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New Radio-opaque Acrylic Bone Cements. I. The Synthesis of Bromine Containing Methacrylates

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Summary

In this work, results are presented concerning the synthesis and characterization (FTIR, ^{1}H-NMR, ^{13}C-NMR) of two bromine containing monomers: 2-(2-bromoisobutyryloxy) ethyl methacrylate (BIEM) and 2-(2-bromopropionyloxy) ethyl methacrylate (BPEM). The synthesis of these monomers has been made with the aim to use them as radio-opaque agents in the composition of PMMA-based bone cements. Copolymers were synthesized by free radical polymerization, using methyl methacrylate (MMA) and one of the bromine containing monomers in different concentrations. Copolymerizations were carried out directly in the thermostatic cell of an NMR spectrometer using deuterated benzene as solvent. The reactivity ratios of the copolymerization systems were determined by ^{1}H NMR analysis.

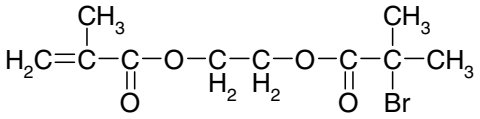
Introduction

Poly(methyl methacrylate)-based bone cements are extensively used in orthopedic surgery for the fixation of artificial joints. To monitor the healing process after the joint replacement by radiography, bone cement must be radio-opaque. Commercial bone cements are usually made radio-opaque by the addition of an inorganic compound, such as barium sulfate or zirconium dioxide [1]. It is known that the incompatibility between the polymeric matrix and inorganic phase may affect the mechanical properties of the cement [2]. The use of X-ray-opaque methacrylates is an alternative to the traditional radio-opaque agents. In this way, some authors obtained a higher opacity for the bone cements using iodine monomers [3-5].

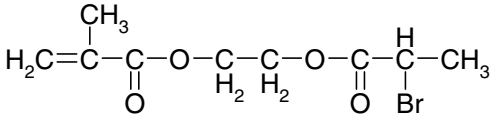
It is known that another element which confers radiopacity is bromine. Thus, the purpose of our work was the synthesis and characterization of bromine containing methacrylates, with the aim of using them in the preparation of acrylic bone cements.

This note reports on the synthesis of 2-(2-bromoisobutyryloxy) ethyl methacrylate (BIEM) and 2-(2-bromopropionyloxy) ethyl methacrylate (BPEM) (Scheme 1).

To our knowledge, only the synthesis of BIEM was recently described by Klumperman et al. [6], whereas BPEM was mentioned in patent application [7]. The copolymerization



BIEM



BPEM

Scheme 1. Chemical structure of BIEM and BPEM

reactivity ratios of BIEM and BPEM have not been reported. Due to the presence of $–CH_2-CH_2-$ spacer group in these two brominated methacrylic monomers, they should have similar reactivities to MMA. To test this, free radical polymerization of BIEM and BPEM will be examined using an NMR technique [8].

Experimental

Materials

Methyl methacrylate (Aldrich), 2-hydroxyethyl methacrylate (Aldrich), 2(2-bromoisobutyryl) acid (Acros Organics), 2-bromopropionic acid (Acros Organics), thionyl chloride (Acros Organics), pyridine (SDS), tetrahydrofuran (Acros Organics), p-xylene (Fluka), azobisisobutylonitrile (Acros Organics) and benzene C_6D_6 (C.E.Saclay) were used as received.

Measurements

^{1}H NMR spectra were recorded on a 400 MHz spectrometer (Bruker Advance 400), using $CDCl_3$ or C_6D_6 as a solvent.

Synthesis of 2-(2-bromoisobutyryloxy) ethyl methacrylate (BIEM)

The synthesis, adapted from that of Klumperman et al [6], comprise of two steps. In the first step, 2-bromoisobutyryl chloride was synthesized by the reaction between 2-bromoisobutyryl 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.

In the second step, 2-(2-bromoisobutyryloxy) ethyl methacrylate (BIEM) was synthesized by the reaction between 2-hydroxyethyl methacrylate (HEMA) and 2-bromoisobutyryl chloride using tetrahydrofuran (THF) as solvent and pyridine (Py) as proton acceptor. This synthesis was carried out in a 500 ml three-neck round-bottom flask. 2-bromoisobutyryl chloride was added drop-wise through a dropping funnel over a period of 3 hours and the reaction was carried at 0°C.

