Synthesis and Mercurophilic Properties of Dicyanoheptafulvene-Incorporated Dithio-Crown-Ethers from Malononitrile and 5,8,11,14,17-Pentaoxa-2,20-dithiabicyclo[19.4.1]hexacosa-21,23,25-trien-26-one and Its Homologues

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5,8,11,14,17-Pentaoxa-2,20-dithiabicylco[19.4.1]hexacosa-21,23,25-trien-26-one and its homologues gave, via remote substitution, 8,8-dicyanoheptafulvene-incorporated dithio-crown-ether derivatives upon heating with malononitrile in acetic anhydride. This means that 7-acetoxy-7-dicyanomethyl-1,3,5-cycloheptatrienes, *ipso*-attacked intermediates of malononitrile to acetoxytropylium derivatives, were not formed on a steric ground. These dithio-crown-ethers efficiently extract and reversibly transport mercury(II) ion.

Previously, we have synthesized remarkably efficient mercurophilic dithio-crown derivatives, 5,8,11,14-tetraoxa-2,17-dithiabicyclo[16.4.1]tricosa-18,20,22-trien-23-one (**1b**) and its homologues,[1] and these compounds showed a reversible complexation, which has been explained in terms of the Coulomb cation–cation repulsive interaction between mercury(II) ion and a hydroxytropylium ion formed upon acid treatment. Meanwhile, we have found a remote condensation of sterically hindered tropones to 8,8-dicyanoheptafulvene derivatives upon treatment with active methylene compounds in acetic anhydride.[2]

Therefore, it is desirable to extend this study to heptafulvene derivatives, which also form a cycloheptatrienylium system upon acidification. Herein, we describe the results, synthesis and mercurophilic properties of such heptafulvene derivatives prepared from appropriate tropones and malononitrile (**2**).

Results and Discussion

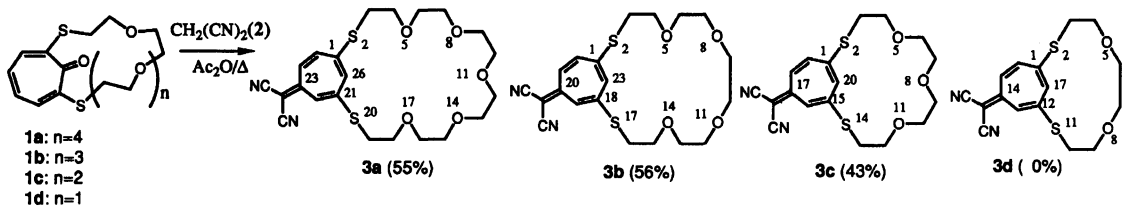
A mixture of 5,8,11,14,17-pentaoxa-2,20-dithiabicyclo[19.4.1]hexacosa-21,23,25-trien-26-one (**1a**) and **2** was heated in acetic anhydride for 1 h to give, via column chromatography, red-colored crystalline heptafulvene (**3a**, mp 70—71 °C), in 55% yield, which was identified to be a remote-condensation product,[2] 23-dicyanomethylene-5,8,11,14,17-pentaoxa-2,20-dithiabicyclo-[19.4.1]hexacosa-1(26),21,24-triene.

Similar treatment of **2** with 5,8,11,14-tetraoxa-2,17-dithiabicyclo[16.4.1]tricosa-18,20,22-trien-23-one (**1b**) and 5,8,11-trioxa-2,14-dithiabicyclo[13.4.1]eicosa-15,17,19-trien-20-one (**1c**) also gave red crystalline products, 20-dicyanomethylene-5,8,11,14-tetraoxa-2,17-dithiabicyclo[16.4.1]tricosa-1(23),18,21-triene (**3b**, mp 133—134 °C) and 17-dicyanomethylene-5,8,11-trioxa-2,14-dithiabicyclo[13.4.1]eicosa-1(20),15,18-triene (**3c**, mp 175—177 °C), in 56 and 43% yields, respectively, but **2** was unreactive with 5,8-dioxa-2,11-dithiabicyclo[10.4.1]-heptadeca-12,14,16-trien-17-one (**1d**)[3] under identical conditions (Scheme 1). Therefore, the reaction of **2** with 5-oxa-2,8-dithiabicyclo[7.4.1]tetradeca-9,11,13-trien-14-one (**1e**) was not attempted.

