Information on the Monomer Sequence of Poly(lactic acid) and Random Copolymers of Lactic Acid and Glycolic Acid by Examination of Static Secondary Ion Mass Spectrometry Ion Intensities

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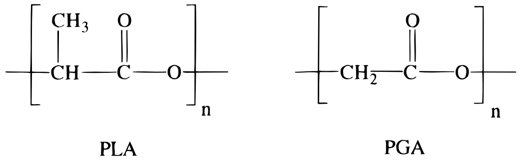
Received May 9, 1995; Revised Manuscript Received September 18, 1995[⊗]

ABSTRACT: Static secondary ion mass spectrometry (SSIMS) has been used to analyze a range of poly(lactic acid)s (PLA) and copolymers of lactic and glycolic acids (PLGA). Ion assignments for the full range of radical cations observed are presented, along with the observation of chain end contribution to the SSIMS spectra in the case of low molecular weight PLA. The ion intensities within different radical cation series in PLGA have been compared with theoretical intensity distributions. In the case of random copolymers, the radical cation intensities are almost identical with the predicted binomial distribution. Dimeric character in some of the polymers is demonstrated using a statistical approach.

Introduction

Poly(D,L-lactic acid) (PLA) is a biodegradable polymer which has been exploited in such applications as drug delivery and biomedical implants.[1−3] Modifications to the degradation kinetics and mechanical properties of PLA can be achieved through blending with another (biodegradable) polymer, or by copolymerizing lactic acid with another monomer. One monomer which has successfully been copolymerized with lactic acid is glycolic acid; the structures of both PLA and poly(glycolic acid) (PGA) are



Both PLA and PGA have been analyzed by static secondary ion mass spectrometry (SSIMS) previously.[4] Since both biological interactions and polymer erosion occur at the polymer/biofluid interface, it is important to understand how changes to the polymeric bulk structure influence the surface properties of the material. XPS and SIMS confirmed that the interfacial compositions of the PLA and PGA homopolymers reflected the bulk compositions, and similar studies have been performed on other biodegradable polymers such as poly(ortho esters)[5,6] and polyanhydrides.[6,7] For instance, it has been shown by this group that immiscible blends of PLA with another biodegradable polymer, poly(sebacic anhydride), form films with a surface excess of PLA, which has significant implications for the initial rate of polymer degradation.[8,9]

In this paper, we highlight the role that SSIMS can play in the analysis of PLA and PLGA. Of particular importance to this paper is the detection of short block sequences of LA or GA within the copolymeric chain which may have implications in terms of preferential surface segregation of polymer chains rich in one of the components, influencing biological interactions with the copolymer and the degradation kinetics.

SSIMS has been used previously to examine the surface chemistry of random copolymers. Often, secondary ions specifically deriving from each of the comonomers can be identified and their intensities compared to provide an estimate of the near surface concentration of each component.[10−12] In some cases it is possible to detect secondary ions that result from two different comonomer units being adjacent to each other.[13,14] Lub *et al.* examined random copolymers of methyl methacrylate (MMA) and ethyl methacrylate (EMA) by SSIMS, and ions derived from MMA−MMA, EMA−MMA, and EMA−EMA diads within the copolymers were identified.[15] The intensities of these peaks were shown to follow a statistical model based upon a random copolymer, with some deviation which can be related to differences in secondary ion yields of the fragments (the ion derived from the MMA−MMA diad always being more intense than expected). To our knowledge this is the only example of a statistical model of ion intensities in the literature.

We show in this paper that a statistical approach can be successfully employed on the SSIMS data from PLGA copolymers to determine short range order and demonstrate deviations from a random structure. The differences in ion intensities can be related to short range structure in the polymer, and we show that in some of these polymers there is some dimeric structure. Confirmation of these results is provided by NMR which can be used to determine an average lactic acid block length. This indicates deviation from a random structure but cannot directly provide evidence of dimeric character in the copolymer.

Experimental Section

Polymers. Homopolymers of poly(D,L-lactic acid) with different molecular weights were obtained from the following sources: low molecular weight samples with a weight average molecular mass M_w 2000 g/L (courtesy of Prof. A. Domb, Hebrew University, Jerusalem, Israel) and 50 000 g/L (Poly-

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[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

