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A Convenient Method To Measure Monomer Reactivity Ratios. Application to Synthesis of Polymeric Biomaterials Featuring Intrinsic Radiopacity

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ABSTRACT: The properties of co- and terpolymers (physical, mechanical, chemical, biocompatibility, etc.) strongly depend on their microstructural details. In the course of our research work on biomaterials that feature intrinsic radiopacity, we became interested in the microstructural details of co- and terpolymers of methyl methacrylate (MMA), 2-hydroxyethyl methacrylate (HEMA), and 2-(2′-iodobenzoyl)-ethyl methacrylate (**1**) or 2-(4′-iodobenzoyl)ethyl methacrylate (**2**). A new method, based on ^{1}H-NMR at 400 MHz, was used to study the copolymerization reactions **1** + HEMA, **1** + MMA, **2** + HEMA, and **2** + MMA. This method was found to be convenient, fast, and accurate, and it is put forward that this approach can also be applied to study other copolymerization reactions. The results, obtained with the error-in-variables method (EVM), are as follows: **1** + HEMA, $r_1 = 1.09 \pm 0.14$, $r_{HEMA} = 1.12 \pm 0.06$; **1** + MMA, $r_1 = 0.54 \pm 0.12$, $r_{MMA} = 0.67 \pm 0.06$; **2** + HEMA, $r_2 = 2.18 \pm 0.72$, $r_{HEMA} = 2.29 \pm 0.38$; **2** + MMA, $r_2 = 0.93 \pm 0.32$, $r_{MMA} = 0.90 \pm 0.13$. Based on these data, a triad analysis was performed. It is concluded that all four copolymerizations afford random-type macromolecules. Therefore, it is most likely that terpolymers consisting of **1** or **2**, HEMA, and MMA will also have a random character. This conclusion is of interest, since it gives a better insight into the different biochemical and physicochemical properties of this type of co-/terpolymers. The results imply that random copolymers, built-up from a hydrophilic and a hydrophobic component, can also exhibit low thrombogenicity; this is in line with recent studies by Mathew et al. (*Biomaterials* **1993**, *14*, 57).

Introduction

Polymeric biomaterials play a vital role in most of the medical subdisciplines. A plethora of polymeric biomaterials has been developed to meet stringent requirements with respect to biocompatibility, chemical resistance, sterilizability, toughness, etc. For example, poly(methyl methacrylate) is used as bone cement in orthopedic surgery, different poly(urethanes) are applied for the manufacture of catheters, and different poly(esters) find widespread use as serum vials or blood collection tubes.

An important drawback of polymeric biomaterials is that they are radiolucent: organic polymers hardly absorb X-radiation, as they lack relatively heavy elements in their primary structure. Yet, when a polymeric biomaterial is used inside the body (either temporarily or permanently), it is often required that the material can be visualized through X-ray fluoroscopy. The common solution to this problem is to add an inorganic additive, usually barium sulfate. Bone cements, for instance, are made radiopaque through addition of ∼7% (by weight) of barium sulfate. However, the use of inorganic additives, dispersed in a polymeric matrix, recently gave rise to concern, since additives appear to have a negative impact on the material's mechanical properties (especially fatigue life).

We have put forward recently that polymerization of monomeric building blocks that contain covalently bound iodine leads to macromolecules with *intrinsic* radiopacity.[1−10] It was shown that polymers composed of methyl methacrylate (MMA), 2-hydroxyethyl methacrylate (HEMA), and an iodine-containing methacrylate (vide infra) exhibit intrinsic X-ray fluoroscopic visibility in combination with good *in vitro* blood compatibility[6−9] and excellent *in vivo* tissue compatibility.[10] The compounds 2-(2′-iodobenzoyl)ethyl methacrylate (**1**) and 2-(4′-iodobenzoyl)ethyl methacrylate (**2**)

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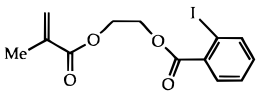

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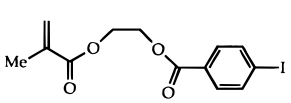

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are convenient iodine-containing monomers, since they can be easily prepared and purified, and co-/terpolymerization with MMA and/or HEMA proceeds with >99% conversion.[7,8] Herein, we specifically focus on the microstructural details of terpolymers MMA/HEMA/**1** and MMA/HEMA/**2**. We report an experimental study that was aimed at determining the reactivity ratios of **1** and **2** with respect to MMA and HEMA. The reactions **1** + HEMA, **1** + MMA, **2** + HEMA, and **2** + MMA were studied with ^{1}H-NMR spectroscopy at 400 MHz, and this technique allowed us to accurately monitor momentary conversion and copolymer composition *while the reaction was ongoing*. The results have both specific and general significance. Specifically, it has been found that the reactions **1** + HEMA, **1** + MMA, **2** + HEMA, and **2** + MMA afford random-type copolymers, and it is therefore argued that terpolymers built-up of **1** or **2**, MMA, and HEMA also have a random character. Generally speaking, our method of determining reactivity ratios by means of ^{1}H-NMR spectroscopy is applicable to a wide range of different copolymer reactions. We believe that this method offers an attractive alternative to more conventional and laborious methods of determining reactivity ratios, which are frequently based on sampling reaction mixtures followed by precipitation and analysis of the copolymer.

