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Structural Analysis of Polymer End Groups by Electrospray Ionization High-Energy Collision-Induced Dissociation Tandem Mass Spectrometry

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Chemical structures of polymer end groups play an important role in determining the functional properties of a polymeric system. We present a mass spectrometric method for determining end group structures. Polymeric ions are produced by electrospray ionization (ESI), and they are subject to source fragmentation in the ESI interface region to produce low-mass fragment ions. A series of source-fragment ions containing various numbers of monomer units are selected for high-energy collision-induced dissociation (CID) in a sector/time-of-flight tandem mass spectrometer. It is shown that high-energy CID spectra of source-induced fragment ions are very informative for end group structure characterization. By comparing the CID spectra of fragment ions with those of known chemicals, it is possible to unambiguously identify the end group structures. The utility of this technique is illustrated for the analysis of two poly(ethylene glycol)-based slow-releasing drugs where detailed structural characterization is of significance for drug formulation, quality control, and regulatory approval. Practical issues related to the application of this method are discussed.

Despite the chemical diversity of polymeric systems, an increasing number of different types of polymers, including most commonly used industrial polymers, can now be analyzed by mass spectrometry. At present, matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometry (TOF MS) is perhaps the most widely used technique for polymer analysis.[1,2] With MALDI-TOF, molecular weight, molecular weight distribution, and polymer composition can be rapidly and accurately determined.[3−18] However, structural information generated from MALDI-TOF is often limited. This is particularly true for end group characterization. At best, the oligomer masses in a MALDI spectrum can only be used to deduce information about the total mass of the end groups of a polymer.

Tandem mass spectrometry combined with MALDI has been developed for polymer structural characterization.[19−22] Very impressive fragment ion spectra can be produced in tandem sector/time-of-flight mass spectrometry with collision-induced dissociation (CID). Derrick and co-workers recently demonstrated the use of high-energy CID in sector/TOF MS for end group characterization.[22] The need of high-energy CID to gain information on end group structures was clearly illustrated.[22] However, in CID spectra of oligomers, ion peaks from end groups tend to mix with many low-mass peaks that are the results of internal fragmentation of the polymer chains, rendering some difficulty in spectral interpretation for end group structure analysis, particularly for unknowns. Since MALDI generates predominately singly charged oligomers, only low-mass polymers are amendable to MALDI MS/MS. These difficulties are also associated with MALDI-TOF having postsource decay or CID capability.

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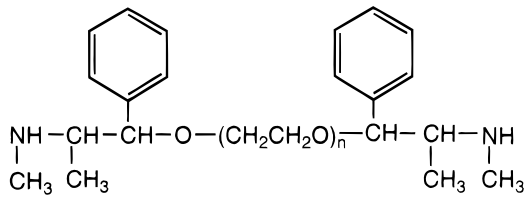
Electrospray ionization (ESI) MS is another important method for polymer analysis.[23−38] In ESI, multiple charged polymeric ions are generated and these ions can be readily fragmented in the source region of an ESI interface.[37] However, polymeric species and their fragments such as those from poly(ethylene glycol)s (PEGs) appear to be difficult to fragment into low-mass ions with low-energy CID. This was observed in the studies of a series of PEGs in an ion trap mass spectrometer.[39] A similar observation was noted in a MALDI Fourier transform ion cyclotron resonance (FT-ICR) experiment[22] and in a fast atom bombardment ionization CID experiment.[40]

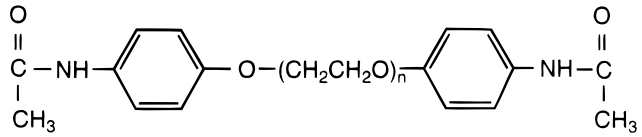
In this report, we present a MS method that provides unambiguous structural characterization of polymer end groups. This method is based on the use of source fragmentation of polymer ions generated by electrospray ionization. The low-mass fragment ions formed in the source are subjected to *high-energy* CID in a tandem sector/time-of-flight mass spectrometer to produce fingerprint spectra of end groups. The application of this method is demonstrated for the end group analysis of two slow-releasing drugs, poly(oxyethylene) bis(acetaminophen) and poly(oxyethylene) bis(ephedrine).

