A PSEUDO THIACROWN COMPOUND FORMED BY HYDROPHOBIC INTERACTION OF ITS LIPOPHILIC PARTS IN WATER: Ag+-SELECITIVE FLUOROPHORE IN WATER

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Abstract- Amphiphilic podand (**3**) was prepared by conventional thioether synthesis in ethanol. It shows exclusive selectivity toward Ag+ ion in a liquid-liquid extraction. It was also found to exhibit selective fluorescence decrease only in the presence of Ag+ ion in water. From the fluorometric titration, the complexing stability constant toward Ag+ in water estimated to be log K_a = 4.2, which value is comparable to cyclic dithia-18-crown-6. This extraordinarily high value was caused by a pseudo cyclic structure formed in water, which was supported by ^{1}H NMR spectral analysis.

Naturally occurring antibiotics, monensin and nigericin are known to form stable complexes with metal cations by pseudo cyclic structure in aqueous media. In general, artificial polyether ligands or podands form stable complexes with metal cations due to their conformational change to pseudo cyclic structures, however, this complexing behavior, in most cases, is limited in organic media.[1] Acyclic polyether compounds having sulfur atom(s) have been found to show high affinity toward heavy metal cations, such as Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Pd^{2+}, and Ag^+.[2] Recently, a number of acyclic[3-10] and cyclic[11,12] compounds

possessing both ligating sites and fluorescent units have been prepared for the determination of cations based on the emission intensity change due to the complexation.[3-10]

From a practical point of view, fluoroionophores are required to dissolve in water and change their spectra by a specific cation added in the system, though there have been few reports for useful fluorophores in aqueous solution.[13,14] Recently, we have conveniently and efficiently prepared thiacrownophanes (**1**) and (**2**) bridged by cyclobutane ring by means of intramolecular [2 + 2] photocycloaddition of styrene derivatives with oligo(oxyethylene) linkage containing sulfur atoms.[15,16] In the liquid-liquid extraction, they showed efficient extractability toward Ag$^+$ with high[15] and exclusive[16] selectivity.

1   **2**
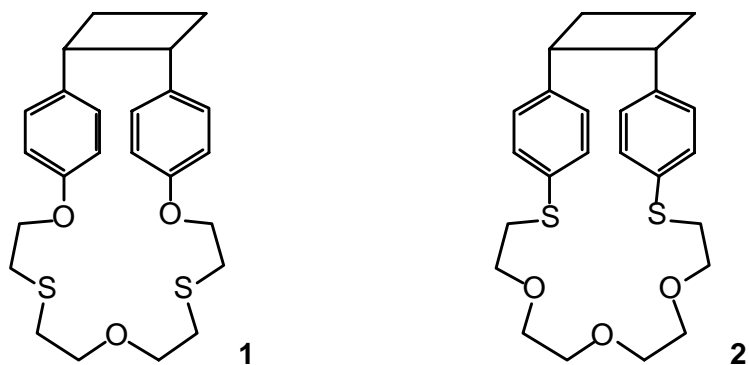
Crownophanes, however, do not appear to be suitable for the application to fluoroionophores, because they produce styrene derivatives through a reverse reaction followed by oligomerization when they are irradiated with UV light.[17] Furthermore, the thiacrownophanes previously obtained were not soluble in water. Thus, we designed that simple podand (**3**) having appropriate hydrophobic residues at the both end of the hydrophilic oligo(oxyethylene) chain, which would be soluble in water and form a pseudo crown ether structure by an intramolecular hydrophobic interaction of its terminal groups in water. It should be one of the simplest strategy to preorganize the linear polyether for incorporating a cation in water. Podand (**4**) was also prepared as a reference compound for comparison with **3** in the aqueous property observed by ^{1}H NMR spectral analysis.

3   **4**
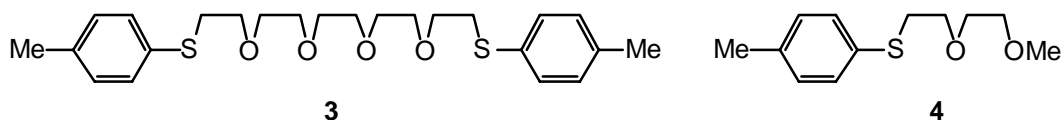
EXPERIMENTAL

Apparatus.   ^{1}H NMR spectra were taken at 500 MHz using tetramethysilane as an internal standard. Elemental analysis was carried out in Technical Research Center for Instrumental Analysis, Gunma University.   Electrospray ionization mass spectra (ESI-MS) were obtained on a following conditions: A sample solution was sprayed at a flow rate of 2 μL min^{-1} at the tip of needle biased by a voltage of 4.5 kV higher than that of a counter electrode.   Metal cations were analyzed by a Shimadzu AA-6500 atomic absorption spectrophotometer.   Fluorescence spectra were measured by a HITACHI F-4500 fluorescence spectrophotometer.

