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Synthesis of Dithio-Crown Ether Derivatives from 5-Hydroxytropolone. Reversible Complex Formation with Mercury Ion[1]

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Condensations of tri-, di-, and mono-ethylene glycol bis-(2-mercaptoethyl) ethers (**6a, b, c**) and bis(mercaptoethyl) ether and the thioether (**6d, e**) with 4,6-bis(chloromethyl)-2,5-dimethoxytropone (**5**), which was prepared from 5-hydroxytropolone in a three-step sequence, gave dithio-crown ethers (**7a, b, c** and **8d, e**), of which, **7a, b, c** selectively formed inclusion complexes with Hg^{2+}. The complexes with **7a, b, c** were quantitatively dissociated by acidification with dil hydrochloric acid. Thus, an effective method for extraction of Hg^{2+} has become available. In this respect, the inclusion complex of a benzenoid dithio-crown derivative did not liberate Hg^{2+}.

Introduction

Crown ethers have been playing important roles in host-guest chemistry since the discovery of their inclusion complex formation with various metal ions.[2,3]

On the other hand, tropolones are well known to form metal complexes with many metal ions,[4,5,6] but only a few systematic studies of the application of this unique affinity have been carried out. An important observation has been reported by Asao and Kikuchi[5] who observed complex formations between 2-methoxytropone and various transition metals, indicating that the free hydroxyl group of tropolones is not necessary for the complex formation.[5] It is worthwhile to investigate the host-guest chemistry of the troponoids carrying the crown ether units, additional ionophoric functions. Herein, we describe the synthesis and some physico-chemical properties of mercury ion-capturing dithio-crown derivatives from 5-hydroxytropolone (**1**).

Results and Discussion

Synthesis of Dithio-crown Derivatives from 5-Hydroxytropolone (1). The precursors of the crown ethers were prepared from **1**: Mannich reaction of **1** with morpholine gave 5-hydroxy-4,6-bis(morpholinomethyl)tropolone (**2**), which gave two isomeric dimethyl ethers (**3** and **4**).[7] Conversion of the major product, 2,5-dimethoxy-4,6-bis(morpholinomethyl)tropone, **3** to 4,6-bis(chloromethyl)-2,5-dimethoxytropone (**5**) was carried out as reported[8] by treatment with ethyl chloroformate.

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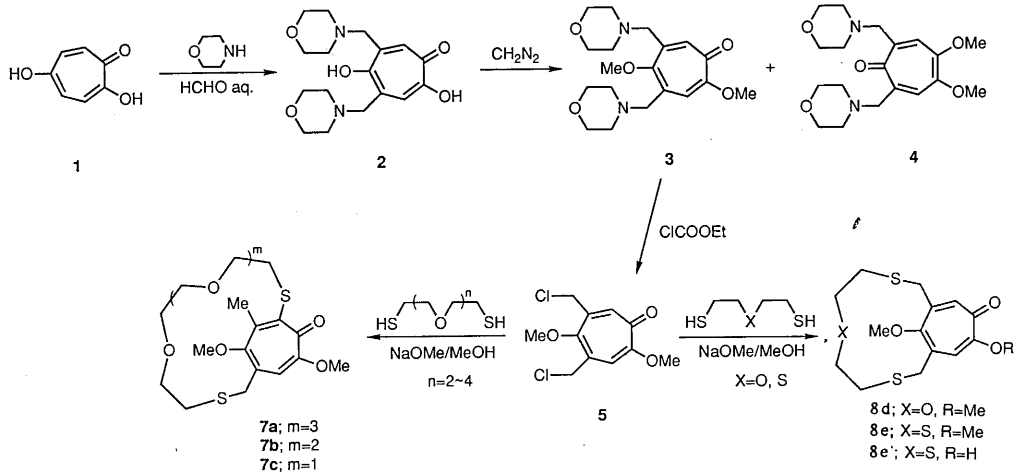


