SYNTHESIS AND POLYMERIZATIONS OF (BIS)PHOSPHONATED-(BIS)METHACRYLAMIDES FOR DENTAL APPLICATIONS

by

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SYNTHESIS AND POLYMERIZATIONS OF (BIS)PHOSPHONATED-(BIS)METHACRYLAMIDES FOR DENTAL APPLICATIONS

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To my family

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ABSTRACT

SYNTHESIS AND POLYMERIZATIONS OF (BIS)PHOSPHONATED-(BIS)METHACRYLAMIDES FOR DENTAL APPLICATIONS

In the first part of this work, novel phosphonate and phosphonic acid-containing bis(methacrylamide)s (1 and 2) were synthesized by amidation of 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride with diethyl 2-aminoethylphosphonate and diethyl 1-aminomethylphosphonate. The phosphonic acid-containing monomers (1a and 2a) were synthesized by hydrolysis of 1 and 2 with trimethylsilyl bromide (TMSBr). Monomers 1 and 2 were found to have high reactivities in photo- and thermal polymerizations. In the second part of this work, two new dental monomers, one a bisphosphonate- the other a bisphosphonic acid-containing bis(methacrylamide), were synthesized. The bisphosphonate monomer (3) was synthesized by amidation of 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride with tetraethyl aminomethyl-bis(phosphonate) and converted to the bisphosphonic acid monomer (3a) by hydrolysis with TMSBr. Thermal polymerization of monomer 3 gave crosslinked polymers. Although monomers 1a, 2a and 3a showed very low polymerization rate and conversion, because of their good performance in terms of solubility, hydrolytic stability, hydroxyapatite (HAP) interaction, acidity and copolymerizability with HEMA, they show potential to be used in self-etching dental adhesives. Finally, two more new dental monomers, one a bisphosphonate- and a bisphosphonic acid containing methacrylamide, were synthesized. The bisphosphonate-containing monomer (4) was obtained by amidation of methacryloyl chloride with tetraethyl aminomethyl-bis(phosphonate) in the presence of triethylamine. Thermal homopolymerization of this monomer gave a soluble polymer. Photopolymerization rate of monomer 4 was found to be lower than HEMA. Hydrolysis of monomer 4 with TMSBr gave monomer 4a as a white solid soluble in water and ethanol. Although monomer 4a showed very low photopolymerization rate and conversion, addition of this monomer to HEMA increased the rate of HEMA. As a result, monomer 4a was also found to be a suitable monomer for self-etching dental adhesives.

ÖZET

DİŞ UYGULAMALARI İÇİN (BİS)FOSFONATLI-(BİS)METAKRİLATLARIN SENTEZLERİ VE POLİMERİZASYONLARI

Bu çalışmanın ilk bölümünde, yeni fosfonat ve fosfonik asit içeren bis(metakrilat)lar (1 ve 2) 2-(2-klorokarbonil-aliloksimetil)-akriloilklorürün dietil 2-aminoetilfosfonat ve dietil 1-aminometilfosfonat ile amidasyon reaksiyonundan sentezlenmişlerdir. Fosfonik asit içeren monomerler (1a ve 2a) ise monomer 1 ve 2'nin trimetilsilil bromür (TMSBr) ile hidrolizi sonucunda elde edilmişlerdir. Monomer 1 ve 2'nin termal ve fotopolimerizasyonda yüksek hızlar gösterdiği görülmüştür. Çalışmanın ikinci bölümünde, iki yeni diş monomeri, biri bisfosfonat diğeri bisfosfonik asit içeren bis(metakrilamit), sentezlenmiştir. Bisfosfonat grubu içeren monomer (3) 2-(2-klorokarbonil-aliloksimetil)-akriloilklorürün tetraetil aminometil-bis(fosfonat) ile amidasyonundan sentezlenmiştir ve daha sonra bu monomer TMSBr ile hidroliz edilerek bisfosfonik asit monomer (3a) elde edilmiştir. Monomer 3'ün termal homopolimerizasyonu çapraz bağlı polimerler vermiştir. Monomer 1a, 2a ve 3a çok düşük polimerizasyon ve dönüşüm göstermelerine rağmen, bu monomerlerin çözünürlük, hidrolize dayanıklılık, HAP ile etkileşim, asidite ve HEMA ile kopolimerleşme yetenekleri, bu monomerlerin 'self-etching' adeziv sistemlerde kullanılma potansiyelini göstermiştir. Son olarak, iki yeni diş monomeri, biri bisfosfonat diğeri bisfosfonik asit içeren metakrilamit, sentezlenmiştir. Bisfosfonat içeren monomer (4), trietilamin varlığında metakriloil klorürün tetraetil aminometil-bis(fosfonat) ile amidasyonu sonucunda elde edilmiştir. Bu monomerin termal kütle homopolimerizasyonu çözünebilen bir polimer vermiştir. Monomer 4'ün fotopolimerizasyon hızı HEMA'dan düşük bulunmuştur. Monomer 4'ün TMSBr ile hidroliziyle monomer 4a, suda ve etanolde çözünen beyaz bir katı elde edilmiştir. Monomer 4a düşük fotopolimerizasyon hızı ve dönüşümü göstermesine rağmen bu monomerin HEMA'ya eklenmesi HEMA'nın hızını arttırmıştır. Sonuç olarak, monomer 4a'nın da 'self-etching' adezivler için uygun bir monomer olduğu bulunmuştur.

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LIST OF ACRONYMS/ABBREVIATIONS

AAm	Acrylamide
AIBN	2,2'-Azobisisobutyronitrile
BAPO	Bis(2,4,6-trimethylbenzoyl)phenylphosphine oxide
Bis-GMA	2,2-Bis[4-(2-hydroxy-3-methacryloyloxy propyloxy) phenyl] propane
DABCO	1,4-Diazobicyclo [2.2.2] octane
DCC	1,3-Dicyclohexylcarbodiimid
DSC	Differential Scanning Calorimetry
FT-IR	Fourier Transform Infrared Spectroscopy
GDMA	Glycerol dimethacrylate
GPC	Gel Permeation Chromatography
HAP	Hydroxyapatite
HEMA	2-Hydroxyethyl methacrylate
Irgacure 651	2,2'-Dimethoxy-2-phenylacetophenone
NMR	Nuclear Magnetic Resonance Spectroscopy
Rp	Rate of polymerization
TBEED	2-(2-tert-Butoxycarbonyl-Allyloxymethyl)-Acrylic Acid tert-Butyl Ester
TBEED-Acid	2-(2-Carboxy-Allyloxymethyl)-Acrylic Acid
TBHMA	Tert-butyl-α-hydroxymethyl acrylate
TEA	Triethylamine
Tg	Glass transition temperature
TGA	Thermal Gravimetric Analysis
TMSBr	Trimethylsilyl bromide
V-50	2,2'-azo-bis(2-amidinopropane)dihydrochloride

1. INTRODUCTION

1.1. Adhesion in Dentistry

Filling composites and enamel-dentin adhesives which are based on mixtures of monofunctional and multifunctional monomers are important components in dentistry. The main problems of filling composites are their polymerization shrinkage, wear due to mechanical stresses, breakdown due to hydrolysis in the aqueous mouth environment and lack of adhesion to tooth tissue [1, 2]. To remedy the last problem, efforts have been made to include binding groups in filling composites [3-5]; but the main approach involves the use of dental adhesives to achieve a strong, durable bond between a filling composite and tooth tissue [6, 7]. Recently, "self-etching adhesives" with proper bond to enamel and dentin are introduced to the market as a solution of this problem [8-11].

1.1.1. Self-Etching Adhesives

Self-etching adhesive systems have been utilized in dentistry to enable a strong and stable bond between a dental filling material and the tooth substance for more than ten years [12]. Commercial self-etching enamel-dentin adhesives are composed of a mixture of self-etching adhesive monomers, crosslinkers, additional monofunctional co-monomers and additives as shown in Figure 1.1 [6, 12-15].

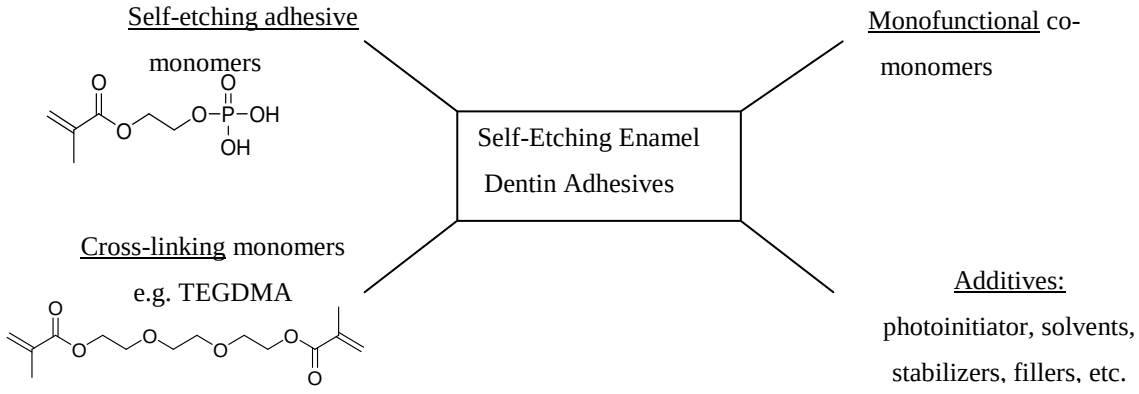


Figure 1.1. Ingredients of self-etching enamel-dentin adhesives.

1.1.2. Adhesive Monomers

The adhesive monomers used in this system should have some properties such as ability to etch the enamel and dentin, ability to form bonds with tooth material, high rate of homo and copolymerization, high mechanical properties, low volume shrinkage, low oral and cytotoxicity and solubility in ethanol, water and adhesive composition.

The general structure of self-etching dental adhesive monomers is shown in Figure 1.2. They contain a polymerizable group, which can react both with other monomers in the adhesive and filling composites by copolymerization, an adhesive group, such as strong acidic groups, which provides the desired adhesion to tooth substance, and a spacer group R [16, 17].

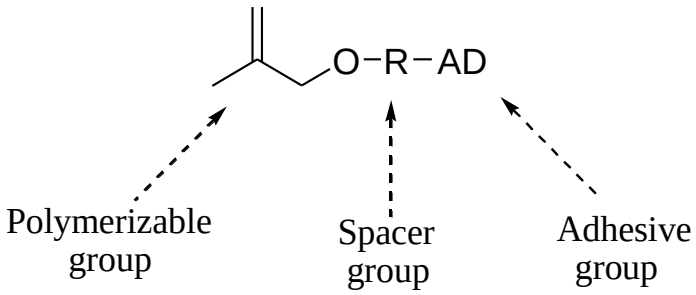


Figure 1.2. General structure of self-etching adhesives.

Free radically polymerizable, methacrylate and methacrylamide functionalized monomers are generally preferred (Figure 1.3).

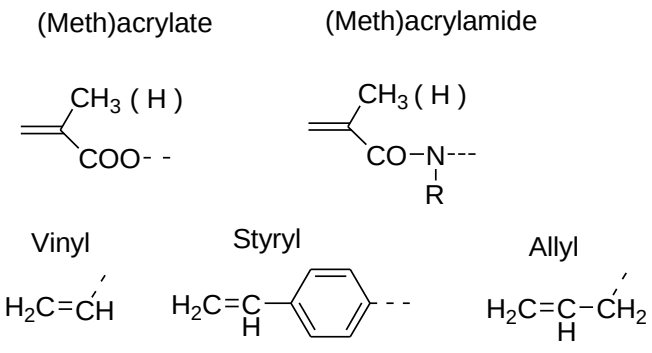


Figure 1.3. Examples of polymerizable groups.

Spacer groups may change the adhesive monomer properties such as solubility, flexibility, volatility and wetting properties. Some common spacer groups are shown in Figure 1.4.

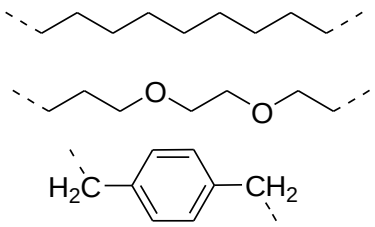


Figure 1.4. Examples of spacer groups (R) in adhesive monomers.

Adhesive groups include mono- or dihydrogenphosphate, phosphonic or carboxylic acid groups (Figure 1.5) [18-28]. These acidic monomers remove the smear layer, demineralize the dentin and enamel, and diffuse into collagen fibrils to form a hybrid layer, providing the desired adhesion. Polymerizable phosphoric and phosphonic acid containing monomers form stronger bond compared to carboxylic acid containing monomers.

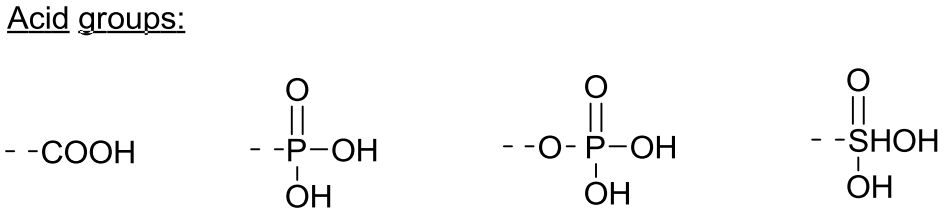


Figure 1.5. Adhesive groups enable chemical adhesion to enamel and dentin.

Some examples of commercial adhesive monomers are 10-methacryloyloxydecyl dihydrogen phosphate (MDP), 4-methacryloyloxyethyl trimellitic acid (4-MET), methacryloyloxyethyl phenyl hydrogen phosphate (MEP-P) and methacryloyloxyethyl dihydrogen phosphate (MEP, HEMA-phosphate), dipentaerythrytolpentaacryloyl dihydrogen phosphate (PENTA-P) (Figure 1.6) [7].

There are also more examples of adhesive monomers which include phosphonic acid groups in the literature. For example, Figure 1.7 shows the structures of some adhesive monomers [18, 24, 29].

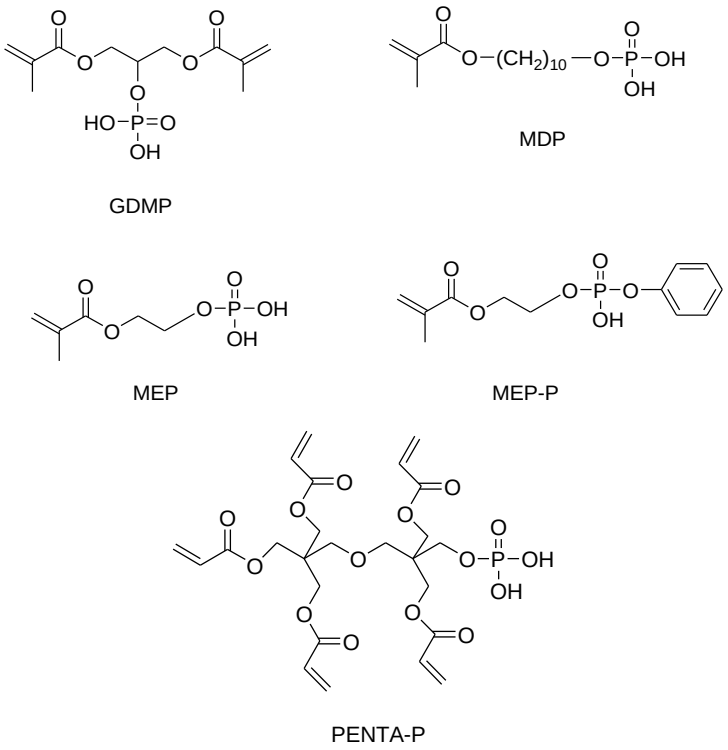


Figure 1.6. Examples of commercial polymerizable phosphonic acids in dentin adhesives.

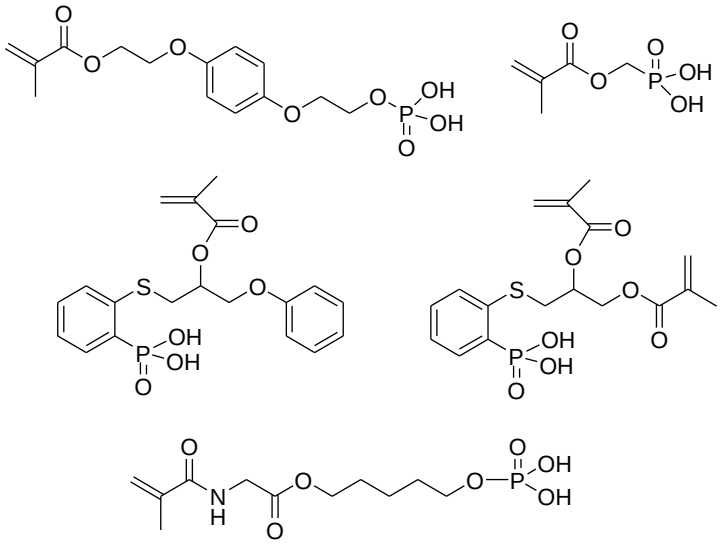


Figure 1.7. Examples of polymerizable phosphonic acids in dentin adhesives.

Some structures of adhesive monomers synthesized by our group are shown as in the following Figure 1.8 [20, 25, 30].

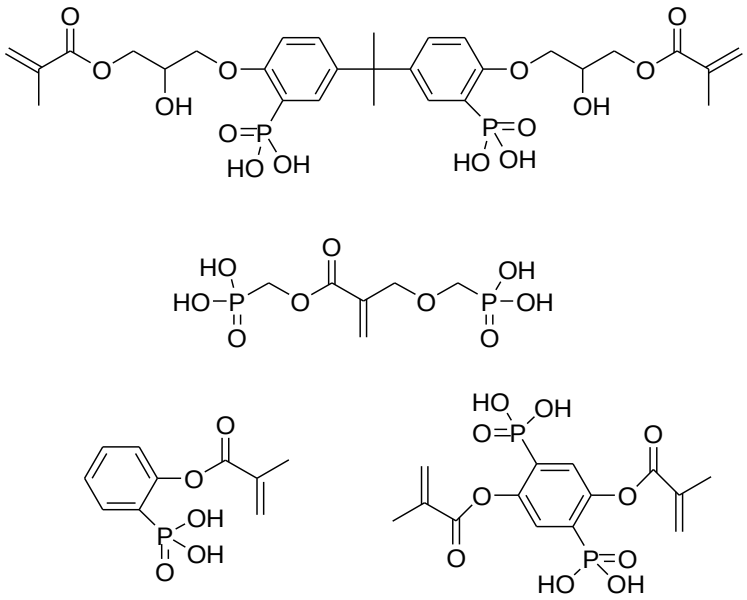


Figure 1.8. Examples of polymerizable acidic phosphates previously synthesized by our group.

1.1.1.1. New Trend: Bisphosphonate Monomers. 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 [31]. 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 (Figure 1.9) [32]. Bisphosphonates have increased enzymatic stability due to hydrolysis-resistant P-C-P group instead of labile P-O-P group in pyrophosphate [32].

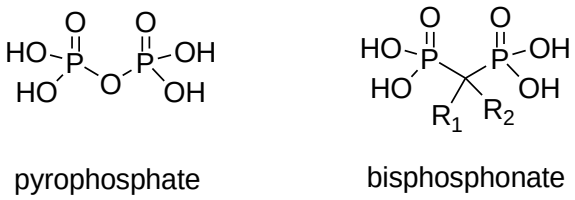


Figure 1.9. Naturally existing pyrophosphate and its synthetic analogues, bisphosphonates.

Moreover, it was also reported that bisphosphonates can inhibit enzymes (metalloproteinases) which degrade the collagen network [33-35]. More recently bisphosphonate-containing monomers were investigated for self-etching dental adhesive applications [36-38]. They facilitate adhesion of dental restoratives and orthodontic appliances to dental tissue. Some examples of self-etching dental adhesive monomers containing bisphosphonates are shown in Figure 1.10.

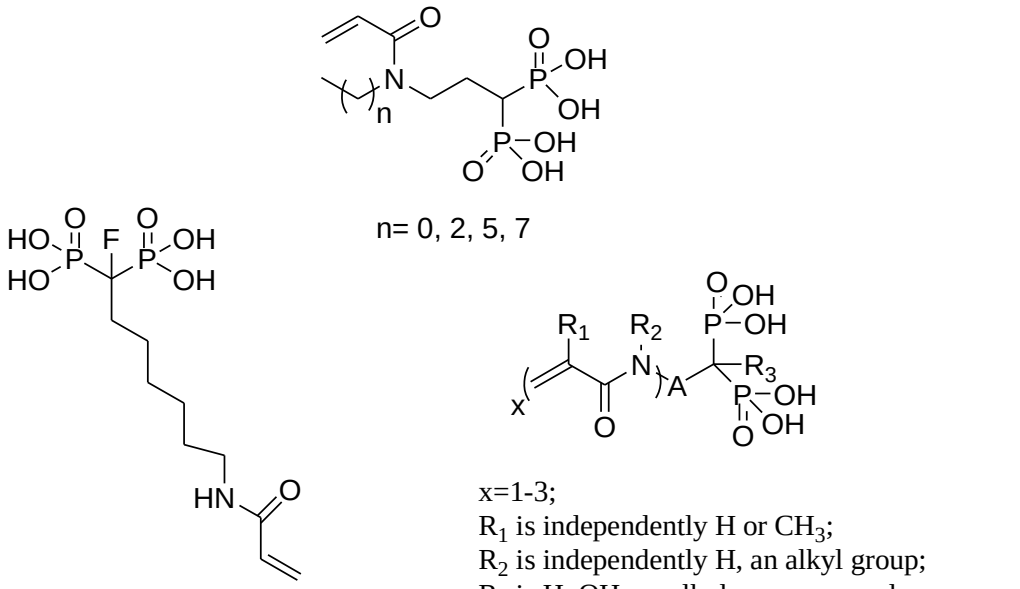


Figure 1.10. Self-etching dental adhesive monomers containing bisphosphonates.

1.1.1.2. Problems of 'Self-Etching' Dental Adhesives. Most of the self-etching adhesive systems are based on acidic monomers in water-HEMA mixtures and have a pH value of 1-2.5. Since water (30-40%) is an important ingredient of these systems, the main problem of 'self-etching' adhesive systems is hydrolysis of the ester groups in (meth)acrylates which these adhesives are based on (Figure 1.11). The hydrolysis of the adhesive monomers changes the chemical composition, the properties of the adhesives and results in inadequate shelf life. Also the hydrolysis reaction may occur in the mouth and lead to breakdown of the adhesive which limits lifetime of filling materials.

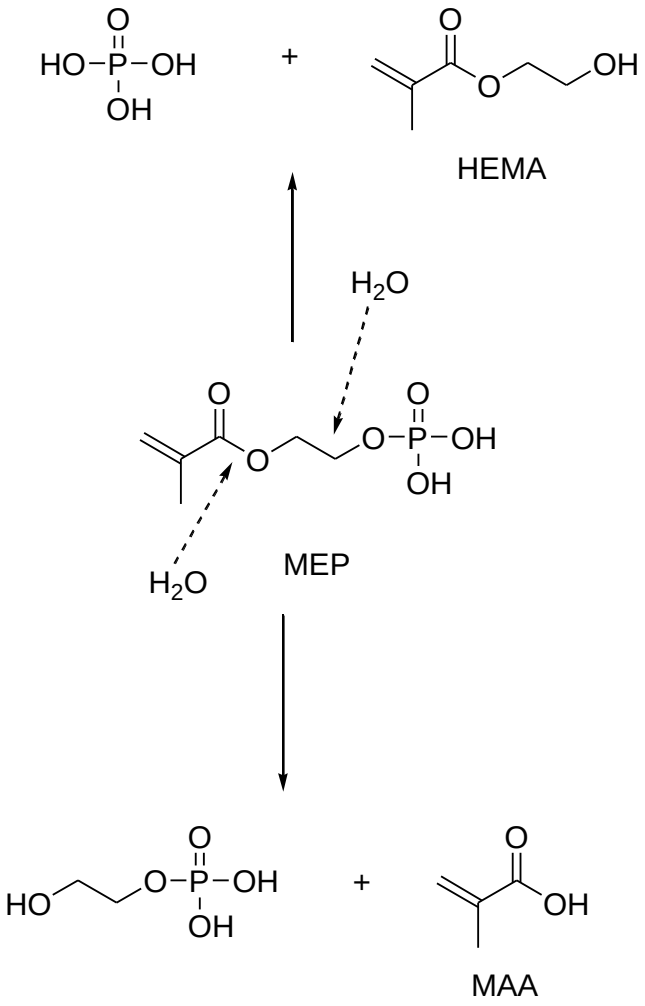


Figure 1.11. Hydrolysis of MEP in the presence of water.

Therefore, in recent years, self-etching adhesive monomers containing hydrolytically stable ether and amide linkages were synthesized to overcome the problem of hydrolysis [16, 29, 30, 39-49]. Ethyl 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylate (EAEPA), 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylic acid (CAEPA), 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylonitrile (NAEPA), 2,4,6-trimethylphenyl 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylate (MAEPA), glycerol dimethacrylamide phosphoric acid(GDMAP) and 4-methacrylamido-4-methylpentylphosphonic acid, 1-(2,5-dimethyl-1,5-hexadienyl)phosphonic acid, 2-(methacrylamidoethyl)phosphonic acid, bis(3-methacyloylamidopropyl)diethylphosphonic acid, N,N'-bis(2-phosphonoethyl)-N,N'-diacryloyl-4,7,10-trioxatridecane-1,13-diamine are hydrolytically stable in aqueous solutions (Figure 1.12) [6, 29, 43, 45].

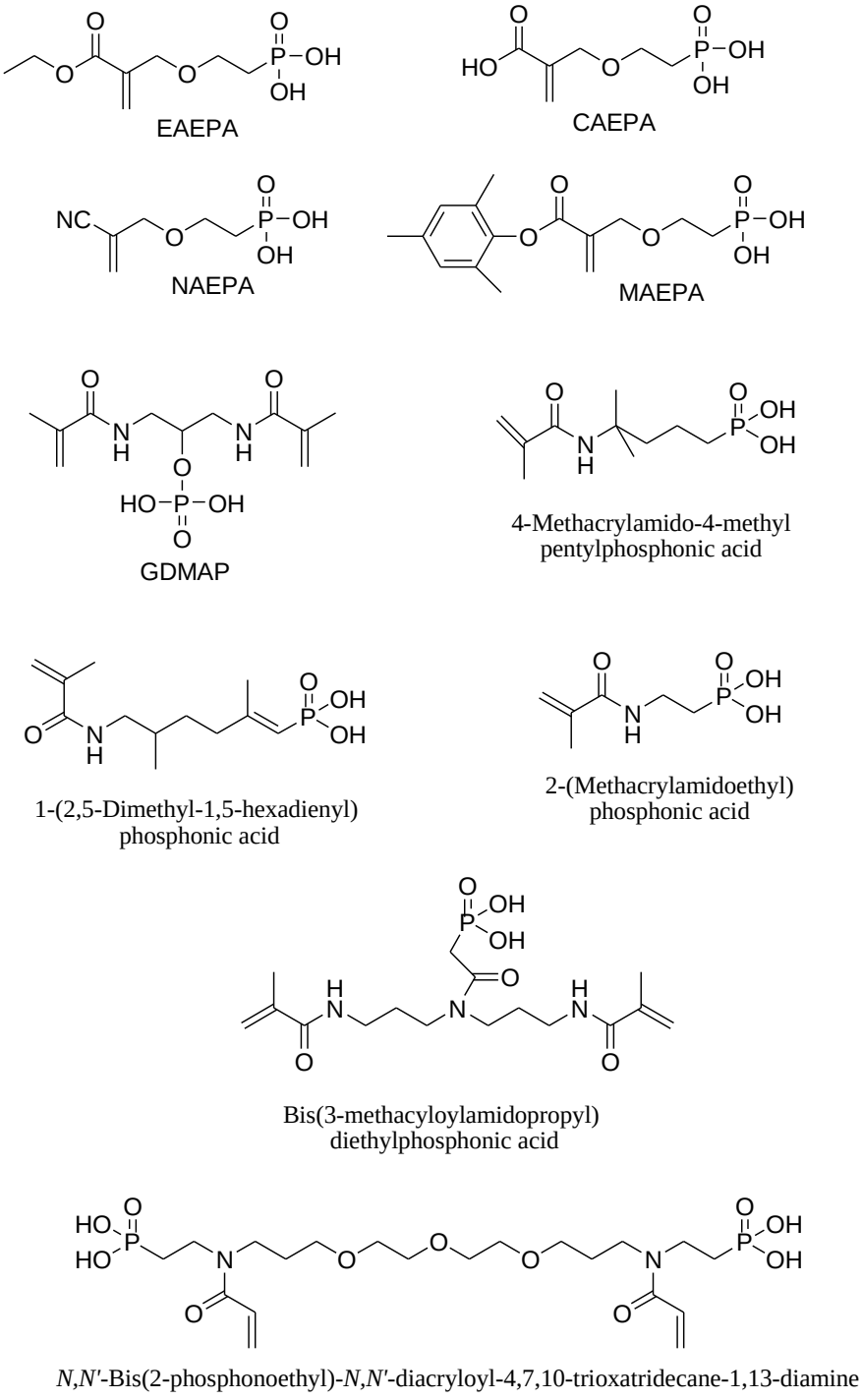


Figure 1.12. Examples of hydrolytically stable monomers.

Our group previously synthesized hydrolytically stable self-etching adhesive monomers shown in Figure 1.13 [30, 48, 49]. These monomers contain good adhesive properties due to their acid groups and high resistance to hydrolysis because of their durable linkages.

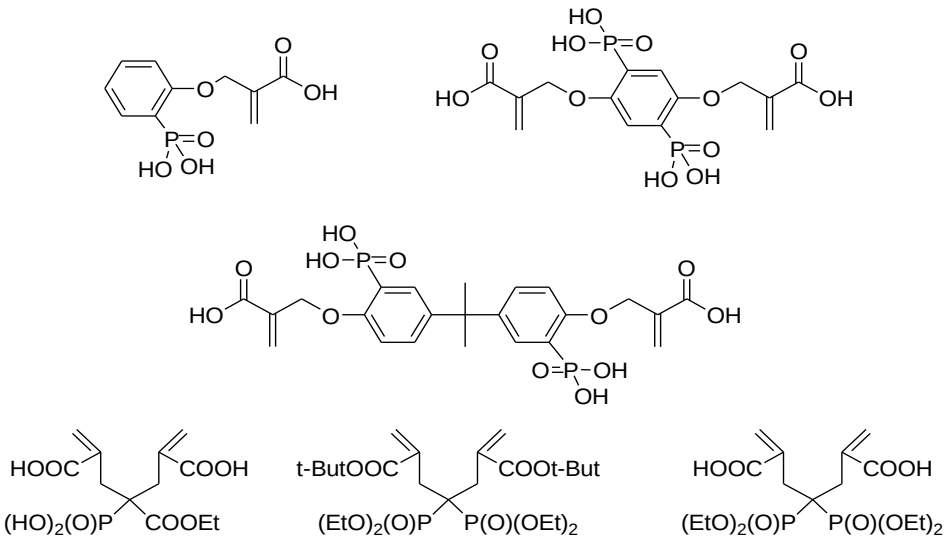


Figure 1.13. The structures of hydrolytically stable adhesive monomers previously synthesized by our group.

