Synthesis, Photopolymerization, and Adhesive Properties of Hydrolytically Stable Phosphonic Acid-Containing (Meth)acrylamides

Ayse Altin,[1] Burcin Akgun,[1] Zeynep Sarayli Bilgici,[1] Sebnem Begum Turker,[2] Duygu Avci[1]

[1]Department of Chemistry, Bogazici University, 34342 Bebek, Istanbul, Turkey
[2]Department of Prosthodontics, Marmara University, 34365 Nisantasi, Istanbul, Turkey
Correspondence to: D. Avci (E-mail: avcid@boun.edu.tr)

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ABSTRACT: Three novel dental monomers containing phosphonic acid groups (**1a** and **2a**, based on diethyl amino(phenyl)methylphosphonate and **3a** based on diethyl 1-aminoheptylphosphonate) were synthesized in two steps: the reaction of α-aminophosphonates with acryloyl chloride (for monomers **1a** and **3a**) or methacryloyl chloride (for **2a**) to give monomers with phosphonate groups, and the hydrolysis of phosphonate groups by using trimethyl silylbromide. Their (and the intermediates') structures were confirmed by FTIR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. All the monomers dissolve well in water ($1<pH<2$) and are hydrolytically stable. Their homo- and copolymerizations with 2-hydroxyethyl methacrylate (HEMA) and HEMA/glycerol dimethacrylate were investigated with photo-DSC. Thermal polymerization of the new monomers in water or in ethanol/water solution was investigated, giving polymers in good yields. X-ray diffraction results showed only dicalcium phosphate dehydrate formation upon interaction of **1a**-**3a** with hydroxyapatite indicating its strong decalcification and that monomer-Ca salts are highly soluble. Some results were also compared to those with a bisphosphonic acid-containing methacrylamide (**4a**) previously reported; and the influence of monomer structure on polymerization/adhesive properties is discussed. These properties, especially hydrolytic stability and good rates of polymerization, make these new monomers suitable candidates as components of dental adhesive mixtures. © 2013 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2014**, *52*, 511–522

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INTRODUCTION In recent years, self-etching adhesives have become popular in restorative dentistry in order to achieve a strong bond between the dental hard tissues (dentin and enamel) and the restorative material.[1–3] Such adhesives are water based and have several components: an acidic monomer [e.g., 4-methacryloxyethyl trimellitic anhydride (4-META) or 10-methacryloyloxydecyl dihydrogen phosphate (MDP)], crosslinking monomers {e.g., 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy) phenyl] propane (bis-GMA), and urethane dimethacrylate}, a monofunctional comonomer (e.g., HEMA), an initiator, and fillers.

Acidic monomers, usually with dihydrogen phosphates, carboxylic or phophonic acid groups, are the most important component in a self-etching adhesive. They are used in the adhesive in order to partially demineralize the tooth tissues as well as to form a strong chemical bond with hydroxyapatite (HAP). Therefore, it is desired that self-etching adhesive monomers have the following properties: (i) high rate of homopolymerizability or copolymerizability with the other monomers in the adhesive, (ii) ability to form strong bonds with tooth tissue, (iii) sufficient stability both in storage and in the mouth. In order to realize the first requirement, (meth)acrylate- and (meth)acrylamide-based acidic monomers are extensively used in dental applications due to their high reactivities.

Extensive research has been conducted to satisfy the second requirement, that is, to develop monomers with acidic functional groups, which may strongly bond to dental tissue, in particular, HAP. For example, bisphosphonates, structural analogs of naturally existing pyrophosphate with increased chemical and enzymatic stability and strong affinity for HAP, can be incorporated into the monomers.[4–7] This interaction can occur by chemical bonds, such as covalent or ionic bonds, stemming from the reaction of acidic and chelating groups with HAP; and physical bonds due to van der Waals forces, London dispersion forces, hydrogen bonding, or charge-transfer complexes.[3] According to the "Adhesion-Decalcification" concept of Yoshida et al., the bonding performance of the adhesives depends on the chemical stability of the monomer-Ca salts formed with the interaction of the acid monomer and HAP.[8–11] Therefore, the structure of the acid monomer is very important and small differences such

as polarity in the monomer structures cause significant differences in their adhesive performances. For example, while 4-META and methacryloxyethyl hydrogen phenylphosphate (Phenyl-P) deposit unstable calcium salts due to dissolution, MDP forms hydrolysis resistant calcium salts due to its hydrophobic decyl group.

Although many commercial dental adhesives accomplish good binding to HAP, the main problem is hydrolysis of the ester groups in (meth)acrylates forming the basis of these monomers, which relates to the third requirement. Adhesive mixtures contain water, and the mouth is an aqueous environment, so ester-based adhesives generally can hydrolyze both in storage and in the mouth, which results in both inadequate shelf life of adhesives and undesirably short useful lifetime of the dental material. To overcome this disadvantage, hydrolytically stable ether- and/or amide-linked monomers were synthesized.[12–22]

Recently we have focused our interest on the design and synthesis of the new acidic monomers, which are expected to meet the requirements mentioned above. In this study, we report on three such monomers. We describe the synthesis, characterization, photopolymerization behavior, hydrolytic stability, adhesive properties, and HAP interactions of the monomers **1a–3a** (Fig. 1). Some of their properties were compared with a bisphosphonic acid-containing methacrylamide (**4a**) previously reported[5] by our group to investigate structure–property relationships. Monomers **1a** and **3a** are novel and **2a** is mentioned in a patent.[23]

EXPERIMENTAL

Materials

Diethyl amino(phenyl)methylphosphonate and diethyl 1-aminoheptylphosphonate were prepared according to literature procedures.[24] Trimethylsilyl bromide (TMSBr) (Aldrich, Taufkirchen, Germany) was distilled before use. Dichloromethane was dried over activated molecular sieves (4 A^0). Methacryloyl chloride, acryloyl chloride, triethyl amine (TEA), 2-hydroxyethyl methacrylate (HEMA), glycerol dimethacrylate (GDMA), 2,2-bis[4-(2-hydroxy-3-methacryloyloxy propoxy) phenyl] propane (bis-GMA), HAP, 2,2′-dimethoxy-2-phenyl acetophenone (DMPA), 2,2′-azobis(2-methylpropionamidine)dihydrochloride (V-50), bis (2,4,6-trimethylbenzoyl)phenylphosphine oxide (BAPO), and all other reagents and solvents were obtained from Aldrich Chemical and used as recieved. MDP was a gift from Ivoclar Vivadent AG.

Characterization

Monomer characterization involved ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy (Varian Gemini 400 MHz) and FTIR spectroscopy (T 380). Elemental analyses were obtained on a Thermo Electron SpA FlashEA 1112 elemental analyser (CHNS separation column, PTFE; 2 m; 6 × 5 mm). Photopolymerizations were performed using a TA Instruments Q100 differential photocalorimeter. The interactions of monomers with HAP were studied by X-ray diffraction (Rigaku D/max-2200/PC). Gel permeation chromatography (GPC) was performed on an Agilent 1100 GPC Instrument equipped with a refractive index detector, using water as a solvent and poly(-acrylic acid sodium salt) standards. Combi Flash Companion Teledyne ISCO Flash Chromatography with octadecyl bonded silica gel (C 18 reverse phase silica gel) as a stationary phase was used for purification of monomers.