Scheme 1; Synthesis of **7** and **8**

When a methanol solution of **5** was allowed to react with oligoethylene glycol bis(mercaptoethyl) ethers (**6a-e**), two types of macrocyclic dithio-crown ethers (**7a-c** or **8d, e**) were formed, respectively; e. g., in the reaction of **5** with triethylene glycol bis(mercaptoethyl) ether (**6a**), the major product obtained was **7a**. The structure of **7a** was deduced from the NMR spectral analysis; i. e., the ^{1}H NHR spectrum of **7a** showed three methyl singlet signals at $\delta = 2.60$, 3.40, and 3.89 along with only one vinyl proton signal on the seven-membered ring. Therefore, an occurrence of an allylic substitution is evident. The position of the newly-generated methyl group was deduced as depicted from the relative reactivity of two chloromethyl groups in **5**, and the chemical shift ($\delta = 6.82$) of the proton on the seven-membered ring which is appropriate for that of vicinal to the methoxy group.

Similar reaction of **5** with diethylene glycol bis(mercaptoethyl) ether (**6b**) and ethylene glycol bis(mercaptoethyl) ether (**6c**) also gave **7b** and **7c**, whose structures were similarly deduced.

The shortest ether investigated was bis(mercaptoethyl) ether (**6d**) which gave another type of product, **8d**. In contrary to **7a-c, 8d** revealed two proton signals on the seven-membered ring at $\delta = 6.87$ and 7.36, along with only two methyl signals at $\delta = 3.21$ and 3.32 in the ^{1}H NMR spectrum, and hence, the depicted structure, that of the normal substitution product, was established.

Furthermore, the reaction of **5** with bis(mercaptoethyl) thioether (**6e**) also gave **8e**, whose structure was similarly deduced as depicted. In a case of **6e**, the products contained a by-product (**8e′**) which was identified as hydrolyzed tropolone derivative as its ^{1}H NMR spectrum revealed an overlapped aromatic proton signal at $\delta = 7.59$ (2H, s), as well as overlapped ^{13}C NMR signals.

It is worth to mention that the mobility of the macrocyclic ethereal rings is reflected to the ^{1}H NMR spectra. Thus, in the ^{1}H NMR spectrum of **7a**, the methylene protons on the carbon bearing the sulfur atom appeared as broadened singlet at $\delta = 3.83$, while in those of the rest of compounds, **7b** and **7c**, the methylene protons appeared as magnetically nonequivalent *AB*-type signals at 3.12 and 4.37 (**7b**) and 3.14 and 4.43 (**7c**), respectively. This phenomenon clearly shows that conformations of the macrocyclic rings in the shorter ethereal derivatives are fixed in respect of the NMR time scale. And, non-crystalline nature of **7a**, of which the crown ether chains are rotating around the troponoid ring, should be a support for this.

Same is true for the case of **8**, formed only from the short ethereal chains; the methylene protons of both **8d** and **8e** appeared as *AB*-type signals.

Unfortunately, the rotational barrier of **7b** could not be estimated; the variable temperature ^{1}H NMR spectra in dimethylformamide-d_7 up to 150℃ disclosed no indication of coalescence of the *AB*-type methylene proton signals. However, according to the variable temperature (−90 ℃ to +30 ℃) ^{1}H NMR spectra of **7a** measured in dichloromethane-d_2, the methylene proton signal on the adjacent carbon bearing the sulfur atom appeared at ca. 3.8 as unified 2H signal, but the signal began to split at −50 ℃, and at −90 ℃, the lower side of the *AB*-doublet signals appeared at $\delta = 4.40$ ($J = 12.5$ Hz). Unfortunately, upper side of the signals, estimated as at ca. 3.28, were underneath the other ethylene proton signals.

