

Synthesis and Polymerization of a New Iodine-Containing Monomer

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ABSTRACT: A new iodine-containing methacrylate monomer, 3,4,5-triiodobenzoyloxyethyl methacrylate (TIBEM), was synthesized by coupling 2-hydroxyethyl methacrylate (HEMA) with 3,4,5-triiodobenzoic acid. The monomer was characterized by ^1H nuclear magnetic resonance, infrared (IR), and ultraviolet spectra. Homopolymerization and copolymerization of the monomer with methyl methacrylate (MMA) were carried out using 2,2'-azobis isobutyronitrile as the initiator. A terpolymer of TIBEM, MMA, and HEMA was also synthesized. The copolymers were characterized by IR, gel permeation chromatography, differential thermal analysis, and thermogravimetric analysis (TGA). High molecular weight

polymers were produced with MMA at different feed compositions of TIBEM. The polymers were found to be freely soluble in common solvents for acrylic polymers. TGA showed little decomposition of the copolymer below 280°C. Copolymers showed good radiopacity at 25 wt % of TIBEM in the feed. These copolymers could find applications in medical and dental areas where radiopacity is a desirable feature of the implants. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 88: 2580–2584, 2003

Key words: X-ray; biomaterials; copolymerization

INTRODUCTION

Polymers having radiocontrast properties are of interest to medicine and dentistry as prostheses made from such polymers can be monitored noninvasively for their fate *in vivo* using X-radiography. Polymers could be rendered radiopaque by blending them with radiopacifying agents like barium sulfate or metal powders such as that of tantalum,^{1,2} or by the incorporation of heavy metal salts such as barium bromide, bismuth halides, or uranyl nitrate into an appropriate polymer ligand via chelation.^{3,4} However, the physical and mechanical properties of the base polymer are often adversely affected by the incorporation of these additives and when the radiopaque additive is a metal salt not covalently bound to the polymer, it tends to leach into the body fluids over long periods, which makes the radiopacity a temporary phenomenon apart from producing systemic toxicity.^{5,6}

Another approach to make the polymer radiopaque is to covalently link a radiocontrast dye to the polymer. This approach is possible only if the polymer possessed a reactive functional group to which the dye could be attached.^{7,8} The best method to produce radiopaque polymers is to synthesize reactive monomers having covalently bound heavy atoms and use these monomers as building blocks for new polymeric

biomaterials that can exhibit intrinsic radiopacity. Thus, polymers containing covalently bound iodine atoms are expected to exhibit good radiocontrast properties.

Ever since the first report on the synthesis and polymerization of iodine-containing monomers from this laboratory,⁹ there has been considerable interest in the synthesis of new iodine-containing polymers. Thus, Kruft et al.^{10–13} and Horak et al.¹⁴ synthesized different iodine-containing methacrylates and studied their polymerization and copolymerization with monomers such as methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (HEMA).

Davy et al.¹⁵ also synthesized and evaluated iodine-containing acrylates for radiopaque denture base applications.

In this article, we report on the synthesis of a new iodine-bearing monomer based on 3,4,5-triiodobenzoic acid and its copolymerization with monomers such as MMA and HEMA.

EXPERIMENTAL

Materials

Iodine monochloride, *p*-aminobenzoic acid, sodium nitrate, and potassium iodide were of analytical grade, and were procured from S. D. Fine Chemicals Ltd., Mumbai, India. Sodium metabisulfite and 2,2'-azobis isobutyronitrile (AIBN) were procured from BDH, Poole, England. MMA, HEMA, dicyclohexyl carbodi-

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imide (DCC), and dimethylamino pyridine (DMAP) were obtained from Sigma Chemical Co., St. Louis, MO, USA. All other solvents and reagents were of the highest purity obtained from local sources.

MMA was washed free of the inhibitor using sodium hydroxide solution followed by water, dried over anhydrous sodium sulfate, and distilled under reduced pressure prior to use. HEMA was distilled under reduced pressure and the middle fraction was employed for the reaction. AIBN was recrystallized twice from methanol before use.

Methods

Preparation of 3,4,5-triiodobenzoic acid

The compound was prepared starting from *p*-amino-benzoic acid according to Vogel.¹⁶ The crude product obtained was recrystallized from dilute ethanol and used in further reactions (mp 289°C).

