The Effects of *O*-Substituents of Hexahomotrioxacalix[3]arene on Potentiometric Discrimination between Dopamine and Biological Organic/Inorganic Cations

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As an interesting type of molecular recognition at a membrane surface, the tri-*O*-acetic acid ester (host 2) of hexahomotrioxacalix[3]arene, when incorporated into poly(vinyl chloride) (PVC) liquid membranes, displays a high potentiometric selectivity for dopamine over, not only other catecholamines (noradrenaline, adrenaline), but also quaternary ammonium guests (tetramethylammonium, choline, and acetylcholine) and inorganic cations (Na^+, K^+, NH_4^+). Interestingly, changes in membrane potential based on the host–guest complexation of host 2 that were observed dopamine/inorganic cation selectivity were not displayed by the related hosts 3 and 4, which contain amide substituents. This paper describes our efforts to separately estimate the two factors contributing to the dopamine selectivities, *i.e.*, the guest lipophilicity factor and the host–guest complexation factor, in an attempt to understand the effects of the *O*-substituents of these hosts. The potentiometric experiments showed that, although the guests had roughly equal lipophilicity, the electromotive force (EMF) response for dopamine by host 2 was excellent. Furthermore, host 2 displayed *ca.* a 20-fold stronger complexation for dopamine, compared to noradrenaline, adrenaline, K^+, and NH_4^+ cations. These results indicate that the high potentiometric selectivity of the ion-selective electrode for dopamine mainly reflect, not the guest lipophilicity factor but the host–guest complexation factor. On the other hand, host 3 displayed *ca.* a 3000-fold stronger binding to Na^+ than dopamine, thus explaining the reasons for the lower dopamine-selectivities of host 3 compared to host 2. It is interesting to note that the high potentiometric selectivities for dopamine were displayed by not only host 2 but also host 5, regardless of the simple structure of the *O*-substituents.

Key words membrane potential; calixarene; dopamine; host–guest system

A variety of methods for the determination of catecholamines (dopamine, noradrenaline, and adrenaline) and their metabolites in biological media have been proposed. Catecholamines are especially important because they are involved in many human physiological and biochemical processes.[1,2] Catecholamines are typically determined by HPLC analysis with electrochemical detection.[3—6] In most cases, the preliminary extraction and purification of catecholamines from biological samples are necessary. On the other hand, the direct potentiometric determination of catecholamines is extremely attractive. However, the development of ion-selective electrodes for catecholamines is difficult, considering their similar structures and relatively hydrophilic nature. Only a few reports of the potentiometric determination of catecholamines have appeared in the literature.[7—10] For the development of sensory elements for dopamine, we focused on the hexahomotrioxacalix[3]arene skeleton, which contains both *ethereal* and *phenolic* oxygens, both of which are capable of forming tripodal hydrogen bonds with the protonated primary amino group of dopamine. It has been reported that the hexahomotrioxacalix[3]arene host **1** (cone conformer),[11] when incorporated into a poly(vinyl chloride) (PVC) liquid membrane displays a high selectivity for dopamine in membrane potential changes, compared to other catecholamines (noradrenaline and adrenaline) and inorganic cations (Na^+ and K^+).[7]

Guest-induced changes in membrane potential at the membrane without hosts are reflected in only the guest lipophilicity factor. On the other hand, changes in a host are reflected in two factors, *i.e.*, the guest lipophilicity factor and the host–guest complexation factor. Mi and Bakker[12] and Ceresa and Pretsch[13] recently reported on the determination of the host–guest complexation factor (complex formation constants) in PVC membranes to characterize the binding capability of ionophores. We present here a quantitative analysis of the two factors that contribute to dopamine selectivity, in an attempt to better understand the effects of the *O*-substituents of hexahomotrioxacalix[3]arene hosts **2**—**5** (Fig. 1). The host–guest complexation factor in PVC membranes constitutes very important information for the further development of sensory elements for dopamine.