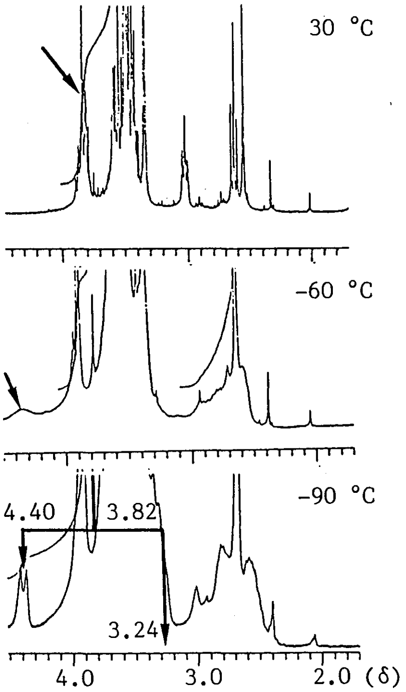


Fig. 1: Variable temperature NMR sepctra of **7a** in CD_2Cl_2

Although another methylene proton was underneath the rest of ethylene glycol proton signals, its chemical shift could be estimated at $\delta = 3.24$ from the chemical shift of the unified methylene protons as $\delta = 3.82$. Since the chemical shift difference of the methylene protons, $\Delta\nu$, can be figured out as 313.2 Hz. From the eq. 1:[9)]

$$\log 1/2\pi\Delta\nu\tau = \log k_0/2\pi\Delta\nu - E_a/2.3RT \tag{1}$$

where $k_0 = 10^{13}$ Hz, $2\pi\Delta\nu\tau = 1.414$, and $T = 223.15$ K, the E_a could be determined as 43.5 kJ/mol at −50 ℃.

Complex Formations with Mercury Ion. The compounds **7** formed inclusion complexes with mercury chloride (Ⅱ). When an aqueous solution containing Hg^{2+} was shaken with a chloroform-*d* solution of **7**, Hg^{2+} was extracted into the chloroform-*d* layer. In the case of **7a**, quantitative liberation of Hg^{2+} occurred by shaking the Hg^{2+}-complex of **7a** with 2 M hydrochloric acid or aqueous sodium chloride (>20%) solution, and the procedure can be repeated. These phenomena can be easily monitored by NMR spectrometry. In particular, diagnostic for Hg^{2+}-complex of **7a** is the appearance of *AB*-type NMR signals at δ 3.66 and 3.90 ($J = 17$ Hz) ascribable to the methylene protons on the carbon bearing the sulfur atom.

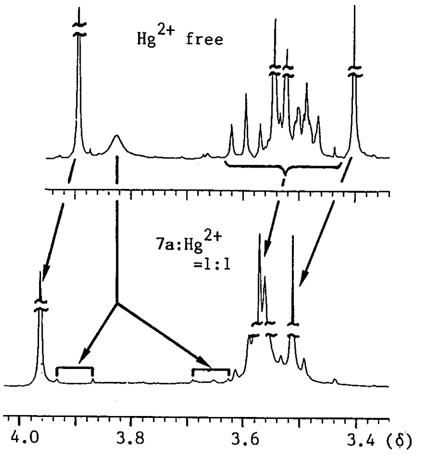


Fig. 2: The ^{1}H NMR spectral change of **7a** by complex formation with Hg^{2+}-

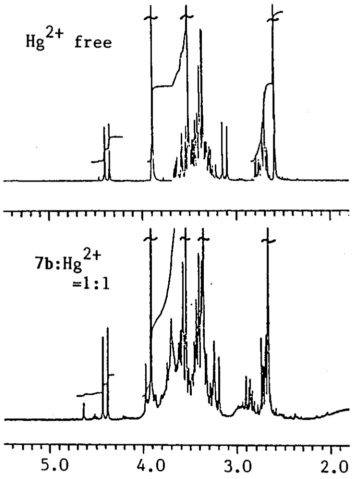


Fig. 3: The ^{1}H NMR spectral change of **7b** by complex formation with Hg^{2+}-

All other NMR signals of host molecules of the complexes more or less caused a down-field shift due to a complex formation with the cationic species.

The liberated Hg^{2+} was titrated UV spectrometrically as a dithizone complex.[10] The ratio of **7a** and **7b** to Hg^{2+} were determined to be 1:1.

Further, the Hg^{2+} was extracted by **7a** as an inclusion complex from Hg^{2+}-containing sea water. Thus, the abundant cations in sea water, Mg^{2+}, did not interfere the extraction of mercury ion.

