RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

ARTICLE

A Multichannel Rotating Electrospray Ionization Mass Spectrometry (MRESI): Instrumentation and Plume Interactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Ran Qiu[a] , Chengsen Zhang [b]*, Zhen Qin[c] and Hai Luo[a] *

A multichannel rotating electrospray ionization (MRESI) mass spectrometry method is described. It is carried out by rotating three spray emitters infused with the same or different kinds of solvents or solutions. Rotation effect is shown as a critical factor in equalizing the sampling processes from different channels. The interactions of plumes generated from different spray emitters in MRESI has been systematically studied. Due to electrostatic repulsion, liquid fusion of charged droplets from different channels does not occur, while volatile reagents can induce reactions between sprays by vaporizing into neutral gas phase molecules which then extracted by other droplets. When the method is coupled to a laser desorption technique, the desorbed analytes can be post-ionized by multiple electrosprays concurrently, providing a more informative MS detection of a complex sample.

Introduction

Ionization techniques play a pivotal role in mass spectrometry (MS), because successful generation of target ions is prerequisite for subsequent MS detection and characterization. Soft ionization methods, of which typical examples are electrospray ionization[1] (ESI) and matrix-assisted laser desorption/ionization[2] (MALDI), have made direct analyses of large biomolecules *via* MS possible. In the past decade, ambient ionization techniques[3-6], of which typical examples are desorption electrospray ionization[7] (DESI), direct analysis in real time[8] (DART) and paper spray ionization[9,10] (PSI) have made MS analyses almost free from labour-consuming sample preparations and thus tremendously enhanced the analytical throughput of MS. The establishment and continuous upgrading of various multichannel spray arrays are also important achievements made in the past few years.[11] Generally, multichannel spray arrays can be categorized into two groups. If at any one time point, only one emitter generates ions for detection while others either do not spray or the plumes are blocked, this kind of array is named "multiplexed ionization methods"[11-20] (Group I). If all the spray emitters generate ions simultaneously for MS measurement, this kind of array is named "parallel sampling" [21-26](Group II). Historically, group I methods were mainly established to couple capillary electrophoresis (CE) or chromatography separations to MS in a higher throughput way. While group II methods were often used for direct MS analyses (in traditional ESI form or in microfluidic chips[27-31]), which made MS detection more sensitive (by generating larger volume of ion plume), informative (ionizing compounds of various polarity) and/or accurate (by spraying mass standards simultaneously to calibrate mass analyser in real time).

One of the key and fundamental issue in multichannel spray arrays is the interaction of plumes generated from different spray emitters. The understandings of whether the sprayed plumes have and when they have cross-talks in ionization process would undoubtedly give practical instructions on better design and application of ionization techniques that based on multichannel sprayers. The slightly biased sampling due to minor different distances from each spray emitter to the MS inlet is also worth special consideration. In this work, to study the interactions of different plumes generated from parallel spray emitters as well as to establish a more sensitive and informative ionization source, a novel multichannel spray array, named multichannel rotating electrospray ionization mass spectrometry (MRESI), was established. The characteristic feature of our instrument is that the electrospray emitters could rotate co-axially corresponding to the inlet of MS to achieve a parallel sampling from different channels. The effect of rotation on the MS signal from different spray emitters was studied. Volatile and non-volatile compounds were employed to present the cross-talks between the plumes from different emitters. In our previous study of post-ionizing a neutral plume desorbed from a complex sample, by changing the spray solvents, the extracted and ionized molecules were different based on their polarity.[32] In MRESI, our newly built instrument, as different solvents were simultaneously sprayed to post-ionize the neutral sample plume generated from laser desorption, analytical

[a] Beijing National Laboratory for Molecular Sciences, College of Chemistry and Molecular Engineering, Peking University, Beijing, 100871, China. hluo@pku.edu.cn
[b] Department of Chemistry, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana, 46202, United States of America. zhang458@iupui.edu.
[c] Institute of Materials, China Academy of Engineering Physics, Mianyang, PO Box 9071-11, China.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

results with a wealth of chemical information could be obtained. To our best knowledge, this work is among the few contributions[20] to systematically study the plume interactions and the first work to discuss the rotation effect in multichannel spray arrays.

Experimental

1 Chemicals and Sample Preparation

High-performance liquid chromatography (HPLC)-grade methanol and acetonitrile were obtained from Fisher Scientific (Pittsburgh, PA, USA). Thymine, histamine, cytochrome *c*, insulin, hexylamine, heptylamine, octanamine, *m*-nitrobenzyl alcohol and caffeine solution (drug standard) were obtained from Sigma-Aldrich (St. Louis, MO, USA). CsCl, glycerol, acetic acid and formic acid were purchased from Acros Organics (Morris Plains, NJ, USA). Histamine ($\alpha,\alpha,\beta,\beta,$-$d_4$) was obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). Purified water was provided by Hangzhou Wahaha Group (Hangzhou, Zhejiang, China). Senz dark chocolate was obtained from a local market and melted in a water bath at 60 °C before analysis. All chemicals were used as received without further purification. Stock solutions were prepared in methanol and water (1:1, v/v) and diluted to the desired concentration before MS analyses.

