A Facile Entry to Macrocyclic Disulfides: An Efficient Synthesis of Redox-Switched Crown Ethers

A. R. Ramesha and Srinivasan Chandrasekaran*,†

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, India

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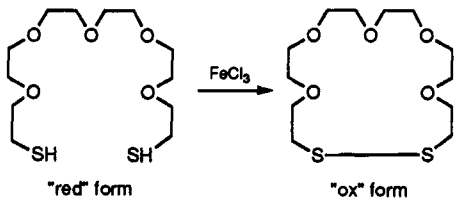
An interesting sulfur transfer reaction with benzyltriethylammonium tetrathiomolybdate has been used efficiently for the synthesis of macrocyclic disulfides. This methodology has been extended to a high-yield synthesis of "redox-switched" crown ethers which have potential application for selective ion transport across liquid membranes.

In the past three decades a large number of synthetic macrocyclic compounds capable of binding cations or anions have been prepared and investigated. Many of these synthetic macrocyclic polyethers,[1] polyamines,[2] polythioethers,[3] and related molecules[4] have been shown to possess interesting and unusual ion binding properties. In recent years, the synthesis and study of a new class of compounds containing a metal–disulfide bond have been pursued due to their probable relevance to certain redox processes in biological systems. For example, it has been postulated that the oxidized form of two-electron copper oxidase (ceruloplasmin) contains in the two copper sites the RSSR[Cu(I)]$_2$ unit.[5]

The term "reversible switching" is used to describe a situation where metal complexation is induced or changed by altering the property of the substrate. This behavior is important in developing models of biochemical reactions where reversible switching occurs. There are a number of ways by which this can be introduced in chemical systems particularly in crown ethers: (a) electrochemical responsive,[6] (b) photochemical responsive,[7] (c) pH responsive,[8] and (d) redox responsive macrocycles.[9a,b]

In each of the above type of macrocycle the metal ion complexation can be switched "on" or "off" by an external source. The most direct change in the cavity shape would be obtained by reversible bond formation and bond scission leading to acyclic–cyclic interconversion. The redox reaction of thiol–disulfide couple in crown ethers has thus attracted a lot of attention in recent years.[9a,b]

Shinkai was the first to report the synthesis of such crown ethers containing a disulfide linkage and he has shown that the "oxidized" form transports Cs^+ ion 6.2 times faster than the reduced form.[9a] Raban reported that the addition of external oxidant like ferric chloride to the reduced form enhances the rate of metal ion transport[9b] (eq 1).



(1)

Results and Discussion

Most of the redox-switched crown ethers are prepared from the corresponding dithiols by conventional oxidation with iodine, ferric chloride, or flavin under high-dilution conditions.[9a,b,10] The major problem associated with this strategy is that in general it leads to the formation of dimers, trimers, and polymers to an appreciable amount thereby reducing the yield of the desired product considerably.[9a] In this paper we describe our results on the facile sulfur transfer reaction mediated by benzyltriethylammonium tetrathiomolybdate (1) for the synthesis of a variety of macrocyclic disulfides and redox-switched crown ethers in high yield without the use of high-dilution techniques.

Earlier we had reported that benzyltriethylammonium tetrathiomolybdate, $(C_6H_5CH_2NEt_3)_2MoS_4$, **1**, is a stable and convenient sulfur transfer reagent which reacts readily with alkyl halides and tosylates to produce the corresponding disulfides in good yield.[11a] The fact that our

† Dedicated to Professor C.N.R. Rao on the occasion of his 60th birthday.

