accurate result (5). The lactate and creatinine sensors illustrate that complex enzymatic systems can be used under nonoptimal conditions and with non-steady-state responses to give a fast analytical readout, which can be important in many cases. For systems independent of reagent addition, it will be an improvement to control the pH of the sensor by the use of buffer deposition in the sensor membrane.

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Design and Synthesis of Lithium Ionophores for an Ion-Selective Electrode by Chemical Modification of Natural Carboxylic Polyether Antibiotic Monensin

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Ion-selective electrodes were prepared with 12 kinds of monensin derivatives obtained by chemical modification of natural antibiotic monensin, and the relationship between the chemical structures of the derivatives and the ion selectivities of those electrodes was investigated for designing Li^+-selective ionophores. Lactonization of monensin and subsequent acylation of its tertiary hydroxyl group are effective for obtaining highly Li^+-selective ionophores. Of all the monensin derivatives synthesized, macrocyclic monensin monoisobutyrate proved to have the highest Li^+ selectivity. The selectivity coefficient of Li^+ to Na^+ (log K^{pot}_{LiNa}) was −1.8 in the poly(vinyl chloride) (PVC) matrix membrane electrode, which was prepared by using the macrocyclic monensin derivative and dibenzyl ether (DBE) as the membrane solvent.

INTRODUCTION

Natural ionophores generally have fairly complicated chemical structures by which they can coordinate ions tridimensionally into themselves by means of oxygen or nitrogen atoms existing in their molecules (*1*, *2*). These structures are stereospecifically accurate and have firm ionic coordination. They are attractive as starting materials for creating many ionophores that have excellent specific ion selectivity. Furthermore, to examine physicochemical properties of the derivatives obtained by chemical modifiation of natural ionophores, it is helpful to understand the complicated and skillful structure of natural molecules.

It has been reported from the crystallographical data (*3*, *4*) that monensin (Figure 1a), possessing some furans, pyrans, and a spiro ring, forms a lipophilic and stable complex with Na^+ by forming a pseudocyclic molecule with a hydrogen bond between the carboxyl group at one end of the molecule and the hydroxyl group at the other end. Some functional groups such as a carboxyl group (C1, see Figure 1a) and three hydroxyl groups (primary, C26; secondary, C7; tertiary, C25) in the monensin molecule can be modified with relative ease; hence, we can produce a number of monensin derivatives.

We previously reported (*5*) that the ion-selective electrode based on C1–C26 lactone monensin (macrocyclic monensin; see Figure 1h) exhibits high Li^+ selectivity, although natural monensin based electrodes show high Na^+ selectivity.

In the present report, 12 kinds of monensin derivatives were synthesized to create highly Li^+-selective ionophores, and the relationship between the molecular structures of the derivatives (discussed mainly with NMR spectroscopy) and their ion selectivities measured by potentiometry was investigated to design Li^+-selective ionophores for an ion-selective electrode. As a result, macrocyclic monensin monoisobutyrate (Figure 1m), which was synthesized from the lactonization of monensin followed by the acylation (isobutyrylation) to the tertiary hydroxyl group, showed excellent Li^+ selectivity.

EXPERIMENTAL SECTION

Reagents. All chemicals used were reagents of the highest grade commercially available. Distilled deionized water had resistivities greater than 1.5×10^7 Ω cm at 25 °C.

Monensin Derivatives. The chemical structures of the derivatives synthesized by chemical modification of natural monensin are indicated in Figure 1b–m. The NMR spectra for structural analysis of these molecules were measured with GX 400 (400 MHz for ^1H) and GSX 270 (270 MHz for ^1H, 68 MHz for ^{13}C) NMR spectroscopy (JEOL Co., Ltd., Tokyo). Monensin methyl ester (b) was synthesized by treating monensin (Sigma Chem. Co., St. Louis, Mo) with methyl iodide and 1,8-diazabicyclo[5.4.0]un-

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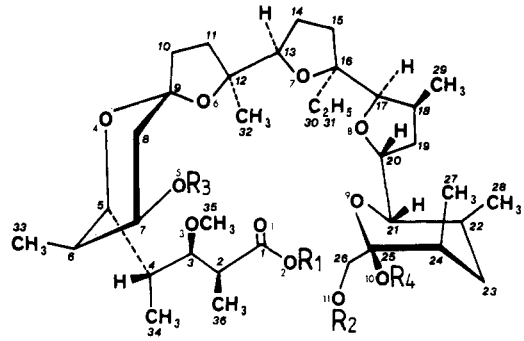

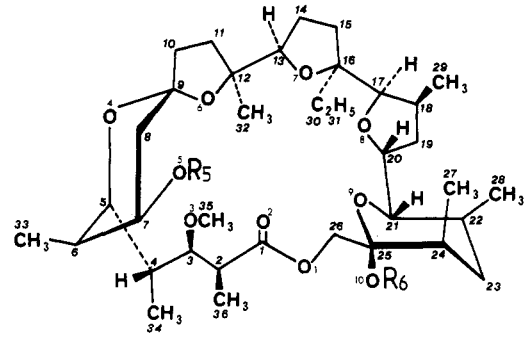

monensin (a)

$R_1 = H$, $R_2 = R_3 = R_4 = H$

monensin methyl ester (b)

$R_1 = {}^{37}CH_3$, $R_2 = R_3 = R_4 = H$

monensin dodecyl ester (c)

$R_1 = {}^{37-48}C_{12}H_{25}$, $R_2 = R_3 = R_4 = H$

monensin methyl ester-1-monoacetate (d)

$R_1 = {}^{37}CH_3$, $R_2 = {}^{39}CH_3{}^{38}CO^{12}$, $R_3 = R_4 = H$

monensin methyl ester-1,2-diacetate (e)

