

Synthesis and Liquid Membrane Transport Properties of Photolabile Molecular Clips Based on Dithiane-spiro-crown Ethers

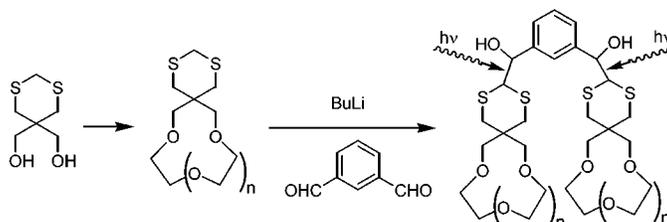
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ABSTRACT



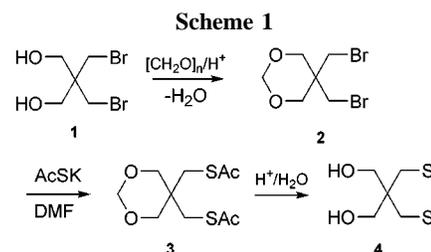
Synthesis of novel dithiane-spiro-crown ethers starting from 5,5-di(hydroxymethyl)-1,3-dithiane is developed. These compounds can be used as building blocks to assemble photolabile bis-crown ethers via addition to dicarbonyl-containing tethers, e.g., isophthalic aldehyde. It is found that unlike their mono-crown precursors such bidentate bis-crowns are capable of efficient liquid membrane transport of, for example, methyl viologen. The transport can be interrupted photochemically, providing a basis for developing smart light-responsive membranes.

Tethered bis-crown ethers have found extensive use in various membrane applications due to their unique ionophoric properties.¹ We suggest that linking two crown moieties with a *photolabile* tether carries the additional benefit of controlling their complexation ability. In this Letter we report on our progress toward development of carriers for smart membranes: synthesis of novel dithiane-spiro-crown ethers **5–7** and their reaction with isophthalic aldehyde to produce tweezers-shaped bis-crown ethers **8–10** capable of photo-induced fragmentation.²

The key starting material, 5,5-di(hydroxymethyl)-1,3-dithiane **4**, was synthesized from commercially available 2,2-bis(bromomethyl)-1,3-propanediol (**1**), which was first pro-

duced via cyclic acetal formation with formaldehyde and then reacted with potassium thioacetate, affording 1,3-dioxane **3**. The critical feature of this synthetic sequence was that during the next, acid-catalyzed step (**3** → **4**) no extra formaldehyde was added and therefore the deprotection of the diol and formation of the dithiane ring occurred via methylenic transfer from oxygen to sulfur atoms (59% yield, Scheme 1).

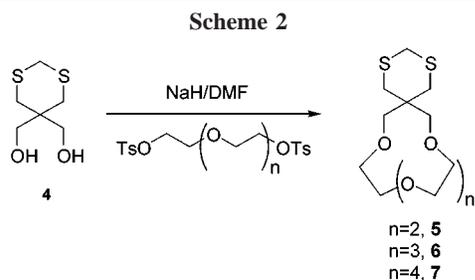
Recognizing the fact that diol **4** allows for direct coupling of dithiane and crown ether moieties through a spiro



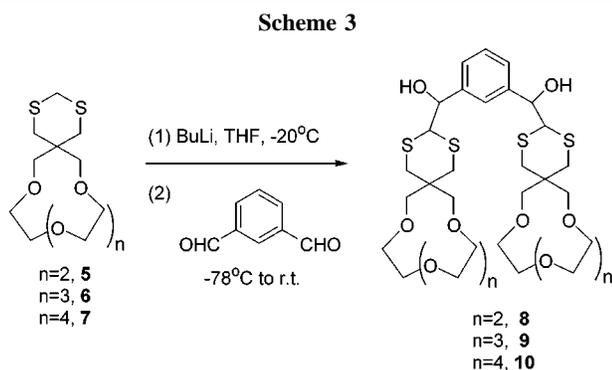
(1) For selected examples of bis-crown-based ionophores, see: Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593.

