Synthesis and Evaluations of Bisphosphonate-Containing Monomers for Dental Materials

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ABSTRACT: Two new bismethacrylamide (**1**, **2**) and two new methacrylamide (**3**, **4**) dental monomers were synthesized. In each group, one monomer contains a bisphosphonate group, the other a bisphosphonic acid group. Monomer **1** and **3** were synthesized by amidation of 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride and methacryloyl chloride with tetraethyl aminomethyl-bis(phosphonate) and converted to the bisphosphonic acid monomers **2** and **4** by hydrolysis with trimethylsilyl bromide. Monomer **1** (m.p.: 71–72 °C), monomer **3** (33–34 °C), and monomer **4** (no m.p.) were obtained as white solids and monomer **2** a viscous liquid, soluble in water. Homopolymerization of **1** gave crosslinked polymers, indicating its low cyclization tendency. The photopolymerization studies indicated that its copolymerizability with 2,2-bis[4-(2-hydroxy-3-methacryloyloxy propyloxy) phenyl] propane and 2-hydroxyethyl methacrylate (HEMA) without changing their rates and conversions significantly means that it could be used as a biocompatible crosslinker. Although monomer **2** showed low polymerizability, because of its good performance in terms of solubility, hydrolytic stability, hydroxyapatite interaction, acidity, and copolymerizability with HEMA, it shows potential to be used in self-etching dental adhesives. The thermal polymerization of **3** resulted in soluble polymers and evaluation of monomer **4** in terms of solubility, acidity, and copolymerizability with HEMA indicated its potential as an adhesive monomer. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000–000, 2012

KEYWORDS: adhesives; bisphosphonic acids; cyclopolymerization; dental adhesives; photopolymerization; radical polymerization

INTRODUCTION Dental composites and "self-etching" enamel-dentin adhesives based on mixtures of monofunctional and multifunctional monomers, are important components in dentistry. The main problems of dental composites are their shrinkage upon polymerization, mechanical wear, breakdown due to hydrolysis in the oral environment, and insufficient adhesion to tooth tissue.[1,2] The main approach to solve the last problem is the use of dental adhesives. The modern "self-etching" dental adhesives are based on acidic monomers containing monohydrogenphosphate or dihydrogenphosphate, phosphonic, sulfonic, or carboxylic acid groups and used to achieve a strong bond between dental filling composites and dental tissues.[3,4] They solubilize the smear layer, demineralize the dentin, and form a thin hybrid layer, providing the desired adhesion. Besides this micromechanical interlocking through hybridization, Inoue et al. reported that the long-term durability of adhesive-dentin bonds depends on the hydrolytic stability of the functional monomer and its chemical interaction potential with the dental tissue.[5] Therefore, extensive research has been conducted to develop new monomers with acidic functional groups, which may strongly bond to HAp. Bisphosphonates, structural analogues of naturally existing pyrophosphate with increased chemical and enzymatic stability, have strong affinity for HAp.[6] Moreover, it was also reported that bisphosphonates can inhibit enzymes (metalloproteinases) which degrade the collagen network.[7–9] Recently, bisphosphonate-containing monomers were investigated for self-etching dental adhesive applications.[10–12] They facilitate adhesion of dental restoratives and orthodontic appliances to dental tissue.

The most common problems of self-etching adhesives are their hydrolysis in the aqueous environment because water is an important ingredient in these systems. In recent years, self-etching adhesive monomers and filling composites containing hydrolytically stable ether and amide linkages were synthesized to overcome the problem of hydrolysis.[10–27]

In this study, we designed two groups of novel dental monomers with improved properties such as hydrolytic stability, ability to form bonds with the tooth material and high rate of copolymerization with dental monomers (Fig. 1). The first group monomers are bismethacrylamides based on ether dimers of alkyl α-hydroxymethyl acrylates (RHMA), with bisphosphonate or bisphosphonic acid functional groups. The second group monomers are methacrylamides based on methacryloyl chloride, with same functional groups.

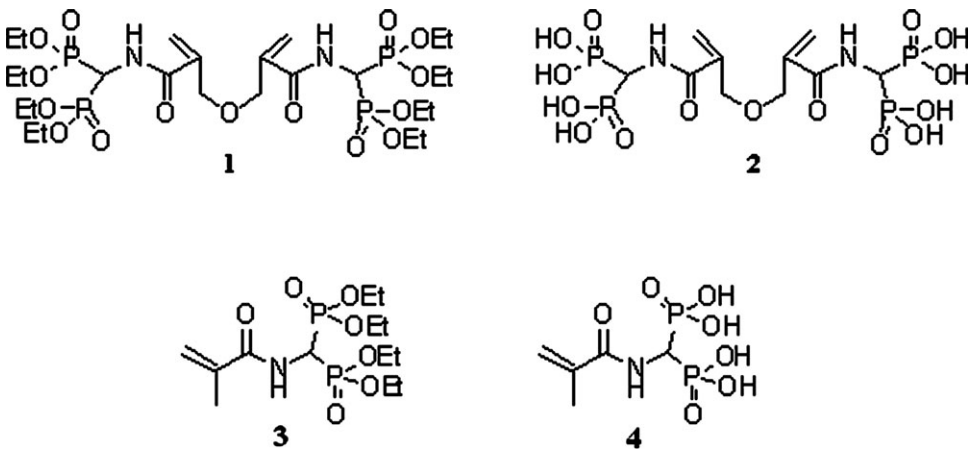

FIGURE 1 Structures of synthesized monomers.

Monomers of both groups are expected to be hydrolytically stable since they contain amide and ether linkages instead of instable ester bonds. The presence of bisphosphonate/bisphosphonic acid group will improve the monomers' capability of etching enamel and dentin and their interaction with HAp.

EXPERIMENTAL

Materials

Tetraethyl aminomethyl-bis(phosphonate), 2-(2-carboxy-allyloxymethyl)-acrylic acid, and 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride were prepared according to literature procedures.[28–30] Methacryloyl chloride, triethyl amine, 2-hydroxyethyl methacrylate (HEMA), 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropyloxy) phenyl] propane (Bis-GMA), hydroxyapatite (HAp), and Na_2SO_4 were purchased from Aldrich and used as received. Trimethylsilyl bromide (TMSBr) (Aldrich, Taufkirchen, Germany) was distilled before use. The thermal initiators 2,2′-azobis(isobutyronitrile) (AIBN) and 2,2′-azobis(*N, N*-amidinopropane) dihydrochloride (V-50) and the photoinitiators 2,2′-dimethoxy-2-phenyl acetophenone (DMPA) and bis(2,4,6-trimethylbenzoyl)phenylphosphine oxide (BAPO) were obtained from Aldrich and used without further purification. Dichloromethane (CH_2Cl_2) was dried over molecular sieves. All other solvents and starting materials were obtained from Aldrich and used as received.