$R_1 = {}^{37}CH_3$, $R_2 = {}^{39}CH_3{}^{38}CO^{12}$, $R_3 = {}^{41}CH_3{}^{40}CO^{13}$, $R_4 = H$

monensin methyl ester-1,3-diacetate (f)

$R_1 = {}^{37}CH_3$, $R_2 = {}^{39}CH_3{}^{38}CO^{12}$, $R_3 = H$, $R_4 = {}^{41}CH_3{}^{40}CO^{13}$

monensin methyl ester-1,2,3-triacetate (g)

$R_1 = {}^{37}CH_3$, $R_2 = {}^{39}CH_3{}^{38}CO^{12}$, $R_3 = {}^{41}CH_3{}^{40}CO^{13}$,

$R_4 = {}^{43}CH_3{}^{42}CO^{14}$

macrocyclic monensin (h)

$R_5 = R_6 = H$

macrocyclic monensin monoacetate (i)

$R_5 = H$, $R_6 = {}^{38}CH_3{}^{37}CO^{11}$

macrocyclic monensin diacetate (j)

$R_5 = {}^{40}CH_3{}^{39}CO^{12}$, $R_6 = {}^{38}CH_3{}^{37}CO^{11}$

macrocyclic monensin monopropionate (k)

$R_5 = H$, $R_6 = {}^{39}CH_3{}^{38}CH_2{}^{37}CO^{11}$

macrocyclic monensin monobutyrate (l)

$R_5 = H$, $R_6 = {}^{40}CH_3({}^{39}CH_2{}^{38}CH_2)_2{}^{37}CO^{11}$

macrocyclic monensin monoisobutyrate (m)

$R_5 = H$, $R_6 = {}^{40\,39}(CH_3)_2{}^{38}CH{}^{37}CO^{11}$

Figure 1. Chemical structures of monensin and its noncyclic and macrocyclic derivatives.

dec-7-ene (DBU) in anhydrous benzene for 4 days at room temperature, followed by silica gel column chromatography (PhH–EtOAc 2:1, 75% yield, colorless oil). For compound b IR ($CHCl_3$) ν_{CO} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (d, J = 9.2 Hz, OH (2nd)), 4.28 (dt, J = 3.1, 8.1 Hz, 20 H), 4.00 (dd, J = 2.2, 9.5 Hz, 5 H), 3.88 (br, 7 H), 3.84 (d, J = 4.8 Hz, 17 H), 3.78 (m, 21 H), 3.77 (br, OH (3rd)), 3.71 (s, 37 H), 3.60 (dd, J = 5.9, 9.5 Hz, 13 H), 3.57 (t, J = 5.1 Hz, 3 H), 3.48 (26 H), 3.33 (s, 35 H), 2.67 (dq, J = 5.1, 7.0 Hz, 2 H), 2.63 (br, OH (1st)). Monensin dodecyl ester (c) was obtained by treating monensin with dodecyl iodide and DBU in anhydrous benzene for 5 days at room temperature, followed by silica gel column chromatography (PhH–EtOAc 3:1, 30% yield, colorless oil). For compound c IR ($CHCl_3$) ν_{CO} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09 (t, J = 7.8 Hz, 37 H), 1.26 (m br, 38–48 H). Acetic anhydride was added to the dry pyridine solution of monensin methyl ester and agitated for 12 h at room temperature. Monensin methyl ester monoacetate (d) (60% yield, colorless oil) and monensin methyl ester 1,2-diacetate (e) (8% yield, colorless oil), monensin methyl ester 1,3-diacetate (f) (8% yield, colorless oil) and monensin methyl ester 1,2,3-triacetate (g) (12% yield, colorless oil) were then separated from the pyridine solution by silica gel column chromatography (PhH–EtOAc 5:1). For compound d IR ($CHCl_3$) ν_{CO} 1738–1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, J = 8.8 Hz, OH (2nd)), 4.29, 3.89 (d, gem, J = 10.3 Hz, 26 H_{AB}), 4.13 (s, OH (3rd)), 2.15 (s, 39 H); compound e IR ($CHCl_3$) ν_{CO} 1738–1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (m, 7 H), 4.24, 3.95 (d, gem, J = 11.0 Hz, 26 H_{AB}), 3.75 (s, 37 H), 2.75 (s, OH (3rd)), 2.13 (s, 39 H), 2.08 (s, 41 H); compound f IR ($CHCl_3$) ν_{CO} 1738–1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78, 4.63 (d, gem, J = 17.0 Hz, 26 H_{AB}), 4.05 (d, J = 10.0 Hz, OH (2nd)), 3.72 (m, 7 H), 3.71 (s, 37 H), 2.70 (m, 24 H), 2.16 (s, 39 H), 2.06 (s, 41 H); compound g IR ($CHCl_3$) ν_{CO} 1738–1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77, 4.64 (d, gem, J = 17.0 Hz, 26 H_{AB}), 4.73 (m, 7 H), 3.75 (s, 37 H), 2.73 (m, 24 H), 2.16 (s, 39 H), 2.06 (s, 41 H and 43 H). Macrocyclic monensin (h) was synthesized from monensin, according to Corey's lactonization method (6), to give compound h after silica gel column chromatography (hexane–EtOAc 4:1, 90% yield, colorless oil). For compound h IR ($CHCl_3$) ν_{CO} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, OH (3rd)), 4.68 (d, J = 10.2 Hz, OH (2nd)), 3.97 (dd, J = 3.0, 11.0 Hz, 21 H), 3.85 (7 H), 4.39, 3.69 (d, gem, J = 11.0 Hz, 26 H_{AB}), 2.83 (dq, J = 2.2, 7.0 Hz, 2 H). Macrocyclic monensin acylates (i–m) obtained by the acylation of macrocyclic monensin (h) with corresponding acid anhydrides in dry pyridine for 4 days at 50 °C gave, after silica gel column chromatography (PhH–EtOAc 5:1) and further purification by reversed-phase high-performance liquid chromatography (column: D-ODS-5, 20 (o.d.) × 250 mm (YMC Co., Ltd., Kyoto); eluent: MeOH, 5 mL/min) with refractive index (RI) detection (RI detector, Model SE-51, Showa Denko Co., Ltd., Tokyo), monoacyl derivatives (monoacetate (i), monopropyrate (k), monobutyrate (l), monisobutyrate (m)) and a diacyl derivative (diacetate (j)). Satisfactory elemental analyses and IR spectroscopic data were obtained for all these acylates. For compound i ^1H NMR (400 MHz, $CDCl_3$) δ 4.50, 4.19 (d, gem, J = 19.0 Hz, 26 H_{AB}), 3.96 (d, OH (2nd)), 3.72 (7 H), 2.86 (24 H), 2.81 (2 H), 2.05 (s, 39 H); compound j ^1H NMR (400 MHz, $CDCl_3$) δ 4.84, 4.67 (d, gem, J = 19.4 Hz, 26 H_{AB}), 4.70 (7 H), 3.00 (24 H), 2.75 (2 H), 2.10 (s, 41 H), 2.05 (s, 39 H); compound k ^1H NMR (400 MHz, $CDCl_3$) δ 4.96, 4.48 (d, gem, J = 17.7 Hz, 26 H_{AB}), 3.95 (d, OH (2nd)), 3.70 (7 H), 2.82 (24 H), 2.78 (2 H), 2.32 (q, J = 7.0 Hz, 39 H); compound l ^1H NMR (400 MHz, $CDCl_3$) δ 4.95, 4.50 (d, gem, J = 17.4 Hz, 26 H_{AB}), 3.95 (d, OH (2nd)), 3.71 (7 H), 2.88 (24 H), 2.80 (2 H), 2.29 (t, J = 7.4 Hz, 39 H); compound m ^1H NMR (400 MHz, $CDCl_3$) δ 4.94, 4.51 (d, gem, J = 17.7 Hz, 26 H_{AB}), 3.94 (d, OH (2nd)), 3.70 (7 H), 2.88 (24 H), 2.80 (2 H), 2.54 (m, J = 6.6 Hz, 39 H).

