Chemical Oscillation Induced Periodic Swelling and Shrinking of a Polymeric Multilayer Investigated with a Quartz Crystal Microbalance

Yecang Tang, Guangming Liu, Changqian Yu, Xiaoling Wei, and Guangzhao Zhang*

Hefei National Laboratory for Physical Sciences at Microscale, Department of Chemical Physics, University of Science and Technology of China, Hefei, China

Poly(acrylic acid-*co*-3-azidopropyl acrylate) and poly(acrylic acid-*co*-propargyl acrylate) have been alternately fabricated into a multilayer via the click reaction. The layer-by-layer deposition was monitored with a quartz crystal microbalance with dissipation (QCM-D) in real time. The response of the multilayer under continuous flow of a bromate−sulfite−ferrocyanide solution with pH oscillation has also been investigated by use of QCM-D. As the pH oscillates between 3.1 and 6.6, either the frequency shift (Δf) or the dissipation shift (ΔD) periodically varies with a constant amplitude, clearly indicating that the multilayer swells and shrinks oscillatedly. The changes of thickness, shear viscosity, and elastic shear modulus further indicate the oscillation.

Introduction

Intelligent polymers in response to an external stimulus such as pH, temperature, and ionic strength have received much attention because they not only can be used to construct new functional polymers but also can help us to understand some phenomena in life science.[1] In comparison with biomacromolecules which function automatically, the conventional polymers exhibit discontinuous action since the response is usually driven by an on−off external stimulus. Recently, chemical oscillation has been used to fabricate polymeric materials with self-action.[2–10] It has been reported that polymeric gels in a closed system driven by the Belousov−Zhabotinsky reaction exhibit self-oscillation.[2–5] Due to the energy dissipation, the oscillation amplitude decays with time. pH-responsive gels with periodical volume changes driven by the Landolt reaction have also been prepared.[6–8] Such gels work in an open system with constant amplitude if the input is continuous. Note that a responsive interface usually exhibits some unique properties in comparison with the bulk materials. However, the oscillating interface or surface has been seldom studied.[7]

The layer-by-layer (LBL) assembly technique has been used to fabricate a multilayer via electrostatic interactions,[11–20] hydrogen bonding,[21–27] and covalent bonding.[28–39] Particularly, multilayers formed by poly(acrylic acid) (PAA) or poly(methyacrylic acid) via cross-linking exhibit good stability in solutions,[26,27,38] and their swelling can be regulated by the polymer structure, pH, and ionic strength of the solution.[34,35] Such a multilayer has been used to load and release some model drugs.[36]

In the present study, we have prepared a multilayer by the click reaction of poly(acrylic acid-*co*-3-azidopropyl acrylate) (poly(AA-*co*-Az)) and poly(acrylic acid-*co*-propargyl acrylate) (poly(AA-*co*-PA)). Since the bromate−sulfite−ferrocyanide (BSF) system oscillates in the pH range of 3.1−6.6 and the pK_a

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of PAA is ~4.5 under this condition,[40,41] the multilayer would exhibit periodic swelling and shrinking under a continuous flow of a BSF solution with pH oscillation. By use of a quartz crystal microbalance with dissipation (QCM-D), we have investigated the response dynamics of the multilayer. Our aim is to understand how the multilayer responds to chemical oscillation.

Experimental Section

Materials. Poly(ethyleneimine) (PEI; $M_w \approx 25\,000$ g/mol), propiolic acid, propargyl alcohol, and *N,N'*-dicyclohexylcarbodiimide (DCC) were all from Acros and used as received. Acrylic acid and acryloyl chloride were distilled prior to use. 4,4'-Azobis(isobutyronitrile) (AIBN) was purified by recrystallization from methanol. *S,S'*-Bis(α,α'-dimethyl-α''-acetic acid) trithiocarbonate was synthesized as described in the literature.[42] The synthesis of poly(AA-*co*-Az) and poly(AA-*co*-PA) were detailed elsewhere,[38] and their weight-average molar mass (M_w) values determined by laser light scattering (LLS) are 1.72×10^5 and 5.6×10^4 g/mol, respectively. The polydispersity indices (M_w/M_n) are 1.9 and 2.0, respectively. The contents of alkyne in poly(AA-*co*-PA) and azide in poly(AA-*co*-Az) determined by ^{1}H NMR are 16 and 14 mol %, respectively. The solvents used were dried and purified following standard procedures. Other chemicals were purchased from Shanghai Chemical Reagent Co. and used as received.

