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Surface-Initiated Polymerization of L-Lactide: Coating of Solid Substrates with a Biodegradable Polymer

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We describe a method of coating solid substrates with a thin film (<100 nm) of a biodegradable polymer, poly(lactic acid) (PLA), using a combination of self-assembled monolayers (SAMs) and surface-initiated polymerization of L-lactide (LA) with tin(II) octoate ($Sn(Oct)_2$).[1] The formation of SAMs, terminated in hydroxyl or amine groups in this study, renders well-defined structural and chemical motifs on solid substrates from which further chemical modifications, such as surface-initiated polymerization, can be achieved. The coating of solid substrates with biocompatible and/or biodegradable polymers has been investigated for applications in the biomedical sciences.[2,3] For example, poly(ethylene glycol) (PEG) is commonly used as a coating for implants to suppress the adhesion of biomolecules and cells.[3a] In the biomedical field, the use of polymers as coating materials ranges from passivation films for prosthetic devices and implants to coatings for drug-delivery devices.[4] For drug-delivery devices, highly uniform polymer films of specific thickness are generally desired either to form a permeable film that allows predetermined dosage of a drug[5] or to encapsulate a drug in a biodegradable coating. PLA is one of the few degradable materials currently used clinically (e.g., sutures), and it is widely used in drug delivery and tissue engineering.[6] The coating of solid substrates (e.g., silicon, gold, or polymers) with biodegradable PLA could potentially yield polymer-coated implants or controlled release devices (e.g., a stent[2d,7] or microchip[4]) for applications in drug delivery or tissue engineering. The coated biodegradable polymer films could also offer model surfaces to further investigate the interactions between man-made surfaces and biomolecules and cells.[2d]

Among the methods for coating solid surfaces, surface-initiated (living) polymerization has been intensively studied.[8] Surface-initiated polymerization gives more robust, dense polymer films in a more controlled manner than other methods such as spin-casting or the "grafting-onto" approach[8a] and is also compatible with patterning techniques such as soft lithography,[9] photolithography,[10] or "dip-pen" nanolithography.[11] Here we report the polymerization of LA from surfaces and the characterization of the resulting polymer films. We chose two solid surfaces that have been used for microfabrication technique-based drug delivery devices: gold and silicon surfaces.[4] These and other surfaces (e.g., glass and polymers) also have been intensively studied for other applications such as microelectromechanical systems (MEMS), microfluidic systems, or DNA chips.

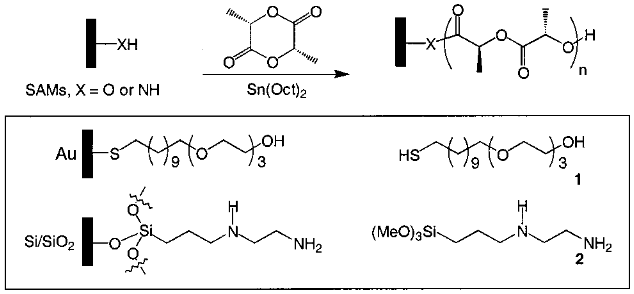

Figure 1. Schematic description of the procedure.

Figure 1 outlines the procedure: (i) the formation of a self-assembled monolayer (SAM) on solid substrates that presents hydroxyl or amine groups depending on the substrates; (ii) the polymerization of added monomers (LA) to coat the substrate. In the first step, we formed a SAM of $HS(CH_2)_{11}(CH_2CH_2O)_3OH$ (**1**) on a gold surface by immersing the gold substrate into a EtOH solution of **1** (2 mM) for 12 h.[12] A SAM of *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane (**2**) was formed on a Si/SiO_2 surface by immersing a plasma-cleaned substrate in an aqueous solution of **2** (1% of **2** in 1 mM acetic acid in deionized water) for 6−12 h.[13] We then placed the SAM-coated substrate in a THF solution of $Sn(Oct)_2$ (0.02 mmol) and LA (10 mmol).[14] After 3 days, the reaction was quenched with 1 N HCl. The substrate was intensively washed with CH_2Cl_2, EtOH, and water and dried under a flow of N_2. We characterized the resulting films by IR spectroscopy, ellipsometry, optical microscopy, and atomic force microscopy (AFM).