Xu *et al*. studied the synthesis of novel hydrolytically stable dental monomers from reactions of amines containing phosphonic acids with methacryloyl chloride Figure 1.14 [3]. The structure of the monomer was characterized by electrospray mass spectrometry (ESMS), Fourier transform infrared, and NMR. The hydrolytic stability of synthesized monomer were compared with the commercial monomer, 2-methacryloyloxyethyl phosphoric acid MEP. Hydrolytic stability were studied with flow injection (FI)/ESMS, ^{1}H-NMR, and ^{31}P-NMR analysis. After storage at 60 ^{o}C for two months, ^{1}H-NMR and ^{31}P-NMR chemical shifts of the monomers 2-methacrylamidoethylphosphonic acid showed little change but those of MEP showed a significant change. FI/ESMS study also indicated nearly complete decomposition of MEP, but synthesized monomer did not decompose, stayed intact.

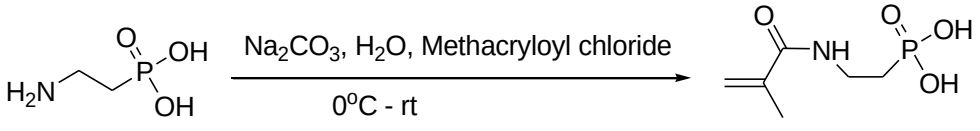


Figure 1.14. One-step reaction of 2-aminoethylphosphonic acid with methacryloyl chloride.

Catel *et al*. also reported synthesis of new acrylamides containing phosphonic acids from the acylation of aminophosphonates by acryloyl chloride in the presence of triethylamine (Figure 1.15) [41]. Finally, phosphonates were hydrolysed by TMSBr to obtain novel self-etching adhesives. This group studied the photopolymerization behavior of the synthesized monomers with *N,N'*-diethyl-1,3-bis(acrylamido)propane by DSC. They prepared new self-etch primers with these acrylamide monomers and measured their dentin shear bond strenght, therefore they found that primers based on (N-methylacrylamido)alkylphosphonic acids provided a strong bond between the tooth substance and a dental composite. They also concluded that the monomer with the longest spacer group results in the highest shear bond strength.

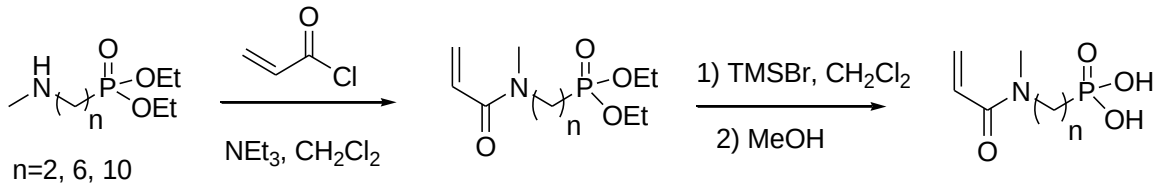


Figure 1.15. Synthesis of acrylamides containing phosphonic acids.

Bala *et al*. studied the synthesis of acrylamide-containing bisphosphonic acid, [1-fluoro-1-phosphono-7-(prop-2-enamido)heptyl]phosphonic acid, for generation of strongly acidic bisphosphonate monomer (Figure 1.16) [36].

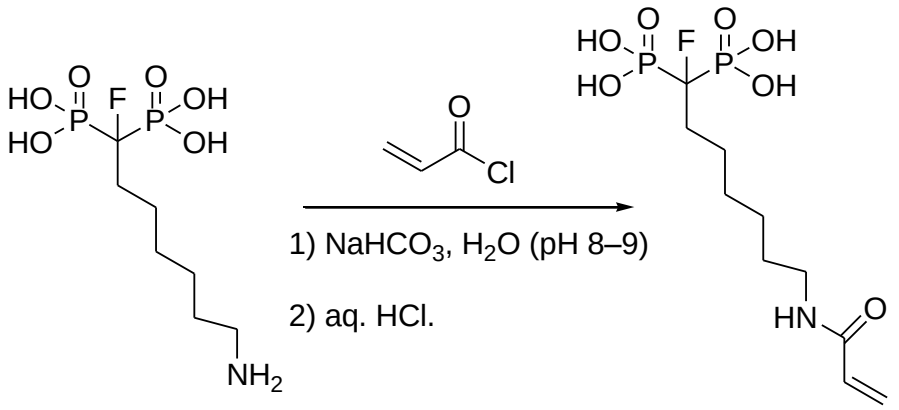


Figure 1.16. Synthesis of [1-fluoro-1-phosphono-7-(prop-2-enamido)heptyl] phosphonic acid.

Catel *et al*. also studied novel self-etching dental adhesive monomers containing bisphosphonates and the reaction was shown in Figure 1.17 [50]. After acylation of aminobisphosphonates, self-etching adhesives were obtained by hydrolysis of ethyl groups with TMSBr. The copolymerization of these monomers with N,N'-diethyl-1,3-bis(acrylamido)propane (DEBAAP) was studied with DSC. They found that the mixtures had a higher reactivity than DEBAAP. They prepared new self-etch dental primers, with these acrylamide monomers and the measurement of their dentin shear bond strength resulted that the mixtures containing bisphosphonic acid provided a strong bond between the tooth substance and a dental composite.

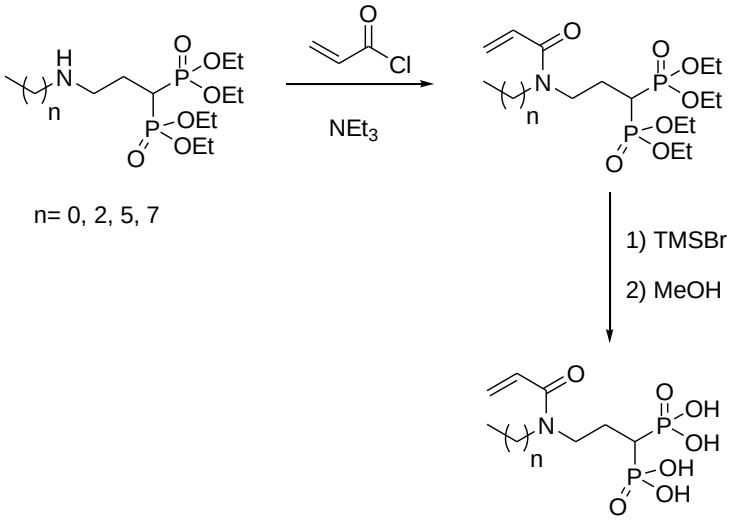


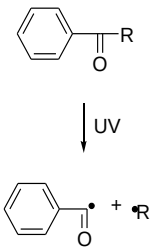
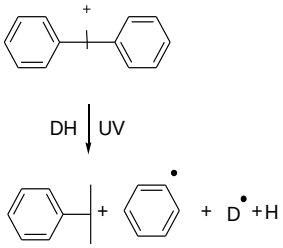
Figure 1.17. Synthesis of bisphosphonate-containing acrylamides.

1.2. Photopolymerization

Photopolymerization, UV radiation curing is a light-induced polymerization of multifunctional monomers or oligomers. This polymerization is very efficient technique in dental applications since it enables a fast, solvent free process at room temperature, a well-accepted technology in dental applications. There are three main components of this system: a photoinitiator which absorbs the incident light and generates radicals or ions, functionalized monomer, a reactive diluent to adjust viscosity [51].

Types of photopolymerization are radical type and cationic type mechanism. In radical type polymerization, initiators such as aromatic ketones are used because they produce free radical and initiate the polymerization of vinyl monomers to obtain a crosslinked polymer. In the other mechanism, cationic type polymerization, a protonic acid is generated by photolysis of triarylsulfonium (TAS) or diaryliodonium salts and this initiates the polymerization of epoxides or viny ethers [52]. Table 1.1 shows the radical and cationic types of photopolymerization.

Table 1.1. Radical and cationic types of photopolymerization.

Mechanism	RADICAL	CATIONIC
Photoinitiator	Aromatic ketone 	Aryliodonium salt 

In dental studies, radical type mechanism is mostly preferred. Two types of mechanism are available to produce free-radical intermediates under incident light exposure [53]. These are called as type-I and type-II. Photofragmentation process produces radical pairs via a highly efficient L-cleavage (type-I) and H-abstraction process (type-II). Examples of type-I and type-II are shown in Figures 1.18 and 1.19.

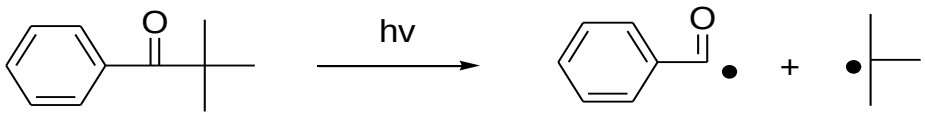


Figure 1.18. Example to type-I initiator.

Finally, commonly used photoinitiators in dentistry and other application are shown in Figure 1.20 [52].

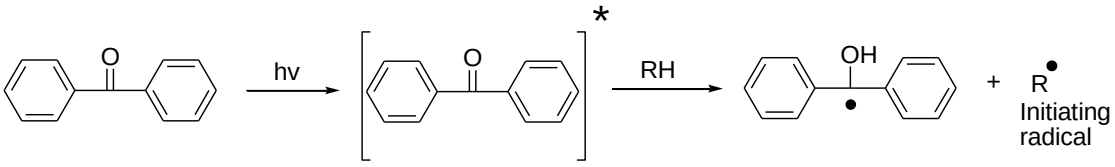


Figure 1.19. Example to type-II initiator.

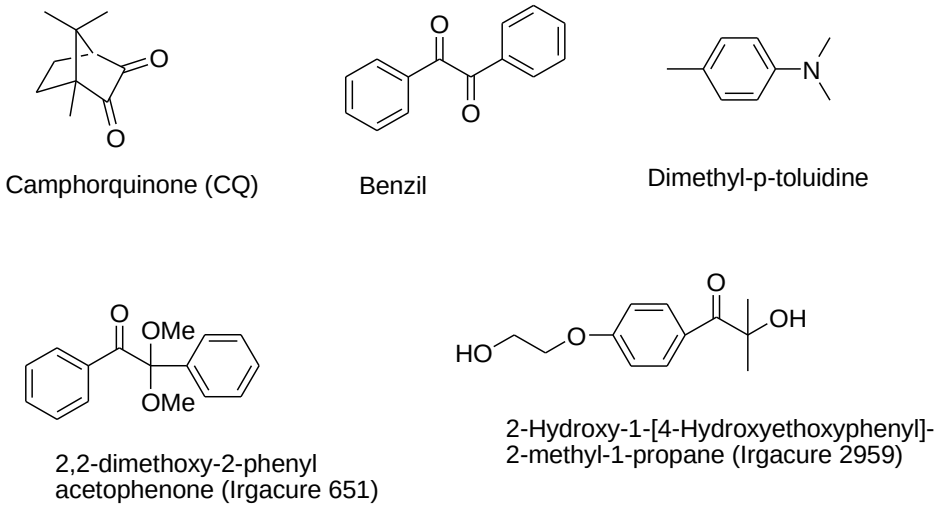


Figure 1.20. Commonly used photoinitiators.

2. OBJECTIVES

The aim of this project is to synthesize new hydrolytically stable reactive (bis)phosphonates and (bis)phosphonic acids-containing monomers and study their polymerization behavior.

The (bis)phosphonate- and (bis)phosphonic acid-containing monomers have potential in dental materials as reactive diluents or crosslinkers and dental adhesives, respectively.

These monomers are derivatives of alkyl α-hydroxymethyl acrylates (RHMA) and are expected to have improved shelf life and bonding reliability, as they will not hydrolyze in aqueous acidic conditions due to the presence of only amide linkage in their structures. Besides hydrolytic stability, the synthesized monomers are expected to have ability to form bonds with the tooth material, high rate of homo and copolymerization, low polymerization shrinkage and high mechanical properties.

3. EXPERIMENTAL

3.1. Materials and Apparatus

3.1.2. Materials

Tetraethyl aminomethyl-bis(phosphonate), diethly 2-aminoethylphosphonate and diethyl 1-aminomethylphosphonate, 2-(2-carboxy-allyloxymethyl)-acrylic acid and 2-(2-chlorocarbonyl-allyloxymethyl)-acryloylchloride were prepared according to literature procedures [54-58]. Triethyl amine (TEA), 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.

3.1.3. Apparatus

^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopy (Varian Gemini 400 MHz) and Fourier transform infrared (FT-IR) spectroscopy (T380) were used for monomer characterization. The photo-polymerizations were performed on a TA Instruments Q100 differential photocalorimeter (DPC). Thermogravimetric analysis was done with a TA Instrument Q50. Elemental analyses were obtained from Thermo Electron SpA FlashEA 1112 elemental analyser (CHNS separation column, PTFE; 2 m; 6 x5 mm). Combi Flash Companion Tledyne ISCO Flash Chromatography was used for purification of monomers. Gel permeation chromatography (Viscotek) was carried out with THF solvent using polystyrene standarts.

3.2. Synthesis of Novel (Bis)Phosphonated (Bis)Methacrylamides

3.2.1. Synthesis of Phosphonated-Bis(methacrylamide)s

3.2.1.1. Synthesis of 2-(2-tert-Butoxycarbonyl-Allyloxymethyl)-Acrylic Acid tert-Butyl Ester (TBEED) [59]. Tert-butyl acrylate (68.85 g, 0.54 mol), paraformaldehyde (16.15 g, 0.54 mol), DABCO (2.69 g, 2.9 wt%) and tert-butyl alcohol (4.31 g, 4.7 wt%) were added to a 250 ml three-necked round bottom flask. The mixture was stirred at 95 ºC for four days. 100 ml of CH_2Cl_2 was added and then mixture was washed three times with 50 ml of 3% HCl and with 50 ml of water. The organic layer was separated, dried with Na_2SO_4 and evaporated under reduced pressure to give crude product. It was purified by column chromotography on silica gel with 99:1 Hexane:MeOH solvent as a white solid in 28.5% yield.

^{1}H-NMR ($CDCl_3$): 1.5 (s, 18H, CH_3), 4.2 (s, 4H, CH_2-O), 5.8, 6.2 (s, 4H, CH_2=C) ppm.

^{13}C-NMR ($CDCl_3$): 28.37 (CH_3), 69.25 (CH_2-O), 81.00 [$(CH_3)_3C$], 124.47 (C=CH_2), 138.82 (C=CH_2), 164.97 (C=O) ppm.

FT-IR: 2978 (C-H), 1710 (C=O), 1638 (C=C), 1152 (C-O-C) cm^{-1}.

3.2.1.2. Synthesis of 2-(2-Carboxy-Allyloxymethyl)-Acrylic Acid (TBEED-acid). To TBEED (10.83 g, 36.3 mmol), CF_3COOH (12.12 g, 106.3 mmol) was added dropwise on ice, under nitrogen. After mixing at room temperature for 24 h, the precipitate formed was filtered and washed with diethyl ether. The white solid product was dried in vacuum. Yield was 94.2%.

^{1}H-NMR (DMSO): 4.17 (s, 4H, CH_2-O), 5.85, 6.18 (s, 4H, CH_2=C) ppm.

^{13}C-NMR (DMSO): 68.3 (CH_2-O), 124.8 (C=CH_2), 137.9 (C=CH_2), 166.7 (C=O) ppm.

FT-IR: 2880 (C-H), 1683 (C=O), 1628 (C=C), 1131 (C-O-C) cm^{-1}.

3.2.1.3. Synthesis of 2-(2-Chlorocarbonyl-Allyloxymethyl)-Acryloyl Chloride. TBEED-acid (0.2 g, 1.072 mmol) was purged with nitrogen for 15 minutes. Dry CH_2Cl_2 (1.28 ml) was added. Then the mixture of oxalyl chloride (0.74 g, 0.5 ml) and dry CH_2Cl_2 (1.88 ml) was added dropwise under ice bath and nitrogen. Ten drops of solution (1 ml of CH_2Cl_2 and 0.2 ml of dimethylformamide) was added and the reaction mixture was stirred for half an hour under ice bath and nitrogen. After half an hour, ice bath was removed and the reaction was stirred for another three and half an hour at room temperature. The solvent and extra oxalyl chloride were evaporated with nitrogen. The product was obtained as yellowish liquid in 100% yield.

^{1}H-NMR ($CDCl_3$): 4.3 (s, 4H, CH_2-O), 6.3, 6.7 (s, 4H, CH_2=C) ppm.

^{13}C-NMR ($CDCl_3$): 69.18 (CH_2-O), 134.42 (C=*C*H_2), 141.35 (*C*=CH_2), 167.23 (C=O) ppm.

FT-IR: 2874 (C-H), 1750 (C=O), 1637 (C=C), 1130 (C-O-C) cm^{-1}.

3.2.1.4. Synthesis of diethly 2-aminoethylphosphonate [55, 56]. Ammnonia (15 ml) was added dropwise to diethyl vinylphosphonate (1.64 g, 0.01 mol) under an ice bath. The reaction mixture was stirred for three days at room temperature. After three days, distilled water (30 ml) was added to the reaction mixture and it was extracted with $CHCl_3$ three times (3x15 ml). The organic layer was collected, dried with Na_2SO_4 and evaporated under reduced pressure to give crude product. The product was distilled under reduced pressure.

^{1}H-NMR ($CDCl_3$): 1.29 (t, 6H, CH_3), 1.85–1.93 (m, 2H, CH_2P), 2.92–3.01 (m, 2H, CH_2N), 4.01–4.13 (m, 4H, CH_2O)

^{31}P-NMR ($CDCl_3$): 30.8

3.2.1.5. Synthesis of diethyl 1-aminomethylphosphonate [56]. Diethyl phthalimidomethylphosphonate (4.869 g, 16.38 mmol), hydrazine hydrate (1.12 ml, 35.68 mmol) and ethanol (69.4 ml) was mixed into a 250 ml of round bottom flax. The mixture was stirred and refluxed at 76 ^{o}C for one hour. White precipitate was obtained in the

mixture. After ethanol was evaporated, $CHCl_3$ was added and filtered out. The organic solvent was evaporated and finally the crude product was distilled under reduced pressure. Pure product was obtained as a colorless liquid in 58% yield.

^{1}H-NMR ($CDCl_3$): 1.29 (t, 6H, CH_3), 2.96 (d, 2H, CH_2P), 4.02-4.19 (m, 4H, CH_2O).

^{31}P-NMR ($CDCl_3$): 28.0.

FT-IR: 3382, 3303 (N–H), 2981-2898 (C–H), 1229 (P=O), 1019 and 952 (P–O–Et) cm^{-1}.

3.2.1.6. Synthesis of monomer 1. To a solution of diethyl 1-aminomethylphosphonate (0.394 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 (2x8 mL), 2M cold HCl (2x12 mL), 2M cold NaOH (3x8 mL) and brine (1x8 mL). After drying the organic phase with anhydrous Na_2SO_4, the solvent was evaporated. The crude product (67% yield) was purified by reversed-phase flash chromatography on C18, eluting with H_2O:MeOH (40:60) to give monomer 1 as a light yellowish viscous liquid.

^{1}H-NMR ($CDCl_3$): 1.24 (t, 12H, CH_3), 3.69-3.73 (m, 4H, CH_2–P), 4.06 (m, 8H, O–CH_2), 4.19 (s, 4H, O–CH_2), 5.55, 6.02 (s, 4H, C=CH_2), 7.47 (bs, 2H, NH) ppm.

^{13}C-NMR ($CDCl_3$): 16.25 (CH_3), 35.34, 33.79 (CH_2–P), 62.39 (O–*C*H_2–CH_3), 69.89 (O–*C*H_2–C), 123.68 (C=*C*H_2), 138.79 (*C*=CH_2), 166.30 (C=O) ppm.

FT-IR: 3306 (N–H), 2983 (C–H), 1662 (C=O), 1619 (C=C), 1532 (NH), 1239 (P=O), 1022 and 952 (P–O–Et) cm^{-1}.

^{31}P-NMR ($CDCl_3$): 22.53 ppm.

ELEM. ANAL., Calcd. for $C_{18}H_{34}N_2P_2O_9$: C, 44.54%; H, 7.27%; N, 5.77%; P, 12.76%; O 29.66%. Found: C, 44.41%; H, 7.50%; N, 5.73%.

3.2.1.7. Synthesis of monomer 1a. TMSBr (0.452 g, 2.953 mmol) was added dropwise to a solution of monomer 1 (0.2384 g, 0.4921 mmol) in 2.12 mL dry dichloromethane in an ice bath and under N_2. Then the solution was refluxed for 4 hours at 40 °C. After evaporation of the solvent, 6.5 mL of methanol was added and the mixture was stirred at room temperature overnight. The methanol was evaporated and the residue was mixed with saturated $NaHCO_3$ solution (3 mL) and washed twice with CH_2Cl_2 (5 mL). The aqueous phase was set to pH=1 with concentrated HCl and treated with saturated NaCl solution (3 mL) and extracted two times with THF (5 mL). The organic phase was dried over Na_2SO_4, concentrated and dried under vacuum. The crude product (94% yield) was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer 1a as a clear, colorless oil in 30% yield.

^{1}H-NMR (D_2O): 3.41, 3.44 (d, 4H, CH_2–P), 4.08 (s, 4H, O–CH_2), 5.54, 5.62, 5.64, 5.77 (s, 4H, C=CH_2) ppm.

^{13}C-NMR (MeOD): 35.22, 36.82 (CH_2-P), 70.05 (CH_2-O), 122.77 (C=*C*H_2), 139.72 (*C*=CH_2), 168.14 (C=O) ppm.

FT-IR: 3273 (N–H), 2921 (C–H), 1657 (C=O), 1608 (C=C), 1536 (NH), 1160 (P=O), 938 and 992 (P–O) cm^{-1}.

^{31}P-NMR (D_2O): 17.80 ppm.

3.2.1.8. Synthesis of monomer 2. To a solution of diethyl 2-aminoethylphosphonate (0.428 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 (2x8 mL), 2M cold HCl (2x12 mL), 2M cold NaOH (3x8 mL) and brine (1x8 mL). After drying the organic phase with anhydrous

Na_2SO_4, the solvent was evaporated. The crude product (41% yield) was purified by reversed-phase flash chromatography on C18, eluting with H_2O:MeOH (40:60) to give monomer 2 as a light yellowish viscous liquid.

^{1}H-NMR ($CDCl_3$): 1.27 (t, 12H, CH_3), 1.98 (m, 4H, CH_2–P), 2.28 (bs, 2H, NH), 3.52 (m, 4H, NH-CH_2), 4.04 (m, 8H, O–CH_2), 4.17 (s, 4H, O–CH_2–C), 5.52, 6.02 (s, 4H, C=CH_2) ppm.

^{13}C-NMR ($CDCl_3$): 16.65 (CH_3), 24.61, 26.08 (CH_2–P), 33.66 (NH–CH_2), 62.03 (O–*C*H_2–CH_3), 70.35 (O–*C*H_2–C), 124.42 (C=*C*H_2), 139.40 (*C*=CH_2), 166.49 (C=O) ppm.

FT-IR: 3305 (N–H), 2982 (C–H), 1663 (C=O), 1619 (C=C), 1532 (NH), 1244 (P=O), 1022 and 952 (P–O–Et) cm^{-1}.

^{31}P-NMR ($CDCl_3$): 29.11 ppm.

ELEM. ANAL., Calcd. for $C_{20}H_{38}N_2P_2O_9$: C, 46.69%; H, 7.84%; N, 5.44%; P, 12.04%; O 27.99%. Found: C, 46.62%; H, 8.13%; N, 5.37%.

3.2.1.9. Synthesis of monomer 2a. TMSBr (0.452 g, 2.953 mmol) was added dropwise to a solution of monomer 2 (0.2522 g, 0.4921 mmol) in 2.12 mL dry dichloromethane in an ice bath and under N_2. Then the solution was refluxed for 4 hours at 40 °C. After evaporation of the solvent, 6.5 mL of methanol was added and the mixture was stirred at room temperature overnight. The methanol was evaporated and the residue was mixed with saturated $NaHCO_3$ solution (3 mL) and washed twice with CH_2Cl_2 (5 mL). The aqueous phase was set to pH=1 with concentrated HCl and treated with saturated NaCl solution (3 mL) and extracted two times with THF (5 mL). The crude product (91% yield) was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer 2a as a clear, colorless oil in 25-30% yield.

^{1}H-NMR (D_2O): 1.77 (m, 4H, CH_2–P), 3.30 (m, 4H, NH-CH_2), 4.04 (s, 4H, O–CH_2–C), 5.50, 5.58, 5.59, 5.74 (s, 4H, C=CH_2) ppm.

^{13}C-NMR (MeOH): 25.63, 27.23 (CH_2-P), 71.33 (CH_2-O), 123.73 (C=*C*H_2), 140.68 (*C*=CH_2), 169.10 (C=O) ppm.

FT-IR: 3253 (N–H), 2976 (C–H), 1649 (C=O), 1606 (C=C), 1545 (NH), 1019 (P=O), 930 and 990 (P–O) cm^{-1}.

^{31}P-NMR (D_2O): 24.92 ppm.

3.2.2. Synthesis of Bisphosphonated-Bis(methacrylamide)s

3.2.2.1. Synthesis of Tetraethyl (*N*,*N*-Dibenzyl)aminomethyl-bis(phosphonate) [54]. Triethyl orthoformate (10.6 g, 71 mmol), diethyl phosphite (25.6 g, 186 mmol), and dibenzylamine (11.8 g, 59.9 mmol) were mixed in a round-bottom flask. The mixture was stirred and refluxed for 5 hours at 150 ^{o}C at oil bath under nitrogen. After 5 hours, the temperature was increased to 160 ^{o}C and the cooler was removed to ged rid of ethanol. The reaction was stirred for 24 hours under nitrogen. $CHCl_3$ (300 mL) was added to the solution and it was washed with 3x60 mL of 5% aqueous NaOH and 2x75 mL of brine. After drying the organic phase with Na_2SO_4, the solvent was evaporated. The crude oil product was purified by column chromatography on silica gel with hexane:EtOH 25:75. Pure product was a viscous, colorless oil in 43% yield.

^{1}H-NMR ($CDCl_3$): 1.32 (td, 12H, CH_3), 3.55 (t, 1H, P-CH-P), 4.07 (m, 4H, N-CH_2-Ph), 4.15 (m, 8H, OCH_2), 7.20-7.45 (m, 10H, Ar-H).

^{31}P-NMR ($CDCl_3$): 20.7.

FT-IR: 3088-3031 (Ar-H), 2981-2901 (C-H), 1246 (P=O), 1018 and 958 (P–O–Et) cm^{-1}.

3.2.2.2. Synthesis of Tetraethyl Aminomethyl-bis(phosphonate) [54]. 10% Pd/C (0.8 g) was kept under nitrogen for ten minutes. Then a solution of tetraethyl (*N*,*N* dibenzyl)aminomethyl-bis(phosphonate) (4.0 g, 8.3 mmol) in dry EtOH (150 mL) was added. Nitrogen was removed and the reaction mixture was refluxed at 85 ^{o}C under

hydrogen atmosphere for 24 hours. After filtration and evaporation of the solvent, the product was obtained as a colorless oil. Yield was 96%.

^{1}H-NMR ($CDCl_3$): 1.36 (t, 12H, CH_3), 3.43 (t, 1H, P-CH-P), 4.23 (m, 8H, OCH_2).

^{31}P-NMR ($CDCl_3$): 20.8.

FT-IR: 3382, 3307 (N–H), 2982-2904 (C–H), 1229 (P=O), 1020 and 954 (P–O–Et) cm^{-1}.

3.2.2.3. Synthesis of monomer 3. 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 (3x8 mL), 2M cold HCl (3x12 mL), 2M cold NaOH (3x8 mL) and brine (1x8 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 3 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.

FT-IR: 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%.

3.2.2.4. Synthesis of monomer 3a. TMSBr (0.904 g, 5.906 mmol) was added dropwise to a solution of monomer 3 (0.372 g, 0.4921 mmol) in 2.12 mL dry dichloromethane in an ice bath and under N_2. Then the solution was refluxed for 4 hours at 40 °C. After evaporation of the solvent, 6.5 mL of methanol was added and the mixture was stirred at room temperature overnight. The methanol was evaporated. The crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer 3a 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.

FT-IR: 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}.

3.2.3. Synthesis of Bisphosphonated-Methacrylamides

3.2.3.1. Synthesis of monomer 4. A solution of methacryloyl chloride (0.16 mL, 1.65 mmol) diluted in anhydrous dichloromethane (1.63 mL) was added dropwise, under N_2, to a mixture 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) in an ice bath. Then the mixture was stirred at room temperature for two hours. Finally the reaction was stopped with addition of distilled water (1.63 mL). The organic layer was extracted with 1x5 ml distilled H_2O, 1x5 ml 2M HCl, 1x5 ml saturated $NaHCO_3$ and 1x5 ml distilled H_2O and dried over Na_2SO_4. After removal of solvent, the crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O:MeOH (50:50) to give monomer 4 as a white solid with a melting point of 33-34 ^{o}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=CH_2), 139.21 (C=CH_2), 167.42 (C=O) ppm.

FT-IR: 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}.

3.2.3.2. Synhtesis of monomer 4a. TMSBr (0.742 g, 4.848 mmol) was added dropwise to a solution of monomer 4 (0.3 g, 0.808 mmol) in 3.5 mL dry dichloromethane in an ice bath and under N_2. Then the solution was refluxed for 2 hours at 40 ^{o}C. After evaporation of the solvent, 11 mL of methanol was added and the mixture was stirred at room temperature overnight. The methanol was evaporated. The crude product was purified by reversed-phase flash chromatography on C18, eluting with H_2O to give monomer 4a 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=CH_2), 138.54 (C=CH_2), 170.85 (C=O) ppm.

FT-IR: 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}.

3.3. Photopolymerizations

3.3.1. Photopolymerization Procedure

The photopolymerizations were carried out using a DSC equipped with a mercury arc lamp. The photoinitiator which was dissolved in CH_2Cl_2 was added with a micro-syringe to give a final concentration in the monomer of 2.0 mol percent after evaporation of the solvent. The sample and the reference pans were placed in the DSC chamber, the

system was purged with nitrogen flow to remove air and CH_2Cl_2 for 10 min before polymerization and purging was continued during polymerization. The samples (3-4 mg) containing 2.0 mol% initiator were irradiated for 10 min at 72 °C and 40 °C with an incident light density of 20 mW/cm^2. 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 kcal/mol for methacrylamide double bonds [58,60].

