(19) Allen, R. D. Ph.D. Dissertation, Virginia Polytechnic Institute, Blacksburg, VA, 1985.
(20) Rudin, A. *The Elements of Polymer Science and Engineering*; Academic: New York, 1982; p 402.
(21) Grassie, N.; Melville, H. W. *Proc. R. Soc. London A*, **1949**, *199*, 24.
(22) Caciolo, P.; Mood, G.; Rizzardo, E.; Serelis, A. K.; Solomon, D. H. *Polym. Bull. (Berlin)* **1984**, *11*, 325.

Functional Capsule Membranes. 26.[1] Permeability Control of Polymer-Grafted Capsule Membranes Responding to Ambient pH Changes[2]

Yoshio Okahata,* Hiroshi Noguchi, and Takahiro Seki

Department of Polymer Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan. *Received April 2, 1986*

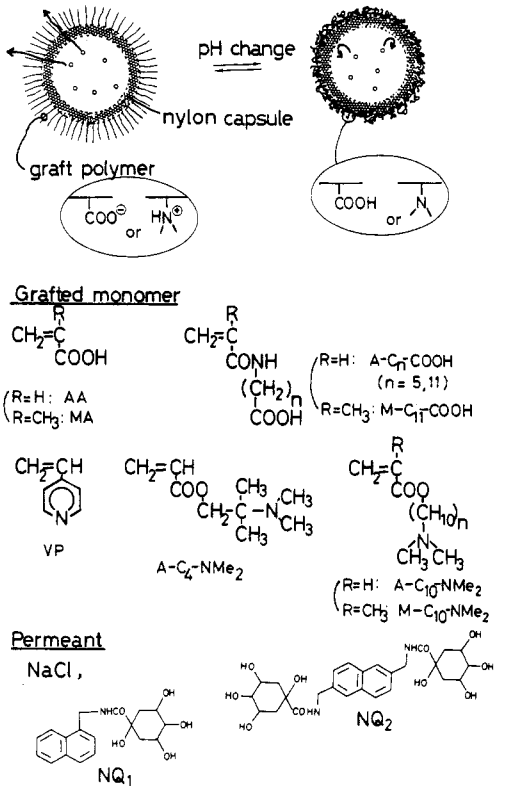
ABSTRACT: Large, ultrathin nylon capsule membranes were grafted with various kinds of polymers having dissociative side chains. The permeability of NaCl and large dyes stored in the inner aqueous core of the capsule could be reversibly controlled by pH changes of the outer medium. The pH dependence of the permeation rate and direct X-ray photoelectron spectroscopic analysis of the capsule surface confirmed that the graft-polymer chains acted as permeation valves where their conformation was changed in response to the dissociation of side chains by an ambient pH. Effects of the hydrophobic nature of the graft polymer, the amount of the graft polymer, and the molecular size of the permeant were also studied.

Introduction

Permeation behavior of microcapsules has been studied extensively because of its importance in designing and constructing sustained drug release devices and artificial cells.[3-5] Despite its potential usefulness, the chemical modification of and permeability control of the capsule membrane have not been fully explored. Capsule membranes are semipermeable and therefore have the disadvantage that they cannot store water-soluble small substances in the inner aqueous core. Conversely utilizing the disadvantage of the porous membrane, Chang and coworkers described the use of a capsule membrane for a model of an artificial cell by entrapping a large enzyme in the inner aqueous phase.[3,6,7] We have developed a nylon capsule whose porous membrane was corked with synthetic lipid bilayers.[8] Permeation of entrapped small substances was decreased very much and reversibly controlled by outside effects such as temperature,[9-11] photoirradiation,[12] and electric field.[13] Their signal-receptive permeability control could be explained by changes in the physical state (molecular packing or orientation) of corking bilayers, which act as a permeation valve.

In this paper, we report that a porous nylon capsule membrane with surface-grafted polyelectrolytes can be used as a pH-sensitive capsule, whose permeability is reversibly regulated by pH changes of the outer medium. We expect the graft polymers to act as permeation valves by changing their conformation in response to ambient pH changes. A schematic illustration of the capsule and structures of grafted monomers and permeants are shown in Scheme I. Acrylic acid (AA), methacrylic acid (MA), and vinyl monomers having a spacer alkyl chain and a carboxylic acid group (A–C_n–COOH (n = 5 and 11) and M–C_{11}–COOH) were selected as graft monomers having carboxylic acid side chains. For the tertiary amino group containing monomers, 4-vinylpyridine (VP) and vinyl monomers having a spacer alkyl chain and a dimethylamino group (A–C_n–NMe_2 (n = 4 and 10) and M–C_{10}–NMe_2) were used. NaCl and large, freely water-soluble

Scheme I



naphthalene molecules (NQ_1 and NQ_2) were used as permeants.

Experimental Section

Materials. 4-Vinylpyridine (VP), acrylic acid (AA), and methacrylic acid (MA) were commercially available (Tokyo Kasei, Japan) and used after distillation.

Vinyl monomers containing a carboxylic acid, ω-(acryloylamino)alkanoic acid (A–C_n–COOH, n = 5, 11) and ω-(methacryloylamino)dodecanoic acid (M–C_{11}–COOH), were prepared

0024-9297/87/2220-0015$01.50/0

Table I
Graft Polymerization onto Nylon Capsule Membranes[a]

monomer	concn, g/15 mL	characterization of grafted polymers: amt, μg per capsule: weighing method[b]	titration method[c]	mol wt[d]	D_p[a]
AA	0.2	3	3	5×10^4	6×10^2
	0.5	8	9		
	1.0	20	18		
	2.0	42	44	6×10^4	8×10^2
MA	0.2	6	8		
	0.5	12	14		
	1.0	42	42		
	2.0	77	70	8×10^4	9×10^2
A–C_5–COOH	1.0	43	40		
A–C_{11}–COOH	0.2	3	4	5×10^4	3×10^2
	0.5	8	7		
	1.0	23	26		
	2.0	44	40		
M–C_{11}–COOH	2.0	40	43	8×10^4	3×10^2
VP	0.2	7	8		
	0.5	14	14		
	1.0	40	40	8×10^4	8×10^2
	2.0	55	58		
A–C_4–NMe_2	1.0	40	45	6×10^4	4×10^2
A–C_{10}–NMe_2	2.0	43	43		
M–C_{10}–NMe_2	0.5	4	3		
	1.0	23	27		
	2.0	38	40	8×10^4	3×10^2

