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Copolymerization of two bromine containing methacrylate monomers with methylmethacrylate. Determination of reactivity ratios by in situ quantitative ^{1}H NMR monitoring

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Abstract: An important method used to make medical implants radiologically visible is based on introduction of radiopaque bromine or iodine containing methacrylic monomers. Thus, 2-(2-bromopropionyloxy) propyl methacrylate (BPPM) and 2-(2-bromoisobutyryloxy) propyl methacrylate (BIPM) were synthesized with the aim to use them as radiopaque agents. The free radical initiated copolymerization of BPPM and BIPM with methyl methacrylate (MMA) were performed directly in a thermostatic cell of the NMR spectrometer. The copolymer compositions obtained from ^{1}H NMR spectra led to the determination of the reactivity ratios (r_{MMA} = 1.08 ± 0.12; r_{BPPM} = 1.01 ± 0.13 and r_{MMA} = 0.95 ± 0.09; r_{BIPM} = 0.95 ± 0.1). The reactivity ratios of these two monomers is similar to that of MMA suggesting that the length of the bromine containing monomers side chain does not affect significantly the reactivity of the methacrylic double bond. From the results we conclude the copolymers to have random structure.

Introduction

At present, a wide range of radiopaque polymer materials are used as medical implants or inserts. As radiopacity is generally proportional to the effective atomic number of a given element, candidate materials for enhancing the radiopacity of medical implants should have higher atomic numbers than the elements, such as hydrogen, carbon, nitrogen and oxygen, present in the body and moreover they should be biocompatible. The preferred elements for biocompatibility and radiopacity are bromine, iodine, barium and bismuth [1, 2].

The main method used to make medical implants radiologically visible is based on blending polymers with conventional radiopaque inorganic salts. Other methods consist of the formation of single-phase radiopaque polymers salt complexes or radiopaque polymers characterized by a radiopacifying element associated with the monomer unit prior to polymerization [2]. An important method, which is developed by many researchers [3-5], consists of the synthesis of radiopaque bromine or iodine containing methacrylic monomers. These monomers were copolymerized with other monomers, especially with methylmethacrylate (MMA) for obtaining the bulk of the implant [5].

In order to obtain homogeneous materials by copolymerization, the halogenated comonomers should have similar reactivities to MMA. This requirement was met by introducing an oxyethyl spacer group between the reactive methacrylic double bond and the brominated moiety of the monomer [6]. The aim of the present work was to extend the range of this type of radiopaque methacrylic monomers, with the synthesis and characterization of 2-(2 bromopropionyloxy) propyl methacrylate (BPPM) and 2-(2 bromoisobutyryloxy) propyl methacrylate (BIPM).

The synthesis of these monomers has been mentioned in a patent application [7]. However, the reactivity ratios for copolymerization of these monomers with MMA were not reported so far. Thus, the free radical copolymerization above mentioned brominated monomers has been examined with a NMR technique which consists of operating the polymerization directly in a thermostatic cell of the spectrometer [7].

Results and discussion

Copolymerization data acquisition

In order to know the bromine containing monomers behavior in radical copolymerization processes with MMA, the reactivity ratios of BPPM and BIPM were determined using ^{1}H NMR spectra.

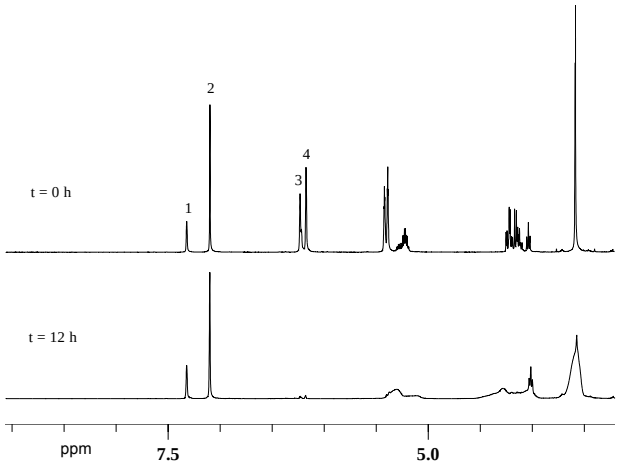


Fig. 1. Some representative ^{1}H NMR spectra of the BIPM-MMA copolymer system (COP 8) at different times of reaction (1-benzene; 2-p-xylene; 3-vinyl proton from BIPM; 4-vinyl proton from MMA)

Figure 1 shows the spectra of the initial BIPM-MMA system and at a reaction time of 12 hours, together with the assignments of the peaks employed in the determination of the monomer concentration. p-Xylene was used as reference for the quantitative analysis of the monomer peaks.

