

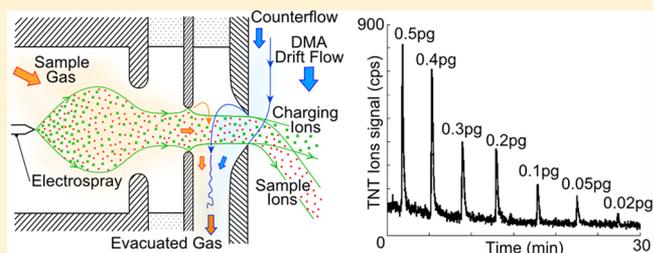
Low-Sample Flow Secondary Electro spray Ionization: Improving Vapor Ionization Efficiency

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ABSTRACT: In secondary electro spray ionization (SESI) systems, gaseous analytes exposed to an electro spray plume become ionized after charge is transferred from the charging electro sprayed particles to the sample species. Current SESI systems have shown a certain potential. However, their ionization efficiency is limited by space charge repulsion and by the high sample flows required to prevent vapor dilution. As a result, they have a poor conversion ratio of vapor into ions. We have developed and tested a new SESI configuration, termed low-flow SESI, that permits the reduction of the required sample flows. Although the ion to vapor concentration ratio is limited, the ionic flow to sample vapor flow ratio theoretically is not. The new ionizer is coupled to a planar differential mobility analyzer (DMA) and requires only 0.2 lpm of vapor sample flow to produce 3.5 lpm of ionic flow. The achieved ionization efficiency is 1/700 (one ion for every 700 molecules) for TNT and, thus, compared with previous SESI ionizers coupled with atmospheric pressure ionization-mass spectrometry (API-MS) (Mesonero, E.; Sillero, J. A.; Hernández, M.; Fernandez de la Mora, J. Philadelphia PA, 2009) has been improved by a large factor of at least 50–100 (our measurements indicate 70). The new ionizer coupled with the planar DMA and a triple quadrupole mass spectrometer (ABSciex API5000) requires only 20 fg (50 million molecules) to produce a discernible signal after mobility and MS² analysis.



Fenn and colleagues noted that vapors put in contact with an electro spray (ESI) cloud were ionized.¹ Chen and colleagues independently proposed a similar approach.² Wu and Hill later named this technique secondary electro spray ionization (SESI).^{3,4}

The exact way ions are produced is still unclear.^{5–11} However, recent experiments suggest that ionization mostly occurs through ion to molecule interactions.^{12,13} SESI produces little fragmentation and simpler aggregation;^{6,12} and the sprayed charging species can be chosen so as to selectively ionize molecules.¹⁴ The term SESI is here limited to the ionization of vapors, while other ambient air electro spray-based ionization techniques such as extractive electro spray ionization (EESI^{15–18}), fused droplet ESI (FD-ESI¹⁹) and laser ablation ESI (LAESI²⁰) also include aerosols that may be ionized by other mechanisms.¹⁸

The theoretically predicted concentration of sample ions (n_s) is uniform within the electro spray plume. It is possible to demonstrate mathematically that space charge repulsion and generation of new sample ions due to charge transfer reactions lead to a balance for which the probability of ionization defined as $p_i = n_s/N_s$ is uniform,¹¹ where N_s and n_s are the concentrations of sample molecules and sample ions.^{11,13} This theoretical value is very low ($\sim 10^{-4}$), and it is in qualitative agreement with the experimental results.¹¹

Despite this, SESI has shown a remarkable sensitivity.²¹ The SESI-ion mobility spectrometry (IMS) scheme of Hill and co-workers⁷ seems to transmit approximately one ion for every

140 sample molecules when the gate of the IMS is opened. This result is not in contradiction with p_i .¹¹ Although the ratio of sample ion to molecule concentration is limited, the ratio of molecules entering the ionizer to ions delivered to the analyzer is not, and the newly formed ions are driven by the electric fields at a much higher flow rate through the IMS that produces an enormous ionic flow rate of a few hundred lpm (estimated from the section area of the drift tube and the drifting speed of the TNT ions). However, the duty cycle of this scheme is very low (near 1%), resulting in a moderated transmission of the SESI-IMS (near 10^{-4}).

