The Analysis of the Surface Chemical Structure of Biomedical Aliphatic Polyanhydrides Using XPS and ToF-SIMS

M. C. DAVIES,[1,*] M. A. KHAN,[1] A. DOMB,[†,2] R. LANGER,[2] J. F. WATTS,[3] and A. J. PAUL[4]

[1]Department of Pharmaceutical Sciences, Nottingham University, Nottingham NG7 2RD, United Kingdom,
[2]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, and
[3]Materials Science Department, Surrey University, Guildford, Surrey GU2 5XH, United Kingdom
[4]CSMA, UMIST, Manchester M60 12D, United Kingdom

SYNOPSIS

The surface chemical structure of a range of aliphatic polyanhydride films has been examined using XPS and ToF-SIMS. The XPS data confirms the purity of the surface, and the experimental surface elemental ratios are in good general agreement with the known stoichiometry of the polyanhydrides. The ToF-SIMS spectra of the polyanhydrides are shown to be significantly different. The SIMS data conforms to a systematic fragmentation, in both negative- and positive-ion SSIMS spectra, occurring throughout the entire series of polyanhydrides examined. Radical cations are observed in the positive-ion spectra. These results are discussed in terms of the general fragmentation patterns observed in the SIMS analysis of polymers. The combined use of ToF-SIMS and XPS is shown to provide a detailed insight into the interfacial chemical structure of these polyanhydrides.

INTRODUCTION

Polyanhydrides have recently shown considerable potential for the controlled release of bioactive molecules.[1-5] The choice of the hydrolytic sensitivity of the anhydride bond coupled with a wide range of aliphatic and aromatic backbone structures available permits the programming of a wide range of polymer degradation[6] and, hence, drug release rates. Polyanhydrides are one of the few synthetic polymers employed in human patients. They have demonstrated good tissue biocompatability *in vivo,* and their breakdown products have shown no adverse toxicological effects.[7]

The bulk and solution stability of the polyanhydrides have been examined in depth previously.[8] As a preface to studying (in the solid state) the mechanism of surface hydrolysis of these polymers *in vitro* and *in vivo,* we report for the first time on the char-

acterization of the surface chemistry of polyanhydride films using time-of-flight secondary ion mass spectrometry (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS). Over the last decade, SIMS and XPS have been shown to be powerful complementary techniques for determining the interfacial chemistries of polymers.[9-11] SSIMS and XPS have proven potent tools for the *in situ* solid-state analysis of the surface chemical structure of a range of biomedical polymers including the polyurethanes[12,13] and polyesters.[14] Hence, these techniques may be used to both confirm polyanhydride structure and provide some insight into the polymer surface chemistry. This article reports an XPS and ToF-SIMS study on a homologous series of aliphatic polyanhydrides of the following general structure:

$$\left[\begin{matrix} O & & O \\ \parallel & & \parallel \\ C - (CH_2)_x - C - O \end{matrix} \right]_n$$
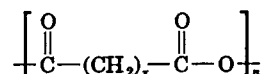
where x is 4, 6, 7, and 8 for poly(adipic anhydride), poly(suberic anhydride), poly(azelaic anhydride) and poly(sebacic anhydride), respectively.

Table I Bulk Data Analysis of Polyanhydrides[a]

| Polymer | Melting Point (°C) | Molecular Wt[b] | | Viscosity[c] (dL/g) | IR[d] (cm^{-1}) |
		M_w	M_n		
Poly(adipic anhydride)	74–75	14,400	4,800	0.19	1810, 1740
Poly(suberic anhydride)	69–71	86,500	17,500	0.81	1810, 1740
Poly(azelaic anhydride)	71–72	40,900	10,650	0.38	1820, 1745
Poly(sebacic anhydride)	69–70	84,500	18,900	0.83	1820, 1745

[a] Polymerized at 180°C for 90 min.
[b] Determined by GPC using chloroform as eluent and with polystyrene standards.
[c] Determined at 23°C in chloroform.
[d] Characteristic for anhydride bonds.

EXPERIMENTAL

Sample Preparation

Poly(adipic anhydride) (PA), poly(suberic anhydride) (PSU), poly(azelaic anhydride) (PAZ), and poly(sebacic anhydride) (PSE) were all prepared as described previously.[15] The crude polymer was purified by quenching in petroleum ether from chloroform solution. The polymers were characterized as previously described,[15] and the data analysis is summarized in Table I.

Solutions of 0.1% w/v polyanhydrides were prepared in analytical-grade chloroform. The polymers were then deposited onto chloroform–acetone cleaned aluminum foil by spin casting. All samples were analyzed within 2 h of preparation.