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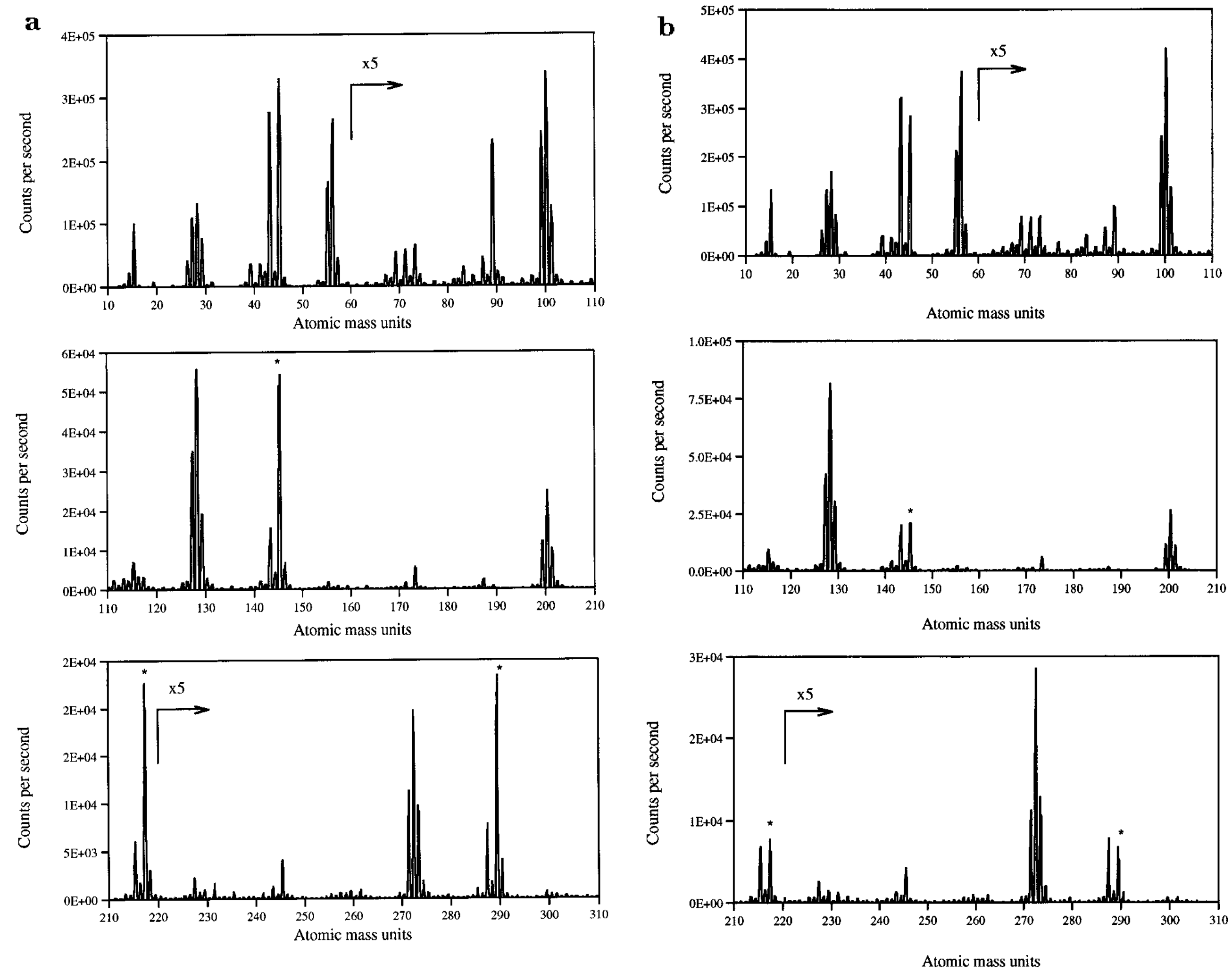


Figure 1. (a) Positive SSIMS spectrum from M_w 50 000 PLA. (b) Positive SSIMS spectrum from M_w 2000 PLA. (nM + H)$^+$ ions are marked with asterisks (n = 2−4).

sciences Inc., Warrington, PA). Copolymers of D,L-lactide and glycolide (PLGA) with a composition of 50:50 mol % and different molecular weights M_w 17 000 (RG 502) and M_w 40 000 (RG 503) were obtained from Boehringer, Ingelheim. PLGA with a monomer ratio of 75:25 and M_w 20 000 (RG 752) was from the same supplier. These polymers are prepared by a ring-opening polymerization of lactide and glycolide using stannous octoate as catalyst. Poly(L-lactic acid) M_w 94 000 and PLGA 75:25 M_w 19 000 were synthesized by a modified polycondensation method.[16]

The PLGA polymers were characterized by size exclusion chromatography on a GPC column (Lichrogel PS mix and Lichrogel PS 40), thermostated at 30 °C using dichloromethane as solvent and a differential refractometer as detector. Molecular weights were calculated using polystyrene reference materials (Merck, Darmstadt, Germany). The ^{13}C-NMR spectra were obtained from $CDCl_3$ solutions containing TMS as reference at 25 °C on a JNMR-GX 400 NMR spectrometer (JEOL, Welwyn Garden City, U.K.).

Surface Analysis. Polymers were dissolved in HPLC grade chloroform (Fisons Scientific Equipment, Loughborough, U.K.) to give 1% w/v solutions. Then 50 μL aliquots of these solutions were cast onto aluminum-coated sample stubs spinning at 5000 rpm. The films were then allowed to dry prior to analysis.

SSIMS spectra were obtained using a VG Ionex SIMSLAB 3B instrument equipped with a differentially pumped EX05 ion gun and a 12−12 M quadrupole mass spectrometer. Argon atoms at 2 keV were used as the primary source with an equivalent current of 1 nA. The total dose per sample was approximately 5 × 10^{12} atoms/cm^2, which is within the regime of the static SIMS experiment.[17] The polymeric film was thin enough to obviate the need for charge compensation. Data acquisition and handling was performed on either a VGS5250 system based on a DEC PDP11 computer or a Spectra V 6.00-D-MS system based on an IBM-PC compatible computer.