Experimental Section

Materials. Commercial MMA and HEMA were purified and stored as described previously.[6−8] Compound **1** was synthesized by esterification of 2-iodobenzoyl chloride and HEMA and purified via chromatography on a silica gel column.[8] Compound **2** was synthesized by esterification of 4-iodobenzoyl chloride and HEMA. After crystallization of the crude product in *n*-hexane, **2** was obtained in pure form. The products were stored at −20 °C. Commercial α,α′-azobis(isobutyronitrile) (AIBN) (purity > 99.5%) was used without further purification.

Instrumentation. The ^{1}H-NMR spectra were recorded on a Varian Unity-Plus system at a frequency of 399.9 MHz. The following NMR acquisition parameters were used: acquisition time, 2.500 s; number of data points used, 32 000; spectral width, 6400.0 Hz. DMSO-d_6 was used as the solvent. Tetramethylsilane was used as the internal standard (δ 0.00 ppm).

Polymerizations. Seven different feed compositions were used: f_1 (or f_2) = 0.100, 0.200, 0.350, 0.500, 0.650, 0.800, and 0.900, with parameter f_1 defined as f_1 = [**1**]/([**1**] + [HEMA] or [MMA]) and parameter f_2 defined as f_2 = [**2**]/([**2**] + [HEMA] or [MMA]). In each case, we mixed monomer **1** or monomer **2**, HEMA or MMA, and stock solution of AIBN in HEMA or MMA, such that the total weight was 2.000 g, and the initiator concentration was 0.1 mol %. Then, 177.2 μL of the reaction mixture and 522.8 μL of DMSO-d_6 were transferred into a 5-mm NMR tube. The whole was well mixed. Purity and composition were checked by ^{1}H-NMR spectroscopy at room temperature. Subsequently, the sample was rapidly heated to 75 °C, and ^{1}H-NMR spectra were recorded at regular time intervals (100−300 s). Thus, the reactions were run in a 5-mm NMR sample tube, inside the NMR magnet, and no manipulation of the sample was necessary.

Determination of Conversion and Copolymer Composition with ^{1}H-NMR

^{1}H-NMR spectroscopy proved to be a very convenient technique to monitor all four copolymerizations. In all cases, it appeared to be possible to accurately measure both conversion *and* copolymer composition in the course of time. Our methodology will be illustrated with two representative examples.

Example I: Copolymerization 1 + HEMA. Figure 1 shows expansions of two 400-MHz ^{1}H-NMR spectra, recorded during copolymerization of **1** + HEMA (mole ratio 1:1). Panels I and II are parts of the spectrum measured at 4.3% conversion (vide infra). Panels III and IV are parts of a spectrum that was recorded at a later stage of the reaction (conversion 22.7%). Note that panels I and III show the same spectral region (δ 3.3−6.4 ppm). Analogously, panels II and IV show the spectral region δ 0.2−2.2 ppm. The assignments of the various monomer signals are given in legends of panels I and II. Panels III and IV clearly show small, broad signals, arising from protons in the polymer then formed. It is of interest to focus on the broad patterns i and ii. Four points should be noted:

(1) Patterns i and ii can be assigned unambiguously, and they are isolated, i.e. there is no overlap with other NMR signals of monomer or polymer protons.

(2) Pattern i arises from the protons of the methyl groups that are directly attached to the polymer chain. Pattern ii arises from protons of one of the side-chain OCH_2 groups of built-in HEMA.

(3) Patterns i and ii are also visible in the low-conversion spectrum (panels I and II), provided that the vertical scale is expanded by 1 order of magnitude. It is possible to obtain accurate and reproducible integrals of these signals.

(4) Pattern iii corresponds with the olefinic protons in the monomeric building blocks. They do not show spectral overlap with polymer signals and gradually disappear as the conversion increases.

Conversion was obtained according to the formula

$$\text{conversion} = \text{int. i}/(\text{int. i} + 1.5\text{int. iii}) \times 100\%$$

where int. i is the integral of pattern i and int. iii is the integral of pattern iii. Furthermore, the parameter F_{HEMA} (i.e., the mole fraction of built-in HEMA in the copolymer) is obtained according to the formula

$$F_{\text{HEMA}} = 1.5(\text{int. ii}/\text{int. i})$$

where int. ii is the integral of pattern ii. Note that this method benefits from the high magnetic field strength in several respects. First, the high magnetic field results in clear dispersion of most (but not all) ^{1}H-NMR spectral patterns, which is essential for accurate measurement of integrals. Second, the high field strength leads to high spectral sensitivity, i.e., sufficient signal-to-noise ratio was obtained in one scan (2.500-s measurement time). This really enabled us to perform momentary measurements of conversion and F_{HEMA}.