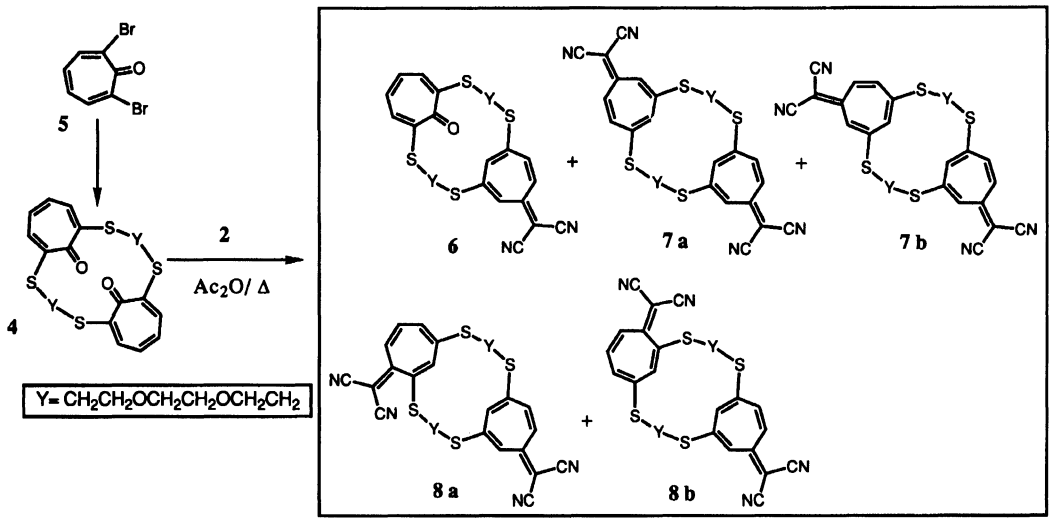
As an example of larger ring derivatives, the 2:2-condensate (**4**) of 2,7-dibromotropone (**5**) to ethylene glycol bis(2-mercaptoethyl) ether[4] was investigated to afford heptafulvenes. Thus, when an acetic anhydride solution of **4** and **2** was refluxed for 1 h under nitrogen atmosphere, five products (**6**, **7a**, **7b**, **8a**, and **8b**) were detected on a high-pressure liguid chromatography, and three of them could be isolated and the structures were identified (Scheme 2). The major product (**6**) was a monosubstituted compound, whose structure was deduced as depicted on the basis of the ^{1}H and ^{13}C NMR spectra. Both crystallines **7a** and **7b** were regioisomeric disubstituted products; structural differentiation of these two was difficult, but the ^{1}H NMR spectrum of **7b**, which revealed no mutual spin-spin splitting with methylene protons of the central ethylene groups at $\delta=3.66$ (4H, s) and 3.67 (4H, s), led us to assign it as the "*cis*"-isomer. On the other hand, the ^{1}H NMR spectrum of the higher mp isomer, **7a**, showed those ethylene groups as an overlapped signal at $\delta=3.67$ (8H, s), and it might be the "*trans*"-isomer.

The remaining **8a** and **8b**, an inseparable mixture, are also regioisomers. Since the ^{1}H NMR spectrum of the mixture showed a large vicinal coupling ($J=12.5$ Hz) between the signals of $\delta=7.08$ (dd) and 6.65 (dd), the remote substitution of the dicyanomethylene group was evident. In addition, an aromatic signal at $\delta=6.87$ (br s) was integrated only for one proton, indicating the presence of an isolated hydrogen adjacent to the dicyanomethylene group of the seven-membered ring. Therefore, the structures of **8a** and **8b** are assigned as depicted.