Characterization

^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy (Varian Gemini 400 MHz) and Fourier transform infrared (FTIR) spectroscopy (T380) were used for monomer characterization. The photopolymerizations were performed on a TA Instruments Q100 differential photocalorimeter. Thermogravimetric analysis (TGA) was done with a TA Instrument Q50. Elemental analyses were obtained from Thermo Electron SpA FlashEA 1112 elemental analyzer (CHNS separation column, PTFE; 2 m; 6 × 5 mm). Combi Flash Companion Teledyne ISCO Flash Chromatography was used for purification of monomers. Gel permeation chromatography (Viscotek) was carried out with THF solvent using polystyrene standards.

Monomer Synthesis

Synthesis of Monomer 1

To a solution of tetraethyl aminomethyl-bis(phosphonate) (0.716 g; 2.36 mmol) and anhydrous pyridine (0.188 g; 2.36 mmol) in 2 mL of dry dichloromethane, 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride (0.239 g; 1.072 mmol) in 2.52 mL of dry dichloromethane was added dropwise in an ice bath under N_2. After stirring overnight at room temperature, 20 mL of chloroform was added and the solution was extracted with distilled water (3 × 8 mL), 2M cold HCl (3 × 12 mL), 2M cold NaOH (3 × 8 mL), and brine (1 × 8 mL). After drying the organic phase with anhydrous Na_2SO_4, the solvent was evaporated. The crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O:MeOH (50:50) to give monomer **1** as a white solid with a melting point of 71–72 °C in 20% yield.

^{1}H NMR ($CDCl_3$): 1.29 (qt, 24H, CH_3), 4.06–4.21 (m, 16H, CH_2—O—P), 4.27 (s, 4H, O—CH_2), 5.08 (d of t, 2H, CH—P), 5.69, 6.10 (s, 4H, C=CH_2), 7.29 (d, 2H, NH) ppm.

^{13}C NMR ($CDCl_3$): 16.62 (CH_3), 42.09, 43.55, 45.01 (CH—P), 63.54 (O—*C*H_2—CH_3), 69.79 (O—*C*H_2—C), 124.63 (*C*=CH_2), 138.28 (C=*C*H_2), 165.58 (C=O) ppm. ^{31}P NMR ($CDCl_3$): 16.06 ppm. FTIR: 3468, 3246 (N—H), 2983, 2908 (C—H), 1672 (C=O), 1628 (C=C), 1517 (NH), 1254 (P=O), 1014 and 967 (P—O—Et) cm^{-1}. Elem. anal, Calcd. for $C_{26}H_{52}N_2P_4O_{15}$: C, 41.27%; H, 6.93%; N, 3.70%; P, 16.38%; O 31.72%. Found: C, 40.85%; H, 7.17%; N, 3.70%.

Synthesis of Monomer 2

TMSBr (0.904 g; 5.906 mmol) was added dropwise to a solution of monomer **1** (0.372 g; 0.4921 mmol) in 2.12 mL dry dichloromethane in an ice bath and under N_2. After stirring for 4 h at 40 °C, the volatile components were removed under vacuum. Methanol (6.5 mL) was added and the mixture was stirred at room temperature overnight. After removal of the solvent, the crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer **2** as a clear, colorless viscous oil in 58% yield.

^{1}H NMR (MeOD:D_2O 1:1 v/v): 4.19, 4.26 (d, 4H, O—CH_2), 4.80 (2H, CH—P), 5.73, 5.81, 5.89, 6.02 (s, 4H, C=CH_2) ppm. ^{13}C NMR (MeOD:D_2O 1:1 v/v): 29.29, 29.85, 30.45 (CH—P), 69.76 (CH_2—O), 123.92, 125.39 (*C*=CH_2), 138.48, 141.11 (C=*C*H_2), 168.19 (C=O) ppm. ^{31}P NMR (D_2O): 13.53 ppm. FTIR: 3306 (N—H), 3000–2600 (OH), 2914 (C—H), 1652 (C=O), 1610 (C=C), 1522 (NH), 1140 (P=O), 998 and 915 (P—O) cm^{-1}.

Synthesis of Monomer 3

To a solution of tetraethyl aminomethyl-bis(phosphonate) (0.303 g; 1.00 mmol) and triethylamine (0.21 mL; 1.50 mmol) in anhydrous dichloromethane (2.8 mL) was added methacryloyl chloride (0.16 mL; 1.65 mmol) in anhydrous dichloromethane (1.63 mL) at 0 °C, under N_2 and the resulting mixture was stirred at room temperature for 2 h. The reaction was stopped by addition of distilled water (1.63 mL). The organic layer was washed with distilled H_2O (1 × 5 mL), 2M HCl (1 × 5 mL), saturated $NaHCO_3$ (1 × 5 mL), and distilled H_2O (1 × 5 mL) and dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent, the crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O:MeOH (50:50) to give monomer **3** as a white solid with a melting point of 33–34 °C in 36% yield.

^{1}H NMR ($CDCl_3$): 1.33 (q, 12H, OCH_2CH_3), 1.98 (s, 3H, CH_3), 4.17 (m, 8H, CH_2—O—P), 5.10 (d of t, 1H, CH—P), 5.42, 5.74 (s, 2H, C=CH_2), 6.45, 6.47 (d, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): 16.28 (OCH_2CH_3), 18.57 (CH_3), 42.17, 43.63, 45.09 (CH—P), 63.53, 63.69 (CH_2—O—P), 120.66 (C=*C*H_2), 139.21 (*C*=CH_2), 167.42 (C=O) ppm. ^{31}P NMR ($CDCl_3$): 16.42 ppm. FTIR: 3471, 3256 (N—H), 2984, 2933 (C—H), 1668 (C=O), 1626 (C=C), 1518 (NH), 1250 (P=O), 1014 and 971 (P—O—Et) cm^{-1}.

Synthesis of Monomer 4

TMSBr (0.742 g; 4.848 mmol) was added dropwise to a solution of monomer **3** (0.3 g; 0.808 mmol) in 3.5 mL dry dichloromethane in an ice bath and under N_2. After stirring for 2 h at 40 °C, the volatile components were removed under vacuum. Methanol (11 mL) was added and the mixture was stirred at room temperature overnight. After removal of the solvent, the crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer **4** as a white solid in 95% yield.