Example II: Copolymerization 1 + MMA. Figure 2 shows expansions of the ^{1}H-NMR spectra recorded during the copolymerization **1** + MMA (mole ratio 1:1). Panels I and II correspond with 4.1% conversion. Panels III and IV correspond with 20.7% conversion. Assignments of the monomer signals are again given in panels I and II. Panels III and IV clearly show several small, broad signals as a result of polymer formation. Pattern i arises from the protons of the methyl groups that are directly attached to the polymer chain. The isolated pattern ii arises from protons of one of the side-chain OCH_2 groups of built-in **1**. The isolated signal at δ 3.4−3.5 ppm is due to the OMe groups of polymerized MMA building blocks. This signal was not

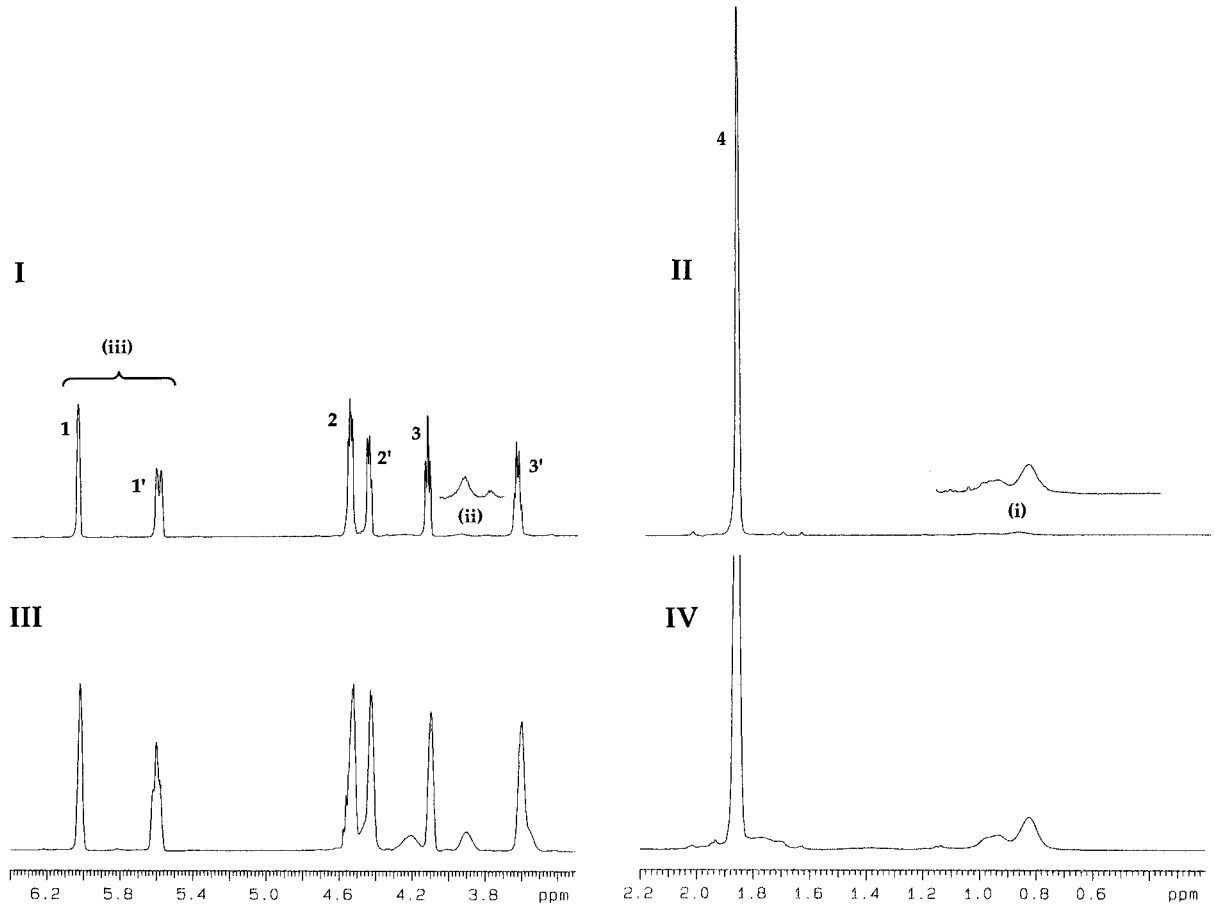

Figure 1. Expansions of the 400-MHz ^{1}H-NMR spectra of **1** + HEMA (mole ratio = 1:1) recorded at 4.3% conversion (panels I, II) and 22.7% conversion (panels III, IV). Panels I and III show spectral region δ 3.3−6.4 ppm. Panels II and IV show spectral region δ 0.2−2.2 ppm. Assignments are as follows: (i) Me groups attached to the polymer chain; (ii) one of the side-chain CH_2 groups of built-in HEMA; (iii) olefinic protons of unreacted monomers **1** and HEMA; 1, olefinic protons of unreacted monomers **1** and HEMA *trans* to Me; 1′, olefinic protons of unreacted monomers **1** and HEMA *cis* to Me; 2 and 2′, side-chain CH_2 groups of unreacted **1**; 3 and 3′, side-chain CH_2 groups of unreacted HEMA; 4, Me group of unreacted **1** and HEMA. Panels I and II contain vertical expansions (×10) of patterns i and ii; note the similarity between these expansions and the corresponding spectral regions in panels III and IV.

used for determination of conversion and polymer composition.

Conversion was calculated as explained above. The composition of the polymer is now expressed as F_1, which was calculated from

$$F_1 = 1.5(\text{int. ii}/\text{int. i})$$

where F_1 is the mole fraction of built-in **1**. Also in this case, patterns i and ii could be assigned unambiguously and do not show spectral overlap.

