Potentiometric Discrimination of Organic Amines by a Liquid Membrane Electrode Based on a Lipophilic Hexaester of Calix[6]arene

Kazunori Odashima,*,† Kenichi Yagi, Koji Tohda,‡ and Yoshio Umezawa*,§

Department of Chemistry, Faculty of Science, Hokkaido University, Kita 10-Jo Nishi 8-Chome, Sapporo, Hokkaido 060, Japan

A novel type of poly(vinyl chloride) matrix liquid membrane electrode that is capable of discriminating the steric shapes of nonpolar moieties of organic amines at neutral pH has been developed. A new lipophilic hexaester of calix[6]arene having a well-defined inclusion cavity for organic guests [37,38,39,-40,41,42-hexakis(decyloxycarbonylmethyloxy)calix[6]-arene] was synthesized and exploited as a sensory element. This electrode displayed the strongest potentiometric responses to the primary amines having no substituent adjacent to the amino group such as 1-octylamine, 2-phenylethylamine, and dopamine. An examination of potentiometric selectivities for different series of organic amines, as well as a ^{1}H-NMR study on the geometry of the host–guest complexes, strongly supported a mode of potentiometric discrimination that depends on the availability of a stable inclusion complex involving the formation of tripodal hydrogen bonds between the NH_3^+ group of the guest and the C=O groups of the host. Such a mode of potentiometric discrimination based on the recognition of the steric shapes of nonpolar moieties was not attained by the electrodes based on dibenzo-18-crown-6 or potassium tetrakis-(*p*-chlorophenyl)borate having no inclusion cavity for organic guests; both of these electrodes showed a selectivity that reflects simple lipophilicity of the guests.

INTRODUCTION

Liquid membrane type ion-selective electrodes (ISEs) provide one of the most versatile sensing methods because it is possible to select various sensory elements according to the structures of the analytes. Based on the recent advance of host–guest chemistry, liquid membrane type ISEs for inorganic metal cations have been extensively developed by the use of crown ethers and related macrocyclic hosts as well as acyclic ligands.[1,2] Many of these ISEs display excellent selectivity for analyte metal cations and are now commercially available.[3-5] A number of ISEs for inorganic anions have also been developed, which are based on trialkyltin chlorides, derivatives of vitamin B_{12} and metalloporphyrin, and diphosphonium and bis(quaternary ammonium) salts.[3-5]

On the other hand, there are still limited examples of ISEs that strongly respond to and discriminate between organic guests. The organic cation-selective electrodes reported so far are based on derivatives of crown ethers[6-14] or natural ionophores.[15-18] Whereas the selectivities of many of these electrodes are controlled mainly by the lipophilicity of guests, several examples of sophisticated function have been reported for potentiometric discrimination between enantiomers of protonated amino acid esters and related guests.[11-18] Of the electrodes developed for organic anions, those based on lipophilic derivatives of macrocyclic polyamines are remarkable.[19-24] Compared to other sensory elements for which potentiometric responses to organic anions have been reported [e.g., derivatives of vitamin B_{12} and metalloporphyrin,[25,26] diphosphonium salts,[27,28] and bis(quaternary ammonium) salts[29]], macrocyclic polyamines display excellent potentiometric selectivities for organic anions.[19-21] This is based on the strong electrostatic interaction with anionic guests by

† Present address: Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo 7-3-1, Bunkyo-Ku, Tokyo 113, Japan.

‡ Present address: Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo 7-3-1, Bunkyo-Ku, Tokyo 113, Japan.

§ Permanent address: Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo 7-3-1, Bunkyo-Ku, Tokyo 113, Japan.

(1) Ammann, D.; Morf, W. E.; Anker, P.; Meier, P. C.; Pretsch, E.; Simon, W. *Ion-Sel. Electrode Rev.* **1983**, *5*, 3-92.
(2) Shono, T. *Bunseki Kagaku* **1984**, *33*, E449-E458.
(3) Koryta, J. *Anal. Chem.* **1990**, *233*, 1-30.
(4) Collison, M. E.; Meyerhoff, M. E. *Anal. Chem.* **1990**, *62*, 425A-437A.
(5) Janata, J. *Anal. Chem.* **1992**, *64*, 196R-216R.
(6) Maeda, T.; Ikeda, M.; Shibahara, M.; Haruta, T.; Satake, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 94-98.
(7) Shirahama, K.; Kamaya, H.; Ueda, I. *Anal. Lett.* **1983**, *16* (*B19*), 1485-1494.
(8) Bocheńska, M.; Biernat, J. F. *Anal. Chim. Acta* **1984**, *162*, 369-371.
(9) Moody, G. J.; Owusu, R. K.; Thomas, J. D. R. *Analyst* **1987**, 121-127.
(10) Hassan, S. S. M.; Elnemma, E. M. *Anal. Chem.* **1989**, *61*, 2189-2192.
(11) Thoma, A. P.; Viviani-Nauer, A.; Schellenberg, K. H.; Bedeković, D.; Pretsch, E.; Prelog, V.; Simon, W. *Helv. Chim. Acta* **1979**, *62*, 2303-2316.
(12) Bussmann, W.; Lehn, J.-M.; Oesch, U.; Plummeré, P.; Simon, W. *Helv. Chim. Acta* **1981**, *64*, 657-661.
(13) Yasaka, Y.; Yamamoto, T.; Kimura, K.; Shono, T. *Chem. Lett.* **1980**, 769-772.
(14) Shinbo, T.; Yamaguchi, T.; Nishimura, K.; Kikkawa, M.; Sugiura, M. *Anal. Chim. Acta* **1987**, *193*, 367-371.
(15) Maruyama, K.; Sohmiya, H.; Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1989**, 864-865.
(16) Tsukube, H.; Sohmiya, H. *Tetrahedron Lett.* **1990**, *31*, 7027-7030.
(17) Tsukube, H.; Sohmiya, H. *J. Org. Chem.* **1991**, *56*, 875-878.
(18) Maruyama, K.; Sohmiya, H.; Tsukube, H. *Tetrahedron* **1992**, *48*, 805-818.
(19) Umezawa, Y.; Kataoka, M.; Takami, W.; Kimura, E.; Koike, T.; Nada, H. *Anal. Chem.* **1988**, *60*, 2392-2396.
(20) Kataoka, M.; Naganawa, R.; Odashima, K.; Umezawa, Y.; Kimura, E.; Koike, T. *Anal. Lett.* **1989**, *22*, 1089-1105.
(21) Naganawa, R.; Kataoka, M.; Odashima, K.; Umezawa, Y.; Kimura, E.; Koike, T. *Bunseki Kagaku* **1990**, *39*, 671-676.
(22) Umezawa, Y.; Sugawara, M.; Kataoka, M.; Odashima, K. In *Ion-Selective Electrodes*; Pungor, E., Ed.; Akadémiai Kiadó (Pergamon Press): Budapest (Oxford), 1989; Vol. 5, pp 211-234.
(23) Odashima, K.; Umezawa, Y. In *Biosensor Technology. Fundamentals and Applications*; Buck, R. P., Hatfield, W. E., Umaña, M., Bowden, E. F., Eds.; Marcel Dekker: New York, 1990; pp 71-93.
(24) Odashima, K.; Sugawara, M.; Umezawa, Y. *Trends Anal. Chem.* **1990**, *10*, 207-215.
(25) Chaniotakis, N. A.; Chasser, A. M.; Meyerhoff, M. E.; Groves, J. T. *Anal. Chem.* **1988**, *60*, 185-188.
(26) Daunert, S.; Bachas, L. G. *Anal. Chem.* **1989**, *61*, 499-503.
(27) Ohki, A.; Yamura, M.; Kumamoto, S.; Maeda, S.; Takeshita, T.; Takagi, M. *Chem. Lett.* **1989**, 95-98.
(28) Ohki, A.; Yamura, M.; Takagi, M.; Maeda, S. *Anal. Sci.* **1990**, *6*, 585-588.
(29) Wotring, V. J.; Johnson, D. M.; Bachas, L. G. *Anal. Chem.* **1990**, *62*, 1506-1510.

0003-2700/93/0365-1074$04.00/0

macrocyclic polyamines, which acquire a strong anion receptor function by multiple protonation at the membrane surface.[19-24] The remarkable feature of the electrodes based on macrocyclic polyamines is their ability to exhibit potentiometric selectivities according to the amount or proximity of negative charges within the guest molecule.[19-21] By far the strongest potentiometric response to ATP^{4-} as compared to ADP^{3-} and AMP^{2-} is a representative example.[19,21] Furthermore, a potentiometric discrimination among similarly charged nucleotides bearing different kinds of base has been shown possible by the use of a cytosine-pendant triamine host having a base-pairing site in addition to an electrostatic binding site for guanine nucleotides.[30] These studies have demonstrated two possible principles for potentiometric discrimination of *organic* analytes, which are based on the recognition of specific functional groups of target organic guests, i.e., negatively charged groups and hydrogen-bonding groups.

In this paper, we report a new mode of potentiometric discrimination of organic guests, which is based on the recognition of steric shapes of nonpolar moieties by inclusion into the cavity of a host having a well-defined structure. Such a mode of potentiometric discrimination has been demonstrated by a poly(vinyl chloride) (PVC) matrix liquid membrane electrode that exploits as the sensory element a long alkyl hexaester of calix[6]arene, **1a**. The sensory element **1a** is a new lipophilic derivative of calix[6]arene, which has a well-defined cavity capable of accommodating organic guests as well as well-arranged ester carbonyl groups capable of forming tripodal hydrogen bonds with a protonated primary amino group. The potentiometric response properties of this electrode for protonated organic amines were compared with those of the electrodes based on dibenzo-18-crown-6 (**2**) as well as potassium tetrakis(*p*-chlorophenyl)borate (**3**). On the basis of a comparison of the selectivities of these electrodes for different series of organic amines, as well as on a ^{1}H-NMR study concerning the geometry of the host–guest complexes, the characteristic potentiometric selectivities of the calixarene electrode were correlated with the recognition of steric shapes of nonpolar moieties by inclusion of these guests into the calix[6]arene cavity.