Synthesis of Monomers

Diethyl Acrylamido(phenyl)methylphosphonate (Monomer 1)

A solution of acryloyl chloride (0.80 mL, 10 mmol) in anhydrous toluene (2 mL) was added dropwise, under N_2, to a solution of diethyl amino(phenyl)methylphosphonate (1.95 g, 8.02 mmol) and TEA (1.30 mL, 9.00 mmol) in anhydrous toluene (7 mL) in an ice bath. Thereafter, more toluene (5 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction was terminated by addition of distilled water (10 mL) and the mixture filtered. The filtered solid was dissolved in chloroform (113 mL) and extracted with distilled water (3 × 40 mL), 2M HCl (3 × 40 mL), saturated $NaHCO_3$ (3 × 40 mL), and distilled water (3 x 40 mL) again. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under vacuum to give monomer **1** as a white solid with a melting point of 154 °C in 30% yield.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.02, 1.24 (t, $^{3}J_{HH} = 7.1$ Hz, $^{3}J_{HH} = 7.2$ Hz, 6H, $OCH_2\underline{CH_3}$), 3.64, 3.83, 4.11 (m, 4H, $O\underline{CH_2}CH_3$), 5.50 (dd, $^{3}J_{HH} = 11.6$ Hz, $^{3}J_{HH} = 9.7$ Hz, 1H, $CH_2{=}\underline{CH}$), 5.61 (dd, $^{2}J_{HH} = 4.7$ Hz, $^{2}J_{HP} = 2.6$ Hz, 1H, $\underline{CH}$—P), 6.23 (d, $^{3}J_{HH} = 11.6$ Hz, 1H, $\underline{CH_2}{=}CH$), 6.25 (d, $^{3}J_{HH} = 9.7$ Hz, 1H, $\underline{CH_2}{=}CH$), 7.21–7.46 (m, 5H, Ar-H), 8.22 (br.s, 1H, N—H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, δ): 16.31 ($OCH_2\underline{CH_3}$), 48.92, 51.04 (CH—P), 63.24 ($O\underline{CH_2}CH_3$), 126.85, 128.46, 128.52,

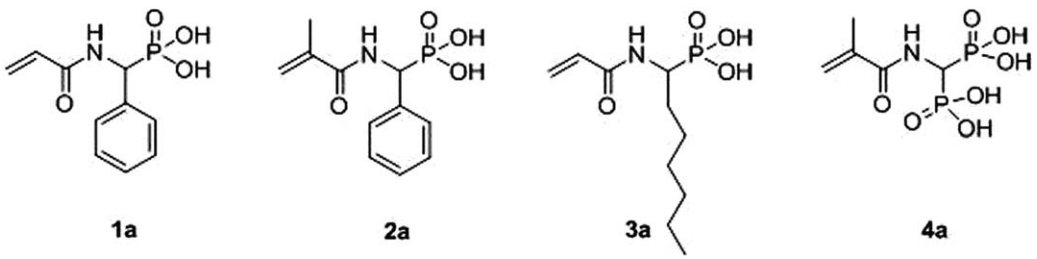

FIGURE 1 Structures of the (bis)phosphonic acid monomers (**4a**) **1a–3a**.

135.07 (Ar-C), 128.02 (CH=$\underline{C}H_2$), 130.41 ($\underline{C}H$=CH_2), 165.19, 165.27 (C=O) ppm. FTIR (ATR): 3262 (N—H), 3052, 3027 (Ar-H), 2985, 2935 (C—H), 1672 (C=O), 1630 (C=C), 1540 (NH), 1216 (P=O), 1015 and 954 (P—O) cm^{-1}. Elem. Anal., Calcd. for $C_{14}H_{20}NO_4P$: C, 56.56%; H, 6.78%; N, 4.71%; O, 21.53%; P, 10.42%. Found: C, 57.62%; H, 7.20%; N, 4.97%.

Acrylamido(phenyl)methylphosphonic acid (Monomer 1a)

TMSBr (0.309 g, 2.018 mmol) was added dropwise to a solution of monomer **1** (0.2 g, 0.673 mmol) in dry dichloromethane (2.90 mL) in an ice bath and under N_2. After stirring for 3 h at room temperature, the volatile components were removed under vacuum. Methanol (9 mL) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by flash chromatography on C18 reverse phase silica gel, eluting with H_2O/MeOH (70/30, v/v) to give monomer **1a** as a white solid with a melting point of 70–71 °C in 54% yield.

^{1}H NMR (400 MHz, D_2O:MeOD, δ): 5.36 (d, $^2J_{HP}$ = 21.1 Hz, 1H, C$\underline{H}$—P), 5.74 (d, $^3J_{HH}$ = 10.5 Hz, 1H, C$\underline{H}_2$=CH), 6.22 (d, $^3J_{HH}$ = 17.6 Hz, 1H, C$\underline{H}_2$=CH), 6.33–6.44 (dd, $^3J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 10.5 Hz, 1H, CH_2=C$\underline{H}$), 7.24–7.46 (m, 5H, Ar-H) ppm. ^{13}C NMR (400 MHz, D_2O:MeOD, δ): 52.72, 54.20 (CH—P), 128.96, 129.11, 129.16, 137.35 (Ar-C), 129.78 (CH=$\underline{C}H_2$), 131.15 ($\underline{C}H$=CH_2), 168.42, 168.50 (C=O) ppm. ^{31}P NMR (400 MHz, $CDCl_3$, δ): 15.26 ppm. FTIR (ATR): 3264 (N—H), 3063, 3028 (Ar-H), 3000–2600 (OH), 2958 (C—H), 1653 (C=O), 1620, 1606 (C=C), 1529 (NH), 1178 (P=O), 983 and 932 (P—O) cm^{-1}

Diethyl Methacrylamido(phenyl)methylphosphonate (Monomer 2)

A solution of methacryloyl chloride (0.60 mL, 6 mmol) diluted in anhydrous toluene (1.2 mL) was added dropwise, under N_2, to a mixture of diethyl amino(phenyl)methylphosphonate (1.20 g, 5. mmol) and triethylamine (0.8 mL, 5.5 mmol) in anhydrous toluene (4.2 mL) in an ice bath. Thereafter, more toluene (3 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction was terminated by addition of distilled water (6 mL) and the mixture was filtered. The filtered solid was dissolved in chloroform (57 mL) and extracted with distilled water (3 × 20 mL), 2M HCl (3 × 20 mL), saturated $NaHCO_3$ (3 × 20 mL), and distilled water (3 × 20 mL). After drying the organic phase with anhydrous Na_2SO_4, the solvent was evaporated under vacuum to give monomer **2** as a white solid with a melting point of 114 °C in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.05, 1.27 (t, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 7.1 Hz, 6H, $OCH_2C\underline{H}_3$), 1.93 (s, 3H, CH_3), 3.67, 3.89, 4.11 (m, 4H, $OC\underline{H}_2CH_3$), 5.32, 5.71 (s, 2H, CH_2=C), 5.53 (dd, $^2J_{HH}$ = 11.6 Hz, $^2J_{HP}$ = 9.5 Hz, 1H, C$\underline{H}$—P), 7.06 (br s, 1H, N—H), 7.27–7.46 (m, 5H, Ar-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, δ): 16.35 ($OCH_2\underline{C}H_3$), 18.97 (CH_3), 49.84, 51.26 (CH—P), 63.36 ($O\underline{C}H_2CH_3$), 120.59 ($\underline{C}H_2$=C), 128.30, 128.41, 128.80, 135.45 (Ar-C), 140.43 (CH_2=$\underline{C}$), 167.89, 167.97 (C=O) ppm. FTIR (ATR): 3280 (N—H), 3048, 3029 (Ar-H), 2982, 2908 (C—H), 1659 (C=O), 1621 (C=C), 1524 (NH), 1234 (P=O), 1021 and 960 (P—O) cm^{-1}. Elem. Anal., Calcd. for $C_{15}H_{22}NO_4P$: C, 57.87%; H, 7.12%; N, 4.50%; O, 20.56%; P, 9.95%. Found: C, 57.82%; H, 7.55%; N, 4.43%.