2 MRESI setup configurations

Fig 1 shows a schematic illustration of the MRESI-MS experimental setup. All the experiments were performed in positive ion mode on an LCQ Advantage MAX ion trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA) which was modified to accept an external pulsed IR laser and an independent designed MRESI source. The MRESI design shown in Fig 1a is a proof-of-concept prototype, which is equipped with three ESI emitters. The construction of the versatile spray ionization emitters was described in the Electronic Supplementary Information (Fig S1-S2 and illustrations therein). All these emitters and the corresponding injection syringes are mounted on the rotating part of the device. The design of this MRESI setup allows spray solvent to be infused into each spray emitter from a separate injection syringe. In order to control the flow rate, a plane bearing is used to transmit the thrust force of the syringe pump to all the syringes (Fig S1). While the method to contact electrical voltage to the rotating emitters, more specifically, to the spray solvents, is accomplished through the slide contact of a brush and a metal ring surrounding on the rim of the rotating part (Fig S2). The typical flow rate of each spray emitter is 20 µl/h. The horizontal distance from each spray emitter to the MS inlet (*l*) is 10 mm. As shown in Fig 1b, the capillary (50 µm inner diameter) tips of the spray emitters are evenly distributed on the circumference with a diameter of 1 mm. The axis of rotation coincides with the centre of the MS inlet. The rotation speed is continuously adjustable by a stepper motor and is optimized to be 4 revolutions per second (rps) in the following experiments unless otherwise specified.

The optimized mass spectrometric parameters were as follows: spray voltage 6.5 kV, capillary voltage 3.0 V, tube lens offset -50.0 V, heated capillary temperature 150 °C. No nebulizing gas was used. The full-scan was carried out in the range of m/z 50-2000 with an ion accumulation time of 30 ms. All data were processed using the instrument software (Xcalibur version 1.4 SR1). Each mass spectrum was the average result in 1-2 min.

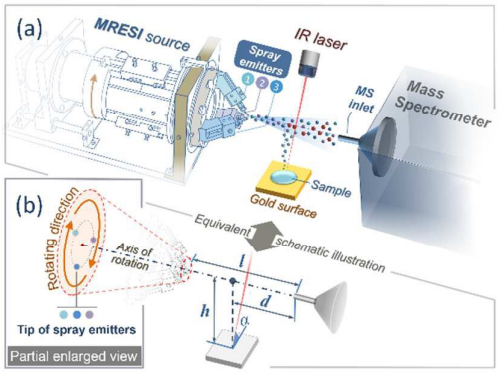

Fig 1. (a) Schematic illustration of the MRESI-MS system coupled with laser desorption technique. (b) Insert displaying partial enlarged view of the motion mode and relative position of the spray emitter tips and the axis of rotation.

In the experiments of coupling the MRESI-MS with a laser desorption system, all the parameters listed above were kept the same. Wet samples were loaded on a gold sample plate 15 mm below the rotation axis (*h*) and desorbed immediately by the Nd:YAG laser (Lai Yin Opto-Electronics Technology, Beijing, China) with 1064 nm at 20 Hz pulse rate. The laser energy was set to 1.1 mJ/pulse. The sample was irradiated at 45° incidence angle (α), and the illuminated spot was 7 mm horizontal from the MS inlet (*d*). The neutral plume desorbed by the laser can be post-ionized by one or up to three electrosprays of the MRESI source with the same or different solvents/solutions.

3 Optimization of spray voltage and flow rate

During the optimization of spray voltage, 10 ppm caffeine solution was infused to all three channels of the MRESI setup and the rotation speed was set at 4 rps. The rotation speed had very little impact on the signal intensity in the range (1-6 rps) we studied.

In MRESI, a stable spray could be observed when the spray voltage was set between 5.5 kV and 7.0 kV. As show in Fig 2a, on the occasion of both static and rotation, the signal intensity increased steadily as the spray voltage increased. A high spray voltage can increase the surface charge density of the electrospray droplets[33, 34], and thus increasing the ionization efficiency. Discharge may occur at higher voltages, resulting in unsteady or even no signals. The spray voltage of 6.5 kV was selected for the following MRESI experiments. It is higher than most ESI and ESI-based techniques (typically 3-5 kV). We presume that as the number of ESI emitters

increase, the electric field at each tip of the ESI emitters becomes deformed.[35] Therefore, the voltage required for the steady spray increases.