EXPERIMENTAL SECTION

Materials and Apparatus. The structures of the hosts and guests used in the present study are shown in Figure 1. The following compounds were purchased and used without further purification for the synthesis of the long alkyl hexaester of calix[6]arene, **1a**: 37,38,39,40,41,42-hexahydroxycalix[6]arene (Catalog No. H 0713) and bromoacetic acid (B 0531) from Tokyo Kasei Kogyo Co. (Tokyo, Japan); 1-decanol (10009-00) from Kanto Chemical Co. (Tokyo, Japan). Ethyl methyl ketone (225-06) was purchased from Nacalai Tesque Inc. (Kyoto, Japan) and distilled just before use. Dibenzo-18-crown-6 (**2**) (15839-9) was obtained from Aldrich Chemical Co. (Milwaukee, WI) and potassium tetrakis(*p*-chlorophenyl)borate (K-T*p*ClPB, **3**) (342-05013) from Dojindo Laboratories (Kumamoto, Japan).

As the guests for the potentiometric measurements, the following amines were purchased and their hydrochloric acid salts prepared: 1-octylamine (**4**) (O 0045), 2-phenylethylamine (**5**) (P 0085), benzylamine (**6**) (B 0406), 1-adamantanamine (**7**) (A 0583), and *tert*-butylamine (**8**) (B 0709) from Tokyo Kasei Kogyo. Co.; dopamine (**9**) (142-12), (*RS*)-noradrenaline (**10**) (010-60), and (*RS*)-adrenaline (**11**) (253-03) from Nacalai Tesque., Inc. (Kyoto, Japan); methyl esters of L-tryptophan (Trp-OCH_3, **12**) (T 5505), L-phenylalanine (Phe-OCH_3, **13**) (P 3126), L-leucine (Leu-OCH_3, **14**) (L 9000), L-valine (Val-OCH_3, **15**) (V 1000), and L-alanine (Ala-OCH_3, **16**) (A 8752) from Sigma Chemical Co. (St. Louis, MO). The following inorganic guests were of the highest

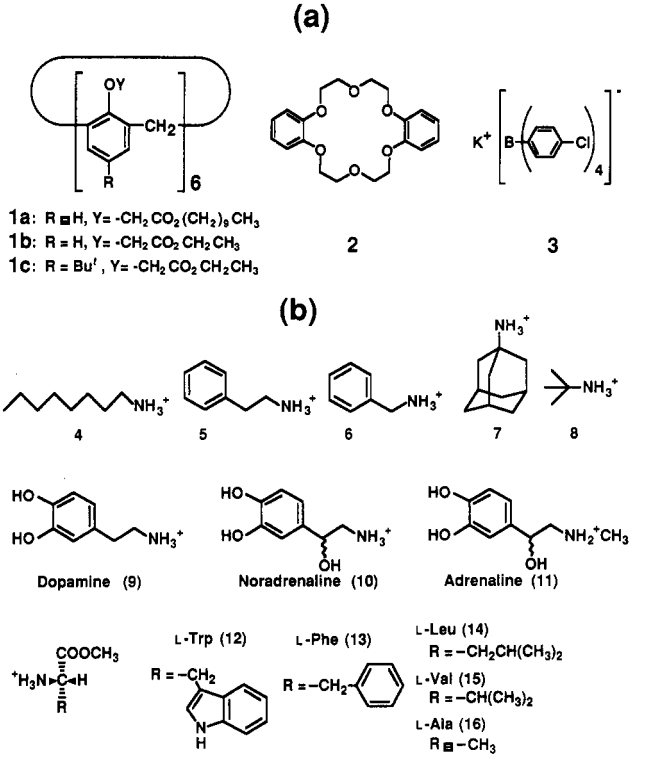

Figure 1. Structures of (a) the sensory elements, i.e., calix[6]arene hexaester **1a**, dibenzo-18-crown-6 (**2**), and potassium tetrakis(*p*-chlorophenyl)borate (**3**), and (b) the three series of organic amine guests examined in the present study.

quality grade available from Wako Pure Chemical Industries (Osaka, Japan): LiCl (123-01162), NaCl (191-01665), KCl (163-03545), RbCl (187-00321), CsCl (035-01952), NH_4Cl (017-02995), $MgCl_2$ (135-00165), $CaCl_2$ (031-00435), $SrCl_2$ (193-04182), and $BaCl_2$ (027-08792).

Dioctyl sebacate [DOS, bis(2-ethylhexyl) sebacate; 041-18643] and poly(vinyl chloride) (PVC; $n_{av} \approx 1100$; 223-00255) were purchased from Wako Pure Chemical Industries. Tris(hydroxymethyl)aminomethane (Tris; 40326-00) and L-ascorbic acid (01452-00) were purchased from Kanto Chemical Co. Deionized and charcoal-treated water (>17.5 MΩ resistance) obtained by a Milli-Q Type I reagent-grade water system (Millipore Corp., Bedford, MA) was used for all potentiometric experiments.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1720-X Fourier transform infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi R-1900 Fourier transform NMR spectrometer (^{1}H, 90 MHz). High-resolution NMR spectra were measured on a JEOL JMS-GX-400 Fourier transform NMR spectrometer (^{1}H, 400 MHz) in the Center for Instrumental Analysis, Hokkaido University. Chemical shifts are reported in δ values in ppm downfield of tetramethylsilane (TMS, 0.03%) as the internal standard.

Synthesis of Calix[6]arene Hexaester 1a. Decyl bromoacetate was prepared by refluxing a mixture of bromoacetic acid, decyl alcohol, and concentrated H_2SO_4 in benzene for 4–6 h with a removal of water by a Dean–Stark apparatus. The reported procedure[31] was employed for the introduction of six decyl acetate units to the calix[6]arene. A suspension of calix[6]arene (0.64 g, 1.0 mmol), decyl bromoacetate (1.71 g, 10.0 mmol), and anhydrous K_2CO_3 (0.73 g, 5.0 mmol) in distilled ethyl methyl ketone (150 mL) was heated at reflux for 70 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and filtered. The solid residue was washed several times with CH_2Cl_2. The combined filtrate and washings were evaporated to give a yellow oil that contained unreacted decyl

(30) Tohda, K.; Tange, M.; Odashima, K.; Umezawa, Y.; Furuta, H.; Sessler, J. L. *Anal. Chem.* **1992**, *64*, 960–964.

(31) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681–8691.

bromoacetate. Purification by column chromatography [silica gel; hexane–ethyl acetate (90:10)] gave the target compound **1a** in 25% yield. Colorless viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 18 H, CH_3), 1.24 (br s, 72 H, $OCH_2CH_2CH_2(CH_2)_6CH_3$), 1.28 (br s, 12 H, $OCH_2CH_2CH_2(CH_2)_6CH_3$), 1.61 (quintet, J = 6.8 Hz, 12 H, $OCH_2CH_2CH_2(CH_2)_6CH_3$), 4.05 (s, 12 H, $ArCH_2$), 4.11 (t, J = 6.8 Hz, 12 H, $OCH_2CH_2CH_2(CH_2)_6CH_3$), 4.23 (s, 12 H, $OCH_2CO_2CH_2$), 6.55 (t, J = 7.8 Hz, 6 H, Ar*H* (para)), 6.70 (d, J = 7.8 Hz, 12 H, Ar*H* (meta)); IR (KBr) 2925, 1761, 1737 (sh), 1461, 1191, 1094, 801 cm^{-1}; FDMS, m/z 1826 (M^+ + 2), 1825 (M^+ + 1), 1824 (M^+). Anal. Calcd for $C_{114}H_{168}O_{18}$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.41.

Electrode Construction. PVC matrix liquid membrane electrodes containing **1a**, **2**, or **3** as well as that containing only the membrane solvent (DOS) and the polymer matrix (PVC) (electrodes 1–4, respectively) were prepared according to the previously reported procedure.[19] The membrane compositions (weight percents of sensory element, membrane solvent, and polymer matrix) of electrodes 1–4 were 5, 68, and 27; 2, 66, and 32; 2, 66, and 32; and 0, 71, and 29, respectively. Each membrane was prepared on a liquid membrane type ISE body kindly supplied from Denki Kagaku Keiki (DKK) Co. (Tokyo, Japan). A 10^{-2} M KCl solution was used as an internal solution. The reference electrode was a double-junction type based on an Ag/AgCl electrode (DKK) containing a 3 M KCl solution in the inner compartment and a 10^{-1} M CH_3CO_2Li solution in the outer compartment. Thus, the electrode cell for the potential measurements was as follows: Ag|AgCl|0.01 M KCl|membrane|sample solution|0.1 M CH_3CO_2Li|3 M KCl|AgCl|Ag.

Potential Measurements. Potential measurements were carried out at room temperature (ambient temperature of 20 ± 3 °C) with an ion meter Model IOC-10 (DKK). All potentials plotted in Figures 4–8 are based on an absolute potential scale. Potentiometric responses to four series of guests were examined, i.e. (1) alkali and alkaline earth metal ions (series 1; Figure 4), (2) simple primary amines (series 2; Figure 5), (3) catecholamines (series 3; Figure 6), and (4) α-amino acid methyl esters (series 4; Figure 7). The buffer solutions used were 0.1 M Tris–HCl buffer (pH 7.0) (series 1 and 2), 0.1 M Tris–HCl buffer (pH 7.0) containing 0.01 M L-ascorbic acid (series 3), or 0.1 M CH_3CO_2Li–CH_3CO_2H buffer (pH 5.0) (series 4). For the solutions of the guests of series 3, L-ascorbic acid was added to prevent oxidation of these catecholic guests. A comparison of potentiometric responses to different series of guests (Figure 8) was also made in the same pH 5 buffer used for the guests of series 4. pH was measured by a pH–mV meter model COM-20 (DKK).