3.4. Free Radical Polymerizations in Bulk and Solution

3.4.1. Polymerization Procedure

The homo- and copolymerizations of monomers 1, 2, 3 with TBEED were carried out in bulk and solution at 80 °C with AIBN as initiator and with standard freeze-evacuate-thaw procedures. The viscous polymer solutions were precipitated into nonsolvents.

The copolymerization of monomers 1a, 2a and 3a with acrylamide (AAm) was carried out in water at 65 °C with V-50. For example, AAm (77.6 mg, 1.092 mmol), monomer 1a (21.4 mg, 0.057 mmol) and V-50 (0.99 mg, 0.0036 mmol) in water were added to a septum sealed tube. The tube was subjected to freeze–evacuate–thaw procedure and placed in a 65 °C oil bath. Crosslinked polymer formed was washed several times with water to remove unreacted monomers and dried under vacuum.

The copolymerization of monomers 1a, 2a and 3a with 2-hydroxyethyl methacrylate (HEMA) was carried out in ethanol at 50 °C with AIBN. For example, HEMA (57.6 mg, 0.443 mmol), monomer 1a (18.3 mg, 0.049 mmol) and AIBN (6.7 mg, 0.041 mmol) in

ethanol were added to a septum sealed tube. The tube was subjected to freeze–evacuate–thaw procedure and placed in a 50 °C oil bath. Crosslinked polymer formed was washed several times with ethanol and dried under vacuum.

The homopolymerization of monomer 4 was carried out in bulk at 65 °C with 2 mol% AIBN as initiator and with standard freeze-evacuate-thaw procedures. The viscous polymer solution was precipitated into hexane with few drops of ether.

3.5. Hydrolytic Stability of Monomers 1a and 3a

The hydrolytic stability of the monomers 1a and 3a was investigated by ^{1}H-NMR measurements of 5 wt% and 2 wt% solutions of the monomers in methanol-d_6/D_2O (1:1 v/v) after storage at 37 °C for 1 month.

3.6. Interaction of Monomers 1a and 3a with Hydroxyapatite

3.6.1. FT-IR Spectroscopy Technique

FT-IR spectrum of the monomer 1a with and without HAP were obtained. 0.1 g of monomer 1a was dissolved in 0.5 g of 20 wt% D_2O/H_2O. To this solution, 15 mg of HAP was added. After the suspension was stirred at 37 ^{o}C for 1 h, the pH value was measured and FT-IR spectrum analysis was performed. Then another 15 mg of HAP was added to the solution and the same procedure was repeated again.

FT-IR spectrum of the monomer 3a with and without HAP were obtained. 0.145 g of monomer 3a was dissolved in 2.9 g of 5 wt% D_2O/H_2O. To this solution, 15 mg of HAP was added. After the suspension was stirred at 37 ^{o}C for 1 h, the pH value was measured and FT-IR spectrum analysis was performed. Then another 15 mg of HAP was added to the solution and the same procedure was repeated again.

4. RESULTS AND DISCUSSION

4.1. Synthesis and Polymerizations of Novel Phosphonated-Bis(methacrylamide)s

4.1.1. Synthesis and Characterizations of Novel Phosphonated-Bis(methacrylamide)s

Amidations with carbodiimides using DMAP as the catalyst are well known [61]. We first synthesized the desired monomers by (i) synthesis of TBHMA-ether derivative from the reaction of t-butyl acrylate and paraformaldehyde in the presence of 1,4-diazobicyclooctane as catalyst, (ii) conversion to a carboxylic acid by cleavage of t-butyl groups using trifluoroacetic acid, (iii) reaction of the carboxylic acid with diethyl 2-aminoethylphosphonate in the presence of N,N'-dicyclohexylcarbodiimide (DCC) and catalytic amounts of DMAP. Although monomers were obtained, they were contaminated with N,N'-dicyclohexylurea which was difficult to separate from the product. Therefore we used an alternative method, where the step (iii) above is replaced by (iii) conversion to an acid chloride by using oxalyl chloride and (iv) reaction of the acid chloride and diethyl 2-aminoethylphosphonate and diethyl 1-aminomethylphosphonate (Figure 4.1).

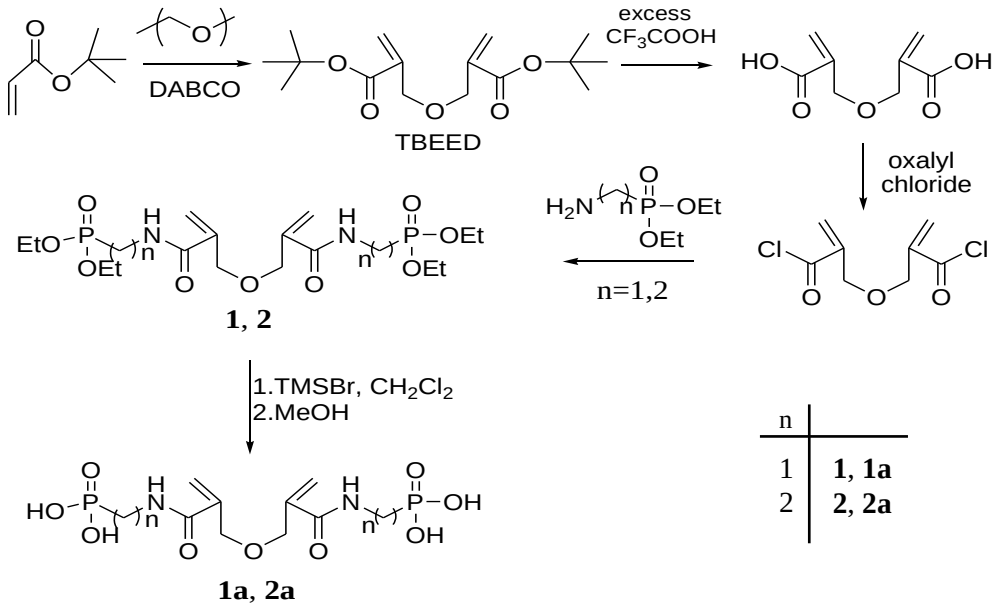


Figure 4.1. Synthesis of monomers 1, 2, 1a and 2a.

The bis(methacrylamide)s were obtained as liquids in crude yields of 67 and 41%, purified by reversed-phase flash chromatography (C18), and satisfactory microanalysis results were obtained before and after purification. The monomers were soluble in acetone, THF, methylene chloride, ethanol and water but insoluble in hexane (Table 4.1). Solubility of monomers in water and ethanol is very important for potential use in dental adhesives which are in aqueous solutions.

Table 4.1. Solubility of monomers 1, 2, 1a and 2a.

Monomers	Solvents						
	H_2O	Methanol	Ethanol	THF	Acetone	Diethyl ether	CH_2Cl_2
1	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+
1a	+	+	-	-	-	-	-
2a	+	+	-	-	-	-	-

The structures of the monomers were confirmed by FT-IR, ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy. For example, ^{1}H-NMR spectrum of monomer 1 shows the characteristic peaks of methyl protons at 1.24 ppm, methylene protons adjacent to phosphorus and oxygens at 3.69-3.73, 4.06 and 4.19 ppm and double bond hydrogens at 5.55 and 6.02 ppm (Figure 4.2). The broad NH peak at 7.47 ppm indicates a monosubstituted carbamide group. The ^{13}C-NMR of monomer 2 is shown in Figure 4.3. The doublet seen at 24.61, 26.08 ppm is due to methylene carbon attached to phosphorus. In the FT-IR spectra of the monomers monomer 1 showed peaks at 3306 cm^{-1} (amide V region), 1662 cm^{-1} (amide I region) and 1532 cm^{-1} (amide II region). Monomer 1 also showed absorption peaks of C=C, P=O and P-O peaks at 1619, 1239, 1022 and 952 cm^{-1} (Figure 4.4).

The phosphonate ester groups of bis(methacrylamide)s 1 and 2 were hydrolyzed under mild conditions with TMSBr. Monomers were first silylated with TMSBr, and then

methanolysis of the silyl ester gave the phosphonic acid monomers 1a and 2a. The monomers were obtained as yellow viscous liquids with the yields of 94 and 91%, respectively. These monomers were further purified by C18 reversed-phase flash chromatography using water to give clear, colorless oils which are soluble in water and ethanol, as expected. The FT-IR spectrum of monomer 1a shows broad bands in the region of 3000-2600 cm^{-1} and 2300-2100 cm^{-1} due to OH stretching and 1670-1600 cm^{-1} due to OH bending modes (Figure 4.4). The strong bands at 1657, 1608 and 1536 cm^{-1} belong to C=O, C=C and NH stretchings, respectively. Also the strong bands at 938 and 992 cm^{-1} correspond to the symmetric and asymmetric vibration of P-O. ^{1}H-NMR spectrum of monomer 1a shows the complete disappearance of phosphonic ester peaks at 1.24 and 4.06 ppm (Figure 4.5). In the ^{31}P-NMR spectrum, one peak at 17.80 ppm confirmed the purity of this monomer.

4.1.2. Thermal Polymerizations of Monomers 1 and 2

It is known that polymerization of 1,6-heptadienes give cyclic polymers. Mathias *et al*. have been investigated cyclopolymerization of ether dimers of several α-hydroxymethylacrylates and observed that cyclization efficiency increases with bulky ester groups such as tert-butyl and adamantyl which sterically inhibits intermolecular addition [57]. They obtained completely soluble high molecular weight polymers at high temperatures and dilute conditions. Even the ether dimer of α-hydroxymethyl acrylic acid with the lowest bulkiness showed high cyclization efficiency. Also,cyclopolymerization of TBEED via atom transfer radical polymerization (ATRP) was reported to give soluble polymers at high conversion with tunable molecular weights, low polydispersities, and living end groups [62].

Thermal bulk and solution polymerizations of monomers 1, 2 and TBEED were carried out using AIBN and standard freeze-evacuate-thaw procedures at 80 °C. The polymerization conditions and results are listed in Table 4.2. Soluble polymers of TBEED could only be obtained at low monomer and initiator concentrations. Molecular weights of the polymers ranged from 13075 to 49118. However, monomers 1 and 2 gave crosslinked polymers under similar and more dilute conditions, indicating lower cyclization tendency of these monomers compared to TBEED. Moszner *et al*. also prepared

bis(methacrylamide)s from TBEED using propyl and diethyl amines and found high crosslinking tendency of the former but no polymerizability at all of the latter [15].

The reactivity of these monomers was found to increase in the following order for polymerizations under the same conditions: TBEED<2<1. For example, gelation time for monomer 1 and 2 were found to be 3 and 16 minutes under the same conditions. However, TBEED gave a soluble polymer with 27% yield at 67 minutes under the same conditions. The lower cyclization efficiency of the synthesized monomers may be due to the steric effect of the substituents. The size or 'effective bulkiness' of the t-butyl substituent is higher than those of monomers 1 and 2 which enhances intramolecular reaction compared to intermolecular reaction.

Copolymerization of TBEED with the synthesized monomers was also carried out to seek the possibility of obtaining soluble polymers. The results of the copolymerizations were summarized in Table 4.2 along with molecular weights of the soluble copolymers obtained. The homopolymer of TBEED and its copolymers were purified by precipitation into methanol: water (5:1) mixture where both monomers are soluble. The copolymers showed similar solubility with poly-TBEED except they were insoluble in hexane where poly-TBEED was soluble. The FT-IR spectrum of one of the copolymers, TBEED:1 (90:10 mol%), shows peaks at 1679, 1537 and 1259 cm^{-1} due to both C=O, NH and P=O stretchings of monomer 1, confirming incorporation of this monomer and no residual double bonds (Figure 4.4). ^{1}H-NMR spectrum of the same copolymer showed methyl, t-butyl and backbone hydrogens between 1.2-2.0 ppm and methylene hydrogens of 1 and TBEED at 4.06-4.50 ppm. The copolymer compositions were determined from integrated ^{1}H-NMR spectra with the ratio of peak areas of methylene protons of the TBEED and 1 at 4.27 ppm to the peak areas of other methylene protons of 1 at 4.06 ppm (Figure 4.6). The amount of 1 units in the copolymers (45 mol%) was greater than in the feed composition (10 mol%), indicating that monomer 1 is clearly much more reactive than TBEED.

Generally, polyphosphonates and polyphosphates are known as flame retardants [63, 64]. During the combustion, poly(phosphoric acid) forms and catalyzes the formation of char to protect the surface from further burning [65].

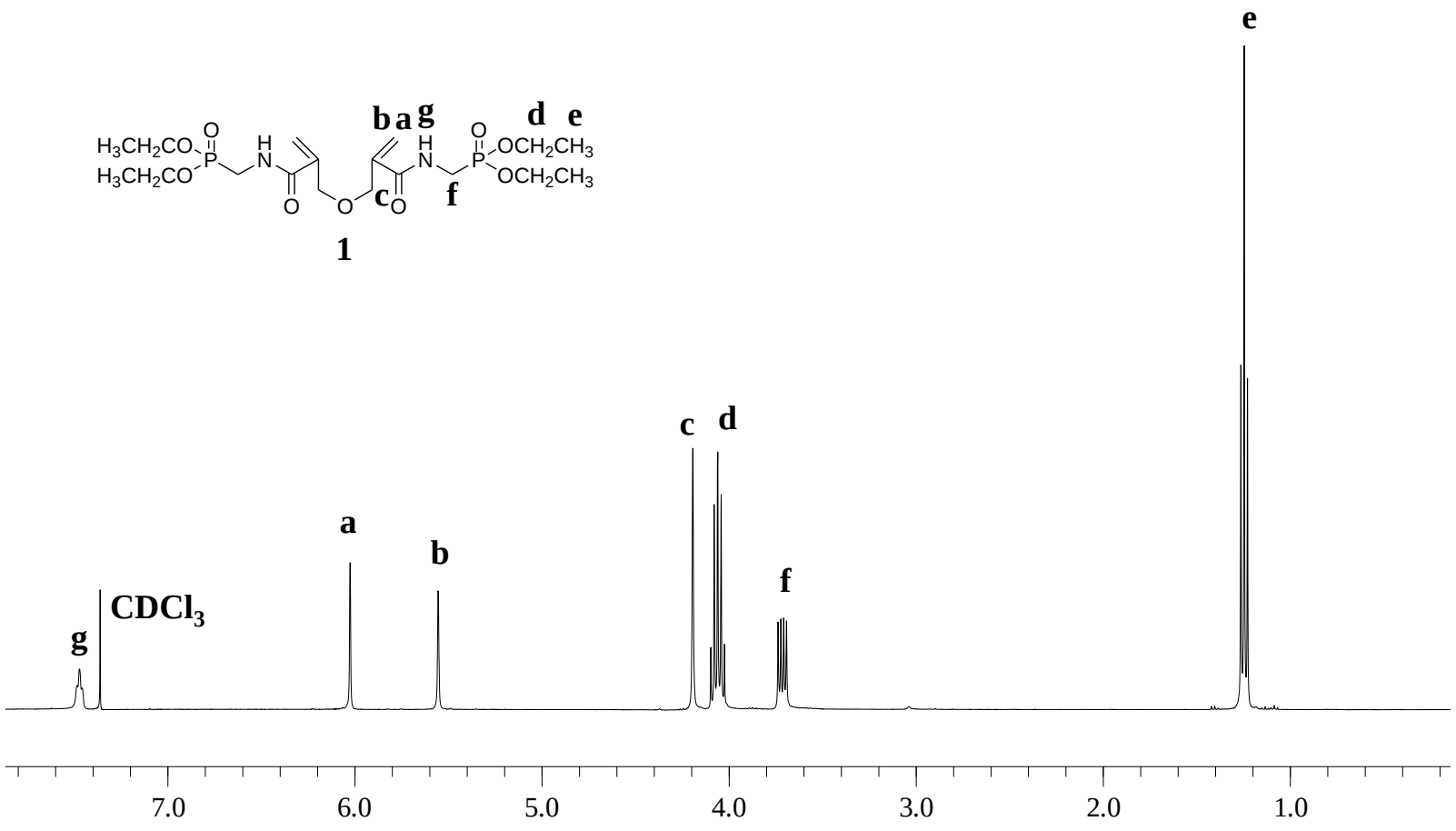
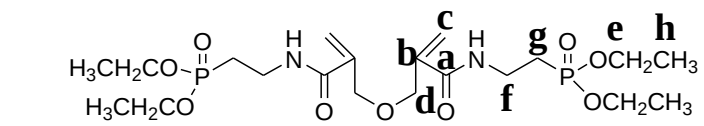


Figure 4.2. ^{1}H-NMR spectrum of monomer 1.



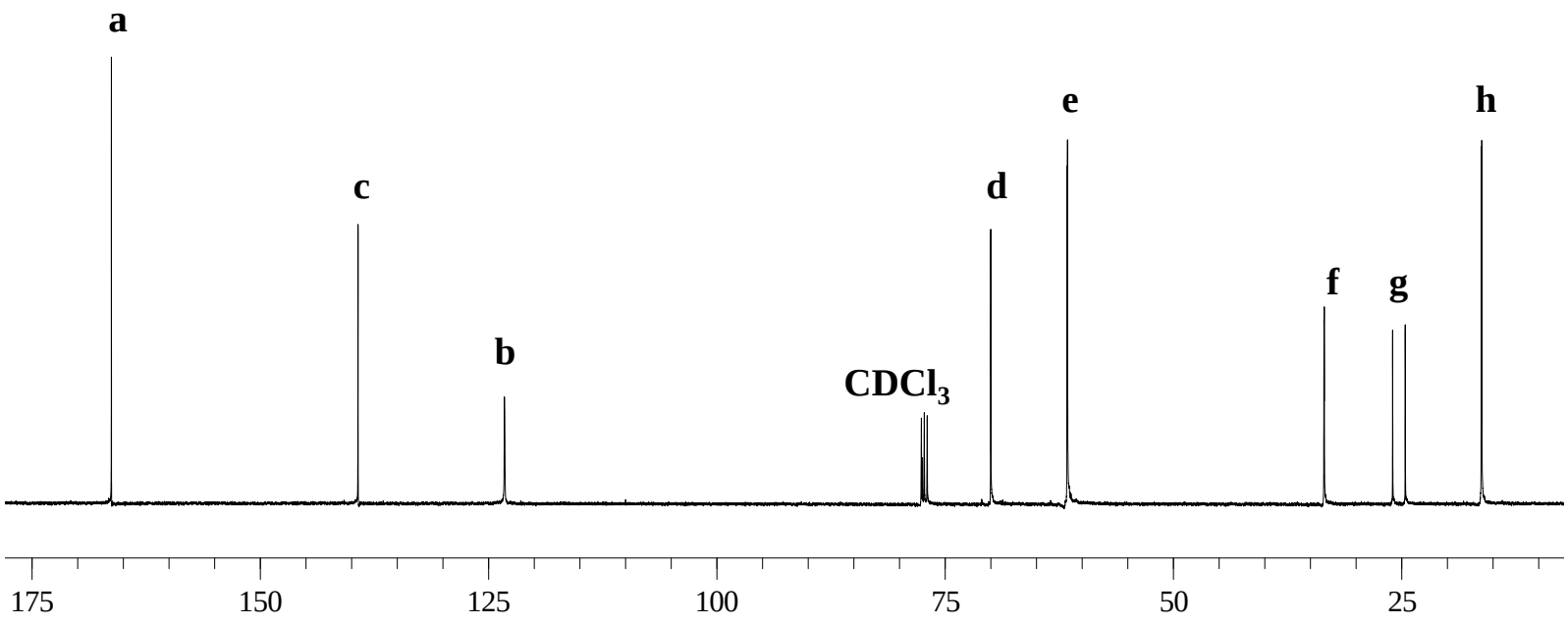


Figure 4.3. ^{13}C-NMR spectrum of monomer 2.

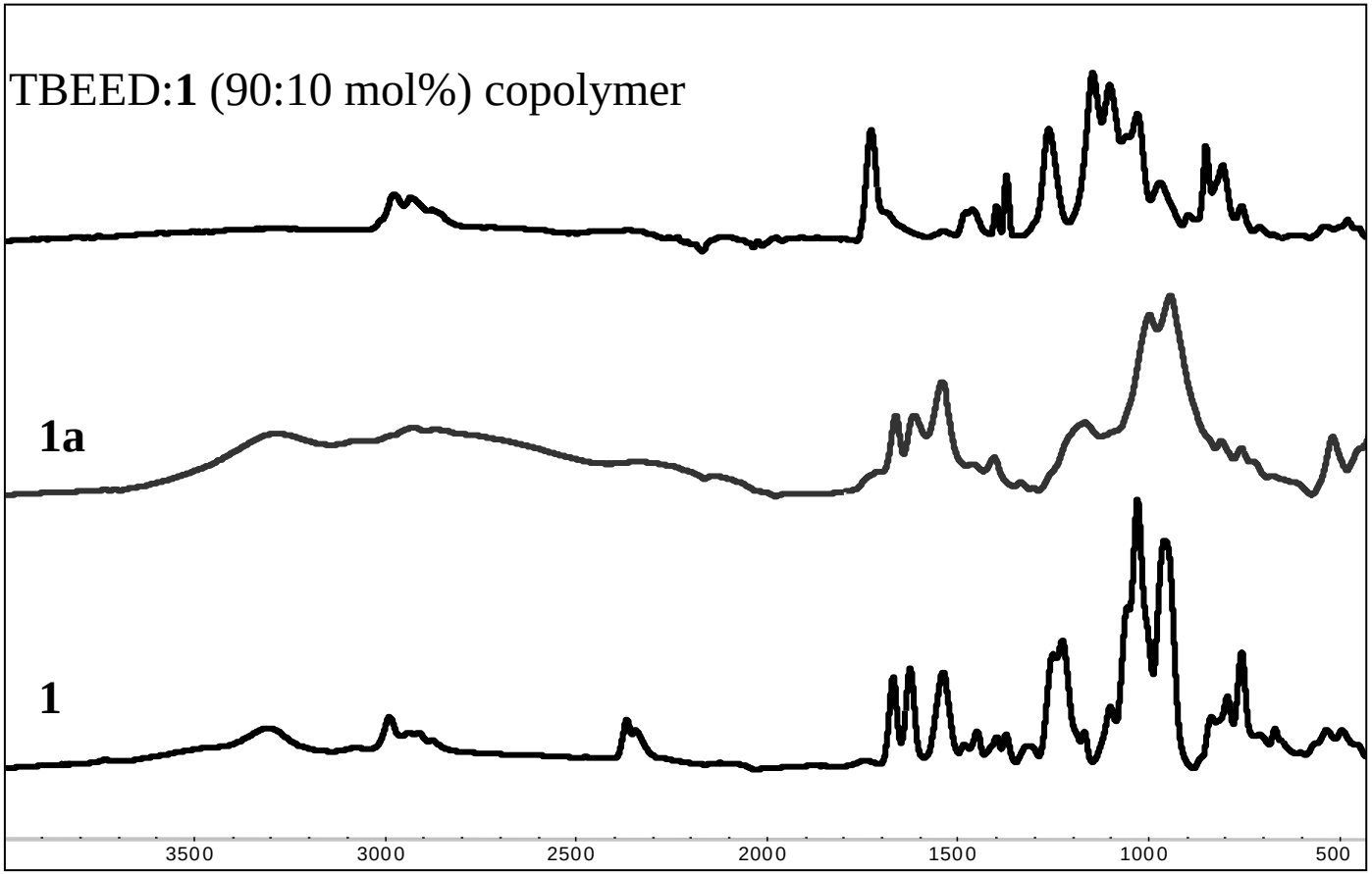


Figure 4.4. FT-IR spectra of monomers 1, 1a and TBEED:1 (90:10 mol%) copolymer.

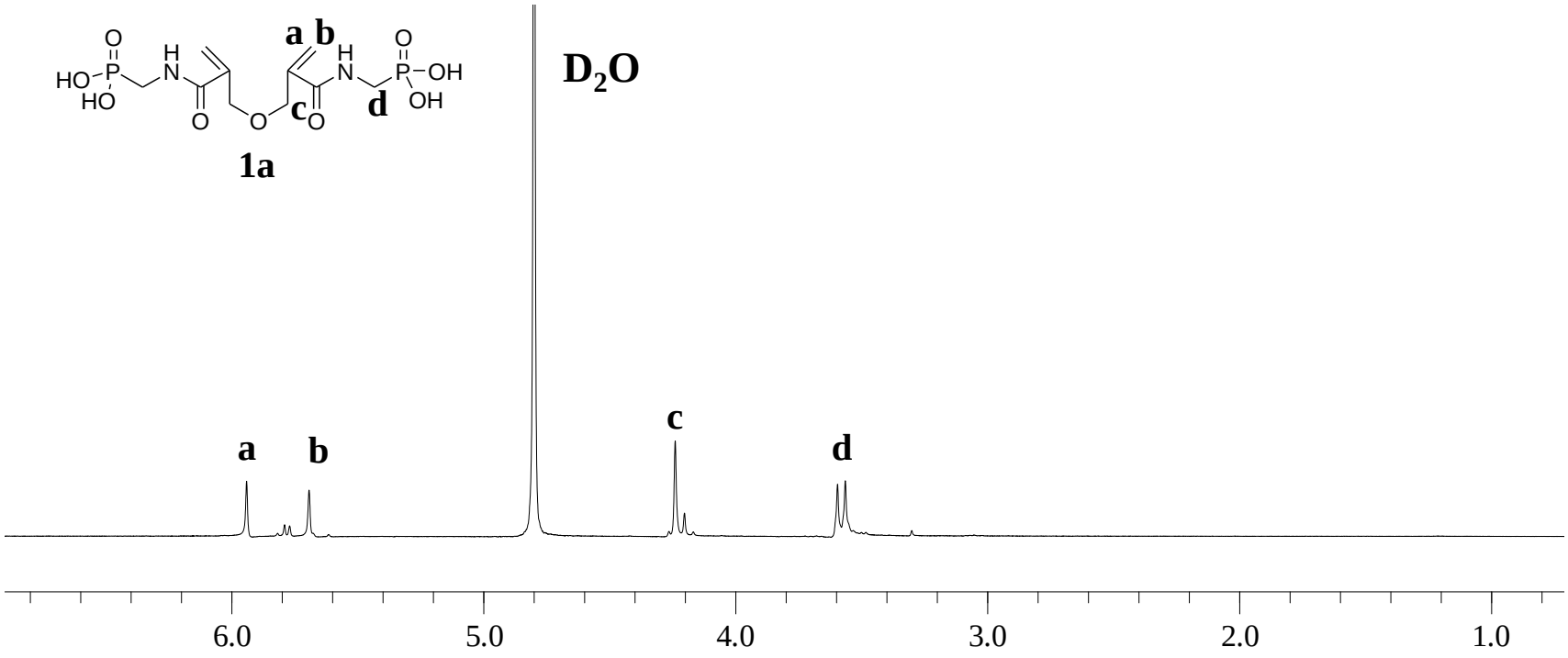


Figure 4.5. ^{1}H-NMR spectrum of monomer 1a.

The thermogravimetric analysis of the homopolymers of 1, 2 and TBEED together with one of the copolymers (TBEED:1, 90:10 mol%) was investigated by TGA under nitrogen at 10 °C/minute (Figure 4.7). Homopolymers of 1 and 2 were found to be more stable, with decomposition starting around at 225 and at 200 °C; the second decomposition step was in the range of 300-400 ^{o}C. The high char yields of these polymers (43.88% for poly-1 and 39.09% for poly-2) are due to formation of phosphonic acids which will contribute to crosslinking in the early stages of degradation. The copolymer of TBEED:1 (90:10 mol%) showed the same thermal degradation behavior with poly-TBEED. Both polymers started to lose weight around 200 °C due to decomposition of the t-butyl groups and then degraded gradually by ring decomposition and/or depolymerization to give char yields of 11.83 and 27.55% for polymer of TBEED and its copolymer with 1. It was observed that addition of 1 to TBEED improved the char yield by 15.72%.

4.1.3. Thermal Copolymerizations of Monomers 1a and 2a

In order to prove the incorporation of monomers 1a and 2a into the copolymers, their thermal solution copolymerizations with AAm and HEMA were conducted. Monomers 1a and 2a were copolymerized with AAm (5:95 mol%) in water at 65°C using V-50 as initiator. Although AAm polymerizes in 4 minutes to give soluble polymers, the copolymers were obtained after 12 h of polymerization. Crosslinked polymers precipitating from water as white solid powders indicated the incorporation of monomers 1a and 2a in copolymers. Monomers 1a and 2a were also copolymerized with HEMA (10:90 mol%) in ethanol at 50°C using AIBN as initiator. We observed that addition of our monomers to HEMA decreased its polymerization rate while HEMA polymerized in 45 minutes copolymers polymerized in more than 12 h giving a white solid crosslinked polymers instead of clear gels. FT-IR spectrum of one of the copolymers (after removal of residual monomers) indicating C=O and N-H peaks of 1a proved the incorporation into the copolymer matrix (Figure 4.8).

4.1.4. Photopolymerizations of Monomers 1, 2, 1a and 2a

We investigated photopolymerization of monomers 1, 2, TBEED and GDMA with photodifferential scanning calorimetry to determine their relative rate of polymerizations.

All the polymerizations were performed under identical conditions of temperature, initiator concentration and light intensity. Figure 4.10 shows the time dependences of the polymerization rate and conversions for monomers 1, 2, TBEED and GDMA.

Table 4.2. Polymerization results of monomers 1, 2, TBEED and their copolymers.

Monomer	[M]	[AIBN]	Solvent	Time (min)	Conversion %	M_n
TBEED	0.89	0.3966	toluene	15	crosslinked	
TBEED	1.71	0.0163	toluene	6	crosslinked	
TBEED	1.30	0.0380	toluene	67	27	28267
TBEED	0.93	0.2037	toluene	205	70	13075
TBEED	1.31	0.0380	toluene	35	38	49118
TBEED	1.33	0.0187	toluene	120	64	33521
1	0.21	0.0015	toluene	1140	crosslinked	-
1	1.26	0.0350	toluene	3	crosslinked	-
TBEED:**1** (80:20 mol%)	0.43	0.0003	toluene	140	crosslinked	-
TBEED:**1** (90:10)	1.30	0.0380	toluene	8	crosslinked	-
TBEED:**1** (90:10)	0.90	0.0217	toluene	5	crosslinked	-
TBEED:**1** (90:10)	0.42	0.0003	toluene	1260	42	-
TBEED:**1** (90:10)	0.43	0.0003	toluene	1140	38	9747
2	-	0.06 wt%	-	180	crosslinked	-
2	0.63	0.019	DMSO	45	crosslinked	-
2	0.39	0.012	EtOH	10	crosslinked	-
2	0.40	-	EtOH	25	crosslinked	-
2	1.30	0.037	toluene	16	crosslinked	-
TBEED:**2** (80:20)	0.80	0.004	DMSO	25	crosslinked	-
TBEED:**2** (90:10)	0.40	0.001	DMSO	50	crosslinked	-
TBEED:**2** (90:10)	0.43	0.00034	toluene	1020	crosslinked	-

It was clearly seen that photopolymerization behavior of the synthesized monomers are different than that of TBEED and similar to GDMA. The photopolymerization of monomers 1, 2 and GDMA starts at a higher rate compared to TBEED. For example, after 5 s of polymerization 22, 10 and 16% of the double bonds were reacted for monomers 1, 2 and GDMA and only 0.1% for TBEED. These values indicate that autoacceleration, that is, an increase in polymerization rate, which is due to crosslinking leading to an increase in viscosity, therefore a decrease in mobility of polymer radicals, which in turn causes a reduced termination rate and increase in radical concentration, occurs earlier in monomers 1, 2 and GDMA. This behavior is typical to multifunctional (meth)acrylates. However, TBEED behaves more like a monofunctional (meth)acrylate. The maximum rates of the commercial and synthesized monomers follow the order: 1> 2~GDMA~TBEED.