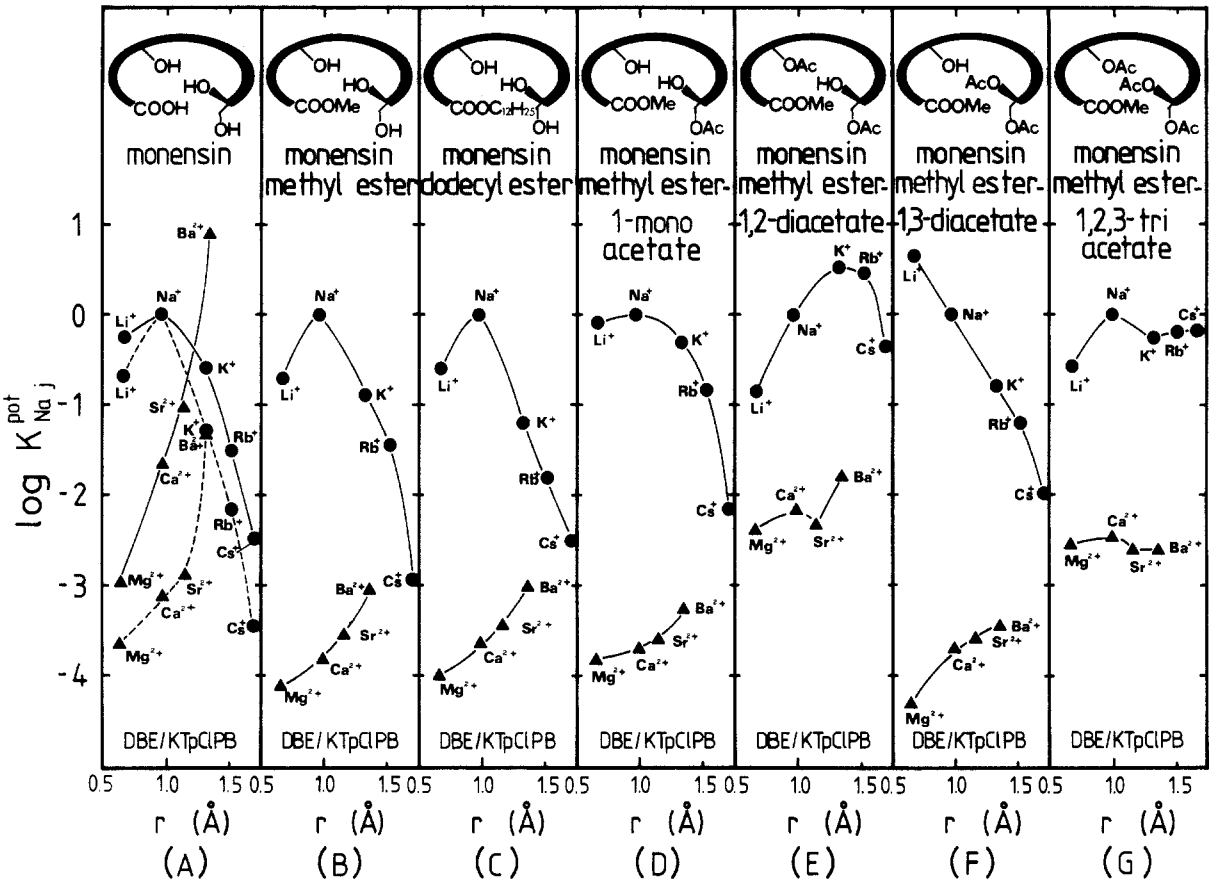

Figure 2. Ion selectivity factors (K^{pot}_{Naj}) for ion-selective electrodes based on monensin and its noncyclic derivatives. (Ion selectivity factors calculated response potentials in a non-pH adjusted 10^{-1} M cation chloride solution are indicated as a broken line.)