Preparation of 3,4,5-triiodobenzoyloxyethyl methacrylate (TIBEM)

To a solution of 3,4,5-triiodobenzoic acid (3.02 g; 6.043 mmol) in 100 mL of dichloromethane in a round-bottomed flask, 1.378 g (6.67 mmol) of DCC and 0.097 g (0.79 mmol) of DMAP were introduced. The solution was stirred magnetically at 0°C and 0.8 g (6.15 mmol) of HEMA was added. The reaction mixture was allowed to stir overnight, the precipitated dicyclohexyl urea was filtered, and the filtrate was washed successively with distilled water (3×), with dilute HCl (3×), with saturated sodium bicarbonate solution (3×), and finally with distilled water. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The solid residue was recrystallized from ethyl acetate. The yield of the monomer was 2.5 g (mp 87°C, yield ~ 63%).

Homopolymerization of TIBEM

Polymerization was carried out in dimethyl formamide (DMF) under a stream of nitrogen in the presence of 1 mol % AIBN as the initiator at 70°C for 5 h following which the temperature was raised to 110°C and the polymerization was continued for 19 h. The polymer formed was precipitated in cold water under stirring. After stirring for 2 h to obtain a good dispersion, the polymer was filtered, washed with ether (unreacted TIBEM goes in ether), and dried in air. Yield ~ 20%.

Copolymerization with MMA

A Pyrex glass tube was charged with 5 g (8.2 mmol) of TIBEM and 15 g (150 mmol) of MMA, or 6.5 g (10.6

mmol) of TIBEM and 13.5 g (135 mmol) of MMA, along with 1 mol % AIBN in 50 mL DMF. The mixture was then polymerized under nitrogen blanket at 70°C for 5 h following which the temperature was raised to 110°C and the polymerization was continued for 19 h. The reaction mixture was then cooled and poured into cold water with stirring. After stirring for 2 h to obtain a good dispersion, the polymer was filtered, washed with ether, and dried. Yield ~ 70%.

Spectral and thermal characterization

Infrared (IR) spectra were recorded in a Fourier transform infrared (FTIR) instrument (Nicolet, model Impact 410, Madison, WI). Ultraviolet (UV) spectra were recorded in a UV-visible (UV-Vis) spectrophotometer (Milton Roy, Genesys 2, Rochester, NY). NMR spectra were recorded in a Bruker 200 MHz spectrometer (Bruker AC-200, Billerica, MA) with tetramethylsilane as the internal standard and CDCl₃ as the solvent. Thermal analyses were carried out using a thermal analyzer (TA Instruments, Inc., SDT 2960, New Castle, DE) at a heating rate of 20°C/min in nitrogen.

Chromatography

Thin layer chromatography (TLC) was done using TLC plates (Silicagel 60, E. Merck, Darmstadt, Germany) using ethyl acetate as the eluent. Gel permeation chromatography (GPC) was performed using Waters HPLC system with 510 pump, 7725 Rheodyne injector, Styragel HR columns, Millennium 32 software, and R401 differential refractometer. Tetrahydrofuran was used as mobile phase at a flow rate of 1 mL/min. The instrument was calibrated using polystyrene standards (Polysciences, Warrington, PA, USA).

RESULTS AND DISCUSSION

The monomer TIBEM is an off-white powder soluble in methanol, ethanol, acetone, and DMF. TLC using ethyl acetate as the eluent showed a single spot with a *R_f* value of 0.7. IR (KBr) spectrum (Fig. 1) shows the following vibrations: 1716 cm⁻¹ (C=O), 1649 cm⁻¹ (C=C), 1600, 1560, 1522, 1446 cm⁻¹ (C=C ring stretching), 3500 cm⁻¹ (C—H stretching, aromatic), 698 cm⁻¹ (out-of-plane C=C bending) 1300–1000 cm⁻¹ (in-plane C—H bending). The ¹H-NMR spectrum is given in Figure 2. The singlet at 8.4 ppm that corresponds to two protons is due to the symmetric aromatic protons. The two singlets at 6.1 and 5.6 ppm each corresponding to a single proton are due to methylene protons of the methacrylate moiety. The two triplets seen at 4.5 and 4.5 together correspond to four protons and are due to ethyl protons of ethyl methacrylate. The singlet at 1.9 correspond to 3 protons is due to methyl protons of methacrylate moiety. Thus the