PEI modified with alkyne (PEI—Alk) was coated on the resonator surface so that the effect of the substrate on the layer growth was minimized.[43] PEI-Alk can cross-link with poly(AA-*co*-Az) via the click reaction to initiate the layer-by-layer desposition. The modification of PEI is as follows. After propiolic acid (0.42 g), DCC (2.66 g), and 4-(dimethylamino)pyridine (10 mg) were dissolved in 40 mL of chloroform at 0 °C for 40 min, a solution of PEI (1.00 g) in 20 mL of chloroform was added dropwise. The mixture was stirred at 25 °C for 24 h. After filtration, the solution was precipitated into diethyl ether. Such a procedure was repeated three times, yielding PEI—Alk. The sample was dried under vacuum and characterized by FTIR and ^{13}C NMR. FTIR (CHCl$_3$, NaCl plates): 2118 cm^{-1} ($\nu_{-C\equiv CH}$). ^{13}C NMR (400 MHz, CDCl$_3$): δ 81.5 (H*C*≡CCONH−), δ 75.7 (HC≡*C*CONH−), δ 164.5 (HC≡C*C*ONH−). These data demonstrate that PEI is modified with alkyne. The content of alkyne in PEI—Alk is 16 mol %.

Characterization. All ^{1}H NMR (300 MHz) analyses were performed on a Bruker AV300 NMR spectrometer. Fourier transform infrared (FTIR) spectra were recorded on a Bruker VECTOR-22 IR spectrometer. LLS measurements were conducted on an ALV/DLS/SLS-5022F spectrometer with a multi-τ digital time correlation (ALV5000) and a cylindrical 22 mW UNIPHASE He—Ne laser ($\lambda_0 = 632$ nm) as the light source. M_w was measured by static LLS in 0.1 M NaCl aqueous solution at 25.0 °C. M_w/M_n was estimated from the relative line width distribution in dynamic LLS.[44] X-ray photoelectron spectroscopy (XPS) measurements were conducted on an ESCALAB-250 spectrometer with a monochromatic Al Kα X-ray source at 1486.6 eV. The analyzer was operated in constant resolution mode at a pass energy of 20 eV with a C1s contamination line at 284.6−285.0 eV as the reference.

QCM-D Measurements. The QCM-D and AT-cut crystal with a fundamental resonant frequency of 5 MHz were from Q-sense AB. The crystal was mounted in a fluid cell with one side exposed to the solution.[45] The measurable frequency shift was within ±1 Hz. When an rf voltage near the resonant frequency is applied across the electrodes, the quartz crystal is excited to oscillate in the thickness shear mode at its fundamental resonant frequency (f_0). The

introduction of a thin layer on the electrodes leads to a decrease in resonant frequency (Δf) which is proportional to the mass (Δm) of the layer. In a vacuum or air, if the layer is rigid, evenly distributed, and much thinner than the crystal, Δf is related to Δm and the overtone number ($n = 1, 3, 5,...$) by the Sauerbrey equation:[46]

$$\Delta m = -\frac{\rho_q l_q}{f_0} \frac{\Delta f}{n} \tag{1}$$

where ρ_q and l_q are the specific density and thickness of the quartz crystal, respectively. The dissipation factor is defined by

$$\Delta D = \frac{E_d}{2\pi E_s} \tag{2}$$

where E_d is the energy dissipated during one oscillation and E_s is the energy stored in the oscillating system. ΔD is measured on the basis of the fact that the voltage over the crystal decays exponentially as a damped sinusoidal when the driving power on the oscillator is switched off. By switching the driving voltage on and off periodically, we can simultaneously obtain a series of changes of the resonant frequency and the dissipation factor. Δf and ΔD values from the fundamental were discarded because they are usually noisy due to insufficient energy trapping.[47]

Considering the Sauerbrey equation is not valid for a viscoelastic polymer layer in a Newtonian liquid, the thickness of the layer was obtained by fitting by theoretical representations based on a Voight model with the Q-tools software from Q-sense AB.[48] Since the bulk solution was dilute, its density ($\rho_l \approx 1000$ kg/m^3) and viscosity ($\eta_l \approx 1 \times 10^{-3}$ Pa·s) were taken to be those of water. The density (ρ_f) of the layer used was ~1000 kg/m^3.