Spectroscopy

The XPS spectra were obtained using a VG Scientific ESCALAB Mk II electron spectrometer employing Mg k_α X rays ($h\nu$ = 1253.6 eV). The X-ray gun was operated at 120 W and placed relative to the sample surface to give a 45° electron take-off angle, thus analyzing the environments of elements present in the top 50 Å of the polymer surface. A survey scan spectrum (1000 eV) and narrow scans in the C1s and O1s regions were recorded for all samples. The analyzer was operated in the fixed analyzer transmission mode with a pass energy of 50 eV (for survey scans) or 20 eV (for C1s and O1s envelopes). Data acquisition and analysis was performed by a VGS 5000 data system based on a DEC PDP 11/73 computer. The peak fitting of the C1s and the O1s envelopes were performed using methodology described elsewhere.[16] The recorded spectra were corrected for sample charging (referenced to C—H/C—C at 285 eV in the C1s envelope).

The ToF-SIMS were obtained using a VG Ionex ToF-SIMSLAB, which has been characterized in detail elsewhere.[17] A 30 keV Ga$^+$ ion beam source was used, and the secondary ions were accelerated to 5 keV prior to mass analysis by applying a bias of the appropriate polarity of the sample. The total primary ion dose for each spectral acquisition was on the order of 1 × 10^{11} particles/cm^2, which falls well within the regime established for "static" SIMS analysis of polymers, as described by Briggs.[18]

RESULTS

XPS

The XPS wide scans for all the polyanhydrides revealed signals from carbon and oxygen only. This indicates that the surface is free from significant levels of inorganic impurities and organic contaminants containing atoms other than C and O. The experimental and theoretical C and O percentage for the polyanhydrides are presented in Table II. There is frequently a certain level of adventitious

Table II Experimental and Theoretical Surface Atomic Composition from Polyanhydride XPS Spectra

| Polyanhydride | Experimental (%) | | Theoretical (%) | |
	C	O	C	O
PA	70.0	30.0	66.6	33.3
PSU	74.1	25.9	72.7	27.3
PAZ	78.2	21.8	75.0	25.0
PSE	77.9	22.1	76.9	23.1

hydrocarbon contamination associated with the XPS analysis of polymers that results in higher than expected hydrocarbon signal at 285 eV. In this case, the origin of the extra hydrocarbon signal may arise from the aluminum window of the X-ray gun or from traces of residual petroleum ether solvent in the polymer after extraction and purification.

The C1s and O1s core level spectra are displayed for PA, PSU, PAZ, and PS in Figure 1. It has been necessary to employ four peaks to achieve the best fit in all polyanhydride C1s spectra. The main peak at 285 eV corresponds to the $\underline{C}$—H. The peak at 289.5 eV arises from O—$\underline{C}$=O. This is substantially greater than the conventional value of 289 eV for this environment.[10] This extra 0.5-eV shift is due to a secondary effect on the carbon-binding energy of O—C=O due to the adjacent carbonyl group. There is also a secondary shift of 0.7 eV for $\underline{C}$—CO$_2$, as originally proposed by Pijpers and Donners.[19] The final shift at 287.1 eV corresponds to $\underline{C}$H$_3$—O—C=O due to the methyl end groups of the polymer chains and is at a consistent level throughout the entire polymer series. The relative intensities of the C1s environments are in good agreement with the anticipated stoichiometry of these polyanhydrides.
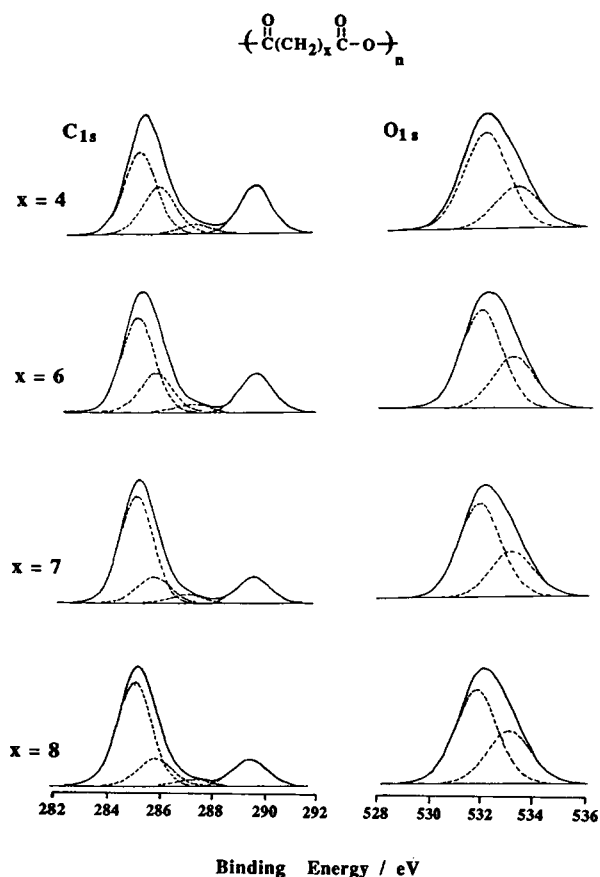
ToF-SIMS

The positive and negative ToF-SIMS spectra of PA, PSU, PAZ, and PS are presented in Figures 2–5 and 6–9, respectively. In agreement with the XPS data, no inorganic or organic contaminating species were detected in the SIMS analysis. No ions were detected above m/z 300, indicating the polymers were free of short-chain oligomers. For clarity, the positive- and negative-ion ToF-SIMS spectra will be discussed separately.

