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Design and Synthesis of Sodium Ion-Selective Ionophores Based on 16-Crown-5 Derivatives for an Ion-Selective Electrode

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To develop an ionophore that is highly selective for sodium for use in an ion-selective electrode, we propose a model based on 16-crown-5 which has a cavity just the size of Na^+ and has a "block" subunit to prevent complex formation with ions larger than Na^+. Based on this molecular model, eight kinds of 16-crown-5 derivatives have been synthesized, and their structural ion selectivity has been evaluated in detail. The 16-crown-5 derivatives having two bulky "block" subunits showed high Na^+ selectivity relative to K^+. In particular, the derivative with two decalino subunits (DD16C5) exhibited the highest Na^+ selectivity of all the ionophores examined. When a phosphate ester-type membrane plasticizer, tris(ethylhexyl) phosphate, was used as the membrane solvent for the ion-sensing membrane based on poly(vinyl chloride), the electrode using DD16C5 exhibited a Na^+ selectivity of over 1000 times relative to alkali metal and alkaline earth metal ions, including K^+, which is the most serious interferant. The evaluation of the relationship between the ionophore chemical structures and the ion-selective features contributes to the host−guest chemistry to give a highly selective ionophore for an alkali metal ion.

Sodium ion is an important chemical species in the metabolism processes of the human body; therefore, measurement of the concentration of sodium ions is useful in controlling human health conditions and diagnosing sicknesses. Recently, Na^+-selective electrodes have been used in hospitals for routine clinical measurement of Na^+ concentration. Using this sensor, an analytical instrument that can rapidly and easily measure the Na^+ concentration in human serum has been constructed. Sodium ion concentration in normal human serum (extracellular fluid) is ∼140 mM, which is a relatively high concentration; thus, an ion-selective electrode having a selectivity coefficient of log $k^{pot}_{Na,K}$ <−0.6 is adequate for this measurement.[1] As for intracellular fluid, the Na^+ concentration is small compared with that of the coexisting K^+ (Na^+, ∼10 mM; K^+, 120 mM). The required Na^+/K^+ selectivity is 4000 in the case where the Na^+ determination is performed with an ion-selective electrode in which the measurement error is assumed to be <1%.[1] Thus, a very highly Na^+ selective electrode is desired for this measurement. Furthermore, in order to construct a long-lifetime and highly reproducible ion-selective electrode, a high lipophililicity value of log $P_{o/w}$ >11.3 is required for the ionophore as one of the ion-sensing electrode membrane components when the electrode is used in the analysis of human serum.[2] In the past, we have obtained a highly Na^+-selective electrode based on a 16-crown-5 derivative [15-(benzyloxy)methyl-15-ethyl-1,4,7,10,13-pentaoxacyclohexadecane] and dibenzyl ether, for which the Na^+/K^+ selectivity was ∼600.[3] Unfortunately, the lifetime of this electrode is not good because of the low lipophilicity of the 16-crown-5 derivative (log $P_{o/w} = 3.4 \pm 0.3$).

Generally, a crown ether forms an 1:1 complex with a metal cation that has an ionic size fitting the cavity size of the crown ether ring, but most of the crown ether compounds also often form a sandwich-type complex with a large cation (a 1:2 or 1:3 ion−ligand complex), because crown ether compounds have a relatively planar and flexible structure, except when the compound has a small ring size. To prevent the formation of a sandwich-type complex, introduction of a bulky blocking wall (a block subunit) into the crown ether (as the shown in Figure 1) is very effective for improving the selectivity as well as the lipophilicity. Cations larger than Na^+ cannot be positioned within an appropriate binding distance of the oxygen atom (the cation binding site in the crown ether ring) due to the presence of the block subunit, as illustrated in Figure 1. Thus, a stable sandwich-type complex with a large cation cannot be formed (block effect). Consequently, a higher selectivity for the cation that fits in the cavity of the crown ether ring can be obtained. We have applied this approach in the design and synthesis of a highly Li^+ selective ionophore and have successfully obtained an ionophore which has a Li^+ selectivity of over 1000 times relative to all other alkali metal and alkaline earth metal ions.[5]

To add an effective block subunit in the crown compound, the following points must be considered: (i) the bulky subunit has to be positioned in the crown compound such that its large physical bulk is oriented in an up-and-down position relative to the crown ring; (ii) in this case, the bulky subunit should be able to support the rigidity of the crown ring so that the ring size is fixed; and (iii) the block subunit is positioned near the oxygen donor atom in the crown ether compound so that the appropriate space for the larger coordinating cation (interfering ion) to bind to the oxygen atom is not offered.

The number of block subunits in the crown ether compound is an important factor as well. Generally, we simply expect that a larger number of block subunits causes a greater block effect. However, if too many block subunits are introduced in the crown ether compounds, the bulky block walls sterically interfere with even the cation having a suitable size to fit the cavity of the crown ring. Thus, the optimum number and suitable type of bulky block subunits have to be introduced in the crown ether.

Based on the model shown in Figure 1, we designed and synthesized eight kinds of novel 16-crown-5 derivatives and evaluated their structural selectivity. 16-Crown-5 derivatives having two block subunits exhibited a very high Na^+ selectivity,

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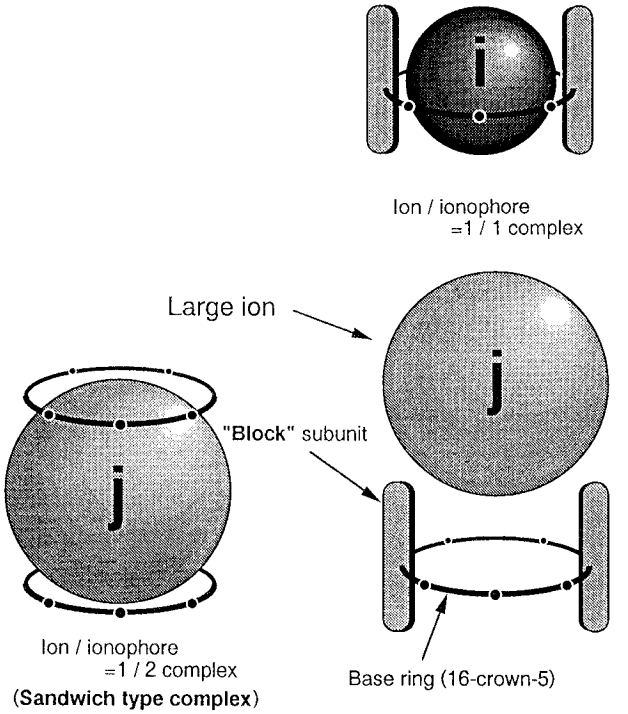

Figure 1. Na^+-selective ionophore model molecules based on 16-crown-5 with and without bulky block subunits. *i*, primary ion (Na^+); *j*, interfering ion (K^+).

especially the derivative with two decalino subunits (DD16C5), which exhibited the highest Na^+ selectivity. The ion-selective electrode based on DD16C5 exhibited 1000 times the Na^+ selectivity relative to that for K^+ and over 1000 times relative to that for other alkali metal and alkaline earth ions when a phosphate ester-type membrane solvent, TEHP, was used as membrane solvent in the polymeric electrode membrane based on PVC. DD16C5 satisfies the requirement for a long-lifetime and highly reproducible ion-selective electrode of adequate lipophilicity ($\log P_{o/w} = 11.8$); therefore, it is an excellent ionophore for Na^+ for application as a membrane component of the Na^+-selective electrodes developed to date.

