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Mechanistic study on the ionization of trace gases by an electrospray plume

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ABSTRACT

The fact that electrosprays of pure solvents can efficiently ionize gas-phase analytes has been known for decades, although this method has not been widely exploited. With the advent of ambient mass spectrometry, this approach is becoming increasingly popular. However, the mechanism by which vapors become ionized in the encounter with electrospray plumes remains largely unknown. This has been our motivation in this study in which we have exposed a set of amine vapors towards electrosprays of water, water/methanol (1/1) and methanol. The ionized vapors were characterized via ion mobility-mass spectrometry. We further tested a recently developed model to predict ionization probabilities for the encounter and charge transfer of vapors with ions or charged droplets emerging from an electrospray source. We found: (i) the highest sensitivity with water sprays and the poorest with methanol; (ii) an approximate correlation of sensitivity with vapor mass, being the heaviest species insoluble in water; (iii) different electrical mobility spectra for the same compounds ionized from the liquid phase and from the gas phase (i.e. one main feature for gas-phase and 3 features for liquid-phase); (iv) a closer agreement with the model for ion-molecule reactions than for droplet–vapor charge exchange. We conclude that the analytes could not possibly be dissolved in the droplets to be reemitted as if they were originally present in the electrospray solution. Our observations suggest that the vapors are ionized via ion-molecule reactions.

1. Introduction

During the early years of electrospray ionization (ESI) development, Fenn and co-workers noted the ability of pure solvent electrosprays to ionize gas-phase species [1]. This peculiarity has been far less exploited than traditional ESI, but nevertheless its analytical merit was later recognized by other authors in a number of applications ranging from the detection of drugs to bacterial volatiles [2–4]. Hill and co-workers termed this approach as secondary ESI (SESI) [5]. Among the advantages noted by some of these authors are (i) high sensitivity (below part-per-trillion, ppt) [6,7], (ii) it is a "gentle" approach, thereby produces simple spectra with few fragmentation [8] and (iii) it implies less bureaucratic burdens as compared to radioactive sources [2,9]. Furthermore, SESI offers a high versatility in comparison with corona or radioactive sources because reactant ions can be easily incorporated into the ES buffer. For example, in the case of ligand-transfer reactions where the generation of gas-phase ligands (e.g. Na$^+$) can be easily accomplished [10], whereas corona and radioactive sources may present more operational restrictions. In other words, SESI may provide higher selectivity than traditional atmospheric pressure chemical ionization (APCI) sources. Perhaps, in contrast with APCI, its main disadvantage is its inability to ionize non-polar substances.

Even though some debate persists around the process by which ESI produces gas-phase ions from species originally present in the liquid phase, this method is fairly well understood [11]. In contrast, the mechanism by which electrosprays ionize gas-phase molecules remains largely unknown. More precisely, it is unclear whether the vapors are charged (i) via chemical ionization with the ions evaporated from the charged drops or (ii) via vapor–droplet interaction and re-emission to the gas phase. In the latter case, after droplet and vapor interaction, the mechanism would be akin to ESI (i.e. generation of gas-phase ions via ion evaporation or charged residue model). In the former case, the process would be closer to APCI, whose fundamentals are well understood. Thus, it is important to understand the driving ionization mechanism of vapors through electrospray clouds because ESI and APCI are fundamentally different processes and therefore rationale choices to optimize the different operating parameters would rely in different principles.

Pioneering systematic studies in the group of J.B. Fenn pointed out the high sensitivity achievable by this approach and suggested that, at least in some cases, ionization of trace gases occurs primarily on the droplets and not in the gas [11]. Later studies concluded that aerosolized samples were ionized "from encounters between particles and ES droplets". However, "when neutral molecules were

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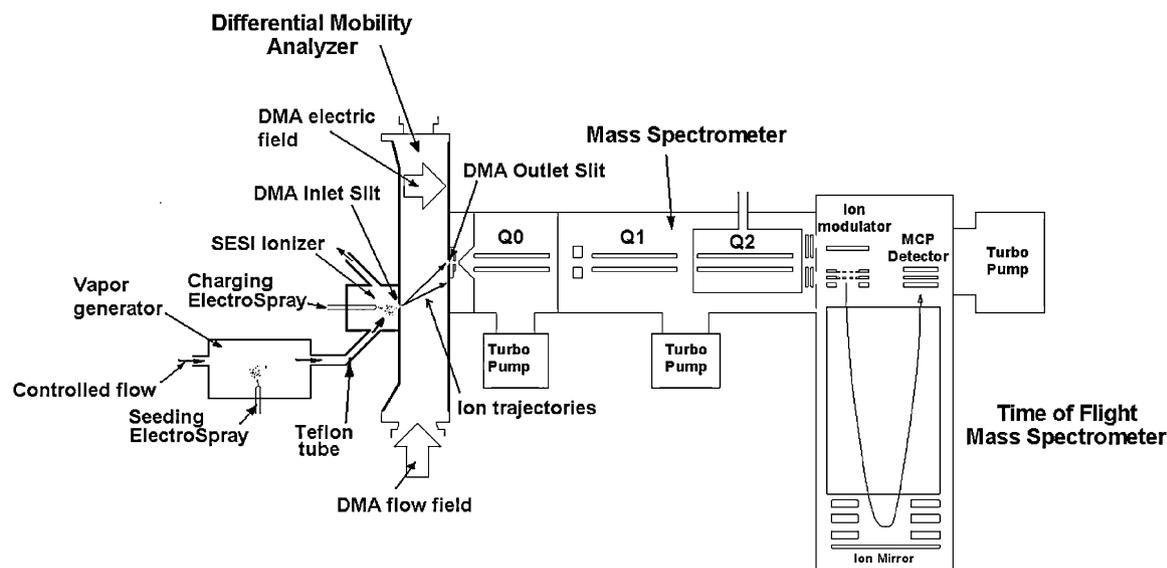 *E-mail address:* pablo.mlsinues@gmail.com (P. Martinez-Lozano Sinues).

