Functional Polymers for Layer-by-Layer Construction of Multilayers via Chemoselective Immobilization

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ABSTRACT: This paper reports detailed synthesis and characterization of polymers with functional groups for chemoselective immobilization. Various types of 1,4-diiodo-2,5-dialkoxybenzene monomers containing hydrophobic and hydrophilic groups with chemoselective functional group pairs were synthesized and copolymerized with 1,2-bis(4-vinylphenyl)ethane by using Heck coupling reaction. It was found that polymers with aldehyde and oxyamine pairs can easily be immobilized layer-by-layer while polymers with ketone functionalities did not afford multilayer deposition. The reproducible deposition process was monitored by UV/vis spectroscopy. Grazing angle reflection−absorption (GARA) FT-IR spectroscopic study confirmed that the multilayer assembly is driven by oxime bond formation. The experimental thickness of each layer was found to be 20 ± 1 Å by ellipsometry, somewhat shorter than that of extended side groups estimated by theoretical calculations. Tapping mode atomic force microscopy showed that the polymer multilayer with chemoselective ligation has the ability to patch up surface defects and provide smooth surface platform for further functionalization.

Introduction

Construction of ultrathin polymer films on solid substrates with one- or two-dimensional control on the molecular level is of great interest for their importance in realizing miniaturization and surface tailoring in electrooptic and biological application.[1,2] A variety of methodologies that lead to polymer multilayers have been demonstrated, including the Langmuir−Blodgett technique,[3] hydrogen bonding assisted assembly,[4] and programmed electrostatic layer-by-layer assembly (PEA).[2,5] These approaches offer an opportunity to fabricate heterostructured multilayers of various materials combination. For example, inorganic nanoparticles and polymers multilayers may be created so that the superior electrooptical properties of inorganic nanoparticles can be incorporated into organic polymeric materials. The most popular approach adapted by numerous groups is based on the PEA technique due to their simplicity in fabrication process.[6] Nevertheless, structural requirements for PEA, such as solubility in aqueous medium, often limit design flexibility. Besides, the stability of the resultant films depends on a number of parameters such as electrolyte concentration and pH value. Most importantly, it is rather difficult to carry out further surface modification with these multilayers. To achieve precise dimensional control and to prepare robust and smooth polymer multilayers, it is crucial to develop an assembly approach via covalent bond formation. The approach has to enable simple yet kinetically favorable film growth control on the nanometer scale. Furthermore, the resulting films must be stable and possess surface functional groups for further modification. Recently, our group demonstrated a new assembly methodology that meets the above requirements. This approach utilizes a highly chemoselective and kinetically facile reaction between aldehyde (or ketone) and alkyloxyamine under very mild conditions to fabricate not only polymer but also polymer/inorganic nanoparticle multilayers.[7,8] The immobilization can be carried out at room temperature in neutral aqueous solutions. Kinetic studies indicated that a few minutes were enough to covalently immobilize a polymer single layer. To further explore the general utility of this unique assembly method, it is necessary to develop synthetic approaches to introduce both oxyamine and aldehyde groups into polymer chains. This paper describes our recent effort in designing and synthesizing several functional polymers for chemoselective immobilization.

Experimental Section

Materials. All the solvents used for the synthesis were HPLC grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under an argon atmosphere prior to use. CH_2Cl_2, DMF, and tributylamine were distilled over calcium hydride. Absolute ethyl alcohol (200 proof) was purchased from Aaper Alcohol and Chemical Co. Flash chromatography was carried using EM science Kieselgel 60 (230−400) mesh. All reagents were purchased from Aldrich, Pfaltz & Bauer, and Fluka and used as received. Diiodohydroquinone[9] and 1,2-bis(4-vinylphenyl)ethane[10] were synthesized according to literature procedures.

10-Bromodecanal (1). To a methylene chloride solution (20 mL) of 10-bromodecanol (2.0 g, 8.43 mmol) was added pyridinium chlorochromate (2.7 g, 12.6 mmol). Upon addition, the orange solution turned dark brown. Stirring was continued at room temperature for 3 h, and the reaction progress was monitored by thin-layer chromatography (TLC) (8:2 hexane: ethyl acetate (EA)). Upon completion, solvent was removed by rotaevaporation to give a dark brown paste which was then purified by column chromatography (2:8 ethyl acetate:hexane) to give a clear oil (1.33 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28−1.41 (b, 10H), 1.58−1.62 (b, 2H), 1.83 (qint, 2H, J = 6.9 Hz), 2.4 (td, 2H, J = 7.3 Hz, J = 1.8 Hz), 3.38 (t, 2H, J = 6.8 Hz), 9.74 (t, 1H, J = 1.8 Hz).

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2-(9-Bromononyl)-1,3-dioxolane (2). 10-Bromodecanal (803 mg, 3.50 mmol) was dissolved in toluene (20 mL) in a 25 mL round-bottomed flask. Ethylene glycol (326 mg, 5.25 mmol) was added along with 10 mg of *p*-toluenesulfonic acid. The flask was then fitted with a Dean Stark trap. The reaction mixture was refluxed under nitrogen for 24 h. The reaction mixture was washed with aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was further extracted with ether. All the organic layers were combined and dried over $MgSO_4$. The solvent was removed to give a clear oil, which was then purified by column chromatography (1:9 ethyl acetate:hexane) to give a clear oil (710 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30−1.43 (m, 12 H), 1.63−1.67, (m, 2H), 1.85 (qint, 2H, J = 7.0 Hz), 3.41 (t, 2H, J = 6.5 Hz), 3.84−3.88 (m, 2H), 3.94−3.98 (m, 2H), 4.84 (t, 1 H, J = 5.0 Hz).

***N*-(10-Bromodecyloxy)phthalimide (3).** *N*-Hydroxyphthalimide (5.44 g, 33.3 mmol) was dissolved in dimethyl sulfoxide (DMSO) (40 mL). Potassium hydroxide (2.8 g, 50.0 mmol) was added to the solution mixture. The reaction mixture was stirred at room temperature for 0.5 h before a solution of 1,10-dibromodecane (12.0 g, 40.0 mmol) in 30 mL of DMSO was added. The reaction mixture was stirred magnetically at room temperature overnight and then poured into 600 mL of water. A solid formed was collected by filtration. The crude product was purified by column chromatography (2:8 ethyl acetate:hexane) to give a clear oil which later solidified (4.4 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31−1.50 (m, 12H), 1.76−1.89 (m, 4 H), 3.41 (t, 2 H, J = 6.9 Hz), 4.20 (t, 2 H, J = 6.8 Hz), 7.73−7.77 (m, 2 H), 7.82−7.86 (m, 2 H).