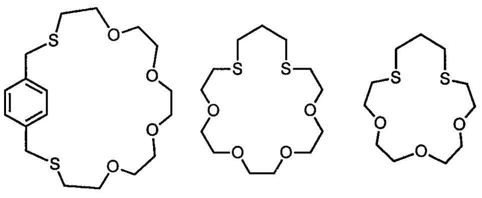
The NMR spectral change of the complex formation of **7a** and **7b** disclosed an information of the molecular structures. At first, the methylene protons at $\delta = 3.83$ of **7a** became an *AB*-type pair of doublets at 3.66 and 3.90 ($J = 17$ Hz). This is due to a freezing of the conformational change, which should be a result of the complex formation with Hg^{2+}. In the case of **7b**, the methylene signals showed down-field shifts by the complex formation,

δ =3.12 and 4.37 to 3.22 and 4.40, respectively. It is clear that the *quasi-axial*-proton, appearing at higher field, suffered a substantial influence from the complex formation.

After all, the complex formation did not cause a significant change in physical and chemical properties of the troponoid structure; the change in the chemical shift of the ^{13}C NMR spectrum of $\delta_{C=O}$ ($CDCl_3$) of **7a** was very small, from 179.1 to 178.2.

Attempted Complex Formation with Other Metal Ions. Then, attempted extractions of other metal ions, such as Li^+, Na^+, K^+, Ag^+, Mg^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Sr^{2+}, Cd^{2+}, Ba^{2+}, La^{3+}, Tl^{3+}, or Fe^{3+}, into chloroform-*d* solution of **7a** from aqueous solution were investigated ^{1}H NMR spectroscopically. However, none of these metals showed a change in the NMR spectra to show the complex formation.

Chemical Properties of Hg^{2+}-Complex with a Benzenoid Dithio-crown Analogue. In view of reversibility of the Hg^{2+}-complexes of **7**, we made a comparative study with *p*-xylylene dithioether (**9**) already prepared by Pedersen11) and two other derivatives, 19-dithio-crown-6-ether (**10**) and 16-dithio-crown-5-ether (**11**).12) In all cases, the Hg^{2+}-complexes formed by mixing with the thioethers could not be regenerated by addition of hydrochloric acid. Thus, the tropone system is essential to reveal this reversibility.



9 **10** **11**

Chart 1: Structures of **9, 10**, and **11**

Conclusion. As described, the troponoid-annexed dithio-crown ethers disclosed a unique property which is certainly unprecedented. It will be worthy of further investigating this repeated mercury ion capturing ability since mercury is one of the most critical heavy metals in the environmental view point. Detailed study with aspects of analytical chemistry will a matter of independent paper.

Experimental

The elemental analyses were carried out by Miss S. Hirashima of the Institute of Advanced Material Study, Kyushu University. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The NMR spectra were measured by means of JEOL FX 100 Model and GSX 270H Model spectrometers in $CDCl_3$ and the chemical shifts are expressed in δ unit. The mass spectra were measured with a JEOL 01SG-2 spectrometer. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds, using a JASCO IR-A102 spectrometer. The UV spectra were measured by a Hitachi U-3200 spectrophotometer. The stationary phase for the column chromatography was Wakogel C-200 and the eluent was a mixture of ethyl acetate and hexane.

Preparation of Dithio-crown Ethers (General Method). A mixed solution of MeOH and benzene (45 cm^3 and 5 cm^3) of **5** (1.13g, 4.30mmol), **6** (1.16g, 4.30mmol) and NaOMe (464 mg, 8.59mmol) were refluxed for 3 h. Purification via silica-gel column chromatography of the mixture gave the products:

7a: A yellow oil, 352 mg; 18%. Found; C, 54.50; H, 6.96%. Calcd for $C_{21}H_{32}O_7S_2$: C, 54.76; H, 7.00%. ^{1}H NMR δ =2.60 (3H, s), 2.66 (2H, t, J=7 Hz), 3.14 (2H, br t, J=1 Hz), 3.40 (3H, s), 3.4-3.7 (6H, m), 3.52 (4H, s), 3.54 (4H, s), 3.59 (2H, t, J=7 Hz), 3.83 (2H, br s), 3.89 (3H, s), and 6.82 (1H, s). ^{13}C NMR δ =20.7, 30.0, 31.9, 33.7, 56.5, 61.0, 70.6 (3C), 70.8, 70.9, 71.0, 71.1, 71.5, 111.9, 128.6, 142.4, 143.8, 154.6, 156.4, and 179.1. IR ν : 2880, 1605, 1550, 1460, 1320, 1280, 1125, and 1000 cm^{-1}. UV λ_{max}^{MeOH} = 247 (ε =13400), 293 (12300), 355 (6320, sh), and 384 nm (6920). UV $\lambda_{max}^{CHCl_3}$ = 240 (ε =12600), 292 (11500), 352 (5970, sh), and 382 nm (6230).