The lower mass region ($< m/z$ 100) of all the polyanhydride positive-ion SIMS spectra is dominated by nonspecific hydrocarbon fragments, i.e., $C_nH_m^+$, which are detected for all polymers. Prominent peaks are observed at m/z 29, 55, 69, 85, 101, and 111 as a "chemical fingerprint" for polyanhydrides in all positive-ion spectra. In contrast, the majority of the diagnostic ions are observed in the m/z 100–300 range. A consistent general fragmentation pattern is observed in the positive-ion spectra of all polymers examined, and the principal ions are shown in Table III. In each case, a dominant ion of the protonated monomer repeat unit, $(M + H)^+$ is observed, i.e., at m/z 129, 157, 171, and 185 for PA, PSU, PAZ, and PS, respectively, corresponding to the following structure:

$$\overset{O}{\overset{\|}{^+C}}-(CH_2)_x-\overset{O}{\overset{\|}{C}}-OH \qquad (MH)^+$$
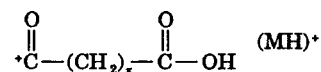
$(M + H)^+$ ions are accompanied by, and dominate, low-intensity $(M - H)^+$ cations. It is particularly interesting to note the presence of the even-numbered ions, e.g., at m/z 128 for PA, which are radical cations, i.e., even-electron ions, corresponding to the mass of the monomer repeat unit, i.e., M^+ as follows:

$$\left[\overset{O}{\overset{\|}{C}}-(CH_2)_x-\overset{O}{\overset{\|}{C}}-O\right]^{+\cdot} \qquad M^{+\cdot}$$
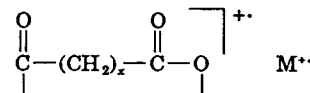
Prominent ions, equivalent to the loss of water from the protonated molecular ion $(MH - H_2O)^+$ or alternatively $(M - OH)^+$, are observed in all positive-ion SIMS spectra. In addition, dominant cations corresponding to the addition of the carbonyl group

$$-\left(\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}-O\right)_n$$

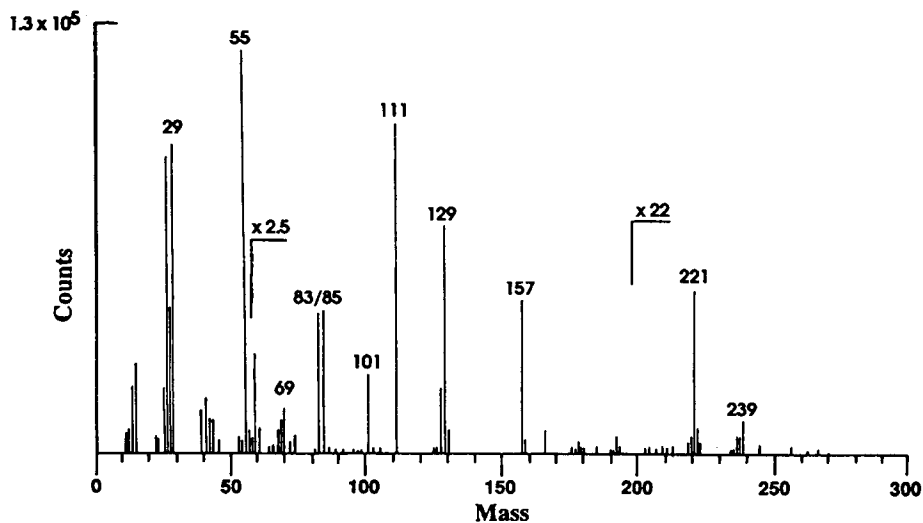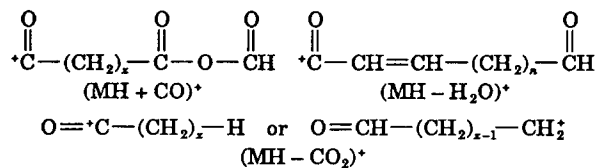**Figure 1**   The C1s and O1s core level envelopes for polyanhydrides PA, PSU, PAZ, and PSE.

Figure 2 Positive-ion ToF-SIMS spectrum of PA.

to the protonated monomer unit, $(MH + CO)^+$, are detected for all polymers. Similarly, low-intensity $(M \pm H - CO_2)^+$ cations are observed. These ions are presented in Table III, and the corresponding structures is depicted as follows:

$$\overset{O}{\overset{\|}{\cdot C}} - (CH_2)_x - \overset{O}{\overset{\|}{C}} - O - \overset{O}{\overset{\|}{CH}} \quad \overset{O}{\overset{\|}{\cdot C}} - CH{=}CH - (CH_2)_x - \overset{O}{\overset{\|}{CH}}$$
$$(MH + CO)^+ \qquad\qquad (MH - H_2O)^+$$

$$O{=}\overset{\cdot}{C} - (CH_2)_x - H \quad\text{or}\quad O{=}CH - (CH_2)_{x-1} - CH_2^+$$
$$(MH - CO_2)^+$$

The m/z 221 ion in Figure 2 is unassignable within the preceding fragmentation pattern. In the higher

mass range, an ion attributable to $(2MH - H_2O)^+$ is observed only for PS in Figure 2 at m/z 239.

