European Polymer Journal 48 (2012) 318–330

Contents lists available at SciVerse ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Synthesis and evaluation of new phosphonic, bisphosphonic and difluoromethylphosphonic acid monomers for dental application

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ARTICLE INFO

Article history:
Received 20 May 2011
Received in revised form 16 September 2011
Accepted 24 September 2011
Available online 2 October 2011

Keywords:
Dental adhesives
Synthesis
Hydroxyapatite
Photopolymerization
Adhesion

ABSTRACT

Syntheses of novel 5-(methacryloyloxy)pentylphosphonic acid **1**, 5-(methacryloyloxy)pentylidenebisphosphonic acid **2** and 1,1-difluoro-5-(methacryloyloxy)pentylphosphonic acid **3** are described. The ability of these monomers to adhere to hydroxyapatite was demonstrated using ^{31}P CP-MAS NMR spectroscopy. Their copolymerization with *N,N′*-diethyl-1,3-bis(acrylamido)propane (DEBAAP) was investigated with photo differential scanning calorimetry. These mixtures exhibit a significantly higher reactivity than DEBAAP alone. Bisphosphonic acid **2** was shown to be significantly more reactive than monomers **1** and **3**. Adhesive properties of these monomers were also studied. Adhesives based on bisphosphonic acid **2** and difluoromethylphosphonic acid **3** provide significantly higher dentin shear bond strength than the one based on phosphonic acid **1**.

1. Introduction

Due to their simplicity of use, dental self-etch adhesives (SEAs) are widely employed to adhere a restorative material to a tooth [1–3]. SEAs are aqueous acidic solutions containing various monomers (acidic, hydrophilic and hydrophobic monomers) which are able to simultaneously etch and infiltrate dental tissues mediating the formation of a bond to the restorative material [4–6]. Key components of dental SEAs are acidic monomers bearing various functions such as carboxylic, sulfonic, phosphonic acids or phosphate esters [1,4,5]. It is well established that SEAs are able to form strong bonds with the tooth [7]. However, durability of the adhesion is a major limitation [8–10]. Indeed, it has been demonstrated that the hybrid layer (interface dentin/adhesive) is sensitive to degradation over time. This is mainly due to the resin hydrolysis [8,10,11], and the degradation of the collagen network by metalloproteinases (MMPs), endogenous enzymes that are released and activated during bonding procedure [12–15]. These two degradation processes are related to water sorption and nanoleakage within the adhesive [8]. It has been reported that some acidic monomers are able to adhere to hydroxyapatite (HAp) crystals by formation of ionic bonds between the acidic group and hydroxyapatite calcium ions [16–18]. Recently, it was suggested that such interactions could reduce nanoleakage and thus extend the bond durability [16,19]. Inoue et al. [19] claimed that the long-term durability of adhesive-dentin bonds depends on the chemical bonding potential of the functional monomer. Therefore, development of new acidic monomers bearing acidic groups which are able to strongly bond to HAp is of high interest.

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doi:10.1016/j.eurpolymj.2011.09.020

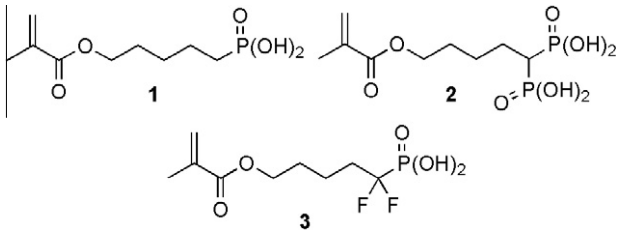

Fig. 1. Structure of acidic monomers **1**-**3**.

In this context, various monomers have been described in the literature [5,20,21]. These include phosphate esters, carboxylic and phosphonic acids. The present study is focused on three phosphonic acid derivatives: methylenephosphonic, difluoromethylphosphonic and bisphosphon ic acid. Although it was already demonstrated that phosphonic acids are able to chemically adhere to HAp [22], the use of difluoromethylphosphonic has not been reported and bisphosphonic acids are barely described for dental application [23–25]. Due to the presence of fluorine atoms, difluoromethylphosphonic acids exhibit a lower pK_a2 value (~5.6) than the corresponding phosphonic acid (~7.6) or phosphate (~6.4) [26]. Consequently, at a given pH, it is expected that difluoromethylphosphonic acids will be found under a diionic form and thus more proned to interact with calcium ions of HAp. Concerning bisphosphonic acids, their great affinity with HAp is largely described in the literature [27–31]. They are able to bind to calcium of hydroxyapatite by chemisorption in a bidental manner. Since additional reports show that bisphosphonates can inhibit MMPs, the use of such acidic monomers in dental SEAs should prevent collagen disruption [32–34].