In general, overall monomer conversion is higher for systems that are polymerized at faster rates. As the polymerization rate increases, the volume relaxation is unable to keep pace with conversion, leading to increased free volume formation. The free volume in excess of equilibrium values causes higher mobility which results in increased conversion. Also, conversion depends on the polymerization temperature and the T_g of the system which indicates its mobility. The T_g of a polymerization system depends on flexibility of monomers. For example, polar groups are responsible for intra-and intermolecular interactions and decrease flexibility of the system and increase T_g. Therefore we can say that hydrogen bonding in monomers 1 and 2 results in an extremely rigid system and decreases conversion of these monomers compared to TBEED which has a flexible structure. Another reason for decreased conversion of monomers 1 and 2 is earlier autoacceleration which decreases mobility of the system.

Although monomers 1 and 2 have similar chemical structures (one methylene unit difference) monomer 1 polymerized faster than monomer 2. Maximum rates of polymerizations for 1 and 2 were 0.075 and 0.051 s^{-1}. The higher polymerizability of monomer 1 compared to monomer 2 may be caused by the more rigid structure of the former.

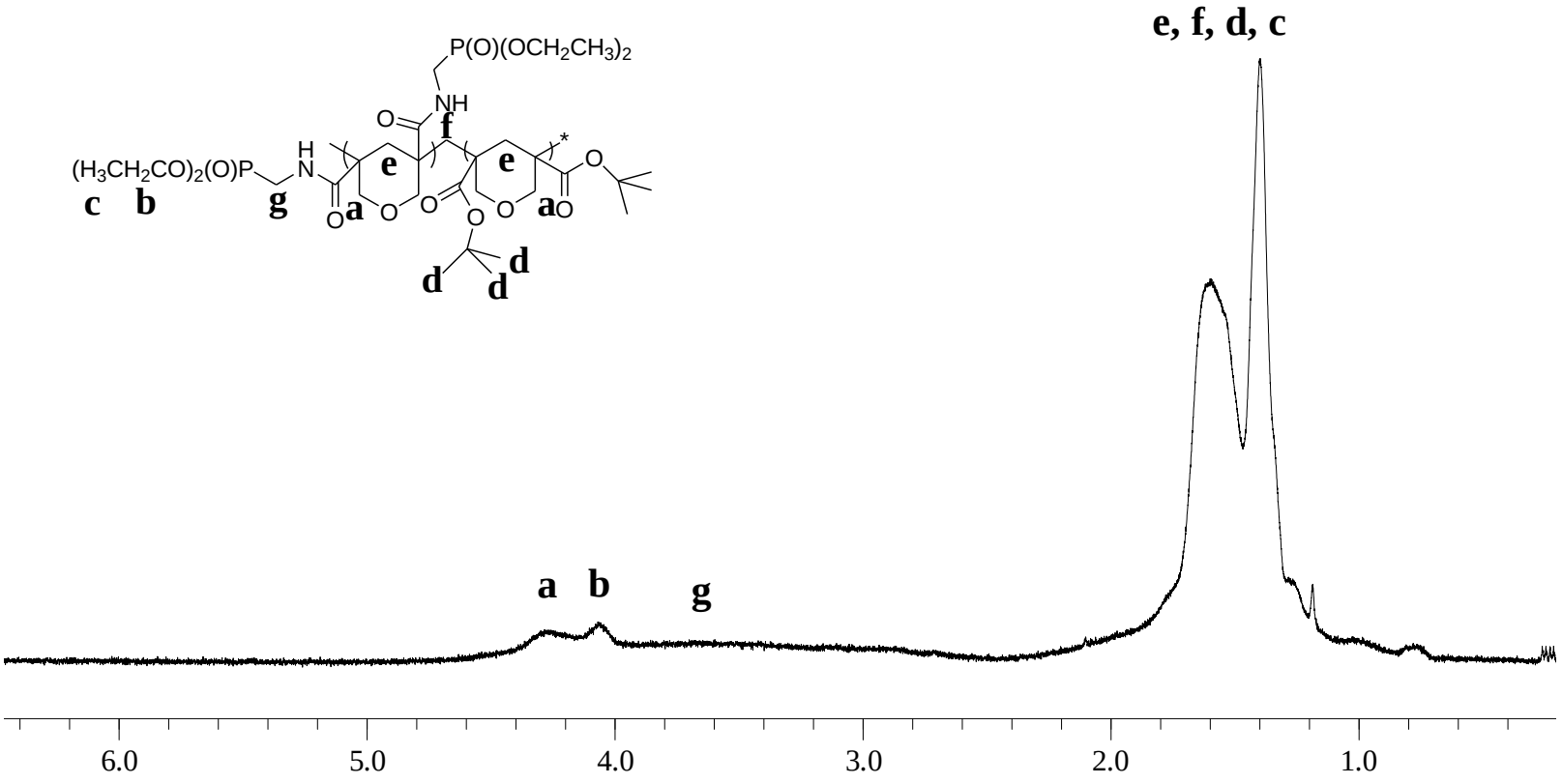


Figure 4.6. ^{1}H-NMR spectrum of TBEED:1 (90:10 mol%) copolymer.

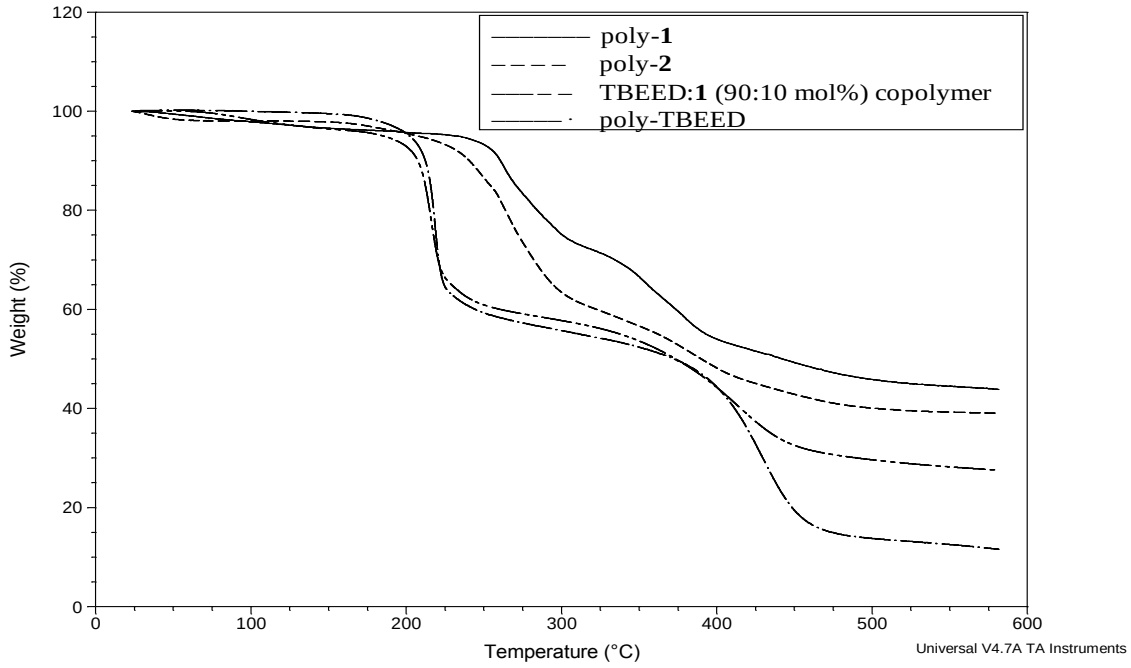


Figure 4.7. TGA results of poly-1, poly-2, poly-TBEED and TBEED:1 (90:10 mol%) copolymer.

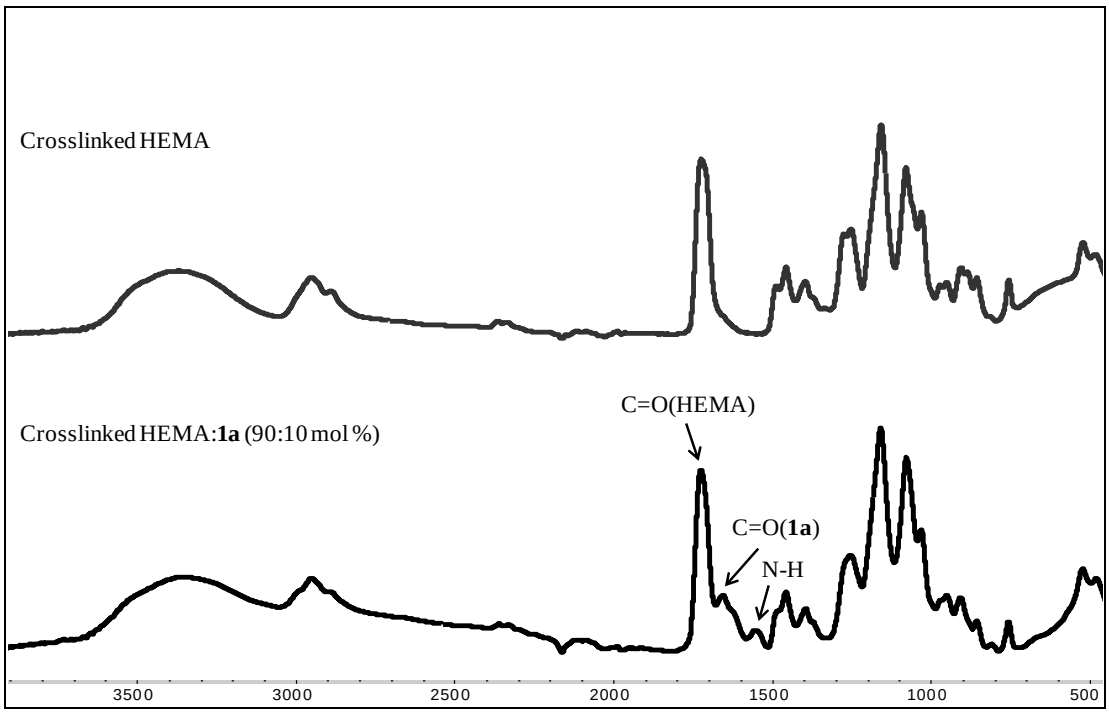


Figure 4.8. FT-IR spectra of homopolymer of HEMA and its copolymer with 1a (HEMA:1a, 90:10 mol%).

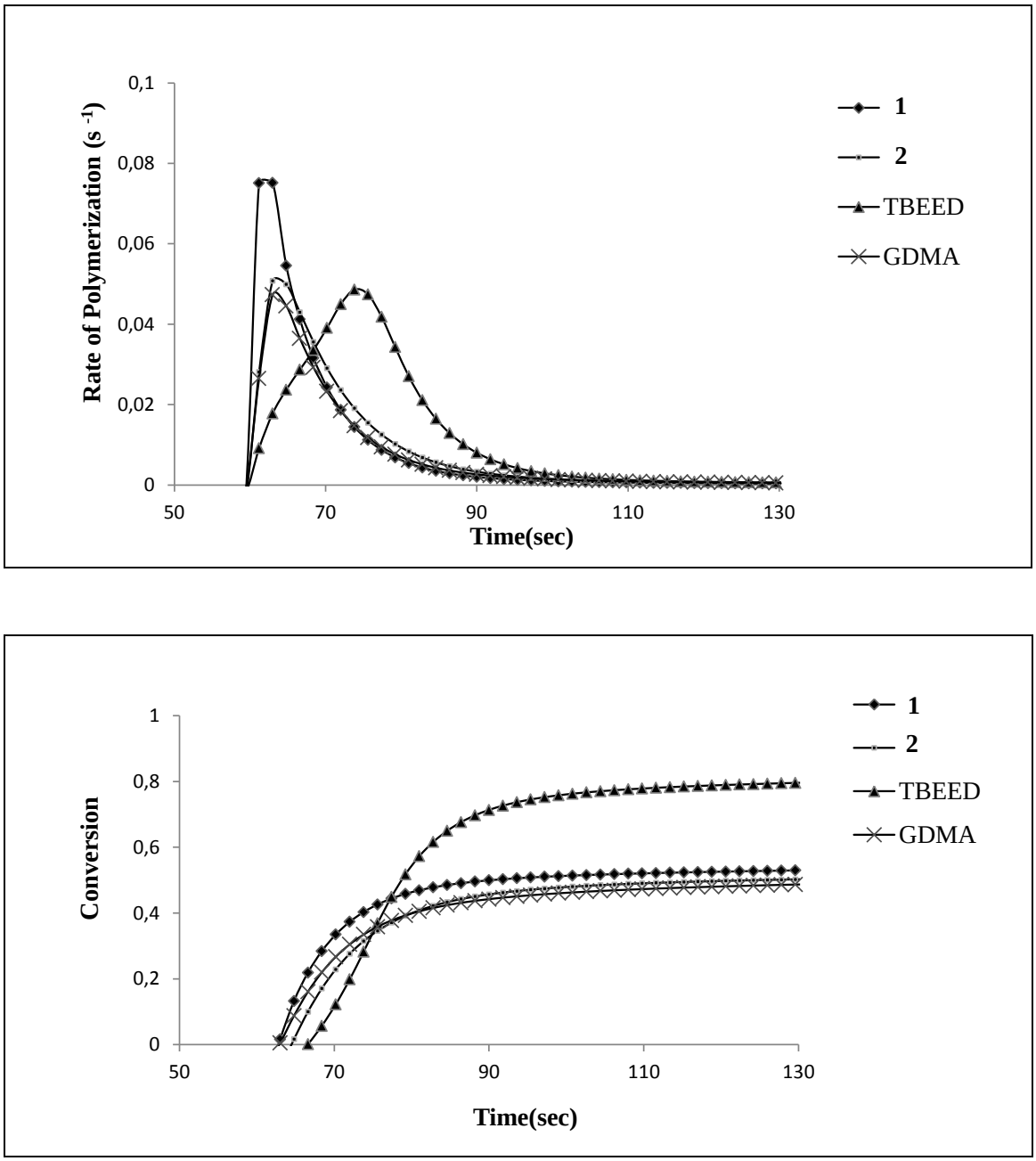


Figure 4.9. Rate-time and conversion-time curves of monomer 1, 2, TBEED and GDMA.

In order to test the use of these monomers as reactive diluents in filling composites and also crosslinking monomers in dental adhesives, we investigated copolymerization of them with Bis-GMA and HEMA. Monomer 1 and 2 showed much higher reactivity than Bis-GMA and HEMA (Table 4.3). The conversions were found to increase in the order: Bis-GMA<2<1<HEMA, as expected. It can be observed that addition of 10 mol% of monomer 1 to Bis-GMA improved both its rate and conversion whereas addition to HEMA

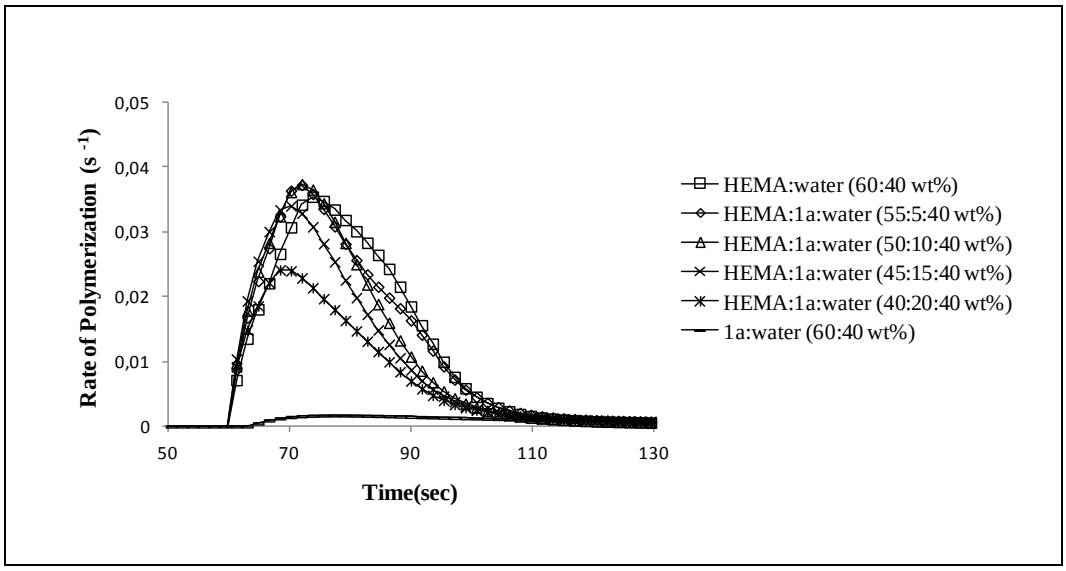
increased its rate without decreasing its conversion. Therefore, the highly reactive monomer 1, enhancing polymerization kinetics of both Bis-GMA and HEMA, may be used for the purposes stated above.

Table 4.3. Photopolymerization results of monomers 1, 2, Bis-GMA, HEMA and their copolymers.

Monomer	$R_p(s^{-1})$	Conversion (%)
1	0.075	49
2	0.051	53
Bis-GMA	0.042	40
HEMA	0.023	90
Bis-GMA:**1** (90:10 mol%)	0.053	59
HEMA:**1** (90:10 mol%)	0.045	86
Bis-GMA:**2** (90:10 mol%)	0.038	41
HEMA:**2** (90:10 mol%)	0.037	69

In order to test the use of monomers 1a and 2a as dental adhesives, the homo- and copolymerization kinetics of these monomers with HEMA, an important component in dental adhesive mixtures, were evaluated. Formulations consisting of mixtures of HEMA and water (60:40 wt%); 1a or 2a and water (60:40 wt%); HEMA, 1a or 2a and water (at different ratios) were prepared. We used a water soluble initiator; BAPO, in our polymerization studies. Table 4.4 and Figure 4.10 show the photopolymerization results. Monomers 1a and 2a were found to be much less reactive than their phosphonate-containing analogs, 2a being the less reactive one. It was observed that addition of 5-15 wt% of 1a to HEMA did not change its rate of polymerization but resulted in gradual decreases in conversion with increasing fraction of 1a. However, addition of 20 wt% of 1a to HEMA decreased both its rate and conversion significantly. On the other hand, addition

of 5-20% of 2a to HEMA decreased its rate significantly without affecting its conversion as much as 1a. The reason for higher conversions obtained for 2a may be due to higher flexibility achieved by two methylene units instead of one in 1a. Additionally, the results (Figure 4.10) clearly show that there is a shift in the peak maximum of HEMA by the addition of monomer 1a. This behavior typical to multifunctional (meth)acrylates confirms the incorporation of monomer 1a into the copolymers. The same behavior was observed for the copolymerization of 2a with HEMA.



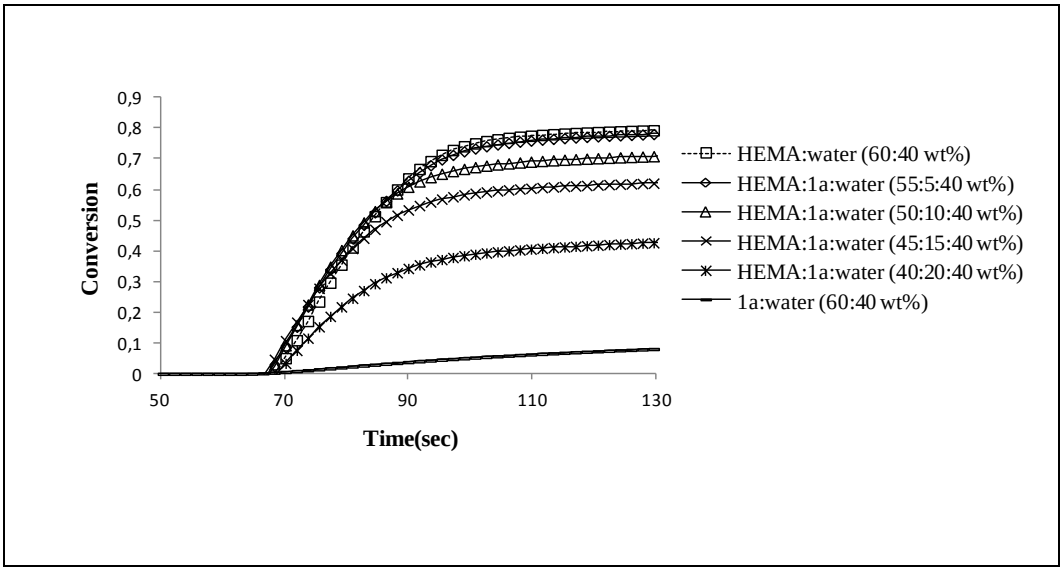


Figure 4.10. Rate-time and conversion-time curves in the homopolymerization and copolymerizations of 1a with HEMA.

Table 4.4. Photo-DSC results of acidic aqueous formulations using BAPO.

1a (wt%)	**2a** (wt%)	HEMA (wt%)	$R_p(s^{-1})$	Conversion (%)
-	-	60	0.0351	92
5	-	55	0.0373	86
10	-	50	0.0374	78
15	-	45	0.0340	68
20	-	40	0.0242	50
60	-	-	0.0017	14
-	5	55	0.0292	96
-	10	50	0.0216	93
-	15	45	0.0155	88
-	20	40	0.0154	79
-	60	-	0.0004	5

4.1.5. Acidity, Interaction with HAP, and Stability of Acid Monomers

It is known that amides are more stable towards hydrolysis by acids compared to carboxylic acid esters. However it was difficult to predict the stability of these monomers which contain acid groups within the same structure. Therefore hydrolytic stability of the acid monomers (1a and 2a) was investigated by recording ^{1}H-NMR spectroscopy of their 20 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 1a and 2a (Figure 4.11). These results showed that the monomers are stable during one month of investigation.

The pH values of aqueous solutions of the monomers (20 wt%) were found to be 1.42 and 1.53 for monomers 1a and 2a, in the range expected from mild self-etching adhesives. The addition of 30-mg HAP, a model compound for dentin and enamel, to the solutions of monomer 1a resulted in an increase in the pH value from 1.42 to 2.74.

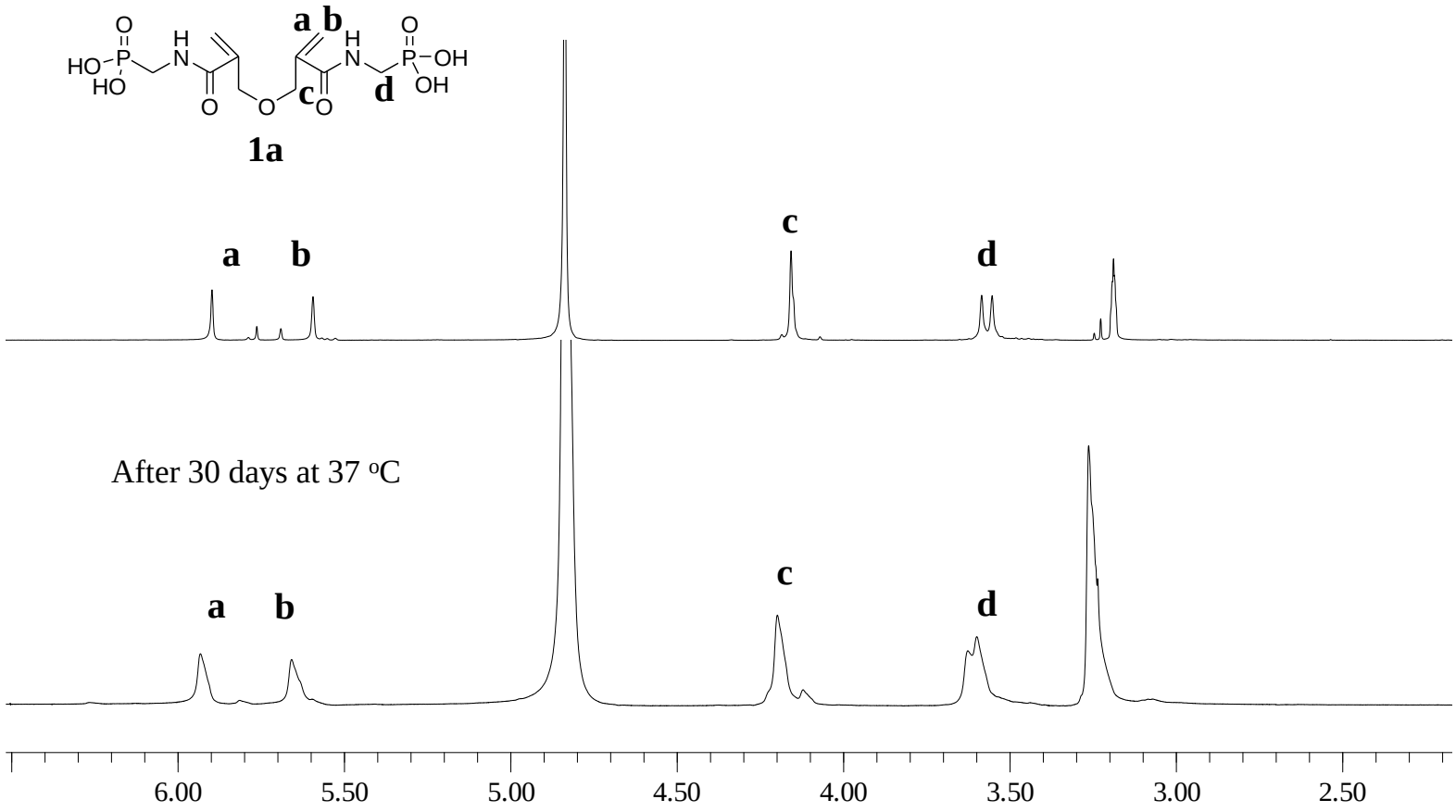


Figure 4.11. Hydrolytic stability of monomer 1a.

The interaction of monomer 1a with HAP was investigated using FT-IR spectrometer (Figure 4.12). The mixtures of monomer 1a and HAP showed peaks due to both components, indicating adsorption of monomer 1a on the HAP surface due to hydrogen bonding or complex formation. Also, the band at 992 cm^{-1} due to asymmetric vibration of P-O in monomer 1a decreased and a new peak appeared around 1053 cm^{-1}. This peak overlaps with PO_4^{3-} peak of HAP at 1016 cm^{-1}. The bands at 600 and 559 cm^{-1} due to HAP were found in both spectra.

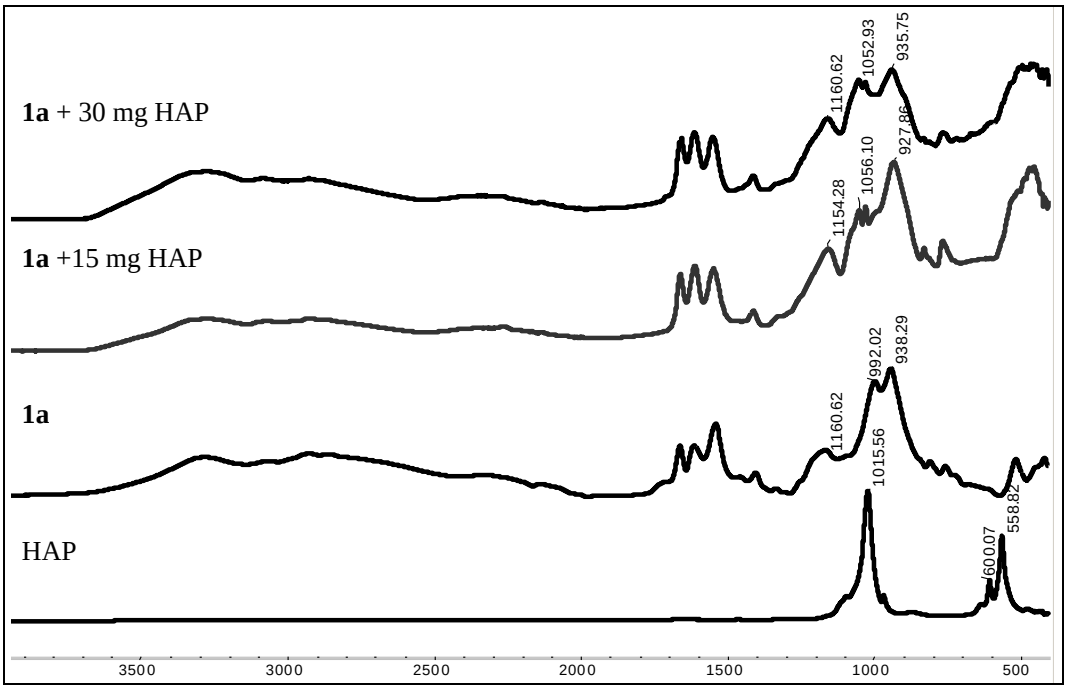


Figure 4.12. FT-IR spectra of HAP, monomer 1a, monomer 1a with 15 mg HAP and monomer 1a with 30 mg HAP.

4.2. Synthesis and Polymerizations of Novel Bisphosphonated-Bis(methacrylamide)s

4.2.1. Synthesis and Characterizations of Novel Bisphosphonated-Bis(methacrylamide)s

A new bisphosphonate-containing bis(methacrylamide) (3) was synthesized in four steps: (i) synthesis of TBHMA-ether derivative from the reaction of t-butyl acrylate and paraformaldehyde in the presence of 1,4-diazabicyclooctane (DABCO) as catalyst, (ii)

conversion to a carboxylic acid by cleavage of t-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) (Figure 4.13). This monomer was obtained as a white solid with a melting point of 71-72 °C in 20% yield after purification by flash chromatography. It was soluble in common organic solvents such as methylene chloride, acetone, ether, ethanol and THF and also soluble in water (Table 4.5).