SESI can also be coupled with atmospheric pressure interface MS (API-MS).^{22–27} To our knowledge, experiments by our colleagues Mesonero et al. represent the best sensitivity achieved by SESI-MS of TNT vapors.²⁸ These results implied however that only 1 out of 10^4 sample molecules was ionized and transferred to the MS. This relatively poor ionization efficiency contrasts with that of Hill's experiments. Two factors could explain this: the high flow of sample gas required (5 lpm) and the poor flow of electrostatically driven ions.

Uniting the high ionization efficiency of the Hill's ionizer with the continuous flow (100% duty cycle) offered by quadrupole MS and differential mobility analyzers

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(DMA)^{29,30} would greatly increase the sensitivity of vapor detectors. ESI-DMA-MS was described in refs 31–36. The SESI-DMA-MS scheme was also described by Martinez-Lozano (Figure 1a illustrates the traditional SESI-DMA interface

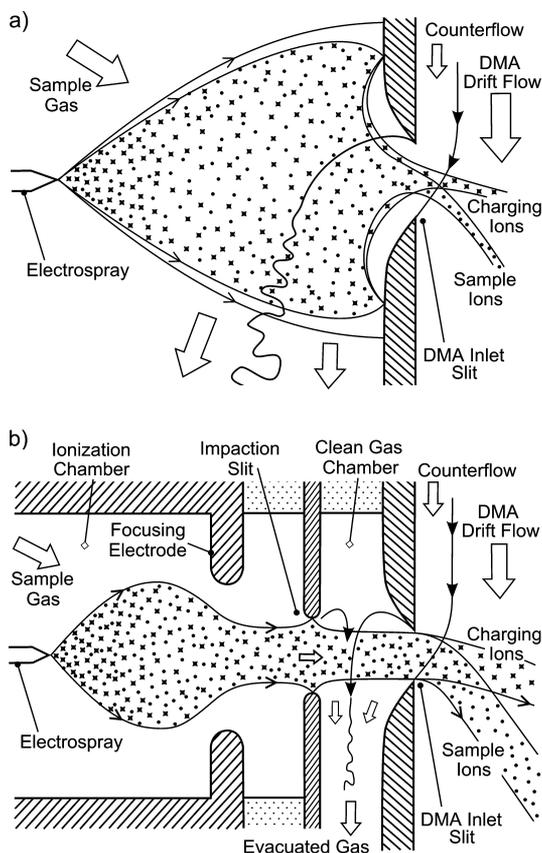


Figure 1. (a) Schematic view of SESI-DMA interface; (b) schematic view of a LF-SESI-DMA interface.

showing the electro spray tip positioned directly in front of the DMA inlet slit).^{12,37} The DMA inlet is small, and a clean counterflow is required to prevent contamination of the drift gas, but it also tends to occupy the electro spray plume. To counteract dilution, the sample flow rate needs to be unusually high, and the charging electro spray tip needs to be separated (at 2 cm) from the DMA inlet slit, thus producing a relatively poor flow of ions through the inlet slit. In this study, we developed and tested a new SESI system design, termed low-flow SESI (LF-SESI), that consumes a very low sample flow rate, produces a high ionic flow rate of sample ions, and couples with a planar DMA.

METHODS

Figure 1b shows the LF-SESI configuration. Sample dilution associated with the counterflow jet is virtually eliminated by performing the functions of the ionizer and the counterflow gas in two different regions: an ionization chamber and a clean gas chamber separated by an impaction plate. The sample flow enters the ionization chamber where it is mixed with the electro spray plume, ideally producing SESI sample ions at the concentration given by p_r .¹¹ A focusing electrode accelerates the ions toward the impaction slit, and the local electric fields drive them through it. Sample gas is also accelerated through the impaction slit and forms a jet that impacts (hence the name)

with the counterflow clean gas and precludes it from entering the ionization chamber. Ions are then pushed toward the DMA inlet slit by the electric fields, while the counterflow jet emerging from the DMA precludes sample gases from contaminating it.