The lower mass ranges of the negative-ion SIMS spectra in Figures 6–9 contain ions at m/z 12, 13, 16, 17, 24, 25, 41, 43, and 45 that may be assigned to C^-, CH^-, O^-, OH^-, C_2^-, C_2H^-, C_2HO^-, $C_2H_3O^-$, and CHO_2^-. The ion at m/z 71 may arise from the fragmentation of the anhydride unit, i.e., $CH_2{=}CHCOO^-$ and is seen for all polyanhydrides. At higher mass ($> m/z$ 100), a general fragmentation pattern was observed, and the major ions are noted in Table IV. In this case, $(M - H)^-$ anions (and not $M + H$) are the dominant diagnostic species for the polymer repeat unit. Ions corresponding
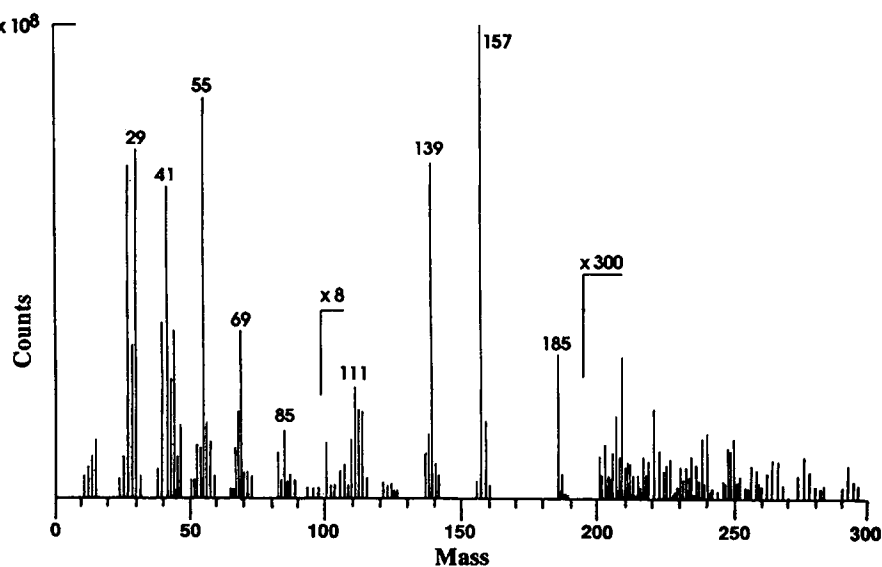

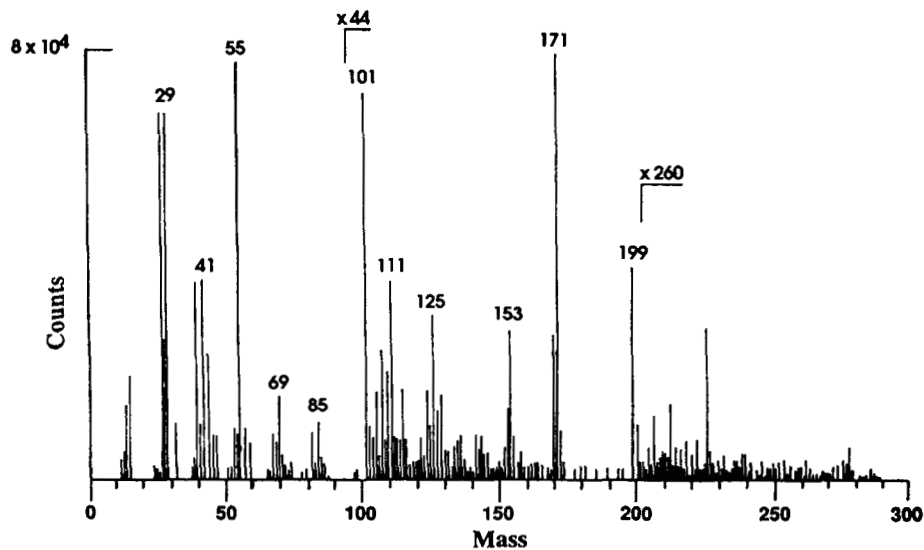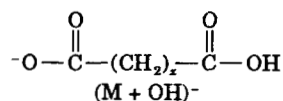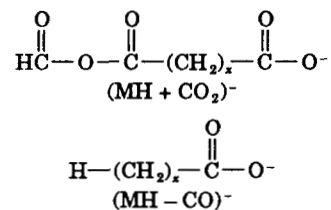**Figure 3** Positive-ion ToF-SIMS spectrum of PSU.

