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ARTICLE

Degradable Polymer Brushes Prepared via Surface-Initiated Controlled Radical Polymerization

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ABSTRACT: Hydrolytically degradable polymer brushes would represent an interesting platform for the development of functional coatings for various biomaterials applications. In this manuscript, the surface-initiated atom transfer radical copolymerization of 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) and poly(ethylene glycol) methacrylate (PEGMA) has been investigated to prepare degradable polymer brushes. The copolymerization of BMDO and PEGMA results in brushes that contain hydrolytically labile ester linkages in the polymer backbone. The thickness of these polymer brushes can be controlled via the polymerization time and the BMDO content by adjusting the monomer feed composition. The degradation of the brushes was investigated by ellipsometry and atomic force microscopy (AFM) experiments. While the brushes were relatively stable under neutral and mild-basic conditions (pH 9), degradation was significantly enhanced under acidic conditions. Degradation was found to be accelerated at low pH values (pH 3−5) and with increasing BMDO content.

Introduction

Polymer brushes are ultrathin surface grafted polymer layers in which all polymer chains are tethered with one of their chain ends to a substrate.[1−3] At sufficiently high grafting densities steric repulsions force the chains to stretch out resulting in a densely packed arrangement of surface grafted polymer chains. The use of controlled/"living" surface-initiated radical polymerization techniques allows to precisely control the thickness, composition and architecture of polymer brushes,[4−6] which makes them very attractive coatings to control the surface properties of a broad range of materials.

Among the different controlled/"living" surface-initiated radical polymerization techniques that are available, surface-initiated atom transfer radical polymerization (SI-ATRP) has been particularly extensively employed due to its robustness and synthetic flexibility. SI-ATRP is frequently used to produce poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(poly(ethylene glycol) methacrylate) (PPEGMA) brushes for a variety of biorelevant applications.[7−14] PHEMA and PPEGMA brushes have poly(ethylene glycol) like properties and have been used to prepare nonbiofouling surfaces,[9,11,14] which can be postmodified to allow protein immobilization[7] or mediate cell-adhesion.[8,11−13] In spite of a broad range of very attractive properties, PHEMA and PPEGMA brushes, being composed of an all carbon backbone, are intrinsically nonbiodegradable, which potentially limits an even wider application of these coatings, e.g., in *in vivo* applications as bioactive coatings on degradable tissue engineering scaffolds. All degradable polymer brushes that have been prepared so far have been obtained via surface-initiated ring-opening polymerization of various cyclic ester monomers.[15−21] While this is a very attractive approach to prepare thin, degradable surface coatings, functional cyclic ester monomers are not readily available and require special syntheses, which largely restricts further functionalization of polyester brushes to the modification of the end group of the surface-tethered polymer chains. The possibility to synthesize hydrolytically degradable polymer brushes via SI-ATRP would greatly facilitate the access to functional degradable polymer brushes, which would be of interest for a range of biomaterials applications.

In this manuscript, we explore the surface-initiated atom transfer radical copolymerization of a cyclic ketene acetal monomer, 5,6-benzo-2-methylene-1,3-dioxepane (BMDO),[22] with PEGMA for the preparation of hydrolytically degradable polymer brushes. While BMDO has been homo- and copolymerized via ATRP in homogeneous solution,[23−29] this monomer, to the best of our knowledge, has not yet been explored to graft hydrolytically degradable brushes from solid substrates. This manuscript will describe the synthesis and characterization of poly(PEGMA$_x$-*co*-BMDO$_y$) brushes prepared via SI-ATRP and will also report on the hydrolytic degradation of these brushes upon exposure to aqueous media of different pH.

Experimental Section

Materials. All chemicals used were purchased from Aldrich unless otherwise stated. Toluene was dried by passage through two columns of molecular sieves using a Pure Solv 400 solvent purification system. Ultrahigh quality Milli-Q water with a resistance of 18.2 MΩ·cm (at 25 °C) was obtained from a Millipore Milli-Q gradient machine fitted with a 0.22 μm filter. The inhibitor in poly(ethylene glycol) methacrylate (PEGMA ~ 360 g·mol^{-1} containing on average six ethylene glycol units) was removed by passing the monomer through a column of activated basic aluminum oxide. The ATRP initiator, (11-(2-bromo-2-methyl)propionyloxy)undecyldimethylchlorosilane, was synthesized as previously described.[30] 5,6-Benzo-2-methylene-1,3-dioxepane (BMDO) was synthesized according to previously reported methods using chloroacetaldehyde dimethyl acetal instead of bromoacetaldehyde diethyl acetal for the acetalization of benzenedimethanol.[25,31]

Instrumentation. Brush thicknesses were determined using a computer-controlled null-ellipsometer (Phillips Plasmon SD 2300) operating with a He−Ne laser at λ = 632.8 nm and an