^{1}H NMR (D_2O): 1.87 (s, 3H, CH_3), 4.66 (t, 1H, CH—P), 5.43, 5.67 (s, 2H, CH_2=C) ppm. ^{13}C NMR (D_2O): 17.47 (CH_3), 46.57 (CH—P), 121.70 (C=*C*H_2), 138.54 (*C*=CH_2), 170.85 (C=O) ppm. FTIR: 3338 (N—H), 3000–2600 (OH), 2920 (C—H), 1651 (C=O), 1610 (C=C), 1533 (NH), 1118 (P=O), 954 and 922 (P—O) cm^{-1}.

Thermal Polymerizations

The thermal homopolymerizations and copolymerizations were carried out with standard freeze-evacuate-thaw procedures:

i. The homopolymerization and copolymerization of monomer **1** was carried out in solution at 80 °C with AIBN as initiator. The homopolymer was not soluble. The copolymerization was done in two different ratios, TBEED:**1**, 90:10 and 80:20 mol %. The copolymers were purified by precipitation into methanol:water (5:1) mixture where both monomers are soluble.
ii. The copolymerization of monomer **2** (18 mg and 0.0338 mmol) with acrylamide (AAm, 45.8 mg, and 0.6445 mmol) was carried out in 0.06 mL of water at 65 °C with V-50 (0.64 mg and 0.0023 mmol). The resulting crosslinked polymer was washed several times with water to remove unreacted monomers and dried under vacuum.
iii. The copolymerization of monomer **2** (22 mg and 0.0413 mmol) with HEMA (48.4 mg and 0.372 mmol) was carried out in 0.03 mL of ethanol at 50 °C with AIBN (6.7 mg and 0.034 mmol). The resulting crosslinked polymer was washed several times with ethanol and dried under vacuum.
iv. The homopolymerization of monomer **3** was carried out in bulk at 65 °C with 2 mol % AIBN as initiator. The polymer was purified by precipitation into hexane with a few drops of ether.

Photopolymerization

The photopolymerizations were carried out using a DSC equipped with a mercury arc lamp. The samples (3–4 mg) containing 2.0 mol % initiator were irradiated for 10 min at 40 and 72 °C with an incident light density of 20 mW cm^{-2} under a nitrogen flow of 20 $mLmin^{-1}$. Rates of polymerization were calculated according to the following formula:

$$\text{Rate} = \frac{(Q/s)M}{n\Delta H_p m}$$

where Q/s is the heat flow per second, M the molar mass of the monomer, n the number of double bonds per monomer molecule, ΔH_p the heat released per mole of double bonds reacted, and m the mass of monomer in the sample. The theoretical value used for ΔH_p was 13.12 $kcalmol^{-1}$ for methacrylamide double bonds.[31,32]

Hydrolytic Stability

The hydrolytic stability of the monomers was investigated by ^{1}H NMR measurements of 2 wt % solutions of the monomers in methanol-d_6/D_2O (1:1 v/v) after storage at 37 °C for 1 month.

RESULTS AND DISCUSSION

Synthesis and Characterization of Monomers

The new bisphosphonate-containing bis(methacrylamide) (**1**) was synthesized in four steps: (i) synthesis of *tert*-butyl α-hydroxymethacrylate-ether derivative (TBEED) from the reaction of *tert*-butyl acrylate and paraformaldehyde in the presence of 1,4-diazabicyclooctane (DABCO) as catalyst, (ii) conversion to a carboxylic acid by cleavage of *tert*-butyl groups using trifluoroacetic acid, (iii) conversion to an acid chloride by using oxalyl chloride, and (iv) reaction of the acid chloride and tetraethyl aminomethyl-bis(phosphonate) (Fig. 2). After purification by flash chromatography, this

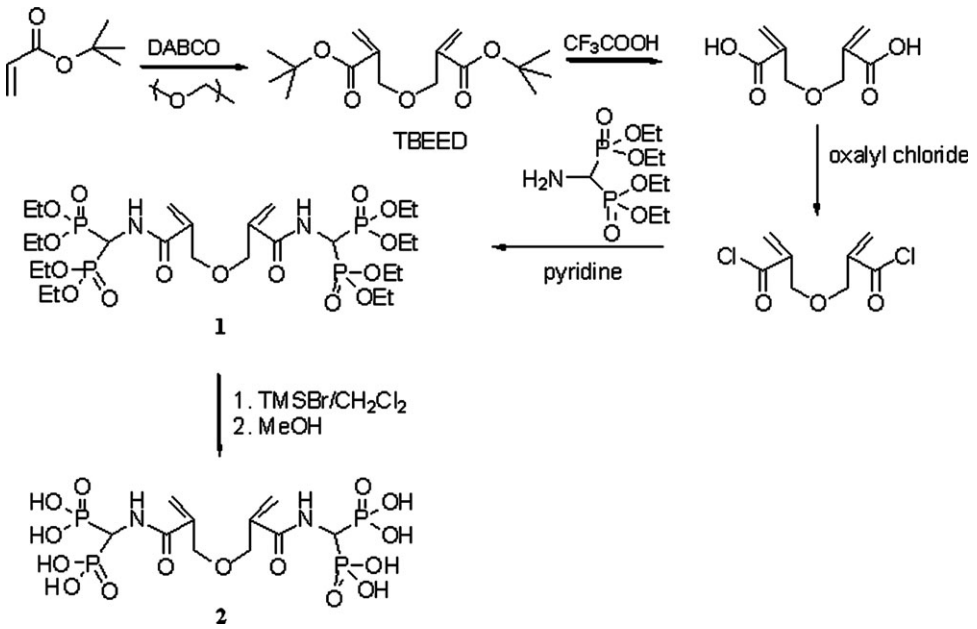

FIGURE 2 Synthesis of monomers **1** and **2**.

monomer was isolated in 20% yield, as a white solid (m.p. 71–72 °C), which is soluble in polar organic solvents such as methylene chloride, acetone, ether, ethanol, and THF and in water (Table 1).

