## Silver Ion Selective Optodes Based on Novel Thia Ether Compounds

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Flow-through type fiber-optic silver ion selective optodes based on novel cyclic and noncyclic thia crown ether compounds and a lipophilic anionic indicator dye have been developed. Pellicular octadecylsilica beads were coated with a lipophilic organic liquid containing the thia ether compound as the silver ion selective ionophore and LAD-3 as the color changeable indicator dye. The optode system was constructed by packing these color changeable ion sensing beads in a flow-through optical cell (cell volume, 7  $\mu$ L) having a quartz window attached directly to the distal end of a bifurcated optical fiber. The optode based on a lipophilic thia crown ether that has two sulfur atoms (tetradecyl-14-dithiacrown-4) exhibited the most sensitive response to silver ion of all the optodes investigated. This optode could detect silver ion in concentrations ranging from  $10^{-6}$  to  $10^{-2}$  M at pH 7.0 with 0.05 M Tris-H<sub>2</sub>SO<sub>4</sub> buffer as the flowing solution by measuring the absorbance change in the sensing beads at 516 nm. This optode showed a highly selective response to Ag<sup>+</sup> without any interference from other transition metal ions, except for  $Hg^{2+}$ , up to  $10^{-3}$  M, as well as alkali metal and alkaline earth metal ions up to 1 M. Optodes employing highly lipophilic ionophores showed good reproducible response to  $Ag^+$  for at least 2 weeks.

The design and synthesis of crown ethers have been widely investigated, and their ion selectivities have been examined using several methodologies such as solvent extraction, liquid membrane transport studies, the potentiometric membrane electrode (ion selective electrode, ISE) method, and so on. In contrast to the many studies based on crown ethers, there are only a few systematic studies based on thia crown ethers, in which the oxygen atoms are partly or completely replaced by sulfur atoms.<sup>1-3</sup> Recently, we reported the design and synthesis of very highly selective Li+ ionophores based on 14-crown-4 derivatives having a bulky subunit which acts as a blocking subunit to prevent the formation of a 2:1 sandwich type complex.<sup>4</sup> This study revealed that a bulky subunit on the ethano bridge of the base crown ring effectively reduced the interference of large ions which do not fit the cavity size of the crown ring. On the basis of these findings, we designed and synthesized 14-membered thia crown ethers having a pinane subunit which was expected to act as an effective "blocking" subunit for preventing complexation with large alkaline

metal cations such as Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup> and applied them to polymeric membrane ISEs. As a result, highly selective ionophores for silver ion were successfully developed.<sup>5</sup>

On the other hand, we have reported ion selective optodes based on neutral ionophores and lipophilic anionic indicator dyes.<sup>6-11</sup> The response characteristics of these types of optodes have been discussed in detail in our reports<sup>6-11</sup> and recent reviews;<sup>12-14</sup> they not only have the advantage of being similar to ISEs, but they also have the possibility of higher sensitivity and selectivity compared to ISEs, in the case where the same ionophore is employed as the sensing material for both optodes and electrodes.

Here we report a silver ion selective optode which utilizes a novel neutral  $Ag^+$  ionophore and a lipophilic anionic dye. Our concept of ionophore design is based on the following two subjects: (1) employing a small cyclic compound (14-membered) with a blocking subunit to obtain high selectivity against large cations and (2) introducing a sulfur atom in the 14-membered cyclic compound and systematically investigating the ion selectivity and sensitivity features in relation to the ionophore structure.

The chemical structures of the ionophore molecules prepared (compounds A-E) are shown in Figure 1. Compound A is one of the ionophores which showed a very highly selective response to  $Ag^+$  when it was used as the membrane component for a silver ion selective polymeric membrane electrode.<sup>5</sup> Compounds B and C have structures similar to that of A, but B has two sulfur atoms compared with A, and C is noncyclic. These compounds were synthesized to evaluate the substituting effect of a donor sulfur atom replacing the oxygen atom and to examine the sensitivity of the  $Ag^+$  optodes. Compounds D and E have a long alkyl chain instead of the bulky pinane subunit compared with B and C, in which the long alkyl chain increases the lipophilicity of the ionophore. Consequently, the optodes based on such ionophores are expected to have long sensor lifetime.

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**Figure 1.** Chemical structures of neutral silver ionophores and a lipophilic anionic dye.