Multilayer Fabrication. The gold-coated resonator was cleaned by using piranha solution composed of 1 part H$_2$O$_2$ and 3 parts H$_2$SO$_4$, rinsed with large amounts of Milli-Q water, and blown dry with a stream of nitrogen gas. The resonator was initially exposed to a PEI—Alk solution with a concentration of 1.0 mg/mL for 20 min, followed by a rinse with water to yield alkyne groups on the resonator surface. After water was replaced with catalyst solution, poly(AA-*co*-Az) and poly(AA-*co*-PA) solutions were alternately introduced for 20 min with catalyst solution rinsing in between. The catalyst solution was composed of CuSO$_4$·5H$_2$O (0.1 mg/mL) and sodium ascorbate (0.2 mg/mL). Poly(AA-*co*-Az) and poly(AA-*co*-PA) were each dissolved in the catalyst solution with a concentration of 0.6 mg/mL. Each solution was adjusted to pH 3.5 using 0.1 M HCl and prepared before deposition of each layer to prevent oxidation of Cu(I). The final multilayer was rinsed alternately with 0.02 M ethylenediaminetetraacetic acid disodium and phosphate buffer (pH 9.1) to remove Cu ions. All experiments were performed at 25 ± 0.02 °C.

Oscillation Behavior of the Multilayer. The oscillation reactions were conducted in a continuously stirred tank reactor (CSTR) by pumping two separate solutions at 0.7 mL/min into the reactor. One solution was composed of Na$_2$SO$_3$ (0.15 M), K$_4$[Fe(CN)$_6$] (0.04 M), and H$_2$SO$_4$ (0.02 M), and the other consisted of KBrO$_3$ (0.13 M).[6,49] The ionic strength was 0.52 mol/kg. Such a solution flowed into the cell of the QCM-D with the resonator coated with the multilayer at a rate of 1.4 mL/min, at which the frequency exhibited the maximum amplitude between pH 3.1 and pH 6.6. The pH change in the CSTR was monitored with a pH meter. The swelling and shrinking of the multilayer as a function of time were examined with the QCM-D.

Results and Discussion

Figure 1 shows the changes in frequency (Δf) and dissipation (ΔD) for the LBL deposition of poly(AA-*co*-Az)/poly(AA-*co*-

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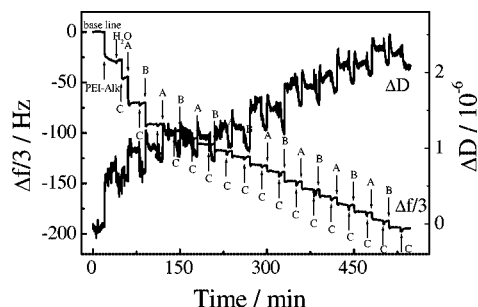
Figure 1. Changes in Δf and ΔD in the formation of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer, where A, B, and C represent poly(AA-*co*-Az), poly(AA-*co*-PA), and the catalyst solution, respectively, and $n = 3$.
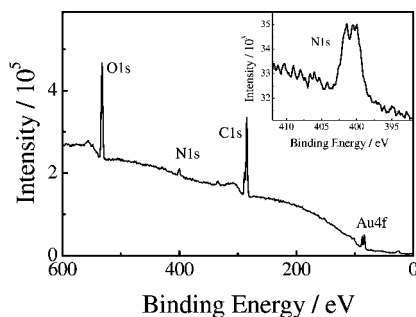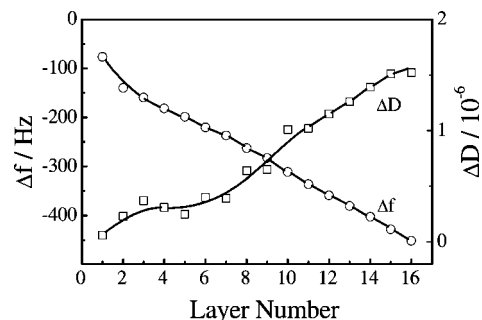

Figure 2. XPS spectrum of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer, where the layer number is 16.

