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Design of New Phosphonic Acid Monomers for Dental Adhesives - Synthesis of (Meth)acryloxyalkyl 3-phosphonopropionates and Evaluation of their Adhesion-promoting Functions

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The aims of this study were to synthesize new phosphonic acid monomers, and to examine their bonding performance. Four kinds of newly designed phosphonic acid monomers were synthesized, and seven experimental composite-type adhesive resins comprising the synthesized monomers (3 wt%), with BPO/DEPT/BPBA initiator were prepared. Tensile bond strengths of the adhesive resins to enamel and metal were measured with a universal testing machine at a crosshead speed of 1.0 mm/min. The synthesized adhesive monomers were light yellow viscous liquids with 32.5%-49.3% yields, and identified by ^{1}H NMR, IR and elemental analysis to be (meth)acryloxyalkyl 3-phosphonopropionates [R-P(=O)(OH)$_2$] (5-MPPP, 6-MHPP, 6-AHPP, 10-MDPP). It was found that the newly developed phosphonic acid monomers with BPO/DEPT/BPBA initiator attained strong adhesion to both unetched, ground enamel and sandblasted Ni-Cr alloy with good durability. They exhibited significantly higher bond strengths than conventional phosphorous-containing monomers such as MEPP and VBPA ($p < 0.01$). These findings indicate that the experimental phosphonic acid monomer-containing adhesive resins have potential prosthodontic and orthodontic applications, especially as self-etching, non-rinsing orthodontic adhesive resins.

Key words: phosphonic acid monomer; polymerization initiator; adhesive resin

INTRODUCTION

To achieve strong, durable adhesion to the hard dental tissues, numerous advances on the molecular design of adhesive monomers have been performed by means of synthetic organic chemistry[1−18]. Nakabayashi[1] firstly suggested that a monomer bearing both hydrophobic and hydrophilic moieties in the molecular structure could provide effective adhesion to dentin. In terms of molecular structure, there are two broad categories of hydrophilic acidic moieties that may be utilized in adhesive monomers. They include the carboxylic acid (-COOH) or its anhydride group, and the phosphoric acid [-O-P(=O)(OH)$_2$] group. Examples of the carboxylic acid type of adhesive monomers that are currently employed in commercially available dentin adhesive formulations are 4-methacryloxyethyltrimellitic anhydride (4-META)[1], an adduct (PMDM)[2,3] of pyromellitic anhydride and 2-hydroxyethyl methacrylate (HEMA), 4-acryloxyethyltrimellic acid (4-AET) and its anhydride (4-AETA)[4,5] and 11-methacryloyloxy-1,1-undecanedicarboxylic acid (MAC-10). Examples of phosphoric acid type adhesive monomers that are employed in contemporary adhesive formulations include 2-methacryloyloxyethylphenyl hydrogen phosphate (Phenyl-P)[6,7], 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP)[8] and dipentaerythritol-pentamethacrylate phosphate ester (PENTA). Glycerine dimethacrylate-11-(phosphoric acid) undecanoic acid ester represents another more recently invented monomer from the latter catrgory[9].

To date, dental adhesion research on the use of phosphoric acid type adhesive monomers has been focused largely on the performance of monomers containing esters of phosphoric acid [R-O-P(=O)(OH)$_2$][6−9], with relatively little work done on the phosphonic acid monomers [R-P(=O)(OH)$_2$] and their adhesion-promoting functions. Although vinylphosphonic acid (VPA) and vinylbenzyl phosphonic acid (VBPA) were initially proposed for bonding to tooth substrates[10], adhesives containing these monomers formulated in ethyl alcohol exhibited minimal adhesion to dental hard tissues. Furthermore, it was thought that the low bond strength was caused by the VBPA and VPA molecular structures that have no flexible alkyl spacer. Interest in the use of phosphonic acid monomers has been revived by the recent demonstration of their superior hydrolytic stability as well as their improved bonding performance in dentin, when they were formulated into water-based adhesives[11-16]. However, the effect of flexible alkyl spacer in the structure of phosphonic acid monomers on adhesion is unknown. Also, little is known about the multi-purpose bonding ability of phosphonic acid monomers with polymerization initiators in hydrophobic adhesive resins. To circumvent the low polymerization reactivity of resin monomers bearing the $-P(=O)(OH)_2$ functional group with conventional polymerization initiators, a new initiator system consisting of benzoyl peroxide (BPO)/*N,N*-di(hydroxyethyl)-*p*-toluidine (DEPT)/1-benzyl-5-phenyl barbituric acid (BPBA) has been previously developed[17].

The objectives of this study were (1) to synthesize four newly designed phosphonic acid monomers that are classified as (meth)acryloxyalkyl 3-phosphonopropionates, and (2) to examine the bonding performance of these new phosphonic acid adhesive monomers to unetched, ground enamel and metal, by comparing to controls that consisted of a conventional phosphoric acid ester-containing methacrylate monomer MEPP (*i.e.* Phenyl-P), and a conventional phosphonic acid monomer VBPA. The conventional MEPP and VBPA were selected as controls that have no flexible alkyl moiety in their molecular structures. All the monomers were polymerized using the same initiator system BPO/DEPT/BPBA[17]. The null hypothesis tested was that there were no differences among the new phosphonic acid monomers and conventional MEPP and VBPA on adhesion to enamel and metal.