For the purification of the BIEM, 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 sodium bicarbonate aqueous solution 10 %. After this, the organic phase was washed with 200 ml distilled water. The organic layer was dried on magnesium sulfate and then filtered. The solvent was evaporated off under reduced pressure. The product structure was identified by FTIR, ^{1}H-NMR and ^{13}C-NMR:

FTIR, υ (cm^{-1}): 2930 (-CH_3), 1145 (C=C), 1716 (-C=O), 1403 (-H_2C-O-), 943 (-CH_2-CH_2-), 650 (-CH-Br);

^{1}H-NMR (400 MHz) $CDCl_3$, δ (ppm): 6.10 (1H, H-C=C), 5.57 (1H, H-C=C), 4.36 (4H, -O-CH_2-CH_2-O-), 1.91 (1H, CH-Br), 1.80 (6H, C=C-CH_3 and -CHBr-CH_3);

^{13}C-NMR (100.6 MHz) $CDCl_3$, δ (ppm): 169.73 (1C, O=C-CH-Br), 166.98 (1C, O=C-C=CH_2), 136.34 (1C, -C=CH_2), 126.36 (1C,CH_2=C-), 63.69 (1C, -O-CH_2-), 62.67 (1C, -CH_2-O-), 40.62 (1C, -HC-Br), 21.70 (1C, CH_3-CH-), 18.61 (1C, CH_3-C=CH_2).

The yield of the reaction for synthesis of 2-(2-bromoisobutyryloxy) ethyl methacrylate was 94%.

Synthesis of 2-(2-bromopropionyloxy) ethyl methacrylate(BPEM)

The synthesis of 2-(2-bromopropionyloxy) ethyl methacrylate comprised the same two steps involved in the precedent synthesis with the difference that, for the second step, 2-bromoisobutyryl acid was replaced with 2-bromopropionic acid. The product structure was identified by FTIR, ^{1}H-NMR and ^{13}C-NMR:

FTIR, υ (cm^{-1}): 2929 (-CH_3), 1147 (C=C), 1718 (-C=O), 1388 (-C-O-), 940 (-CH_2-CH_2-), 645 (-C-Br);

^{1}H-NMR (400 MHz) $CDCl_3$, δ (ppm): 6.06 (1H, H-C=C), 5.53 (1H, H-C=C), 4.37 (4H, -O-CH_2-CH_2-O-), 1.88 (9H, CH_3-C=C and CH_3-CBr-CH_3);

^{13}C-NMR (100.6 MHz) $CDCl_3$, δ (ppm): 171.51 (1C, O=C-C-Br), 167.38 (1C, O-C-O=CH_2), 136.40 (1C, -C=CH_2), 126.41 (1C, CH_2=C-), 63.76 (1C, -O-CH_2-), 61.68 (1C, -CH_2-O-), 55.16 (1C, -C-Br), 30.65 (2C, CH_3-CBr-CH_3), 18.67 (1C, CH_3-C=CH_2).

The yield of the reaction for synthesis of 2-(2-bromopropionyloxy) ethyl methacrylate was 95%.

Copolymerization

The copolymerizations between MMA and one of the monomers synthesized (either BIEM or BPEM) were carried out directly in the thermostatic cell of a NMR spectrometer at 60°C. The reactions are monitored for 12 hours by ^{1}H-NMR. The mixture of co-monomers, AIBN (1.5 wt % with respect to the mixture of monomers) and p-xylene as an internal reference component (0.1 mol/l) was dissolved in deuterated benzene, into a 5 ml volumetric flask.

It was not possible to monitor the reaction using dimethyl sulfoxide (DMSO) as deuterated solvent. Our supposition was that DMSO and the bromine containing monomer reacted following the mechanism of a Kornblum reaction, with generation of aldehyde or ketone derivatives [9].

The initial concentrations of the reagents at ambient temperature are well known. Using MMA and each one of the bromine containing monomers, 10 copolymers were synthesized (Table 1).

Table 1. Molar concentrations of the monomers involved in copolymerization

Copolymers	BPEM – MMA	
	[BPEM], mol/l	[MMA], mol/l
COP 1	0.120	0.963
COP 2	0.300	0.690
COP 3	0.498	0.515
COP 4	0.703	0.308
COP 5	0.901	0.117
	BIEM – MMA	
	[BIEM], mol/l	[MMA], mol/l
COP 6	0.101	0.903
COP 7	0.298	0.700
COP 8	0.500	0.500
COP 9	0.698	0.301
COP 10	0.901	0.108

Results and discussion

The ^{1}H NMR spectra are analyzed using a software named *XWINNMR*, provided by Bruker. The evolution of the vinyl proton peaks of the bromine containing monomer and of the methyl methacrylate was determined with reference to the p-xylene proton peak, which will remain constant throughout the experiment (Figure 1).