7b: Yellow plates (AcOEt-Hexane), mp 132.5-133 ℃, 107 mg; 6.3%. Found: C, 54.68; H, 6.77%. Calcd for $C_{19}H_{28}O_6S_2$: C, 54.79; H, 6.78%. ^{1}H NMR δ =2.60 (3H, s), 2.6-2.9 (3H, m), 3.12 (1H, d, J=14 Hz), 3.2-3.7 (13H, m), 3.51 (3H, s), 3.89 (3H, s), 4.37 (1H, d, J=14 Hz), and 6.76 (1H, s). ^{13}C NMR δ =20.5, 30.8, 31.2, 33.9, 56.3, 60.7, 70.0, 70.1, 70.3, 70.4, 70.6, 70.7, 111.4, 128.5, 142.4, 143.3, 154.1, 156.1, and 178.7. IR ν : 2900, 1620, 1600, 1550, 1325, 1195, 1120, and 1100 cm^{-1}. UV λ_{max}^{MeOH} =247 (ε =9270), 292 (9100), 354 (4390, sh), and 384 nm (5120).

7c: Yellow prisms (AcOEt-Hexane), mp 94-95 ℃, 615 mg; 46%. Found: C, 54.78; H, 6.52%. Calcd for $C_{17}H_{24}O_5S_2$: C, 54.82; H, 6.49%. ^{1}H NMR δ =2.4-2.6 (1H, m), 2.70 (3H, d, J=1 Hz), 2.7-2.8 (1H, m), 2.9-3.0 (1H, m), 3.1-3.7 (9H, m), 3.14 (1H, d, J=13 Hz), 3.54 (3H, d, J=1 Hz), 3.90 (3H, s), 4.43 (1H, d, J=13 Hz), and 6.72 (1H, s). ^{13}C NMR δ =21.9, 30.0, 32.6, 35.2, 56.4, 60.8, 70.2, 70.9, 71.6, 73.1, 113.7, 129.8, 143.9, 146.2, 155.0, 156.8, and 178.7. IR ν : 2940, 1615, 1595, 1555, 1470, 1405, 1335, 1200, 1100, and 1000 cm^{-1}. UV λ_{max}^{MeOH} =378 (ε =7380), 296 (10900), and 251 nm (15100).

8d: Yellow plates (AcOEt-Hexane), mp 151-153 ℃, 268 mg; 25%. Found: C, 54.77; H, 6.19%. Calcd for $C_{15}H_{20}O_4S_2$: C, 54.85; H, 6.14%. ^{1}H NMR δ = 2.4-2.8 (4H, m), 3.0-3.6 (4H, m), 3.21 (1H, d, J=14 Hz), 3.32 (1H, dd, J=14, 1 Hz), 3.62 (3H, s), 3.96 (3H, s), 4.17 (1H, d, J=14 Hz), 4.50 (1H, d, J=14 Hz), 6.87 (1H, s), and 7.36 (1H, s). ^{13}C NMR δ =28.3, 29.0, 34.2, 34.3, 56.3, 62.1, 68.5, 68.8, 114.2, 133.0, 137.4, 145.3, 155.6, 161.7, and 179.2. IR ν : 2950, 2840, 1615, 1600, 1570, 1200, and 1080 cm^{-1}. UV λ_{max}^{MeOH} =248 (ε =25800), 305 (8690), and 366 nm (6790).