Fig. 1. Scheme of the experimental set-up. Minute concentrations of gas-phase analytes are delivered from the vapor generator towards the charging electrospray. Some of the analytes are ionized, whose electrical mobility is subsequently analyzed in the DMA. In a second stage, their mass to charge ratio is measured in a quadrupole time-of-flight mass spectrometer.

the analyte in the drying gas, the resulting spectra did not so clearly distinguish between the possible ionization mechanisms" [13]. More recently, this issue has been also investigated, but more work remains to be done to better understand this process [7–9,14].

In the present work we have tackled this problem by investigating the effect of a number of different experimental parameters in the ionization probability in ESI and SESI. For this purpose, we have used a differential mobility analyzer (DMA) as stand-alone ion mobility instrument or interfaced with a quadrupole time-of-flight (QTOF). We further compared our experimental results against theoretical predictions of ionization probabilities through small drops and ions [15].

2. Materials and methods

The DMA-QTOF system utilized in this study has been recently presented in this journal [16] and we will not discuss it in much detail here. Fig. 1 shows the schematical experimental set-up. On left hand side of the sketch we represent the vapor delivery and SESI system, which is similar to the one described in [6] to assess the sensitivity of SESI towards explosive vapors. Briefly, the target vapors were delivered in controlled amounts via electrospray (seeding electrospray). This electrospray chamber was heated with heating tape up to 100 °C to ensure complete evaporation of the drops. The delivered gas-phase compounds were diluted and dragged downstream with a controlled flow (3 L/min) of nitrogen through a 50 cm long, 6 mm Teflon tube towards the DMA electrospray chamber (charging electrospray). The 3 L/min of nitrogen containing trace amounts of amines discharged into the chamber at approximately the same axial position as the electrospray tip. Turbulence within the chamber ensures that the amine vapors can interact either with the charged droplets or with the ultimately produced ions. As shown in [6], this provides ample time for the analytes to reach the ionization chamber as neutrals. The charging ES consisted in either H_2O (0.5% formic acid), H_2O/MeOH (1:1, 0.5% formic acid) and MeOH (0.5% formic acid), infused at typical flow rates of 80–90 nL/min. The distance between the emitter and the DMA sampling slit was optimized to maximize the signal to ~2 cm. The recirculating drift gas within the DMA was nitrogen. Its temperature was fixed at the converging region of the DMA at

28 °C via a proportional–integral–derivative controller developed in house. The drying counterflow preventing neutral species to enter the DMA was set at 0.7 L/min. Similar SESI experiments were conducted in a different platform, consisting in replacing the MS by an electrometer, whereby the mobility spectra where recorded.

A set of amines – primary, secondary and tertiary – including isomers were selected as test vapors. These nitrogen compounds have high gas-phase and liquid-phase basicities to ensure thermodynamically favorable protonation reactions whichever is the applying mechanism. Dimethylamine, ethylamine, trimethylamine, diethylamine, triethylamine, dibutylamine, tert-octylamine, octylamine and trihexylamine were diluted in methanol in concentrations ranging from 0.025 to 2 mM, which electrosprayed at typical flow rates in the range of 150–300 nL/min and diluted in 3 L/min of N_2, resulted in gas phase concentrations in the range of ~30 ppt to ~4 ppb. For example, a 0.025 mM solution electrosprayed at 150 nL/min and diluted in 3 L/min of nitrogen delivers some 30 ppt (i.e. 3.75×10^{-12} mol/min of amine diluted in ~0.12 mol/min of nitrogen). The main relevant properties of these amines for the current study are listed in Table 1.

In another set of experiments, with the aim of comparing differences between ESI and SESI, the amines were analyzed via traditional ESI. Thus, the samples dissolved in methanol were electrosprayed in lieu of the charging ES. The rest of the parameters remained identical, except for the absence of the carrier gas flowing through the ES chamber.

3. Results and discussion

3.1. SESI solvent impact on ionization efficiency

Fuerstenau found dramatic response differences for cocaine vapors towards different SESI solvents [12]. This led him to hypothesize that the higher sensitivity found for chloroform may be due to the higher solubility of cocaine in this solvent, implying that the ionization was occurring at the surface of the droplet and not in the gas-phase by chemi-ionzation. Similarly, Brenner et al. [8] observed an impact on the ionization efficiency of a set of gas chromatography eluents. Following this approach, we have explored the responsiveness of a set of amines towards aqueous

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Table 1
Relevant physicochemical properties of the amines tested in this study.

