Monomers for adhesive polymers, 18. Synthesis, photopolymerization and adhesive properties of polymerizable α-phosphonooxy phosphonic acids

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ABSTRACT
Four polymerizable α-phosphonooxy phosphonic acids 7a, 7b, 9 and 16 were synthesized in seven steps. They were characterized by 1H, 13C and 31P NMR spectroscopy and by high-resolution mass spectroscopy. The copolymerization of acidic monomers 7a, 7b, 9 and 16 with 2-hydroxyethyl methacrylate was studied using a differential scanning calorimeter. Due to the presence of two acidic groups, those monomers are significantly more reactive than 10-methacryloyloxydecylphosphonic acid (MDPA) and 10-methacryloyloxydecyl dihydrogen phosphate (MDP). Self-etch adhesives based on monomers 7a, 7b, 9 and 16 were formulated and used to mediate a bond between a dental composite and the dental hard tissues (dentin and enamel). These adhesives exhibit excellent performances and provide significantly higher dentin and enamel shear bond strength than adhesives based on MDP or MDPA.

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1. Introduction
Self-etch adhesives (SEAs) are nowadays often used to achieve a bond between the dental hard tissues (dentin and enamel) and a restorative material (composite).[1–3] A SEA is an aqueous formulation containing different monomers (acidic, monofunctional and crosslinking monomers), cosolvents (ethanol, acetone, etc.) and additives (photoinitiator(s), co-initiator(s), stabilizers, fillers, etc.). Contrary to total-etch adhesives, SEAs are able to simultaneously demineralize and infiltrate the dental tissues. The acidic monomer is responsible for the etching of the tooth surface. Monomers such as polymerizable dihydrogen phosphates, carboxylic or phosphonic acids can be found in SEA formulations.[4] In SEAs, the acidic monomer should exhibit good etching properties, sufficient storage stability and a low oral toxicity.[5] It also has to show a high rate of homo- or copolymerization with the comonomers of the formulation. Van Meerbeek et al. [6–9] demonstrated that the ability of the acidic monomer to strongly interact with the calcium of hydroxyapatite (HAP) has a significant impact on the adhesive performance. Therefore, acidic monomers exhibiting strong chelating properties were synthesized and tested in SEAs. It has been demonstrated that the adhesion of SEAs can be improved when polymerizable diphosphonic acids,[10–12] β-ketophosphonic acids [13] or phosphonic acids bearing urea groups [14] are used as acidic monomer.

Gem-phosphonate phosphates were found to be potential antiatherosclerotic agents.[15] Due to the presence of both a phosphonic acid and a dihydrogen phosphate group on the same carbon, such compounds should present excellent chelating properties. To the best of our knowledge, polymerizable gem-phosphonate-phosphates have not yet been reported in the literature. In this context, we took an interest in the synthesis of polymerizable α-phosphonooxy phosphonic acids 7a, 7b, 9 and 16 (Figure 1). In this article, the synthesis, photopolymerization behavior and adhesive properties of monomers 7a, 7b, 9 and 16 are described.

2. Experimental
2.1. Abbreviations
Butylated hydroxytoluene (BHT), camphorquinone (CQ), dichloromethane (DCM), double-bond conversion (DBC), N,N′-diethyl-13-bis-(acrylamido)propane (DEBAAP), diethyl ether (Et2O), 4-dimethylaminopyridine (DMAP), dimethylformamide (DMF), ethanol (EtOH), ethyl acetate (EA), ethyl 4-(dimethylamino)benzoate (EMBO), geminal (gem), Hydroxyapatite (HAP), 2-hydroxyethyl methacrylate (HEMA), Bis(2,4,6-trimethylbenzoyl)-phenylphosphineoxide (Irgacure 819), bis-(4-methoxybenzoyl)diethylgermanium (Ivocerin'), 10-methacryloyloxydecyl dihydrogen phosphate (MDP), 10-methacryloyloxydecylphosphonic acid...
matography was performed on silica gel 60 F-254 plates. 

Thin layer chro-

2.2. Materials

DCM, THF and MeOH were dried over molecular sieves. TMSBr was distilled prior to use. 2-Isocyanatoethyl methacrylate was purchased from ABCR. tert-Butylchlorodiphenylsilane was purchased from TCI. All other reagents were purchased from Sigma–Aldrich and were used without further purification. BHT (Sigma–Aldrich), Bis-GMA (Esschem), CQ (Rahn), DEBAAP (Ivoclar-Vivadent AG), EMBO (Sigma–Aldrich), HEMA (Evonik), Irgacure 819 (BASF) and MDP (Orgentis Chemical GmbH) were used in the adhesive formulations and for the photopolymerization studies. MDPA was synthesized according to a procedure reported in the literature.[16] Column chromatography were performed on Macherey-Nagel silica gel 60 (40–63 μm). Thin layer chromatography was performed on silica gel 60 F-254 plates.

2.3. Methods

"DESIGNED MONOMERS AND POLYMERS"

2.4. Syntheses

2.4.1. Synthesis of the acidic monomer 7a

2.4.1.1. 6-(tert-Butyl-diphenylsilyloxy)hexanoic acid 1a. tert-Butylchlorodiphenylsilane (58.03 g, 0.21 mol) was added, under argon atmosphere, to a solution of 6-hydroxycaproic acid (25.0 g, 0.19 mol) and imidazole (28.98 g, 0.43 mol) in DMF (180 mL). The solution was stirred for 15 h at 50 °C. The solution was poured into 400 mL of brine and the mixture was extracted with EA (3 x 500 mL). The organic layers were gathered and washed with deionized water (2 x 500 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent = DCM/MeOH: 98/2). 46.1 g (0.12 mol) of the desired carboxylic acid 1a were isolated.

Yield: 66%. Aspect: colorless oil. 1H-NMR (400 MHz, CDCl3): δ = 1.04 (s, 9H, CH3 tBu); 1.36–1.47 (m, 2H, CH2); 1.52–1.67 (m, 4H, CH2); 2.33 (t, JHH = 7.6 Hz, 2H, CH2COOH); 3.65 (t, JHH = 6.4 Hz, 2H, CH2OSi); 7.34–7.45 (m, 6H, CHAr); 7.63–7.69 (m, 4H, CHAr).

2.4.1.2. 6-(tert-Butyl-diphenylsilyloxy)hexanoyl chloride 2a. Oxaly chloride (2.78 mL, 32.4 mmol) was added dropwise to a solution of carboxylic acid 1a (10.0 g, 27.0 mmol) in anhydrous toluene (100 mL). The solution was stirred for 4 h at room temperature. The solution was concentrated under reduced pressure. 10.5 g (27.0 mmol) of 2a were obtained.

Yield: 100%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 0.105 (s, 9H, CH3 tBu); 1.37–1.48 (m, 2H, CH2); 1.51–1.61 (m, 2H, CH2); 1.69 (qt, JHH = 7.6 Hz, 2H, CH2); 2.86 (t, JHH = 7.4 Hz, 2H, CH2COCl); 3.66 (t, JHH = 6.2 Hz, 2H, CH2OSi); 7.35–7.46 (m, 6H, CHAr); 7.62–7.69 (m, 4H, CHAr).

2.4.1.3. Diethyl 6-(tert-butyl-diphenylsilyloxy)-1-oxo-hexylphosphonate 3a. Triethyl phosphite (4.61 mL, 26.9 mmol) was added dropwise, under argon atmosphere, at 0 °C, to a solution of acyl chloride 2a (10.5 g, 26.9 mmol) in anhydrous DCM (20 mL). The solution was stirred for 1 h at room temperature. The solution was concentrated under reduced pressure. 13.1 g (26.8 mmol) of α-ketophosphonate 3a were obtained.

