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

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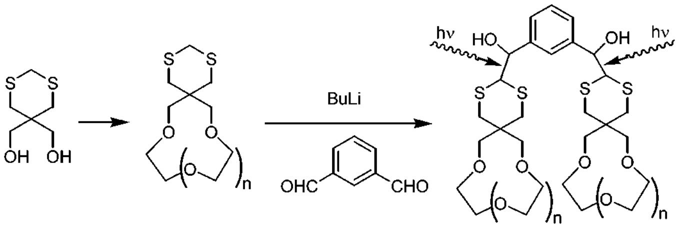
ABSTRACT



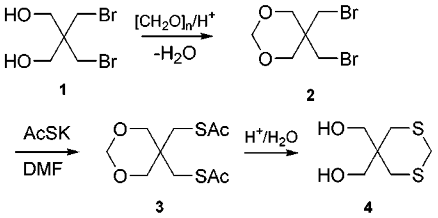
Synthesis of novel dithiane-spiro-crown ethers starting from 5,5-di(hydroxymethyl)-1,3-dithiane is developed. These compounds can be used as building blocks to assemble photolabile bis-crown ethers via addition to dicarbonyl-containing tethers, e.g., isophthalic aldehyde. It is found that unlike their 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 photoinduced 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 protected 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

Scheme 1



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[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.

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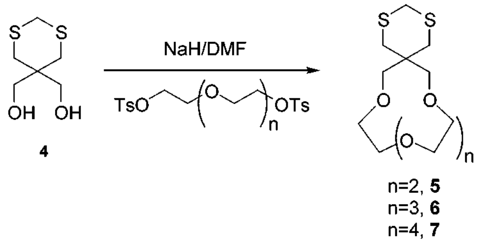
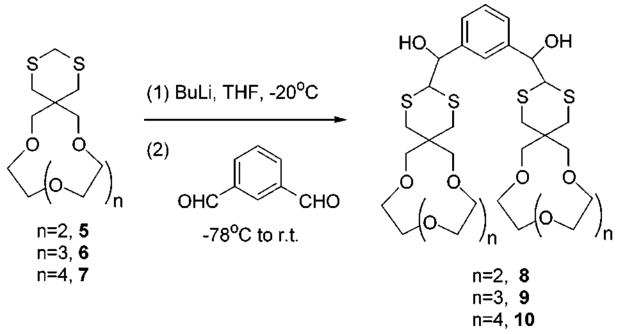
connection, we synthesized dithiane-bearing crowns **5**−**7** via the alkylation of **4** with (poly)ethylene glycol ditosylates in DMF in the presence of sodium hydride (Scheme 2).[3]

Scheme 2



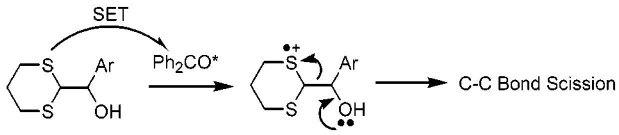
Crown ethers **5**−**7** were purified by column chromatography and then utilized as building blocks to assemble bis-crown ethers **8**−**10** (Scheme 3). First, the corresponding dithiane anions were generated with butyllithium at −20 °C in THF. The lithiodithianes were then quenched with isophthalic aldehyde at −78 °C to furnish bis-crowns **8**−**10** (60−80%).[4]

Scheme 3



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]

Scheme 4



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

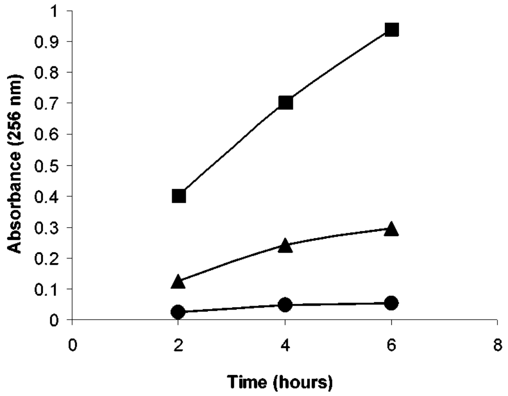


Figure 1. Methyl viologen transport through the liquid (chloroform) membrane assisted by **10** (■). The efficiency of transport by irradiated **10** is significantly reduced (▲). Poor mono-crown carrier **7** is shown for comparison (●).

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(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$_4$Cl and then extracted into ether. The ethereal layer was washed 4× with NH$_4$Cl 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}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$_4$Cl, extracted into ether, dried, and concentrated. Flash column chromatography (1:50 MeOH:CHCl$_3$) gave 0.150 g of a clear oil (94%): ^{1}H NMR (CD$_3$-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 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.

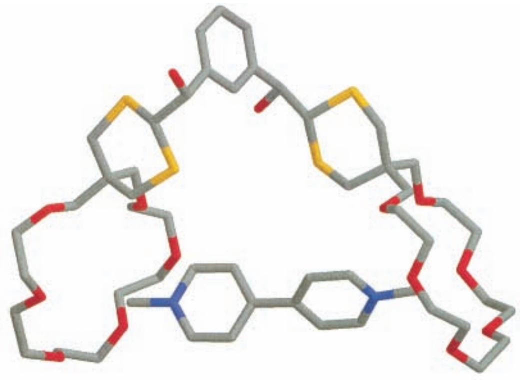

Figure 2. PM3 geometry of **10**·methyl viologen (hydrogen atoms are not shown for clarity).

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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(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 cm^2. pH of 8 in both the donor and the receiving solutions was maintained by 10 mM K_2HPO_4. 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.