[a] The respective monomer was graft polymerized in H_2O and/or THF solution (15 mL) onto EDM-grafted nylon capsule membranes. Initiator: potassium persulfate (50 mg) and sodium hydrogen sulfite (20 mg), at room temperature for 4 h. [b] Capsules were weighed before and after polymerization. [c] Grafted polymers were titrated by acid or base in aqueous solution. [d] Average molecular weight was obtained by gel-permeation chromatography (standard: poly(ethylene oxide)).

from acryloyl chloride or methacryloyl chloride and the respective ω-aminoalkanoic acid in chloroform at room temperature for 12 h in the presence of triethylamine. A–C_5–COOH: yield 6.9 g (49%); mp 78–80 °C. A–C_{11}–COOH: yield 7.0 g (47%); mp 95–96 °C. M–C_{11}–COOH: yield 3.0 g (57%); mp 63–65 °C.

Vinyl monomers containing a tertiary amino group, 2-(dimethylamino)-2-methylisopropyl acrylate (A–C_4–COOH), ω-(dimethylamino)decyl acrylate (A–C_{10}–NMe_2), and ω-(dimethylamino)decyl methacrylate (M–C_{10}–NMe_2), were prepared from acryloyl chloride or methacryloyl chloride and the respective (dimethylamino)alkyl alcohol in chloroform at room temperature for 12 h in the presence of triethylamine. A–C_4–NMe_2: yield 18 g (71%); bp 50–54 °C (0.4 mmHg); A–C_{10}–NMe_2: yield 4.6 g (56%); bp 125–130 °C (0.6 mmHg); M–C_{10}–NMe_2: yield 4.9 g (51%); bp 130–140 °C (0.2 mmHg).

The structure and purity of all monomers were confirmed by NMR spectra, thin-layer chromatography with a flame-ionization detector, gas chromatography, and elemental analysis (C, H, N).

Preparations of fully water-soluble naphthalene molecules, 1-(quinamidomethyl)naphthalene (NQ_1) and 2,6-bis(quinamidomethyl)naphthalene (NQ_2), are reported elsewhere.[11]

Capsule Membranes. Large nylon-2,12 capsule membranes (2.5-mm diameter, 5 μm thick) were obtained from ethylenediamine and 1,10-bis(chlorocarbonyl)decane by interfacial polymerization according to previous papers.[8-13] Graft polymerization of vinyl monomers onto the capsule membrane was carried out as follows. In order to introduce vinyl groups onto the capsule membrane, capsules were soaked for 30 min at room temperature in a tetrahydrofuran (THF) solution (25 mL) of cerium(IV) ammonium nitrate (0.5 g) and ethylene glycol dimethacrylate (EDM, 1.0 g). The amount of EDM introduced was estimated to be 1–2 μg per capsule. The dry weight of a capsule was 20 ± 2 μg. The capsules were grafted with the respective vinyl monomer (0.2–2.0 g) in an aqueous and/or tetrahydrofuran solution (15 mL) in the presence of a redox radical initiator (50 mg of potassium persulfate and 20 mg of sodium hydrogen sulfite) at room temperature for 4 h under nitrogen. The capsules were washed with an excess of water or acetone to remove nongrafted polymers and unreacted monomers. The amount of grafted polymers could be controlled by the monomer concentration in the polymerization (see Table I).

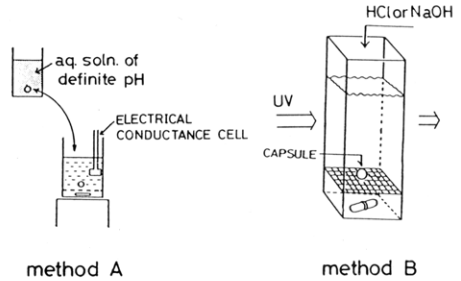


Figure 1. Apparatus for permeation measurements. NaCl permeation was detected by electrical conductance, and pH changes were carried out by dipping in a buffer solution (0.01 M) containing 0.2 M NaCl for 1 min (method A). Permeation of NQ_1 and NQ_2 was followed spectrophotometrically, and the pH of the outer medium was directly changed by the addition of acid or alkali (method B).

The capsules were dialyzed for 2–3 days against an aqueous solution of the respective permeant (0.2 M NaCl, 1 mM NQ_1, or 1 mM NQ_2) to give capsules containing permeants in the inner aqueous core.

Characterization of Capsule Membranes. The nylon capsule membrane had an asymmetrical structure with a large number of pores: the highly dense and very thin inner layer (thickness <1 μm, pore diameter 1–2 nm) and the macroporous thick part of the outside (thickness 4–5 μm, pore diameter 0.1–0.3 μm).[15] These pores arise naturally during the formation of the capsule membrane by the interfacial polymerization. The nylon capsule had small amounts of residual COOH and NH_2 end groups (ca. 1×10^{-4} equiv/g) by acid–base titration.[15,16] In order to avoid the effect of ionization on permeation experiments, the residual end groups were converted to $COOCH_3$ and $NHCOCH_3$ groups by methyl esterification and acetylation, respectively.