Before each set of measurements, the electrode was soaked overnight in an appropriate buffer solution containing no guest. In the measurements for sample solutions containing a guest, the equilibration time after the electrode was dipped into the solution was 20 s to 10 min, depending on the difference in the equilibration time due to the difference in the concentration of the guest. The response time $t(\Delta t,\Delta E)$, defined in previous articles[32–34] as the time at which the differential quotient ($\Delta E/\Delta t$) of the potential–time curve becomes smaller than a prechosen value ($\Delta E/\Delta t < 0.5$ or $\Delta E < 0.5$ mV within Δt = 1.0 min in the present study), was generally short and within 1 min at a concentration of 1.0×10^{-4} M for all guests examined.

Selectivity Coefficients. Potentiometric selectivity coefficients ($K_{i,j}^{pot}$) were determined for each series of guests at room temperature (ca. 20 °C) by the matched potential method according to Gadzekpo and Christian[35] or by the separate solution method according to Srinivasan and Rechnitz[36] (see also refs 37 and 38).

(a) Matched Potential (MP) Method. In the matched potential method, the selectivity coefficient is defined as the ratio of the concentrations of the primary and interfering ions which give the same potential change under the same condition, i.e., under a fixed concentration of the primary ion as a background.[35] For each series of guests, the selectivity coefficients were determined under the following conditions by the procedure described previously.[19,38]

Series 1 (alkali and alkaline earth metal ions; Table I): A 1.0×10^{-5} M concentration of Cs^+ ion was used as a background. The $K_{Cs^+,j}^{pot}$ values were calculated from the concentration of the interfering ion which induced the same amount of potential change as that induced by increasing the concentration of Cs^+ ion to 1.2×10^{-5} M.

Series 2 (simple primary amines; Table II): A 1.0×10^{-4} M concentration of 2-phenylethylamine (**5**) was used as a background. The $K_{5\cdot H^+,j}^{pot}$ values were calculated from the concentration of the interfering ion which induced the same amount of potential change as that induced by increasing the concentration of guest **5** to 2.0×10^{-4} M.

Series 3 (catecholamines; Table III): A 1.0×10^{-4} M concentration of dopamine (**9**) was used as a background. The $K_{9\cdot H^+,j}^{pot}$ values were calculated from the concentration of the interfering ion which induced the same amount of potential change as that induced by increasing the concentration of guest **9** to 1.5×10^{-4} M.

Series 4 (α-amino acid methyl esters; Table IV): A 1.0×10^{-4} M concentration of Trp-OCH_3 (**12**) was used as a background. The $K_{12\cdot H^+,j}^{pot}$ values were calculated from the concentration of the interfering ion which induced the same amount of potential change as that induced by increasing the concentration of guest **12** to 1.2×10^4 M.

Potentiometric selectivity coefficients for different groups of guests (Table V) were determined at pH 5.0 in the same buffer as used for the guests of series 4. A 1.0×10^{-4} M concentration of **5** was used as a background. The $K_{5\cdot H^+,j}^{pot}$ values were calculated from the concentration of the interfering ion which induced the same amount of potential change as that induced by increasing the concentration of guest **5** to 2.0×10^{-4} M. In addition, potentiometric selectivity coefficients were also determined for a combination of dopamine (**9**) and K^+ ion using the same buffer (values in the parentheses in Table V). In this case, K^+ ion, which induced a stronger response, was used as a primary ion and a 1.0×10^{-4} M concentration of it was used as a background. The $K_{K^+,9\cdot H^+}^{pot}$ value was calculated from the concentration of the interfering ion ($9\cdot H^+$) which induced the same amount of potential change as that induced by increasing the concentration of K^+ ion to 2.0×10^{-4} M.

(b) Separate Solution (SS) Method. Selectivity coefficients were also determined by the separate solution method[36] according to the conventional Nicolsky–Eisenman equation, although some of the interfering ions did not give calibration curves with an ideal linearity and Nernstian slope (see ref 38 for a relevant discussion). The concentration of the primary and interfering ions used for the calculation was 1.0×10^{-2} M for all data in Tables I–V.

^{1}H-NMR Measurements. For the ^{1}H-NMR experiments, hydrochlorides of 2-phenylethylamine (**5**), 1-adamantanamine (**7**), and *tert*-butylamine (**8**) were used as the guests. The sample solutions were prepared by diluting with a mixed solvent of $CDCl_3$–CD_3OD (90:10) an appropriate amount of stock solutions of host **1a** (1.5×10^{-2} M) and/or guest (1.5×10^{-1} M) in the same mixed solvent. The measurements were conducted on a 400-MHz Fourier transform NMR spectrometer in the Center for Instrumental Analysis, Hokkaido University, at an ambient temperature of 24 ± 1 °C with a resolution of 0.0012 ppm. Tetramethylsilane (neat) was used as an external standard. Since the chemical shift of $CHCl_3$ based on the external tetramethylsilane was constant (6.73 ± 0.01 ppm) for every sample, it had served as an internal standard. For a relevant discussion, see ref 39.

(32) Uemasu, I.; Umezawa, Y. *Anal. Chem.* **1982**, *54*, 1198–1200.
(33) Lindner, E.; Tóth, K.; Pungor, E.; Umezawa, Y. *Anal. Chem.* **1984**, *56*, 808–810.
(34) Lindner, E.; Tóth, K.; Pungor, E. *Pure Appl. Chem.* **1986**, *58*, 469–479.
(35) Gadzekpo, V. P. Y.; Christian, G. D. *Anal. Chim. Acta* **1984**, *164*, 279–282.
(36) Srinivasan, K.; Rechnitz, G. A. *Anal. Chem.* **1969**, *41*, 1203–1208.
(37) International Union of Pure and Applied Chemistry, Analytical Chemistry Division, Commission on Analytical Nomenclature *Pure Appl. Chem.* **1976**, *48*, 127–132.
(38) Umezawa, K.; Umezawa, Y. In *CRC Handbook of Ion-Selective Electrodes: Selectivity Coefficients*; Umezawa, Y., Ed.; CRC Press: Boca Raton, FL, 1990; pp 3–9.
(39) Ono, S.; Mitsumori, F.; Arata, Y.; Fujiwara, S. *Bunseki Kagaku* **1977**, *26*, 766–772; *Chem. Abstr.* **1978**, *88*, 56763k.

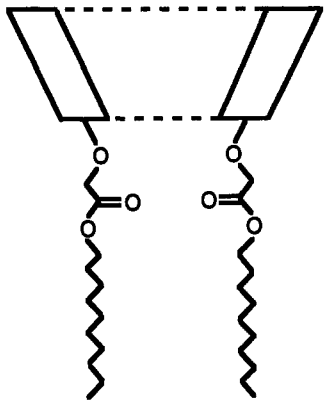

Figure 2. Schematic representation of the inward-directed carbonyl groups in an acetate ester derivative of calixarene (cone conformer). These carbonyl groups, linked by a methylene unit to the hydroxyl groups at the lower rim of the calixarene cavity, form a pseudocavity that functions as a convergent binding site for cationic guests.

RESULTS AND DISCUSSION

Design and Synthesis of Lipophilic Hexaester of Calix[6]arene 1a as the Sensory Element for Organic Amines. Calixarenes, a class of metacyclophanes produced by the condensation–macrocyclization of phenol and aldehyde, have focused increasing attention as a class of host compounds having a well-defined cavity, which is composed of aromatic rings linked by methylene units at the meta positions.[40,41] Extensive studies have been carried out on the selective complexation and transport of alkali metal ions by calixarene derivatives, especially those exhaustively derivatized with acetate ester units at the lower rim.[40,41] This type of calixarene esters has inward-directed carbonyl oxygens, which function as well-defined convergent binding sites for the metal ions that sterically fit well with the pseudocavity constructed by these oxygens (Figure 2). Actually, the calix[4]arene tetraesters and the calix[6]arene hexaesters have been shown to display selectivities for sodium and cesium ions, respectively, in the complexation, extraction, and transport experiments.[40,41] These results have stimulated a number of groups to apply this type of calixarene ester as sensory elements of liquid membrane type ISEs. Thus, the electrodes for sodium,[42–47] potassium,[48] and cesium ions[49] have been reported. Some ketonic analogues, which have a structural feature common to the calixarene esters (Figure 2), have also been used as sensory elements for sodium ion.[46,50,51] In all of these studies, the calixarene structure was used as a rigid support for the carbonyl groups that function as convergent binding sites for metal ions.

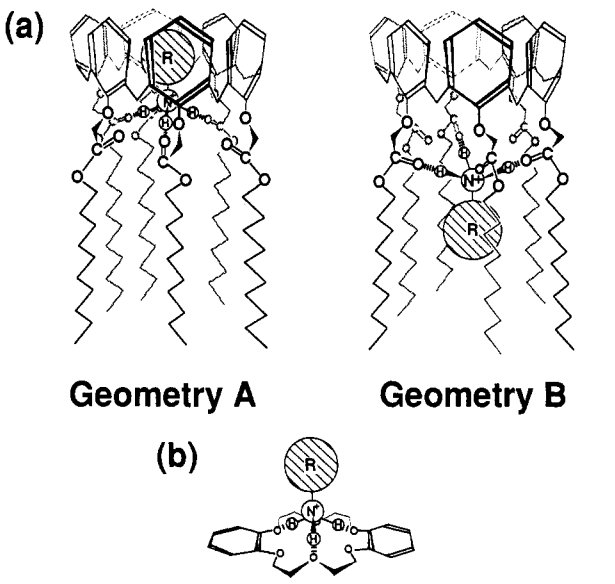

Figure 3. Schematic representations of the complexation geometries of the host–guest complexes: (a) Two possible geometries of the host–guest complex between the calix[6]arene hexaester **1a** and a protonated primary amine guest. (b) Plausible geometry of the host–guest complex between dibenzo-18-crown-6 (**2**) and a protonated primary amine guest.

