Reflexive Interfaces of Poly(trimethylene carbonate)-Based Polymers: Enzymatic Degradation and Selective Adsorption

Junji Watanabe,[†,‡] Hideaki Kotera,[§] and Mitsuru Akashi*[,†,‡,§]

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamada-oka, Suita, Osaka 565-0871, Japan; 21st Century COE for "Center for Integrated Cell and Tissue Regulation", School of Engineering, Osaka University, 2-1 Yamada-oka, Suita, Osaka 565-0871, Japan; and Division of Applied Science, School of Engineering, Osaka University, 2-1 Yamada-oka, Suita, Osaka 565-0871, Japan

Received May 7, 2007; Revised Manuscript Received July 19, 2007

ABSTRACT: A reflexive interface was designed and prepared based on poly(trimethylene carbonate) (PTMC), which was polymerized from the hydroxyl groups of cholesterol or poly(ethylene glycol) monomethyl ether (mPEG) by conventional ring-opening polymerization techniques. Resulting polymer coatings were analyzed in terms of surface wettability and polymer weight loss during degradation using contact angle and quartz crystal microbalance measurements. The adsorption of hydrophilic and hydrophobic dyes on the membrane was evaluated by UV−vis spectrometry and was found to be largely dependent on the polarity of the terminal unit such as the cholesterol or mPEG segment. For example, mPEG ($M_n = 5000$ g/mol)−PTMC membranes, abundant with surface mPEG segments, demonstrated quick, spontaneous surface enrichment in water. In terms of results, surface wettability increased and enzymatic degradation decreased due to a lack of enzymatic accessibility. Moreover, such membranes could adsorb hydrophobic dyes from aqueous solutions, demonstrating interfacial stabilization by mPEG segments. Resulting polymers could be interesting candidates for commercial applications and of specific interest in biomedical applications.

1. Introduction

Poly(trimethylene carbonate) (PTMC) is a widely investigated biodegradable polymer,[1−4] and several studies have shown its suitability as a biomaterial.[5−7] PTMC displays a low glass transition temperature (T_g) and thus possesses high molecular mobility at ambient conditions. Meijer et al. utilized the mobility of PTMC in conjunction with terminal hydrogen-bonding units as an approach for supramolecular assemblies,[8] and Hilborn et al. reported a biocompatible interface using phosphorylcholine (PC) functional PTMC oligomers.[9−12] In the latter study, when immersed in water, terminal polar groups were shown to spontaneously rearrange onto the outermost surface to reduce the surface free energy. From these results, we were inspired by the properties such as a rapid, spontaneous fashion and repetition. Thus, we call the surface quick rearrangement based on PTMC a reflexive interface, and it could be designed using PTMC. Yui et al. described fundamental strategies regarding reflexive polymers, which are summarized in an excellent textbook by Mrsny and Park.[13] Stimuli-responsive polymers were furthermore used to prepare functional polymer interfaces.[14,15] On one hand, the alternate adsorption process is a promising technique that modifies polymer interfaces,[16] while polymer coating is a typical surface modification technique, and the resulting surfaces are capable of further functionality. Serizawa and Akashi reported the regulation of alkaline hydrolyses on poly(lactic acid) stereocomplexes[17] and stereoregular polymerization of poly(methyl methacrylate)[18] in their pioneering work using an alternate adsorption process. The regulation of interface properties was crucial to further improve polymer functionalities.

In the present study, we focus on segmented functional PTMC-based polymers, which show spontaneous surface rearrangements dependent on wet conditions. The design of the terminal unit was shown to be the dominant factor to facilitate the reflexive function. Poly(ethylene glycol) monomethyl ether (mPEG) was utilized as a macroinitiator for conventional ring-opening polymerization (ROP) using stannous octoate as a catalyst. PEG is a known hydrophilic polymer, and its rotational correlation times have in an earlier study been shown to increase with the PEG molecular weight.[19] Therefore, we synthesized various PTMC−PEG block copolymers utilizing PEG as a macroinitiator to study coating reflexive properties from resulting materials. Cholesterol was used as an initiator to provide a more hydrophobic reference surface than PTMC. Initially, the PEG−PTMC surface was hydrophobic since PTMC would enrich the surface and thereby reduce the surface free energy in air; however, by soaking the surface in an aqueous solution, the surface properties changed into hydrophilic PEG segments that enriched the surface. The changes in surface polarity were characterized using static contact angle measurements and evaluated by enzyme accessibility and also selective adsorption using hydrophobic and hydrophilic dyes. Reflexive polymers are of importance as biomaterials and in industrial applications.