Figure 4 Positive-ion ToF-SIMS spectrum of PAZ.

to $(M + OH)^-$ are also observed for all polymers, i.e., at m/z 145 for PA. This ion may be assigned the following structure:

$$^-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_x-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$
$$(M + OH)^-$$

The loss and addition of carbon dioxide gives rise to prominent $(M - CO_2 \pm H)^-$ and $(MH + CO_2)^-$ anions. Additionally, ions corresponding to $(M \pm H$

$- CO)^-$ and $(MH + CO_2 + CO)^-$ were observed in polyanhydride negative-ion SIMS spectra, e.g.,

$$H\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_x-\overset{\overset{\displaystyle O}{\|}}{C}-O^-$$
$$(MH + CO_2)^-$$

$$H-(CH_2)_x-\overset{\overset{\displaystyle O}{\|}}{C}-O^-$$
$$(MH - CO)^-$$

The presence of the m/z 113 and 127 ions in the PSE negative-ion spectra may arise from the loss of

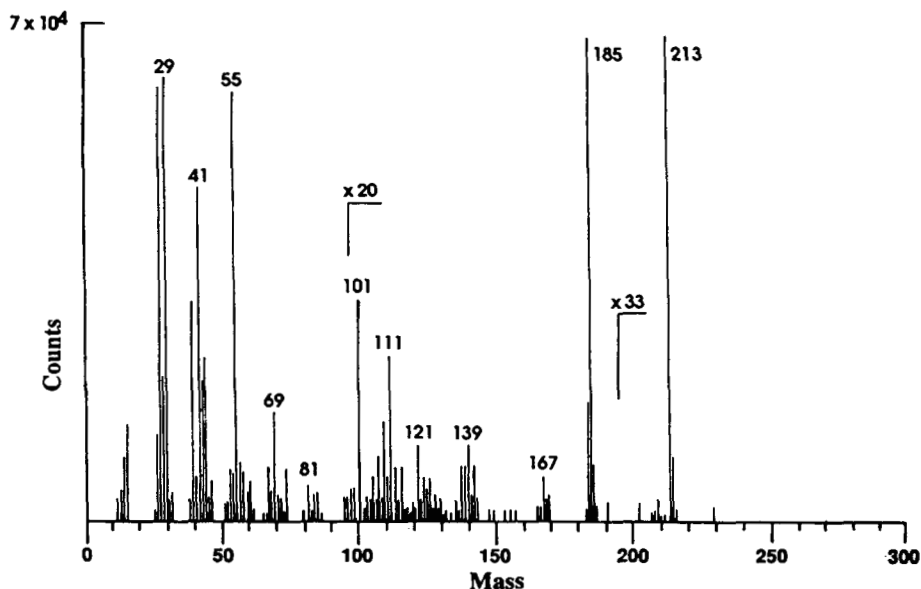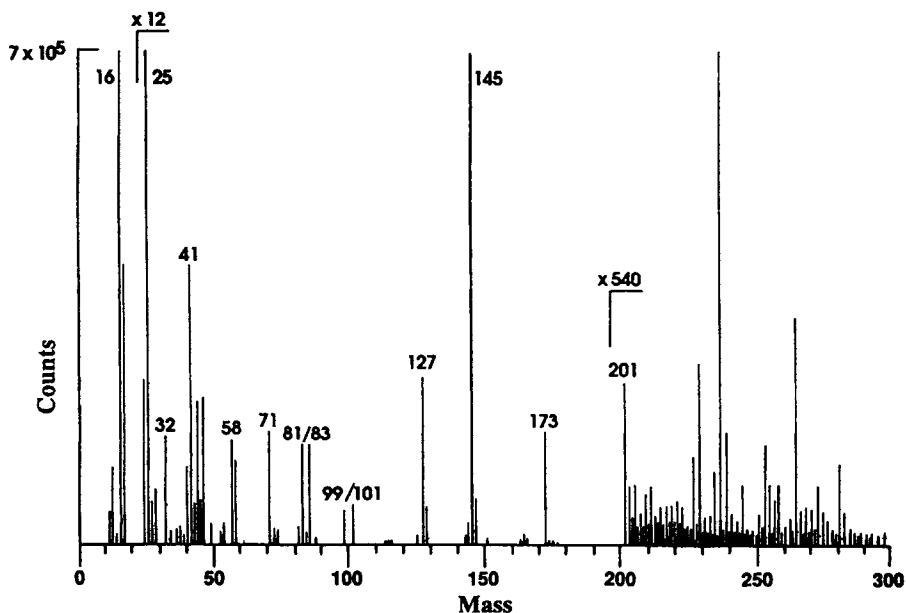**Figure 5** Positive-ion ToF-SIMS spectrum of PSE.

Figure 6 Negative-ion ToF-SIMS spectrum of PA.

methylene groups from the $(M - CO_2 \pm H)^-$. Also, the ions corresponding to $(2M - CO \pm H)^-$ are detected at m/z 227/229 for PA only.