Methacrylamido(phenyl)methylphosphonic Acid (Monomer 2a)

TMSBr (0.295 g, 1.927 mmol) was added dropwise to a solution of monomer **2** (0.2 g, 0.642 mmol) in dry dichloromethane (2.80 mL) in an ice bath and under N_2. After stirring at 40 °C for 2 h, the volatile components were removed under vacuum. Methanol (8.5 mL) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by flash chromatography on C18 reverse phase silica gel, eluting with H_2O/MeOH (35/65, v/v) to give monomer **2a** as a white solid with a melting point of 63–64 °C in 56% yield.

^{1}H NMR (400 MHz, D_2O, δ): 1.99 (s, 3H, C$\underline{H}_3$), 5.28 (d, $^2J_{HP}$ = 18.1 Hz, 1H, C$\underline{H}$—P), 5.54, 5.78 (s, 2H, C$\underline{H}_2$=C), 7.36–7.57 (m, 5H, Ar-H) ppm. ^{13}C NMR (400 MHz, MeOD, δ): 14.48 (CH_3), 27.23, 27.36 ($CH\underline{C}H_2$), 23.71, 29.92, 30.50, 32.89 ($CH_2CH_2CH_2CH_2$), 47.44 (CH—P), 127.21(C=CH_2), 131.85 ($\underline{C}$=CH_2), 168.10, 168.14 (C=O) ppm. FTIR (ATR): 3245 (N—H), 3000–2600 (OH), 2926, 2858 (C—H), 1655 (C=O), 1627 (C=C), 1547 (NH), 1097 (P=O), 998 and 937 (P—O) cm^{-1}

Diethyl 1-Acrylamidoheptylphosphonate (Monomer 3)

A solution of acryloyl chloride (0.33 mL, 4.06 mmol) diluted in anhydrous dichloromethane (3.3 mL) was added dropwise, under N_2, to a mixture of diethyl 1-aminoheptylphosphonate (0.64 g, 2.53 mmol), and triethylamine (0.5 mL, 3.43 mmol) in anhydrous dichloromethane (7.4 mL) in an ice bath. The mixture was stirred at room temperature for 2 h. The reaction was terminated by addition of distilled water (3.3 mL). After addition of chloroform (35 mL), the organic layer was extracted several times with distilled water (3 × 12 mL), 2M HCl (3 × 12 mL), saturated $NaHCO_3$ (3 × 12 mL), and distilled water (3 × 12 mL) and dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give monomer **3** as a yellow viscous liquid in 49% yield.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.79 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_2C\underline{H}_3$), 1.13–1.30 (m, 14H, $OCH_2C\underline{H}_3$, ($C\underline{H}_2$)$_4$), 1.58, 1.73 (m, 2H, $CHC\underline{H}_2$), 4.06 (m, 4H, $OC\underline{H}_2CH_3$), 4.47 (m, 1H, CH—P), 5.58 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 9.2 Hz, 1H, CH_2=C$\underline{H}$), 6.25 (d, $^3J_{HH}$ = 10.6 Hz, 1H, C$\underline{H}_2$=CH), 6.27 (d, $^3J_{HH}$ = 9.2 Hz, 1H, C$\underline{H}_2$=CH), 7.45, 7.48 (d, $^3J_{HH}$ = 9.9 Hz, 1H, N—H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, δ): 12.78 (CH_3), 15.58 ($OCH_2\underline{C}H_3$), 21.66 ($CH\underline{C}H_2$), 24.87, 27.84, 28.51, 30.54 ($CH_2CH_2CH_2CH_2$), 43.31, 44.79 (CH—P), 61.19, 62.08 ($O\underline{C}H_2CH_3$), 125.47 (CH=$\underline{C}H_2$), 129.59 ($\underline{C}H$=CH_2), 164.59, 164.64 (C=O) ppm. FTIR (ATR): 3253 (N—H), 2980, 2928 (C—H), 1664 (C=O), 1630 (C=C), 1539 (NH), 1222 (P=O), 1022 and 959 (P—O) cm^{-1}.

1-Acrylamidoheptylphosphonic Acid (Monomer 3a)

TMSBr (0.490 g, 3.203mmol) was added dropwise to a solution of monomer **3** (0.326 g, 1.068 mmol) in dry dichloromethane (4.60 mL) in an ice bath and under N_2. After stirring

for 3 h at room temperature, the volatile components were removed under vacuum. Methanol (14.4 mL) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by flash chromatography on C18 reverse phase silica gel, eluting with H_2O/MeOH (45/55, v/v) to give monomer **3a** as a white solid with a melting point of 50–51 °C in 80% yield.

^{1}H NMR (400 MHz, MeOD, δ): 0.89 (t, $^3J_{HH} = 6.9$ Hz, 3H, $CH_2C\underline{H}_3$), 1.23–1.46 (m, 8H, $(C\underline{H}_2)_4$), 1.65, 1.88 (m, 2H, $CHC\underline{H}_2$), 4.29 (dt, $^3J_{HH} = 12.8$ Hz, $^2J_{HP} = 4.2$ Hz, 1H, CH—P), 5.66, 5.68 (dd, $^3J_{HH} = 9.8$ Hz, $^3J_{HH} = 2.5$ Hz, 1H, $C\underline{H}_2$=CH), 6.21, 6.25 (dd, $^3J_{HH} = 15.1$ Hz, $^3J_{HH} = 2.5$ Hz, 1H, $C\underline{H}_2$=CH), 6.31, 6.35 (dd, $^3J_{HH} = 15.1$ Hz, $^3J_{HH} = 9.8$ Hz, 1H, CH_2=C$\underline{H}$) ppm. ^{13}C NMR (400 MHz, MeOD, δ): 14.48 (CH_3), 27.23, 27.36 ($CH\underline{C}H_2$), 23.71, 29.92, 30.50, 32.89 ($CH_2CH_2CH_2CH_2$), 47.44 (CH—P), 127.21 (C=$\underline{C}H_2$), 131.85 ($\underline{C}$=CH_2), 168.10, 168.14 (C=O) ppm. ^{31}P NMR ($CDCl_3$): 22.76 ppm. FTIR (ATR): 3245 (N—H), 3000–2600 (OH), 2926, 2858 (C—H), 1655 (C=O), 1627 (C=C), 1547 (NH), 1097 (P=O), 982 and 933 (P—O) cm^{-1}

Methacrylamidomethylenediphosphonic Acid (Monomer 4a)

Monomer **4a** was synthesized in our previous study.[5]

Interactions of Monomers with Hydroxyapatite

FTIR Spectroscopy Technique

HAP particles (0.2 g) were dispersed in 1.00 g of monomer/EtOH/H_2O (15/45/40 wt %) solution under stirring as described by Yoshihara et al.[9] After 24 h, the monomer-coated HAP particles were isolated by centrifugation and washed with water (× 3) and then with ethanol and dried at room temperature.

XRD Technique

HAP samples were prepared as in the case of FTIR spectroscopy technique, washed with ethanol (× 3) and water (× 3), and dried at room temperature before analysis. The crystal phases on the monomer-coated HAP particles were identified by a powder XRD operated under 40 kV acceleration and 40 mA current and scanning rate of 2° min^{-1} for $2\theta/\theta$ scan.

Hydrolytic Stability

The hydrolytic stabilities of monomers were studied by ^{1}H NMR measurements of 5 wt % solutions of the monomers in methanol-d_4/D_2O (1/1, v/v) after storage at 37 °C for 20 days.