The copolymerizations **2** + HEMA and **2** + MMA were monitored analogously. For all four monomer pairs, conversion of 5% was reached within 15 min. This ^{1}H-NMR approach to monitor ongoing copolymerizations is convenient because of its speed, accuracy, and reproducibility.

Results and Discussion

Table 1 compiles the results obtained by studying the reactions **1** + HEMA and **1** + MMA. Momentary conversion (η) and momentary copolymer composition (F_1) were measured as described above. Each reaction was followed until conversion reached ∼10%. Table 1 summarizes the results of these experiments. Note that, for $f_1 = 0.500$, the reaction was monitored up to conversion of ∼33%. Table 2 analogously compiles the data for **2** + HEMA and **2** + MMA. It was possible to calculate the complete set of monomer reactivity ratios from the data in Tables 1 and 2. To do this, we selected data corresponding with η in the range of 4%−6%. These entries are bold in Tables 1 and 2. Note that this selection is quite critical. For lower η, integration of the polymer resonances becomes troublesome, and for higher η, it is no longer possible to neglect the so-called composition drift effect.[11] We have used both the Tidwell−Mortimer method[12] and the error-in-variables model (EVM)[11] to calculate the reactivity ratios. All reactivity ratios were obtained by fitting the composition data in the terminal model, as was independently introduced in 1944 by Alfrey and Goldfinger,[13] Wall,[14] and Mayo and Lewis.[15]

Tidwell and Mortimer used a curve-fitting method that calculates the values of r_1 and r_2 by minimizing the sum of the squares of the differences between the observed and computed polymer composition.[12] EVM differs from other statistical methods in that it correctly considers error in the independent variable, i.e., the monomer feed composition.[11] If the error in the dependent variable (i.e., copolymer composition) is substantially larger than that in the independent variable, ordinary nonlinear least-squares is an adequate method for parameter estimation. However, bias can result if the errors are approximately the same, thus making EVM preferable.

