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Degradation kinetics of acid-sensitive hydrogels

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ABSTRACT

Dimethacrylate or divinyl-functionalized acetal-based crosslinkers were synthesized as building elements of acid-sensitive crosslinked hydrogels. Each crosslinker was prepared under catalytic acidic conditions with different functional groups installed at the acetal position. The hydrophilicity of the crosslinkers was tuned to control acidic-hydrolysis rate. We report the synthesis of hydroxyethyl dimethacrylate-functionalized dimethyl ketal (CL1), *meta*- or *para*-methoxybenzaldehyde based acetals (CL2m and CL2p), poly(ethylene glycol) dimethacrylate-functionalized dimethyl ketal-based crosslinker (CL3), and divinyl-functionalized *meta*-methoxybenzaldehyde-based acetal crosslinker (V-CL2m). An examination of acetal hydrolysis kinetics of the monomers was performed in aqueous buffer solutions using ^{1}H NMR (proton nuclear magnetic resonance) and UV–Vis (ultraviolet–visible) spectroscopy at various pH ranges. The hydrolysis rates were strongly dependent on the structure of the acetal. Network films containing CL2m were prepared by thermally initiated polymerization with either hydroxyethylmethacrylate (HEMA) or methylmethacrylate (MMA). A study of the hydrolysis kinetics of these crosslinked films was performed using GC–MS (gas chromatography and mass spectroscopy) to understand the effect of monomer hydrophilicity, crosslinking density, and polymerization mechanism at different pHs. The crosslinked films composed of the hydrophilic monomer, HEMA, show faster hydrolysis than those containing more hydrophobic monomers (e.g. MMA). The hydrolysis rate decreases as the crosslinking density increases. In the case of thiol-ene networks formed by reacting pentaerythritol tetrakis(3-mercaptopropionate) and V-CL2m, each repeating unit is composed of an acid-degradable acetal-moiety. Hydrolysis of the thio-ene network films results in depolymerization into two lower molecular weight components, pentaerythritol tetrakis(3-(6-hydroxyhexylthio)propanoate) and *meta*-methoxybenzaldehyde.

1. Introduction

pH-sensitive polymers or gels have been intensively studied among the stimuli-responsive systems that can show spontaneous physical or chemical changes in response to small external stimuli such as temperature, mechanical stress, and ionic strength. These pH-sensitive polymer systems can be used in bio-related areas such as in drug-delivery systems (DDS), as well as diagnostic and sensing applications because of the various pH ranges found in human organs and pH differences between normal tissue and tumor tissue [1–6]. For example, using changes in pH as the external stimuli can drive reversible changes in volume by tuning the ionization states of polyelectrolytes or to irreversibly change solubility via cleavage of acid-degradable crosslinked positions in the crosslinked or linear polymer [7]. Polymers containing acid-degradable linkages have also been exploited in lithographic patterning where high temperature or strong acids are often required to strip the resist after patterning [8–10]. The use of these acid-sensitive materials not provide protection of the silicon substrate from undesired damage but also leads to milder condition for post-process substrate cleaning and hence lower production costs.

There are a variety of acid-degradable systems based on chemistries including tertiary esters, orthoesters, acetal/ketals, imines, hydrazones, and cis-aconityls – many of these are also frequently used as protective groups in organic synthesis [7]. For example, polystyrene based nanogels crosslinked by tertiary ester dimethacrylates have been reported and their degradation was demonstrated by treating the samples at 90 °C for 24 h leading to their conversion from spherical gel particles to soluble linear polymer [11]. Acid-sensitive brush polymers were grown from

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silicon substrates utilizing a tertiary ester-based tethering group. Layers with different brush thickness were demonstrated and these brushes could be easily removed by treatment with aqueous media [12]. Among the many acid-sensitive functional groups, acetal based crosslinkers have various advantages including ease of synthesis, useful hydrolysis at room temperature that occurs within reasonable time at various acidic pH ranges, stability at neutral or mildly alkaline conditions, and versatile tuning of degradation rate by changing the substituent group at the acetal position.

The degradation rates of hydrogels or polymers which are covalently bonded with acid-degradable monomers have been studied using a variety of methods. Hydrophilic water-soluble materials can be easily characterized in water-based pH buffer solutions without any complications due to diffusion. These measurements can be made using ^{1}H NMR by observing the disappearance of proton signal corresponding to acid-sensitive functional groups [13], or by tracking molecular weight changes using gel permeation chromatography (GPC) [14]. Acid-degradable linear polymers have been synthesized via step-polymerization involving the Michael addition reaction with acetal containing monomers [13], direct acetal forming polymerization using diols with divinyl ether [15] or acyclic diene metathesis (ADMAT) from divinyl monomers with Grubbs' catalyst [2]. All of these procedures require long reaction times, high monomer purity, and precise control of stoichiometry for high molecular weight. Most linear step-growth polymers will not retain their shape after degradation because the resulting products consist of smaller molecules which are be easily washed away after hydrolysis. In the case of materials crosslinked by simple radical polymerization, the monomers themselves can be selected from those having more than one polymerizable group. After hydrolysis only the crosslinker units will be severed while the linear portion of the polymer remains mainly intact. This can lead to partial shape retention and lends utility of these types of materials to be used in molding operations where the networks can be formed by thermal or UV-initiated polymerization. For these reasons and others, acid-degradable crosslinked films are ideal candidates for the development of self-exfoliating garments, which can facilitate the selective removal of contaminated areas by acidic stimuli but maintain its overall original integrity. The pH range which triggers this degradation could be specifically varied depending on external stimuli.