(2) Photoinduced cleavage in hydroxy- or amino-alkyl dithianes: (a) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924. (b) Wan, Y.; Mitkin, O.; Barnhurst, L.; Kurchan, A.; Kutateladze, A. *Org. Lett.* **2000**, *2*, 3817. (c) Vath, P.; Falvey, D. E.; Barnhurst, L. A.; Kutateladze, A. G. *J. Org. Chem.* **2001**, *66*, 2886. (d) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 1841.

connection, we synthesized dithiane-bearing crowns **5–7** via the alkylation of **4** with (poly)ethylene glycol ditosylates in DMF in the presence of sodium hydride (Scheme 2).³

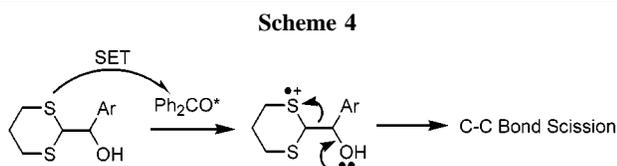


Crown ethers **5–7** were purified by column chromatography and then utilized as building blocks to assemble bis-crown ethers **8–10** (Scheme 3). First, the corresponding



dithiane anions were generated with butyllithium at -20°C in THF. The lithiodithianes were then quenched with isophthalic aldehyde at -78°C to furnish bis-crowns **8–10** (60–80%).⁴

As expected from our earlier studies on photoinduced C–C bond cleavage in α -hydroxyalkyldithianes, bis-crowns **8–10** undergo efficient photofragmentation in the presence of an external ET-sensitizer, benzophenone. The general mechanism for cleavage, exemplified by the photoinduced C–C bond scission in a parent compound, the dithiane–benzaldehyde adduct, is shown in Scheme 4. After initial excitation,



triplet benzophenone is quenched via single electron transfer from the dithiane moiety, followed by the mesolytic C–C

bond cleavage in the generated cation-radical. The benzophenone anion-radical generally accelerates the second step by deprotonating the hydroxy group.⁵

To evaluate the liquid membrane transport properties and the possibility of photochemically shutting off the transport, we chose methyl viologen as a guest molecule. In addition to structural considerations, our choice of guest was influenced by our finding that methyl viologen itself can sensitize C–C bond cleavage in dithiane–carbonyl adducts. We found that bis-crown **10** (based on 19-crown-6) transported methyl viologen with greater efficiency than either the 16-crown-5 host **9** or 13-crown-4 host **8**. Figure 1 shows this efficient

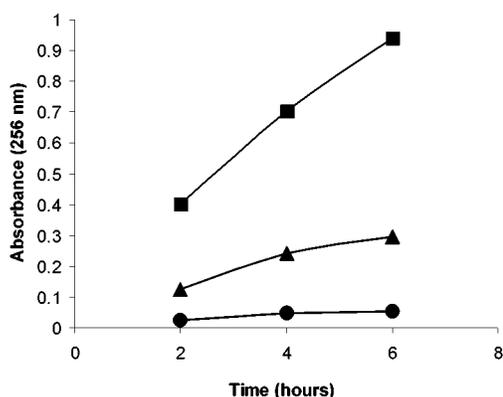


Figure 1. Methyl viologen transport through the liquid (chloroform) membrane assisted by **10** (■). The efficiency of transport by irradiated **10** is significantly reduced (▲). Poor mono-crown carrier **7** is shown for comparison (●).

transport from the donor aqueous phase to the receiving aqueous phase through the chloroform solution of bis-crown

(3) **Typical procedure: 8,11,14,17-Tetraoxa-2,4-dithiaspiro[5.12]octadecane (5).** A solution of 5,5-di(hydroxymethyl)-1,3-dithiane **4** (0.40 g, 2.2 mmol) in 40 mL of DMF was stirred under a nitrogen atmosphere. This solution was treated with hexane-washed NaH (0.21 g, 8.8 mmol). After 15 min of stirring, tri(ethylene glycol) di-*p*-tosylate (0.96 g, 2.1 mmol) was added and allowed to stir at room temperature overnight. The resulting mixture was carefully treated with NH_4Cl and then extracted into ether. The ethereal layer was washed 4× with NH_4Cl and 2× with water to remove all DMF, dried, and concentrated. Flash column chromatography (1:1 ethyl acetate:hexanes) gave 0.54 g of a light yellow oil (88%): $^1\text{H NMR}$ (CDCl_3 , 400 Hz) 3.64–3.72 (m, 18H), 2.72 (s, 4H); MS (EI) m/z (relative intensity) 294 (M^+ , 30), 144 (60), 98 (100), 85 (60).