Hydroxyl-terminated molecules (including polymers) have been used as co-initiators in the polymerization of LA in bulk or solution polymerization.[15,16] For example, LA was polymerized from the hydroxyl end group of poly(ethylene glycol) (PEG) to form block copolymers in solution.[16] Regarding the mechanism of the polymerization of LA, Penczek et al. reported that the polymerization is initiated by a −Sn(OR) species that derives from a carboxylic acid (Oct)−alkoxide (OR) exchange reaction.[17] These results suggested that PLA could possibly be grown from hydroxyl-terminated surfaces.

We formed hydroxyl-terminated SAMs on a gold substrate and performed the polymerization of LA with $Sn(Oct)_2$ at 40 °C. Because of the instability of the Au−S bond above 60 °C,[18] reports on the surface-initiated polymerization on gold are few.[9a,d,18a,b,19] It is, therefore, noteworthy that the PLA was grown at a low temperature, considering that the bulk or solution polymerization of LA is usually performed at high temperature (>80 °C). Figure 2 shows the polarized infrared external reflectance spectroscopy (PIERS) spectrum of a PLA film (12 nm thick based on the ellipsometric measurement) on Au after 3 days.[20] The C−H stretching peaks at 2961 and 2930 cm^{-1} and the CO ester peak at 1735 cm^{-1} indicated the presence of a PLA film on the surface. When the same conditions were applied to a gold substrate without a SAM of **1**, we did not observe film formation. The film was thoroughly washed with CH_2Cl_2; at this step, unbound PLA was removed from the

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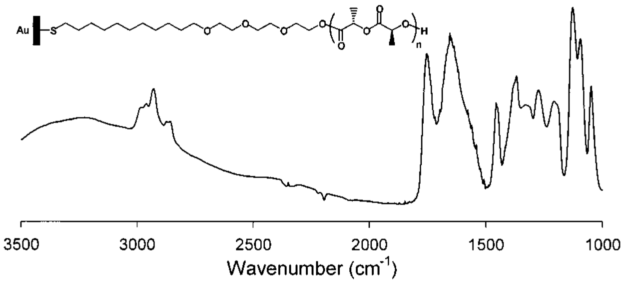

Figure 2. PIERS spectrum of PLA grown on a gold substrate. The film was grown on gold by placing a substrate presenting hydroxyl-terminated SAMs in a THF solution of $Sn(Oct)_2$ (0.2 mmol) and LA (10 mmol) and heating at 40 °C for 3 days.

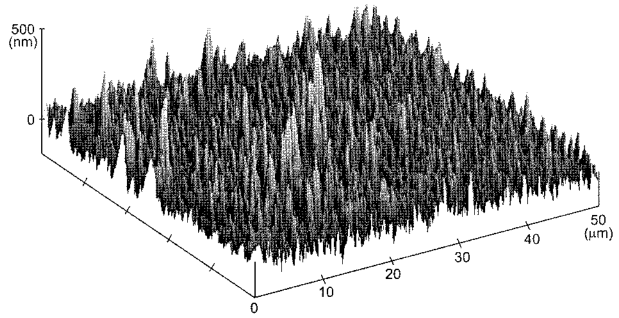

Figure 3. AFM image of PLA grown on Si/SiO_2. The film was grown on Si/SiO_2 by placing a substrate presenting amine-terminated SAMs in a THF solution of $Sn(Oct)_2$ (0.2 mmol) and LA (10 mmol) and heating at 80 °C for 3 days.

surface. A peel test was used to determine whether the film could be removed with an adhesive.[21] The film, however, stayed at the surface, suggesting that the polymer was grown from the surface hydroxyl group.

The same general conditions were applied to Si/SiO_2 surfaces presenting amine-terminated SAMs (0.02 mmol of $Sn(Oct)_2$ and 10 mmol of LA in THF). Because the SAMs on Si/SiO_2 surfaces are more robust, the temperature was set at 80 °C. Ellipsometric measurements revealed that films grown on Si/SiO_2 surfaces were much thicker than those grown on gold surfaces: films as thick as 70 nm could be grown on Si/SiO_2, compared to a maximum of about 12 nm on Au. On the basis of the report that the polymerization rate from an amine-terminated molecule is roughly the same as that from an hydroxyl-terminated molecule in solution,[17] we believe that the temperature played an important role in the polymerization.