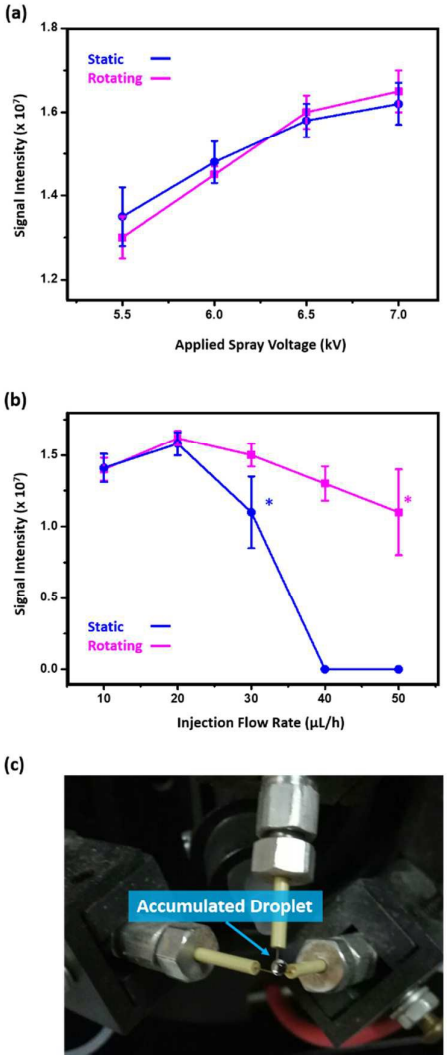

Fig 2 Caffeine solution (10 ppm) was analyzed by MRESI under static (blue) and rotating (pink) conditions. (a) Optimization of spray voltage. (b) Optimization of flow rates "*" denotes under this flow rates and higher, accumulated droplet would form and the MS detection would then be interrupted. (c) Picture taken with an accumulated droplet. Error bars indicate standard deviations in 6 repetitive experiments.

When the emitters were static, and the flow rate became higher, due to the size of the micro-droplets in the plumes became larger, a droplet of liquid would accumulate at the tip end of the parallel emitters (Fig 2c). Once such accumulated droplet formed, no MS signal could be obtained. As shown in Fig 2b, rotation can partially prevent such phenomenon *via* mechanical movement. Under static condition, when the flow rate was 30 μl/h, occasionally accumulated droplet was obtained and the MS signals were absent. When the flow rate was higher than 30 μl/h, it was more frequent to obtain such accumulated droplet, which made continuous MS detection impossible. Under rotating condition, slightly higher flow rates (30 and 40 μl/h) were applicable, but much higher flow rates could also lead the formation of the accumulated droplet and then stop the ionization process. The results show our instrument can operate at slightly higher flow rates in rotating mode than in static mode.

4 Optimization of rotation speed

The photograph of the MRESI setup (forepart) is shown in Fig 3a. All tips of the spray emitters are toward the extension capillary of the MS inlet. The light scattering of the ESI plume generated by all three spray emitters helps to track the trajectories of the plumes. Gaps among electrosprays due to their electrostatic repulsion could be obvious under both static condition (Fig 3b) and rotating condition (Fig 3c). This phenomenon results in a sampling difference from different channels under static conditions. Although the positions of spray emitter tips are carefully adjusted, their ESI plume is still off-axis corresponding to the MS inlet, as shown in Fig 3b, probably affected by environmental factors (such as random gas flow in ambient atmosphere, or by the deformation of the overall electric filed). Under rotating condition, however, all tips of three spray emitters move exactly on the same trajectory, thus exchange the positions of their ESI plume quickly. Thus, the off-axis of the ESI plume will not affect the sampling process from different channels.

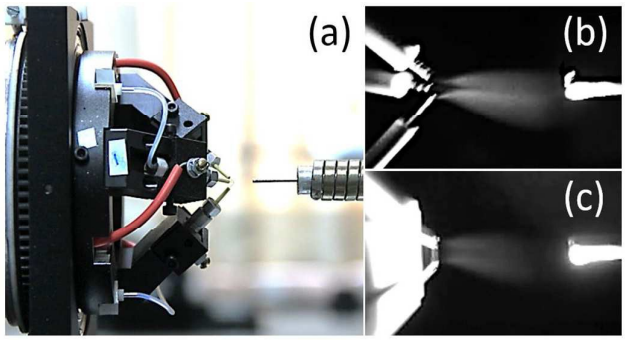

Fig 3 (a) Picture of the spray emitters in the MRESI setup. The tips of emitters are toward the extension capillary of the MS inlet. Pictures of ESI plumes taken under (b) static condition and (c) rotational condition.

The rotation effect was shown to have a significant impact on the sampling of analytes from different channels. In the initial experiment, two of the emitters were employed and infused with histamine (HIM) and deuterated histamine (HIM-d4) solutions of the same concentration. In comparison of the mass spectra obtained under static and rotating conditions, we found that rotating the spray emitters was beneficial to equalize the sampling efficiencies from different sprays. As shown in Fig 4, under static condition, the TIC was most contributed by $[HIM+H]^+$ (m/z 112) with minor contribution from $[HIM\text{-}d_4+H]^+$.(m/z 116). The intensity ratio

of $[HIM+H]^+$/$[HIM\text{-}d_4+H]^+$ was about 7. This phenomenon can be explained by the electric force deforming the cone at the tip of the capillary nozzle, which made one of the spray plumes travel off-axis trajectory regarding the MS inlet. When we switched it to rotating condition, a dramatic change of both the EICs of $[HIM+H]^+$ and $[HIM\text{-}d_4+H]^+$ could be observed, resulting in an approximately equal intensity ratio of $[HIM+H]^+$ / $[HIM\text{-}d_4+H]^+$. As shown in Fig 4b, the 1 min average mass spectrum indicated the equalized sampling for both $[HIM+H]^+$ and $[HIM\text{-}d_4+H]^+$ under rotation condition.