Figure 3. Layer number dependence of the Δf and ΔD of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer. The odd and even layer numbers correspond to the deposition of poly(AA-*co*-Az) and poly(AA-*co*-PA), respectively, and $n = 3$.

Figure 4. Layer number dependence of t of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer, where curves A and B are obtained from the Sauerbrey equation and Voight model, respectively.

Figure 5. Oscillation of pH measured at 25 °C under the continuous flow of BSF solution, where [KBrO$_3$] = 0.065 M, [K$_4$[Fe(CN)$_6$]] = 0.02 M, [Na$_2$SO$_3$] = 0.075 M, [H$_2$SO$_4$] = 0.01 M, and r = 1.4 mL/min.
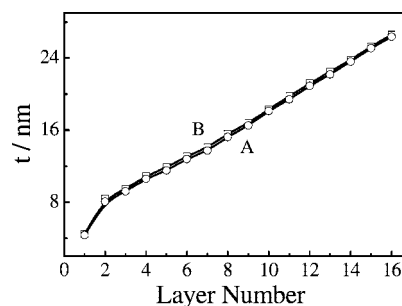
PA), where $n = 3$. The decrease in Δf and increase in ΔD clearly indicate that the polymers gradually deposit onto the resonator surface. Since PAA chains cannot construct a multilayer by electrostatic interaction themselves,[38] the multilayer is formed via 1,3-dipolar cycloaddition reaction of azide and alkyne.[37] The peaks in the responses of the frequency and dissipation after the addition of a polymer solution are attributed to the small changes of density and viscosity in the solution.

The click reaction in the multilayer was examined by XPS. Figure 2 shows the XPS spectra for the outermost surface of a 16-layer film. The small peak for Au4f is attributed to the resonator surface uncovered by the multilayer. The inset shows a broad N1s peak near 400 eV. By a multipeak fitting, the peak can be separated into two peaks at 400.1 and 401.7 eV, corresponding to the triazole ring. The absence of the peak at ~405 eV indicates no azide groups on the film.[39,50] Therefore, 1,2,3-triazole linkages are formed in the film. Note that the azide and alkyne groups cannot completely react with each other at any layer, leading to excessive cross-linkable groups, so that the multilayer can be continuously built up. In addition, XPS does not reveal Cu ion peaks, indicating that the Cu ion has been completely removed.
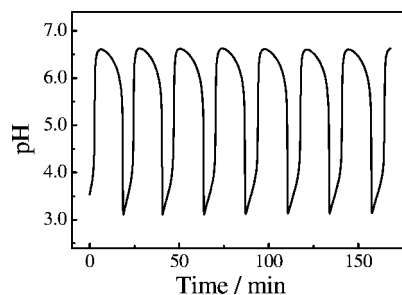
Figure 3 shows Δf and ΔD of poly(AA-*co*-Az)/poly(AA-*co*-PA) as a function of the layer number. The odd and even layer numbers correspond to the deposition of poly(AA-*co*-Az) and poly(AA-*co*-PA), respectively. For the first and second layers, Δf and ΔD markedly change. Besides the click reaction, complexation between PEI−Alk and PAA copolymer via electrostatic interaction also occurs. The changes in Δf and ΔD are the result of their combination. When the layer number is above 2, Δf monotonously decreases with the layer number, indicating that the multilayer grows in a linear mode. It is known that Δf is the response of the mass or thickness of the layer on

the resonator surface, whereas ΔD reflects the structure of the layer.[51] Δf for poly(AA-*co*-Az) and poly(AA-*co*-PA) layers are ~−21 and −24 Hz, respectively. In other words, Δf slightly changes with the layer number when the number is above 2. This fact indicates that the amount of adsorbed copolymer in each layer is close. On the other hand, the small change in ΔD (~0.09) implies that the structure of the films is compact. This is because PAA copolymers are collapsed at pH 3.5. The cross-linking between the neighboring layers via the click reaction of azide and alkyne further leads the films to be compact.