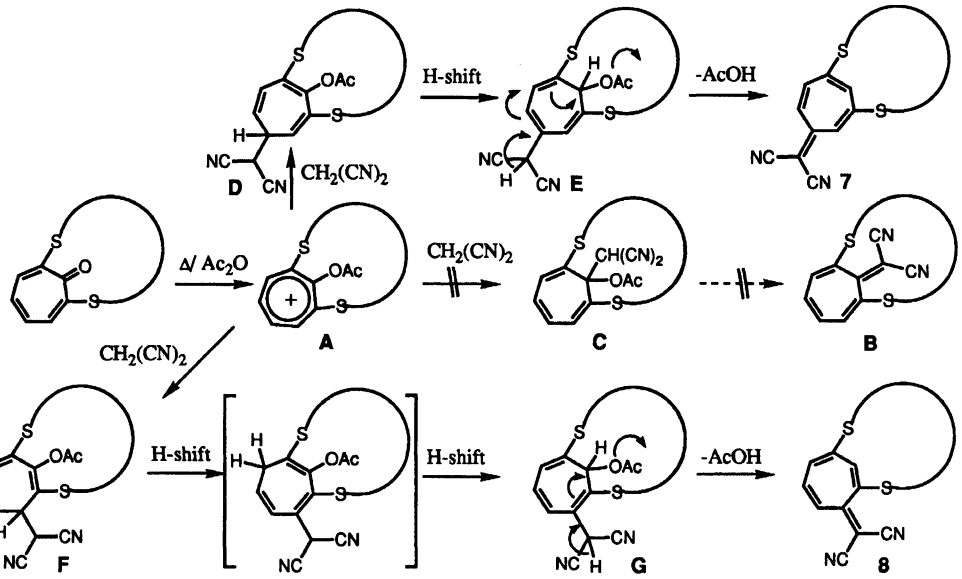
The reaction mechanism is provided in Scheme 3, where the first step of the reaction is the formation of an acetoxytropylium ion (**A**), and the absence of the product (**B**) might be attributable to steric hindrance in the *ipso*-attacked intermediate (**C**). On the other hand, an intermediate (**D**) leading to the remote-condensate is eligible for a thermally-allowed [1,5] hydrogen shift to an intermediate (**E**), a precursor of **7**.[5] In the case of **8**, a simple [1,5] sigmatropic hydrogen shift of the proto-adduct (**F**) can not form the intermediate (**G**). There-



Scheme 1.



Scheme 2.



Scheme 3.

fore, repeated sigmatropies or a stepwise ionic mechanism should be involved for all these remote substitution reactions.

Complex Formation with Mercury Ion. On the analogy to the tropone analogues, these heptafulvenes formed complexes with mercury ion.[6] Extraction of mercury ion into the chloroform-*d* solutions containing **3a**—**3c** was checked by ^{1}H NMR spectroscopy; **3a** and **3b** revealed a clear ^{1}H NMR change to indicate complex formation, but the change of **3c** by complexation was not significant. Yet, **3a**—**3c** all formed complexes with mercury(II) salt. As a representative example, the ^{1}H NMR spectral change of **3a** by complexation is shown in Fig. 1.

However, according to experiments using a U-type cell,[7] all of **3a**—**3c** transported mercury ion selectively,