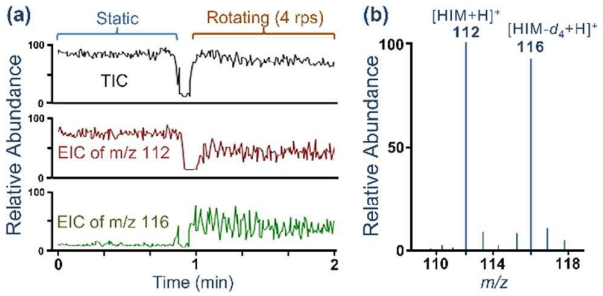

Fig 4 (a) Total ion chromatogram (TIC), extracted ion chromatogram (EIC) of HIM (m/z 112) and HIM-d_4 (m/z 116) obtained by MRESI-MS under static and rotating conditions. (b) Averaged mass spectrum of HIM and HIM-d_4 obtained in 1 min. HIM and HIM-d_4 were sprayed from two ESI emitters in MRESI, respectively.

We further employed all three emitters to study the influence of rotation speed. In one case, we observed the signal intensity of an analyte from one emitter, while the other two emitters infused with spray solvent. As shown in Fig 5a, the signal intensity of protonated octanamine (m/z 130) was stable under rotation speeds from 1 to 6 rps, which means the rotation speed had very little impact on the signal intensity of the analyte from each emitter. In another case, 1 ppm hexylamine, heptylamine, and octanamine were sprayed from three channels of MRESI. Fig 5b shows their relative abundance under different rotation speed. Once started to rotate, the relative abundance of $C_6H_{13}NH_3^+$ (m/z 102), $C_7H_{15}NH_3^+$ (m/z 116), and $C_8H_{17}NH_3^+$ (m/z 130) obtained were nearly the same. Although a higher rotation speed may provide a closer sampling rate among channels, we set the rotation speed at a moderate 4 rps in most of our experiments considering about the physical deterioration of mechanical parts in MRESI at high rotation speed.

The effect of rotation on equalizing the sampling efficiency of different channels can be readily explained from the design of the MRESI device (Fig 1b). Ideally, as the tips of all three spray emitters follow a motion mode similar to a conical pendulum, they move along the same trajectory. In other words, the tips cover the same positions after they move one or more cycle(s), and thus on average they transmit approximately the same amount of ions to the MS inlet in a given period of time. In addition, the averaged mass spectra were not obviously affected by the rotation speed, as the time for averaging a mass spectrum (more than 30 s) could cover dozens of circles even the rotation speed was as low as 1 rps. This special feature of rotation which can eliminate the minor position differences between the tips of spray emitters sets the MRESI source apart from all the static multichannel electrospray ion sources.

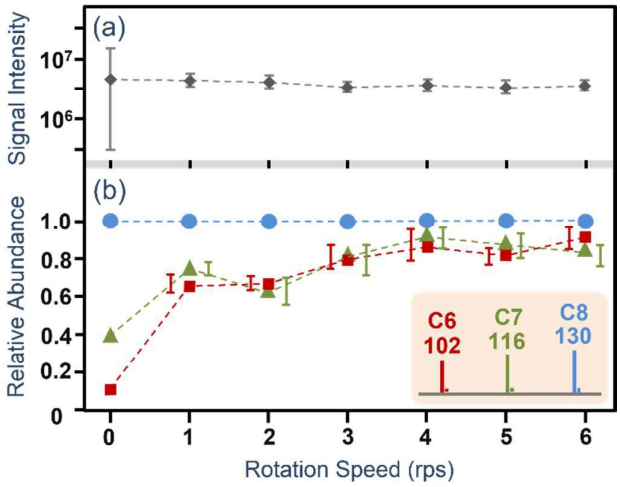

Fig 5. The effect of rotation speed on the MRESI MS signal intensity. (a) One channel of MRESI was infused with 1 ppm octanamine and the other two channels were infused with MeOH/water (1:1, v/v); (b) The three channels of MRESI were infused with 1 ppm hexylamine (red squares), heptylamine (green triangles) and octanamine (blue circles), respectively. The changes of the relative signal abundances of the three amines with the rotation speed. Insert: The averaged mass spectrum when the rotation speed is 4 rps.

Results and Discussions

In MRESI-MS, as the plumes generated from different channels coexisted in the space between the instrument and the MS inlet, the interactions between (among) them should be a serious issue. This potential interaction or reaction was investigated by several experiments, and the verification method was to detect whether the product of the reaction could be obtained in MRESI-MS analyses. During the desolvation process in ESI, charged droplets, gas phase molecules and ions coexisted before entering the mass spectrometer. Here, the possible reactions under MRESI condition, such as liquid phase reaction caused by fusion of spray droplets and gas phase ion-molecular reaction during the desolvation process were tested. Note that ESI process is on milliseconds time scale, the feasibility of all the chosen reaction systems has been successfully demonstrated using other ESI based ionization method, such as LDSPI[32, 36], reactive-DESI[37] or nanoESI from theta-shaped capillaries

[38, 39]. The effects of rotation on each occasions were discussed accordingly.

