector mass spectrometers

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ABSTRACT

A simple and inexpensive direct liquid introduction system that can be used for tandem mass spectral analysis and for interfacing liquid chromatography on quadrupole and magnetic-sector mass spectrometers is described. The interface consists of a transfer fused-silica capillary that is introduced directly into the chemical ionization source of the mass spectrometer through the conventional gas chromatography–mass spectrometry interface, replacing the capillary column. The coupling uses no desolvation chamber and the transfer capillary is heated over the whole length of the interface. Experiments on the effect of interface temperature and flow-rate demonstrate that the system is extremely stable under optimal operating conditions, which are similar on different spectrometers. The chemical ionization plasma generated by the mobile phase under typical operation consists mainly of protonated monomers, and its composition is similar on different spectrometers, as shown by the comparison of spectra obtained. The system can be used with a series of mobile phases, and the ionization features that they produce are comparable. The system is stable, reproducible and allows picogram range sensitivity to be achieved in mass spectrometric, tandem mass spectrometric or liquid chromatographic–mass spectrometric experiments.

INTRODUCTION

The development of techniques allowing the introduction of liquid samples into the ion source of a mass spectrometer has considerably increased the range of compounds that can be analysed by mass spectrometry (MS). Although substantial efforts have been devoted to developing interfaces in order to couple liquid chromatography (LC) to MS, there are several other applications that can benefit from such liquid introduction techniques. Mass spectral applications that require the introduction of liquid samples can be classified into three general classes and theses are (i) the identification of organic compounds by techniques of MS or MS–MS, (ii) real-time monitoring of chemical reactions occurring in solution and (iii) interfacing of liquid chromatography to mass spectrometry.

Since the initial experiments reported by Tal'roze *et al.* [1] and by Baldwin and McLafferty [2] in the early 1970s, many reports describing liquid introduction techniques or LC interfaces have appeared in the literature, and these techniques have

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been the subject of periodic reviews over the last ten years [3–8]. Several approaches can be used to conduct experiments that require the introduction of a liquid into the ion source of a mass spectrometer, and these include direct liquid introduction (DLI) systems [1–3,8–10], moving belts [11], thermospray [12,13], electrospray [14], ion spray [15,16], fast atom bombardment [17], monodisperse aerosol interfaces [6] and many others. For example, fast atom bombardment (FAB) MS has been used successfully in its conventional form as an introduction system for MS and MS–MS analysis [18] and in the continuous-flow (CF) mode for real-time reaction monitoring (peptide hydrolysis) [19] and interfacing LC to MS (LC–FAB-MS) [20]. The use of FAB as an introduction system is advantageous since it allows an ion beam to persist for a long period of time (10–15 min), during which mass spectral techniques such as exact mass measurements or collision-induced dissociation experiments (MS–MS) can be performed.

A survey of the existing liquid introduction systems shows that the DLI systems using a simple metal or fused-silica capillary [9,10,21–26] to transfer the solvent or an analyte in solution into the ion source of the mass spectrometer are the most appealing. They are inexpensive and can be adapted easily to any type of mass spectrometer whether it be a quadrupole or a magnetic-sector instrument. This simple type of interface uses flow-rates in the range of 1–10 μl/min, which are within the pumping capacity of most mass spectrometers that use an electron ionization (EI) or a chemical ionization (CI) ion source, as shown by Tal'roze *et al.* [1] and by Baldwin and McLafferty almost twenty years ago. The simplicity of this interface has permitted the construction of home-built devices for the analysis of thermally labile or polar compounds [22] or high-molecular-weight materials (CF-FAB) [18].

The use of a DLI interface can lead to three conditions of stability that are interesting for mass spectral analysis. These interfaces can produce a stable liquid surface under vacuum as in FAB, a stable stream of liquid droplets, that can further be desolvated [21], as produced by pneumatic nebulizers [14,15] with or without electrical assistance, or alternatively a steady stream of gas as obtained with capillary thermal nebulizers [27].