The main objective of this work is to evaluate the influence of the nature of the acidic group on the reactivity of the monomers as well as on their adhesive properties. Hence, a comparative study involving monomers in which the only structural difference is the nature of the acidic group appears to be an interesting approach to evaluate these parameters.

In this paper, synthesis, characterization and adhesive properties of the new acidic monomers **1**–**3** are described and the copolymerization of these monomers with *N*,*N*′-diethyl-1,3-bis(acrylamido)propane (DEBAAP) is investigated (Fig. 1). The influence of the nature of the acidic group on both adhesive properties and reactivity will be discussed.

2. Experimental

2.1. Materials

Triethylamine was distilled over calcium hydride prior to use. All reagents were purchased from Sigma–Aldrich and were used without further purification. 5-bromo-1-(tetrahydropyran-2-yloxy) pentane **4**, [35] DEBAAP [36], diisopropyl 1-methylsulfanyl-1,1-difluoromethyl phosphonate **11** [37] and diisopropyl 1,1-difluoro-5-hydroxypentylphosphonate **12** [37] were prepared according to literature procedures. Both THF and dichloromethane were purified with a PURESOLVTM apparatus developed by Innovative Technology Inc. Column chromatography was performed on Merck Silica Gel Si 60 (40–63 μm). Hydroxyapatite particles (surface area of 42 $m^2\,g^{-1}$) were provided according to the method described in below.

2.2. Measurements

^1H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded on a Bruker DPX 250 (250 MHz) or AC 400 (400 MHz) spectrometers with TMS as internal reference for ^1H NMR and ^{13}C NMR chemical shifts. H_3PO_4 (85%) and $CFCl_3$ were respectively used as external references for ^{31}P NMR and ^{19}F NMR chemical shifts. Data are given in the following order: chemical shift in ppm, multiplicity (s, singlet; d doublet; t, triplet; q, quadruplet; sx, sextet; m, multiplet), coupling constant in Hertz, assignment broad and ^1H decoupling. ^{31}P MAS NMR was recorded on an Advance 400 MHz Bruker equipped with a MAS 4 mm double probe. The sample spinning speed at the magic angle to the external magnetic field was 12 kHz. ^{31}P CP-MAS NMR spectra with decoupling proton was taken at 162,1 MHz, 3 s recycle delays and 1800 μs contact time, where the signal 3072 pulses were accumulated. ^{31}P NMR chemical shift are reported in ppm. All NMR spectra were recorded in a room for exclusive use of NMR, where the room temperature was kept at 300 K by means of an air conditioner. FTIR absorption spectra were recorded on a Perkin–Elmer Spectrum One FTIR Spectrometer with an ATR accessory. The mentioned IR absorptions are observed as strong bands in cm^{-1}. High-resolution mass spectra (HRMS) were obtained with a Waters Q-TOF Micro instrument in electrospray ionization positive (ES+) or negative (ES-) mode and lockspray with orthophosphoric acid. These analyses were performed with an infusion introduction of 10 L min^{-1}, a source temperature of 80 °C, a desolvation temperature of 120 °C and an external calibration with NaI.

2.3. Preparation of the hydroxyapatite powder

Stoichiometric calcium hydroxyapatite was prepared by a conventional aqueous precipitation method using a diammonium phosphate $(NH_4)_2HPO_4$ and a calcium nitrate tetrahydrate $Ca(NO_3)_2$, $4H_2O$ salts (Merck, Germany). Salts were first dissolved under stirring in pure water at a controlled and adjusted temperature of 45 °C in jacketed reactors. The Calcium/Phosphorus reagents molar ratio was fixed at 10:6. The concentrations of the calcium nitrate and the diammonium hydrogen phosphate were equal to 2.3 M and 1.4 M, respectively. Then, the phosphate aqueous solution was transferred to the calcium nitrate aqueous solution using a