

SYNTHESIS OF NOVEL AMPHIPHILIC COMPOUNDS CONTAINING AZA-12-CROWN-4 OR D-GLUCOSAMINE AND THEIR ION PERMEABILITY

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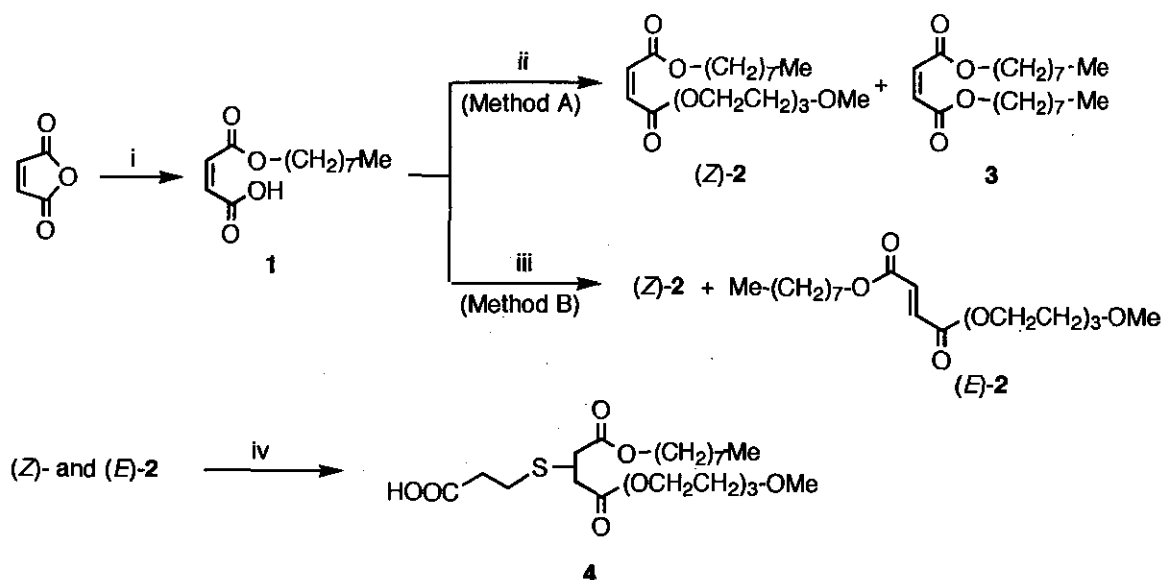
Abstract --- New amphiphilic compounds (**Types 1, 2, and 3**) composed of triethylene glycol monomethyl ether, octanol, and aza-12-crown-4 or D-glucosamine were synthesized. Aza-12-crown-4 was connected to an amphiphilic alkyl chain by the -CO-N- linkage in **Type 1** and by -C-N- in **Type 2**, and D-glucosamine was connected to it by -CO-N- in **Type 3**. The ion permeability of these compounds was elucidated by means of the black lipid membrane method with an alternating current (a.c.). Only **Type 2** compound showed significant transmembrane currents when incorporated into the lipid bilayer membrane in aqueous NaCl, KCl, and RbCl solutions.

Naturally occurring channels mediate the passage of ions and small molecules from one side of biological membrane to the other, and thus they play important roles in the generation of electrical signals in the nervous and signal transduction systems.¹ Gramicidin,² a pentadecapeptide, and amphotericin,³ a macrocyclic polyene antibiotic, form channels in different manners when incorporated into membranes. Synthesis and design of artificial ion channel-forming molecules are important strategies for a deeper understanding of the functions of channels in biological membranes. The single ion

channel properties of artificial peptides and non-peptide have independently been demonstrated by DeGrado,⁴ Montal,⁵ and Kobuke.⁶ Fuhrhop and co-workers have extensively studied on the synthesis of bolaamphiphiles and their ion channel properties in monolayer lipid membrane.⁷ Further, interesting papers concerning the ion permeability of synthetic molecules based on crown ethers in vesicles and lipid bilayer membranes have been reported by Nolte,⁸ Voyer,⁹ Lehn¹⁰, Fyles,¹¹ and Gokel.¹² In the preceding paper,¹³ we reported on the formation of the black membrane using a microfabricated orifice and measurement of the transmembrane current of natural channel-forming molecule with an a.c.. In this paper, we describe the synthesis of new amphiphilic compounds composed of triethylene glycol monomethyl ether, octanol, and aza-12-crown-4 or D-glucosamine and the elucidation of their ion permeability by means of the black lipid membrane method with an a.c.. The aim of this research is to examine the influence of (a) the linkage mode between the polar head and amphiphilic alkyl chain and (b) the molecular structure of the polar head moiety upon the ion permeability.