The fluid flow in the impaction region has to be sufficiently stable to avoid convective and diffusion penetration of counterflow gas into the ionization chamber. From this perspective, the impaction slit should be as small as possible. Producing the required ionic flow rate requires the use of very intense electric fields and a very thin impaction plate. The distance between the impaction plate and the DMA inlet electrode is 2 mm, and the impaction plate is 0.5 mm wide. The impaction slit is 5 mm long and 1 mm thick. Its voltage is controlled by means of an EMCO power supply that floats above the DMA inlet electrode voltage and provides a constant differential potential of 1.5 kV. In these conditions, and with a sample flow of 0.2 lpm, the local Re is near 100.

The concentration of sample ions is theoretically homogeneous in the ionization region, and therefore, one only needs to worry about the ionic flow rate, but the electric field produced by an ESI is relatively weak. Matching this weak electric field produced by the electro spray with the intense electric fields required near the impaction region is achieved by means of an electrostatic focus. The focusing electrode is located in the ionization chamber and focuses the electro spray plume toward the impaction slit. It produces an intense electric field near the impaction region and a weaker electric field on the electro spray side. Our simplified numerical study showed that the electric flux per unit of slit length goes approximately with

$$\phi = e^{-1.5\lambda} d(E_1 E_2)^{1/2} \quad (1)$$

where d and λ are the width and the ratio of thickness to width of the slit, and E_2 , E_1 are the field strengths on each side of the planar plate. In our prototype, the size of the focusing slit was chosen with the aim of providing a similar electric flux to that of the impaction slit (which has intense electric fields on both sides of the plate) but requires an electric field strength 10 times weaker in its upstream side. The focusing electrode is 2 mm from the impaction plate, and its voltage is controlled by another EMCO adding 1.5 kV. The focusing slit dimensions are 4 and 5 mm. The electro spray tip can be positioned by means of an in-house micrometric positioning system that works as a Bowden cable does. The optimum position of the electro spray is approximately 6 mm from the focusing electrode, and a voltage of 3 kV produces a stable ESI current of approximately 65 nA.

No new sample ions can be produced in the absence of sample molecules in the clean gas region. However, space charge due to charging ions still tends to dilute the ions as they cross it. The passage of ions through the clean region should thus be as fast as possible, and the concentration of charging agents should be minimized. The strong electric field produced by the voltage difference between the impaction plate and the DMA inlet electrode allows us to reduce the time of residence through this region. Also, the concentration of charging ions can be reduced by locating the electro spray tip farther from the focusing electrode that redirects the electro spray plume toward the slits.

The ionizer was heated by means of an electrically isolated resistor. The DMA was operated at a moderate temperature (70 °C) that was controlled by another resistor acting in the recirculation circuit. Heating the ionizer to a uniform

temperature, while keeping the DMA warm, produced a strong and localized thermal gradient between the impaction plate and the DMA inlet electrode. The thin impaction plate had to be actively heated to prevent vapor condensation and accumulation and to ensure that the thermal gradient remained only in the clean gas region.

EXPERIMENTS

The LF-SESI was designed to optimize exploitation of limited amounts of sample. We used a stainless steel (SS) mesh where the sample was deposited by pipetting known amounts of a sample solution that dries at ambient temperature and forms a solid deposition. Vapor molecules were produced in a leak-proof heater designed to vaporize the solid samples (the vaporizer). A flow of N_2 , controlled by means of a flow meter, was continuously introduced in the vaporizer which was directly connected with the ionizer. The vaporizer and the lines carrying the sample gases were heated to 200 °C. The ionization chamber temperature was limited by the boiling point of the electrospray solution (MeOH–H₂O–HCl 9:1:0.01%), and its temperature was reduced to 90 °C.