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angle of incidence of 70°. Film thicknesses were calculated using a double layer silicon/polymer brush model. The refractive indices used for the calculations were $n = 3.7$ for the silicon substrate and $n = 1.45$ for the polymer. X-ray photoelectron spectroscopy (XPS) was carried out using an Axis Ultra instrument from Kratos Analytical equipped with a conventional hemispheric analyzer. The X-ray source employed was a monochromatic Al Kα (1486.6 eV) source operated at 100 W and 10^{-9} mbar. Water contact angle measurements were performed using a DataPhysics OCA 35 contact angle measuring instrument. Atomic force microscopy (AFM) was performed in Tapping-mode on a Veeco Multimode Nanoscope IIIa SPM controller (Digital instruments, Santa Barbara, CA) using NSC14/no Al Mikromasch (Tallinn, Estonia) cantilever.

Immobilization of the ATRP Initiator. First, the silicon wafers were sonicated for 5 min in acetone and dried. Subsequently, the slides were immersed in piranha solution (H_2SO_4/H_2O_2 (7:3, v:v) for 30 min at 150 °C in order to remove any organic residues from the silicon oxide surface and to promote the formation of silanol groups (*CAUTION! piranha solution reacts violently with organic materials*). The slides were then thoroughly washed with water, methanol and chloroform and subsequently dried under nitrogen. Next, the clean wafers were kept overnight and in the dark in a 10 mM solution of the ATRP initiator in anhydrous toluene. Afterward, the slides were extensively rinsed with chloroform, dried under nitrogen, and transferred to the appropriate reactors for the polymerizations.

Synthesis of Poly(PEGMA$_x$-*co*-BMDO$_y$) Brushes. Surface-initiated atom transfer radical copolymerization of PEGMA and BMDO was performed in bulk at 90 °C, using a reaction system consisting of the monomer(s) (PEGMA and BMDO), $Cu^{I}Cl$ and 2,2′-bipyridyl (bipy) in the following molar ratio: 100:1:2. First, PEGMA, BMDO and bipy were introduced into a Schlenk tube sealed with a septum, and mixed until complete homogenization. Then, the mixture was degassed by three freeze−pump−thaw cycles and $Cu^{I}Cl$ was added under nitrogen. After being stirred for 10 min at room temperature, the resulting solution was transferred with a cannula to the nitrogen-purged reaction vessel containing the ATRP initiator modified slides. The reactor was placed in a thermostated bath at 90 °C and the reaction was allowed to proceed with stirring for the desired time. The polymerization was quenched by exposing the substrates to air and then the slides were rinsed thoroughly with water and methanol and finally dried under a flow of nitrogen. Using the protocol outlined above a series of copolymer brushes was prepared by varying the relative amounts of the two monomers in the feed. Throughout the manuscript, these brushes are referred to as PPEGMA, P(PEGMA$_{90}$-*co*-BMDO$_{10}$), P(PEGMA$_{75}$-*co*-BMDO$_{25}$) and P(PEGMA$_{50}$-*co*-BMDO$_{50}$). In these abbreviations, the subscripts indicate the mole fraction of the respective monomer in the feed. Patterned polymer brushes for AFM studies were prepared from patterned ATRP initiator modified substrates, which were obtained as previously described.[32]

Hydrolytic Degradation of Poly(PEGMA$_x$-*co*-BMDO$_y$) Brushes. Degradation studies were carried out with copolymer brushes of different composition, which were obtained after a polymerization time of 30 min. Polymer brush coated substrates were immersed in aqueous solutions of different pH, which were prepared by dilution of concentrated HCl or NaOH solutions. At different time intervals, the substrates were taken out of the solutions, washed thoroughly with water and methanol and dried under a flow of nitrogen. The thicknesses of the polymer brushes were subsequently measured by ellipsometry or AFM.

Results and Discussion

Brush Synthesis. The preparation of the P(PEGMA$_x$-*co*-BMDO$_y$) brushes was carried out as shown in Scheme 1, starting with the grafting of the ATRP initiator on the silicon wafer. The successful grafting of the ATRP initiator on the surface was evidenced by an increase in the static water contact angle from 4° for the clean wafers (after piranha treatment) to 77° for the ATRP initiator modified slides.