Synthesis of New Amphiphilic Compounds (Types 1, 2, and 3). The carboxylic acid (4) bearing an amphiphilic alkyl chain was synthesized according to modified Fuhrhop's method¹⁴ as shown in Scheme 1. The treatment of maleic anhydride with octanol gave the half-ester (1)¹⁵ in a 61% yield. Compound (1) was allowed to react with triethylene glycol monomethyl ether in the presence of *p*-toluenesulfonic acid (*p*-TsOH) under reflux condition to give the diester ((*Z*)-2) in a 12% yield (method A). During this reaction, the ester exchange reaction occurred to give the symmetric diester (3)¹⁶ in a 20% yield. On the other hand, the half-ester (1) was treated with triethylene glycol monomethyl ether in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give a mixture of *Z* and *E* isomers ((*Z*)- and (*E*)-2) in a total 40% yield (method B). Two isomers can be easily distinguished by ¹H nmr spectral data. The olefinic protons of (*Z*)-2 appeared at 6.23 and 6.28 ppm as two doublets, while those of (*E*)-2 appeared at 6.87 ppm as a singlet. When pure (*Z*)-2, obtained from method A, was treated with DCC and DMAP without triethylene glycol monomethyl ether under the same condition, the *Z*-to-*E* isomerization was observed although the mechanism remained obscure. From

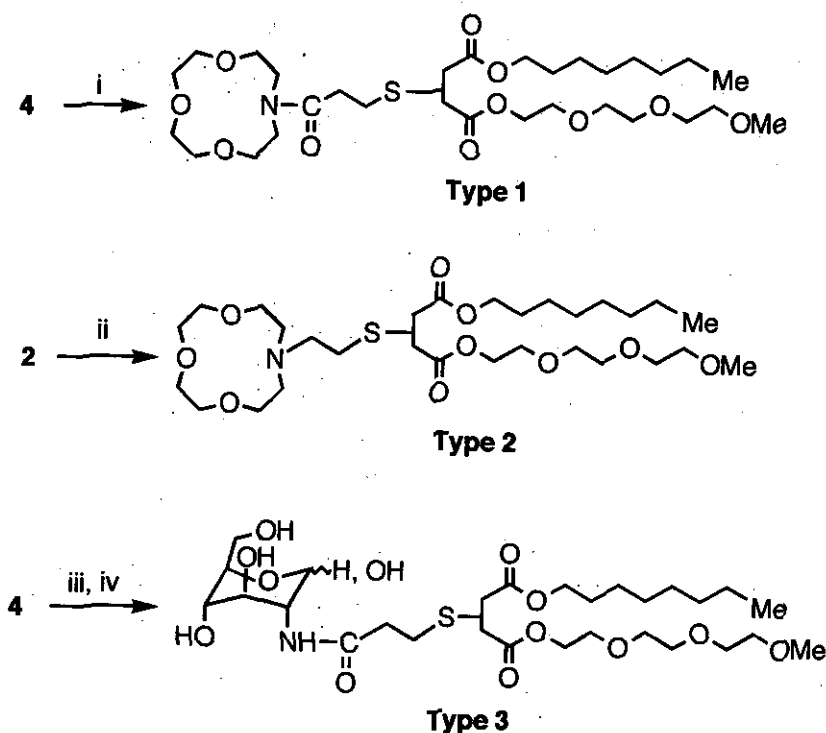
these experiments, method B was found to be preferable to method A from the viewpoint of yield and manipulation. The sodium salt of 3-mercaptopropionic acid easily underwent the Michael addition to a mixture of (*Z*)- and (*E*)-**2** in the presence of piperidine as a catalyst to give the amphiphilic carboxylic acid (**4**) in an 80% yield. The direction of the Michael addition to an olefine could not be determined at this time, because any attempts to separate a mixture by silica gel column and gel-permeation chromatographies were unsuccessful. The synthetic procedure for the desired amphiphilic compounds (**Types 1, 2, and 3**) is depicted in Scheme 2. The carboxylic acid (**4**) was allowed to react with aza-12-crown-4 in the presence of DCC and *N*-hydroxysuccinimide (HOSu) in dry THF.