EXPERIMENTAL SECTION

Reagents. The highest grade commercially available reagents were used for syntheses of the new compounds and preparation of the aqueous test electrolytes. The distilled and deionized water used had a resistivity of 1.5×10^7 Ω cm at 25 °C. The electrode membrane solvent bis(1-butylpentyl) adipate (BBPA) was purchased from Fluka AG (Buchs, Switzerland). Poly(vinyl chloride) (PVC, high molecular weight type), used as the electrode membrane material, was obtained from Sigma Chemical Co. (St. Louis, MO).

Synthesis of 16-Crown-5 Derivatives. The procedures for the preparation of new ionophores as follows:

(i) DTM16C5A (2,2,3,3,8,8,9,9-Octamethyl-1,4,7,10,13-pentaoxacyclohexadecane). Sodium hydride (NaH; 2.56 g, 64.0 mmol) was added to a solution of pinacol (6.30 g, 53.3 mmol) in tetrahydrofuran (THF; 130 mL) and stirred for 30 min at room temperature. A solution of benzyl bromide (8.21 g, 48 mmol) in 60 mL of THF was added gradually to this mixture and was then stirred at 80 °C for 20 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The solvent was then evaporated and the obtained residue purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent to yield 3-(benzyloxy)-2,3-dimethyl-2-butanol (**1**; 7.01 g, 71.0%) as a colorless oil.

NaH (2.88 g, 72.0 mmol) was gradually added to a solution of **1** (10.0 g, 48.0 mmol) in 200 mL of THF and stirred for 50 min. A solution of allyl bromide (8.72 g, 72 mmol) in 90 mL of THF was then added and stirred at 50 °C for 20 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The ethyl acetate was evaporated and the obtained residue purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent to yield 6-(benzyloxy)-5,5,6,-trimethyl-4-oxaheptene (**2**; 8.37 g, 70.22%) as a colorless oil.

Product **2** (8.37 g, 33.7 mmol) was added to a solution of sodium borohydride ($NaBH_4$) in 20 mL of THF. While the mixture was being stirred in an ice bath, a solution of boron trifluoride etherate complex [$BF_3(C_2H_5)_2O$; 2.87 g, 20.2 mmol] in 30 mL of THF was added gradually over 1 h. After **2** was consumed (determined by TLC), 3 M NaOH (0.54 g, 13.48 mmol) was added, followed by the 30% H_2O_2 (4.6 mL, 40.4 mmol). The reaction mixture was stirred for 3 h. The reaction product was then extracted three times with ethyl acetate and the obtained residue purified by a silica gel column chromatography with hexane−ethyl acetate (6:1) as the eluent to yield 6-(benzyloxy)-5,5,6-trimethyl-4-oxaheptanol (**3**; 4.92 g, 54.8%) as a colorless oil.

A solution of **3** (3.63 g, 13.6 mmol) in 15 mL of methanol was added to a suspension of 7.5 wt % Pd−C (1.8 g, 50 wt %) in 20 mL of methanol. The methanol mixture was stirred at room temperature under 1 atm H_2 for 22 h. After the solid was filtered off, the liquid was evaporated to yield 2,3,3-trimethyl-4-oxa-2,7-heptanediol (**4**; 2.00 g, 83.4%). NaH (1.35 g, 33.7 mmol) was added to a solution of pinacol (1.66 g, 14.1 mmol) in THF (50 mL) and stirred for 30 min. A solution of benzyl bromide (7.77 g, 33.7 mmol) in 75 mL of THF was added gradually to this mixture. The mixture was then stirred at 60 °C for 5 days. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The solvent was then evaporated and the obtained residue purified by silica gel column chromatography with hexane−ethyl acetate (4:1) as the eluent to yield 1,8-bis(benzyloxy)-4,4,5,5-tetramethyl-3,6-dioxaoctane (**5**; 337.6 mg, 6.22%) as a colorless oil.

A solution of product **5** (842.3 mg, 2.18 mmol) in 10 mL of methanol was added to a suspension of 7.5 wt % Pd−C (420 mg, 50 wt %) in 4 mL of methanol. The mixture was stirred at room temperature under 1 atm H_2 for 20 h. After the solid was filtered off, the mixture was evaporated to yield 4,4,5,5- tetramethyl-3,6-dioxa-1,8-octanediol (**6**; 2.00 g, 59.6%).

Tosyl chloride (544.5 mg, 2.86 mmol) was added to a solution of **6** (267.8 mg, 1.30 mmol) in 3 mL of pyridine and stirred for 3 h in an ice bath. The reaction mixture was evaporated and the residue extracted three times with ethyl acetate. The solvent was collected and evaporated. The obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (2:1) as the eluent to yield 4,4,5,5-tetramethyl-3,6-dioxa-1,8-octanediol ditosylate (**7**; 314.6 mg, 47.1%) as a white solid.

NaH (97.8 mg, 2.45 mmol) was added to a solution of **4** (107.7 mg, 0.61 mmol) in THF (3 mL) and stirred for 30 min. A solution of **7** (314.6 g, 0.6 mmol) in 5 mL of THF was then added to this mixture and stirred at 70 °C for 22 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The ethyl acetate was then evaporated and the obtained residue purified by silica gel column chromatography with hexane−ethyl acetate (1:1) as the eluent to yield 2,2,3,3,8,8,9,9-octamethyl-1,4,7,10,13-pentaoxacyclohexadecane (DTM16C5A; 18.4 mg, 8.69%) as a colorless oil. Analytical data for DTM16C5A are as follows: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.20 (s, 24H, 8 $-CH_3$), 1.75 (m, 2H, $-CH_2CH_2CH_2$), 3.30−3.80 (m, 12H, $-OCH_2-$). Anal. Calcd for $C_{19}H_{38}O_5$ (346.51): C, 65.86; H, 11.05. Found: C, 65.89; H, 11.01.