MATERIALS AND METHODS

Synthesis of new phosphonic acid monomers

A schematic illustration of the synthesis of the new phosphonic acid monomers used in this study is shown in Fig. 1. The phosphonic acid monomers (3 in Fig. 1) were synthesized by esterification of 2-carboxyethylphosphonic acid (2-CEPA) [or 3-phosphonopropionic acid (1 in Fig. 1)] with mono-hydroxyalkyl(meth)acrylate (2 in Fig. 1), according to a previously disclosed patent[18].

5-Methacryloxypentyl 3-phosphonopropionate (5-MPPP)

A mixture of 1,5-pentamethylene glycol (520 g, 5 mol), methacrylic acid (258 g, 3 mol), *p*-toluene sulfonic acid (25g) and butylated hydroxytoluene (BHT) (1g) was stirred for 5 h at 90-110℃ under 70-100 mm Hg vacuum. The reaction mixture was separated through column chromatography, and pure 5-hydroxypentyl methacrylate (5-HPMA) [2 in Fig. 1 ($R=CH_3$, $n=5$)] (250 g) was obtained as a mono-ester. A mixture of triethylphosphite (332 g, 2 mol) and β-propiolactone (144 g, 2 mol) was refluxed at 155-160℃ for 16 h. After distillation, ethyl 3-diethoxyphosphonopropionate (3-EDEPP) (1' in Fig. 1) (150 g) was obtained as a translucent liquid (b.p. 128-133℃ under 2-3 mm Hg). The 3-EDEPP (150 g, 0.63 mol) was hydrolyzed with 38% hydrobromic acid aqueous solution and purified by recrystalization from acetone with ethyl acetate, and 2-CEPA (70 g) was obtained. The 5-HPMA (94.6 g, 0.55 mol) was reacted with 2-CEPA (1 in Fig. 1) (77 g, 0.50 mol) in toluene (100 g) at 80-90℃ for 6 h under vacuum (200-300 mm Hg), and a yellowish oily residue (150 g) was obtained. After alkali and ether extractions, a light yellow viscous product (70 g) was obtained.

6-Methacryloxyhexyl 3-phosphonopropionate (6-MHPP)

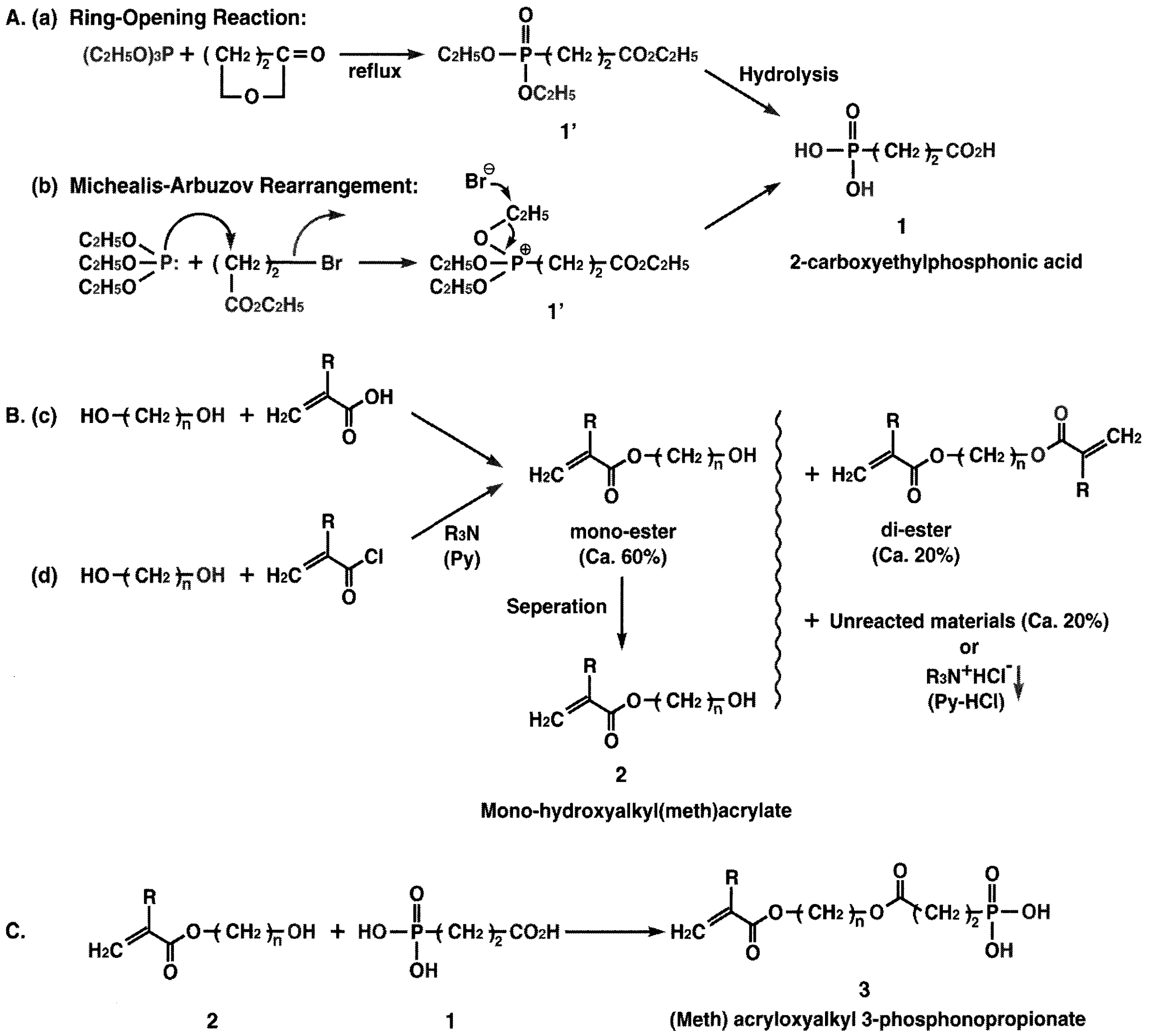
Methacrylic chloride (209 g, 2.0 mol) was added drop-wise to a stirred mixture of 1,6-hexamethylene glycol (238 g, 2.0 mol), pyridine (118 g, 1.5 mol) and tetrahydrofuran (1.2 L) for 2-3 h at 10-15℃. The reaction was continued at 15℃ for 4 h under 70-100 mm Hg vacuum, and the precipitated pyridine hydrochloride (Py-HCl) and solvent was removed. The residual mixture was separated through column chromatography, and pure 6-hydroxyhexyl methacrylate (6-HHMA) [2 in Fig. 1 ($R=CH_3$, $n=6$)] (70 g), a mono-ester, was obtained. A mixture of triethylphosphite (664.6 g, 4.0 mol) and ethyl 3-bromopropionate (362, 2.0 mol) was refluxed for 4 h. After distillation, 3-EDEPP (b.p. 127-130℃/2-3 mm Hg) (240 g) was obtained. The 3-EDEPP was hydrolyzed with 38% hydrobromic acid aqueous solution and purified by recrystalization from acetone with ethyl acetate, and 2-CEPA (110 g) was obtained. The reaction of 6-HHMA (102 g, 0.55 mol) with 2-CEPA (77 g, 0.50 mol) was conducted in toluene (100 g) at 80-100℃ under 200-300 mm Hg for 6 h, and a light yellow viscous product (70 g) was obtained.