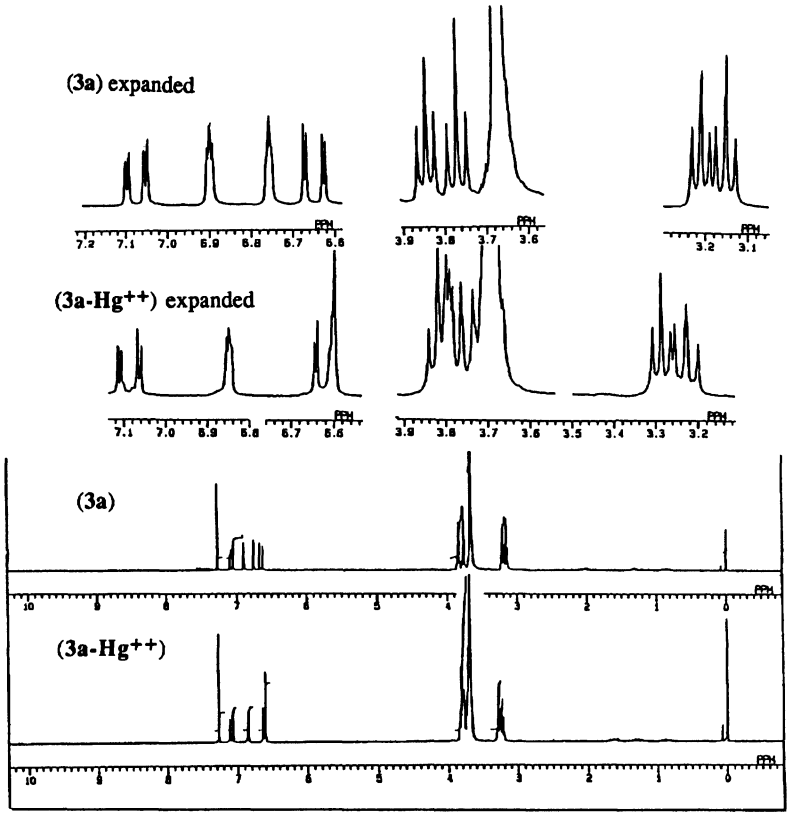


Fig. 1. The ^{1}H NMR spectral change of **3a** by complexation with mercury(II) salt.

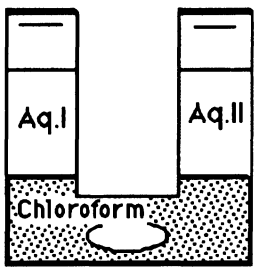
Table 1. Transportation Experiments of Several Metal Ions by Use of Dithio-Crown Heptafulvene Derivatives

Crown deriv.	$T(Zn^{2+})$	$T(Cu^{2+})$	$T(Ni^{2+})$	$T(Hg^{2+})$	$T(Ag^{+})$
Method of analysis	a)	b)	c)	a)	a)
3a	d)	d)	d)	3.18	d)
3b	d)	d)	d)	0.79	d)
3c	d)	d)	d)	0.64	d)

a) diphenylthiocarbazone; b) sodium diethyldithocarbamate; c)1-(2-pyridylazo)-2-naphthol; d) no detectable amount transported.

and, in parallel to that with **1**, copper ion did not interfere with the transportation. Moreover, zinc, nickel, and silver ions were not transported under the same conditions. The amount of metal ions transported was determined photometrically and is complied in Table 1, where the relative rates of transportation of mercury(II) ion with different size ether rings are expressed with the figures of T(M); T means a total amount (micromol per hour) of ions transported by means of a U-type cell (Fig. 2) under the specified conditions (See Experimental).

The extraction into an organic layer containing the crown ethers and the reverse-extraction into an aqueous layer (2 M HCl) occurred quite smoothly. Indeed, the most satisfactory results obtained with **3a** are far better than any previous ones ever encountered. Furthermore, the 2 : 2-condensates (**6**—**8**) also formed complexes with mercury ion.



Aq. I (10 cm^3) : MCl_2 or $AgNO_3$ (0.05 mmol)
Aq. II(10 cm^3) : 2M HCl
$CHCl_3$(20 cm^3) : **3** (0.05mmol)

Fig. 2. Dimensions and quantities used for transportation experiments.

It is also noteworthy that the transportation efficiency dropped sharply when **3b** or **3c** was used; under the same conditions, the transportation rate for **3b** or