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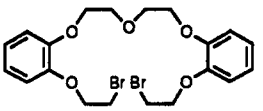
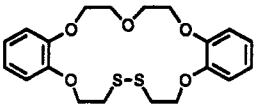
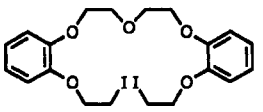
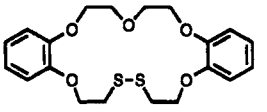
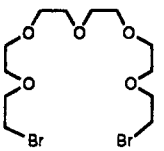
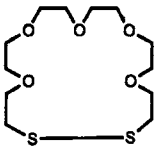
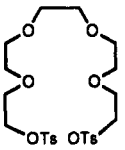
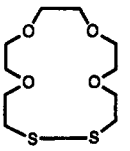
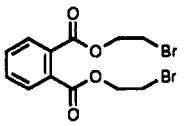
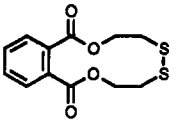
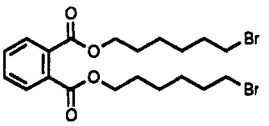
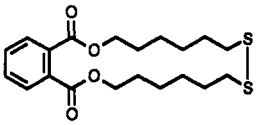
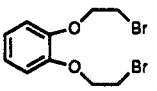
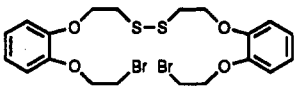
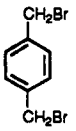
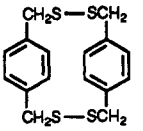
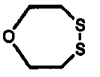
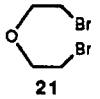
Table 1. Reaction of 1 with Dihalides at Room Temperature (25 °C)

entry	substrate	time (h)	product	yield (%)
1	 **2**	8	 **3**	74
2	 **4**	4	 **3**	69
3	 **5**	2	 **6**	77
4	 **7**	16	 **8**	86
5	 **7**	7	 **10**	68
6	 **11**	7	 **12**	67
7	 **13**	7	 **14**	45
8	 **15**	0.5	 **16**	52
9	$BrCH_2CH_2Br$ **17**	1	 **18**	58
10	 **19**	8	 **20**	54
11	 **21**	4	 **20**	69

reaction does not go via the intermediacy of thiols offers a great advantage in synthesizing cyclic disulfides of different ring size without the formation of competing side products. This methodology has been extended to the synthesis of a variety of dithia-crown ethers and medium to large ring (7–20-membered rings) systems having the disulfide linkage (Table 1).

Treatment of dibromo ether **2** or diiodo ether **4** with 2 equiv of **1** either in chloroform or acetonitrile as the solvent at room temperature (25 °C) yielded the dibenzo 18-crown-6 analogue (Cr) with a disulfide bond (Cr_{ox}) **3** in

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very good yield. Interestingly, these reactions were carried out by rapid addition of dihalide to the reagent in solution. When the same reaction was performed by slow addition of the substrate under high dilution, both intra- and intermolecular products were obtained. This is a rather surprising observation and the reasons for this unusual behavior are not clear.

Under similar conditions dibromide **5** and the ditosylate **7** afforded the 18-crown-6 analogue **6** (77%) and 15-crown-5 analogue **8** (86%), respectively. It is of interest to note that the dibromo ester **11** on treatment with **1** yields the 20-membered macrocyclic disulfide **12** as the only product in 67% yield. However, attempts to form a 20-membered ring with two disulfide linkages by intermolecular followed by intramolecular reaction of **13** was not successful even with excess of the reagent. Since the formation of 10-membered cyclic disulfide is not favorable,[11b] the reaction stops after the initial intermolecular reaction to produce the dibromo disulfide **14** in 45% yield. p-Xylene dibromide (**15**) and 1,2-dibromoethane (**17**) on the other hand react with **1** readily to give cyclic disulfides **16** and **18**, respectively. Digol dichloride (**19**) or digol dibromide (**21**) under similar conditions gave only the seven-membered cyclic disulfide **20**.

Thus, this methodology involving benzyltriethylammonium tetrathiomolybdate as a sulfur transfer reagent provides a simple, versatile, and general route to the synthesis of a wide variety of macrocyclic disulfides and redox-switched crown ethers of different sizes.

Experimental Section

General Remarks. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. TLC were performed on 0.25-mm E. Merck precoated silica plates (60F-254). All the products were purified by flash chromatography on silica gel. The melting points and boiling points reported are uncorrected. Benzyltriethylammonium tetrathiomolybdate was prepared as described earlier.[11a] Acetonitrile and chloroform were distilled over phosphorus pentoxide and stored over 4-Å molecular sieves.