Figure 4 shows the hydrodynamic thickness (t) of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer obtained from the Sauerbrey equation and the fitting based on the Voight model are almost the same. Since the Sauerbrey equation is suitable for a rigid film, the agreement of the thickness values in Figure 4 further indicates the film is not viscoelastic but rigid. On the other hand, the thickness linearly increases with the layer number when the

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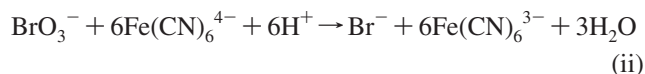(51) Voinova, M. V.; Rodahl, M.; Jonson, M.; Kasemo, B. *Phys. Scr.* **1999**, *59*, 391–396.
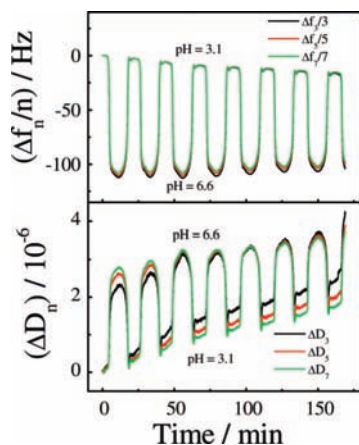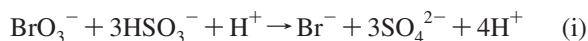
Figure 6. Time dependence of Δf and ΔD of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer under the continuous flow of BSF solution, where $r = 1.4$ mL/min, $T = 25$ °C, and $n = 3, 5,$ and 7.

layer number is above 2. This is because the contents of azide (14 mol %) and alkyne (16 mol %) in the copolymers are close; each layer reacts almost the same as other polymers to form the next layer.

We used BSF solution composed of $KBrO_3$, Na_2SO_3, $K_4[Fe(CN)_6]$, and H_2SO_4 to induce the swelling and shrinking of the multilayer. The mechanism of the Landolt reaction is complex. However, it involves two processes, that is, the oxidation of sulfite by bromate (i) and the oxidation of the ferrocyanide by bromate (ii).

$$BrO_3^- + 3HSO_3^- + H^+ \rightarrow Br^- + 3SO_4^{2-} + 4H^+ \quad \text{(i)}$$

$$BrO_3^- + 6Fe(CN)_6^{4-} + 6H^+ \rightarrow Br^- + 6Fe(CN)_6^{3-} + 3H_2O \quad \text{(ii)}$$

The first process produces protons (positive feedback), while the second consumes protons (negative feedback). As a result, the reaction provides pH oscillation.[6,49] Figure 5 shows that the pH of the BSF solution varies between 3.1 and 6.6 with an oscillation period of ~23 min at a flow rate (r) of 1.4 mL/min. Such a chemical oscillation has enough time to drive the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer to change conformation.

Figure 6 shows the time dependence of Δf and ΔD of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer driven by BSF solution. Clearly, both Δf and ΔD periodically vary in concordance with the pH oscillation in Figure 5. As the pH increases from 3.1 to 6.6, Δf abruptly decreases. In contrast, Δf sharply increases with pH decreasing from 6.6 to 3.1. On the other hand, ΔD oscillates with pH in the opposite trend. This oscillation relates to the conformational change of PAA at different pH values. It has been reported that the pK_a of the PAA solution in the absence of added salt ranges from 5.5 to 6.5. In the presence of salts, it can drop to ~4.5, especially in the case of a PAA multilayer.[40,41] Here, the pK_a should be ~4.5. Accordingly, $\sim10\%$ of the carboxyls are deprotonated at pH 3.2, but they are almost completely ionized as the pH is increased to 6.6.[52] The decrease of Δf with pH increasing from 3.1 to 6.6 reflects the swelling of the multilayer due to the electrostatic repulsion. In other words, more water molecules are coupled with carboxyls. As the pH decreases from 6.6 to 3.1, water gradually becomes a poor solvent, and the dehydration of the films occurs, leading the thickness to decrease. That is why Δf increases. Note that the multilayer
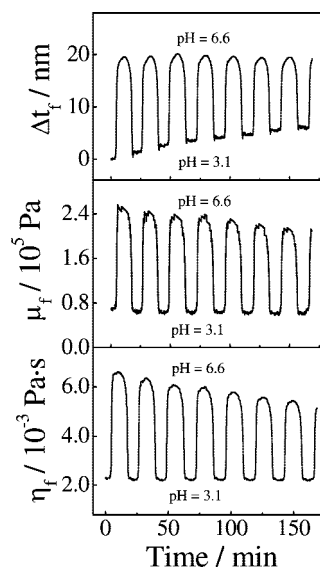
Figure 7. Time dependence of Δt_f, η_f, and μ_f of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer under the continuous flow of BSF solution, where $r = 1.4$ mL/min and $T = 25$ °C.