Examination of the actual configuration of most gas chromatography (GC)–MS systems, using direct coupling of the capillary GC column into the ion source, immediately leads to the conclusion that these systems could be used as the basis for capillary DLI interfaces using thermal nebulization. It is in that perspective that the present work was untertaken in order to evaluate the feasibility of using conventional GC–MS interfaces for the introduction of liquid samples into quadrupole and magnetic-sector mass spectrometers. Experiments have been conducted in order to characterize the optimal operating conditions of such an interface coupled with a CI source and to use it as a liquid sample introduction system for MS and MS–MS analyses as well as a simple interface to perform LC–MS experiments on specific analytical systems.

EXPERIMENTAL

Instrumentation

The instruments used in this study were a VG-TRIO-1 quadrupole mass spectrometer equipped with differential pumping (240 L/s source, 50 L/s analyser) and a

LAB BASE data system, and a VG-AutoSpec-Q magnetic-sector hybrid mass spectrometer of EBEqQ geometry. Both instruments were interfaced to Hewlett-Packard 5890 gas chromatographs equipped with capillary GC columns. The TRIO-1 was slightly modified by the addition of a Penning CP25EK high-vacuum gauge (Edwards Vacuum) on the pumping circuit leading to the CI source, which was slightly altered to increase its pumping speed and sensitivity. The VG-AutoSpec-Q was used without modification. The combined EI–CI source was used for DLI-MS experiments. In DLI-MS–MS experiments, kinetic energy spectra (MIKES/CA) were obtained by isolating the ion of interest with the two sectors E_1 and B and by scanning the voltage on the second electric sector E_2 over the whole range of energies. The collision energy in the FF3 cell was 8 KeV, and helium was used as a collision gas at a pressure corresponding to a beam attenuation of 50%. Single- or multiple-scan experiments were performed with the SIOS interface using the VAX-based OPUS data system in the MCA mode.

DLI experiments

The DLI experiments performed in this study were done by directly introducing a 50 or 75 μm I.D. fused-silica transfer capillary into the ion source of either mass spectrometer. On both instruments, the transfer capillary was introduced by the GC oven through the conventional GC–MS interface where it replaced the GC capillary column and was adjusted into the ion source exactly like the GC column. The capillary was directly connected at the other end (in or outside GC oven) to a 60-nl Valco C14W manual injector valve through which the solution containing the sample was introduced. The mobile phase of variable composition was supplied to the DLI system by a Harvard Model 22 low-pressure syringe pump as shown in Fig. 1. All solvents were HPLC grade and degassed in an ultrasonic bath for 15 min before use. Typical flow-rates used were between 0.5 and 3 μl/min. For LC–MS experiments, the Harvard pump was replaced by a high-pressure syringe pump. The transfer capillary was heated over the length of the interface and maintained at the optimal temperature on both spectrometers using the standard GC–MS interface heaters and controls on the respective instruments. The CI ion source was operated using the DLI mobile

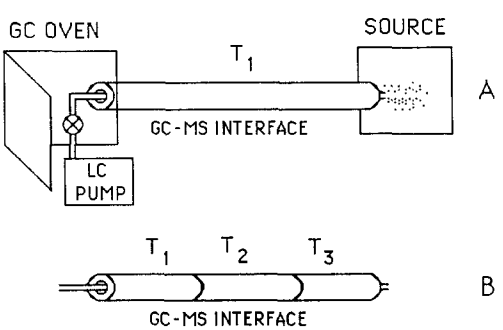

Fig. 1. Typical GC–MS interfaces that exist on mass spectrometers. (A) GC–MS interface on VG-TRIO-1 quadrupole mass spectrometer. (B) GC–MS interface on VG-AutoSpec magnetic-sector mass spectrometer. T_1, T_2 and T_3 represent thermal zones in the interface.

phase as a reagent gas with or without a make-up CI gas. Return to the GC–MS mode was done by simply replacing the DLI capillary with the GC capillary column. Essentially no time was wasted in resetting the interface temperature when changing the operating mode since temperatures were very similar in both types of experiments.