11-Hydroxy-3,6,9-trioxaundecyl-1-*p*-toluenesulfonate (4).[11] A solution of tetraethylene glycol (TEG) (17 g, 88 mmol) in methylene chloride (50 mL) was prepared and cooled to 0 °C in an ice bath. *p*-Toluenesulfonyl chloride (6.7 g, 35 mmol) in pyridine (12 mL, 148 mmol) was added dropwise to the solution. Stirring at room temperature was continued overnight. The excess pyridine was neutralized with 1 N hydrochloric acid (15 mL). Water (100 mL) was added, and the organic phase was extracted with methylene chloride (5 × 60 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated at reduced pressure. Column chromatography on silica gel with a eluent gradient consisting of ethyl acetate and hexanes (8:2) yielded 7.32 g (60%) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.57−3.69 (m, 14H), 4.15 (t, 2H, J = 4.9 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.78 (d, 2H, J = 7.78 Hz).

1,4-Diiodo-2,5-bis(11-hydroxy-3,6,9-trioxaundecyl)benzene (5). A solution of tetraethylene glycol monotoluenesulfonate (**4**) (5.55 g, 15.9 mmol), 1,4-diiodo-2,5-dihydroxybenzene (2.88 g, 8.0 mmol), and potassium carbonate (6.61 g, 47.8 mmol) in acetone (90 mL) and anhydrous *N*,*N*-dimethylformamide (DMF) (2.7 mL) was refluxed overnight while magnetically stirring under a N_2 atmosphere. The reaction mixture was concentrated under reduced pressure, and water was added. The organic phase was extracted with methylene chloride (5 × 60 mL), and the combined organic layers were dried over Na_2SO_4. Eluent gradient chromatography on silica gel with methanol and ethyl acetate (1:9) yielded 3.10 g (54%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57−3.60 (m, 4H), 3.66−3.71 (m, 16H), 3.76−3.78 (m, 4H) 3.86 (t, 4H, J = 4.8 Hz), 4.09 (t, 4H, J = 4.7 Hz), 7.22 (s, 2H).

Toluene-4-sulfonic Acid 2-(2-{2-[2-(2-Oxopropoxy)-ethoxy]ethoxy}ethoxy)ethyl Ester (9). To a solution of 4.54 g (23.4 mmol) of tetraethylene glycol in 30 mL of anhydrous 1,4-dioxane, pulverized sodium hydroxide (2.52 g, 63.1 mmol) was suspended. 3.24 g (18.7 mmol) of 2-chloro-1-(chloroethyl)-ethyl methoxymethyl ether (**6**) was added to the mixture at once. The reaction mixture was heated to 60 °C and stirred magnetically for 5 h. During the reaction, a white precipitate was formed. Water was added to dissolve the precipitate, and the organic was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated followed by drying under vacuum (4.10 g, crude). 2.23 g of the crude product (**7**) was hydrolyzed with 5 mL of 1 N HCl at 60 °C for 1 h. The reaction mixture was neutralized with aqueous Na_2CO_3. Water was removed by vacuum distillation. Ethyl acetate was added to dissolve the product. Insoluble solid in ethyl acetate was removed by filtration, and the filtrate was concentrated and dried over Na_2SO_4 (2.02 g, crude). 2.02 g of the crude product (**8**) was dissolved in 20 mL of CH_2Cl_2, and 2.31 g (12.14 mmol) of *p*-toluenesulfonyl chloride in 3.84 g of pyridine was added. After stirring magnetically overnight at room temperature, the excess pyridine was neutralized by 1 N HCl. The organic was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated. The pure product was obtained by column chromatography (55:45 ethyl acetate:hexane) (818 mg, 18% for three steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.42 (s, 3H), 3.57−3.68 (m, 14H), 4.10 (s, 2H), 4.13 (m, 3H), 7.32 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.4 Hz).

Monomer A. To a solution of 1,4-diiodo-2,5-dihydroxybenzene (384 mg, 1.06 mmol) in 5 mL of DMSO was added postassium hydroxide (178 mg, 3.18 mmol). A solution of 2-(9-bromononyl)-1,3-dioxolane (**2**) (710 mg, 2.54 mmol) in 5 mL of DMSO was then added immediately. The reaction mixture was stirred magnetically at room temperature overnight and then poured into 100 mL of water. A solid formed was collected by filtration. Pure product was obtained by two times of recrystallization from hexane (500 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32−1.50 (m, 24H), 1.64−1.68 (m, 4H), 1.76−1.82 (quint, 4H, J = 7.0 Hz), 3.84−3.86 (m, 4H), 3.92 (4H, J = 6.5 Hz), 3.96−3.98 (m, 4H), 4.84 (t, 2H, J = 5.0 Hz), 7.17 (s, 2H). $[M + H]^+$: Calcd 759.15; Found 759.0.

Monomer B. To a solution of 1,4-diiodo-2,5-dihydroxybenzene (1.24 g, 3.42 mmol) in 15 mL of DMSO, 587 mg of KOH (powder) was added while magnetically stirring. 3.14 g (8.21 mmol) of *N*-(10-bromodecyloxy)phthalimide (**3**) in 12 mL of DMSO was added to the solution, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into 300 mL of water, and the organic was extracted with Et_2O. Organic layers were combined and dried over $MgSO_4$. $MgSO_4$ was filtered out, and the filtrate was concentrated. The residue was recrystallized from $CHCl_3$ and hexane to give a pure product (1.17 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26−1.49 (m, 24H), 1.80 (quint, 8H, J = 7.0 Hz), 3.92 (t, 4H, J = 6.4 Hz), 4.20 (t, 4H, J = 6.8 Hz), 7.17 (s, 2H), 7.74−7.77 (m, 2H), 7.83−7.85 (m, 2H). $[M + H]^+$: Calcd 965.17; Found 965.0.