Yield: 100%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.04 (s, 9H, CH3 tBu); 1.32–1.44 (m, 2H, CH2); 1.37 (t, JHH = 7.1 Hz, 6H, POCH2CH3); 1.50–1.67 (m, 4H, CH2); 2.83 (t, JHH = 7.3 Hz, 2H, CH2COP); 3.65 (t, JHH = 6.3 Hz, 2H, CH2OSi); 4.17–4.27 (m, 4H, POCH2CH3); 7.33–7.46 (m, 6H, CHAr); 7.62–7.69 (m, 4H, CHAr). 31P NMR (162 MHz, CDCl3): δ = -2.7. 13C NMR (101 MHz, CDCl3): δ = 16.4 (d, JCP = 5.6 Hz, POCH2CH3); 19.2 (Si(CH3)2); 22.2 (d, JCP = 3.9 Hz, CH2COP); 25.2 (CH2); 26.9 (Si(CH3)2); 32.2 (CH2); 43.4 (d, JCP = 54.0 Hz, POCH2CH3); 63.6 (CH2OSi); 63.7 (d, JCP = 7.3 Hz, POCH2CH3); 127.6 (CHAr); 129.6 (CHAr); 134.0 (CHAr); 135.6 (CHAr); 211.2 (d, JCP = 165.2 Hz, COP).
2.4.1.4. Diethyl 6-(tert-butyl-diphenylsilyloxy)-1-diethylphosphonooxy-hexylphosphonate 4a. A solution of α-ketophosphonate 3a (13.1 g, 26.6 mmol) in Et₂O (40 mL) was slowly added at 0 °C to a solution of diethyl phosphate (3.43 mL, 26.6 mmol) and diethylamine (2.75 mL, 26.6 mmol) in Et₂O (60 mL). The reaction mixture was stirred for 30 min at 0 °C and for 24 h at room temperature. The solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent = EA). 12.0 g (19.1 mmol) of the compound 4a were isolated.

Yield: 72%. Aspect: slightly yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 1.04 (s, 9H, CH₃tBu); 1.26–1.66 (m, 18H, CH₂ and POCH₂CH₃); 1.76–1.99 (m, 2H, CH₂); 3.65 (t, 3JCH = 6.4 Hz, 2H, CH₂OSi); 4.05–4.25 (m, 8H, POCH₂CH₃); 4.56–4.68 (m, 1H, CH₂); 7.34–7.45 (m, 6H, CHAr); 7.63–7.69 (m, 4H, CHAr).

2.4.1.5. Diethyl 6-hydroxy-1-diethylphosphonooxy-hexylphosphonate 5a. A solution of TBAF (7.23 g, 23.0 mmol) in THF (25 mL) was added dropwise to a solution of compound 4a (12.0 g, 19.1 mmol) in THF (50 mL). The reaction mixture was stirred for 3 h at room temperature. A saturated solution of ammonium chloride (4 mL) was added. The solution was concentrated under reduced pressure. Deionized water (60 mL) was added and the solution was extracted with EA (3 × 60 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent = EA/MeOH: 95/5). 2.84 g (6.2 mmol) of monomer 5a were isolated.

Yield: 78%. Aspect: colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 1.28–1.76 (m, 18H, CH₂ and POCH₂CH₃); 1.81–2.03 (m, 5H, CH₂ and CH₃); 4.07–4.28 (m, 10H, POCH₂CH₃ and CH₂OCO); 4.57–4.72 (m, 1H, CHP); 5.53–5.59 (m, 1H, CH₂=C); 6.10 (s, 1H, CH₂=C). ¹³C NMR (101 MHz, CDCl₃): δ = 16.0 (d, 3JCP = 169.9 Hz, POCH₂CH₃); 63.8 (CH₂OSi); 64.0 (d, 3JCP = 5.9 Hz, POCH₂CH₃); 73.2 (d, 3JCP = 6.7 Hz, POCH₂CH₃); 127.6 (C₆H₅); 129.5 (C₆H₅); 131.4 (C₆H₅); 133.5 (C₆H₅).

2.4.1.6. Diethyl 6-methacryloyloxy-1-diethylphosphonooxy-hexylphosphonate 6a. Methacrylic anhydride (1.31 mL, 8.8 mmol) was added, under argon atmosphere, to a solution of alcohol 5a (3.12 g, 8.0 mmol), DMAP (49 mg, 0.40 mmol) and triethylamine (1.23 mL, 8.8 mmol) in dry DCM (30 mL). The reaction mixture was stirred for 6 h at room temperature. The solution was concentrated under reduced pressure. EA (70 mL) was added and the solution was washed with a saturated solution of sodium bicarbonate (2 × 70 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent = EA/MeOH: 95/5). 2.84 g (6.2 mmol) of monomer 6a were isolated.

Yield: 78%. Aspect: slightly yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 1.28–1.76 (m, 18H, CH₂ and POCH₂CH₃); 1.81–2.03 (m, 5H, CH₂ and CH₃); 4.07–4.28 (m, 10H, POCH₂CH₃ and CH₂OCO); 4.57–4.72 (m, 1H, CHP); 5.53–5.59 (m, 1H, CH₂=C); 6.10 (s, 1H, CH₂=C). ¹³C NMR (101 MHz, CDCl₃): δ = 16.0 (d, 3JCP = 169.9 Hz, POCH₂CH₃); 16.1 (d, 3JCP = 4.8 Hz, POCH₂CH₃); 16.4 (d, 3JCP = 5.8 Hz, POCH₂CH₃); 16.5 (d, 3JCP = 5.8 Hz, POCH₂CH₃); 19.2 (Si(CH₃)₃); 25.3 (d, 3JCP = 10.5 Hz, CH₂CH₂CH₂P); 26.5 (d, 3JCP = 16.9 Hz, CH₂CH₂CH₂P); 127.6 (C₆H₅); 129.5 (C₆H₅); 131.4 (C₆H₅); 133.5 (C₆H₅).

2.4.1.7. 6-Methacryloyloxy-1-phosphonooxy-hexylphosphonic acid 7a. TMSBr (4.75 mL, 36.0 mmol) was added, under argon atmosphere, to a solution of monomer 6a (2.75 g, 6.0 mmol) in anhydrous DCM (40 mL). After stirring for 5 h at 30 °C, the mixture was concentrated under reduced pressure. Methanol (40 mL) was added and the mixture was stirred for 30 min at RT. The solvent was evaporated and the product was dried to a constant weight under vacuum. 1.96 g (5.7 mmol) of the monomer 7a were isolated.

Yield: 95%. Aspect: highly viscous yellow oil. ¹H NMR (400 MHz, MeOD): δ = 1.28–1.78 (m, 6H, CH₂); 1.79–1.98 (m, 5H, CH₂ and CH₃); 4.15 (t, 3JCH = 6.6 Hz, 2H, CH₂OCO); 4.36–4.48 (m, 1H, CHP); 5.59–5.63 (m, 1H, CH₂=C); 6.08 (s, 1H, CH₂=C). ¹³C NMR (100 MHz, MeOD): δ = 17.0 (CH₂); 24.7 (d, 3JCP = 10.3 Hz, CH₂CH₂CH₂P); 25.4 (CH₂); 28.1 (CH₂); 30.6 (CH₂); 64.4 (CH₂OCO); 73.0 (dd, 3JCP = 166.1 Hz, 7.2 Hz, CHP); 124.6 (CH₂=C); 136.5 (CH₂=C); 167.5 (C=O). HRMS (m/z): calculated for C₁₀H₁₉O₉P₂: 345.0504; found, 345.0504 [M-H]⁻.
2.4.2. Synthesis of the acidic monomer 7b

2.4.2.1. 10-(tert-Butyl-diphenylsilyloxy)decanoic acid 1b. 10-(tert-Butyl-diphenylsilyloxy)decanoic acid 1b was synthesized, from 10-hydroxydecanoic acid (10.0 g, 53.1 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)-hexanoic acid 1a. 17.3 g of 1b were isolated.