EXPERIMENTAL SECTION

All high-energy CID experiments were carried out by using the ZabSpec (ZAB) sector/orthogonal acceleration (OA) time-of-flight mass spectrometer (Micromass, Manchester, U.K.). Electrospray ionization was used for creating protonated gas-phase ions. Source fragmentation of the polymer ions was controlled by adjusting the voltage difference (V_{CID}) between the atmospheric plate and the skimmer in the ESI interface. The precursor ions were accelerated by a voltage of 4000 V and mass selected with the EBE mass spectrometer. The ions were introduced into the collision cell floated at 3600 V. Thus, for high-energy CID, the laboratory kinetic energy of a multiple charged precursor ion with a charge state of z was 400z eV. Argon was used as the collision gas, and on average, the intensity of the precursor ions was attenuated by ~30%. The ions exiting the collision cell were guided into the OA-TOF spectrometer and pulsed into the flight tube for mass separation. Ions were detected with a microchannel plate detector.



Poly(oxyethylene) bis(ephedrine)



Poly(oxyethylene) bis(acetaminophen)

Figure 1. Structures of the polymers used in this work.

Poly(oxyethylene) bis(acetaminophen), poly(oxyethylene) bis(ephedrine), acetaminophen, and ephedrine were purchased from Sigma Chemical Corp, (St. Louis, MO) and used without purification. The structures of these two polymers are shown in Figure 1.

HPLC-grade acetonitrile, HPLC-grade water, and ammonium acetate were purchased from Fisher Scientific Co. (Nepean, ON, Canada). Solutions for ESI MS analysis were prepared by dissolving an analyzed compound in a mixture of 80% (v/v) acetonitrile and 20% (v/v) 0.25 mM ammonium acetate in water. The sample solution (100 μM) was delivered from a syringe to the ESI source at a flow rate of 6 μL/min using the continuous infusion method.

RESULTS

Poly(oxyethylene) Bis(ephedrine). Electrospray ionization of the studied polymers (average molecular weight ~3500 u) resulted in the mass spectra displaying several polymer distributions arisen from oligomers with different charge states (not shown). The oligomers at a charge state of +4 were chosen for CID. Oligomers with lower charge states did not fragment as efficiently as the +4 ions for these samples. Figure 2A shows the low-mass region of the high-energy CID spectrum of an ion at m/z 1014 from poly(oxyethylene) bis(ephedrine). A series of peaks from G_n ions (i.e., m/z at 148, 192, and 236) and A_n ions (i.e., m/z at 45, 89, 133, and 177) (see Discussion and Figure 7 for fragment ion notations) were observed with a mass difference corresponding to the monomer unit of the polymer (i.e., 44 u). These fragment ions are generated by cleavage of the polymer backbone and may contain end group information.[40] However, no intense peaks corresponding to the ephedrine structure can be assigned. This illustrates a major shortcoming of the method using CID MS/MS of high-mass oligomers for structural characterization of end groups. The lack of a sufficient number of fragment ions from the particular structures of end groups is quite understandable, in light of the fact that the internal energy gained from the CID

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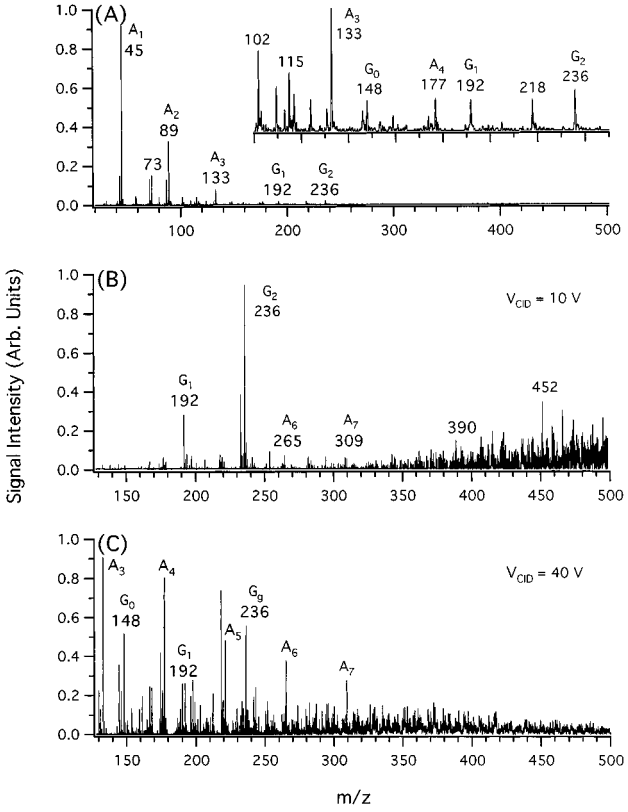