The optical response principle of this type of optode is based on the following ion pair formation reaction:<sup>7,8</sup>

$$pi^{z+} + mS_o + nAH_o = S_m i_p A_{n,o} + zpH^+$$
(1)

where S is a silver ion selective neutral ionophore, the subscript o describes the organic phase, iz+ is the ion to be sensed (Ag+ in this case), AH is a lipophilic anionic dye, and SiA is the complex formed by S,  $i^+$ , and A<sup>-</sup>. In this equation, the *p*:*m* complex (ionionophore) and electroneutrality (zp = n) in the organic phase were assumed. The response mechanism of these types of optodes is fully discussed in detail in our previous reports7-10 and other references.<sup>15,16</sup> Based on this reaction, the silver ion concentration can be determined by measuring the absorbance change of the color changeable dye due to the formation of an anion  $(A^{-})$  by the deprotonation of the indicator dye which acts as a counterion when the cation-ionophore complex is formed in the organic phase. The silver ion selective optodes developed were the flow-through type,8 prepared by coating a lipophilic organic liquid incorporating the silver ionophore and the anionic dye on pellicular octadecylsilica (ODS) beads. As a result, all optodes using thia ether compounds A-E exhibited good Ag<sup>+</sup> selectivity over other cations. Sensor performance characteristics such as response time, selectivity, and the relationship between the chemical structures of these ionophores and the response of the optodes were also discussed, together with experimental results with the prepared optodes, so that the differences in their response characteristics were characterized. Furthermore, the stoichiometry of the silver ion-ionophore complex was investigated by solvent extraction measurements based on <sup>1</sup>H NMR spectroscopy and the theoretical curve fitting technique based on the response of the optode.

#### **EXPERIMENTAL SECTION**

**Reagents.** Reagents of the highest grade commercially available were used for synthesis of the novel silver ionophores

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and preparation of the aqueous test electrolytes. The distilled and deionized water used had resistivity values of more than 1.5  $\times 10^7 \Omega$  cm at 25 °C. The pellicular ODS beads were purchased from Merck AG (Darmstadt, Germany; Perisorb RP-18, 30–40  $\mu$ m particle size, ~2  $\mu$ m surface modified layer thickness).

**Synthesis of Membrane Components.** *Lipophilic Anionic Dye. N*-(2,4-Dinitro-6-(octadecyloxy)phenyl)2,4-dinitro-6-(trifluoromethyl)phenylamine (LAD-3) was synthesized according to our previous report.<sup>8</sup> Novel silver ion selective ionophores were synthesized as follows.

Compound A. (1R,2R,3S,5R)-(-)-Pinanediol (2 g, 11.7 mmol) and sodium hydride (NaH) (1.41 g, 35.2 mmol) were added to 10 mL of absolute tetrahydrofuran (THF) and stirred for 30 min at ambient temperature. Allyl bromide (3.41 g) was added dropwise to this reaction mixture, and the resultant mixture was stirred for 6 h at 60 °C. After addition of 2 mL of methanol to the mixture and concentration, the product, 2,3-bis(allyloxy)pinane, was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (9:1) as the eluent (85.1% yield). This product (10.0 mmol, 2.5 g), NaBH<sub>4</sub> (9.00 mmol, 0.34 g), and boron trifluoride ethyl ether complex (12.0 mmol, 1.7 g) were added to 10 mL of THF and stirred at ambient temperature for 3 h. After addition of small amounts of deionized water ( $\sim 1$  mL), 7 mL of NaOH aqueous solution (3 N) and 7.14 g of 30% H<sub>2</sub>O<sub>2</sub> aqueous solution were added to the reaction mixture, and the resultant mixture was stirred for 3 h. The product, 2,3-bis(3-hydroxypropoxy)pinane, was extracted from the reaction mixture with ethyl acetate and purified by silica gel chromatography with hexane-ethyl acetate (1:4) as the eluent (81.4% yield). 2,3-Bis(3-hydroxypropoxy)pinane (0.64 g, 2.23 mmol) was dissolved in absolute pyridine, and p-toluenesulfonyl chloride (1.02 g, 5.34 mmol) was added at 0 °C. This reaction mixture was stirred for 3 h. After the reaction, pyridine was evaporated, and the resulting residue was extracted three times with chloroform. After the organic phase was dried using Na<sub>2</sub>-SO<sub>4</sub> and evaporation, the obtained residue was purified by silica gel column chromatography with hexane-ethyl acetate (4:1) as the eluent to yield 2,3-bis(3-tosyloxypropoxy)pinane (yield 0.31 g, 23.4%). 1,2-Ethanedithiol (81 mg, 0.86 mmol) and NaH (103 mg, 2.57 mmol) were added to 15 mL of absolute THF and stirred for 30 min at 50 °C. 2,3-Bis(3-tosyloxypropoxy)pinane (510 mg) was added dropwise to this reaction mixture, and the resultant mixture was refluxed for 48 h at 50 °C. After addition of 2 mL of methanol to the mixture and concentration, the final product, (1R,2R,15S,17R)-2,18,18-trimethyl-3,7,14-trioxa-10-thiatricyclo- $[15.1.1.0^{2,15}]$  nonadecane (A), was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (9:1) as the eluent (14.9% yield). Analytical data obtained with <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) and elemental analysis for A are as follows:  $\delta 0.95$  (s, 3H, CH<sub>3</sub>), 1.22-1.33 (d, 6H, CH<sub>3</sub>), 1.45-2.43 (m, 10H, CH, CH<sub>2</sub>), 2.58-2.88 (m, 8H, SCH<sub>2</sub>), 3.13-3.80 (m, 5H, OCH, OCH<sub>2</sub>). Anal. Calcd for  $C_{18}H_{32}O_{3}S$  (MW = 328.52) C, 65.81; H, 9.82. Found: C, 65.73; H, 9.75.