Compound	MW (Da)	Gas-phase basicity (kJ/mol) [37]	Dipole moment (Debye) [38]	Polarizability (Å³) [39]	Measured electrical mobility, Z (cm²/Vs)	Reduced Z from [40] (cm²/Vs)	MeOH sensitivity (counts/ppt)[c]	H₂O/MeOH sensitivity (counts/ppt)[c]	H₂O sensitivity (counts/ppt)[c]	ADO rate constants for the proton transfer reaction from [H(H₂O)₁₀]⁺ (cm³ molecule⁻¹ s⁻¹)	Solubility in water (25 °C, 1 atm) [log (molefraction)] [39]
Ethylamine	45.08	878	1.22	5.86	2.04	1.92	0.286	1.008	1.48	1.24×10^{-9}	−0.12
Dimethylamine	45.08	896.5	1.01	5.99	2.13	2.02	0.74	1.989	3.178	1.17×10^{-9}	−0.32
Trimethylamine	59.11	918.1	0.612	7.95	2.24	2.36	0.903	2.626	4.019	1.04×10^{-9}	−0.17
Diethylamine	73.14	919.4	0.92	9.65	2.06	2.01	1.465	4.965	8.062	1.14×10^{-9}	Miscible
Triethylamine	101.19	951	0.66	13.44	2.03	1.95	3.424	10.83	14.88	1.10×10^{-9}	−1.8
Tert-octylamine	129.25		1.22[a]	16.85	1.68		0.934	2.083	2.798	1.25×10^{-9}	−2.51
Octylamine	129.25	895	1.22[a]	16.85	1.51		2.078	8.151	11.41	1.25×10^{-9}	−3.15
Dibutylamine	129.25	935.3	0.98	16.97	1.70	1.7	5.082	17.66	22.63	1.19×10^{-9}	−2.95
Trihexylamine	269.51		0.66[b]	35.4	1.29		4.791	35.69	40.01	1.35×10^{-9}	−8.5

[a] In the absence of tabulated values, we assumed to be that of ethylamine.
[b] In the absence of tabulated values, we assumed to be that of triethylamine.
[c] All regression coefficients >0.99.