Figure 2. Fragment ion spectra of poly(oxyethylene) bis(ephedrine) obtained by using ESI tandem sector/time-of-flight mass spectrometry. (A) High-energy CID spectrum of an oligomer ion at *m*/*z* 1014 with a +4 charge state, (B) source-induced CID spectrum of the polymer at V_{CID} = 10 V, and (C) source CID spectrum of the polymer at V_{CID} = 40 V.

process redistributes among many energy levels of such a large ion. Chain clearage appears to be the dominant process in CID.

It would appear that further dissociation of the fragment ions after mass selection should potentially generate structural information on the end group. Unfortunately, the ZAB-TOF system used does not provide MS/MS/MS capability. Thus, an alternative tandem mass spectrometric experiment was examined. In this case, we used source fragmentation in the ESI interface of this instrument to produce fragment ions from a polymer, followed by high-energy CID of these fragments. Panels B and C of Figure 2 show the source fragmentation spectra of poly(oxyethylene) bis(ephedrine) obtained by using two different source voltages (V_{CID}). A number of fragment ions are generated in source fragmentation; however, the ions from the G_n series at *m*/*z* 148, 192, and 236 are preferentially formed (see Figure 2B). As V_{CID} increases, lower mass fragments become more intense. We then recorded the high-energy CID MS/MS spectra of these fragment ions. By examination of all the recorded spectra, some fragmentation patterns can be readily recognized. This is illustrated in Figure 3. The intense source-fragment ion at *m*/*z* 236 shown in both Figure 2B and C gives rise to a relative simple CID spectrum (see Figure 3A). The peak at *m*/*z* 148 is generated by the elimination of two monomer units from the *m*/*z* 236 ion. The source-fragment ion at *m*/*z* 192, which is 44 u or one monomer unit less than the *m*/*z* 236 species, produces many peaks in the CID spectrum, as shown in Figure 3B. Of particular interest, a fragment ion at *m*/*z* 148 is also observed and is likely from the loss of 44 u from *m*/*z* 192. The

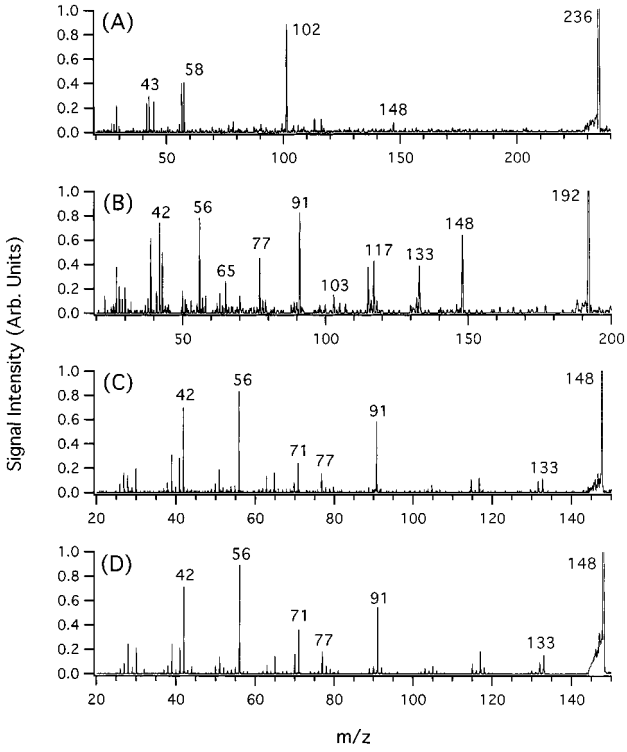

Figure 3. High-energy CID spectra of source-induced fragment ions at (A) *m*/*z* 236, (B) 192, and (C) 148 derived from poly(oxyethylene) bis(ephedrine). (D) CID spectrum of the source-induced fragment ion at *m*/*z* 148 originated from ephedrine.

next source-fragment ion in the series at *m*/*z* 148 generates a CID spectrum that has many resemblances to the low-mass region of the CID spectrum from *m*/*z* 192. No intense fragment ion peak from the loss of 44 u is found. From these results, we can tentatively assign the *m*/*z* 148 ion as an ion from the end group of the polymer.