Reagents.   Ethanol was dehydrated by the treatment with Na, followed by distillation.   Guaranteed reagent grade CH_2Cl_2 was distilled before use. $AgNO_3$, $Pb(NO_3)_2$, $Cu(NO_3)_2$, $Mn(NO_3)_2$, $Zn(NO_3)_2$, $Ni(NO_3)_2$, $Co(NO_3)_2$, and $Fe(NO_3)_3$ were of commercially available highest grade and used after vacuum drying.   All aqueous solutions were prepared with distilled, deionized water.   Commercially available acetonitrile for spectrochemical analysis was used without further purification.

Preparation of 1,16-bis(4'-methylphenyl)-1,16-dithia-4,7,10,13-tetraoxahexadecane (3).   Na (2.78 g, 0.12 mol) was added to ethanol (100 mL) under a nitrogen atmosphere at rt.   To this solution 4-methythiophenol (10.00 g, 0.08 mol) in ethanol (100 mL) was added with stirring at rt and then 50 ^{o}C for 1 h.   To the mixture pentaethyleneglycol ditosylate (11.00 g, 0.02 mol) dissolved in ethanol-dioxane (1:1 mixed solvent, 30 mL) was added at rt and then the mixture was stirred at 50 ^{o}C for 4 h.   After cooling, the mixture was neutralized with hydrochloric acid (water:ethanol = 1:1) and filtered and the filtrate was evaporated.   The residue was chromatographed (SiO_2, toluene-ethyl acetate) to give **3** (5.25 g, 59%) as transparent viscous liquid.   ^{1}H NMR ($CDCl_3$); 7.28 (4H, d, $J=8.0$), 7.09 (4H, d, $J=8.0$), 3.64-3.59 (16H, m), 3.07(4H, t, $J=7.0$), 2.31 (6H, s).   Anal. Calcd for $C_{24}H_{34}O_4S_2$: C, 63.96; H, 7.60. Found: C, 63.57; H, 7.56.

Preparation of 1-(4'-methylphenyl)-1-thia-4,7-dioxaoctane (4).   This compound was prepared by a reaction of the corresponding tosylate and 4-methythiophenol in a similar manner to that of **3**.   It was transparent viscous liquid.   Yield, 36%; ^{1}H NMR ($CDCl_3$); 7.28 (2H, d, $J=8.2$), 7.10 (2H, d, $J=8.2$), 3.64

(2H, t, J=7.0), 3.61-3.59 (2H, m), 3.53-3.52 (2H, m), 3.38 (3H, s), 3.09 (2H, t, J=7.0), 2.32 (3H, s). Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02.   Found: C, 63.33; H, 7.90.

Solvent extraction of heavy metal nitrates.   A CH_2Cl_2 solution of acyclic polyether (1 x 10^{-4} mol dm^{-3}, 5.0 mL) and an aqueous metal nitrate solution (0.1 mol dm^{-3}, 5.0 mL), whose pH value was adjusted as high as possible not to precipitate the hydroxides, were shaken in a 20-mL test tube with a ground-glass stopper at an ambient temperature (18-20 ^{o}C) for 2 h.   Two liquid phases were separated and evaporated *in vacuo*.   The residue was dissolved in 0.1 mol dm^{-3} HNO_3 for analysis by atomic absorption spectrometry.

ESI-MS measurement of podand 1 in the presence of $AgNO_3$.   The sample solution was 1:1 (v/v) $MeCN-H_2O$ containing of the same concentration of podand and the salt (1 x 10^{-4} mol dm^{-3} in each).

RESULTS AND DISCUSSION

Podand (**3**) with two 4-methylphenylthia residues as terminal hydrophobic parts and compound (**4**) with one 4-methylphenylthia residue were designed and prepared by the conventional reaction of the aromatic thioalcohol with the corresponding oligoethylene glycol ditosylate or monotosylate in the presence of sodium ethoxide in ethanol.