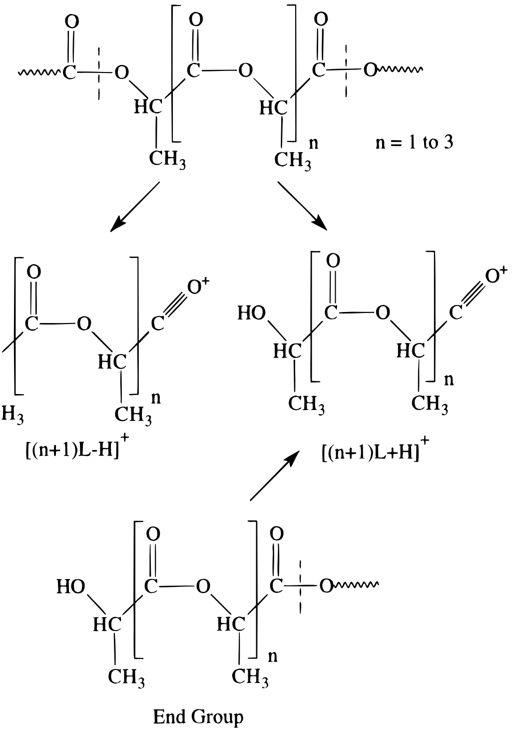
Results and Discussion

PLA Homopolymer. In the discussion following we will only refer to the positive ion SSIMS spectra of the compounds under investigation. Negative ion SSIMS spectra were also collected and found to be in close agreement with previous studies.[4] However such data are not relevant to the investigation presented here.

All of the polymer films analyzed were found by SSIMS to give no signals diagnostic of organic or inorganic contaminants. No intense signal was found at m/z 27 in the SSIMS positive ion spectra indicating that the films were defect free and continuous, completely covering the aluminum substrate.

The spectrum of PLA M_w 50 000 is shown in Figure 1 with the spectrum of the M_w 2000 polymer for comparison. In all features the M_w 94 000 PLA spectrum (not shown) is identical to that of the M_w = 50 000. The SSIMS spectra of poly(lactic acid) (M_w ~2500), not shown, have been reported previously by this group,[4] and the spectra presented here are in generally good agreement with that work. There are, however, some differences in intensity between the spectra in our present work and those published previously. Most notably, it is found that the intensity of the radical cations at m/z 100 and 128 are much greater than their neighboring ions in this work. In addition, the strong cation at m/z 83[4] in the positive ion spectrum for PLA is of low intensity in the present work. These differences may arise from the fact that different spectrometers were used to acquire the spectra but may also be due to a low level of contamination in the previous samples (as evidenced by the larger than expected hydrocarbon peak in the C_{1s} XPS spectra[4]).

The most significant differences between the spectra of high molecular weight and oligomeric PLA shown in Figure 1 are the ion intensities appearing at m/z 145, 217, and 289. These ions correspond to the $(n\mathrm{L} + \mathrm{H})^+$ series where $n = 2-4$; there is also a corresponding $(n\mathrm{L} - \mathrm{H})^+$ sequence which is apparent at m/z 143, 215, and 287. To avoid confusion in the remainder of the text, the letter "L" refers to a monomer unit of lactic acid, and the letter "G" will be used to refer to a monomer unit of glycolic acid. The letter "M" will be used as a general term for both lactic and glycolic acid monomer units. In the lower molecular weight polymer, and also in previous spectra of PLA oligomers,[4] the intensities of the $(n\mathrm{L} + \mathrm{H})^+$ peaks are greater than those of the $(n\mathrm{L} - \mathrm{H})^+$ ions, but in the case of high molecular weight PLA (both the 50 000 and the 94 000) these ion pairs are of roughly equal intensity.



We propose that this change in intensity is caused by a strong contribution of end-group-derived ions in the case of the low molecular weight material. This is illustrated by the reaction scheme above. Previously,[4] these $(n\mathrm{L} \pm \mathrm{H})^+$ ions were assigned to fragments containing an intact carboxyl group existing as the free acid with the positive charge residing on a carbon atom. The structures we have given here involve cleavage of the carboxyl group at the carbon–oxygen single bond, and in the assigned structures we have postulated that the positive charge resides on a heteroatom. This kind of cleavage is commonly found in the mass spectra of aliphatic acids and esters.[18] Formation of the $(n\mathrm{L} \pm \mathrm{H})^+$ ions from the main chain involves scission of two ester groups. The loss or gain of a hydrogen atom produces either an alcohol or a ketone group at the uncharged end of the fragment. In the case of high molecular weight PLA these two processes appear to occur with an equal probability, since for any given $(n\mathrm{L} + \mathrm{H})^+$, the $(n\mathrm{L} - \mathrm{H})^+$ peak is of roughly equal intensity.