6-Acryloxyhexyl 3-phosphonopropionate (6-AHPP)

This phosphonic acid monomer was prepared by esterfication of 6-hydroxyhexylacrylate [2 in Fig. 1 ($R=H$, $n=6$)] (60.2 g, 0.35 mol) with 2-CEPA (46 g, 0.30 mol) for 6 h at 80-110℃ under 200-300 mm Hg in a manner that was similar to the synthesis of 6-MHPP. A light yellow viscous product (30 g) was obtained.

10-Methacryloxydecyl 3-phosphonopropionate (10-MDPP)

Esterification of 1,10-decamethylene glycol (349 g, 2.0 mol) and methacrylic acid (103 g, 1.2 mol) was conducted for 6 h at 90℃ under 80 - 100 mmHg. The reaction mixture was separated through column chromatography, and pure 10-hydroxydecylmethacrylate (10-HDMA) [2 in Fig. 1 ($R=CH_3$, $n=10$)] (100 g, 0.41 mol) was obtained. The 10-HDMA (85 g, 0.35 mol) was reacted with 2-CEPA (46 g, 0.30 mol) in



Abbr.	R	n
5-MPPP	$-CH_3$	5
6-MHPP	$-CH_3$	6
6-AHPP	-H	6
10-MDPP	$-CH_3$	10

Fig. 1 A schematic representation of the synthesis of four kinds of experimental phosphonic acid monomers of (meth)acryloxyalkyl 3-phosphonopropionates (3). A: For the formation of carbon-phosphorus bonds [>P(=O)-C], the ethyl-diethylphosphonate (1') can be synthesized by either (a) a ring-opening reaction of β-propiolactone with triethylphosphite or (b) the Michaelis-Arbuzov rearrangement that involves the reaction of triethylphosphite with ethyl-ethylcarboxylate bromide. During the transformation, a trivalent phosphorus [P(III)] is converted into a pentavalent phosphorus [P(V)] that is involved the conversion of >P-O-C linkage into >P(=O)-C. B: Since the esterification of di-hydroxyalkylene glycol with (meth)acrylic acid (c) or (meth)acrylic chloride (d) produces mono-OH-(meth)acylate (ca. 60%), di-(meth)acylate (ca. 20%) and unreacted materials (ca. 20%) or precipitated pyridine hydrochloride (Py-HCl), the reaction products have to be separated chromatographically to obtain the pure mono-hydroxyalkyl(meth)acrylate (2). C: The new phosphonic acid monomers (3) were synthesized by the esterification of 2-carboxyethylphosphonic acid (1) with mono-hydroxyalkyl(meth)acrylates (2).

toluene (80g) at 80 - 90℃ for 7 h under 200 - 300 mmHg vacuum, and a light yellow viscous liquid (45 g) was obtained. The purified product could be crystallized under room temperature.

Identification of synthesized (meth)acryloxyalkyl 3-phosphonopropionates

The structures of the synthesized products were identified by proton nuclear magnetic resonance spectroscopy (^1H NMR). The NMR spectra were taken with a JNM-AL300 (300 MHZ) spectrometer (JEOL, Tokyo, Japan) with tetramethylsilane (TMS) as an internal standard. Infra-red (IR) spectra measurements were performed on a Fourier transform-infra red (FT-IR) spectrometer (FT-300; Horiba Co. Ltd., Kyoto, Japan). Elemental analysis was conducted using an Elemental Organic Analyzer (CHN CORDER, Model MT-3, Yanaco Analytical Instruments Co., Kyoto, Japan).