The characterization of the graft polymer was studied after complete hydrolysis of nylon capsule membranes under strong acidic conditions at 60 °C for 1 day. The residual graft polymer was analyzed by gel-permeation chromatography (column: TSK-GEL G-6000PW, Toyo Soda Co. Ltd., Tokyo; eluent: 0.2 M phosphate buffer (pH 6.8) + 20% CH_3CN). The average molecular weight of the graft polymer was estimated to be 50 000–80 000 (D_p = 300–800) [standard: poly(ethylene oxide)]. The graft amount of polymers was changed by varying monomer concentrations and determined by two methods: the weight of capsules before and after graft polymerization, and acid–base titration of the grafted polyelectrolyte. The amounts obtained from the two methods show satisfactory agreement. The results are summarized in Table I.

The surface structure of the polymer-grafted capsule membrane was analyzed by X-ray photoelectron spectroscopy (XPS). The capsule was soaked in acidic (pH 2) or alkaline (pH 12) solution for 1 min and crushed on filter paper. The surface of the capsule membrane was analyzed by XPS (instrument: ESCA 750, Shimadzu Co., Ltd., Kyoto) and the N_{1s}/O_{1s} elemental ratio was obtained.

Permeation Measurements. Permeation of NaCl from inside the capsule membrane was followed by detecting increases in the electrical conductance in the outer water phase after a capsule was dropped into the distilled water of the permeation cell (see method A in Figure 1). pH changes in the outer medium were effected as follows: the capsule was removed from the cell, immersed in a solution of definite pH for 1 min, and then returned to the cell. The dipping solution was buffered by 0.01 M acetate (pH 3–5)–Tris (pH 6–8)–phosphate (pH 8–10) and contained 0.2 M NaCl in order to prevent the release of NaCl from inside the capsule during immersion.

Permeation of water-soluble naphthalene molecules (NQ_1 and NQ_2) was followed by detecting increases in the absorbance at 220 or 227 nm, respectively, in the outer aqueous phase (method B in Figure 1). pH values of the outer medium were directly changed by the addition of aliquots of 1 M HCl and 1 M NaOH

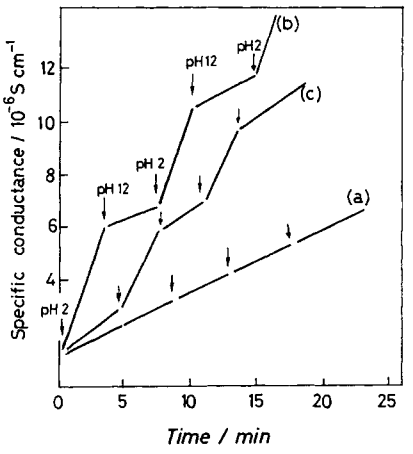


Figure 2. pH-sensitive permeation of NaCl responding to ambient pH changes at 25 °C. The capsule was alternately dipped in an aqueous solution of pH 2 or pH 12 (arrows): (a) ungrafted capsule; (b) PVP-grafted capsule; (c) PMA-grafted capsule.

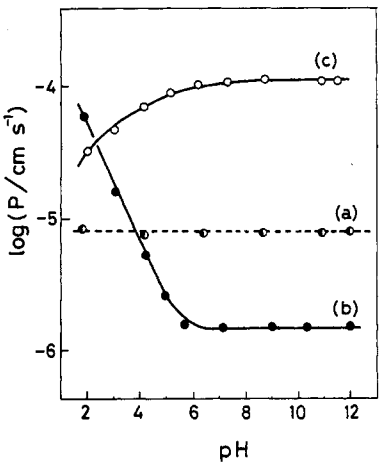


Figure 3. pH–rate profiles of NaCl permeation at 25 °C (acetate, Tris, phosphate buffer was used (0.01 M)): (a) ungrafted capsule; (b) PVP-grafted capsule; (c) PMA-grafted capsule.

or by the use of a 0.01 M buffer solution (acetate (pH 3–5)–Tris (pH 6–8)–phosphate (pH 8–10)).

Apparent permeation rates, P (cm s^{-1}), were calculated from the initial slope of the increase of the electrical conductance or the absorbance using the equation[8-13]

$$P = \frac{1}{6}\frac{kd}{C_0} \quad (1)$$

where k and d are the initial slope of a permeant release and the capsule diameter (2.5 mm), respectively. C_0 denotes the change of the electrical conductance or the absorbance after the capsule was crushed, which means the concentration of permeants stored in the inner aqueous phase. Permeation measurements were carried out at least in triplicate under the individual conditions and gave good reproducibility. The P values in the tables and figures are the average of three data points and contain an experimental error of ±5%.

Results and Discussion

pH-Sensitive Permeation of NaCl. The effect of ambient pH on NaCl permeation from the inside of the capsule was studied. Figure 2 shows reversible changes in the permeation of NaCl when the polymer-grafted capsule was alternately dipped in an aqueous solution of pH 2 or pH 12 containing 0.2 M NaCl as shown in method A in Figure 1. In the case of the ungrafted original capsule membrane, the permeation was not affected by an ambient pH change of pH to 2 or 12.

When the capsule grafted with 40 μg of poly(vinylpyridine) (PVP) was soaked in acidic solution (pH 2), NaCl permeation was very fast. When the PVP-grafted capsule was dipped into basic solution (pH 12), the permeability was immediately decreased by a factor of 16 but reverted to the same fast rate when the capsule was returned to the solution of pH 2. In the case of the capsule grafted with 42 μg of poly(methacrylic acid) (PMA) the reverse occurred: the permeability was reduced in the acidic medium (pH 2) and increased in the basic medium (pH 12), and the magnitude of variations in permeability with changes in pH was not as large as those in the PVP-grafted capsule. This permeability regulation of the polymer-grafted capsules in response to pH changes could be reproduced repeatedly without damaging the capsule.

Figure 3 shows pH–rate profiles of the NaCl permeation. The PVP-grafted capsule membrane formed a high barrier to NaCl permeation in the neutral pyridine form of the grafted polymer (above pH 7), but not in the cationic pyridinium form (below pH 6), relative to that of the ungrafted capsule. The permeability of the PMA-grafted capsule was decreased when the polymer was in the neutral carboxylic acid form (below pH 5) and increased for the anionic carboxylate form (above pH 6). The permeability of the ungrafted original capsule did not change over the whole pH 2–12 range.