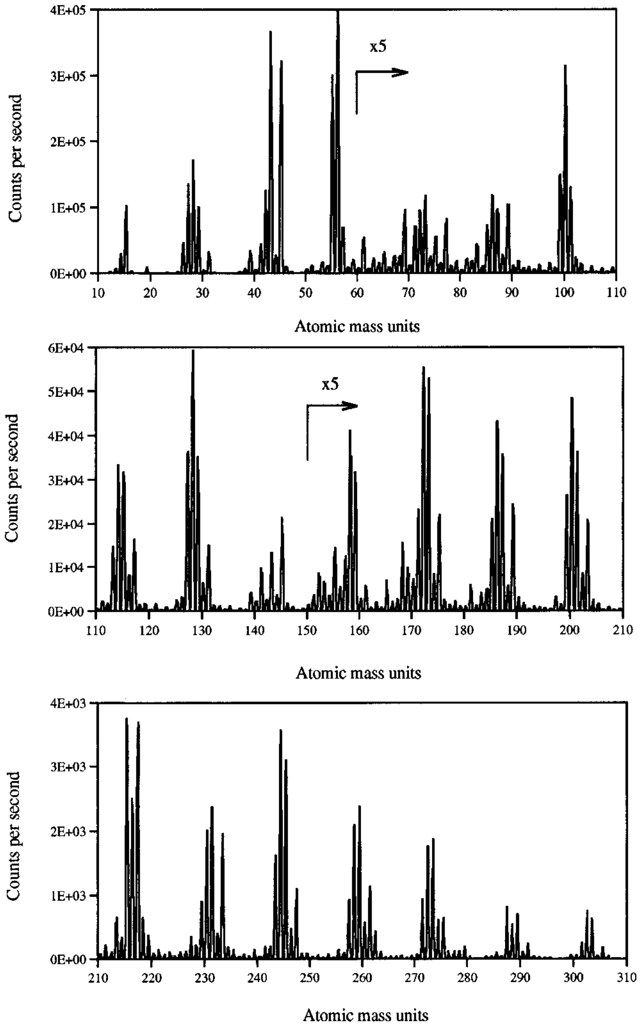
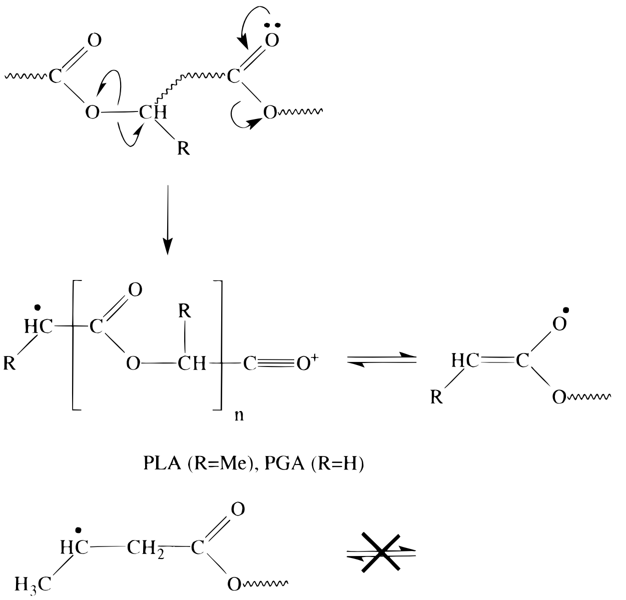


Figure 2. Positive SSIMS spectrum of 50% LA M_w 17 000 copolymer.

Contribution to the $(n\mathrm{L} + \mathrm{H})^+$ can also occur from the free alcohol end group, as shown in the reaction scheme. The end group, following the single bond cleavage shown, would result in the formation of cations assigned solely to the $(n\mathrm{L} + \mathrm{H})^+$ ion. This effect would be particularly apparent in low molecular weight PLA where there are a greater number of end groups per unit volume. Since there are approximately 28 repeat units of lactic acid in one polymer chain of PLA M_w 2000, one might expect the intensity of ions derived from the end group to be small. However, it has been shown in other polymeric systems that end groups and pendant groups often give rise to ions which have a disproportionately large ion yield.[19,20] Such an effect may be rationalized by considering that a single bond cleavage requires less energy than multiple bond cleavages, and single bond scissions will be able to occur at a greater range of sites in the vicinity of a primary ion impact event. This will greatly increase the number of ions produced from end groups and explains the large intensities of the m/z 145, 217, and 289 ions in the SSIMS spectra of oligomeric PLA.

PLGA Copolymers. The ion series $(n\mathrm{L} - \mathrm{O})^{\bullet+}$ is particularly notable in the SSIMS spectra of PLA: these ions appear with the two related even electron ions $(n\mathrm{L} - \mathrm{OH})^{+}$ and $(n\mathrm{L} - \mathrm{O} + \mathrm{H})^{+}$ which differ by one atomic mass unit from the radical cation. Strong ions can be observed for $n = 1-5$ at *m*/*z* 56, 128, 200, 272, and 344, respectively. An analogous series is found in PGA at *m*/*z* 42, 100, 158, 216, and 274, respectively. However, no such series can be found for poly(hydroxybutyrate) (PHB) or poly(caprolactone) (PCL), both closely related polyesters. In the previous paper,[4] these fragments were assigned to cyclic species. The high intensity of such cations can be readily explained by a resonant stabilization of the radical following a homolytic cleavage of the ester bond; see reaction schemes below. This kind of stabilization is not possible for PHB, and hence the positive SSIMS spectrum for this polymer does not display strong radical cations of this type. The long-lived radical cations from PLA and PGA may well cyclize either prior to or following emission from the surface, but since ring closure would result in a loss of resonant stabilization we now think this is unlikely.