Preparation of other reagents

Silane-treated fillers [a mixture of 75% silane-treated silica (mean particle size: 1.5 μm) and 25% silane-treated $BaSO_4$][17] were prepared by treating the filler mixture with γ-methacryloxypropyltrimethoxy silane (KBM-503, Shinetsu Chemical Co. Ltd., Niigata, Japan). Dimethacryloxyethyl isophorone diurethane [IPDI-HEMA: an adduct of isophorone diisocyanate (IPDI) and HEMA in a 1:2 molar ratio, a translucent viscous liquid containing 20 wt% ethyleneglycol dimethacrylate (EGDMA)][17], MEPP (commonly known as Phenyl-P)[6,7], VBPA[10], BPBA (mp 156.5-159.0℃, white needle crystals)[17,19] were prepared according to the respective methods reported previously. Triethyleneglycol dimethacrylate (TEGDMA) (Shin Nakamura Chemicals Co. Ltd., Wakayama, Japan), BPO (Nihon Oil and Fat Co. Ltd., Tokyo, Japan), DEPT and BHT (Wako Pure Chemical Industries, Ltd., Osaka, Japan) were purchased and used without further purification.

Preparation of experimental adhesive resins

Six experimental chemically-cured, self-etching, composite-type adhesive resin cements consisting of powder and liquid were prepared from the silane-treated silica and $BaSO_4$, IPDI-HEMA, TEGDMA, EGDMA, BPO, DEPT, BPBA, BHT and one of the six phosphorus-containing acidic resin monomers (5-MPPP, 6-MHPP, 10-MDPP, 6-AHPP, MEPP or VBPA). The seventh formulation was prepared without any of these phosphorus-containing resin monomers and served as the control. The compositions of these seven composite formulations are listed in Table 1.

Tensile bond strength measurement

Freshly extracted bovine incisors were used as substitutes for human specimens[20], due to the large number of teeth required in this study. The bovine teeth with their roots removed were embedded in epoxy resin. Flat enamel bonding substrates were prepared by grinding the labial enamel surfaces with 600-grit silicon carbide abrasive papers under running water, and then air-dried. This bonding substrate was designated as "unetched ground enamel".

A dental Ni-Cr alloy (Shofu Summalloy Nickel, Shofu Inc., Kyoto, Japan) was cast with a casting machine (Shofu Argon Caster, Shofu Inc., Kyoto, Japan) to form metal rods (4.5±0.1 mm in diameter, 6.0±0.1 mm in height) and metal plates (3.0 × 8.0 × 10.0 mm). Flat bonding surfaces on these rods and plates were prepared by first grinding with 600-grit silicon carbide abrasive papers and then sandblasting with 50 μm aluminum oxide, and cleaned ultrasonically in water for 5 min. This bonding substrate was designated as "sandblasted Ni-Cr alloy".

After drying the prepared substrates, a mixed slurry of the respective adhesive resin was placed between the sandblasted Ni-Cr alloy rod and either the surface of the sandblasted alloy plate or the ground enamel surface. In particular, the ground enamel was bonded without additional phosphoric acid etching. The mixed adhesive resins (P/L=3.5) were

Table 1 Composition of the experimental composite-type adhesive resins examined in this study

Powder (wt%)†		Liquid (wt%)†	
Silane-treated filler	98.9	IPDI-HEMA	65.0
BPBA	1.0	TEGDMA	20.0
DEPT	0.1	EGDMA	9.5
		Acidic monomer (5-MPPP, 6-MHPP, 6-AHPP, 10-MDPP, MEPP, VBPA)	5.0
		BPO	0.5
		BHT	500 ppm

†Powder/Liquid ratio: 3.5/1

Abbreviations: BPBA: 1-benzyl-5-phenylbarbituric acid, DEPT: *N,N*-(dihydroxyethyl)-*p*-toluidine, IPDI-HEMA: adduct of isophorondiisocyanate and 2-hydroxyethyl methacrylate in 1:2 molar ratio, TEGDMA: triethyleneglycol dimethacrylate, EGDMA: ethyleneglycol dimethacrylate, BPO: bezoylperoxide, BHT: butylated hydroxytoluene. 5-MPPP: 5-methacryloxypentyl 3-phosphono propionate, 6-MHPP: 6-methacryloxyhexyl 3-phosphonopropionate, 6-AHPP: 6-acryloxyhexyl 3-phosphonopropionate, 6-MHPP: 6-methacryloxyhexyl 3-phosphonopropionate, 10-MPPP: 10-methacryloxydecyl 3-phosphono propionate, MEPP (*i.e.* Phenyl-P): methacryloxyethyl phenyl hydrogen phosophate[6,7], VBPA: vinylbenzyl phosphonic acid[10].

cured for 5-8 min at 23±1℃. After 30 min, the bonded specimens ($n=10$) were immersed in distilled water at 37℃ for 24 h and then subjected to a thermal cycling test for 2000 cycles (1 cycle: in 4℃ and 60℃ water for 1 min each). Tensile bond strengths were measured using a universal testing machine (Model 5567, Instron Corp., Canton, MA USA) at a crosshead speed of 1 mm/min.

The fractured surfaces of the specimens were examined with a stereomicroscope, and the failure modes were classified as adhesive, cohesive or mixed failures. The bond strength data were analyzed using a one-way analysis of variance (ANOVA) design. Statistical significance was set in advance at the 0.01 probability level. Multiple comparisons were performed using Student-Newman-Keule tests at $\alpha = 0.01$.

