

Articles

Spectroscopically Encoded Resins for High Throughput Imaging Time-of-Flight Secondary Ion Mass Spectrometry

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Spectroscopic barcoding was recently introduced as a new pre-encoding strategy wherein the resin beads are not just carriers for solid phase synthesis, but are, in addition, the repository of the synthetic scheme to which they were subjected. To expand the repertoire of spectroscopically barcoded resins (BCRs), here we introduce a new family of halogenated polystyrene-based polymers designed for high-throughput combinatorial analysis using not only infrared and Raman spectroscopy but also imaging time-of-flight secondary ion mass spectrometry (ToF-SIMS). In particular, we have established that (a) the halogen content of these new resins can be used as an encoding element in quantitative imaging ToF-SIMS and (b) the number of styrene monomers used to generate unique vibrational fingerprints can be significantly reduced by using monomers in different molar ratios. The combination of quantitative imaging ToF-SIMS and vibrational spectroscopy is anticipated to dramatically increase the repertoire of possible BCRs from a few hundreds to several thousands.

Introduction

Encoded combinatorial chemistry¹ has emerged over the past decade as a strategy for tracking the chemical identity of individual compounds in a chemical library. The main objective has been that large numbers of compounds can be tested simultaneously, and only those with the desired properties would be decoded. This approach benefits from the multitude of microcarriers available, their amenability to split/pool synthesis,² and their compatibility with a broad spectrum of encoding/code readout strategies.^{3–20} The microcarriers can be encoded during library synthesis by adding a detectable chemical tag at each synthesis cycle that encodes for that particular step (parallel encoding approach). Alternatively, the microcarriers can be encoded before the synthesis (pre-encoding approach),^{21–27} in which case they must be decoded at each synthetic cycle to keep track of their chemical history (directed sorting strategy).²⁸

Parallel encoding requires the physical separation of the tags from the microcarrier, followed by their analysis to

uncover the chemical identity of the encoded material. Common molecular tags include oligonucleotide,⁸ haloaryls,⁹ trityls,¹⁰ secondary amines,¹¹ fluorescent dyes,¹² or peptides.^{2d,13} Although the detection methods for the elucidation of the codes are generally difficult to automate,¹⁴ they include a broad spectrum of techniques, such as mass spectrometry,^{10,15} high-resolution magic angle spinning⁴ and gel phase^{3,5} ¹H- and ¹³C NMR, ¹⁹F NMR,¹⁶ energy-dispersive X-ray spectroscopy,¹⁷ X-ray photoelectron spectroscopy,¹⁸ infrared and Raman spectroscopy,^{6,7,19} and fluorescence spectroscopy.²⁰ Pre-encoding requires simply matching the microcarrier's preset code with the corresponding library member. The encoding methods in this case include optical,^{12,21} colloidal,²² organic²³ and inorganic²⁴ dye, graphical,²⁵ size²⁶ and shape,²⁷ and radio frequency²⁸ encoding.

We have recently reported on a new class of resins prepared from spectroscopically active styrene monomers, the combination of which resulted in resins possessing each a unique vibrational fingerprint (Figure 1). This vibrational signature was then converted into a barcode in which the position of each bar matches the peak wavenumber in the corresponding spectrum. The first generation of barcoded resins (BCRs), composed of 24 new polymers, featured Merrifield-like physical and chemical properties.^{29a} The second generation, composed of 25 BCRs, had the properties of PS–PEG graft copolymers.^{29b} This family was designed

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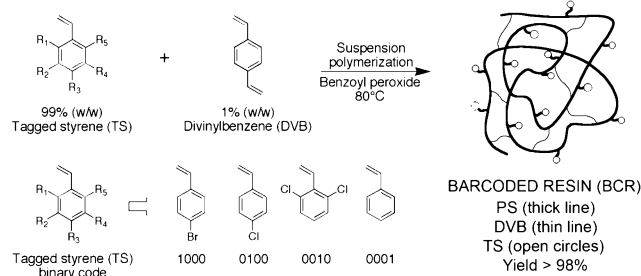


Figure 1. General synthetic strategy for the preparation of halogenated barcoded resins for imaging ToF-SIMS (PS, polystyrene backbone).

to address limitations associated with Merrifield type resins, notably the question of (a) compatibility with biological assays and directed sorting using flow cytometry and (b) general reliability of the barcoding strategy.^{29b} Although two dozen barcoded supports is sufficient to develop efficient deconvolutive screening strategies, such as dual recursive deconvolution (DRED),^{7d,e} the majority of current applications in combinatorial screening and biomedical diagnostics would require hundreds to thousands of unique BCRs.

