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Extending the range of compounds amenable for gas chromatography–mass spectrometric analysis

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Abstract

Gas chromatography–mass spectrometry (GC–MS) suffers from a major limitation in that an expanding number of thermally labile or low volatility compounds of interest are not amenable for analysis. We found that the elution temperatures of compounds from GC can be significantly lowered by reducing the column length, increasing the carrier gas flow rate, reducing the capillary column film thickness and lowering the temperature programming rate. Pyrene is eluted at 287 °C in standard GC–MS with a 30 m×0.25 mm I.D. column with 1-μm DB5ms film and 1-ml/min He column flow rate. In contrast, pyrene is eluted at 79 °C in our ''Supersonic GC–MS'' system using a 1 m×0.25 mm I.D. column with 0.1-μm DB5ms film and 100-ml/min He column flow rate. A simple model has been invoked to explain the significantly (up to 208 °C) lower elution temperatures observed. According to this model, every halving of the temperature programming rate, or number of separation plates (either through increased flow rate or due to reduced column length), results in ~20 °C lower elution temperature. These considerably lower elution temperatures enable the analysis of an extended range of thermally labile and low volatility compounds, that otherwise could not be analyzed by standard GC–MS. We demonstrate the analysis of large polycyclic aromatic hydrocarbons (PAHs) such as decacyclene with ten fused rings, well above the current GC limit of PAHs with six rings. Even a metalloporphirin such as magnesiumoctaethylporphin was easily analyzed with elution temperatures below 300 °C. Furthermore, a range of thermally labile compounds were analyzed including carbamates such as methomyl, aldicarb, aldicarbsulfone and oxamyl, explosives such as pentaerythritol tetranitrate, Tetryl and HMX, and drugs such as reserpine (608 a.m.u.). Supersonic GC–MS was used, based on the coupling of a supersonic molecular beam (SMB) inlet and ion sources with a bench-top Agilent 6890 GC plus 5972 MSD. The Supersonic GC–MS provides enhanced molecular ion without any ion source related peak tailing. Thus, the lower GC separation power involved in the analysis of thermally labile and low volatility compounds is compensated by increased separation power of the MS gained from the enhanced molecular ion. Several implications of these findings are discussed, including our conclusion that *slower* chromatography leads to better analysis of thermally labile compounds.
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1. Introduction

Gas chromatography–mass spectrometry (GC–MS) is a central analytical technique that serves a

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broad range of applications [1,2]. However, current GC–MS technology suffers from a major limitation in that a relatively small range of volatile, thermally stable compounds are amenable for analysis. A growing portion of analytically important analytes includes thermally labile compounds and/or compounds of insufficient volatility that require liquid chromatography mass spectrometry (LC–MS) for their analysis.

The major strength of GC–MS using electron ionization (EI) is its ability to identify compounds through the use of extensive and established 70-eV EI libraries. Such library-based compound identification can be performed with minimal analyst intervention. However, EI mass spectra suffer from frequent absence of the molecular ion (M^+), and this drawback reduces the confidence level in the sample identification. As a result, an additional analysis with chemical ionization is sometimes required, which is incompatible with library identification, and could require a lengthy procedure of ion source replacement.

These two major GC–MS shortcomings become more apparent and are further exacerbated due to recent advances in capillary column technology, in which the temperature range of GC columns is steadily increased. Less volatile compounds tend to be more fragile and have a higher probability of being thermally labile. Furthermore, in order to prevent ion source induced peak tailing (and contamination) with less volatile compounds, the temperature of the ion source must be increased which causes a reduction in the relative abundance of the molecular ion *for all* sample compounds (due to increased sample vibrational energy content) [3–6]. Consequently, the limitations of GC–MS in light of expanding number of thermally labile compounds and compounds that show no molecular ion in their 70-eV EI mass spectra become more problematic. Thus, the use of LC–MS is currently growing at a faster pace than GC–MS, despite its added cost, greater complexity and lack of library identification.

Clearly, any advance in extending the range of compounds amenable for GC–MS analysis and thus alleviating this Achilles heel of GC–MS can considerably contribute to its use and variety of applications, and increase its advantage compared to LC–MS. Preferably, such an extension in the range of compounds should also give an increased quality of library searchable mass spectra that always show a sufficiently abundant molecular ion for high confidence identifications.

In the last decade we developed and explored the performance capabilities of a new type of GC–MS, based on the use of a supersonic molecular beam (SMB). SMB was used for interfacing the GC to the MS [7–13] and as a medium for ionization of sample compounds while in the SMB, either by electron ionization [14–16] or by hyperthermal surface ionization (HSI) [15,17–22]. While our research has employed a quadrupole mass analyzer [7–13], GC–MS with SMB was also implemented with a time-of-flight mass analyzer [23,24]. Supersonic helium or hydrogen seeded molecular beam provides unidirectional motion with equal velocity of its entire species and thus a controlled hyperthermal kinetic energy (1–20 eV) of the heavier (seeded) organic sample compounds. In addition, SMBs are characterized by intra-molecular vibrational supercooling of its seeded compounds due to relatively low collision energies of sample compounds and carrier gas species during the supersonic expansion. SMBs are further characterized by mass focusing similar to that of a jet separator, and the capability to handle very high column flow rates of up to 240 ml/min [7,10]. We note that increased column flow rate does not adversely affect the sensitivity since it is involved with slightly less make up gas and thus the same supersonic nozzle flow rate, regardless of the column flow rate. SMB has been demonstrated to improve several major GC–MS performance aspects including:

(1) The M^+ intensity is enhanced in EI with SMB (named "cold EI") and it is practically always exhibited. This feature originates from intra molecular vibrational cooling of sample compounds in the supersonic expansion [15].

(2) Effective fast and ultra-fast GC–MS is enabled, compatible with any mass analyzer including quadrupole devices, and without limitations on column diameter, length or flow rate [7–13].

(3) Low detection limits can be achieved for a wide range of drugs and aromatics using HSI [7,25], while the EI sensitivity is similar to that of standard

''thermal'' EI [25]. Enhanced single ion monitoring (SIM) sensitivity is exhibited in EI of alkanes due to the large enhancement in M^+ abundance [25].

(4) Thermally labile molecules are amenable for analysis [7,8].

Dagan and Amirav explored GC–MS of thermally labile and relatively non-volatile compounds using GC–MS with SMB. Ovalene and even phthalocyanine were analyzed with a short (50 cm) Megabore (0.53 mm I.D.) capillary column, 240-ml/min He column flow rate and isothermal analysis conditions at 430 °C [7]. Subsequently, Dagan and Amirav further investigated the GC–MS analysis of a range of thermally labile carbamates, steroids and drugs (antibiotics) [8]. The increased analysis capability of these thermally labile compounds was attributed mostly to the reduction of the time spent in the column, although the high column flow rate at the injector and the elimination of degradation in the ion source were also found to be important parameters [8]. Grob was the first to explore the factors that affect the analysis of thermally labile compounds (phenylurea herbicides) by capillary column GC–FID [26]. In his paper, he emphasized the importance of lowering the elution temperature by using higher column flow rates. The importance of using thin adsorption films and shorter columns was also addressed, and the use of cold-on-column injection was demonstrated to suppress intra injector degradation. Trehy et al. used short columns for fast GC–MS analysis of thermally labile aldicarb and discussed the importance of increased optimal carrier gas velocity at sub-ambient pressures with vacuum outlet conditions of GC–MS instruments [27]. The reduction of the time spent at the column was invoked as the major factor for improved performance with thermally labile compounds. Rossi et al. reported the use of short column GC–MS with near or sub ambient column head pressure for the analysis of underivatized steroids [28,29].

However, despite the considerable importance of the subject of thermally labile and low volatility analysis, only a few GC–MS investigations were performed aimed at better understanding of this subject. To date, no appropriate solution has been found to solve this critical GC–MS limitation. We feel that the major reason for the long prevalence of this major GC–MS limitation is that the vast majority of capillary GC–MS systems are operated with direct introduction of the GC column outlet gas flow to an MS chamber equipped with a small vacuum pump (for the obvious reason of cost reduction). A second probable reason is that most GC–MS users are not used to considering sacrificing GC resolution to obtain other benefits. Consequently, the industry standard column is 30 m in length with 0.25 mm I.D. for achieving direct and easy coupling of the GC and MS, which gives a positive column head pressure and typical maximum flow rate of 1–2 ml/min. As a result, GC–MS is currently limited to the type of compounds that can be handled by these ''industry standard'' columns and column flow rates. The goal of this paper is to explore all the parameters, in addition to analysis time, that affect our ability to analyze thermally labile and low volatility compounds by GC–MS, and suggest a viable approach for their useful analysis and thus, a solution for extending the range of GC–MS applications.

2. Experimental supersonic GC–MS system

Recently, we have incorporated GC–MS with SMB into a new instrument and approach, which we have entitled ''Supersonic GC–MS''. This instrument has been described in detail previously [25]. In brief, its design involves the modification of a commercially available Agilent (Wilmington, DE) GC–MS system (6890 GC plus 5972 MSD) to include an SMB interface and ion sources. The Supersonic GC–MS transfer line, a 20-cm-long piece of 0.53 mm I.D. deactivated Silcosteel tube provided by Restek (Bellefonte, PA), was connected at the vacuum end with a nozzle (0.1 mm I.D.) and was operated at a typical temperature of 200–250 °C with 130-ml/min combined makeup and column He flow rate. After the supersonic expansion from the nozzle, the free jet was skimmed, differentially pumped, and passed into a fly-through EI ion source (home-made, 10-mA ionizing electron emission current with 70-eV electron energy) located perpendicular to the quadrupole MS inside the vacuum chamber of the original 5972 mass selective detector (MSD) instrument. The original 5972 MSD was used essentially as is, except

the original EI ion source was replaced by our home-made 90° ion mirror and ion optics [25]. An optional HSI ion source, combined with the ion mirror (for the EI-produced ions), was also fitted inside the quadrupole mass analyzer in lieu of the original EI ion source.

The Supersonic GC–MS requires added differential pumping with the inclusion of a 60 l/s air-cooled diffusion pump (or, recently, a 70-l/s Turbo-molecular pump) and a 537-l/min rotary pump. All of the gas flow rates, heated zones, sampling, etc., are performed in the same way as with the original system and are computer-controlled via the original Agilent Chemstation software. Data analysis was also performed with the Chemstation software in combination with either NIST'98 or Wiley mass spectral libraries. The Agilent 6890 GC was used either with its standard split/splitless injector or with an Optic-2 temperature programmable injector (Atas, Veldhoven, The Netherlands). A home-made ChromatoProbe could also be coupled with this injector [30]. This ChromatoProbe is similar to our previous ChromatoProbe, which is available from Varian, except that it is slightly longer due to the longer liner in the Optic injector.