Monomer C. Compound **5** (1 g, 1.4 mmol), *N*-hydroxyphthalimide (710 mg, 4.2 mmol), and triphenylphospine (1.3 g, 4.9 mmol) were dissolved in 41 mL of anhydrous THF under a positive N_2 pressure. The solution was cooled in ice bath, and then 0.82 mL (5.6 mmol) of diethyl azodicarboxylate (DEAD) was added dropwise. After the addition of DEAD was completed, the reaction mixture was warmed to room temperature and stirred overnight. 100 mL of water was added to the reaction mixture, and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure, and eluent gradient column chromatography with ethyl acetate and hexanes (85:15) yielded 1.13 g (80%) of the pure product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56−3.58 (m, 8H), 3.62−3.65 (m, 4H), 3.68−3.71 (m, 4H), 3.81−3.84 (m, 8H), 4.05 (t, 4H, J = 4.8 Hz), 4.33−4.35 (m, 4H), 7.18 (s, 2H), 7.69−7.73 (m, 4H), 7.79−7.82 (m, 4H). $[M + H]^+$: Calcd 1005.56; Found 1005.00.

Monomer D. To a solution of 520 mg (0.73 mmol) of compound **5** and 466 mg (2.26 mmol) of 1,3-dicylcohexylcarbodiimide (DCC) in 15 mL of dry CH_2Cl_2 was added 212 mg (1.83 mmol) of levulinic acid. A catalytic amount of 4-(dimethylamino)pyridine was added to the reaction mixture while magnetically stirring at room temperature. After 3 h of stirring, the reaction mixture was stored in a refrigerator overnight. A solid formed was filtered out, and the filtrate was concentrated. The pure product was obtained by column chromatography (8:2 ethyl acetate:hexane) (614 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 6H), 2.53 (t, 4H, J = 6.5 Hz), 2.68 (t, 4H, J = 6.6 Hz), 3.57−3.63 (m, 16H), 3.70−3.72 (m, 4H), 3.81 (t, 4H, J = 4.8 Hz), 4.04 (t, 4H, J = 4.8 Hz), 4.16 (t, 4H, J = 4.9 Hz). $[M + H]^+$: Calcd 911.11; Found 910.7.

Monomer E. In a two-neck round-bottom flask equipped with condenser, 150 mg of NaH (60% dispersed in mineral oil) (3.75 mmol) was suspended in 5 mL of anhydrous THF. 1.071 g (1.5 mmol) of compound **5** dissolved in 5 mL of anhydrous THF was added to the suspension very slowly under N_2 flow while magnetically stirring at room temperature. Upon addition, bubbling was observed and the suspension became a clean solution. Within a few minutes, a highly viscous brown liquid, immiscible with THF, was formed. The reaction mixture was refluxed before 0.887 g (4.5 mmol) of bromoacetaldehyde diethylacetal was added. The reaction mixture was refluxed overnight. The viscous brown liquid disappeared, and a solid precipitate formed. The solid was filtered out, and water was added to the residue. The organic was extracted with ethyl acetate, and the combined organic layer was dried over Na_2SO_4. Na_2SO_4 was filtered out, and the filtrate was concentrated. The pure product was obtained by column chromatography (7:3 ethyl acetate:hexane) (1 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, 12H, J = 7.1 Hz), 3.49 (d, 4H, J = 5.3 Hz), 3.51−3.67 (m, 28H), 3.72−3.75 (m, 4H), 3.83 (t, 4H, J = 4.8 Hz), 5.06 (t, 4H, J = 4.8 Hz), 4.59 (t, 2H, J = 5.2 Hz), 7.19 (s, 2H). $[M + Cl]^-$: Calcd 981.64; Found 981.2.

Monomer F. To a solution of 1,4-diiodo-2,5-dihydroxybenzene (347 mg, 0.96 mmol) and 398 mg (2.88 mmol) of potassium carbonate in 15 mL of acetone and 0.45 mL of DMF was added 818 mg (2.02 mmol) of compound **9**. The reaction mixture was refluxed overnight. Potassium carbonate was filtered out, and water was added to the filtrate. The organic was extracted with ethyl acetate and CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. Na_2SO_4 was filtered out, and the filtrate was concentrated. The pure product was obtained by column chromatography (9:1 ethyl acetate:methanol) (385 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 6H), 3.63−3.67 (m, 20H), 3.74−3.77 (m, 4H), 3.85 (t, 4H, J = 4.8 Hz), 4.08 (t, 4H, J = 4.8 Hz), 4.10 (s, 4H), 7.21 (s, 2H). $[M + H]^+$: Calcd 827.26; Found 826.7.