Scheme 1 Reagents and conditions : i) HO-(CH₂)₇-Me in dry benzene, reflux ; ii) H-(OCH₂CH₂)₃-OMe / *p*-TsOH in dry benzene, reflux ; iii) H-(OCH₂CH₂)₃-OMe / DCC / DMAP in CH₂Cl₂, room temperature; iv) HSCH₂CH₂COOH / NaOH / piperidine in 2-propanol, reflux.

The crude product was purified by gel permeation chromatography on Sephadex LH-20 with MeOH as an eluant to afford **Type 1** compound in a 25% yield. In its spectrum, the absorption band due to the C=O stretching vibration of the carboxylic acid of the starting material (**4**) disappeared, and the new band attributable to the amide carbonyl group appeared at 1650 cm⁻¹. The Michael addition of *N*-(2-mercaptoethyl)aza-12-crown-4 to a

mixture of (*Z*)- and (*E*)-**2** was carried out in the presence of five molar amounts of piperidine to give **Type 2** compound in a 20% yield after purification by column chromatography on silica gel. The long period of heating caused the partial hydrolysis of the diester. Kopecek and co-workers have reported that treatment of an amino sugar with the activated ester in dry DMSO gave the amide-linked compound.¹⁷ This method, therefore, was applied to the synthesis of **Type 3** compound. The carboxylic acid (**4**) was converted into the corresponding *O*-succinimido ester using *N*-[(3-(dimethylamino)propyl)-*N'*-ethylcarbodiimide hydrochloride (water-soluble carbodiimide: WSC·HCl)-HOSu method. The isolated OSu ester was coupled with D-glucosamine hydrochloride in the presence of triethylamine in dry DMSO to afford the desired **Type 3** compound in a 28% yield.



Scheme 2 Reagents and conditions: i) aza-12-crown-4/DCC/HOSu in dry THF room temperature; ii) *N*-(2-mercaptoethyl)aza-12-crown-4/piperidine in 2-propanol, reflux; iii) WSC·HCl/HOSu in DMF-CH₂Cl₂ mixture, room temperature; iv) D-glucosamine in dry DMSO, room temperature.

Measurement of the Ion Permeability. The ion permeability of newly synthesized compounds was elucidated by measurement of the transmembrane current using the black membrane method with an a.c.¹³ Phospholipid (PC; 7.5 mg/ml an egg yolk lecithin in decane) and cholesterol solutions (8.7 mg/ml in decane) were mixed in the molar ratio of 4:1; we hereafter referred to this solution as 'the control solution'. A small aliquot of new compounds in MeOH or DMSO was premixed with the control solution at the molar ratio of 1:3000 (compound/phospholipid). The capacitance (C_C) and the resistance (R_C) of Teflon cup were measured to be 145 pF and 58.9 G Ω , respectively, using a glass plate without an orifice. The R_C value was large enough as expected, and thus it was neglected in the following arguments. First, transmembrane currents by addition of three types of new amphiphilic compounds were measured in 10 mM aqueous NaCl solution as the electrolyte solution, and the results are shown in Figure 1. In the case of **Types 1** and **3**, no enhancement of the trans-membrane current was observed, that is, the conductance level of these compounds was almost the same as that of the control. On the contrary, **Type 2** showed remarkable enhancement of the transmembrane current. The channel conductance was calculated to be 415 pS, which was 3.6 times compared to the control, although the conductance was far below that of gramicidin D.