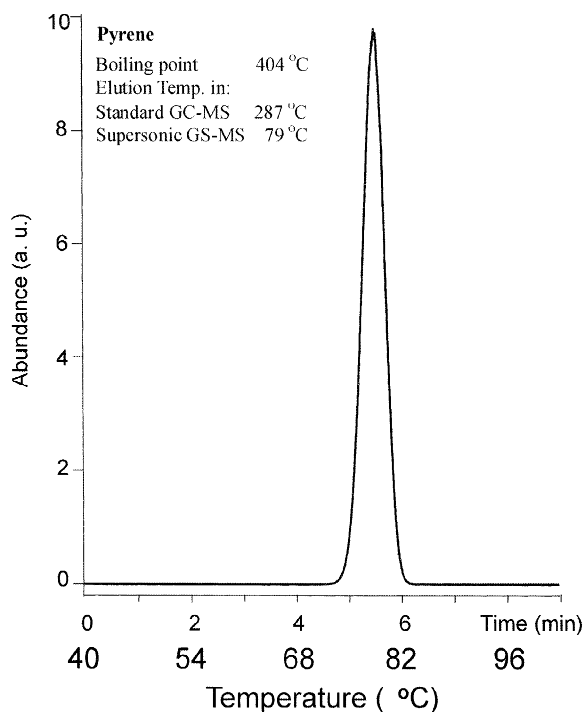

Fig. 1. Low temperature (79 °C) elution of pyrene obtained with Supersonic GC–MS using 1 m×0.25 mm I.D. column with 0.1-μm DB-XLB film and 100-ml/min helium column flow rate. The temperature programming rate was 7 °C/min and the peak width at half maximum is 3.3 °C. Pyrene (10 ng) was injected (1 μl splitless of 10-ppm methanol solution).

3. Results

3.1. Lowering the GC column elution temperatures

Commonly used GC–MS typically uses a column of 30 m×0.25 mm I.D., 0.25–1-μm film of dimethylsiloxane with 5% phenyl composition and 1-ml/min helium column flow rate. Under these conditions each sample compound elutes in its own relatively narrow elution temperature window. Keeping all other conditions constant, the elution temperature can be somewhat increased through the use of a more polar film, but essentially nothing is done to lower the elution temperature compared to that achieved with standard GC–MS columns.

In Fig. 1, the elution of pyrene is shown, achieved with the Supersonic GC–MS with a 1 m×0.25 mm I.D. column of 0.1-μm DB-XLB film (similar to DB5ms) and 100-ml/min helium column flow rate. Pyrene has a boiling point of 404 °C and it eluted at 287 °C in a Saturn 2000 standard GC–MS (Varian, Walnut Creek, CA) using a 30 m×0.25 mm I.D. column of 1-μm DB5ms film (Agilent, Folsom, CA) and 1-ml/min helium column flow rate. In contrast, pyrene eluted at 79 °C with the Supersonic GC–MS, which is 208 °C lower than that obtained with the traditional GC–MS.

Such significantly lower elution temperature is hard to perceive for GC–MS and is thus like a new phenomenon (although, as will be described, no "new science" was used). For example, a 200 °C lower elution temperature enables GC–MS analysis at lower column temperatures than with many supercritical fluid chromatography (SFC) analyses, as pyrene was eluted in more than 1 h at a higher temperature of 100 °C in SFC–MS [31].

In Fig. 2, the effects of column flow rate, length, film thickness and GC oven temperature program rate on pyrene elution temperature are given, through

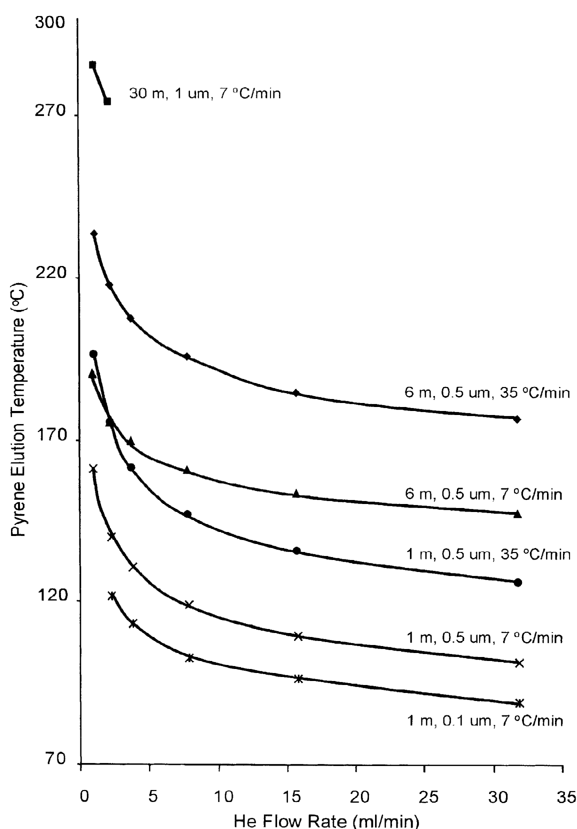

Fig. 2. Pyrene elution temperature versus the column flow rate with the indicated column lengths, DB5ms film thickness and temperature program rates.

plotting pyrene elution temperatures versus the column flow rate (columns with 0.25 mm I.D. and DB5ms film type were used in these experiments). As demonstrated, the reduction of column length and the increase of column flow rate resulted in considerably lower pyrene elution temperatures. Furthermore, slowing down the chromatography by using lower GC oven temperature program rate of 7 instead of 35 °C/min, resulted in ~32 °C lower elution temperatures. The reduction of film thickness from 0.5 to 0.1 μm also resulted in lower pyrene elution temperature by ~13 °C.

Thus, for a given stationary phase type, four parameters were found to affect the elution temperature: column length, column flow rate (flow velocity), GC oven temperature program rate and adsorption (sorption) film thickness.

At first glance one may think that the use of thin films could lower the column capacity and as a result severely hamper the chromatography versus standard conditions. However, high column flow rate (as used with the Supersonic GC–MS) acts to maintain the column capacity and preserve good peak shapes even when a large amount of analyte is injected. In Fig. 3, the elution peak shape of 500 ng n-$C_{32}H_{66}$ (linear chain alkane) is shown, achieved with the Supersonic GC–MS at 1-ml/min He column flow rate (upper trace A) and 16 ml/min (lower trace B). As can be seen, no peak fronting (saturation) is observed using 16-ml/min column flow rate, in contrast to the highly fronted peak obtained (as expected) with 1-ml/min column flow rate. The column capacity

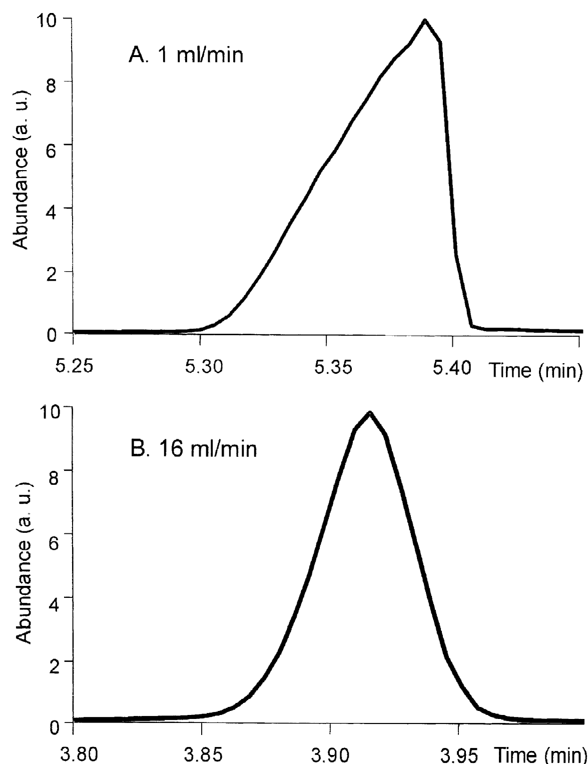

Fig. 3. Column flow-rate effect of increased column capacity. n-$C_{32}H_{66}$ (500 ng) was injected into 6 m×0.25 mm I.D. column with 0.5-μm DB5ms film using either 1-ml/min (upper trace A) or 16-ml/min (lower trace B) flow rate and transfer line temperature of 280 °C. The chromatography peak width obtained with 1 ml/min is distorted with peak fronting while with 16 ml/min a symmetric peak is obtained although broader than the peak width obtained with 1 ml/min with low sample amount.

relates to the film volume of a separation plate, thus, since at high column flow rate the plate height is increased, the column capacity is increased correspondingly. As a result, thinner column films can be used with the Supersonic GC–MS for further lowering the elution temperature without a sacrifice in column capacity (provided that high column flow rate is employed).

On the other hand, the reduced column length and increased column flow rate result in reduced GC separation power that is, however, compensated by increased MS separation power as will be described below (Section 4).

3.2. A simple model to explain the lower GC elution temperatures

GC elution temperatures were theoretically and experimentally investigated by Blumberg and Klee [32–35]. These authors explored the elution temperature dependence on column replacement with ''retention time locking'' [35] in order to maintain similar order of elution (pattern) and as a result approximately constant elution temperatures regardless of the variation in the column length, I.D. and flow rate. They also extensively investigated the optimization of temperature programming rate under various GC parameters [32–34]. However, their goal was to maintain optimal GC resolution, which is in contrast to our goal of trading GC resolution for achieving lower elution temperatures while compensating for the lost GC separation power by improved separation power of the MS.

We wish to invoke a simple model that will explain and account (at least qualitatively and potentially semi quantitatively) for the significantly lower elution temperatures obtained for pyrene (Fig. 2) and other such samples. This model is further aimed at providing some insight and guidelines on the effects of the various GC parameters on the elution temperatures for optimal control for the purpose of lowering the GC elution temperatures.

The GC elution temperature is determined by the time that sample molecules are adsorbed (or absorbed) on the column stationary phase, assuming negligible carrier gas passage time through the column. This time depends exponentially on the GC oven temperature. Let us assume that a given molecule, such as pyrene, elutes after time t_e at isothermal GC oven temperature T_{gc}. For better understanding let us further assume a constraint of equal elution time t_e under different chromatography conditions. As a result, if the number of adsorption sites (which relates to separation plates) is to be reduced by a factor of two, the sample molecules will double their average residence (adsorption) time on each adsorption site. The number of adsorption sites can be reduced by a factor of two either by cutting the column length by a factor of two or by doubling the column flow rate (so that the separation plate height is doubled, see discussion below). In order to achieve doubled average adsorption time per adsorption site the GC oven temperature must be lowered by a given temperature difference named ΔT. This ΔT can be experimentally determined using a given set of experimental conditions of column type, film thickness, length and flow rate, as it is the change in the oven temperature which doubles isothermal elution times. We experimentally measured this ΔT for pyrene and found it to be 19.3 °C at ~220 °C. Thus, each 19.3 °C GC oven temperature variation doubles (or halves) the pyrene elution time. We found that for various alkanes from C_{16} to C_{32} ΔT ranges from 15 to 17 °C and it slowly increased with the alkane chain length. For more polar compounds, such as corticosterone and high explosives, ΔT was found to be well above 20 °C. Thus, we feel that we can safely use an average value of $\Delta T = 20$ °C. According to Blumberg and Klee [33,34] and references therein, typical values for ΔT (which they define as ''thermal constant'' that is ~1.4 ΔT) are in the range of 16 °C for non-polar compounds, and up to ~28 °C for late eluting polar pesticides (in agreement with our findings), and these values linearly increase with the elution temperature.

With this information and model we can start to explain the various effects that govern the GC elution temperatures under GC oven temperature programming conditions.

(A) Temperature program rate. If we reduce by a factor of two the temperature program rate, the average time that the sample compound is adsorbed on each adsorption site is doubled and thus the elution temperature will be lower by ΔT. As a result, each factor of two *slower temperature program* rate results with further ΔT *lower elution temperature,*

with a penalty of slower analysis and broader GC–MS peaks.