General Procedure of Heck Polymerization. Monomer (492 mg, 0.65 mmol for monomer **A**) was weighted into a 10 mL round-bottom flask. 1,2-Bis(4-vinylphenyl)ethane (152 mg, 065 mmol), palladium(II) acetate (0.03 equiv, 4.5 mg, 0.02 mmol), tri-*o*-tolylphosphine (0.12 equiv, 24 mg, 0.08 mmol), tributylamine (3 equiv, 361 mg, 1.95 mmol), and dry DMF (3 mL) were added. The flask was fitted with condenser and heated in an oil bath at 60−70 °C for 24 h under static nitrogen. The solution mixture turned dark yellow as the reaction progressed and became very viscous with formation of some black precipitate. The reaction mixture was then poured into methanol (150 mL) with stirring. Upon addition, an orange-brown precipitate formed. Stirring continued in the absence of light for 12 h. The precipitate was collected by filtration, redissolved in CH_2Cl_2, and filtered through Celite to remove residual catalyst. The solution was concentrated and precipitated by excess methanol. To obtain pure polymer, the precipitation was carried out twice. A similar procedure was used to obtain polymers **B**, **C**, **D**, and **E**. Polymer **A**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34−1.40 (br, 20H), 1.54 (br, 4H), 1.64 (br, m, 4H), 1,87 (br, 4H), 2.94 (br, 4H), 3.83 (br, 4H), 3.95 (br, 4H), 4.05 (br, 4H), 4.83 (t, 2H, J = 4.8 Hz) 7.11−7.46 (br, m, 14H). Polymer **B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26−1.87 (br, m, 32H), 2.93 (br, 4H), 4.05 (br, m, 4H), 4.19 (t, 4H, J = 6.6 Hz), 7.10−7.47 (br, m, 14H), 7.72 (br, 2H), 7.81 (br, 2H). Polymer **C**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.92 (br, 4H), 3.57−3.66 (br, m, 16H), 3.72 (t, 4H, J = 4.8 Hz), 3.82 (t, 4H, J = 4.5 Hz), 3.90 (t, 4H, J = 4.5 Hz), 4.33 (t, 4H, J = 4.5 Hz), 7.04−7.44 (br, m, 14H), 7.68 (m, 2H), 7.77 (m, 2H). Polymer **D**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14 (s, 6H), 2.56 (t, 4H, J = 6.8 Hz), 2.69 (t, 4H, J = 6.5 Hz), 2.92 (br, 4H), 3.59−3.70 (br, m, 16H), 3.77 (br, m, 4H), 3.91 (t, 4H, J = 4.8 Hz), 4.18 (t, 4H, J = 4.8 Hz), 4.22 (t, 4H, J = 4.8 H),7.03−7.24 (br, m, 14 H). Polymer **F**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H), 2.92 (br, m, 4H), 3.63−3.69 (20 H), 3.76 (br, m, 4H), 3.91 (t, 4H, J = 4.8 Hz), 4.06 (s, 4H), 4.21 (t, 4H, J = 4.8 Hz) 7.06−7.45 (br, m, 14H).

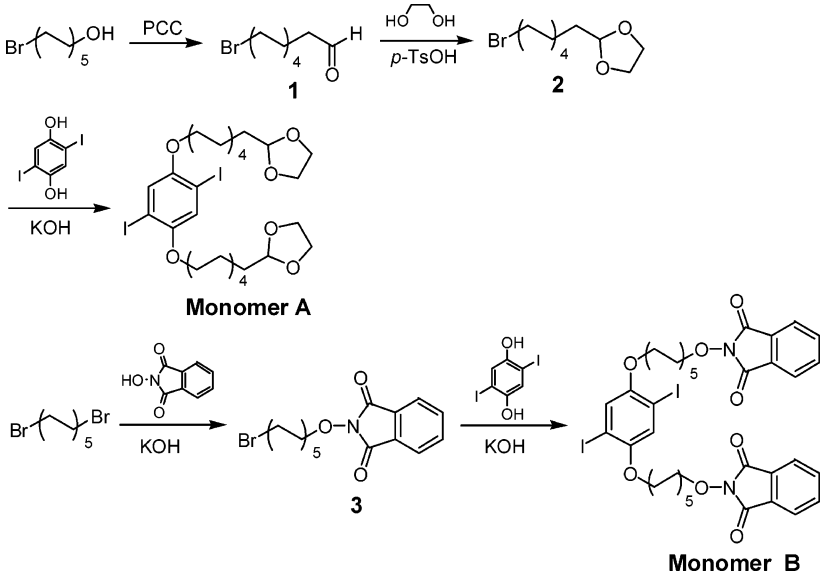
Aldehyde-Substituted Polymer (Polymer G). Polymer **A** (81 mg) was dissolved in a solution of methylene chloride (8 mL), acetone (10 mL), and water (2 mL). To the solution, 1 mL of concentrated HCl was added. The reaction mixture was heated and stirred magnetically at 45−50 °C for 24 h. Saturated $NaHCO_3$ was added to the reaction mixture until the reaction mixture became neutral. The organic layer was extracted with CH_2Cl_2 (3 × 30 mL). Combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the product was dried under vacuum for 24 h to afford polymer **G** (76 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23−1.54 (br, m, 24H), 1.84 (br, 4H), 2.36 (br, m, 4H), 2.92 (br, 4H), 4.03 (br, 4H), 7.08−7.45 (br, m, 14H), 9.72 (s, 2H).

Aminooxy-Substituted Polymer (Polymers H and I). Polymer **C** (86 mg) was dissolved in THF (3 mL). Hydrazine (excess) was diluted with 2 mL of THF and added dropwise into the solution mixture. The reaction mixture was heated to 45 °C and stirring continued for 12 h, and some white precipitate was formed over time. The white precipitate was removed by filtration. 5 mL of water was added, and the organic layer was extracted with CH_2Cl_2 (3 × 30 mL). Combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the product was dried under vacuum for 24 h to afford polymer **I** (65 mg). Polymer **H** was prepared with using polymer **B** instead of polymer **C** in a similar way. Polymer **H**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22−1.88 (br, m, 32H), 2.93 (br, m, 4H), 3.66 (t, 4H, J = 6.5 Hz), 4.05 (br, m, 4H), 7.14−7.45 (br, m, 24H). Polymer **I**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (m, 4H), 3.62−4.2 (br, m, 32H), 7.01−7.44 (br, m, 14H).

Multilayer Assembly. To afford multilayer assembly, substrates were functionalized with oxyamine surface groups. First, glass substrates were sonicated in 5 wt % KOH for 3 h while silicone wafers were dipped in $NH_4OH/H_2O_2/H_2O$ (1/1/5) for 6 h at 80 °C. These substrates were immersed in a toluene solution of *N*-[11-(chlorodimethylsilanyl)undecyloxy]-acetimidic acid ethyl ester[12] for 12 h. Protected oxyamine surface groups were further treated with concentrated HCl/ethanol (1/25) for 12 h followed by sequential washing with 0.1 N Na_2CO_3, water, and ethanol. The substrates derivatized with oxyamine groups were immersed in a chloroform solution of the aldehyde-substituted polymer (**G**) (2 mg/mL) for 30 min at room temperature. The film was then put in a chloroform bath and rigorously shaken for 5 min before drying with nitrogen. The film was subsequently immersed into a solution of oxyamine-substituted polymer (**I**) (2 mg/mL) for 30 min at room temperature to form the second polymer layer. Repetition of alternative dipping in aldehyde- and aminooxy-derivatized polymer gave the corresponding multilayer films. In the case of gold/silicon wafer substrate for GARA FT-IR spectroscopy, surface functionalization was carried out in the same way described in the ref 7.