For unambiguous structural assignment, fragment ion spectra of standard compounds can be obtained and compared to a spectrum of an unknown. In this case, a high-energy CID spectrum of an ion originated from the standard compound, ephedrine, was recorded under the same experimental conditions. This is shown in Figure 3D. The spectra shown in Figure 3C and D are perfectly matched, confirming the end group structure.

Poly(oxyethylene) Bis(acetaminophen). Figure 4A shows the expanded high-energy CID spectrum of a poly(oxyethylene) bis(acetaminophen) oligomer at *m*/*z* 1007 with a charge state of +4. At the mass range up to *m*/*z* ~133, this CID spectrum is almost the same as that of Figure 2A obtained from poly(oxyethylene) bis(ephedrine), despite the significant differences in end group structures of the two polymers. Unfortunately this is also the mass region that one hopes to obtain useful information on end group structures. It is clear that high-energy CID MS/MS of oligomers has its limited use in end group structure characterization for these two slow-releasing drugs. Since many PEG-based slow-releasing drugs use a similar or longer PEG chain for drug attachment, it is likely that we will have difficulty in generating useful end group information on other PEG drugs by CID MS/MS.

Panels B and C of Figure 4 show the source-fragmentation spectra of poly(oxyethylene) bis(acetaminophen) obtained using

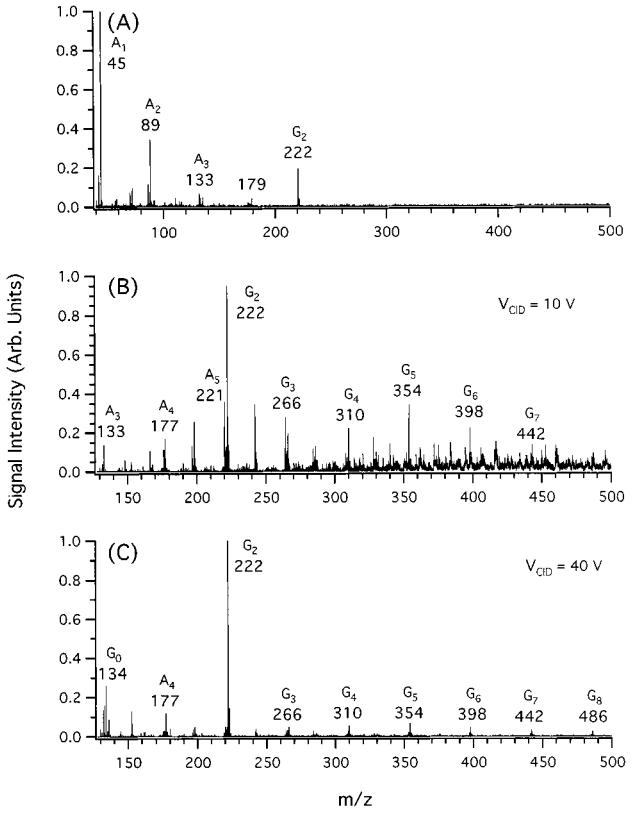

Figure 4. Fragment ion spectra of poly(oxyethylene) bis(acetaminophen). (A) High-energy CID spectrum of an oligomer at *m*/*z* 1007 with a +4 charge state, (B) source-induced CID spectrum of the polymer at $V_{CID} = 10$ V, and (C) source CID spectrum of the polymer at $V_{CID} = 40$ V.