To expand the repertoire of BCRs, we envision two approaches: The first consists of simply increasing the number of tagged styrene monomers to meet the size of the library to be encoded; however, this approach is limited by the number of monomers amenable to incorporation in a polymer blend suitable for solid-phase synthesis, and could in practice result in ~ 1000 usable BCRs. The second approach stems from our earlier reports, which indicated that the vibrational spectrum (and barcodes) of a copolymer is a linear combination of the parent homopolymer's frequencies in addition to new vibrations unique to the copolymer. Here, we capitalize on the latter observation and set out to generate a new family of resins that differ not only by their monomer content but also by the ratio of the monomers used. In principle, any combination of monomers we have previously investigated would have proved the concept; however, the family of monomers we selected is not only spectroscopically unique but also readily and quantitatively identified by imaging time-of-flight secondary ion mass spectrometry (ToF-SIMS).³⁰ As elaborated in the discussion section, the combination of IR/Raman spectroscopy with ToF-SIMS is anticipated to increase the number of usable barcodes by several orders of magnitude, which should address numerous applications in target-oriented^{28a,b,31} and diversity-oriented³² libraries and biomedical diagnostics.^{22a,b}

Results

BCR Preparation. The beaded polymers were prepared according to the general scheme shown in Figure 1. Since the IR and Raman spectra of (co-)polymers in powder form are essentially identical to those obtained in beaded form and also much faster to prepare, only a few representative copolymers were prepared in beaded form for imaging ToF-SIMS (see Supporting Information). Table 1 summarizes the composition of the 35 polymers prepared and their Raman/IR barcodes. These polymers can be subdivided into eight families (entries 1, 2–5, 6–9, 10–13, 14–19, 20–25, 26–31, 32–35) differing by their tagged styrene (TS) molar

content. The molar ratio of TS monomers within each family was varied as shown in Table 1.

Digital Code and Spectroscopic Barcode Generation.

We have arbitrarily assigned a basic binary code for each of the four monomers (Figure 1). The presence (1) or absence (0) of a particular styrene monomer within a given polymer determines the first half of the eight-digit code assigned to each resin. The second half refers to the respective monomer volume ratio that can be 0 (0), 20 (1), 40 (2), 60 (3), 80 (4), or 100% (5). The infrared⁶ and Raman⁷ spectra of the BCRs were recorded and baseline-corrected. These vibrations were converted into barcodes in which the position of each bar matches the peak wavenumber in the corresponding spectrum (Table 1). The barcodes are independent of the peak intensity in the parent vibrational spectrum.

Robustness of the Vibrational Barcode. Unlike our previous BCRs,²⁹ several of the polymers described here are composed of the same TS monomers. For instance, entries 2–5, 6–9, 10–13, 14–19, 20–25, 26–31, and 32–35 are families of polymers composed of the same styrene monomers. The difference within these families stems from the ratio of each of the constituent TS monomers. To determine the level of similarity between BCRs within and across these families of polymers, a similarity coefficient (S)³³ between each resin pair was calculated as described earlier.^{29b} The resulting Raman and infrared similarity tables comparing all possible resin pairs (Tables 1 and 2, Supporting Information) were plotted as contour maps in which the highest similarity intersections appear in red and the lowest appear in blue (Figure 2).

Quantitative I-ToF-SIMS Measurements. The halogenated resins were probed with a 25-keV Ga^+ liquid metal ion beam focused to a spot size of 200 nm with a DC beam current of 1.5 nA. In all measurements, the incident ion dose was kept at or below the static limit of 1×10^{12} ions/cm². To maximize signal intensities from the resins, charge compensation was performed by irradiating the sample with a pulsed e-beam of 30 eV having a DC current of 50 nA. The e-beam was allowed to strike the sample for 50 μs after each liquid metal ion gun pulse, during which period the sample stage voltage was held at 0 V. A detailed description of the ToF-SIMS instrument used in this study was described elsewhere.^{30a} Figure 3 shows a ToF-SIMS of copoly(styrene/10% 4-bromostyrene/1% divinylbenzene) and the corresponding imaging ToF-SIMS generated by measuring the negatively charged ions released from the bead surface.