Instrumentation. ^{1}H NMR spectra were recorded on a Bruker AM 400 or AM 500 spectrometer. Molecular weights and distributions of polymers were determined by using gel permeation chromatography (GPC) with a Waters Associates liquid chromatograph equipped with a Waters 510 HPLC pump, a Waters 410 differential refractometer, and a Waters 486 tunable absorbance detector. THF was used as the eluent and polystyrene as the standard. UV/vis spectra were collected by using a Shimadzu UV-2401PC recording spectrophotometer. The GARA FT-IR spectroscopy experiments were performed with a Nicolet Magna-IR 560 Fourier transform infrared spectrometer fitted with an 85° grazing angle reflectance accessory (SpectraTech) and an internal mercury cadmium tellurite (MCT) detector. The reflectance signal was averaged for 10 000 scans at 4 cm^{-1} resolution. Ellipsometric film thickness measurements were made on a Gaertner model L116C single-color optical ellipsometer equipped with a helium−neon laser operating at 632.8 nm and interfaced to a personal computer. Measurements were made at an incident angle of 70°. The real and imaginary indices of refraction were measured at 10 or more locations on each substrate before monolayer formation. An average of these numbers were then input to the software to determine the thickness of resulting film, which was also measured at least 10 or more points. The tapping mode AFM imaging of the sample was performed

Scheme 1. Synthetic Routes for Monomers A and B



under ambient conditions with a multimode nanoscope IIIA Digital Instrument multimode scanning probe microscope. Rectangular silicon cantilevers with a nominal spring constant of 40 N/m were used with a type J scanner. The drive frequency was ca. 320 kHz. The images were acquired with typical scan rates of 0.5−1.0 Hz with a frame rate of 512.

Results and Discussion

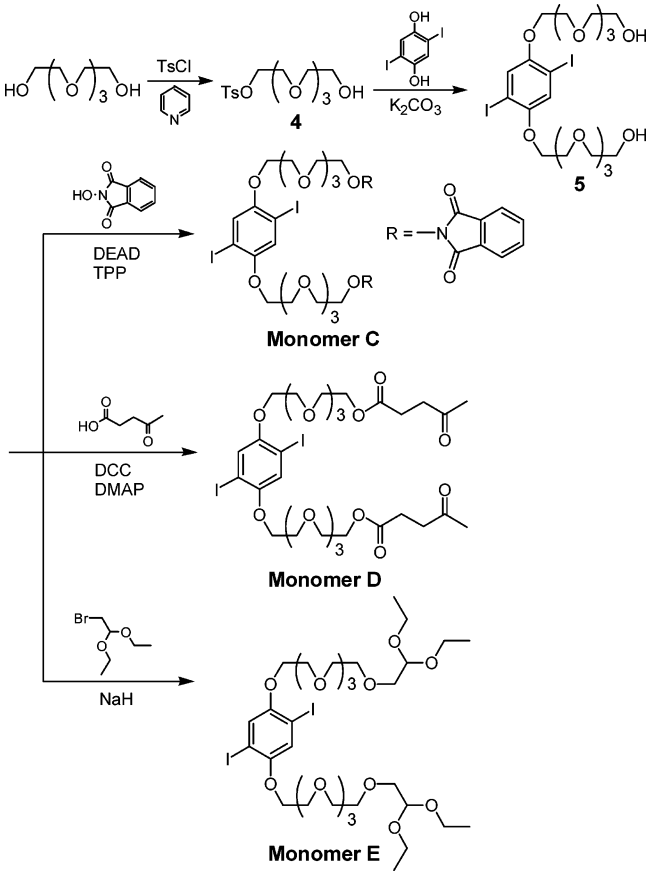
Synthesis of Polymers. A series of polymers with functional side groups for chemoselective immobilization were synthesized according to the reaction Schemes 1−5. The polymer backbone designed possesses enough rigidity to avoid complexity in reaction on surface caused by the random-coiled chain conformation[13] and flexibility to promote solubility as well as to provide smooth surface after immobilization.[8] Additionally, a visible chromophore in the repeating unit gives easy monitoring of the deposition process of each layer. Both hydrophobic methylene groups and hydrophilic tetraethylene oxides were chosen as side groups of these polymers. Since the polymer multilayers to be produced via chemoselective immobilization are cross-linked, the change in side group properties can affect the swellability of the matrix and can be useful in exploring drug entrapment.

Various types of 1,4-diiodo-2,5-dialkoxybenzene monomers were synthesized, as outlined in Schemes 1−3. Aldehyde and oxyamine functions need to be protected by dioxolane and phthalimide, respectively, to survive in the polymerization condition. The 1,4-diiodo-2,5-dialkoxybenzene monomers with hydrophobic side groups with chemoselective pairs were synthesized by reactions between bromoalkyldioxolane or bromoalkyloxyphthalimide and diiodohydroquinone. These reactions were straightforward, and monomers **A** and **B** were obtained in good yield.

However, when the side groups were hydrophilic tetraethylene oxides, similar reaction procedures failed to produce the corresponding final monomers. Alternatively, compound **5** was prepared as a key molecule to monomers **C**−**E**.

Under typical Mitsunobu reaction conditions,[14] compound **5** was reacted with *N*-hydroxyphthalimide to afford monomer **C**. Furthermore, reactions with levulinic acid and bromoacetaldehyde diethylacetal afforded monomers **D** and **E**, respectively, in high yield.

Scheme 2. Synthetic Routes for Monomers C−E



As an electrophile of chemoselective pair, ketone is reported to be equally useful as aldehyde for ligation with oxyamine. In addition, unlike aldehyde, ketone is compatible with the Heck polymerization condition.[15] Thus, polymers **D** and **F** were designed and synthesized. The synthetic strategy to prepare monomer **F** is worthy of particular note and merits further elaboration. A traditional synthetic approach to transform alcohol to ketone requires a few steps of chemistry that are often time-consuming.