RESULTS AND DISCUSSION

The DLI system used in this study, which resembles several systems that have been reported in the literature [10,22,26], consists of a fused-silica capillary which is introduced directly into a CI source through a standard GC–MS interface. This capillary replaces the GC column in the interface and is connected to an injector and a pumping system as shown in Fig. 1. The characteristics of the system are (i) the absence of a desolvation chamber which is often used in DLI systems [7,9,12,21,25] and (ii) the fused-silica transfer capillary is heated over the whole length of the interface, which is of the order of 60 cm. The interface can have one temperature zone, as in Fig. 1A (TRIO-1), or several, as in Fig. 1B (AutoSpec-Q).

The main factors that influence the performance of DLI systems using capillary thermal nebulizers are the temperature of the capillary and the flow of the mobile phase into the ion source of the mass spectrometer. The temperature of the interface governs the rate of evaporation of the mobile phase, whereas the flow-rate affects the pressure within the ion source and thus the composition of the CI plasma. It is, therefore, essential for the optimization of the DLI system that the optimal interface temperature and flow-rate be determined in order to operate under stable experimental conditions [8,28,29].

The effect of the interface temperature on the stability of the DLI systems was studied in initial experiments on the quadrupole spectrometer that has a single thermal zone (Fig. 1A). The results obtained when the temperature was varied at constant flow-rate (*ca.* 1 μl/min) of the mobile phase indicated that the stability of the system, as measured by the ratio of the standard deviation of the total ion current (TIC) (σ) over the TIC, varied as a parabolic function of the interface temperature. Typically the ratio σ/TIC was of the order of a few percent between 150 and 180° (3% at 170°C [27]), where source conditions were found to be extremely stable. Partial to severe instability was encountered on both sides of this temperature range. These observations can be rationalized by the fact that at lower temperatures the evaporation of the mobile phase is too slow compared with the flow in the system, creating erratic evaporation in the ion source [10]. At temperature values well above 170°C, the evaporation rate is too high and the vaporization zone resides well within the capillary, creating instability in the flow.

The temperature effect observed when the DLI system was used on the AutoSpec-Q mass spectrometer showed similar behavior, but the results obtained for the stability of the system with the interface temperature were slightly different. This can be explained by the fact that the GC–MS interface on this particular mass spectrometer is constructed in three segments that can be maintained at different temperatures (Fig. 1). With this instrument a stability region also exists for a range of temperature between 180 and 240°C for segment T_3, when the temperatures of fragments T_2 and T_1 are maintained at 210 and 220°C, respectively. Temperature T_3 appears to be most critical, and if it is set outside this range instability in the operating conditions is observed, as with the other interface.

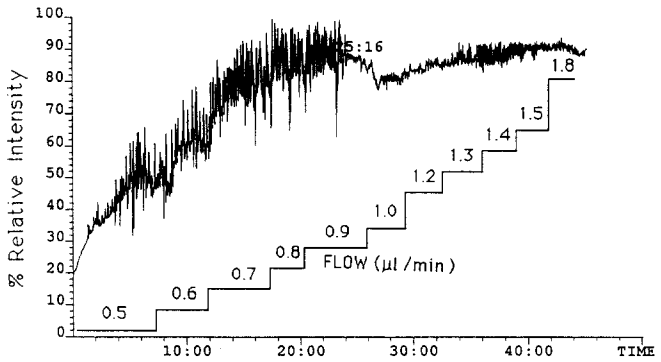

Fig. 2. Stability of the TIC in the ion source of the AutoSpec-Q with the flow-rate in the DLI interface. Time in min.

Another factor that affects the stability and the operating conditions is the flow-rate. Its value has to be such that the thermal input through the interface is sufficient to vaporize the mobile phase while the pressure within the CI source is adequate to maintain ionization and sensitivity. The pressure in the ion source depends on the flow-rate and the pumping capacity, and it must stay within a given range in order to produce a stable and reproducible plasma composition. If LC–MS experiments are to be conducted, additional constraints will be imposed on the flow-rate, since it will have to be such that the chromatographic conditions are also optimized.