2. Materials and Methods

2.1. Materials. Trimethylene carbonate (TMC) was purchased from Boehringer Ingelheim. Cholesterol (Chol, Wako Pure Chemical Industries), poly(ethylene glycol) monomethyl ether at 350 g/mol (mPEG8, Alfa Aesar), poly(ethylene glycol) monomethyl ether at 5000 g/mol (mPEG114, Fluka), and stannous octoate (tin(II) 2-ethyl hexanoate, Wako) were used for the polymerizations. Organic solvents were purchased from Wako and used as received. To examine enzymatic degradation, Dulbecco's phosphate buffered saline (PBS, #14200-075, Invitrogen) was used with a pH of 7.1.

---

* Corresponding author: e-mail akashi@chem.eng.osaka-u.ac.jp; phone +81-6-6879-7356; Fax +81-6-6879-7359.

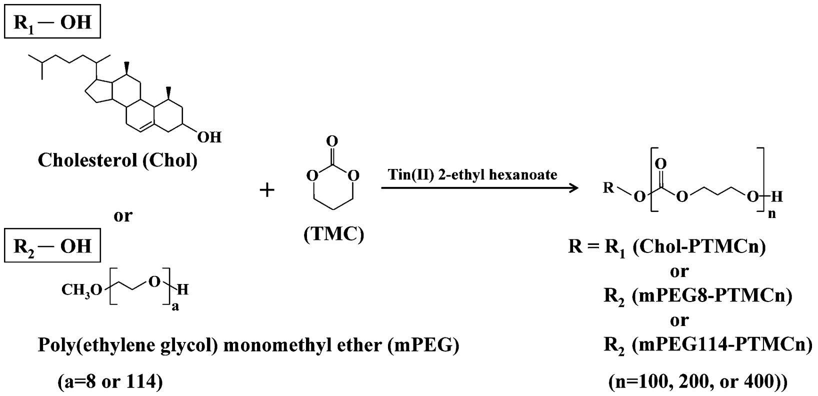
[†] Department of Applied Chemistry.

[‡] 21st Century COE for "Center for Integrated Cell and Tissue Regulation".

[§] Division of Applied Science.

10.1021/ma071030q CCC: $37.00 © 2007 American Chemical Society
Published on Web 11/02/2007

Scheme 1. Synthetic Route Showing Both Poly(trimethylene carbonate) and a Functional Initiator Unit



As an enzyme, Lipase (Wako, pig pancreas, 10 units/mg) was used with a concentration of 10 mg/mL in PBS, and its supernatant was used in enzymatic degradations.

2.2. Instrumentation. ^{1}H NMR spectra were recorded using a JNM-GSX (JEOL, 400 MHz) with $CDCl_3$ as a solvent. Gel permeation chromatography (GPC) measurements were performed on an HLC-8220GPC (Tosoh) with a TSK-GEL SuperH4000 column to determine molecular weights and their distributions. As an eluent, *N*,*N*-dimethylformamide (DMF) with 10 mmol/L lithium chloride was used. The flow rate was 1 mL/min, and a universal calibration with polystyrene standards (Shodex) was performed. FT-IR spectra were recorded using the attenuated total reflection (ATR) method by the use of an FT-IR spectrometer (Spectrum 100, Perkin-Elmer). Static contact angle measurements were performed using a DropMaster 500 (Kyowa Interface Science) with ultrapure water. UV−vis spectra were recorded from 400 to 700 nm using a U-3010 (Hitachi) spectrophotometer. To monitor changes in weight on a substrate, a quartz crystal microbalance (QCM) substrate with a parent frequency of 9 MHz (USI System) was used, and the change in the frequency was monitored by a frequency counter (53131A, Agilent Technologies).

2.3. PTMC-Based Polymer Syntheses. Poly(trimethylene carbonate) (PTMC) with a segmented functional unit was synthesized by a conventional bulk ring-opening polymerization.[20,21] A typical procedure using cholesterol as an initiator is as follows: A total of 2.04 g (20 mmol) of TMC and 0.039 g (0.2 mmol) of cholesterol were added to a round-bottom flask equipped with a magnetic stir bar. Tin(II) 2-ethyl hexanoate (10 μL of a toluene solution (0.33 mol/L)) was added, and the flask was evacuated with a vacuum pump for 1 h. After the removal of toluene, the flask was heated to 150 °C for 6 h. After cooling, the mixture was dissolved in chloroform and poured into an excess of methanol to obtain cholesterol-terminated PTMC, and the resulting product was abbreviated as Chol-PTMC100. The last three-digit number displays the molar ratio between TMC and the hydroxyl group in the feed. The composition of the obtained Chol-PTMC100 was confirmed by FT-IR, ^{1}H NMR, and GPC. Yield: 62%. IR (ATR, cm^{-1}): 1730 (C═O). ^{1}H NMR ($CDCl_3$, ppm): δ 1.00−1.50 (m, H, cholesterol), 2.05 (m, 2H, $-CH_2-$ in PTMC), 4.24 (t, 4H, $-OCH_2-$ in PTMC), 5.39 (s, 1H, CH═C in cholesterol). The number- and weight-average molecular weight were 22 900 and 32 900 g/mol, respectively, and the polydispersity (PDI) was 1.44.