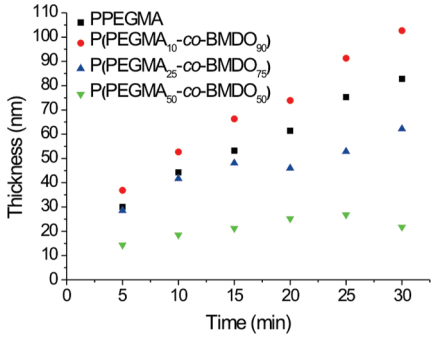
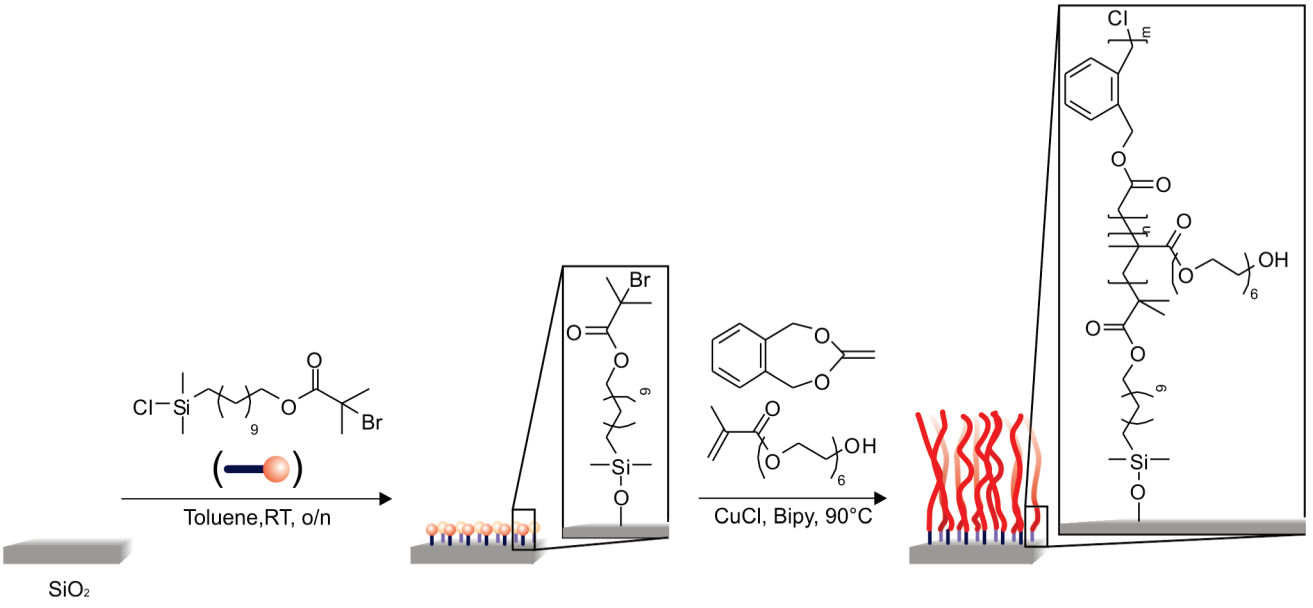


Figure 1. Evolution of the ellipsometric film thickness as a function of polymerization time for surface-initiated copolymerizations performed with different monomer feed compositions.

