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Variable Ion Selectivity in [*n*.3.3](1,3,5)Crownophanes: The “Breathing” Process

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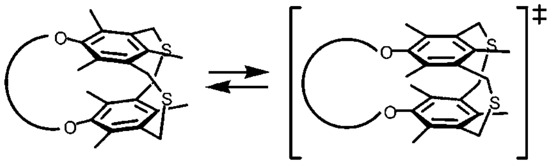
ABSTRACT



A series of dithia[*n*.3.3](1.3.5)crownophanes were synthesized by cesium carbonate-assisted intramolecular cyclization reactions in 10–31% yields. Their complexation behavior exhibits an unusual ion-selectivity preference due to the presence of a “breathing” process of the dithia[3.3]metacyclophane moiety, which indirectly controls the ion selectivity through the adjustment of the cavity size of the crown unit. This breathing mechanism is also supported by observation made in X-ray crystallographic analysis.

Studies of classic crown ethers reveal that the cavity size of a crown ether is one of the main factors in governing its complexation to a metal ion.[1] On the other hand, one of the key features in the chemistry of cyclophanes is their conformational behavior.[2] The conformational mobility of cyclophanes and their aromatic interactions were in fact employed in a recent approach to a nanomechanical molecular cyclophane system.[3] Crownophanes, having a flexible polyether chain and a cyclophane skeleton, are a unique kind of hybridized molecular host that exhibits interesting properties.[4] The bis-cyclobutyl bridges in crownophane **1** dictate its rigid molecular structure, and its crown unit complexes Li$^+$ strongly and specifically.[5] 2,11-Dithia[3.3]metacyclophane is known to exist as a syn conformer both in the solid state and in solution,[6,7] and its conformational behavior involves a tilting motion of the two aromatic rings resulting in a variation of the tilting angle α. Crownophane **2** was reported to exhibit interesting complexation behaviors mediated by the mobility of the cyclophane moiety and form a novel supramolecular polymeric structure.[8,9] A [*n*.3.3](1,3,5)-crownophane (Figure 1b) exhibiting conformational mobility

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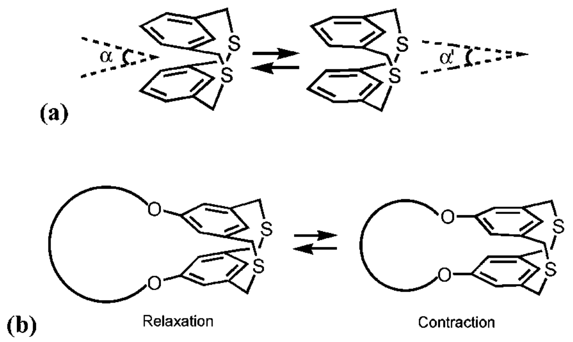
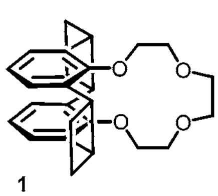


Figure 1. (a) Tilting of aromatic rings in *syn*-**1** and (b) conformational changes in a breathing process in [*n*.3.3](1,3,5)crownophanes.

in the cyclophane unit as in Figure 1a will result in a variably sized cavity in its crown unit. Such a ligand is expected to show a decrease in the complexation selectivity toward metal ions. On the basis of the "breathing" mechanism, it may, however, complex effectively to a series of metal ions with various ion radii. This may be the desirable result in the case of nonselective yet effective complexation of a mixture of metal ions. We report in this communication the complexation behavior of a series of [*n*.3.3](1,3,5)crownophanes **4**.



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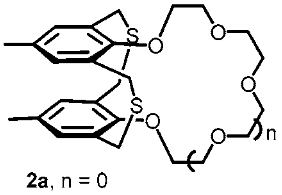
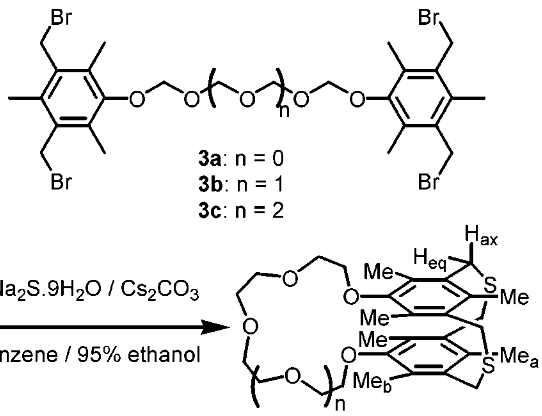