Instead, monoacetonyl TEG can be synthesized by using 2-chloro-1-(chloromethyl)ethyl methoxymethyl

Scheme 3. Synthetic Routes for Monomer F

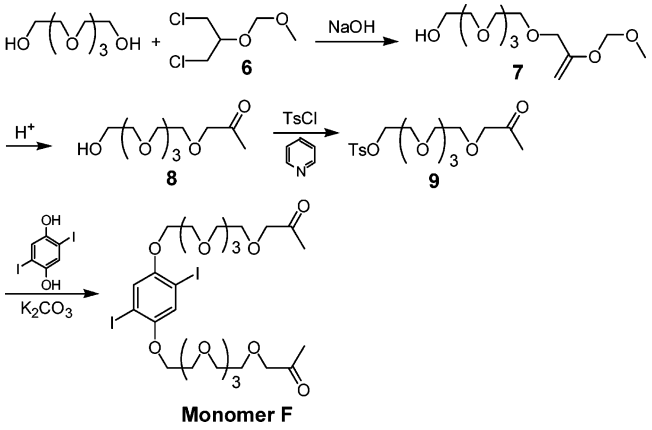


Table 1. Summary of Molecular Weights and Polydispersity Indices of Polymers

polymer	$\bar{M}_n$ (g/mol)	$\bar{M}_w$ (g/mol)	PDI
A	7 600	22 300	2.93
B	5 100	12 200	2.39
C	7 800	14 200	1.82
D	12 800	22 900	1.79
F	12 500	28 500	2.28

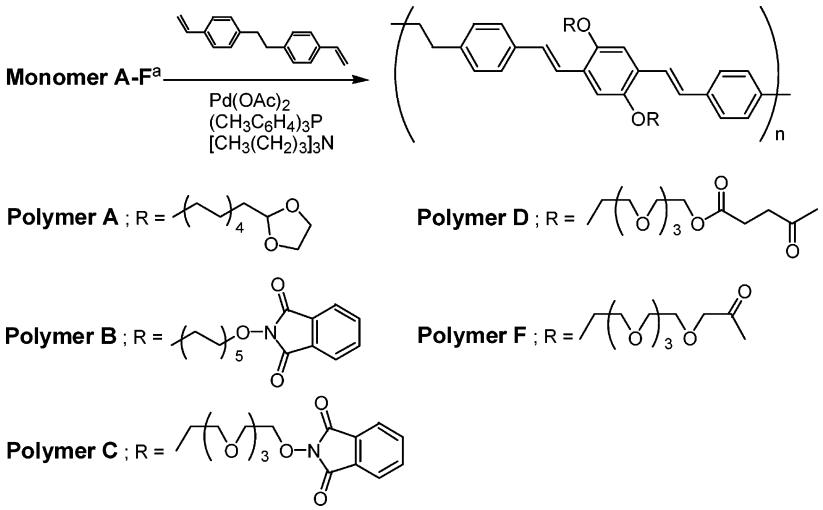
ether (**6**)[16] according to Scheme 3. Compound **6** can be simply prepared from the epichlorohydrin and chloromethyl methyl ether with dodecyltrimethylammonium chloride as a catalyst and had been demonstrated to be very effective acetonylation agent for various types of active proton-containing compounds. Under basic conditions (NaOH) in dioxane, compound **6** was reacted with TEG to produce compound **7**, and further acid hydrolysis afforded monoacetonyl TEG (**8**). To simplify the separation process, the remaining hydroxyl group of compound **8** was converted to the corresponding toluenesulfonate without further purification. The final monomer **F** was obtained by simple nucleophilic substitution reaction with diiodohydroquinone. The utility of compound **6** was further extended to the synthesis of monomer containing tetraethylene oxide ketone. These interesting acetonylation reactions circumvented possible difficulties with traditional oxidations and Grignard reaction from TEG. The preparation of monomer **F** by reacting compound **5** with **6** in basic conditions was also attempted; however, no reaction was observed.

These monomers were copolymerized with 1,2-bis(4-vinylphenyl)ethane by the palladium-mediated Heck coupling reaction.[9] Polymerization was carried out in DMF with a catalyst system composed of palladium acetate (3 mol %), tributylamine (3 equiv), and tri-*o*-tolylphosphine (12 mol %). The polymerization proceeded smoothly, resulting in polymers in high yield. The final polymers had molecular weight ranging from M_w = 12 200 to 28 500 by GPC against polystyrene standards (Table 1). Polymerization of monomer **E** with 1,2-bis(4-vinylphenyl)ethane failed because this particular aldehyde protecting group was not stable under the reaction conditions, and a polymer gel was formed. The structures of the polymers were characterized by different spectroscopic techniques. The ^{1}H NMR spectra of these polymers generally showed the chemical shifts in the range 7.1−7.5 ppm as a broad multiplet corresponding to the aromatic and vinyl protons. Ethylene protons in the polymer repeating unit consistently appeared at 2.9 ppm for all the polymers. Removal of the protecting groups was carried out in basic and acidic conditions for phthalimide and dioxolane groups, respectively, until the proton resonances of corresponding protecting groups were unobservable by ^{1}H NMR spectroscopy. All polymers showed two UV/vis absorption maxima at ca. 390 and 340 nm in $CHCl_3$ solution, as shown in Figure 1 and Table 2.

In the case of polymers **G**, **H**, and **I**, absorption characteristics are reminiscent of those of protected polymers. Considering the structure of the polymer backbone with two chromophores, 1,4-di(2-phenylvinyl)-2,5-dialkoxybenzene[17] in repeating unit and iodostilbene[18] end group, it is reasonable to assign the absorption at ca. 390 nm to the former and ca. 340 nm to the mixture of both chromophores. The ratio of absorbance at the two λ_{max} is summarized in Table 2. Although not quantitative, the increase in the ratio of absorbance at ca. 390 nm to that at 340 nm correlates to the increase in the molecular weight.

Multilayer Assembly. As discussed in the previous report,[8] building multilayers driven by chemoselective ligation is kinetically facile and very simple in processing. More importantly, further surface functionalization is highly feasible which gives a great deal of design flexibility to prepare a variety of surfaces. One of our concerns is whether polymers with hydrophilic side

Scheme 4. Polymerization of Monomers by Heck Coupling Reaction



[a] Polymer from monomer **E** was not obtained.