Results and Discussion

Synthesis of Host Molecules The synthesis of host **2**

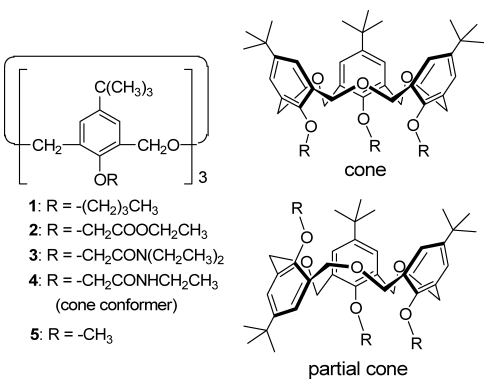

Fig. 1. Structure of Host Molecules and Schematic Representations of the *Cone* and *Partial Cone* Conformations

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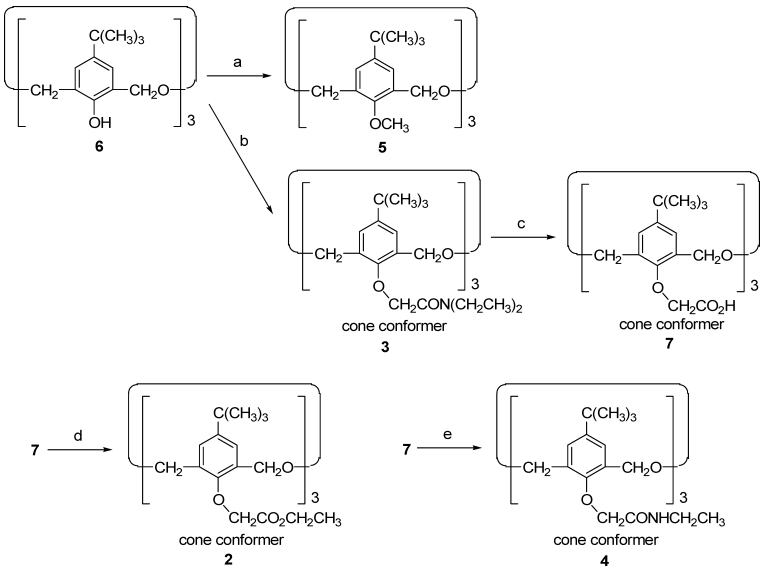

Reagents and reaction conditions: (a) MeI, NaH, DMF, 85 °C, 2 h, 67%; (b) *N*,*N*-diethylchloroacetamide, NaH, THF, reflux, 6 h, 79%; (c) KOH, dioxane/H_2O, reflux, 5 d, 91%; (d) EtI, DBU, benzene, reflux, 19 h, 67%; (e) $EtNH_2 \cdot HCl$, BOP, Et_3N, DMF, rt, 12 h, 76%.

Chart 1. Synthesis of Host Molecules

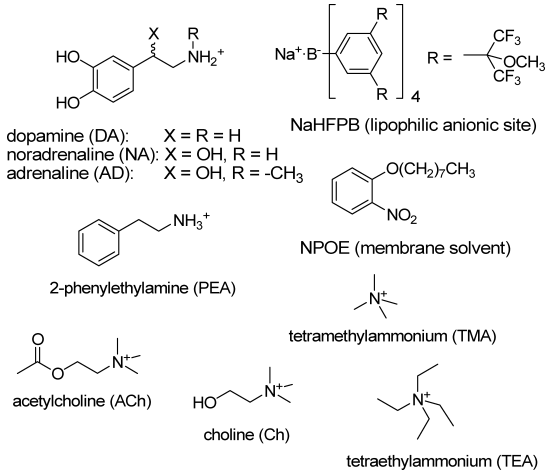

Fig. 2. Structures of Catecholamines, Organic Guests, and Membrane Components Used in the Present Study

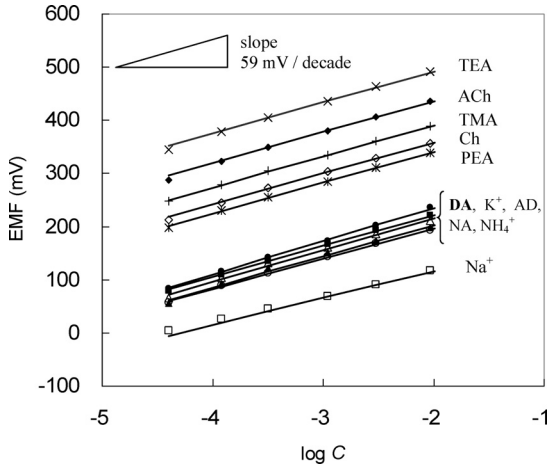

Fig. 3. Membrane Potential (Electromotive Forces; EMF) *vs.* Concentration Curves for a Blank Membrane without a Host