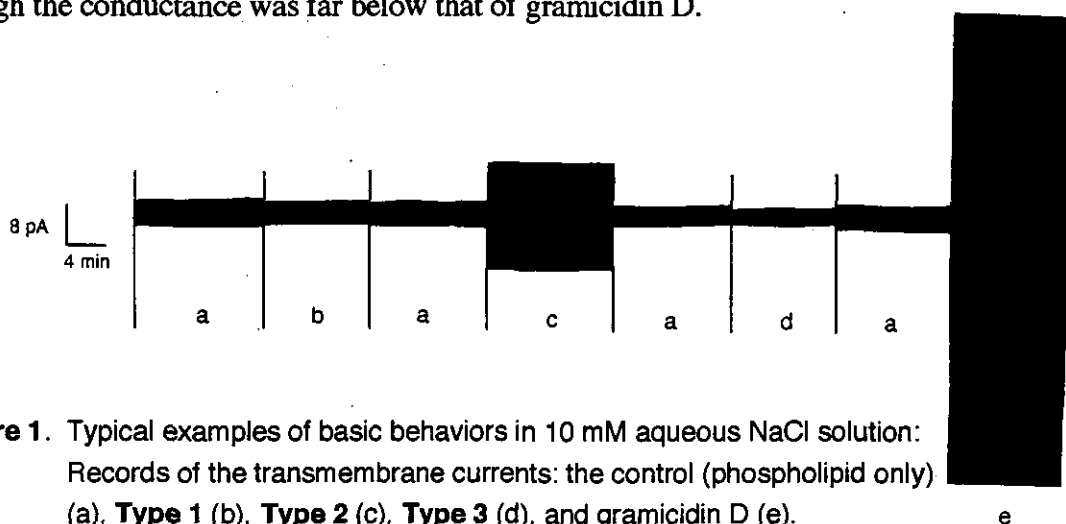


Figure 1. Typical examples of basic behaviors in 10 mM aqueous NaCl solution: Records of the transmembrane currents: the control (phospholipid only) (a), **Type 1** (b), **Type 2** (c), **Type 3** (d), and gramicidin D (e).

Similar measurements of membrane currents were performed in 10 mM aqueous KCl and RbCl solutions (not shown here). Again, **Types 1** and **3** showed no enhancement of the membrane current, while **Type 2** showed the membrane conductance by a factor of 4 in

aqueous KCl solution (conductance: 460 pS) and 2.3 in aqueous RbCl solution (conductance: 255 pS) compared to the control. Repeated experiments gave the same results. In the case of **Type 2** the duration of these conductance levels continued for 1 to 2 h, suggesting that the aggregation state of **Type 2** in the lipid bilayer would be very stable. There was striking difference in the ion permeability between **Type 1** and **Type 2**. Only difference of them is the linkage mode, viz., the amide bond (-CO-N-) for **Type 1** and the C-N single bond for **Type 2**. The preference of the planar conformation due to the amide bond results in deformation of the azacrown ether ring. It seems to make the aggregation state of **Type 1** unstable. In the case of **Type 3**, it might be too hydrophilic to incorporate into the lipid bilayer membrane.

In conclusion, **Type-2** compound showed significant ion permeability when incorporated into the lipid bilayer membrane. Further, it was found that both the linkage mode and the molecular structure of the polar head moiety were remarkably influenced upon the ion permeability.

EXPERIMENTAL

Mp was recorded on a Mel-Temp apparatus in open capillaries and is uncorrected. ^1H Nmr spectra were recorded with a JEOL JNM-GX 270 spectrometer using tetramethylsilane as an internal standard. Ir spectra were taken on JASCO A-100 and JIR-3510 infrared spectrophotometers. Silica gel (MERCK, Silica gel 60) and alumina (MERCK, Aluminium oxide 90 active, neutral) were used for column chromatography. Thin layer chromatography (tlc) analysis was carried out with Kieselgel 60/Kieselgur F254 and Aluminiumoxid 60 F254 with a 0.2 mm layer thickness. Elemental analyses were performed by Yanaco MT-3 CHN corder.