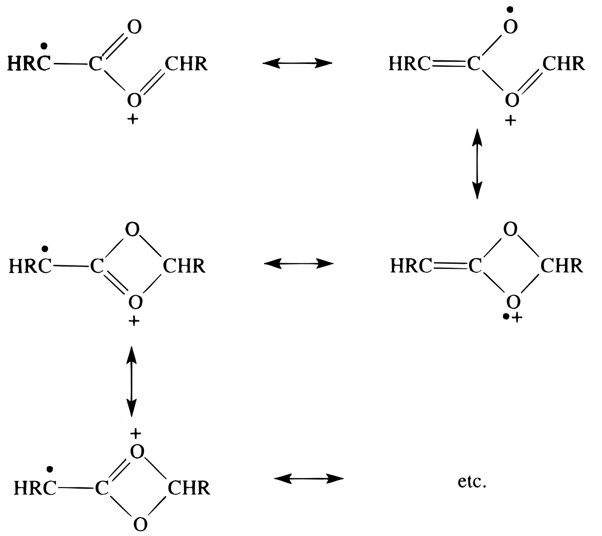


PLA also produces a radical cation at *m*/*z* 100, which has been assigned to the $(2\mathrm{L} - \mathrm{CO_2})^{\bullet+}$ ion,[4] but could also be the $(2\mathrm{L} - \mathrm{C_2H_4O})^{\bullet+}$ ion. The analogous PGA ions, $(2\mathrm{G} - \mathrm{CO_2})^{\bullet+}$ and $(2\mathrm{G} - \mathrm{CH_2O})^{\bullet+}$, would appear respectively at *m*/*z* 72 and 86, and only the *m*/*z* 72 ion appears in previously published PGA SSIMS spectra,[4] which suggests that the $(2\mathrm{M} - \mathrm{CO_2})^{\bullet+}$ assignment is correct. In Figure 2, the positive ion spectra of the commercially produced 50% LA (M_w 17 000) copolymer is shown. Ions at both *m*/*z* 72 and 86 are evident; these are respectively the $(2\mathrm{G} - \mathrm{CO_2})^{\bullet+}$ ion and the $(\mathrm{GL} - \mathrm{CO_2})^{\bullet+}$ ion which consists of one monomer unit of lactic and one of glycolic acid. The ion at *m*/*z* 86 almost certainly derives from lactic acid and glycolic acid monomer units which were adjacent to each other within the copolymer prior to ion impact.

Actual structures have not been assigned to these species, and it is interesting that the only signal caused by other ions with the general formula $(n\mathrm{M} - \mathrm{CO_2})^{\bullet+}$ appears for $n = 1$ at *m*/*z* 28; the $n > 2$ ions do not appear. The stability of these odd electron species must be intrinsic to the structure of the $(2\mathrm{M} - \mathrm{CO_2})^{\bullet+}$ ion. A large number of canonical forms for this ion may be drawn if an intermediate four-membered cycle is allowed to exist; only a few of the possible structures are shown below. The existence of such resonance hybrids will contribute to the stability of the radical cation. It is not possible for such structures to exist for $(n\mathrm{M} - \mathrm{CO_2})^{\bullet+}$ except in the case $n = 2$, and this would explain why only this ion is observed. Verification of this possibility could be achieved by using tandem secondary ion mass spectrometry[21] on PLA which has had one of the two different oxygen environments selectively substituted with the $^{18}\mathrm{O}$ isotope. If the cyclic structure exists, there should be a "scrambling" of the isotopically different oxygen atoms which would be evident in further fragmentation of the ion.

Table 1. Radical Cation Masses for Ions of the Type $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ Observed from Lactic Acid−Glycolic Acid Random Copolymers

no. of glycolic acid units	$(2\mathrm{M} - \mathrm{O})^{\bullet+}$	$(3\mathrm{M} - \mathrm{O})^{\bullet+}$	$(4\mathrm{M} - \mathrm{O})^{\bullet+}$
0	128	200	272
1	114	186	258
2	100	172	244
3		158	230
4			216



The spectra of all of the lactic−glycolic acid copolymers demonstrate radical cations of the type $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ that are formed from all the possible combinations of lactic and glycolic monomer units; an example spectrum is shown in Figure 2. Table 1 lists the ion masses for each composition of monomer units. The existence of these ions in strong intensity is a good indication of the random nature of these copolymers. The mixture of lactic (L) and glycolic (G) units in the cation are the same as the original composition of the parent polymer chain section. Furthermore, the intensity of ions with differing L or G contents within each $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ series can be directly related to the polymer composition if we make the following assumptions for this type of ion:

(1) Fragmentation, ionization, and sputtering occur with equal probability regardless of the type of monomer unit (lactic or glycolic acid) at the site, or adjacent to the site, of bond scission.

(2) All radical cations have the same stability—once again regardless of the composition of the fragment ion.

Given these assumptions, within one $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ cluster the fraction of ions with one particular composition should be directly proportional to the number of sites containing that composition in the polymer, which can be predicted on statistical grounds.