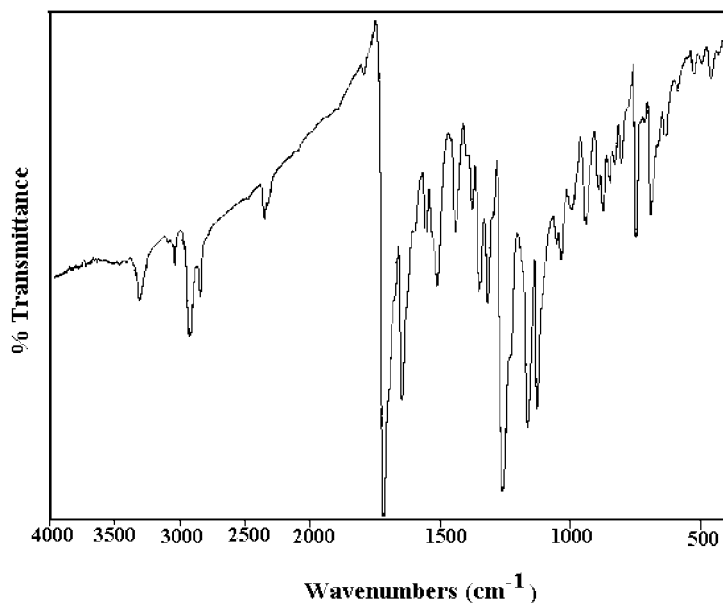


Figure 1 IR spectrum of TIBEM.

NMR spectrum confirms the formation and purity of the monomer 3,4,5-triodobenzoyloxyethyl methacrylate.

Homopolymerization of the monomer TIBEM did not lead to good conversion even after continuing the polymerization for 24 h. Copolymerization with a monomer such as MMA led to better conversion under the same conditions. The poor homopolymerization is due to bulky iodine atoms on the molecule exerting a strong hindrance during the chain propagation. Figure 3 shows the IR spectrum of the

copolymer of TIBEM with MMA. The spectrum shows an intense peak at 1728 cm^{-1} which corresponds to the $\text{C}=\text{O}$ stretching vibration of both MMA and TIBEM. The peak at 1649 cm^{-1} has almost disappeared, demonstrating the complete conversion of the $\text{C}=\text{C}$ bond in the monomers. The $\text{C}=\text{C}$ (aromatic ring) stretching vibrations are seen at 1565 and 1522 cm^{-1} . Out-of-plane ring $\text{C}=\text{C}$ bending is seen at 700 cm^{-1} . Thus, the IR spectrum shows the formation of the copolymer between MMA and TIBEM.

