Cluster and protein nanoparticle studies with a bipolar electrospray source and high resolution tandem mobility analysis

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Aerosol Technology, Bilbao, 18/June/2018
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- Electrospray as a source of clusters and nanometer particles, and its limitations
- Charge reduction
- Bipolar Electrosprays as a clean source of clusters
- Bipolar electrospray as a source of proteins
- Efforts to develop a DMA for high resolution analysis of viral particles by extending the size range to 100 nm without degrading resolution
- Producing monodisperse particles of several (or many) nm to characterize the viral analyzer
- Bipolar electrospray as a source of polymer ions
- Some useful features of another high resolution DMA: The half-Mini DMA
- Semiconducting outlet and the transmission problem (Atoui, Bezantakos-Biskos)
- Wider size range via axisymmetric inlet
- Fast response time — Quick spectral acquisition; kinetic studies, DMA²
- Parallel plate DMAs: high inlet transmission; freezing of fast kinetics, etc.
- Emulating the triple quadrupole at atmospheric pressure: DMA-Oven-DMA
The readily recognizable and interpretable clusters produced by electrosprays are very few due to multiple charging:
From salt \((A^+B^-)\), clusters \((A^+B^-)^n(A^+)^z\)

- Mobility spectrum
- tandem mobility-mass spectrum
Eliminating (or reducing) the complication of multiple charges

• Charge reduction of the \((A^+B^-)_n(A^+)_z\) series via a radioactive source or other charge reducing ions produces clusters with numerous impurities due to lack of control of the neutralizing ions

• Charge reduction with controlled clusters \((A^+B^-)_n(B^-)_z\) produced by a negative electrospray of the same salt \((A^+B^-)\) would be more effective as it yields clusters of the form \((A^+B^-)_nA^+\) or \((A^+B^-)_nA^-\) and perhaps a smaller proportion of multiply charged clusters

• We have accordingly develop a bipolar electrospray source to do so
Bipolar electrospray source of singly charged particles

Almost exclusively simply charged clusters: \((A^+B^-)_nA^+\) or \((A^+B^-)_nA^-\)
Charge reduction of electrosprayed biomolecules or other polymers

- Positive electrospray: SAMPLE. Water with 25-100 mM of completely volatile salt (ammonium acetate, triethyl ammonium formate, etc.)

- Negative electrospray (neutralizing ions): alcohol with 25-100 mM of completely volatile salt (ammonium acetate, triethyl ammonium formate, etc.)

- Practical difficulty of water ES handled with very small tips (~15 \( \mu \text{m} \))

Immunoglobulin G: IgG

- \( \sim 8 \text{ nm diameter} \)

Control charge reduction level via position of negative spray
Size-analysis of viral particles at the maximal possible resolution for infection diagnosis

• Prior DMA work with ES-charge reduction-ES: Substantial literature: Zachariah’s group, Biswas-Hogan, etc., with TSI’s GEMMA.
• Similar studies by Zymansky, Almaier with TSI and Reischl DMA
• With best DMA conditions and very clean viral samples, FWHM (mobility) may be as small as ~4%
• Recent work by Jarrold et al. (Indiana) shows viral mass distributions as narrow as 2%. Remarkable progress as charge and mass/charge distributions need to be measured with high accuracy.
• Corresponding mobility distribution should be even smaller than 2%. Our goal is to determine how narrow this distribution is in practice.
Requirements

• Techniques for effective cleaning of viral particles: These exist as demonstrated in MS work by Heck and colleagues and Jarrold and colleagues, and also (probably) by various authors for DMA analysis (Wick, Almaier, Zachariah, etc.)

• A DMA of high resolving power, ideally with intrinsic FWHM<2-3%, with a size range from 20-70 nm. This will be discussed by Perez Lorenzo on Tuesday

• In addition to an excellent DMA, we need a narrow size standard of ~10-100 nm particles
Large size standard from salt clusters via Tandem DMA
Size standard from polymers (Poly-PEG 8k) via bipolar electrospray source

- Negative spectrum ~13% of positive.
- Interesting simplified approach to study charging probability
Tandem DMA size standard from Poly-PEG-8k

- Peak width FWHM ~4.5%
The transfer function of the TDMA is considerably wider than that of either of the two separate DMAs connected in tandem