Knowing the peak intensities of the vinyl protons and the peak intensity of the p-xylene proton it is possible to determine the molar conversion rate at a given time. From a practical point of view, the slope at the origin of each curve of conversion was obtained right after the inhibition period which is not exceeding 5 minutes and for a total conversion not exceeding 15 % (Figure 2).

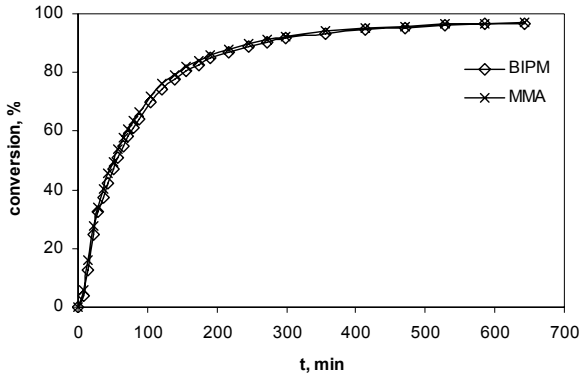


Fig. 2. Evolution of the molar conversion vs. time for the system BIPM – MMA.

Determination of monomer reactivity ratios

The monomer reactivity ratios for the copolymerization of MMA with BPPM and BIPM were determined from the copolymer composition as a function of various monomer feed ratios (Table 1). The well-known Finemann-Ross (FR) [10] and Kelen-Tüdös (KT) [11] methods were used to determine the monomer reactivity ratios r_1 and r_2.

Tab. 1. FR and KT parameters for the copolymerization of BPPM-MMA and BIPM-MMA.

f	F	F-R parameters		K-T parameters	
		H	G	ξ	η
Copolymers BPPM-MMA					
0.113	0.096	0.132	-1.056	0.111	-0.883
0.43	0.481	0.385	-0.465	0.266	-0.321
1.004	0.901	1.114	-0.110	0.512	-0.051
2.322	2.3	2.342	1.312	0.688	0.385
8.615	8.708	8.574	7.642	0.890	0.793
Copolymers BIPM-MMA					
0.116	0.102	0.132	-1.018	0.110	-0.851
0.424	0.545	0.330	-0.354	0.237	-0.254
1	0.926	1.077	-0.077	0.503	-0.036
2.333	2.355	2.312	1.343	0.685	0.398
8.174	7.772	8.598	7.131	0.890	0.738

Alpha (α) is equal to 1.063 for the BPPM-MMA system and 1.065 for the BIPM-MMA system.

The equation involved in Finemann-Ross method is:

$$f \cdot \frac{(F-1)}{F} = \left(\frac{f^2}{F} \right) \cdot r_1 - r_2 \qquad (1)$$

where *F* is the ratio of mole fraction of BPPM (BIPM) to the mole fraction of MMA in the feed and *f* is the ratio of mole fraction of BPPM (BIPM) to the mole fraction of MMA in the copolymer. A plot of $G=f(F-1)/F$ against $H=f^2/F$ gives a straight line with slope equal to r_1 and intercept equal to r_2. The FR plots obtained by linear regression analysis for copolymer system BPPM-MMA and BIPM-MMA are given in Figures 3 and 4, respectively.

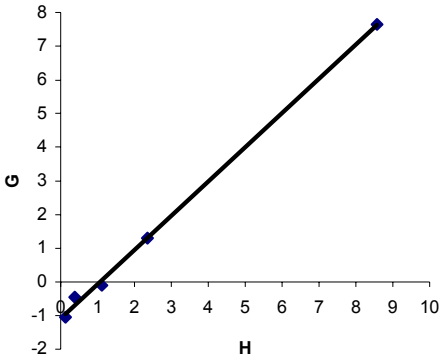


Fig. 3. FR plot for poly(BPPM-co-MMA).