Scheme 1



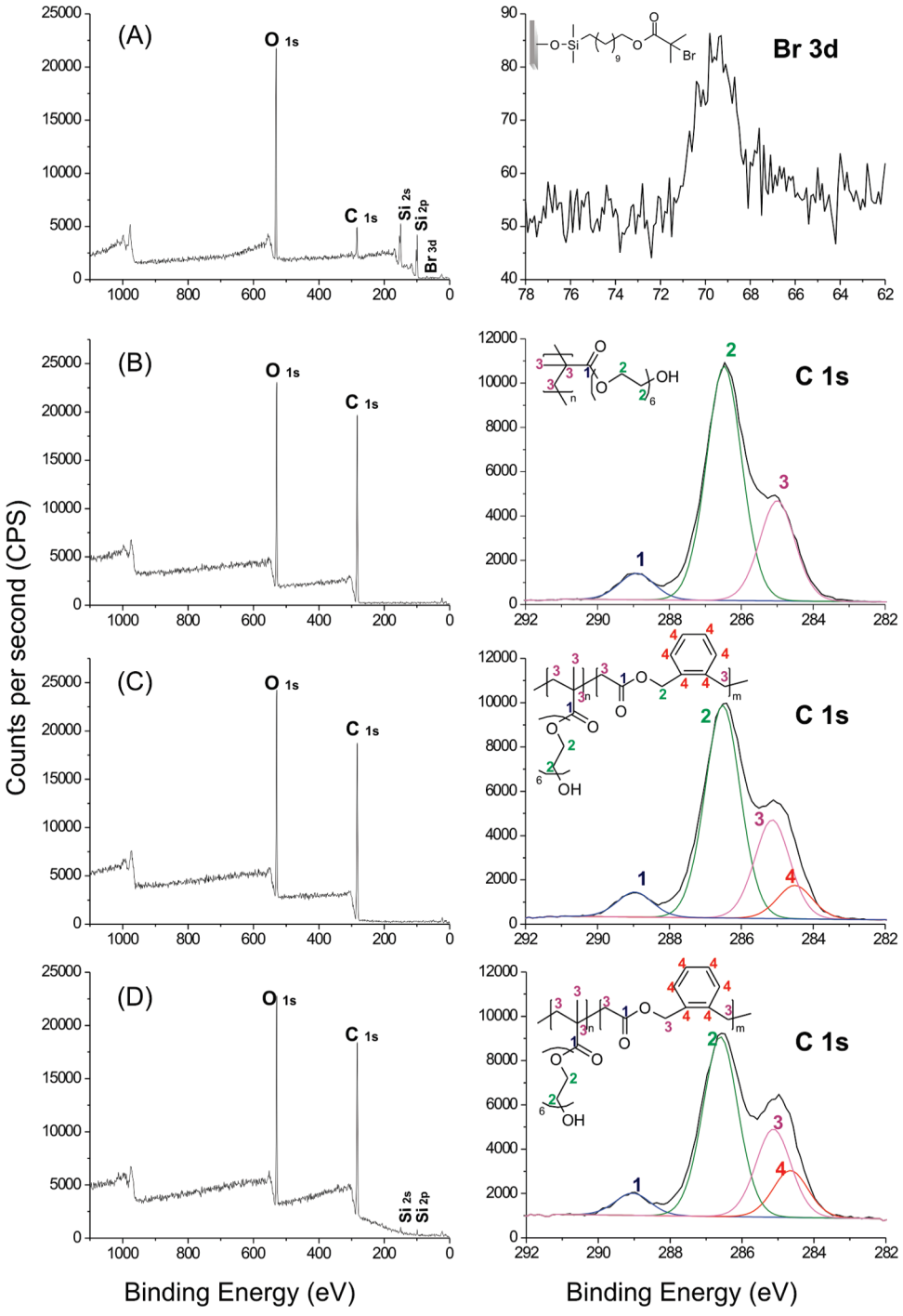


Figure 2. XPS survey spectra (left) and high-resolution elemental scans (right) of (A) a silicon substrate modified with the ATRP initiator, (B) a PPEGMA brush, (C) a P(PEGMA$_{75}$-*co*-BMDO$_{25}$) brush, and (D) a P(PEGMA$_{50}$-*co*-BMDO$_{50}$) brush. All experiments were performed with polymer brushes obtained after a polymerization time of 30 min.

The clean surfaces are hydrophilic since they are rich in silanol groups, while the functionalized wafers are more hydrophobic due to the grafting of the ATRP initiator. XPS analysis of the ATRP initiator modified substrate revealed a characteristic peak at around 70 eV corresponding to the bromine atom of the ATRP initiator (Figure 2). The ATRP initiator modified wafers were then used to initiate the atom transfer radical copolymerization of BMDO and PEGMA using a Cu(I)Cl/bipyridyl catalyst system at 90 °C. The catalyst system used in this work is similar to the one previously reported by Lutz and co-workers for the terpolymerization of BMDO with methacrylate monomers in solution.[28] It is important to note that not all of the BMDO incorporated into the copolymer brush necessarily leads to the formation of ester bonds in the backbone of the polymer chains. Atom transfer radical copolymerization of BMDO may also lead to the introduction of a small fraction of nonopened cyclic acetals, which are incorporated via a vinyl addition reaction.[25,26,28]

Figure 1 shows the evolution of the ellipsometric film thickness as a function of polymerization time for different copolymerizations. For all copolymerizations, a linear increase in brush thickness with polymerization time was observed, which reflects the controlled nature of the ATRP

Table 1. Static Water Contact Angles of Different Polymer Brushes before and after Degradation in pH 3 Solution at 25 °C for 30 days[a]

	water contact angle (deg)	
polymer brush	before degradation	after degradation
PPEGMA	52 ± 0.3	46 ± 0.2
P(PEGMA$_{90}$-*co*-BMDO$_{10}$)	51 ± 1.1	44 ± 0.9
P(PEGMA$_{75}$-*co*-BMDO$_{25}$)	51 ± 0.9	48 ± 0.7
P(PEGMA$_{50}$-*co*-BMDO$_{50}$)	54 ± 0.6	54 ± 0.9

[a] All experiments were performed with polymer brushes obtained after a polymerization time of 30 min.

process. At any polymerization time, the thickness of the copolymer brushes decreased with increasing amount of BMDO in the feed, except for the P(PEGMA$_{90}$-*co*-BMDO$_{10}$) brushes. The decrease in brush thickness with increasing BMDO content reflects the lower reactivity of BMDO compared to PEGMA and is consistent with earlier reports, which described a decrease in the molecular weight of BMDO/methyl methacrylate copolymers prepared via ATRP with increasing BMDO content.[26] The origin of the unexpected but reproducible higher thicknesses of the P(PEGMA$_{90}$-*co*-BMDO$_{10}$) copolymer brushes is not clear at this moment and is the subject of ongoing investigations; we hypothesize that it may be due to a different viscosity of the polymerization mixture as it was observed that viscosity influences surface-initiated polymerizations.[33]