1 Plume Interactions When Non-Volatile Reagents Analyzed

We investigated the interactions between plumes generated from different parallel emitters in MRESI through a rapid noncovalent interaction, *i.e.* the formation of magic number clusters. In our previous work, the formation of different thymine (denoted as T) quintets had been successfully probed by LDSPI-MS and reactive-DESI-MS. For example, in LDSPI-MS experiment, 100 μL thymine solution (100 ppm) was deposited on the substrate plate, and irradiated by IR-laser. A neutral plume was generated from laser desorption and it would be post-ionized by an ESI plume, which was sprayed from 100 ppm CsCl solution. As shown in Fig 6a, the base peak at m/z 762 was identified as the $[T_5+Cs]^+$, indicating the formation of thymine quintet. While in Fig 6b, the MRESI mass spectrum was obtained by spraying 100 ppm CsCl and 100 ppm thymine in two separate ESI emitters. The ions Cs^+ and $[T_5+NH_4]^+$ could be observed, but not $[T_5+Cs]^+$ ion. Under static conditions, the ratio of m/z 133 and m/z 647 deviates largely in repeated experiments (from about 5 to as high as 20), while under rotating condition, such ratio become stable and close to 1 regardless of minor environmental fluctuations. Fig 6c shows an overlaid ESI mass spectrum of CsCl solution and thymine. In comparison of Fig 6b and Fig 6c, the mass spectrum recorded in MRESI was identical to that overlaid ESI mass spectrum, indicating that the plumes generated from different spray emitters in MRESI have almost no cross-talks in this condition.

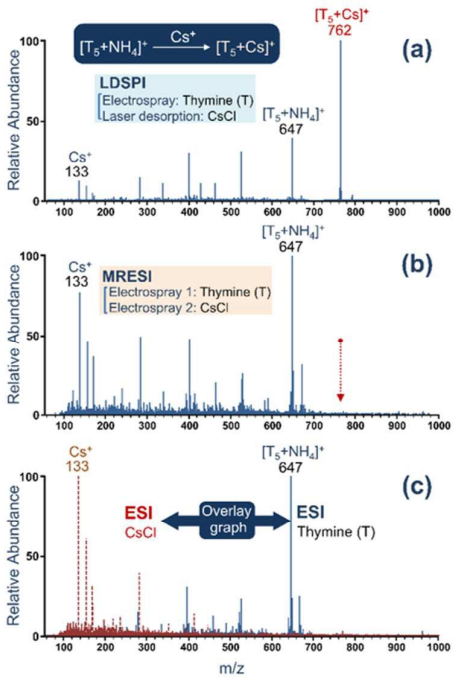

Fig 6 (a) LDSPI mass spectrum obtained by laser desorption of deposited CsCl solution and post-ionized by ESI plume of thymine (T) solution. (b) MRESI mass spectrum obtained by spraying CsCl and T solutions via two ESI emitters, respectively. (c) Overlaid ESI mass spectra when CsCl and T separately analyzed.

In LDSPI, microdroplets in the neutral plume from laser desorption could coalesce with the microdroplets in the charged plume of ESI. Subsequently, the "picked-up" analytes would be ionized in the fused microdroplets through the mechanism of ESI. In MRESI, however, charged microdroplets from parallel emitters would not mix due to electrostatic repulsion. No formation of magic number cluster $[T_5+Cs]^+$ was a direct evidence to support this statement. The results here demonstrated that when non-volatile reagents were analyzed in multichannel spray emitters, the effect of cross-talks could be neglected.

Charge state distribution (CSD) of proteins[40-42] in ESI based MS analyses is an important topic in proteomics. Several non-volatile compounds can induce "supercharging effect" [43-46]in ESI, which make proteins or peptide hold more charges than usual. We also employed supercharging reagents in MRESI experiments. As shown in Fig S5, supercharging reagents (glycerol, *m*-nitrobenzyl alcohol) and denatured cytochrome *c* were separately sprayed from two emitters, no supercharging effect could be observed in the spectra. These results again support our statement that non-volatile reagents would not cause cross-talks in MRESI.

2 Plume Interactions When Volatile Reagents Analyzed

The CSD changes of proteins in ESI-MS can indicate the structural changes of proteins and recent nanoESI experiments via theta-shaped capillaries[38, 39] re-affirmed the protein folding and unfolding could happen in milliseconds. To test the interaction of plumes in MRESI, protein denaturation by volatile acid was chosen as the example. As shown in Fig 7a, when one emitter sprayed cytochrome *c* solution (10 ppm) and another emitter sprayed pure solvent (1:1, MeOH/water), protein ions with +7, +8 and +9 charges were significant in the mass spectrum. When added 0.1% formic acid in the spray solvent, in addition to protein ions with +7, +8 and +9 charges, ions with charges from +10 to +15 could also be observed (Fig 7b). Similar spectra were obtained under both static and rotating conditions. This result indicated cytochrome *c* was partially denatured (unfolded) in the MRESI process. Similar results when insulin was used as the analyte were described in Fig S3. In LDSPI, cytochrome *c* solution was deposited on the substrate plate, and spray solvent with 0.1% formic acid was sprayed to generate post-ionization plume. The resulting mass spectrum was shown in Fig 7c, besides +7, +8 ions corresponding to folded protein configuration, a sigmoidal pattern of ions with charges from +11 to +17 could be seen, which indicated the proteins here wre more severely denatured than those in MRESI.