Yield: 76%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 1.05 (s, 9H, CH3 tBu); 1.2–1.4 (m, 10H, CH2); 1.50–1.69 (m, 4H, CH2); 2.35 (t, JHH = 7.6 Hz, 2H, CH2COOH); 3.65 (t, JHH = 6.5 Hz, 2H, CH2OSi); 4.17–4.27 (m, 4H, POCH2CH3); 7.35–7.46 (m, 6H, CHAr); 7.65–7.70 (m, 4H, CHAr). 31P NMR (162 MHz, CDCl3): δ = −1.0 (s, 3H, CH3P). 13C NMR (101 MHz, CDCl3): δ = 19.2 (SiC(CH3)3); 25.1 (CH2); 25.7 (CH2); 26.9 (CH2); 28.4 (CH2); 29.0 (CH2); 29.2 (CH2); 29.3 (CH2); 32.5 (CH2); 41.1 (CH2COCl); 64.0 (CH2OSi); 127.6 (CAr); 129.5 (CAr); 134.2 (CAr); 135.6 (CAr); 137.3 (COCl).

2.4.2.2. 10-(tert-Butyl-diphenylsilyloxy)-decanoyl chloride 2b. 10-(tert-Butyl-diphenylsilyloxy)-decanoyl chloride 2b was synthesized, from 10-(tert-butyl-diphenylsilyloxy)decanoic acid 1b (2.0 g, 4.7 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)-hexanoyl chloride 2a. 2.1 g of 2b were isolated.

Yield: 100%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 1.06 (s, 9H, CH3 tBu); 1.22–1.40 (m, 10H, CH2); 1.56 (qt, JHH = 6.8 Hz, 2H, CH2); 1.71 (qt, JHH = 7.3 Hz, 2H, CH2); 2.89 (t, JHH = 7.3 Hz, 2H, CH2COCl); 3.66 (t, JHH = 6.5 Hz, 2H, CH2OSi); 4.07–4.26 (m, 8H, POCH2CH3); 7.35–7.46 (m, 6H, CHAr); 7.57–7.71 (m, 4H, CHAr); 13C NMR (101 MHz, CDCl3): δ = 19.2 (Si(CH3)3); 25.1 (CH2); 25.7 (CH2); 26.9 (CH2); 28.4 (CH2); 29.0 (CH2); 29.2 (CH2); 29.3 (CH2); 32.5 (CH2); 41.1 (CH2COCl); 64.0 (CH2OSi); 127.6 (CAr); 129.5 (CAr); 134.2 (CAr); 135.6 (CAr); 137.3 (COCl).

2.4.2.3. Diethyl 10-(tert-Butyl-diphenylsilyloxy)-1-oxo-decylphosphonate 5b. Diethyl 10-(tert-butyl-diphenylsilyloxy)-1-oxo-decylphosphonate 5b was synthesized, from 10-(tert-butyl-diphenylsilyloxy)-decanoyl chloride 2b (2.0 g, 4.7 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)-1-oxo-decylphosphonate 3a. 2.4 g of 3b were isolated.

Yield: 94%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 1.04 (s, 9H, CH3 tBu); 1.19–1.38 (m, 10H, CH2); 1.37 (t, JHH = 7.1 Hz, 6H, POCH2CH3); 1.49–1.66 (m, 4H, CH2); 2.83 (t, JHH = 7.3 Hz, 2H, CH2COOCH2); 3.64 (t, JHH = 6.5 Hz, 2H, CH2OSi); 4.17–4.27 (m, 4H, POCH2CH3); 7.34–7.45 (m, 6H, CHAr); 7.65–7.70 (m, 4H, CHAr). 31P NMR (162 MHz, CDCl3): δ = −1.1 (d, JPP = 21.8 Hz, CHOP). 13C NMR (101 MHz, CDCl3): δ = 19.2 (Si(CH3)3); 25.1 (CH2); 25.7 (CH2); 26.9 (CH2); 28.4 (CH2); 29.0 (CH2); 29.2 (CH2); 29.3 (CH2); 32.5 (CH2); 41.1 (CH2COCl); 64.0 (CH2OSi); 127.6 (CAr); 129.5 (CAr); 134.2 (CAr); 135.6 (CAr); 137.3 (COCl).

2.4.2.4. Diethyl 10-(tert-butyl-diphenylsilyloxy)-1-diethylphosphonoxy-decylphosphonate 4b. Diethyl 10-(tert-butyl-diphenylsilyloxy)-1-diethylphosphonoxy-decylphosphonate 4b was synthesized, from diethyl 10-(tert-butyl-diphenylsilyloxy)-1-oxo-decylphosphonate 3b (15.4 g, 28.2 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)-1-diethylphosphonoxy- hexylphosphonate 4a. 16.1 g of 4b were isolated.

Eluent: EA. Yield: 83%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.04 (s, 9H, CH3 tBu); 1.19–1.66 (m, 26H, CH2 and POCH2CH3); 1.76–1.98 (m, 2H, CH2); 3.64 (t, JHH = 6.5 Hz, 2H, CH2OSi); 4.07–4.26 (m, 8H, POCH2CH3); 4.57–4.69 (m, 1H, CHP); 7.33–7.46 (m, 6H, CHAr); 7.63–7.70 (m, 4H, CHAr). 31P NMR (162 MHz, CDCl3): δ = −1.0 (d, JPP = 21.6 Hz, CHOP). 13C NMR (101 MHz, CDCl3): δ = 16.0 (d, JCP = 4.4 Hz, POCH2CH3); 16.1 (d, JCP = 4.2 Hz, POCH2CH3); 16.4 (d, JCP = 5.8 Hz, POCH2CH3); 16.5 (d, JCP = 5.7 Hz, POCH2CH3); 19.2 (Si(CH3)3); 25.4 (d, JCP = 10.7 Hz, CH2CH2CH2CH3); 25.8 (CH2); 26.9 (Si(CH3)3); 29.3 (2C, CH2); 29.4 (CH2); 29.5 (CH2); 31.0 (CH2); 32.6 (CH2); 62.8 (d, JCP = 6.6 Hz, POCH2CH3); 64.0 (d, JCP = 5.8 Hz, POCH2CH3); 64.0 (CH2OSi); 73.2 (dd, JCP = 169.7 Hz, JCP = 7.4 Hz, CHP); 127.6 (CAr); 129.5 (CAr); 134.2 (CAr); 135.6 (CAr).
6b was synthesized, from diethyl 10-hydroxy-1-diethylphosphonoxy-decylphosphonate 5b (2.3 g, 5.1 mmol), according to the same procedure described for the synthesis of diethyl 6-methacryloyloxy-1-diethylphosphonoxy-hexylphosphonate 6a. 2.3 g of 5b were isolated.