Dopamine (●, DA), noradrenaline (▲, NA), adrenaline (■, AD), 2-phenylethylamine (✳, PEA), acetylcholine (◆, ACh), choline (◇, Ch), tetramethylammonium (+, TMA), tetraethylammonium (×, TEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+) were used as guests.

has been described previously.[14] However, this method gave only a 9% yield of the cone conformer of **2**, because the *O*-alkylation of **6** with ethyl bromoacetate gave the partial-cone conformer in preference to the cone conformer (Fig. 1). Thus, we prepared the cone conformer of **2** by an alternate procedure (Chart 1). The starting compound, **6**, was prepared according to the literature.[15] The *O*-alkylation of **6** with *N*,*N*-diethylchloroacetamide gave only cone conformer of **3** in 79% yield.[16] Hydrolysis of **3** with KOH gave **7** in 91% yield.[17] Finally, esterification of **7** with ethyl iodide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave **2** in 67% yield.[18] On the other hand, when the reaction was conducted in the presence of sodium, potassium, cesium carbonate, or triethylamine, **2** was produced in <18% yield. This result indicates that alkali metal cations interact with **7** and the complex exerts a steric effect on the esterification, and triethylamine is too slow to be useful for the esterification reaction.[19] This procedure led to an improved yield of **2** from 9 to 48% (3 steps from **6**). Host **4** was also synthesized by a condensation reaction between **7** and ethylamine hydrochloride in 76% yield. Hosts **3**[16] and **5**[11] were prepared by the reported methods.

Potentiometric Measurements We investigated the potentiometric selectivities of hosts **2**, **3**, **4**, and **5**, when incorporated into the matrix of PVC liquid membranes. The membrane components and guest compounds are shown in Fig. 2. We chose tetraethylammonium ion (TEA^+) as a reference ion, because the complexation of TEA^+ with the hosts is negligible. Nernstian responses to all ions examined were obtained in the membrane without hosts (Fig. 3). The relative magnitudes of the membrane potential changes are listed in Table 1 as potentiometric selectivity coefficients ($\log K^{pot}_{TEA,X}$).[20—24] Except for 2-phenylethylamine (PEA), host **2** in the PVC matrix liquid membrane displayed *ca.* a

Table 1. Potentiometric Selectivity Coefficients ($\log K^{pot}_{TEA,X}$) for PVC Matrix Liquid Membranes in Which Hosts **2**—**5** Were Incorporated and a Blank Membrane without a Host[a)]

Guests (X)	$\log K^{pot}_{TEA,X}$				
	Host **2**	Host **3**	Host **4**	Host **5**	Blank
TEA	0	0	0	0	0
PEA	2.9	3.1	0.5	1.9	−1.5
DA	0.3	0.3	−2.4	−0.4	−4.0
NA	−1.6	−1.1	—[b)]	−1.7	−4.6
AD	—[b)]	−2.5	−4.0	—[b)]	−4.3
ACh	−1.3	—[b)]	−1.5	−1.2	−0.8
Ch	−2.7	—[b)]	−2.1	−2.6	−1.9
TMA	−1.6	—[b)]	−1.5	−1.4	−1.0
NH_4^+	−1.8	−0.6	−4.1	−2.2	−4.8
K^+	−1.5	0.2	−3.5	−1.6	−4.2
Na^+	−1.6	1.7	−3.0	−2.8	−6.1

a) Potentiometric selectivities are given by selectivity coefficients ($K^{pot}_{TEA,X}$), determined using TEA as a standard. *b*) Could not be estimated because of the large deviation from the Nernstian slope due to weak complexation. Dopamine (DA), noradrenaline (NA), adrenaline (AD), 2-phenylethylamine (PEA), acetylcholine (ACh), choline (Ch), tetramethylammonium (TMA), tetraethylammonium (TEA)