XPS analysis of the different polymer brushes (Figure 2) indicated the presence of carbon and oxygen in ratios that are in good agreement with the elemental composition of the monomers in the feed. As expected, the carbon to oxygen atomic concentration ratio increased with increasing amount of BMDO in the feed (data not shown). For the PPEGMA polymer brushes, the C_{1s} signal can be fitted with three different Gaussian peaks corresponding to three different types of carbon atoms which, in order of decreasing energy, can be assigned to the ester groups, the ethylene glycol units and the aliphatic carbon atoms of the polymer brush. These assignments are in good agreement with previously reported XPS analyses of PPEGMA brushes.[7,10] For the P(PEGMA$_x$-*co*-BMDO$_y$) brushes, a fourth Gaussian peak can be fitted in the C_{1s} signal, which appears at a lower energy than the aliphatic carbon unit and corresponds to the aromatic carbons of BMDO. The relative intensity of the C_{1s} signal due to the aromatic carbons was found to increase with increasing amounts of BMDO in the monomer feed, reflecting the increased incorporation of this monomer in the polymer brushes. In addition to confirming the chemical composition of the copolymer brushes, the XPS spectra also show that the brushes are free of any residual catalyst, as no copper and nitrogen signals could be observed.

The polymer brushes were further characterized by water contact angle measurements, the results of which are summarized in Table 1. As Table 1 indicates the different copolymer brushes have water contact angles that are similar to that of PPEGMA and do not drastically change upon variation in the copolymer composition.

Degradation Studies. The P(PEGMA$_x$-*co*-BMDO$_y$) brushes contain four potential cleavage sites; three ester linkages, which are located in the ATRP initiator, the PEGMA side chain as well as in the copolymer backbone, respectively, together with the Si−O−Si bond that connects the ATRP initiator with the silicon substrate. To evaluate their hydrolytic stability, the copolymer brushes were exposed to aqueous solutions of different pH and the film thickness was measured as a function of time and compared with that of a PPEGMA homopolymer brush reference sample. The results of these experiments are summarized in Figure 3 and Figure 4. To facilitate comparison, Figure 3 and Figure 4 plot the relative thickness h/h_0 (measured thickness after x days/initial thickness) as a function of the degradation time. The data in these figures show that the different polymer brushes are quite stable for up to 1 month upon incubation in Milli-Q water or pH 9 conditions. At lower pH (pH 3 and 5), however, degradation is more significant and increases with decreasing pH and increasing BMDO content. The decrease in film thickness of the PPEGMA brush (especially at pH 3 and pH 5) can be due to both hydrolysis of the PEGMA side chains, as well as to cleavage of the Si−O−Si or ester linkage at the initiator. The rate of degradation of the BMDO containing brushes, however, is significantly higher than that of the PPEGMA reference sample and also gradually increases with increasing amounts of BMDO in the feed, which is consistent with the incorporation of hydrolytically cleavable ester bonds in the main chain of the copolymer brushes. With exception of the P(PEGMA$_{50}$-*co*-BMDO$_{50}$) brush degradation at ~ pH 7