4-Methylphenyl residues can be act not only as a significant hydrophobic group but also a fluorescent group.   In analogy with general acyclic polyethers, **3** seems to incorporate cations in organic solvents due to its cation-ligating parts.   To examine this ability, we first employed the compound as an extractant toward metal cations in liquid-liquid extraction experiments.   Results are summarized in Table 1 with some reference compounds.

Commercially available cyclic dithia-15-crown-5 (**5**) was used as a reference compound for evaluating the extractability of podand (**3**).   As shown in Table 1 all the compounds examined exclusively extracted Ag^+ ion.   Compound (**3**) showed higher extractability toward Ag^+ than **4**, indicating that a ligand is required to possess two sulfur atoms in the molecule for efficient complexation with Ag^+ ion.   The extractability of compound (**3**) was also higher than that of cyclic ligand **5**, suggesting that Ag^+ ion is

favorably complexed with **3**, and **3** is considered to form a pseudo cyclic structure around the cation as previously reported podands.[1]   The ability of **3**, on the contrary, was slightly inferior to that of cyclic thiacrownophane (**2**) due to its pseudo cyclic structure at the complexation.

Table 1.   Extraction of metal cations with ligands

Ligand	Extractability (%)[a]							
	Ag^+	Pb^{2+}	Cu^{2+}	Mn^{2+}	Zn^{2+}	Ni^{2+}	Co^{2+}	Fe^{3+}
2	50(6.5)	0(4.5)	0(4.5)	0(6.0)	0(6.0)	0(7.0)	0(7.0)	0(1.5)
3	35(5.7)	0(4.4)	0(4.4)	0(7.1)	0(6.0)	0(6.7)	0(6.8)	0(1.8)
4	6(5.3)	0(4.5)	0(4.4)	0(7.1)	0(6.0)	0(6.7)	0(6.8)	0(1.7)
5	15(5.0)	0(5.0)	0(4.3)	0(6.2)	0(5.7)	0(7.0)	0(7.0)	0(1.8)

a) Extraction conditions: Aq. phase (5 mL), [metal nitrate]= 1.0×10^{-1} mol dm^{-3}; Org. phase, CH_2Cl_2 (5 mL), [ligand]= 1.0×10^{-4} mol dm^{-3}; *ca.* 20 °C, shaken for 1 h.   The values are based on the concentration of the crown compounds.   Values in parentheses are equilibrium pH of aqueous phase.

5
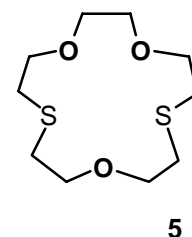
The complexing behavior of **3** was examined by ESI-MS analysis in an aqueous solution with $AgNO_3$.   Figure 1 showed significant 1:1 (1:Ag^+) complex without any peak of free **3**, indicating strong binding ability of **3** with Ag^+ even in a typical polar solvent.
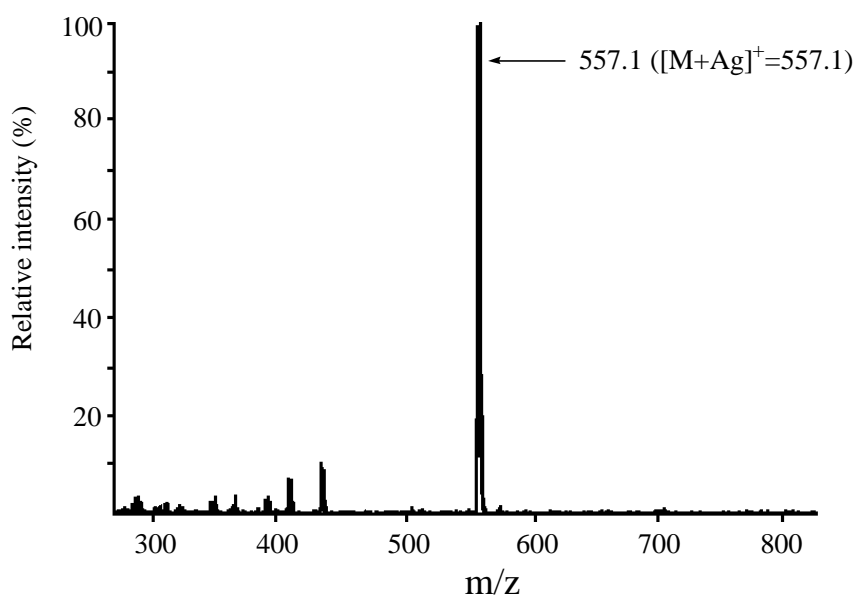

557.1 ([M+Ag]$^+$=557.1)

Figure 1.   ESI-MS spectrum of acyclic dithiacrown (**3**) in H_2O containing $AgNO_3$.