The planar DMA can be operated either alone, by measuring the current of ions exiting through the DMA exit slit with an electrometer, or in tandem with an MS, by integrating the DMA with an API-MS.³⁰ The counterflow of clean gas exiting through the DMA inlet slit was 0.4 lpm, and the sample gas was 0.2 lpm. The operation of the SESI-DMA-MS system was previously described by Martinez Lozano,¹² but here we introduced the improved LF-SESI. In the DMA alone setup, a vacuum pump reduces the pressure in the electrometer such that the DMA outlet is sonically choked, producing a flow of 3.5 lpm as if it were connected with the API-MS. The DMA alone setup serves to measure more directly the current of ions outputted from the DMA. The mobility spectrum of the charging electrospray was first characterized by scanning the DMA voltage and recording the electrometer signal when no TNT was introduced. The DMA voltage corresponding to the TNT ions was later identified by scanning the DMA voltage immediately after introducing 20 ng of TNT in the vaporizer. Once the TNT voltage was identified, the DMA voltage was fixed to continuously monitor the signals produced by the TNT ions. By introducing known amounts of TNT in the vaporizer and then collecting the current in the electrometer after tuning the DMA voltage to selectively pass only TNT ions, we measured the gain (ratio of sample ions delivered to the electrometer to sample molecules delivered to the vapor generator) of the LF-SESI ionizer and the DMA together. The efficiency of the ionizer was further estimated using the previously measured DMA transmission.³⁸

In the final setup, the LF-SESI-DMA was coupled to an API5000 (ABSciex) MS. This MS was shared with our colleague Mesonero, who had already optimized its parameters to selectively pass the (TNT-H)⁻ precursor ion (226.1 Da), fragment it, and pass the NO₂⁻ product ion (46.1 Da).²⁸ With the MS set to monitor only TNT ions, the DMA voltage was scanned immediately after introducing 5 pg of TNT, to identify the voltage corresponding to TNT. During the rest of the experiments, this voltage was fixed to measure the intensity of the peak of TNT (the DMA voltage was 1510 V, and the DMA pump velocity was 12 000 rpm). By measuring the ions counted at the MS detector after LF-SESI-DMA-MS/MS analysis (fragment 46.1 Da), we were able to measure the overall gain of the vapor analyzer LF-SESI-DMA-MS/MS system. Compar-

ing the gain of the ionizer DMA alone system with that measured after incorporating the MS, we were also able to estimate the MS transmission.

SAFETY CONSIDERATIONS

High voltages and high temperatures are applied to the DMA and the LF-SESI. Care must always be taken to avoid electric discharges and injury and burns.

RESULTS AND DISCUSSION

The main goal of the experimental part of this study was to characterize the efficiency of the new ionizer. The experiments of our colleagues Mesonero et al. are, to our knowledge, the closest previous approach to our study. Although they produced the vapors continuously at controlled concentrations by means of a second electrospray and at high flow rate and we produce the vapors by means of a vaporizer for which only the total amount of TNT can be controlled (and not the concentration of vapors), the ionization efficiency can be estimated and compared for the two systems. We share in common the same MS, and we use the same MS settings. Luckily for us, the fact that TNT ions analyzed by SESI-MS/MS²⁸ and by SESI-DMA-MS/MS appear with the same precursor and product ions (TNT – H)⁻ and NO₂⁻ shows that the DMA does not chemically affect the ions. Note here that we are introducing high-purity samples of TNT and that signals grow linearly with the amount of TNT pipetted, which allows us to be almost sure that we are indeed detecting TNT. We cannot tell if ions are fragmented in the MS inlet, which would imply that the SESI produces clusters that contain TNT and not simply (TNT – H)⁻, but that question goes beyond the scope of this study. For simplicity, we shall refer to all these hypothetical forms of charged TNT as TNT ions.