2a, n = 0
2b, n = 1



Scheme 1. Synthesis of Crownophanes **4**

4a: n = 0
4b: n = 1
4c: n = 2

Synthesis of some closely related [*n*.3.3](1,3,5)cyclophanes has been reported.[10] In our work, crownophanes **4** were prepared by an intramolecular cyclization of compound **3**[11] in the presence of $Na_2S{\cdot}9H_2O$ in a mixture of 95% ethanol and benzene under high dilution conditions (Scheme 1).[12] Compounds **4a**[13] and **4b**[14] were obtained in 15 and 20% yields, respectively. Cyclophane **4c**[15] was, however, isolated in a very low yield (≈1%) under such conditions. Addition of cesium carbonate[12] to the reaction mixture resulted in a significantly increased yield (31%) of **4c**. Surprisingly, presence of cesium carbonate did not have an appreciable effect on the yields of **4a** and **4b**.

The structures of **4a** and **4b** were characterized by X-ray crystallography. However, no suitable crystals of **4c** could be isolated for a similar study. For **4a**, interestingly, two independent conformers **4a-(I)** and **4a-(II)** were observed in the crystal (Figure 2). In **4a-(I)**, both the thia-bridges adopt a *pseudochair* conformation with C−S bond lengths and C−S−C bond angles very similar to those observed in reported medium-sized dithia[3.3]metacyclophanes.[6−8] In conformer **4a-(II)**, one of the sulfur atoms is triply disordered. This is a unique example of the bridge wobbling processes of a thia-bridge in the solid state.[16,17] The two benzene rings in **4a-(I)** and **4a-(II)** are not parallel to each other but tilt at angles of 16.1 and 13.6°, respectively. The X-ray single-crystal structure of **4b** (Figure 2) shows that

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[11] A dimeric product was also isolated. This will be published elsewhere.

[12] **General Synthetic Procedure for 4a−c.** A solution of sodium sulfide nonahydrate (480 mg, 2.0 mmol) and cesium carbonate (652 mg, 2.0 mmol) in 95% ethanol (300 mL) and a solution of tetrabromide **3** (1.0 mmol) in benzene (300 mL) in separate rotaflow dropping funnels were added dropwise simultaneously at the same rate to nitrogen purged 95% ethanol (1 L). After the addition, the mixture was stirred overnight and the bulk of the solvent was removed under reduced pressure. Water and dichloromethane were added to the residue, and the mixture was stirred until all solids were dissolved. The organic layer was separated, dried, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/hexane (1:4 and then 3:7) as the eluent.

[13] **4a** (10%): mp 222−224 °C; ^1H NMR ($CDCl_3$) δ 2.26 (s, 12 H), 2.47 (s, 6 H), 3.74 (t, 4 H), 3.79 (d, 4 H, J = 14.9 Hz), 3.80 (s, 4 H), 3.88 (t, 4 H), 4.22 (d, 4 H, J = 14.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.39, 18.73, 31.62, 69.89, 70.31, 71.13, 128.18, 131.28, 132.75, 152.91; MS (EI) (*m/z*) 502 (M^+, 92); IR (KBr) 2949, 2923, 2862, 1451, 1369, 1301, 1259, 1233, 1104, 1014, 1013, 925 cm^{-1}. Anal. Cacld for $C_{28}H_{38}O_4S_2$: C, 66.89; H, 7.62. Found: C, 67.07; H, 7.78.

[14] **4b** (30%): mp 221−223 °C; ^1H NMR ($CDCl_3$) δ 2.27 (s, 12 H), 2.46 (s, 6 H), 3.66−3.69 (m, 4 H), 3.76 (d, 4 H, J = 15.3 Hz), 3.77 (s, 8 H), 3.87−3.91 (m, 4 H), 4.27 (d, 4 H, J = 15.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.26, 18.74, 31.65, 69.94, 70.40, 71.30, 71.41, 128.33, 131.00, 132.73, 153.38; IR (KBr) 2937, 2906, 2868, 1563, 1453, 1375, 1356, 1303, 1258, 1234, 1134, 1097, 1055, 940, 840 cm^{-1}; MS (EI) (*m/z*) 546 (M^+, 24). Anal. Cacld for $C_{30}H_{42}O_5S_2$: C, 65.90; H, 7.74. Found: C, 66.03; H, 7.54.