(ii) DTM16C5B (2,2,3,3,11,11,12,12-Octamethyl-1,4,7,10,13-pentaoxacyclohexadecane). To a solution of pinacol

(7.27 g, 61.5 mmol) and malonaldehyde bis(dimethyl acetal) (5.0 g, 30.45 mmol) in benzene (150 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (100 mg), and the mixture was stirred at 90 °C for 2 h. The reaction mixture was then evaporated and partitioned three times with chloroform. The chloroform was then evaporated and the residue purified by silica gel column chromatography with hexane−ethyl acetate (4:1) as the eluent to yield 2,2′-methylenedi-4,4,5,5-tetramethyl-1,3-dioxolane (**8**; 7.87 g, 95.0%) as white crystals.

A solution of lithium aluminum hydride (752 mg, 19.8 mmol) in 10 mL of ether was added to a solution of aluminum chloride (10.57 g, 79.3 mmol) in 130 mL of ether and stirred in a water bath for 30 min. Product **8** (3.0 g, 11 mmol) was then added and the solution stirred for 3 h. After the addition of water (25 mL), followed by addition of 10% H_2SO_4 solution (25 mL), the organic layer was decanted and the water phase extracted three times with ethyl acetate. The organic solvent was then collected and evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (1:1) as eluent to yield 2,3,3,9,9,10-hexamethyl-4,8-dioxa-2,10-undecanediol (**9**; 2.46 g, 80.9%) as a white solid.

NaH (290 mg, 7.2 mmol) was added to a solution of **9** (500 mg, 1.8 mmol) in THF (10 mL) and stirred at 40 °C for 1 h. A solution of diethylene glycol dimesylate (474.3 g, 1.8 mmol) in 10 mL of THF was then added to this mixture. The mixture was then stirred at 70 °C for 20 h, and a small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The organic solvent was then evaporated and the obtained residue purified by silica gel column chromatography with hexane−ethyl acetate (1:4) as the eluent to yield 2,2,3,3,11,11,12,12-octamethyl-1,4,7,10,13-pentaoxacyclohexadecane (DTM16C5B; 23.4 mg, 3.7%) as a colorless oil. Analytical data for DTM16C5B are as follows: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.16 and 1.20 (s, 24H, 8 $-CH_3$), 1.72 (m, 2H, $-CH_2CH_2CH_2$), 3.54−3.68 (m, 12H, $-OCH_2-$). Anal. Calcd for $C_{19}H_{38}O_5$ (346.51): C, 65.86; H, 11.05. Found: C, 66.01; H, 11.07.

(iii) DD16C5 (2,6,13,16,19-Pentaoxapentacyclo[18.4.4.4^{7,12}.0^{1,20}.0^{7,12}]dotriacontane). To a solution of *cis*-1,6-dihydroxybicyclo[4.4.0]decane (4.19 g, 24.6 mmol) and malonaldehyde bis(dimethyl acetal) (2.0 g, 12.2 mmol) in benzene (60 mL) was added a small amount of *p*-toluenesulfonic acid monohydrate (400 mg), and the solution was stirred at 90 °C for 2 h. The reaction mixture was evaporated and partitioned three times with chloroform. The organic solvent was then evaporated. The residue was dissolved in a small amount of chloroform (20 mL), and then methanol (20 mL) was added and the mixture cooled at 0 °C for 2 h. The resulting white crystals were filtered out and identified as 12,12′-methylenedi-11,13-dioxatricyclo[4.4.3.0^{1,6}]tridecane (**10**: 2.35 g, 51.4%).

A solution of lithium aluminum hydride (436 mg, 11.47 mmol) in 10 mL of ether was added to a solution of aluminum chloride (6.12 g, 45.89 mmol) in 130 mL of ether and stirred in a water bath for 30 min. Product **10** (2.4 g, 6.37 mmol) was then added and the solution stirred for 3 h. After the addition of water (25 mL), followed by addition of 10% H_2SO_4 solution (25 mL), the solvent was decanted and the water phase extracted three times with ethyl acetate. The organic solvent was evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (4:1) as eluent to yield 6,6′-(propylenedioxy)di-*cis*-1-hydroxydecane (**11**; 821.1 mg, 33.8%) as a white solid.

NaH (250 mg, 6.25 mmol) was added to a solution of **11** (380.4 mg, 1.0 mmol) in THF (8 mL) and stirred at 40 °C for 1 h. A solution of diethylene glycol dimesylate (262.1 g, 1.0 mmol) in 6 mL of THF was added to this mixture. The mixture was then stirred at 70 °C for 20 h. A small amount of methanol (20 mL) was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The organic solvent was then evaporated, and the obtained residue was purified by HPLC with acetone as the eluent to yield 2,6,13,16,19-pentaoxapentacyclo[18.4.4.4^{7,12}.0^{1,20}.0^{7,12}]dotriacontane (DD16C5; 68.5 mg, 15.2%) as a colorless oil. Analytical data for DD16C5 are as follows: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.10−2.35 (m, 34H, $-CH_2-$), 3.25−4.00 (m, 12H, $-OCH_2-$). Anal. Calcd for $C_{27}H_{46}O_5$ (450.67): C, 71.96; H, 10.29. Found: C, 72.01; H, 10.33.

(iv) C14-DTM16C5B (2,2,3,3,11,11,12,12-Octamethyl-6-tetradecyl-1,4,7,10,13-pentaoxacyclohexadecane). Trityl chloride (7.62 g, 27.3 mmol) was added to a solution of 1,2-hexadecanediol (7.0 mg, 27.08 mmol) in 300 mL of pyridine and stirred at 60 °C for 12 h. The reaction mixture was then evaporated, and the residue was extracted three times with ethyl acetate. The organic solvent was evaporated and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (6:1) as the eluent to yield 1-trityloxyhexadecan-2-ol (**12**; 10.0 g, 73.8%) as a white solid.

Mesyl chloride (7.90 g, 68.99 mmol) was added to a solution of (benzyloxy)ethanol (10 g, 65.7 mmol) in 60 mL of pyridine and stirred for 30 min in an ice bath. The reaction mixture was then evaporated, and the residue was extracted three times with ethyl acetate. The solvent was collected and evaporated. The obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (2:1) as the eluent to yield 2-(benzyloxy)-ethanol mesylate (**13**; 12.4 mg, 82.1%) as a colorless oil.

To a solution of product **12** (5.3 g, 10.58 mmol) in THF (60 mL) was added NaH (508 mg, 12.7 mmol), and the mixture was stirred at 40 °C for 1 h. A solution of **13** (2.68 g, 11.6 mmol) in 20 mL of THF was added to this mixture. The mixture was then stirred at 70 °C for 20 h. A small amount of methanol (20 mL) was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (19:1) as the eluent to yield 5-(benzyloxy)-2-tetradecyl-1-(trityloxy)-3-oxapentane (**14**; 4.05 g, 60.2%) as a colorless oil.