However, the well-defined structure of the calixarene cavity could also be exploited for inclusion of organic guests. Especially, the cavity of calix[6]arene is sufficiently large to accommodate organic guests, whereas that of calix[4]arene is too small for ordinary organic guests. In addition, a hexakis(acetate ester) of calix[6]arene affords an excellent binding site for protonated primary amines, because the NH_3^+ moiety of these guests can bind strongly to the inward-directed ester carbonyl groups of the host by a tripodal hydrogen bonding. As depicted schematically in Figure 3a, there are two possible geometries for the complexation between the calix[6]arene hexaester host and a protonated primary amine guest: geometry A, which involves a tripodal hydrogen bonding with an inclusion of the nonpolar moiety of the guest into the calix[6]arene cavity, and geometry B, which involves a tripodal hydrogen bonding from the opposite side, in other words, without the inclusion into the cavity. Discrimination of organic amine guests according to the steric shapes of their nonpolar moieties could be expected on the basis of the complexation geometry A involving the guest inclusion. Such a shape-descriminating effect would not be expected for a simple 18-crown-6 derivative that also has hexagonally arranged oxygen atoms for binding with a protonated primary amine guest but does not have a cavity which is sufficiently large to accommodate organic guests (Figure 3b).

In the present study, a new lipophilic hexaester of calix[6]arene [37,38,39,40,41,42-hexakis(decyloxycarbonylmethyloxy)calix[6]arene, **1a**] was synthesized by introducing six decyl acetate units to hexahydroxycalix[6]arene by employing the reported procedure.[31] This lipophilic calix[6]arene hexaester having C_{10} alkyl chains was exploited as the sensory element of a PVC matrix liquid membrane electrode. The potentiometric response properties of this electrode were examined for three series of organic amines as well as for alkali and alkaline earth metal ions. The selectivities for the inorganic metal ions were compared with the reported selectivities of the electrode based on the same type of calix[6]arene hexaester but having C_2 chains (**1b**).[49] The selectivities for the organic amine guests were compared with those of the electrodes based on dibenzo-18-crown-6 (**2**) or potassium tetrakis(*p*-chlorophenyl)borate (**3**). In addition, a ^{1}H-NMR study was carried out to correlate the characteristic

(40) Gutsche, C. D. *Calixarenes*; Monographs in Supramolecular Chemistry, Vol. 1; Royal Society of Chemistry: London, 1989.
(41) *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Topics in Inclusion Science, Vol. 3; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991.
(42) Kimura, K.; Matsuo, M.; Shono, T. *Chem. Lett.* **1988**, 615–616.
(43) Kimura, K.; Miura, T.; Matsuo, M.; Shono, T. *Anal. Chem.* **1990**, *62*, 1510–1513.
(44) Tanaka, M.; Kobayashi, T.; Yamashoji, Y.; Shibutani, Y.; Yakabe, K.; Shono, T. *Anal. Sci.* **1991**, *7*, 817–818.
(45) Diamond, D.; Svehla, G.; Seward, E. M.; McKervey, M. A. *Anal. Chim. Acta* **1988**, *204*, 223–231.
(46) Cadogan, A. M.; Diamond, D.; Smyth, M. R.; Deasy, M.; McKervey, M. A.; Harris, S. J. *Analyst* **1989**, 1551–1554.
(47) Cunningham, K.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Anal. Proc.* **1991**, *28*, 294–296.
(48) Cadogan, A.; Diamond, D.; Cremin, S.; McKervey, A. M.; Harris, S. J. *Anal. Proc.* **1991**, *28*, 13–14.
(49) Cadogan, A.; Diamond, D.; Smyth, M. R.; Svehla, G.; McKervey, M. A.; Seward, E. M.; Harris, S. J. *Analyst* **1990**, *115*, 1207–1210.
(50) Brunink, J. A. J.; Haak, J. R.; Bomer, J. G.; Reinhoudt, D. N.; McKervey, M. A.; Harris, S. J. *Anal. Chim. Acta* **1991**, *254*, 75–80.
(51) Telting-Diaz, M.; Diamond, D.; Smyth, M. R.; Seward, E. M.; McKervey, A. M. *Electroanalysis* **1991**, *3*, 371–375.

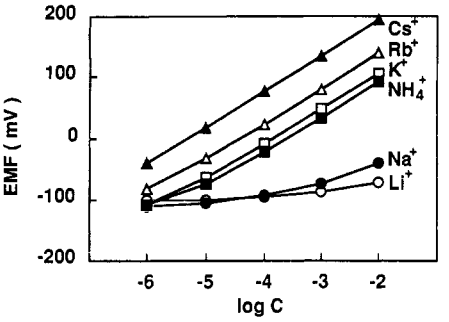

Figure 4. Potential vs concentration curves for alkali metal and ammonium cations, obtained at pH 7.0 by electrode 1 based on the calix[6]arene hexaester **1a**. Measured in 0.1 M Tris–HCl buffer (pH 7.0) at room temperature (ca. 20 °C).

response behaviors of the calixarene electrode with the geometries of the host–guest complexes.

Potentiometric Responses and Selectivity for Inorganic Metal Ions. As described earlier, calixarene esters as well as their analogues have recently been applied as sensory elements of liquid membrane type ISEs for alkali metal ions.[42–51] Especially noteworthy is the application of lipophilic tetraesters of calix[4]arene for sodium ion-selective electrodes,[42–47] which display a higher Na^+/K^+ selectivity as compared to those of the electrodes based on lipophilic derivatives of bis(14-crown-4).[52] Higher homologues of calix[4]arene ester such as dioxocalix[4]arene tetraesters[48] and calix[6]arene hexaesters[49] have also been used as sensory elements for potassium and cesium ion-selective electrodes, respectively.

Figure 4 shows potentiometric response curves for alkali metal and ammonium ions, obtained at pH 7.0 (0.1 M Tris–HCl buffer) by electrode 1 based on **1a**. The strongest response was observed for Cs^+ ion with a detection limit below 10^{-6} M. A linear response with a slope of 59 mV/decade, close to the theoretical value according to the Nernst equation (58.17 mV/decade at 20 °C), started from ca. 10^{-5} M. Nernstian responses were also observed for Rb^+ and K^+ ions as well as NH_4^+ ion though from a higher concentration (ca. 10^{-4} M). On the other hand, the response to Na^+ ion was much weaker and that to Li^+ ion was almost negligible (Figure 4). The responses to all of the alkaline earth metal ions (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) were negligible (figure not shown). Electrode 4 with a membrane containing no specific sensory element showed negligible responses to all of the alkali and alkaline earth metal ions tested (figure not shown).

The selectivity of potentiometric responses by electrode 1 was in the order of $Cs^+ > Rb^+ > K^+ \geq NH_4^+ \gg Na^+ > Li^+ \gg Mg^{2+}$, Ca^{2+}, Sr^{2+}, Ba^{2+} (no response). The selectivity coefficients ($K_{Cs^+,j}^{pot}$) determined by the matched potential (MP) method as well as by the separate solution (SS) method are listed in Table I. The $K_{Cs^+,j}^{pot}$ values reported for the electrode based on the corresponding calix[6]arene hexaester having C_2 chains (**1b**)[49] are also listed in Table I for comparison. These two calix[6]arene hexaester electrodes showed the same response order and gave similar $K_{Cs^+,j}^{pot}$ values for most of the metal ions tested. Most of these $K_{Cs^+,j}^{pot}$ values are also in the same order of magnitude with those of the electrodes based on bis(18-crown-6)'s.[53–57] The potentiometric selectivity of the calix[6]arene electrodes reflects the selectivity observed in the complexation, extraction, or transport of these ions.[31,50,58–60] The preference for Cs^+ ion can be reasonably explained by a good steric fit with the pseudocavity constructed by the six inward-directed ester carbonyl groups (see Figures 2 and 3a).

Table I. Potentiometric Selectivity Coefficients for Alkali and Alkaline Earth Metal Ions at pH 7.0

	electrode 1 based on **1a**[a]		
guest	MP method[b]	SS method[c]	electrode based on **1b**[d]
Cs^+	1	1	1
Rb^+	$(2.50 \pm 0.18) \times 10^{-1}$	$(8.00 \pm 0.68) \times 10^{-2}$	1.41×10^{-2} [e]
K^+	$(3.97 \pm 0.21) \times 10^{-2}$	$(2.34 \pm 0.52) \times 10^{-3}$	2.09×10^{-3} [e]
NH_4^+	$(1.25 \pm 0.09) \times 10^{-2}$	$(2.00 \pm 0.56) \times 10^{-3}$	1.48×10^{-3} [e]
Na^+	$<10^{-4}$	$(2.04 \pm 0.18) \times 10^{-5}$	1.35×10^{-4} [e]
Li^+	$<10^{-4}$	$(1.38 \pm 0.26) \times 10^{-5}$	6.31×10^{-5} [e]
Ba^{2+}	$<10^{-4}$		
Sr^{2+}	$<10^{-4}$		
Ca^{2+}	$<10^{-4}$		4.07×10^{-4} [f]
Mg^{2+}	$<10^{-4}$		9.12×10^{-5} [f]

[a] **1a**, calix[6]arene hexaester with C_{10} alkyl chains. The potentiometric selectivity coefficients ($K_{Cs^+,j}^{pot}$) obtained by electrode 1 were determined in 0.1 M Tris–HCl buffer (pH 7.0) at room temperature (ca. 20 °C). The average values of three or five runs are shown with the mean deviations. [b] Determined by the matched potential (MP) method with 1.0×10^{-5} M Cs^+ ion (primary ion) as a background. See Experimental Section for the details. [c] Determined by the separate solution (SS) method with 1.0×10^{-2} M primary and interfering ions. [d] **1b**, calix[6]arene hexaester with C_2 alkyl chains. The reported values of selectivity coefficients ($K_{Cs^+,j}^{pot}$) obtained by an electrode based on the same type of calix[6]arene hexaester but with shorter alkyl chains.[49] Membrane composition: **1b**:NPOE:PVC = 2:360:180. (NPOE, 2-nitrophenyl 1-octyl ether). [e] The $K_{Cs^+,j}^{pot}$ values for the monocations were determined by the separate solution method using 1×10^{-1} M chloride salts of each cation. [f] The $K_{Cs^+,j}^{pot}$ values for the dications were determined by the mixed solution fixed interference method.