Shear Bond Strength Measurements

Caries-free human molars were used in this study. The roots of each tooth were embedded in autopolymerizing acrylic resin (Meliodent, # 64713278; Heraeus Kulzer, Hanau, Germany). A horizontal dentin bonding surface was prepared with a high speed of diamond disc [Isomet 1000 Precision saw (Buehler, Easton Ill)]. A phosphoric acid gel was applied on the dentin surface for 15 s. The etchant gel was then removed with a water spray, and the excess of moisture was removed. The adhesive was then rubbed on the etched dentin with a microbrush for 10 s. The adhesive layer was air-dried for 15 s and light cured for 10 s with a LED curing light. A 3-mm thick Teflon mold (Gapi, Bergamo, Italy) with a central 2-mm diameter circular hole was fixed on the surface. The nanohybrid composite was placed into the mold. The samples were polymerized for 40 s with LED curing light. The samples were finally stored in water at 37 °C for 24 h before being tested. The shear bond strength (SBS) was measured using a universal testing machine (Zwick) at a crosshead speed of 0.8 mm min^{-1}. Ten samples were tested for each adhesive.

Photopolymerizations

Photopolymerizations were conducted using a DSC equipped with a mercury arc lamp. The samples (3–4 mg) containing 2.0 mol % initiator were irradiated for 10 min with an incident light intensity of 20 mW cm^{-2} and a nitrogen flow of 20 mL min^{-1}. Photopolymerization rates were calculated using the following formula:

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

where Q/s is the heat flow per second, M is the molar mass of the monomer, n is the number of double bonds per monomer molecule, ΔH_p is the heat released per mole of double bonds reacted, and m is the mass of monomer in the sample. The values used for the ΔH_p of acrylamide and methacrylamide double bonds were 20.6 and 13.1 kcal mol^{-1} [25].

Thermal Polymerizations

Thermal homopolymerizations of monomers (**1a**, **2a**, and **3a**) were carried out in solutions of water or EtOH/water (2.5/1, v/v) containing V-50 at 65 °C using the standard freeze-evacuate-thaw procedure. Large amounts of THF (**1a**) or water (**2a**, **3a**) were then added to precipitate the polymers. After filtration, the polymer was dried under vacuum.

RESULTS AND DISCUSSION

Synthesis and Characterization of Monomers

Two α-primary aminophosphonates (diethyl amino(phenyl)-methylphosphonate and diethyl 1-aminoheptylphosphonate) were used as starting materials for the synthesis of the monomers. They were prepared in a solvent-free one-pot reaction of benzaldehyde or heptaldeyde, ammonium carbonate, and diethyl phosphite in the presence of catalytic $Al(OTf)_3$ (Fig. 2).[24]

The new phosphonic acid-containing (meth)acrylamides (**1a–3a**) were prepared in two steps (Fig. 2). In the first step, acryloyl or methacryloyl chloride was reacted with diethyl amino(phenyl)methylphosphonate and diethyl 1-amino heptylphosphonate in the presence of TEA to give phosphonate-containing monomers (**1–3**). The monomers **1** and **2** were solids with melting points of 154 and 114 °C, respectively, and isolated in 30 and 40% yields, whereas monomer **3** was a viscous liquid in 49% yield.

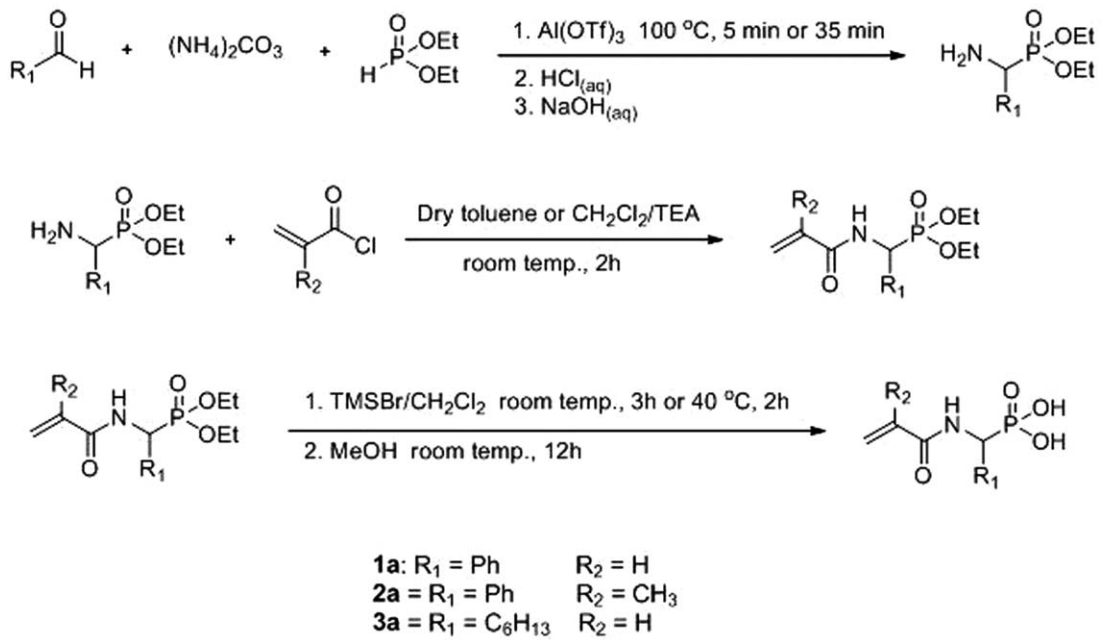

FIGURE 2 Synthesis of α-aminophosphonates and phosphonic acid monomers **1a–3a**.

In the second step, the silylation of phosphonate monomers (**1–3**) using TMSBr, followed by methanolysis of the silyl ester groups provided the new acid monomers **1a–3a** in 54–80% yields after purification with C18 reversed-phase flash chromatography. The monomers **1a–3a** were obtained as white solids with melting points of 70–71, 63–64, and 50–51 °C, respectively. The solubility of phosphonic acid monomers in water, EtOH, acetone, THF, diethyl ether, and CH_2CL_2 (3 mg/5 mL), were investigated (Table 1). All monomers are soluble in EtOH and water, which is very important for dental adhesive applications; but insoluble in diethyl ether and CH_2CL_2. Solubility of monomer **1a** was also determined as 0.2, 0.6, and 1.2 mg mL^{-1} at pH values of 4, 7, and 10. Monomers **1a–3a** are also soluble in THF and acetone whereas monomer **4a** is not, due to its more polar nature.

The monomers (**1–3** and **1a–3a**) were characterized using FTIR, ^1H, ^{13}C, and ^{31}P NMR spectroscopies, as well as elemental analysis. In the ^1H NMR spectra of monomers **1** and **2**, we observed two different triplet peaks for methyl protons and three different multiplets for methylene protons, indicating special conformations of these monomers. Diastereotopic protons were observed for one methylene at 3.64 and 3.83 ppm and protons of the other methylene were observed at 4.11 ppm for monomer **1** (Fig. 3). The rigid structure of the molecule provided by the benzyl group may be the reason for this behavior. Moreover, monomers **1** and **2** also have a peak seen as doublet of doublet for methine proton due to phosphorus and resonance form of amide linkage. The broad NH peak at 8.22 ppm in the ^1H NMR spectra of monomers **1** indicates a monosubstituted carbamide group. The ^{13}C NMR spectrum of monomer **3** is shown in Figure 4. The doublet seen at 43.31, 44.79 ppm is due to the carbon attached to phosphorus. In the FTIR spectra of the monomers, monomer **3** showed peaks at 3253 cm^{-1} (amide V region), 1630 cm^{-1} (amide I region) and 1539 cm^{-1} (amide II region). Monomer **3** also showed absorption peaks of C═C, P═O, and P—O peaks at 1630, 1222, 1022, and 959 cm^{-1}.