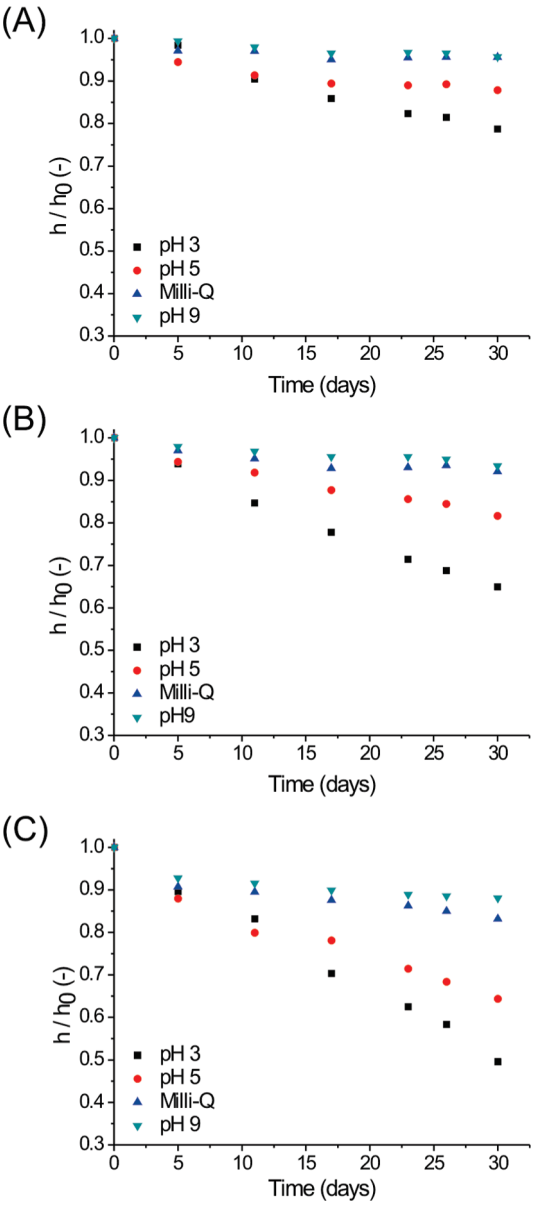


Figure 3. Degradation kinetics of (A) a PPEGMA brush, (B) a P(PEGMA$_{75}$-*co*-BMDO$_{25}$) brush, and (C) a P(PEGMA$_{50}$-*co*-BMDO$_{50}$) brush at 25 °C and different pH conditions.

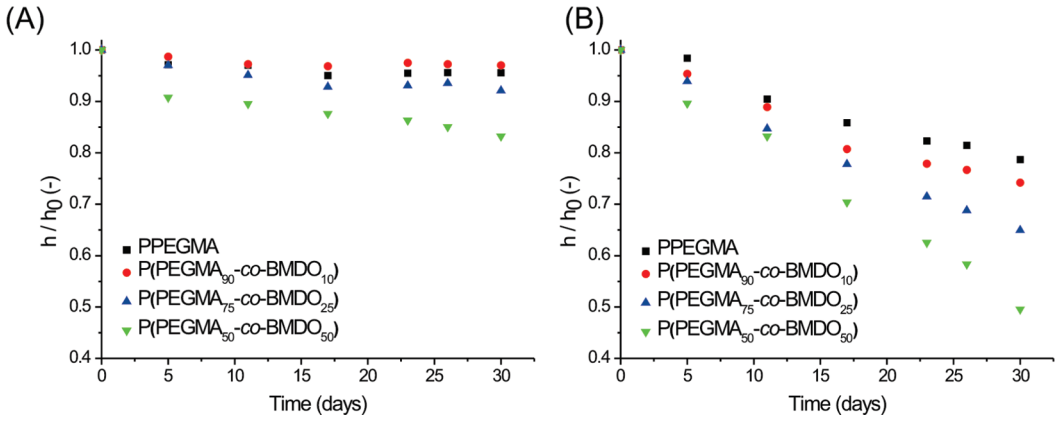


Figure 4. Degradation kinetics of P(PEGMA$_x$-*co*-BMDO$_y$) brushes of different compositions in (A) Milli-Q water and (B) pH 3 solution at 25 °C.

