

RESEARCH ARTICLE

Comparison of Different Ion Mobility Setups Using Poly (Ethylene Oxide) PEO Polymers: Drift Tube, TIMS, and T-Wave

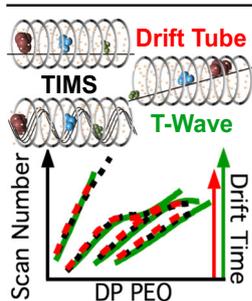
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Abstract. Over the years, polymer analyses using ion mobility-mass spectrometry (IM-MS) measurements have been performed on different ion mobility spectrometry (IMS) setups. In order to be able to compare literature data taken on different IM(-MS) instruments, ion heating and ion temperature evaluations have already been explored. Nevertheless, extrapolations to other analytes are difficult and thus straightforward same-sample instrument comparisons seem to be the only reliable way to make sure that the different IM(-MS) setups do not greatly change the gas-phase behavior. We used a large range of degrees of polymerization (DP) of poly(ethylene oxide) PEO homopolymers to measure IMS drift times on three different IM-MS setups: a homemade drift tube (DT), a trapped (TIMS), and a traveling wave (T-Wave) IMS setup. The drift time evolutions were followed for increasing polymer DPs (masses) and charge states, and they are found to be comparable and reproducible on the three instruments.

Keywords: Ion mobility, Mass spectrometry, TIMS, Drift tube, Traveling wave, Synthetic polymers, Poly (ethylene oxide)

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Introduction

Different homemade or commercial ion mobility spectrometry (IMS) setups have been used over the years to perform different synthetic polymer mixture analyses [1–4] as well as polymer topology and conformation characterizations [5–13].

Homemade drift tube (DT) setups were the first to be used as ion mobility-mass spectrometry couplings (IM-MS) to analyze different synthetic oligomers with different cationizing agents [5–7, 10]. Throughout the following years, commercially available differential mobility analyzers (DMA) and traveling wave ion mobility-mass spectrometers (T-Wave) were used to characterize different polymer mixtures and polymer

topologies [9, 11–13]. Recently, new advances in IMS setups led to a substantial increase in resolving power through a trapped ion mobility separation device coupled to a mass spectrometry (TIMS) setup [14–17]. More detailed structural information and better conformational separation can hence be obtained by precisely tuning the IMS parameters.

To compare literature IMS values and trends between different instruments, parameters such as ion heating and IMS drift behaviors have to be correlated between the different setups. First attempts to evaluate ion heating, which can influence ion conformations or induce fragmentation depending on instrument settings have been made on different instrument (and IMS) setups [18–25]. As the temperatures of these small model ions cannot be easily extrapolated to different, larger analytes or ion systems, straightforward instrument comparisons on identical analytes seem to be the only way to ensure that the different IMS setups, coupled to different mass spectrometer setups, do not significantly affect the gas-phase behavior.

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Here, we introduce the use of synthetic homopolymers to assess the comparability of IMS results obtained with different IMS setups. Synthetic homopolymers are well-suited simple model systems covering a large mass range (sample dispersity) and charge state distributions when using an electrospray ionization source (ESI) with no change in intramolecular interactions according to literature [1, 3, 6, 9, 12, 26]. We use three different IM-MS setups to measure poly(ethylene oxide) PEO arrival time distributions (ATDs) and elution voltages when complexed with different numbers of sodium cations. A homemade DT setup [27], the recently developed TIMS[14–17] (prototype, Bruker Daltonics, USA) device and a commercially available T-Wave setup (SYNAPT G2 HDMS, Waters, UK) are compared using raw extracted drift time data (or equivalent).

Experimental

Sample Preparation

Poly(ethylene oxide) PEO ($\text{CH}_3\text{O-PEO-H}$) 750 g/mol and 2000 g/mol samples were bought from Aldrich (Saint Louis, MO, USA). The samples were diluted to 5×10^{-6} M in pure methanol spiked with 10^{-5} M Na^+ cations (NaCl salt).