Electrode Preparation and emf Measurements. Ion-selective membranes of PVC matrix type were prepared according to a previously reported procedure (*7*). The membrane compositions were 3 wt % ionophore, 1 wt % potassium tetrakis(*p*-chlorophenyl)borate (KTpC1PB), 70 wt % membrane solvent, and 26 wt % PVC (high molecular weight type, Sigma Chemical Co.). Membrane solvents were DBE (ϵ (dielectric constant) = 4; Tokyo Chemical Industry Co., Tokyo), bis(2-ethylhexyl) sebacate (BEHS), ϵ = 4; Tokyo Chemical Industry), diisodecyl phthalate (DIDP, ϵ = 4; Tokyo Chemical Industry), 2-nitrophenyl octyl ether (NPOE, ϵ = 24; Fluka AG, Buchs, Switzerland), and 2-nitrophenyl phenyl ether (NPPE, ϵ = 24; Eastman Kodak Co., Rochester, NY). The membrane thickness was ca. 100 μm. A 7 mm diameter circle was cut out from the prepared membrane and mounted on a Philips IS-561 electrode body for ion-sensitive electrode preparation. The reference electrode was a double-junction type based on an Ag–AgCl electrode (HS-305DS, TOA Electronics, Ltd., Tokyo). Thus the electrode cells for the emf measurements were as follows; Ag;AgCl, 3 M KCl|0.3 M NH_4NO_3|sample|membrane|0.1 M LiCl, AgCl;Ag. The measurement of response potential (emf) based on prepared electrodes was performed according to the previous report (*8*). The sample solutions were cation chlorides, and the activity coefficients were calculated from the equation proposed by Kielland et al. (*9*). The selectivity coefficients of ISE (K^{pot}_{ij}; i, primary ion; j, interfering ion) were calculated from response potentials in a 1×10^{-1} M cation chloride solution by the separate solution method (SSM) based on the recommendation of IUPAC (*10*) and JIS (*11*).

RESULTS AND DISCUSSION

The ion selectivity factors, K^{pot}_{Naj} (*j*, interfering ion), of the electrodes based on natural monensin and six kinds of noncyclic monensin derivatives are shown in Figure 2. As reported previously (*8*), the natural monensin based electrode exhibits high selectivity for Na^+ and Ba^{2+} (Figure 2, column A). Especially, the high Ba^{2+} selectivity is due to the complex formation of negatively charged monensin deprotonated at the carboxylic group with Ba^{2+} as a divalent cation. Therefore, the ion-selectivity factors of the electrode based on natural monensin vary with the degree of deprotonation at the carboxyl group, namely, with the change of sample solution pH. For this reason, the selectivity coefficients (column A) of natural monensin were calculated from response potentials in 0.1 M cation chloride solution adjusted pH 7.0 with 0.1 M Tris/HCl. The selectivity coefficients calculated response potentials in a non-pH-adjusted 10^{-1} M cation chloride solution (prepared with deionized water) are also indicated as a broken line in Figure 2, column A. The electrode based on monensin methyl ester (b), which was obtained from methyl esterification of the carboxyl group of natural monensin and no longer has a negative charge, reduces the binding power to divalent cations such as Ba^{2+}. Consequently, Ba^{2+} selectivity decreased when compared with Na^+ selectivity (column B). However, we reported previously (*8*) that the potential responses (emf) of the electrode based on monensin methyl ester (b) to monovalent cations hardly changed from that of the electrode based on natural monensin. All synthesized 12 monensin derivatives except natural monensin are so-called "neutral carrier ligands" (*12*). The response potentials of the electrodes obtained by using these electrically neutral compounds to 0.1 M cation chloride solutions prepared with a pH adjusting buffer (0.1 M Tris/HCl, pH 7.0) are in accordance with those to the same solution prepared without a pH-adjusting buffer. Thus, the selectivity coefficients were the same for both solutions with and without the buffer. The high Na^+ selectivity of natural monensin hardly changes with the esterification of the carboxyl group of monensin molecule (columns B and C). The ^1H NMR spectra (δ 2.5–5.5 ppm region) of ion-free form and NaI complex form of monensin methyl ester (b) are shown in Figure 3. Using $CDCl_3$ as the solvent for NMR measurements, C26 methylene protons (2 H) of ion-free