Compound **B**. 2-Mercaptoethanol (60 mg, 0.77 mmol) and NaH (92 mg, 2.31 mmol) were added to 15 mL of absolute THF and stirred for 30 min at 50 °C. 2,3-Bis(3-tosyloxypropoxy)pinane (457 mg) was added dropwise to this reaction mixture, and the resultant mixture was refluxed for 72 h at 60 °C. After addition of 2 mL of methanol to the mixture and concentration, the final product,

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(1*R*,2*R*,15*S*,17*R*)-2,18,18-trimethyl-3,14-dioxa-7,10-dithiatricyclo-[15.1.1.0<sup>2.15</sup>]nonadecane (**B**), was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (15:1) as the eluent (13.6% yield). Analytical data obtained with <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) and elemental analysis for **B** are as follows:  $\delta$  0.95 (s, 3H, CH<sub>3</sub>), 1.21– 1.38 (d, 6H, CH<sub>3</sub>), 1.55–2.40 (m, 10H, CH, CH<sub>2</sub>), 2.63–3.00 (m, 4H, SCH<sub>2</sub>), 3.30–3.99 (m, 9H, OCH, OCH<sub>2</sub>). Anal. Calcd for C<sub>18</sub>H<sub>32</sub>O<sub>2</sub>S<sub>2</sub> (MW = 344.58): C, 62.74; H, 9.36. Found: C, 62.69; H, 9.29.

Compound C. 2.3-Bis(3-(methylthio)propoxy)pinane (C) was synthesized as follows. 3-(Methylthio)-1-propanol (3.0 g, 28.3 mmol) was dissolved in absolute pyridine, and p-toluenesulfonyl chloride (5.32 g, 28.3 mmol) was added at 0 °C. This reaction mixture was stirred for 1 h. After the reaction, pyridine was evaporated, and the resulting residue was extracted three times with ethyl acetate. After the organic phase was dried using Na<sub>2</sub>-SO4 and evaporation, the obtained residue was purified by silica gel column chromatography with hexane-ethyl acetate (4:1) as the eluent to yield 3-(methylthio)-1-propanol mono-p-toluenesulfonate (yield 7.0 g, 95.1%). (1R,2R,3S,5R)-(-)-Pinanediol (980 mg, 5.8 mmol) and NaH (414 mg, 17.4 mmol) were added to 20 mL of absolute N.N-dimethylformamide (DMF) and stirred for 30 min at 50 °C. 3-(Methylthio)-1-propanolmono-p-toluenesulfonate (3.0 g) was added dropwise to this reaction mixture, and the resultant mixture was stirred for 24 h at 50 °C. After addition of 2 mL of methanol to the mixture and concentration. the final product, 2,3-bis(3-(methylthio)propoxy)pinane (C), was extracted from the reaction mixture with ethyl acetate and purified by silica gel chromatography with hexane-ethyl acetate (4:1) as the eluent (7.6% yield). Analytical data obtained with <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) and elemental analysis for C are as follows:  $\delta$ 0.95 (s, 3H, CH<sub>3</sub>), 1.25-1.35 (d, 6H, CH<sub>3</sub>), 1.45-1.55 (d, 1H, CH), 1.70-1.95 (m, 6H, CH<sub>2</sub>), 2.00-2.15 (m, 8H, SCH<sub>3</sub>), 2.30-2.45 (m, 1H, CH), 2.55-2.65 (m, 4H, SCH<sub>2</sub>), 3.20-3.30 (m, 1H, OCH), 3.45-3.60 (m, 2H, OCH2), 3.70-3.80 (m, 2H, OCH2). Anal. Calcd for  $C_{18}H_{34}O_2S_2$  (MW = 346.60): C, 62.38; H, 9.89. Found: C, 62.29; H, 9.80.

