



Tandem Fourier transform mass spectrometry of block and random copolymers

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ABSTRACT

In recent years, many fragmentation techniques have been developed for use with Fourier transform mass spectrometry (FTMS) in sequencing polymers. Tandem mass spectrometric techniques such as collision-induced dissociation (CID) and electron capture dissociation (ECD) were used to fragment high mass polyether and polyacrylate copolymer ions produced using external electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) sources. High resolution FTMS analysis of fragments produced by collision cell CID (QCID) is available in a new generation hybrid FTMS instrument. Although tandem QCID-TOF techniques have been used heavily to explore copolymer fragmentation, we report the first QCID-FTMS analysis of such systems. The high fragmentation efficiency of QCID combined with the high mass resolution and mass accuracy of FTMS reveals a novel fragmentation pattern of selected oligomers. This method provided evidence of re-combination of fragments in the gas phase, in that some fragments have higher mass and charges than the isolated precursor ions. QCID fragmentation of oligomers of varying size was studied in the presence of Li, Na, or Cs salts. The ECD-FTMS spectra of polyacrylates showed only side group losses. Accordingly, this technique can be used for an unknown polyacrylate sample analysis and has the potential for side group determination.

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1. Introduction

After the introduction of soft ionization methods, such as electrospray ionization (ESI) [1] and matrix assisted laser desorption/ionization (MALDI) [2,3] techniques, and mass analyzers, such as time-of-flight (TOF) [4] and Fourier transform mass spectrometers (FTMS) [5], mass spectrometry became the main tool in “top-down” proteomics and polymer analysis [6].

In recent years, many fragmentation techniques have been developed for use with Fourier transform mass spectrometry (FTMS) in sequencing peptides and polymers. The most commonly used methods include sustained off-resonance irradiation collision-induced dissociation (SORI-CID) [7,8], infrared multiphoton dissociation (IRMPD) [9], and electron capture dissociation (ECD) [9,10]. Recently, hybrid FTMS instruments that have the capability of performing collision-induced dissociation in a hexapole collision cell (QCID) which is filled with argon gas and kept at a pressure of 10^{-2} mbar [11] were introduced. This relatively high pressure increases the probability of collisions between selected precursor ion and gas molecules when compared with the SORI-CID technique, where collision occurs in the ion cyclotron cell (ICR) using collision gas pressures of up to 10^{-5} mbar [12]. However,

analysis time employing QCID is shorter, since the ICR cell is separated from the collision cell by ion optics and constantly held under high vacuum (10^{-10} mbar). This differs from SORI-CID where analysis time depends on high-vacuum pump efficiency because of the need to rapidly pump the analyzer region down to 10^{-10} mbar after the gas pulse, required for SORI. The disadvantage of QCID when compared to SORI-CID is that the ion's path length during which collisions occur is limited by the collision cell length. In SORI-CID, the path length of precursor ions is basically unlimited. This results from the fact that collisions occur in the trapped ion cell, enabling many collisions with gas molecules resulting in higher collision energies for fragmentation.

Until now, most of the literature on MS/MS analysis has focused on sequencing of biomolecules [8–10]. In contrast, the present research deals with the equally challenging problem of sequencing synthetic polymers. This is a consequence of the stability of the covalent bonds connecting monomer units. Therefore, the tandem MS technique employed must impart high enough energy to the oligomer ions to break those bonds. Often when fragmentation does occur, a limited number of fragments are detected and their low abundances require a large number of measurements, in order to increase the signal to noise ratio of resulting spectra. In the past, such analyses were very time consuming [13]. With development of new hybrid instruments, required analyses time has been reduced significantly [14]. Electron-capture dissociation (ECD) is a technique in tandem MS that produces fragments through a non-ergodic mechanism making this technique unique for frag-

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mentation [15]. As most often implemented, ECD requires the use of multiply charged ions produced by electrospray ionization (ESI) [16]. There are a few reports of successful fragmentation of copolymer and polymer samples using ECD-FTMS [17–21]. On the other hand, tandem MS characterizations of the polymers were said to be “unreliable” due to occurrence of recombination processes following molecular ion dissociation. As mentioned above, although ECD fragmentation was applied to analysis of a number of synthetic polymer samples [19,20], including polyethers [16,18], in contrast to its applications to biomolecules [22–24], the analytical utility of ECD for polymers may be less useful.

Polyether CID fragmentation has been investigated using the previously mentioned techniques, providing a source of comparison for this study's results [7,16,18,25–27]. The main focus of the present research is analysis of QCID and ECD-FTMS of polyacrylates [28]. Specifically, the homopolymer poly(methyl methacrylate), the random copolymer methyl methacrylate–butyl methacrylate and the block copolymer methyl methacrylate–butyl methacrylate were studied. A previous study performed on polyacrylates by Jackson, Slade, and Scrivens showed that different ionization agents cause various fragmentation patterns for multiply-charged oligomers fragmented and analyzed using an orthogonal time-of-flight mass spectrometer [29]. For this reason, we also explored the influence of cationizing agents on polyacrylate fragmentation patterns by replicate FTMS analyses in the presence of LiCl, NaCl, and CsCl salts. Lithium and cesium cations were chosen for this study because they are the smallest and largest, respectively, of readily available alkali metal cations, while sodium cation was chosen as the middle ion because, as a ubiquitous element, it often contaminates synthetic polymers during their synthesis. As a consequence, sodiated peaks are often present in spectra even when no sodium has been added [30]. Thus, when sodium chloride is added, and samples analyzed by MALDI, the relative abundances of the sodium cationized oligomers are enhanced. Interestingly, in the present research it appears that the results allow *rapid differentiation of block and random copolymers by suitable analysis of their fragmentation patterns*.