The effect of the flow-rate was investigated on the AutoSpec-Q mass spectrometer at optimum temperature of the interface (T_1 = 220°C, T_2 = 210°C, T_3 = 190°C). The fluctuation of the TIC, including the mobile phase components, observed with flow-rate is shown in Fig. 2. For values of the flow-rate below 1.0 µl/min the system is quite unstable, as witnessed by the important variation in the signal. As the flow approaches the value of 1.1 µl/min, the noise on the TIC rapidly disappears and the standard deviation becomes of the order of a few percent, indicating that the overall operating conditions have stabilized. If the flow is increased above 1.3 µl/min, the noise reappears but to a much lesser extent, indicating that the system is slightly perturbed but still relatively stable. The range of flows corresponding to stable operating conditions is found to be 1.0–1.6 µl/min on the AutoSpec-Q mass spectrometer and 0.8–2.0 µl/min on the TRIO-1, corresponding, dependent on solvent, to indicated source pressures of $1 \cdot 10^{-5}$ to $6 \cdot 10^{-5}$ and $2 \cdot 10^{-5}$ to $2 \cdot 10^{-4}$ Torr, respectively, which indicates that flow conditions are probably similar on most instruments. This flow is compatible with the use of 0.25 mm I.D. packed capillary columns that operate at optimum flow-rates between 1 and 2 µl/min.

The flow-rate in a DLI system using CI also determines the pressure in the ion source and consequently the composition of the plasma. In order to assess the influence of the flow on ionization, the composition of the plasma was measured at varying source pressures corresponding to different flow-rates. In these experiments, several mobile phase compositions were studied, and typical results obtained with the binary mixture acetonitrile–water (75:25) are shown in Fig. 3. The figure gives the ion profiles on the TRIO-1 (Fig. 3A) and on the AutoSpec-Q (Fig. 3B) as a function of the

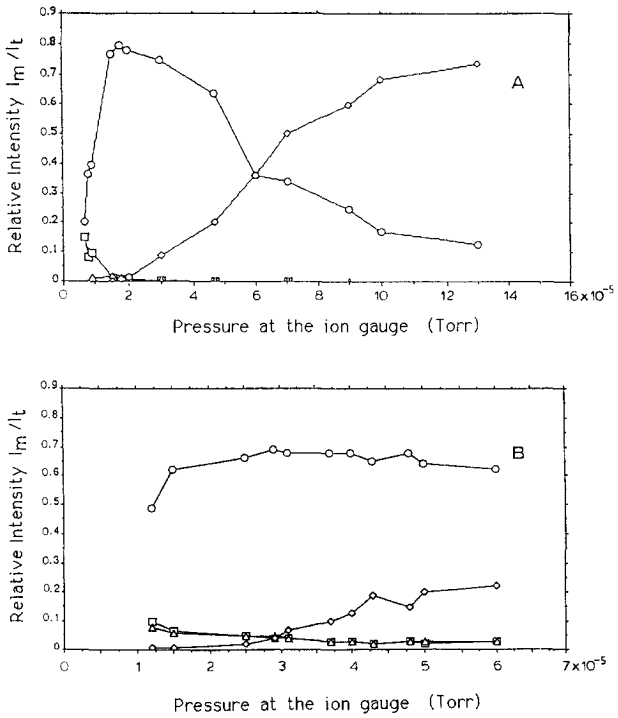

Fig. 3. Variation of the composition of the CI plasma with pressure (flow-rate) in the ion source. (A) TRIO-1: ○ = CH_3CNH^+ = m/z 42; ◇ = $(CH_3CN)_2H^+$ = m/z 83; □ = H_3O^+ = m/z 19; △ = H_2O^+ = m/z 18. (B) AutoSpec: ○ = CH_3CNH^+; ◇ = $(CH_3CN)_2H^+$; □ = H_3O^+; △ = H_2O^+. I_m represents the current of the individual mass and I_t the total ion current.

pressure in the source. It can be observed from Fig. 3A that the major ion in the plasma at the lower pressures ($<4 \cdot 10^{-5}$ Torr) corresponds to protonated acetonitrile at m/z 42, and that for pressures below this value the intensity of the protonated dimer of acetonitrile at m/z 83 is small. As the pressure is increased above that value, the intensity of the dimer increases and it becomes the most important ion. Ions at m/z 18 and 19 corresponding to H_2O^+ and H_3O^+ have much weaker intensities than those related to acetonitrile.