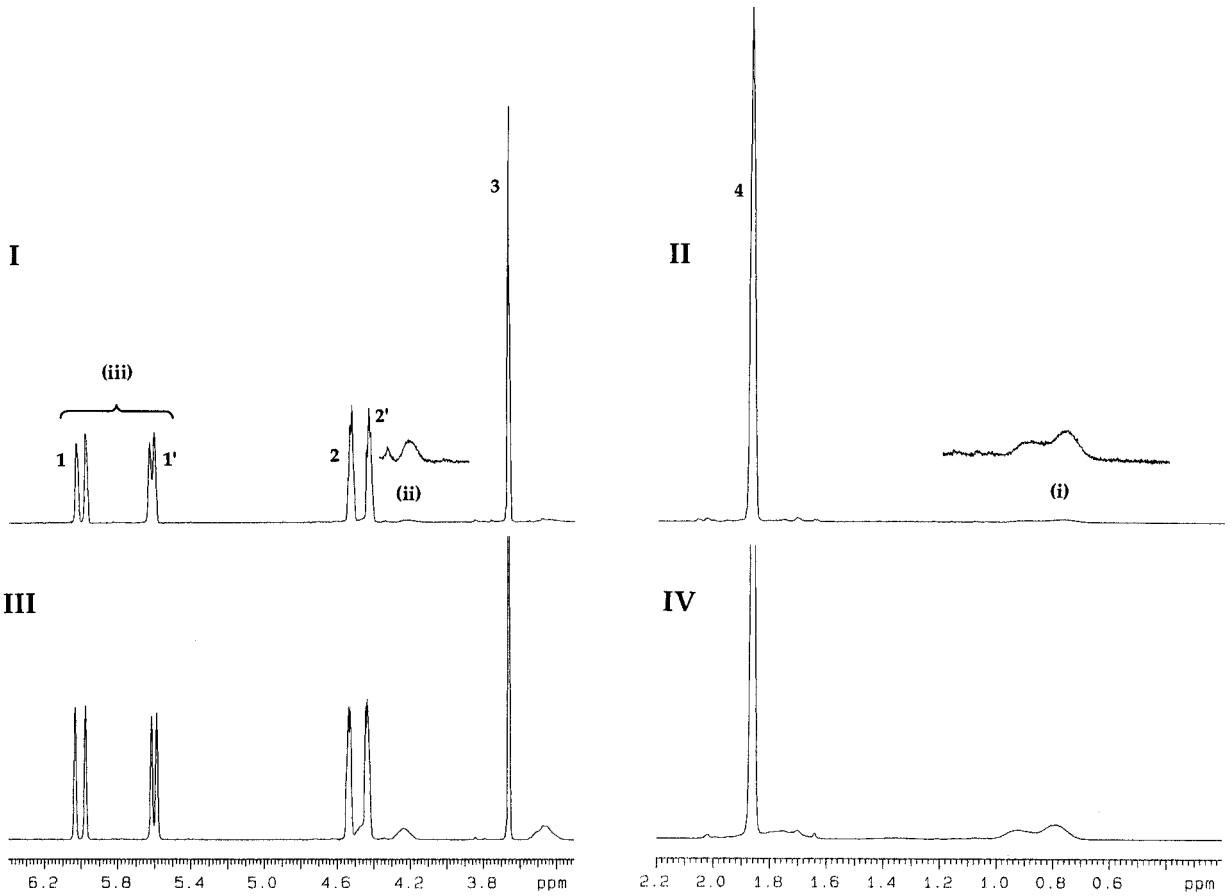

Figure 2. Expansions of the 400-MHz ^{1}H-NMR spectra of **1** + MMA (mole ratio = 1:1) recorded at 4.1% conversion (panels I, II) and 20.7 % conversion (panels III, IV). Panels I and III show spectral region δ 3.3−6.4 ppm. Panels II and IV show spectral region δ 0.2−2.2 ppm. Assignments are as follows: (i) Me groups attached to the polymer chain; (ii) one of the side-chain CH_2 groups of built-in **1**; (iii) olefinic protons of unreacted monomers **1** and MMA; 1, olefinic protons of unreacted monomers **1** and MMA *trans* to Me; 1′, olefinic protons of unreacted monomers **1** and MMA *cis* to Me; 2 and 2′, side-chain CH_2 groups of unreacted **1**; 3, MeO group of MMA; 4, Me group of monomer **1** and MMA. Panels I and II contain vertical expansions (×10) of patterns i and ii; note the similarity between these expansions and the corresponding spectral regions in panels III and IV.

The reactivity ratios determined with EVM were computed using estimated random errors of 1% and 5% for the monomer feed composition and the copolymer composition, respectively, as proposed in ref 11. Table 3 shows the reactivity ratios as determined with EVM. The reactivity ratios as determined with the Tidwell−Mortimer method were found to be highly comparable with those found with EVM.[16] Figure 3A shows F_1 vs f_1 and the fitted curves for **1** + HEMA and **1** + MMA; Figure 3B shows F_2 vs f_2 and the fitted curves for **2** + HEMA and **2** + MMA. The reactivity ratios found for the copolymerization reaction **1** + HEMA are $r_1 = 1.09 \pm 0.14$ and $r_{HEMA} = 1.12 \pm 0.06$. These data reveal that both monomers have virtually equal reactivities toward both propagating radical species. Therefore, the copolymer composition equals the monomer feed with a random placement of the two building blocks along the copolymer chain. Such behavior is referred to as random or Bernouillian.

For the reaction **1** + MMA, the reactivity ratios were found to be $r_1 = 0.54 \pm 0.12$, and $r_{MMA} = 0.67 \pm 0.06$, which reveals a slight deviation from Bernouillian behavior.[17] The reactivity ratios for the reaction **2** + HEMA are $r_2 = 2.18 \pm 0.72$ and $r_{HEMA} = 2.29 \pm 0.38$. Also in this case, a slight difference from Bernouillian behavior is noted. Our studies on the copolymerization **2** + MMA revealed $r_2 = 0.93 \pm 0.32$ and $r_{MMA} = 0.90 \pm 0.13$, which again reveals Bernouillian behavior.

Figure 4A shows how the mole fraction of **1**-centered triads varies as a function of f_1 (feed composition) for the reaction **1** + HEMA. Figure 4B plots these data for the reaction **1** + MMA. Both graphs show that the mole fraction of alternating **1**-centered triads decreases smoothly with increasing f_1. Simultaneously, the mole fraction of homotriads increases smoothly. Figure 4C and D analogously shows the calculated distribution of **2**-centered triads for **2** + HEMA, and **2** + MMA, respectively. Highly comparable results were obtained for the triad analyses of **2** + HEMA and **2** + MMA (viz. Figure 4C,D). The mole fraction of heterotriads having one HEMA or MMA unit reaches a maximum of 0.5 at about $f_1 = 0.48$ for **1** + HEMA (Figure 4A), at about $f_1 = 0.65$ for **1** + MMA (Figure 4B), at about $f_2 = 0.32$ for **2** + HEMA (Figure 4C), and at about $f_2 = 0.52$ for **2** + MMA (Figure 4D). Note the symmetrical appearance of the graphs in Figure 4A and D, which is in accordance with the ideal behavior of the copolymerizations **1** + HEMA and **2** + MMA.

The 95% confidence limit gives an idea of the experimental error and the accuracy of the experimental conditions used to generate the composition data.[18] When the experimental error is reasonably small and the data have been taken under the appropriate conditions, the approximation can be remarkably good. This is illustrated by the dimensions of the elliptical diagram generated by applying the mathematical treatment suggested by Behnken[18] and Tidwell and Mortimer.[12] The 95% confidence region is to be interpreted as follows: on indefinitely repeating the experiment, calculating the confidence region in the same way each

Table 1. Results for Copolymerization of 1 + HEMA and 1 + MMA: Momentary Conversion (η) and Momentary Composition of the Copolymer (F_1) for Different Feed Compositions (f_1)[a]