We characterized the surface properties of the resulting film by optical and atomic force microscopy. Tapping mode AFM micrographs of the film (70 nm thick) showed a nanomorphology consisting of polymer brushes (Figures 3 and 4a).[22] The roughness of the film (rms) was 38 nm from the AFM measurement. We did not observe any smooth polymer surfaces. Presumably, the structure of the resulting polymers, a nanobrush, is due to the crystalline nature of PLA:[23] stereoregular (isotactic) PLA readily crystallizes with high melting point (~190 °C) and a glass transition temperature (T_g) of around 60 °C. We believe that the crystallinity of PLA prevented polymer chains from entangling each other and/or collapsing.[24] Instead, polymer chains aggregate (crystallize) to form polymer nanobrushes.

We annealed the polymer brushes by heating the substrate at 180 °C for 5 min and then at 130 °C for 2 h. By comparison with the surface morphology of the PLA film before annealing, the annealed film showed evenly distributed circular structures (Figure 4b). More importantly, the magnified image showed that these circular structures were composed of stacked flat layers (which surface roughness is less than 1 nm). The smallest height of the layers we have observed was 5 nm. The polymer film as a whole became rougher: the rms was 52 nm after annealing. It is known that the polymerization of L-lactide with $Sn(Oct)_2$ yields an isotactic PLA, which has a high crystallinity.[25] The crystalline structure of PLA consists of helical chains, and the crystalline domains grow as spherulites that are composed of lamellae formed by the helical chains.[23,26] We presume that the annealing resulted in more domains composed of crystalline, elongated structures containing some lamella-like structures. This result demonstrates one method for changing the surface morphology (and presumably crystallinity) of polymers that are covalently bonded to the surfaces.

In conclusion, we have demonstrated the surface-initiated polymerization of LA on Au and Si/SiO_2 surfaces. The synthesis of surface-bound block or random copolymers (e.g., poly(lactic-*co*-glycolic acid) (PLGA)), as well as the determination of the living characters of the polymerization, is under investigation.

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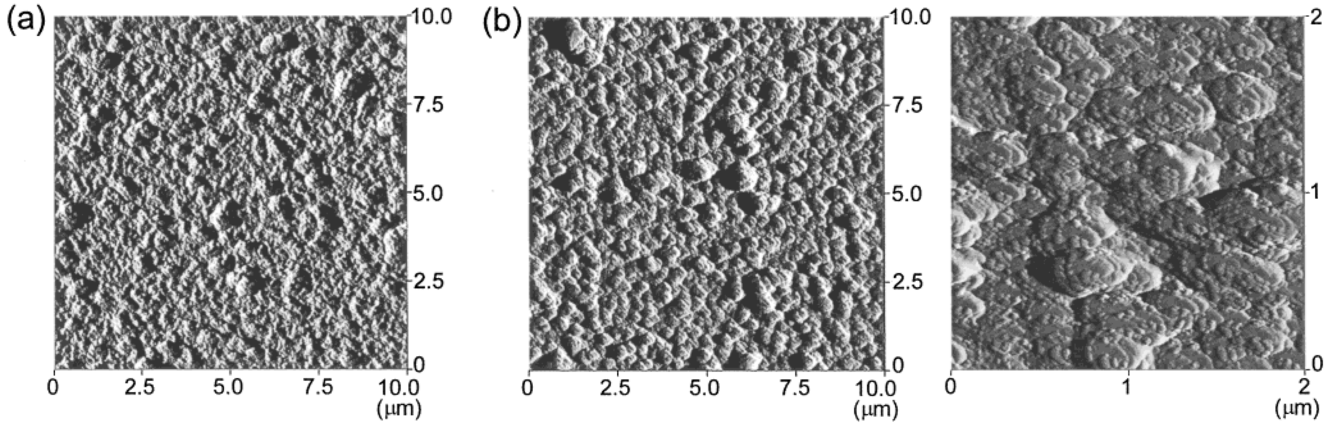

Figure 4. AFM images of the PLA films before annealing (a) and after annealing (b). The films were heated at 180 °C for 5 min and then at 130 °C for 2 h.

References and Notes

(1) We used $Sn(Oct)_2$ because it is commonly used in pharmaceutical and biomedical applications and has FDA approval as a food stabilizer. See: Wong, W. H.; Mooney, D. J. In *Synthetic Biodegradable Polymer Scaffolds*; Atala, A., Mooney, D. J., Eds.; Birkhauser: Boston, 1997.