Compound D. 1,2-Hexadecanediol (6 g, 23.2 mmol) and NaH (1.39 g, 58 mmol) were added to 100 mL of absolute THF and stirred for 30 min at 45 °C. Allyl bromide (2.81 g) was added dropwise to this reaction mixture, and the resultant mixture was stirred for 20 h at 45 °C. After addition of 2 mL of methanol to the mixture and concentration, the product, 5-tetradecyl-4,7-dioxa-1,9-decadiene, was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (9:1) as the eluent (8.7% yield). This product (3.36 mmol, 1.0 g), NaBH<sub>4</sub> (3.02 mmol, 14 mg), and boron trifluoride ethyl ether complex (4.03 mmol, 572 mg) were added to 100 mL of THF and stirred at ambient temperature for 1 h. After addition of small amounts of deionized water, 4.5 mL of NaOH aqueous solution (3 N) and 0.8 mL of 30% H<sub>2</sub>O<sub>2</sub> aqueous solution were added to the reaction mixture, and the resultant mixture was stirred for 1 h. The product, 5-tetradecyl-4,7-dioxa-1,10-decanediol, was extracted from the reaction mixture with ethyl acetate and purified by silica gel chromatography with hexane-ethyl acetate (1:4) as the eluent (21.5% yield). 5-Tetradecyl-4,7-dioxa-1,10-decanediol (1.0 g, 2.67 mmol) was dissolved in absolute pyridine, and p-toluenesulfonyl chloride (1.02 g, 5.34 mmol) was added at 0 °C. This reaction mixture was stirred for 30 min. After the reaction, pyridine was evaporated, and the resulting residue was extracted three times with ethyl acetate. After the organic phase was dried using Na<sub>2</sub>SO<sub>4</sub> and evaporation, the obtained residue was purified by silica gel column chromatography with hexane-ethyl acetate (4:1) as the eluent to yield 5-tetradecyl-4,7-dioxa-1,10-decanediol bis-p-toluenesulfonate (yield 1.1 g, 65.0%). 1,2-Ethanedithiol (140 mg, 1.46 mmol) and NaH (105 mg, 4.38 mmol) were added to 5 mL of absolute THF and stirred for 30 min at 50 °C. 5-Tetradecyl-4,7-dioxa-1,10-decanediol bis-p-toluenesulfonate (1.0 g) was added dropwise to this reaction mixture, and the resultant mixture was refluxed for 48 h at 70 °C. After addition of 2 mL of methanol to the mixture and concentration, the final product. 2-tetradecyl-1.4-dioxa-8.11-dithiacyclotetradecane (D), was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (19:1) as the eluent (5.0% yield). Analytical data obtained with <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) and elemental analysis for D are as follows; & 0.83-0.95 (t, 3H, CH<sub>3</sub>), 1.15-1.35 (m, 24H, CH<sub>2</sub>), 1.40–1.55 (m, 2H, CH), 1.70–2.00 (m, 4H, CH<sub>2</sub>), 2.55-2.85 (m, 8H, SCH<sub>2</sub>), 3.55-3.70 (m, 7H, OCH, OCH<sub>2</sub>). Anal. Calcd for  $C_{24}H_{48}O_2S_2$  (MW = 432.77): C, 66.61; H, 11.18. Found: C, 66.46; H, 10.99.

Compound E. 1,2-Hexadecanediol (540 mg, 2.1 mmol) and NaH (150 mg, 6.3 mmol) were added to 5 mL of absolute DMF and stirred for 30 min at 50 °C. 3-(Methylthio)-1-propanol monop-toluenesulfonate (1.11 g) was added dropwise to this reaction mixture, and the resultant mixture was refluxed for 24 h at 70 °C. After addition of 2 mL of methanol to the mixture and concentration, the product, 7-tetradecvl-6.9-dioxa-2.13-dithia tetradecane (E), was extracted from the reaction mixture with chloroform and purified by silica gel chromatography with hexane-ethyl acetate (19:1) as the eluent (45% yield). Analytical data obtained with <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) and elemental analysis for E are as follows:  $\delta$  0.83-0.93 (t, 3H, CH<sub>3</sub>), 1.25-1.43 (m, 26H, CH<sub>2</sub>), 1.78-1.92 (m, 4H, CH<sub>2</sub>), 2.05-2.10 (s, 6H, SCH<sub>3</sub>), 2.50-2.63 (m, 4H, SCH<sub>2</sub>), 3.30-3.72 (m, 7H, OCH, OCH<sub>2</sub>). Anal. Calcd for  $C_{24}H_{50}O_2S_2$  (MW = 434.79): C, 66.30; H, 11.59. Found: C, 66.19; H, 11.48.