For a random copolymer the predicted spectral intensity can be calculated by using a simple binomial distribution. If $p(\mathrm{L})$ represents the probability of finding a lactic acid unit at any given site in the copolymer, then $1 - p(\mathrm{L})$ is the probability of finding a glycolic acid unit in a particular site. The predicted intensity distribution for the $(4\mathrm{M} - \mathrm{O})^{\bullet+}$ series in the 75% lactic acid copolymer would then be $I\{(4\mathrm{G} - \mathrm{O})^{\bullet+}\} = (0.25)^4 = 0.004$, $I\{(3\mathrm{GL} - \mathrm{O})^{\bullet+}\} = 4 \times 0.75 \times (0.25)^3 = 0.05$, $I\{(2\mathrm{G}2\mathrm{L} - \mathrm{O})^{\bullet+}\} = 6 \times (0.75)^2 \times (0.25)^2 = 0.21$, etc. where $I\{\mathrm{X}\}$ represents the peak area of component X divided by the total peak area for all ions ion the $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ group. These distributions were calculated for the $(2\mathrm{M} - \mathrm{O})^{\bullet+}$, $(3\mathrm{M} - \mathrm{O})^{\bullet+}$, and $(4\mathrm{M} - \mathrm{O})^{\bullet+}$ series.

Peak areas for all the $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ radical cations within the SSIMS spectra of each of the copolymers were measured. The spectra of the M_w 19 000 75% LA and M_w 40 000 50% LA copolymers were repeated three times on different samples to test the reproducibility of the spectral intensities. In the pure PLA spectrum, there are significant contributions from ions at *m*/*z* 100, as mentioned previously, and *m*/*z* 216 which also influence the observed intensity distributions in the copolymers. These ions do not belong to the series we are interested in but appear at the same mass; hence their contribution to the observed peak intensity needs to be eliminated. We removed these contributions by comparing the ion intensity at these two masses to the intensity of the $(n\mathrm{L} - \mathrm{O})^{\bullet+}$ peaks at *m*/*z* 128 and 272, and then in each data set we subtracted the proportion of the peak intensity at *m*/*z* 100 and 216 that was predicted to have come from purely lactic acid containing sites in the polymer (66% of the *m*/*z* 128 peak area was subtracted from the *m*/*z* 100 peak area, and 17% of the *m*/*z* 272 peak area from the *m*/*z* 216 peak area).

Following these corrections Figure 3 shows that very good agreement was found between the predicted and observed normalized peak intensities for all $(n\mathrm{M} - \mathrm{O})^{\bullet+}$ ions in the case of the 19 000 M_w 75% LA copolymer. There was a slight difference in absolute ion intensities and those calculated, especially across the *m*/*z* 216−272 $(4\mathrm{M} - \mathrm{O})^{\bullet+}$ series. The low-mass ions were slightly more intense than expected, and the higher mass ions slightly weaker. Since the sensitivity of quadrupole mass spectometers is mass dependent,[22] this effect is to be expected and will become more prominent as the mass range over which a series is spread increases.

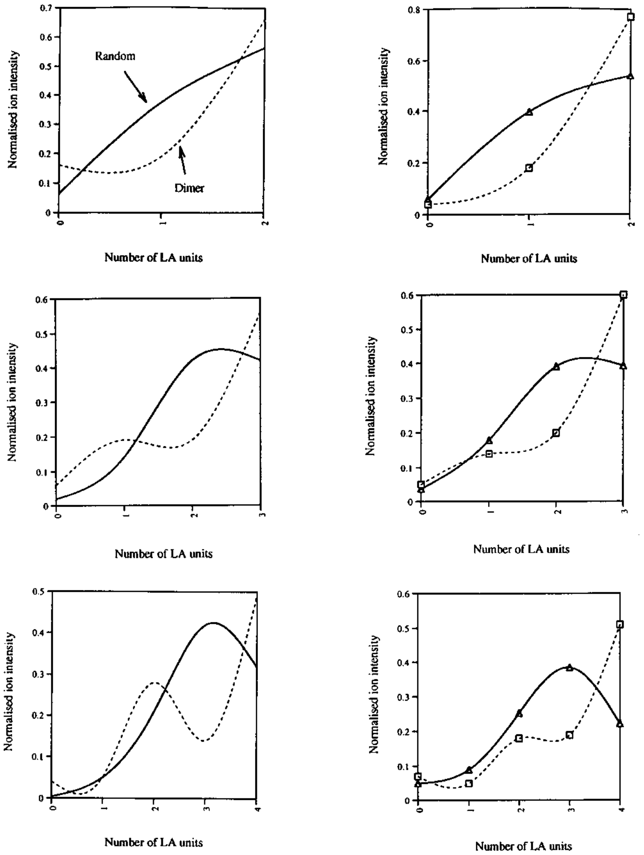
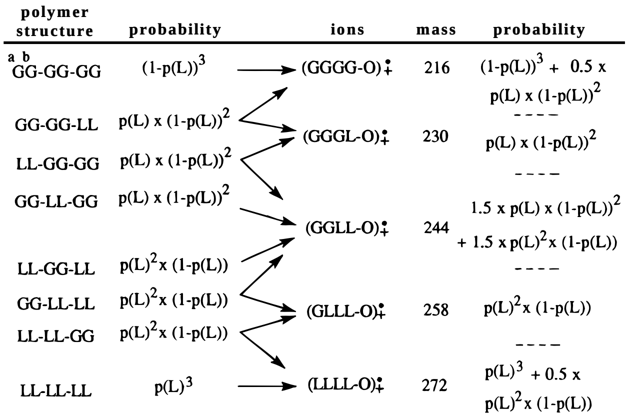