The distribution of ions in the source of the AutoSpec-Q is shown in Fig. 3B and is similar to that observed on the TRIO-1. The figures appear different because the pressure range shown in Fig. 3B ($1 \cdot 10^{-5}$ to $6 \cdot 10^{-5}$ Torr) is narrower than that in Fig. 3A ($2 \cdot 10^{-5}$ to $1.6 \cdot 10^{-4}$ Torr). The upper limit for pressure on the magnetic-sector spectrometer is lower than on the quadrupole because of the high voltage. The ion profiles in the source of this magnetic-sector mass spectrometer compare well with the ion intensities found at a pressure of $2 \cdot 10^{-5}$ on the quadrupole instrument, and it can be seen that the protonated dimer starts to increase while the protonated monomer starts to decrease as the pressure increases. The ions generated by water at m/z 18 and 19 are again weak as observed in the other source. The pressures indicated in the figures are not actual source pressures but those corresponding to readings on the vacuum gauges and are not exactly matched since the gauges are located at different positions on each spectrometer.

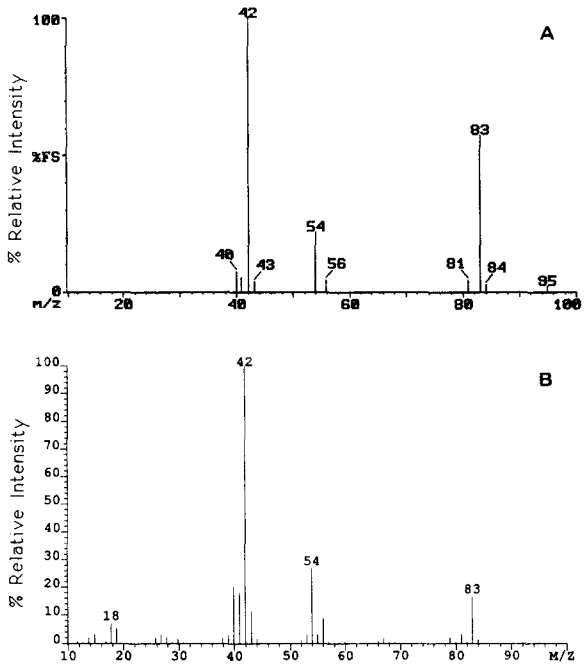

Fig. 4. Composition of the CI plasma obtained with a mobile phase acetonitrile–water (75:25) under typical operating conditions of the DLI system. (A) Composition on the VG-TRIO-1 mass spectrometer. (B) Composition on the AutoSpec-Q; CH_3CNH^+ = m/z 42.

The ionization conditions should be similar on both instruments since the operating conditions of the DLI systems are close. The mass spectrum corresponding to the plasma generated in both systems by the binary mobile phase, under optimized conditions, is given in Fig. 4A and B. Examination of the figures reveals that the ion populations are identical, which suggests that the DLI system will probably yield similar results on almost any mass spectrometer with a direct GC–MS capillary interface. For the acetonitrile–water (75:25) mixture the most important ionic species is CH_3CNH^+, but this ion is also quite important in other phases that we have analyzed, including ternary mixtures containing acetonitrile (acetonitrile–water–acetic acid). Thus, the qualitative results that can be obtained using these systems with different mobile phases containing acetonitrile should be similar. It is noteworthy that the presence of important ionic species higher than the dimer is not observed in our DLI-MS system even in the absence of a desolvation chamber. This observation is contrary to other reports using DLI interfaces in which the protonated dimer is by far the most important ionic species [30,31]. This disparity can be rationalized by the fact that our capillary is heated over a considerable length, and this causes higher clusters to dissociate before they enter the ion source.