**Preparation of Ag<sup>+</sup> Sensing Beads.** The chemical structures of the ionophores and dye used in this investigation are shown in Figure 1. The Ag<sup>+</sup> sensing lipophilic organic liquid was prepared by dissolving the neutral ionophore and the color changeable dye (LAD-3) in the lipophilic organic liquid of bis(2-ethylhexyl)sebacate (BEHS) in a 10 mL glass vessel. The Ag<sup>+</sup> sensing ODS beads were prepared simply by coating the surface of the pellicular ODS beads with the Ag<sup>+</sup> sensing organic liquid in the glass vessel. Concentrations of the ionophore and dye in BEHS were 0.109 mol/L in all the optodes prepared.

Structure of the Flow-Through Type  $Ag^+$  Optode. The prepared  $Ag^+$  optode was the same as the previously reported lithium, chloride, or calcium ion selective optode.<sup>8–10</sup> For the flowthrough system, 0.05 M Tris-H<sub>2</sub>SO<sub>4</sub> buffer solution adjusted to pH 7.0 was flowed at a flow rate of 1.0 mL/min using a pulse-free liquid delivery pump (Trirotor 2, JASCO, Tokyo, Japan). All sample solutions were prepared with 0.05 M Tris-H<sub>2</sub>SO<sub>4</sub> buffer solution adjusted to pH 7.0 and introduced into the flow system through an HPLC injector having a 2 mL injection loop.

**Preparation of Test Solutions.** All test solutions were prepared with nitrate salts of Li, Na, K, Ca, Mg, Ag, Cr, Mn, Cu, Zn, Pb, Hg, and Cd (except for Pb and Hg, for which acetates

were used) using a 0.05 M Tris $-H_2SO_4$  buffer solution adjusted to pH 7.0. In this case, test samples including Cr<sup>3+</sup>, Mn<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pb<sup>2+</sup>, and Hg<sup>2+</sup> were made up to 10<sup>-3</sup> M, because these ions precipitate at >10<sup>-3</sup> M at pH 7.0.

**Determination of Lipophilicites of Membrane Components.** The lipophilicites, log  $P_{o/w}$ , ( $P_{o/w}$  is the distribution coefficient between the organic liquid and water), of the synthesized neutral silver ionophores, the lipophilic anionic dye, and lipophilic organic liquids were determined with the *R*/values from reversed-phase thin-layer chromatography (RP-TLC) according to the method reported by Simon et al.<sup>17</sup> The RP-TLC used octadecylsilane-modified reversed-phase silica plates (KC18F; Whatman, Maidstone, England), cut to  $18 \times 20$  cm<sup>2</sup> and developed chromatographically with ethanol—water 90:10 as the mobile phase.

Stoichiometry Studies on Ion–Ionophore Complex. Five milliliters of chloroform containing  $2 \times 10^{-5}$  mol of ionophore and 5 mL of aqueous solution containing AgNO<sub>3</sub> and picric acid (1:3 mol/mol) were mixed and shaken for 10 min. In this procedure, the AgNO<sub>3</sub> concentration in the aqueous phase was varied relative to the ionophore concentration in the organic phase. The mixture was then centrifuged for 5 min, and the organic phase was concentrated. The resulting residue was dissolved in CDCl<sub>3</sub>, and the <sup>1</sup>H NMR spectra were measured with a JEOL GSX-270 spectrometer (JEOL, Tokyo, Japan).

#### **RESULTS AND DISCUSSION**

Detection Limit of the Optodes Based on Novel Thia Crown Ether Compounds. As described in the introduction section, the novel thia ether ionophores shown in Figure 1, A-E, which are cyclic and noncyclic 14-membered thia crown ether derivatives, were synthesized. All optodes prepared with these ionophores responded selectively to  $Ag^+$ . Detection limits of the optodes were affected by the chemical structures of the ionophores, in which different numbers of sulfur atoms as well as macrocyclic or noncyclic structures are present. In the bulk optode system, the detection limit is governed mainly by the complexation constant in relation to the ionophore and the coordinating ion.<sup>7,8</sup>

As expected, the optodes based on pinane-14-crown-4 derivatives of B and C exhibited lower detection limits than that based on A, as shown Figure 2. This fact reveals that ionophores having two sulfur atoms have higher complexation constants than those having one sulfur atom. The macrocyclic structure of the ionophore also affects the detection limit of the optode. As shown in Figures 2, macrocyclic ionophore-based optodes exhibited lower detection limits compared with those based on noncyclic ones (see response curves of the optodes based on **B** and **C**). The macrocyclic structures of the ionophores are very effective in regulating flexibility at the binding site position, especially for the 14-crown-4 skeleton, which has a small ring size. Thus the cyclic ionophore B is considered to have larger complexation constants for  $Ag^+$  than ionophore C. A similar difference in the detection limit for  $Ag^+$  was observed with the optode based on **D** and **E**, which have a long alkyl group as a side chain of the 14-membered dithia ethers. In this case, only a slight difference in the detection limit was observed when a pinane subunit was substituted for the tetradecyl subunit (see response curves of the optodes based on



Figure 2. Response curves obtained with the optodes based on A, B, and C.