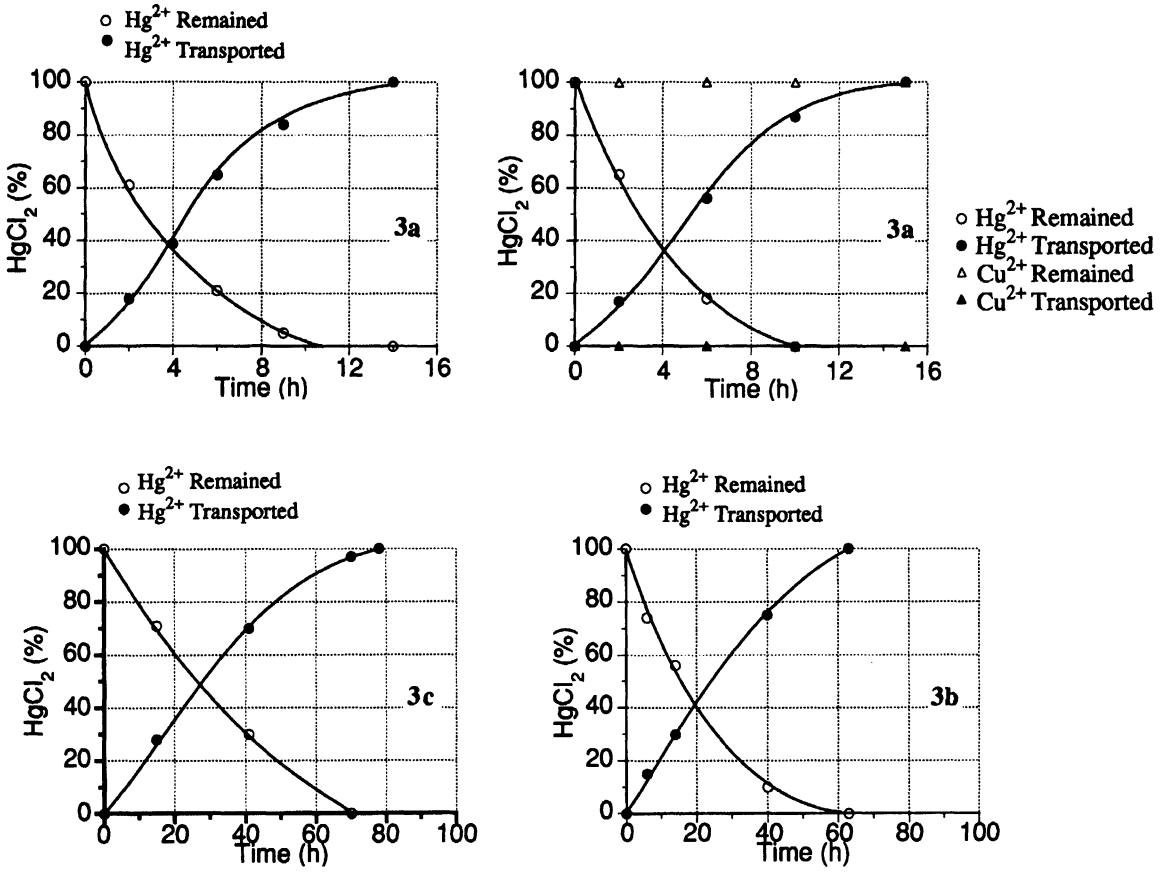


Fig. 3. Transportation experiments of Hg^{2+} with **3a**, **3b**, and **3c**.

3c was less than 30% of that for **3a**. These results are summarized in Fig. 3.

In the case of the troponoid analogues, **1b** was a better mediator for transportation of mercury ion than **1a**. The best-fitted ring sizes between **1** and **3** were different. Therefore, both electron-withdrawing dicyanomethylene and carbonyl moieties on the seven-membered rings take part in the complexation. In other words, the sites of complexation for mercury(II) ion are different between **1** and **3**.[8)]

Consequently, the marked selective and reversible complex formation of **1** with mercury salt is now extended to **3**. The results clearly show that protonation is responsible for the ready liberation of mercury ion by generating a 6π-cationic system with the seven-membered ring to cause Coulomb repulsion with the complexed mercury ion. This should be responsible for the difference from the benzenoid counterpart.

Experimental

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 $CDCl_3$; the chemical shifts are expressed in units of δ. The mass spectra were measured with a JEOL 01SG-2 spectrometer, except for FAB-MS measurements of high-resolution molecular weight determinations which were performed by a JEOL JMS SX 102A model spectrometer being controlled by a JEOL DA-7000 Data System (Tokyo), of the Pharmaceutical School of Kyushu University. 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 using Hitachi U-3200 and U-3410 spectrophotometers. The stationary phase for column chromatography was Wakogel C-300 and the eluent was a mixture of ethyl acetate and hexane.