Octyl hydrogen malenate (1): A mixture of maleic anhydride (0.98 g, 0.01 mol) and octanol (1.3 g, 0.01 mol) in dry benzene (50 ml) was refluxed for 8 h. H_2O (80 ml) was added to the mixture, the aqueous layer was neutralized with 5% NaOH solution to pH 10, and then two layers were separated. The aqueous layer was acidified with 5% HCl solution to pH 3, and extracted with benzene (50 ml x 2). The organic layer was washed

with H₂O (30 ml), brine (50 ml) and dried over anhydrous Na₂SO₄. Evaporation of the solvent and subsequent vacuum distillation gave the product (1) (1.39 g, 61%) as an oil; mp 29-30 °C, bp 235-238 °C/3 torr; ¹H nmr(CDCl₃) δ: 0.93 (3H, t, J=7 Hz, CH₃), 1.15-1.45 (12H, m, CH₂), 1.67 (2H, m, OCH₂CH₂), 4.25 (4H, t, J=7 Hz, OCH₂), and 6.13 ppm (2H, s, CH=CH); ir(neat) ν_{max}: 3100 (br), 1730, 1655, and 730 cm⁻¹.

Octyl 3,6,9-trioxadecyl malenate (2); Method A: A mixture of compound (1) (0.68 g, 3 mmol), triethylene glycol monomethyl ether (0.5 g, 3 mmol), and *p*-TsOH (1.0 g) in benzene (200 ml) was refluxed for 4 h with aid of the Dean-Stark apparatus. After evaporation of the solvent, the residue was dissolved in AcOEt (250 ml), and the organic layer was washed with 5% NaHCO₃ (30 ml x 3). The crude product was purified by column chromatography on silica gel with AcOEt-hexane (1:2) mixture to give the pure product (*Z*)-2 (134 mg, 12 %) as an oil; ¹H nmr(CDCl₃) δ: 0.85 (3H, t, J=7 Hz, CH₃), 1.24-1.45 (12H, m, CH₂), 1.65 (2H, q, J=7 Hz, OCH₂CH₂), 3.38 (3H, s, OCH₃), 3.56 (2H, m, CH₂OCH₃), 3.62-3.67 (6H, m, OCH₂CH₂O), 3.75 (2H, t, J=5 Hz, CO₂CH₂CH₂O), 4.18 (4H, t, J=7 Hz, CO₂CH₂CH₂), 4.35 (2H, t, J=5 Hz, CO₂CH₂CH₂O), 6.23 (1H, d, J=11.5 Hz, CH=CH), and 6.28 ppm (1H, d, J=11.5 Hz, CH=CH); ir(neat) ν_{max}: 1730 cm⁻¹. Anal. Calcd for C₁₉H₃₄O₇·0.1H₂O: C, 61.0; H, 9.1. Found: C, 60.7; H, 9.1. In this reaction, dioctyl maleate (3) was isolated in a 20% yield as by-product after vacuum distillation; bp 240-245 °C/2x10⁻³ torr; ¹H nmr(CDCl₃) δ: 0.92 (3H, t, J=7 Hz, CH₃), 1.2-1.4 (20H, m, CH₂), 4.13 (4H, t, J=5 Hz, OCH₂), and 6.23 ppm (2H, s, CH=CH); ir(neat) ν_{max}: 1740 cm⁻¹.

Method B: A mixture of compound (1) (228 mg, 1 mmol), triethylene glycol monomethyl ether (164 mg, 1 mmol), and DMAP (122 mg, 1 mmol) in CH₂Cl₂ (50 ml) was cooled to 0 °C on an ice bath. After addition of DCC (205 mg, 1 mmol), the reaction mixture was stirred for 5 min at 0 °C and then for another 3 h at room temperature. The resulting precipitate, *N,N'*-dicyclohexylurea, was filtered off. The organic layer was washed with 5% HCl (50 ml) and dried over anhydrous Na₂SO₄. Column chromatography on silica gel afforded a mixture of (*Z*)- and (*E*)-2 in the ratio of 85:15 (150 mg, 40 %) as an oil; ¹H nmr(CDCl₃) δ: 0.85 (3H, t, J=7 Hz, CH₃), 1.2-1.4 (12H, m, CH₂CH₂), 1.6-1.75 (2H, m, OCH₂CH₂CH₂), 3.38 (3H, s, OCH₃), 3.5-3.6 (2H, m,

CH_2OCH_3), 3.6-3.7 (6H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.7-3.8 (2H, m, $\text{CO}_2\text{CH}_2\text{CH}_2\text{O}$), 4.1-4.25 (4H, m, $\text{CO}_2\text{-CH}_2\text{CH}_2$), 4.3-4.4 (2H, t, $J=5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2\text{O}$), 6.23 (0.85H, d, $J=11.5$ Hz, $Z\text{-CH=CH}$), 6.28 (0.85H, d, $J=11.5$ Hz, $Z\text{-CH=CH}$), and 6.87 ppm (0.3H, s, $E\text{-CH=CH}$).