Product **14** was dissolved in mixture of THF−H_2O−AcOH (4:1:7 v/v/v; 120 mL) and stirred at 60 °C for 4 h. After evaporation of the solvent, the residue was extracted three times with ethyl acetate. Then organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (6:1) as the eluent to yield 5(benzyloxy)-2-tetradecyl-3-oxapentan-1-ol (**15**; 4.88 g, 69.3%) as a colorless oil.

A solution of **15** (5.72 g, 14.56 mmol) in 30 mL of ethanol was added to a suspension of 7.5 wt % Pd−C (2.8 g, 50 wt %) in 30 mL of ethanol. The reaction mixture was then stirred at room temperature under 1 atm H_2 for 20 h. After the solid was filtered off, the mixture was evaporated to yield 2-tetradecyl-3-oxa-1,5-pentanediol (**16**; 4.21 g, 95.4%) as a colorless oil.

Mesyl chloride (3.34 g, 29.16 mmol) was added to a solution of **16** (4.20 g, 13.88 mmol) in 40 mL of pyridine and stirred for 30 min in an ice bath. The reaction mixture was then evaporated, and the residue was extracted three times with ethyl acetate. The organic solvent was evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (1:1) as the eluent to yield 2-tetradecyl-3-oxa-1,5-pentanediol dimesylate (**17**; 4.81 g, 75.5%) as a colorless oil.

NaH (290 mg, 7.2 mmol) was added to a solution of **9** (500 mg, 1.8 mmol) in THF (15 mL) and stirred at 40 °C for 1 h. A solution of **17** (830 mg, 1.8 mmol) in 12 mL of THF was then added to this mixture. The mixture was then stirred at 70 °C for 20 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The solvent was then evaporated,

and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent. Further purification by HPLC using acetone as the eluent yielded 2,2,3,3,11,11,12,12-octamethyl-6-tetradecyl-1,4,7,10,13-pentaoxacyclohexadecane (C14-DTM16C5B; 180 mg, 18.3%) as a colorless oil. Analytical data for C14-DTM16C5B are as follows: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (t, 3H, $-CH_3$), 1.14 and 1.18 (s, 24H, 8 $-CH_3$), 1.20−1.56 (m, 26H, $-CH_2-$), 1.69 (m, 2H, $-CH_2-$), 3.30−3.74 (m, 11H, $-OCH_2-$). Anal. Calcd for $C_{33}H_{66}O_5$ (542.89): C, 73.01; H, 12.25. Found: C, 72.98; H, 12.28.

(v) C14-DD16C5 (6-Tetradecyl-2,6,13,16,19-pentaoxapentacyclo[18.4.4.4^{7,12}.0^{1,20}.0^{7,12}]dotriacontane). NaH (220 mg, 5.40 mmol) was added to a solution of **11** (513.9 mg, 1.35 mmol) in THF (10 mL) and stirred at 40 °C for 1 h. A solution of **17** (619.4 mg, 1.35 mmol) in 12 mL of THF was then added to this mixture. The mixture was then stirred at 70 °C for 3 days. A small amount of methanol (12 mL) was added to quench the excess NaH. After evaporation of THF, the residue was extracted three times with ethyl acetate. The solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent. Further purification by HPLC using acetone as the eluent yielded 6-tetradecyl-2,6,13,16,19-pentaoxapentacyclo[18.4.4.4^{7,12}.0^{1,20}.0^{7,12}]-dotriacontane (C14-DD16C5; 140.1 mg, 16.0%) as a colorless oil. Analytical data for C14-DD16C5 are as follows: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (t, 3H, $-CH_3$), 1.18−2.40 (m, 60H, $-CH_2-$), 3.10−3.92 (m, 11H, $-OCH_2-$). Anal. Calcd for $C_{41}H_{74}O_5$ (647.04): C, 76.11; H, 11.53. Found: C, 76.51; H, 11.56.

(vi) Nor16C5 (8,11,14,17,20-Pentaoxaspiro[5.15]-1,4-methano-2-heneicosene). NaH (310 mg, 7.68 mmol) was added to a solution of 2,3-bis(hydroxymethyl)-5-norbornene (493.6 mg, 3.2 mmol) in THF (10 mL) and stirred for 1 h at room temperature. A solution of tetraethylene glycol ditosylate (1.609 g, 3.2 mmol) in 10 mL of THF was then added to this mixture. The mixture was then stirred at 70 °C for 20 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted twice with ethyl acetate. The solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (1:2) as the eluent. Further purification by HPLC using methanol as the eluent yielded 8,11,14,17,20-pentaoxaspiro[5.15]-1,4-methano-2-heneicosene (Nor16C5; 253.8 mg, 25.38%) as a colorless oil. Analytical data for Nor16C5 are as follows: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.70−0.80 (m, 1H, −CH−), 1.32−1.58 (m, 3H, −CH−, $-CH_2-$), 2.68 and 2.79 (br, 2H, $-CH_2-$), 3.12−3.88 (m, 20H, $-OCH_2-$), 6.00−6.16 (m, 2H). Anal. Calcd for $C_{17}H_{28}O_5$ (312.41): C, 65.36; H, 9.03. Found: C, 65.38; H, 9.07.

(vii) C18-16C5 (15-Octadecyl-1,4,7,10,13-pentaoxacyclohexadecane). Malonic acid diethyl ester (1.60 g, 9.98 mmol) was added to the suspension of NaH (0.390 g, 9.9 mmol) in 20 mL of ethanol. A solution of 1-bromooctadecane (3.24, 9.7 mmol) in 30 mL of ethanol was then added, and the mixture was refluxed at 80 °C for 14 h. After evaporation of ethanol, the residue was extracted three times with chloroform. The organic solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (hexane−ethyl acetate 9:1) to yield diethyl 2-octadecylmalonate (**18**; 1.91 g, 47.8%). Product **18** (420.6 mg, 1.02 mmol) was added to a suspension of $LiAlH_4$ (58.0 mg, 1.53 mmol) in 5 mL of THF in an ice bath and stirred for 3 h. A small amount of water (1 mL) was then added to this mixture to quench the reaction. After evaporation of THF, the residue was extracted twice with chloroform to yield 2-octadecyl-1,3-butanediol (**19**; 220 mg, 65.7%) as a white crystal. NaH (98.6 mg, 2.47 mmol) was added to a solution of **19** (336.47 mg, 1.03 mmol) and stirred at room temperature for 1 h. A solution of tetraethylene glycol ditosylate (389.78 mg, 68.7 mmol) was then added, and the mixture was refluxed at 80 °C for 14 h. A small amount of methanol (10 mL) was added to quench the excess NaH. After evaporation of THF, the residue was extracted twice with chloroform. The organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent to yield 15-octadecyl-1,4,7,10,13-pentaoxacyclohexadecane C18-16C5; 107.9 mg, 21.6%) as a white crystal. Analytical data for C18-16C5 are as follows: ^{1}H-NMR (270 MHz, $CDCl_3$) and δ 0.87 (m, 3H, $-CH_3$), 1.25 (s, 34H, 17 $-CH_2$), 1.82 (b, 1H, −CH−), 3.44−3.72 (m, 20H, 10 $-CH_2-$). Anal. Calcd for $C_{29}H_{58}O_5$ (486.78): C, 71.56; H, 12.01. Found: C, 71.58; H, 12.05.