	1 + HEMA		**1** + MMA	
f_1[b]	η (%)	F_1[c]	η (%)	F_1[c]
0.100	4.7	0.142	3.7	0.142
	6.0	**0.092**	**5.7**	**0.135**
	7.4	0.105	7.6	0.154
0.200	3.0	0.201	4.0	0.234
	4.6	**0.186**	**6.1**	**0.221**
	8.2	0.172	8.7	0.232
0.350	**4.5**	**0.345**	3.7	0.343
	7.7	0.344	**4.9**	**0.354**
	9.9	0.345	6.6	0.351
0.500	**4.3**	**0.504**	3.8	0.522
	6.7	0.505	4.1	0.538
	8.9	0.491	**4.9**	**0.534**
	13.2	0.496	7.9	0.568
	17.2	0.508	20.7	0.523
	22.7	0.475	32.1	0.523
	26.8	0.462		
	33.4	0.467		
0.650	3.5	0.622	3.4	0.605
	4.8	**0.634**	**4.9**	**0.597**
	5.8	0.600	6.3	0.654
0.800	3.4	0.790	3.8	0.670
	4.9	**0.798**	**5.1**	**0.715**
	7.4	0.780	6.2	0.697
0.900	**5.6**	**0.928**	3.7	0.721
	8.2	0.933	**4.9**	**0.789**
	12.9	0.910	5.3	0.763

[a] Entries in bold were used in the calculations of the reactivity ratios. [b] Error was determined to be <1%. [c] Error was determined to be <2%.

Table 2. Results for Copolymerization of 2 + HEMA and 2 + MMA: Momentary Conversion (η) and Momentary Composition of the Copolymer (F_2) for Different Feed Compositions (f_2)[a]

	2 + HEMA		**2** + MMA	
f_2[b]	η (%)	F_2[c]	η (%)	F_2[c]
0.100	2.9	0.057	4.8	0.119
	4.8	**0.053**	**5.6**	**0.111**
	6.7	0.094	6.5	0.119
0.200	4.2	0.148	3.3	0.216
	6.2	**0.136**	4.7	0.206
	7.9	0.164	**6.1**	**0.195**
0.350	3.5	0.275	4.3	0.389
	4.8	**0.287**	**5.4**	**0.394**
	7.1	0.296	7.1	0.388
0.500	3.8	0.489	4.7	0.482
	6.3	**0.507**	**5.3**	**0.508**
	8.1	0.516	7.1	0.497
0.650	3.4	0.733	**4.9**	**0.660**
	5.2	**0.679**	7.0	0.667
	6.9	0.696	8.3	0.671
0.800	**4.7**	**0.850**	2.7	0.774
	7.5	0.843	**5.5**	**0.750**
	10.2	0.829	8.7	0.765
0.900	4.2	0.921	3.5	0.833
	6.3	**0.930**	**5.6**	**0.879**
	8.7	0.926	7.4	0.882

[a] Entries in bold were used in the calculations of the reactivity ratios. [b] Error was determined to be <1%. [c] Error was determined to be <2%.

time, the two values of r_1 and r_2 will be within the ellipse 95% of the time.

We have used the reactivity ratio values as determined by EVM to provide the 95% confidence limits defined by the area of the elliptical diagrams in Figure 5. The dimensions of the elliptical diagrams for all four monomer pairs (Figure 5) confirm the excellent approximation of the reactivity ratios, as indicated by the relatively small dimensions of the ellipses.

Table 3. Reactivity Ratios of 1 + HEMA, 1 + MMA, 2 + HEMA, and 2 + MMA As Determined with the Error-in-Variables Model (EVM)

reaction	reactivity ratios[a,b]
1 + HEMA	$r_1 = 1.09 \pm 0.14$, $r_{HEMA} = 1.12 \pm 0.06$
1 + MMA	$r_1 = 0.54 \pm 0.12$, $r_{MMA} = 0.67 \pm 0.06$
2 + HEMA	$r_2 = 2.18 \pm 0.72$, $r_{HEMA} = 2.29 \pm 0.38$
2 + MMA	$r_2 = 0.93 \pm 0.32$, $r_{MMA} = 0.90 \pm 0.13$

[a] Including standard deviations. [b] For all four monomer pairs, the 95% confidence intervals for both reactivity ratios are shown in Figure 5.

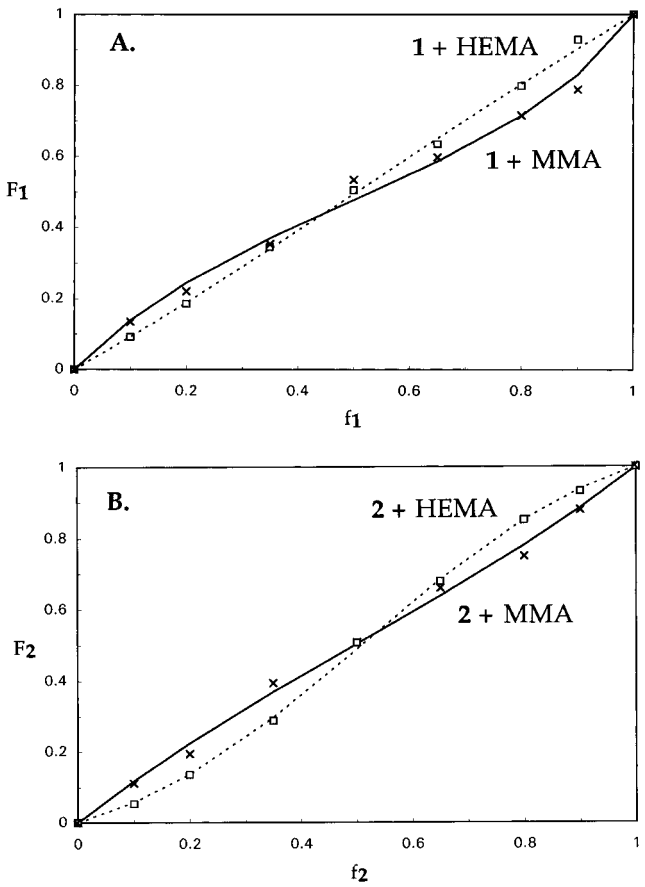

Figure 3. Experimental data F_1 vs f_1 (or F_2 vs f_2) and fitted curves (A) for **1** + HEMA (dotted line) and **1** + MMA (bold line) and (B) for **2** + HEMA (dotted line) and **2** + MMA (bold line).