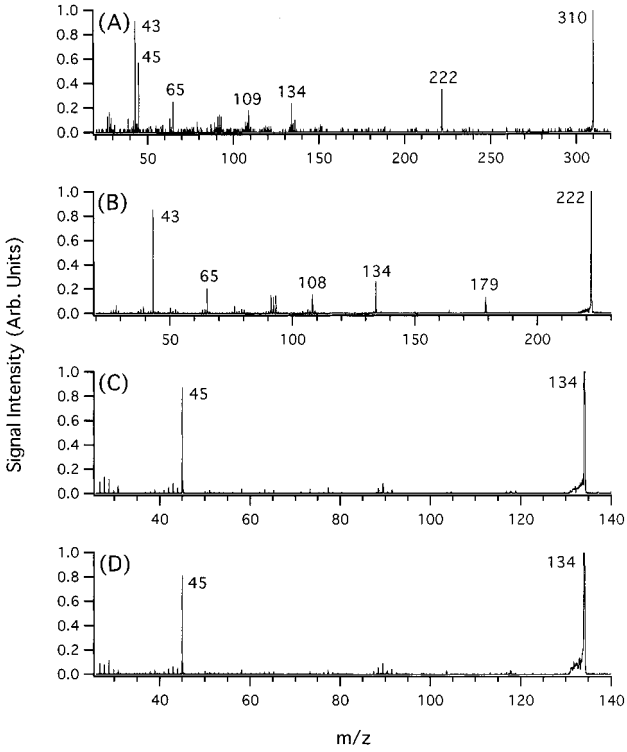

Figure 5. High-energy CID spectra of source-induced fragment ions at (A) *m*/*z* 310, (B) 222, and (C) 134 derived from poly(oxyethylene) bis(acetaminophen). (D) CID spectrum of the source-induced fragment ion at *m*/*z* 134 originated from acetaminophen.

two different source voltages (V_{CID}). These spectra are different from those of poly(oxyethylene) bis(ephedrine) (see Figure 2B and C). The more intense source-fragment ions were subjected to CID, and some of the resulting spectra are shown in Figure 5. In this case, we show the CID spectra of *m*/*z* 310 and 222 to illustrate that further dissociation of almost all source-fragment ions can be readily achieved with the high-energy CID in the sector/TOF instrument. Panels C and D of Figure 5 show the CID spectrum of the *m*/*z* 134 ion originated from poly(oxyethylene) bis(acetaminophen) and acetaminophen, respectively. In this case, confirmation of the end group identity was also achieved.

DISCUSSION

The above examples demonstrate that the method of source-fragmentation MS/MS can be very useful in obtaining structural information of polymer end groups. In applying this method for end group analysis, several important issues need to be considered. The first one is related to the generation of source-fragment ions for different types of polymers. It appears that source fragmentation is quite efficient for a number of polymeric systems.[27−38] In fact, source fragmentation is one of the major concerns in determining molecular weights of polymer by ESI. For polymers that do not fragment efficiently, variation of ESI conditions such as the change of solvents and types of cation can influence the extent of source fragmentation.[32,37]

For two identical end groups, the described method herein does not indicate the number of the end groups linked to the polymer. In addition to that, careful examination of the source fragmentation (Figures 2B and 4B) or high-energy CID fragmentation (Figures 2A and 4A) spectra of both polymers reveals, according to the A_n ion series, that another candidate for the end group can be postulated. A consecutive loss of the monomer unit (44 u) from all A_n ions implies that an $H(OCH_2CH_2)_n$ terminal satisfies requirements to be considered as an alternative end group. However, complementary information can be obtained from an ESI MS or MALDI MS spectrum of the intact polymer that provides the total mass of the end groups attached to the polymer terminals. Thus, the correct number and identity of the end groups can be conclusively determined by the combination of polymer MS and ESI source fragmentation/MS/MS. In the case of poly(oxyethylene) bis(acetaminophen) and poly(oxyethylene) bis(ephedrine), the desired polymeric product has ephedrine or acetaminophen linked to the polymer at both ends. Dosage determination of these slow-releasing drugs is partly dependent upon the success of derivatization of the polymer. For the two samples examined in this work, both ESI and time-lag focusing MALDI-TOF mass analysis of the oligomers indicated that there are two drugs attached to both ends.[41]

For a nonsymmetric polymer with different end groups in α and β terminals, it remains to be seen whether a combination of polymer MS and ESI source-fragmentation MS/MS can provide an unambiguous assignment of the end groups to the proper terminals. In this case, the end group assignment would depend on the concomitant generation of source-fragment ions that contain the respective α and β terminal end groups.