The pH–rate profiles clearly show that ionization of the graft polymers on the capsule membrane plays an important role in the observed pH-sensitive permeation. When the graft polymer is in the ionized form (cationic PVP below pH 6; anionic PMA above pH 6), the polymer chains may be repelled by charge repulsions between ionic side chains or by hydrophilic properties, and NaCl would then permeate smoothly through the charged, hydrophilic, and swelled membrane relative to the ungrafted capsule, as shown on the left-hand side of Scheme I. On the other hand, when the graft polymer is in the neutral form (PVP above pH 7; PMA below pH 5), the relatively hydrophobic, entangled polymer covers the porous membrane, and NaCl permeation is significantly reduced (see the right-hand side of Scheme I). The graft polymers act as a permeation valve on the capsule membrane by changing their conformation in response to pH changes in the outer medium.

The magnitude of pH-sensitive permeation changes of the PMA-grafted capsule was not as large as those of the PVP-grafted capsule. The effect of the hydrophobic nature of the graft polymer on the permeation change will be discussed later.

XPS Analyses of Capsule Membrane Surfaces. An attempt was made to directly analyze by XPS the conformational change of graft polymers on the capsule membrane by pH changes. The polymer-grafted capsule was soaked in acidic (pH 2) or alkaline (pH 12) solution for 1 min, crushed on filter paper, and dried. XPS spectra of the surface of ungrafted and PVP-grafted capsule membranes are shown in Figure 4 as typical examples. The spectra were obtained at the take-off angle (θ) of 90°, which corresponds to a probing depth of 3–6 nm. The observed peaks include those of C_{1s} (not shown), N_{1s}, and O_{1s}. The N/O elemental ratio was determined from the area ratio of the N_{1s} and O_{1s} peaks after correction for the relative photoelectron signal intensity and is summarized in Table II together with results for the PMA-grafted capsule.

The N/O ratio of the original capsule was 0.35, which roughly corresponds to the composition of nylon-2,12 membrane independent of the pH value of the dipping solution. The PVP-grafted capsule showed N/O = 0.31 after being treated in acidic solution. When the PVP-

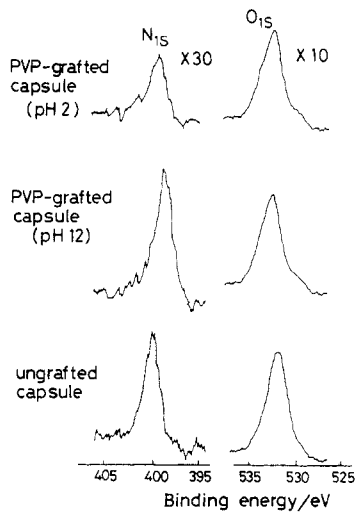


Figure 4. X-ray photoelectron spectra of the surface of capsule membranes. Take-off angle of photoelectron is 90°. The surface of the PVP-grafted capsule was analyzed in the dry state after dipping in the aqueous solution of pH 2 or pH 12 for 1 min. The spectra of the ungrafted capsule were not changed by pH.

Table II
Elemental Ratios of Surfaces of Capsule Membranes

capsule	N_{1s}/O_{1s}[a] pH 2[b]	pH 12[b]
ungrafted	0.35	0.35
PVP grafted[c]	0.31	0.41
PMA grafted[d]	0.071	0.12

[a] Calculated from peak areas of XPS spectra after correction for the relative photoelectron signal intensity. [b] The capsule was soaked in a pH 2 or pH 12 solution, and XPS spectra were obtained in the dry state. [c] Graft amount: 7–8 μg per capsule. [d] Graft amount: 42 μg per capsule.

grafted capsule was soaked in pH 12 solution, the N/O ratio increased from 0.31 to 0.41. This indicates that PVP polymers containing N but not O cover the membrane surface at pH 12 relative to pH 2. In the case of the PMA-grafted capsule, the N/O ratio decreased after treatment at pH 2 relative to that at pH 12. Thus, the decrease of the N/O ratio suggests that PMA polymers containing O but not N cover the surface of the capsule membrane in the neutralized form at pH 2. Although the XPS results show the surface structure in the dry state and do not reflect directly the membrane surface in the solution, they seem to well reflect the results of pH-sensitive permeations due to the conformational change of the graft polymer on the capsule membrane responding to ambient pH (see Scheme I).

Arrhenius Plots of NaCl Permeation. Figure 5 shows Arrhenius plots of NaCl permeation across the PVP-grafted capsule membrane at pH 2 and 12 together with that of the ungrafted capsule. The activation energy (E_a, kcal mol^{-1}) obtained from Arrhenius slopes is also included in the figure. The E_a values of NaCl permeation through the PVP-grafted capsule at pH 12 (18 kcal mol^{-1}) and at pH 2 (3.7 kcal mol^{-1}) were larger and smaller than that of the ungrafted capsule (E_a = 10 kcal mol^{-1}), respectively. Thus, NaCl can permeate smoothly through the hydrophilic, swelled membrane grafted with ionized PVP polymers with a small E_a value relative to the ungrafted capsule. On the contrary, it is difficult to diffuse and permeate through the hydrophobic capsule membrane covered with neutralized PVP polymers, and a large E_a value is given. A similar tendency of E_a values responding to pH changes was also observed in the PMA-grafted capsule membrane.

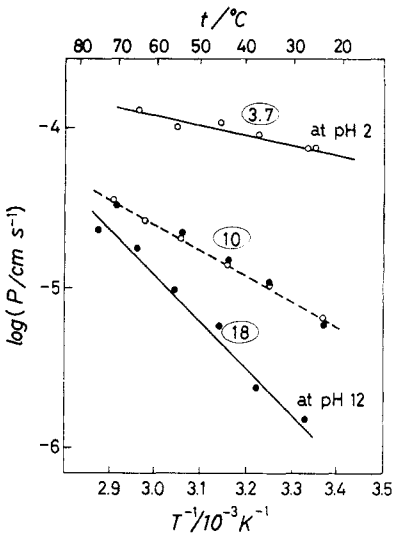


Figure 5. Arrhenius plots of NaCl permeation from the PVP-grafted capsule membrane. A dashed line shows the Arrhenius plot of the ungrafted capsule. Numbers in the figure are activation energies (E_a) in kcal mol^{-1} obtained from the slope.