The DP of PTMC was altered by adjusting the amount of initiator [I] to TMC [TMC]. In the case of mPEG8 and mPEG114, the synthetic procedure was slightly modified. The polymerization temperature and time were changed to 130 °C and 8 h, respectively. Also, the resulting polymer (mPEG114-PTMC) was recovered by centrifugation (9000 rpm × 20 min) after the reprecipitation. The overall synthetic route is illustrated in Scheme 1.

2.4. Preparation of PTMC-Based Reflexive Interfaces and Their Properties. PTMC-based coatings were prepared on poly(ethylene terephthalate) (PET) (Wako) or QCM substrates using the following procedure: The polymer to be coated was dissolved in chloroform to a final concentration of 0.5 or 1 wt % for PET and 0.2 wt % for QCM. The polymer was spin-coated using a Spin Coater 1H-7D (MIKASA) at 1500 rpm for 60 s.

The reflexive function was evaluated by the contact angle change in water. The polymer-coated substrate (PET) was immersed in ultrapure water at 37 °C. After a given time, the substrate was picked up and surplus water was removed by drying with N_2 gas. The static contact angle was then measured.

Polymer-coated QCM substrates were used to study the enzymatic degradation, and the change in the frequency shift was correlated to the weight loss using Sauerbrey's eq (1 Hz corresponds to 1.15 ng).[22] Polymer-coated QCM substrates were immersed in PBS lipase solutions at 37 °C. After a given time, the QCM substrate was rinsed in ultrapure water and then dried with N_2 gas. The frequency was monitored and plotted as a function of the degradation time. The PBS lipase solution was changed at intervals of 6 h to maintain its enzymatic activity.

Allura Red AC (AR, food additive dye, C.I. #16035, $\lambda_{max} = 504$ nm, solubility in water = 12 g/dL) and Basic Blue 7 (BB7, pigment, C.I. #42595, $\lambda_{max} = 616$ nm, solubility in water = 2 g/dL) were used to estimate dye adsorption properties. First, a stock solution of each dye (AR and BB7) was prepared in ultrapure water at a final concentration of 0.1 mg/mL. The stock solution was diluted by ultrapure water before use. PTMC-based polymer membranes were prepared by the solvent evaporation technique, and disks were punched out with a diameter of 10 mm. Disks were immersed into the dye solution in a cuvette at room temperature, and the UV−vis spectrum of the supernatant was monitored at given times.

3. Results and Discussion

3.1. Diversity of PTMC-Based Reflexive Polymers. Table 1 summarizes the synthetic results of PTMC-based polymers, which were polymerized by ROP in the presence of a tin(II) catalyst. Initiation was done from either cholesterol (Chol) or poly(ethylene glycol) monomethyl ether (mPEG). In the case of Chol-PTMC, the physical state at room temperature varied from a solid wax to a rubbery wax depending on the molecular weight. The number-average molecular weight as expected increased with the feed ratio of [TMC]/[I], and the PDI was in general around 1.5 for yields around 50%. A series of mPEG-PTMC were similar in terms of molecular weight changes and yields; however, mPEG8-PTMC100 was a viscous liquid because the molecular weight of the resulting polymer was low ($M_n \sim 10\,000$ g/mol). The physical state of mPEG8-PTMC200 changed to a solid rubber due to the higher molecular weight. mPEG114-PTMC100 was shown to dissolve or aggregate in methanol; presumably, this polymer matched the solvent affinity of methanol. Polymer aggregates were confirmed by the Tyndall phenomenon using a laser pointer; however, for higher molecular weights (mPEG114-PTMC400) the resulting polymers were recovered by precipitation in methanol. The aforementioned result indicates that the solvent affinity of the polymer decreased, and the polymer could form a precipitate.