For a comparative analysis of the BCRs' halogen content, the detector gain, the image field of view, and the density of primary ion dose on the resin surface must be kept constant whenever possible. Whereas the average total ion counts varied significantly among BCRs (standard deviations 12–39%), their normalization to units of the bead's surface area improved dramatically the quantitative analysis (standard deviation 5–11%), as shown in Table 2.

To further establish the reliability of ToF-SIMS as a quantitative analytical tool for the characterization of the BCRs, the halogen content of eight resins was derived from the measured signal intensities and was found in excellent agreement with the calculated values (Table 3).

Table 1. Polymers Prepared, Their Composition, Digital Codes, and Raman/Infrared

Entry	Digital code ^a		Raman Barcode	Infrared Barcode
	Binary code	Content code		
1	0001	0005		
2	0011	0014		
3	//	0023		
4	//	0032		
5	//	0041		
6	0101	0104		
7	//	0203		
8	//	0302		
9	//	0401		
10	1001	1004		
11	//	2003		
12	//	3002		
13	//	4001		
14	0111	0113		
15	//	0122		
16	//	0212		
17	//	0131		
18	//	0221		
19	//	0311		
20	1011	1013		
21	//	1022		
22	//	2012		
23	//	1031		
24	//	2021		
25	//	3011		
26	1101	1103		
27	//	1202		
28	//	2102		
29	//	1301		
30	//	2201		
31	//	3101		
32	1111	1112		
33	//	1121		
34	//	1211		
35	//	2111		

^a The presence (1) or absence (0) of a particular styrene monomer within a given polymer determines the first half of the eight-digit code assigned to each resin. The second half refers to the respective monomer volume ratio that can be 0 (0), 20 (1), 40 (2), 60 (3), 80 (4), or 100% (5).

Table 2. Quantitative Analysis of Chlorinated BCRs with Imaging ToF-SIMS

entry	BCR composition (v/v) ^a			relative calcd Cl atom content ^b	av cts ^c	relative meas Cl atom content ^d	cts × μm ⁻² (× 100) ^{c,e}	relative corrected Cl atom content ^f
	0100	0010	0001					
1	10		90	1.0	1240 ± 149	1.0	1.2 ± 0.1	1.0
2	20		80	2.0	3667 ± 1430	3.0	2.4 ± 0.3	2.0
3		20	80	3.2	6211 ± 745	5.0	4.0 ± 0.2	3.3

^a Monomer volume composition; see Figure 1 for binary code assignment. ^b Relative halogen atom content based on molarity of tagged styrene monomers. ^c Average of three measurements. The standard deviation was calculated according to the equation in ref 34. ^d Relative halogen atom content based on measured counts. ^e Counts normalized to the surface area of the bead, which was approximated to its circular footprint and calculated from the measured bead diameter ($2\pi r^2$). ^f Relative halogen atom content based on measured counts per bead's surface area.

Figure 4 shows imaging ToF-SIMS of five halogenated BCRs randomly distributed on a silicon wafer. The images reveal the chloride (green) and the bromide (red) ion distribution. On the basis of the composition and intensity of the measured Cl/Br signals, the BCRs were rapidly classified. Table 4 shows the BCRs' composition, their

relative halogen atom content (mole equivalents), and the measured relative halogen atom content. Note that bromide and chloride ion contents per surface area are not comparable because of a difference in their desorption/ionization energies. Here again, the calculated and measured relative halogen atom content are in excellent agreement. The analysis