(B) Column length. Column length determines the number of adsorption sites or separation plates. Consequently, if we cut the column length into half we reduce the number of adsorption sites by a factor of two, and for the same analysis time, the sample molecules will elute at ΔT lower elution temperature through spending doubled time (on average) on each adsorption site. This effect is additive and thus if we cut a standard column from 30 m to 94 cm (30 m divided by 2^5) we should have 5 ΔT lower elution temperature which could be ~100 °C. Cutting the column length is also beneficial to enable high column flow rate with given upper inlet pressure limitation. In fact, lowering of the elution temperatures by using short columns is a common state-of the-art technique used in enantiomers separation by GC [36–38]. Figs. 8 and 9 in Ref. [38] clearly demonstrate that the reduction of the column length from 20 to 2 m or from 40 to 4.5 m, resulted in lower elution temperatures of 60 and 40 °C, respectively, combined with similar elution times.

(C) Column flow rate (velocity). Column flow rate is the most important parameter for extending the range of compounds amenable for analysis since: (a) it increases the column capacity and thus enables the use of lower film thickness with further lowered elution temperature; (b) it reduces the time spent at the injector and thus the degree of injector degradation; (c) it enables lower ''elution temperatures'' from the injector liner during temperature programmed injection and thus significantly reduces intra injector degradation; and (d) flow rate can be quickly programmed and thus the trade-off of separation and elution temperature can be programmed and better optimized. We use in this discussion flow rate and not flow velocity. Blumberg recently showed [39] that under high-pressure drop conditions and the use of thin film, the separation plate height linearly increases with flow rate (Eq. (33) in Ref. [39]). For the case of low-pressure drop, the carrier gas velocity is in any case proportional to the flow rate and thus beyond the optimal Van Deemter velocity, and the plate height is linearly increased with both carrier gas velocity and flow rate. The number of adsorption sites linearly relates to the carrier gas velocity and not to the number of separation plates (at high pressure drop), but the latter can serve as a good approximation. Consequently, each doubling of the carrier gas flow rate (sufficiently above the optimal value) results, under conditions of constant chromatography time, in doubled adsorption time per adsorption site and, thus, in lowered elution temperature by ΔT. Similar to reduced column length this effect is additive, and an increase of the column carrier gas flow rate by a factor of 32 (2^5) implies (again, sufficiently above the optimal value) lower elution temperature by close to 100 °C.

(D) Adsorption (sorption) film thickness. As shown in Fig. 3, thinner adsorption film can be used at high column flow rates without sacrificing column capacity. It is known that thinner films enable shorter adsorption (sorption) times per separation plate. The magnitude of this effect is not well characterized but we found that each doubled film thickness results in increased elution temperature by up to 10 °C. Grob and Grob found that changing the film thickness by a factor of two results in a change of the elution temperature by 16 °C, other conditions being equal [40]. This difference could originate in part due to different film types used, as well as lower ΔT at our experiments with high column flow rates and shorter columns used.

(E) Carrier gas and absorption film type. Hydrogen can be used as a carrier gas and results in significantly lower elution temperatures than achieved with helium. However, hydrogen is a reactive gas that promotes extensive sample degradation even with relatively stable pesticides [41,42] and thus, its general use cannot be recommended with thermally labile compounds. Film type is an obvious factor that affects the elution temperature. However, non-polar films usually provide lower elution temperatures, especially for polar or semi polar compounds and thus the standard non-polar films such as dimethylsiloxane with or without 5% phenyl seem preferable.

When all these effects are combined, one can use a column length of 1 m with flow rate of 100 ml/min, and thereby anticipate elution temperature reduction of over 200 °C. This is as observed, although the reduction of film thickness was not accounted for.

So far we assumed that ΔT is compound and

temperature independent. However, as observed [33], ΔT linearly increases with the elution temperature. Blumberg (private communication) found that $\Delta T = 0.7Rt_e^2/\Delta H$ where ΔH is the enthalpy of vaporization. If we apply Trouton's rule of approximate equality of entropy of vaporization for all organic compounds to thermal desorption of organic compounds from the column surface (thus, $\Delta H \sim t_e$), we obtain $\Delta T \sim t_e$. We also independently arrived at this conclusion. Thus, ΔT will be higher for less volatile compounds, as desirable for the extension of range of compounds amenable for analysis.

It is emphasized that our model as presented above should not be used "as is" to quantitatively account for the results shown in Fig. 2, since any change in the parameters shown was also coupled to a change in the elution time, and thus, the central assumption of constant elution time was not maintained. For example, in a different set of experiments a 6 m× 0.25 mm I.D. column with 0.5-μm DB5ms film was used. With 8-ml/min helium column flow rate and the use of 20 °C/min temperature-programming rate (120 °C initial oven temperature), pyrene eluted at 189.6 °C after 3.48 min. Upon doubling the column flow rate to 16 ml/min, pyrene eluted at 180.0 °C, which is only 9.6 °C lower (and not 19.3 °C as our ΔT for pyrene) after 3.00 min, which is 0.48 min earlier. However, when the temperature-programming rate was adjusted to 16 °C/min pyrene elution time was restored to 3.45 min (sufficiently close to 3.46 min) and under these conditions pyrene eluted at 175.2 °C, which is now a 14.4 °C lower elution temperature. Since ΔT linearly depends on the temperature, its value of 19.3 °C which was measured around 220 °C should be 17.7 °C around 180 °C, and thus, our model value is in reasonable (or closer) agreement with our 14.4 °C experimental value of lowered elution temperature.

3.3. Extending the range of low volatility compounds amenable for GC–MS analysis

If, as demonstrated in Figs. 1 and 2, the GC elution temperature can be significantly reduced, considerably less volatile compounds can be analyzed. In Fig. 4, the analysis of underivatized corticosterone is demonstrated together with the effect of column flow rate on its elution temperature and resulting degree of column bleed interference. Corticosterone is a steroid that cannot be analyzed with standard GC–MS due to both complete intra-GC column degradation and too high elution temperature [8]. In the upper trace A, its analysis with the Supersonic GC–MS is demonstrated using a 6 m column at 1-ml/min He flow rate. As the figure shows, it elutes at 340 °C GC oven temperature and thus with considerable amount of column bleed that hampers the quality of its mass spectrum. In trace B (bottom) the analysis of corticosterone is shown with 16-ml/min column flow rate, which provided 8.5 times higher average column flow velocity. As a result, corticosterone eluted at 278 °C, which is 62 °C lower than with 1 ml/min. The integrated peak area is now increased by about an order of magnitude (it is also a little broader) and the adverse effect of column bleed on its mass spectrum is practically eliminated. Furthermore, an isomer of corticosterone can be easily observed and confirmed due to its similar molecular ion (but different fragment ion intensities). An impurity is also observed at ~252 °C elution temperature. Thus, the GC–MS analysis of corticosterone was improved by lowering its elution temperature.

Since the temperature (and thus column temperature) has an exponential effect on compound degradation, lowering the elution temperature is far more important than speeding up the chromatography. This approach is in contrast to the concept of fast chromatography since, as discussed above, the faster the chromatography through higher temperature programming rate the higher the sample elution temperature. An important feature observed is that the obtained mass spectrum of corticosterone shows a sizable molecular ion at m/z 346, which is not found in the NIST mass spectral library. All the other peaks are with similar relative abundance (except m/z = 328 which is also enhanced for the vibrationally cold corticosterone in the SMB) and thus high identification matching factor of 920 is observed.

The presence of an enhanced molecular ion is of major significance for our ability to extend the range of compounds amenable for analysis. The enhanced molecular ion is very desirable because it provides the increased separation power of the MS to compen-

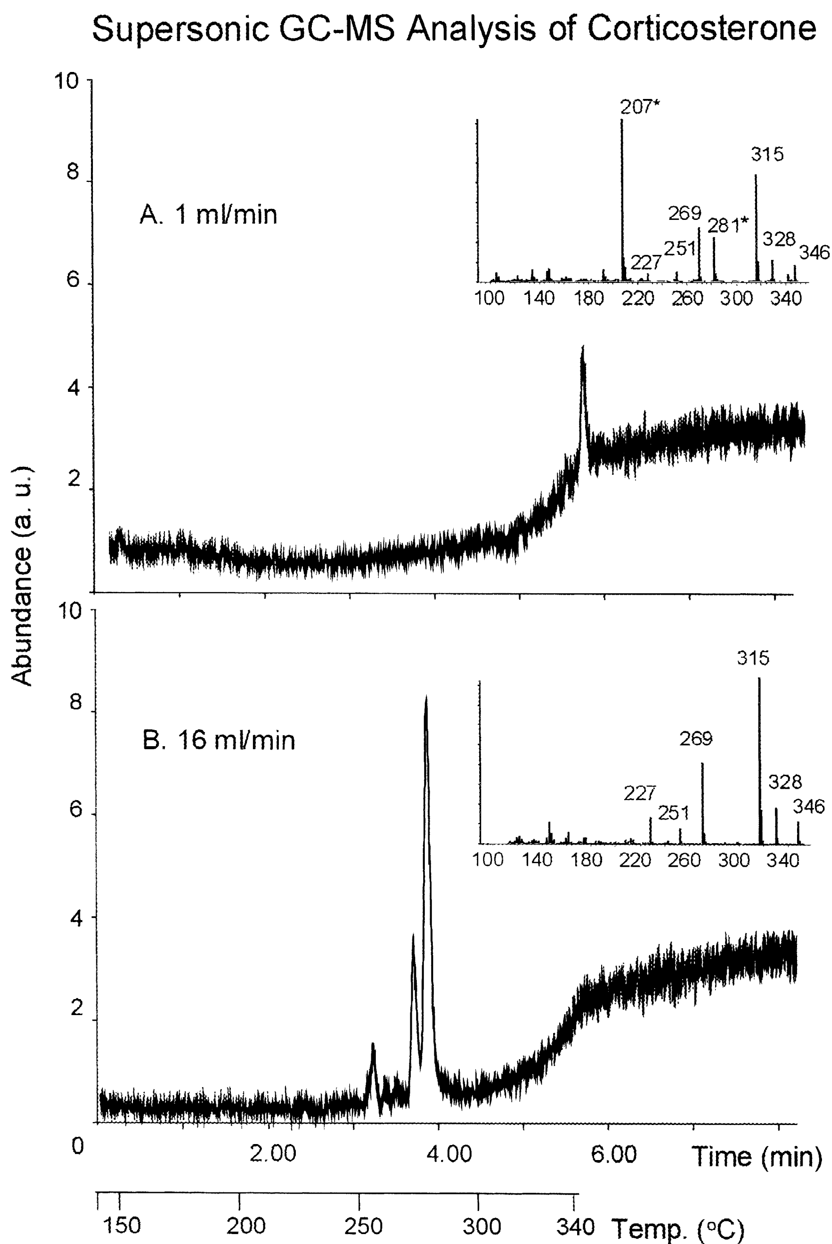

Fig. 4. Analysis of underivatized corticosterone with Supersonic GC–MS using 1-ml/min column flow rate (upper trace A) and 16 ml/min flow rare (lower trace B). A 6 m×0.25 mm I.D. column was used with 0.5-μm DB5ms film. The transfer line and nozzle temperatures were 200 °C, and the fixed injector temperature was 200 °C. Note the effect of lowering the corticosterone elution temperature on its recovery and elimination of column bleed effects (*m/z* 207 and 281). The smaller earlier eluting peak is of an isomer of corticosterone found in the commercial sample (Sigma, St. Louis, MO, USA). * In the mass spectra marks mass spectral peaks of column bleed. Corticosterone (10 ng) was analyzed through the injection of 1 μl of 100-ppm methanol solution with split ratio of 10:1.

sate for the loss of GC separation power. We previously determined that matrix interference is exponentially reduced with mass by about a factor of 20 per 100 a.m.u. [6] and thus, the molecular ion provides a significant improvement in the reduction of matrix interference.