2. Materials and methods

All polymer-cation solutions used in electrospray (ESI) experiments were of a concentration ratio of 8 μM polymer to 200 μM cation in methanol. The methanol used was purchased from EMD Chemicals (Gibbstown, NJ). The poly(ethylene glycol) and poly(methyl methacrylate) have average molecular weights of 3000 g/mol and 5000 g/mol, respectively, and were both purchased from Fluka (now Sigma–Aldrich, St. Louis, MO). Random poly(ethylene oxide-propylene oxide) was obtained from Polysciences (Warrington, PA) ($M_w \sim 2900$) while block copolymers poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) ($M_w \sim 2900$) and poly(propylene oxide)-block-poly(ethylene oxide)-block-poly(propylene oxide) ($M_w \sim 3300$) were acquired from Sigma–Aldrich. Block copolymer poly(methyl methacrylate-*b-n* butyl methacrylate) ($M_w \sim 4000$) was purchased from Polymer Standard Service–USA (Warwick, RI) and random poly(methyl methacrylate-*n* butyl methacrylate) ($M_w \sim 3000$) was a generous gift from Dr. William J. Simonsick of DuPont. The lithium chloride and sodium chloride used were purchased from Sigma–Aldrich, while the cesium chloride was purchased from Shelton Scientific (Shelton, CT).

For matrix-assisted laser desorption ionization (MALDI), polymers were mixed with dihydroxy-benzoic acid (Alfa Aesar, Ward Hill, MA) and cationization agent in methanol with an approximate molar ratio of 1:400:30 (analyte:DHB:salt) respectively. Solutions were aerosprayed onto stainless steel plates.

Polymers were analyzed using a Bruker APEX Qe 9.4T FTMS (Billerica, MA) with a dual external ionization ESI and MALDI source. The instrument is equipped with Nd:YAG laser operated at a wavelength of 355 nm. Detailed schematics of the instrument appear elsewhere [11]. For tandem FTMS, a full spectrum of the polymer was obtained and several oligomers of high abundance were selected to isolate and fragment. These were isolated using a quadrupole ion filter and fragmented using the desired method. In this paper, MS/MS data from a representative oligomer is reported. For CID, the pressure of argon gas within the collision cell was held at 10^{-2} mbar. The collision energy ranged from 55 to 80 eV, as calculated in the laboratory frame, and was adjusted to give the highest fragmentation efficiency. Electron energy for electron capture dissociation was between 3 and 4 eV employing an electron pulse length of 50 ms.

3. Results and discussion

3.1. ESI-QCID-FTMS of polyacrylates

For the initial collision cell CID Fourier transform mass spectrometry (QCID-FTMS) experiments, the homopolymer poly(methyl methacrylate) (PMMA, $M_w = 5000$) was chosen. Before looking at the more complicated copolymer samples using electrospray ionization (ESI) QCID PMMA was analyzed. For these measurements, lithium, sodium, and cesium salts were added in order to determine the fragmentation pattern and efficiency for each of the cations. QCID was performed on the doubly-charged oligomers consisting of 37 methyl methacrylate (MMA) monomeric units and on the triply-charged oligomers consisting of 50 MMA monomeric units. The 50 monomer chain was chosen because it represented the average weight of the polymer used. However, the doubly-charged oligomer of that length produced a mass-to-charge ratio too large for the quadrupole to isolate efficiently. Therefore, the abundant and efficiently isolated oligomer containing 37 monomeric units was chosen for the doubly-charged analysis instead.

Fig. 1A represents a full mass range ESI-FT mass spectrum of sodium-cationized PMMA. Fig. 1B–D shows the fragmentation spectra of the doubly-charged 37-mer oligomers obtained in the presence of each of the cations. Table 1 displays all of the fragments present in each of these three spectra. The QCID process of fragmentation is ergodic [31]. In such a case, the energy from the collision is spread out across the oligomer, breaking the weakest bond. The large size and low charge density of Cs would make its coordination bonds with the carbonyl groups along the chain weak [31]. Thus, it is quite favorable for a Cs^+ ion to be removed by a collision. As a result the peak corresponding to the loss of one Cs^+ ion ($m/z = 3842.9$, Fig. 1D) is more abundant than those corresponding to other fragments. In all three spectra, there are fragments that are longer or more highly charged than the precursor ion. This indicates that some of the fragments produced by the collision combine while still in the gas phase. Depending upon the lengths and number of ions present on the fragments, longer, more highly charged oligomers result. This is more frequent when Li^+ and Na^+ are used as the cationizing agents because these cations are not as easily removed as Cs^+ [31–33]. The results of the fragmentation of the triply-charged 50-mer using each cation are shown in Fig. 1E–G and are summarized in Table 2. These are similar to the results of the doubly-charged 37-mer in that cesiated species readily loses the cation and fragment less than oligomers cationized by Li^+ or Na^+ . However, there are more fragments present for Cs^+ with the 50-mer than there are for the 37-mer and no peak representing the loss of two Cs^+ ions is present. This is consistent with reports that Cs^+ coordinates readily with longer oligomers

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