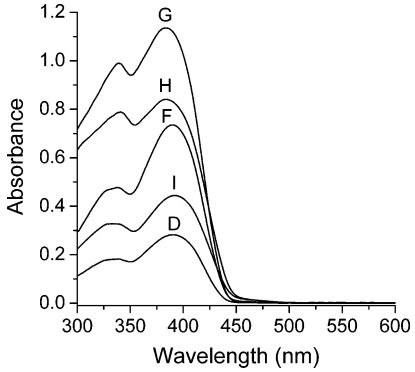


Figure 1. Electronic absorption spectra of polymers in $CHCl_3$.

Scheme 5. Deprotection of Dioxoloane and Phthalimide

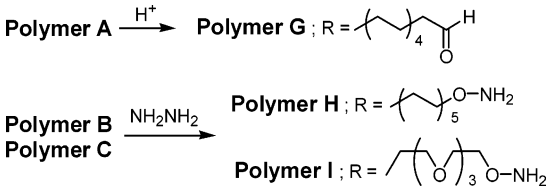


Table 2. UV/vis Absorption of Polymers in $CHCl_3$

polymer	λ_1 (nm)[a]	λ_2 (nm)[b]	A_1/A_2[c]
D	391	339	1.55
F	389	338	1.54
G	393	334	1.36
H	383	341	1.07
I	384	339	1.15

[a] Wavelength at the absorption maximum. [b] Wavelength at the second absorption maximum. [c] The ratio of absorbance at λ_1 to λ_2.

groups proceed with layer-by-layer deposition by chemoselective ligation.

The reaction between oxyamine and aldehyde is facile. When two polymer solutions (polymers **G** and **I**) in deutrated chloroform are mixed in a NMR tube, instantaneous precipitation was observed. The proton resonance of aldehyde at 9.71 ppm disappeared accordingly when the concentration of oxyamine is greater than the stoichiometric amount. On the other hand, the mixture of tetraethylene oxide ketone functionalized polymers (polymer **D** or **F**) and oxyamine partner did not give a similar phenomenon even after 24 h at room temperature. Thus, the reactivity of the ketone moiety is not sufficient for layer-by-layer immobilization of polymers. This chemoselective immobilization approach is flexible in substrate. Gold, glass, and silicon surfaces can be used. To immobilize polymers, substrates were functionalized to provide oxyamine moieties on the surface. In the case of glass substrate or silicon wafer, a hydroxyl group was generated by ultrasonication in aqueous potassium hydroxide solution. Further functionalization of the surface was carried out by immersing the hydrophilic substrate into toluene solution of protected aminooxyalkyldimethylsilyl chloride, followed by deprotection in an acidic condition[12] to generate free oxyamine. Subsequent alternating dipping in $CHCl_3$ solutions of polymers **G** and **I**, rinsing with $CHCl_3$, and drying with a stream of N_2 provided highly reproducible layer deposition. Since all the polymers described herein show significant absorption at ca. 390 nm, the deposition process was conveniently monitored by UV/vis spectroscopy. Figure 2 represents an increase in the absorbance as a function of the number of polymer layers.

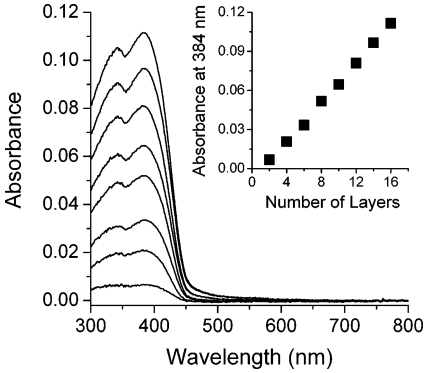


Figure 2. Electronic absorption spectra of multilayers of polymers **G** and **I**. The inset represents the increase in absorbance at 384 nm as a function of the number of layers.

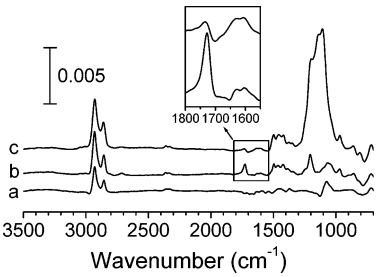


Figure 3. GARA FT-IR spectra of multilayers of polymers **G** and **I**: a, alkyloxyaminothiol; b, polymer **G**; c, polymer **I**.

A linear increase in absorbance with the number of layers was observed even with opposite hydrophilicity in side groups and is indicative of consistent layer-by-layer deposition throughout the process. Note that the increase in optical density of the first couple of layers is smaller than the rest. It is expected that the functionalized glass substrate with oxyamine contains local defects due to surface roughness and imperfect surface coverage. Most probably, a few layers of polymer were consumed to patch up the defects on the substrates. This surface healing phenomenon is one of the important properties of this methodology and was confirmed by tapping mode AFM studies.

To assess that the deposition is driven by covalent bond formation, the films were characterized by GARA FT-IR spectroscopy. Spectrum a in Figure 3 shows a self-assembled monolayer of aminooxyalkylthiol on a gold/silicon wafer substrate. When polymer **G** was deposited (spectrum b), the characteristic peaks of aldehyde appeared at 1726 (C═O stretching), 2710, and 2815 cm^{-1} (C−H stretching). These peaks disappeared at the subsequent deposition of polymer **I**, and a broad peak corresponding to the oxime was observed at 1630 cm^{-1} instead (spectrum c). The peak at 1100 cm^{-1}, the C−O stretching of aliphatic ether, increased strongly while alkane C−H stretching at 2930 cm^{-1} increased gradually as polymers were deposited. This result clearly manifests formation of oxime bond during the deposition process.

The thickness of each polymer layer was determined by ellipsometry. To conduct this experiment, a silicon wafer with hydrophilic surface was used as a substrate. As shown in Figure 4, a linear increase in the thickness as a function of the number of layers was obtained.