Synthesis of Dibromide 2. 1,5-Bis(2-hydroxyphenoxy)-3-oxapentane[12] (2.89 g, 10 mmol) was added to a slurry of 1,2-dibromoethane (30 mL), DMF (30 mL), and K_2CO_3 (4.5 g) over a period of 8 h at 80 °C in small portions, and the mixture was stirred at 80–100 °C overnight. Excess dibromoethane and DMF were removed under reduced pressure. Extraction of the viscous material with CH_2Cl_2 (2 × 50 mL) afforded a brown solid. Flash column chromatography on silica gel (ethyl acetate:petroleum ether (60–80 °C), 1:4) afforded the dibromide **2** as a white solid (1.30 g, 20%): mp 87–88 °C; IR (Nujol) 1593, 1509, 1260, 1221, 1125, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.96 (s, 8H), 4.08–4.40 (m, 8H), 3.84–4.08 (m, 4H), 3.60 (t, 4H, J = 5 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 149.5, 148.3, 122.7, 121.7, 116.4, 115.2, 69.8, 69.2, 29.6; MS (m/z) 504 (M^+, 26), 267 (44), 199 (23), 163 (56), 149 (100), 136 (85), 109 (71); HRMS calcd for $C_{20}H_{24}O_5Br_2$ 504.0160, found 503.9972.

Representative Procedure for the Synthesis of Dithia Crown Ether Analogues. Synthesis of Dibenzo Dithia-18-Crown Ether 3. Dibromide **2** (1.008 g, 2 mmol) and benzyltriethylammonium tetrathiomolybdate (**1**, 2.492 g, 4.1 mmol) were dissolved in dry CH_3CN (or $CHCl_3$, 10 mL) and stirred at 25 °C for 8 h. Most of the acetonitrile was removed under reduced pressure. The black residue was extracted with ether (2 × 15 mL). The black mass was slurried with CH_2Cl_2 (2 mL) extracted with ether (10 mL) and filtered through Celite. Repeated extraction (5 × 20 mL) afforded 98% of the crude material. Flash chromatography of the residue (CH_2Cl_2:petroleum ether (60–80 °C), 1:1) afforded the dithia crown ether **3** as white crystals (0.603 g, 74%): mp 127–28 °C; IR (Nujol) 1593, 1503, 1455, 1254, 1221, 1121, 1050, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.88 (s, 8H), 3.80–4.36 (m, 12H), 3.22 (t, 4H, J = 5 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 149.2, 148.1, 122.0, 121.3, 115.6, 114.0, 70.0, 68.9, 68.0, 39.3; MS (m/z) 408 (M^+, 100), 349 (46), 136 (73), 87 (43); HRMS calcd for $C_{20}H_{24}O_5S_2$ 408.1072, found, 408.1065.

Synthesis of Diiodide 4. A mixture of dibromide **2** (0.504 g, 1 mmol), NaI (0.5 g, 3.33 mmol) and dry acetone (20 mL) were stirred at 25 °C overnight (18 h). Acetone was removed on a rotary evaporator and the solid mass was dissolved in water and extracted with ether (2 × 25 mL). Flash chromatography of the residue (ethyl acetate:petroleum ether (60–80 °C), 1:4) afforded the diiodo compound **4** as a white solid (0.502 g, 84%): mp 65–66 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.92 (s, 8H), 4.08–4.36 (m, 8H), 3.90–4.08 (m, 4H), 3.40 (t, 4H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.3, 148.0, 122.5, 121.7, 116.3, 115.1, 70.5, 69.9, 69.1, 1.76; MS (m/z) 598 (M^+, 64), 335 (44), 155 (100), 121 (98), 80 (38).

Synthesis of Dibromo Diester 9. Phthalic anhydride (1.52 g, 10.27 mmol), 2-bromoethanol (3.52 g, 28.3 mmol), p-toluenesulfonic acid hydrate (0.210 g), and toluene (50 mL) were refluxed in a Dean–Stark apparatus for 14 h. The light brown colored solution was poured into crushed ice and extracted with ether (3 × 25 mL). After washing with saturated $NaHCO_3$ solution and drying over anhydrous Na_2SO_4, the residue was purified by flash chromatography on silica gel (ethyl acetate:petroleum ether (60–80 °C), 1:20) and afforded the dibromo compound **9** as a pale yellow viscous oil (1.1 g, 26%): IR (neat) 1728, 1602, 1584, 1449, 1380, 1290, 1119, 1077, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.48–7.84 (m, 4H), 3.64 (t, 4H, J = 6.4 Hz), 4.64 (t, 4H, J = 5.14 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 167.5, 132.0, 129.1, 64.5, 29.0; MS (m/z) 381 (M^+ + 1, 2), 299 (10), 255 (30), 175 (44), 149 (77), 107 (100).