In Fig. 5, we show what we consider as the current record in the analysis of low volatility compounds by GC–MS. In this case, the analysis of perylene, coronene, magnesiumoctaethylporphin, decacyclene and tetraphenylporphin is demonstrated. Standard GC–MS cannot typically analyze polycyclic aromatic hydrocarbons (PAHs) with more than six rings. In contrast, coronene with seven fused rings is an early eluter (elutes below 200 °C) in Fig. 5, and decacyclene with ten rings is easily amenable for analysis with elution temperature below 300 °C. We note that there is growing need for the analysis of large PAHs with more than six fused aromatic rings [43]. Even porphirins and metalloporphirins become amenable for Supersonic GC–MS analysis as demonstrated in Fig. 5, and other metalloporphirins such as zinctetraphenylporphin eluted at the elution temperature of tetraphenylporphin without noticeable metal effect. Metalloporphirins were previously analyzed in oil shale with GC–MS by Blum et al. [44]. These authors used a high pumping capacity differentially pumped (two 800-l/s diffusion pumps) MS system with home-made high temperature transfer line (400 °C), high temperature GC (410 °C) and high flow-rate hydrogen as the carrier gas (>10 ml/min).

The true low volatility limit of the Supersonic GC–MS is probably significantly better than demonstrated in Fig. 5. Since the Supersonic GC–MS ion source has no limitation on compound volatility (absence of ion source related peak tailing), it can be operated with any low volatility compound that can be eluted by the GC. Currently, the upper GC column temperature specification is 480 °C with the HT5 columns of SGE (SGE, Ringwood, Australia), which is much higher than what was used in Fig. 5.

However, the ultimate limitation in the GC–MS analysis of organic compounds is often determined by the thermal stability of the analyzed compound, and as the molecular size is increased its tendency to become thermally labile is also significantly increased.

3.4. Extending the range of thermally labile compounds amenable for GC–MS analysis

The reduction of elution temperature enables a wider range of thermally labile compounds to be analyzed by the Supersonic GC–MS because considerably less sample degradation occurs in the column. An additional important aspect of the Supersonic GC–MS is that sample dissociation in the ion source is inherently eliminated through the use of SMB. Increased column flow rate also contributes to the reduction of sample degradation at the injector due to shorter time spent at the hot injector by the sample molecules. Furthermore, in the case of a temperature-programmed injector, sample compounds are transferred into the column through crude intra-liner chromatography, and their ''elution temperature'' from the liner into the column is predicted to be lowered with increased liner (column) flow rate at the same way as demonstrated for the separation column in Fig. 2. Intra injector degradation can be practically eliminated through the use of cold-on-column injection but such use is not generally recommended with dirty samples.

In Fig. 6, we demonstrate the elimination of intra column thermal degradation of aldicarb through lowering its elution temperature by increasing column flow rate from 1 to 16 ml/min. Aldicarb is a widely used thermally labile carbamate pesticide, which cannot be analyzed at all by standard GC–MS. With a short column (6 m) at 1-ml/min flow rate, only ~10% of the aldicarb is eluted and detected. While we obtain ~4% relative abundance of its molecular ion at $m/z=190$ we prefer to use the mass chromatogram of its most abundant ion at $m/z=144$ as shown in the upper trace A. In the middle trace B we show the mass chromatogram at $m/z=115$ of aldicarb's degradation product aldicarbnitrile. Aldicarbnitrile is also found in aged aldicarb solutions, especially in methanol solutions (acetonitrile is a better solvent) and it can also be formed by thermal degradation in the GC injector. In trace B we observe a peak of aldicarbnitrile at ~0.8 min, which emerges in part due to ''aging'' in its methanol solution and in part due to thermal degradation at the 120 °C injector temperature. The most important observation drawn from Fig. 6 is the broad peak of aldicarbnitrile appearing from ~140 °C up to

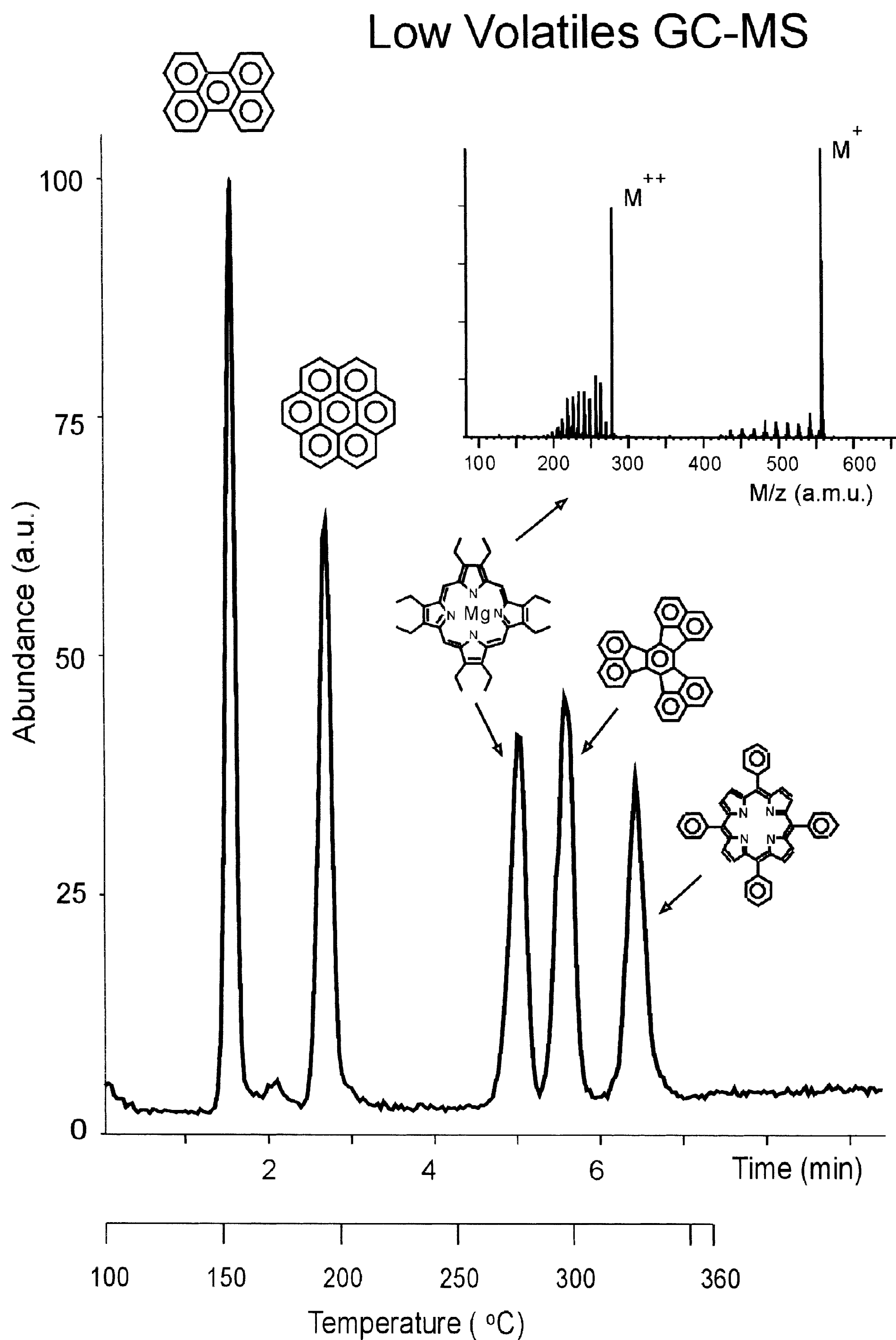

Fig. 5. Analysis of low volatiles with the Supersonic GC–MS. A 1 m×0.25 mm I.D. column was used with 0.1-μm DB-XLB film, 100-ml/min helium column flow rate and temperature programming rate of 35 °C/min. The transfer line and nozzle temperatures were 370 °C and the injector temperature was 320 °C. The obtained "cold EI" mass spectrum of magnesiumoctaethylporphin is shown in the insert. Approximately 30 ng of each compound were analyzed through splitless injection of 2 μl of 15-ppm methanol sample solution.

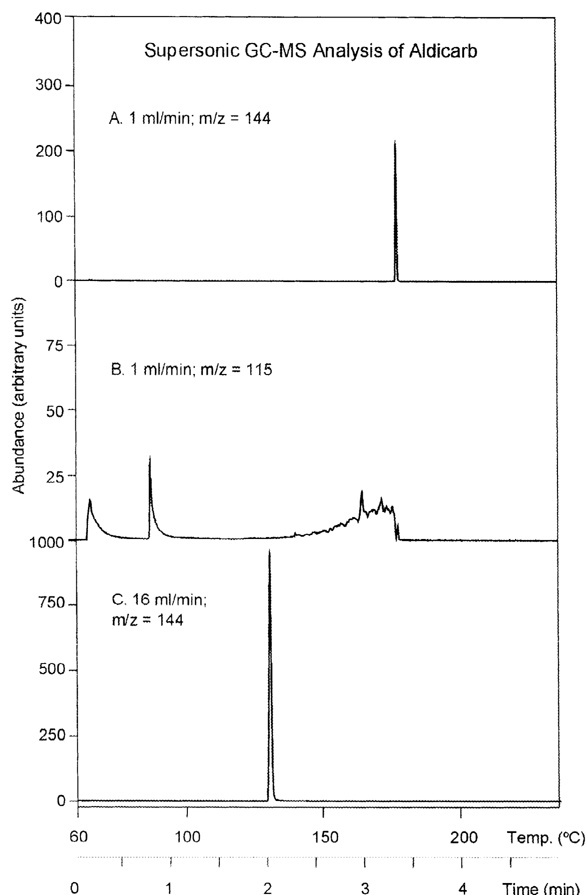

Fig. 6. A demonstration of intra-column degradation of a thermally labile compound (aldicarb) and the elimination of this degradation through lowering its elution temperature with increased column flow rate. A 6 m×0.25 mm I.D. column was used with 0.5-μm DB5ms film and temperature programming rate of 35 °C/min. The transfer line and nozzle temperatures were 200 °C and the injector temperature was 120 °C. The indicated column flow rates were 1 ml/min for traces A and B and 16 ml/min for trace C. Trace B shows the production of aldicarbnitrile which is a known thermal degradation product of aldicarb. Aldicarb (20 ng) was analyzed through the injection of 1 μl of 100-ppm methanol solution with a split ratio of 5:1.

the elution of aldicarb at 178 °C. This broad hump is clearly due to intra-column degradation of aldicarb. Upon the increase of the column flow rate from 1 to 16 ml/min, the elution temperature of aldicarb is reduced to ~130 °C, well below the onset of aldicarb degradation. As a result, the integrated aldicarb peak area is increased 10-fold and the broad hump of aldicarbnitrile is completely eliminated. The earlier peak of aldicarbnitrile was also reduced and became independent of injector temperature and thus fully assigned to residual "aging" of aldicarb in solution (this small peak is completely absent in acetonitrile solution). Thus, a compound such as aldicarb, which is fully decomposed in standard GC–MS, can be quantitatively analyzed with the Supersonic GC–MS through the lowering of its elution temperature.