(viii) MD-16C5 (2, 5, 8, 11, 15-Pentaoxatricyclo [14.4.4.0] tetracosane). To the DMF solution of triethylene glycol (3.13 g, 20.8 mmol) in an ice bath was added NaH (1.25 g, 31.2 mmol), and the mixture was stirred for 30 min. Benzyl bromide (3.56 g, 20.8 mmol) was then added to the reaction mixture. The reaction mixture was then stirred at 80 °C for 2 h. A small amount of methanol was added to quench the excess NaH. After evaporation of DMF, the residue was extracted twice with ethyl acetate. The organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (9:1) as the eluent to yield 8-(benzyloxy)-3,6-dioxaoctanol (**20**; 2.83 g, 28.3%) as a colorless oil.

NaH (0.71 g, 17.7 mmol) was added to the THF solution of **20** (2.83 g, 11.8 mmol) in an ice bath and stirred for 30 min. Allyl bromide (1.71 g, 1.2 mmol) was then added slowly to this mixture. The reaction mixture was then refluxed for 2 h, and a small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted twice with ethyl acetate. The organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (1:1) as the eluent to yield 12-(benzyloxy)-4,7,10-trioxa-1-dodecene (**21**; 2.52 g, 76.1%) as a colorless oil.

To the THF suspension of $NaBH_4$ (0.139 g, 4 mmol) and BF_3 ethereal complex (0.757 g, 5.33 mmol) was added a THF solution of **21** (2.52 g, 9.0 mmol), and the mixture was stirred for 2 h. A small amount of water was then added to this mixture, followed by of 2.1 mL of NaOH (3 M) solution and 1.51 mL of 30% H_2O_2 solution, and this mixture was stirred for 2 h. The reaction mixture was then extracted with ethyl acetate and the organic solvent evaporated. The residue was purified by silica gel column chromatography (hexane−ethyl acetate 9:1) to yield 12-(benzyloxy)-4,7,10-trioxadodecanol (**22**; 0.86 g, 32.5%).

To the methanol solution of **22** (583 mg, 1.95 mmol) was added 10% Pd−C (291 mg, 50 wt %), and the reaction mixture was stirred at room temperature under 1 atm H_2 for 3 h. After the solid was filtered off, the mixture was evaporated to yield 3,6,9-trioxa-1,12-dodecanediol (**23**; 383 mg, 94.3%) as a colorless oil. Tosyl chloride (1.052 g, 5.52 mmol) was added to a solution of **23** (383 mg, 1.84 mmol) in 10 mL of pyridine and stirred for 1 h in an ice bath. The reaction mixture was then evaporated, and the residue was extracted three times with ethyl acetate. The organic solvent was evaporated, and the obtained residue was purified by silica gel column chromatography with hexane−ethyl acetate (1:2) as the eluent to yield 3,6,9-trioxa-1,12-dodecanol ditosylate (**24**; 612 mg, 64.4%) as a colorless oil. NaH (188.8 mg, 4.72 mmol) was added to a solution of *cis*-decalindiol (201 mg, 1.18 mmol) in THF (20 mL) and stirred for 1 h. A solution of **24** (612 mg, 1.18 mmol) in 7 mL of THF was then added to this mixture and stirred at 70 °C for 24 h. A small amount of methanol was added to quench the excess NaH. After evaporation of THF, the residue was extracted twice with ethyl acetate. The organic solvent was then evaporated, and the obtained residue was purified by silica gel column chromatography (hexane−ethyl acetate 1:9) to yield 2,5,8,11,15-pentaoxatricyclo[14.4.4.0] tetracosane (MD-16C5; 40 mg, 10.0%) as a colorless oil. Analytical data for MD-16C5 are as follows: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.22−2.18 (m, 18H, dec-H and $-CH_2-$), 3.30−3.88 (m, 16H, 8 $-OCH_2$). Anal.