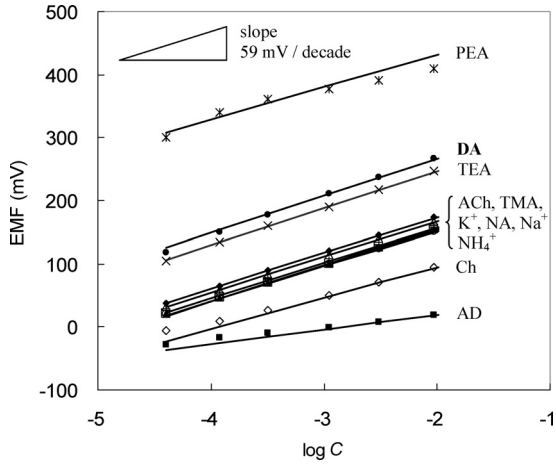

Fig. 4. Membrane Potential (Electromotive Forces; EMF) *vs.* Concentration Curves for Host **2**

Dopamine (●, DA), noradrenaline (▲, NA), adrenaline (■, AD), 2-phenylethylamine (✳, PEA), acetylcholine (◆, ACh), choline (◇, Ch), tetramethylammonium (+, TMA), tetraethylammonium (×, TEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+) were used as guests.

>40-fold higher potentiometric selectivity for dopamine (DA) over other catecholamines [noradrenaline (NA) and adrenaline (AD)], inorganic cations (Na^+, K^+, and NH_4^+), and quaternary ammonium guest [tetramethylammonium (TMA^+), choline (Ch), and acetylcholine (ACh)] (Fig. 4). Nernstian responses were observed for all guests, except for AD due to the weak complexation between host **2** and AD. On the other hand, host **3** also displayed *ca.* a >25-fold higher potentiometric selectivity for DA over other catecholamines and quaternary ammonium guests. However, host **3** suffered from severe interference by inorganic cations, particularly Na^+ (Fig. 5). Apparently, the cause of the sub-Nernstian response of host **3** toward quaternary ammonium guests was interference by Na^+ from the internal solution of the electrode and weak complexation between host **3** and quaternary ammonium guests, thereby prohibiting the potentiometric selectivity coefficients from being calculated. Compared with hosts **2** and **3**, host **4** showed a decrease in potentiometric response for

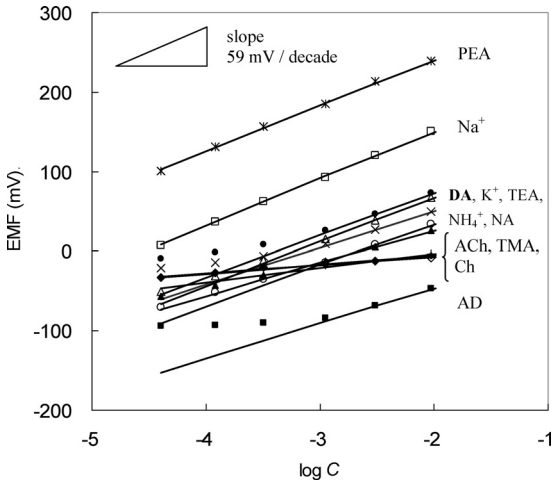

Fig. 5. Membrane Potential (Electromotive Forces; EMF) *vs.* Concentration Curves for Host **3**

Dopamine (●, DA), noradrenaline (▲, NA), adrenaline (■, AD), 2-phenylethylamine (✳, PEA), acetylcholine (◆, ACh), choline (◇, Ch), tetramethylammonium (+, TMA), tetraethylammonium (×, TEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+) were used as guests.

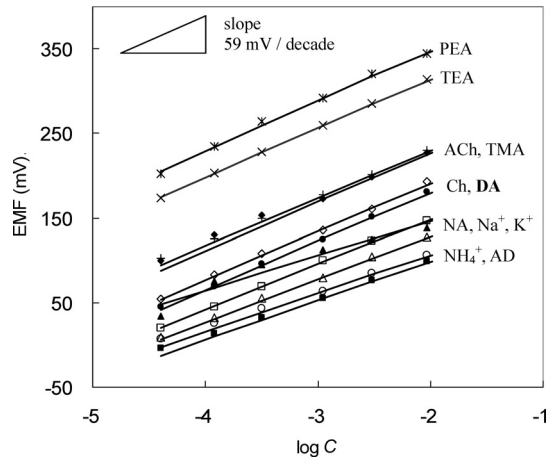

Fig. 6. Membrane Potential (Electromotive Forces; EMF) *vs.* Concentration Curves for Host **4**

Dopamine (●, DA), noradrenaline (▲, NA), adrenaline (■, AD), 2-phenylethylamine (✳, PEA), acetylcholine (◆, ACh), choline (◇, Ch), tetramethylammonium (+, TMA), tetraethylammonium (×, TEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+) were used as guests.

almost all of the guests [$\log K^{pot}_{TEA,X}$ (host **4**)] and no potentiometric selectivity for DA was found (Fig. 6). On the other hand, it is interesting that high potentiometric selectivities for DA were displayed, not only by host **2**, but also host **5**, which is not restricted to the cone conformer (Fig. 7). Host **5** also shows a sub-Nernstian response toward AD due to the weak nature of its complexation.