and organic electrosprays. Fig. 2 (top) shows the calibration curves (signal intensity vs. vapor concentration) obtained for the nine amines tested using H_2O, H_2O/MeOH (1/1) and methanol solvents in the charging ES. Fig. 2 (bottom) displays the sensitivity values (i.e. slopes found after linear regression fitting) as a function of vapor mass for the three solvents tested. To facilitate the comparison between the three solvents, the lower-right pane shows the sensitivity ratio of water over the other solvents vs. vapor mass. The response of the system was linear in the range tested (up to $\sim$2 orders of magnitude), much in the same way as in our previous studies with explosives [6] and fatty acids [17] in negative ion mode. Interestingly, we found for the nine amines tested a similar behavior, with increasing sensitivity as MeOH < H_2O/MeOH (1/1) < H_2O. This is in line with APCI studies [18] – via corona discharge – who found a dramatic sensitivity drop ($\sim \times 10$) by introducing MeOH vapors in the ppm range as compared to ionization efficiencies obtained in pure water (3 ppm) for an analyte with low proton affinity [19]. Conversely with [12], we observed the highest sensitivity for H_2O electrosprays, even though the heaviest amines are immiscible in water (Table 1). This observation precludes the scenario in which the vapor is first dissolved in the droplet. However, as noted in [15], our observation do not necessarily exclude an active role of the droplets during the ionization process. For example, one can expect a scenario in which only the amine group reaches the droplet surface to receive a proton, while the non-polar hydrocarbon chain remains in the gas-phase. However, recent H_2O/MeOH ESI mixtures modeling have shown that demixing of the two solvents takes place during the nanodroplets life time, where methanol tends to form an external layer at the periphery [20]. Therefore, if the vapors would hit the outmost external layer of the drops to acquire a charge, one would expect similar sensitivities for H_2O/MeOH (1/1) and for pure MeOH, which is clearly not the case. Reasoning in terms of chemical ionization, the charging agents evaporated from the ES droplet are different from one buffer to another. The simulations performed in [20] were based on ammonium ions, but most likely we should expect similar dynamics for the evaporation of ions. The simulations predict that typically, the ejected ions are of the form $[(H_2O)_x H]^+$ for H_2O, $[(MeOH)_x H]^+$ for MeOH and $[(H_2O)_x(MeOH)_y H]^+$ for H_2O/MeOH (1/1) electrosprays. However in the latter case, due to the presence of gas-phase methanol evaporating at high rates from the droplets and to its higher proton affinity than water, a shift towards methanol clusters is to be expected [21]. This complicates the picture because if the vapors are ionized via ion-molecule reactions, it is unknown if the proton transfer reaction may occur from the primary water–methanol clusters or from the secondary methanol clusters. Fig. 3 compares the mobility spectra for the buffers used in this study. They show comparable features with a maximum arising at 1.175 V of the DMA scanning voltage. However, the signal intensity is the highest for water, the lowest for methanol and intermediate – although closer to water – for the 1:1 (v/v) mixture. Accordingly, the different production rate of ions across the different buffers was accompanied with a correlation of electrospray ion currents: $\sim$1 μA for H_2O, $\sim$250 nA for H_2O/MeOH and $\sim$10 nA for MeOH. It is tempting to link the sensitivity differences observed for the three buffers with their ion production. However, the model against which we will compare these results, predicts that in the equilibrium, the ionization probability is independent of the charging species concentration. Nevertheless, a higher linear dynamic range can be still expected for H_2O due to the higher availability of reactant species. The reasons behind the dramatic sensitivity differences observed are therefore still unclear. Perhaps, the concentration ratio of charge transferring species to non-transferring species – that would have the only effect of diluting the ions by coulombic repulsion – could also affect the probability of ionization. Similarly to our own results, it has been found that the charge
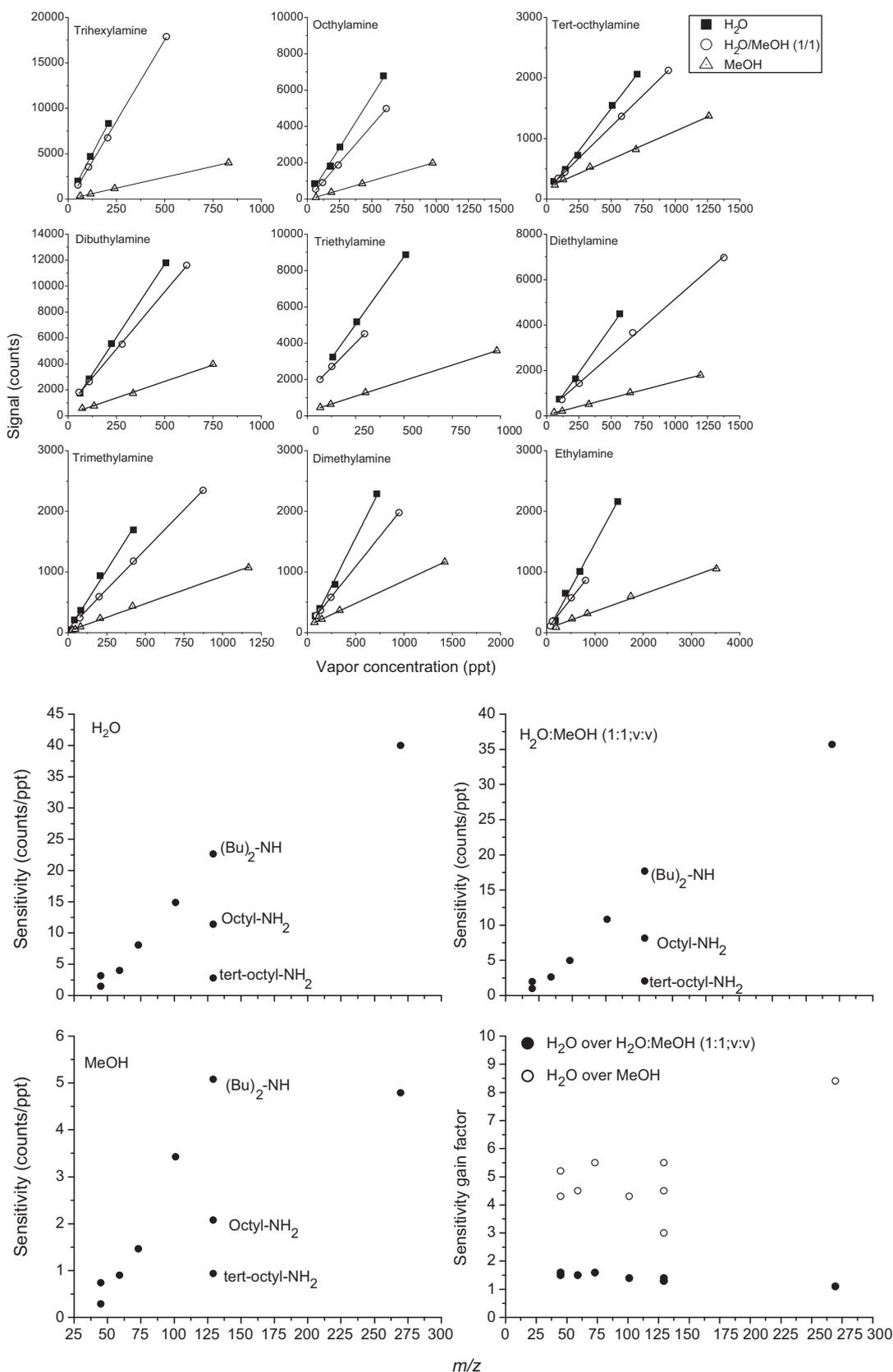
Fig. 2. (Top) Sensitivity measurements for a set of vaporized amines towards electrosprays of water, water/methanol and methanol. (Bottom) Compilation of the sensitivity measurements (slopes from linear fitting of top figure) vs. vapor mass for the three solvents tested. The lower right panel shows the sensitivity ratio water to water/methanol (1/1), and water to methanol.
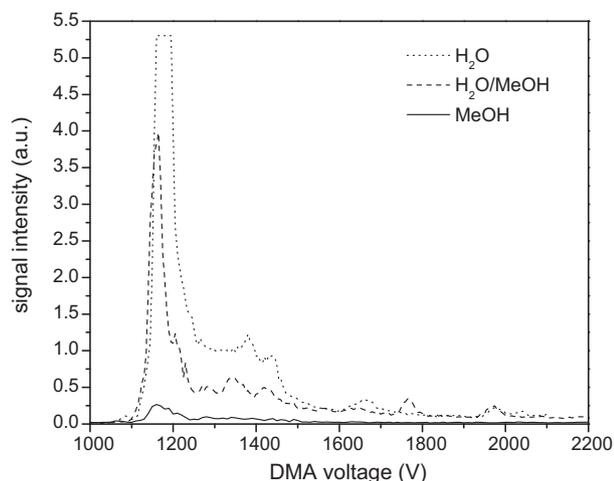
Fig. 3. Electrical mobility spectra of the charging buffers used in this study. Note that the spectrum of H₂O/MeOH (1:1) is closer to that of water than to that of MeOH.

transfer rates between ionic species generated by electrospray and amine vapors varied with reagent ion's chemical composition and size, but the reasons for this phenomenon are still to be elucidated [14].