Figure 3. Comparison of calculated and experimental values for 75% LA copolymer normalized ion intensities: left side, calculated values; right side, experimental values (squares, RG752; triangles, 19 000 M_w); top, *m*/*z* 100−128 series; middle, *m*/*z* 158−200 series; bottom, *m*/*z* 216−272 series. All lines are interpolations through data points.

Table 2. Example Calculation of Ion Intensities Derived from "Random Dimeric" PLGA Copolymers for the Ion Series $(4\mathrm{M} - \mathrm{O})^{\bullet+}$



polymer structure	probability		ions	mass	probability
$^{a\ b}$GG-GG-GG	$(1\text{-}p(L))^3$	→	$(GGGG\text{-}O)^{\bullet+}$	216	$(1\text{-}p(L))^3 + 0.5 \times p(L) \times (1\text{-}p(L))^2$
GG-GG-LL	$p(L) \times (1\text{-}p(L))^2$	↗ ↘			----
			$(GGGL\text{-}O)^{\bullet+}$	230	$p(L) \times (1\text{-}p(L))^2$
LL-GG-GG	$p(L) \times (1\text{-}p(L))^2$	↗ ↘			----
GG-LL-GG	$p(L) \times (1\text{-}p(L))^2$	↘	$(GGLL\text{-}O)^{\bullet+}$	244	$1.5 \times p(L) \times (1\text{-}p(L))^2 + 1.5 \times p(L)^2 \times (1\text{-}p(L))$
LL-GG-LL	$p(L)^2 \times (1\text{-}p(L))$	↗			----
GG-LL-LL	$p(L)^2 \times (1\text{-}p(L))$	↗ ↘	$(GLLL\text{-}O)^{\bullet+}$	258	$p(L)^2 \times (1\text{-}p(L))$
LL-LL-GG	$p(L)^2 \times (1\text{-}p(L))$	↗ ↘			----
LL-LL-LL	$p(L)^3$	→	$(LLLL\text{-}O)^{\bullet+}$	272	$p(L)^3 + 0.5 \times p(L)^2 \times (1\text{-}p(L))$

All of the other copolymers exhibited substantial deviations from the binomial model. Since all of the copolymers except for the 75% LA 19 000 M_w were synthesized using lactic and glycolic acid dimers, it is possible that some retained dimeric short range structure exists in the polymers. To investigate this possibility, the normalized ion intensity distributions for ions arising from a randomly repeating dimeric unit were calculated. An example of how this calculation was performed is shown in Table 2. The example shown is for the series $(4\mathrm{M} - \mathrm{O})^{\bullet+}$, and three dimeric repeat units have to be taken into account since cleavage can occur either (a) between adjacent dimer units or (b) within one dimer unit to produce the radical cations. Since we are assuming that there is an equal probability of either type of cleavage occurring, if more than one composition of ion can be formed from a particular dimer sequence, then both are produced with half the intensity of sequences where it is only possible to produce one kind of ion.

The interpolated results of these calculations are shown in Figure 3 along with the experimental results for the 75% LA copolymers. The results from the three experiments performed on the copolymer synthesized from the monomer demonstrate good reproducibility and, as mentioned previously, follow the pattern expected for a truly random copolymer. The 20 000 M_w 75% LA copolymer shows some dimer character, the experimental results are suggestive of a mixture between random and random dimeric character which probably is caused by transesterification processes

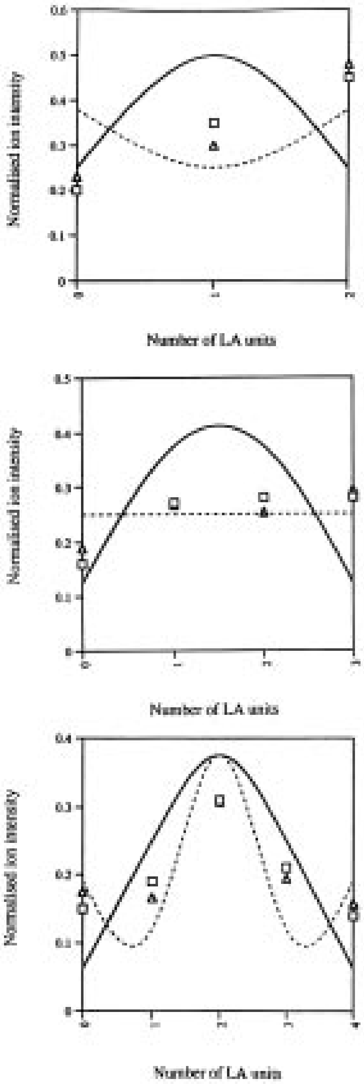


Figure 4. Comparison of calculated and experimental values for 50% LA copolymer normalized ion intensities: top, *m*/*z* 100−128 series; middle, *m*/*z* 158−200 series; bottom, *m*/*z* 216−272 series. Experimental values are shown as points (squares, RG502; triangles, RG503); theoretical values are shown as lines interpolated through data points.

during synthesis. Also notable is the higher than expected intensity of the purely lactic acid-containing fragments; this may be indicative of a preferential surface segregation of polymer segments which solely contain lactic acid units.