^1H NMR spectrum of monomer **1a** shows the complete disappearance of phosphonic ester peaks at 1.02, 1.24, 3.64, 3.83, and 4.11 ppm (Fig. 3). The FTIR spectrum of monomer **1a** shows broad peaks in the region of 3000–2600 and 2300–2100 cm^{-1} due to OH stretching, 1670–1600 cm^{-1} due to OH bending and strong peaks at 1653, 1620, and 1529 cm^{-1} due to C═O, C═C, and NH stretching,

TABLE 1 Solubility of Monomers **1a–4a** in Selected Solvents

Monomer	H_2O	EtOH	THF	Acetone	Diethyl Ether	CH_2Cl_2
1a	+	+	+	+	–	–
2a	+	+	+	+	–	–
3a	+	+	+	+	–	–
4a	+	+	–	–	–	–

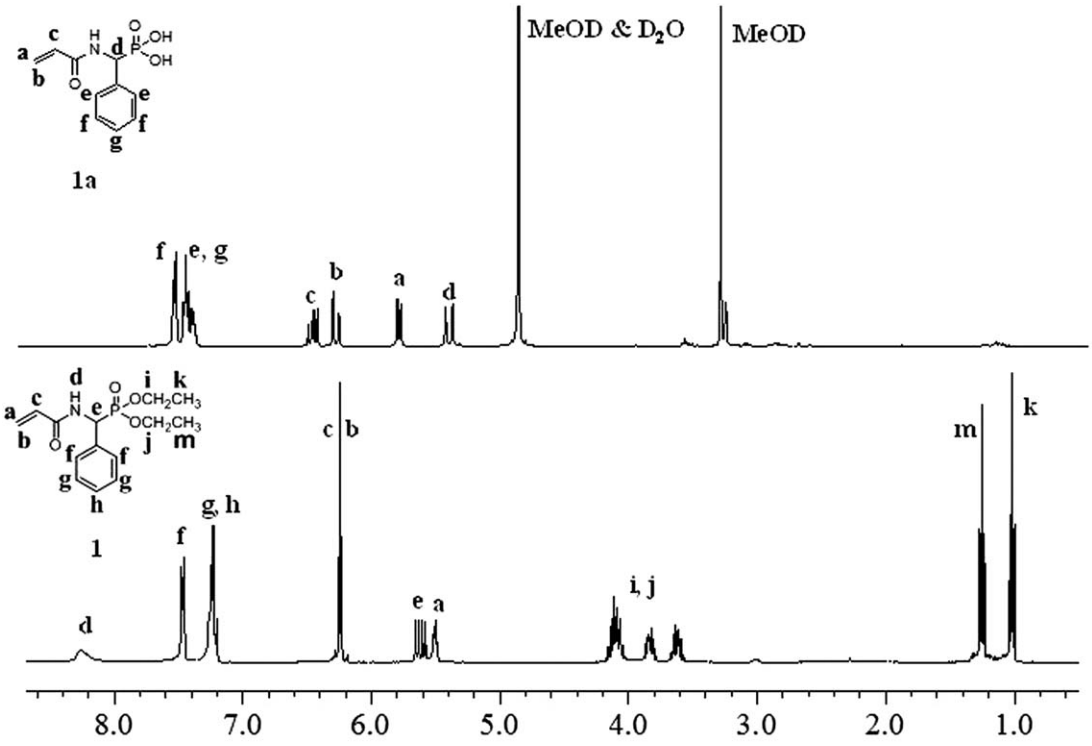

FIGURE 3 ^{1}H NMR spectra of monomers **1** and **1a**.

respectively. Also the strong bands at 983 and 932 cm^{-1} correspond to the symmetric and asymmetric vibration of P—O. In the ^{13}C NMR spectrum of monomer **3a**, the disappearance of the characteristic peaks of the ethyl groups of the phosphonates at 15.58, 61.19, and 62.08 ppm shows that the deprotection is complete (Fig. 4).

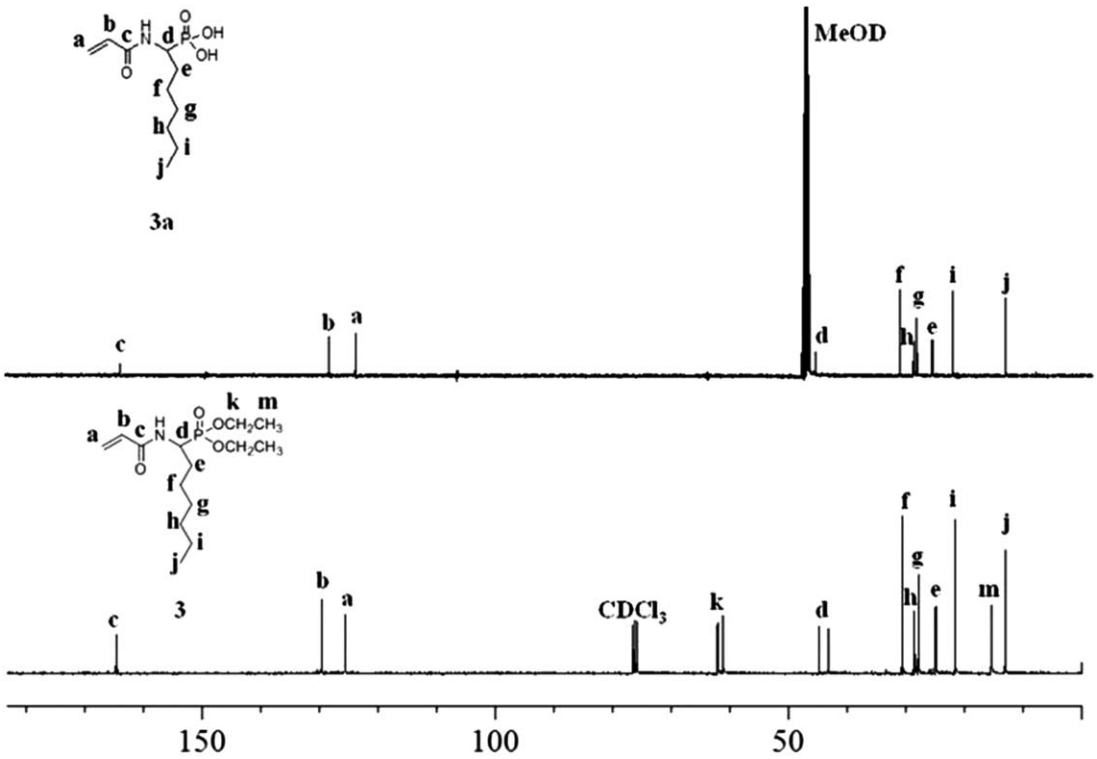

FIGURE 4 ^{13}C NMR spectra of monomers **3** and **3a**.

Acidity and Interactions of Monomers with Hydroxyapatite

The pH values of aqueous solutions of the monomers (2 wt %) were found to be 1.38, 1.42, 1.54, and 1.21 for monomers **1a–4a**, respectively, in the range expected for mild self-etching adhesives. These results show that bisphosphonic acid monomer (**4a**) is more acidic in comparison with the others, due to electron withdrawing effect of the second phosphonic acid group in its structure. The substitution of the phenyl group by the hexyl group results a decrease in pH, due to electron donating effect of alkyl chain.