exhibits a relatively quick response to the pH change. The response times for the swelling and deswelling are ~98 and 25 s, respectively.

The oscillation of ΔD reflects the viscoelasticity change of the multilayer. As discussed above, the multilayer is compact at pH 3.5. As the pH increases to 6.6, ΔD increases, indicating the hydration of the polymer chains. This causes the multilayer to be more viscous and damps the shear wave more. In contrast, as the pH decreases from 6.6 to 3.1, polymer chains are dehydrated and shrunk, leading to the decrease in ΔD. Note that the amplitude of Δf or ΔD slightly drops as the oscillation cycle increases. This is probably because the multilayer does not reach equilibrium in the swelling or shrinking state in the observation time. We have also examined the multilayer with layer numbers of 4, 8, and 12 (not shown). The multilayer exhibits similar behavior. Generally, the amplitude increases with the layer number because the thickness increases with the layer number.

Figure 7 shows the changes of the thickness (Δt_f), shear viscosity (η_f), and elastic shear modulus (μ_f) of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer fit by the Voight model. It can be seen that Δt_f, η_f, and μ_f exhibit periodic oscillation. As the pH oscillates between 3.1 and 6.6, Δt_f exhibits a periodic change with an amplitude of ~17 nm. This clearly indicates the swelling and shrinking of the multilayer. Note that the spikes in the curves about Δf and ΔD in Figure 6 do not translate into the curves in Figure 7. The spikes can be attributed to the small changes in density and viscosity of the BSF solution during pH oscillation. Since the density and viscosity were fixed at certain values in the fitting by the Voigt model, the spikes cannot be observed in the changes of η_f and μ_f in Figure 7.

The maximum swelling ratio (SW) is estimated to be 164% by using SW = $(t_{6.6}/t_{3.1}) \times 100$,[35] where $t_{6.6}$ and $t_{3.1}$ are the film thickness values at pH 6.6 and 3.1. Such a swelling ratio is comparable to that for a PAA film reported in a previous work.[53] As the pH increases from 3.1 to 6.6, the electrostatic repulsion between two neighboring layers becomes stronger, and the multilayer adopts a weakly compressible state, so that μ_f increases. In contrast, μ_f decreases as the pH decreases from 6.6 to 3.1.

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Similarly, the oscillation of pH leads to the periodic dehydration and hydration of the multilayer, so that η_f varies periodically. It has been reported that the η_f and μ_f of a cross-linked protein film are 6×10^{-3} Pa·s and 3×10^5 Pa, respectively.[54] The values are comparable to our results. In short, the periodic oscillations of η_f and μ_f further indicate the periodic swelling and shrinking of the poly(AA-*co*-Az)/poly(AA-*co*-PA) multilayer. With the continuous swelling and shrinking, the present multilayer may find applications in the fields of actuators, biosensors, and drug delivery. For example, it could serve as a drug delivery system where the accurate timed drug release can be controlled by the pH oscillation.

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Conclusion

A polymeric multilayer has been prepared by layer-by-layer deposition via the click reaction. The films exhibit periodic swelling and shrinking under continuous flow of bromate−sulfite−ferrocyanide solution. The response can be well characterized with a QCM-D. Such a film might find an application in the fields of actuators, biosensors, and drug delivery.

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