[15] **4c** (31%): mp 184−186 °C.; ^1H NMR ($CDCl_3$) δ 2.25 (s, 12 H), 2.46 (s, 6 H), 3.65−3.68 (t, 4 H), 3.71−3.78 (m, 16 H), 3.85−3.88 (t, 4 H), 4.25 (d, 4 H, J = 15.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.19, 18.76, 31.62, 70.77, 70.89, 71.14, 71.41, 128.25, 131.12, 132.68, 153.17; IR (KBr) 2923, 2876, 1561, 1452, 1381, 1351, 1301, 1263, 1235, 1147, 1102, 1020, 990, 944 cm^{-1}; MS (EI) (*m/z*) 590 (M^+, 66). Anal. Cacld for $C_{32}H_{46}O_6S_2$: C, 65.05; H, 7.85. Found: C, 64.93; H, 8.02.

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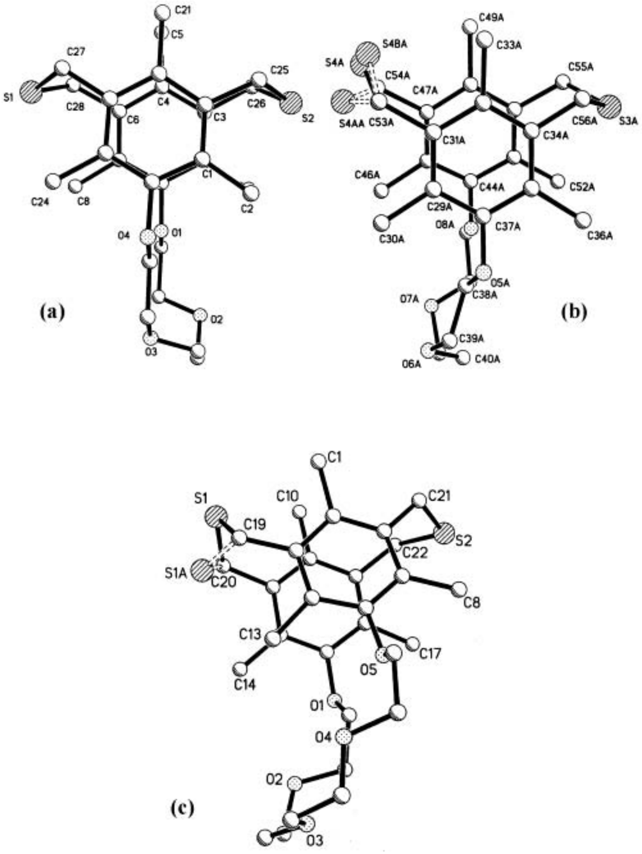

Figure 2. ORTEP drawing of crownophane (a) **4a-(I)**, (b) **4a-(II)**, and (c) **4b**.

one of the sulfur atoms is disordered. Similar to **4a**, the two benzene rings in **4b** are not parallel and form an angle of 12.9°. The tilting angles in both **4a** and **4b** are larger than that in *syn*-9,18-dimethyl-2,11-dithia[3.3]metacyclophane (11.5°).[17] This implies that the long polyether chain in **4** has a tendency to push the two aromatic rings apart, resulting in a larger tilting angle α. The crystal structures of both **4a** and **4b** indicate a conformational preference for the relaxation mode (Figure 1b). Assuming that this preference was also observed in solution, the breathing process in these [*n*.3.3]-(1,3,5)crownophanes would then involve the relaxation mode as the conformational minimum and the contraction mode as the transition state.

The association constants of crownophanes **4a**−**c** were measured using the solvent extraction method.[19] It was surprising to observe that **4a** does not bind to any alkali metal ion, although **4b** and **4c** can extract a series of alkali metal ions from a water solution. In comparison to the structurally rigid **1** with a crown cavity fitting Li^+ perfectly, the crown unit in **4a** is enlarged by an outward tilting of its C1 and C1′ carbons. The crown cavity **4a** is believed to be too large for Li^+ but too small for the other alkali metals. The breathing flexibility in **4a** may be restricted due to the relatively short polyether linkage. The logarithm of association constants (log K_{ass}) of **4b**, **4c**, 15-crown-5 (15-C-5), and 18-crown-6 (18-C-6) are summarized in Table 1. For crownophane **4c**, the order of association constants is $Cs^+ > Rb^+ > K^+ > Na^+$, corresponding to the decreasing order in ionic size of the metal ions. In contrast, **4b** has a maximum log K_{ass} for K^+, followed by Na^+, Rb^+, and Cs^+.