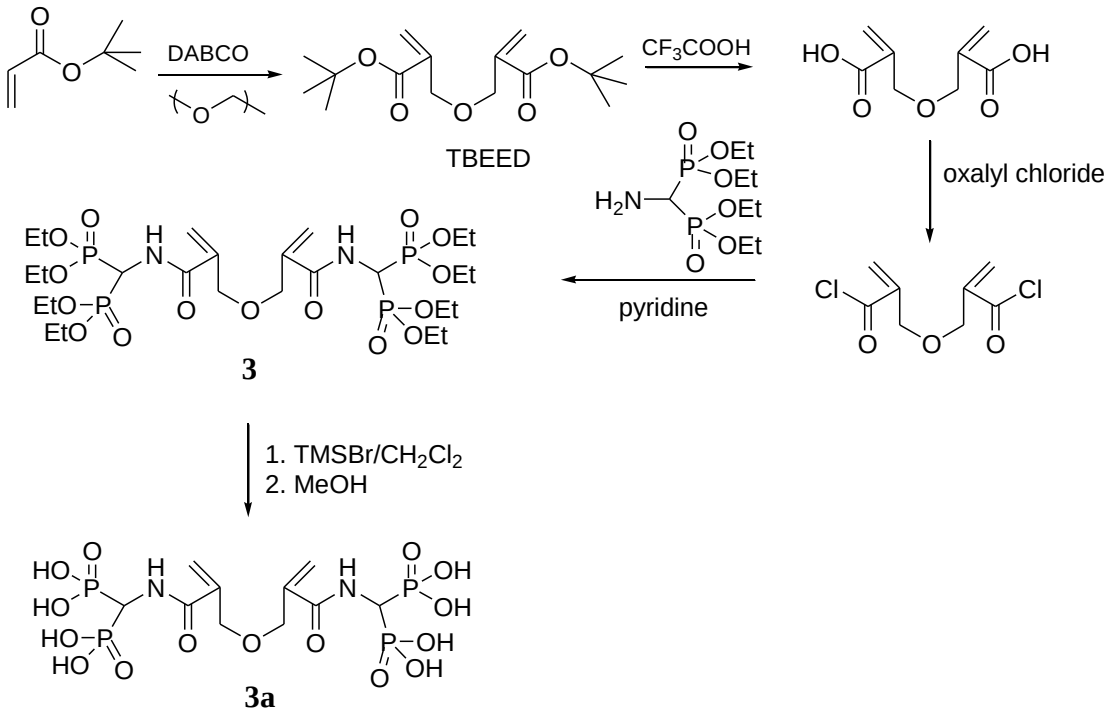


Figure 4.13. Synthesis of monomers 3 & 3a.

Table 4.5. Solubility of monomers 3 & 3a.

Monomers	H_2O	Ethanol	THF	Acetone	Diethyl ether	CH_2Cl_2
3	+	+	+	+	+	+
3a	+	+	-	-	-	-

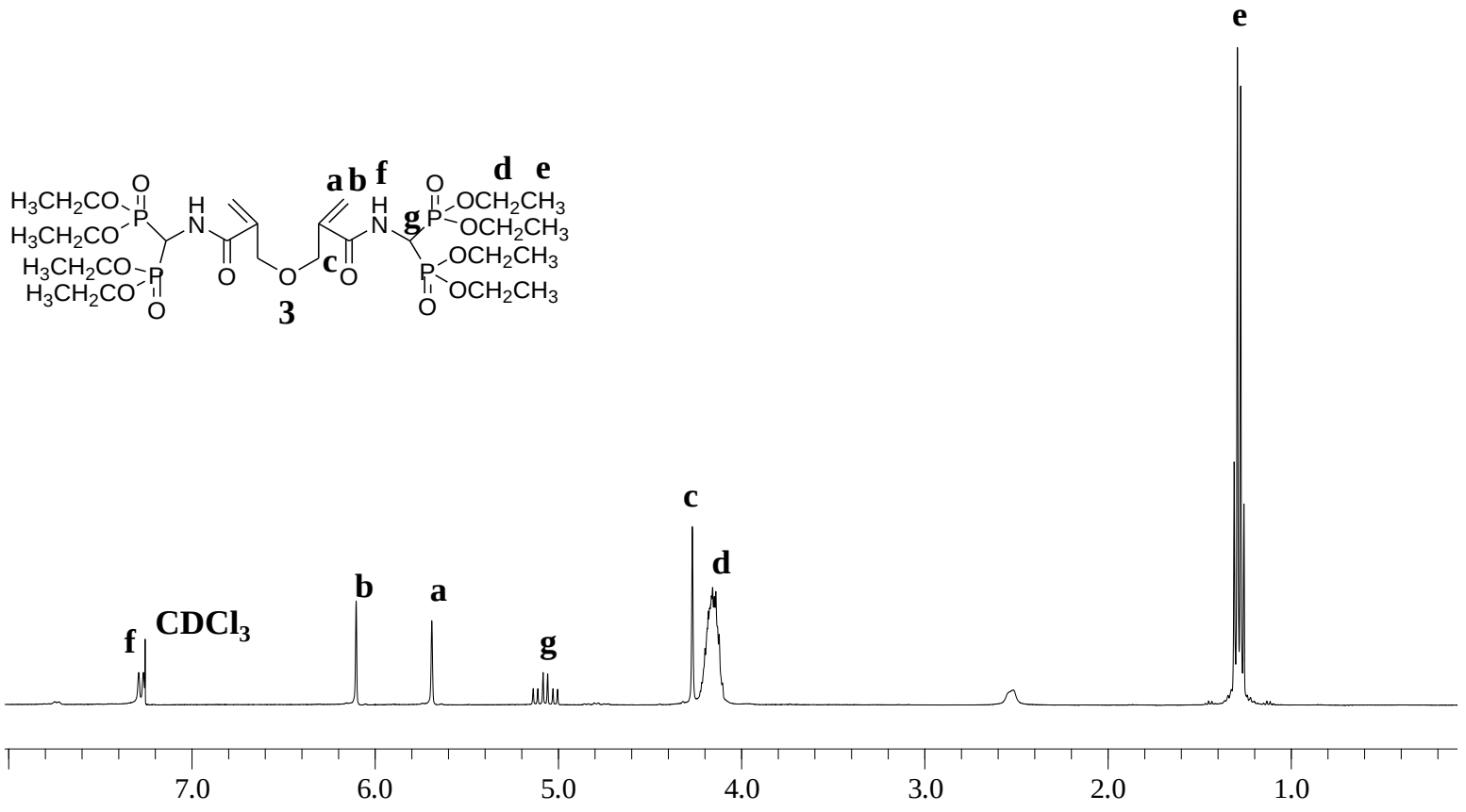
The characterization of this monomer was carried out by FT-IR, ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy, as well as elemental analysis. The spectral data are in agreement with the expected structure of the monomer. For example, the single bisphosphonate proton is

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 oxygens at 4.06-4.21 and 4.27 ppm and double bond hydrogens at 5.69 and 6.10 ppm (Figure 4.14). The peak at 7.29 ppm is typical for the NH peak of carbamide group. The ^{13}C-NMR of this monomer is shown in Figure 4.15. The triplet seen at 42.09, 43.55 and 45.01 ppm is due to methine carbon attached to two phosphorus. ^{31}P-NMR chemical shift of this compound is 16.06 ppm. In the FT-IR 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 3 also showed absorption peaks of C=C, P=O and P-O peaks at 1628, 1254, 1014 and 967 cm^{-1} (Figure 4.16).

The silylation of monomer 3 with TMSBr and methanolysis of the silyl ester groups gave a new bisphosphonic acid-containing bis(methacrylamide) (3a). This monomer was obtained as clear viscous oil in 58% yield after purification by C18 reversed-phase flash chromatography. Monomer 3a dissolves very well in water which is very important for dental adhesive applications. The FT-IR spectrum of monomer 3a 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 stretchings, respectively (Figure 4.16). 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 3a shows the complete disappearance of bisphosphonic ester peaks at 1.29 and 4.06-4.21 ppm (Figure 4.17). Monomer 3a 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.

4.2.2. Thermal Polymerizations of Monomer 3

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 [57]. It was observed that bulky ester groups such as tert-butyl and adamantyl sterically inhibit intermolecular addition and increase cyclization efficiency.



3

Figure 4.14. ^{1}H-NMR spectrum of monomer 3.

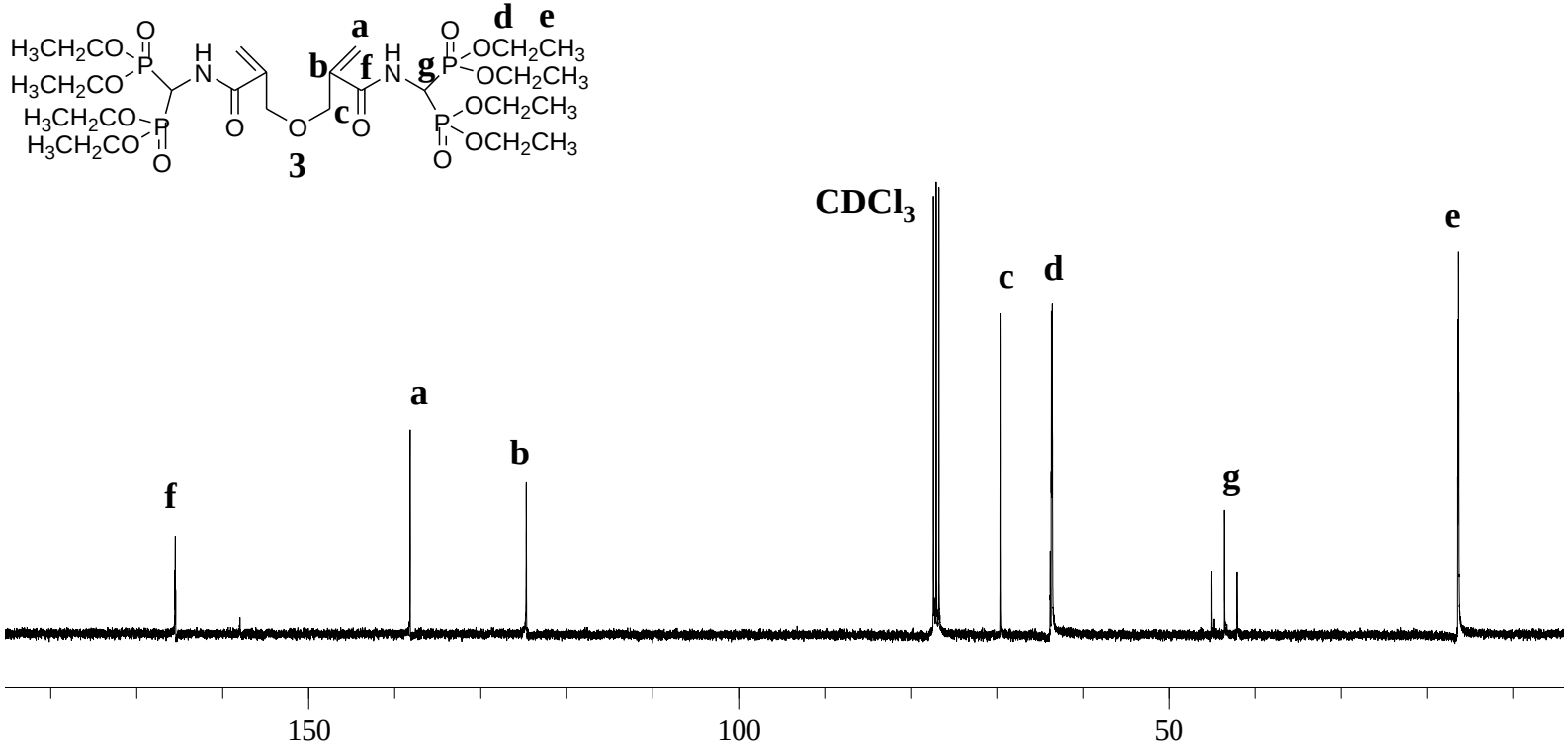


Figure 4.15. ^{13}C-NMR spectrum of monomer 3.

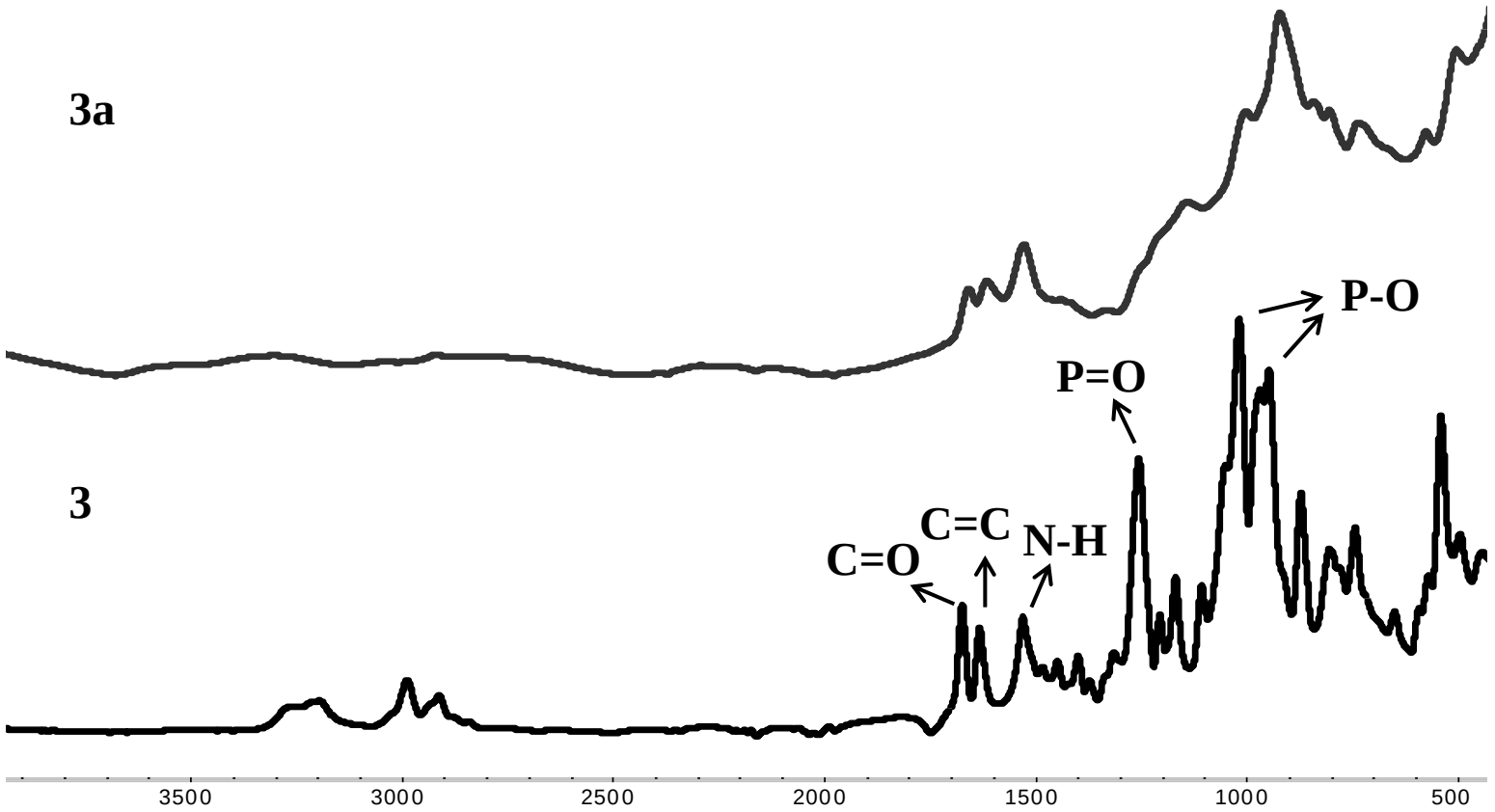


Figure 4.16. FT-IR spectra of monomers 3 & 3a.

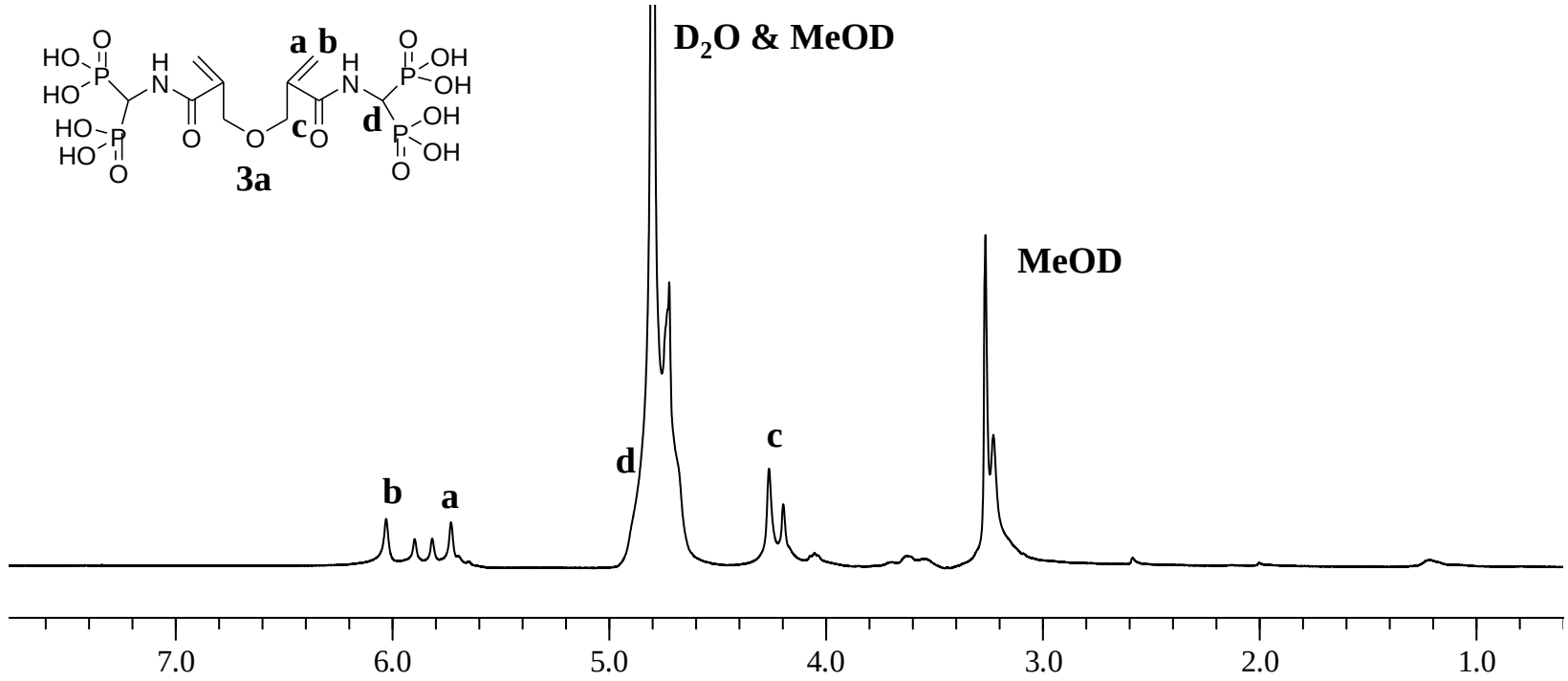


Figure 4.17. ^{1}H-NMR spectrum of monomer 3a.

Cyclization efficiency increases at high temperatures and dilute conditions. Moszner *et al*. prepared bis(methacrylamide)s from TBEED using propyl and diethyl amines and found high crosslinking tendency of the former but no polymerizability at all of the latter due to steric hinderance of N,N-disubstituted methacrylamide structures [15].

Thermal solution homo- and copolymerizations of monomer 3 were conducted under the same conditions as TBEED and 1 to see the effect of substituents. The polymerization conditions and characteristics of the polymers are shown in Table 4.6. All three monomers showed very high polymerization rates, giving polymers in 3-180 minutes. Although monomer 3 has higher bulkiness compared to 1, they both gave crosslinked polymers under similar conditions, indicating their low cyclization efficiency. TBEED gave soluble or crosslinked polymers under similar conditions. Our attempt to obtain soluble polymers by decreasing the polymerization time resulted in only a milky solution, which we conjecture to contain very low-molecular weight polymers. Although poly-1 was obtained as a clear gel, poly-3 was a white solid powder, indicating a low molecular weight crosslinked polymer, showing the importance of chain transfer reaction during polymerization of monomer 3. The labile hydrogen between two phosphonate groups in monomer 3 is probably the reason for the chain transfer reaction, giving unexpectedly high crosslinking tendency despite a bulky bisphosphonate substituent.

The chemical shift difference $\Delta\delta$ (δC_β-δC_α) measurable by ^{13}C-NMR can be used to assess the effects of substituents on the free radical polymerizability of monomers, since the electron withdrawing power of the substituents affects the double bond [66, 67]. Substituents with stronger the electron-withdrawing power (indicated by smaller the chemical shift differences) lead to higher the radical polymerizability, dominating over the chain transfer reactions and resulting in higher molecular weight polymers. Bulky substituents, on the other hand, increase differences in chemical shifts, decrease polymerizability, leading to both high cyclization efficiency and high chain transfer rate. Table 4.7 shows the chemical shift differences of vinyl carbons for monomer 3 together with its phosphonated bis-methacrylamide analogs. The higher chemical shift value of monomer 1 compared to 2 can be ascribed to the steric effect: the bulky phosphonate group in monomer 2 is one carbon further away from the double bond. Therefore, monomer 3 with a bulky bisphosphonate group would be expected to have higher chemical shift value;

however, it showed the lowest. This is probably due to the doubled electron withdrawing power of the phosphonate groups overcoming the steric effect. Even so, monomer 3 did not show as high polymerizability as expected from its chemical shift, presumably due to early termination by the above-mentioned tendency of chain transfer.

Table 4.6. Thermal polymerization results of monomer 3 & its copolymers.

Monomer	[M]	[AIBN]	Solvent	Time (min)	Conversion (%)	M_n
3	1.26	0.0350	toluene	180	crosslinked	-
3	1.26	0.0350	toluene	120	-	Very low MW
TBEED:**3** (90:10 mol%)	1.30	0.0380	toluene	21	crosslinked	-
TBEED:**3** (90:10)	1.30	0.0380	toluene	28	54	22450
TBEED:**3** (90:10)	1.30	0.0380	toluene	45	43	26650
TBEED:**3** (80:20)	1.30	0.0380	toluene	122	19	20029

Table 4.7. Chemical shift differences, $\Delta\delta$ (δC_β-δC_α), of vinyl carbons for monomers 1, 2 & 3.

Monomers	**1**	**2**	**3**
$\Delta\delta$	15.11	14.98	13.65

Monomer 3 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 FT-IR spectrum of one of the copolymers, TBEED:3 (80:20 mol%), with a peak at 1018 cm^{-1} due to P-O stretching supported the incorporation of monomer 3 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 20000) than that of homopolymer of TBEED indicated the importance of chain transfer reactions.

The thermal stability of poly-3 and copolymer of 3 with TBEED (TBEED:3, 80:20 mol%) was investigated by thermogravimetric analysis (TGA) under nitrogen at 10 °C/minute and compared to those of poly-1 and poly-TBEED (Figure 4.18). Poly-3 and poly-1 were found to be more stable than poly-TBEED, starting to decompose around at 200 °C and at 225 °C. Poly-3 degraded smoothly over a broad temperature range while poly-1 features stepwise degradation. Both polymers also gave higher char yields (43.88% for poly-1 and 53.42% for poly-3) compared to poly-TBEED (11.83%) at 575 °C. These high char yields are probably due to the formation of bisphosphonic acid which causes crosslinking reactions during degradation. The char yields above are consistent with the expectation that this mechanism should be more effective in poly-3 with its four phosphonate groups of its monomer unit. Both poly-TBEED and copolymer of 3 with TBEED (TBEED:3, 80:20 mol%) started to lose weight around 200 °C due to decomposition of the *t*-butyl ester group and then degraded gradually by ring decomposition and depolymerization to give char yields of 11.83 and 25.82%, respectively. These results indicated that addition of 3 to TBEED improved the char yield by 13.99%.

4.2.3. Thermal Copolymerizations of Monomer 3a

Thermal homopolymerization of monomer 3a was not investigated due to its very low photopolymerization rate. However, in order to check the incorporation of this monomer into the copolymers, its thermal solution copolymerizations with AAm and HEMA were investigated. Monomer 3a was copolymerized with AAm (5:95 mol%) in water at 65°C with V-50 as initiator. Although AAm homopolymerizes in 4 minutes to give soluble polymers, its copolymerization with 3a took more than 12 h. Crosslinked copolymers precipitated as white solid powders which indicate the incorporation of monomer 3a. Monomer 3a was also copolymerized with HEMA (10:90 mol%) in ethanol at 50°C with AIBN as initiator. The addition of monomer 3a to HEMA decreased its polymerization rate: HEMA homopolymerizes in 45 minutes giving clear gels, but the copolymer formed in more than 12 h giving a white solid crosslinked polymer. FT-IR spectrum of one of the copolymers (after removal of residual monomers) indicated C=O and N-H peaks of monomer 3a, which proved its incorporation into the copolymer (Figure 4.19).

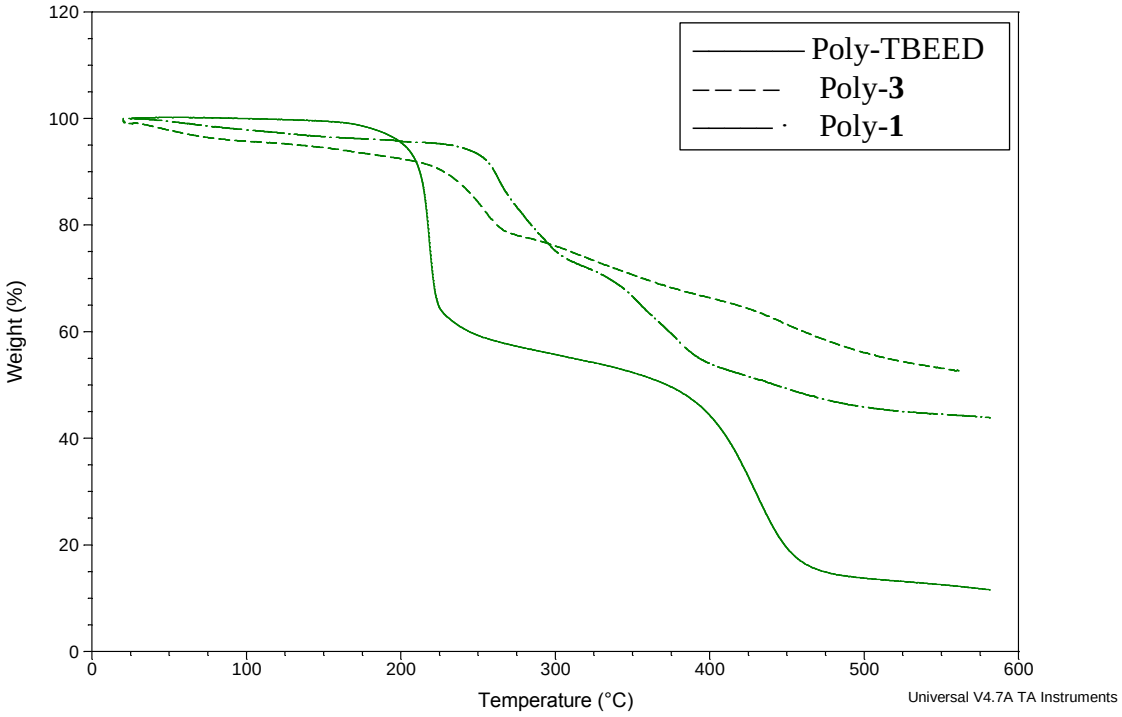


Figure 4.18. TGA results of poly-1, poly-3 and poly-TBEED.

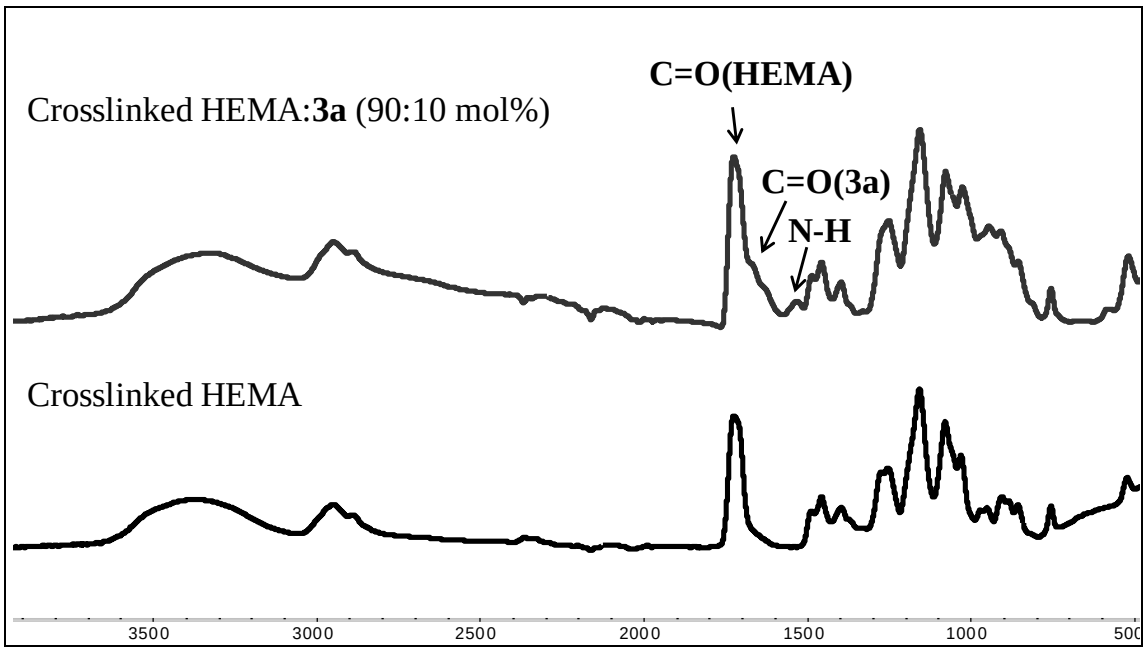


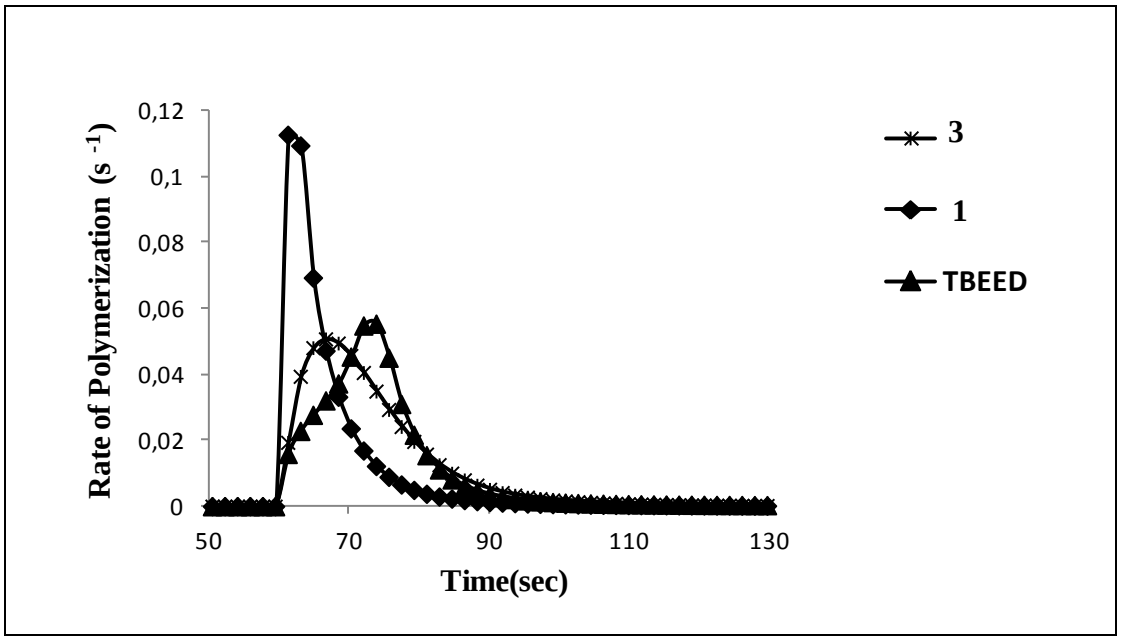
Figure 4.19. FT-IR spectra of homopolymer of HEMA and its copolymer with 3a (HEMA:3a, 90:10 mol%).