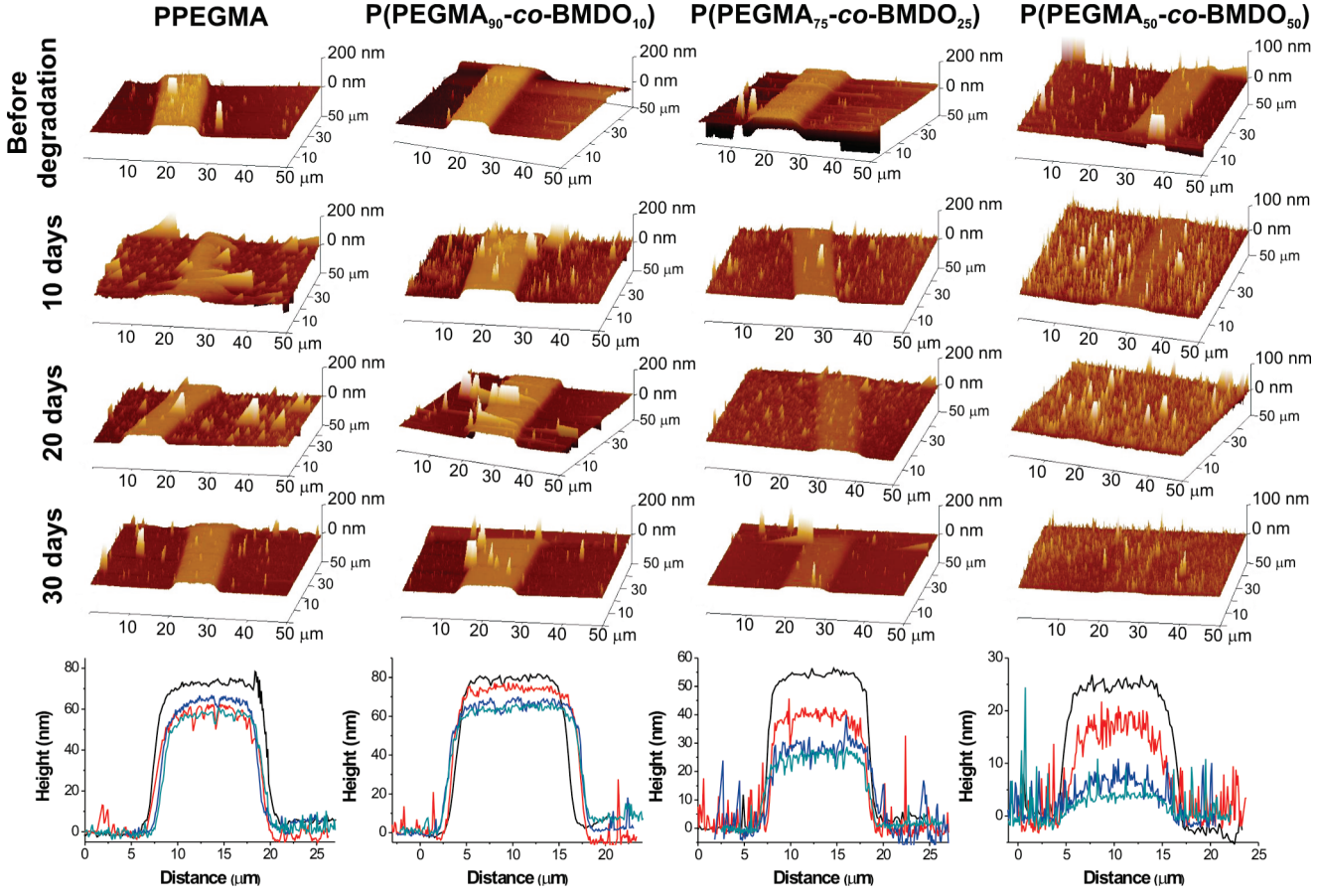


Figure 5. 3D AFM images and 2D cross-sectional profiles of different P(PEGMA$_x$-*co*-BMDO$_y$) brushes taken at different time intervals upon exposure to a pH 3 solution at 25 °C. Cross-sectional profiles: black lines, before degradation; red lines, after 10 days; blue lines, after 20 days; green lines, after 30 days.

(Milli-Q water) was negligible on the time scale of the experiment (one month), which may be undesirable for real biomaterials applications. The degradation kinetics of the brushes may be enhanced, however, by the use of other cyclic ketene acetal or cyclic acrylate monomers or via copolymerization of suitable monomers with nucleophilic side chain functional groups that can facilitate hydrolysis by means of neighboring group participation.[34] Analysis of the water contact angles of samples that were exposed to a pH 3 solution revealed a small decrease in the water contact angle (Table 1).

To complement the results of the ellipsometry experiments summarized in Figure 3 and Figure 4, the degradation behavior of a series of micropatterned polymer brushes was studied by atomic force microscopy (AFM). Figure 5 shows 3D images and 2D cross-sectional profiles of four different brushes that were incubated in a pH 3 solution as a function of exposure time. The AFM images qualitatively confirm the results discussed earlier and indicate only a minor variation in film thickness for the PPEGMA brush. For the BMDO containing copolymer brushes, in contrast, significant decreases in film thickness were observed, which became more pronounced at higher BMDO contents, reflecting the incorporation of this hydrolytically degradable monomer in the polymer brush main chain.

Conclusions

In this report, we have described the synthesis of polymer brushes containing hydrolytically labile ester linkages in the polymer backbone via surface-initiated atom transfer radical copolymerization of 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) and poly(ethylene glycol) methacrylate (PEGMA). Analysis of the growth kinetics revealed a linear increase in the thickness of these copolymer brushes with increasing polymerization time, which is in agreement with the controlled nature of the ATRP process. XPS experiments further indicated that the degree of incorporation of BMDO can be adapted by varying the feed composition of the polymerization reaction mixture. While these copolymer brushes are relatively stable upon exposure to neutral and mild-basic (pH 9) aqueous media, considerable decreases in film thickness were observed when samples were immersed in acidic aqueous solutions. The decrease in film thickness, i.e. the extent of degradation, was found to increase with decreasing pH and increasing BMDO content. These degradable P(PEGMA$_x$-*co*-BMDO$_y$) brushes may represent an interesting platform for the development of degradable coatings, e.g. for controlled drug release or tissue engineering applications.