- Let the response function of the first and second DMAs be governed by Brownian diffusion (Gaussian)
  \[ \left( \frac{a}{\pi} \right)^{1/2} \exp\left[ -a(Z-Z_1)^2 \right], \left( \frac{b}{\pi} \right)^{1/2} \exp\left[ -b(Z-Z_1)^2 \right], \]  \( (1) \)

- The TDMA response is the convolution:
  \[ \int_{-\infty}^{\infty} dZ \left( \frac{a}{\pi} \right)^{1/2} \exp\left[ -a(Z-Z_1)^2 \right] \left( \frac{b}{\pi} \right)^{1/2} \exp\left[ -b(Z-Z_2)^2 \right], \]  \( (2a) \)

- which is itself the Gaussian
  \[ \left[ \left( \frac{c}{\pi} \right)^{1/2} \exp\left[ -c(Z-Z_1)^2 \right] \right]; \ c=ab/(a+b). \]  \( (2b) \)

- (2) implies that the composite FWHM of the tandem DMA is:
  \[ \text{FWHM}_{1-2}=( \text{FWHM}_1^2 + \text{FWHM}_2^2 )^{1/2}. \]  \( (3) \)

- if \( \text{FWHM}_1 = \text{FWHM}_2 = 3\% \), then \( \text{FWHM}_{1-2} = 4.24\% \)
Conclusion on producing narrow size standards to characterize high resolution viral DMA

• Tandem DMA selection of monomobile ionic liquid clusters as large as may be isolated (or deconvoluted) from neighboring clusters appears as the best option available to certify resolving powers >33; perhaps as high as 40 or 50.
Requirements for a DMA of high resolving power and wide size range (1-70 nm)

• Upper size range: resolution $< q/Q$

$$Z_{min} = Rq \frac{\ln(R_2/R_1)}{2\pi LV_{max}}$$

• Length $L > 10$ cm

• Good centering of electrodes

• Ideal response at moderate flow rates

• Large sheath gas flow rate: If $q = 1.5$ lpm and $\text{Res} = 50$, then $Q > 75$ lpm
Ideal response at moderate sample/sheath flow rates $q/Q$

- A substantially non-ideal response observed in half-Mini DMA at $q/Q > 0.02$.

- Resolved via symmetric aerosol entry
Could established long DMAs achieve the desired resolution? Lessons from TSI’s 3071 (long) DMA.

- Q max too small, as transition to unsteady or turbulent flow sets in at 30-40 lpm (a).
- Problem removed by avoiding unnecessary discontinuities at laminarization screens (b).
- Apparently no solution without laminarization trumpet.

IgG protein: monomer, dimer, trimer
A new instrument needs to be developed for viral analysis at high resolution

• Perez DMA to be described Tuesday by L.J. Perez-Lorenzo
Some recent developments in the Half-Mini DMA

• Semiconducting outlet for high transmission
• Axisymmetric aerosol sample inlet (ALREADY DISCUSSED)
• Fast measurements, and the importance of an ideal and fast response for distorsion reductions
• The DMA-fragmentation-DMA analog of the triple quadrupole mass spectrometer
Safe operation and good transmission with a semiconductor outlet

- Bezantakos, Andreas, Biskos, Attoui
How fast can one scan a DMA?

- Given a fast detector, and an ideal DMA response, the peaks remain narrow upon fast scanning. They are just linearly displaced.
- However, non-ideal DMA response results in peak broadening.

\[ V \rightarrow V - \Delta t(dV/dt) \]
Why not small and hand-held?

Re = $2 \times 10^4 \text{m/s} \times 0.3 \text{ cm}/(0.15 \text{ cm}^2/\text{s}) = 40,000$

Max electric field: $E \sim 6 \text{kV/0.3 cm} = 20 \text{kV/cm}$

Analysis time: $2 \text{ cm}/20000 \text{cm/s} = 0.1 \text{ ms}$

Transmission: Annular chamber perimeter
Emulating the triple quadrupole MS at ambient pressure

Ion Mobility Spectrometer-Fragmenter-Ion Mobility Spectrometer Analogue of a Triple Quadrupole for High-Resolution Ion Analysis at Atmospheric Pressure

Mario Amo-González, Irene Camicero, Sergio Pérez, Rafael Delgado, Gary A. Eiceman, Gonzalo Fernández de la Mora, and Juan Fernández de la Mora

Figure 1 shows the schematic of the DMA-F-DMA instrument.

- Anal Chem, web edition
TDMA without chemistry