Concluding Remarks

The results of this study show that the reactions **1** + HEMA, **1** + MMA, **2** + HEMA, and **2** + MMA produce copolymers with a random character. Therefore, terpolymers built-up of **1** or **2**, HEMA, and MMA are also expected to have a random arrangement of these building units along the polymer chain. In our previous work, we specifically focused on the terpolymer **1**:HEMA:MMA (mole ratio = 20:15:65).[8] It was concluded that this material has low thrombogenicity, as compared to poly(ethylene), poly(urethane), and poly(vinyl chloride). It is tempting to speculate what the surface of the terpolymer in contact with blood will look like. Most probably, hydrophilic HEMA units are exposed at the surface, but it is unlikely that the entire surface is covered by HEMA. In view of the random character of the terpolymer, it is also unlikely that hydrophilic and hydrophobic microdomains are present. This is of interest, since it has been reported that microphase

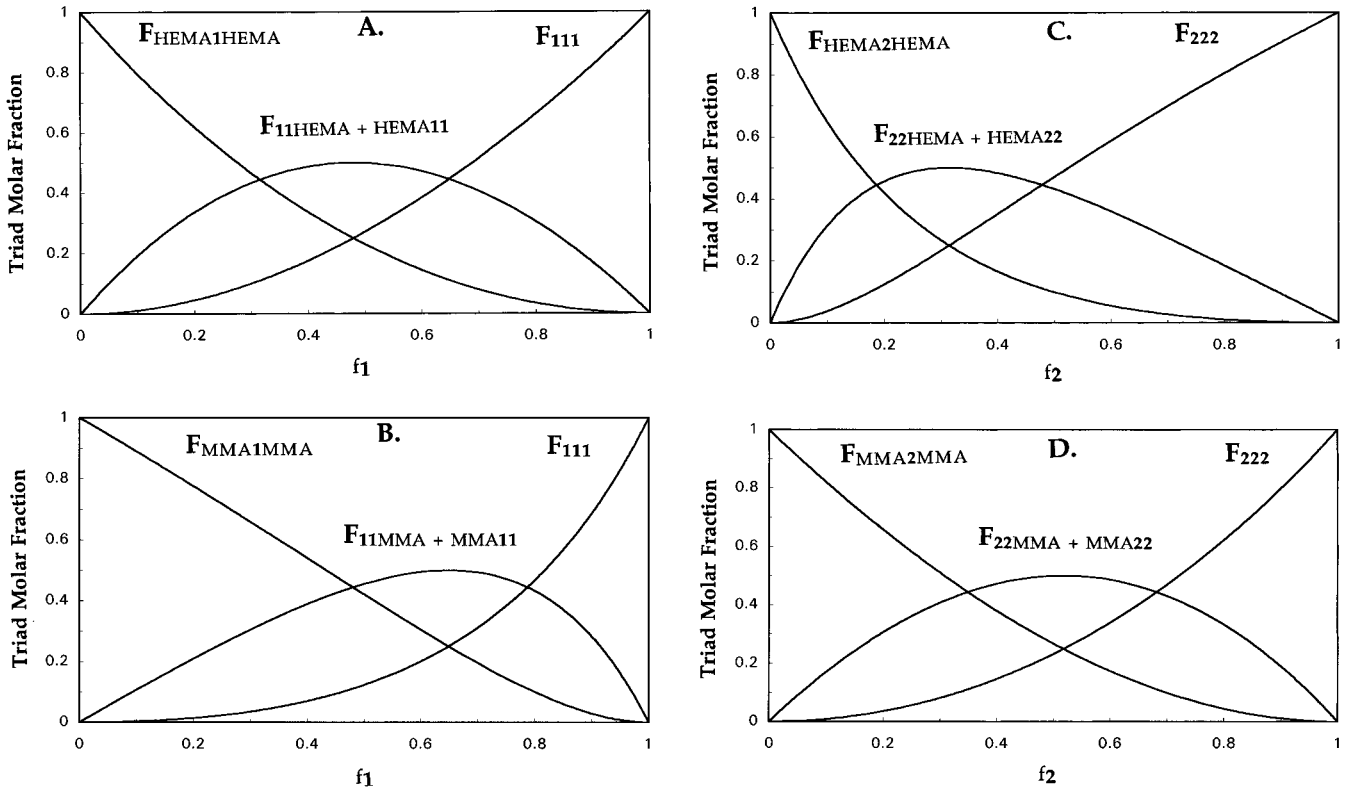

Figure 4. Variation of the mole fraction of **1**-(or **2**-)centered triads with the feed composition (f_1 or f_2) (A) for **1** + HEMA, (B) for **1** + MMA, (C) for **2** + HEMA, and (D) for **2** + MMA.