RESULTS

Synthesis of new phosphonic acid monomers

The phosphonic acid monomers were synthesized as pale yellow viscous liquids with yields of 32.5%-49.3%. They were spectrally identified as new compounds by ^{1}H NMR and IR spectra in typical assignments of ^{1}H NMR chemical shift (δ) of 7.6 ppm [2H, $-P(=O)(OH)_2$] and IR band of 1292-1296 cm^{-1} (ν P=O). Since IR spectra measured in this study were recorded between 4,000-800 cm^{-1}, the IR bands of 750-650 cm^{-1} assigned for carbon-phosphorus bond (C-P) could not be detected. However, the IR bands of 1070-1050 cm^{-1} assigned for phosphate bond (C-O-P) were also not recorded. Accordingly, synthesized monomers were confirmed to be novel (meth) acryloxyalkyl 3-phosphonopropionates [3 in Fig. 1, 5-MPPP ($R=CH_3$, n=5), 6-MHPP ($R=CH_3$, n=6), 6-AHPP (R=H, n=6), 10-MDPP ($R=CH_3$, n=10)]. The identification characteristics of experimental phosphonic acid monomers are summarized in Table 2.

The viscous appearance of the four experimental phosphonic acid monomers was caused by the presence of long alkyl chains between the phosphonic acid moieties and the (meth)acryloyl groups. Although

Table 2 Characteristics of the synthesized (meth)acryloxyalkyl 3-phosphonopropionates

Monomer	Appearance	Yield (%)	^{1}H NMR spectra (δ, ppm)	IR spectra (neat, cm^{-1})	Elemental Analysis
5-MPPP	Light yellow Viscous liquid	49.3	1.3-1.8 [6H, $-CH_2-(\underline{CH_2})_3-CH_2-$], 1.9 (3H, $-C\underline{H_3}$), 2.1-2.7 (4H, $-OOC-C\underline{H_2}-C\underline{H_2}-P$), 4.0, 4.1 (4H, $-COO-C\underline{H_2}- \times 2$), 5.6, 6.0 (2H, $C\underline{H_2}=C<$), 7.6 [2H, $-P(=O)(O\underline{H})_2$]	1295 (ν P=O), 1009, 940 (ν P-$\underline{OH}$), 1638 (ν C=C)	Theoretical calculations for $C_{12}H_{21}O_7P$: C, 42.30%; H, 7.39%. Experimental: C, 41.95%; H, 7.13%
6-MHPP	Light yellow Viscous liquid	43.5	1.3-1.8 [8H, $-CH_2-(\underline{CH_2})_4-CH_2-$], 1.9 (3H, $-C\underline{H_3}$), 2.1-2.7 (4H, $-OOC-C\underline{H_2}-C\underline{H_2}-P$), 4.0, 4.1 (4H, $-COO-C\underline{H_2}- \times 2$), 5.6, 6.0 (2H, $C\underline{H_2}=C<$), 7.6 [2H, $-P(=O)(O\underline{H})_2$]	1292 (ν P=O), 1008, 939 (ν P-$\underline{OH}$), 1637 (ν C=C)	Calculations for ($C_{13}H_{23}O_7P$): C, 48.44%; H, 7.14%; Experimental: C, 48.13%; H, 7.01%.
6-AHPP	Light yellow Viscous liquid	32.5	1.3-1.8 [8H, $-CH_2-(\underline{CH_2})_4-CH_2-$], 2.1, 2.7 (4H, $-OOC-C\underline{H_2}-C\underline{H_2}-P$), 4.0, 4.1 (4H, $-COO-C\underline{H_2}- \times 2$), 5.8, 6.2 (3H, $C\underline{H_2}=C\underline{H}-$), 7.6 [2H, $-P(=O)(O\underline{H})_2$]	1294 (ν P=O), 1008, 939 (ν P-$\underline{OH}$), 1637 (ν C=C)	Calculations for ($C_{12}H_{21}O_7P$): C, 46.75%; H, 6.82%. Experimental: C, 46.50%; H, 6.70%.
10-MDPP	Light yellow Viscous liquid, but can be crystallized under room temperature	39.7	1.3-1.8 [16H, $-CH_2-(\underline{CH_2})_8-CH_2-$], 1.9 (3H, $-C\underline{H_3}$), 2.1-2.7 (4H, $-OOC-C\underline{H_2}-C\underline{H_2}-P$), 4.0, 4.1 (4H, $-COO-C\underline{H_2}- \times 2$), 5.6, 6.0 (2H, $C\underline{H_2}=C<$), 7.6 [2H, $-P(=O)(O\underline{H})_2$]	1296 (ν P=O), 1011, 940 (ν P-$\underline{OH}$), 1639 (ν C=C)	Calculations for ($C_{17}H_{31}O_7P$): C, 53.96%; H, 8.20%. Experimental: C, 53.65%; H, 8.04%.

Abbreviations: 5-MPPP: 5-methacryloxypentyl 3-phosphonopropionate, 6-MHPP: 6-methacryloxyhexyl 3-phosphonopropionate, 6-AHPP: 6-acryloxyhexyl 3-phosphonopropionate, 6-MHPP: 6-methacryloxyhexyl 3-phosphonopropionate, 10-MPPP: 10-methacryloxydecyl 3-phosphono propionate the yields of these experimental phosphonic monomers were not so high, the elemental analysis data and ^{1}H NMR spectra for these experimental monomers revealed that they were synthesized with high purity.

Tensile bond strength measurement

The tensile bond strengths of the seven composite-type adhesive resins comprising 5-MPPP, 6-MHPP, 6-AHPP, 10-MDPP, MEPP, VBPA and None (control), with BPO/DEPT/BPBA initiator system[17] to unetched, ground enamel after 0 and 2000 thermal cycles are presented in Table 3. The tensile bond strengths of the seven adhesive resin formulations to sandblasted Ni-Cr alloy after 0 and 2000 thermal cycles are shown in Table 4.