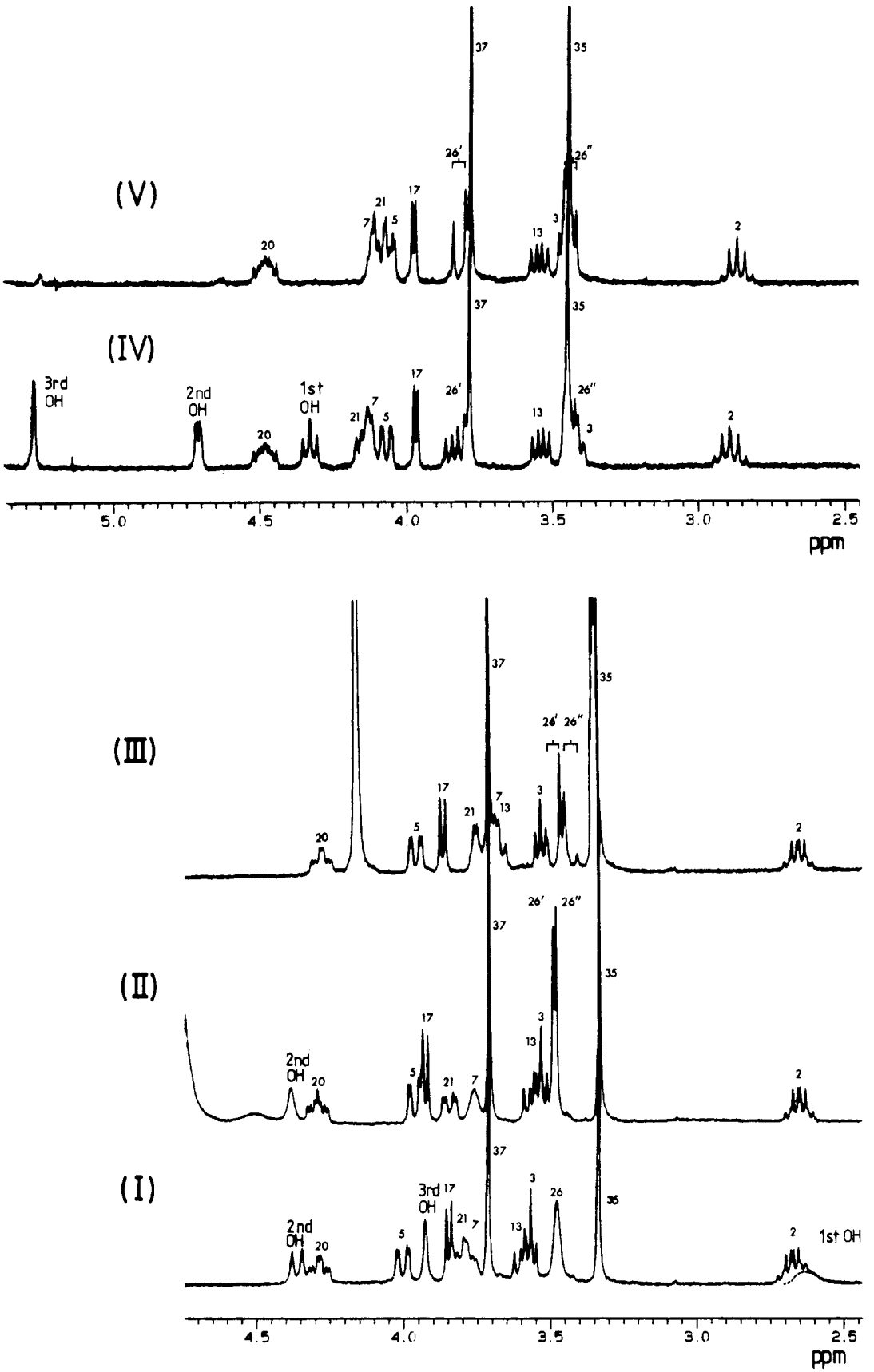

Figure 3. 270-MHz ^1H NMR spectra (2.5–5.5 ppm region) in $CDCl_3$ of monensin methyl ester and monensin methyl ester NaI complex: (I) spectrum of monensin methyl ester; (II) spectrum after treatment of the sample with H_2O; (III) spectrum after treatment of the sample with CD_3OD; (IV) spectrum of monensin methyl ester NaI complex; (V) spectrum of monensin methyl ester NaI complex after treatment with CD_3OD.

monensin methyl ester gave a broad singlet signal. This indicates that the primary hydroxyl group is rotating freely without forming an intramolecular hydrogen bond. In addition, the torsion angle between the O5–H bond and C7–H bond was calculated to be approximately 130° using the coupling constant of 10.2 Hz (J OH (2nd)). Therefore, the