Potentiometric Responses and Selectivity for Simple Primary Amines. As discussed earlier, electrode 1 based on **1a** is expected to be capable of discriminating the steric shapes of nonpolar moieties of protonated primary amine guests, provided that the host–guest complexation occurs with geometry A depicted in Figure 3a. From this viewpoint, the response behaviors of this electrode for simple primary amines (**4**–**8**) were examined at pH 7.0 (0.1 M Tris–HCl buffer) and compared with those of electrode 2 based on **2**, electrode 3 based on **3**, and electrode 4 containing no specific sensory element. At pH 7.0, guests **4**–**8** (pK_a = 9.5–11) are almost completely in their monocationic forms by protonation. Potentiometric response curves for electrodes 1–4 are shown in Figure 5a–d, respectively. Responses to the positive direction (cationic responses) were observed in all cases. For electrodes 1 and 2, the selectivity coefficients ($K_{5\text{-}H^+,j}^{pot}$), determined by the matched potential method as well as by the separate solution method with 2-phenylethylamine (**5**) as a primary ion, are listed in Table II.

Electrode 1 based on **1a** displayed a characteristic potentiometric selectivity for the protonated primary amines (RNH_3^+). As shown in Figure 5a and Table II, the magnitude of the response was in the order of 1-octylamine (**4**, R = $(CH_2)_7CH_3$) ≥ 2-phenylethylamine (**5**, R = $CH_2CH_2C_6H_5$) ≫ benzylamine (**6**, R = $CH_2C_6H_5$) ≫ 1-adamantanamine (**7**, R

(52) Shono, T.; Okahara, M.; Ikeda, I.; Kimura, K.; Tamura, H. *J. Electroanal. Chem.* **1982**, *132*, 99–105.
(53) Kimura, K.; Tamura, H.; Shono, T. *J. Electroanal. Chem.* **1979**, *105*, 335–340.
(54) Tamura, H.; Kimura, K.; Shono, T. *Nippon Kagaku Kaishi* **1980**, 1648–1650.
(55) Kimura, K.; Ishikawa, A.; Tamura, H.; Shono, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 447–450.
(56) Fung, K. W.; Wong, K. H. *J. Electroanal. Chem.* **1980**, *111*, 359–368.
(57) Ikeda, T.; Abe, A.; Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1983**, 369–372.
(58) Chang, S.-K.; Cho, I. *Chem. Lett.* **1984**, 477–478.
(59) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211–214.
(60) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388–390.

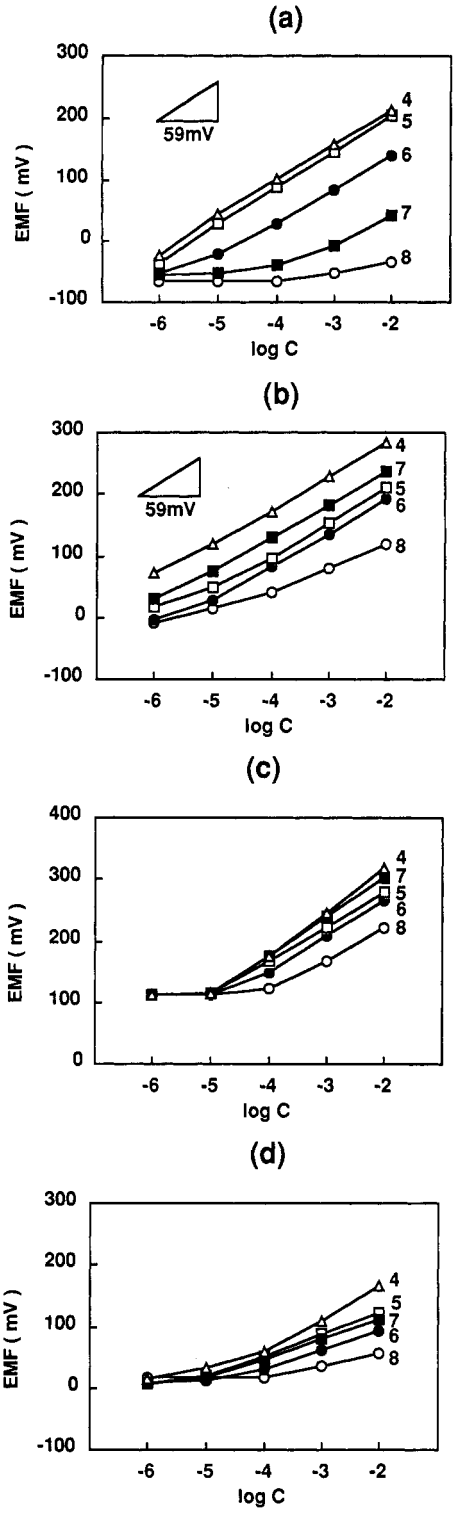

Figure 5. Potential vs concentration curves for simple amines at pH 7.0: (a) Electrode 1 based on the calix[6]arene hexaester **1a**. (b) Electrode 2 based on dibenzo-18-crown-6 (**2**). (c) Electrode 3 based on potassium tetrakis(*p*-chlorophenyl)borate (**3**). (d) Electrode 4 with a membrane containing only DOS and PVC. Measured in 0.1 M Tris–HCl buffer (pH 7.0) at room temperature (ca. 20 °C).

= 1-adamantyl) > *tert*-butylamine (8, R = $C(CH_3)_3$). The strongest responses were obtained for guests 4 and 5 with a detection limit below 10^{-6} M. Responses with a theoretical Nernstian slope were observed from ca. 10^{-5} M concentration for guest 4 (58 mV/decade) and from ca. 10^{-6} M concentration for guest 5 (59 mV/decade). A Nernstian response was also observed for guest 6 though from a higher concentration (ca. 10^{-4} M). On the other hand, the responses to guests 7 and 8 were much weaker, and by comparing with the corresponding curves in Figure 5d, could be ascribed to the responses due to the membrane solvent (DOS) and/or polymer matrix (PVC) and not to the sensory element **1a**.

Table II. Potentiometric Selectivity Coefficients for Simple Amines (4–8) at pH 7.0[a]

	calix[6]arene hexaester 1a		dibenzo-18-crown-6 (2)	
guest[b]	MP method[c]	SS method[d]	MP method[c]	SS method[d]
4	2.60 ± 0.14	1.41 ± 0.20	20.0 ± 0.03	20.0 ± 0.09
5	1	1	1	1
6	(2.90 ± 0.19) × 10^{-1}	(7.76 ± 0.33) × 10^{-2}	4.77 ± 0.24	(4.70 ± 0.20) × 10^{-1}
7	<10^{-2}	(1.55 ± 0.19) × 10^{-3}	20.0 ± 0.11	2.86 ± 0.08
8	<10^{-2}	(7.41 ± 0.22) × 10^{-5}	(3.48 ± 0.03) × 10^{-1}	(2.69 ± 0.10) × 10^{-2}

[a] The potentiometric selectivity coefficients ($K_{5\text{-}H^+,J}^{pot}$) were determined in 0.1 M Tris–HCl buffer (pH 7.0) at room temperature (ca. 20 °C) with 2-phenylethylamine (**5**) as a primary ion. The average values of three or five runs are shown with the mean deviations. [b] All of the amine guests are almost completely in their monocationic forms by protonation under the experimental pH. [c] Determined by the matched potential (MP) method with 1.0 × 10^{-4} M guest **5** (primary ion) as a background. See Experimental Section for the details. [d] Determined by the separate solution (SS) method with 1.0 × 10^{-2} M primary and interfering ions.

Electrode 2 based on the 18-crown-6 derivative **2** showed a quite different selectivity for the primary amine guests. The magnitude of the response was in the order of **4** (R = $(CH_2)_7CH_3$) > **7** (R = 1-adamantyl) > **5** (R = $CH_2CH_2C_6H_5$) ≥ **6** (R = $CH_2C_6H_5$) ≫ **8** (R = $C(CH_3)_3$) (Figure 5b, Table II). In this case, the response was much stronger than that by electrode 4 for all of the guests examined. Again, the strongest response was observed for guest 4 with a detection limit below 10^{-6} M. A linear response of 58 mV/decade started from ca. 10^{-4} M. Since appreciable responses have also been observed for the other guests at 10^{-6} M, the crown ether electrode can be regarded to have a higher sensitivity (lower detection limit) as compared with that of the calixarene electrode.

Electrode 3 based on a conventional cation exchanger (**3**) showed a selectivity similar to that of the crown ether electrode. However, the responses started at ca. 10^{-5} M and the sensitivity was much inferior to that of the crown ether electrode. The slopes of the curves at the high concentration range (>10^{-4} M) were 56–66 mV/decade, which were close to or greater than the theoretical value. Electrode 4 with a membrane containing no specific sensory element also showed responses to the primary amine guests, but the responses and selectivity were both much inferior to those of the other three electrodes except for guests 7 and 8 in comparison with electrode 1 (vide supra).