Selectivity in Host–Guest Complexation The potentiometric selectivity coefficients for the membrane with host [$\log K^{pot}_{TEA,X}$ (host)] reflect the two factors *i.e.*, the guest lipophilicity factor [$\log K^{pot}_{TEA,X}$ (blank)] and the host–guest complexation factor. In order to quantitatively understand the selectivities on the basis of the hosts' binding capabilities, we calculated the stability constants ($\log K_s$) for the host–guest complexes by separately estimating the two factors (Table 2).[13] It was shown through potentiometric experiments that, although the magnitudes of the guest lipophilicity were al-

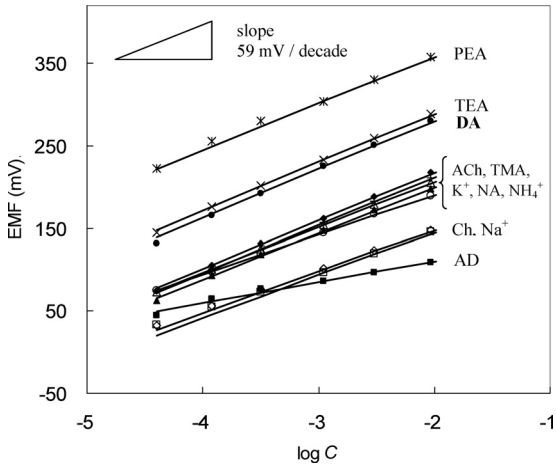

Fig. 7. Membrane Potential (Electromotive Forces; EMF) *vs.* Concentration Curves for Host **5**

Dopamine (●, DA), noradrenaline (▲, NA), adrenaline (■, AD), 2-phenylethylamine (✳, PEA), acetylcholine (◆, ACh), choline (◇, Ch), tetramethylammonium (+, TMA), tetraethylammonium (×, TEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+) were used as guests.

Table 2. Stability Constants ($\log K_s$) for Host–Guest Complexes in PVC Matrix Liquid Membranes

Guests	$\log K_s$			
	Host **2**	Host **3**	Host **4**	Host **5**
TEA	—	—	—	—
PEA	6.5	6.8	4.1	5.3
DA	6.5	6.5	3.8	5.7
NA	5.1	5.6	—*a)*	4.8
AD	—*a)*	4.0	2.4	—*a)*
ACh	1.7	—*a)*	1.5	1.6
Ch	1.3	—*a)*	1.9	1.3
TMA	1.6	—*a)*	1.7	1.7
NH_4^+	5.2	6.4	2.9	4.6
K^+	4.9	6.4	2.9	4.6
Na^+	6.6	9.9	5.3	5.3

a) Could not be estimated because of the large deviation from the Nernstian slope due to weak complexation. Dopamine (DA), noradrenaline (NA), adrenaline (AD), 2-phenylethylamine (PEA), acetylcholine (ACh), choline (Ch), tetramethylammonium (TMA), tetraethylammonium (TEA).

most the same [$\log K^{pot}_{TEA,X}$ (blank): NA, NH_4^+, AD, K^+, DA] (Fig. 3), host **2** displayed *ca.* >20-fold stronger complexation for DA. These results indicate that the high potentiometric selectivities for DA against similarly lipophilic guests and highly lipophilic quaternary ammonium guests mainly reflects the host–guest complexation factor. In contrast, the high potentiometric selectivity for DA against Na^+ (highly hydrophilic) was found to be mainly due to the guest lipophilicity factor. The stability constants for the **2**–DA and **3**–DA complexes were calculated to be $\log K_s$=6.5, respectively. However, host **3** displayed *ca.* a 3000-fold stronger binding to Na^+ than DA, which explains the lower DA-selectivities of host **3** than host **2**. On the other hand, the stability constants for the **4**–guest complexes provide an explanation for why host **4** showed no potentiometric selectivity for DA. Thus, the binding capability of host **4** was less for all guests than hosts **2** and **3**. Compared with host **2**, the stability constant for the **5**–DA complex was calculated to be $\log K_s$=5.7, which was somewhat smaller than that for host **2**. This can be attributed to the flexible conformation of host **5**.