Table 1. PTMC-Based Reflexive Copolymers

abbrev	feed ratio [TMC]/[I]	physical state at RT	mol wt[a] M_n	mol wt[a] M_w	mol wt[a] M_w/M_n	yield (%)
Chol-PTMC100	100	wax	22 900	32 900	1.44	62
Chol-PTMC200	200	solid (rubbery)	29 300	43 700	1.49	48
Chol-PTMC400	400	solid (rubbery)	35 500	55 100	1.55	62
mPEG8-PTMC100	100	viscous liquid	10 100	14 400	1.43	61
mPEG8-PTMC200	200	solid (rubbery)	32 700	50 600	1.55	74
mPEG8-PTMC400	400	solid (rubbery)	39 300	58 500	1.49	79
mPEG114-PTMC100	100	solid (rubbery)	23 400	31 900	1.36	[b]
mPEG114-PTMC200	200	solid (rubbery)	28 600	38 000	1.33	15
mPEG114-PTMC400	400	solid (rubbery)	36 200	53 500	1.48	70

[a] Determined by GPC in DMF with 10 mmol/L LiBr (polystyrene standard). M_n and M_w show number- and weight-average molecular weight, respectively. M_w/M_n is polydispersity. [b] The resulting polymer could not be recovered in methanol.

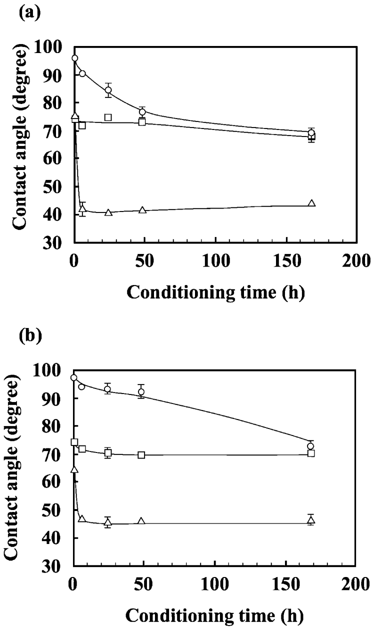


Figure 1. Static contact angle measurement of reflexive polymers incubated at 37 °C; repeating units of TMC were (a) 200 and (b) 400 in feed. Symbols show Chol-PTMC (○), mPEG8-PTMC (□), and mPEG114-PTMC (△). The polymer coating was carried out at the concentration of 1 wt %. Average value of five measurements and their standard deviation are indicated.

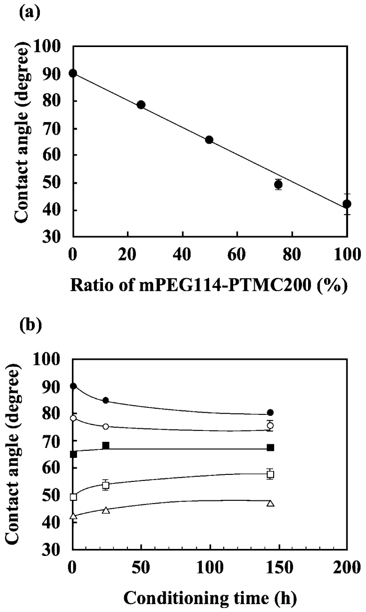


Figure 2. Changes in static contact angle by polymer blending. Chol-PTMC200 and mPEG114-PTMC200 were blended in chloroform, and final polymer concentration was 0.5 wt %. The polymer-coated substrates were incubated at RT: (a) ratio of mPEG114-PTMC and by (b) conditioning time. mPEG114-PTMC200 content was 0 (●), 25 (○), 50 (■), 75 (□), and 100 (△). Average value of five measurements and their standard deviation are indicated.

3.2. Reflexive Function by Static Contact Angle Measurements. Figure 1 displays changes in the static contact angle of PTMC-based polymers when immersed in water. In general, the outermost surface of the polymer rearranges to reduce the surface free energy. In the case of mPEG114-PTMC200 (Figure 1a), the initial contact angle was roughly 75°, and immediately following water immersion the contact angle reduced to 42°. The time to reach the complete surface rearrangement was 5 h. The rearranged surface was found to maintain its surface wettability, indicating that the mPEG114 segment was enriched at the outermost surface. The effect of the chain length of mPEG was noticeably observed. The initial contact angle of mPEG8-PTMC200 roughly showed 74°, and the contact angle did not change by water conditioning. The static contact angle of the PTMC homopolymer was measured to be 70°; thus, the mPEG8 segment could not efficiently wet the surface. In fact, the reason for higher contact angles on mPEG114-PTMC200 and mPEG8-PTMC200 relative to pure PTMC was not clear; coating conditions and the resulting surface roughness may play a role in the higher contact angles. On the other hand, Chol-PTMC200 showed a change in wettability. The initial contact angle of 90° was reduced to 70° when the polymer was immersed in water. The previous result suggests that the cholesterol, in air, is enriched at the outermost surface layer and in water migrates to the bulk polymer. The surface layer is now instead enriched with PTMC, which provides a lower surface free energy in water than in cholesterol.