The potentiometric selectivities of electrode 2 based on **2** and electrode 3 based on **3** seem to be controlled mainly by the lipophilicity of the guests. This is consistent with the fact that both of these sensory elements bind with a protonated amine guest only through its NH_3^+ group without any interaction with the nonpolar moiety. On the other hand, electrode 1 based on **1a** displayed a potentiometric selectivity, which is quite different from that expected from simple lipophilicity of the guests as observed for electrodes 2 and 3. An important factor controlling the characteristic selectivity of electrode 1 is evidently the steric bulkiness around the NH_3^+ group of the guests. The guests that induced the strongest responses are the ones that do not have a bulky substituent at the α-carbon adjacent to the NH_3^+ group [**4**, R = $(CH_2)_7CH_3$; **5**, R = $CH_2CH_2C_6H_5$]. Guest **6** (R = $CH_2C_6H_5$) having a bulky phenyl group at the α-carbon gave a weaker response. No net response was observed for the guests having a tertiary alkyl structure at the α position [**7**, R = 1-adamantyl; **8**, R = $C(CH_3)_3$].

Calix[6]arene hexaester **1a** belongs to a category of hosts designated as "neutral carriers", which includes valinomycin and crown ethers as representative examples. A number of studies have shown that the potentiometric selectivities of the electrodes based on neutral carriers reflect the complexing selectivities of these hosts.[1,61] In the case of **1a**, it would be reasonable to assume that the complexing ability for each guest would be greatly affected by the feasibility of forming an inclusion complex without the tripodal hydrogen bonding being sterically hindered, in other words, by the feasibility of adopting the complexation geometry A depicted in Figure 3a.

From this viewpoint, the tertiary alkyl structure at the α position in guests **7** and **8** is unfavorable because it would sterically hinder the tripodal hydrogen bonding when the nonpolar moieties of these guests are accommodated within the calix[6]arene cavity. The phenyl group attached directly to the α-carbon as in guest **6** is also unfavorable because it causes a bent structure that would lead to an incomplete tripodal hydrogen bonding when the phenyl group is accommodated within the calix[6]arene cavity. Guest **5**, having an additional methylene unit between the NH_3^+ and phenyl groups, is capable of adopting an extended conformation as in guest **4**, having a nonbranched alkyl chain. In contrast to the case of guest **6**, such an extended conformation in guests **4** and **5** would not lead to a severe steric hindrance for the formation of tripodal hydrogen bonds. Thus, the characteristic potentiometric selectivity of electrode 1 for the primary amine guests can be reasonably interpreted by the feasibility of forming a stable inclusion complex with a tripodal hydrogen bonding. A series of extraction experiments that might be related to such a mode of structure discrimination have been recently reported by Chang et al.[62]

Potentiometric Responses and Selectivity for Catecholamines. Catecholamines (**9**–**11**), which comprise an important group of neurotransmitters as well as adrenal medulla hormones, have as a basic skeleton the structure of 2-phenylethylamine **5**, which induced the strongest response to electrode 1 based on **1a**. The response behaviors of electrodes 1–4 for guests **9**–**11** were examined at pH 7.0, at which all of these guests are almost completely in their monocationic forms by protonation. Since catecholamines are sensitive to oxidation, a 0.01 M concentration of L-ascorbic acid was added as a reducing agent to the buffer solution (0.1 M Tris–HCl). The measurements were carried out within 8 h after the preparation of the guest solutions. Potentiometric response curves for electrodes 1–4 are shown in Figure 6a–d, respectively. Cationic responses were observed in all cases. For electrodes 1 and 2, the selectivity coefficients ($K_{9,H^+,J}^{pot}$), determined by the matched potential method as well as by the separate solution method with dopamine (**9**) as a primary ion, are listed in Table III.

Electrode 1 based on **1a** showed the strongest response to **9**, which has a primary amino group and no substituent at the β-carbon. The response started at ca. 10^{-5} M, and a theoretical Nernstian slope was observed from ca. 10^{-3} M. The responses to noradrenaline (**10**) and adrenaline (**11**), with a hydroxyl group at the β-carbon, were much weaker but still much stronger than the responses by electrode 4 with a membrane containing no specific sensory element (Figure 6, a vs d). Electrodes 2 and 3 based on **2** and **3**, respectively, also showed the strongest responses to **9** (Figure 6b and c), though much weaker than the response by electrode 1 (Figure 6a). The

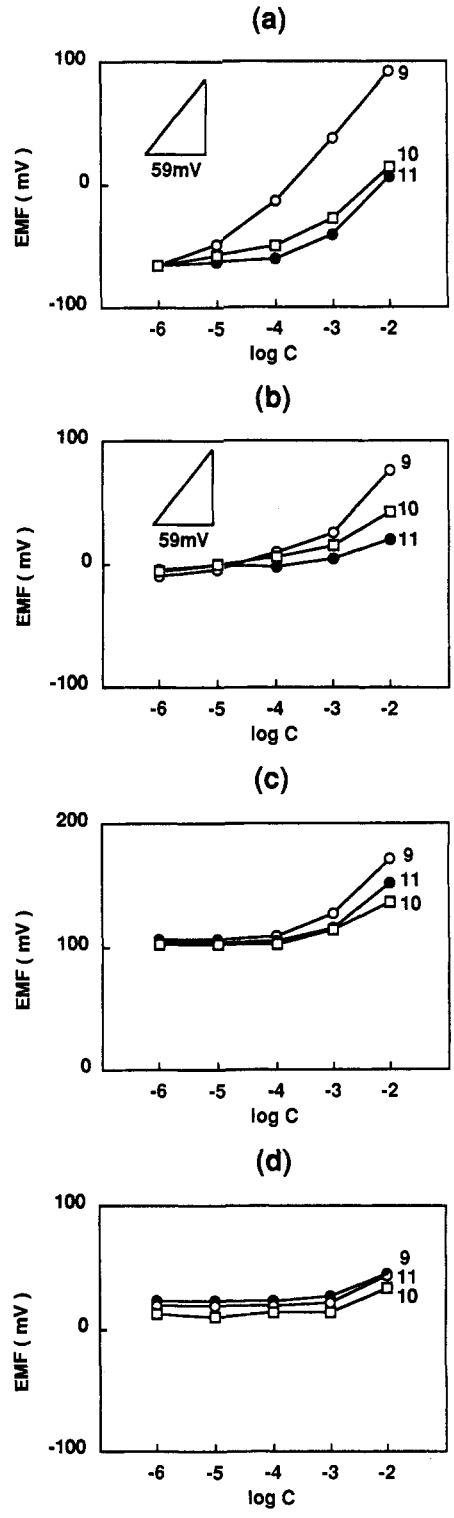

Figure 6. Potential vs concentration curves for catecholamines at pH 7.0: (a) Electrode 1 based on the calix[6]arene hexaester **1a**. (b) Electrode 2 based on dibenzo-18-crown-6 (**2**). (c) Electrode 3 based on potassium tetrakis(*p*-chlorophenyl)borate (**3**). (d) Electrode 4 with a membrane containing only DOS and PVC. Measured at room temperature (ca. 20 °C) in 0.1 M Tris–HCl buffer containing 0.01 M L-ascorbic acid (pH 7.0).

responses and selectivity were both much inferior with electrode 4.

The distinct potentiometric discrimination between **9** and the other guests (**10**, **11**) by electrode 1 can be explained, again, on the basis of geometry A depicted in Figure 3a. Guest **9**, which has a structure common to **5**, would form a stable inclusion complex with host **1a**. On the other hand, the β-substituted structure in guests **10** and **11** is unfavorable

(61) Eisenman, G. *Ion-Selective Electrodes*; Durst, R. A., Ed.; Special Publication 314; National Bureau of Standards: Washington, D.C., 1969; Chapter 1.

(62) Chang, S. K.; Jang, M. J.; Han, S. Y.; Lee, J. H.; Kang, M. H.; No, K. T. *Chem. Lett.* **1992**, 1937–1940.

Table III. Potentiometric Selectivity Coefficients for Catecholamines (9–11) at pH 7.0[a]

	calix[6]arene hexaester 1a		dibenzo-18-crown-6 (2)	
guest[b]	MP method[c]	SS method[d]	MP method[c]	SS method[d]
9	1	1	1	1
10	$(1.99 \pm 0.19) \times 10^{-1}$	$(3.80 \pm 0.30) \times 10^{-2}$	$(9.35 \pm 0.16) \times 10^{-1}$	$(2.20 \pm 0.16) \times 10^{-1}$
11	$(2.69 \pm 0.12) \times 10^{-1}$	$(2.82 \pm 0.11) \times 10^{-2}$	$(8.82 \pm 0.20) \times 10^{-1}$	$(8.13 \pm 0.18) \times 10^{-2}$

[a] The potentiometric selectivity coefficients ($K_{9,H^+_J}^{pot}$) were determined at room temperature (ca. 20 °C) in 0.1 M Tris–HCl buffer containing 0.01 M L-ascorbic acid (pH 7.0). Dopamine (9) was used as a primary ion. The average values of three or five runs are shown with the mean deviations. [b] All of the amine guests are almost completely in their monoprotonated forms by protonation under the experimental pH. [c] Determined by the matched potential (MP) method with 1.0×10^{-4} M guest 9 (primary ion) as a background. See Experimental Section for the details. [d] Determined by the separate solution (SS) method with 1.0×10^{-2} M primary and interfering ions.

because the tripodal hydrogen bonding would be sterically hindered when the nonpolar moieties of these guests are accommodated within the calix[6]arene cavity. The secondary amino structure in guest 11 is another unfavorable factor for the tripodal hydrogen bonding between the host and guest. Thus, the characteristic potentiometric selectivity of electrode 1 for 9 can be reasonably interpreted, again, by the feasibility of forming a stable inclusion complex with a tripodal hydrogen bonding.