References and Notes

(1) Milner, S. T. *Science* **1991**, *251*, 905–914.
(2) Zhao, B.; Brittain, W. J. *Prog. Polym. Sci.* **2000**, *25*, 677–710.
(3) Brittain, W. J.; Minko, S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 3505–3512.
(4) Edmondson, S.; Osborne, V. L.; Huck, W. T. S. *Chem. Soc. Rev.* **2004**, *33*, 14–22.
(5) Pyun, J.; Kowalewski, T.; Matyjaszewski, K. *Macromol. Rapid Commun.* **2003**, *24*, 1043–1059.
(6) Barbey, R.; Lavanant, L.; Paripovic, D.; Schüwer, N.; Sugnaux, C.; Tugulu, S.; Klok, H.-A. *Chem. Rev.* **2009**, DOI: 10.1021/cr900045a.
(7) Tugulu, S.; Arnold, A.; Sielaff, I.; Johnsson, K.; Klok, H.-A. *Biomacromolecules* **2005**, *6*, 1602–1607.
(8) Tugulu, S.; Silacci, P.; Stergiopulos, N.; Klok, H.-A. *Biomaterials* **2007**, *28*, 2536–2546.
(9) Tugulu, S.; Klok, H.-A. *Biomacromolecules* **2008**, *9*, 906–912.
(10) Xu, F. J.; Zhong, S. P.; Yung, L. Y. L.; Kang, E. T.; Neoh, K. G. *Biomacromolecules* **2004**, *5*, 2392–2403.
(11) Xu, F. J.; Li, Y. L.; Kang, E. T.; Neoh, K. G. *Biomacromolecules* **2005**, *6*, 1759–1768.
(12) Raynor, J. E.; Petrie, T. A.; Garcia, A. J.; Collard, D. M. *Adv. Mater.* **2007**, *19*, 1724–1728.
(13) Wischerhoff, E.; Uhlig, K.; Lankenau, A.; Borner, H. G.; Laschewsky, A.; Duschl, C.; Lutz, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5666–5668.
(14) Ma, H. W.; Hyun, J. H.; Stiller, P.; Chilkoti, A. *Adv. Mater.* **2004**, *16*, 338–341.
(15) Choi, I. S.; Langer, R. *Macromolecules* **2001**, *34*, 5361–5363.
(16) Yoon, K. R.; Koh, Y. J.; Choi, I. S. *Macromol. Rapid Commun.* **2003**, *24*, 207–210.
(17) Yoon, K. R.; Yoon, O. J.; Chi, Y. S.; Choi, I. S. *Macromol. Res.* **2006**, *14*, 205–208.
(18) Yoon, K. R.; Lee, Y.-W.; Lee, J. K.; Choi, I. S. *Macromol. Rapid Commun.* **2004**, *25*, 1510–1513.
(19) Zeng, H.; Gao, C.; Yan, D. *Adv. Funct. Mater.* **2006**, *16*, 812–818.
(20) Möller, M.; Nederberg, F.; Lim, L. S.; Kånge, R.; Hawker, C. J.; Hedrick, J. L.; Gu, Y. D.; Shah, R.; Abbott, N. L. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3529–3538.
(21) Husemann, M.; Mecerreyes, D.; Hawker, C. J.; Hedrick, J. L.; Shah, R.; Abbott, N. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 647–649.
(22) Bailey, W. J.; Ni, Z.; Wu, S.-R. *Macromolecules* **1982**, *15*, 711–714.
(23) Yuan, J.-Y.; Pan, C.-Y.; Tang, B. Z. *Macromolecules* **2001**, *34*, 211–214.
(24) Yuan, J.-Y.; Pan, C.-Y. *Eur. Polym. J.* **2002**, *38*, 1565–1571.
(25) Wickel, H.; Agarwal, S. *Macromolecules* **2003**, *36*, 6152–6159.
(26) Wickel, H.; Agarwal, S.; Greiner, A. *Macromolecules* **2003**, *36*, 2397–2403.
(27) Huang, J.; Gil, R.; Matyjaszewski, K. *Polymer* **2005**, *46*, 11698–11706.
(28) Lutz, J. F.; Andrieu, J.; Üzgün, S.; Rudolph, C.; Agarwal, S. *Macromolecules* **2007**, *40*, 8540–8543.
(29) Siegwart, D. J.; Bencherif, S. A.; Srinivasan, A.; Hollinger, J. O.; Matyjaszewski, K. *J. Biomed. Mater. Res. Part A* **2008**, *87A*, 345–358.
(30) Sanjuan, S.; Perrin, P.; Pantoustier, N.; Tran, Y. *Langmuir* **2007**, *23*, 5769–5778.
(31) Grewe, R.; Struve, A. *Chem. Ber. Recl.* **1963**, *96*, 2819–2820.
(32) Tugulu, S.; Harms, M.; Fricke, M.; Volkmer, D.; Klok, H.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7458–7461.
(33) Farquet, P.; Kunze, A.; Padeste, C.; Solak, H. H.; Gürsel, S. A.; Scherer, G. G.; Wokaun, A. *Polymer* **2007**, *48*, 4936–4942.
(34) McCoy, C. P.; Morrow, R. J.; Edwards, C. R.; Jones, D. S.; Gorman, S. P. *Bioconjugate Chem.* **2007**, *18*, 209–215.