To investigate the interaction of the synthesized monomers with HAP, we used FTIR spectroscopy and XRD techniques. HAP particles were treated with a mixture of monomer/EtOH/H_2O for 24 h and washed with water and ethanol. The solid and the liquid separated from the mixture were analyzed by FTIR (Fig. 5). The adhesive monomer's characteristic C═O band was observed on the solid part, indicating very low adsorption of monomers on the HAP surface due to hydrogen bonding or complex formation. FTIR analysis of the liquid part showed characteristic stretching bands of the monomers and some changes of the P═O and P—O peaks when compared with the corresponding monomer. For example, the peaks at 983 and 932 cm^{-1} due to symmetric and asymmetric vibration of P—O in monomer **1a** decreased and a new peak appeared around 1026 cm^{-1}. This peak overlaps with PO_4^{3-} peak of HAP at 1022 cm^{-1}. These results indicated that the synthesized monomers can decalcify HAP and are also slightly adsorbed to HAP surfaces.

XRD patterns of monomer (**1a–3a**)-treated HAP particles were explained according to the Adhesion-Decalcification concept proposed by Yoshida et al.[8] To compare the performance of the synthesized monomers, MDP, which has been shown to have excellent binding ability, was used as a control monomer. Untreated HAP showed peaks at $2\theta = 26^\circ$ and 32° (Fig. 6). Upon treatment with MDP, peaks around $2\theta =$ 4.8° and 7.1° appeared which are assigned to the formation of hydrolytically stable MDP-Ca salts. These peaks are due to assembling of MDP molecules into nanolayers caused by Ca ions released upon partial dissolution of HAP. This nanolayering forms a strong phase at the adhesive interface. XRD spectra of HAP treated with acidic monomer (**1a–3a**) solutions showed no peaks around $2\theta = 2$–8° which can be assigned to monomer-Ca salts (Fig. 6). However, a new peak was detected at around $2\theta = 11.6^\circ$ due to deposited $CaHPO_4.2H_2O$ (DCPD), indicating presence of demineralization which also contributes to chemical bonding. Similar results were observed for the commercial adhesive Phenyl-P in which no ionic bonding to HAP was detected.[26] These results can be explained by (i) decalcification of HAP by the synthesized monomers and (ii) higher solubilities of monomer-Ca salt than DCPD in water-EtOH solution. The intensity of the peak corresponding to DCPD is lower for monomer **3a**, which can be explained by the less acidic property of this monomer. Its decalcification ability is probably lower than the other two monomers. All these results indicate that the synthesized monomers will have bond strengths lower than MDP. However, a comparison between the synthesized monomers and MDP may not be totally appropriate, since the latter has a phosphoric acid group instead of a phosphonic acid group.

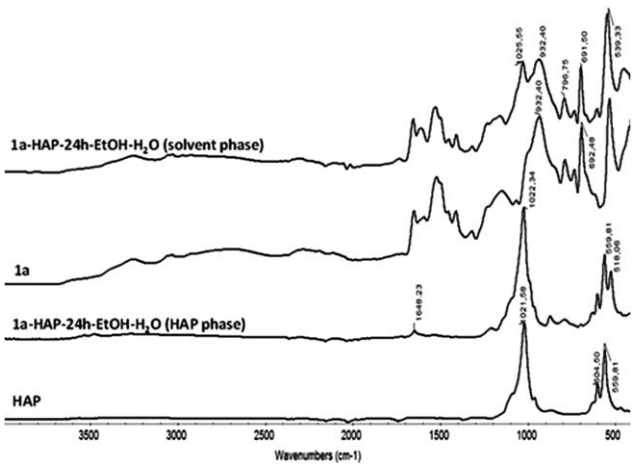

FIGURE 5 FTIR spectra of HAP, **1a**-HAP-24 h-EtOH (HAP), **1a**, **1a**-HAP-24 h-EtOH (solution).

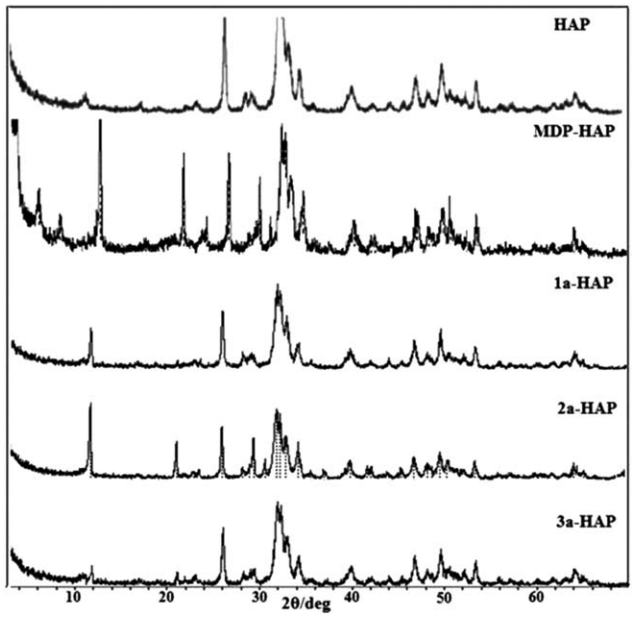

FIGURE 6 XRD patterns of HAP, MDP-HAP, **1a**-HAP, **2a**-HAP, and **3a**-HAP samples.

Hydrolytic Stability

All the synthesized monomers have phosphonic acid groups attached to the double bond through amide linkage so these monomers are expected to be resistant to hydrolysis. In fact, ^1H NMR spectra of the monomers in aqueous methanol at 37 °C taken 20 days apart confirmed our expectation; no hydrolysis was observed.

TABLE 2 Compositions of the Evaluated Adhesives

Components	Proportions (wt %)
Acidic monomer	11.1
HEMA	20.0
GDMA	11.0
bis-GMA	33.1
EtOH	24.0
BAPO	0.80

Adhesive Properties

In order to evaluate the adhesive properties of the synthesized acidic monomers in dental adhesives, experimental adhesives were formulated. Each formulation contains a phosphonic acid monomer, crosslinking monomers (GDMA and bis-GMA), a comonomer (HEMA), a photoinitiator (BAPO), and EtOH in the same molar ratios (Table 2). A reference adhesive containing MDP was also prepared to compare the efficiency of the synthesized monomers with a commercial one. The adhesives were then used to induce formation of a bond between the dental tissues and restorative materials. SBS tests were carried out using a universal testing machine (Instron) to evaluate the performance of adhesives. The results of SBS tests reported in Table 3 show the significant influence of the acidic monomer structure on the adhesion performance. Each adhesive based on the synthesized monomers has lower adhesion properties to dentin than the formulations containing the reference, MDP. These results can be explained by the higher acidity of MDP compared to the synthesized monomers which allows deeper penetration of MDP into dentin and also by lower solubility of MDP's salts which formed after interaction with HAP.

Photopolymerizations

Photopolymerizations of the synthesized monomers were investigated with photodifferential scanning calorimetry. First, the monomers were homopolymerized at 40 °C in water using BAPO as a photoinitiator. For comparison with these monomers, commercial dental monomer HEMA was also polymerized under the same conditions. Figure 7 shows photopolymerization results such as the time to reach the maximum polymerization rate (t_{max}), maximum rate of polymerization (R_{pmax}), and conversion. It was clearly seen that all three synthesized monomers exhibit improved t_{max} compared to HEMA, the acrylate monomers **1a** and **3a** having shorter t_{max} than the methacrylate monomer **2a**, consistent with the trend that acrylates are more reactive than comparable methacrylates. Therefore, it is expected that monomers **1a** and **3a** will have higher rates of polymerization values compared to **2a**. This expectation was amply borne out by the maximum rate of polymerization of **3a**, but not by that of **1a**. The lower reactivity of monomer **1a** is probably due to its very rigid structure compared to monomer **3a**. The bisphosphonic acid-containing monomer (**4a**) was found to be much less reactive than phosphonic acid-containing ones (**1a–3a**). This can be also explained due to steric effect of bulky bisphosphonic acid group compared to that of phosphonic acid.