The results above demonstrated that when volatile reagents were analyzed in multichannel spray array, the cross-talks between plumes generated from parallel emitters could be a serious issue. Although the charged microdroplets generated from different spray emitters would not mix during MRESI process, volatile reagents, such as formic acid in this example, would become gas phase molecules and adsorbed by other microdroplets. Subsequently, the adsorbed molecules would induce reactions, such as protein denaturation. To confirm this proposed route, another way to

introduce pure gas phase formic acid into MRESI spray plumes was tried and also caused protein denaturation (Fig S4). Note that the gas phase transition route was less efficient in terms of mass transferring than direct coalescence of microdroplets which happened in LDSPI. This statement could be verified by the fact that protein denaturation in MRESI was much less complete than that in LDSPI. The results demonstrated that in multichannel spray arrays, both under static and rotating condition, when volatile and reactive reagents were analyzed, cross-talks between (among) different spray emitters should be considered.

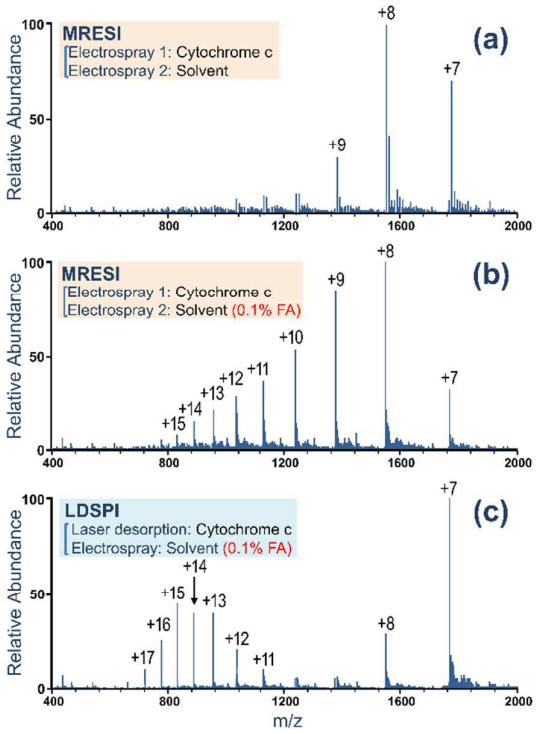

Fig 7 (a) MRESI mass spectrum obtained by spraying cytochrome *c* and empty solvent (1:1, MeOH/water), respectively, in two ESI emitters. (b) MRESI mass spectrum obtained by spraying cytochrome *c* and 0.1% formic acid solution, respectively, in two ESI emitters. (c) LDSPI mass spectrum obtained by laser desorption of deposited cytochrome *c*, then post ionized by ESI plume which 0.1% formic acid solution was sprayed.

3 Analyses with Different Solvents as Post-ionization Sprays

One advantage of multichannel spray arrays was when solvents of various polarity were used to generate post-ionizing sprays, analytes of various polarity could be simultaneously extracted in the charged ESI plume, ionized and detected by MS. Previously, in laser desorption dual-spray post-ionization[32] (LDDPI) MS, less polar acetonitrile and more polar 1:1 MeOH/water were used as solvents in ESI post-ionization plumes to selectively extract and ionize less polar lipids and more polar carbohydrates, respectively. In MRESI coupled to laser desorption (LD-MRESI), melted chocolate was chosen as the sample, and it was desorbed by laser to generate neutral plume for post-ionization. When both acetonitrile and 1:1 MeOH/water were simultaneously sprayed from two emitters, both lipids and carbohydrates could be extracted and ionized (Fig 8a). When only acetonitrile was sprayed, only less polar lipids could be detected by MS (Fig 8b). When only 1:1 MeOH/water was sprayed, only more polar carbohydrates could be detected by MS (Fig 8c). In LDDPI, a simple switch step was needed to change from one solvent (or solution) to another. So the MS signals corresponding to different polarities could only be obtained *quasi-simultaneously*. When two emitters sprayed at one time (which is similar to MRESI operated under static condition), signals from either one spray could be obtained, while signals from the other spray were absent. Which spray "masked" the other one depends on the positions of the two emitters relative to the MS inlet. Under this occasion, simultaneous sampling and ionization by different sprays were not applicable. However, LD-MRESI (under rotating condition) can *simultaneously* detect multiple components extracted and ionized by different sprays in one step (Fig 8a).