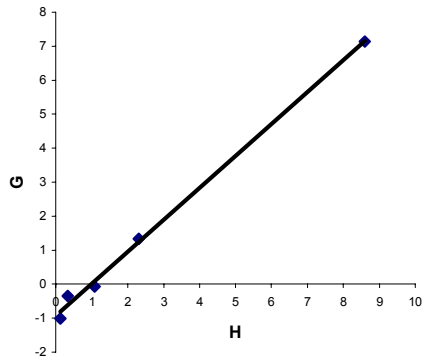


Fig. 4. FR plot for poly(BIPM-co-MMA).

In Kelen-Tüdös method, the equation is:

$$\eta = \left(r_1 + \frac{r_2}{\alpha} \right) \cdot \zeta - \frac{r_2}{\alpha} \qquad (2)$$

where $\eta=G/(\alpha+H)$, $\xi=H/(\alpha+H)$, $G=f(F-1)/F$, $H=f^2/F$ and α is the geometric means of the minimum and maximum H values. By plotting η against ξ a straight line is obtained which with slope equal to $(r_1+r_2)/\alpha$ and intercept equal to $-r_2/\alpha$. The KT plots for copolymer system BPPM-MMA and BIPM-MMA are presented in Figures 5 and 6.

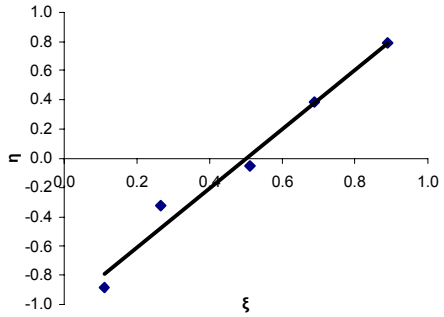


Fig. 5. KT plot for poly(BPPM-co-MMA).

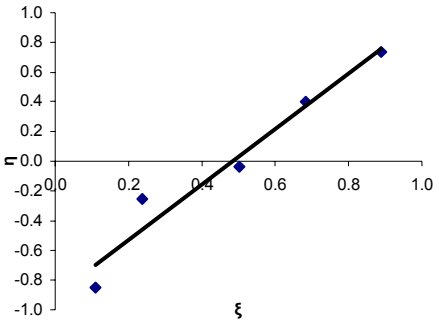


Fig. 6. KT plot for poly(BIPM-co-MMA).

The values of reactivity ratios with standard errors obtained from KT and FR methods are summarized in Table 2.

Tab. 2. Comparison of reactivity ratios by various methods.

System	Method	r_1	r_2	$r_1.r_2$
Poly(BPPM-co-MMA)	FR	1.01 ± 0.03	1.08 ± 0.12	1.09
	KT	1.01 ± 0.24	1.08 ± 0.13	1.09
Poly(BIPM-co-MMA)	FR	0.94 ± 0.02	0.94 ± 0.09	0.88
	KT	0.96 ± 0.18	0.96 ± 0.02	0.92

It is obvious that in this case, when both reactivity ratios are approximately equal to 1, BIPM-MMA copolymer system is favored to form short homogeneous sequences. Taking into account the errors, it can be said that the reactivity ratios for the system BPPM-MMA, and by this the behavior of the monomers is similar to the case of the system BIPM-MMA when the composition of the copolymer being same during the reaction is equal at any time with the feed compositions.

It is possible that the reactivity of the two prepared monomers is different when a bulk polymerization is involved. This fact could not be verified using NMR spectroscopy, because the copolymers obtained are not soluble in deuterated solvents usually used in NMR technique. In this case, the reactivity ratios values determined are specific for the copolymerization in deuterated benzene.

Conclusions

2-(2-Bromopropionyloxy) propyl methacrylate (BPPM) and 2-(2-bromoisobutyryloxy) propyl methacrylate (BIPM) were synthesized and characterized by ^{1}H NMR and ^{13}C NMR spectral techniques. Copolymers of BPPM and BIPM with MMA having various compositions were prepared in solution by free radical polymerization at 60 ˚C. The reactivity ratios of these two brominated comonomers were estimated using Fineman-Ross and Kelen-Tüdös methods. Their reactivity is similar to that of MMA suggesting that the length of the bromine containing monomers side chain does not affect significantly the reactivity of the methacrylic double bond.