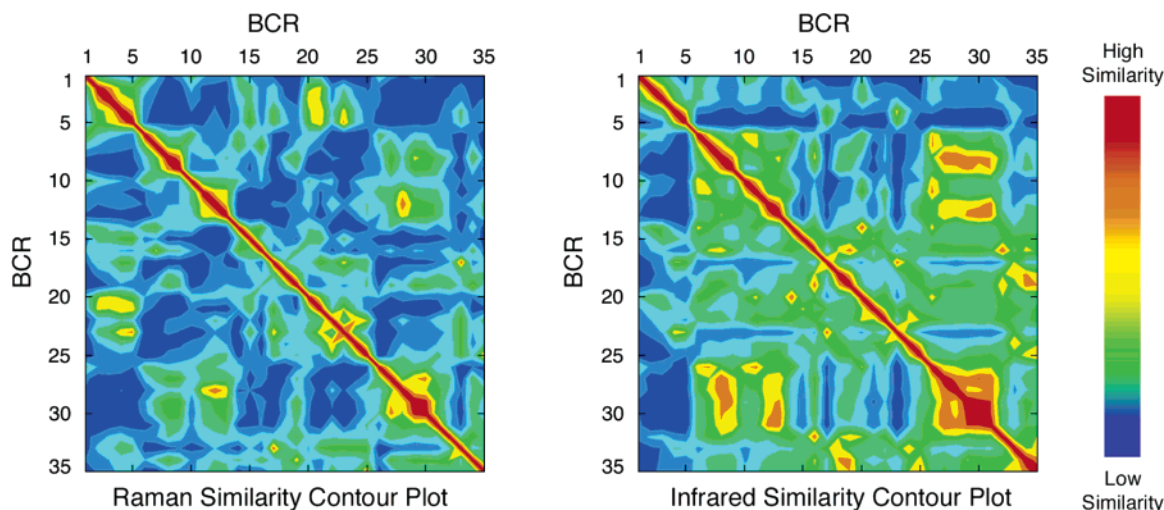


Figure 2. Raman and infrared similarity contour plots of the polymers listed in Table 1. The highest similarity intersections are depicted in red, and the lowest, in blue.

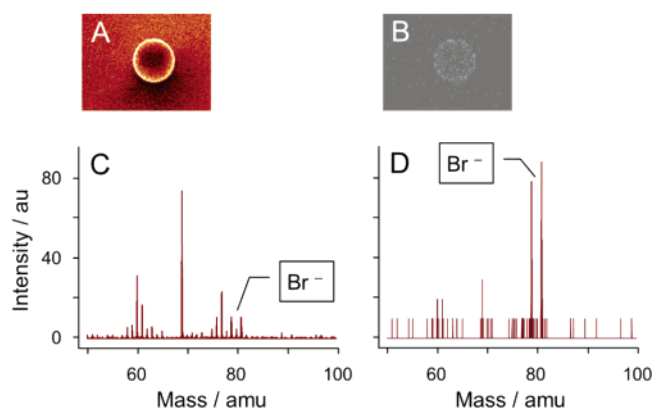


Figure 3. Negative ion imaging ToF-SIMS (A, B) and corresponding integrated ToF-SIMS spectra (C, D) of copoly(styrene/10% 4-bromostyrene/1% divinylbenzene). Comparison of the total ion image integrated over the entire field of view (A) versus that integrated over the bead surface (B) shows that the bromide ions are predominantly desorbed from the BCR surface.

Table 3. ToF-SIMS Measurement of the Br/Cl Content of Eight Halogenated BCR's (± 5 –10%)

BCR composition (v/v) ^a				relative halogen atom content			
				calcd ^b		meas ^c	
1000	0100	0010	0001	Br	Cl	Br	Cl
80			20	4.0		4.2	
60	20		20	3.1	0.9	2.8	1.0
60		20	20	3.1	1.7	3.1	1.9
40	40		20	2.2	1.9	1.8	2.1
40	20	20	20	2.1	2.6	2.0	2.7
20	60		20	1.1	3.1	1.0	3.1
	80		20		4.3		4.2
	40	40	20		5.7		5.6

^a Monomer volume ratio; see Figure 1 for binary code assignment. ^b Relative halogen atom content based on molarity of tagged styrene monomers calculated from the density, molecular weight, and volume ratio of the relevant styrene monomers. ^c Relative halogen atom content based on measured counts.

efficiency was ~ 2 beads/min, which could reach its full potential of 600 beads/min by imaging denser arrays of BCRs.^{30b}

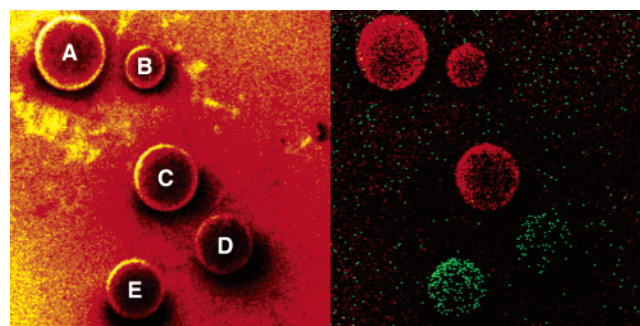


Figure 4. Imaging ToF-SIMS of five BCRs on a silicon substrate showing the total ion image (left) and the chloride (green)/bromide (red) ions distribution (right) in a $1700 \times 1700 \mu\text{m}^2$ field of view with a primary ion dose of 1.0×10^{10} ions/cm².