4.2.4. Photopolymerizations of Monomers 3 and 3a

To determine the effect of monomer structure on polymerization reactivity, the conversion and polymerization rate of monomers TBEED, 1, 3 and 3a were monitored using photo-DSC, as function of time. Figure 4.20 shows the results for monomers 1, 3 and TBEED. We see a significant difference in radical polymerizability between these monomers: The maximum rates of polymerizations for 1, 3 and TBEED were found to be 0.1127, 0.0508 and 0.0554 s^{-1}. The lower polymerizability of TBEED and monomer 3 may be explained on the basis of steric effect of tert-butyl groups and both steric and chain transfer effects of bisphosphonate groups. Also, it was observed that although the maximum rate of polymerization of monomer 1 is higher than TBEED and monomer 3, conversion at maximum rate is lower. At maximum rate of polymerizations 10 mol%, 47 mol% and 24 mol% of the double bonds were reacted for monomers 1, TBEED and 3. The reason for increased conversion at maximum rate for monomers 3 and TBEED indicates a delayed gel effect due to lower crosslinking tendencies of these monomers compared to monomer 1.

In order to test the use of monomer 3 as reactive diluent in filling composites and also crosslinking monomers in dental adhesives, we investigated its copolymerization with Bis-GMA and HEMA. The results (Figure 4.21 and Table 4.8) show that the polymerization rate of monomer 3 is lower than Bis-GMA but slightly higher than HEMA. The conversions follow the order: HEMA>3>Bis-GMA. Addition of 10 mol% of monomer 3 to Bis-GMA slightly decreased its rate without changing its conversion. However, addition of 10 mol% of monomer 3 to HEMA did not change its rate but decreased its conversion due to crosslinking.

In order to test the potential of monomer 3a to be used in dental adhesives, the homo- and 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, 3a and water (at different ratios) were photopolymerized. Figure 4.22 and Table 4.9 show that addition of 5-20 wt% of 3a to HEMA resulted to gradual decreases in both conversion and rate of polymerization. Also, slight shift in the peak maximum indicated the incorporation of monomer 3a into copolymers.



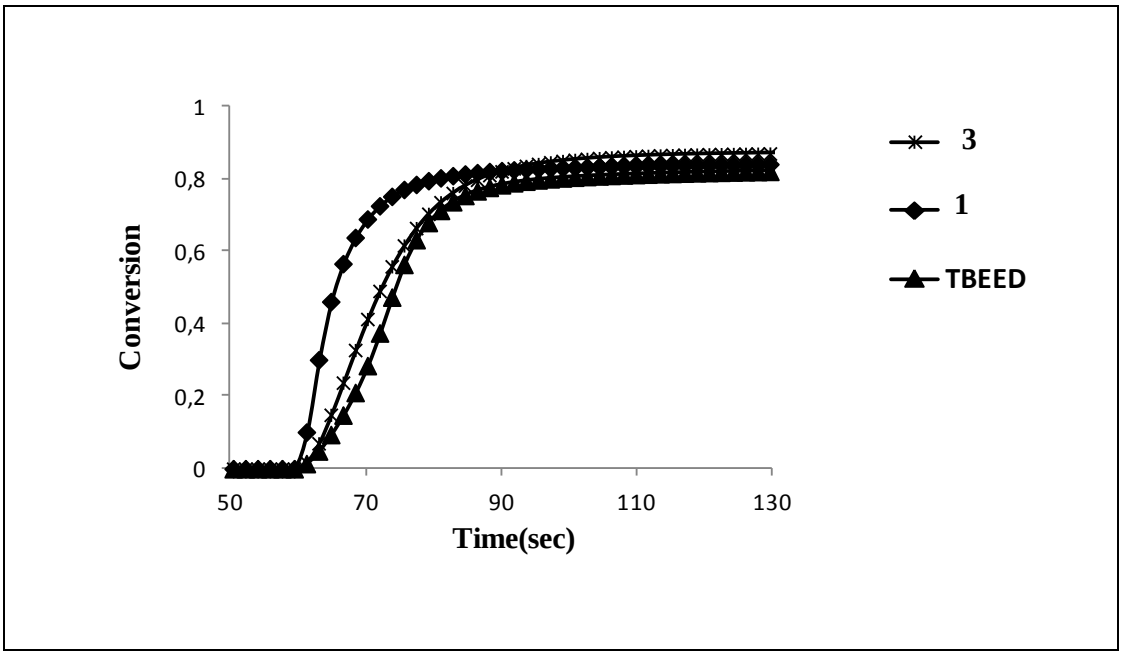
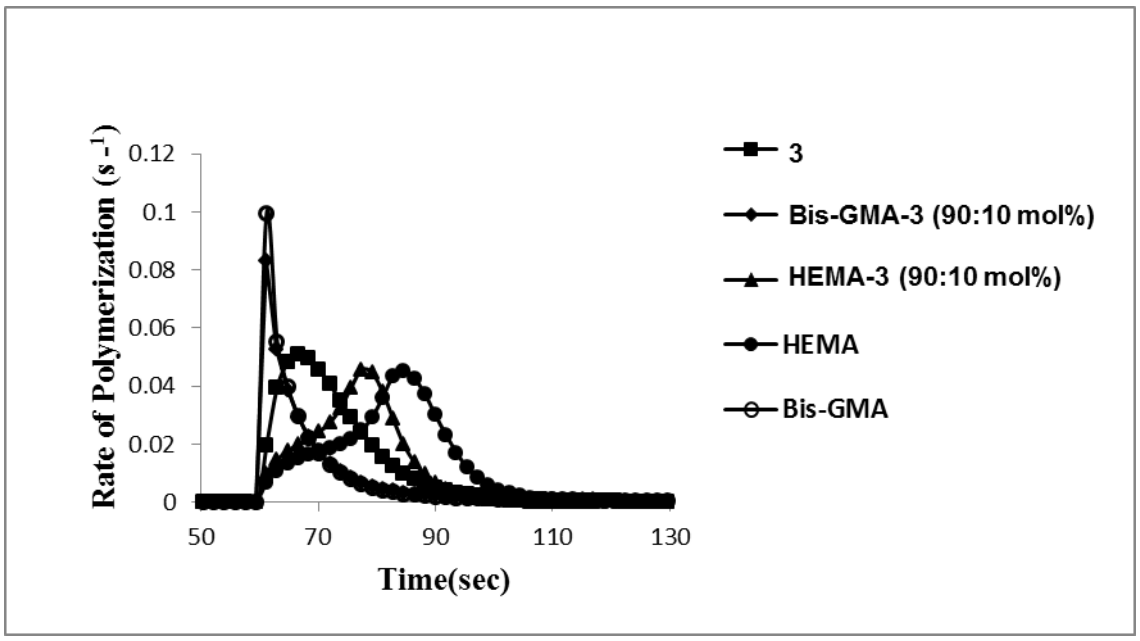


Figure 4.20. Rate-time and conversion-time curves in the polymerizations of 3, 1 and TBEED at 72 ^{o}C.

4.2.5. Acidity, Interaction with HAP and Stability of Monomer 3a

The pH value of aqueous solution of monomer 3a (5 wt%) was found to be 1.10, indicating its enamel etching ability. The addition of 15, 30 and 60 mg HAP, a model

compound for dentin and enamel, to the solutions of this monomer resulted in increases in the pH values to 1.65, 1.90 and 3.34, respectively.



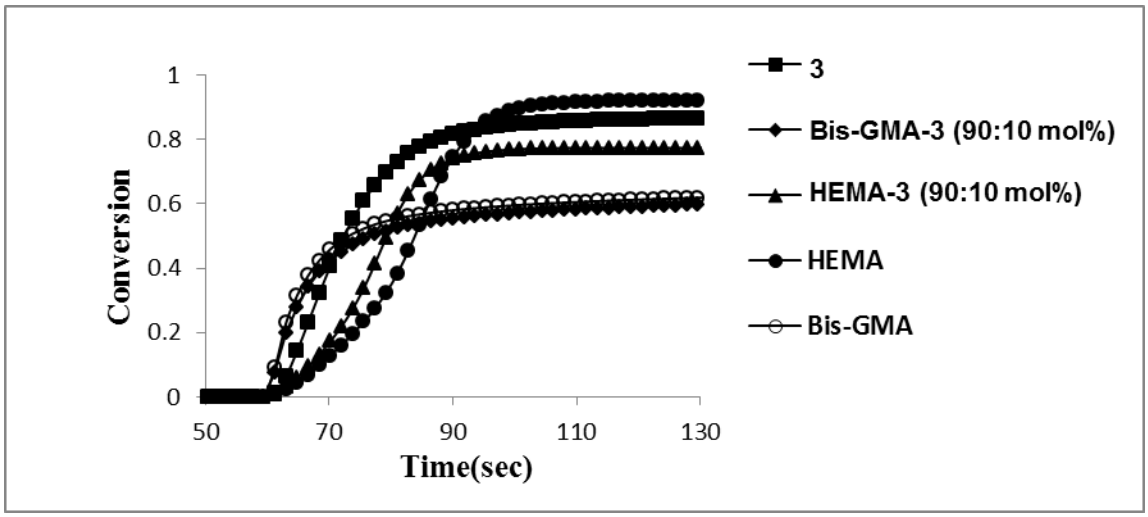


Figure 4.21. Rate-time and conversion-time curves in the homopolymerization and copolymerizations of 3 with HEMA and Bis-GMA at 72 ^{o}C.

The interaction of monomer 3a with HAP was investigated using FT-IR spectrometer (Figure 4.23). The FT-IR spectrum of HAP-3a mixture showed peaks due to HAP and monomer 3a, a decrease at the peak at 998 cm^{-1} due to asymmetric vibration of P-O in monomer 3a and a new peak around 1027 cm^{-1}, overlapping with PO_4^{3-} peak of HAP at

1016 cm^{-1}. The decrease of the P-O peak and the appearance of the new peak indicate adsorption of monomer 3a on the HAP surface due to hydrogen bonding or complex formation.

Table 4.8. Photopolymerization results of monomers 3, 1 & their copolymer with HEMA and Bis-GMA at 72 ^{o}C.

Monomer	$R_p(s^{-1})$	Conversion (%)
3	0.051	84
1	0.113	84
Bis-GMA	0.099	67
HEMA	0.045	92
Bis-GMA:**3** (90:10 mol%)	0.083	65
HEMA:**3** (90:10 mol%)	0.046	77
Bis-GMA:**1** (90:10 mol%)	0.109	68
HEMA:**1** (90:10 mol%)	0.051	90

Table 4.9. Photo-DSC results of acidic aqueous formulations using BAPO at 40 ^{o}C.

Monomer	$R_p(s^{-1})$	Conversion (%)
HEMA:water (60:40 wt%)	0.035	86
HEMA:**3a**:water (55:5:40 wt%)	0.031	80
HEMA:**3a**:water (50:10:40 wt%)	0.028	79
HEMA:**3a**:water (45:15:40 wt%)	0.028	76
HEMA:**3a**:water (40:20:40 wt%)	0.025	70

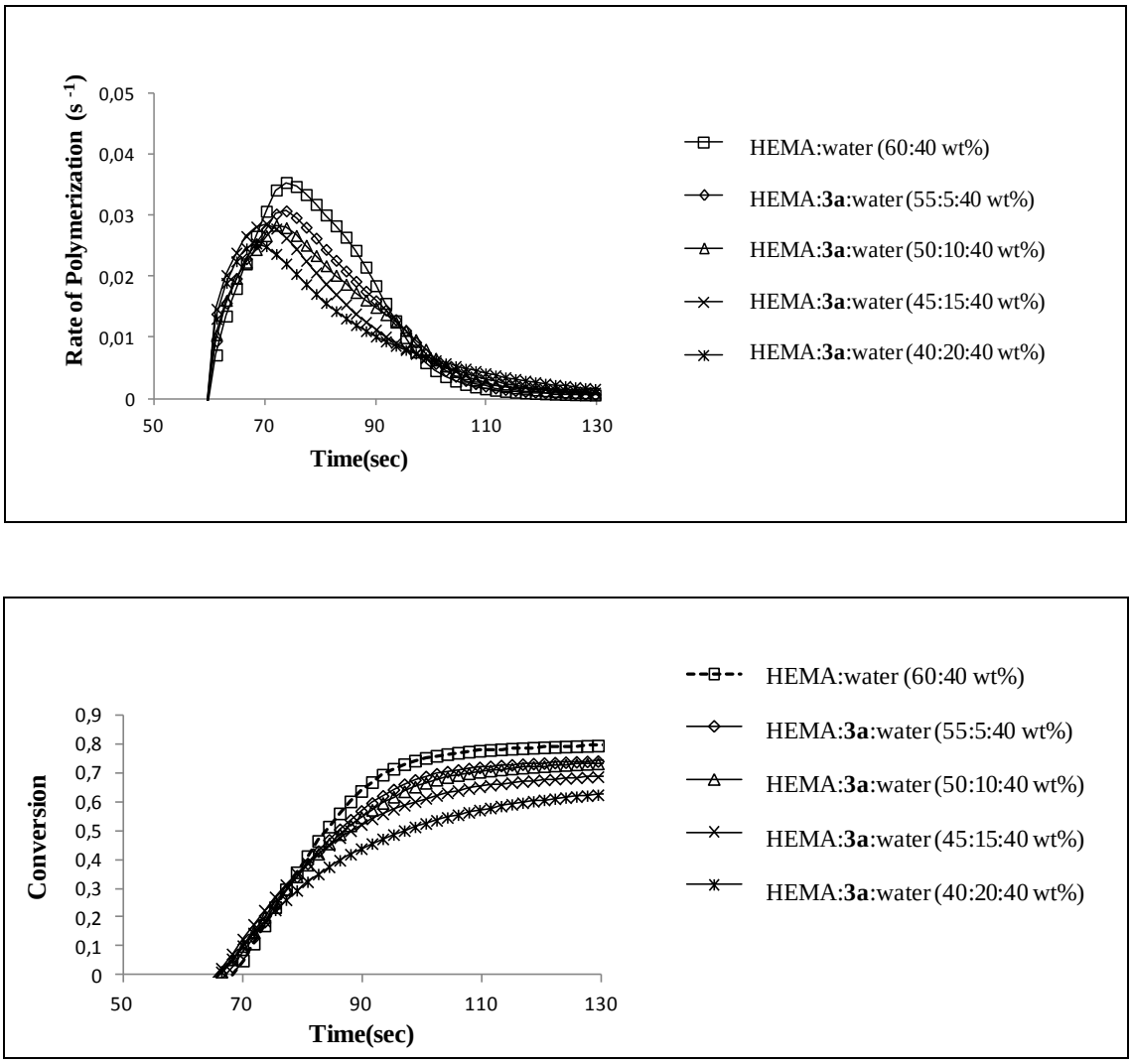


Figure 4.22. Rate-time and conversion-time curves in the homopolymerization and copolymerizations of 3a with HEMA using BAPO at 40 ^{o}C.

We expected that monomer 3a would be more hydrolytically stable compared to commercial dentin adhesives 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 monomer 3a which contain acid groups within the same structure. Therefore hydrolytic stability of the acid monomer 3a 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 3a, showing its stability for at least one month.

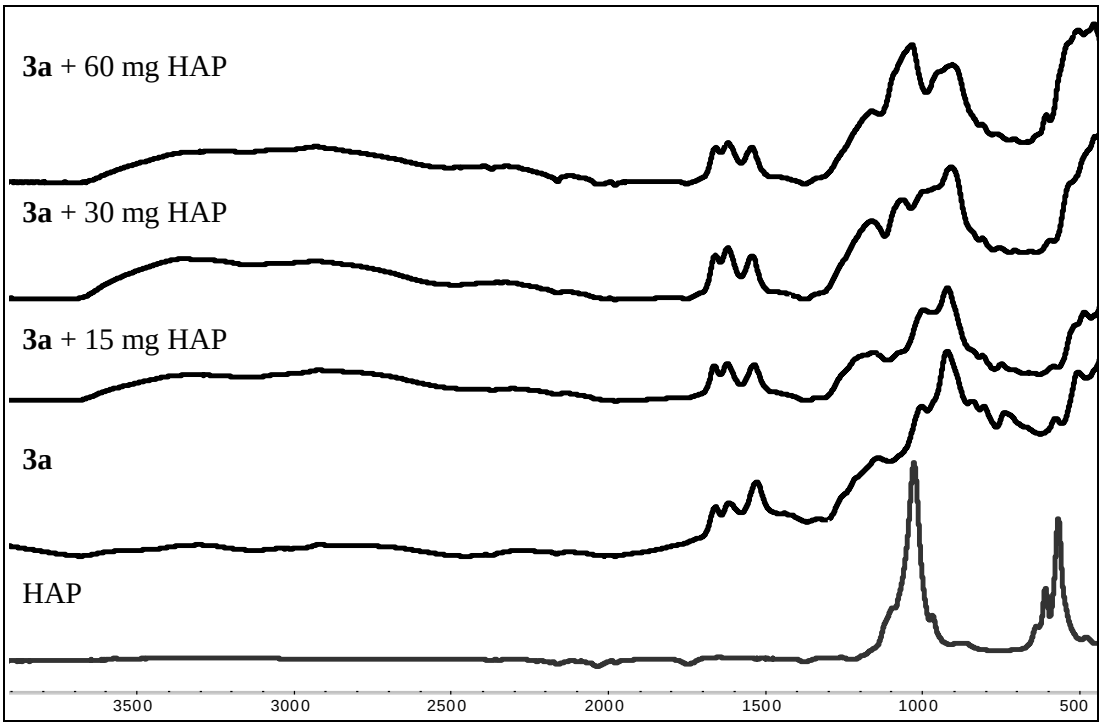


Figure 4.23. FT-IR spectra of HAP, monomer 3a, monomer 3a with 15 mg HAP, monomer 3a with 30 mg HAP and 3a with 60 mg HAP.

4.3. Synthesis and Polymerizations of Novel Bisphosphonated-Methacrylamides

4.3.1. Synthesis and Characterizations of Novel Bisphosphonated-Methacrylamides

A new bisphosphonate-containing methacrylamide (4) was synthesized in one step by the reaction of methacryloyl chloride and tetraethyl aminomethyl-bis(phosphonate) in the presence of triethylamine (Figure 4.24). This monomer was obtained as a white solid with a melting point of 33-34 ^{o}C in 36% yield after purification by flash chromatography. It was soluble in common organic solvents such as hexane, methylene chloride, acetone, ether, ethanol, THF and also soluble in water (Table 4.10).

The structure of monomer 4 was proved by FT-IR, ^{1}H and ^{13}C spectroscopy. In the ^{1}H-NMR the single bisphosphonate proton is present as a doublet of triplet at 5.10 ppm.

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 ppm (Figure 4.25). NH peak of carbamide group appears at 6.46 ppm as doublet. The ^{13}C-NMR of this monomer is shown in Figure 4.26. Methine carbon attached to two phosphorus appears as triplet at 42.17, 43.63 and 45.09 ppms as expected. The monomer structure was also confirmed by FT-IR spectra which showed characteristic peaks at 3400-3300 cm^{-1} (amide V region), 1668 cm^{-1} (amide I region) and 1518 cm^{-1} (amide II region). Monomer 4 also showed absorption peaks of C=C, P=O and P-O peaks at 1626, 1250, 1014 and 971 cm^{-1} (Figure 4.27).

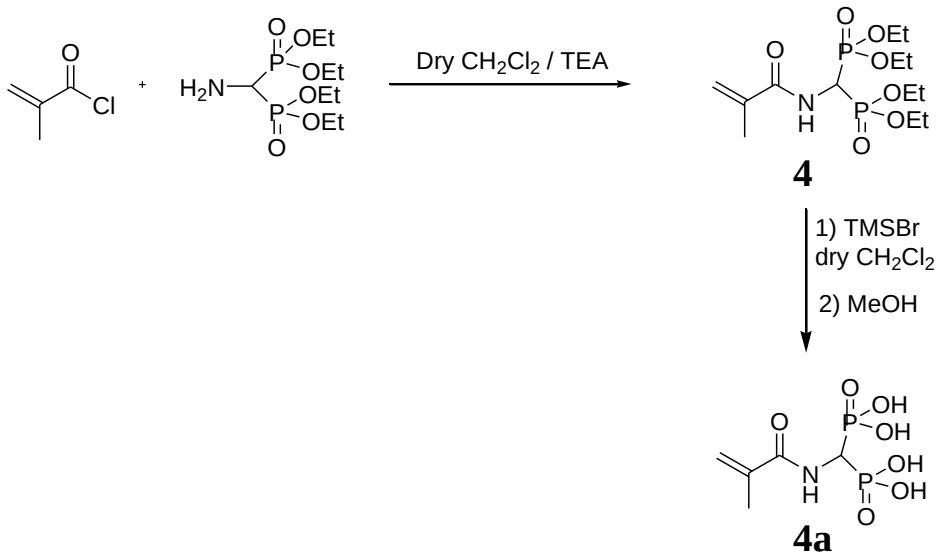


Figure 4.24. Synthesis of monomers 4 and 4a.

Table 4.10. Solubility of monomers 4and 4a.

Monomer	H_2O	Ethanol	THF	Acetone	Diethyl Ether	CH_2Cl_2	Hexane
4	+	+	+	+	+	+	+
4a	+	+	-	-	-	-	-

A new bisphosphonic acid containing methacrylamide, monomer 4a, was synthesized by the silylation of monomer 4 with TMSBr and methanolysis of the silyl ester groups (Figure 4.24). This monomer was obtained as a white solid in 95% yield after purification by C18 reversed-phase flash chromatography. Monomer 4a dissolves very well in water which is very important for dental adhesive applications (Table 4.10). The FT-IR spectrum of monomer 4a 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 1651, 1610 and 1533 cm^{-1} due to C=O, C=C and NH stretchings, respectively (Figure 4.27). Also the strong bands at 954 and 922 cm^{-1} correspond to the symmetric and asymmetric vibration of P-O. ^{1}H-NMR spectrum of monomer 4a shows the complete disappearance of bisphosphonic ester peaks at 1.33 and 4.17 ppm (Figure 4.28).

4.3.2. Thermal Homopolymerization of Monomer 4

Thermal bulk homopolymerization of monomer 4 were conducted with 2 mol% of AIBN at 65 ^{o}C using standard freeze-evacuate-thaw procedures (Figure 4.29). Bulk polymerization of monomer 4 gave a soluble polymer in ten minutes with 40% conversion, indicating its high reactivity. The polymer was obtained as a white solid after precipitation into hexane with few drops of ether. The polymer was soluble in dichloromethane, acetone, ether and water but insoluble in hexane.

^{1}H-NMR spectrum of the poly-4 is shown in Figure 4.30. The double bond peaks at 5.42 and 5.74 ppm completely disappeared after polymerization. The number average molecular weight (M_n) for this polymer was around 32000 as estimated by size exclusion chromatography.

4.3.3. Photopolymerizations of Monomers 4 and 4a

Photopolymerizations of monomers 4 and HEMA were investigated with photodifferential scanning calorimetry to determine their relative rate of polymerizations. All the polymerizations were performed under identical conditions of temperature, initiator concentration and light intensity. Figure 4.31 shows the time dependences of the polymerization rate and conversions for monomers 4, HEMA and their copolymer.

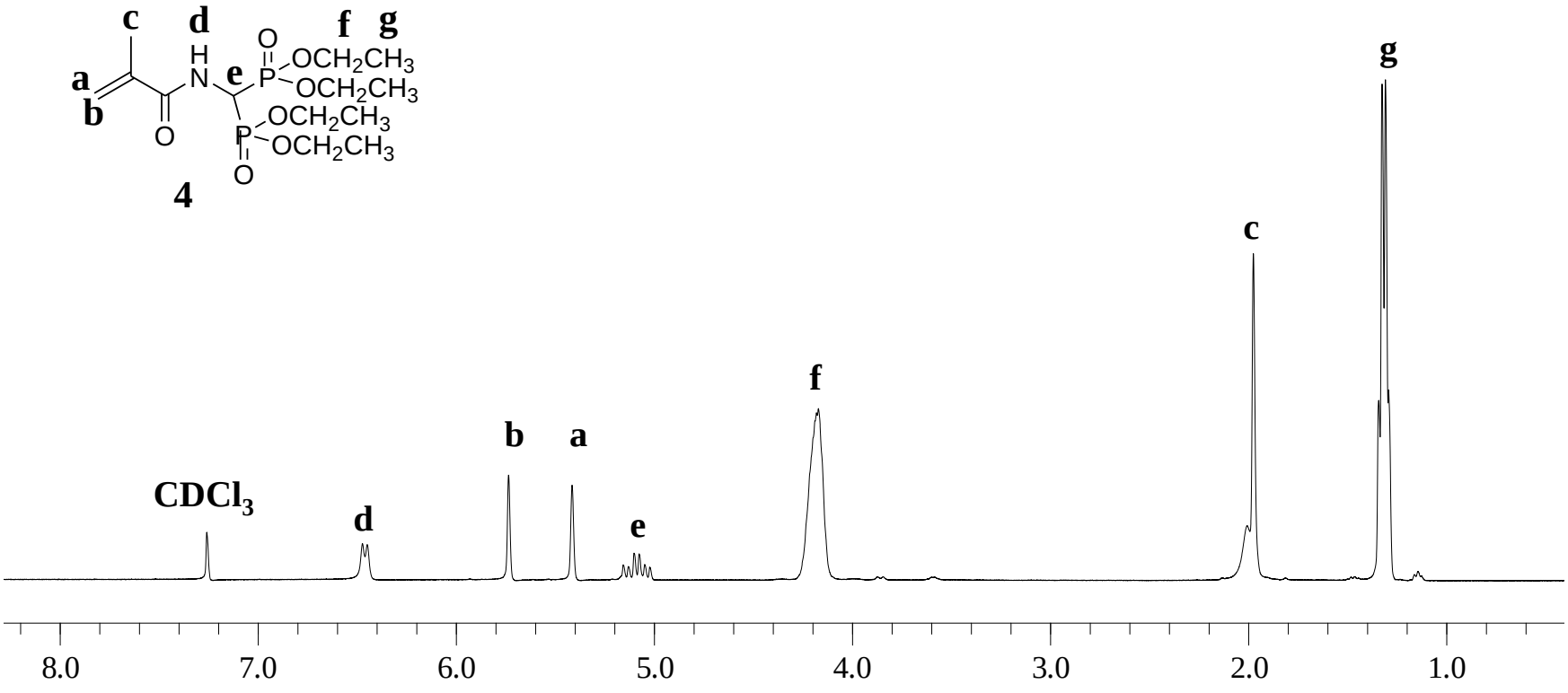


Figure 4.25. ^{1}H-NMR spectrum of monomer 4.

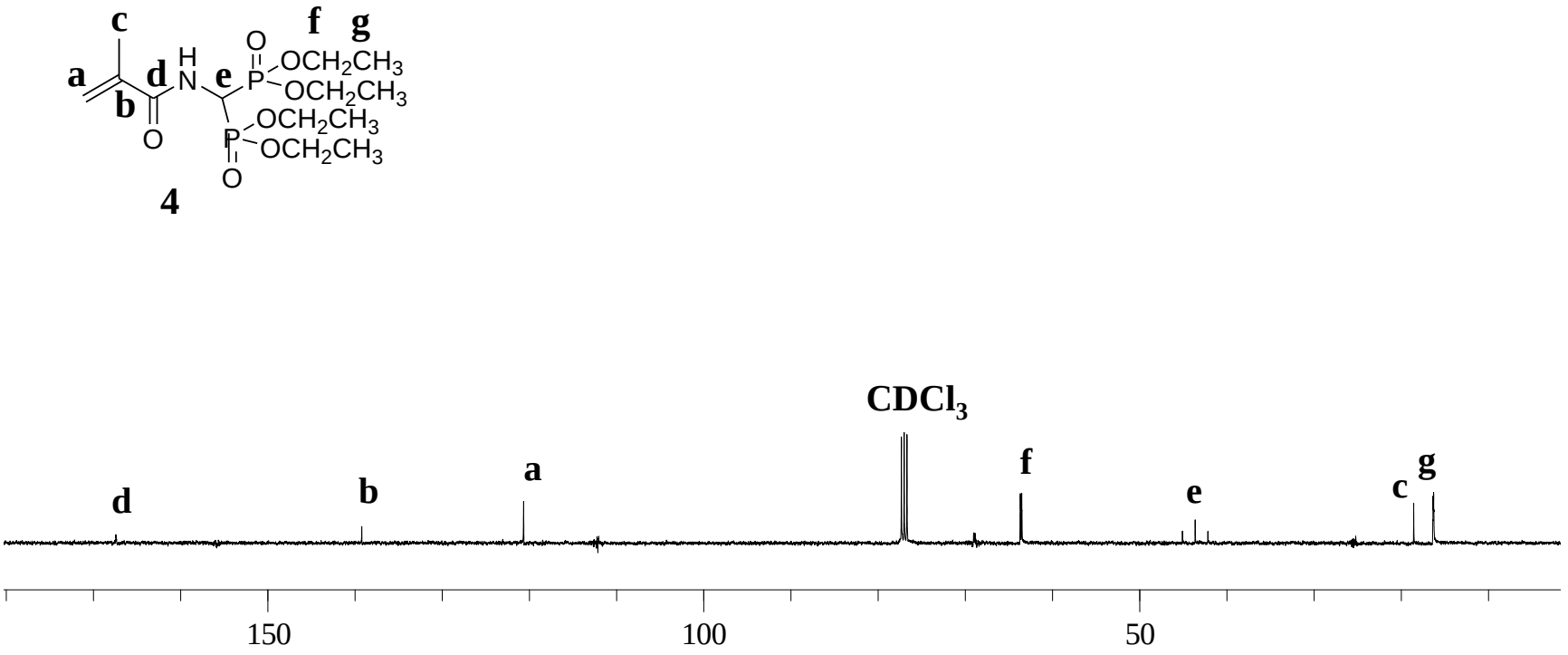


Figure 4.26. ^{13}C-NMR spectrum of monomer 4.