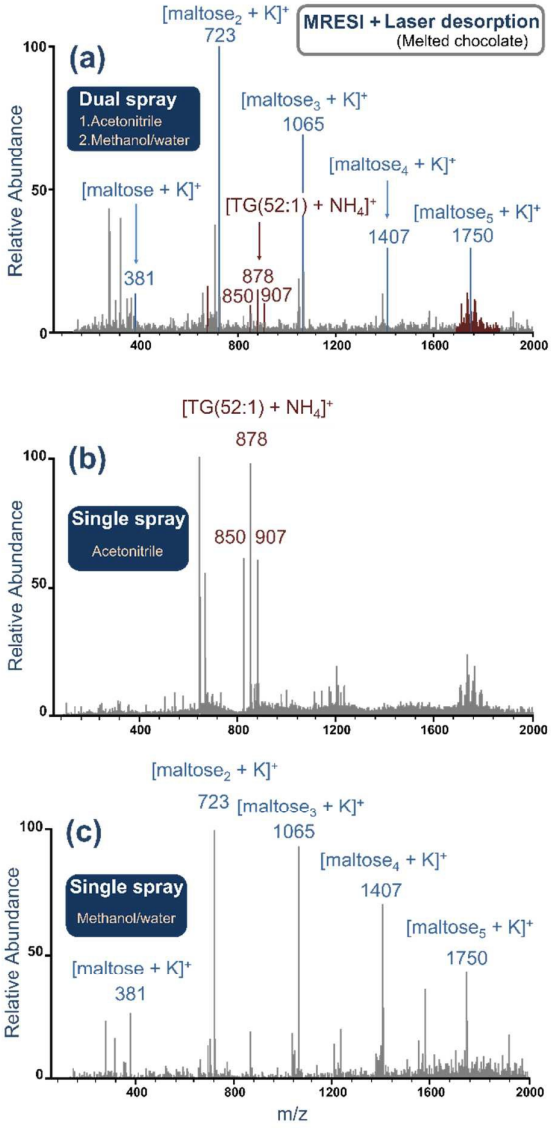

Fig 8 LD-MRESI for analysis of a real sample (melted chocolate). (a) When both acetonitrile and 1:1 MeOH/water were simultaneously used as post-ionization plumes. (b) When acetonitrile was used as post-ionization plume. (c) When 1:1 MeOH/water was used as post-ionization plume.

Conclusions

In conclusion, a novel multichannel spray array, named multichannel rotating electrospray ionization (MRESI) was established. Key parameters, such as applied high voltage, flow rate and rotation speed, were optimized to offer the best analytical performance. Rotation could make plumes from different spray emitters much more evenly distributed in the space between MRESI instrument and MS inlet. This feature has made sampling among different spray emitters more equalized. Through proof-of-principle examples of magic number clusters formation, supercharging effect and protein denaturation, the interactions of plumes generated from different spray emitters were studied. Due to electrostatic repulsion among charged micro-droplets, when non-volatile reagents were analyzed, cross-talks among spray emitters could be neglected. While volatile reagents were analyzed, potential cross-talks should be considered and avoided if necessary (*e.g.*, by using alternative non-volatile substitutes). This conclusion would be instructive to future designs and applications of advanced multichannel spray arrays. When solvents of different polarity were simultaneously used in MRESI as post-ionization sprays to ionize laser desorbed neutral plume, analytes of different polarity could be detected by MS in one step. Being a more informative and higher throughput ionization method compared to both LDSPI and LDDPI, LD-MRESI has been demonstrated to be a potent analytical tool to analyze real samples.

Acknowledgements

The financial support from the National Natural Science Foundation of China (nos. 20727002 and 21075005), and the NSFC Funding (21445005) were acknowledged.