In order to investigate qualitatively the variability of the ionization conditions in the DLI system, several compounds were analyzed using mobile phases of varying compositions. Typical spectra obtained in these experiments are shown in Fig. 5. The figure shows the mass spectra of *p*-hydroxybenzoic acid and vanillic acid obtained

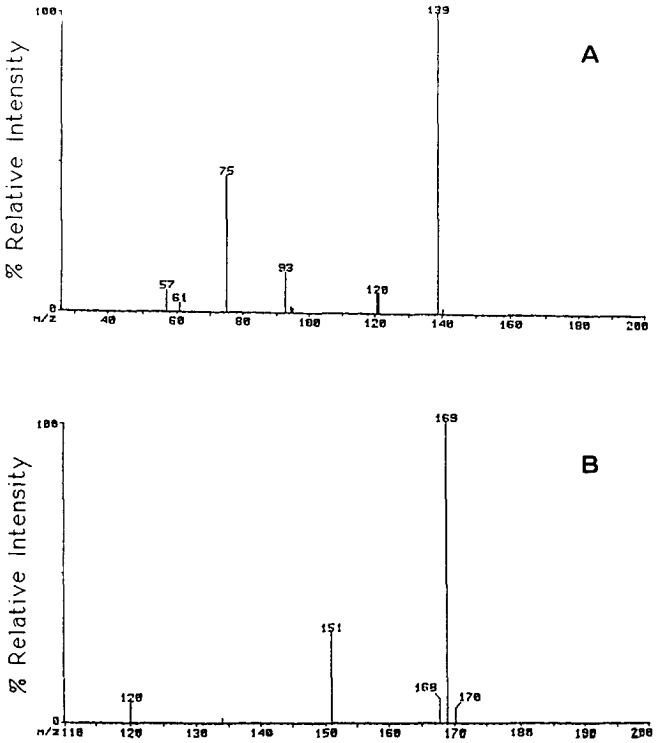

Fig. 5. Mass spectrum of (A) *p*-hydroxybenzoic acid obtained with pure water as mobile phase and (B) vanillic acid obtained with pure acetonitrile.

using pure water (Fig. 5A) and pure acetonitrile (Fig. 5B), respectively. It can be concluded from the data that, although the extent of fragmentation can vary slightly from one composition to another because of different proton affinities, the general features of the spectrum, presence of $[M+H]^+$ and $[M+H-H_2O]^+$, are generally the same. The mass spectra obtained with the same mobile phase but on different instruments can be compared. The spectra of ibuprofen obtained using the DLI interface (acetonitrile–water, 75:25) on the TRIO-1 (80 ng) and the AutoSpec-Q (6 ng) are shown in Fig. 6A and B, respectively. It is noteworthy that the relative intensity of the $[M+H]^+$ ion is considerably greater than that reported in the literature in similar systems using concentrations ten times greater [32]. Furthermore, the data reveal that the patterns obtained on different instruments are extremely similar, which suggests that the DLI system can be transported between instruments without noticing major changes. This supports the assumption made previously from the comparison of the plasma compositions.

The operating conditions having been determined, the DLI interface can be used for several types of applications. Beside its obvious use as an LC–MS interface as already shown [27], it can be used for real-time monitoring of reactions in solution and as a liquid introduction system for MS and MS–MS analysis.The latter application is interesting since, as is done with FAB, the DLI system can be helpful in mass

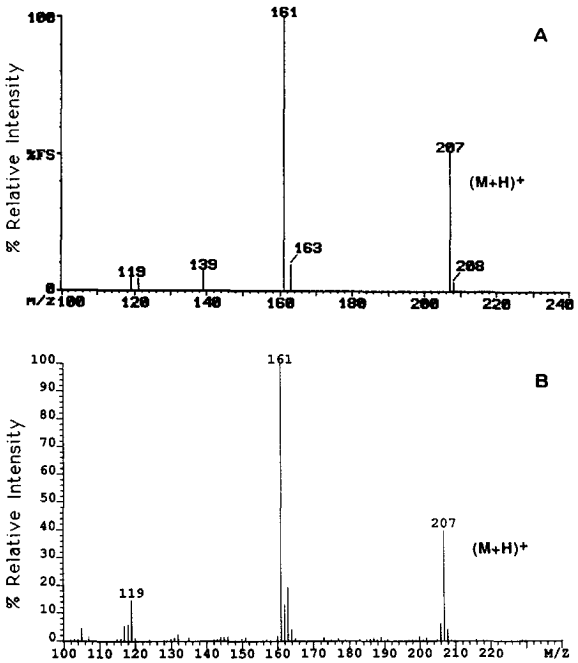

Fig. 6. Mass spectrum of ibuprofen obtained with acetonitrile–water (75:25). (A) Spectrum on TRIO-1; (B) spectrum on AutoSpec-Q.