Ion Mobility-Mass Spectrometry: Drift Tube IMS (DT)

The samples were infused at a flow rate of 150 $\mu\text{L/h}$ into a homemade ion mobility-mass spectrometer fitted with an ESI source [27]. The instrument is based on a Maxis Impact (Bruker, Germany) Quadrupole Time-of-Flight mass spectrometer (Q-ToF) in order to detect ions after IMS separations. The DT setup contains two 79 cm-long drift tubes separated by a dual-stage ion funnel assembly. Both extremities of both drift tubes are fitted with grids in order to define precisely the drift distance. After the IMS separations, the ions pass through another dual funnel assembly, which is followed by a stacked-ring radio-frequency ion guide before entering the original transfer optics of the Q-ToF. The drift time measurements reported in this article were obtained in the second drift region, using a N_2 drift gas pressure of 3.9 Torr and a drift voltage of 500 V. The temperature of the measurements was 296.15 K. The capillary voltage was set to 1.99 kV and the pressure in the first vacuum chamber was 3.5 Torr.

The ATDs were extracted from the IM-MS measurements and fitted with Gaussian functions in order to accurately determine the arrival times using two homemade software applications, in order to determine accurate drift times. Data processing was performed using Excel 2011 and IgorPro 6.34A.

Ion Mobility-Mass Spectrometry: Trapped IMS (TIMS)

The samples were infused at a flow rate of 150 $\mu\text{L/h}$ into a prototype TIMS ion mobility-mass spectrometer (Bruker Daltonics, USA) fitted with an ESI source. The TIMS and the

DT ESI sources are very similar because they are both Bruker-based setups. The TIMS samples were ionized using a capillary voltage of 4.7 kV, a nebulizer pressure of 7.3 psi, a drying gas flow rate of 4.0 L/min, and a drying temperature of 180 °C. The ToF pulses per IM scan were set to 1500 and the TIMS ramp duration was set to 1300. The start and end voltages of the TIMS ramp were -195 V and -20 V, respectively. The TIMS drift gas was N_2 .

The interpretation of the TIMS data was performed using a beta version of Bruker's DataAnalysis 5.0 software. TIMS provides scan numbers corresponding to elution voltage values, instead of drift times, that could be converted into collision cross-sections (CCSs) after calibration. Data processing was performed using Excel 2011 and IgorPro 6.34A.

Ion Mobility-Mass Spectrometry: Traveling Wave IMS (T-Wave)

The samples were infused at a flow rate of 250 $\mu\text{L/h}$ into a SYNAPT G2 HDMS ion mobility-mass spectrometer (Waters, UK) fitted with an ESI source. The capillary voltage was 3 kV, the sampling cone voltage was set to 40 V, and the extraction cone was 4 V. The source and desolvation temperatures were set to 100 °C and 200 °C, respectively. The desolvation gas flow was 500 L/h. The voltages for the trap and transfer collision energies (CE) were 4 V and 2 V, respectively, and the trap bias was 45 V. The IMS wave height was 40 V and the wave speed was set to 1200 m/s. The trap Ar gas flow was set to 2 mL/min, the He gas flow was 180 mL/min, and the N_2 pressure in the IMS cell was set to 2.6 mbar.

The interpretation of the T-Wave data was performed using Waters' MassLynx 4.1 software. ATD peaks were fitted using PeakFit v.4.11 to determine accurate drift times. Data processing was performed using Excel 2011 and IgorPro 6.34A.

Results and Discussion

In a DT setup, the ions drift at a stationary velocity through the gas-filled drift region. A constant electric field moves the ions towards the detector, allowing the IMS separation.