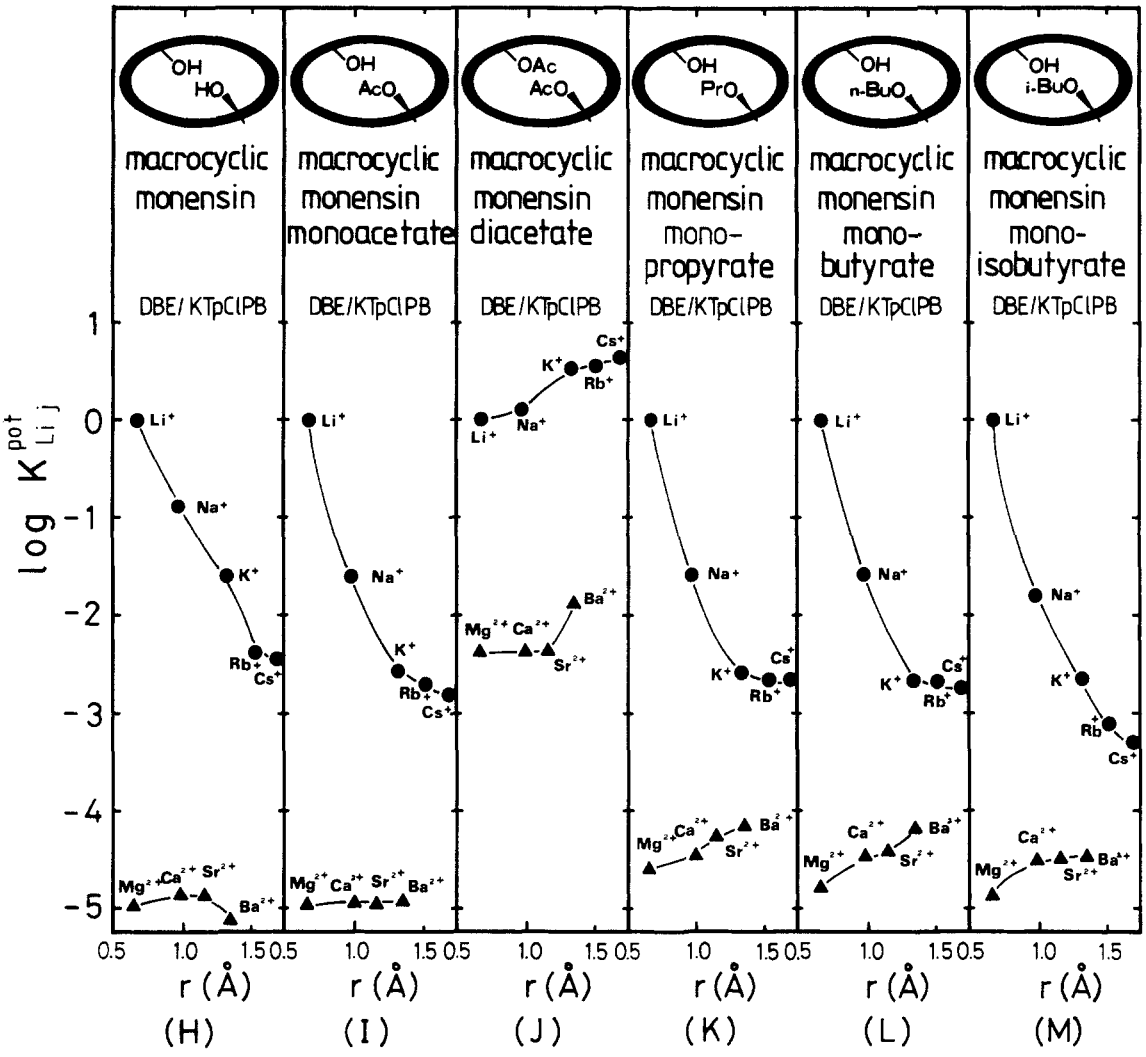

Figure 4. Ion selectivity factors (K^{pot}_{Lij}) for ion-selective electrodes based on macrocyclic monensin and its acyl derivatives.

presence of a hydrogen bond between the hydrogen of the secondary hydroxyl group and the oxygen of the tertiary hydroxyl group was recognized by the reported molecular structure of natural monensin (*13*, *14*) (Figure 3, I). When light water was added to the $CDCl_3$ solution containing ion-free monensin methyl ester, the ^1H NMR signal of the secondary hydroxyl group became a broad singlet. This phenomenon suggests that the hydrogen bond between the secondary and tertiary hydroxyl groups was severed. In this case, the ^1H NMR signal of the C26 methylene protons showed an AB coupling pattern (Figure 3, II). The addition of CD_3OD to this solution also produces an AB coupling pattern having the coupling constant of C26 methylene protons $J(26H_{AB})$ = 12 Hz (Figure 3, III). This fact indicates that the primary hydroxyl group coordinates to the oxygen of the carboxyl group by interposing a solvent molecule (H_2O or CD_3OD) with two hydrogen bonds (O11H~ O (solvent) H or D~ O2). The ^1H NMR spectrum of a monensin methyl ester–NaI complex in $CDCl_3$ is shown in Figure 3, part IV. The ^1H NMR signal of C26 methylene protons shows an AMX coupling pattern ($J(26H_{AM})$ = 11.8 Hz, J(26H, OH5) = 6.2 Hz). These results conclude that the hydrogen bonds of monensin methyl ester (OH5–O10, O11H–O(solvent)H-O2, O11H–O1) make the cavity for cation coordination and also make the tight complex similar to the reported configuration of natural monensin (*3*, *4*, *15*). In such a complex configuration, the esterification of the carboxyl group hardly affects the complex's formation ability to Na^+. In fact, the selectivity coefficients (K^{pot}_{NaK}) of the electrode based on monensin dodecyl ester (c) which possesses a long and bulky side chain at the C1 carboxyl position were almost the same as that of the electrode based on the methyl ester derivative b. Monensin dodecyl ester is much more lipophilic than methyl ester derivative; hence, the Na^+-selective electrode based on compound c is expected to have a long lifetime. On the other hand, Na^+ selectivity of the electrode using monensin methyl ester monoacetate (d), which is obtained by the acetylation of the primary hydroxyl group at the other end of monensin molecule compared to the carboxyl group, was reduced (column D). This result indicates that the primary hydroxyl group of natural monensin is important to the coordination of Na^+. The X-ray diffraction data of monensin–Na^+ complex (*2*, *3*, *15*) also support this consideration. Monensin methyl ester 1,2-diacetate (e), monensin methyl ester 1,3-diacetate (f), and monensin methyl ester 1,2,3-triacetate (g) were obtained by further acetylation of monensin methyl ester monoacetate (d). The electrodes based on compounds e and g in which the acetyl group was introduced to the secondary hydroxyl group did not exhibit any ion selectivity (columns E and G). The acetylation of the secondary hydroxyl group blocks any ion coordination. On the other hand, the electrode using monensin methyl ester 1,3-diacetate (f), which is obtained by the acetylation of primary and tertiary hydroxyl groups, apparently shows Li^+ selectivity (column F). This suggests that the carbonyl oxygen of the acetyl group introduced to the tertiary hydroxyl group contributes to the coordination for Li^+. The chemical modification of the tertiary hydroxyl group also improves Li^+ selectivity of macrocyclic monensin. (The reason will be

Table I. Assignments of ^{13}C NMR Spectra of Macrocyclic Monensin and Macrocyclic Monensin LiCl Complex in CD_3OD, Relative to TMS (δ 0.00) Internal Standard

multiplicity	carbon no.	chemical shift (δ) ion free	chemical shift (δ) LiCl salt	$\Delta\delta$
s	1 (carbonyl)	178.83	177.85	0.98
s	9	109.46	109.00	0.46
s	25	97.76	99.44	-1.68
t	17	87.54	84.98	2.56
s	16, 12	87.37	88.92	-1.56
s		86.85	86.62	0.23
d	13	84.55	79.57	4.98
d	3	80.52	82.36	-1.84
d	20	78.04	78.73	-0.69
d	21	75.82	74.29	1.53
d	7	72.65	70.58	2.07
t	26	69.49	67.88	1.61
d	5	68.88	70.58	-1.70
q	35	58.75	58.69	0.06

discussed later.)