(2) (a) Ikada, Y. *Biomaterials* **1994**, *15*, 725. (b) Kim, B. S.; Hrkach, J. S.; Langer, R. *Biomaterials* **2000**, *21*, 259. (c) Ishaug-Riley, S. L.; Okun, L. E.; Prado, G.; Applegate, M. A.; Ratcliffe, A. *Biomaterials* **1999**, *20*, 2245. (d) Black, F. E.; Hartshorne, M.; Davies, M. C.; Roberts, C. J.; Tendler, S. J. B.; Williams, P. M.; Shakesheff, K. M. *Langmuir* **1999**, *15*, 3157.

(3) (a) Merrill, E. W. In *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*; Harris, J. M., Ed.; Plenum Press: New York, 1992; pp 199−220. (b) James, C. D.; Davis, R.; Meyer, M.; Turner, A.; Turner, S.; Withers, G.; Kam, L.; Banker, G.; Craighead, H.; Isaacson, M.; Turner, J.; Shain, W. *IEEE Trans. Biomed. Eng.* **2000**, *47*, 17. Mizutani, F.; Sato, Y.; Yabuki, S.; Sawaguchi, T.; Ijima, S. *Electrochim. Acta* **1999**, *44*, 3833.

(4) Santini, J. T., Jr.; Richards, A. C.; Scheidt, R.; Cima, M. J.; Langer, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2396. Santini, J. R., Jr.; Cima, M. J.; Langer, R. *Science* **1999**, *397*, 335. Armani, D. K.; Liu, C. *J. Micromech. Microeng.* **2000**, *10*, 80.

(5) Nagale, M.; Kim, B. Y.; Bruening, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 11670.

(6) Langer, R. *Acc. Chem. Res.* **2000**, *33*, 94. Langer, R. *J. Controlled Release* **1999**, *62*, 7 and references therein.

(7) Klugherz, B. D.; Jones, P. L.; Cui, X.; Chen, W.; Meneveau, N. F.; DeFelice, S.; Connolly, J.; Wilensky, P. L.; Levy, R. J. *Nature Biotechnol.* **2000**, *18*, 1181.

(8) For surface-initiated anionic polymerization, see: (a) Jordan, R.; Ulman, A.; Kang, J. F.; Rafailovich, M. H.; Sokolov, J. *J. Am. Chem. Soc.* **1999**, *121*, 1016. (b) Ingall, M. D. K.; Honeyman, C. H.; Mercure, J. V.; Bianconi, P. A.; Kunz, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 3607.

(9) (a) Husemann, M.; Mecerreyes, D.; Hawker, C. J.; Hedrick, J. L.; Shah, R.; Abbott, N. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 647. (b) Jeon, N. L.; Choi, I. S.; Whitesides, G. M.; Kim, N. Y.; Laibinis, P. E.; Harada, Y.; Finnie, K. R.; Girolami, G. S.; Nuzzo, R. G. *Appl. Phys. Lett.* **1999**, *75*, 4201. (c) Lackowski, W. M.; Ghosh, P.; Crooks, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 1419. (d) Kratzmüller, T.; Appelhans, D.; Braun, H.-G. *Adv. Mater.* **1999**, *11*, 555.

(10) (a) Husemann, M.; Morrison, M.; Benoit, D.; Frommer, J.; Mate, C. M.; Hinsberg, W. D.; Hedrick, J. L.; Hawker, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 1844. (b) Prucker, O.; Schimmel, M.; Tover, G.; Knoll, W.; Rühe, J. *Adv. Mater.* **1998**, *10*, 1073.

(11) Hong, S.; Zhu, J.; Mirkin, C. A. *Science* **1999**, *286*, 523.

(12) Gold films (100 nm) were deposited by electron beam evaporation on silicon wafers that had been primed with titanium (5 nm).

(13) Chrisey, L. A.; Lee, G. U.; O'Ferrall, C. E. *Nucleic Acids Res.* **1996**, *24*, 3031.

(14) All the preparations were performed under a nitrogen atmosphere in a glovebox. The reaction was kept at 40 °C for gold substrates and 80 °C for Si/SiO_2 substrates.

(15) Wang, Y.; Hillmyer, M. A. *Macromolecules* **2000**, *33*, 7395.