For the production of end group fingerprint spectra, the method described does not require the use of an on-line separation

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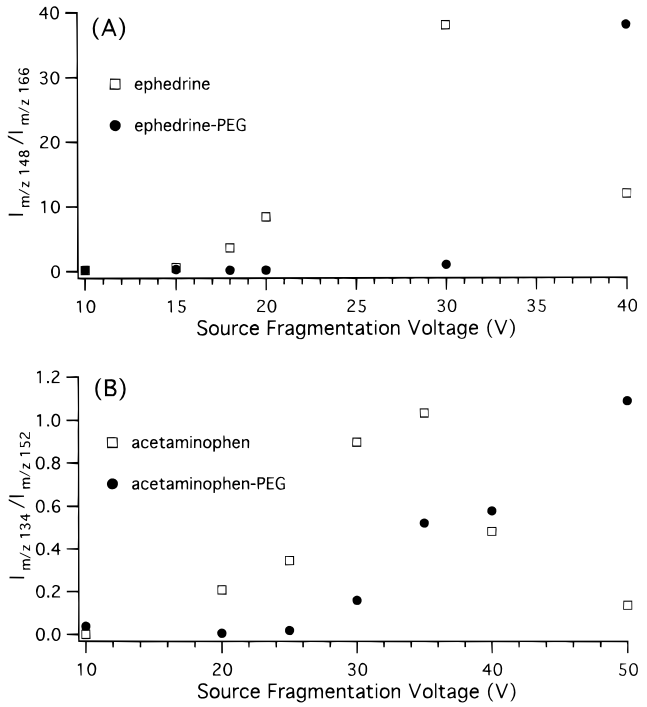

Figure 6. Ion stability diagrams of source fragmentation from (A) poly(oxyethylene) bis(ephedrine) and ephedrine and (B) poly(oxyethylene) bis(acetaminophen) and acetaminophen.

technique. This provides the advantage of simplicity and no need of compromising ESI condition and separation conditions. Infusion experiment also provides polymeric ion signals over a long period, ensuring the selection of many different source-fragment ions for CID. However, one has to be aware of the possible presence of any low-mass impurities in the polymer sample that may cause complications in spectral interpretation. For instance, the fragment ion peak observed at m/z 148 in Figure 2 could be simply from ephedrine that might be present in the sample. While off-line separation by liquid chromatography to get rid of low-mass impurities prior to MS/MS experiments is an obvious option, another way to check the origins of low-mass peaks is to examine the source-fragmentation behaviors of different species with common groups. This is illustrated in Figure 6.

Figure 6 shows the distributions of important diagnostic ions formed in source fragmentation. The two sets of data shown in Figure 6A were obtained by source fragmentation of ESI-generated ephedrine and poly(oxyethylene) bis(ephedrine), respectively. In the case of ephedrine, the intensity of the ion R^+ at m/z 148 was measured relative to the intensity of the protonated molecular ion of ephedrine ROH_2^+ at m/z 166 at various fragmentation voltages (V_{CID}). For ephedrine-attached PEG, the signal at m/z 166 was at the background level and the ratio of peak intensities at m/z 148 and 166 was calculated for comparison. Figure 6A illustrates that, at V_{CID} of 30 V, only the formation of the m/z 148 ion originated from ephedrine takes place. A further increase in V_{CID} causes dissociation of the m/z 148 ion derived from ephedrine and formation of the m/z 148 ion initiated from ephedrine−PEG. The corresponding graphs for acetaminophen and acetaminophen-attached PEG are presented in Figure 6B. The intensity of the ion R^+ (m/z 134) was measured relative to the intensity of the ion at m/z 152 (i.e., the protonated molecular ion peak in the case