In addition to their application as radiopaque materials, this type of bromine containing copolymers may be used as atom transfer radical polymerization initiators for the preparation of graft copolymers as recently suggested by Li et al [9].

Experimental part

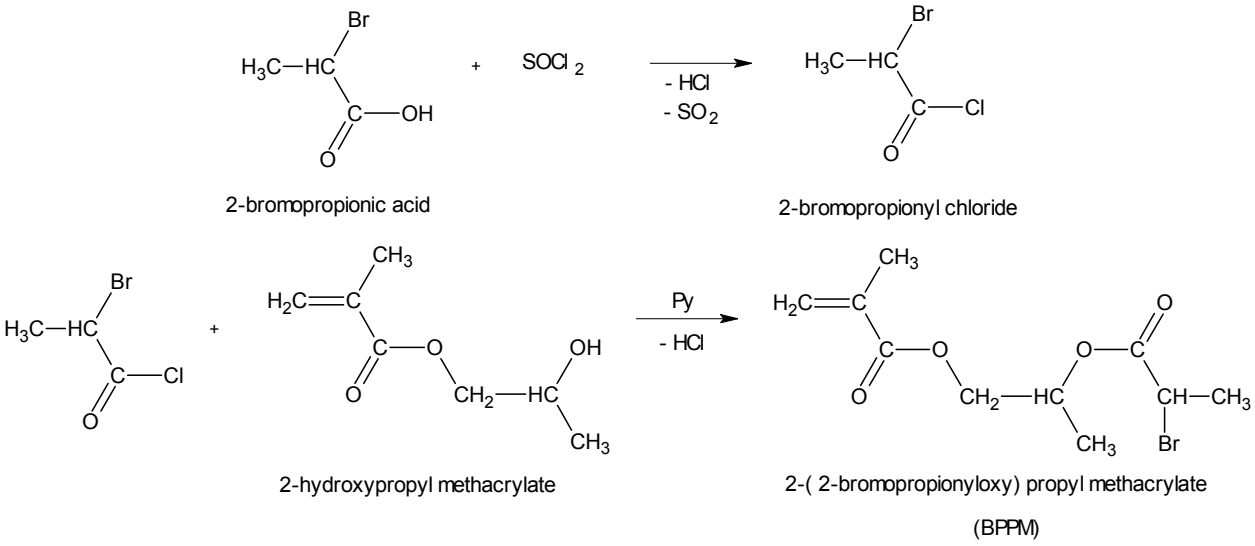
Materials

Methyl methacrylate (Aldrich, 99%), 2-hydroxypropyl methacrylate (Aldrich, 99%), 2-bromoisobutyryl bromide (Aldrich, 98%), 2-bromopropionic acid (Acros Organics, 99%), thionyl chloride (Acros Organics), pyridine (Aldrich, 99%), tetrahydrofuran (Acros Organics, 99,9%), p-xylene (Fluka, 99%), 2,2'-azobisisobutyronitrile (Acros Organics) and deuterated benzene (C.E.Saclay) were used as received.

Synthesis of 2-(2-bromopropionyloxy) propyl methacrylate (BPPM)

The synthesis, transposed from that of Klumperman et al [8], comprises of two steps (Scheme 1). First, 2-bromopropionyl chloride was synthesized by the reaction between 2-bromopropionic acid and thionyl chloride. For this, a dry 250 ml two-neck round-bottom flask was used. Thionyl chloride was added drop-wise over a period of 2 hours. The reaction was carried out under stirring at 0 °C. The unreacted thionyl chloride was removed by distillation under vacuum.

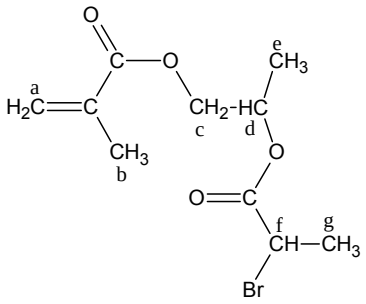
Second, 2-(2-bromopropionyloxy) propyl methacrylate (BPPM) was synthesized by the reaction between 2-hydroxypropyl methacrylate (HPMA) and 2-bromopropionyl chloride using tetrahydrofuran (THF) as solvent and pyridine (Py) as HCl acceptor. This synthesis was carried out in a 500 ml three-neck round-bottom flask. 2-bromopropionyl chloride was added drop-wise through a dropping funnel over a period of 3 hours and the reaction was carried out at 0 °C.