spectral experiments that need a stable ion beam that can persist for a resonable period of time. In mass spectral techniques such as accurate mass measurement or mass-analyzed ion kinetic energy spectroscopy experiments, it is extremely useful to be able to maintain a steady ion beam of good intensity. Use of a direct insertion probe or a heated batch inlet system is not always desirable. Some compounds are too volatile for probe work and only give a transient signal, and others are too labile to be heated in a batch reservoir. Thus, the DLI inlet can be used with success in these types of analyses.

In order for the DLI interface to be useful for these applications it is necessary

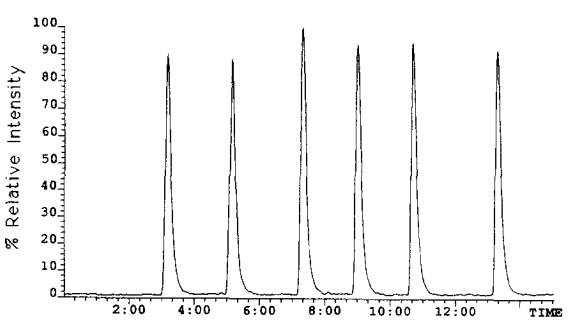

Fig. 7. TIC on AutoSpec-Q for repetitive injections of 60 nl of ibuprofen (100 pg/nl). Time in min.

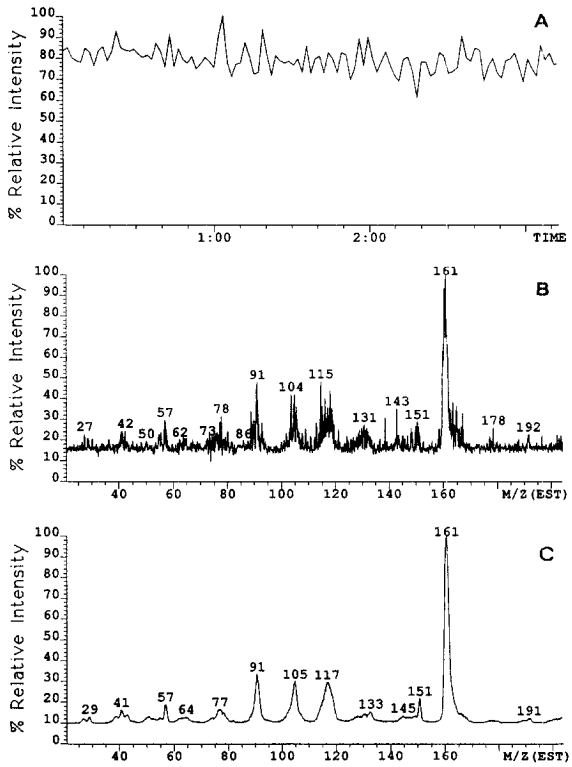

Fig. 8. MS–MS analysis of a solution of ibuprofen (100 pg/nl) in the DLI mode. (A) Mass chromatogram of $[M+H]^+$ at m/z 207. Time in min. (B) Collisionally activated spectrum of $[M+H]^+$ at m/z 207, single scan. (C) Average of ten scans.