Octyl 3,6,9-trioxadecyl (2-carboxyethylthio)succinate (4): To a hot solution of compound (2) (350 mg, 0.9 mmol) in 2-propanol (100 ml) at 80 °C were added 3-mercaptopropionic acid (100 mg, 0.9 mmol), sodium hydroxide (36 mg, 0.9 mmol), and a few drops of piperidine. After refluxing for 1.5 h, the solvent was evaporated under reduced pressure, and the residue was dissolved in H_2O (10 ml). The aqueous layer was acidified with 5% HCl to pH 2 and extracted with AcOEt (200 ml). The organic layer was washed with H_2O (20 ml x 3) and dried over anhydrous Na_2SO_4 . Column chromatography on silica gel with CHCl_3 -acetone-EtOH (100:40:8) mixture afforded the product (4) (360 mg, 80 %) as colorless oil; ^1H nmr(CDCl_3) δ : 0.85 (3H, t, $J=7$ Hz, CH_3), 1.24-1.45 (12H, m, CH_2CH_2), 1.65 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2$), 2.45-2.60 (4H, m, COCH_2), 2.80-2.92 (2H, m, SCH_2), 3.28 (3H, s, OCH_3), 3.45-3.72 (11H, m, $\text{OCH}_2\text{CH}_2\text{O}$, SCH), and 4.00-4.23 ppm (4H, m, $\text{CO}_2\text{CH}_2\text{CH}_2$); ir(neat) ν_{max} : 3000 (br), 2910, and 1730 cm^{-1} . Anal. Calcd for $\text{C}_{19}\text{H}_{34}\text{O}_7\cdot\text{H}_2\text{O}$: C, 53.0 ; H, 8.5. Found: C, 53.0; H, 8.3.

Octyl 3,6,9-trioxadecyl{2-[(1,4,7-trioxa-10-azacyclodec-10-yl)carbonyl]ethylthio}succinate (Type 1): Compound (4) (350 mg, 0.73 mmol) in dry THF (30 ml) was mixed with aza-12-crown-4 (128 mg, 0.73 mmol) and HOSu (104 mg, 0.9 mmol). To the mixture cooled to -10 °C was added DCC (186 mg, 0.9 mmol), and the reaction mixture was stirred overnight. The resulting N,N' -dicyclohexylurea was filtered off, THF was evaporated under reduced pressure, and then the residue was dissolved in AcOEt (80 ml). The AcOEt layer was stored in a refrigerator, and the solid was again filtered off. The organic layer was washed with 5% NaHCO_3 (20 ml x 3), H_2O (30 ml), and then dried over anhydrous Na_2SO_4 . The crude product was purified by gel permeation chromatography on LH-20 with MeOH as an eluant to give the pure product **Type 1** as colorless oil (90 mg, 19 %) ; ^1H nmr(CDCl_3) δ : 0.88 (3H, t, $J=7$ Hz, CH_3), 1.24-1.45 (10H, m, CH_2CH_2), 1.65 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2$), 2.63-2.78 (4H, m, $2\times\text{COCH}_2$),

2.93-3.05 (2H, m, SCH₂), 3.38 (3H, s, OCH₃), 3.54-3.75 (27H, m, OCH₂CH₂O, NCH₂, SCH), and 4.05-4.35 ppm (4H, m, CO₂CH₂CH₂); ir(neat) $\nu_{\max}$: 2950, 1740, 1650, and 1250 cm⁻¹. Anal. Calcd for C₃₀H₅₅NO₁₁S: C, 56.5; H, 8.7; N, 2.2. Found: C, 56.2; H, 8.5; N, 1.9.