Potentiometric Responses and Selectivity for α-Amino Acid Esters. Potentiometric responses to α-amino acid esters were also examined in the present study. Since the basicity of α-amino acid esters is much weaker (pK_a = 7–7.5) than that of ordinary aliphatic amines (pK_a = 9.5–11), the pH of the sample solutions was set to 5.0 using a 0.1 M CH_3CO_2-Li–CH_3CO_2H buffer. At this pH, all of these guests are almost completely in their monocationic forms by protonation. Potentiometric response curves for electrodes 1–4 are shown in panels a–d of Figure 7, respectively. Cationic responses were observed in all cases. For electrodes 1 and 2, the selectivity coefficients ($K_{12,H^+_J}^{pot}$), determined by the matched potential method as well as by the separate solution method with Trp-OCH_3 (12) as a primary ion, are listed in Table IV.

For this series of guests, the responses by electrode 1 based on 1a (Figure 7a) were inferior to those of electrode 2 based on 2 or electrode 3 based on 3 (Figure 7b and c). Actually, the responses by electrode 1 were only a little greater than those by electrode 4 with a membrane containing no specific sensory element (Figure 7d). This is consistent with the above observation that electrode 1 did not give a strong response to benzylamine (6) having a bulky substituent (phenyl group) attached directly to the α-carbon (Figure 5a). α-Amino acid esters fall into such a category of guests, which would lead to an incomplete tripodal hydrogen bonding when accommodated within the calix[6]arene cavity. This could be an unfavorable factor for the complexation geometry A (Figure 3a) and hence for a strong potentiometric response.

The magnitude of the potentiometric response to the α-amino acid esters [$^+H_3NCH(R)CO_2CH_3$] by electrode 1 was in the order of 12 (Trp-OCH_3, R = 3-indolylmethyl) > 13 (Phe-OCH_3, R = $CH_2C_6H_5$) > 14 (Leu-OCH_3, R = $CH_2CH(CH_3)_2$) > 15 (Val-OCH_3, R = $CH(CH_3)_2$) > 16 (Ala-OCH_3, R = CH_3). This selectivity reflects the lipophilicity of each guest and was very similar to that of electrodes 2–4. These results suggest a possibility of the predominance of geometry B over geometry A in the formation of host–guest complexes between calix[6]arene hexaester 1a and protonated α-amino acid esters. Recently, Chang et al.[63] reported on a selective transport of amino acid esters through a chloroform liquid membrane by using a calix[6]arene hexaester having C_2 alkyl chains (1c). The selectivity of transport was found to be

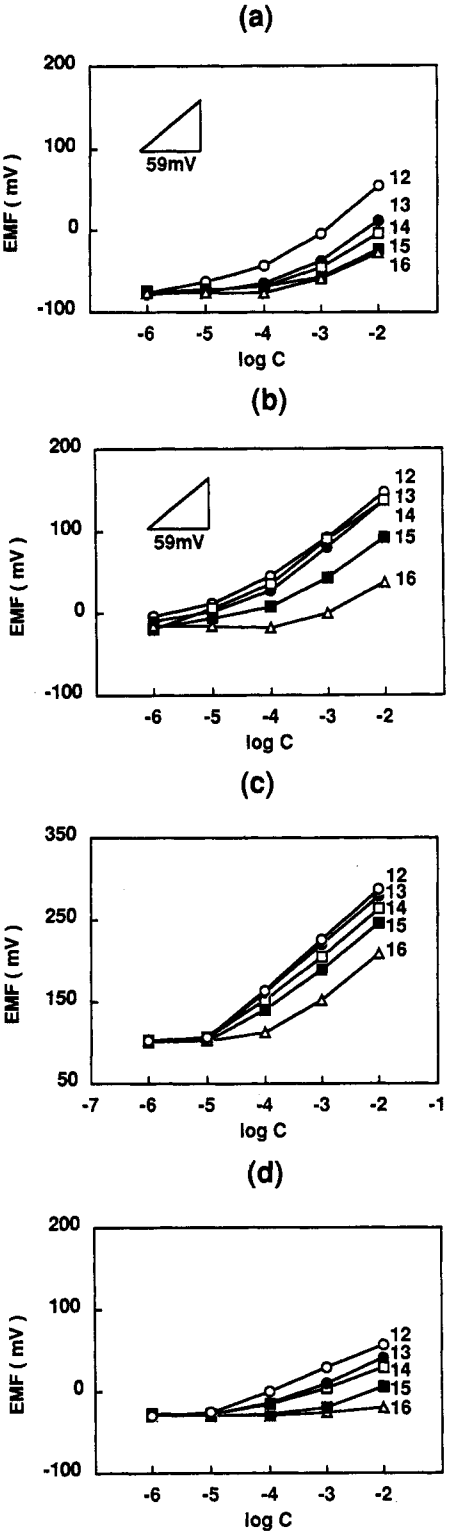

Figure 7. Potential vs concentration curves for α-amino acid methyl esters at pH 5.0: (a) Electrode 1 based on the calix[6]arene hexaester 1a. (b) Electrode 2 based on dibenzo-18-crown-6 (2). (c) Electrode 3 based on potassium tetrakis(*p*-chlorophenyl)borate (3). (d) Electrode 4 with a membrane containing only DOS and PVC. Measured in 0.1 M CH_2CO_2Li–CH_3CO_2H buffer (pH 5.0) at room temperature (ca. 20 °C).

(63) Chang, S. K.; Hwang, H. S.; Son, H.; Youk, J.; Kang, Y. S. *J. Chem. Soc., Chem. Commun.* 1991, 217–218.

Table IV. Potentiometric Selectivity Coefficients for α-Amino Acid Esters (12–16) at pH 5.0[a]

	calix[6]arene hexaester 1a		dibenzo-18-crown-6 (2)	
guest[b]	MP method[c]	SS method[d]	MP method[c]	SS method[d]
12	1	1	1	1
13	$(6.22 \pm 0.31) \times 10^{-1}$	$(1.80 \pm 0.31) \times 10^{-1}$	$(9.13 \pm 0.08) \times 10^{-1}$	$(6.30 \pm 0.10) \times 10^{-1}$
14	$(5.14 \pm 0.10) \times 10^{-1}$	$(9.55 \pm 0.26) \times 10^{-2}$	$(8.80 \pm 0.12) \times 10^{-1}$	$(6.30 \pm 0.21) \times 10^{-1}$
15	$(2.86 \pm 0.19) \times 10^{-1}$	$(4.17 \pm 0.22) \times 10^{-2}$	$(5.62 \pm 0.21) \times 10^{-1}$	$(1.00 \pm 0.16) \times 10^{-1}$
16	$(1.92 \pm 0.16) \times 10^{-1}$	$(3.35 \pm 0.23) \times 10^{-2}$	$(1.22 \pm 0.03) \times 10^{-1}$	$(1.15 \pm 0.15) \times 10^{-2}$

[a] The potentiometric selectivity coefficients ($K_{12\text{-}H^+,J}^{pot}$) were determined in 0.1 M CH_3CO_2Li–CH_3CO_2H buffer (pH 5.0) at room temperature (ca. 20 °C) with Trp-OCH_3 (12) as a primary ion. The average values of three or five runs are shown with the mean deviations. [b] All of the amine guests are almost completely in their monoprotonated forms by protonation under the experimental pH. [c] Determined by the matched potential (MP) method with 1.0×10^{-4} M guest 12 (primary ion) as a background. See Experimental Section for the details. [d] Determined by the separate solution (SS) method with 1.0×10^{-2} M primary and interfering ions.

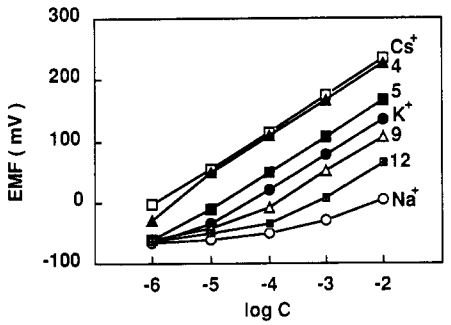

Figure 8. Potential vs concentration curves for representative guests of series 1–4, obtained at pH 5.0 by electrode 1 based on the calix[6]arene hexaester 1a. Measured in 0.1 M CH_3CO_2Li–CH_3CO_2H buffer (pH 5.0) at room temperature (ca. 20 °C).

closely related to the lipophilicity of each guest. This work may also support the predominance of geometry B in the host–guest complexation between a calix[6]arene hexaester and a protonated α-amino acid ester.

Comparison of Potentiometric Responses to Different Series of Amines. Potentiometric responses of electrode 1 based on 1a to different series of guests were compared under the same conditions. Since α-amino acid ester guests having pK_a's of 7–7.5, which are lower than those of ordinary aliphatic amines (9.5–11), require pH 5.0 for a complete protonation, the experimental condition for the comparison between the guests of different series was set to pH 5.0 using a 0.1 M CH_3CO_2Li–CH_3CO_2H buffer. This pH, more acidic than pH 7.0, has as another advantage that the oxidation of catecholamine guests is much slower and no colorization of the sample solution occurs at least for several hours after the preparation. Therefore, L-ascorbic acid as a reducing agent was not added in this case.