After processing the aldicarbnitrile data contained in Fig. 6 we also found that the rate of aldicarbnitrile formation (from aldicarb) is exponentially increased with a resulting factor of 5 per 20 °C, which is significantly larger than a typical factor of 2 reduction in elution time per 20 °C. Consequently, slower GC oven temperature programming rate is beneficial for aldicarb analysis, since the resulting lower elution temperature is more valuable than the shorter analysis time for the preservation of aldicarb.

In a more extreme example using a 1 m column with 100-ml/min flow rate (as the case in Fig. 1), large thermally labile drugs can be analyzed, such as reserpine with molecular weight of 608 a.m.u. In Fig. 7, the analysis of reserpine, stanozolol (underivatized anabolic steroid) and clenbuterol (β-agonist drug) is shown. Reserpine is the industry-standard test molecule for LC–MS performance, and we consider its analysis by the Supersonic GC–MS to be the largest drug analyzed by GC–MS. The mass spectra of these three labile drugs are also shown in Fig. 7, and they all demonstrate either dominant or abundant molecular ion. The existence of molecular ion in the mass spectra proves that the drugs are detected in their intact form. Additionally, the molecular ions permit improved detection in that no matrix interference is likely to occur in their mass chromatograms [6].

In Fig. 8, the analysis of high explosives is demonstrated. Explosives are known to be unstable and thus their analysis requires attention [45–47]. In the lower trace the explosives analysis was performed with a 6 m column using 1-ml/min column flow rate. Triacetonetriperoxide (TATP), nitroglycerin (NG) and 1,3,5-triazine hexahydro-1,3,5-trinitro (RDX) relative peak height is low, while pentaerythritol tetranitrate (PETN) is fully decomposed. Tetryl eluted at 236 °C with a sharp peak, but its mass spectrum indicates that its sharp appearance is deceptive. In fact, the absence of a molecular ion and existence of intense $m/z = 242$ ion serves as

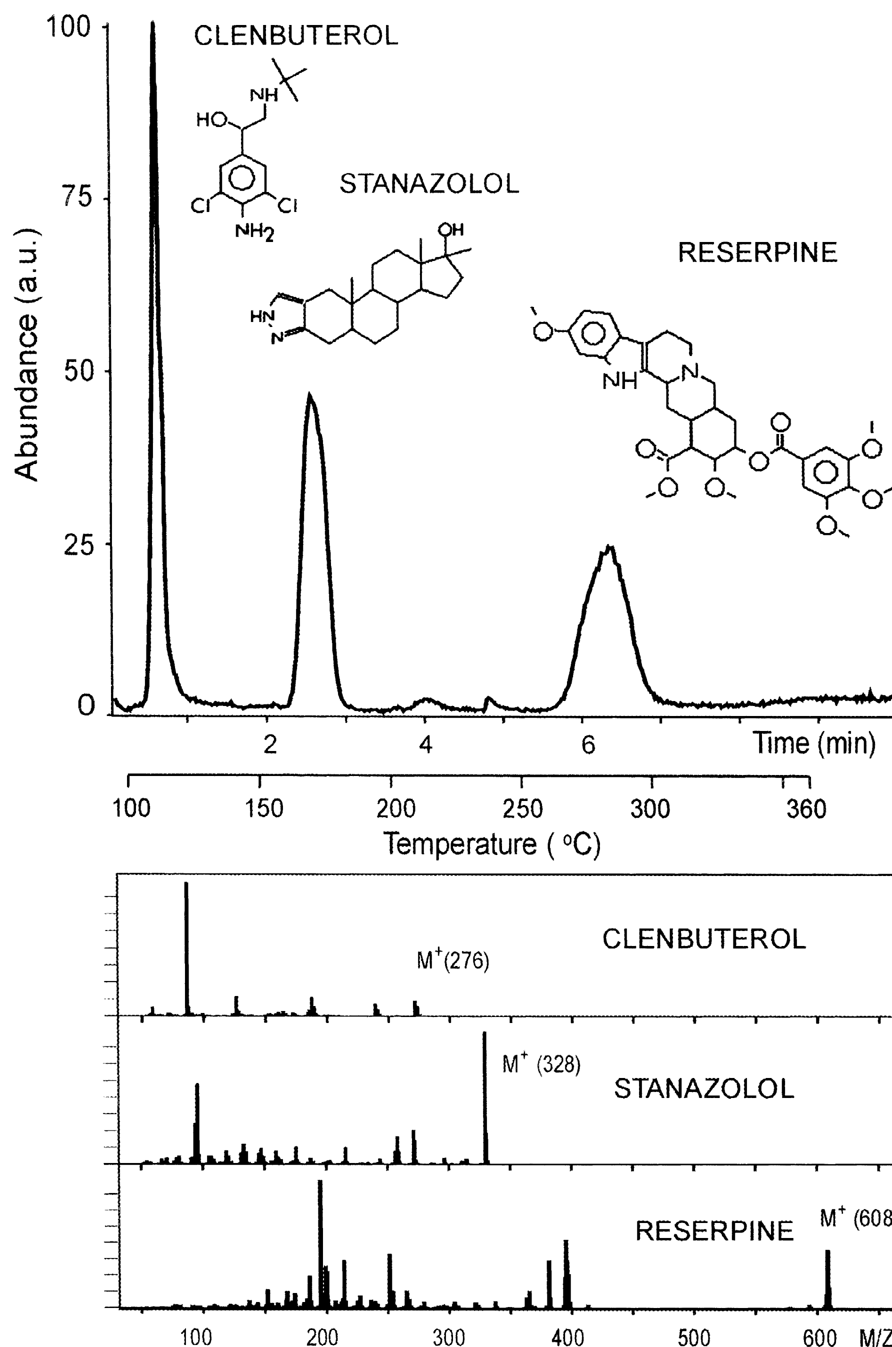

Fig. 7. Analysis of the indicated thermally labile drugs with the Supersonic GC–MS and their "cold EI" mass spectra. A 1 m×0.25 mm I.D. column with 0.1-μm DB-XLB film and 100-ml/min helium column flow rate was used with temperature programming rate of 30 °C/min. The transfer line and nozzle temperatures were 280 °C. Optic PTV injector was used, programmed from 100 to 280 °C at 5 °C/s. A 40-ng sample of each drug was analyzed through the splitless injection of 0.8 μl of 50-ppm methanol sample solution.

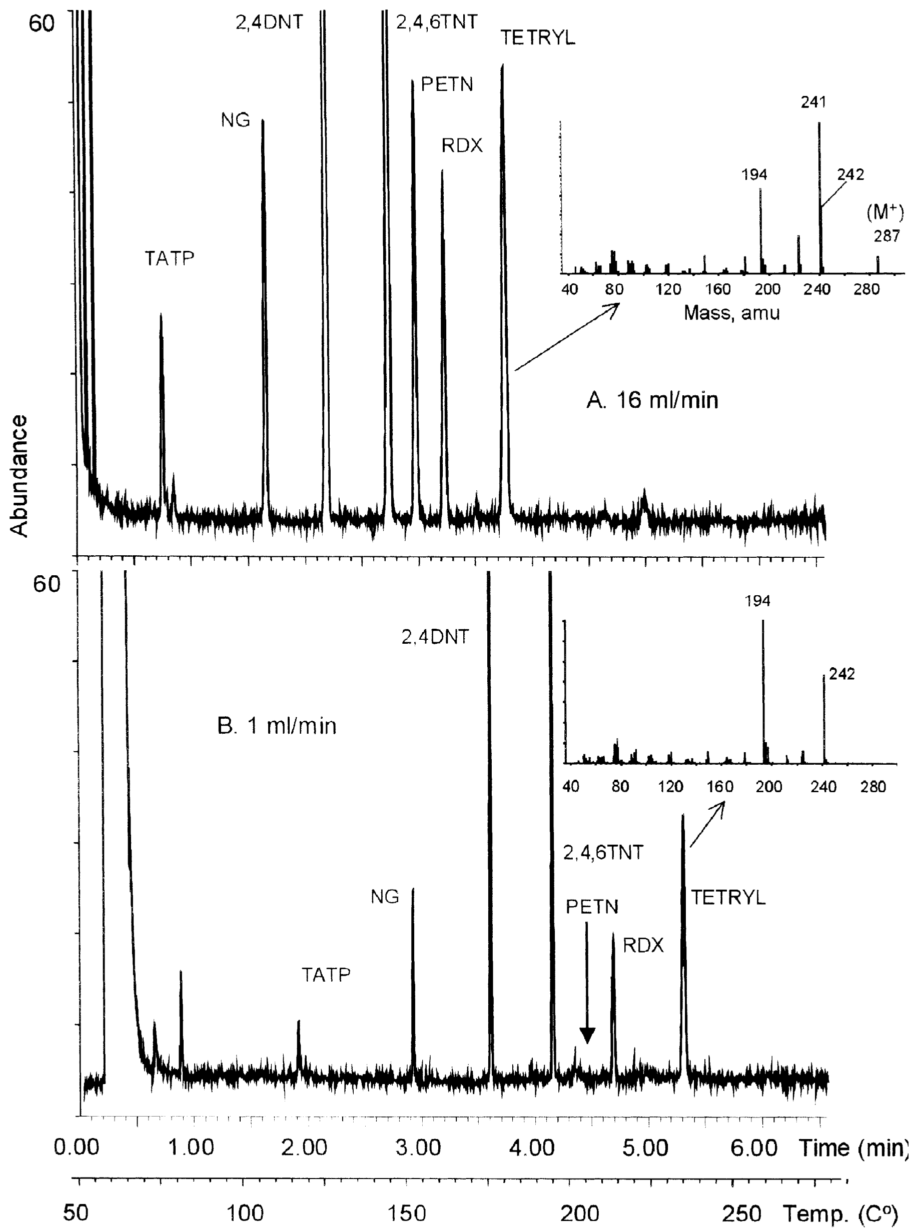

Fig. 8. Analysis of high explosives with the Supersonic GC–MS using increased column flow rate for lowering the explosives' elution temperature and their degree of degradation. The mass spectra of Tetryl are added in the inserts. A 6 m×0.25 mm I.D. column was used with 0.5-μm DB5ms film and temperature programming rate of 35 °C/min. The transfer line and nozzle temperatures were 200 °C while the injector temperature was fixed at 180 °C. The indicated column flow rates were 1 ml/min for lower trace B and 16 ml/min for upper trace A. Approximately 20 ng of each explosive were analyzed through the injection of 1 μl of 100-ppm acetone sample solution with a split ratio of 5:1. NG, nitroglycerin; PETN, pentaerythritol tetranitrate; RDX, 1,3,5-triazine hexahydro-1,3,5-trinitro; TATP, triacetonetriperoxide.

evidence that it is degraded in the column due to hydrolysis, thus producing *N*-methylpicramide through a loss of NO_2 and gain of a hydrogen [45]. In the upper trace the same analysis is performed with 16-ml/min column flow rate. All of the explosives can be analyzed intact, including tetryl as shown by the presence of its molecular ion at m/z 287. Clearly, the increased flow rate of 16 ml/min resulted in ~50 °C lower elution temperature, which better enables the analysis of high explosives. Even HMX can be analyzed by Supersonic GC–MS, but it showed some column-induced peak tailing, and thus we chose not to include it in this explosive mixture (100 ppm in acetone; kindly donated by T. Tamiri, Division of Identification and Forensic Science, Israel Police Headquarter, Jerusalem).