(4) Compounds **8–10** were purified by column chromatography without separating individual diastereomers. **Typical procedure:** {3-[Hydroxy-(8,11,14,17-tetraoxa-2,4-dithiaspiro[5.12]octadec-3-yl)methyl]phenyl)-(8,11,14,17-tetraoxa-2,4-dithiaspiro[5.12]octadec-3-yl)methanol (**8**). A solution of **5** (0.130 g, 0.44 mmol) in 10 mL of freshly distilled THF was cooled to -20°C , and 1.6 M *n*-butyllithium (0.41 mL, 0.66 mmol) was added while stirring under a N_2 atmosphere. The reaction mixture was stirred at this temperature for 2 h, after which the reaction was further cooled to -78°C , and isophthalaldehyde (0.030 g, 0.22 mmol) in 2 mL of THF was added via syringe. The resulting mixture was allowed to slowly warm to room temperature over a period of 2 h and then stirred overnight. The resulting yellow solution was washed 2× with 10 mL of saturated NH_4Cl , extracted into ether, dried, and concentrated. Flash column chromatography (1:50 MeOH: CHCl_3) gave 0.150 g of a clear oil (94%): $^1\text{H NMR}$ ($\text{CD}_3\text{-CN}$, 400 Hz) 7.41 (b, 1H), 7.30 (d, $J = 1.2$ Hz, 3H), 4.82 (m, 2H), 4.16 (dd, $J_1 = 1.6$ Hz, $J_2 = 6.8$ Hz, 2H), 3.53–3.62 (m, 32H), 3.44 (s, 2H), 2.70–2.78 (m, 4H), 2.52–2.58 (m, 4H).

(5) For further mechanistic details of the photocleavage, see refs 2a,c.

10.⁶ In contrast, the chloroform solution of the corresponding mono-crown **7**, twice as concentrated for fair comparison, does not transport methyl viologen appreciably. Irradiation of the chloroform solution containing the host–guest complex (**10**•methyl viologen) led to a significant decrease in transport efficiency as evidenced by the leveling off optical density of the receiving aqueous phase.⁷

Similar photochemically induced disruption of liquid membrane transport was observed with benzophenone as an external sensitizer. It should be noted that the addition of benzophenone had a negligible effect on the transport rate by **10**, while the transport rate by the less efficient bis-crown carriers **8** and **9** was improved in the presence of benzophenone. Clearly, in the latter case, benzophenone additionally stabilizes the weaker complex of methyl viologen with **8** or **9**, thus serving the dual function of a co-complexing sensitizer. As expected, the rate of viologen transport by the corresponding mono-crown ethers **5**, **6**, and **7** was insignificant and the addition of benzophenone caused only a minor enhancement.

Figure 2 shows a PM3-optimized geometry of the complex between methyl viologen and **10**. It helps visualize a nice

(6) The photochemically interrupted transport experiments were carried out in a Pyrex U-tube (300 nm cutoff), while slowly stirring the central chloroform solution with a magnetic stirrer. Irradiations were performed with a medium-pressure mercury lamp. The temperature was maintained by immersing the tube into a regulated water bath. Initial concentration of viologen in the donor solution was 1 mM. Carrier concentration: 5.1 mM for **10** or 10.4 mM for **7**. Donor solution volume: 4 mL. Receiving solution volume: 4 mL. Carrier solution volume: 12 mL. Interface area: 1.77 cm². pH of 8 in both the donor and the receiving solutions was maintained by 10 mM K₂HPO₄. The progress was monitored by the increase in UV absorption of the receiving solution at $\lambda = 256$ nm.

(7) Judging by NMR, the photofragmentation was driven to >90% conversion. At this point we can only speculate on the nature of the residual transferability by irradiated **10**. One possibility is that overoxidation of the dithiane moiety in the released mono-crown ether **7** produces a small amount of a better complexing byproduct.

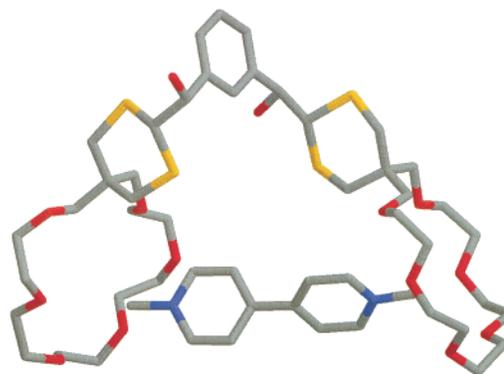


Figure 2. PM3 geometry of **10**•methyl viologen (hydrogen atoms are not shown for clarity).

fit accounting for the efficient transport by the bis-crown carrier. Obviously, analogous *trimolecular*-sandwiched complexes with two mono-crown ethers are less favorable due to entropic factors.

To summarize, we have developed a simple modular approach to photolabile bis-crown ethers allowing us to photochemically interrupt transport through liquid membranes.

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Supporting Information Available: Experimental details. This material is available via the Internet at <http://pubs.acs.org>

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