When using appropriate experimental conditions (especially a low, constant, and uniform electric field), the relationship between the average drift time obtained with a DT and the CCS is linear [28], DT IMS setups can then be used to extract absolute CCS or mobility (K) values without the need of a calibration. The ATDs are then measured for one given set of conditions (temperature, drift gas pressure,...), varying only the DT voltages. The extracted arrival times for each DT voltage are plotted as a function of the inverse drift voltage and the curves are fitted with linear regressions. The slopes of the linear regressions are then proportional to the CCS of the ions [27]. The Mason-Schamp equation [28] (Equation 1) can be used to convert the CCS values into K values and vice-versa.

$$K = \frac{3}{16} \frac{e}{N} \left[\frac{2\pi}{\mu k_B T} \right]^{\frac{1}{2}} \frac{z}{CCS} \quad (1)$$

where e is the charge of an electron, k_B is the Boltzmann constant, T is the temperature and N is the gas number density.

Whereas the DT setup works with a constant electric field moving the ions through a drift gas, a TIMS IMS setup uses a linearly increasing electric field (electric field gradient) that traps the ions according to their mobilities. The TIMS setup uses the electrical field gradient to trap the ions at a stationary point within the drift cell (or TIMS tunnel) by achieving a counterflow of drift gas (or downstream flow) towards the detector. The lower mobility ions (i.e., those with larger CCS and/or lower charge state) will be pushed further into the TIMS tunnel until they are trapped (halted) by the electric field, which is able to counterbalance the forward movement of the ions [14, 15]. The higher mobility ions (i.e., those with smaller CCS and/or the higher charges) will be trapped earlier in the TIMS tunnel where lower electric fields are applied. Then, the ions are eluted in a stepwise manner according to their mobilities towards the detector by decreasing the electric field trapping the ions. This elution voltage is linked to the TIMS ramp (applied electric field gradient), i.e., the voltage steps applied over a given time, and determines the IMS resolving power. The gentler the slope of the TIMS ramp and the more scans that are sampled during the ramp, the higher the resolving power.

In order to extract CCS values from a TIMS experiment, CCS calibrating ions [Agilent Tune Mix [29] or other] need to be measured using the same IMS parameters as for the samples. However, we prefer discussing data as TIMS scan numbers, linked to the elution voltages. Consequently, we do not induce any bias due to a calibration process.

Note that the latest beta version of the TIMS software used during this study provides the TIMS scan numbers in the inverse order rather than the physical order of elution, i.e., the low mobility ions elute first and should be correlated to the smallest scan numbers; they are, however, shown in the common drift time order, meaning that increasing TIMS scan numbers are associated with ions decreasing in mobility. The TIMS scan numbers can thus be combined to the DT drift times (in ms), as shown in Figure 1. Data is plotted as a function of the degree of polymerization (DP, number of polymerized monomer units) of the polymer chain for different charge states of PEO complexed by sodium cations (1+ to 4+).

As it has already been discussed in literature [9, 10, 12, 30], the drift times (or CCSs) of polymer-cation complexes globally and generally monotonically increase when increasing the number of monomer units and the mass. Moreover, increasing the charge state increases the mobility K of the ions as well, leading to lower drift times (*cf.* Mason-Schamp Equation [28], Equation 1). A balance between the Coulomb repulsion, the solvation of the charges, and the entropy contributions define the drift time (or CCS) evolution when the DP increases. Hence, polymer-cation complexes undergo structural

rearrangements for higher charge states at different DP values. These structural rearrangements are observed as breaks in the monotone trends of the CCS (or drift time) evolutions. The three-dimensional structures of the complexes change in order to attain new three-dimensional arrangements, which are able to better stabilize the Coulomb repulsion.

PEO complexed by two sodium cations [PEO + 2Na⁺]²⁺ shows such a structural rearrangement in the analyzed mass range (Figure 1). The [PEO + 3Na⁺]³⁺ complexes start their structural rearrangement at the end of the analyzed mass range, whereas the [PEO + 4Na⁺]⁴⁺ complexes do not exhibit any changes in their drift time evolution in the investigated DP range. Obviously, the singly charged complexes [PEO + 1Na⁺]⁺ are not subjected to any Coulomb repulsion.