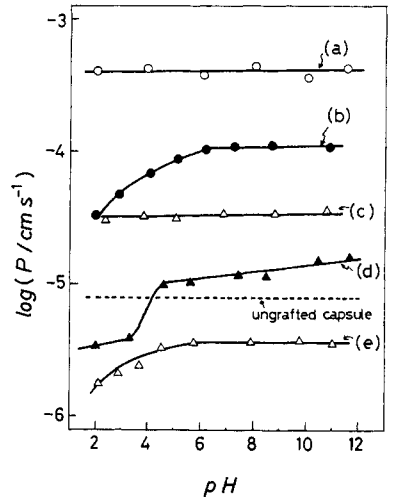


Figure 6. pH–rate profiles of NaCl permeation from the capsule grafted with polymers containing a carboxylic acid at 25 °C: (a) PAA-grafted capsule; (b) PMA-grafted capsule; (c) A–C_5–COOH-grafted capsule; (d) A–C_{11}–COOH-grafted capsule; (e) the M–C_{11}–COOH-grafted capsule.

Effect of Hydrophobic Nature of Graft Monomers. In the above pH-sensitive permeation control, the PVP-grafted capsule gave a larger permeability change than the PMA-grafted capsule. The highly hydrophobic nature in the neutral form and the highly hydrophilic nature in the ionized form of graft polymers will be required in order to act as an effective permeation valve. pH–rate profiles of NaCl permeation from the capsule grafted with various types of polymers containing a carboxylic acid are shown in Figure 6. Capsules grafted with 38–44 μg of polymers were used (see Table I). When the capsule grafted with poly(acrylic acid) (PAA) or poly[ω-(acryloylamino)hexanoic acid] (A–C_5–COOH) was employed, the NaCl permeation was hardly changed by the ambient pH over the whole pH 2–12 range. In the case of the capsule grafted with poly[ω-(acryloylamino)dodecanoic acid] (A–C_{11}–COOH) or poly[ω-(methacryloylamino)undecanoic acid] (M–C_{11}–COOH), the permeability decreased below pH 5, as well as that of the PMA-grafted capsule.

PAA or poly(A–C_5–COOH) seems to be insufficiently hydrophobic to cover the capsule membrane in the neutral form, and the permeability is hardly reduced in the acidic

Table III
Permeation Rates of NaCl, NQ_1, and NQ_2 from Capsule Membranes at 25 °C

capsule	NaCl P, 10^{-6} cm s^{-1} pH 2	NaCl P, 10^{-6} cm s^{-1} pH 12	NaCl P_{fast}/P_{slow}[a]	NQ_1 P, 10^{-6} cm s^{-1} pH 2	NQ_1 P, 10^{-6} cm s^{-1} pH 12	NQ_1 P_{fast}/P_{slow}[a]	NQ_2 P, 10^{-6} cm s^{-1} pH 2	NQ_2 P, 10^{-6} cm s^{-1} pH 12	NQ_2 P_{fast}/P_{slow}[a]
ungrafted (original)	7.9	7.8	1.0	3.5	3.6	1.0	1.6	1.5	1.0
PAA grafted	390	380	1.0	180	170	1.1	84	80	1.0
PMA grafted	32	120	3.9	3.1	99	32	1.1	100	91
A-C_5-COOH grafted	3.1	4.5	1.4	2.5	100	40	0.56	125	220
A-C_{11}-COOH grafted	16	4.0	4.0	0.13	3.0	22	0.16	0.63	3.9
PVP grafted	63	4.0	16	50	5.0	10	45	0.20	225
M-C_{10}-NMe_2 grafted	50	1.3	38	2.5	0.14	18	0.92	0.16	5.8

[a] P_{fast}/P_{slow} represents the ratio of permeation rates: $P_{pH\,12}/P_{pH\,2}$ or $P_{pH\,2}/P_{pH\,12}$ for the capsule grafted with carboxylate polymer or amino polymer, respectively.

medium. Although PMA can reduce the permeability in the acidic pH region, the neutralized PMA seems to be still hydrophilic to entirely cover the capsule membrane because the permeability in the acidic pH region is not reduced below that of the ungrafted capsule. On the contrary, when the capsule was grafted with M-C_{11}-COOH polymers having both the hydrophobic methacrylic main chain and the long spacer alkyl chain, the anionic polymer seems to cover the membrane surface because of the high hydrophobicity of the anionic form, so that the permeability above pH 6 does not increase above that of the ungrafted capsule. Thus, the A-C_{11}-COOH polymer, containing the acrylic polymer chain and the long spacer alkyl group, has a suitable hydrophobicity in the neutralized form to cover the membrane and a suitable hydrophilicity in the anionic form not to prevent NaCl permeation. In order to introduce a hydrophobic nature to the graft polymer, methyl groups in polymer main chains should be more effective than spacer alkyl groups in side chains, because the grafted PAA and A-C_5-COOH cannot act as a permeation valve but the PMA polymer can.

Similar results were obtained from the capsule grafted with polymers containing a tertiary amino group (Figure 7). When the relatively hydrophilic A-C_4-NMe_2 was grafted on the capsule membrane, the permeability was hardly decreased in the alkaline pH region. The polymer of M-C_{10}-NMe_2 could largely reduce the permeability as well as the PVP polymer in the alkaline pH region above the respective pK_a value of the tertiary amino group, because the neutralized, hydrophobic graft polymer could entirely cover the porous capsule membrane.