TABLE 3 Shear Bond Strength Measurements

Acidic Monomer	Mean SBS (MPa)	SD (MPa)
MDP	27.0	8.3
1a	13.7	2.3
2a	18.0	9.0
3a	15.9	3.1

The overall conversions of the synthesized monomers were found to be low: 41, 46, and 50% for monomers **1a**, **2a**, and **3a**, respectively. These low conversions were expected due to the high T_g of the polymerizing systems which depends on flexibility of monomers.[27] In fact, the order of conversions, **3a** > **2a** > **1a** > **4a**, is correlated well with the flexibility of the monomers. The hydrogen bonded and aromatic ring structures in monomers probably result in extremely rigid systems and decreased conversion.

In order to test the potential of the synthesized monomers to be used in self-etching dental adhesives, their copolymerization kinetics with HEMA were also investigated. Various formulations consisting of mixtures of HEMA and water (60/40 wt %); HEMA, **1a–3a** and water (at different ratios) were photopolymerized (Fig. 8). The data indicated that replacement of 15 wt % of HEMA with one of the synthesized monomers in the formulation showed a remarkable effect on both maximum polymerization rate and conversion values. Although monomers **1a**, **2a**, and **4a** in water have lower maximum rates of polymerizations than HEMA in water, their mixtures with HEMA gave values higher than both HEMA in water and monomers in water. These results can be explained by the flexibility increase of the polymerizing systems. The more flexible monomer **3a** with comparable values of maximum polymerization rates is not affected. The overall conversions were found to be 57, 67, 68, and 77% for copolymers of **4a**, **1a**, **2a**, and **3a** with HEMA.

Bulk copolymerization of the acid monomers with a mixture of HEMA and GDMA were also studied in the presence of DMPA to compare reactivity of the synthesized monomers (Fig. 9). The mixtures of HEMA/monomer/GDMA (5/2/3 mol/mol/mol) and HEMA/GDMA (7/3 mol/mol) were photopolymerized at 40 °C. It was observed that the mixtures containing the acid monomers showed improved t_{max} (4.8 s) values compared to HEMA/GDMA. Maximum rates of polymerizations follow the same order: HEMA/**3a**/GDMA > HEMA/**2a**/GDMA > HEMA/**1a**/GDMA, as in monomer/water systems. The more flexible monomer **3a** has similar maximum rate compared to HEMA/GDMA mixture.

Thermal Polymerizations

Thermal homopolymerizations of monomers **1a**, **2a**, and **3a** were investigated in water at 65 °C with V-50 as initiator. The polymerization conditions and the characteristics of the polymers are listed in Table 4. Although monomer **1a** gave

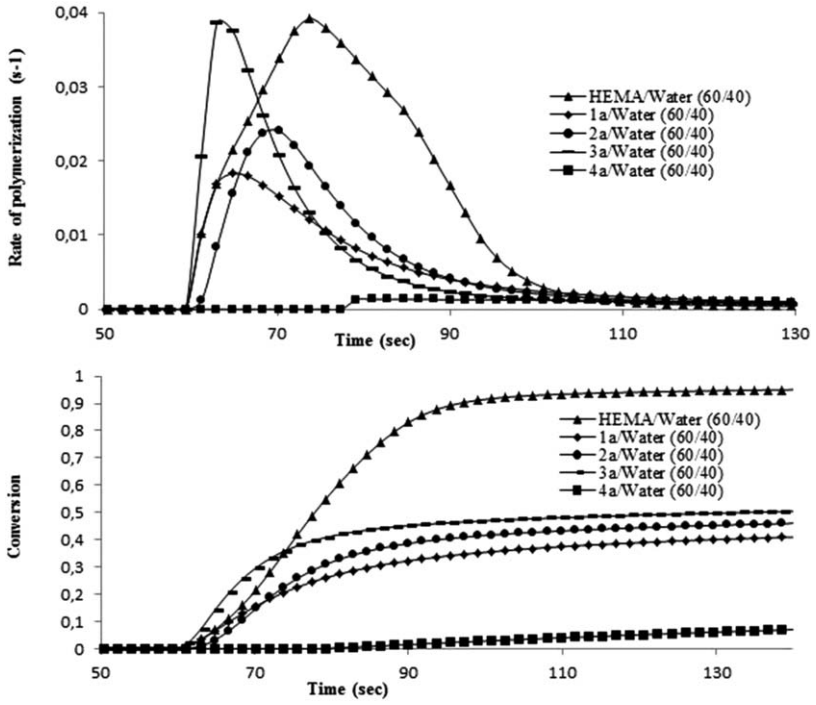

FIGURE 7 Rate–time and conversion–time curves for homopolymerizations of **1a**, **2a**, **3a** and **4a** using BAPO at 40 °C.

soluble polymers in water, polymers of **2a** and **3a** precipitated as insoluble solids during polymerization. The conversions reached very high values (85–89%) within 24 h. Soluble polymers of **3a** were obtained during solution polymerization of this monomer in EtOH/water (2/1, v/v). Although poly-**1a** is soluble in water, poly-**2a** and poly-**3a** are not, due to their more hydrophobic character. All polymers are soluble in ethanol.

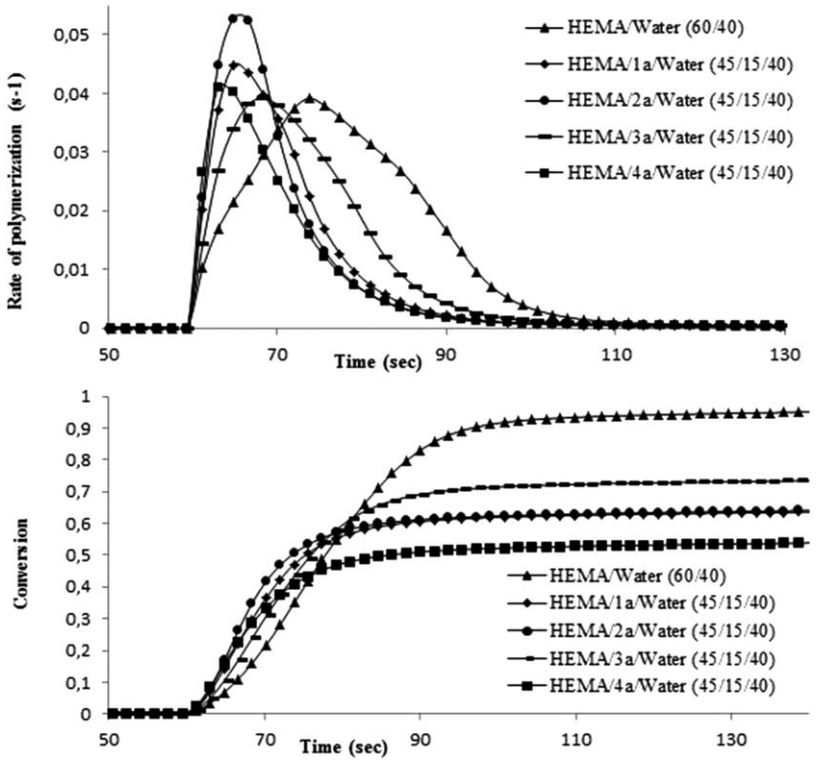

FIGURE 8 Rate–time and conversion–time curves for copolymerizations of **1a**, **2a**, **3a**, and **4a** with HEMA using BAPO at 40 °C.