The characterization of this monomer was carried out by FTIR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy, as well as elemental analysis. The spectral data are in agreement with the expected structure of the monomer. For example, the single bisphosphonate proton is supported by the presence of a doublet of triplet at 5.08 ppm. Other characteristic peaks of this monomer were methyl protons at 1.29 ppm, methylene protons adjacent to oxygen at 4.06–4.21 and 4.27 ppm and double bond hydrogen at 5.69 and 6.10 ppm (Fig. 3). The peak at 7.29 ppm is typical for the NH peak of carbamide group. In the ^{13}C NMR spectrum, the triplet seen at 42.09, 43.55, and 45.01 ppm is due to methine carbon attached to two phosphorus (Fig. 4). The peak of the phosphorus atom at 16.06 ppm in the ^{31}P NMR spectrum is characteristic for the phosphonate group. In the FTIR spectra, this monomer showed characteristic peaks at 3400–3300 cm^{-1} (amide V region), 1672 cm^{-1} (amide I region), and 1517 cm^{-1} (amide II region). Monomer **1** also showed absorption peaks of C=C, P=O, and P—O peaks at 1628, 1254, 1014, and 967 cm^{-1}.

TABLE 1 Solubility of Monomers **1–4**

	H_2O	Ethanol	THF	Acetone	Diethyl ether	CH_2Cl_2
1	+	+	+	+	+	+
2	+	+	−	−	−	−
3	+	+	+	+	+	+
4	+	+	−	−	−	−

The silylation of monomer **1** with TMSBr and methanolysis of the silyl ester groups provided the new bisphosphonic acid-containing bis(methacrylamide) (**2**). This monomer was obtained as clear viscous oil in 58% yield after purification by C18 reversed-phase flash chromatography. Monomer **2** dissolves very well in water, which is very important for dental adhesive applications (Table 1). The FTIR spectrum of monomer **2** shows broad peaks in the region of 3000–2600 cm^{-1} and 2300–2100 cm^{-1} due to OH stretching, 1670–1600 cm^{-1} due to OH bending and strong peaks at 1652, 1610, and 1522 cm^{-1} due to C=O, C=C, and NH stretching, respectively. Also the strong bands at 998 and 915 cm^{-1} correspond to the symmetric and asymmetric vibration of P—O. ^{1}H NMR spectrum of monomer **2** shows the complete disappearance of bisphosphonic ester peaks at 1.29 and 4.06–4.21 ppm (Fig. 5). Monomer **2** also showed two sets of double bond and methylene peaks due to different resonance forms of the amide linkage and one form is strengthened after hydrolysis.

The new bisphosphonate-containing methacrylamide (**3**) was synthesized in one step by the reaction of methacryloyl chloride and tetraethyl aminomethyl-bis(phosphonate) in the presence of triethylamine (Fig. 6). This monomer was obtained as a white solid with a melting point of 33–34 °C in 36% yield after purification by flash chromatography. It is well soluble in common organic solvents such as hexane, methylene chloride, acetone, ether, ethanol, THF, and in water (Table 1). The structure of monomer **3** was proved by FTIR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy. In the ^{1}H NMR spectrum, the single bisphosphonate proton is present as a doublet of triplet at 5.10 ppm (Fig. 7). Besides, the structure of this monomer is supported by the presence of methyl protons at 1.33 and 1.98 ppm, methylene protons at 4.17 ppm and double bond hydrogens' at 5.42 and 5.74

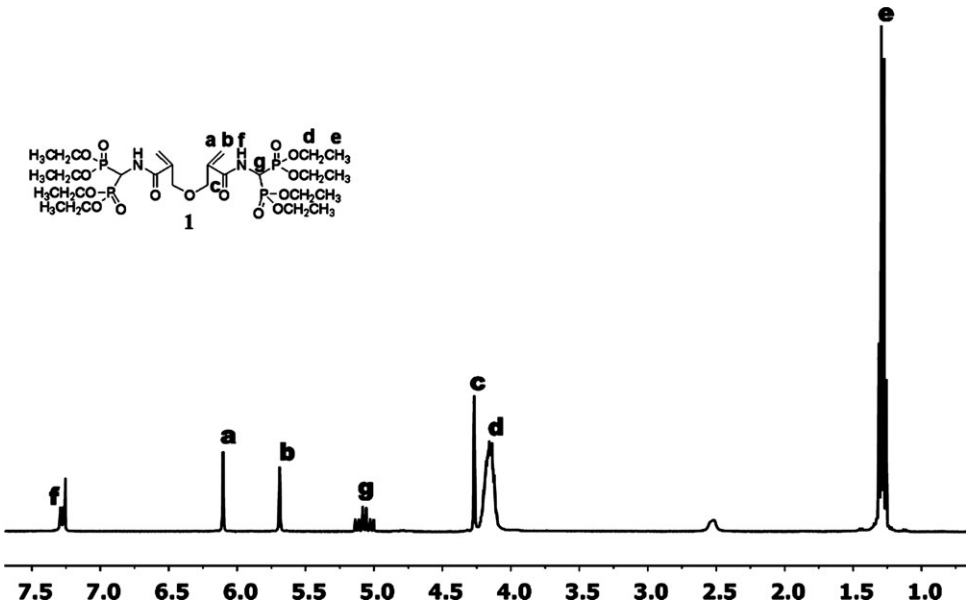

FIGURE 3 ^{1}H NMR spectrum of monomer **1**.

ppm. In the ^{31}P NMR spectrum, one peak at 16.42 ppm confirmed the purity of this monomer. Satisfactory microanalysis results were obtained for this monomer.

Monomer **3** was converted to the new bisphosphonic acid containing methacrylamide, monomer **4**, by the reaction with TMSBr (Fig. 6). After purification by flash chromatography, monomer **4** was isolated with excellent yield (95%) as a white solid, soluble in water. Upon heating to 250 °C, no melting point was observed. In the ^{1}H NMR, the disappearance of the characteristic peaks of the ethyl groups of the phosphonates at 1.33 and 4.17 ppm shows that the deprotection is complete (Fig. 8). The double bond protons are characterized as two singlets at 5.43 and 5.67 ppm. The triplet at 4.66 ppm stands for the methine attached to the two phosphorus atoms.

Acidity, Interactions with HAP, and Stability of Acid Monomers

The pH value of aqueous solution of monomer **2** (5 wt %) and **4** (2 wt %) was found to be 1.10 and 1.21, indicating their enamel etching ability. The addition of 15, 30, and 60 mg HAp, a model compound for dentin and enamel, to the solutions of monomer **2** resulted in increases in the pH values to 1.65, 1.90, and 3.34, respectively.