Conclusion

The results reported herein demonstrate the effects of the *O*-substituents of the hexahomotrioxacalix[3]arene hosts. The findings indicate hosts **2** and **5** displayed high potentiometric selectivities for DA, compared to hosts **3** and **4**, which contain amide substituents. The improved potentiometric selectivity for DA can be attributed to strong binding to DA and weak binding to inorganic cations because of the absence of amide substituents. The modification of the *O*-substituents of the host to attain some level of selectivity over inorganic cations will be necessary for the practical use of this procedure in biological media. From the synthetic viewpoint, host **5** is more useful for the development of sensory elements for DA than host **2**, because it is difficult to restrict it to the cone conformer. Efforts to understand the binding capabilities of the hosts on the basis of the structure of stable complexes are currently in progress.

Experimental

General Information Melting points were measured with a Yanaco MP-500V melting point apparatus and were uncorrected. Infrared spectra were recorded on a FT-IR-5300 spectrometer. Mass spectra were recorded on JEOL AX-505 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL LAMBDA GSX/400 spectrometer at ambient temperature of *ca.* 25 °C. Chemical shifts are reported in δ values in ppm downfield from tetramethylsilane (TMS) as the internal standard unless stated otherwise. Data are reported as chemical shift with multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, m=multiplet, br=broad), coupling constant(s) (Hz), integration and assignment. Solvents for extraction and chromatography were of reagent grade. Dimethoxyethane (DME) and benzene were distilled over calcium hydride. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl after treatment with $LiAlH_4$. Triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled over potassium hydroxide. Anhydrous chloroform ($CHCl_3$), *N*,*N*-dimethylformamide (DMF), and acetone were purchased from Wako Pure Chemical Industries (Osaka, Japan) and used as supplied.

7,15,23-Tri-*tert*-butyl-25,26,27-tris(ethoxycarbonylmethoxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (2) A solution of **7** (20 mg, 0.0267 mmol) and DBU (13 mg, 0.0880 mmol) in benzene (2 ml) was heated at reflux under an atmosphere of N_2. To this mixture was added ethyl iodide (21 mg, 0.133 mmol) and the whole was heated at reflux for 19 h. The mixture was diluted with AcOEt (20 ml) and washed successively with water (15 ml×2) and brine (10 ml), dried over anhyd $MgSO_4$, and evaporated. The residual white solid was purified by preparative TLC (silica gel, $CHCl_3$/AcOEt=9/1) to give **2** as colorless crystals, which was recrystallized from diethyl ether to give a white solid (15 mg, 67%). The characterization data were reported.[14]

7,15,23-Tri-*tert*-butyl-25,26,27-tris(*N*-ethylaminocarbonylmethoxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (4) A solution of **7** (74 mg, 0.0987 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (1.31 g, 2.96 mmol), ethylamine hydrochloride (241 mg, 2.96 mmol), and Et_3N (600 mg, 5.93 mmol) in DMF (6 ml) was stirred at room temperature for 12 h under an atmosphere of N_2. After water (20 ml) was added, the mixture was extracted with AcOEt (15 ml×2). The combined organic layers were washed successively with water (15 ml), satd. aq. $NaHCO_3$ (15 ml), water (15 ml), and brine (10 ml), dried over anhyd $MgSO_4$, and evaporated. The residual pale yellow crystals were recrystallized twice from methanol to give **4** as white needles (62 mg, 76%): mp 189—192 °C. IR (KBr disk) ν_{max} cm^{-1}: 3324 (νNH, br), 1659 ($\nu_{C=O}$, amide). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.11 (27H, s, *t*-Bu), 1.29 (9H, t, *J*=7.3 Hz, C$\underline{H}_3$), 3.46 (6H, m, *J*=6.1, 7.3 Hz, NC$\underline{H}_2$), 4.13 (6H, s, ArOC$\underline{H}_2$), 4.35 (6H, d, *J*=12.2 Hz, ArC$\underline{H}_2$O), 4.73 (6H, d, *J*=12.2 Hz, ArC$\underline{H}_2$O), 6.94 (6H, s, Ar$\underline{H}$), 7.76 (3H, t, *J*=6.1 Hz, N$\underline{H}$). MS (FAB) *m/z*: 832 $[M+H]^+$. *Anal.* Calcd for $C_{48}H_{69}N_3O_9\cdot H_2O$: C, 67.82; H, 8.42; N, 4.94. Found: C, 67.35; H, 8.43; N, 5.09.