The TIMS scan number and DT drift time correlation provided in Figure 1 shows that the scan numbers (or elution voltages) and drift times evolve similarly for all the charge states, disregarding the small discrepancies that could be due to the different data processing software and data fitting possibilities.

A similar comparison can be established when comparing TIMS and T-Wave IMS data (see Figure 2 or Figure S11 and Figure S12 in the Supplementary Information for simultaneous TIMS, DT, and T-Wave comparisons). T-Wave setups use periodic voltage pulses resulting in voltage waves propagating the ions through a static drift gas towards the mass detector at the end of the instrument. T-Wave specific parameters, especially nitrogen gas pressure, wave height, and wave speed, determine the T-Wave IMS resolution. Higher charged and smaller ions (i.e., ions having a small CCS) spend more time surfing the front of the wave [31, 32], which results in the ions being more often accelerated than lower charged and bigger ions (i.e., ions having a large CCS). The latter are more often surfing on the tail of the wave and are thus more often decelerated. The wave height and the wave speed determine the rollover behavior of the ions, i.e., the ions' surpassing of waves and their alternating surfing on either side of the waves.

As the ion trajectories are difficult to describe [33], T-Wave IMS measurements need CCS calibrations for each set of parameters used in the IMS cell in order to correlate the observed drift times into CCS values. Once again, in order not to influence the comparisons by any bias due to a CCS calibration process, we plot the measured T-Wave drift times as a function of the DP (number of polymerized monomer units). Figure 2 represents the comparison of the TIMS scan numbers and the T-Wave drift times (in ms) for different charge states of PEO complexed by sodium cations (1+ to 4+).

At a first glance, the TIMS scan number (or elution voltage) and the T-Wave drift time evolutions are similar for all the analyzed charge states. Only minor discrepancies, which should mostly be due to an imperfect correlation of the two axes (TIMS scan numbers and T-Wave drift times), can be observed between the TIMS and T-Wave trends.

Information independent of different data fitting possibilities and other potential software inequalities among the three IMS setups are the structural rearrangements found in the IMS

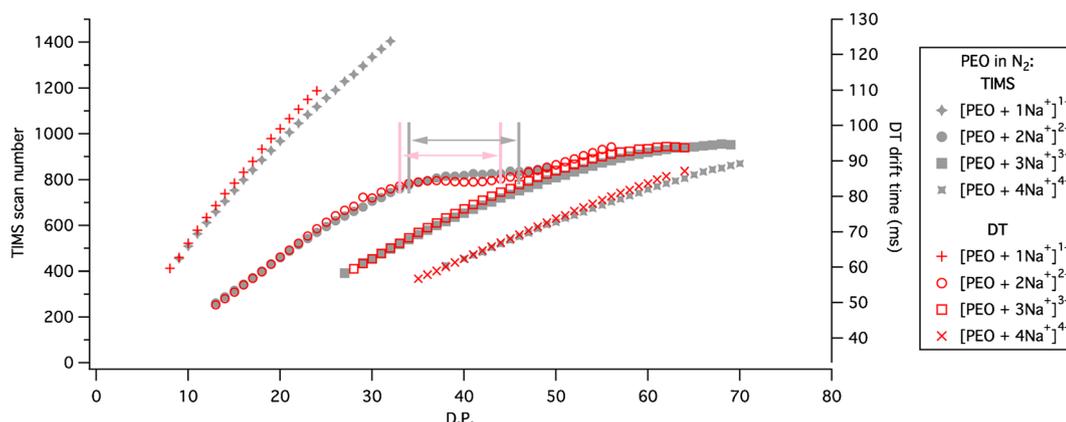


Figure 1. Correlation of the N₂ TIMS (trapped ion mobility spectrometry) scan numbers (filled gray markers; left axis) and the N₂ DT (drift tube) drift times (red markers; right axis) of poly(ethylene oxide) PEO polymers complexed by 1 to 4 Na⁺ cations plotted as a function of the degree of polymerization (polymer chain length, DP). The gray and pink arrows indicate the DP region of the structural rearrangement of the [PEO + 2Na⁺]²⁺ complexes as measured on the TIMS and the DT instruments, respectively