The selectivity coefficients of the electrodes based on macrocyclic monensin derivatives are shown in Figure 4. The macrocyclization (C1–C26 lactonization) of monensin reduces the cavity in comparison with that of a pseudocyclic form of natural monensin. Consequently, the macrocyclic monensin shows Li^+ selectivity (Figure 4, column H). Table I shows ^{13}C NMR (CD_3OD) chemical shift values of the ion-free macrocyclic monensin and its LiCl complex in CD_3OD. In general, the ^{13}C NMR signal for a carbonyl carbon shifts downfield when carbonyl oxygen coordinates to a metal cation (*16*, *17*). However, the ^{13}C signal of C1 lactone carbonyl of macrocyclic monensin shifted slightly upfield (0.98 ppm) by Li^+ complexation. Thus, the C1 lactone carbonyl oxygen does not coordinate to Li^+ directly. The ^{13}C NMR signals for C25, C16, C3, and C5 of the macrocyclic monensin shifted downfield, while signals for C17, C13, C21, C7, and C26 greatly shifted upfield. The conformational rearrangements (*18*) of macrocyclic monensin by complexation with Li^+ affects the ^{13}C NMR chemical shifts, so that the coordination donor site oxygens could not be identified for this molecule with these ^{13}C NMR data.

Macrocyclic monensin possesses two kinds of hydroxyl groups, secondary and tertiary. Judging from the reaction products, the tertiary hydroxyl group acylation occurs prior to the secondary hydroxyl group acylation of the macrocyclic monensin molecule because of the large steric hindrance for the acylation to the secondary hydroxyl group. In fact, the macrocyclic monensin derivative acylated only at the secondary hydroxyl group was not obtained. Therefore, it is considered that the secondary hydroxyl group points toward the cavity. This understanding is reasonable compared with the reported steric structure of a pseudocyclic monensin–Na^+ complex (*3*, *4*, *15*). The electrode based on macrocyclic monensin monoacetate (i) which acylated only to the tertiary hydroxyl group shows higher Li^+ selectivity (Figure 4, column I) than that of the electrode based on macrocyclic monensin (h). The ^{13}C NMR signal for the C37 acetyl carbonyl carbon (δ 177.11 ppm) of macrocyclic monensin monoacetate–Li^+ complex shifted 5.5 ppm downfield in comparison with the signal for its ion-free form (i) (δ 171.60 ppm), while the signal for the C1 (carbonyl) carbon was hardly shifted (<1.0 ppm) by the Li^+ complexation. This large downfield shift (5.5 ppm) concludes that the C37 acetyl carbonyl oxygen of macrocyclic monensin monoacetate (i) apparently contributes to the complexation of Li^+. A similar shift (4–6 ppm) was also reported at the coordination site carbonyl carbon of valinomycin molecule (*19*). The acylation of the tertiary hydroxyl group of macrocyclic monensin is effective for improving Li^+ selectivity. On the other hand, the electrode based on macrocyclic monensin diacetate (j) does not show any specific ion selectivity (Figure 4, column J). An acetyl group introduced to the secondary hydroxyl group orientates itself toward the cavity of the macrocyclic molecule; hence, because the steric

Table II. Ion Selectivity Factors (K^{pot}_{Lij} and K^{pot}_{Naj}) for the Electrodes Based on Monensin and Its Derivatives (Membrane Solvent: DBE)