Figure 2a shows the signals of ions arriving at the MS detector after DMA-MS/MS selection as a function of time when increasing amounts of TNT (0.5, 1, 2, 5, 10, and 50 pg) were sequentially vaporized. Each peak corresponds with the introduction of a given amount of TNT; the signal quickly rose when the mesh was introduced and then it returned to background levels as TNT was depleted. After each sequence was completed, we waited 30 min for the background signals to return to initial levels and then proceeded with the next sequence. The sequence was repeated three times to prove its repeatability, each of which is represented with differing broken lines. The timing of the three sequences was similar, and they are represented together to graphically illustrate that similar amounts of TNT produced similar signals.

Figure 2b shows the total ion counts, integrated over 2 min after the mesh was introduced, as a function of the amount of TNT deposited in the stainless steel mesh. The number of ions was proportional to the amount of TNT, and the gain of the system was approximately 2.8×10^4 counts/pg. The system required about 10^5 molecules for each detected ion, 36 times less than the system used by Mesonero et al. Considering that we used the same MS and MS sensor, this improvement can be mostly explained by a combination of three factors: the reduced sample flow rate, which accounts for a factor of 20, the improved electrostatic design which could be responsible for another factor of 3.5, and the DMA transmission which accounts for another factor of 0.5.³⁸ The ionizer presented here would be 70 times more efficient than its predecessor. Note however that we are not considering the uncontrolled changes

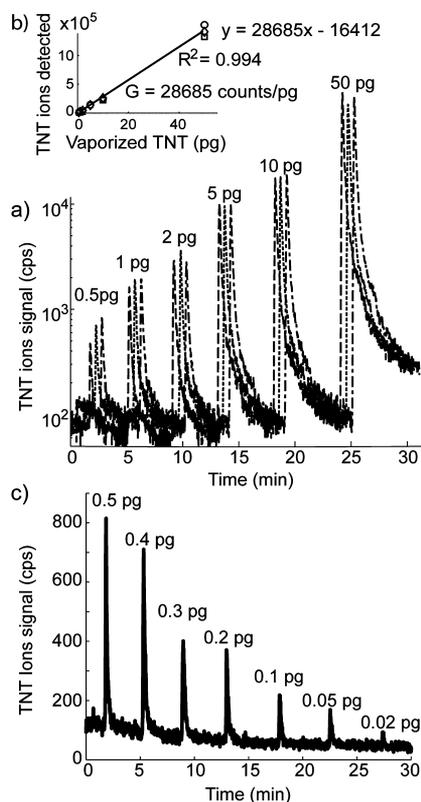


Figure 2. (a) Three curves of time evolution of the TNT signal measured in the LF-SESI-DMA-MS/MS system when different amounts of TNT were introduced in the vaporizer, each curve corresponding to an experiment. (b) Total ion counts (integrated over 2 min) detected as a function of the amount of TNT introduced in the vaporizer. (c) Time evolution of the TNT signal when lower amounts of TNT were introduced in the vaporizer.

in the transmission of the MS during the different experiments. We speculate that the ionization efficiency is improved by a factor of 50–100 over the previous ionization scheme.

To measure the minimum detectable signal, we pipetted lower amounts of TNT. Figure 2c shows the signal produced in this experiment. The peak produced by 0.02 pg (20 fg) of TNT was still detected. This small but still discernible peak was produced by approximately 53 million molecules.

Working in DMA alone mode, we also measured the total charge arriving at the electrometer as a function of the amount of TNT deposited in the mesh (we used 3 meshes with 0 ng of TNT, 2 with 2 ng, 4 with 5 ng, 6 with 10 ng, and 6 with 20 ng). Background levels of TNT or other species were much higher in this DMA alone experimental setup, but it had the advantage that we were able to measure the amount of ions produced more directly. The total amount of current arriving at the detector showed how many ions were actually produced, delivered to the DMA, selected according to their mobility, and finally detected at the electrometer. Although much higher amounts of TNT were being introduced, the signal was still linear, showing that the ionizer worked in a broad range of concentrations. The gain of the system was approximately 0.3 nC/ng ($y = 0.2819x + 0.4122$; $R^2 = 0.937$). This means that approximately 1400 molecules deposited in the mesh were required for each ion detected. Bearing in mind that the DMA transmission was approximately 50%,³⁸ we can conclude that the ionizer produced approximately one ion for every 700 molecules.