Eluent: EA. Yield: 86%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 1.23–1.72 (m, 26H, CH2 and POCH2CH2); 1.77–1.98 (m, 5H, CH2 and CH3); 4.08–4.25 (m, 10H, POCH2CH2 and CH2OCO); 4.58–4.68 (m, 1H, CHP); 5.53–5.57 (m, 1H, CH2=C); 6.10 (s, 1H, CH2=C). 13P NMR (162 MHz, CDCl3): δ = −1.0 (d, 3JCP = 21.7 Hz, CHOP); 20.3 (d, 3JCP = 21.7 Hz, CHP); 55.1 (CH2); 55.3 (CH2); 75.9 (CH2OCO); 125.1 (CH2=C); 126.0 (CH2=C); 136.5 (CH2=C); 167.6 (C=O).

2.4.2.7. 10-Methacryloyloxy-1-phosphonoxy-decylphosphonic acid 7b. 10-Methacryloyloxy-1-phosphonoxy-decylphosphonic acid 7b was synthesized, from diethyl 10-methacryloyloxy-1-diethylphosphonoxy-decylphosphonic acid 6b (1.95 g, 3.8 mmol), according to the same procedure described for the synthesis of 6-methacryloyloxy-1-phosphonoxy-hexylphosphonic acid 7a. 1.52 g of 7b were isolated.

Yield: 100%. Aspect: highly viscous yellow oil. 1H NMR (400 MHz, MeOD): δ = 1.26–1.73 (m, 14H, CH2); 1.75–1.96 (m, 5H, CH2 and CH3); 4.13 (t, 3JHH = 6.6 Hz, 2H, CH2OCO); 4.35–4.46 (m, 1H, CHP); 5.59–5.62 (m, 1H, CH2=C); 6.07 (s, 1H, CH2=C). 13P NMR (162 MHz, MeOD): δ = 0.3 (d, 3JCP = 18.7 Hz, CHOP); 19.5 (d, 3JCP = 18.7 Hz, CHP). 13C NMR (101 MHz, MeOD): δ = 17.1 (CH2); 25.1 (d, 3JCP = 10.4 Hz, CH2CH2CH2); 25.7 (CH2); 28.3 (CH2); 28.9 (CH2); 29.0 (CH3); 29.1 (CH2); 29.2 (CH2); 30.7 (CH2); 64.6 (CH2OCO); 73.2 (dd, 3JCP = 165.9 Hz, 2JCP = 7.2 Hz, CH2); 124.7 (CH2=C); 136.5 (CH2=C); 167.5 (C=O). HRMS (m/z): calcd for C14H27O5P2 401.1130; found, 401.1127 [M-H].

2.4.3. Synthesis of the acidic monomer 9

2.4.3.1. Diethyl 6-[2-(methacryloyloxyethylamino)carbonyloxy]-1-diethylphosphonoxy-hexylphosphonate 8. A solution of dibutyltin dilaurate (25.5 mg, 0.041 mmol) in anhydrous DCM (2.0 mL) was added, under argon atmosphere, to a solution of diethyl 6-hydroxy-1-diethylphosphonoxy-hexylphosphonate 5a (2.3 g, 8.1 mmol) in anhydrous DCM (10.0 mL). 2-Isocyanatoethyl methacrylate (1.14 mL, 8.1 mmol) was subsequently added dropwise to the mixture. The solution was stirred for 3 h at RT and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: EA/MeOH: 9/1), 4.3 g of the desired compound were isolated.

Yield: 93%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.28–1.74 (m, 18H, CH2 and POCH2CH3); 1.80–1.98 (m, 5H, CH2 and CH3); 3.40–3.54 (m, 2H, CH2NH); 4.00–4.26 (m, 12H, POCH2CH2CH2OCONH and CH2OCO); 4.56–4.67 (m, 1H, CHP); 5.24 (s, 1H, NH); 5.57–5.61 (m, 1H, CH2=C); 6.13 (s, 1H, CH2=C). 13P NMR (162 MHz, CDCl3): δ = −1.1 (d, 3JCP = 22.2 Hz, CHOP); 20.1 (d, 3JCP = 22.2 Hz, CHP). 13C NMR (101 MHz, CDCl3): δ = 16.0 (d, 3JCP = 4.6 Hz, POCH2CH3); 16.1 (d, 3JCP = 4.4 Hz, POCH2CH3); 16.4 (d, 3JCP = 5.8 Hz, POCH2CH3); 16.5 (d, 3JCP = 5.8 Hz, POCH2CH3); 18.3 (CH2); 25.0 (d, 3JCP = 10.5 Hz, CH2CH2CH2); 25.7 (CH2); 28.5 (CH2); 30.8 (CH2); 40.0 (CH2NH); 62.8 (d, 3JCP = 6.1 Hz, POCH2CH3); 62.8 (d, 3JCP = 7.2 Hz, POCH2CH3); 63.8 (CH2OCO); 64.1 (d, 3JCP = 6.1 Hz, POCH2CH3); 65.0 (CH2OCO); 73.0 (dd, 3JCP = 169.9 Hz, 2JCP = 7.3 Hz, CHP); 126.0 (CH2=C); 136.0 (CH2=C); 156.7 (C=O); 167.2 (C=O).

2.4.3.2. 6-[2-(Methacryloyloxyethylamino)carbonyloxy]-1-phosphonoxy-hexylphosphonic acid 9. 6-[2-(Methacryloyloxyethylamino)-carbonyloxy]-1-phosphonoxy-hexylphosphonic acid 9 was synthesized, from diethyl 6-[2-(methacryloyloxyethylamino)-carbonyloxy]-1-diethylphosphonoxy-hexylphosphonate 8 (1.0 g, 1.8 mmol), according to the same procedure described for the synthesis of 6-methacryloyloxy-1-phosphonoxy-hexylphosphonic acid 7a. 750 mg of 9 were isolated.

Yield: 94%. Aspect: highly viscous yellow oil. 1H NMR (400 MHz, MeOD): δ = 1.26–1.74 (m, 6H, CH2); 1.77–1.97 (m, 5H, CH2 and CH3); 3.38 (t, 3JHH = 5.5 Hz, 2H, CH2NH); 4.03 (t, 3JHH = 6.5 Hz, 2H, CH2OCO); 4.17 (t, 3JHH = 5.5 Hz, 2H, CH2OCONH); 4.34–4.47 (m, 1H, CHP); 5.61–5.65 (m, 1H, CH2=C); 6.11 (s, 1H, CH2=C). 13P NMR (162 MHz, MeOD): δ = 0.3 (CHOP); 19.3 (CHP). 13C NMR (101 MHz, MeOD): δ = 17.0 (CH2); 24.8 (d, 3JCP = 10.4 Hz, CH2CH2CH2); 25.3 (CH2); 28.6 (CH2); 30.6 (CH2); 39.3 (CH2NH); 63.2 (CH2OCO); 64.5 (CH2OCO); 73.0 (dd, 3JCP = 166.0 Hz, 2JCP = 7.2 Hz, CHP); 125.1 (CH2=C); 136.2 (CH2=C); 157.9 (C=O); 167.3 (C=O). HRMS (m/z): calcd for C11H23NO2P2 432.0825; found, 432.0822 [M-H].

2.4.4. Synthesis of the acidic monomer 16

2.4.4.1. 11-Phthalimido-undecanoic acid 10. A mixture of 11-aminoundecanoic acid (3.04 g, 15.1 mmol) and phthalic anhydride (2.24 g, 15.1 mmol) was heated for 1 h at 150 °C. DCM (25 mL) was added and the resulting solution was dried over sodium sulfate. The solution was filtered and concentrated under reduced pressure. 4.9 g (14.8 mmol) of carboxylic acid 10 were obtained.
2.4.4.1. 11-Phtalimido-undecanoyl chloride 11.