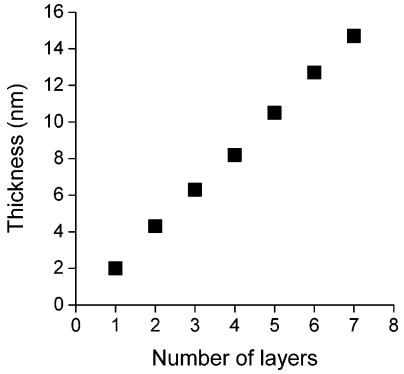


Figure 4. Ellipsometric thickness of multilayers of polymers **G** and **I**. The thickness of aminooxyalkyldimethylsiloxane layer (ca. 1.5 nm) was excluded.

The calculated thickness of each layer from the slope was 20 ± 1 Å. The experimental thickness is somewhat shorter than the theoretical thickness of 30 Å for polymer **G** and 36 Å for polymer **I** estimated by molecular mechanics calculations when side groups are extended. In conjunction with electronic absorption spectra of the multilayers, we can conclude that each layer is uniform and free of possible aggregation.

Surface topographies of the polymer multilayers were investigated by tapping mode AFM studies. To elucidate change in the surface morphology as the film grows, rough glass was used as a substrate instead of flat substrates such as gold or silicon wafer.

Figure 5a shows AFM image of hydrophilic glass substrate. The surface of glass substrate contained significant amount of defects including nodules[19] with height ranging from 5 to 15 nm. These defects on the surface were mostly covered when six layers of polymer were immobilized (Figure 5b) with surface roughness about 3 nm. However, traces of the nodules were still observable. Note that the thickness of six polymer layers is smaller than that of large nodules on glass substrate. The resulting multilayer film surfaces are smooth and contain functional groups, either −CHO or $-ONH_2$, for further surface reactions.

Conclusions

Several functional polymers with side groups for chemoselective immobilization were synthesized and characterized. It was found that reaction between aldehyde and oxyamine is facile, and the resulting multilayer films are smooth and functionalizable. A linear relationship between layer number and the thickness of films was observed. However, polymers containing side ketone groups have a sluggish reaction with oxyamine under neutral conditions and is not suitable to prepare multilayer polymer films. The importance of the discovery of building polymer multilayers via chemoselective ligation lies on the fact that robust smooth and end-functionalizable platform can easily be generated. The resulting polymer films allow further surface reactions under mild conditions. Further utility of this deposition approach will enable us to

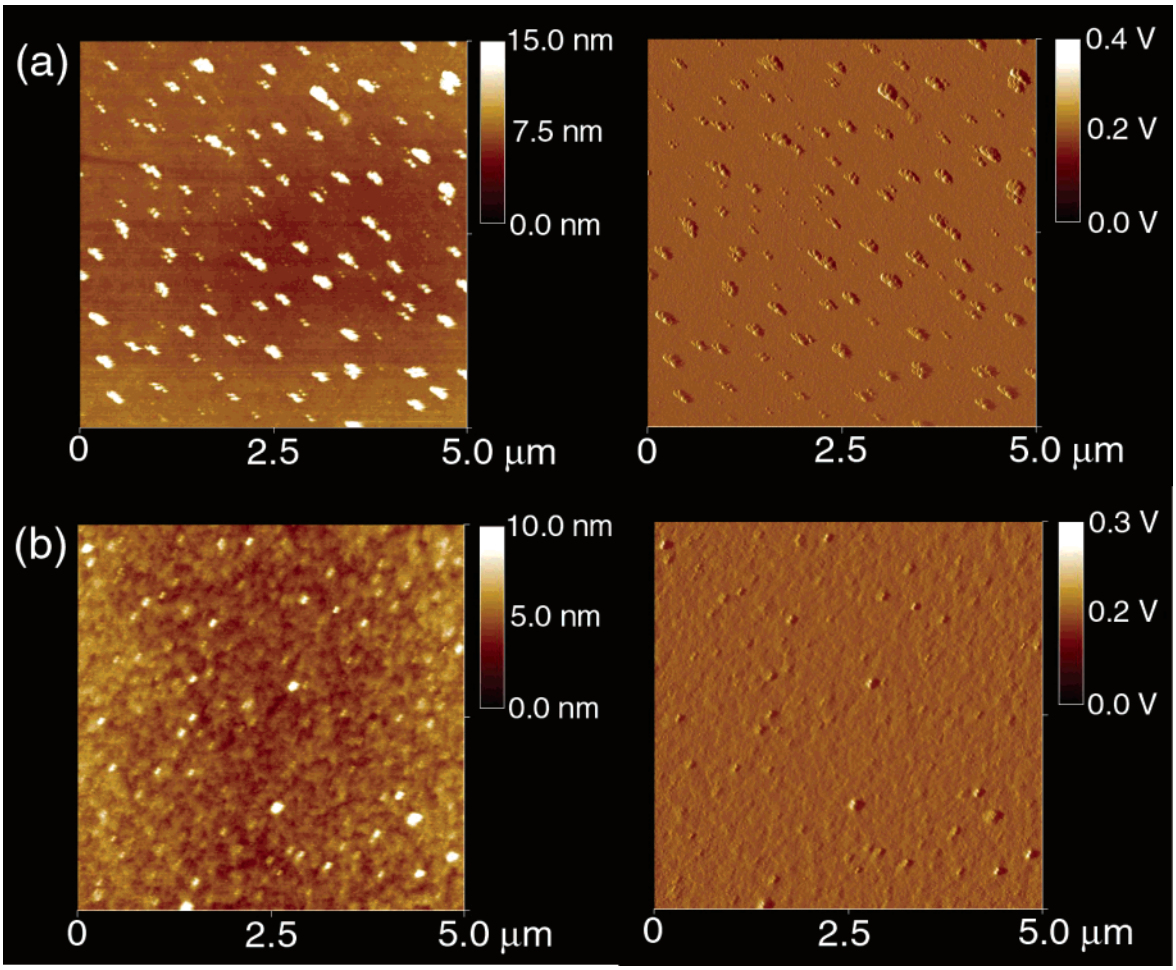


Figure 5. Tapping mode AFM images of hydrophilic glass (a) and six polymer layers (b). Images on the left and right are topographic and amplitude tapping mode, respectively.

rationally design materials with desired physical properties, such as miniaturized electrooptic devices and highly functionalizable biocompatible surfaces for medical and sensing applications. Further work along these lines is in progress.

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