Permeability-controllable pH regions could be changed when both acidic PMA and basic PVP were employed as graft polymers. The pH–rate profile of NaCl permeation through the capsule grafted with both PMA and PVP is shown in Figure 8. The permeability was decreased in the neutral region (pH 4–9) and increased in both the acidic (below pH 3) and the alkaline (above pH 10) regions. The same pH–rate profiles were obtained independent of the method of graft polymerization: the capsule was graft polymerized in the mixture of MA and VP monomers or the PMA(or PVP)-grafted capsule was again grafted with PVP (or PMA) polymers. Thus, graft polymers such as copoly(MA–PV) and mixtures of PVP and PMA can cover the porous capsule membrane and reduce the NaCl permeation in the neutral region (pH 4–9) due to the hydrophobic polyion complexes between anionic MA and cationic VP groups.

Effect of Molecular Size of Permeants. In order to study the effect of the molecular size of permeants on pH-sensitive permeability changes, relatively large substances such as water-soluble naphthalene molecules (NQ_1 and NQ_2) were used as permeants instead of NaCl. Permeation rates and their ratio at pH 2 and pH 12 of NaCl, NQ_1, and NQ_2 are summarized in Table III. When the small electrolyte NaCl was employed as a permeant, the extent of permeability change by ambient pH, P_{fast}/P_{slow}, increased with increasing hydrophobic nature of the grafted monomer. On the contrary, permeation of the large NQ_2 was only slightly changed by ambient pH when a capsule grafted with a very hydrophobic polymer such as

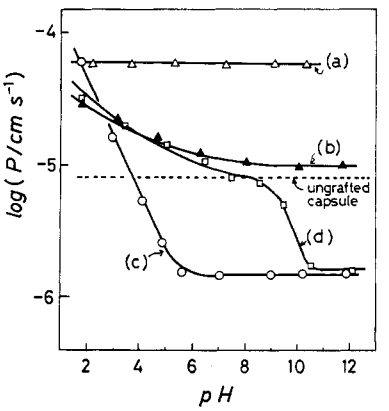


Figure 7. pH–rate profiles of NaCl permeation from the capsule grafted with polymers containing a tertiary amino group at 25 °C: (a) A-C_4-NMe_2-grafted capsule; (b) A-C_{10}-NMe_2-grafted capsule; (c) PVP-grafted capsule; (d) M-C_{10}-NMe_2-grafted capsule.

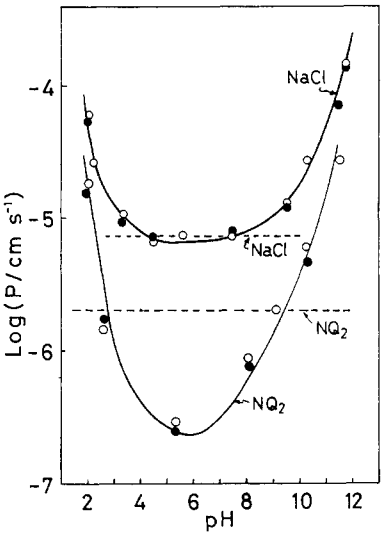


Figure 8. pH dependences of NaCl and NQ_2 permeations from the capsule grafted with both PMA and PVP at 25 °C. Open symbols, capsule grafted with copoly(MA-VP); filled symbols, capsule grafted with mixtures of PMA and PVP. Dashed lines show permeations of NaCl and NQ_2 for the ungrafted capsule membrane.

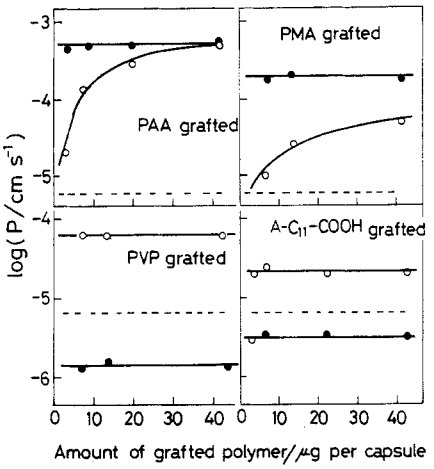


Figure 9. Effect of amount of grafted polymer on pH-sensitive permeation of NaCl at 25 °C: broken lines, permeation rates of the ungrafted capsule independent on ambient pH; filled circles, permeation rates at pH 12; open circles, permeation rates at pH 2.

A–C_{11}–COOH and M–C_{10}–NMe_2 was employed (P_{fast}/P_{slow} = 3.9–5.8). This indicates that a large permeant could not permeate smoothly through the capsule membrane covered with the ionized but still hydrophobic graft polymer. In the case of permeation of larger permeants, a graft polymer having a suitable hydrophobic nature such as A–C_5–COOH and PVP acted as an effective permeation valve and gave a very large permeability change (a factor of 220–225 between pH 2 and pH 12 for the NQ_2 permeation).

The pH–rate profile of the permeation of the large NQ_2 through a capsule grafted with PMA/PVP or copoly(MA–VP) is shown in Figure 8 together with that of NaCl. The permeability decrease of NQ_2 in the neutral-pH region was larger than that of NaCl because the large permeant has difficulty in diffusing through a membrane covered with hydrophobic polyion complexes of PMA^- and PVP^+.

Effect of Amounts of Graft Polymers. The molecular weight and amount of grafted polymer on the capsule membrane should affect the function of polymer chains as permeation valves. It was difficult to regulate the molecular weight (polymer chain length) in radical graft polymerization but relatively easy to control the amount of graft polymers by the change of the monomer concentration. Effects of amounts of graft polymers on pH-sensitive permeations are summarized in Figure 9. The permeability change of NaCl between pH 2 and pH 12 was not affected by the amount of graft polymers when the capsule was grafted with relatively hydrophobic polymers such as PVP and A–C_{11}–COOH. When hydrophilic polymers such as PAA and PMA were grafted on the capsule membrane, however, the pH-sensitive permeability change became large with decreasing graft amount of polymers. Thus, the permeability of the capsule grafted with 42 μg of PAA was not changed between pH 2 and 12, and the capsule grafted with 3–9 μg polymers showed clearly the pH-sensitive permeation due to the decrease in the permeability in the acidic media. This means that a small amount of polymer is enough to reduce the permeability in the neutralized form of hydrophilic graft polymers. The capsule membrane seems to become swelling or hydrophilic by the introduction of a large amount of hydrophilic graft polymers, so that even the neutralized COOH-polymers cannot reduce the permeability. In the case of a capsule grafted with hydrophobic polymers, the graft polymer did not swell the membrane and the permeability did not increase with increasing graft amount.