GENERAL DISCUSSION

While the XPS provides significant information regarding the quantitative elemental composition and

chemical functionalities, the molecular specificity of the SIMS technique has been aptly demonstrated. Interestingly, the SIMS spectra indicate that there is a general mechanism of fragmentation for this series of polymers. Similar findings have been observed for a range of other polymer series including the polyalkylmethacrylates,[20] nylons,[21] polyesters,[14] and polyethers.[13] The existence of ions within the mass spectra attributable to fragments of M, the
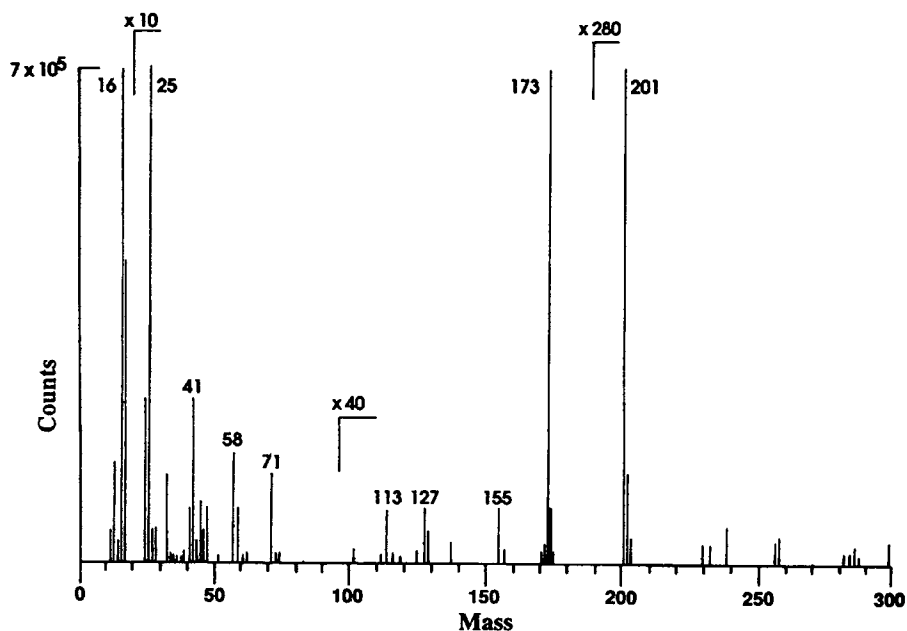

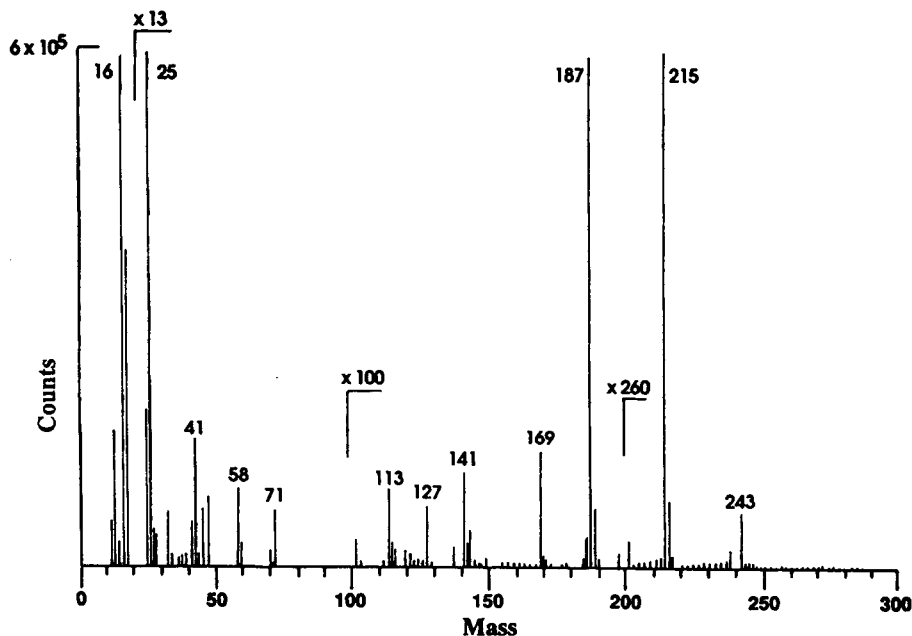**Figure 7** Negative-ion ToF-SIMS spectrum of PSU.