In Fig. 9, the analysis of eight common underivatized steroids is shown together with mass spectra of testosterone and corticosterone. Since the analysis of corticosterone was already demonstrated in Fig. 4, it is not surprising that smaller and thus generally more volatile steroids can be analyzed as well. The ''cold EI'' mass spectra of these steroids is either characterized by enhanced molecular ion and minor depletion of low mass fragments in comparison with the NIST mass spectra (e.g. corticosterone) or is very similar to the NIST mass spectrum (testosterone) if a dominant molecular ion is presented in the standard thermal EI mass spectrum.

In Fig. 10, the GC–MS analysis of ten carbamates is demonstrated. The carbamate mixture was purchased from Accustandards (New Haven, CT, USA) at 100-μg/ml concentration in acetonitrile and was used as is with split injections or diluted as needed with acetonitrile. Fast, universal analysis of pesticides with the Supersonic GC–MS is discussed in detail elsewhere [6]. Carbamate pesticides is a widely used family of pesticides that pose major analytical difficulty in their analysis since they are thermally labile compounds that require LC (usually with post column derivatization and UV fluorescence detection) for their analysis. We found that carbaryl and carbofuran are relatively stable and can be analyzed by standard GC–MS although with some injector and column degradation. However, sulfur carbamates such as methomyl, aldicarb, oxamyl and aldicarbsulfone (aldicarb degradation product) are considerably more thermally labile. Song and McNair recently reported the fast GC analysis of carbamates with cold on-column injection [48]. These authors used a short column with relatively high column flow rate, but unlike our suggestion in this paper, they employed a fast temperature programming rate. As shown in Fig. 10, split injection gives a nice chromatogram with relatively uniform response. This chromatogram is even better than that obtained with SFC–MS [31]. However, carbamate pesticides are both thermally labile and chemically labile. Thus, while their intra-column degradation is eliminated at high column flow rate, and their intra-injector degradation is minimized with split injection (upper chromatogram), some pesticide dependent degradation occurs at the liner during the longer residence time of splitless injection as shown in the bottom chromatogram. We found that most of this intra-injector liner degradation occurs presumably on metal impurities in the glass liner. Thus, the degree of this degradation was reduced through the use of a home-made flame-annealed fused-silica liner (which was used in the case of the bottom chromatogram in Fig. 10). Otherwise, oxamyl and aldicarbsulfone relative peak height could be significantly lower. We also tested cold-on-column injection, which can eliminate or minimize injector degradation [26,46], but this injection mode is unacceptable for real world dirty sample analysis due to increased column maintenance. In Fig. 11, the analysis of the ten carbamate pesticides mixture is demonstrated in cucumber extract at a spiking level of 400 ng/g. Each pesticide is characterized by two mass chromatograms of its molecular ion and an additional prominent high mass fragment. In cases when the molecular ion was too weak or absent, another high mass fragment was employed. The use of two high mass chromatograms for pesticide identification is explained in detail elsewhere [6]. Fig. 11 serves an additional purpose of demonstrating that the extension of range of compounds amenable for analysis could be used for ''real world'' analysis of these compounds in relatively complex matrices.

4. Discussion

The subject of extension of the range of compounds amenable for GC–MS analysis raises several

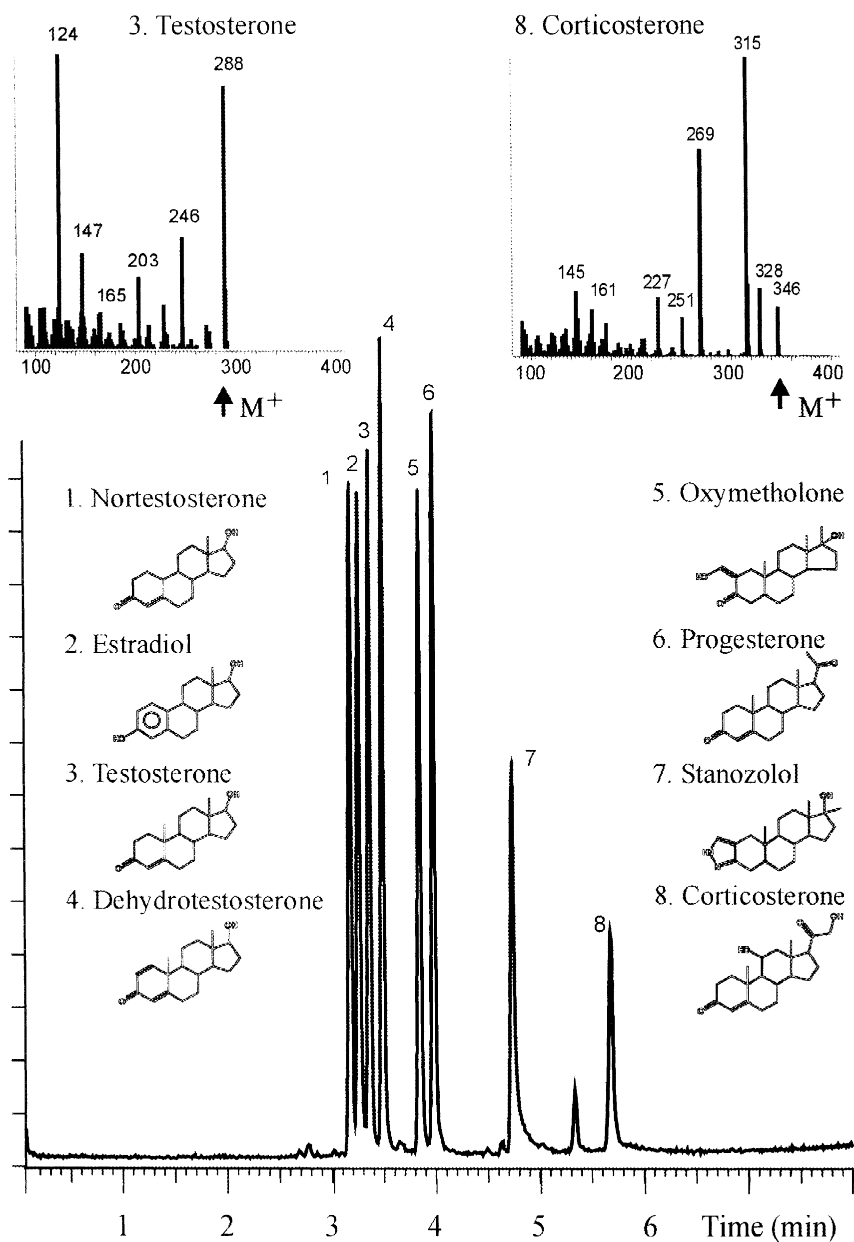

Fig. 9. Analysis of underivatized steroids with Supersonic GC–MS. A 6 m×0.25 mm I.D. column was used with 0.1-μm DB-XLB film, temperature programming rate of 20 °C/min and column flow rate of 4 ml/min. The transfer line and nozzle temperatures were 200 °C. Optic PTV injector was used, programmed from 150 to 280 °C at 5 °C/s. "Cold EI" mass spectra of testosterone and corticosterone are also shown. A 10-ng sample of each steroid was analyzed through the injection of 1 μl of 100-ppm methanol sample solution with a split ratio of 10:1.

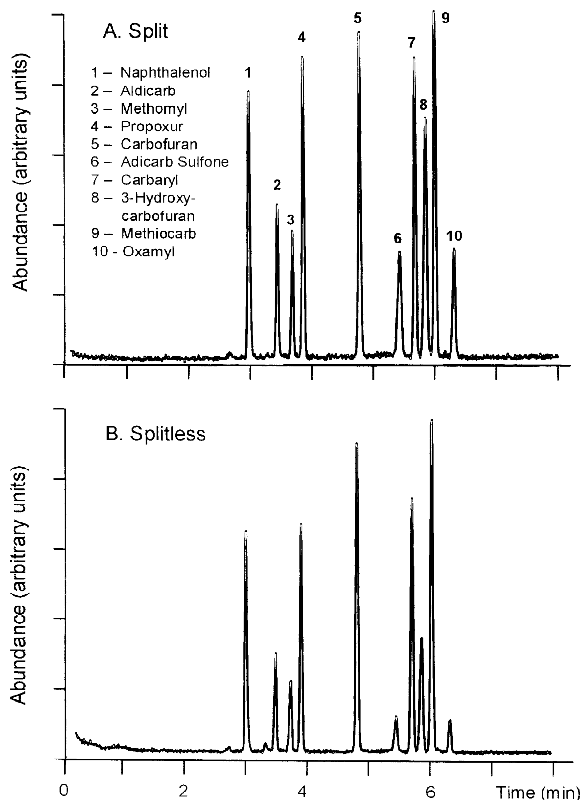

Fig. 10. Carbamate pesticide analysis with the Supersonic GC–MS. A 6 m×0.25 mm I.D. column was used with 0.1-μm DB-XLB film, temperature programming rate of 15 °C/min and column flow rates of 12 ml/min. The transfer line and nozzle temperatures were 200 °C and the Optic PTV injector was programmed from 80 to 150 °C at 5 °C/s. The upper trace A was obtained with injection split ratio of 20:1 of 100-ng/μl sample while the lower trace was obtained with splitless injection of 1 μl 5-ng/μl sample using a home made flame annealed fused-silica liner.

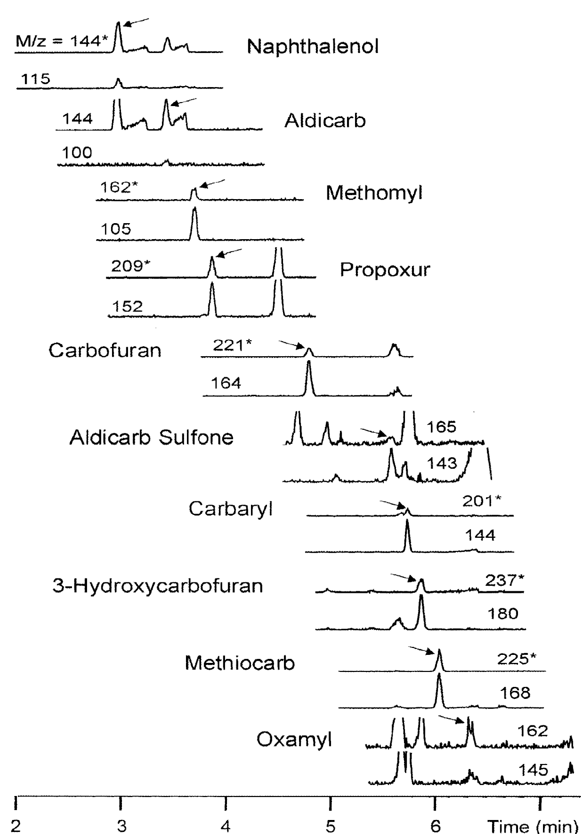

Fig. 11. Carbamate pesticide analysis in cucumber with the Supersonic GC–MS. Cucumber extract was spiked with the carbamate pesticide mixture at 400-ng/g concentration level in the cucumber. A 6 m×0.25 mm I.D. column was used with 0.1-μm DB-XLB film, temperature programming rate of 15 °C/min and column flow rates of 12 ml/min. The transfer line and nozzle temperatures were 200 °C and the Optic PTV injector was programmed from 80 to 150 °C at 5 °C/s, hold 60 s and up to 200 °C at 5 °C/s (1 μl injected volume). An inlet pressure pulse of 50 p.s.i. was employed for 5 s. Two mass chromatograms per pesticide are shown using the molecular ion (marked by *) and one additional high mass fragment or two high mass fragments if the molecular ion was too weak.

interesting aspects and questions for discussion such as detailed below.