8e: Yellow crystals (AcOEt-Hexane), mp 167-167.5 ℃, 115 mg; 18%. Found: C, 52.18; H, 5.86%. Calcd for $C_{15}H_{20}O_3S_3$: C, 52.30; H, 5.85%. ^{1}H NMR δ =2.2-2.9 (8H, m), 3.20 (1H, d, J=13 Hz), 3.26 (1H, dd, J=13, 1 Hz), 3.64 (3H, s), 3.97 (3H, s), 4.26 (1H, d, J=13 Hz), 4.52 (1H, d, J=13 Hz), 6.96 (1H, s), and 7.51 (1H, s). ^{13}C NMR δ =30.3 (2C), 31.7, 31.8, 32.0, 32.6, 56.4, 62.5, 113.6, 132.4, 138.7, 145.3, 155.4, 162.2, and 179.1. IR ν : 2950, 2850, 1605, 1595, 1560, 1390, 1285, 1205, and 1005 cm^{-1}. UV λ_{max}^{MeOH} =250 (ε =24800), 308 (7950), 370 (5590), and 388 nm (3860, sh).

8e': Yellow crystals, mp 225-228 ℃, 159 mg; 26%. Found: *m/z*, 330.0390 (M$^+$). Calcd for $C_{14}H_{18}O_3S_3$: 330.0415 (M). ^{1}H NMR δ =2.2-2.8 (8H, m), 3.30 (2H, d, J=13 Hz), 3.67 (3H, s), 4.44 (2H, d, J=13 Hz), and 7.59 (2H, s). ^{13}C NMR δ =30.4 (2C), 31.8 (2C), 32.5 (2C), 62.9, 125.8 (2C), 143.0 (2C), 155.9, and 169.4 (2C). IR ν: 3600-3300, 2940, 1615, 1600, 1535, and 1240 cm^{-1}. UV λ_{max}^{MeOH} = 262 (ε = 20600), 313 (6980), 342 (8380), 400 (4050, sh), and 415 nm (4680).

Variable Temperature ^1H NMR measurement of 7b. To deoxygenated DMF-d_7 solution, **7b** (ca. 30 mg) was introduced and sealed off. The ^1H NMR spectra were measured in the range of 50 to 150 ℃ as usual.

Variable Temperature ^1H NMR measurement of 7a. To deoxygenated CD_2Cl_2 solution, **7a** (ca. 30 mg) was introduced and sealed off. The ^1H NMR spectra were measured in the range of 30 to −90 ℃ as usual. Spectral change could be seen in Fig. 1.

The $HgCl_2$-Complex Formation with 7a. A $CDCl_3$ solution (2 cm^3) of **7a** (40 mg, 8.7×10^{-2} mmol) and an aqueous solution (2 cm^3) of $HgCl_2$ (56 mg, 0.21 mmol) was vigorously shaken for 10 min. The $CDCl_3$ layer was analyzed by means of ^1H NMR spectroscopy to show a formation of Hg^{2+}-complex of **7a** [^1H NMR δ = 2.69 (3H, s), 2.81 (2H, t, J = 6 Hz), 3.21 (2H, br t-like), 3.3-3.7 (16H, m), 3.51 (3H, s), 3.66 (1H, d, J = 17 Hz), 3.90 (1H, d, J = 17 Hz), 3.96 (3H, s), and 6.83 (1H, s). ^{13}C NMR δ = 20.7, 30.4, 32.7, 34.1, 56.3 60.9, 68.1, 69.5, 69.6, 70.0, 70.1 (3C), 70.3, 113.3, 129.4, 140.4, 145.2, 154.7, 156.6, and 178.2].

Liberation of Hg^{2+} from the 7a-Complex. **a)** The $CHCl_3$ solution containing the Hg^{2+}-complex of **7a** was treated with 2 N HCl (2 cm^3) for 1 h under vigorous stirring. The organic layer was separated, dried on $MgSO_4$, and evaporated in vacuo. The NMR spectrum of the resultant yellow oil was identical in every respect with that of **7a**. The recovery of **7a** was quantitative. Quantitative analysis of Hg^{2+} was carried out by means of UV spectrophotometry as the dithizone salt to show the ratio of **7a**: Hg^{2+} = 1:1.

b) The Hg^{2+}-complex of **7a** in $CHCl_3$ was vigorously stirred with 20%-NaCl, and the separated $CHCl_3$ layer was dried on $MgSO_4$ and evaporated in vacuo. The NMR spectrum of the residue was free from the Hg^{2+}.