Figure 8 Negative-ion ToF-SIMS spectrum of PAZ.

mass of the monomer unit, is emerging as a common feature in polymer SSIMS analysis and underlines the power of the technique for determination of surface chemical structure. While the formation of (M ± H) $^\pm$ ions greatly aids the interpretation of mass spectra, the fragmentation mechanism is far from simple. In this case, the main focus of chain cleavage and ion formation appear to be in the region of the heteroatoms within the anhydride unit itself rather

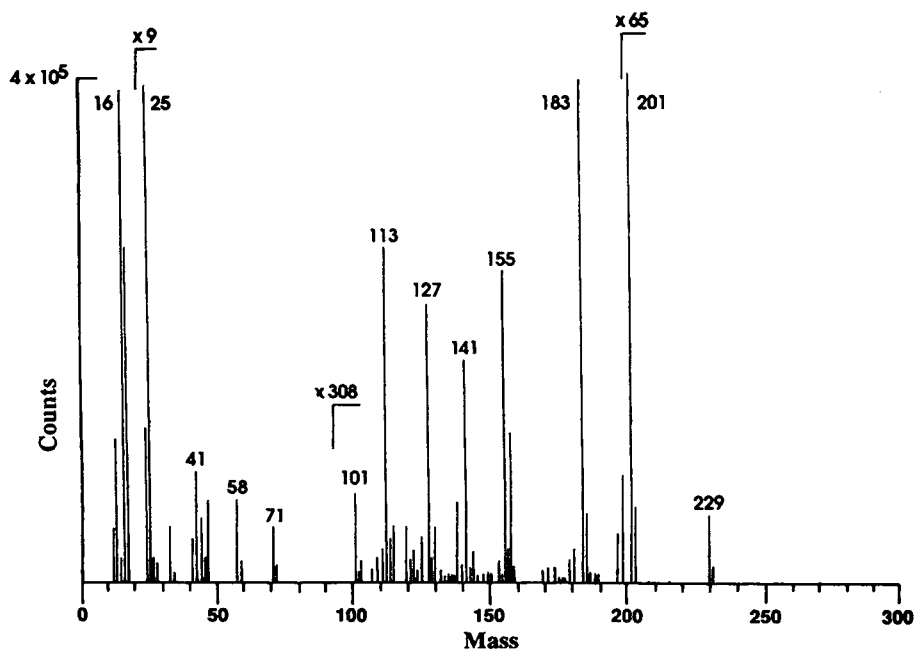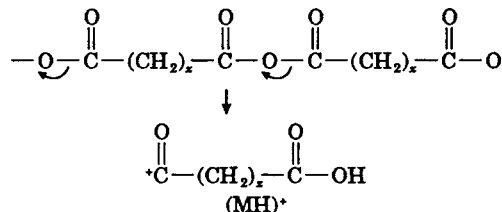than the alkyl portions of the monomer unit via chain scission, e.g.,

Figure 9 Negative-ion ToF-SIMS spectrum of PSE.

Table III   Major Positive Ions in Polyanhydride SIMS Spectra

Ion	PA	PSU	PAZ	PSE
$M + H^+$	129	157	171	185
$M^{\cdot+}$	128	156	170	184
$M - OH^+/MH - H_2O^+$	111	139	153	167
$MH + CO^+$	157	185	199	213
$M - CO_2 \pm H$	83/85	111/113	125/127	139/141

Similar observations have been made for structurally related polymers such as the polyethers, polyesters, and poly(ethylene terephthalate), which contain heteroatoms within the main polymer chain. The presence of the radical cations, albeit at low intensity, within the positive mass spectra is an interesting feature of the positive-ion spectra. The existence of these odd-electron species was only recognized recently in the SIMS analysis of biomedical polyesters[14] and in a review of previous SIMS work on standard polymers.[22] Even-electron species are dominated by odd-electron ions in other forms of mass spectrometry such as electron impact MS[23] of organics and pyrolysis MS of polymers. However, it appears clear from this study and the SIMS literature on polymers[14,22] that the reverse is true of SIMS analyses of polymers.

In a previous study on polyesters, the $M-O^{\cdot+}$ radical cation was observed but not $M^{\cdot+}$ as for polyanhydrides. Additionally, the formation of these even-electron ions was dependent on the chain length of the monomer unit where $M-O^{\cdot+}$ was detected for polylactic acid and polyglycolic acid but not for the higher molecular weight monomers of polyhydroxybutyrate, polyhydroxyvalerate, and polycaprolactone.[24] A similar monomer molecular weight dependence for odd- and even-electron species is observed by examination of the reported positive-ion SIMS spectra of a series of nylons.[21] In this study, there appears to be no such dependence as $M^{\cdot+}$ is recorded for even the highest molecular weight monomer unit, i.e., for PSE. Interestingly,

the intensity ratio of the ions $(M + H)^+/M^{\cdot+}$ remains relatively constant at 4.3, 4.5, 4.0, and 4.3 for PA, PSU, PAZ, and PSE, respectively. It is clear that while the presence of the radical cations aids the interpretation of the fragmentation pattern, an understanding of the formation of odd- and even-electron species within the complex and multiple mechanisms of ion formation in the SIMS analysis of polymers remains to be resolved.