11-Phtalimido-undecanoyl chloride 11 was synthesized, from 11-pteroidal-undecenoic acid 10 (8.4 g, 25.3 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)hexanoyl chloride 2a. 8.9 g of 11 were isolated.

Yield: 100%. Aspect: colorless oil. 1H NMR (400 MHz, CDCl3): δ = 1.22–1.39 (m, 12H, CH2); 1.36 (t, JCHp = 7.3 Hz, CH2); 1.58–1.77 (m, 4H, CH2); 2.87 (t, JCHp = 7.3 Hz, 2H, CH2COCl); 3.67 (t, JCHp = 4.7 Hz, CH2P); 7.67–7.74 (m, 2H, CHAr); 7.81–7.87 (m, 2H, CHAr).

2.4.4.2. Diethyl 11-phtalimido-1-oxo-undecylphosphonate 13.

Diethyl 11-phtalimido-1-oxo-undecylphosphonate 13 was synthesized, from 11-phtalimido-undecanoyl chloride 11 (1.0 g, 2.9 mmol), according to the same procedure described for the synthesis of 6-(tert-butyl-diphenylsilyloxy)-1-oxo-hexylphosphonate 2a. 1.22 g of 13 were isolated.

Yield: 95%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.18–1.74 (m, 28H, POCH2CH3); 1.76–1.98 (m, 2H, CH2); 3.67 (t, JCHp = 7.2 Hz, 2H, CH2 N); 4.07–4.26 (m, 8H, POCH2CH3); 4.57–4.68 (m, 1H, CHP); 7.68–7.73 (m, 2H, CHAr); 7.81–7.87 (m, 2H, CHAr).

13P NMR (162 MHz, CDCl3): δ = −1.0 (d, JCP = 21.6 Hz, CHP); 20.3 (d, JCP = 21.6 Hz, CHP). 13C NMR (101 MHz, CDCl3): δ = 6.0 (d, JCP = 4.9 Hz, POCH2CH3); 16.1 (d, JCP = 4.7 Hz, POCH2CH3); 16.4 (d, JCP = 5.8 Hz, POCH2CH3); 16.5 (d, JCP = 5.5 Hz, POCH2CH3); 25.4 (d, JCP = 10.4 Hz, CH2CH2CH2CHP); 26.9 (CH2); 28.6 (CH2); 29.1 (CH2); 29.2 (CH2); 29.4 (CH2); 34.0 (CH2COOH); 38.1 (CH2 N); 123.2 (CAr); 132.2 (CAr); 133.8 (CAr); 168.5 (C=O); 179.7 (C=O).

2.4.4.3. Diethyl 11-phtalimido-1-oxo-undecylphosphonate 14.

Hydrazine monohydrate (0.13 mL, 2.54 mmol) was added to a solution of compound 13 (1.0 g, 1.70 mmol) in EtOH (10 mL). The mixture was refluxed for 2 h and the solvent removed under reduced pressure. A solution of NaOH (2 N in distilled water, 20 mL) was added and the mixture was extracted with Et2O (3 x 15 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. 650 mg (1.41 mmol) of the desired product was isolated.

Yield: 83%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.20–1.66 (m, 30H, POCH2CH3, CH2 and CH3); 1.77–1.99 (m, 2H, CH2); 2.67 (t, JCHp = 6.9 Hz, 2H, CH2NH2); 4.07–4.27 (m, 8H, 2H, POCH2CH3); 4.56–4.69 (m, 2H, CH2P).

13P NMR (162 MHz, CDCl3): δ = −1.0 (d, JCP = 21.8 Hz, CHP); 20.3 (d, JCP = 21.8 Hz, CHP). 13C NMR (101 MHz, CDCl3): δ = 6.0 (d, JCP = 4.5 Hz, POCH2CH3); 16.1 (d, JCP = 4.4 Hz, POCH2CH3); 16.4 (d, JCP = 5.7 Hz, POCH2CH3); 16.5 (d, JCP = 5.5 Hz, POCH2CH3); 25.3 (d, JCP = 10.6 Hz, CH2CH2CH2CHP); 26.9 (CH2); 29.1 (CH2); 29.2 (CH2); 29.4 (CH2); 29.5 (CH2); 31.0 (CH2); 33.8 (CH2); 40.3 (CH2 N); 62.7 (d, JCP = 6.7 Hz, POCH2CH3); 63.9 (d, JCP = 5.9 Hz, POCH2CH3); 73.2 (dd, JCP = 169.7 Hz, JCP = 7.4 Hz, CHP); 123.1 (CA); 132.2 (CA); 133.8 (CA); 168.4 (C=O).

2.4.4.4. Diethyl 11-methacrylamido-1-diethylphosphonoxy-undecylphosphonate 15.

Methacrylonitrile (0.23 mL, 2.29 mmol) was added, under argon atmosphere and at 0°C, to a solution of amine 14 (1.00 g, 2.18 mmol) and triethylamine (0.33 mL, 2.39 mmol) in dry DCM (9 mL). The reaction mixture was stirred for 6 h at RT. The solution was washed with HCl 1 N (10 mL), NaOH 1 N (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent = EA/MeOH: 95/5). 920 mg (1.74 mmol) of monomer 15 was isolated.

Yield: 80%. Aspect: slightly yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.19–1.64 (m, 28H, POCH2CH3 and CH2); 1.75–1.94 (m, 2H, CH2); 1.94 (s, 3H, CH3); 3.28 (q, JCHp = 6.7 Hz, 2H, CH2N); 4.05–4.23 (m, 8H, POCH2CH3); 4.55–4.66 (m, 1H, CHP);
5.28 (s, 1H, C=CH2); 5.64 (s, 1H, C=CH2); 5.85 (s, 1H, NH). \(^{31}P\) NMR (162 MHz, CDCl\(_3\)): \(\delta = -1.1\) (d, \(3J_{pp} = 21.8\) Hz, CHOP); 20.2 (d, \(3J_{pp} = 21.8\) Hz, CHP). \(^1^C\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 16.0\) (d, \(3J_{pp} = 4.5\) Hz, POCH\(_2\)CH\(_3\)); 16.1 (d, \(3J_{pp} = 4.4\) Hz, POCH\(_2\)CH\(_3\)); 16.4 (d, \(3J_{pp} = 5.8\) Hz, POCH\(_2\)CH\(_3\)); 16.5 (d, \(3J_{pp} = 5.7\) Hz, POCH\(_2\)CH\(_3\)); 18.7 (CH\(_3\)); 25.3 (d, \(3J_{pp} = 10.5\) Hz, CH\(_2\)CH\(_2\)CHP); 26.9 (CH\(_2\)); 29.1 (CH\(_3\)); 29.2 (CH\(_3\)); 29.3 (CH\(_3\)); 29.4 (CH\(_2\)); 29.4 (CH\(_2\)); 29.5 (CH\(_2\)); 31.0 (CH\(_2\)); 39.7 (CH\(_2\)); 62.8 (d, \(2J_{pp} = 6.2\) Hz, POCH\(_2\)CH\(_3\)); 62.9 (d, \(2J_{pp} = 7.3\) Hz, POCH\(_2\)CH\(_3\)); 64.0 (d, \(2J_{pp} = 5.9\) Hz, POCH\(_2\)CH\(_3\)); 73.2 (dd, \(2J_{pp} = 169.5\) Hz, 2\(J_{pp} = 7.2\) Hz, CHP); 119.0 (C=CH\(_2\)); 140.3 (C=CH\(_2\)); 168.4 (C=O).