data evolutions. Indeed, if polymer analyses in the gas phase can be compared across different IMS setups, the structural rearrangements should not vary with the IMS setup as these DP regions are defined by the enthalpic and entropic contributions (physicochemical properties), determined by the polymerized monomer units of the analyzed polymer (i.e., PEO). Such a statement is nevertheless based on the assumption that similar effective temperatures could be reached and on the assumption of the absence of metastable or kinetically trapped conformations that could have been formed during the ESI process or during ion transfers. However, the ESI sources, ion optics, analyses timeframes, and the gas pressures and temperatures inevitably differ on the three IMS setups used in this study. It is still noteworthy, however, that the TIMS and the homemade DT IMS setups use similar Bruker-based ESI sources, the sources varying only in the applied voltages, their reversed ways of applying the polarity of the electrical potential, and their gas pressure conditions.

Figure 3 represents the [PEO + 2Na⁺]²⁺ drift time (DT, T-Wave) and scan number (TIMS) evolutions as a function of the

DP for the different IMS setups. The evolutions before and after the structural rearrangements are fitted with linear regressions in order to easily determine visually the DP ranges where the structural rearrangements occur (detachment of the data points from the linear regression fits, i.e., the linear drift time or scan number evolution before and after the structural rearrangements). The comparisons shown in Figure 1 (DT – TIMS) and Figure 2 (T-Wave – TIMS) allow the fitting of the few data points of the TIMS scan number evolution after the structural rearrangement; the comparison assuring that the structural rearrangement is finished at higher DP values for the TIMS measurement. Table 1 summarizes the DP ranges of the structural rearrangement of the [PEO + 2Na⁺]²⁺ complexes measured by the different IMS setups. These DP ranges are determined through the deviations of the IMS data points from the linear regressions represented in Figure 3. They are as well represented as arrows in Figure 1 and Figure 2.

Comparing the starts and the ends of the structural rearrangement, a slight shift is noticeable when going from the DT to the TIMS and the T-Wave IMS setup ($DP_{\text{start}} = 33, 34, 35$

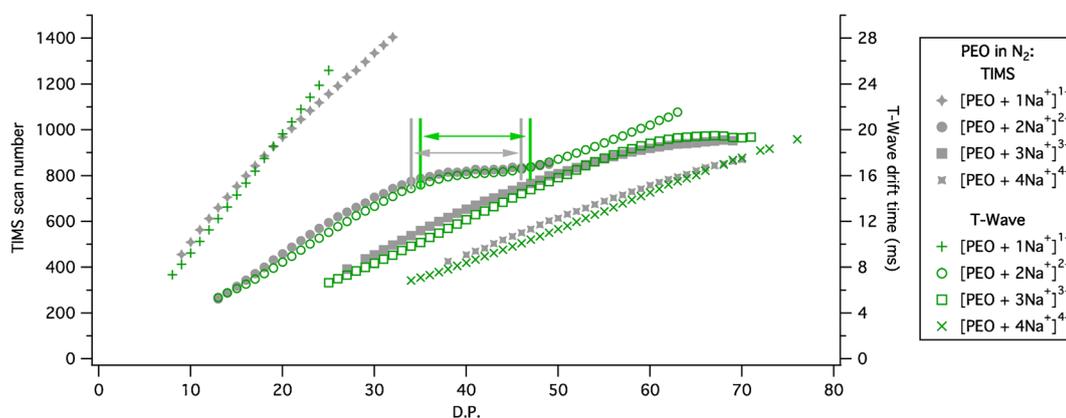


Figure 2. Correlation of the N₂ TIMS scan numbers (filled gray markers; left axis) and the N₂ T-Wave drift times (green markers; right axis) of PEO polymers complexed by 1 to 4 Na⁺ cations plotted as a function of the DP (polymer chain length). The gray and green arrows indicate the DP region of the structural rearrangement of the [PEO + 2Na⁺]²⁺ complexes as measured on the TIMS and the T-Wave instruments, respectively