Scheme 1. Synthesis of 2-(2-bromopropionyloxy) propyl methacrylate.

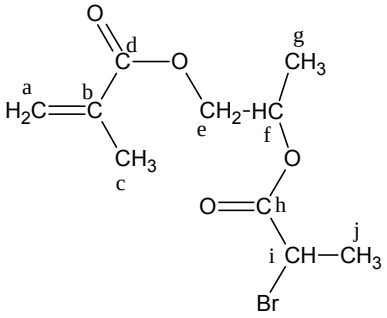
For the purification of BPPM, the reaction solution was introduced into a separation funnel with a mixture of 300 ml water and 300 ml ethylic ether and stirred for 40 minutes. The water mixture was extracted. Then, the resulting organic layer was washed two times sequentially with 150 ml of 1M hydrochloric acid and 100 ml of a saturated 10 % sodium bicarbonate aqueous solution. After this, the organic phase was washed with 200 ml distilled water. The organic layer was dried over magnesium sulfate and then filtered. The solvent was evaporated under reduced pressure. After

the drying process, column chromatography was used for separation and purification of bromine monomer. The product structure was identified by ^{1}H NMR and ^{13}C NMR: *^{1}H NMR (400 MHz) $CDCl_3$, δ (ppm):* 6.04 (a); 5.52 (a); 5.17 (f); 4.29 (c); 4.13 (d); 1.87 (b); 1.73 (e); 1.24 (g) (Scheme 2).



Scheme 2. Chemical structure of BPPM with noted protons for ^{1}H NMR spectra analysis.

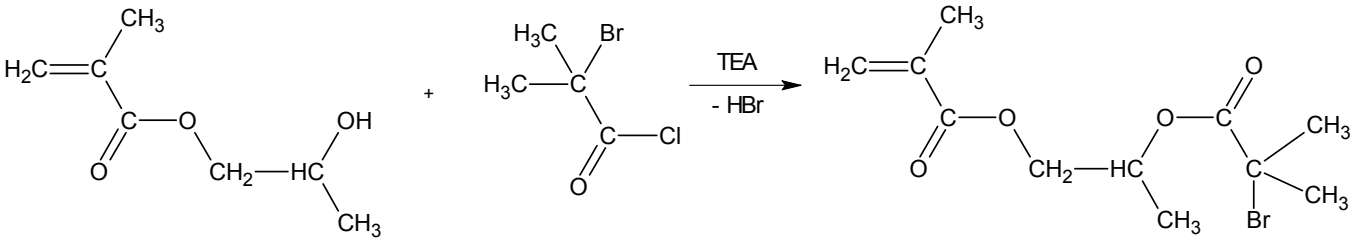
^{13}C NMR (100.6 MHz) $CDCl_3$, δ (ppm): 169.44 (h); 166.74 (d); 135.68 (b); 126.07 (a); 69.77 (e); 65.81 (f); 39.86 (i); 21.34 (j); 18.13 (c); 16.07 (g) (Scheme 3).



Scheme 3. Chemical structure of BPPM with noted carbon atoms for ^{13}C NMR spectra analysis.

Synthesis of 2-(2-bromoisobutyryloxy) propyl methacrylate (BIPM)

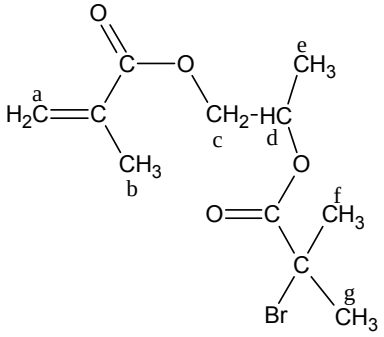
BIPM was synthesized by esterification of hydroxypropyl methacrylate with 2-bromoisobutyryl bromide, (Scheme 4). 2-Hydroxypropyl methacrylate (HPMA), triethyl amine (TEA) and tetrahydrofuran (THF) as solvent were added into a dry 250 ml three-neck round-bottom flask.