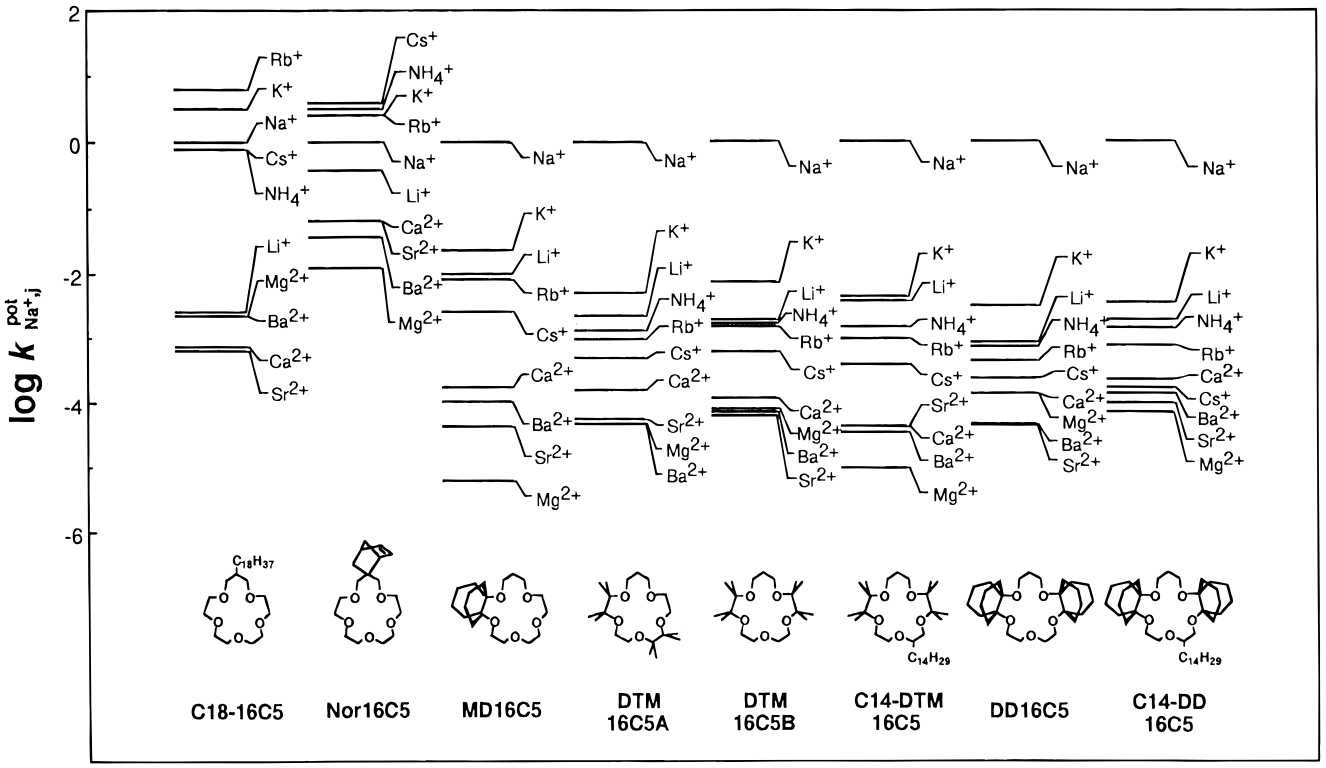

Figure 2. Ion selectivity factors (log $k^{pot}_{Na,j}$, j is the interfering ion) of the electrodes based on 16-crown-5 derivatives as novel Na^+-selective ionophores.

Calcd for $C_{19}H_{34}O_5$ (342.48): C, 66.64; H, 10.01. Found: C, 66.67; H, 10.04.

Electrode Preparation and emf Measurements. Ion-sensitive membranes of the PVC matrix type were prepared according to the previously described procedures.[6] The polymeric membrane composition was normally 3 wt % ionophore, 67.9 wt % membrane solvent BBPA, 29.1 wt % PVC, and 10 mol % (relative to the ionophore) potassium tetrakis(*p*-chlorophenyl)borate (KTpClPB, Dojindo Laboratories, Kumamoto, Japan) unless otherwise stated. The membrane thickness was ~100 μm. A 6 mm diameter circle was cut from a prepared membrane and placed on the tip of the PVC ion-selective electrode body assembly (Liquid Electrode Membrane Kit, DKK Co., Ltd., Tokyo, Japan). The prepared electrodes were immersed in 0.1 M NaCl solution for over 24 h for preconditioning before use. The external reference electrode was a double-junction type Ag/AgCl electrode (HS-305DS, Toa Electronics, Ltd., Tokyo, Japan). The electrode response potential (emf) measurements were performed according to the reported procedure at 25 ± 0.5 °C using the electrochemical cell system,[6]

Ag|AgCl|3 M KCl||0.3 M NH_4NO_3||test solution|
membrane|0.1 M NaCl|AgCl|Ag

All test solutions were made from chloride salts without any pH-adjusting buffer reagent. The selectivity coefficients k^{pot}_{ij}, where i is the primary ion (Na^+) and j is the interfering ion, were calculated from the response potentials in an alkali metal or alkaline earth metal chloride solution using the fixed interference method (FIM; j = 0.1 M) according to the recommendations of IUPAC and JIS.[7,8]

Determination of Lipophilicities of Ionophores. The lipophilicities of several synthesized ionophores, log $P_{o/w}$ ($P_{o/w}$ is the distribution coefficient between organic liquid and water), were determined with R_f values of reversed-phase thin-layer chromatography (RP-TLC) according to the method reported.[2] The RP-TLC used octadecylsilane-modified silica plates (KC18F, Whatman) that were cut to a length of 20 cm and developed chromatographically with ethanol−water (9:1) as the mobile phase.

RESULTS AND DISCUSSION

Structural Ion Selectivity Features of 16-Crown-5 Derivatives. Based on the molecular model shown in Figure 1, we have designed and synthesized eight kinds of 16-crown-5 compounds, and their ion selectivity features were examined with an ion-selective electrode method using these ionophores. Figure 2 shows the ion selectivity coefficients of the electrode based on these synthesized ionophores, and their chemical structures are also indicated in Figure 2.

One of the synthesized ionophores, C18-16C5, having a normal alkyl group as a lipophilic side chain in the normal 16-crown-5, is not a good fit for this model. In fact, the electrode based on C18-16C5 was more selective for Rb^+ than for Na^+. The ionic diameter of Rb^+ is ~2.9 Å, and therefore it does not fit in the cavity of 16-crown-5 (1.8−2.4 Å). Because the octadecyl group (normal alkyl group) in the C18-16C5 cannot function as the block subunit, this ionophore preferably forms a 1:2 Rb^+−ionophore sandwich complex.

Comparing the ion selectivity of the electrode based on Nor16C5 and MD16C5, which has one bulky subunit, it is clear that a greater block effect can be found by introducing the bulky group into the ethylene part rather than in the pivotal position of the propylene part of the crown ether ring. It is true that the norbornene group is sterically very bulky, but the electrode based on Nor16C5 did exhibit selectivity for alkali metal ions with larger ionic diameter than that of Na^+. We have fully discussed this structural feature in our previous report on highly selective ionophores for Li^+,[5] i.e., that introducing a bulky block subunit close to the binding site oxygen atom in the crown ether compound gave a better block effect. On the other hand, a

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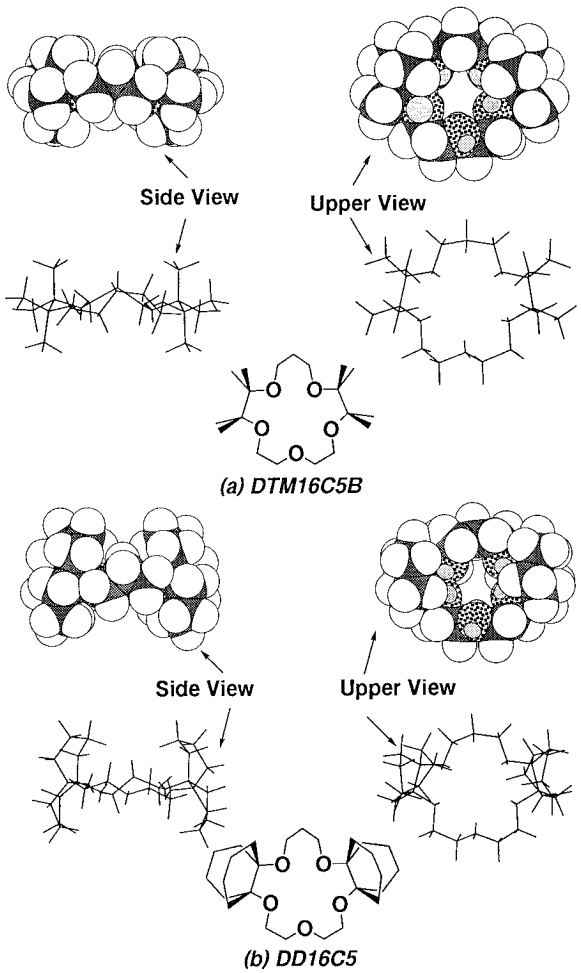

Figure 3. Space-filling (CPK) model views of DTM16C5B (a) and DD16C5 (b).

decalino group in the ethylene part in the crown ether is a very effective block subunit. The electrode based on MD16C5 showed Na^+/K^+ and Na^+/Rb^+ selectivities of 40 and 160, respectively, and it is obvious that introduction of a decalino group has lowered the stability of the sandwich complex.