When compared with the control formulation (*i.e.* no acidic adhesive monomer included), both the bond strengths of the sandblasted Ni-Cr alloy rod to the unetched ground enamel and the sandblasted Ni-Cr alloy plates were significantly affected by the inclusion of acidic adhesive monomers. For the unetched ground enamel substrate, with the exception of 5-MPPP, significant differences were observed between the tensile bond strengths attained with the new, experimental phosphonic acid monomers (10.2-11.5 MPa) and the conventional phosphoric acid ester MEPP (6.0-6.8 MPa) and the conventional phsophonic acid monomer VBPA (5.0-5.5 MPa), both with and without thermal cycling ($p<0.01$). For the sandblasted Ni-Cr alloy substrate, all the new, experimental phosphonic acid monomers exhibited significantly higher tensile bond strengths (40.8-44.8 MPa) than either MEPP (31.0-31.8 MPa) or VBPA (30.2-30.3 MPa), as a control adhesive monomer, both with and without thermal cycling ($p<0.01$). The tensile bond strengths of the newly synthesized phosphonic acid monomers to the metal alloy were, in general, 3.5-4 times as high as their corresponding tensile bond strengths to enamel. Examination of the fractured surfaces after tensile bond testing revealed that adhesive failures occurred predominantly with the enamel substrate, while 80-100% cohesive failure occurred within the adhesive layer with the metal substrate when these experimental phosphonic acid monomers were included in the resin formulations (Tables 3 and 4).

Table 3 Effect of several adhesive monomers on tensile bond strengths of experimental composite-type adhesive resins between sandblasted Ni-Cr alloy rod and unetched ground enamel after 0 and 2000 thermal cycles

Adhesive Monomers	Unetched enamel ($n=10$)*			
	0 cycle†	A/M/C (%)§	2000 cycles†	A/M/C (%)§
5-MPPP	8.3 (3.6)^{ab}	100/0/0	8.5 (3.5)^{ab}	100/0/0
6-MHPP	10.6 (3.6)^{a}	90/10/0	10.2 (3.5)^{a}	100/0/0
6-AHPP	11.5 (4.3)^{a}	100/0/0	11.2 (3.3)^{a}	100/0/0
10-MDPP	10.8 (3.6)^{a}	90/10/0	11.5 (3.8)^{a}	90/10/0
MEPP	6.0 (1.5)^{b}	100/0/0	6.8 (2.2)^{b}	100/0/0
VBPA	5.0 (2.0)^{b}	100/0/0	5.5 (2.2)^{b}	100/0/0
None	0.5 (0.2)^{c}	100/0/0	0^{c}	100/0/0

*Unetched enamel: bovine enamel ground with 600-grit SiC abrasive paper and bonded without acid etching.

†Values are means (standard deviation). Groups from the same column that are identified with the same superscript letters are not significantly different ($p<0.01$).

§Failure modes: percent of Adhesive failure/Mixed failure/Cohesive failure in adhesive.

Table 4 Effect of several adhesive monomers on tensile bond strengths of experimental composite-type adhesive resins between sandblasted Ni-Cr alloy rod and sandblasted Ni-Cr alloy plate after 0 and 2000 thermal cycles

Adhesive monomers	Ni-Cr alloy (n=10)*			
	0 cycle†	A/M/C (%)§	2000 cycles†	A/M/C (%)§
5-MPPP	40.8 (9.7)^{a}	0/10/90	40.8 (10.2)^{a}	0/20/80
6-MHPP	42.8 (10.8)^{a}	0/10/90	42.5 (12.5)^{a}	0/10/90
6-AHPP	41.9 (9.5)^{a}	0/0/100	42.6 (10.7)^{a}	0/0/100
10-MDPP	42.4 (11.2)^{a}	0/0/100	44.8 (12.0)^{a}	0/0/100
MEPP	31.0 (6.4)^{b}	0/30/70	31.8 (8.8)^{b}	0/40/60
VBPA	30.3 (4.8)^{b}	0/40/60	30.2 (4.8)^{b}	0/40/60
None	5.2 (1.2)^{c}	100/0/0	4.2 (1.4)^{c}	100/0/0

*Ni-Cr alloy: Shofu Summalloy Ni (Shofu Inc., Kyoto, Japan) rod cast was sandblasted with aluminum oxide.

†Values are means (standard deviation); groups of the same column that are identified with the same superscript letters are not significantly different ($p<0.01$).

§Failure modes: percent of Adhesive failure/Mixed failure/Cohesive failure in adhesive.

DISCUSSION

Numerous challenges on the design of adhesive monomers have been performed to upgrade their adhesion-promoting functions[1-18]. Improved performances of recently developed dental adhesives are attributed to the development of adhesive monomers that have the ability to bond to a variety of different substrates. In the present study, four kinds of newly designed phosphonic acid monomers [R-P(=O)$(OH)_2$], *i.e.* (meth)acryloxyalkyl 3-phosphonopropionates (5-MPPP, 6-MHPP, 6-AHPP, 10-MDPP in Fig. 1C) were synthesized, and their bonding performances to unetched enamel and sandblasted Ni-Cr alloy, together with BPO/DEPT/BPBA initiator[23] were investigated.