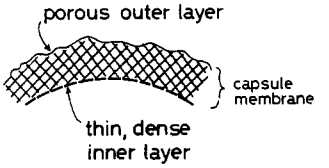


Figure 10. Schematic illustration of a cross section of nylon-2,12 capsule membranes.

Figure 9 clearly indicates that a small amount (2–5 μg per capsule) of graft polymer is effective in controlling the permeability, independent of the hydrophobic nature of the graft polymer. This value roughly means that 10^{13} polymer chains are grafted on a capsule membrane (dry weight = 20 μg, surface area = 3×10^{-5} m^2) when the average molecular weight of the graft polymers is 7×10^4 (see Table I). Thus, one polymer chain is calculated to be grafted per 1×10^3 repeating units of nylon-2,12 membranes and per 0.39 nm^2 of the membrane surface. Nylon capsule membranes are known to have an asymmetrical structure:[15] the highly dense and very thin inner layer (0.1–0.3 μm thick, 1–2-nm pore size) and the macroporous, thick part of the outer side (4–5 μm thick, 0.1–0.3-μm pore diameter) schematically shown in Figure 10. A large number of pores are connecting the outside to the inside of the capsule and arise naturally during the formation of the capsule. Since a very small amount of graft polymer (2–5 μg per capsule or one polymer chain per 10^3 repeating units of nylon-2,12) is effective in reducing the permeability by a factor of 10–200, the polymer grafted at the inner dense layer may act as an effective permeation valve, and the polymer grafted at the outer sponge layer may be ineffective in changing the permeability. When the hydrophilic polymer (PAA or PMA) was grafted over 20 μg per capsule, the polymer grafted in the sponge layer swelled the membrane and could not reduce the permeability in the neutral form.

Recently, Osada and co-workers graft polymerized very high molecular weight linear PMA ($M_w > 10^6$) onto the porous poly(vinyl alcohol) (PVA) film (pore size 8 μm; film thickness 1 mm) by plasma polymerization.[14] Water permeation across the PMA-grafted PVA film was decreased and increased by a factor of 100–200 in the alkaline and acidic pH regions, respectively. They explained that very long graft-polymer chains can cover the pores of a PVA film in the ionized, extended form above pH 8; on the contrary, the neutralized, entangled polymers cannot cover the large pores of the film and permeability increases in the acidic pH region. The pH-sensitive behavior of the PMA-grafted PVA film is quite opposite to that of our PMA-grafted capsule membrane. This can be explained by the chain length of the graft polymers and the pore size of membranes. Thus, the very long, extended graft polymers can cover the large pores of a PVA film, and the entangled polymers can cover the small pores (1–2 nm) of capsule membranes, but not the large pores (8 μm) of PVA films.

Summary

Although a nylon capsule membrane is simply semipermeable, the polymer-grafted capsule can control the permeability by changing their conformation in response to ambient pH changes. Thus, the graft polymer acts as a permeation valve on the capsule membrane. The following results were concluded. (1) A permeability controllable pH region can be selected by the graft homo- or copolymers having dissociative side chains. (2) A small amount of polymer grafted near the inner dense thin layer of the capsule membrane is effective for a permeation

valve. (3) The more hydrophobic polymers are more effective in controlling the permeation of small NaCl. For relatively large permeants, a graft polymer having a suitably hydrophobic nature can largely change the permeability by ambient pH.

The valve of the graft polymer can also be opened or shut reversibly by temperature changes[17] or redox reactions[1] in addition to ambient pH changes, when poly(*N*-alkylacrylamide) or viologen-containing polymers are grafted on the capsule membrane, respectively. The capsule membrane having a signal-receptive permeation valve should be useful for new drug release devices. Since graft polymers are covalently bonded onto the capsule membrane, the capsule can be used repeatedly without damaging the permeation valve.

Acknowledgment. We thank Prof. T. Kajiyama and N. Higashi (Kyushu University) for the use of the XPS instruments. We also thank Prof. Y. Osada (Ibaragi University) for his helpful discussion.

Registry No. ACl, 814-68-6; A-C_5-COOH, 20766-85-2; A-C_{11}-COOH, 45235-77-6; A-C_4-COOH, 73029-81-9; A-C_{10}-NMe_2, 105430-98-6; M-C_{10}-NMe_2, 105430-93-1; NQ_1, 99646-33-0; NQ_2, 97732-71-3; MACl, 920-46-7; NaCl, 7647-14-5; $NH_2(CH_2)_5CO_2H$, 60-32-2; $NH_2(CH_2)_{10}CO_2H$, 693-57-2; $Me_2NC(Me)_2CH_2OH$, 7005-47-2; $Me_2N(CH_2)_{10}OH$, 27397-09-7; $NH_2(CH_2)_2NH_2$·ClCO-$(CH_2)_{10}$COCl·AA copolymer, 91310-37-1; $NH_2(CH_2)_2NH_2$·ClCO-$(CH_2)_{10}$COCl·MA copolymer, 91310-36-0; $NH_2(CH_2)_2NH_2$·ClCO-$(CH_2)_{10}$COCl·VP copolymer, 91310-35-9; $NH_2(CH_2)_2NH_2$·ClCO-$(CH_2)_{10}$COCl·A-C_5-COOH copolymer, 105430-94-2; NH_2-$(CH_2)_2NH_2$·ClCO$(CH_2)_{10}$COCl·A-C_{11}-COOH copolymer, 105430-95-3; $NH_2(CH_2)_2NH_2$·ClCO$(CH_2)_{10}$COCl·M-C_{11}-COOH copolymer, 105430-96-4; $NH_2(CH_2)_2NH_2$·ClCO$(CH_2)_{10}$COCl·A-C_4-NMe_2 copolymer, 105430-97-5; $NH_2(CH_2)_2NH_2$·ClCO$(CH_2)_{10}$COCl·A-C_{10}-NMe_2 copolymer, 105430-99-7; nylon 2,12 (SRU), 41724-60-1; nylon 2,12 (copolymer), 41510-72-9.