The potentiometric response curves obtained for representative guests of series 1–4 are shown in Figure 8. The strongest responses were observed for Cs^+ and 4 with a detection limit below 10^{-6} M. Linear responses with a theoretical Nernstian slope started from ca. 10^{-6} M and 10^{-5} M for Cs^+ and guest 4, respectively. Guest 5 and K^+ also showed strong responses with a Nerstian slope starting from ca. 10^{-5} M. In the case of 9, the Nernstian response started from a higher concentration (ca. 10^{-4} M). Guest 12 gave a linear Nernstian response only in a highest concentration range (>10^{-3} M). The response to Na^+ ion was very weak and

Table V. Potentiometric Selectivity Coefficients of the Calix[6]arene Electrode for Different Groups of Amines at pH 5.0[a]

	calix[6]arene hexaester 1a	
guest[b]	MP method[c]	SS method[e]
4	5.36 ± 0.05	10.72 ± 0.08
5	1	1
9	$<10^{-2}$ (0.63 ± 0.02)[d]	$(9.89 \pm 0.04) \times 10^{-2}$
12	$<10^{-2}$	$(1.82 \pm 0.02) \times 10^{-2}$
Cs^+	8.10 ± 0.11	14.79 ± 0.03
K^+	$<10^{-2}$ (1)[d]	$(3.02 \pm 0.01) \times 10^{-1}$
Na^+	$<10^{-2}$	$(1.91 \pm 0.01) \times 10^{-3}$

[a] The potentiometric selectivity coefficients ($K_{5\text{-}H^+,J}^{pot}$) were determined in 0.1 M CH_3CO_2Li–CH_3CO_2H buffer (pH 5.0) at room temperature (ca. 20 °C) with 2-phenylethylamine (5) as a primary ion. The average values of two or three runs are shown with the mean deviations. [b] Amine guests: 1-octylamine (4), 2-phenylethylamine (5), dopamine (9), and L-tryptophan methyl ester (Trp-OCH_3, 12). All of the amine guests are almost completely in their monoprotonated forms by protonation under the experimental pH. [c] Determined by the matched potential (MP) method with 1.0×10^{-4} M guest 5 (primary ion) as a background. See Experimental Section for the details. [d] Determined by the matched potential method with 1.0×10^{-4} M K^+ ion (primary ion) as a background. See Experimental Section for the details. [e] Determined by the separate solution (SS) method with 1.0×10^{-2} M primary and interfering ions.

did not give a Nernstian slope at the highest concentration. The selectivity coefficients ($K_{5\text{-}H^+,J}^{pot}$), determined by the matched potential method with 5 as a primary ion, are listed in Table V.

The strongest responses to Cs^+ ion and 4 can be explained by the best fit to the pseudocavity composed of the ester carbonyl groups of the host, which would lead to a strongest charge–dipole or hydrogen-bonding interaction to Cs^+ ion and the NH_3^+ group of guest 4, respectively. The weaker response to 9 as compared to 5 would be ascribed to the more hydrophilic nature of the former guest due to the hydroxyl groups on the benzene ring. The hydrophilicity of the guest could be an unfavorable factor for a selective permeation of the complexed cationic guest to the organic phase at the membrane boundary, leaving the counteranion to the aqueous side.

Since dopamine (9) is a compound of interest from the viewpoint of practical analysis, the selectivity coefficient for this guest was also determined with K^+ ion as a primary ion (values in the parentheses in Table V). Considering these selectivity coefficients, the stronger response to K^+ ion as compared to 9 would make it difficult to detect a 10^{-3} M concentration of dopamine from a sample solution containing a physiological concentration of K^+ ion (5×10^{-3} M in the case of blood plasma).

^{1}H-NMR Study on the Geometry of Host–Guest Complexes of the Calix[6]arene Hexaester. The potentiometric selectivities observed in the present study by electrode 1 based on 1a are consistent with the relative feasibility for each guest to form an inclusion complex with a strong tripodal hydrogen bonding (geometry A in Figure 3a). To obtain information on the complexation geometry of host 1a, a ^{1}H-NMR study was carried out using hydrochlorides of 2-phenylethylamine (5·HCl), 1-adamantanamine (7·HCl), and *tert*-butylamine (8·HCl).

Parts a and b of Figure 9 show the aromatic regions of ^{1}H-NMR spectra measured in $CDCl_3$–CD_3OD (90:10) for host 1a alone (1.5×10^{-3} M) and a mixture of host 1a (1.5×10^{-3} M) and guest 5·HCl (1.5×10^{-2} M), respectively. In the presence of the host, the aromatic signals of the guest existing in 10 molar excess of the host separated into two sets of signals in ca. 9:1 integration ratio (Figure 9b). The two aliphatic

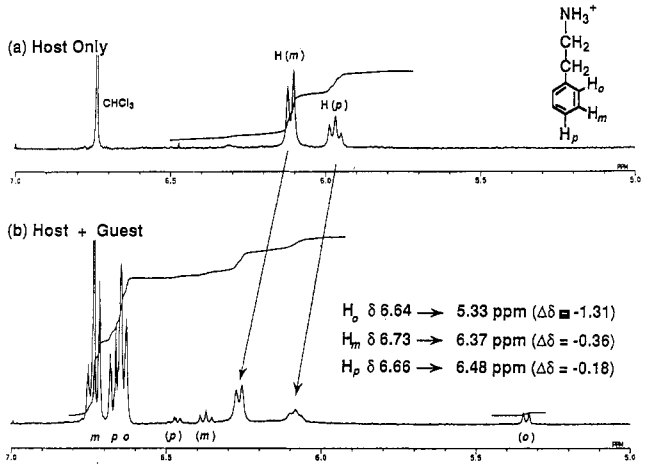

Figure 9. Changes in ^{1}H-NMR spectra by the host–guest complexation between the calix[6]arene hexaester (**1a**) and 2-phenylethylamine hydrochloride (**5**·HCl) in $CDCl_3$–CD_3OD (90:10) at an ambient temperature of 24 ± 1 °C: (a) [**1a**] = 1.5 × 10^{-3} M. (b) [**1a**] = 1.5 × 10^{-3} M, [**5**·HCl] = 1.5 × 10^{-2} M.

signals of the guest also separated in the same integration ratio in the presence of the host (spectrum not shown). Such a separation into two sets of signals indicates that the formation–dissociation rate of the host–guest complex between **1a** and **5**·H^+ is slower than the NMR chemical shift fast-exchange limit. The set of signals with the greater integration, which appeared at positions identical to those in the absence of the host (spectrum not shown), can be assigned to the uncomplexed guest. On the other hand, the set of signals with the smaller integration can be assigned to the guest that is complexed with the host in 1:1 stoichiometry. The fact that the whole signals of the two aromatic protons of the host shifted upon the addition of the guest (Figure 9, a vs b) also supports the formation of a 1:1 host–guest complex.

The host-induced upfield shifts of the aromatic signals of the complexed guest indicate a strong ring current effect on the guest accommodated into the calix[6]arene cavity composed of six benzene rings. By far the greatest upfield shift of the ortho proton signal of the guest ($\Delta\delta$ = −1.31 ppm) as compared to that of the meta and para proton signals ($\Delta\delta$ = −0.36 and −0.18 ppm, respectively) supports the predominance of the complexation geometry involving the guest inclusion (geometry A in Figure 3a). The downfield shifts ($\Delta\delta \approx +1$ ppm) of the aliphatic signals of the complexed guest (spectrum not shown) indicate the formation of hydrogen bonds through the NH_3^+ group as well as a deshielding effect due to the aromatic rings of the host. This is also consistent with the complexation geometry A between host **1a** and guest **5**·H^+.

In the cases of 1-adamantanamine (**7**·HCl) and *tert*-butylamine (**8**·HCl), neither an upfield shift due to the inclusion nor a downfield shift due to the hydrogen bonding and inclusion was induced by host **1a** under the same conditions. This indicates the lack of complex formation in either geometry A or B, which could lead to the lack of potentiometric responses.

CONCLUSIONS

Potentiometric discrimination of organic amines has been effected by a PVC matrix liquid membrane electrode that exploits as the sensory element a long alkyl hexaester of calix[6]arene, **1a**. A new mode of potentiometric discrimination, which is based on the recognition of the steric shapes of nonpolar moieties by inclusion into a well-defined cavity of the host, has been strongly supported by a combination of the following key experimental results: (i) The strongest responses were observed for the amines, which do not have a bulky substituent at the α-carbon and hence would not hinder the formation of a stable inclusion complex with geometry A depicted in Figure 3a (guests **4**, **5**, and **9**). (ii) Responses to the amines that have a bulky substituent at the α-carbon (guests **6** and **12**–**16**) gave only moderate or weak responses. (iii) The amines that have a tertiary alkyl structure at the α-position (guests **7** and **8**) did not give net responses as compared to the electrode containing no specific sensory element. (iv) The capability of the formation of host–guest inclusion complexes and the availability of potentiometric responses have been correlated by ^{1}H-NMR measurements.

From the practical viewpoint, it is interesting that the present calix[6]arene electrode displayed a potentiometric selectivity to dopamine over the other catecholamines, i.e., adrenaline and noradrenaline. However, the stronger response to K^+ ion would cause a limitation in using the present electrode to detect dopamine in blood samples. Chemical modification of the host to attain some level of selectivity over inorganic ions will be necessary for practical use. Despite such a limitation at present, a new mode of potentiometric discrimination has been demonstrated that would be potentially applicable to a wide range of organic analytes, which generally contain nonpolar moieties having specific steric structures.

ACKNOWLEDGMENT

We gratefully acknowledge Ms. Yumiko Misu, the Center for Instrumental Analysis, Hokkaido University, for the measurement of ^{1}H-NMR spectra, and Denki Kagaku Keiki (DKK) Co. (Tokyo, Japan) for kindly supplying liquid membrane type ISE bodies. This work was supported by grants from the Ministry of Education, Science and Culture, Japan [Grant-in-Aid for Scientific Research on Priority Areas ("Multiplex Organic System") to K.O. (02231201, 03215201) and Grant-in-Aid for Scientific Research (B) to Y.U. (03453038)]. Support from the Terumo Life Science Foundation (Tokyo, Japan) to K.O. and from the Nakano Foundation (Aichi, Japan) to Y.U. is also acknowledged.

RECEIVED for review September 16, 1992. Accepted January 5, 1993.