2.4.7. 11-Methacrylamido-1-phosphonoxy-undecylphosphonic acid 16. 11-Methacrylamido-1-phosphonoxy-undecylphosphonic acid 16 was synthesized, from diethyl 11-methacrylamido-1-diethylphosphonoxy-undecylphosphonic acid 15 (900 mg, 1.71 mmol), according to the same procedure described for the synthesis of 6-methacryloyloxy-1-phosphonooxy-1-diethylphosphonooxy-undecylphosphonic acid 7a. 710 mg of 16 were isolated.

Yield: 100%. Aspect: highly viscous slightly yellow oil.

\(^{1}H\) NMR (400 MHz, MeOD): \(\delta = 1.15 - 1.59\) (m, 16H, CH\(_2\)); 1.65 - 1.87 (m, 5H, CH\(_3\) and CH\(_2\)); 3.12 (t, \(3J_{HH} = 7.2\) Hz, 2H, CH\(_2\)N); 4.25 - 4.35 (m, 1H, CHP); 5.25 (s, 1H, C=CH\(_2\)); 5.56 (s, 1H, C=CH\(_2\)). \(^{31}P\) NMR (162 MHz, MeOD): \(\delta = 0.3\) (d, \(3J_{PP} = 18.6\) Hz, CHOP); 19.5 (d, \(3J_{PP} = 18.6\) Hz, CHP). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 15.8\) (CH\(_3\)); 23.5 (d, \(3J_{pp} = 10.3\) Hz, CH\(_2\)CH\(_2\)CHP); 25.0 (CH\(_3\)); 27.3 (CH\(_3\)); 27.4 (CH\(_3\)); 27.5 (CH\(_3\)); 27.6 (CH\(_2\)); 27.6 (CH\(_2\)); 29.1 (CH\(_3\)); 37.8 (CH\(_2\)); 71.6 (dd, \(2J_{pp} = 165.9\) Hz, \(2J_{pp} = 7.2\) Hz, CHP); 117.4 (C=CH\(_2\)); 138.3 (C=CH\(_2\)); 168.4 (C=O). HRMS (m/z): calcd for C\(_{13}\)H\(_{26}\)NO\(_2\)P\(_2\): 414.1447; found, 414.1443 [M-H]–.

2.5. Photopolymerization procedure

Photopolymerizations were carried out on a Perkin Elmer differential scanning calorimeter (DSC), Pyris Diamond. 0.5 mol% of Ivocerin® (photoinitiator) were added to each comonomer mixture. A sample (ca. 0.8 mg) of each mixture was placed in an uncovered aluminum DSC pan. The DSC chamber was purged with nitrogen for 5 min before polymerization. One minute after the beginning of the acquisition, the samples were irradiated for 2 min at 37 °C with a LED curing light (Bluephase, Ivoclar Vivadent AG). The incident light intensity was 20 mW cm\(^{-2}\). Each experiment was repeated at least three times. The heat flux was monitored as a function of time using the DSC under isothermal conditions. The DSC was calculated as the quotient of the overall enthalpy evolved (\(\Delta H_p\) (J g\(^{-1}\))) and the theoretical enthalpy obtained for 100% conversion of the mixtures (\(\Delta H_{0p}\) (J g\(^{-1}\))) (Equation (1)).

\[
\Delta H_p = \frac{\Delta H_{0p}}{\Delta H_{0p}}
\] (1)

\(\Delta H_{0p}\) was calculated according to the following formula (Equation (2)):

\[
\Delta H_{0p} = \sum \Delta H_{0i} \cdot \frac{P_i}{M_i}
\] (2)

where \(\Delta H_{0i}\) is the theoretical enthalpy of monomer \(i\) (\(i = \text{methacrylate or methacrylamide}, \Delta H_{0i} = 54.8\) kJ mol\(^{-1}\) \(^{[17]}\)), \(M_i\) its molar mass and \(P_i\) the amount used in the formulation (wt%).

The rate of polymerization \(R_p\) was calculated according to the following formula (Equation (3)):

\[
R_p = \frac{Q}{(m \Delta H_{0p})}
\] (3)

where \(Q\) is the heat flow per second during the reaction and \(m\) the mass of the mixture in the sample.

2.6. SBS measurement

Freshly extracted bovine mandibular incisors were embedded in unsaturated polyester resin (ViscoVoss). Flat dentinal and enamel surfaces were prepared with 120-grit and 400-grit wet silicon carbide paper on the labial side of the embedded teeth. The adhesive was first rubbed on the prepared dentin or enamel surface with a microbrush for 20 s. The adhesive layer was strongly air dried and light cured for 10 s with a LED curing light (Bluephase G2, polywave LED with a spectrum from 385 to 515 nm and 2 maxima at 410 and 470 nm, Ivoclar Vivadent AG). A poly(ethylene) mold with a central 2.38-mm diameter circular hole was fixed on the surface. A composite (Tetric EvoCeram, Ivoclar Vivadent AG) was inserted in the mold and light-cured for 20 s. The samples were then stored in water at 37 °C for 24 h before being tested. The SBS was measured using a universal testing machine (Zwick, Germany) at a crosshead speed of 0.8 mm min\(^{-1}\). 10 samples were tested for each adhesive.

3. Results and discussion

3.1. Syntheses

Monomer 7a was prepared, starting from 6-hydroxy-caproic acid, in seven steps (Scheme 1). The alcohol group was first protected using tert-butylidiphenylchlorosilane, and the resulting triethyl phosphite to the acyl chloride 2a in a quantitative yield. The addition of silyl ether and oxalyl chloride provided the corresponding acyl chloride in unsaturated polyester resin (ViscoVoss). Flat dentinal and enamel surfaces were prepared with 120-grit and 400-grit wet silicon carbide paper on the labial side of the embedded teeth. The adhesive was first rubbed on the prepared dentin or enamel surface with a microbrush for 20 s. The adhesive layer was strongly air dried and light cured for 10 s with a LED curing light (Bluephase G2, polywave LED with a spectrum from 385 to 515 nm and 2 maxima at 410 and 470 nm, Ivoclar Vivadent AG). A poly(ethylene) mold with a central 2.38-mm diameter circular hole was fixed on the surface. A composite (Tetric EvoCeram, Ivoclar Vivadent AG) was inserted in the mold and light-cured for 20 s. The samples were then stored in water at 37 °C for 24 h before being tested. The SBS was measured using a universal testing machine (Zwick, Germany) at a crosshead speed of 0.8 mm min\(^{-1}\). 10 samples were tested for each adhesive.
chromatography, compound 4a was isolated in 72% yield. Then, the tert-butylidiphenylsilyl protecting group was cleaved using TBAF in THF. The resulting alcohol 5a was obtained in 86% yield. Methacrylate 6a was synthesized by acylation of 5a with methacryloyl anhydride in the presence of triethylamine and of a catalytic amount of DMAP. Silylation of 6a using TMSBr, followed by the methanalysis of the silyl ether, finally provided the desired acidic monomer 7a in 95% yield. Monomer 7b was prepared, from 10-hydroxydecanoic acid, according to a similar synthetic pathway (Scheme 1). It was isolated in a 47% global yield. Acidic monomer 9 was synthesized in two steps, starting from alcohol 5a (Scheme 2). Methacrylate 8 was first prepared by reacting 5a with 2-isocyanatoethyl methacrylate using dibutyltin dilaurate as a catalyst. It was obtained, after purification, in 93% yield. The dealkylation of the phosphonate and phosphate groups subsequently gave the desired monomer 9. It is well-known that the use of (meth)acrylic monomers in SEAs present some drawbacks. Indeed, SEAs being acidic aqueous solutions, such monomers tend to hydrolyse upon storage. A low acidic monomer concentration or a storage in the refrigerator are required to prevent the deterioration of the adhesive. On the other hand, (N-alkyl)(meth)acrylamides are known to be significantly more stable than (meth)acrylates in aqueous acidic medium.[11,18–23] Therefore, such monomers have been incorporated in several commercially available SEAs. In this context, we took an interest in the seven-step synthesis of methacrylamide 16 (Scheme 3). The first step consisted in reacting 11-aminoundecanoic acid with phthalic anhydride at 150°C. This reaction led to the formation of phthalimide 10, which was obtained in 98% yield. The gem-phosphonate-phosphate 13 was then prepared in three steps, from carboxylic acid 10, according to a similar synthetic pathway than the one previously described for compounds 4a and 4b (Scheme 1). The phthalimide group was successfully cleaved using hydrazine in EtOH. The corresponding amine 14 was isolated in 83% yield. A subsequent acylation using methacryloyl chloride, followed by deprotection of both dialkyl phosphonate and phosphate groups, finally led to the targeted acidic methacrylamide 16. All new monomers were characterized by 1H-NMR, 31P-NMR and 13C-NMR spectroscopy. For example, the 1H-NMR spectrum of monomer 7b is shown in Figure 2. It is characterized by nine methylene groups at 1.26–1.73 ppm (m, 14H), 1.75–1.96 ppm (m, 2H) and 4.13 ppm (t, 2H). The signal at 4.35–4.46 ppm corresponds to the proton of the CH bearing both acidic groups. The protons of the methacrylate group are identified by the presence of signals at about 1.92 (methyl group), 5.60 and 6.07 ppm.