References and Notes

(1) For part 25 of this series, see: Okahata, Y.; Ariga, K.; Seki, T. *J. Chem. Soc., Chem. Commun.* **1986**, 73.
(2) Preliminary report: Okahata, Y.; Ozaki, K.; Seki, T. *J. Chem. Soc., Chem. Commun.* **1984**, 519.
(3) Chang, T. M. S. *Artificial Cells*; Charles C. Thomas: Springfield, IL, 1972.
(4) Chang, T. M. S. *Artif. Organs* **1979**, *3*, 1.
(5) Kondo, T., Ed. *Microencapsulation*; Techno Inc.: Tokyo, 1979.
(6) Rothenthal, A. M.; Chang, T. M. S. *J. Membr. Sci.* **1980**, *6*, 329.
(7) Yu, Y. T.; Chang, T. M. S. *FEBS Lett.* **1981**, *125*, 94.
(8) For a review, see: Okahata, Y. *Acc. Chem. Res.* **1986**, *19*, 57.
(9) Okahata, Y.; Lim, H.-J.; Nakamura, G.; Hachiya, S. *J. Am. Chem. Soc.* **1983**, *105*, 4855.
(10) Okahata, Y.; Lim, H.-J.; Hachiya, S.; Nakamura, G. *J. Membr. Sci.* **1984**, *19*, 237.
(11) Okahata, Y.; Iizuka, N.; Nakamura, G.; Seki, T. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1591.
(12) Okahata, Y.; Lim, H.-J.; Hachiya, S. *J. Chem. Soc., Perkin Trans. 2* **1984**, 989.
(13) Okahata, Y.; Hachiya, S.; Ariga, K.; Seki, T. *J. Am. Chem. Soc.* **1986**, *108*, 2863. Okahata, Y.; Hachiya, S.; Seki, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1377.
(14) Osada, Y.; Honda, K.; Ohta, M. *J. Membr. Sci.* **1986**, *27*, 327.
(15) Seki, T.; Okahata, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1986**, *24*, 61.
(16) Seki, T.; Okahata, Y. *Macromolecules* **1984**, *17*, 1880.
(17) Okahata, Y.; Noguchi, H.; Seki, T. *Macromolecules* **1986**, *19*, 493.

"Complete" Thermocontrol of Ion Permeation through Ternary Composite Membranes Composed of Polymer/Liquid Crystal/Amphiphilic Crown Ethers[1]

Seiji Shinkai,*[2] Shinichiro Nakamura,[2] Kouji Ohara,[2] Shinji Tachiki,[2] Osamu Manabe,[2] and Tisato Kajiyama[3]

Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan, and the Department of Applied Chemistry, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan. *Received July 7, 1986*

ABSTRACT: Composite membranes composed of polymer (polycarbonate (PC))/liquid crystal (*N*-(4-ethoxybenzylidene)-4′-butylaniline (EBBA))/amphiphilic crown ethers (**1a**, **2a**, and **2b**) have been prepared. The DSC study established that **1a** (single-chain amphiphile) is dispersed homogeneously in the PC/EBBA composite membrane, whereas **2a** and **2b** (double-chain amphiphiles) exist as phase-separated aggregates in the membrane. Also prepared were ternary composite membranes containing natural ionophores such as X-537A (lasalocid) or monensin, which were dispersed homogeneously in the PC/EBBA composite membrane. Above T_{KN} (crystal–nematic liquid crystal phase transition temperature of EBBA), ion permeation through these composite membranes was very fast (19–34-fold compared with the conventional membranes). This is due to the high fluidity of EBBA forming a continuous phase in the composite membrane. Permeation of K^+ ion through PC/EBBA/**1a** and PC/EBBA/natural ionophore was observed below and above T_{KN}, and the Arrhenius plots consisted of two straight lines intersecting at T_{KN}. This indicates that carrier-mediated K^+ permeation is directly affected by the molecular motion of the liquid crystal phase. Surprisingly, K^+ permeation through PC/EBBA/**2a** and PC/EBBA/**2b** was "completely" suppressed below T_{KN} and increased with increasing transport temperature above T_{KN}. Furthermore, Cs^+, which forms sandwich-type complexes with 18-crown-6 and its analogues, could permeate through PC/EBBA/**2a** but not at all through PC/EBBA/**1a** above T_{KN}. The difference in the permeation mechanism between PC/EBBA/**1a** and PC/EBBA/**2a** is discussed in relation to the dispersion state of the crown ethers. The Arrhenius thermodynamic parameters show a good enthalpy–entropy compensation relationship expressed by $E_a = 5.42 \log A + 50.4$, but the permeability coefficient for K^+ (P_{K^+}) was affected more significantly by the log A term. Finally, the PC/EBBA/**2a** membrane, which exhibits an all-or-nothing change in the ion permeability, was applied to the reversible thermocontrol of K^+ permeation and to the temperature-dependent "catch-and-release" of K^+ ion. This is the first example for "complete" thermocontrol of ion permeation through the polymer composite membrane.

Biological membranes are composed of various kinds of phospholipids, cholesterols, and proteins, and the fundamental functions such as permeation and selectivity are closely associated with the gel–liquid crystal phase transition. Therefore, the phase transition would be one of the most essential functions provided by phospholipid bio-

0024-9297/87/2220-0021$01.50/0