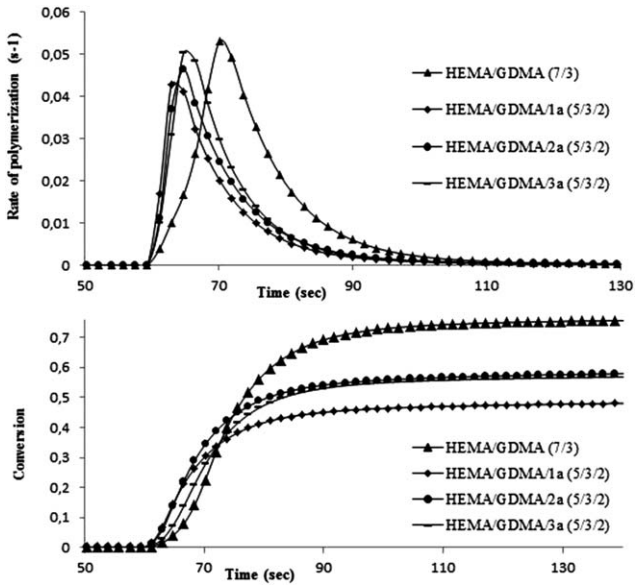

FIGURE 9 Rate–time and conversion–time curves for copolymerizations of **1a**, **2a**, and **3a** with HEMA and GDMA using DMPA at 40 °C.

^{1}H NMR spectrum of poly-**1a** indicated disappearance of double bond peaks of the monomer at 5.74, 6.22, and 6.33–6.44 ppm after polymerization (Fig. 10). The C═O stretching (amide I) vibrations were observed at 1654 and 1642 cm^{-1} in the FTIR spectra of monomer **3a** and its polymer (Fig. 11). The NH bending (amide II) in the monomer and the polymer appears at 1536 and 1528 cm^{-1}, respectively. These differences are probably due to the differences of intermolecular and intramolecular hydrogen bonding strengths. The small peak observed at 1621 cm^{-1}, which corresponds to C═C is absent in the polymer spectrum. The number average molecular weight (M_n) for this polymer was found to be 200,000 g mol^{-1}, as estimated by GPC. The determination of the molecular weight of poly-**2a** and poly-**3a** was not possible due to insolubility of these polymers in water or THF. The glass transition temperatures (T_g) of the synthesized polymers were measured by DSC to be 62 and 37 °C for poly-**2a** and **3a**, respectively. The lower T_g of poly-**3a** is due to the alkyl side chain in its structure. No T_g was observed for poly-**1a**. In order to further investigate the reactivity of the synthesized monomers, monomer **1a** was copolymerized with HEMA (1:9 mol ratio) in water (Table 4). FTIR spectrum of the crosslinked polymer obtained in 15 min showed

TABLE 4 Thermal Polymerization Results[a]

Monomer	[V-50]	Solvent	Time (h)	Conversion (%)	M_n
1a	0.025	H_2O	24	85	200,000
2a	0.025	H_2O	24	87	–
3a	0.025	H_2O	24	89	–
3a	0.05	EtOH/H_2O (2.5/1, v/v)	7 min	44	–
HEMA	0.025	H_2O	15 min	Crosslinked	–
HEMA/**1a** (9/1 mol %)	0.025	H_2O	15 min	Crosslinked	–

[a] 65 °C [*M*]= 1 mol L^{-1}.

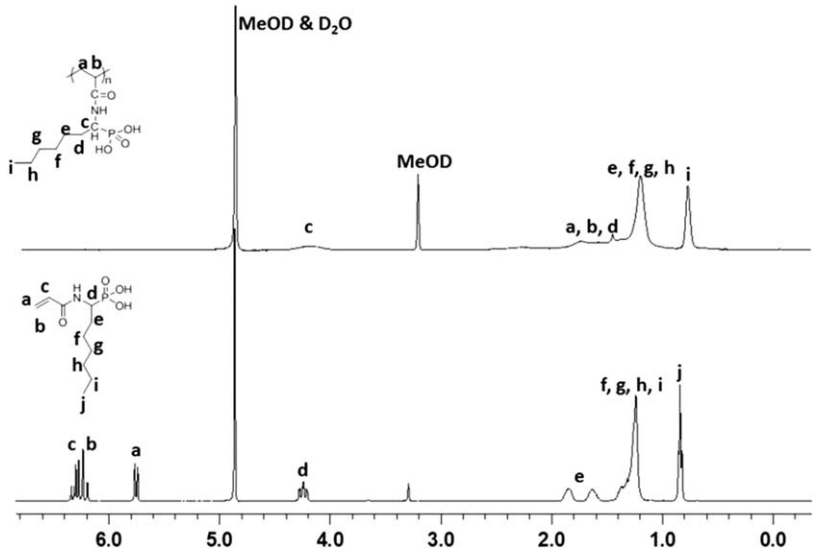

FIGURE 10 ^{1}H NMR spectra of **3a** and poly-**3a**.

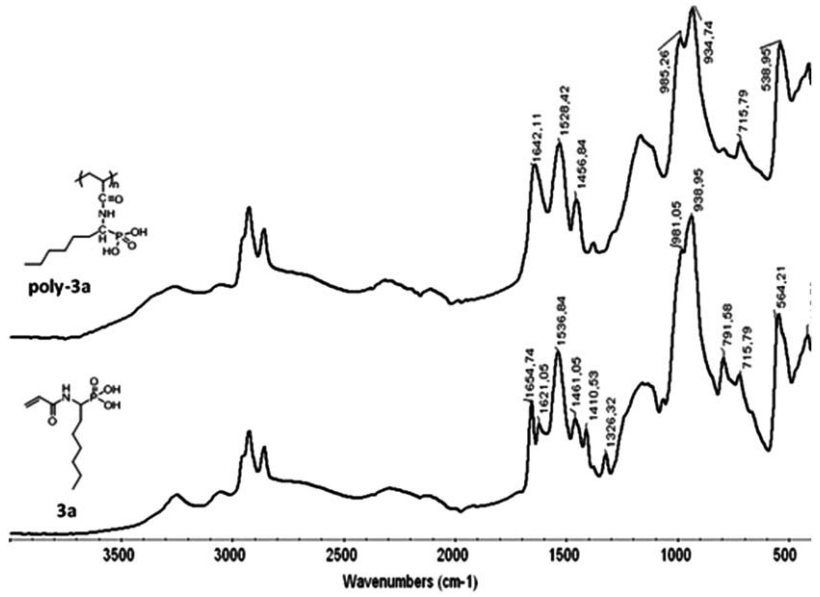

FIGURE 11 FTIR spectra of **3a** and poly-**3a**.

new C═O and NH peaks, indicating incorporation of **1a** in the copolymer.

CONCLUSIONS

Three novel phosphonic acid-containing (meth)acrylamides were synthesized and evaluated for possible applications in dental adhesives. The pH values of the monomers were found to be in the range of mild self-etching adhesives and shown to be controlled by changing the substituent (alkyl or aryl) at the α-carbon to the nitrogen. Monomers are hydrolytically stable, showing promise of good shelf life and bonding reliability. Thermal solution polymerizations of the synthesized polymers gave good yields. Photopolymerization results indicated that all monomers were found to be homo- and copolymerizable efficiently with HEMA or HEMA-GDMA mixtures. Even though monomers **1a**, **2a**, and **4a** in water have lower maximum rates of polymerizations than HEMA in water, their mixtures with HEMA gave values higher than both HEMA in water and monomers in water. As the flexibility of the monomer or mobility of the polymerizing system increases both the conversion and polymerization rate increases. These monomers were found to strongly decalcify HAP and result in the formation of DCPD instead of hydrolytically stable monomer Ca salts. Dentin SBS test showed the effect of the acidic monomer structure on the adhesion performance. In summary, our investigations indicate that these three phosphonic acid-containing (meth)acrylamides constitute a new class of monomers for potential use in dental adhesives.

ACKNOWLEDGMENTS

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