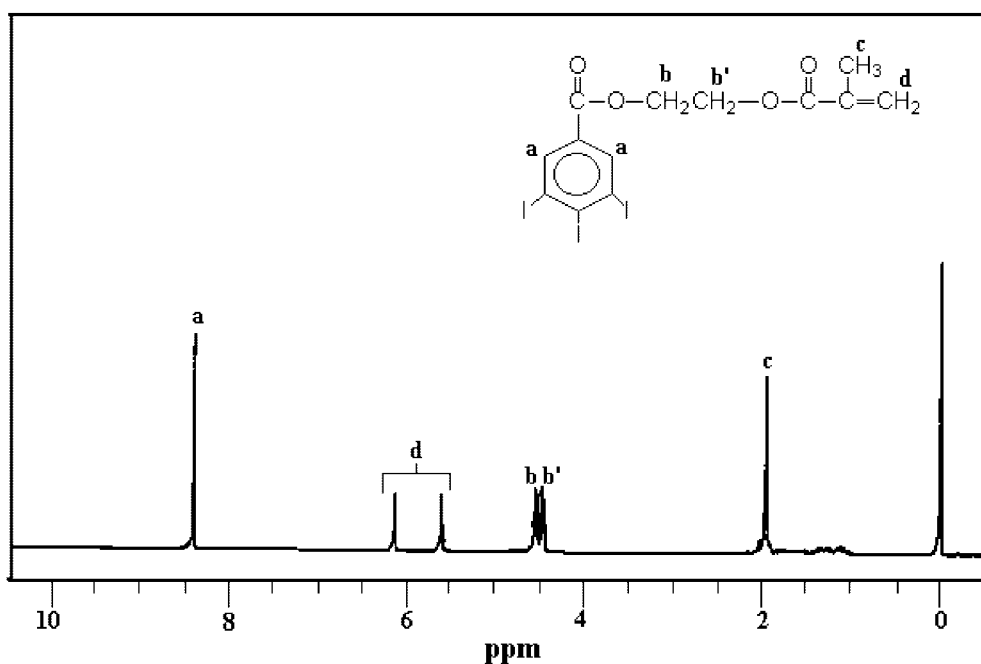


Figure 2 ^1H -NMR spectrum of TIBEM.

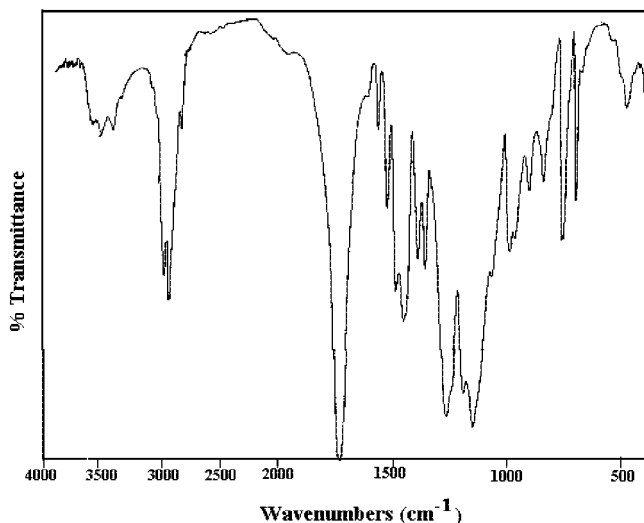


Figure 3 IR spectrum of the copolymer of MMA and TIBEM.

Due to the presence of the benzene ring in TIBEM, UV spectroscopy was employed to determine the copolymer composition. The UV spectrum of triiodobenzoic acid in DMF showed a sharp peak at 268 nm due to the $\pi-\pi^*$ transitions of the benzene ring, which was also seen in the spectrum of TIBEM in DMF [Fig. 4(a)]. The UV spectrum of PMMA was devoid of this peak. The copolymer of TIBEM with MMA showed this sharp absorption at 268 nm [Fig. 4(b)]. By constructing a calibration curve for TIBEM in DMF, attempts were made to quantify the composition of the copolymer. The results are shown in Table I. These results demonstrate that incorporation of TIBEM into the copolymer with MMA was nearly quantitative.

Table II shows the molecular weights of the copolymer obtained by GPC. For a comparison, values for PMMA prepared under similar reaction conditions are also given. It is seen that high molecular weight copolymers of TIBEM could be produced with MMA as the comonomer.

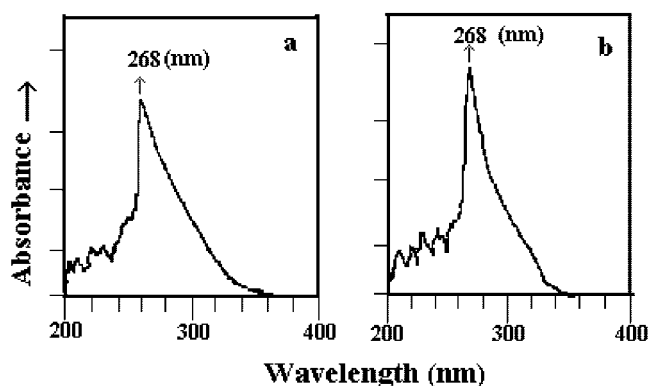


Figure 4 UV spectrum of TIBEM (a) and copolymer of MMA and TIBEM (b) in DMF.