In this article, the combined application of XPS and SIMS appears to provide an in-depth analysis of the polyanhydride surface structure. The molecular information from the SIMS experiment (combined with the quantitative elemental XPS data) has also been shown to provide the simple detection of and the distinction between the different monomer units present at copolymer surfaces of aliphatic and aromatic polyanhydrides.[25] The acquisition of data specific to the monomer and the anhydride unit will allow the future study of these interesting biomedical polymers with particular reference to the surface degradation reactions that occur on exposure to an aqueous environment. As this hydrolysis occurs in the region of the anhydride unit, XPS and SSIMS may have a further interesting role in the study of biodegradation of polyanhydrides.

CONCLUSIONS

XPS and ToF-SIMS have proven potent tools for the characterization of the surface chemical struc-

Table IV   Major Negative Ions in Polyanhydride SIMS Spectra

Ion	PA	PSU	PAZ	PSE
$M - H^-$	127	155	169	183
$M + OH^-$	145	173	187	201
$MH + CO_2^-$	173	201	215	229
$M - CO_2 \pm H^-$	83/85	—/113	—/127	—/141
$M - CO \pm H^-$	99/101	127/129	141/143	155/157
$MH + CO_2 + CO^-$	201	—	243	—

ture of polyanhydrides. The molecular specificity of SIMS combined with the quantitative elemental and functional group information from XPS provide a detailed analysis of the polyanhydride interfacial chemistry. The surface analysis readily distinguishes between the series of polyanhydrides. The comprehensive fragmentation patterns observed are typical of the SIMS analysis of polymers. Interestingly, radical cations are observed (albeit at low intensity) and provide further evidence for their existence in SIMS spectra of polymers. The molecular information of the SIMS spectra has been employed to identify ions specific to the monomer components of polyanhydride copolymer surfaces,[25] and these studies are continuing.

REFERENCES

1. K. W. Leong, J. Kost, E. Mathiowitz, and R. Langer, *Biomaterials*, **7**, 364, (1986).
2. M. Chausim, D. Louis, and R. Langer, *Biopharm. Manufact.*, **1**, 33 (1988).
3. A. Domb and R. Langer, *Macromolecules*, **21**, 1925 (1988).
4. J. Kost, K. W. Leong, and R. Langer, in *Polymers in Medicine: Biomedical and Pharmaceutical Applications*, E. Chiellini, Ed., Plenum Press, New York, 1986, Vol. II, p. 387.
5. R. Langer, D. Lund, K. W. Leong, and J. Folkman, *J. Controlled Release*, **2**, 331 (1985).
6. K. W. Leong, B. C. Brott, and R. Langer, *J. Biomed. Mater. Res.*, **19**, 941 (1985).
7. K. W. Leong, P. D'Amore, M. Marletts, and R. Langer, *J. Biomed. Mater. Res.*, **20**, 51 (1986).
8. A. Domb and R. Langer *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, **15**, 358 (1988).
9. D. T. Clark and J. W. Feast, Eds., *Polymer Surfaces*, Wiley, Chichester, 1987.
10. D. Briggs, in *Practical Surface Analysis by Auger and X-ray Photoelectron Spectroscopy*, D. Briggs and M. P. Seah, Eds., Wiley, Chichester, 1983, Chapter 8.
11. D. Briggs, *Surf. Interface Anal.*, **9**, 391 (1983).
12. M. J. Hearn, D. Briggs, S. C. Yoon, and B. D. Ratner, *Surf. Interface Anal.*, **10**, 384 (1987).
13. M. J. Hearn, B. D. Ratner, and D. Briggs, *Macromolecules*, to appear.
14. M. C. Davies, R. D. Short, M. A. Khan, J. F. Watts, A. Brown, A. J. Eccles, P. Humphrey, J. C. Vickerman, and M. Vert, *Surf. Interface Anal.*, **14**, 115 (1989).
15. A. J. Domb and R. Langer, *J. Polym. Sci., Part A. Chem Ed.*, **25**, 3373 (1987).
16. P. M. A. Sherwood, in *Practical Surface Analysis by Auger and X-ray Photoelectron Spectroscopy*, D. Briggs and M. P. Seah, Eds., Wiley-Interscience, New York, 1985, p. 445.
17. A. J. Eccles and J. C. Vickerman, *J. Vac. Sci. Technol.*, to appear.
18. D. Briggs and M. J. Hearn, *Vacuum*, **36**, 1005 (1986).
19. A. P. Pijpers and W. A. Donners, *J. Polym. Sci., Chem. Ed.*, **23**, 453 (1985).
20. M. J. Hearn and D. Briggs, *Surf. Interface Anal.*, **11**, 198 (1988).
21. D. Briggs, *Org. Mass Spectrom.*, **22**, 91 (1987).
22. R. D. Short and M. C. Davies, *Int. J. Ion Process. and Format.*, **89**, 149 (1989).
23. F. W. McLafferty, *Interpretation of Mass Spectra*, Benjamin, New York, 1966.
24. M. C. Davies, M. A. Khan, R. D. Short, C. Pouton, S. Akhtar, and J. F. Watts, *Biomaterials*, **11**, 228 (1990).
25. M. C. Davies, M. A. Khan, A. Domb, E. Ron, and R. Langer, in preparation.