4.1. Magnitude of extended range of analysis

The range of compounds amenable for GC–MS analysis is a subjective and ill-defined factor. We consider the upper size of compounds amenable for standard GC–MS analysis to be ~700 a.m.u. for non-polar compounds such as linear chain alkanes while for polar compounds such as drugs it is only ~400 a.m.u. For linear chain alkanes, the limit is imposed with respect to volatility, while for polar compounds it is imposed by thermal lability. Coniglio and Nouviaire plotted available boiling points of linear chain alkanes versus the number of carbon atoms and extrapolated them to large size alkanes [49]. From their data, we conclude that the relative increase of boiling point per added carbon atom is considerably reduced for high carbon numbers. As a

result, while the boiling point of $C_{40}H_{82}$ is close to 800 K, the boiling point of $C_{100}H_{202}$ is only ~900 K. Consequently, it is reasonable to conclude that upon lowering the elution temperature by 200 °C one can more than double or even triple the range and upper size of non-polar compounds amenable for analysis.

We note that this prediction is actually proven since it is well known that standard GC–FID can analyze aliphatic compounds in excess of C_{120} in various simulated distillation (SIMDIS) analyses. These analyses employ a short (5 m) capillary column with 0.53 mm I.D., 0.1-μm inert film thickness, carrier gas flow rate of ~10 ml/min and upper GC oven temperature of ~430 °C. Currently our Supersonic GC–MS is limited to 700 a.m.u. in view of our quadrupole mass analyzer limitation. However, we believe that it can analyze the full range of SIMDIS requirements combined with the provision of molecular weight information. Consequently, we feel that the Supersonic GC–MS approach can approximately double the size and range of compounds amenable for analysis although this conclusion remains to be proven in practice.

4.2. How much GC resolution can one trade off?

The extension of GC–MS range of compounds presented in this paper is based mostly on a trade-off of GC separation resolution for wider analytical scope. The lowering of pyrene elution temperature by 208 °C (demonstrated in Fig. 1) was obtained with a significant reduction of the number of separation plates. We calculated 78 separation plates based on pyrene peak width under isothermal elution at the column length and flow-rate conditions as in Fig. 1. However, since most GC–MS analyses are based on temperature programming, the separation capability is not as severely impaired as initially perceived, since the peak width of pyrene in Fig. 1 is only 3.3 °C wide. In fact, since the GC with reduced separation power should be applied for the analysis of compounds that cannot be analyzed by standard GC–MS it is worthwhile to compare it with LC. We feel that the demonstrated GC resolution in Figs. 4–12 is acceptable in comparison with equivalent LC or LC–MS analyses (or SFC–MS analysis [31]).

4.3. The trade-off of GC resolution for enhanced MS separation power

The basic assumption presented in this manuscript is that in GC–MS, unlike with GC–FID (or other non-selective detectors), the GC separation power can be reduced for many types of analyses in order to extend the range of compounds amenable for analysis. With the Supersonic GC–MS the enhancement of the molecular ion further improves the separation power of the MS for several reasons: (a) matrix interferences are exponentially reduced with mass and they are often minimal at the mass chromatogram at the molecular ion [6]; (b) extended range of compounds in many cases also involves relatively large compounds on the GC–MS scale. Higher mass peaks have even less chance of interferences; and (c) the separations of GC and MS are more independent and orthogonal at the molecular ions.

4.4. A comparison of Supersonic GC–MS analysis with LC–APCI-MS analysis and other LC–MS methods

Currently, modern LC–MS systems are operated either with electrospray or with atmospheric pressure chemical ionization (APCI). APCI [50,51] is based on thermal vaporization of the sample compounds at about atmospheric pressure. In the Supersonic GC–MS sample compounds undergo several (intra GC column) adsorption desorption cycles (as low as 78 in this paper), but these cycles are performed at relatively low temperatures, although for a total residence time of several hundred seconds. In contrast, APCI is based on fast (sub second) vaporization of the sample compounds followed by their rapid (<1 s) transfer to a corona discharge with high flow rate of nitrogen gas that also serves for the APCI spray formation. However, APCI involves typical temperatures of 450–500 °C, which are much higher than the GC analyses demonstrated in this paper. Thus, although APCI takes ~3–4 orders of magnitude shorter time spent at the heated zone, the ~200 °C higher temperature involved makes it equivalent or even harsher than Supersonic GC–MS in terms exposure of the sample compounds to high

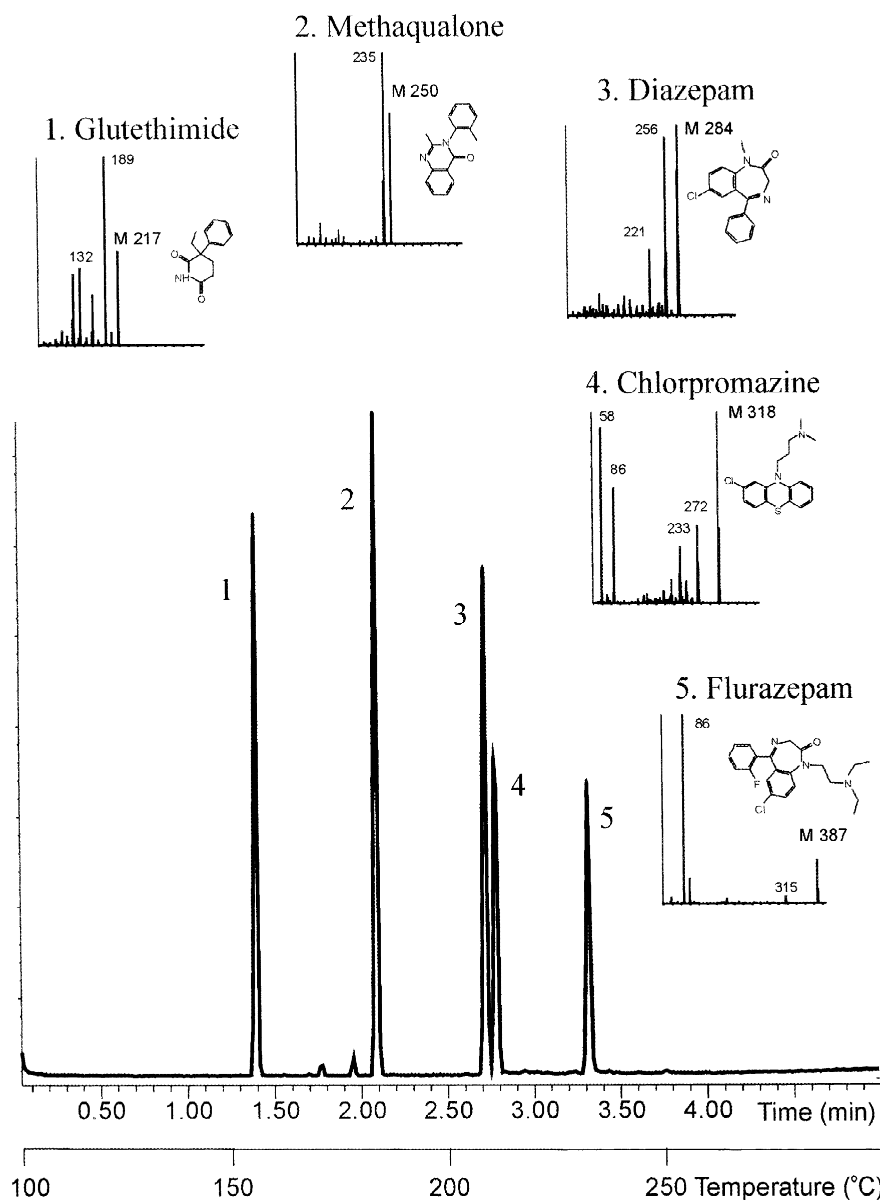

Fig. 12. Fast analysis of depressant drugs with Supersonic GC–MS. A 6 m×0.25 mm I.D. column was used with 0.1-μm DB-XLB film, temperature programming rate of 20 °C/min and column flow rates of 4 ml/min. The "cold EI" mass spectrum of flurazepam is shown in the upper insert. Note the low (230 °C) elution temperature of the last to elute flurazepam benzodiazapine drug. A 10-ng sample of each drug was analyzed through the injection of 1 μl of 100-ppm methanol sample solution with a split ratio of 10:1.

temperature. Since most chemical degradation processes are accelerated by more than three orders of magnitude per 200 °C temperature rise, we claim that in terms of range of thermally labile compounds amenable for analysis, the Supersonic GC–MS is equivalent to LC–APCI-MS. However, each method has its advantages. LC–MS usually employs electrospray for the analysis of thermally labile compounds

that APCI cannot handle, whereas Supersonic GC–MS has no alternative. Furthermore, LC is a better separation tool for polar thermally labile compounds than GC. In addition, when a compound degrades in the GC column it forms noise and it is lost whereas if it degrades in APCI it retains its clean LC peak and some mass spectral information is retained. On the other hand, Supersonic GC–MS has a few advantages such as better integration in analysis methods that include small and relatively volatile compounds or in the analysis of samples that contain non-polar compounds that are not amenable for APCI. Perhaps the most important attribute of the Supersonic GC–MS is its compatibility with reliable sample identification using large available EI mass spectral libraries and its compatibility with AMDIS deconvolution software [52–54] that enables automated identification of co-eluting compounds even under limited GC resolution. In this regard, Supersonic GC–MS can be compared to particle beam LC–MS [55–62], which also provides library searchable EI mass spectra. We note that in particle beam EI each sample compound undergoes over ten cycles of adsorption/desorption in the ion source that could last for more than 10 s and thus result in peak tailing induced by the ion source. Since these adsorption/desorption cycles are performed on hot ion source metal surfaces they are more likely to lead to degradation than on the deactivated GC column surface. Furthermore, in order to eliminate peak tailing, the particle beam EI ion source is maintained at temperatures that are usually higher than the upper Supersonic GC–MS oven temperature in order to suppress peak tailing of the last to elute compound. Using these conditions the molecular ion is often lost while in the Supersonic GC–MS it is practically always exhibited and enhanced. Thus, we believe that the Supersonic GC–MS can be used for the analysis of the range of particle beam LC–MS compounds and can provide for these compounds higher quality mass spectra.

Recently, EI was coupled with LC–MS using supersonic molecular beams [63]. This relatively new approach of LC–EI-MS shares (with the Supersonic GC–MS) the same advantages of high quality EI mass spectra, and its range of compounds amenable for analysis is somewhat larger than that of the Supersonic GC–MS since it also involves fast, high temperature vaporization as in APCI.