Figure 3. Response curves obtained with the optodes based on  ${\rm D}$  and  ${\rm E}.$ 

**B** and **D** or **C** and **E** that are shown in Figures 2 and 3). This fact suggests that the bulky pinane subunit does not affect the stability of the  $Ag^+$  complex itself.

**Selectivity of the Optode.** The ion selectivity of an optode using a crown ether as the ion selective ionophore was generally governed by the cavity size fit effect of the macrocycle. As for 14-crown-4, Li<sup>+</sup> has the best fit to the cavity size.<sup>8</sup> However, all optodes prepared based on 14-membered thia crown compounds responded selectively to Ag<sup>+</sup>, and no response to Li<sup>+</sup> was observed.

<sup>(17)</sup> Laubli, M. W.; Dinten, O.; Pretsch, E.; Simon, W. Anal. Chem. 1985, 57, 2756.

It is an interesting fact that the replacement of one oxygen atom with a sulfur atom in the 14-crown-4 creates a Ag<sup>+</sup> selective ionophore, and such an ionophore completely lost its lithium ion selectivity. Based on the space-filling molecular models of monothia 14-crown-4 and normal 14-crown-4, it is suggested that the ring size of monothia 14-crown-4 (1.0-1.3 Å) is slightly smaller than that of normal 14-crown-4 (1.2-1.5 Å). Thus the loss of lithium ion selectivity of monothia 14-crown-4 was caused not only by a change in the donor property but also by loss of the size fit effect for lithium ion.

When **A** was used as the membrane component for the optode, it responded only to  $Ag^+$ , and no response was observed to other cations such as Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, and Ca<sup>2+</sup> (up to 1 M) and Cr<sup>3+</sup>, Mn<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pb<sup>2+</sup>, and Hg<sup>2+</sup> (up to 10<sup>-3</sup> M). When a mixed solution of these cations was used as the sample solution, there was no response unless the sample contained Ag<sup>+</sup>. This is due to the low stability of the complex formed between **A** and all these cations except for Ag<sup>+</sup>. Noncyclic compounds **C** and **E**, which have two sulfur atoms, also showed no response for other cations, even though they have a higher affinity for Ag<sup>+</sup> than **A**.

Only two optodes based on B and D responded slightly to Hg2+  $(f(r) \approx 0.050 \text{ AU} \text{ at } 10^{-3} \text{ M})$ , but their Hg<sup>2+</sup> response was irreversible and nonreproducible. Thus, the selectivity coefficient, log  $k_{Ag^+,Hg^{2+}}^{opt}$ , was calculated as ca. -2, but this value is nonreproducible. A mercury sample solution was prepared with a buffer solution of pH 7.0. At this pH, slight hydrolysis of  $Hg^{2+}$  can be produced; thus hydrolyzed species such as HgO may act as a poison species in the sensing organic phase. Very recently, Lerchi et al. reported a PVC type bulk optode membrane for Ag+ having a subnanomolar detection limit.<sup>18</sup> They used as neutral ionophores dithiocarbamate derivatives which have four sulfur atoms. Their optode system is affected by large mercury ion interference when it is used for the determination of silver ion. Chemical ion sensors generally require having ion detectability. The present optode based on A, which has one sulfur atom, responds to Ag<sup>+</sup> only at pH 7.0, even if the sample contains mercury ion (up to  $10^{-3}$  M), though the detection limit is only  $10^{-4}$  M Ag<sup>+</sup>.