While networks that controllably degrade in the presence of external stimuli have many potential applications, there has been little activity in studying the acid-catalyzed hydrolysis kinetics of ketal and acetal functional groups present in network films [16]. It is challenging to quantitatively measure how quickly acid-sensitive groups can be hydrolyzed in crosslinked systems, mainly due to the slow diffusion of aqueous buffer solutions and the relatively small mass loss during the decomposition of the crosslinker units. In the case of acid-sensitive nano- or micro-gel particles, the degradation rate can be indirectly examined by observing particle size changes, for example by using dynamic light scattering (DLS) while taking into account any swelling effect [17]. The hydrolysis of acid-degradable crosslinked polymer films can be discontinuously measured by monitoring fractional mass loss by repeatedly incubating gels in buffer solution and drying [16]. However, if the mass loss during hydrolysis is very small, it can be very difficult to measure the mass change after each degradation cycle.

Herein, we report the synthesis and characterization of novel, acid sensitive methacrylate-functionalized acetal and ketal-based crosslinker monomers. We use ^{1}H NMR and UV–Vis spectroscopy to perform a measurement of the kinetics of their room temperature hydrolysis. Acid-degradable network films composed of hydrophilic HEMA or hydrophobic MMA with the synthesized crosslinkers were prepared and their degradation kinetics were investigated using GC–MS. This paper provides facile way to prepare acid-sensitive crosslinkers and by performing an in-depth measurement of hydrolysis kinetics we provide a new understanding how to control the rate of network decomposition.

2. Experimental

2.1. Materials and instruments

Hydroxyethylmethacrylate (HEMA, Acros Organics, 97%), methyl methacrylate (MMA, Acros Organics, 99%), poly(ethylene glycol) methacrylate (PEG-MA, average M_n: 360 g/mol, Aldrich), 2,2-dimethoxypropane (DMP, Acros Organics, 98%), *p*-toluenesulfonic acid monohydrate (*p*TSA, Aldrich, 98.5%), molecular sieves (4 Å) (Alfa Aesar), *p*-methoxybenzaldehyde (*p*MBA, Alfa Aesar, 98%), *m*-methoxybenzaldehyde (*m*MBA, Alfa Aesar, 98%), 5-hexen-1-ol (TCI, 95%), triethylamine (TEA, Acros Organics, 99%), anhydrous tetrahydrofuran (THF) (EMD chemicals, 99.9%), cyclohexane (Fisher Scientific, 99%), pentaerythritol tetrakis(3-mercaptopropionate) (PTMPA, Aldrich, 95%), pH buffer solution (pH1~5, Fluka) were used without further purification. Azobisisobutyrontitrile (AIBN, Aldrich, 98%) was recrystallized before use.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. Chemical shifts were given relative to residual solvent peaks in deuterated solvents, chloroform ($CDCl_3$) and deuterated oxide (D_2O). All the NMR data for confirmation of synthesis are available in supporting information (S2–S8). UV–Vis spectroscopy were recorded on a Cary 50 UV–Vis absorption spectrometer with 1 cm path length quartz cuvettes at room temperature. GC–MS was measured using a HP 5890 GC–MS (Agilent DB-5ms column consisting of a fused silica capillary, 30 m length, 0.2 mm inner diameter and 0.325 μm film thickness) injecting 2 μL of dilute solution and ramping from room temperature to 350 °C.

2.2. Synthesis of crosslinkers

CL1: Synthesis based on a literature procedure was followed and optimized [9]. In a 250 mL round bottom flask, 0.55 g of *p*TSA (2.91 mmol, 0.07 equiv.) were dissolved in THF and molecular sieves were then added to the solution. After 15 min, 13.53 g HEMA (104 mmol, 2.5 equiv.) and 4.3 g 2,2-DMP (41.6 mmol, 1 equiv.) were added and the mixture was stirred for 6 h at room temperature. The reaction was quenched by adding ~3 mL TEA (pH > 7), the molecular sieves were removed by filtration and solvent was evaporated in vacuum. After removing solvent, the transparent liquid residue was purified by column chromatography with silica gel (ethyl acetate:hexane:TEA = 1:9:0.1, v/v). The resulting product was obtained as a slightly yellow viscous oil (40% yield). ^{1}H NMR of CL1 (400 MHz, $CDCl_3$, TMS standard, r.t.): δ = 6.10 (m; 2H), 5.55 (m; 2H), 4.26 (t; 4H), 3.69 (t; 4H), 1.93 (s; 6H), 1.37 (s; 6H).

CL3: We utilized a similar procedure to synthesize CL3 as described above for CL1 except substituting 5 g PEG-MA (13.89 mmol, 2.3 equiv.) in place of HEMA. The reaction was quenched by adding with ~0.5 mL TEA (pH > 7) and the molecular sieves were removed by filtration and solvent was evaporated in vacuum. Product was obtained as a viscous yellow liquid. By comparing the integration ratio in ^{1}H NMR ($CDCl_3$) spectra (see Supplemental data in S3) it was confirmed that it is mixture of unreacted PEG-MA and CL3 (3.38:1). CL3, with the unfunctionalized PEG-MA impurity was used without further purification.

CL2p and CL2m: *p*MBA or *m*MBA 5 g (36.7 mmol, 1 equiv.) and 19.1 g HEMA (146.8 mmol, 4 equiv.) were charged in a 100 mL round bottom flask and placed in an ice-bath in the presence of