Reaction of 1 with 2 in Ac_2O to form 3 (General Method). An anhydrous Ac_2O solution (2 cm^3) of **1** (80-90 mg, 0.2 mmol) and **2** (60 mg, 0.9 mmol) was heated under N_2 atmosphere at 130—140 °C for 1—3 h. The mixture was then heated in vacuo to remove volatile materials, and the residue thus obtained was chromatographed on a silica-gel column to give **3**.

3a: Red crystals, mp 70—71°C, 55%. ^{1}H NMR δ=3.15 (2H, t, J=6.6 Hz), 3.21 (2H, t, J=5.5 Hz), 3.67 (16H, s), 3.77 (2H, t, J=6.6 Hz), 3.84 (2H, t, J=5.5 Hz), 6.65 (1H, dd, J=12.5 and 2.2 Hz), 6.76 (1H, br s), 6.90 (1H, dd, J=2.2 and 1.8 Hz), and 7.07 (1H, dd J=12.5 and 2.2 Hz). ^{13}C NMR δ=32.5, 32.9, 66.3, 68.3, 69.5, 70.7 (3C), 71.0 (4C), 71.2, 115.5, 115.6, 121.6, 127.3, 132.3, 137.5, 149.1, 154.5, and 158.5. MS m/z (%) 464 (M^+, 88), 242 (61), 218 (63), 140 (57), 45 (100), 44 (96), 43 (40), and 28 (58). IR ν 2872, 2200, 1624, 1561, 1520, 1439, 1392, 1354, 1275, 1110, 1039, 849, and 824 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=312.5 nm (ε=23300), 332

(17600), and 438 (23300). Found: m/z, 465.1504 ($M+H^+$) (FAB-MS). Calcd for $C_{22}H_{29}O_5N_2S_2$: M+H, 465.1518.

3b: Red crystals, mp 133—134 °C, 56%. ^{1}H NMR δ=3.14 (2H, t, J=5.9 Hz), 3.21 (2H, t, J=5.5 Hz), 3.62—3.71 (12H, m), 3.76 (2H, t, J=5.9 Hz), 3.84 (2H, t, J=5.5 Hz), 6.64 (1H, dd, J=12.5 and 1.8 Hz), 6.88 (2H, br s), and 7.10 (1H, dd, J=12.5 and 2.2 Hz). ^{13}C NMR δ=32.7, 33.9, 66.2, 67.8, 70.2, 70.3, 70.6, 70.8, 71.0, 71.1, 71.2, 115.6, 115.7, 121.3, 128.0, 132.1, 137.6, 148.8, 154.8, and 158.6. MS m/z (%) 421 (26), 420 (M^+, 100), 244 (19), 242 (54), 218 (49), 172 (26), 140 (47), and 45 (42). IR ν 2200, 1555, 1510, 1394, 1362, 1274, 1144, and 1100 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=312 nm (ε=16900), 332 (16800), and 438 (23300). Found: m/z, 421.1261 ($M+H^+$) (FAB-MS). Calcd for $C_{20}H_{25}O_4N_2S_2$: M+H, 421.1255.

3c: Red crystals, mp 175—177 °C, 43%. ^{1}H NMR δ=3.21 (2H, t, J=5.5 Hz), 3.23 (2H, t, J=5.5 Hz), 3.56—3.68 (8H, m), 3.77 (2H, t, J=5.5 Hz), 3.83 (2H, t, J=5.5 Hz), 6.71 (1H, dd, J=12.1 and 2.2 Hz), 7.02 (1H, br s), 7.09 (1H, dd, J=12.1 and 2.2 Hz), and 7.13 (1H, dd, J=2.2 and 1.5 Hz). ^{13}C NMR δ=33.3, 33.9, 65.8, 68.9, 70.4, 70.5, 70.9, 71.2, 71.5, 115.6, 115.7, 124.9, 128.6, 132.6, 137.7, 150.0, 153.3, and 158.6. MS m/z (%) 376 (M^+, 100), 242 (87), 218 (62), 172 (40), 140 (78), 45 (76), 43 (40), and 28 (39). IR ν: 2919, 2864, 2198, 1505, 1396, and 1359 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=314 nm (ε=9400), 337 (9400), and 446 (14000). Found: m/z, 377.0993 ($M+H^+$) (FAB-MS). Calcd for $C_{18}H_{21}O_3N_2S_2$: M+H, 377.0994.