The two 50% LA copolymers were both produced from the acid dimers, and the spectra for both copolymers were essentially identical. The results are given in Figure 4 where the normalized ion intensities are compared with the predicted intensities. Both the $(3M - O)^{\bullet+}$ and $(4M - O)^{\bullet+}$ sequences follow intensity distributions that are indicative of a strong dimeric character within the copolymers. The $(2M - O)^{\bullet+}$ sequence, however, does not seem to fit either theoretical distribution, and this may be a result of the corrections made to the *m*/*z* 100 ion intensity to account for the $(2L - CO_2)^{\bullet+}$ ion. We assumed that the intensity of this ion was proportional to the intensity of the $(2L - O)^{\bullet+}$ *m*/*z* 128 ion, and this assumption is possibly erroneous. The distribution of ions in the $(2M - O)^{\bullet+}$ sequence can also be accounted for by considering that there is preferential surface segregation of lactic acid-containing units, as seen in the 75% LA copolymer. Some evidence of this may be found in the $(3M - O)^{\bullet+}$ sequence where the *m*/*z* 200 ion is often the most intense, but the $(4M - O)^{\bullet+}$ sequence does not give any indication of surface segregation and so this possibility does not appear to be supported by the other distributions in the same spectra.

Confirmation of these results is supplied by the NMR data. This revealed that the bulk composition of the copolymers was as expected and also demonstrated the nonrandom nature of some of the dimeric polymers. The average block length of PLGA copolymers can be evaluated using ^{13}C-NMR spectroscopy. The peak intensities of the carboxyl signals of the lactyl units (∼169 ppm) allow the calculation of the average block length L according to the following relationship.[23,24]

$$L = (I_{LL}/I_{GL}) + 1$$

I_{LL} and I_{GL} are the peak intensities of the LL and GL diads, respectively. The 75% LA copolymer synthesized by polycondensation shows an average block length of 1.9, which corresponds to an almost random distribution. The 50% LA M_w 17 000 copolymer obtained by a ring-opening polymerization yields $L = 2.7$, which is indicative of a nonrandom distribution.

Using appropriate preparation methods, SSIMS promises to be a reproducible method of analyzing and quantifying short range order in copolymers of lactic and glycolic acid in the bulk as well as at the surface. Such features may influence the degradation kinetics or the mechanical properties of the copolymers which have direct relevance to their use as drug delivery materials or as biodegradable surgical implants. NMR data do not provide evidence of a dimeric structure. Although this type of structure may be postulated from the polymerization route employed, the NMR data do not rule out the possibility of scrambled trimeric or higher order structures. SSIMS data provide this evidence, and statistical calculations based on trimeric and other structures show significant deviations from the experimental data. The detection of short range retention of dimeric structure using SSIMS for these copolymers is highly useful, since although NMR is able to detect this nonrandomness, it is unable to show whether there is any preferential surface segregation of PLA or PGA blocks in the dimeric systems, and this will be of utility in the interpretation of surface properties of these copolymers.

A number of issues have to be addressed before it is possible to routinely use this type of analysis for the copolymeric systems discussed here. These include possible surface segregation phenomena and the mass dependent sensitivity of quadrupole mass analyzers. The first of these points can only be investigated by analysis of a wide range of well-characterized copolymers; the second can be dealt with by the use of time of flight SIMS or by characterizing the spectrometer involved with a suitable set of standard materials.

Conclusions

A range of poly(lactic acid)s and copolymers of lactic acid and glycolic acid with differing molecular weights and compositions have been investigated with SSIMS. Some discussion on the assignment of structures to ions observed in the PLA spectra has been presented. It is found that the $(nL + H)^+$ series of ions is much stronger in low molecular weight PLA, and the contribution from polymer end-group-derived ions has been forwarded as an explanation for this observation. It is possible that these ions can be used as a probe for the evolution of low molecular weight species or chain ends at the surface of PLA during polymer degradation.

The strong presence of radical cations from both PLA and PGA has been well documented, and in this paper a possible explanation for the special stability of these ions is proposed. Further study of PLA and PGA by a tandem SIMS technique is necessary for a better understanding of the structures of these ions.

One random lactic/glycolic acid copolymer has been analyzed, and radical cation intensities have been excellently modeled using simple mathematics. The copolymers that were synthesized from the dimers of lactic and glycolic acids demonstrated short term order that was consistent with a "scrambled" random dimeric structure. We believe that this is the first time that deviations from a random copolymer structure have been demonstrated with the use of SSIMS. The utility of SSIMS in this respect is potentially greater than NMR in that the latter technique cannot provide information on the type of short range structure present. Further experiments are proposed which include the analysis of a much wider range of random copolymer compositions and the analysis of random dimeric copolymers which have varying levels of transesterification.

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MA950622I