that its operation be stable and reproducible. The reproducibility of sample injection has been studied with injections of ibuprofen. Fig. 7 gives the single-ion chromatogram of m/z 207 ($[M+H]^+$) reproduced from the TIC for several consecutive 60-nl injections of a solution of ibuprofen (100 ng/μl). As is observed from the figure, the reproducibility of the system is excellent considering that the peaks are reproduced from scanning data. An example of the use of the DLI system for MS–MS analysis is presented in Fig. 8. The figure shows the results of experiments in which MS–MS data were obtained when a solution of ibuprofen was continuously introduced into the ion source using the DLI interface. Fig. 8A shows the TIC of the primary ion current at m/z 207 ($[M+H]^+$), Fig. 8B a single scan of a MIKES/CA spectrum of m/z 207, and Fig. 8C gives the spectrum obtained by averaging ten scans of the electric sector. The data of Fig. 8A demonstrate that the stability of the system is very good since the TIC was reproduced from MIKES/CA spectra and the relative concentration of the $[M+H]^+$ ion in the plasma was extremely low. The results also indicate that the liquid introduction system allows MS–MS spectra to be easily obtained from very small amounts of material (*ca.* 1 ng) and that it is possible to integrate the signal to increase signal-to-noise ratio bacause of the persistence of the signal. Thus the DLI system represents an excellent introduction system for mass spectral analysis of compounds in solution or in mixtures.

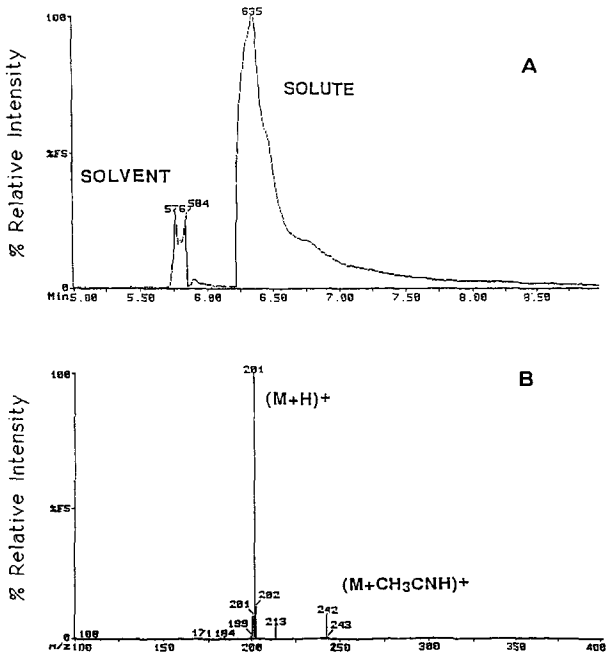

Fig. 9. Analysis of solution of 1,12-diaminododecane in hexane injected in acetonitrile–water (75:25). (A) TIC of DLI injection. (B) Mass spectrum of 1,12-diaminododecane.

The thermal nebulizer capillary DLI interface offers other advantages for the routine analysis of volatile compounds present in solutions. This can be seen from the data presented in Fig. 9, which shows the injection of a liquid solution of 1,12-diaminododecane in hexane. The TIC trace represented in Fig. 9A shows that the interface separates the solute from the solvent and that both compounds are analyzed separately in the mass spectrometer. The spectrum given in Fig. 9B corresponds to the spectrum of 1,12-diaminododecane in the mixture. Examination of the spectrum reveals that it is relatively pure and that interference from the solvent is almost absent. Several samples contained in solvents have been analyzed by direct liquid injection, and the phenomenon shown in Fig. 9 is almost always observed because of some activity in the transfer capillary. However, this phenomenon is not observed when the sample is continuously admitted into the ion source.

CONCLUSIONS

The simple DLI system using a conventional GC–MS interface that has been described in this work can be very useful to interface LC to MS and also as a stand-alone system that can be used for mass spectral analyses by MS or MS–MS. The system is easy to operate, offers very good stability when operated under optimum conditions and is transportable from one instrument to another. As has been shown in this study, the performance is equally good on the magnetic-sector or quadrupole mass spectrometers and the data obtained using both systems compare well. The mass

spectra obtained with several mixtures commonly used as mobile phases in LC are qualitatively similar. The system, although similar to other systems that have been reported, presents particular features since the plasma generated contains mostly protonated monomers. The system is reproducible and allows picogram sensitivity to be achieved in the MS–MS or LC–MS mode, using 0.25-mm packed capillary columns [27]. Over the period of 16 months that we have used the system, the capillary has never blocked with our analytical applications.

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