To further investigate surface rearrangements, the DP of PTMC was changed as shown in Figure 1b. The typical trend was similar to Figure 1a; however, the time to allow surface rearrangement was found to increase with molecular weight. In particular, Chol-PTMC400 displayed a slow change in the contact angle during an incubation for 150 h. Moreover, the final contact angle in mPEG114-PTMC400 was around 45°, which was slightly higher than that of mPEG114-PTMC200. This result indicates that PTMC entanglements suppress its reflexive function and that lower molecular weights, Chol-PTMC200 and mPEG114-PTMC200, have a more spontaneous rearrangement.

To further regulate surface wettability, Chol-PTMC200 and mPEG114-PTMC200 were blended at a given ratio, and the final polymer concentration was 0.5 wt % using chloroform. Figure 2a shows the change in the contact angle of polymer blend surfaces. The contact angle correlates with the blend ratio. These results indicate that the static contact angle could be tuned

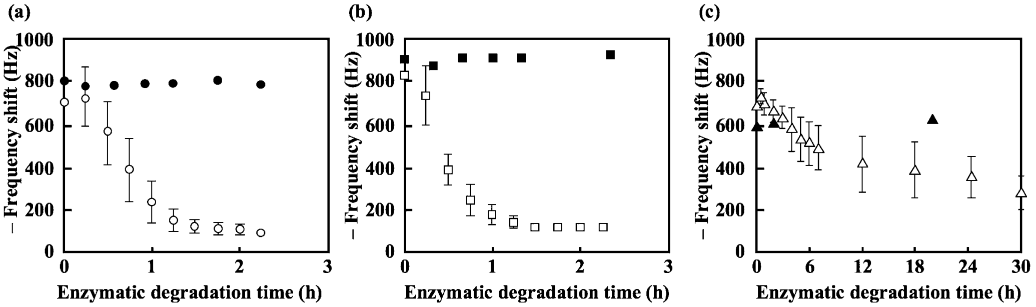


Figure 3. Enzymatic degradation of reflexive polymers was monitored by quartz crystal microbalance. The change in frequency was plotted as a function of degradation time. Open symbol shows Chol-PTMC400 (○), mPEG-PTMC400 (□), and mPEG114-PTMC400 (△). Each closed symbol shows a reference without lipase. The polymer coating was carried out at the concentration of 0.2 wt %. Average value of three measurements and their standard deviation are indicated.

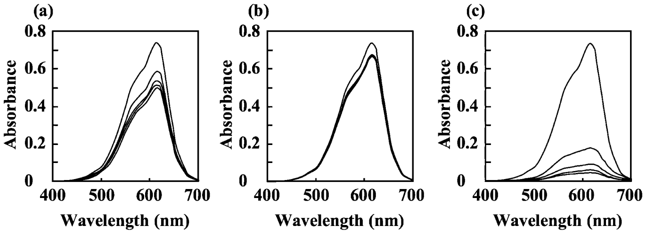


Figure 4. Basic Blue7 as a model dye absorption in reflexive polymer membranes: (a) Chol-PTMC400, (b) mPEG8-PTMC400, and (c) mPEG114-PTMC400. The initial dye solution was prepared by mixing the stock solution of Basic Blue7 (250 μL) and ultrapure water (750 μL). The spectra of Basic Blue7 dye in cuvettes were monitored at 0, 1, 12, 24, and 48 h from the top spectrum.