2-hydroxypropyl methacrylate + 2-bromoisobutyryl bromide → 2-(2-bromoisobutyryloxy) propyl methacrylate (BIPM)

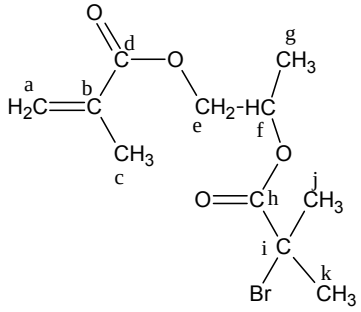
Scheme 4. Synthesis of 2-(2-bromoisobutyryloxy) propyl methacrylate.

This mixture was stirred at room temperature under nitrogen flow. 2-bromoisobutyryl bromide was added drop-wise through a dropping funnel over a period of 15 minutes. The reaction was carried out for 48 hours at room temperature. The resulting solid phase of triethylene ammonium bromide was separated by filtration and then the solvent (THF) from the liquid phase was evaporated. In the next step, the product was washed sequentially with diethyl ether and a 10% solution of potassium carbonate in a separation funnel. The organic layer was dried over magnesium sulfate and then filtered. The solvent was evaporated under reduced pressure. After the drying process, column chromatography was used for separation and purification of bromine monomer. The product structure was identified by ^{1}H NMR and ^{13}C NMR: *^{1}H NMR (400 MHz) $CDCl_3$, δ (ppm):* 6.05 (a); 5.51 (a); 4.21 (c); 4.15 (d); 1.85 (f,g); 1.25 (b,e) (Scheme 5).



Scheme 5. Chemical structure of BIPM with noted protons for ^{1}H NMR spectra analysis.

^{13}C NMR (100.6 MHz) $CDCl_3$, δ (ppm): 170.89 (h); 166.85 (d); 135.73 (b); 126.1 (a); 69.87 (e); 65.83 (f); 30.52 (i); 18.14 (j,k); 15.88 (c,g) (Scheme 6).



Scheme 6. Chemical structure of BIPM with noted carbon atoms for ^{13}C NMR spectra analysis.

Copolymerization

Copolymerization reactions of the prepared monomers with MMA were carried out directly in the thermostatic cell of a NMR spectrometer at 60 °C under quantitative conditions. The total monomer concentration was 1M in all cases, using 1 ml as the volume size of the polymerization batches. Deuterated benzene (C_6D_6) as solvent, 2,2'-azobisisobutyronitrile (AIBN) as radical initiator in concentration 1.5 wt % with respect to the mixture of monomers and p-xylene as an internal reference component

with concentration of 0.1 M were used. The feed molar composition of monomer and comonomer is given in Table 3.

Tab. 3. Molar concentrations of the monomers involved in copolymerization.

Copolymers	BPPM – MMA	
	[BPPM],mol/l	[MMA], mol/l
COP 1	0.102	0.901
COP 2	0.301	0.700
COP 3	0.500	0.499
COP 4	0.701	0.302
COP 5	0.898	0.104
	BIPM – MMA	
	[BIPM], mol/l	[MMA], mol/l
COP 6	0.105	0.905
COP 7	0.297	0.700
COP 8	0.500	0.500
COP 9	0.700	0.300
COP 10	0,900	0.110

^{1}H NMR analysis

The experiments were carried out in a 400 MHz Bruker Advance 400 spectrometer. The sample temperature was maintained at 60 °C using the heat controller of NMR equipment. For the calibration of NMR spectrometer, a solution of monomer and p-xylene in deuterated benzene without initiator was used for each copolymer systems. Spectra were thus obtained and signals were analyzed using electronic integration and the concentrations were determined as follows:

$$[X]_t = \frac{M_t}{R} \qquad (3)$$

where X is molar ratio of BPPM, BIPM and MMA respectively, at the time *t*; M_t corresponds to the contribution of protons assigned to BPPM, BIPM and MMA and *R* is the reference peak (p-xylene). Further experimental details can be found in a recently published article [7].

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