### 3.2. Photopolymerization in bulk

In order to study the reactivity of acidic monomers 7a, 7b, 9 and 16, their copolymerization with HEMA (acidic monomer/HEMA: 2/8, mol/mol) was investigated using photo-DSC. Each monomer mixture was polymerized under the same conditions (irradiation time: 2 min; light intensity: 20 mW cm⁻²). Ivocerin® (0.5 mol%) was added as photoinitiator.[24] The copolymerization of MDPA and MDP with HEMA was also studied. For each mixture, the
Table 1. $R_{pmax}$, $t_{Rpmax}$ and DBC measured for different HEMA comonomer mixtures.

| Mixtures (mol/mol) | $t_{Rpmax}$ (s) | $R_{pmax}$ (s$^{-1}$) | DBC (%) |
|--------------------|-----------------|----------------------|---------|
| 7a/HEMA (8/2)      | 4.8             | 0.101 ± 0.001        | 80.5 ± 1.0 |
| 7b/HEMA (8/2)      | 4.8             | 0.091 ± 0.001        | 77.1 ± 1.0 |
| 9/HEMA (8/2)       | 3.8             | 0.105 ± 0.001        | 79.0 ± 0.1 |
| 16/HEMA (8/2)      | 5.8             | 0.085 ± 0.001        | 75.4 ± 1.0 |
| MDP/HEMA (8/2)     | 15.4            | 0.055 ± 0.001        | 85.1 ± 2.0 |
| MDPA/HEMA (8/2)    | 14.7            | 0.056 ± 0.001        | 84.2 ± 1.0 |

Figure 3. $R_p$ vs. irradiation time for the polymerization of 7b/HEMA, MDP/HEMA, MDPA/HEMA and HEMA.

Scheme 1. Synthesis of acidic monomers 7a and 7b.
mixtures containing α-phosphonoxy phosphonic acids 7a, 7b, 9 and 16 led to lower DBCs (75.4% < DBCs < 80.5%) than for the mixtures based on MDPA (84.2%) and MDP (85.1%). Amongst the synthesized monomers, 9 was found
to be the most reactive. This result can be explained by the presence of the additional urethane group, which can also participate in hydrogen bond interactions. No significant difference was observed between the reactivity of methacrylate 7b and of the corresponding methacrylamide 16. Results obtained with 7a and 7b also showed that the spacer length has almost no influence on the polymerization rate.

### 3.3. Adhesive properties

In order to evaluate the adhesive properties of monomers 7a, 7b, 9 and 16, SEAs were formulated (Table 2). Each SEA contained an acidic monomer (15 wt%), crosslinking monomers (Bis-GMA and DEBAAP), photoinitiators (CQ/EMBO and Irgacure 819), solvents (water and i-ProOH) and additives (BHT as inhibitor). SEAs based on MDPA and MDP were also prepared. These adhesives were used to mediate a bond between a composite (Tetric EvoCeram®) and dental hard tissues (dentin and enamel). The SBS was subsequently measured (Table 3). SEAs containing the new polymerizable α-phosphonoxy phosphonic acids 7a, 7b, 9 and 16 provided significantly higher dentin and enamel SBS than the adhesives based on MDPA and MDP. The results confirm that the presence of two acidic groups has a considerable influence on the adhesive properties. Excellent chelating ability as well as improved etching properties of monomers 7a, 7b, 9 and 16 are probably responsible for the outstanding performances of SEAs 1–4. These adhesives led to similar dentin and enamel SBS. Consequently, neither the spacer length nor the nature of the polymerizable group nor the presence of a carbamate group had an influence on the SBS values. It should be emphasized that MDP is one of the most frequently used acidic monomer in commercial SEAs. α-Phosphonoxy phosphonic acids are therefore excellent candidates to improve the performance of current adhesives.

### Table 2. Composition of six experimental SEAs.

| Component | SEA 1 (wt%) | SEA 2 (wt%) | SEA 3 (wt%) | SEA 4 (wt%) | SEA 5 (wt%) | SEA 6 (wt%) |
|-----------|-------------|-------------|-------------|-------------|-------------|-------------|
| 7a        | 15.00       | –           | –           | –           | –           | –           |
| 7b        | –           | 15.00       | –           | –           | –           | –           |
| 9         | –           | –           | 15.00       | –           | –           | –           |
| 16        | –           | –           | –           | 15.00       | –           | –           |
| MDP       | –           | –           | –           | –           | 15.00       | –           |
| MDPA      | –           | –           | –           | –           | –           | 15.00       |
| DEBAAP    | 40.00       | 40.00       | 40.00       | 40.00       | 40.00       | 40.00       |
| Bis-GMA   | 22.40       | 22.40       | 22.40       | 22.40       | 22.40       | 22.40       |
| Water     | 15.00       | 15.00       | 15.00       | 15.00       | 15.00       | 15.00       |
| i-ProOH   | 5.00        | 5.00        | 5.00        | 5.00        | 5.00        | 5.00        |
| CQ        | 0.90        | 0.90        | 0.90        | 0.90        | 0.90        | 0.90        |
| EMBO      | 0.42        | 0.42        | 0.42        | 0.42        | 0.42        | 0.42        |
| Irgacure  | 1.25        | 1.25        | 1.25        | 1.25        | 1.25        | 1.25        |
| 819       |              |             |             |             |             |             |
| BHT       | 0.03        | 0.03        | 0.03        | 0.03        | 0.03        | 0.03        |

### Table 3. Results of dentin and enamel SBS tests.

| SEA | Acidic monomer | Dentin SBS (MPa) | Enamel SBS (MPa) |
|-----|---------------|------------------|-----------------|
| 1   | 7a            | 37.3 ± 5.1       | 29.1 ± 4.5      |
| 2   | 7b            | 36.5 ± 4.1       | 25.8 ± 2.8      |
| 3   | 9             | 38.5 ± 3.8       | 29.8 ± 3.0      |
| 4   | 16            | 33.8 ± 3.7       | 27.9 ± 2.9      |
| 5   | MDP           | 27.7 ± 4.8       | 22.6 ± 4.0      |
| 6   | MDPA          | 22.0 ± 3.3       | 16.4 ± 2.8      |