We expected that monomers **2** and **4** would be more hydrolytically stable compared with commercial dentin adhesives

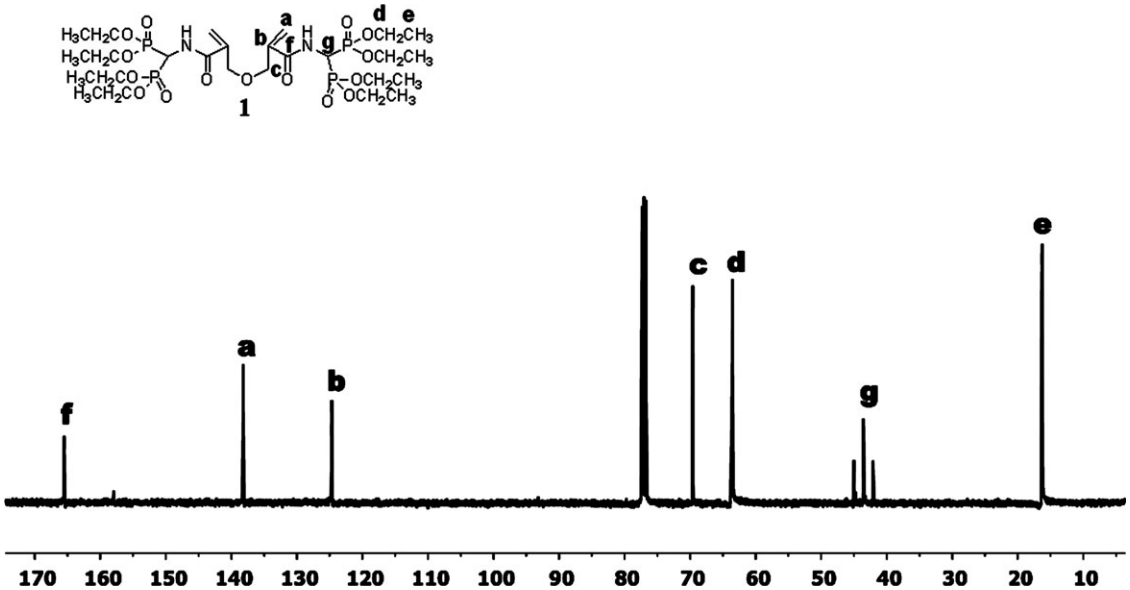

FIGURE 4 ^{13}C NMR spectrum of monomer **1**.

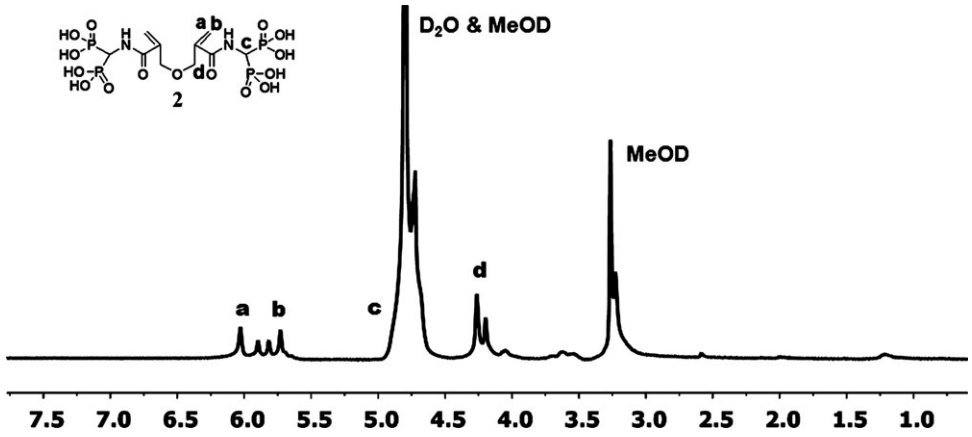

FIGURE 5 ^{1}H NMR spectrum of monomer **2**.

such as 2-(methacryloyloxy)-ethyl dihydrogen phosphate (MEP) or 10-(methacryloyloxy)-decyl dihydrogen phosphate (MDP) due to the presence of amide linkages instead of ester linkages, since it is known that amides are more hydrolytically stable than esters under acidic conditions due to lower reactivity of amide carbonyl. However, it was difficult to predict the stability of monomers **2** and **4**, which contain acid groups within the same structure. Therefore, hydrolytic stability of the acid monomer **2** was investigated by recording ^{1}H NMR spectroscopy of their 2 wt % solutions in methanol-d_6/D_2O (1:1) after storage at 37 °C. After 30 days of storage, the ^{1}H NMR spectrum showed no decrease of the peaks assigned to monomer **2**, showing its stability for at least one month.

Thermal Polymerizations

In general, polymerization of ether dimers of α-hydroxymethacrylates, which have 1,6-heptadiene structure gives soluble or crosslinked polymers depending on monomer structure and polymerization conditions.[29] It was observed that bulky ester groups such as *tert*-butyl and adamantyl sterically inhibit intermolecular addition and increase cyclization efficiency. In addition, cyclization efficiency increases at high temperatures and dilute conditions. Moszner et al. and our group prepared bis(methacrylamide)s from TBEED using propyl amine, diethyl 2-aminoethylphosphonate, and diethyl 1-aminomethylphosphonate and found high crosslinking tendency of these monomers.[27,33]

Thermal solution homopolymerizations and copolymerizations of monomer **1** were conducted under the same conditions as TBEED to see the effect of bisphosphonate substituent (Table 2). Monomer **1** gave crosslinked polymers, indicating its low cyclization efficiency. Our efforts to decrease polymerization time to obtain soluble polymers were not successful, giving just milky solutions. However, TBEED gave soluble or crosslinked polymers under similar conditions. Although crosslinked polymers of TBEED were obtained as clear gels, crosslinked polymers of monomer **1** were white solid powders. The labile hydrogen between two phosphonate groups in monomer **1** probably results in chain transfer reaction, giving unexpectedly high crosslinking

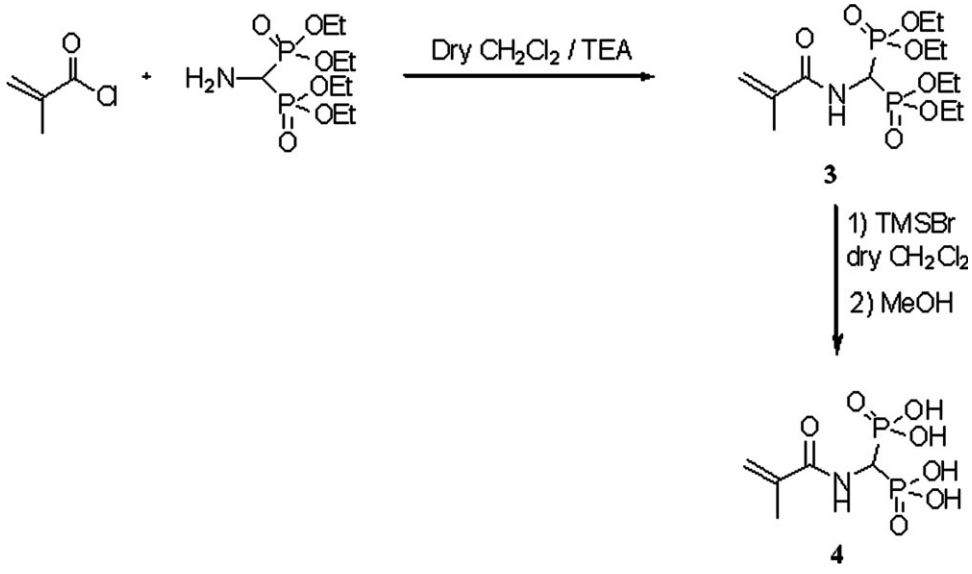

FIGURE 6 Synthesis of monomers **3** and **4**.