We have reported another highly effective block subunit: a 2,2,3,3-tetramethyl group (abbreviated as "tetramethyl group") similar to that of the decalino group. We designed two derivatives of 16-crown-5 having two tetramethyl groups and synthesized DTM16C5A and DTM16C5B. Considering of the preparation procedures, facilitated by a procedure developed recently by Sachleben et al.,[9] the total synthetic yield of DTM16C5B obtained was much higher than that of DTM16C5A. The electrodes based on these two derivatives did not show considerable differences in their ion selectivity features, as shown in Figure 2. The Na^+/K^+ selectivity of these electrodes is 100−130; that is, 2−3 times more Na^+-selective compared to the electrode based on 16-crown-5 having one decaline group, MD16C5. With the introduction of two block subunits into the 14-crown-4 as a Li^+ ionophore, a positive block effect is not observed in the Li^+/Na^+ selectivity.[5] On the contrary, it is obviously effective to introduce two block subunits into the Na^+ ionophore based on 16-crown-5.

The 16-crown-5 derivative with two decalino groups, DD16C5, showed a Na^+/K^+ selectivity of over 300. This selectivity is about 3 times that of MD16C5, which has one decalino group. As shown in Figure 3 for the CPK models of DTM16C5B and DD16C5, the differences in effectiveness of the block effect with a tetramethyl group and a decalino group are understandable when one compares the heights of their bulky blocking walls in the crown ring plane and their rigid structures. The lipophilicity of DD16C5 was log $P_{o/w}$= 11.8, and this value fulfills the requirement for application in the analysis of human serum (log $P_{o/w}$ = 11.3),[2] while the log $P_{o/w}$ value for DTM16C5B is 6.3−6.4, not sufficiently lipophilic for the analysis. Thus, C14-DTM16C5, which has a long alkyl group (tetradecyl group) introduced into the DTM16C5, was synthesized. This compound exhibited a log $P_{o/w}$ value of 12.4. Comparing the ion selectivities of DTM16C5B and C14-DTM16C5, it was observed that the latter ionophore exhibited slightly better Na^+ selectivity relative to all other tested cations, as shown in Figure 2. This result indicates that the tetradecyl group showed the block effect to some extent.

Similarly, C14-DD16C5, a DD16C5 derivative having a tetradecyl group as the lipophilic side chain was also synthesized. The log $P_{o/w}$ value of C14-DD16C5 was very high (20.4), but its Na^+/K^+ selectivity was slightly lower compared to that of DD16C5. This fact indicates that introduction of additional numbers of block subunits into DD16C5 resulted in a negative effect on the Na^+/K^+ selectivity, which interfered with the cavity space fit of Na^+. A similar result was observed in the investigation of the lithium ionophore design based on 14-crown-4.[5] Thus, it is understandable that for a sodium ionophore design based on 16-crown-5, there is also a suitable position and an optimum number of block subunits in the crown ring.

Optimization of the Electrode Membrane Based on DD16C5 and Its Response Characteristics. Among eight kinds of newly synthesized ionophores, DD16C5 exhibited the best Na^+ selectivity relative to other tested cations. Thus, in order to find the best response membrane composition, we conducted an optimization study using DD16C5 as an ion-sensing component for the electrode membrane. In the case of the electrode membrane employing BBPA as a low polarity membrane solvent (ϵ = 4; ϵ is the dielectric constant), when the quantity of the ionophore DD16C5 was varied to 1, 3, 5, 10, and 20 wt %, the resulting ion selectivity features were not varied significantly in these electrodes (in the case where the DD16C5 content in the membrane was >20 wt %, the membrane plasticity was decreased and the strength of the membrane was reduced). The lipophilic anionic additive, KTCPB, was added to the electrode membrane to prevent anionic interference from the test solution; however, if the addition is too much, it will decrease the selectivity for the primary ion, because KTCPB acts as a cation exchanger in its anion form ($TCPB^-$). When the quantity of KTCPB was varied to 5, 10, 20, 30, 50, and 100 mol % relative to the molar quantity of the ionophore, it was observed that 5−10 mol % is the optimum quantity of KTCPB to be added to the electrode membrane based on DD16C5. When the quantity of KTCPB was 20 mol % and 30−50 mol %, ~8% and 10−20% decreases were observed in the Na^+/K^+ selectivity, respectively. For the membrane with 100 mol% KTCPB, the electrode membrane selectivity was close to the selectivity of the TCPB anion itself, for which the Na^+/K^+ selectivity was only approximately 2.

As for the plasticizer for the PVC matrix membrane, besides BBPA which has been discussed up to this point, we have also examined three other types of membrane solvents (plasticizers): DBE, NPOE, and TEHP. BBPA, which is often used in practical applications, is a highly lipophilic ester-type plasticizer with low polarity (ϵ = 4); DBE is an ether-type plasticizer with low polarity (ϵ = 4); and NPOE is a relatively high polarity ether-type plasticizer (ϵ = 24). TEHP is a phosphate-type ester, and it is known that the P═O group in the phosphate has a relatively strong ability to bind alkali metal ions such as Li^+.[10] Among these three membrane solvents (BBPA, DBE, and NPOE), the electrode using BBPA as the membrane solvent exhibited a slightly better Na^+ selectivity, but the electrode using TEHP as a membrane

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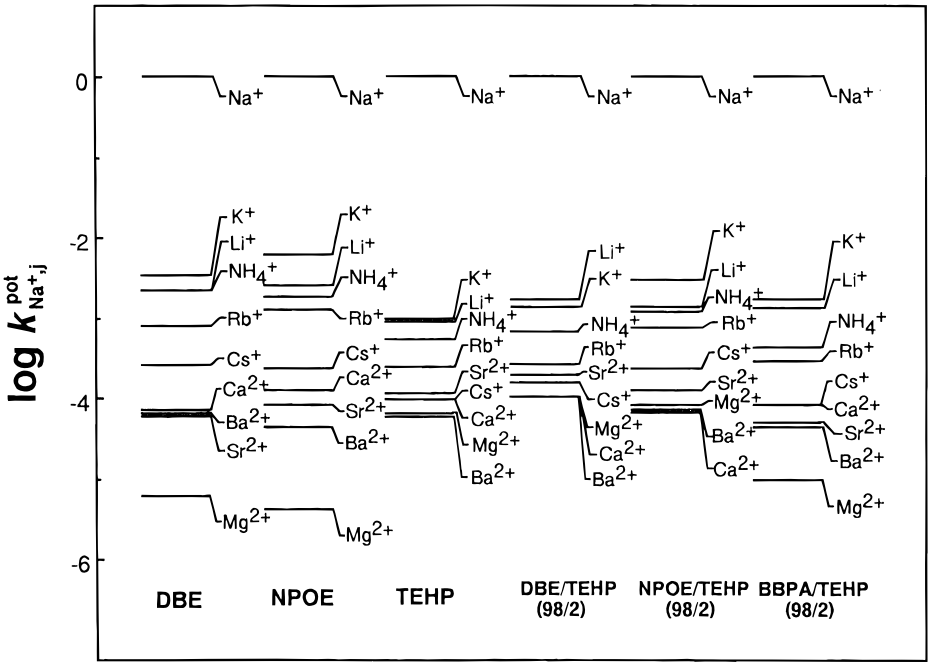