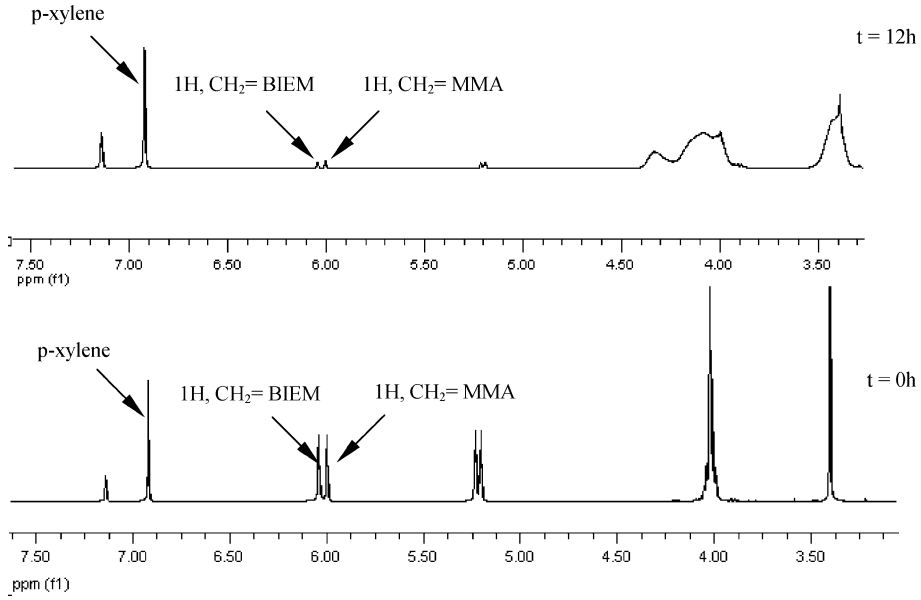


Figure 1. ^{1}H-NMR spectra of COP 8 system BIEM – MMA

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 *t* time using the equations 1 and 2.

$$X(MMA,t) = 100 \cdot \left(1 - \frac{\left(\frac{H_{MMA}}{H_x} \right)_t}{\left(\frac{H_{MMA}}{H_x} \right)_{t=0}} \right) \qquad (1)$$

$$X(BIEM,t) = 100 \cdot \left(1 - \frac{\left(\frac{H_{BIEM}}{H_x} \right)_t}{\left(\frac{H_{BIEM}}{H_x} \right)_{t=0}} \right) \qquad (2)$$

With
H_{MMA} – the value of integral of MMA vinyl proton ;
H_{BIEM}– the value of integral of BIEM vinyl proton ;
H_x – the value of integral of p-xylene proton ;
X(MMA, t) – conversion rate of MMA after t minutes ;
X(BIEM, t) –conversion rate of BIEM after t minutes.
From the slopes at origin (P_{BIEM}, P_{BPEM} and P_{MMA}) of the conversion curves versus time, for the MMA and the bromine containing monomers, it is possible to determine the instantaneous composition of the copolymer in the form of molar fraction (F_{BIEM}, F_{BPEM} and F_{MMA}) (Equation 3).

$$F_{BIEM} = \frac{P_{BIEM,0} \cdot [BIEM]}{P_{BIEM,0} \cdot [BIEM] + P_{MMA,0} \cdot [MMA]} \qquad (3)$$

From a practical point of view, the slope at the origin of each curve of conversion was obtained by extrapolation right after the period of inhibition not exceeding 5 minutes and for a total conversion rate not exceeding 15 % (Figure 2).

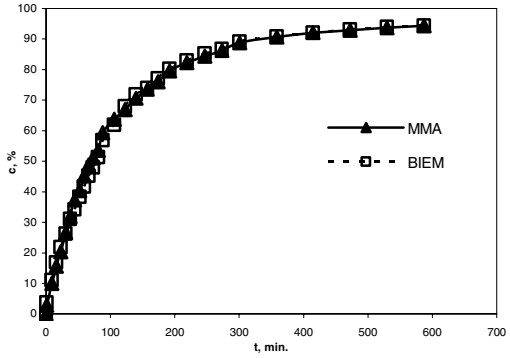


Figure 2. Evolution of the molar conversion of COP 8 system BIEM – MMA

From kinetic data and using the methods of Fineman-Ross, inverted Fineman-Ross and Kelen-Tudos [10], we have determined the reactivity ratios for the two copolymerization systems, BIEM/MMA and BPEM/MMA respectively (Table 2).

Table 2. Reactivity ratios for the two copolymerization systems BIEM/MMA and BPEM/MMA

Reactivity ratios	Fineman-Ross	Inverted Fineman-Ross	Kelen-Tudos
r_{BIEM}	1.01	1.05	1.01
r_{MMA}	0.84	0.85	0.82
r_{BPEM}	1.02	0.97	0.99
r_{MMA}	1.01	0.99	0.98

From this table, it can be noticed that for a given monomer, the reactivity ratios, calculated by the different methods, are consistent and that the reactivity ratios of the brominated monomers, both near to one, are close to those of MMA. According to the classical copolymerization theories, this means that one has a random distribution of the brominated monomer units in the copolymer chain with no risk of compositional drift as a function of conversion. Therefore, at conversions approaching 100%, which is required for surgical applications, there will be only trace amounts of brominated species left as monomer.

It is possible that the reactivity of the two prepared monomers to be 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.

Conclusion

2-(2-bromoisobutyryloxy) ethyl methacrylate (BIEM) and 2-(2-bromopropionyloxy) ethyl methacrylate (BPEM) were synthesized and characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR. Copolymers of these brominated acrylic monomers with methyle methacrylate have been prepared by free radical polymerization in benzene at 60°C. The reactivity ratios of the comonomers were estimated using Fineman-Ross and Kelen-Tudos methods. The r_{BPEM} and r_{BIEM} values are close to r_{MMA} value, meaning that one has a random distribution of the brominated monomer units in the copolymer chain.

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