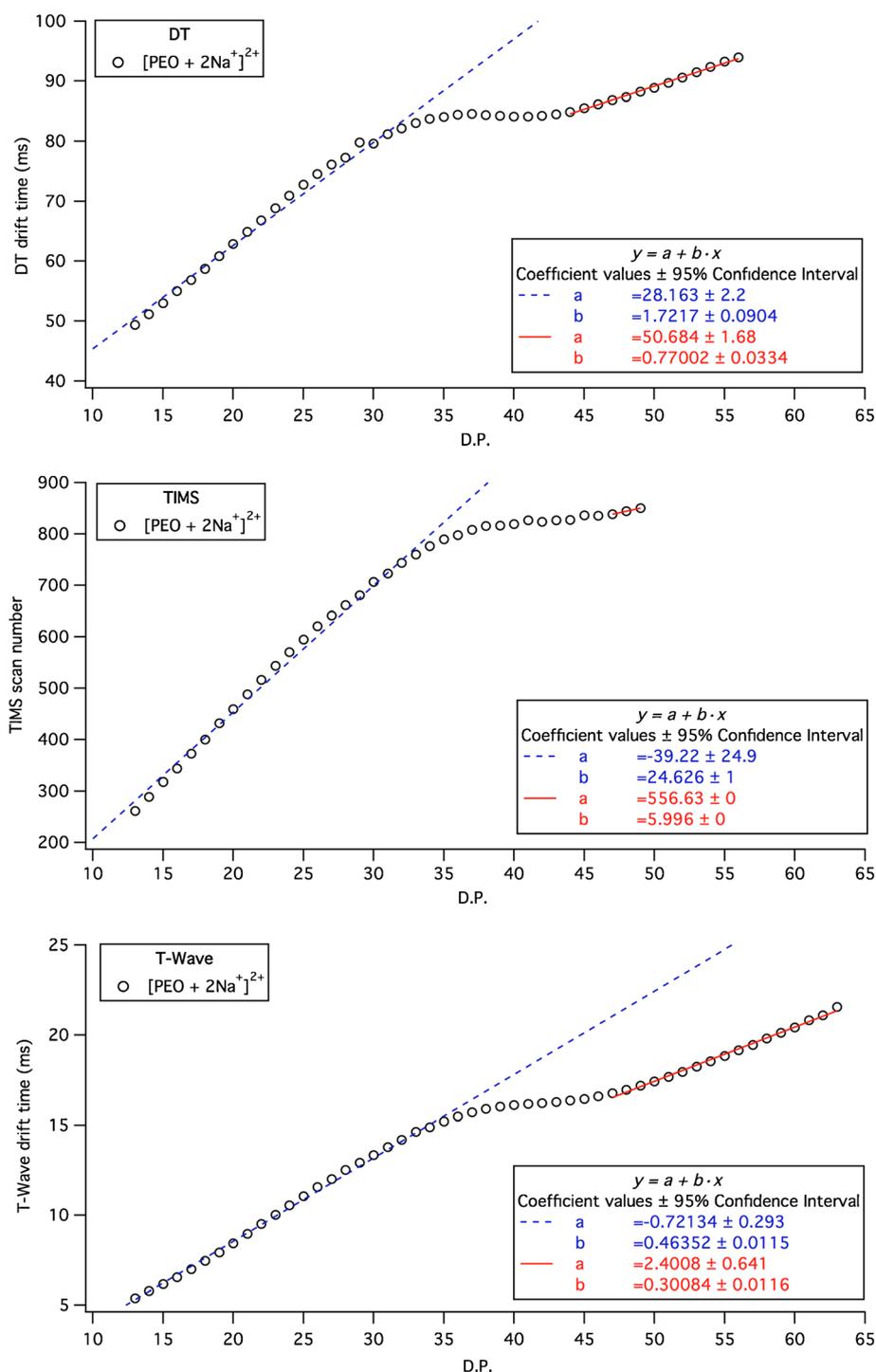


Figure 3. [PEO + 2Na⁺]²⁺ complexes' drift time and scan number evolutions as a function of the DP. From top to bottom: DT, TIMS, and T-Wave. The trends before and after the structural rearrangements are fitted using linear fit functions ($y = a + b \cdot x$). The blue and red coefficients correspond to the blue (dotted line) and red (plain line) fit lines, respectively

and $DP_{\text{end}} = 44, 46, 47$, respectively). These small differences could be explained by software data extraction and ATD fitting disparities, as already discussed before. Slight ion temperature differences could as well explain the small IMS measurement differences.

Nevertheless, the values of the number of polymerized monomer units constituting the structural rearrangement ΔDP

(Equation 2) are in good agreement among the three IMS setups. As these values are dictated by the physicochemical properties of PEO (considering enthalpic and entropic contributions), they should not and indeed do not significantly change as a function of the IMS setup, provided that similar effective ion temperatures could be reached for exploring the free potential energy surface of all structures with minimized

Table 1. Summary of the DP ranges of the structural rearrangement of the $[\text{PEO} + 2\text{Na}^+]^{2+}$ complexes measured using three IMS setups: drift tube, trapped ion mobility spectrometry, and traveling wave IMS. The ΔDP of the structural rearrangement represents the difference of the DP values of the end and the start of the structural rearrangement (number of polymerized monomer units constituting the structural rearrangement; Equation 2), assigned according to the linear fits depicted in Figure 3

Ion mobility setup	DP at the start of the structural rearrangement	DP at the end of the structural rearrangement	ΔDP of the structural rearrangement ^a
DT	33	44	11
TIMS	34	46	12
T-Wave	35	47	12

^a ΔDP is calculated by subtracting the DP at the start and at the end of the structural rearrangement. See Equation 2 and text for details