Table 4. ToF-SIMS Identification and Classification of BCRs Imaged in Figure 4 Based on Their Halogen Atom Content

BCR8	composition (v/v) ^a				relative halogen atom content		cts $\times \mu\text{m}^{-2}$ ($\times 100$) ^d
	1000	0100	0010	0001	calcd ^b	meas ^c	
A			20	80	3.2	3.1	7.1
B		20		80	2	1.8	4.2
C		10		90	1	1	2.3
D	10			90	2	2	0.2
E	20			80	1	1	0.1

^a Monomer volume composition; see Figure 1 for binary code assignment. ^b Relative halogen atom content based on molarity of tagged styrene monomers. ^c Relative halogen atom content based on measured counts per bead's surface area. ^d Counts normalized to the surface area of the bead, which was approximated to its circular footprint and calculated from the measured bead diameter ($2\pi r^2$).

Discussions

Expanding the Repertoire of BCRs. The defining characteristic of the barcoded resins is their preparation from spectroscopically active styrene monomers displaying unique IR and Raman vibrational fingerprints. The styrene monomers' substitution pattern is the source of spectral diversity of the resulting polymers. The frequencies used to generate the barcodes are mainly due to aromatic ring skeletal bending

and C–H stretching modes (Table 3, Supporting Information). The vibrational spectra (and barcodes) of the corresponding copolymers are, in all cases studied, a linear combination of the parent homopolymers' frequencies, in addition to new vibrations unique to the copolymers.^{29b} The goal of the present study is to (a) assess the feasibility of combining spectroscopic encoding with quantitative imaging ToF-SIMS for the unequivocal identification of the BCRs and (b) to expand the repertoire of BCRs by using "SIMS-active" TS monomers in different ratios. Table 1 shows 35 new polymers prepared from 4 basic monomers, 4-bromostyrene, 4-chlorostyrene, 2,6-dichlorostyrene, and styrene, and the corresponding Raman and IR spectroscopic barcodes. Incorporation of halogenated styrene monomers was dictated by their amenability to quantitative imaging ToF-SIMS. Although several polymers are composed of the same styrene monomers, their vibrational fingerprint was sufficiently unique for their unequivocal identification. We attributed this result to subtle changes in the chemical/physical properties of the polymers as a result of their relative TS monomer composition and content. To establish the uniqueness of each of the BCRs, we calculated the similarity among all the resins synthesized (Table 1). In 100% of the cases, the highest similarity coefficients (*S* values) were obtained for resins with identical digital codes (diagonal values in Tables 1 and 2, Supporting Information). To simplify the comparison of the IR and Raman similarity tables, the *S* values were normalized and presented as contour plots (Figure 2).

Several important conclusions were drawn from this analysis. First, the contour plots show high similarity along the diagonal, demonstrating that resins with identical digital codes maintain the highest level of similarity, despite their relatively similar composition (see Table 1, entries 2–5, 6–9, 10–13, 14–19, 20–25, 26–31, 32–35). Second, the Raman and infrared contours are significantly different, therefore allowing us to use them synergistically for the unequivocal identification of a barcoded resin. To illustrate this synergy, consider the extreme case in which BCR #30 (digital code 11012201) showed high infrared similarity with BCRs #8 (01010302), #12 (10013002), #26 (11011103), #27 (11011202), #28 (11012102), and #29 (11011301). The Raman similarity contour, however, ruled out every possibility except the correct one, BCR #30. Third, given that the TS monomers could be used in various molar ratios, many more BCRs can be generated from a smaller set of TS monomers. For instance, 92 378 ($C(10 + 10 - 1, 10)$) unique BCRs could be generated from 10 TS monomers used in weight ratios varying from 0 to 100% in increments of 10%, as opposed to only 1023 ($2^{10} - 1$) when the monomers are used in a simple binary combination.²⁹