Octyl 3,6,9-trioxadecyl[2-(1,4,7-trioxa-10-azacyclodec-10-yl)ethylthio]succinate (Type 2): To a mixture of compound (2) (187.2 mg, 0.5 mmol) and *N*-(2-mercaptoethyl)aza-12-crown-4 (118 mg, 0.5 mmol) in 2-propanol (50 ml) at 80 °C was added piperidine (213 mg, 2.5 mmol). After refluxing for 4 h, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with CHCl₃-acetone-EtOH (100:5:1) mixture to give the pure product **Type 2** as colorless oil (120 mg, 20 %); ¹H nmr(CDCl₃) δ : 0.88 (3H, t, J=7 Hz, CH₃), 1.27-1.45 (10H, m, CH₂CH₂), 1.65 (2H, q, J=7 Hz, CO₂CH₂CH₂), 2.35-2.47 (2H, m, COCH₂), 2.65-2.80 (2H, m, SCH₂), 3.38 (3H, s, OCH₃), 3.54-3.72 (29H, m, OCH₂CH₂O, NCH₂, SCH), 4.06-4.13 (2H, m, CO₂CH₂CH₂CH₂), and 4.25 ppm (2H, t, J=5 Hz, CO₂-CH₂CH₂O); ir(neat) $\nu_{\max}$: 2900, 1730, and 1120 cm⁻¹. Anal. Calcd for C₂₉H₅₅NO₁₀S·H₂O: C, 55.5; H, 9.15. Found: C, 55.35; H, 9.0.

***N*-(3-[1-Octyloxycarbonyl-2-(3,6,9-trioxadecyloxycarbonyl)ethylthio]propanoyl)-2-amino-2-deoxy-D-glucopyranose (Type 3):** To a mixture of compound (4) (200 mg, 0.42 mmol), HOSu (96 mg, 0.83 mmol) in dry DMF (30 ml) cooled to -10 °C on an ice-salt bath was added WSC·HCl (159 mg, 0.83 mmol) in CH₂Cl₂ (20 ml). The reaction mixture was stirred for 20 h at room temperature. After removal of the solvent, the residue was dissolved in CHCl₃ (100 ml). The organic layer was washed with H₂O (20 ml) and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave the corresponding *O*-succinimido ester as an oil in quantitative yield, which was used to the next reaction without purification. To a solution of the *O*-succinimido ester in dry DMSO (10 ml) cooled to 0 °C was added a mixture of 2-amino-2-deoxy-D-glucopyranose hydrochloride (102 mg, 0.47 mmol) and Et₃N (47.6 mg, 0.47 mmol) in dry DMSO (3 ml). After stirring for 24 h at room temperature, the solvent was removed under reduced pressure, and then the residue was dissolved in CHCl₃ (50 ml). The organic layer was washed with H₂O (20 ml) and then dried over anhydrous Na₂SO₄. The crude product

was purified by gel permeation chromatography on TOYOPEARL HW-40 with MeOH as an eluant to give the product **Type 3** as viscous oil (75 mg, 28 %); ^1H nmr(CDCl_3) δ : 0.88 (3H, t, $J=7$ Hz, CH_3), 1.20-1.38 (10H, m, CH_2CH_2), 1.65 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2$), 2.55-2.75 (4H, m, COCH_2) 2.93-3.04 (2H m, SCH_2) 3.40 (3H, s, OCH_3) 3.53-3.90 (20H, m, $\text{OCH}_2\text{CH}_2\text{O}$, ring protons, SCH), 4.10 (2H, t, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 4.24 (2H, t, $J=5$ Hz, $\text{COOCH}_2\text{CH}_2\text{O}$), and 5.23 ppm (2H, br s, sugar); ir(neat) ν_{max} : 3300, 2950, 1730, 1650, and 1240 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{51}\text{NO}_{13}\text{S}\cdot 1.5\text{H}_2\text{O}$: C 50.3; H 8.1; N 2.1. Found: C, 50.15; H, 7.85; N, 2.2.

Measurement of the Ion Permeability: When new synthetic compounds were incorporated into the lipid bilayer membrane, the membrane currents were measured according to the procedure described in the previous paper.¹³

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