ionophore	log K^{pot}_{Lij} [log K^{pot}_{Naj}][a] $j = Li^+$	$j = Na^+$	$j = K^+$	$j = Rb^+$	$j = Cs^+$	$j = Mg^{2+}$	$j = Ca^{2+}$	$j = Sr^{2+}$	$j = Ba^{2+}$
monensin (A)[b]	0 [-0.24]	0.24 [0]	-0.32 [-0.56]	-1.3 [-1.5]	-2.2 [-2.4]	-2.7 [-2.9]	-1.4 [-1.6]	-0.76 [-1.0]	1.1 [0.88]
monensin methyl ester (B)	0 [-0.72]	0.72 [0]	-0.16 [-0.88]	-0.68 [-1.4]	-2.2 [-2.9]	-3.4 [-4.1]	-3.1 [-3.8]	-2.8 [-3.5]	-2.4 [-3.1]
monensin dodecyl ester (C)	0 [-0.60]	0.60 [0]	-0.60 [-1.2]	-1.2 [-1.8]	-1.9 [-2.5]	-3.4 [-4.0]	-3.0 [-3.6]	-2.8 [-3.4]	-2.4 [-3.0]
monensin methyl ester 1-monoacetate (D)	0 [-0.10]	0.10 [0]	-0.20 [-0.30]	-0.74 [-0.84]	-2.1 [-2.2]	-3.7 [-3.8]	-3.6 [-3.7]	-3.5 [-3.6]	-3.2 [-3.3]
monensin methyl ester 1,2-diacetate (E)	0 [-0.84]	0.84 [0]	1.4 [0.52]	1.3 [0.45]	0.48 [-0.36]	-1.6 [-2.4]	-1.4 [-2.2]	-1.5 [-2.3]	-0.96 [-1.8]
monensin methyl ester 1,3-diacetate (F)	0 [0.64]	-0.64 [0]	-1.4 [-0.76]	-1.8 [-1.2]	-2.6 [-2.0]	-4.9 [-4.3]	-4.3 [-3.7]	-4.2 [-3.6]	-4.0 [-3.4]
monensin methyl ester 1,2,3-triacetate (G)	0 [-0.56]	0.56 [0]	0.32 [-0.24]	0.36 [-0.20]	0.38 [-0.18]	-1.9 [-2.5]	-1.8 [-2.4]	-2.0 [-2.6]	-2.0 [-2.6]
macrocyclic monensin (H)	0 [0.88]	-0.88 [0]	-1.6 [-0.72]	-2.4 [-1.5]	-2.4 [-1.5]	-5.0 [-4.1]	-4.8 [-3.9]	-4.8 [-3.9]	-5.1 [-4.2]
macrocyclic monensin monoacetate (I)	0 [1.6]	-1.6 [0]	-2.6 [-1.0]	-2.7 [-1.1]	-2.8 [-1.2]	-5.0 [-3.4]	-4.9 [-3.3]	-4.9 [-3.3]	-4.9 [-3.3]
macrocyclic monensin diacetate (J)	0 [0.12]	0.12 [0]	0.52 [0.64]	0.56 [0.68]	0.64 [0.76]	-2.4 [-2.3]	-2.4 [-2.3]	-2.4 [-2.3]	-1.9 [-1.8]
macrocyclic monensin monopropyrate (K)	0 [1.6]	-1.6 [0]	-2.6 [-1.0]	-2.6 [-1.0]	-2.6 [-1.0]	-4.6 [-3.0]	-4.4 [-2.8]	-4.3 [-2.7]	-4.2 [-2.6]
macrocyclic monensin monobutyrate (L)	0 [1.6]	-1.6 [0]	-2.7 [-1.1]	-2.7 [-1.1]	-2.7 [-1.1]	-4.8 [-3.2]	-4.5 [-2.9]	-4.4 [-2.8]	-4.2 [-2.6]
macrocyclic monensin monoisobutyrate (M)	0 [1.8]	-1.8 [0]	-2.6 [-0.80]	-3.1 [-1.3]	-3.3 [-1.5]	-4.9 [-3.1]	-4.5 [-2.7]	-4.5 [-2.7]	-4.5 [-2.7]

[a] Data obtained by the separate solution method (SSM, 0.1 M cation chloride, refs 10 and 11). [b] The selectivity coefficients of the electrode using natural monensin were calculated from response potentials in 0.1 M cation chloride solution adjusted pH 7.0.

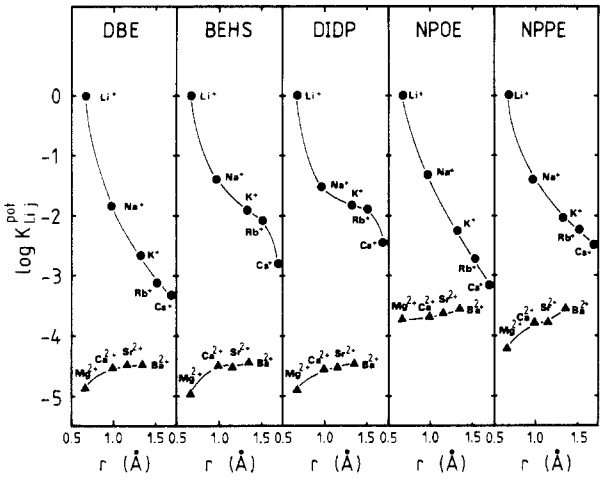

Figure 5. Selectivity factors (K^{pot}_{Li}) for PVC membranes with DBE, BEHS, DIDP, *o*-NPOE, and *o*-NPPE as plasticizer with macrocyclic monensin monoisobutyrate.

hindrance, the diacetate derivative lost its ability to complex any cation. This explanation is also the case in the electrode based on the monensin methyl ester 1,2-diacetate (e) and 1,2,3-triacetate (g) (Figure 2, columns E and G). In order to obtain stronger Li^+-selective monensin derivative, several kinds of acyl groups were introduced to the tertiary hydroxyl group of macrocyclic monensin. The ion-selectivity factors (K^{pot}_{Lij}) of the electrodes based on macrocyclic monensin acetyl (i), propionyl (k), butyryl (l), and isobutyryl (m) derivatives are shown in Figure 4. Among these electrodes, the electrode based on the butyryl derivative showed the best Li^+ selectivity (column M). Introducing a bulky acyl group such as isobutyryl to the tertiary hydroxyl group of the macrocyclic molecule is effective in improving the Li^+ selectivity. The introduced acyl side chain at the tertiary hydroxyl group, which is perpendicular to the cavity of the macrocyclic molecule, blocks the complexation with an ion whose ionic radius is larger than that of Li^+, namely Na^+ and K^+. The ion-selectivity coefficients of the electrodes based on macrocyclic monensin monoisobutyrate (m) with various membrane solvents are shown in Figure 5. The electrodes with relatively high polarity membrane solvents (NPOE and NPPE) give larger K^{pot}_{Lij} values for divalent cations. Therefore, a lower polarity membrane solvent is preferable and the best Li^+ selectivity was obtained with DBE as the membrane solvent. The response slope of this electrode is 59.0 mV/pLi^+ (theoretical response slope: 59.2 mV/pLi^+ at 25 °C), ranging from 1×10^{-5} to 1×10^{-1} M Li^+. The effectiveness of the membrane solvent, DBE, is recognized in the other Li^+-selective ionophore based electrodes (*20*). Since the reason for its effectiveness is not clear, we are attempting to synthesize and evaluate several DBE derivatives.

The ion selectivity factors (K^{pot}_{Lij} and K^{pot}_{Naj}) of the electrodes based on natural monensin and all monensin derivatives discussed here are summarized in Table II. In conclusion, well-designed chemical modifications of natural ionophores are effective in obtaining excellent specific ion selective ionophores for an ion-selective electrode.

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