TABLE I
Compositions of Copolymers of TIBEM with MMA and HEMA

No.	Copolymer	TIBEM in feed (mol %)	TIBEM in polymer (mol %)
1	TIBEM-co-MMA	5.2	4.4
2	TIBEM-co-MMA	7.3	6.5
3	TIBEM-co-MMA-co-HEMA	6.0	5.4

Figure 5 gives TGA and differential thermal analysis (DTA) curves of the copolymer. Significant weight loss starts at 280°C and 50% loss occurs at 374°C. The enhanced thermal stability could be due to the presence of aromatic moiety in the copolymer. The DTA curve shows endotherm corresponding to the decomposition of the copolymer around 280°C. From the DTA curve, the glass transition temperature of the copolymer is found to be around 110°C which is well within in the range reported for other 3-iodine-containing polymers by others.¹⁷

Copolymers with 5.2 and 7.3 mol % TIBEM in the feed gave good images by X-radiography. Benzina et al.¹² and the present authors⁸ have earlier shown that materials with about 15 wt % iodine are well detected by fluoroscopy. This would work out to about 7 mol % of TIBEM in the copolymer. The incorporation efficiency of TIBEM in the copolymerization reactions studied seems to be excellent. This means that there will be very little wastage of the monomer in the polymerization process.

TIBEM could also be copolymerized with other monomers such as HEMA using conventional free radical initiators to produce high molecular weight polymers, which are less rigid and more flexible in nature. For instance, a terpolymer of TIBEM with MMA and HEMA was synthesized by polymerizing 4.6 g (7.5 mmol) TIBEM, 8.6 g (86 mmol) MMA, and 4.1 g (31.5 mmol) of HEMA using 1 mol % AIBN as initiator in the same way the synthesis of the copolymer was carried out. The terpolymer possessed good molecular weight characteristics (Table II) as well as good thermal stability. Incorporation of TIBEM into the terpolymer was almost quantitative (Table I). Benzina et al.¹² and the present authors⁸ have observed that when the benzene ring contains three iodine atoms that are in close proximity to the vinyl bond (e.g.,

TABLE II
Molecular Weights of Polymers Estimated by GPC

Polymer	M_n	M_w	Polydispersity M_w/M_n
PMMA	23013	50840	2.209
TIBEM-co-MMA (1)	15066	39119	2.596
TIBEM-co-MMA-co-HEMA	13215	38752	2.932

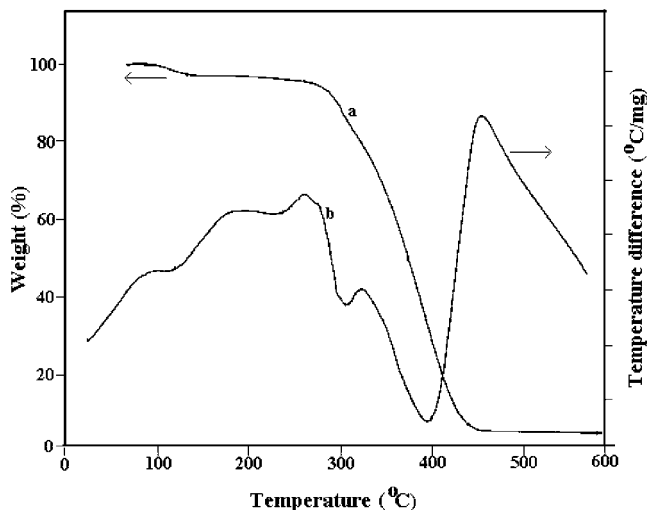


Figure 5 TGA–DTA traces of TIBEM/MMA copolymer having 4.4 mol % TIBEM in the copolymer.

2,4,6-triiodophenyl methacrylate), the molecule was highly resistant to free radical polymerization. When the iodine atoms in the ring are in the 2,3,5 positions, the corresponding ethyl and propyl methacrylates were more susceptible to polymerization and copolymerization yielding high molecular weight polymers.^{12,17} The 3,4,5-triiodo monomer has a better compact molecular structure with respect to the bulky iodine atoms and was susceptible to copolymerization with other vinyl monomers, although homopolymerization was not very facile as seen in this study. With excellent thermal stability and good polymerization behavior with other vinyl monomers, the new iodine-containing monomer is a promising candidate for the preparation of implants possessing X-ray opacity.

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