For radical polymerizable monomers bearing both hydrophilic and hydrophobic moieties in their structure[1], the acidic hydrophilic moiety is significantly important because of its adhesion-promoting function. The (meth)acryloxyalkyl 3-phosphonopropionates (3 in Fig. 1) were synthesized by esterification (Fig. 1C) of mono-hydroxyalkyl (meth)acrylates (2 in Fig. 1) with 2-carboxyethylphosphonic acid (2-CEPA) (1 in Fig. 1). The phosphonic acid moiety [-P(=O)$(OH)_2$] was produced from the 2-CEPA [HOOC-$(CH_2)_2$-P(=O)$(OH)_2$] (1 in Fig. 1) that was prepared by hydrolysis of ethyl 3-diethylphosphonopropionate [EtOOC-$(CH_2)_2$-P(=O)$(OEt)_2$] (1' in Fig. 1). The latter, in turn, was synthesized by either (a) a ring-opening reaction of β-propiolactone with triethylphosphite or (b) the Michaelis-Arbuzov reaction[21,22] of triethylphosphite with ethyl 3-bromopropionate (Fig. 1A). For the formation of the carbon-phosphorus bond [>P(=O)-C], the alkyl-dialkylphosphonate [R_1 OOC-R_2 -P(=O)$(OR_1)_2$] is a valuable synthetic intermediate. The Michaelis-Arbuzov reaction, that is still frequently used in organophosphorus chemistry, involves the rearrangement of an alkyl halide (R-Hal) with a trialkyl phosphite [$(R'O)_3P$], yielding a dialkyl alkylphosphonate [R-P(=O)$(OR')_2$][21]. Thus, during the transformation, a trivalent phosphorus [P(III)] is converted into a pentavalent phosphorus [P(V)] that is involved in the conversion of the $P(OR')_3$ linkage into [>P(=O)-C][21], and can involve complicated competing eliminations[21].

Hydrophobic alkyl and polymerizable (meth)acryloyl moieties can be produced from the mono-hydroxyalkyl (meth)acrylate (OH-monomer 2, Fig. 1C) that is also a useful synthetic intermediate for extending the carbon-chain in the structure of adhesive monomers. The mono-OH-monomer (2 in Fig. 1) was synthesized by esterification of alkylene glycol with (c) (meth)acrylic acid or (d) (meth)acrylic chloride (Fig. 1B). Since mono- and di-esters can be produced in this reaction, unreacted (meth)acrylic acid or precipitated pyridine hydrochloride (Py-HCl) and unreacted materials (ca. 20%) were removed, and the di-ester (ca. 20%) was chromatographically separated to yield pure mono-hydroxyalkyl (meth)acrylates (2 in Fig. 1), wherein the C-number of alkyl moiety was C5, C6 and C10. It was thought that high purity of the synthesized (meth)acryloxyalkyl 3-phosphonopropionates (3 in Fig. 1) was caused by the chromatically purified mono-OH-monomers.

Currently, adhesive resins are widely used to bond orthodontic brackets to enamel. Recently developed self-etching primers are attractive in that they may create micromechanical retention in dental hard tissues without the use of a separate acid-etching step[4,11-16,23-26]. This enables them to bond orthodontic brackets[27,28] or stainless rod[29] to unetched enamel[27-29]. A self-etching primer comprising 10-MDP provided an effective adhesion of composite type resin cement to titanium[30]. Because of their self-etching capabilities, it was anticipated that the experimental phosphonic acid monomer-containing adhesive resins have potential prosthodontic and orthodontic applications. Accordingly, we examined the bonding performance of these experimental adhesive resins on adhesion between sandblasted Ni-Cr alloy and either unetched, ground enamel or sandblasted Ni-Cr alloy, with or without thermal cycling. Similar to conventional phosphate monomers [R-O-P(=O)$(OH)_2$], it was anticipated that the experimental phosphonic acid monomers [R-P(=O)$(OH)_2$] should possess adhesion-promoting functions. To clarify this issue, formulation of powder-liquid type self-curing adhesive resins were employed using these phosphonic acid monomers, and their bonding performance was examined for potential prosthodontic and orthodontic applications. The phosphonic acid monomers 6-MHPP, 6-AHPP and 10-MDPP exhibited strong adhesion to both unetched enamel and sandblasted Ni-Cr alloy with good durability after 2000 thermal cycles, and their bond strengths were significantly higher than that of the conventional MEPP and VBPA. The tensile bond strength of 5-MPPP to enamel was higher, but not significantly different than the conventional monomers. Conversely, its bond strength to the sandblasted Ni-Cr alloy was significantly higher than the conventional monomers. Thus, we may reject the null hypothesis that there are no differences between the new phosphonic acid monomers and conventional MEPP and VBPA on adhesion to enamel and metal.

Regarding the structure of adhesive monomers, it is known that bond strength is affected by the flexible spacer group as well as acidic groups. Omura and Yamauchi[8] reported that bond strength of 10-MDP (=C10: 10 carbon-number of methylene chain) or 6-methacryloxyhexyl dihydrogen phosphate (6-MHP) (=C6) to dentin or Ni-Cr alloy was higher than that of 2-methacryloxyethyl dihydrogen phosphate (10-MEP) (=C2), and concluded that methylene chain as the spacer group in phosphate monomers was necessary for both adhesion to dentin and metal. Furthermore, our previous work[31] found that the tensile bond strength to Ni-Cr alloy after 20,000 thermal cycling was strongly correlated with the C-number (C2-C10) of the methylene chain in (meth)acryloxyalkyltrimellitic anhydride ($r=0.937$), when BPO/DEPT/BPBA-type initiator was used. We attributed the enhanced bonding efficacy of the new phosphonic acid monomers in this study to their flexible (meth)acryloxyalkyl moiety as well as their phosphonic acid moiety. The bonding durability of 10-MDPP that encompasses the more flexible C10 moiety is anticipated to be similar to that of 10-MDP[8]. Conversely, it was thought that the lower bond strengths obtained by conventional MEPP and VBPA were caused by the absence of flexible alkyl spacer when compared with the new phosphonic acid monomers.