Reaction of 4b with 2 in Ac_2O. Formation of 6, 7a, 7b, 8a, and 8b. An anhydrous Ac_2O solution (2 cm^3) of **4b** (90.0 mg) and **2** (63 mg) was refluxed for 1 h. The mixture was then heated to remove the volatile material, and the residue thus obtained was chromatographed on a silica-gel column and further purified via high-pressure liquid chromatography to afford the products.

6: Red crystals, mp 147—150 °C, 27.4 mg, 30%. ^{1}H NMR δ=3.03—3.14 (8H, m), 3.57—3.70 (8H, m), 3.76—3.91 (8H, m), 6.44 (1H, br s), 6.62 (1H, d, J=12.1 Hz), 6.79 (1H, br s), 6.93—7.05 (3H, m), and 7.23—7.33 (2H, m). ^{13}C NMR δ=32.3, 32.5, 33.4, 33.6, 65.6, 68.2, 68.4, 68.7, 69.0, 70.6, 70.9, 71.0 (2C), 115.7, 115.8, 120.6, 127.9, 128.1, 128.2 (2C), 128.3, 131.9, 137.5, 149.4, 150.8, 151.0, 154.8, 158.5, and 178.7. MS m/z (%) 616 (M^+, 9), 196 (16), 61 (100), 60 (42), 59 (23), 45 (73), 44 (19), 43 (68), and 27 (29). IR ν 2918, 2856, 2200, 1622, 1577, 1511, 1437, 1351, 1275, 1113, 1038, 975, 849, 816, 768, and 746 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=311 nm (ε=17300), 337 (20500), 407 (18000), and 440 (27300). Found: m/z, 617.1276 ($M+H^+$) (FAB-MS). Calcd for $C_{29}H_{33}O_5N_2S_4$: M+H, 617.1272.

7a: Red crystals, mp 203—205 °C, 7.0 mg, 7%. ^{1}H NMR δ=3.10 (4H, t, J=5.9 Hz), 3.20 (4H, t, J=5.9 Hz), 3.67 (8H, s), 3.77 (4H, t, J=5.9 Hz), 3.83 (4H, t, J=5.9 Hz), 6.62 (2H, br s), 6.67 (2H, dd, J=12.1 and 1.8 Hz), 6.89 (2H, dd, J=2.4 and 1.8 Hz), and 7.08 (2H, dd, J=12.1 and 2.4 Hz). ^{13}C NMR δ=33.2 (2C), 33.8 (2C), 67.2 (2C), 68.6 (2C), 69.4 (2C), 70.9 (4C), 115.2 (2C), 115.5 (2C), 121.4 (2C), 128.0 (2C), 132.3 (2C), 137.5 (2C), 149.0 (2C), 153.8 (2C), and 158.5 (2C). MS m/z (%) 664 (M^+, 13), 140 (18), 61 (100), 60 (39), 59 (22), 45 (70), 44 (30), 43 (20), and 23 (27). IR ν 2922, 2854, 2202, 1561, 1512, 1357, 1274, 1105, 1037, 806, 694, and 560 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=312 nm (ε=27500), 330 (26700), and 439 (34600). Found: m/z, 665.1402 ($M+H^+$) (FAB-MS). Calcd for $C_{32}H_{33}O_4N_4S_4$: M+H, 665.1385.