Comparing the gain of the DMA alone with that of the DMA-MS system, we estimate that the MS passed one fragment ion (46.1 Da) after introducing approximately 140 ions through the orifice plate (approximately 0.7%). Although it was not the original purpose of this study, we also found that adding an electrode in order to electrostatically focus the initially axisymmetric electrospray plume toward the linear DMA inlet slit also improved its sensitivity in conventional ESI-DMA³⁹ by a factor of 10.

At first glance, these improvements might appear to be surprising, but they actually agree with the theoretical expected values. The ratio of ion concentration and neutral vapor concentration is approximately $p_i \sim 10^{-4}$ for the SESI ionization of TNT. This value was measured,²⁸ and theoretically estimated,¹¹ thus supporting the validity of the approach. In our configuration we were producing an ionic flow rate of $Q_i = 3.5$ lpm (the ionic flow was limited by the analyzer capacity) at an ionic concentration $p_i \sim 10^{-4}$ times lower than the neutral vapor concentration which was entering the ionizer at a flow rate of $q_s = 0.2$ lpm. The predicted ratio of molecules entered to ions delivered is then $q_s/(Q_i p_i) = 570$. This result, so close to the measured value, indicates that the LF-SESI was indeed working as expected.

CONCLUSIONS

One first conclusion of the present work is that, although space charge dilutes the ions and seems to limit the ionization efficiency achievable with SESI, a LF-SESI could approach the ideal of 100% if the sample gas could be introduced at a sufficiently low flow rate. We found that a few tens of millions of TNT molecules (a few tens of femtograms) are sufficient to produce a discernible signal using a DMA-MS/MS analyzer with high resolution and transmission.

The LF-SESI technique could potentially open new fields of vapor research and analysis. To give an example, if this analyzer were used in combination with an ideal trap concentrating the sample collected in 1 m³, species having 10⁻² ppq of partial pressure could hypothetically produce a detectable signal (assuming that the ionization probability and background levels were similar to what we have measured here for TNT). Another example is in the emerging field of single cell analysis.^{20,40} If an average cell of 20 μm in diameter could be fully volatilized for single cell analysis, it would produce approximately 10¹¹ molecules (calculated using the density and molar mass of water). Also, species present at concentrations above 10⁻⁴ would be detected as long as they behaved similarly to TNT molecules. A lot of work, however, would still need to be done to actually achieve these estimated performances. Although the gain when detecting other species could be of approximately the same order as that of TNT, one would realistically expect that background levels would greatly differ from one application to another. If we could reduce the background to the ideal of zero, a few million molecules, or possibly even just one million, would produce a discernible signal of a few tens of ion counts. In this ideal case, and using an equally ideal preconcentration trap sampling 1 m³ of room air, the sensitivity would be in the range of 10⁻¹⁹ (10⁻⁴ ppq!); and the detection limit in a single cell could be in the ppm range. Of course, the detection limit of such an ideal analyzer would be lessened by the background levels and depend on its ability to differentiate species. Although we are performing multiple stage analysis (DMA-MS/MS), the real sensitivity of the system is limited by the background levels. This

background could be produced by TNT contamination itself or by other contaminants. In our case, the temperature of the ionizer was limited by the boiling point of the electrospray solvents. Increasing this temperature could potentially reduce background levels and improve the detection limit of the vapor analyzer. The results presented here suggest that further improvements in the selectivity of the analyzer will also improve its background levels and hence its detection limits and that therefore using the DMA in tandem with the MS is a valuable approach.

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Notes

The authors declare no competing financial interest.

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