4.5. Range extension and its correlation with speed of analysis

Contrary to the common perception we found that there is an inherent contradiction between faster GC–MS analysis and the preservation of intact thermally labile compounds. Despite the shorter time spent by the compounds at the heated column in fast GC–MS methods, *the slower the temperature program rate (thus chromatography), the better the samples are preserved.* The reason for this ''unexpected'' claim is that 20 °C lower elution temperature protects the labile sample molecules more than the traded factor of two shorter analysis time. Most degradation processes are characterized by higher activation energy than their vaporization energy. Thus, lowering the species elution temperature has greater protecting effect than time on their degradation. This conclusion is also based on our observation of stronger temperature dependence of aldicarb decomposition rate to aldicarbnitrile (factor of 5 per 20 °C) than its elution time (assumed factor of 2 per 20 °C). It is further based on our greater current success in the analysis of compounds such as corticosterone and aldicarbsulfone in a few minutes with temperature programming than in the past in a few seconds under higher isothermal temperature analysis [8]. Consequently, we recommend the reduction of temperature programming rate for the analysis of thermally labile compounds. However, slow analysis also involves broadened GC peaks and thereby a loss of sensitivity in addition to loss of time. Thus, the temperature program rate should be a compromise between these conflicting parameters.

4.6. Supersonic GC–MS and other methods of fast GC–MS analysis

Currently, several methods and instrumentations are claimed to excel in the provision of fast GC–MS analysis. The simplest approach for achieving fast GC–MS analysis employs short microbore (0.1 mm I.D.) columns together with faster GC oven temperature programming rate [64–66]. This way the analy-

sis time is reduced, the GC resolution is maintained and the elution temperatures are also preserved. Thus, on the one hand the faster analysis slightly helps, while on the other hand, the limited microbore column flow rate deteriorates the injector liner induced degradation so that overall practically no change is obtained in the range of compounds amenable for analysis. An alternative method named ''Flash GC'' is based on the use of thin metal tubes for fast resistive heating of the GC analytical column [67,68]. Clearly, according to the discussion above, this method reduces the range of compounds amenable for GC–MS analysis since it induces higher elution temperatures. More recently, another method was revived based on vacuum chromatography [69] and the use of 10 m columns with 0.53 mm I.D. and a short microbore transfer line restrictor at the inlet [70,71]. In Ref. [71] it is specifically mentioned that the use of that column enables the reduction of the elution temperatures by 50–70 °C *if slow temperature programming is used*. According to the discussion above, the use of this column (named ''Rapid MS'') may result in ~60 °C lower elution temperatures, emerging from eight times reduction in the number of separation plates in comparison with standard GC–MS (three times shorter column with 2.1 times bigger I.D. and 25% less plates per meter due to the use of vacuum chromatography). However (and as mentioned in Ref. [71]), if the temperature program rate is increased as suggested in order to speed up the analysis, than no gain is obtained in the range of compounds amenable for analysis and the elution temperatures are preserved. Thus, for both microbore and vacuum chromatography approaches it is either faster chromatography or lower elution temperatures but not both. In contrast, with the Supersonic GC–MS, fast GC–MS can be combined with extended range of compounds. If desirable, for the expense of further lowering of the elution temperature (for example by additional 60 °C), one can simultaneously decrease the time of analysis (by a factor of 8 in this example), which is faster also due to the lower elution temperatures. These conditions are sufficient for solving ''borderline'' compounds' analysis problems, yet with sufficient chromatography resolution as demonstrated in Figs. 8–12.

4.7. The unique role of increased column flow rate on the extension of range of compounds amenable for GC–MS analysis

Column flow rate is, in our opinion, the most important parameter for extending the range of compounds amenable for analysis since high column flow rate: (a) increases the column capacity and thus enables the use of thinner films with lower elution temperature without losing column capacity; (b) enables lower ''elution temperatures'' from the injector liner (using a temperature programmable injector) and thus reduced intra injector degradation. While cold on-column is claimed to be the best injection method for labile compounds, its applicability for real world samples is known to be limited. As a result, the use of temperature programmed injectors provides the best practical method and device for the analysis of thermally labile compounds. For optimal injection the injector temperature program rate should be limited to less than 10 °C per liner ''void time'' (ratio of liner volume to flow rate) as recommended for the GC column [32–35]. With 16-ml/min flow rate this is easy to achieve with 5 °C/s, even with standard liner volumes of 0.5 ml as needed for dirty sample analysis. In fact, high flow rate enables lower ''elution'' temperature of sample compounds from the liner into the column the same way as occurs for elution from the column; (c) although usually ignored, degradation can also occur at the transfer line between the GC and MS since it is maintained at a high temperature as required to prevent peak tailing for the last to elute sample compound. With Supersonic GC–MS only 4 cm column is maintained at the transfer line temperature, while the rest of the transfer line is based on uncoated deactivated fused silica operated at 130-ml/min make-up gas. This high transfer line gas flow rate enables its operation at lower temperatures without inducing peak broadening or tailing for the same reasons described above for the lowered column elution temperatures; and (d) flow rate can be quickly programmed and thus the trade-off of separation and elution temperature can be programmed and better optimized. Consequently, the ability to handle increased flow rate enables not only the analysis of lower volatility and more labile com-

pounds but also higher ratio of volatility in a single run. The analysis can begin with standard column flow rate for handling relatively volatile compounds and either gradually or at once near the end of the analysis the flow rate can be increased for analyzing compounds that otherwise would not elute in time. Flow programming, unlike temperature programming, allows fast changes to either direction in less than a second. However, shorter columns should also be preferred for enabling higher flow-rate pulsed injection and a wider range of upper to lower flow-rate ratios, unless a Megabore column with 0.53 mm I.D. is used with its low flow-rate impedance.

Since the analysis of thermally labile compounds requires a complete solution of all its aspects, including the injection, high column flow rate is considered by us to be the most important parameter as it also helps the injection.

4.8. Implications for GC analysis

GC analysis, unlike GC–MS analysis, must rely on full chromatographic separation of the analyzed compounds for their quantitative determination. Thus, the trade-off of GC resolution for lowered elution temperature and consequently greater range of compounds amenable for analysis is generally unacceptable. However, in a few cases GC resolution can be traded for lower elution temperatures and a few examples are: (a) simulated distillation analysis is performed with lower GC resolution since otherwise most of the analyzed compounds would not elute from the GC in reasonable time. In this case chromatographic separation of isomers is not attempted while the separation of carbon number is preserved; (b) sometimes simple mixtures are analyzed as in the case of synthetic organic chemistry and GC resolution can and should preferably be traded to enable the GC–FID analysis of new thermally labile compounds; and (c) if a GC selective detector is used GC resolution can be traded for enhanced separation power of the selective detector over FID. Chamber and Duffy have analyzed, based on this manuscript, aldicarb, methomyl and methiocarb using the pulsed flame photometric detector (sulfur selective detection) in combination with a 4 m×0.25 mm I.D. column with 0.25-μm DB5 film and 5-ml/min He column flow rate (140 °C injector temperature) [72]. We note that GC analysis unlike GC–MS analysis is generally not limited in the use of short columns and or high column flow rates.

4.9. Increased range of GC–MS applications

In general we feel that lowering the GC elution temperatures by more than 200 °C is a significant quantitative change that in view of its magnitude can result in a qualitative change of GC–MS applicability to significantly greater number of applications. However, it is important to realize that the extension of the range of compounds amenable for analysis requires a full method which addresses *all the relevant aspects* including: (a) use of a temperature programmable injector with high liner flow rate and the of use inert liner; (b) lowering the GC elution temperature; (c) use of high flow rate at the GC–MS short transfer line; (d) use of a GC–MS interface such as the supersonic molecular beam interface to enable high column flow rate without flow splitting and/or EI ion source sensitivity reduction; (e) elimination of intra ion source related peak tailing combined with retaining of the molecular ion and effective library search capability; (f) elimination of intra ion source sample degradation; and (g) provision of increased relative abundance of the molecular ion and other high mass fragments in order to compensate the reduced GC resolution with enhanced separation power of the MS. Once all these issues are properly addressed, as in our system, the door is open for a large number of either improved or new applications of GC–MS. Pesticide analysis for example could be performed with a single universal Supersonic GC–MS run for all the important groups of pesticides [6]. Explosives and underivatized steroid analyses were demonstrated in this paper. From these analyses it can be concluded that significantly greater range of drugs can be analyzed with the Supersonic GC–MS, including benzodiazepines. In Fig. 12, the analysis of depressant drugs is demonstrated, with elution temperature of 230 °C for the last to elute flurazepam benzodiazepine drug. Reasonably good chromatography and nice peak shapes with high quality mass spectra are shown, despite some sacrificed GC resolution. A few other life science related classes of compounds can potentially be analyzed such as prostaglandines,

porphyrins and triglycerides. Certainly, much larger aliphatic and other petrochemicals can be analyzed including heavy oils, waxes and polymers. Synthetic organic chemists can benefit from the extended range in the analysis of new, larger or more thermally labile compounds such as 5,10-epoxide of decaline which was analyzed with the Supersonic GC–MS [73,74]. In general, any compound that is currently hard with standard GC–MS since it either elutes too late or it is partially or mostly degraded in the GC injector, column or MS ion source could be analyzed with the Supersonic GC–MS.

4.10. Applicability to other GC–MS systems

In this paper, the parameters that affect the elution temperature and consequently the range of compounds amenable for analysis were discussed. While Supersonic GC–MS excels in this extension, other GC–MS systems can also be used for such extension. Standard GC–MS systems can be operated with 15 m×0.25 mm I.D. columns with thin film (0.1–0.25 μm) and column flow rate of 2 ml/min that is acceptable. This way sample elution temperatures will be reduced by more than 20 °C. Furthermore, 3 m×0.15 mm I.D. columns can be used with convenient positive head pressure with 1–2-ml/min column flow rate, for achieving more than 50 °C lower elution temperatures. The use of such column combined with slow temperature programming rate of both the GC injector and oven enables the proper analysis of borderline compounds that are currently partially degraded. Alternatively, standard 0.25 mm I.D. columns at any length (but preferably short ones such as 4 m, with thin film) can be used with an open split interface without any flow-rate restriction for achieving over 100 °C lower elution temperature. The use of open split interface could be in the form of a T flow splitter into both MS and another GC detector such as the pulsed flame photometric detector (PFPD) that can further improve (lower) the MS identification limits of organo-phosphorus and organo-sulfur compounds [75]. We note that in some applications such as pesticide analysis in complex agricultural matrices, matrix related chemical noise is dominant hence the use of open split may not reduce the sensitivity as much as the split ratio. Recently, Shimadzu introduced the 2010 GC–MS system that has differential pumping as a standard feature, while ThermoFinnigan offered for a few years their Trace MS with optional differential pumping. Differential pumping enables column flow rates of 10 ml/min and with such flow rates standard columns with 0.25 mm I.D. can be used with 3-m length with positive injector head pressure. Thus, under these conditions standard GC–MS with differential pumping capabilities can be used for the significant extension of range of compounds amenable for analysis. The lack of enhancement of the MS separation power (especially if higher ion source temperatures are needed to avoid peak tailing) can reduce the appeal of the trade-off of GC resolution but it is better to analyze a given compound even with poor mass spectrum than not at all.

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