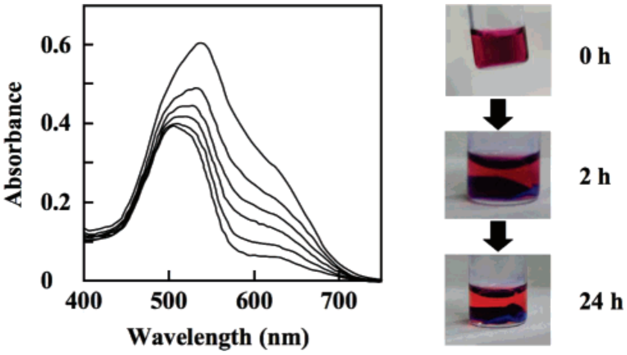


Figure 5. Selective adsorption in mPEG114-PTMC400. The initial dye solution was prepared by mixing the stock solutions of Allura Red (250 μL) and Basic Blue7 (500 μL) dyes and ultrapure water (1750 μL). The spectra were monitored at 0, 1, 2, 4, 7, and 12 days from the top spectrum. The typical photos were take after 24 h, which initial dye solution was prepared by mixing of the stock solutions of Allura Red (250 μL) and Basic Blue 7 (250 μL).

by changing the blend ratio to obtain final contact angles between 40° and 90°. Figure 2b shows water conditioning of the polymer blend, and the rearrangement was stabilized within 50 h as described above, yielding final contact angles with an average of a 10° change.

3.3. Reflexive Functions by Enzymatic Degradation. The reflexive function was further investigated by studying enzymatic degradation on QCM substrates and specifically observing the weight change of membranes with or without lipase. The change in frequency after polymer coating was roughly 800 Hz, showing a 15 nm thickness, and the polymer layer was considered to have multilayers. Shown in Figure 3 is the change in frequency shift plotted as a function of degradation time. In the case of Chol-PTMC400, the frequency immediately decreased within 1 h after which the frequency change stabilized. As a reference, the same PTMC-based polymer membrane was not degraded in a PBS solution without lipase as the frequency was constant at 800 Hz for 2 h. The previous result indicates that lipase is essential for the degradation of Chol-PTMC400 and that the time required to reach complete degradation was 2 h. In general, degradation of polymers occurs either from the surface or from the bulk,[1] and PTMC has been shown to undergo surface erosion in lipase solutions.[23,24] Particularly, higher repeating TMC units (over 100) could not be degraded in aqueous media, if lipase was not added. The PTMC could be easily degraded in the presence of lipase via surface erosion. In our study, the degradation depends on the molecular weight of PTMC and was shown to degrade with a surface erosion type mechanism. Figure 3b shows the result of mPEG8-PTMC400, and the frequency was shown to decrease with increasing degradation times. Additionally, the degradation profile was similar to Chol-PTMC400. On the other hand, mPEG114-PTMC400 showed a different degradation profile (Figure 3c). Now, the degradation time was delayed until 24 h, and the total amount of degraded membrane was slightly lower than that of mPEG8-PTMC400, suggesting a durable mPEG114-PTMC400 surface. We explain the different behaviors with the increased hydrophilic segment by mPEG114 such that enzymatic degradation is suppressed due to the enzyme's lower accessibility to the membrane. Taking the results into account, PTMC-based polymers showed reflexive functions based on terminal functional units.

3.4. Selective Adsorption Properties Using Dyes. So far, PTMC-based polymers showed diverse surface wet abilities also reflecting their respective enzymatic degradation. The next question was whether these polymers could act as temporary reservoirs for drugs, thereby increasing their use as biomaterials. In this study, basic blue 7 (BB7) was used as a hydrophobic model drug. Figure 4 shows changes in absorbance of the supernatant in mixtures with PTMC-based polymer membranes, and the maximum absorption of BB7 is observed at 616 nm. In the case of Chol-PTMC400, the spectrum changed after mixing the membrane and the dye. The change in adsorption was significantly observed within 1 h; however, the effect of the adsorption was saturated after 1 h. Although Chol-PTMC400 showed a hydrophobic surface, the total amount of adsorbed BB7 was low. On the other hand, mPEG8-PTMC400 could not adsorb the BB7 dye on the surface. This spectrum only changed initially but remained constant for a total incubation time exceeding 48 h. Interestingly, mPEG114-PTMC400 showed a quick and complete adsorption (Figure 4c). Moreover, the time to reach the complete adsorption was strongly dependent on the total amount of solution. The data shown in Figure 4 were obtained with a total volume of 1 mL. The anomalous adsorption demonstrated the drug loading capability in spite of the hydrophobic nature of the drug. The surface of mPEG114-