To evaluate the fluorophoric property of **3** toward the metal cations in water, a variety of alkali (Na^+, K^+) or other metal cations (Ag^+, Pb^{2+}, Ni^{2+}, Zn^{2+}, and Cu^{2+}) were added into an aqueous solution containing psuedo cyclic compound (**3**) (2×10^{-5} mol dm^{-3}). In agreement with the results with the extraction, a perfect selective fluorescent behavior was observed at Ag^+ addition.
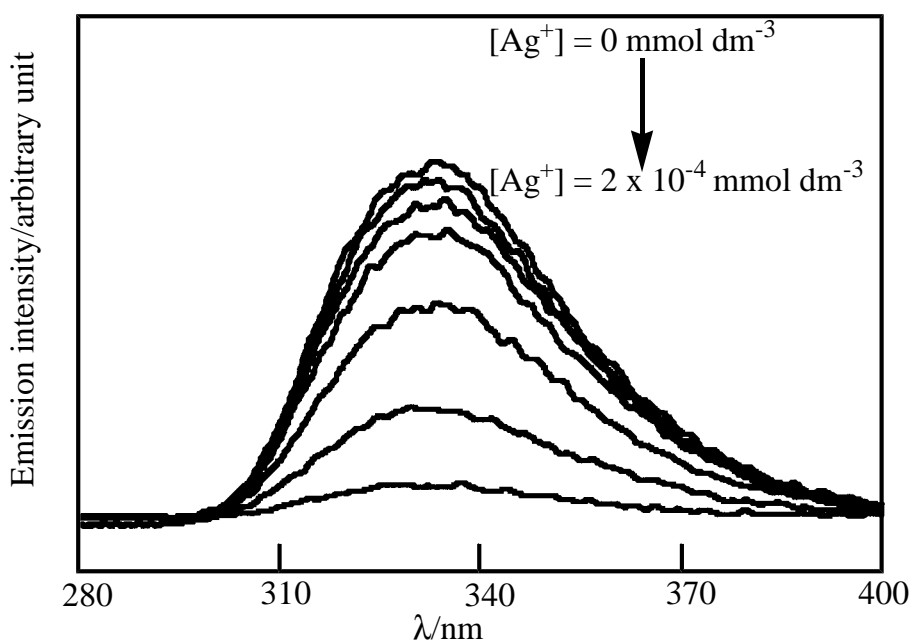

Figure 2. Fluorescence spectra of podand (**3**) with $AgClO_4$ in water.
[podand (**3**)] = 2×10^{-5} mol dm^{-3}. $\lambda_{ex} = 265$ nm.

As shown in Figure 2, the fluorescence emission intensity remarkably decreases with increasing Ag^+ ion concentration while the absorption spectra hardly changed. It was found from the calibration curve of concentration vs fluorescence intensity that ppm order of Ag^+ ion should be detected in water (Figure was not shown). The stability constant (log K_a) of **3** with Ag^+ ion was determined to be 4.2 based on the spectral change[18] and the information of 1:1 complexation between **3** and Ag^+ ion was obtained from ESI-MS analytical data (Figure 1).

The constant is close to that estimated between cylic dithia-18-crown-6 and Ag^+ (log $K_a = 4.3$) in water.[19] This suggests that Ag^+ ion is incorporate into the pseudo cyclic cavity formed by the intramolecular hydrophobic interaction of its two aromatic nuclei in water, which was supported by ^{1}H NMR analysis as follows. A D_2O solution of podand (**3**) (2×10^{-5} mol dm^{-3}) and that of the reference podand possessing