Halogenated BCRs for Imaging ToF-SIMS. Since both chloride and bromide ions yield intense and isotopically unique peak distribution via SIMS, they were unambiguously identified and imaged. No fragments associated with the TS monomers were detected; only halogen ions were selectively desorbed from the BCR surface (Figures 3 and 4). The intensities of the halogen atom signals were proportional to their concentration in the polymer matrix, thus establishing the possibility of developing an encoding scheme based on

Br/Cl ions signal intensities (Tables 3 and 4). Finally, imaging ToF-SIMS of BCRs does not require pretreatment of the resins to dissociate the halogen ions. As a result, cross-contamination is minimized, and the spatial integrity of the signals is preserved.

Conclusion

Spectroscopic barcoding²⁹ was recently introduced as a new pre-encoding strategy wherein the resin beads are not just carriers for solid phase synthesis, but are, in addition, the repository of the synthetic scheme to which they were subjected. The goal of the present study is to expand the potential repertoire of BCRs from a few hundreds to several thousands using a minimal number of TS monomers. Thus, a new family of BCRs containing various combinations and molar ratios of halogenated styrene monomers was designed and synthesized. These polymers were characterized by infrared and Raman spectroscopies and ToF-SIMS. Their spectroscopic barcodes and halogen atom content could be identified with 100% confidence. Because of the amenability of the BCRs to directed sorting strategies,²⁸ the synthetic steps common to all the beads or any subset thereof can be combined, thereby reducing the overall synthetic effort (e.g., by using split/pool synthesis²). As a result, each individual compound or group of compounds could be synthesized on a bead characterized by a unique barcode. Directed sorting,²⁸ bead loading (up to 1 mmol/g), and size (100–1000 μm)³⁵ offer the possibility to control the amount of each synthetic intermediate and library member. As a result, routine spectroscopic characterizations at any stage of the library synthesis and on-bead or solution-phase biological evaluations could be carried out. Readout of the barcodes can be done using single-bead microspectroscopy^{6,7} or dramatically speeded up using hyperspectral imaging of dozens of beads simultaneously.^{7d,e} Bead synthesis can be automated at the laboratory scale to produce at least 50 BCRs per day in 25-g batches³⁶ and more in a production setting. Thus, the preparation of 1000 BCRs on a laboratory scale would require 20–30 days without extensive assistance. It should be noted, however, that a 1000-member library in which each member is present in 100 copies would require only ~ 100 mg of all the BCRs (assuming beads with ~ 150 - μm diameter). The beads' pore size can be readily controlled between 5 and 500 nm³⁷ to improve on-bead biological assays.³⁸

Imaging ToF-SIMS of densely arrayed samples was established as a high-throughput method for combinatorial analysis.^{15a,30} In our early work, ligands synthesized on polymer resins were identified through direct measurement of their mass spectra at a rate of 10 beads/s,^{30b–d} and up to 10 000 spectra/s can be acquired. Moreover, this method is noninvasive since the spectral information is sampled over an area of $\sim 1 \mu\text{m}^2$ due to the focused nature of the interrogating probe. We have shown that cluster ionization sources, such as Au_n^+ and C_{60}^+ greatly enhance secondary ion yield of organic molecules,^{30d} and we anticipate being able to exert the same effect on the halogenated BCRs. As a result, the accuracy, sensitivity, and S/N ratio could be significantly improved, and other types of monomers that

do not yield strong signals under Ga⁺ bombardment may be used as encoding material when cluster ionization source is employed.

We anticipate that the combination of spectroscopic barcoding with imaging ToF-SIMS will add a new dimension to the barcoding strategy. Because of the improved sensitivity of ToF-SIMS equipped with cluster ionization sources, a smaller fraction of the polymer blend (<10%) could be used for SIMS encoding and the remainder for spectroscopic barcoding, thus not only expanding the repertoire of BCRs but also minimizing the effect of halogenated styrene monomers on the chemical and physical properties of the BCRs. Furthermore, these BCRs are particularly amenable to imaging ToF-SIMS because they do not require any pretreatment prior to analysis.

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Supporting Information Available. Procedures for the preparation of the polymers, procedures for IR and Raman measurements, Raman and IR peak assignment, similarity tables, and Raman and IR spectra of the polymers listed in Table 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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