In general polymer chemistry, it is known that the radical copolymerization rate of acrylic ester derivatives ($CH_2=CH\text{-}COO\text{-}R$) with radical polymerizable monomers have faster reactivity than that of methacrylic ester derivatives [$CH_2=C(CH_3)\text{-}COO\text{-}R$][32]. Comparing the structure of an acrylic ester 6-AHPP with a methacrylic ester 6-MHPP, although it was considered that the copolymerization reactivity could affect on bonding performance, there was no significant difference between 6-AHPP and 6-MHPP on the bond strength ($p<0.01$).

Similar to the chemical interaction of carboxylic acid as acidic group with hydroxyapatite[33,34], we further speculated that synthesized phosphonic acid monomers as a ligand monomer achieved good chemical interaction with both hydroxyapatite in tooth and metal oxide on the metal surface that via the hypothetical mechanism depicted in Fig. 2. Although good chemical affinity was achieved, similar to the incompatibility between conventional phosphate monomers and dual-cured composites[35-37], the four experimental phosphonic acid monomers will have low polymerization reactivity caused by the neutralization of the acidic [$\text{-}P(=O)(OH)_2$] moiety with the basic, binary, redox BPO/DEPT initiator system[6,17]. It is known that the acidic group (electron acceptor) reacts with an aromatic tertiary amine (electron donor) to form a yellowish charge-transfer complex (CT-complex)[2,17]. Yamauchi *et al.*[6] found that the BPO/tertiary amines/*p*-toluenesulfinic acid sodium salt (*p*-TSNa) ternary initiator system provided good adhesion of a phosphate monomer (Phenyl-P) to dentin. To circumvent the compromised adhesion caused by the formation of CT-complexes, BPO/DEPT/BPBA was previously developed as a new polymerization initiator system[17]. This initiator system was employed for the polymerization of the adhesive resin cements formulated in this study so that the experimental phsphonic acidic monomers could perform their essential adhesion-promoting function. This ternary initiator system markedly reduced the adverse effects on both polymerization and adhesion[17], and increased the cohesive strengths of adhesive layer between the adherents (Fig. 2). Indeed, co-initiators such as *p*-TSNa and BPBA are of significant importance for adhesive resin compositions in which acidic adhesive monomers are incorporated. Our results demonstrated that the experimental phosphonic acid monomers are compatible with this ternary initiator system and together, they contributed to the improved adhesion.

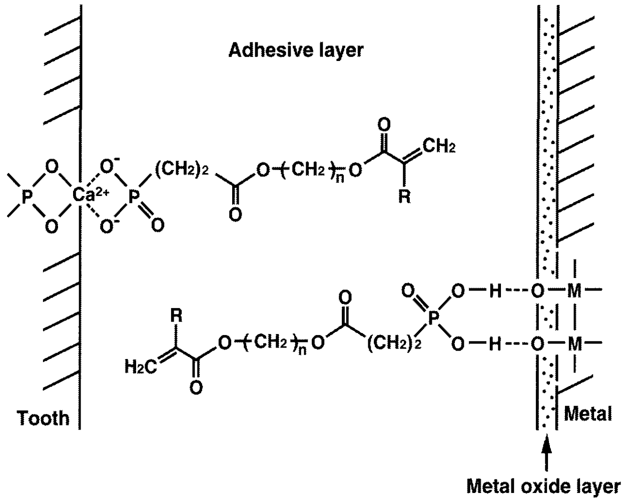


Fig. 2 A schematic illustration of the hypothetical interaction of the phosphonic acid moiety of (meth)acryloxyalkyl 3-phosphonopropionates with hydroxyapatite and metal. It is speculated that the bonding effect of synthesized monomers is achieved via ionic interactions of phosphonic acid moiety with the adherents along the bonding interface.

Apart from the good chemical interaction or adhesion-promoting functions of acidic moieties, hydrolytic stability of these monomers is also an important issue, particularly when they are formulated as water-based self-etching primers or adhesives[11-16]. Accordingly, it is worth noting that the recently synthesized phosphonic acid monomers are hydrolytically stable in a water-based adhesives[11-14]. In the single-bottle type adhesives, the acidic monomers are combined with water during the manufacturing process, and hydrolysis of the conventional phosphate ester-type monomers occur readily, particularly when they are stored without refrigeration[14-16]. Moreover, as phosphonic acid monomers are still ionic monomers, it is important in future studies to examine their vulnerability to water sorption after polymerization[38-41], a universal problem that challenges the longevity of contemporary dental resins containing hydrophilic components. Water sorption causes plasticizing of adhesive interfaces and the sequential reduction in their physical properties. Only when these problems are resolved can the full potential of new phosphonic acid monomers be realized in future dental adhesive formulations.

CONCLUSION

Within the limits of this study, it is concluded that (meth)acryloxyalkyl 3-phosphonopropionates, in particular those with long alkyl spacers such as 6-MHPP, 6-AHPP and 10-MDPP provided strong adhesion to unetched ground enamel and sandblasted Ni-Cr alloy when they are formulated into self-cured adhesive resin formulations using the ternary initiator system BPO/DEPT/BPBA. These findings indicate that the experimental adhesive resins formulated using the phosphonic acid monomer/initiator combination have potential prosthodontic and orthodontic applications, especially as self-etching, non-rinsing orthodontic adhesive resins.

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