one 4-methylphenylthia residue (**4**) (4 x 10^{-5} mol dm^{-3}) was used for the analysis. The chemical shift of **3** for the aromatic protons, 6.92 and 6.68 ppm, respectively, were shifted to 0.32 and 0.42 ppm upper field than those of **4** (7.24 and 7.10 ppm), while chemical shifts for the aromatic protons of **3** and **4** in $CDCl_3$ were almost the same (see EXPERIMENTAL). Such chemical shift change was often observed in cyclophane chemistry. As mentioned above, we have prepared thiacrownophane (**2**) from linear precursor (**6**) by intramolecular [2 + 2] photocycloaddition. The ^1H NMR spectra ($CDCl_3$) of **6** showed ABq signals at δ 7.45 and 7.22 ppm for the aromatic protons. These signals were shifted to upfield δ 7.13 and 6.82 ppm in **2**, respectively, which is a characteristic of cyclophane structure due to the interaction between two layered aromatic nuclei.[16]
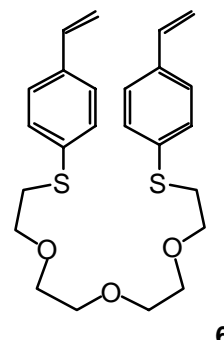
From these results it was considered that an intramolecular layered aromatic interaction of podand (**3**) mentioned above was obviously caused by the hydrophobic interaction in water. This is a driving force to form the pseudo cyclic structure in water and this pseudo cycle formation is one of the important preorganization to incorporate a certain cation in water.

On the other hand, stability constant (log K_a) of **3** with Ag^+ was determined to be 2.8 in acetonitrile. Generally, complexing stability constants of a crown compound including an acyclic polyether with a cation in organic solution are higher than those obtained in aqueous solution, though the constant in MeCN lower than that of in water. This lower value is considered to rise from the lack of the preorganization due to the hydrophobic interaction in MeCN. In fact, the chemical shift of **3** for the aromatic protons hardly shifted to upper field compared to those of **4**.

In conclusion, the podand possessing 4-methylphenylthia residues showed perfect selectivity toward Ag^+ ion in both the liquid-liquid extraction and fluorometric detection. It was found that the intramolecular hydrophobic interaction of 4-methylphenylthia residues of **3** plays a significant role in the complexation between podand and Ag^+ ion in water.

REFERENCES

1. G. W. Gokel and S. H. Korzeniowski, "Macrocyclic Polyether Syntheses," Springer-Verlag, Berlin Heidelberg New York, 1982, Chap. 7.

2.   F. Voegtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 753.

3.   B. Valeur, J. Pouget, J. Bourson, M. Kaschke, and N. P. Ernsting, *J. Phys. Chem.*, 1992, **96**, 6545.

4.   Y. Kakizawa and T. Nakamura, *Chem. Lett.*, **1993**, 1671.

5.   H.-D. Becker, *Chem. Rev.*, 1993, **93**, 145.

6.   R. Tahara, K. Hasebe, and H. Nakamura, *Chem. Lett.*, **1995**, 753.

7.   B. Bodenant and F. Fages, *Tetrahedron Lett.*, 1995, **61**, 3956.

8.   J. A. Sclfani, M. T. Marato, T. M. Sisk, and S. A. Van Arman, *Tetrahedron Lett.*, 1996, **37**, 2193.

9.   H. Weizman, O. Ardon, B. Mester, J. Libman, O. Dwir, Y. Hadar, Y. Chen, and A. Schanzer, *J. Am. Chem. Soc.*, 1996, **118**, 12368.

10. J. Ishikawa, H. Sakamoto, S. Nakao, and H. Wada, *J. Org. Chem.*, 1999, **64**, 1913.

11. R. Ostaszewski, L. Prodi, and M. Montalti, *Tetrahedron*, 1999, **55**, 11553.

12. I. Jacquet, J.-M. Lehn, P. Marsau, H. Andrianatoandro, Y. Barrans, J.-P. Desvergne, and H. Bouas-Laurent, *Bull. Soc. Chim. Fr.*, 1996, **133**, 199.

13. J. A. Sclafani, M. T. Maranto, T. M. Sisk, and S. A. Van Arman, *Tetrahedron Lett.*, 1996, **37**, 1515.

14. M. T. Albelda, M. A. Berbardo, P. Díaz, E. García-España, J. S. de melo, F. Pina, C. Soriano, and S. V. Luis, *Chem. Commun.*, **2001**, 1520.

15. S. Inokuma, A. Kobayashi, R. Katoh, T. Yasuda, and J. Nishimura, *Heterocycles*, 1995, **40**, 401.

16. S. Inokuma, T. Funaki, M. Tanakajima, K. Isawa, and J. Nishimura, *Heterocycles*, 2001, **55**, 1635.

17. S. Inokuma, M. Takezawa, H. Satoh, Y. Nakamura, T. Sasaki, and J. Nishimura, *J. Org. Chem.*, 1998, **63**, 5791.

18. H. Shizuka, K. Kameta, and T. Shinozaki, *J. Am. Chem. Soc.*, 1985, **107**, 3956.

19. H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600.