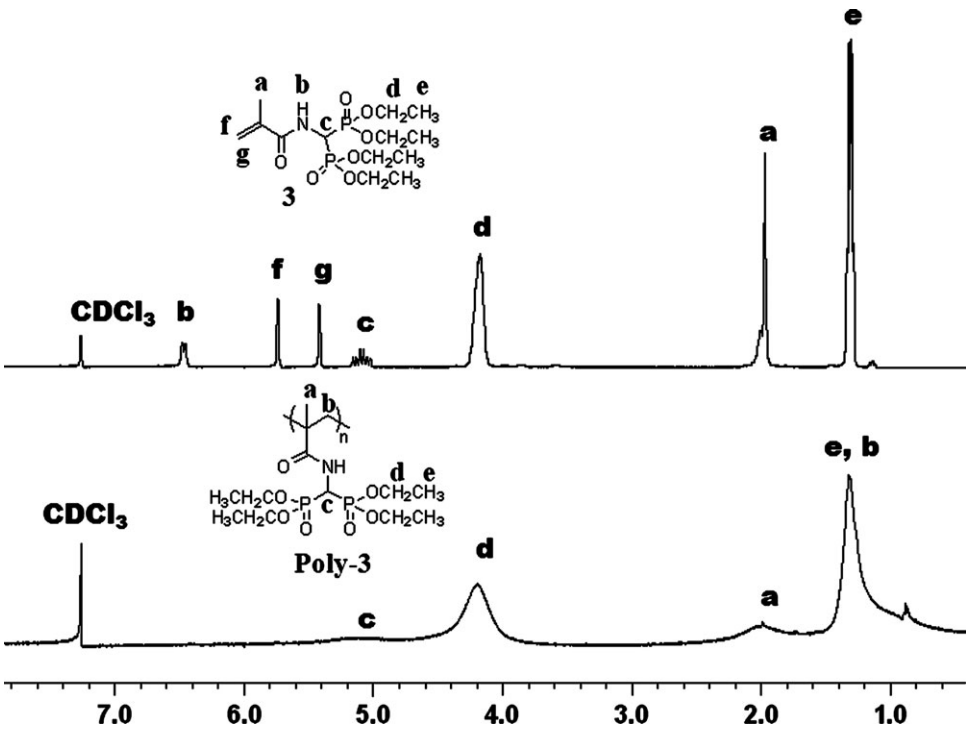

FIGURE 7 ^{1}H NMR spectra of monomer **3** and poly-**3**.

tendency despite a bulky bisphosphonate substituent and low molecular weight crosslinked polymers. To check the possibility of hydrogen abstraction, the photopolymerization of this monomer in the presence of benzophenone (BP) was tried. Although no polymerization was observed without BP, utilization of BP (2 mol %) resulted in 33% conversion, indicating presence of the labile hydrogens under our photopolymerization conditions.

Monomer **1** was copolymerized with TBEED so that we could obtain soluble polymers. The copolymers showed similar solubility with poly-TBEED except they were insoluble in hexane where poly-TBEED was soluble. The FTIR spectrum of one of the copolymers, TBEED:**1** (80:20 mol %), with a peak at 1018 cm^{-1} due to P—O stretching supported the incorporation of monomer **1** into the copolymer. However, it was difficult to calculate copolymer composition using ^{1}H NMR due to overlapping peaks. The lower number average molecular weight (M_n) of the copolymers (around 20,000) than that of homopolymer of TBEED indicated the importance of chain transfer reactions.

The thermal stability of poly-**1** was investigated by TGA under nitrogen at 10 °C min^{-1} and compared with that of poly-TBEED. Poly-TBEED started to lose weight (40%) around 200 °C due to decomposition of *tert*-butyl ester

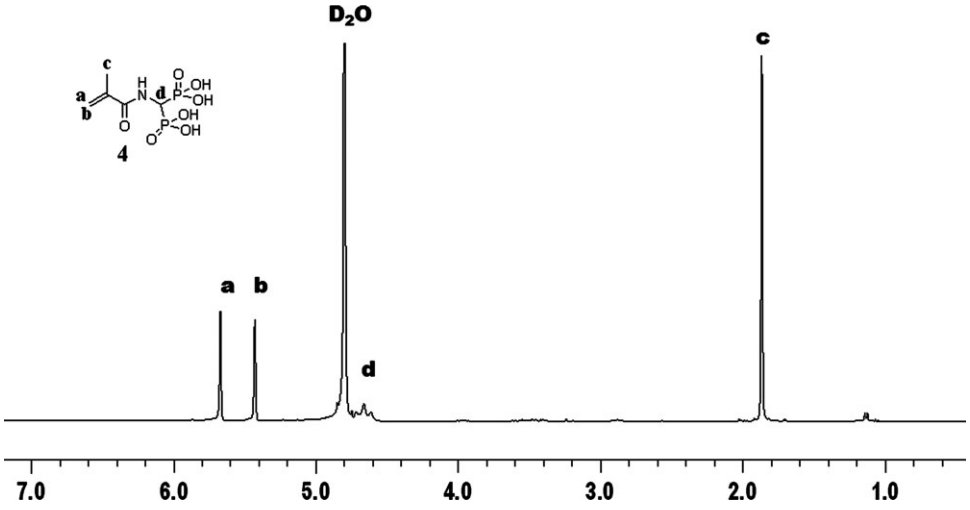

FIGURE 8 ^{1}H NMR spectrum of monomer **4**.