Notes and references

1 J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong, C. M. Whitehouse, *Science* **1989**, 246, 64-71.
2 R. Abate, A. Ballistreri, G. Montaudo, D. Garozzo, G. Impallomeni, G. Critchley, K. Tanaka, *Rapid Commun Mass Spectrom* **1993**, 7, 1033-1036.
3 G. A. Harris, A. S. Galhena, F. M. Fernandez, *Anal Chem* **2011**, 83, 4508-4538.
4 L. P. Li, B. S. Feng, J. W. Yang, C. L. Chang, Y. Bai, H. W. Liu, *Analyst* **2013**, 138, 3097-3103.
5 R. G. Cooks, Z. Ouyang, Z. Takats, J. M. Wiseman, *Science* **2006**, 311, 1566-1570.
6 R. G. Cooks, A. K. Jarmusch, C. R. Ferreira, V. Pirro, *Proc Natl Acad Sci USA* **2015**, 112, 5261-5262.
7 Z. Takats, J. M. Wiseman, B. Gologan, R. G. Cooks, *Science* **2004**, 306, 471-473.
8 R. B. Cody, J. A. Laramee, H. D. Durst, *Anal Chem* **2005**, 77, 2297-2302.
9 H. Wang, J. Liu, R. G. Cooks, Z Ouyang, *Angew Chem Int Ed* **2010**, 49, 877-880.
10 C. Zhang, N. E. Manicke, *Anal Chem* **2015**, 87, 6212-6219.
11 C. J. Chen, F. A. Li, G. R. Her, *Electrophoresis* **2008**, 29, 1997-2003.
12 L. Leclercq, C. Delatour, I. Hoes, F. Brunelle, X. Labrique, J. Castro-Perez, *Rapid Commun Mass Spectrom* **2005**, 19, 1611-1618.
13 D. Morrison, A. E. Davies, A. P. Watt, *Anal Chem* **2002**, 74, 1896-1902.
14 F. Foret, P. Kusy, *Electrophoresis* **2006**, 27, 4877-4887.
15 Q. F. Xue, F. Foret, Y. M. Dunayevskiy, P. M. Zavracky, N. E. McGruer, B. L. Karger, *Anal Chem* **1997**, 69, 426-430.
16 L. Y. Yang, T. D. Mann, D. Little, N. Wu, R. P. Clement, P. J. Rudewicz, *Anal Chem* **2001**, 73, 1740-1747.
17 H. H. Liu, C. Felten, Q. F. Xue, B. L. Zhang, P. Jedrzejewski, B. L. Karger, F. Foret, *Anal Chem* **2000**, 72, 3303-3310.
18 V. de Biasi, N. Haskins, A. Organ, R. Bateman, K. Giles, S. Jarvis, *Rapid Commun Mass Spectrom* **1999**, 13, 1165-1168.
19 L. Fang, J. Cournoyer, M. Demee, J. Zhao, D. Tokushige, B. Yan, *Rapid Commun Mass Spectrom* **2002**, 16, 1440-1447.
20 T. Nissila, N. Backman, M. Kolmonen, A. Leinonen, A. Kiriazis, J. Yli-Kauhaluoma, L. Sainiemi, R. Kostiainen, S. Franssila, R. A. Ketola, *Int J Mass Spectrom* **2012**, 310, 65-71.
21 J. Shiea, D. Y. Chang, C. H. Lin, S. J. Jiang, *Anal Chem* **2001**, 73, 4983-4987.
22 J. T. Shia, C. H. Wang, *J Mass Spectrom* **1997**, 32, 247-250.
23 C. M. Hong, F. C. Tsai, J. Shiea, *Anal Chem* **2000**, 72, 1175-1178.
24 S. Q. Su, G. T. T. Gibson, S. M. Mugo, D. M. Marecak, R. D. Oleschuk, *Anal Chem* **2009**, 81, 7281-7287.
25 B. B. Schneider, D. J. Douglas, D. D. Y. Chen, *Rapid Commun Mass Spectrom* **2002**, 16, 1982-1990.
26 L. F. Jiang, M. Moini, *Anal Chem* **2000**, 72, 20-24.
27 X. J. Feng, B. F. Liu, J. J. Li, X. Liu, *Mass Spectrom Rev* **2015**, 34, 535-557.
28 S. M. Miladinovic, L. Fornelli, Y. Lu, K. M. Piech, H. H. Girault, Y. O. Tsybin, *Anal Chem* **2012**, 84, 4647-4651.
29 Y. F. Li, N. Zhang, Y. M. Zhou, J. N. Wang, Y. M. Zhang, J. Y. Wang, C. Q. Xiong, S. M. Chen, Z. X. Nie, *J Am Soc Mass Spectrom* **2013**, 24, 1446-1449.
30 Y. Lu, F. Liu, N. Lion, H. H. Girault, *J Am Soc Mass Spectrom* **2013**, 24, 454-457.
31 L. P. Mark, M. C. Gill, M. Mahut, P. J. Derrick, *Eur J Mass Spectrom* **2012**, 18, 439-446.
32 J. Liu, C. S. Zhang, J. M. Sun, X. X. Ren, H. Luo, *J Mass Spectrom* **2013**, 48, 250-254.
33 D. B. Hager, N. J. Dovlchl, J. Klassen, P. Kebarle. *Anal Chem* **1994**, 66, 3944-3949.
34 R. L.Grimm, J. L. Beauchamp. *J Phys Chem B* **2003**, 107, 14161-14163.
35 Y. Tatemoto, R. Ishikawa, M. Takeuchi, T. Takeshita, K. Noda, T, Okazaki. *Chem Eng Technol* **2007**, 30, No. 9, 1274-1279.
36 J. Liu, B. Qiu, H. Luo, *Rapid Commun Mass Spectrom* **2010**, 24, 1365-1370.
37 Z. Qin, J. Liu, B. Qiu, H. Luo, *J Mass Spectrom* **2012**, 47, 552-554.
38 D. N. Mortensen, E. R. Williams, *Anal Chem* **2015**, 87, 1281-1287.
39 C. M. Fisher, A. Kharlamova, S. A. McLuckey, *Anal Chem* **2014**, 86, 4581-4588.
40 S. K. Chowdhury, B. T. Chait, *Biochem Bioph Res Commun* **1990**, 173, 927-931.
41 A. T. Iavarone, E. R. Williams, *J Am Chem Soc* **2003**, 125, 2319-2327.
42 A. Kharlamova, J. C. DeMuth, S. A. McLuckey, *J Am Soc Mass Spectrom* **2012**, 23, 88-101.

43 A. T. Iavarone, E. R. Williams, *J Am Chem Soc* **2003**, 125, 2319-2327.
44 A. T. Iavarone, J. C. Jurchen, E. R. Williams, *J Am Soc Mass Spectrom* **2000**, 11 (11), 976-985.
45 A. T. Iavarone, J. C. Jurchen, E. R. Williams, *Anal Chem* **2001**, 73 (7), 1455-1460;
46 A. T. Iavarone, E. R. Williams, *Int J Mass Spectrom* **2002**, 219 (1), 63-72.

ESI needs to move! A multichannel rotating electrospray ionization (MRESI) mass spectrometry method is described. Plume interactions are also systematically studied.