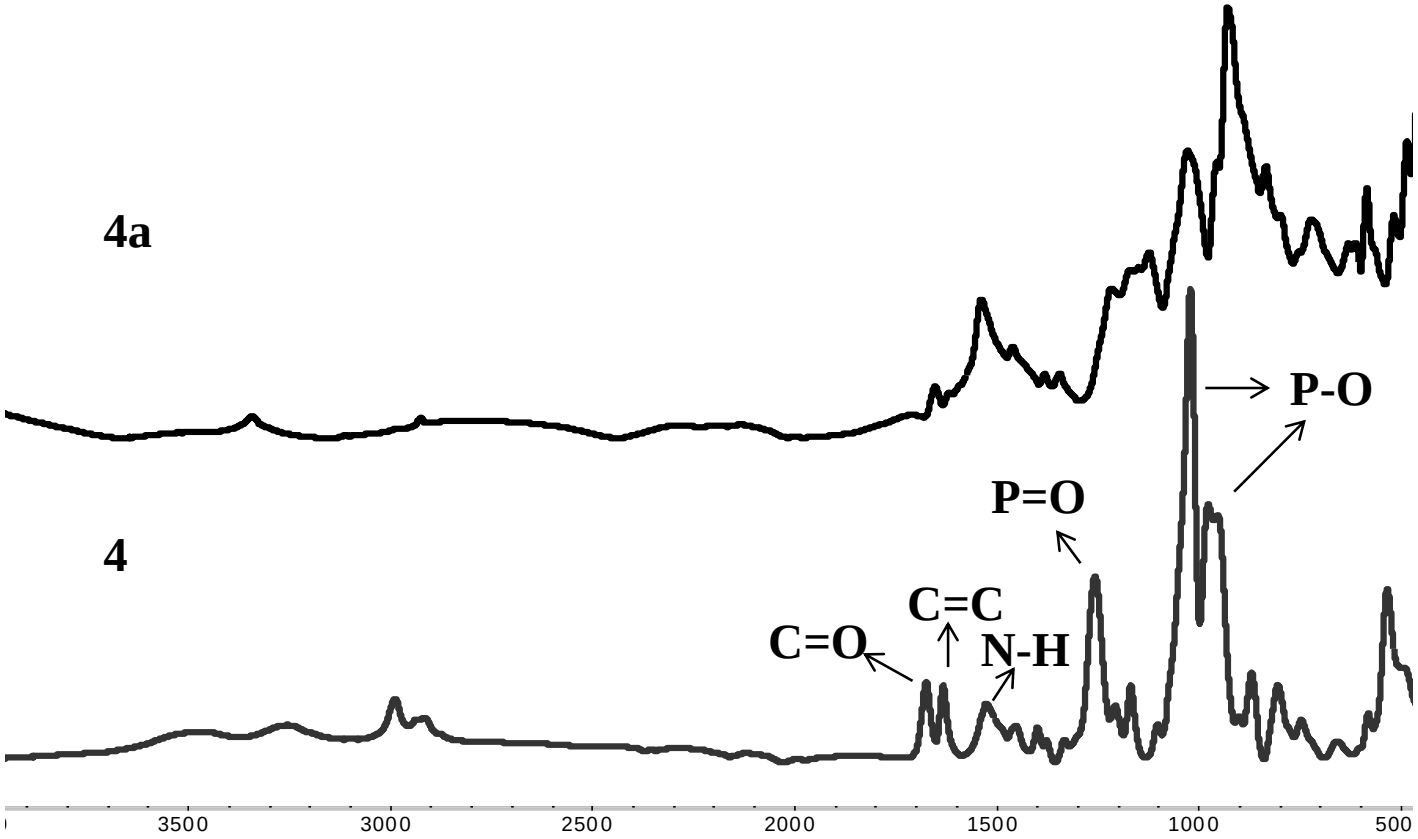


Figure 4.27. FT-IR spectra of monomers 4 and 4a.

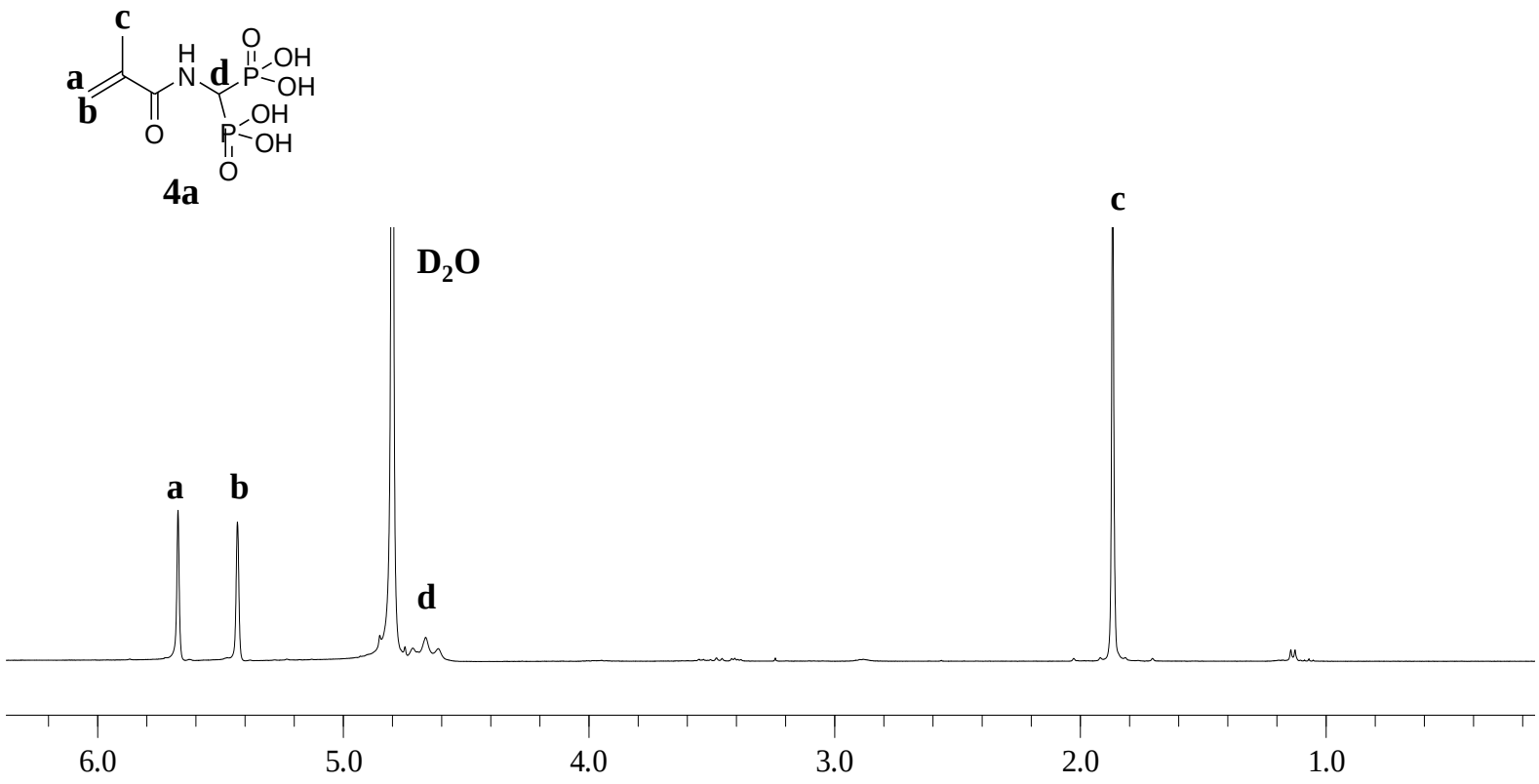


Figure 4.28. ^{1}H-NMR spectrum of monomer 4a.

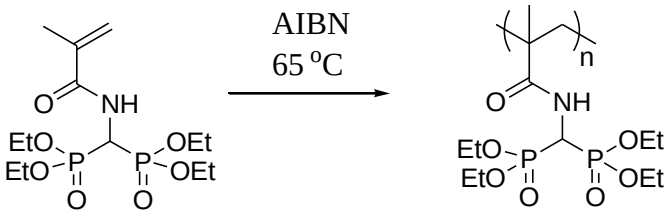


Figure 4.29. Polymerization scheme of monomer 4.

Photopolymerization rate of monomer 4 was found to be lower than HEMA, with the maximum rate of polymerizations of 0.013 and 0.034 s^{-1} for monomer 4 and HEMA. The conversions reached were 64 and 82% for monomer 4 and HEMA. The lower rate of photopolymerization of monomer 4 compare to HEMA is expected: due to steric effect of the bulky bisphosphonate group. Addition of monomer 4 to HEMA decreased the rate of HEMA slightly but it did not change the conversion significantly.

In order to test the potential of monomer 4a to be used in dental adhesives, the homo- and 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%); 4a and water (60:40 wt%); HEMA, 4a and water (45:15:40 wt%) were photopolymerized. Figure 4.32 shows that addition of 15 wt% of 4a to HEMA resulted in an increase in rate of polymerization but a decrease in conversion. However, homopolymerization of 4a showed very low polymerization rate, its copolymer with HEMA resulted in higher reactivity than homopolymerization of HEMA, and therefore this indicated the incorporation of monomer 4a into the copolymer.

The pH value of aqueous solution of monomer 4a (2 wt%) was found to be 1.21, indicating its enamel etching ability.

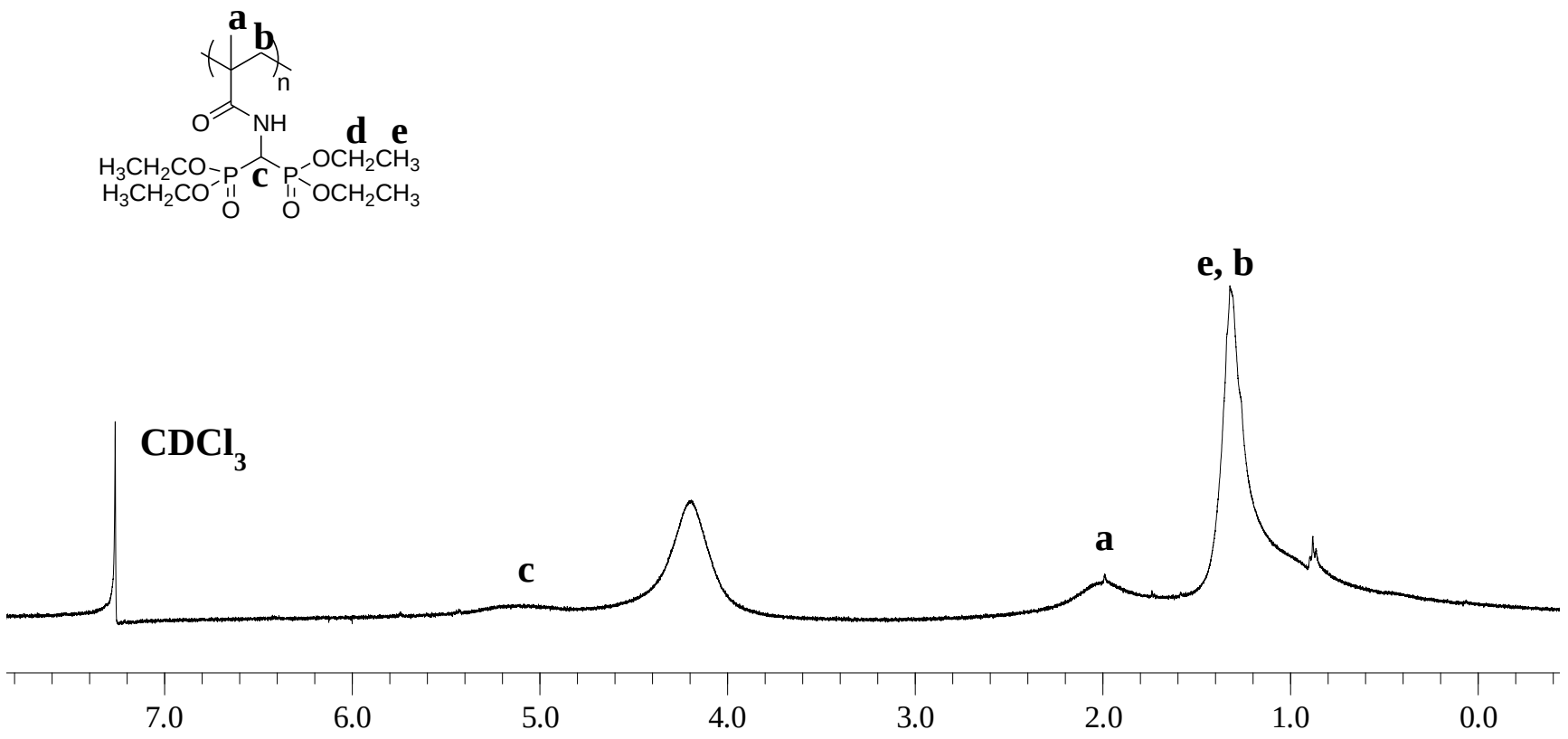
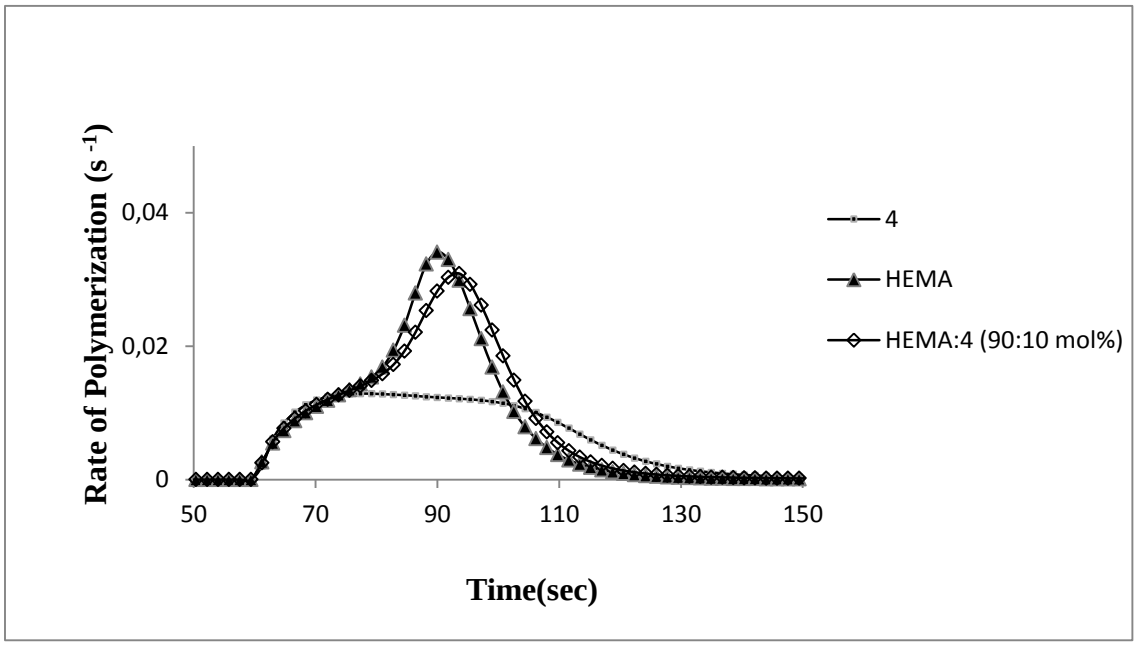


Figure 4.30. ^{1}H-NMR spectrum of poly-4.



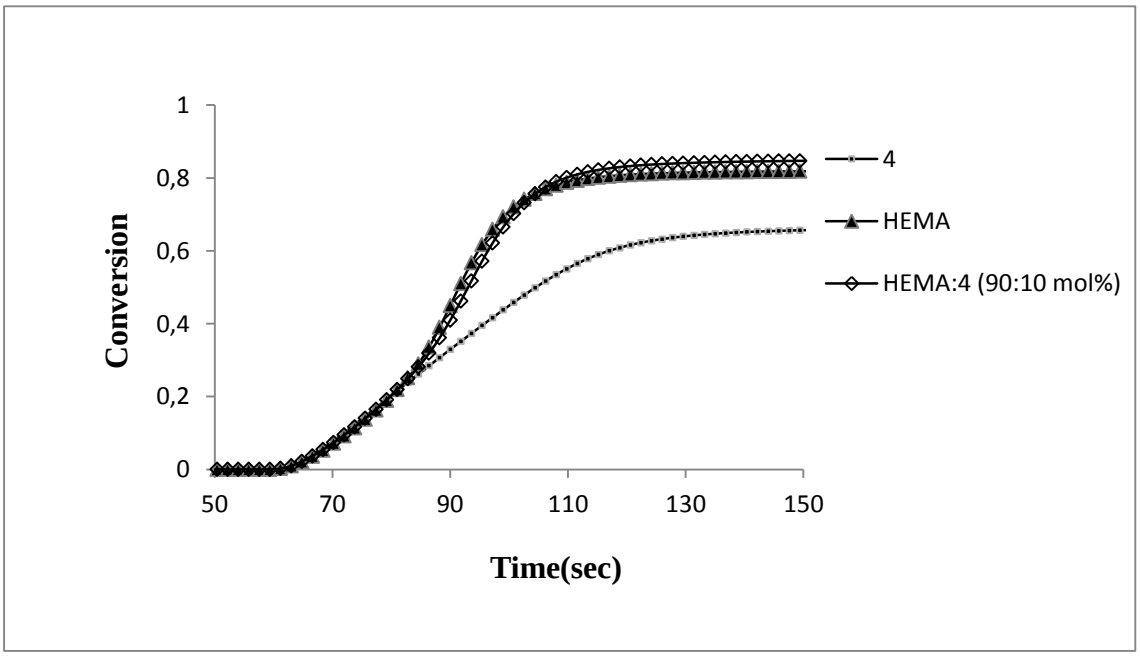


Figure 4.31. Rate-time and conversion-time curves during polymerizations of 4, HEMA and HEMA:4 (90:10 mol%) at 40 ^{o}C.

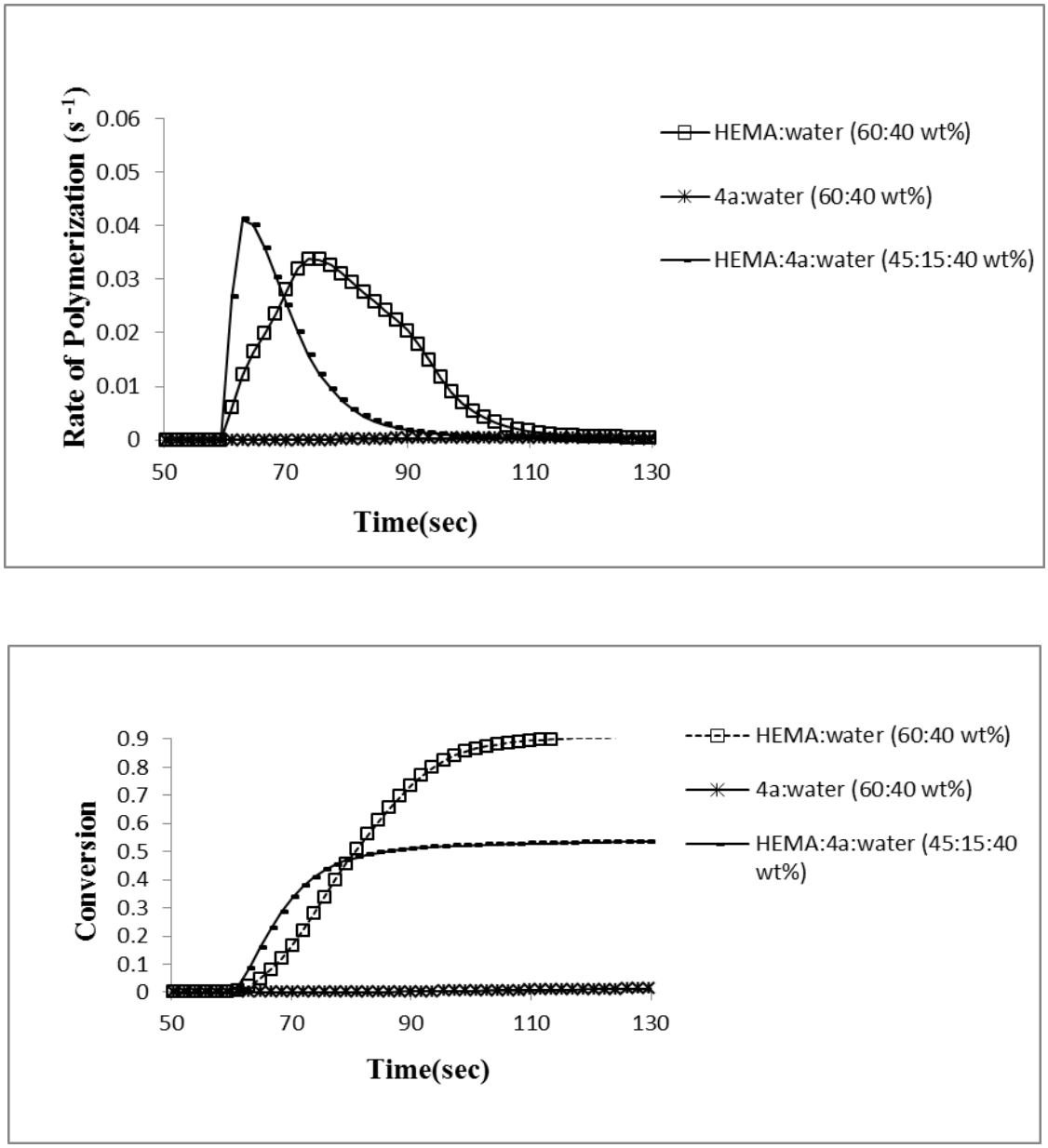


Figure 4.32. Rate-time and conversion-time curves during homopolymerizations and copolymerizations of 4a with HEMA using BAPO at 72°C.

5. CONCLUSION

Two novel bis(methacrylamide)s containing phosphonate groups, monomers 1 and 2, were synthesized and evaluated in terms of cyclopolymerizability compared to TBHMA-ether dimer. High reactivity and crosslinking tendency of these monomers may be due to small size or lower 'effective bulkiness' of the substituent and/or hydrogen bonding. Because these monomers were found to be more reactive than Bis-GMA and HEMA, their potential in dental systems as reactive diluents or crosslinkers was also evaluated. Utilizing one of these monomers resulted in improvements in photopolymerization kinetics of both Bis-GMA and HEMA. Hence, these highly reactive and hydrolytically stable monomers show great promise to be used as reactive diluents or crosslinkers in dental applications.

Two novel bis(methacrylamides) containing phosphonic acid groups, 1a and 2a, were synthesized and evaluated in dental adhesives. Although these monomers showed very low polymerization rates and conversions, because of their etching and binding ability, hydrolytic stability and copolymerizability with dental monomers such as HEMA gives them potential to be used as adhesive monomers in dental adhesives.

A novel bisphosphonate and a bisphosphonic acid-containing bismethacrylamide, 3 and 3a, were synthesized at high purity and in good yield. Polymerization studies of the bisphosphonate-containing one indicated high reactivity, crosslinking and chain transfer tendency. The photopolymerization reactivity of this monomer was comparable to TBEED but lower than its phosphonated analog. The copolymerization results with Bis-GMA and HEMA indicated that this highly reactive monomer may possess potential as reactive diluent for dental composites. Bisphosphonic acid-containing bismethacrylamide shows good performance in terms of solubility, hydrolytic stability, acidity, interaction with HAP and copolymerizability with HEMA and may have potential to be used in self-etching dental adhesives.

Finally, a novel bisphosphonate and a bisphosphonic acid-containing methacrylamide, 4 and 4a, were obtained in good yield and high purity. Homopolymerization studies of the bisphosphonate-containing monomer 4 showed high reactivity and gave a soluble polymer in a short time. Also, the photopolymerization

reactivity of this monomer showed that this monomer can be used as a reactive diluent for dental composites. Bisphosphonic acid-containing methacrylamide has good performance in solubility, acidity and copolymerizability with HEMA. Copolymerization of this monomer with HEMA resulted in higher reactivity than HEMA in photopolymerization. These results indicated that monomer 4a may have potential to be used in self-etching dental adhesives.

APPENDIX A: SPECTROSCOPY DATA

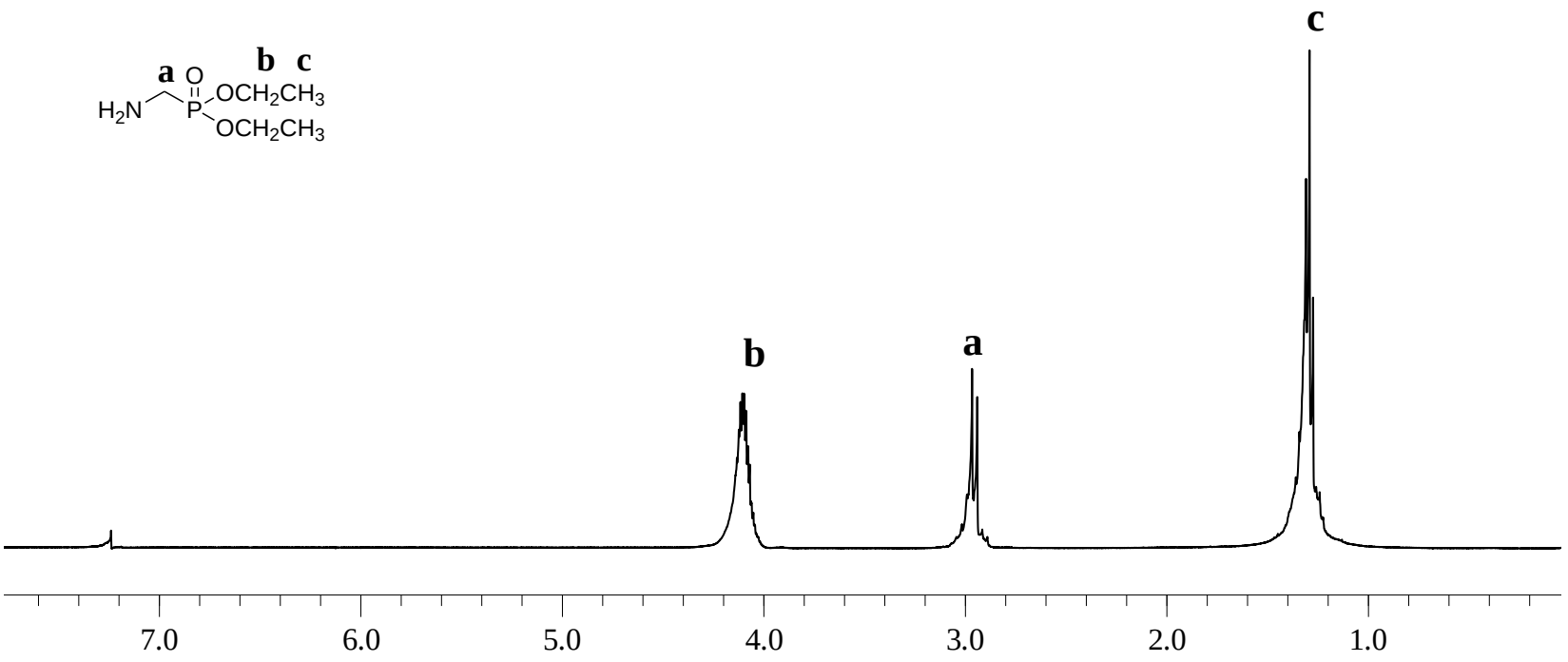


Figure A.1. ^{1}H-NMR spectrum of diethyl 1-aminomethylphosphonate.

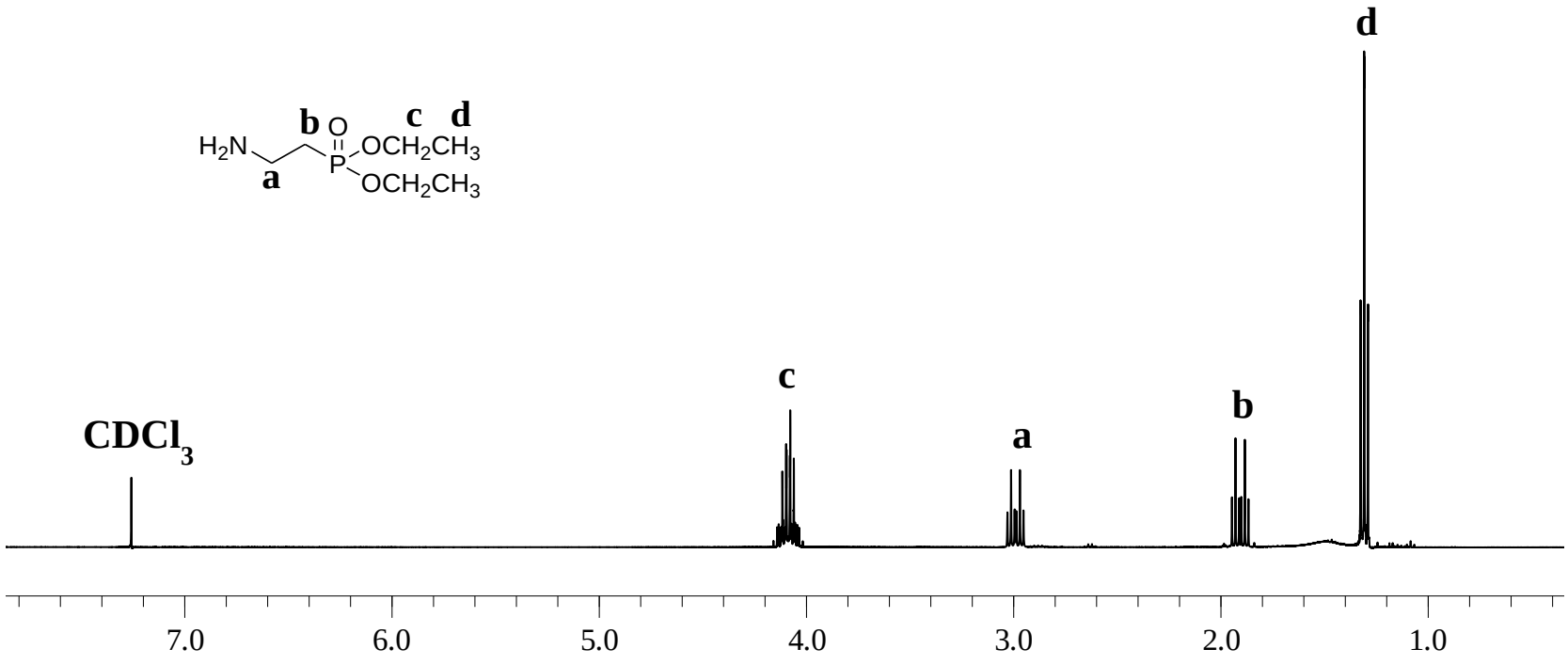


Figure A.2. ^{1}H-NMR spectrum of diethly 2-aminoethylphosphonate.