Response Profile of the Optode. Figure 4 shows the response profiles of the optodes based on B and D; their response times were  $\sim 4$  min and one run required  $\sim 20$  min. The optode based on **B** exhibited poor reproducibility. The response of this optode gradually decreased with time. On the other hand, the optode based on D showed very good reproducibility of its response. This optode exhibited the same sensitivity (error,  $\pm 3\%$ in absorbance value) for Ag<sup>+</sup> over 2 weeks. These experimental results can be explained by the lipophilicity of the ionophores. A lipophilicity parameter, log  $P_{0/w}$ , was measured with prepared ionophores, and the results were as follows: A,  $4.9 \pm 0.3$ ; B, 5.2 $\pm$  0.3; C, 4.3  $\pm$  0.3; D, 9.6  $\pm$  0.3; and E, 9.1  $\pm$  0.3. Obviously the optode based on a highly lipophilic ionophore such as **D** showed very good reproducibility. In the bulk optode system, a change in ionophore concentration in the organic phase (effusion of the membrane components from the sensing layer) can be directly correlated with the resulting absorbance values (see theoretical response eq 2). From a practical point of view, the lifetime of the bulk optode is one of the important characteristics, the lipophilicity of the sensory elements is an important factor in



Figure 4. Response profiles obtained with the optodes based on B and D.

obtaining stable and reproducible response of the optode. Judging from our experimental results, ionophores with low lipophilicity (log  $P_{o/w} < 5$ ) should not be employed as the sensory elements of the bulk optodes, because the response reproducibility and the stability are poor.

Stoichiometry of Ion–Ionophore Complex. Using cyclic and noncyclic 14-membered dithia crown ether derivatives D and E, liquid–liquid  $Ag^+$  extraction measurements were performed with test samples containing different concentration ratios of the ionophore and silver picrate, and the chemical shift values in <sup>1</sup>H NMR spectra of the extracted complex species were measured (see Experimental Section).

Figure 5 shows the relationship between the concentration ratio (Ag<sup>+</sup>-ionophore (mol/mol)) and chemical shift values of the proton which is connected to the carbon neighboring the sulfur atom. A bend in the curve was observed at a concentration ratio of 1 for both D and E. In addition, the integral value ratio of the picrate anion and the ionophore at this point was calculated to be 1 ( $1 \mod 1 \mod 1$ ). Compounds **D** and **E** are thus considered to form a 1:1 or 2:2 complex with Ag<sup>+</sup> in the organic phase (chloroform). When the concentration ratio was increased, the NMR signal was multiplied. These results were attributed to the rigidity of the ion-ionophore complex produced. As shown in Figure 5 (right), the end methyl proton of the noncyclic E has the same chemical shift (singlet) when the complex is not formed; however, increasing the concentration ratio separated them slightly. Maximum chemical shift changes in relation to the complexation with Ag<sup>+</sup> were 0.37 ppm for D and 0.29 ppm for E. These values suggest that **D** interacts with Ag<sup>+</sup> more strongly than does E. This understanding is reasonable because the optode based on D showed a lower detection limit than that based on E (see Figure 3).

Figure 6 shows the relationship between the experimental values ( $\bigcirc$ ) and theoretical response curves calculated with the theoretical response eq 2 (see ref 8 for details) for the present optode system,

<sup>(18)</sup> Lerchi, M.; Reitter, E.; Simon, W.; Pretsch, E.; Chowdhury, D. A.; Kamata, S. Anal. Chem. 1994, 66, 1713.



Figure 5. Solvent extraction curves of D and E and silver picrate in CDCI<sub>3</sub> based on <sup>1</sup>H NMR measurements.



Figure 6. Theoretical response curves and experimental values (O) obtained with the optodes based on D and E.

$$a_{ix+}^{p} = \frac{a_{H+}^{n}\Psi f(r)}{K(a_{S}^{tot} - m\Psi f(r))^{m}(a_{AH}^{tot} - n\Psi f(r))^{n}}$$
(2)  
$$(a_{S}^{tot} > m\Psi f(r) \ge 0, \quad a_{AH}^{tot} > n\Psi f(r) \ge 0)$$

where *a* and *K* represent the activities and the ion pair extraction equilibrium constant, respectively, f(r) is Kubelka–Munck's factor, and  $\Psi$  is an instrumental factor taking into account the straying and scattering of incident light.<sup>19</sup>

According to the results with <sup>1</sup>H NMR spectroscopy shown in Figure 5, the stoichiometry of the ion–ionophore complex can be assumed to be 1:1 or 2:2. By varying the *p*, *m*, and *n* (see eq 1) values in eq 2 as 1:1:1 or 2:2:2, theoretical response curves were obtained as shown in Figure 6, in which the following factors were used:  $\Psi = 5.31 \times 10^{-2}$ ,  $K = 1.80 \times 10^{-3}$  for **D**; and  $\Psi = 4.70 \times 10^{-2}$ ,  $K = 3.60 \times 10^{-5}$  for **E**;  $a_{AH}^{tot} = 0.109$  mol/L and  $a_{H^+} = 10^{-7}$  mol/L for both ionophores **D** and **E**. As shown in Figure 6, the experimental values were in good agreement with the

theoretical response curves when p:m:n = 2:2:2. Thus **D** and **E** form complexes with  $Ag^+$  as a 2:2 type ion-ionophore complex. The tridimensional complex structures could not be determined, because they form a fine powder that could not be used for threedimensional X-ray analysis. A typical 2:2 type  $Ag^+$ -thia crown complex was reported by Chayama et al.,<sup>3</sup> in which the two Ag atoms formed an intermolecular sandwich complex with two ligand molecules. We consider that the complex formed with **D** or **E** and silver ion is similar to this model.