Complex Formation of 7b and $HgCl_2$. A $CDCl_3$ solution (1.5 cm^3) of **7b** (25 mg, 6.0×10^{-2} mmol) and an aqueous solution (2 cm^3) of $HgCl_2$ (99 mg, 0.36 mmol) were vigorously shaken for 5 min. The $CDCl_3$ layer was analyzed by means of ^1H NMR spectroscopy to show a formation of Hg^{2+}-complex of **7b** [^1H NMR δ = 2.68 (3H, s), 2.6-3.0 (3H, m), 3.22 (1H, d, J = 14 Hz), 3.1-4.0 (13H, m), 3.55 (3H, s), 3.92 (3H, s), 4.40 (1H, d, J = 14 Hz), and 6.93 (1H, s)].

Liberation of Hg^{2+} from the 7b-Complex. To the $CHCl_3$ solution of Hg^{2+}-complex of **7b** was added 2 N HCl under vigorous stirring. Evaporation of the $CHCl_3$ layer left a colorless oil, in 70% yield, of which the NMR spectrum was identical with that of **7b**. Quantitative analysis of Hg^{2+} in the aqueous layer was similarly carried out by means of UV spectrophotometry as the dithizone salt to show the ratio of **7b**: Hg^{2+} = 1:1.

Complex Formation of 7a and $HgCl_2$ in the Presence of Na^+. A $CDCl_3$ solution (1.5 cm^3) of **7a** (18.5 mg 4.0×10^{-2} mmol) and an aqueous solution (2 cm^3) of $HgCl_2$ (124 mg, 0.46 mmol) and NaCl (60 mg) were vigorously shaken for 10 min. The $CDCl_3$ layer was analyzed by means of ^1H NMR spectroscopy to show a formation of Hg^{2+}-complex of **7a.**

The Complex Formation of 7a with $HgCl_2$ in Sea Water. A $CDCl_3$ solution (1 cm^3) of **7a** (10 mg, 2.4×10^{-2} mmol) and a sea water (2 cm^3), collected in Hakata Bay, of

$HgCl_2$ (36 mg, 0.13 mmol) was vigorously shaken for 10 min. The $CDCl_3$ layer was analyzed by means of ^1H NMR spectroscopy to show a formation of Hg^{2+}-complex of **7a.**

Attempted $HgCl_2$-Complex Formation with 8d and 8e. Each $CDCl_3$ solution (1.5 cm^3) of **8d** (23 mg, 7.0×10^{-2} mmol) or **8e** (25 mg, 7.3×10^{-2} mmol) was mixed with an aqueous solution (2 cm^3) of $HgCl_2$ (90 mg, 0.33 mmol) and vigorously shaken for 10 min. The $CDCl_3$ layer analyzed by means of ^1H NMR spectroscopy showed no indication of the Hg^{2+}-complex formation.

Complex Formation and Attempted Liberation of Hg^{2+} with 9, 10, and 11. A $CDCl_3$ solution (2 cm^3) of **9, 10,** or **11** (7.5×10^{-2} mmol) and an aqueous solution (2 cm^3) of $HgCl_2$ (60 mg, 0.22 mmol) was vigorously shaken for 10 min. The $CDCl_3$ layer was analyzed by means of ^1H NMR spectroscopy to show a formation of Hg^{2+}-complex. The Hg^{2+}-complex of each **9, 10**, or **11** was then treated with 2 N HCl, and fractionated. The organic layer was separated, dried on $MgSO_4$, and evaporated in vacuo. The residues, thus obtained, showed the identical NMR spectra with those of **9, 10,** and **11**.

Attempted Complex Formation with Other Metal Ions. To a $CDCl_3$ solution of **7a**, an aqueous solution (2 cm^3) of each metal salt, i.e., LiBr, NaCl, KCl, $AgNO_3$, $MgCl_2$, $CoCl_2$, $NiCl_2$, $CuCl_2$, $ZnCl_2$, $SrCl_2$, $CdCl_2$, $BaCl_2$, La $(OAc)_3$, $TlCl_3$, or $FeCl_3$, was added under vigorous stirring. Organic layer was then collected, dried on $MgSO_4$, and evaporated in vacuo. The ^1H NMR spectroscopic analysis revealed no noticeable change in each case.

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