(16) (a) Nagasaki, Y.; Kataoka, K. *Polym. Prepr.* **1998**, *2*, 190. (b) Li, S. M.; Rashkov, I.; Espartero, J. L.; Manolova, N.; Vert, M. *Macromolecules* **1996**, *29*, 59. (c) Rashkov, I.; Manolova, N.; Li, S. M.; Espartero, J. L.; Vert, M. *Macromolecules* **1996**, *29*, 50. (d) Stevels, W. M.; Ankone, M. J. K.; Dijkstra, P. J.; Feijen, J. *Macromol. Chem. Phys.* **1995**, *196*, 3687. (e) Guerra, R. S. D.; Cristallini, C.; Rizzi, N.; Barsacchi, R.; Guerra, G. D.; Tricoli, M.; Cerrai, P. *J. Mater. Sci.: Mater. Med.* **1994**, *5*, 891. (f) Kricheldorf, H. R.; Meier-Haack, J. *Makromol. Chem.* **1993**, *194*, 715. (g) Zhu, K. J.; Xiangzhou, L.; Shilin, Y. *J. Appl. Polym. Sci.* **1990**, *39*, 1.

(17) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **2000**, *33*, 7359.

(18) (a) Kim, J.-B.; Bruening, M. L.; Baker, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 7616. (b) Shah, R. R.; Merreceyes, D.; Husemann, M.; Rees, I.; Abbott, N. L.; Hawker, C. J.; Hedrick, J. L. *Macromolecules* **2000**, *33*, 597. (c) Bain, C. D.; Troughton, E. B.; Tao, Y.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 321.

(19) Weck, M.; Jackiw, J. J.; Rossi, R. R.; Weiss, P. S.; Grubbs, R. H. *J. Am. Chem. Soc.* **1999**, *121*, 4088.

(20) PIERS spectra were obtained in single reflection mode using a dry air purged Digilab Fourier transform infrared spectrometer. The p-polarized light was incident at 80° relative to surface normal of the substrate, and a narrow band mercury−cadmium−telluride (MCT) detector was used. A spectrum of a SAM of *n*-octadecanethiolate-d_{37} on gold was taken as reference. We averaged 1024 scans to yield the spectrum at a resolution of 4 cm^{-1}. The IR spectrum of PLA polymerized in the solution shows the aliphatic peaks at 2995 and 2940 cm^{-1} and the ester peak at 1760 cm^{-1}. See: Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *Macromolecules* **1995**, *28*, 425. Ellipsometric measurements were made on a RudolfResearch type 43603-200E ellipsometer using a He−Ne laser ($\lambda = 632.8$ nm) at an incident angle of 70.0° relative to the surface normal of the substrate.

(21) Ingall, M. D. K.; Joray, S. J.; Duffy, D. J.; Long, D. P.; Bianconi, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 7845.

(22) The resulting polymer films were intensively washed with THF, EtOH, H_2O, CH_2Cl_2, EtOH, and CH_2Cl_2 sequentially and dried under a flow of N_2 (200 kPa). Figures 3 and 4a show the AFM images of the same polymer film grown on Si/SiO_2 surface. The images were taken with CH_2Cl_2-washed films. The AFM image of the PLA film grown on a gold surface showed the same surface morphology. The columnar morphology of the films is, we believe, due to the crystalline nature of PLA, but we do not exclude the possibility of a low grafting density.

(23) Thakur, K. A. M.; Kean, R. T.; Zupfer, J. M.; Buehler, N. U.; Doscotch, M. A.; Munson, E. J. *Macromolecules* **1996**, *29*, 8844.

(24) *rac*-Lactide did not polymerize at 80 °C but did polymerize at 100 °C in the presence of *n*-BuOH (as a co-initiator). The resulting polymer films showed relatively smooth surfaces: for example, the rms value of a 32 nm thick polymer film was in the range 4−10 nm. The detailed data on the comparison between polymer films from L-lactide and those from *rac*-lactide (including study on the difference in reactivity) will be published separately.

(25) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Lindgren, T. A.; Doscotch, M. A.; Siepmann, J. I.; Munson, E. J. *Macromolecules* **1997**, *30*, 2422.

(26) Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S.-H. *Macromolecules* **1987**, *20*, 904. Tonelli, A. E.; Flory, P. J. *Macromolecules* **1969**, *2*, 225. de Santis, P.; Kovacs, A. J. *Biopolymers* **1968**, *6*, 299.

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