3.2. Mobility spectra of SESI vs. ESI

We have just shown that water-insoluble amines are detected with high sensitivity using water-based electrosprays. This suggests that SESI ionization mechanism does not involve the dissolution of the analyte vapors into the charged droplets. However, it is yet unclear whether the protonation takes place via ion-molecule reactions or via interaction of the amine group with the periphery of the charged droplets. To further investigate this

point, we compared the electrical mobility spectra from protonated amines ionized either by SESI or by ESI. Thus, the amines dissolved in methanol ($\sim$30 μM) were analyzed by the traditional ESI mode and by exposing the amine vapors to an electrospray of methanol. Our working hypothesis was that, supposing that SESI mechanism is closer to that of ESI than to that of APCI, their mobility spectra should be comparable.

One of the main advantages of ion mobility analysis via DMAs is that the ions produced in the API source are analyzed at almost identical conditions as they were produced; thereby their original structure is more likely preserved as compared to other approaches subjecting the ions to declustering potentials or abrupt changes of pressure. Fig. 4 shows the mobility spectra for a set of protonated amines [M+H]⁺ produced either via ESI or SESI. The signal intensity has been normalized to facilitate the comparison of the different appearing features. Note that the DMA was calibrated with tetraheptylammonium ions [22] (corrected for temperature and gas composition as a hard-sphere) and thus the x-coordinate shows the inverse of electrical mobility, instead of the scanning DMA voltage.

We found that SESI and ESI produce significantly different mobility spectra patterns. The SESI spectrum is dominated by a single peak with a long low-mobility tail, whereas in the case of ESI, the spectra display two or three additional peaks at lower mobilities. These lower mobility peaks are either proton bound n-mers or amine–solvent clusters evaporated from the ESI drops. These clusters are fragmented in the transition between the atmospheric pressure (DMA) and the vacuum (mass spectrometer), and for this reason are finally detected in the mass spectrometer as the protonated amine.

In the case in which SESI would be driven by the impact of the neutral vapors with the charged droplets, to be finally re-emitted by ion evaporation, one would expect a mobility spectrum akin to that obtained by ESI, in which the ionized amine would evaporate with solvent molecules attached to it or alternatively protonated n-mers.
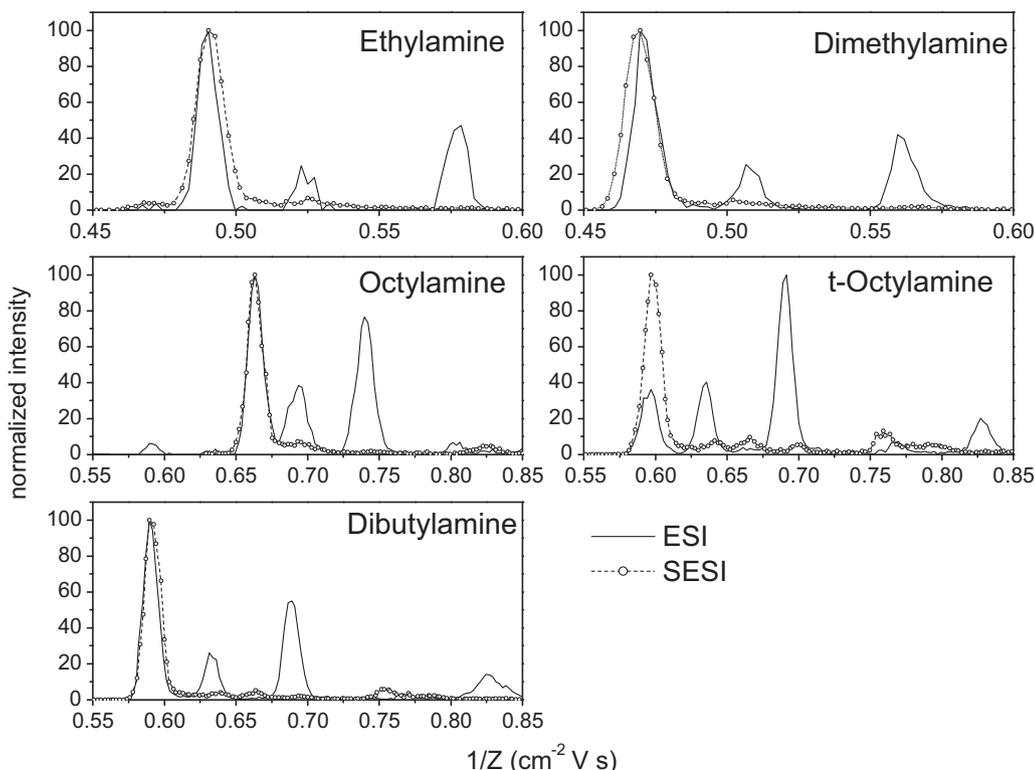