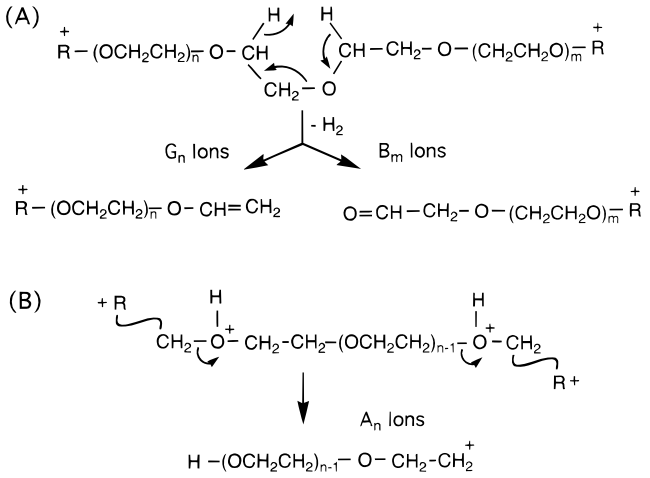

Figure 7. Polymer ion fragmentation schemes. (A) Formation of G_n and B_m ions and (B) formation of A_n ions.

of acetaminophen) at various fragmentation voltages (V_{CID}). Figure 6 clearly shows that in both cases higher V_{CID} is required to produce a significant amount of end group-related species from the polymer. Thus, the presence of strong ion signals at m/z corresponding to the intact molecular ion peak of end group initiators (i.e., m/z 166 for ephedrine and m/z 152 for acetaminophen) and end group-containing fragment ions (i.e., m/z 148 for ephedrine and m/z 134 for acetaminophen) at low source voltages would suggest the presence of some impurities in the sample. Sample cleanup or more vigorous sample cleanup (if already done once) prior to MS/MS experiments is needed.

Considering the CID spectra of oligomers, the presence of the fragment ions not related to the end groups raises the question about the nature of these ions. Figure 7 shows the proposed mechanism for the formation of the ions present in CID spectra of poly(oxyethylene) bis(ephedrine) and poly(oxyethylene) bis(acetaminophen). In an electrospray ionization process, an oligomer of a polymer accommodates four protons for +4 ions. Considering the proton affinity of amines or amides versus that of ethers,[42] protonation should take place at the NH functionality of a polymer end group. It is represented in Figure 7 by the end group R carrying the charge. Such protonated sites possess a well-stabilized charge center and will favor charge-remote fragmentation in CID.[40] The reaction scheme for this process is shown in Figure 7A. Charge-remote decompositions can account for all major CID fragments from the G_n series containing end group information. Note that ions from the B_n series are not observed in the CID spectra. The remaining labile protons randomly move along a polymer chain and interact with ether oxygen atoms. The random location of protons creates many possible reaction sides. Figure 7B illustrates formation of the A_n series ions. They are generated by charge-site-catalyzed (inductive) cleavages.[40] The incipient ionic products of these decompositions would be primary carbonium cations. Such ions are prone to further fragmentation and isomerization and may rearrange to more stable structures during or after formation. The ions from the A_n series do not contain end group information.

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CONCLUSIONS

A method based on electrospray ionization sector/time-of-flight mass spectrometry has been developed for obtaining structural information on polymer end groups. This method relies on the use of source fragmentation to generate low-mass fragment ions from polymer ions formed by electrospray ionization. Two types of ions, similar to those observed in high-energy CID of oligomer ions, are generated from source fragmentation of poly(oxyethylene) bis(acetaminophen) and poly(oxyethylene) bis(ephedrine). One group of ions generated by the cleavage of the polymer chain does not contain end group information, whereas the second group contains end groups. High-energy CID of the second group ions produced spectra bearing information of end groups. These spectra can be used as a fingerprint to compare with the CID spectra of standard compounds for unambiguous structural identification of end groups. This method, along with oligomer mass information obtained from techniques such as ESI MS or MALDI-TOF, should be useful for studying "unknown" end group structures. This method does rely on the availability of CID library spectra in order to find a satisfactory match. Fortunately, in polymer analysis, some prior knowledge of the end group chemistry is always available from the polymer chemistry used for the synthesis. The initiators and their analogues are available and can be used to generate a CID library for spectral comparison. The laborious aspect of the method will depend on the complexity of the polymeric system under investigation. The applications of this method for structural characterization of other types of polymers will be reported elsewhere.

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