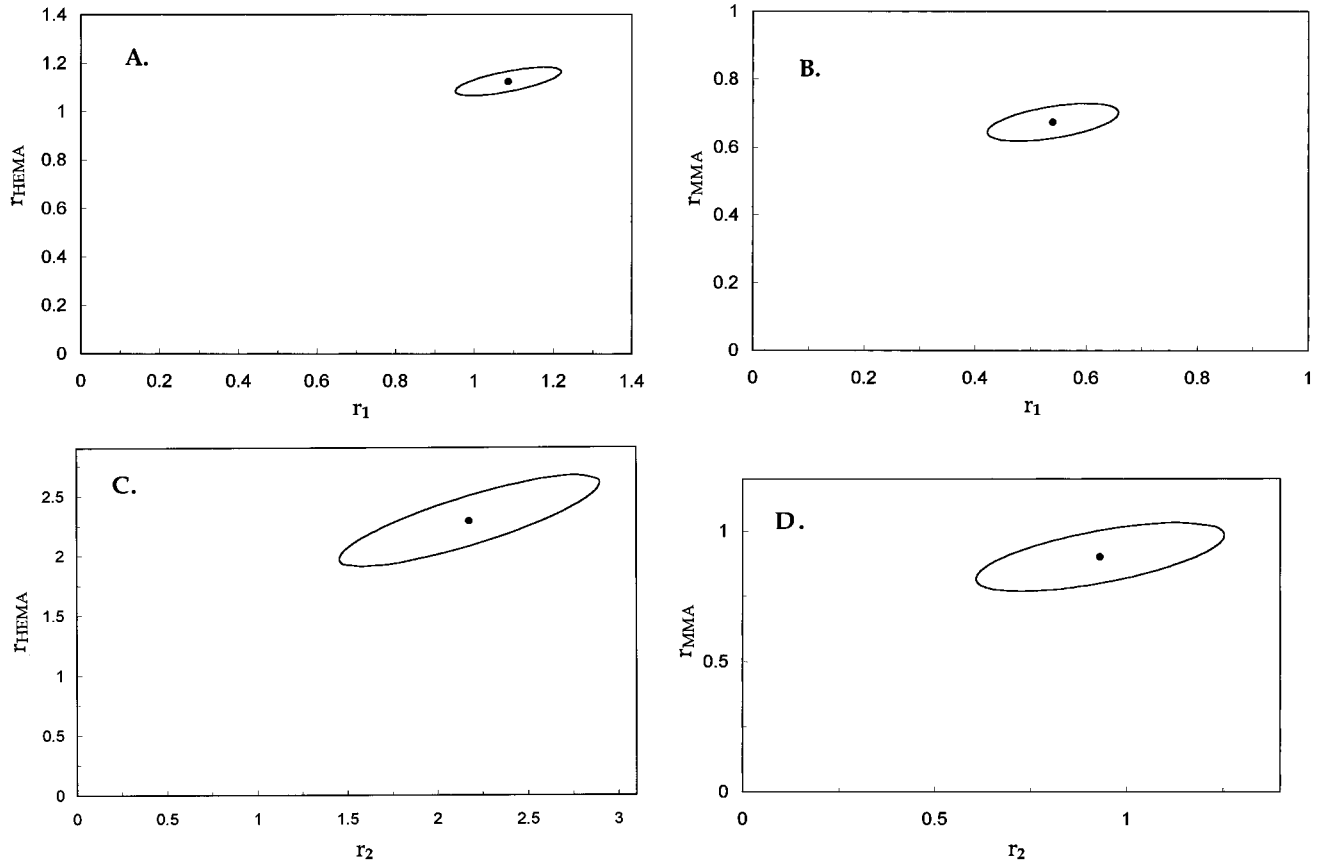

Figure 5. The 95% confidence diagram for the reactivity ratios as determined by EVM of (A) **1** + HEMA, (B) **1** + MMA, (C) **2** + HEMA, and (D) **2** + MMA. Note the relatively small dimensions of the ellipses, which confirms the excellent approximation of the reactivity ratios.

separation affects adsorption of plasma proteins and thereby influences adhesion and activation of blood platelets.[19,20] A balance between hydrophilicity and hydrophobicity is proposed as one of the prerequisites for polymeric materials to exhibit low thrombogenicity.[19,21,22] Our present results appear to reinforce the

conclusion of Mathew *et al.*,[23,24] that polymers that expose hydrophilic and hydrophobic building units in a nonordered manner at their surface also exhibit low thrombogenicity.

We believe that the NMR spectroscopic method introduced here is suitable to study other copolymerizations as well. Potential limitations appear to be that it must be possible to assign polymer signals in an unambiguous way and that no overlap with other signals occurs. Such overlap would hamper accurate signal integration. The method obviously benefits from a strong magnetic field, which results in high spectral dispersion and high sensitivity (signal/noise for ^{1}H). The latter aspect is important to realize short sampling times (typically 2.5 s). Further work along these lines is currently in progress in our laboratory.

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