Fig. 4. Mass-selected mobility spectra of a set of amines ionized from the liquid phase (ESI) and from the vapor phase interacting with methanol electrospray (SESI).
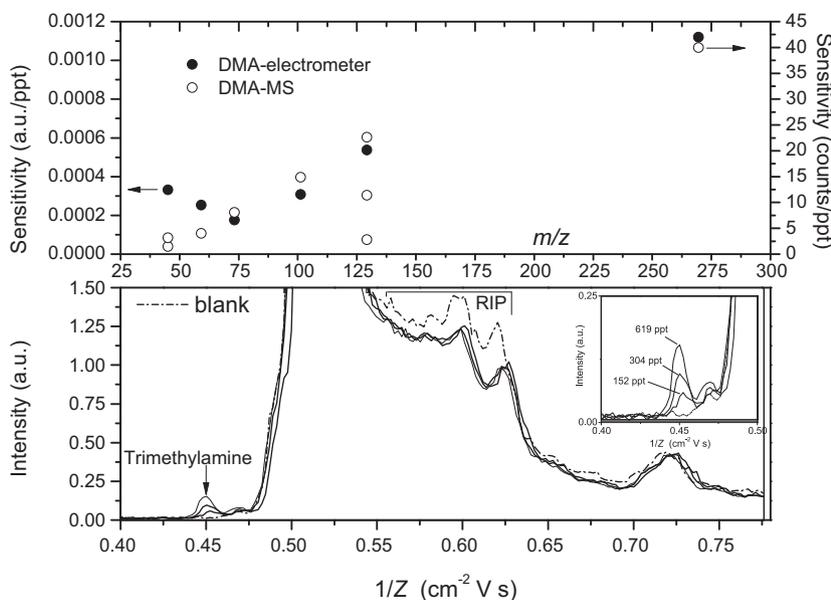
Fig. 5. (Bottom) Mobility spectra of trimethylamine vapors injected at increasing concentrations into a SESI source located at the front-end of a DMA-electrometer system. The enhancement of the peak at $0.45\,cm^{-2}\,V\,s$ is accompanied with a decrease of the reactant ion peaks at lower mobilities in the region of 0.55–$0.62\,cm^{-2}\,V\,s$ for water electrosprays. (Top) The sensitivity measurements repeated for DMA-MS and the stand alone DMA shows that the mass spectrometer discriminates slightly against the lightest species, confirming that the correlation between sensitivity and vapor mass is a mechanistic effect.

This is negated by Fig. 4, even though the vapor concentrations tested were as high as ~3.5 ppb. The presence in SESI of essentially one single peak at the highest mobility – hence corresponding to the bare ion – suggests that the leading mechanism is gas-phase proton transfer reaction between the vapor molecules and ionic species generated from the droplets.

3.3. Experimental vs. theoretical ionization probability

Another observation made during the experiments presented in Fig. 2 is the very different sensitivity (curve slope for a given SESI solvent) for the different amines tested. In consistency with

previous work [17,23], we find a crude correlation between sensitivity and vapor mass.

To confirm that this effect was not biased by a potential discrimination of the mass spectrometer itself in favor of the heaviest species, we conducted similar sensitivity measurements via SESI-DMA-electrometer as detailed in Section 2. The outlet of the DMA is a critical orifice, whereby the ions exit with approximately equal transmission efficiency regardless of their mass. As an example, Fig. 5b (bottom) shows the mobility spectra for the pure acidified water electrospray (blank) and those obtained delivering controlled amounts of trimethylamine. The solvent electrospray is characterized by a number of overlapped peaks over $0.45\,cm^{-2}\,V\,s$, with a maximum in signal intensity at
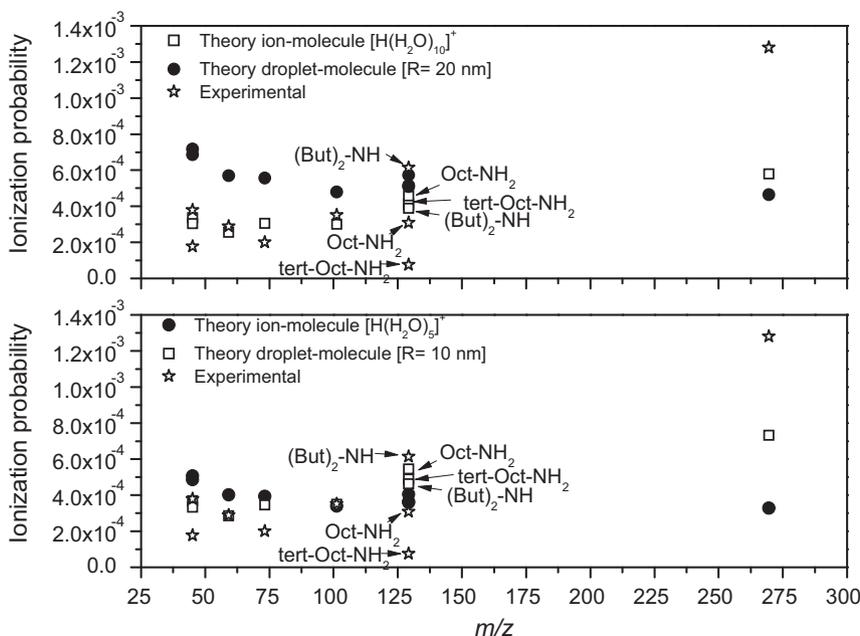

Fig. 6. Comparison of the experimental ionization probabilities against Eq. (1) for collisions of vapors with charging ions or electrospray droplets.

around 0.55 cm^{-2} V s (saturated signal not shown). Upon injection of trimethylamine vapors, a clear peak arises at ~0.45 cm^{-2} V s accompanied with a signal drop in the range of ~0.55–0.62 cm^{-2} V s (labeled as RIP, reactant ion peak).