### 4. Conclusion

The polymerizable α-phosphonoxy phosphonic acids 7a, 7b, 9 and 16 were successfully synthesized in seven steps. The copolymerization of these monomers as well as of MDPA and MDP with HEMA was investigated. The addition of monomers 7a, 7b, 9 and 16 to HEMA led to an acceleration of the polymerization. Acidic monomers 7a, 7b, 9 and 16 were found to be significantly more reactive than MDP and MDPA. The strong ability of these monomers to form hydrogen bonds, which can be ascribed to the presence of two acidic groups, is thought to be responsible for their high reactivity. The adhesive properties of acidic monomers 7a, 7b, 9 and 16 were also evaluated. SEAs based on these α-phosphonoxy phosphonic acids led to significantly higher dentin and enamel SBS than adhesives containing the phosphonic acid MDPA or the dihydrogen phosphate MDP. Monomers 7a, 7b, 9 and 16 are therefore excellent candidates for the formulation of high performance adhesives.

### Disclosure statement

No potential conflict of interest was reported by the authors.

### References

[1] Moszner N, Hirt T. New polymer-chemical developments in clinical dental polymer materials: enamel–dentin adhesives and restorative composites. J Polym. Sci. Part A: Polym. Chem. 2012;50:4369–4402.
[2] Van Meerbeek B, Yoshihara K, Yoshida Y, et al. State of the art of self-etch adhesives. Dent. Mater. 2011;27:17–28.
[3] Van Landuyt KL, Snauwaert J, De Munck J, et al. Systematic review of the chemical composition of contemporary dental adhesives. Biomaterials. 2007;28:3757–3785.
[4] Moszner N, Catel Y. Phosphorus-based polymers: from synthesis to applications. In: Monge S, David G, editors. RSC polymer chemistry series 11. Cambridge (UK): Royal Society of Chemistry; 2014; Chapter 8; p. 151–166.
[5] Moszner N, Salz U. Recent developments of new components for dental adhesives and composites. Macromol. Mater. Eng. 2007;292:245–271.
[6] Van Landuyt KL, Yoshida Y, Hirata I, et al. Influence of the chemical structure of functional monomers on their adhesive performance. J. Dent. Res. 2008;87:757–761.
[7] Yoshida Y, Van Meerbeek B, Nakayama Y, et al. Adhesion to and decalcification of hydroxyapatite by carboxylic acids. J. Dent. Res. 2001;80:1565–1569.
[8] Yoshida Y, Nagakane K, Fukuda R, et al. Comparative study on adhesive performance of functional monomers. J. Dent. Res. 2004;83:454–458.

[9] Yoshihara K, Yoshida Y, Hayakawa S, et al. Self-etch monomer-calcium salt deposition on dentin. J. Dent. Res. 2011;90:602–606.

[10] Bilgici ZS, Turker SB, Avci D. Novel bisphosphonated methacrylates: synthesis, polymerizations, and interactions with hydroxyapatite. Macromol. Chem. Phys. 2013;214:2324–2335.

[11] Catel Y, Degrange M, Le Pluart L, et al. Synthesis, photopolymerization, and adhesive properties of new bisphosphonic acid monomers for dental application. J. Polym. Sci. Part A: Polym. Chem. 2009;47:5258–5271.

[12] Catel Y, Fischer U, Moszner N. Monomers for adhesive polymers, 13. Synthesis, radical photopolymerization and adhesive properties of polymerizable 2-substituted 1,3-propylienediphosphonic acids. Des. Monomers Polym. 2014;17:286–299.

[13] Catel Y, Bock T, Moszner N. Monomers for adhesive polymers, 15: Synthesis, photopolymerization, and adhesive properties of polymerizable β-ketophosphonic acids. J. Polym. Sci. Part A: Polym. Chem. 2014;52:3550–3563.

[14] Tauscher S, Catel Y, Moszner N. Monomers for adhesive polymers, 17: Synthesis, photopolymerization and adhesive properties of polymerizable phosphonic acids bearing urea groups. Des. Monomers Polym. 2016;19:77–88.

[15] Nguyen LM, Nie J, Niesor E, et al. Gem-diphosphonate and gem-phosphonate-phosphate compounds with specific high density lipoprotein inducing activity. J. Med. Chem. 1987;30:1426–1433.

[16] Derbanne MA, Besse V, Le Goff S, et al. Hydrolytically stable acidic monomers used in two steps self-etch adhesives. Polym. Degrad. Stab. 2013;98:1688–1698.

[17] Anseth KS, Wang CM, Bowman CN. Kinetic evidence of reaction-diffusion during the polymerization of multi(methyl)acrylate monomers. Macromolecules. 1994;27:650–655.

[18] Moszner N, Zeuner F, Angermann J, et al. Monomers for adhesive polymers, 4: Synthesis and radical polymerization of hydrolytically stable cross-linking monomers. Macromol. Mater. Eng. 2003;288:621–628.

[19] Catel Y, Degrange M, Le Pluart L, et al. Synthesis, photopolymerization and adhesive properties of new hydrolytically stable phosphonic acids for dental applications. J. Polym. Sci. Part A: Polym. Chem. 2008;46:7074–7090.

[20] Moszner N, Angermann J, Fischer U, et al. Monomers for adhesive polymers, 9. Synthesis, radical photopolymerization, and properties of (meth)acrylamido dihydrogen phosphates. Macromol. Mater. Eng. 2013;298:454–461.

[21] Klee JE, Lehmann U. N-alkyl-N-[(phosphonoethyl) substituted (meth)acrylamides – new adhesive monomers for self-etching self-priming one part dental adhesive. Beil. J. Org. Chem. 2009;5:72.

[22] Catel Y, Fischer UK, Moszner N. Monomers for adhesive polymers: 11. Structure–adhesive properties relationships of new hydrolytically stable acidic monomers. Polym. Int. 2013;62:1717–1728.

[23] Altin A, Akgun B, Bilgici ZS, et al. Synthesis, photopolymerization, and adhesive properties of hydrolytically stable phosphonic acid-containing (meth)acrylamides. J. Polym. Sci. Part A: Polym. Chem. 2014;52:511–522.

[24] Moszner N, Zeuner F, Lamparth I, et al. Benzoylgermanium Derivatives as Novel Visible-light Photoinitiators for Dental Composites. Macromol. Mater. Eng. 2009;294:877–886.

[25] Berchtold KA, Nie J, Stansbury JW, et al. Novel monovinyl methacrylic monomers containing secondary functionality for ultrarapid polymerization: steady-state evaluation. Macromolecules. 2004;37:3165–3179.

[26] Jansen JFGA, Dias AA, Dorschu M, et al. Fast monomers: factors affecting the inherent reactivity of acrylate monomers in photoinitiated acrylate polymerization. Macromolecules. 2003;36:3861–3873.

[27] Lee TY, Roper TM, Jönsson ES, et al. Influence of hydrogen bonding on photopolymerization rate of hydroxalkyl acrylates. Macromolecules. 2004;37:3659–3665.

[28] Zhou H, Li Q, Lee TY, et al. Photopolymerization of acid containing monomers: real-time monitoring of polymerization rates. Macromolecules. 2006;39:8269–8273.