Figure 4. Ion selectivity factors (log $k^{pot}_{Na,j}$, j = interfering ion) of the electrodes based DD16C5 with different membrane solvents (DBE, dibenzyl ether; NPOE, 2-nitrophenyl octyl ether; TEHP, tris(ethylhexyl) phosphate).

solvent showed better Na^+ selectivity, even compared to that based on BBPA, as shown in Figure 4. The Na^+/K^+ selectivity of the electrode based on DD16C5 and TEHP was 1000; therefore, it is one of the best Na^+ electrodes reported to date. This membrane solvent, TEHP, was also tested for the Li^+ electrode based on a highly Li^+-selective ionophore, monodecalino-14-crown-4. However, a positive result was not observed in its ion selectivity features, including Li^+/Na^+ selectivity.[5] In the case of 14-crown-4 as a Li^+ ionophore, the coordination number of 4 is the best fit for a small ion (Li^+), so the other binding site offered by the solvent molecule (TEHP) was not needed. On the contrary, in the case of the Na^+ ionophore based on 16-crown-5, even in the case of DD16C5, the TEHP molecule effectively coordinates with Na^+, together with the ionophore which has five oxygens. As shown in Figure 4, when 2 wt % TEHP was used with BBPA, DBE, or NPOE as the membrane solvent, an increase in Na^+/K^+ selectivity was also observed. In relation to this fact, the following two subjects are considered to affect Na^+ coordination: (1) The coordination number 5 offered by the 16-crown-5, which is the lowest suitable number for Na^+. In fact, some bis(benzo-12-crown-4) compounds have a coordination number of 8.[11] (2) The larger the ring size in the crown compound, the larger will be the open space in the upper and lower sides of the crown ether plane. The 16-membered crown does not have a large ring size, but the space fit for the P═O in the TEHP molecule to coordinate with the DD16C5−Na^+ complex is sterically possible.

The response of the electrode based on DD16C5 and TEHP to a human blood fluid level Na^+ concentration was examined. The response curve of the electrode in test solutions containing 120 mM K^+, 2 mM Li^+, 3 mM Mg^{2+}, and 1 mM Ca^{2+}, a composition similar to that of a typical normal human intracellular fluid,[1] showed an almost Nernstian response down to a Na^+ concentration of 10^{-4} M, as shown in Figure 5. The mathematically calculated required selectivity coefficient of log $k^{pot}_{Na,K}$ for the determination of Na^+ in a human intracellular fluid is −3.5, with 1% error in the worst case.[1] The electrode based on DD16C5 and TEHP could determine the Na^+ in a human intracellular fluid. In addition, with this response curve in Figure 5, a Na^+/K^+ selectivity of over 1000 was also determined.

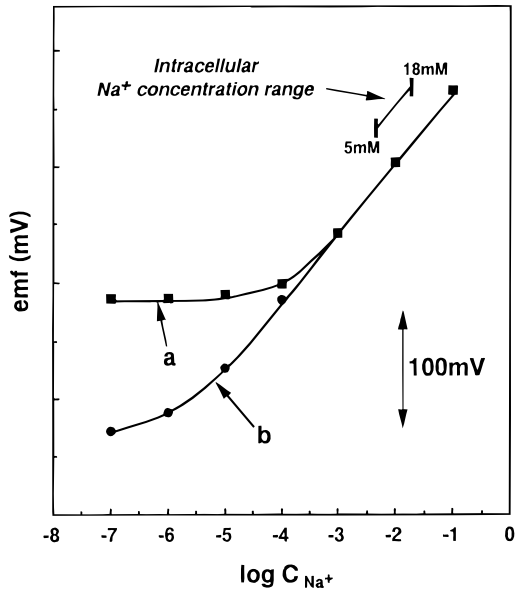

Figure 5. Typical response curves for Na^+ obtained with the electrode based on DD16C5. Curves a and b indicate the response curves for Na^+ with and without interfering ions, respectively, similar to the normal ion concentration levels of human intracellular fluid (120 mM K^+, 2 mM Li^+, 3 mM Mg^{2+}, and 1 mM Ca^{2+}).

Until recently, in relation to the development of a Na^+-selective electrode, many ionophores for Na^+, including diamide,[12,13] hemispherand,[14] biscrown,[10,11] monensin derivative,[15,16] calixarene,[17−20] and 16-crown-5 derivatives,[3,21,22] were synthesized and utilized as

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the Na^+ sensing component for the electrode. In these reported data, only the calixarene-type ionophore had a Na^+/K^+ selectivity of more than 1000 ($\log k^{pot}_{Na,K} < -3.0$).[20] But, unfortunately, our examination of the electrode obtained from the developer showed a different selectivity value ($\log k^{pot}_{Na,K} = -2.6$ to 2.8) compared to the reported value ($\log k^{pot}_{Na,K} < -4.0$). In our opinion, they omitted the preconditioning step using an electrolyte containing Na^+, so they actually measured the non-steady-state potential response values.

CONCLUSIONS

In this report, we propose a simple Na^+ ionophore molecular model and successfully develop a highly selective ionophore for Na^+ based on this model. The examination of the ionophore chemical structures and their ion selectivity features contributes to host−guest chemistry, especially for alkali metal cation ligand or complex design. In this case, the block subunit, which plays a very important role in providing a large positive effect on the ion-selective characteristic of the ionophore molecule, is unfortunately not yet a common useful factor in the host molecule design. However, in the near future, most of the reseachers involved in host−guest chemistry will recognize the importance of this subject. Using a methodological approach similar to that discussed in the present research, we have also successfully developed highly selective ionophores for Li^+, Ca^{2+}, and Mg^{2+}. The appropriate ionophore design and synthesis could be realized to offer many useful chemical ion sensors having high selectivity for analytes, such as selectivities of over 1000 relative to other interferents.[5,23]

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