7b: Red crystals, mp 174—175 °C, 3.0 mg, 3%. ^{1}H NMR δ=3.13 (4H, t, J=5.9 Hz), 3.20 (4H, t, J=5.9 Hz), 3.66 (4H, s), 3.67 (4H, s), 3.77 (4H, t, J=5.9 Hz), 3.82 (4H, t, J=5.9 Hz), 6.62 (2H, br s), 6.66 (2H, dd, J=12.1 and 1.8 Hz), 6.89 (2H, t, J=1.8 Hz), and 7.08 (2H, dd, J=12.1 and 1.8 Hz). ^{13}C NMR δ=32.9 (2C), 33.9 (2C), 67.1 (2C), 68.4 (2C), 69.1 (2C), 70.9 (4C), 115.3 (2C), 115.4 (2C), 121.5 (2C), 127.7 (2C), 132.3 (2C), 137.3 (2C), 148.9 (2C), 153.8 (2C), and 158.4 (2C). MS m/z (%) 664 (M^+, 6), 66 (15), 61(100), 60 (39), 59 (22), 45 (64), 44 (14), 43 (22), and 27 (24). IR ν 2911, 2858, 2202, 1559, 1516, 1437, 1392, 1358, 1299, 1272, 1127, 1113, and 1038 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=312 nm (ε=35600), 330 (34900), and 438 (45800). Found: m/z, 665.1381 ($M+H^+$) (FAB-MS). Calcd for $C_{32}H_{33}O_4N_4S_4$: M+H, 665.1385.

8a and 8b: A red oil, 4.0 mg, 4%. ^{1}H NMR δ=3.07 (2H, t, J=6.1 Hz), 3.10 (2H, t, J=6.1 Hz), 3.13 (2H, t, J=6.1 Hz), 3.18 (2H, t, J=5.8 Hz), 3.60—3.64 (8H, m), 3.66 (2H, t, J=6.4 Hz), 3.70 (2H, t, J=6.4 Hz), 3.78 (2H, t, J=6.1 Hz), 3.81 (2H, t, J=5.8 Hz), 6.55—6.61 (2H, m), 6.65 (1H, dd, J=12.5, 2.0 Hz), 6.72 (1H, br s), 6.75—6.77 (2H, m), 6.86 (1H, br s), and 7.08 (1H, dd, J=12.5, 2.3 Hz). MS m/z (%) 664 (M^+, 20) 66 (42), 61 (100), 60 (39), 59 (26), 45 (81), 43 (23), and 27 (29). IR ν 2920, 2858, 2202, 1623, 1599, 1555, 1515, 1438, 1391, 1353, 1275, 1105, 1065, 1038, 859, and 747 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$=266 nm (ε=16900), 312 (26500), 416 (22200), and 439 (28700). Found m/z, 665.1402 ($M+H^+$) (FAB-MS). Calcd for $C_{32}H_{33}O_4N_4S_4$: M+H, 665.1402.

Transportation Experiment of Various Metal Ions with 3a, 3b, and 3c Using a U-Type Cell. By similar procedures as described in the previous paper,[4] spectrophotometric determinations of metal ions before and after the transportations via complexation with **3a**, **3b**, and **3c** were carried out:

Ni^{2+} Ion: 10 cm^3 of aqueous $NiCl_2$ solution (0.05 mol dm^{-3}) was employed, and determined UV-spectrometrically at a λ_{max} of 570 nm as a complex with 1-(2-pyridylazo)-2-naphthol.[9]

Zn^{2+} Ion: 10 cm^3 of aqueous $ZnCl_2$ solution (0.05 mol dm^{-3}) was employed, and determined UV-spectrometrically at a λ_{max} of 535 nm as a complex with diphenylthiocarbazone.[10]

Ag^+ Ion: 10 cm^3 of aqueous $AgNO_3$ solution (0.05 mol dm^{-3}) was employed, and determined UV-spectrometrically at a λ_{max} of 470 nm as a complex with diphenylthiocarbazone.[11]

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3) This should be due to severe steric strain in the intermediate, 1,3-disubstituted 2-acetoxycycloheptatrienylium ion.

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7) The U-type cell used was the same as the previous apparatus, described in Ref. 4.

8) Nearly perpendicular geometries of the seven-membered rings to the dithio-crown rings were observed in the crystal structures of **1b** and **3a**, and this conformation is likely to be general in these mercurophilic dithio-crown derivatives. The X-ray crystallographic study will be reported elsewhere in the near future.

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