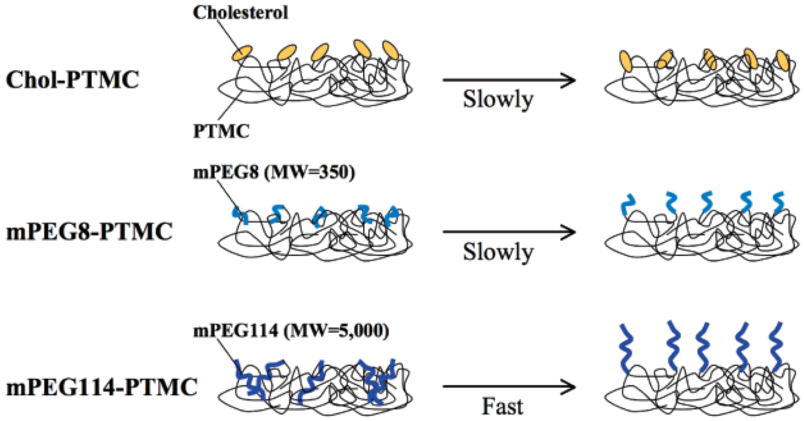


Figure 6. Schematic illustration of reflexive polymer interfaces from dry state to water environment. Repeating unit of PTMC was 400 as one of the typical compositions. The molecular rearrangement and its surface enrichment were spontaneously formed to reduce surface free energy.

PTMC is enriched with mPEG114, thereby increasing the interfacial affinity between the membrane surface and the dye solution. In general, hydrophobic dye adsorption on substrates from media is regulated by partition and diffusion coefficients. Particularly, the partition coefficient is crucial to solid−liquid interfaces. In the present study, mPEG114-PTMC provided a good interface, with a major mPEG segment, and mPEG segments acted as bridges between polymeric substrates and dye solution. A similar dye, methylene blue (basic blue 9, solubility in water = 3.5 g/dL), could not significantly be adsorbed in mPEG114-PTMC400. The methylene blue is a little bit hydrophilic in comparison with BB7. Taking this into account, the hydrophobicity plays an important role. The hydrophobic dyes stained whole part of the polymer, so the precise location could not be distinguished. However, this effect is reduced in mPEG8-PTMC400. We conclude that the chain length of the mPEG segment is the dominant factor for interface stabilization in an aqueous solution. Hilborn et al. reported that ionomers with PTMC backbones could form spontaneous routes for water intrusion.[10] Moreover, the prepared porous structure could be applicable for the loading and release of drugs. In this study, we could not observe the release of the loaded dye from the membrane. The lower release function was regulated by the partition coefficient of the BB7 dye.

We also investigated the selective adsorption from mixtures of hydrophobic (BB7) and hydrophilic (Allura Red (AR)) dyes, whose concentrations were almost the same. The maximum absorption wavelength of each dye was 616 and 504 nm, respectively. In the presentation, the initial spectrum was overlaid, and Figure 5 shows typical spectra from the selective adsorption in a total volume of 2.5 mL. The spectrum was immediately changed, and the absorbance at 616 nm was attributed to BB7. In mPEG114-PTMC400, BB7 was preferentially adsorbed and disappeared from the supernatant after 12 days. On the other hand, if the mPEG114-PTMC200 was used, the adsorption ratio would be enhanced as imagined from Figure 1. Moreover, Chol-PTMC400 and mPEG8-PTMC400 could not adsorb dyes as shown in Figure 4a,b. AR spectra remained stable throughout the experiment. The selective adsorption could also be observed visually as the color of the supernatant changed to red (AR) as BB7 was adsorbed (total volume of 0.5 mL). The results suggest that PTMC-based polymers may provide a reservoir for poorly water-soluble drugs.

Figure 6 summarizes the postulated mechanism on the actions that take place on the PTMC-based polymer surface when immersed in water. In all cases (Chol-, mPEG8-, and mPEG114-PTMC), the polymer-coated surface spontaneously rearranges to reduce the surface free energy. In the case of mPEG114-PTMC, the surface rearrangement was particularly fast, and the response was quick when introduced to water. Furthermore, the resulting mPEG114-PTMC provided resistance to enzymatic degradation and preferential adsorption of poorly water-soluble drugs. Taking these results into account, the mPEG114 segment stabilizes the polymer−water interface. Further investigations and anomalous properties will be reported in forthcoming papers.

4. Conclusions

Reflexive functions of PTMC-based polymers were presented investigating surface wettabilities, enzymatic degradation, and selective adsorption. PTMC-based polymers were synthesized by the ring-opening polymerization of trimethylene carbonate using either cholesterol or poly(ethylene glycol) monomethyl ether as initiators. The use of an mPEG with a $M_n \sim 5000$ g/mol was efficient to induce a rapid reflexive function. The surface enrichment of the hydrophilic segment followed immediately after immersion into water to reduce the surface free energy. The time to reach a complete surface enrichment is affected not only by the polymer's molecular weight but also by the functional terminal unit. Future studies will involve polymeric designs that enhance reflexive functions.