TABLE 2 Thermal Polymerization Results of Monomers **1**, **3**, TBEED, and TBEED:**1** (90:10 mol %)

Monomer	[*M*]	Temperature (°C)	[AIBN]	Solvent	Time (min)	Conversion (%)	M_n
TBEED	1.26	80	0.0350	Toluene	6	Crosslinked	–
TBEED	1.31	80	0.0380	Toluene	35	38	49,118
TBEED	1.30	80	0.0380	Toluene	21	Crosslinked	–
1	1.26	80	0.0350	Toluene	180	Crosslinked	–
1	1.26	80	0.0350	Toluene	120	No polymer	
TBEED:**1** (90:10 mol %)	1.30	80	0.0380	Toluene	21	Crosslinked	–
TBEED:**1** (90:10 mol %)	1.30	80	0.0380	Toluene	28	54	22,450
TBEED:**1** (90:10 mol %)	1.30	80	0.0380	Toluene	45	43	26,650
3	–	65	2 mol %	–	10	40	32,000
3	–	65	2 mol %	–	13	21	–

group and then degraded (40%) at around 375 °C. Poly-**1** was found to be more stable than poly-TBEED, starting to decompose around 225 °C and then degraded gradually to give higher char yield of 53.42% compared with poly-TBEED (11.83%) at 575 °C. This high char yield is probably due to the formation of bisphosphonic acid, which causes crosslinking reactions during degradation.

Thermal bulk homopolymerization of monomer **3** with AIBN gave soluble polymers in 10 min at 40% conversion, indicating its high reactivity (Table 2). The polymer was soluble in dichloromethane, acetone, ether, and water but insoluble in hexane. ^{1}H NMR spectrum of this polymer indicated complete disappearance of the double bond peaks at 5.42 and 5.74 ppm after polymerization (Fig. 7). The number average molecular weight (M_n) for this polymer was around 32,000 as estimated by gel permeation chromatography. The DSC analysis for this polymer showed no glass-transition temperature from 0 to 160 °C.

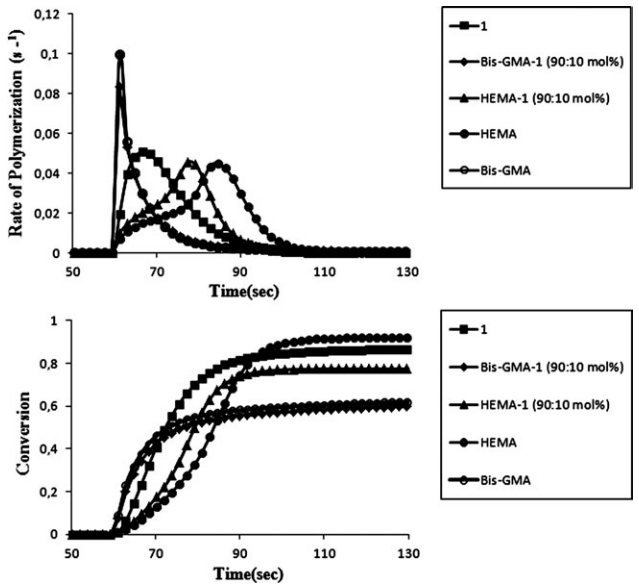

FIGURE 9 Rate-time and conversion-time curves in the homopolymerization and copolymerizations of **1** with HEMA and Bis-GMA at 72°C.

Photopolymerization

The polymerizability of monomer **1** was found to be similar to TBEED with the maximum rates of polymerizations of 0.0508 and 0.0554 s^{-1} and conversions of 87 and 82% for **1** and TBEED. At maximum rate of polymerizations, 47 and 24 mol % of the double bonds were reacted for monomers TBEED and **1**. The reason for lower conversion at maximum rate for monomer **1** indicates earlier gelation due to higher crosslinking tendency of this monomer compared with TBEED.

To test the use of monomer **1** as reactive diluent in filling composites and also crosslinking monomer in dental adhesives, we investigated its copolymerization with Bis-GMA and HEMA. The results (Fig. 9 and Table 3) show that the polymerization rate of monomer **1** is lower than Bis-GMA but slightly higher than HEMA. The conversions follow the order: HEMA> **1**> Bis-GMA. Addition of 10 mol % of monomer **1** to Bis-GMA slightly decreased its rate without changing its conversion. However, addition of 10 mol % of monomer **1** to HEMA did not change its rate but decreased its conversion due to crosslinking.

To test the potential of monomer **2** to be used in dental adhesives, the copolymerization kinetics of this monomer with HEMA using a water-soluble initiator BAPO were investigated. Various formulations consisting of mixtures of HEMA and water (60:40 wt %); HEMA, **2** and water (at different ratios) were photopolymerized. Figure 10 shows that addition of 5–20 wt % of **2** to HEMA resulted to gradual decreases in both conversion and rate of polymerization.

TABLE 3 Photopolymerization results of HEMA, Bis-GMA, **1**, Bis-GMA:**1** (90:10 mol %), and HEMA:**1** (90:10 mol %) at 72°C

Monomer	R_p (s^{-1})	Conversion (%)
1	0.051	84
Bis-GMA	0.099	67
HEMA	0.045	92
Bis-GMA:**1** (90:10 mol %)	0.083	65
HEMA:**1** (90:10 mol %)	0.046	77

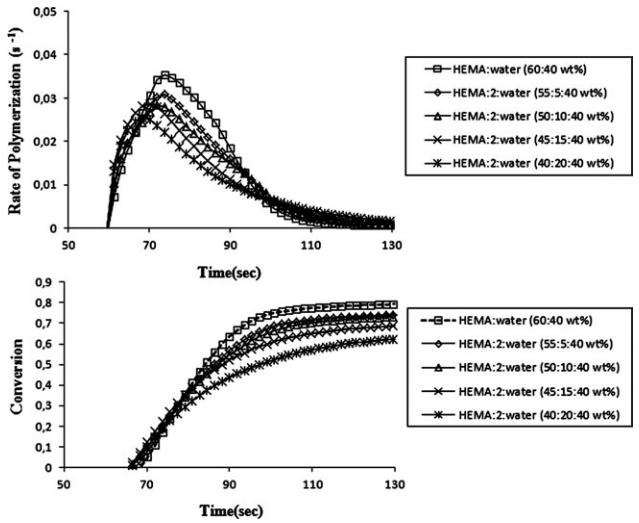

FIGURE 10 Rate-time and conversion-time curves in the copolymerizations of **2** with HEMA using BAPO at 40°C.

In addition, slight shift in the peak maximum indicated incorporation of monomer **2** into copolymers.