Reagents for Potentiometric Measurements The following compounds were purchased and used without further purification: Sodium tetrakis[3,5-bis(1,1,1,3,3,3-hexafluoro-2-methoxy-2-propyl)phenyl]borate

trihydrate (NaHFPB) and *o*-nitrophenyl octyl ether (NPOE) from Dojindo Laboratories (Kumamoto, Japan); poly(vinyl chloride) (PVC, high molecular weight) and (*RS*)-noradrenaline hydrochloride from Fluka (Buchs, Switzerland); (*RS*)-adrenaline hydrochloride from Sigma (St. Louis, MO, U.S.A.); dopamine hydrochloride, 2-phenylethylamine hydrochloride, choline chloride, and acetylcholine chloride from Tokyo Kasei Kyogyo Co. (Tokyo, Japan); tetramethylammonium chloride, tetraethylammonium chloride, KCl, and NH_4Cl from Nacalai Tesque Inc. (Kyoto, Japan); CH_3COOLi and NaCl from Wako Pure Chemical Industries (Osaka, Japan).

PVC Matrix Liquid Membrane PVC matrix liquid membranes were prepared according to the literature[13] with minor modifications. Membranes of *ca.* 0.1 mm thickness were obtained by pouring a solution of *ca.* 300 mg of the membrane components, dissolved in *ca.* 3 ml of THF, into a flat Petri dish (34 mm i.d.). The solvent was allowed to be evaporate at room temperature for 2 d. The resulting, 7 mm diameter membranes were punched from the master membranes and the disks were soaked in a 1.0×10^{-2} M NaCl solution overnight as a conditioning process. The membranes had the following composition: The membrane without a host compound contained NPOE/PVC/NaHFPB=67 : 33 : 0.5 wt%. The membranes with a host compound contained host/NPOE/PVC/NaHFPB=0.8—1.0 : 65 : 33 : 0.5 wt%.

Electrode System Each membrane was fixed on a liquid membrane type ion-selective electrode body type IS 561 (Willi Möller AG, Zürich, Switzerland). A 1.0×10^{-2} M NaCl solution was used as an internal solution. The reference electrode was a double-junction type based on a Ag/AgCl electrode (DDK·TOA Co., Tokyo, Japan) containing a satd. aq. KCl solution in the inner compartment and a 1 M CH_3CO_2Li solution in the outer compartment. The electrode cell used for the potential measurements was as follows: Ag | AgCl | satd. aq. KCl | 1 M CH_3CO_2Li | sample solution | membrane | 1.0×10^{-2} M NaCl | AgCl | Ag.

Potential Measurements Membrane potentials were measured for unbuffered aqueous solutions of guests. All measurements were carried out with gentle stirring at room temperature (*ca.* 25 °C) with a pH–mV meter model HM-60V (TOA Electronics Ltd., Tokyo, Japan). Deionized and charcoal-treated water (specific resistance, 18.2 $M\Omega cm^{-1}$) was obtained with a MILLI-Q Labo (Millipore, Bedford, MA, U.S.A.). Sample solutions of each guest were prepared by adding an aliquot (10, 20, 50, 200, 500, 1800 μl) of a 1.0×10^{-1} M guest solution to 25 ml of water. Membrane potentials for each guest cation were measured in the order of increasing lipophilicity of the guest (Na^+, NA, NH_4^+, AD, K^+, DA, PEA, Ch, TMA, ACh, TEA). The potentials were measured for 1—10 min. During this period, the potential drift was around 1 mV/min in most cases. The potential measurement for each guest was repeated two or three times. Selectivity coefficients of the electrode were determined by the separate solution method,[25] using the conventional Nicolsky–Eisenman equation, although some of the interfering ions did not give calibration curves with an ideal linearity and Nernstian slope. The concentration of the primary and interfering ions used for the calculation was 1.0×10^{-2} M for all data. The selectivity coefficients were determined as the average of two or three independent measurements.

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