Acknowledgment. Part of this study was financially supported by a Grant-in-Aid for the 21st Century COE Program "Center for Integrated Cell and Tissue Regulation" from The Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Drs. T. Kida, M. Matsusaki, and H. Ajiro, Osaka University, for their helpful discussions.

References and Notes

(1) Pitt, C. G.; Hendren, R. W.; Schindler, A.; Woodward, S. C. *J. Controlled Release* **1984**, *1*, 3−14.
(2) Zhu, K. J.; Hendren, R. W.; Jensen, K.; Pitt, C. G. *Macromolecules* **1991**, *24*, 1736−1740.
(3) Tsutsumi, C.; Nakagawa, K.; Shirahama, H.; Yasuda, H. *Macromol. Biosci.* **2002**, *2*, 223−232.
(4) Yasuda, H.; Aludin, M.-H.; Kitamura, N.; Tanabe, M.; Shirahama, H. *Macromolecules* **1999**, *32*, 6047−6057.
(5) Matsuda, T.; Kwon, I.-K.; Kidoaki, S. *Biomacromolecules* **2004**, *5*, 295−305.
(6) Vandermeulen, G.; Rouxhet, L.; Arien, A.; Brewster, M. E.; Préat, V. *Int. J. Pharm.* **2006**, *309*, 234−240.
(7) Dinarvand, R.; Alimorad, M. M.; Amanlou, M.; Akbari, H. *J. Biomed. Mater. Res.* **2005**, *75A*, 185−191.
(8) Dankers, P. Y. W.; Zhang, Z.; Wisse, E.; Grijpma, D. W.; Sijbesma, R. P.; Feijen, J.; Meijer, E. W. *Macromolecules* **2006**, *39*, 8763−8771.

(9) Nederberg, F.; Bowden, T.; Nilsson, B.; Hong, J.; Hilborn, J. *J. Am. Chem. Soc.* **2004**, *126*, 15350−15351.

(10) Atthoff, B.; Nederberg, F.; Söderberg, L.; Hilborn, J.; Bowden, T. *Biomacromolecules* **2006**, *7*, 2401−2406.

(11) Nederberg, F.; Bowden, T.; Hilborn, J. *Macromolecules* **2004**, *37*, 954−965.

(12) Nederberg, F.; Watanabe, J.; Ishihara, K.; Hilborn, J.; Bowden, T. *Biomacromolecules* **2005**, *6*, 3088−3094.

(13) Yui, N.; Mrsny, R. J.; Park, K. In *Reflexive Polymers and Hydrogels: Understanding and Designing Fast Responsive Polymeric Systems*; CRC Press: Boca Raton, FL, 2004.

(14) Yoshida, R.; Uchida, K.; Kaneko, Y.; Sakai, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Nature (London)* **1995**, *374*, 240−242.

(15) Kaneko, T.; Asoh, T.; Fukushige, Y.; Akashi, M. *Macromolecules* **2006**, *39*, 2298−2305.

(16) Decher, G. *Science* **1997**, *277*, 1232−1237.

(17) Serizawa, T.; Arikawa, Y.; Hamada, K.-I.; Yamashita, H.; Fujiwara, T.; Kimura, Y.; Akashi, M. *Macromolecules* **2003**, *36*, 1762−1765.

(18) Serizawa, T.; Hamada, K.-I.; Akashi, M. *Nature (London)* **2004**, *429*, 52−55.

(19) Otsuka, H.; Nagasaki, Y.; Kataoka, K. *Langmuir* **2004**, *20*, 11285−11287.

(20) Zou, T.; Li, F.; Cheng, S.-X.; Zhuo, R.-X. *J. Biomater. Sci., Polym. Ed.* **2006**, *17*, 1093−1106.

(21) Ould-Ouali, L.; Ariën, A.; Rosenblatt, J.; Nathan, A.; Twaddle, P.; Matalenas, T.; Borgia, M.; Arnold, S.; Leroy, D.; Dinguizli, M.; Rouxhet, L, Brewster, M.; Préat, V. *Pharm. Res.* **2004**, *21*, 1581−1590.

(22) Sauerbrey, G. *Z. Phys* **1959**, *155*, 206.

(23) Pêgo, A. P.; Poot, A. A.; Grijpma, D. W.; Feijen, J. *J. Macromol. Biosci.* **2002**, *2*, 411−419.

(24) Zhang, Z.; Kuijer, T.; Bulstra, S. K.; Grijpma, D. W.; Feijen, J. *Biomaterials* **2006**, *27*, 1741−1748.

MA071030Q