The top panel in Fig. 5 shows the sensitivity measured with the DMA-electrometer overlapped with that measured with the DMA-MS. It follows that only the lightest vapors ($<m/z$ 75) may be penalized by the mass spectrometer, showing that the increasing sensitivity with mass is a mechanistic effect. We attempted to run the same experiments using MeOH, but confirming our results of Fig. 2, the sensitivity was too low to enable a proper calibration in the linear regime above the background level. Similarly, we could not accomplish the calibration of the less sensitive C8 isomers.

To further discuss these results, we will make use of recent theoretical expressions developed by Fernandez de la Mora [15] to predict ionization probabilities (p_i) of vapors interacting with electrospray clouds:

$$p_i = \frac{n_s}{n_v} = \frac{k\varepsilon_0}{qZ_s} \tag{1}$$

where n_s is the concentration of ionized vapors, n_v is the concentration of neutral vapor, k is the collision rate between the vapor and the charging agents – either droplets (k_d) or ions (k_i), $-\varepsilon_0$ is the vacuum permittivity, Z_s is the electrical mobility of the ionized vapor and q its net charge. Z_s was experimentally measured using as reference the tetraheptyl ammonium and the values are listed in Table 1.

To estimate the ionization probability for ion-molecule reactions (k_i) we computed the collision frequency using the average-dipole-orientation theory [24]:

$$k_i = \left(\frac{2\pi q}{\mu^{1/2}}\right)\left[\alpha^{1/2} + c\mu_D\left(\frac{2}{\pi k_B T}\right)^{1/2}\right] \tag{2}$$

where μ is the reduced mass of the ion–vapor pair, α is the polarizability of the vapor molecule, μ_D is the dipole moment, c is a parameter compensating for the effectiveness of the charge "locking in" the dipole, k_B is the Boltzmann constant and T is the temperature. Table 1 lists the different properties for the amines tested and their resulting collision frequencies. For the calculation we have assumed that the charging ions are of the form $(H_2O)_n H^+$. The average mobility of the charging species in Fig. 4 is 1.7 cm^{-2}/V s (~0.6 cm^{-2} V s). This corresponds ideally (ignoring polarization effects and being the diameter of the neutral gas 0.3 nm) [19] to ions of about 0.9 nm. Assuming that the ejected hydronium ions are spherical and that their density is that of the bulk water ($\rho = 1$ g/mL), we can roughly estimate n to be ~10 water clusters.

In the case where the vapor becomes ionized upon impact with charged droplets, the collision frequency is given by (Eq. (17) in [15]):

$$k_d = R^2 \sqrt{\frac{8\pi k_b T}{m_g}} \tag{3}$$

where T is the gas temperature, R the drop radius and m_g the mass of the carrier gas. To test this model, in the absence of buffer conductivity measurements (which fixes drop radius [25]), R was considered to be 20–10 nm. This is close to the critical size at which ion evaporation occurs [26].

Experimental ionization probabilities can be derived from the measured sensitivity slopes (counts/ppt) as instructed in [6]. Note that the DMA-MS slopes were corrected with the DMA-electrometer measurements from Fig. 5 to account for slight discrimination against the lightest species. The transmission efficiency of the DMA-QTOF system was fixed at to 1.5 × 10^{-4} to estimate the experimental ionization probabilities. Fig. 6 compares the experimental ionization probability with the theoretical values predicted by (1) when the charging agents are solvated ions of the form $[(H_2O)_{10}H]^+$ or charged water droplets (half of the Rayleigh limit) of 20 nm in radius (top), and $[(H_2O)_5H]^+$ ions and droplet of $R = 10$ nm (bottom).

Although quantitatively there may be some uncertainties associated with the actual size of the droplets or the transmission efficiency of the mass spectrometer, the qualitative trends should remain unchanged and are therefore valuable for comparison purposes. The model predicts ionization probabilities of the order 10^{-3}–10^{-4}, but the trends are somewhat opposite: increasing p_i with vapor mass for ion-molecule reactions and decreasing for the capture of vapors in droplets. The experimental values show a closer behavior to that predicted for chemi-ionization, suggesting that this may be the leading mechanism. However, there are some important discrepancies. For example, the experimental correlation of p_i with mass is steeper than that predicted for the model. In addition, Eq. (1) predicts slightly different ionization probabilities for the 3 different C8 isomers tested, stemming mainly from the different electrical mobilities. However, the experimental values depart significantly from this trend, indicating that other effects may be applying. One possible explanation is the steric hindrance exerted by the different nitrogen substituents. For example, we found the lowest sensitivity for tert-octylamine, which in fact presents the nitrogen atom highly hindered by the hydrocarbon group. In the case of octylamine, we speculate that the long hydrocarbon chain may shield the amine group more efficiently than two shorter chains as is the case of dibutylamine. Steric hindrance has been found to have a dramatic impact in chemical ionization [27], thus it is to be expected the same effect if SESI is driven by ion-molecule reactions. It is perhaps counterintuitive to expect such a dramatic steric effect in the case in which the neutral molecule (~1 nm diameter) collides with a droplet with at least 100× its collision cross section (d ~10 nm). For this reason, we are inclined to think that this observation points again towards ion-molecule reactions. Moreover, we tested if the same dramatic responsiveness differences (tert-octylamine < n-octylamine < dibutylamine) would be observed via ESI. The response was comparable for n-octylamine and tert-octylamine and about twice as sensitive for dibutylamine. This is in line with [28], who found a correlation between electrospray response and basicity in solution. This suggests that a gas-phase rather than a solution effect is responsible for the ionization in SESI. This notion is further strengthened by the fact that Mesonero and co-workers [23] found a correlation between explosive mass and sensitivity using methanol electrosprays carrying the analyte vapors through tubing heated at 155 °C. While the exact temperature of the core of the gas is unknown, it was likely well above the boiling point of methanol (65 °C), thereby only ions (and no droplets) could possibly emerge from the capillary's tip.