Synthesis of Cyclic Disulfide 10. To a solution of dibromo diester **9** (0.38 g, 1 mmol) in CH_3CN (10 mL), was added tetrathiomolybdate **1** (1.276 g, 2.1 mmol) in one portion. After stirring for 6 h (25 °C) the reaction was worked up as described above and the product was purified by flash column chromatography on silica gel (ethyl acetate:petroleum ether, (60–80 °C), 1:40) to afford the cyclic disulfide **10** as a colorless oil (0.193 g, 68%): IR (neat) 2932, 1728, 1272, 1125, 1074, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.50–7.90 (m, 4H), 4.65 (t, 4H, J = 5.1 Hz), 3.10 (t, 4H, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 167.3, 132.8, 129.9, 66.5, 36.5; MS (m/z) 284 (M^+, 22), 193 (100%), 149 (80), 118 (20), 84 (56), 76 (22), 60 (47); HRMS calcd for $C_{12}H_{12}O_4S_2$ 284.0177, found 284.0171.

Synthesis of Dibromo Diester 11. Phthalic anhydride (1.48 g, 10 mmol), 6-bromo-1-hexanol (4.52 g, 25 mmol), p-toluenesulfonic acid (0.200 g), and toluene (50 mL) were refluxed in a Dean–Stark apparatus for 14 h. The colored solution was poured into crushed ice and extracted with ether (3 × 25 mL). The ether layer was washed with $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (ethyl acetate: petroleum ether (60–80 °C), 5:95) to afford the dibromo compound **11** as a viscous liquid (2.95 g, 60%): IR (neat) 2920, 1773, 1725, 1122, 1269, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.40–7.80 (m, 4H), 4.30 (t, 4H, J = 6 Hz), 3.40 (t, 4H, J = 6 Hz), 1.40–2.00 (m, 16H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 167.3, 132.0, 130.8, 128.6, 65.3, 33.6, 32.5, 28.2, 27.5, 25.0; MS (m/z) 492 (M^+, 27), 331 (7), 311 (100), 165 (100), 83 (100), 55 (81); HRMS calcd for $C_{20}H_{28}O_4Br_2$ 492.0336, found 492.1352.

Synthesis of Cyclic Disulfide 12. Dibromo diester **11** (0.492 g, 1 mmol) was added to a solution of **1** (1.27 g, 2.1 mmol) in CH_3CN (10 mL), and the mixture was stirred for 7 h. CH_3CN was removed under vacuum and after the usual workup the crude product was purified by flash chromatography on silica gel (ethyl acetate:petroleum ether (60–80 °C), 1:6) to afford cyclic disulfide **12** as a viscous liquid (0.265 g, 67%): IR (neat) 2900, 1710, 1260, 1160, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.40–7.90 (m, 4H), 4.22 (t, 4H, J = 4 Hz), 2.40–2.90 (dt, 4H, J = 6 Hz), 1.10–2.00 (m, 12H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 167.1, 131.9, 130.6, 128.5, 65.3, 38.9, 33.5, 31.6, 29.2, 28.9, 28.7, 28.1, 27.7, 25.6, 25.1, 24.0, 22.4, 13.8; MS (m/z) 396 (M^+, 14), 149 (100), 115 (43), 83 (28), 55 (45), 41 (25); HRMS calcd for $C_{20}H_{28}O_4S_2$ 396.1429, found 396.1438.

Synthesis of Dibromo Disulfide 14. Dibromide **13** (0.324 g, 1 mmol) was added to a solution of **1** (1.52 g, 2.5 mmol) in CH_3CN (15 mL). The reaction mixture was stirred for 8 h and worked up as described above. Flash column chromatography of the residue on silica gel (ethyl acetate:petroleum ether (60–80 °C), 5:97) afforded dibromo disulfide **14** (0.116 g, 42%) as an oil: IR (neat) 2900, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.92 (8H, s), 4.08–4.40 (m, 8H), 3.80 (t, 4H, J = 6.4 Hz), 3.08 (t, 4H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 148.8, 148.3, 122.6, 121.9, 116.1, 115.3, 69.8, 67.6, 42.1, 37.9.

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Supplementary Material Available: Listing of spectral data for compounds **6**, **8**, **16**, **18**, and **20**, as well as copies of the ^1H and ^{13}C NMR spectra of compounds **2–4**, **9–12**, and **14** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.