Gibbs free energy. Polymer analyses thus seem to be exploitable and comparable through the different measurement setups.

$$\Delta\text{DP} = \text{DP}_{\text{end structural rearrangement}} - \text{DP}_{\text{start structural rearrangement}} \quad (2)$$

Conclusions

Poly(ethylene oxide) PEO polymers complexed by sodium cations (1+ to 4+) were used to demonstrate that the drift time or scan number evolutions as a function of the polymer chain length (degree of polymerization) are not significantly influenced by the IMS setup (drift tube, trapped, and traveling wave IMS). Only minor discrepancies were noticed and were mostly assumed to be dependent on software data extraction and data processing differences. Small IMS measurement differences could as well be due to slight ion temperature differences in the three used IMS setups.

In order to better evaluate if synthetic polymer analyses can be compared on different IMS setups, the DP regions of structural rearrangements were investigated in more detail. During these structural rearrangements, the polymer chain rearranges in order to better stabilize the cation charges and to diminish the Coulomb repulsion. As expected, the DPs constituting the structural rearrangements (ΔDP) are in good agreement on the three instruments (DT, TIMS, and T-Wave).

As poly(ethylene oxide), and very probably other synthetic polymers, show an overall ion mobility behavior that is independent of and reproducible on the different investigated instrumentation setups, they should be considered as relevant IM calibrating ions. Nevertheless, more complex systems such as different polymer topologies should as well be compared on different IMS setups to ensure that cross-platform data still is comparable, given that slight shifts were noticed depending on the instrument.

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Compliance with ethical standards

Conflict of interest disclosure The authors declare no competing financial interest.

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