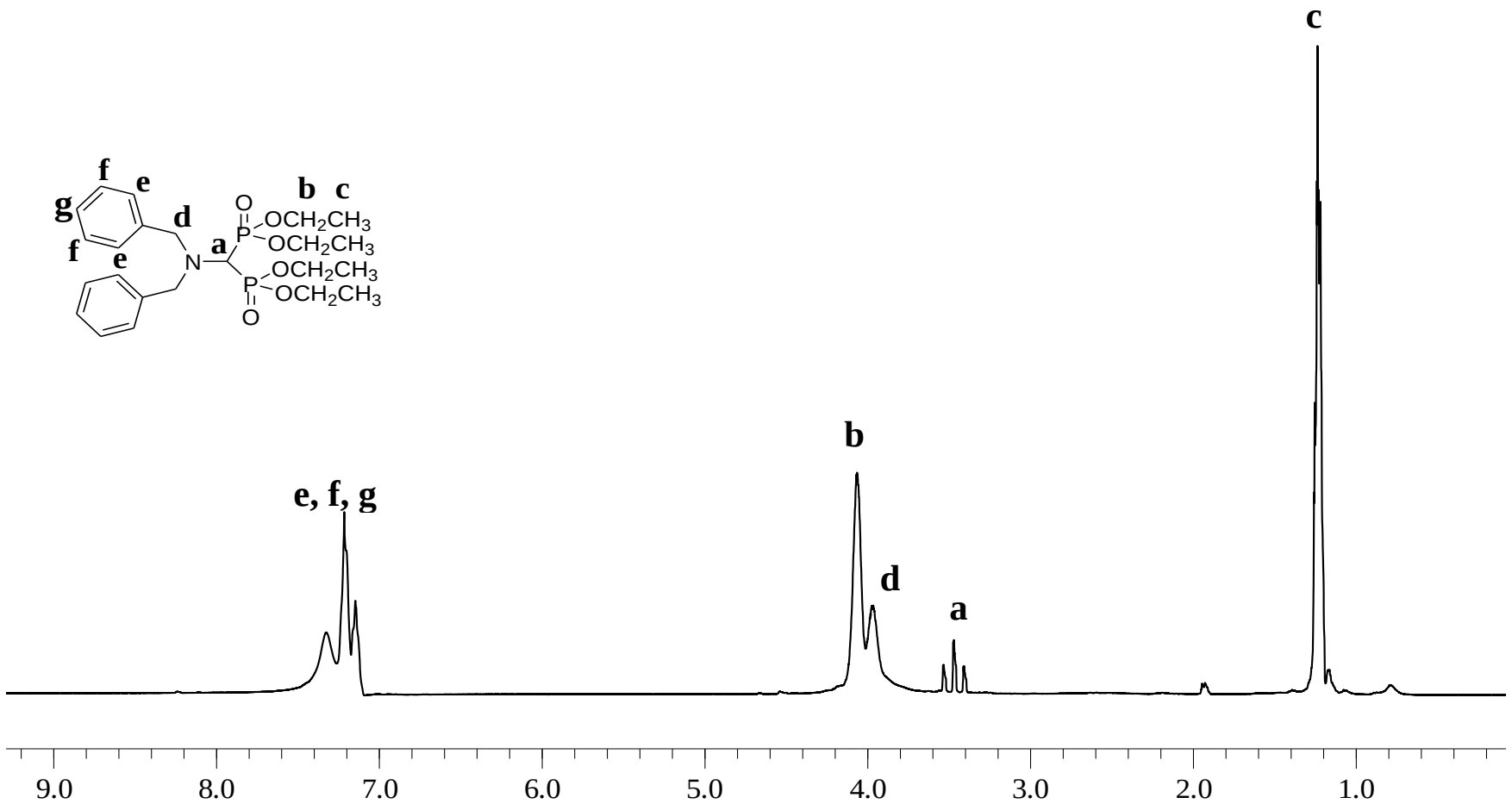


Figure A.3. ^{1}H-NMR spectrum of Tetraethyl (*N*,*N*-Dibenzyl)aminomethyl-bis(phosphonate).

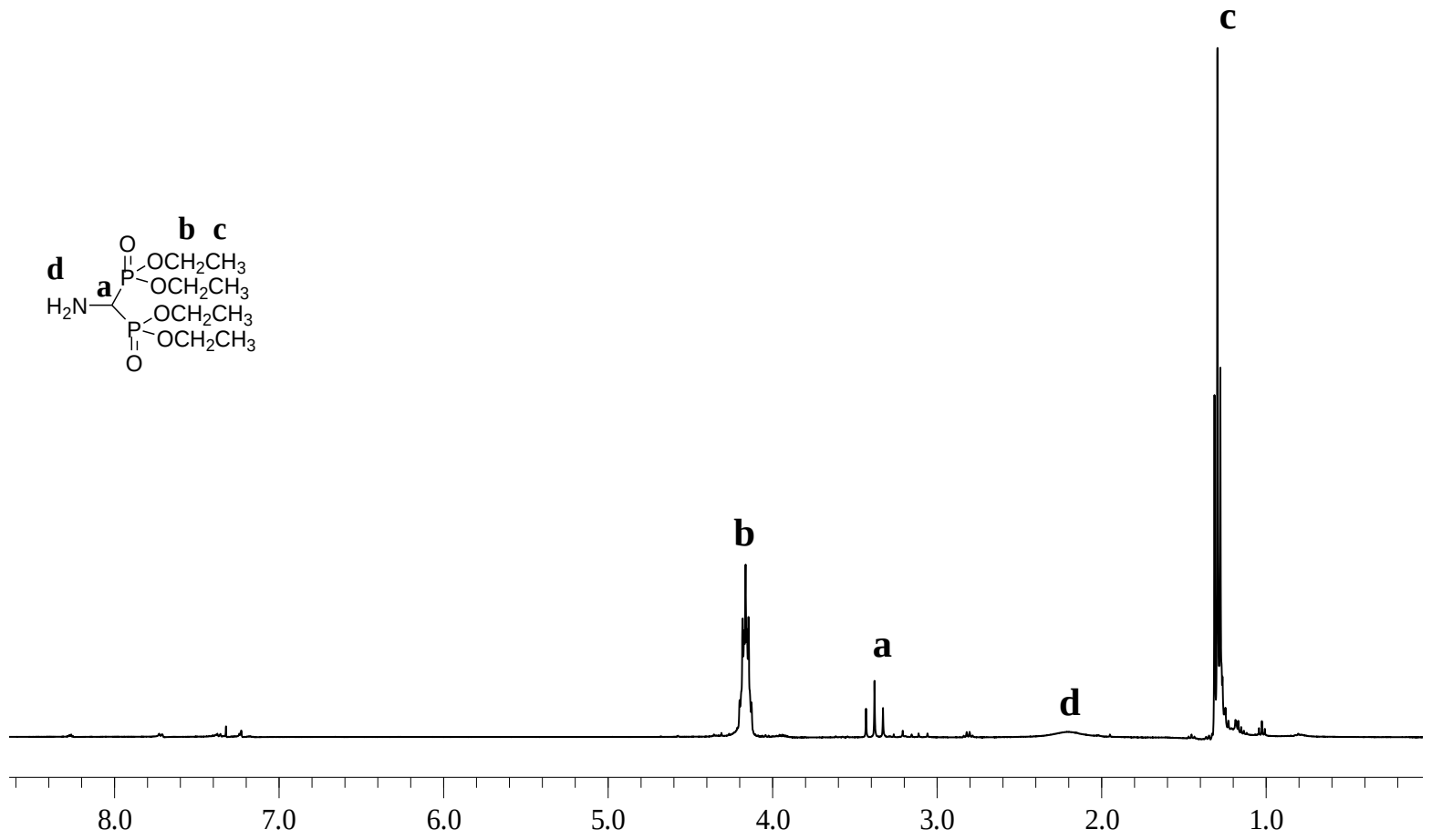


Figure A.4. ^{1}H-NMR spectrum of Tetraethyl Aminomethyl-bis(phosphonate).

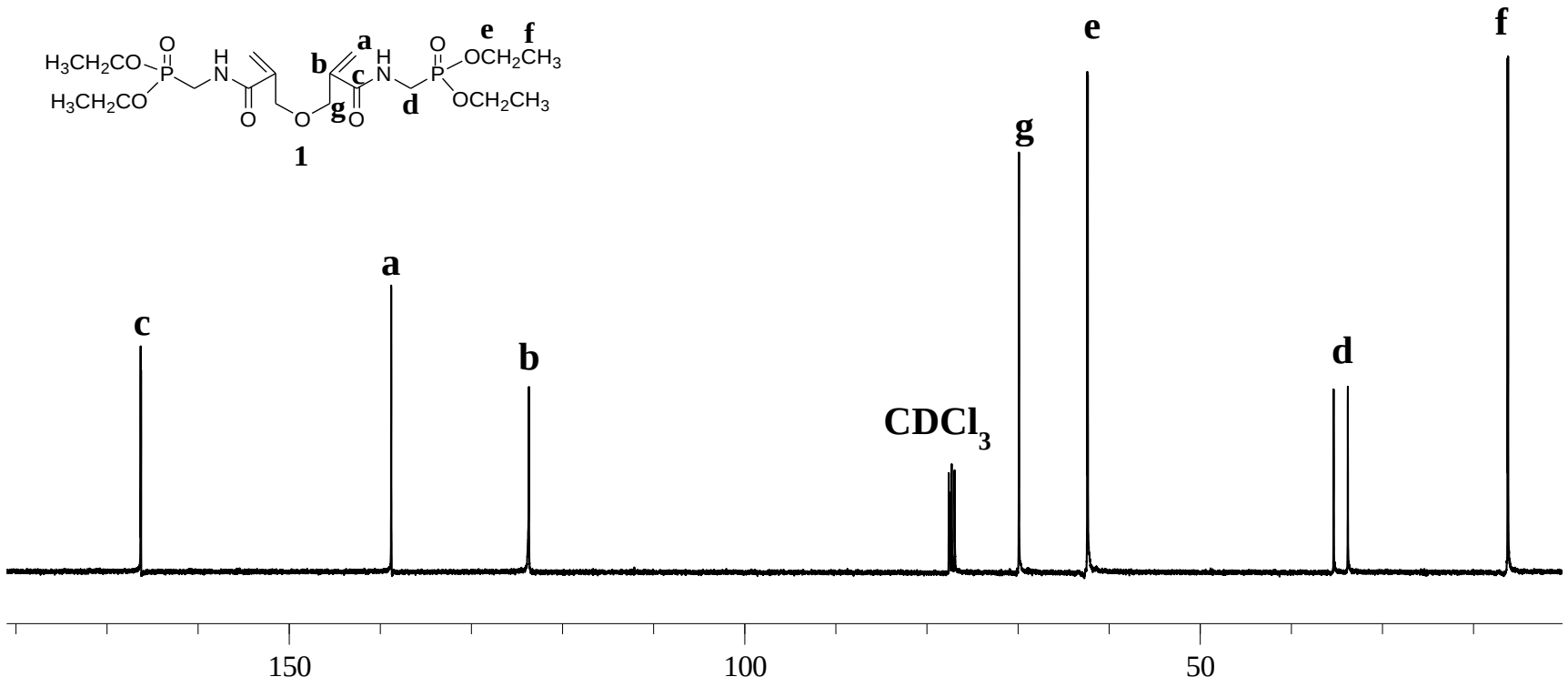


Figure A.5. ^{13}C-NMR spectrum of monomer 1.

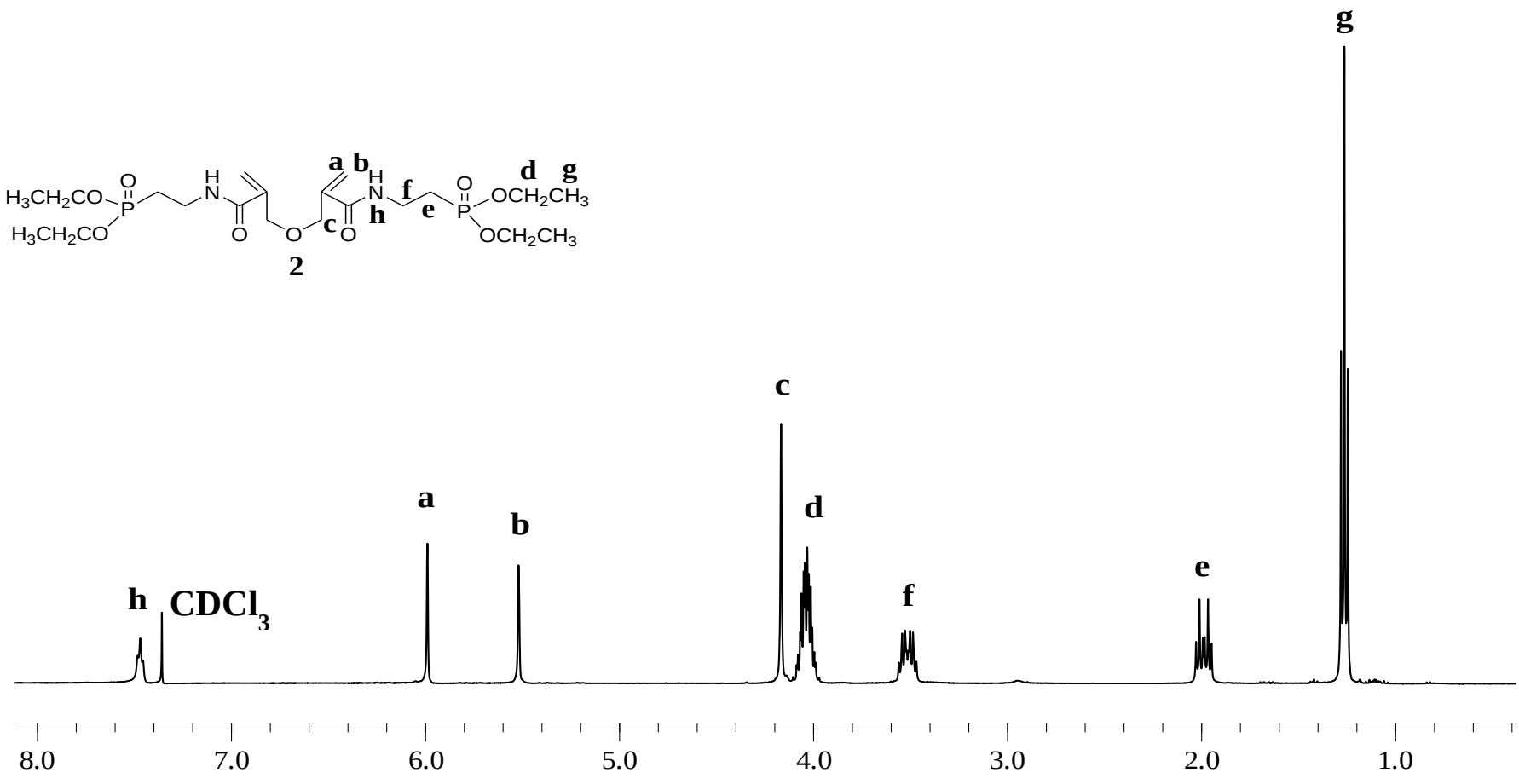


Figure A.6. ^{1}H-NMR spectrum of monomer 2.

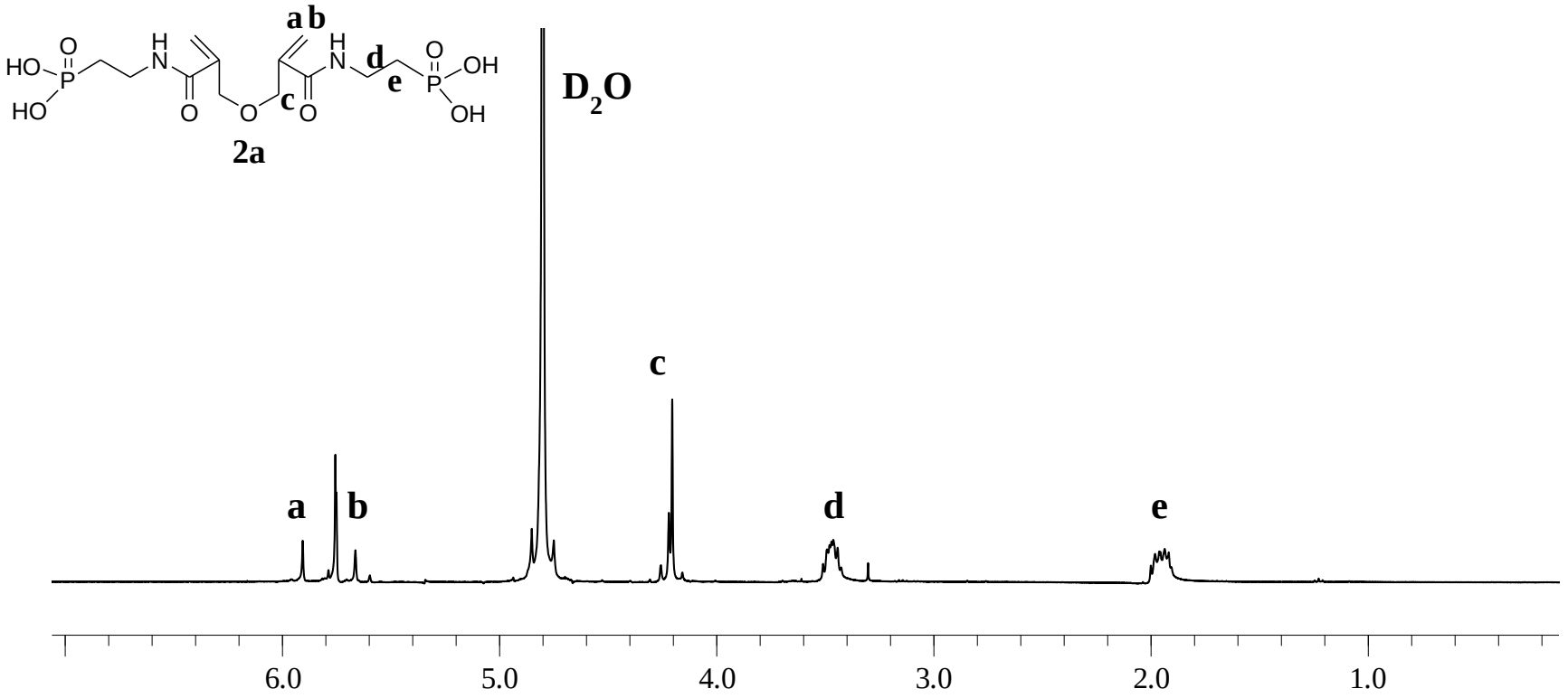


Figure A.7. ^{1}H-NMR spectrum of monomer 2a.

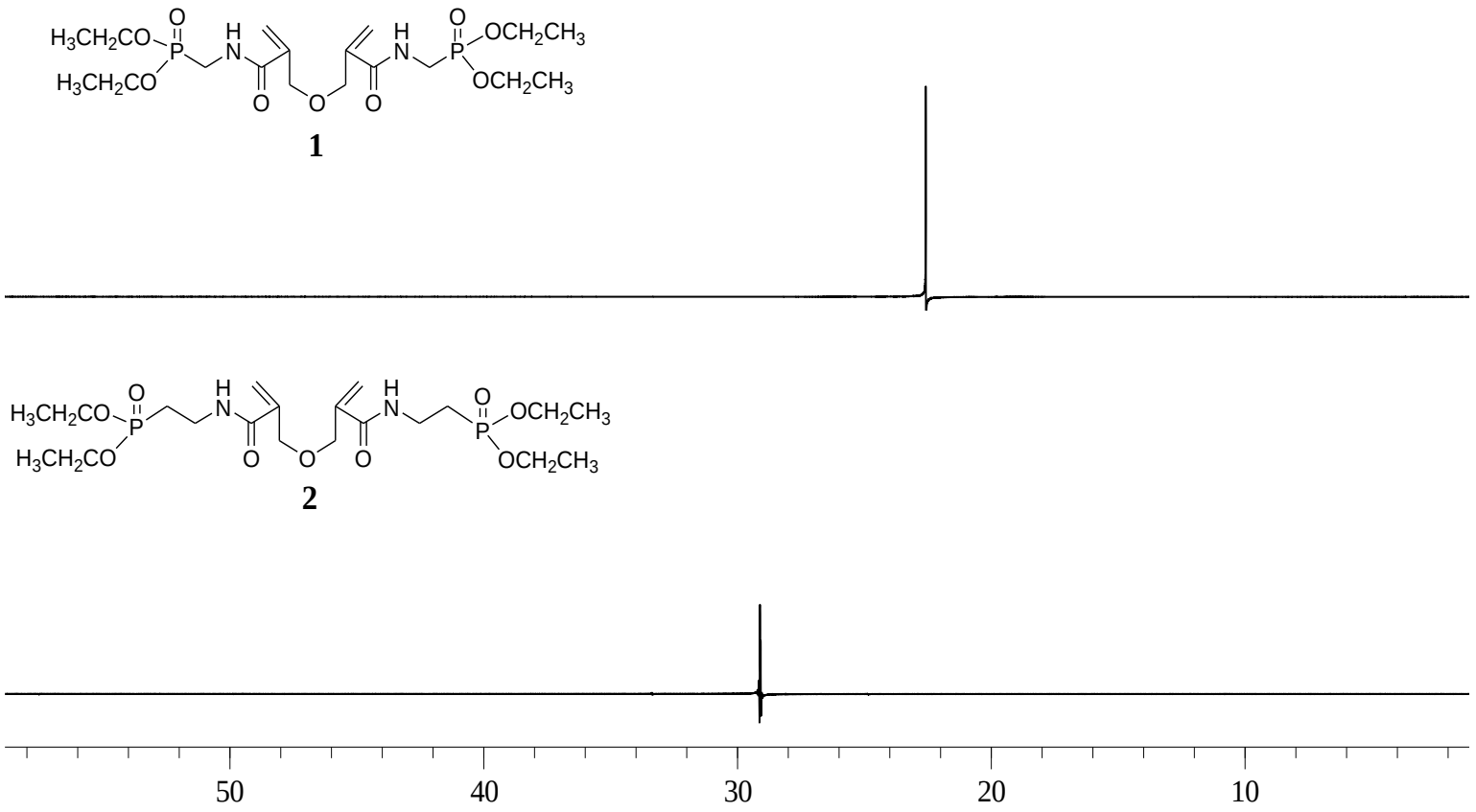


Figure A.8. ^{31}P-NMR spectra of monomers 1 and 2.

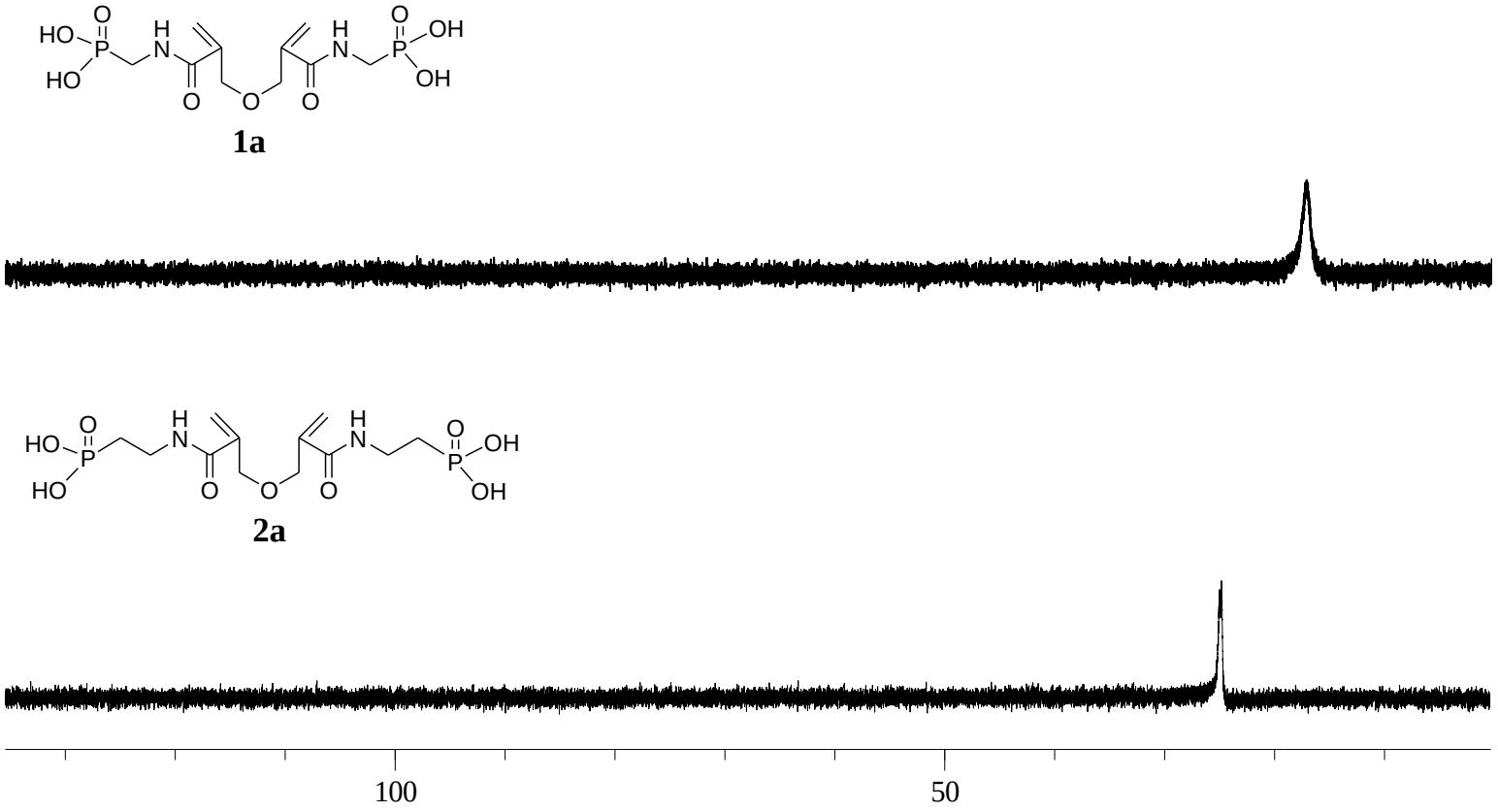


Figure A.9. ^{31}P-NMR spectra of monomers 1a and 2a.

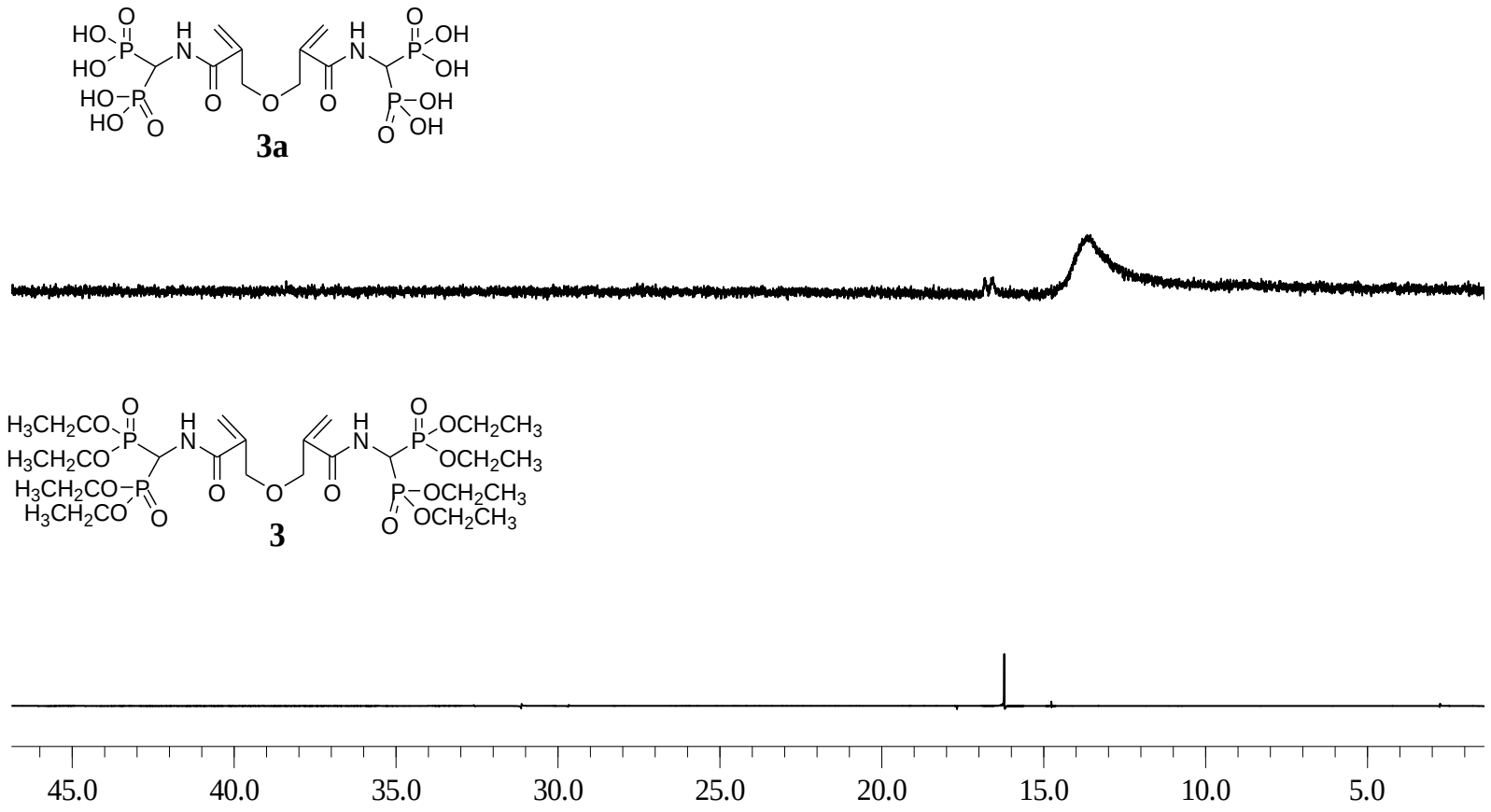


Figure A.10. ^{31}P-NMR spectra of monomers 3 and 3a.

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