Table 1. Comparison of log K_{ass} of Crownophanes **4b**, **4c**, 15-Crown-5, and 18-Crown-6

crown	Na^+	K^+	Rb^+	Cs^+
4b	3.68	4.62	3.61	2.27
15-C-5[a]	4.52	4.40	4.29	3.74
4c	3.85	5.00	5.15	5.29
18-C-6[a]	3.89	6.20	5.96	5.17

[a] See ref 18.

As the crown unit in **4b** structurally resembles that of 15-crown-5, whereas **4c** could be considered as a derivative of 18-crown-6, a comparison of their ion selectivity is of special interest (Table 2). The average cavity diameter of **4b** is estimated from its crystal structure (Figure 2c) to be about 2.28 Å,[20] which is between the ionic diameters of K^+ (2.66 Å) and Na^+ (1.90 Å). On the basis of the size-match principle, **4b** is not expected to behave like 15-C-5, the strongest preference of which is for Na^+ (Table 1), and may not show a strong preference to either Na^+ or K^+. Our experimental observation was that **4b** shows the strongest affinity for K^+ (Table 1) with an ion selectivity ratio of 0.11 for Na^+/K^+, about 8 times more selective than its preference for Na^+ over K^+ for 15-crown-5 (Table 2). It is evident that **4b** adopts the most stable conformation in a relaxation mode (Figure 1b) via the breathing mechanism to provide a larger cavity size for a preference of K^+ to Na^+. In fact, in comparison to 15-C-5, **4b** generally shows higher ion selectivity (Table 2) for K^+/Rb^+, Rb^+/Cs^+, K^+/Cs^+, and $Na^+/$

Table 2. Comparison of Ion Selectivity of Crownophane **4b** and 15-Crown-5 and of Crownophane **4c** and 18-Crown-6

ion pairs	15-C-5[a]	**4b**	18-C-6[a]	**4c**
Na^+/K^+	1.32	0.11	4.9×10^{-3}	0.07
K^+/Rb^+	1.29	10.2	1.74	0.71
Rb^+/Cs^+	3.55	21.9	6.17	0.72
Na^+/Rb^+	1.70	1.17	8.51	0.05
K^+/Cs^+	4.57	224	10.7	0.51
Na^+/Cs^+	6.03	25.7	0.05	0.04

[a] See ref 18.

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(20) The cavity diameter was estimated by averaging the difference between the diagonal distance of two oxygen atoms and the van der Waals diameter of an oxygen atom (2.80 Å).

Cs^+, with the highest selectivity index of 224 for K^+/Cs^+. The length of the polyether chain in **4b** seems to restrict the degree of the breathing mechanism (angle α) resulting in its ion selectivity compared to the more conformationally flexible 15-crown-5.

18-Crown-6 shows a significant preference for K^+ to Rb^+ and Cs^+, but crownophane **4c** exhibits nonselective and similar binding preference to all three alkali metal ions (Table 2). We believe that the longer polyether chain in **4c** allows a more flexible breathing process (varying angle α), supported by the fact that **4c** has larger association constants than **4b** for all the alkali metal ions (Table 1), including the relatively smaller Na^+. On the other hand, **4c** exhibits the largest association constant for the large Cs^+, again indicating that the breathing process could result in a large relaxation mode (Figure 1b) to bind to Cs^+. Incidentally, this preferential ion selectivity for Cs^+ is in accordance with the observation that in the synthesis of **4c**, the product yield was significantly improved upon addition of cesium carbonate. In addition to the higher polarizability of the Cs^+, which makes it more effective in intramolecular cyclization reactions,[21] the template effect of the Cs^+ is believed to play a key role in the enhanced yield of **4c** under these conditions.

In conclusion we have demonstrated the potential in using the conformational mobility (breathing process) of the cyclophane component of a crownophane in functioning as a “tuning” factor to adjust its complexation behavior and ion selectivity. The crownophane **4b** illustrates an increase in ion selectivity over the more conformationally mobile 15-crown-6, while the behavior of **4c** indicates that a more flexible breathing process will result in nonselective but effective binding to a series of metal ions. In view of the extensive literature in both cyclophane and crown chemistry, the function of conformational characteristics in a cyclophane in controlling the cavity size of a crown unit would provide a comprehensive area in modulating the complexation properties of crownophanes.

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Supporting Information Available: Crystallographic data (CIF format) of **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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