Homopolymerizations and copolymerization behavior of monomer **3** with HEMA were also investigated with photo-differential scanning calorimetry using DMPA as photoinitiator (Fig. 11). The rate of polymerizations for monomer **3** features a lower maximum (0.013 s^{-1}), which however keeps flat for a long time, in contrast to the narrow peaks for HEMA or the HEMA-**3** mixture (maximum 0.034 s^{-1}). This results in total conversion of **3** that is not significantly less than HEMA or the HEMA-**3** mixture (64 vs. 82%). The lower maximum rate of photopolymerization of monomer **3**

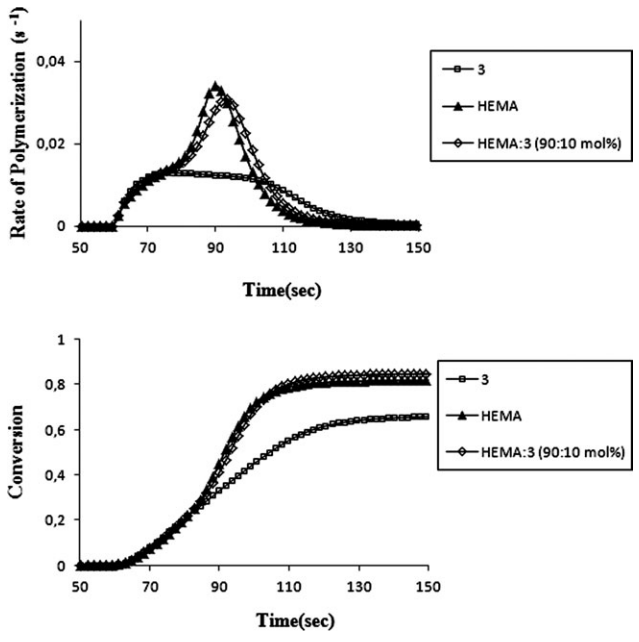

FIGURE 11 Rate-time and conversion-time curves during polymerizations of **3**, HEMA and HEMA:**3** (90:10 mol %) at 40°C.

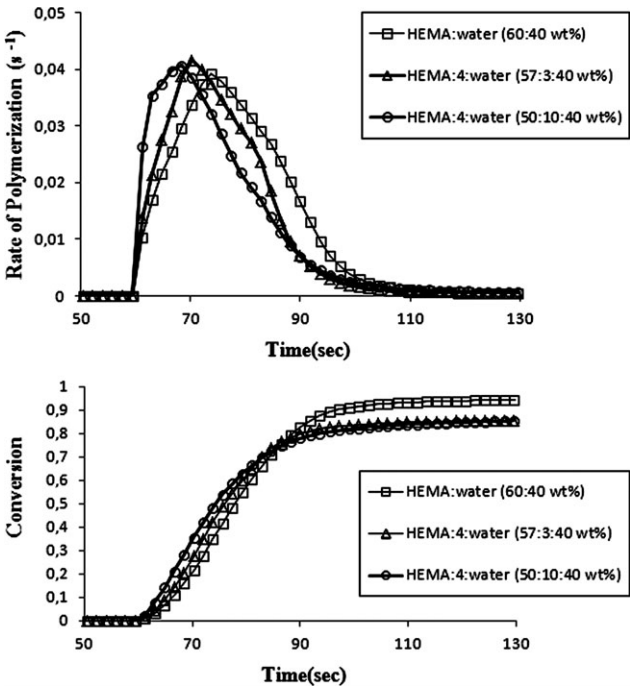

FIGURE 12 Rate-time and conversion-time curves during copolymerizations of **4** with HEMA using BAPO at 72°C.

compared with HEMA may possibly be explained due to steric effect of the bulky bisphosphonate group. Addition of 10 mol % of monomer **3** to HEMA, decreased its rate without changing its conversion significantly.

Monomer **4** was also copolymerized with HEMA using a water soluble initiator BAPO to observe its performance as dental adhesive monomer. The formulations consisting of mixtures of HEMA and water (60:40 wt %); HEMA, **4** and water (50:10:40 wt %), and HEMA, **4** and water (57:3:40 wt %) were photopolymerized. Addition of 3 and 10 wt % of monomer **4** to HEMA resulted in slight improvements in the rate of polymerization w.r.t. pure HEMA, without changing its conversion (Fig. 12).

Thermal Copolymerizations of Monomer 2

Thermal homopolymerization of monomer **2** was not investigated due to its very low photopolymerization rate. However, to check the incorporation of monomer **2** into the copolymers, its thermal solution copolymerizations with AAm and HEMA were investigated. Monomer **2** was copolymerized with AAm (5:95 mol %) in water at 65 °C with V-50 as initiator. Although AAm homopolymerizes in 4 min to give soluble polymers, its copolymerization with **2** took more than 12 h. Crosslinked copolymers precipitated as white solid powders which indicate the incorporation of monomer **2**. Monomer **2** was also copolymerized with HEMA (10:90 mol %) in ethanol at 50 °C with AIBN as initiator. The addition of monomer **2** to HEMA decreased its polymerization rate: HEMA homopolymerize in 45 min giving clear gels, but the copolymer formed in more than 12 h giving a white solid crosslinked polymer. FTIR spectrum of one of the copolymers (after removal of residual monomers) indicated OH, C=O peaks of HEMA at

3309 and 1720 cm^{-1} and additional peaks due to C=O and N—H peaks of monomer **2** at 1657 and 1530 cm^{-1}, which proved its incorporation into the copolymer.

CONCLUSION

We have successfully synthesized four novel monomers at high purity. The first two are bismethacrylamides, and the second group is methacrylamides, in each group one monomer containing a bisphosphonate and the other a bisphosphonic acid functional group.

The polymerization studies of the bisphosphonate-containing bismethacrylamide indicated high reactivity, crosslinking and chain transfer tendency. The photopolymerization reactivity of this monomer was comparable to TBEED. The copolymerization results with Bis-GMA and HEMA indicated that this highly reactive monomer might possess potential as reactive diluent for dental composites. The bisphosphonate-containing methacrylamide was also found to be highly reactive but gave soluble polymers.

The bisphosphonic acid-containing monomers showed good performance in terms of solubility, acidity, and copolymerizability with HEMA. Hydrolytic stability was found to be good for the bismethacrylamide, and conjectured to be so for the methacrylamide, since the former has two bisphosphonic acid groups. The first monomer, as representative of both bisphosphonic acid-containing monomers, was also found to interact with HAp, which serves as representative of dental tissue.

We conclude that the shelf life and bonding reliability of dental monomers can be increased by utilizing these four monomers.

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