For all the above, we think that the mechanism of SESI is more similar to APCI than to ESI. This piece of information is obviously welcome to make rationale choices to optimize the different operating conditions. The principles governing gas-phase chemical ionization are well understood, and the choice of the ES buffer should be based on the gas-phase solvent-analyte thermochemistry, rather than for example analyte solubility. Hence, we anticipate a larger analyte coverage using H_2O-based electrosprays than for example MeOH due to the higher gas-phase proton affinity and regardless of the liquid solvating power. However, this prediction should still be validated with a wider range of analytes.

To conclude, it is pertinent to put these results in perspective as compared to other electrospray-based ambient ionization techniques. In particular, with those termed fused-droplet (FD) ESI [29] or a similar technique referred to as extractive ESI (EESI) [30]. The key difference between these techniques and SESI is that the samples are delivered in the condensed-phase (usually in aerosol form),

whereas SESI has been typically restricted to gas-phase analytes. Regardless of the acronym of choice, this seems to be a critical difference because it has been assumed that aerosolized analytes are thought to interact with the charged droplets [29,31], whereas, in view of our results, gaseous analytes seem to be ionized via ion-molecule reactions. As a matter of fact, mechanistic EESI studies have suggested the liquid–liquid extraction pathway [32,33]. However, a recent thorough investigation comparing ESI, EESI and SESI have suggested that perhaps the picture is more complex than initially expected [34]. For example, consistently with our own results, they found significant differences between SESI and ESI. Moreover, the results obtained via EESI resembled more to SESI than to ESI, which led them to conclude that "the mechanism of EESI for volatile amines is dominated by gas-phase charge transfer ionization" (ion-molecule reactions were assumed to be the only one mechanism in SESI). These findings may perhaps lead to the re-evaluation of the role of EESI solvent when the aerosolized sample contains volatile analytes, which is often the case. In support of their results, our work suggests that chemical ionization appears to dominate in SESI and therefore for at least some analytes in EESI. We therefore believe that it would be a conservative approach to keep this in mind when one desires to probe vapors or aerosols (including those containing volatile species), regardless of the acronym of choice to dub the process. This is for example the case of breath analysis. While it is known that breath can carry molecules of negligible vapor pressure such as cytokines [35] that can only be transported as aerosols, the vast majority of the species detected as a result of exhaling towards an electrospray plume have molecular weights well below that of proteins and come as vapors [36]. These compounds are therefore most likely ionized via ion molecule reactions rather than by dissolution and further ESI-like ion production.

4. Conclusions

We have examined the responsiveness of a set of gas-phase amine analytes towards electrospray clouds with the aim to gain insights into the ionization process. We conclude that:

1) Water-immiscible compounds were efficiently ionized via SESI using water-based electrosprays. This discards the postulation in which gas-phase analytes require to be dissolved in the electrospray charged droplets to be ionized.

2) Ionization efficiencies were higher for H_2O than for MeOH (4–6 fold). Even though the reasons behind this best performance for water-based electrosprays remain unclear, this is of practical interest for SESI users at least targeting amino compounds.

3) We found a crude correlation between sensitivity and vapor mass. We compared our experimental probability of ionization results with the theoretical predictions for the ionization of this set of amines by ion molecule reactions and by electrospray nanodroplets. The trend found experimentally is in reasonable agreement with the model for ion-molecule reactions, whereas the predicted trend vapor-mass for vapor-droplet interactions was reversed.

4) We found dramatic differences ($\sim \times 10$) in ionization efficiencies for three isomeric species. We interpret this observation as a result of steric effects, much in the same way as it occurs in chemical ionization. No such dramatic effect was observed when the same samples were electrosprayed from the liquid phase, providing further evidence of the difference of SESI and ESI.

5) DMA-MS analysis of a set of amines ionized either by SESI or ESI revealed different mobility spectra. ESI spectra showed the monomer ion peak along with other features arising at lower mobilities (solvent attached ions or multimers), whereas SESI spectra was dominated by the bare ion peak. We speculate that

this observation, together with those presented above, is more compatible with an APCI-like scenario than with the interaction of vapor-droplets.

6) In view of all the above, we believe that it would be most appropriate to make a distinction when the analytes are delivered to an electrospray plume in vapor form or in the condensed phase. However, as shown in [34], in the latter case it should be taken into account that species with sufficient volatility may escape from the sample aerosol and be ionized via SESI. Our results suggest that in this case ion-molecule reactions may prevail.

Acknowledgements

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