#### CONCLUSIONS

Flow-through type Ag<sup>+</sup> selective optodes based on novel thia ether derivatives and a lipophilic anionic dye were developed. The performance characteristics of the present optodes are summarized in Table 1. All these optodes responded to Ag<sup>+</sup> selectively. Among them, the optode based on tetradecyl-14dithiacrown-4 (**D**) exhibited a stable response for Ag<sup>+</sup> for at least 2 weeks with high sensitivity (detection limit,  $10^{-6}$  M Ag<sup>+</sup>) and selectivity (no response to most cations except Hg<sup>2+</sup>, log K<sup>opt</sup>Ag<sup>+</sup>Hg<sup>2+</sup>  $\approx -2$ ). On the other hand, the optode based on monothia crown

<sup>(19)</sup> Kubelka, P.; Munk, Z. Z. Tech. Phys. 1931, 12, 593.

# Table 1. Comparison of Performance Characteristics of the Optodes Based on Thia Ether Ionophores $(A-E)^a$ and a Lipophilic Anionic Dye (LAD-3)<sup>a</sup>

| ionophore<br>used for<br>the optode | limit of<br>detection<br>for Ag <sup>+</sup> (M) | response<br>reproducibility | interference  |
|-------------------------------------|--|-----------------------------|---|
| $A (4.9 \pm 0.3)^{b}$               | $\simeq 10^{-4}$                                 | poor                        | no interference <sup>d</sup>  |
| <b>B</b> $(5.2 \pm 0.3)^{b}$        | $\simeq 10^{-6}$                                 | poor                        | $\mathrm{Hg}^{2+}$ (log $k_{\mathrm{Ag}^+,\mathrm{Hg}^{2+}}^{\mathrm{opt}} \simeq -2$ ) |
| $C (4.3 \pm 0.3)^{b}$               | $\simeq 10^{-5}$                                 | poor                        | no interference <sup>d</sup>  |
| <b>D</b> $(9.6 \pm 0.3)^{b}$        | $\simeq 10^{-6}$                                 | good <sup>c</sup>           | $Hg^{2+} (\log k_{Ag^+, Hg^{2+}}^{opt} \simeq -2)$                                      |
| $E (9.1 \pm 0.3)^{b}$               | $\simeq 10^{-5}$                                 | good                        | no interference <sup>d</sup>  |

<sup>*a*</sup> See Figure 1 for the chemical structures. <sup>*b*</sup> Log  $P_{o/w}$  value, see Experimental Section (log  $P_{o/w}$  for LAD-3, 7.8 ± 0.4). <sup>*c*</sup> Sensor response was almost contant for at least 2 weeks (5–7 h use per day). <sup>*d*</sup> No response was observed for a test sample containing  $10^{-1}$ M Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, and Ca<sup>2+</sup> and  $10^{-3}$  M Cr<sup>3+</sup>, Mn<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pb<sup>2+</sup>, and Hg<sup>2+</sup>.

derivative A exhibited excellent  $Ag^+$  selectivity against other cations including  $Hg^{2+}$  but not high sensitivity (detection limit,  $10^{-4} M Ag^+$ ).

Stoichiometry of the ion-ionophore complex has been confirmed by liquid-liquid extraction measurements and the theoretical response curve fitting technique. The latter technique was first used for the determination of complex stoichiometry, and it was demonstrated that this method using the present optode system based on a color changeable dye is useful for the determination of ion-complex stoichiometry even when the complex component such as an ionophore is very small (milligram order). In our case, it was found that **D** forms a 2:2 complex with Ag<sup>+</sup> in the organic phase. The selectivities of these optodes were governed by the complex affinity based on the HSAB concept rather than the size fit effect of the neutral ionophore; thus optodes employing thia ether derivatives generally respond to Ag<sup>+</sup> selectively.

Futhermore, lipophilicity of the sensory elements seriously affects the sensor lifetime. Sensory components such as a neutral ionophore and a dye with low lipophilicity (log  $P_{o/w} < 5$ ) showed nonreproducible response values and should not be employed for the bulk optodes.

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