

Synthesis of New *cis*- and *trans*-Bis(crown ether)s and Their Binding Properties with Alkali Metal Cations

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Received August 19, 1997

Noncovalent binding of alkali metal cations to crown ethers is one of the most classical examples in host-guest chemistry.¹ The stability and selectivity upon complexation generally depends on the complementary sizes of metal cations and crown ether cavities. The size correlation is not, however, well fitted to the relatively large crown rings due to the conformational flexibilities. A large number of bis(crown ether)s have been reported² and their binding affinities were dramatically increased toward alkali metal cations larger than the cavity sizes of the monocrown ethers. We previously reported symmetric and asymmetric bis(crown ether)s in which two crown ethers are covalently held together by highly rigid Kemp's Triacid.³ We describe here the syntheses and cation-binding properties of two geometrical isomers of bis(benzocrown ether)s **6** and **7** derived from a new structurally well-defined molecule, 1,2,3,4,5,6,7,8-octahydro-1,8-dipropyl-1,8-dicarboxylic acid (**5**).

The synthetic procedure of 1,8-dicarboxylic acid **5** is similar to that of analogous 1,5-dicarboxylic acid.⁴ Esterification (SOCl₂/methanol) followed by allylation (LDA/allyl bromide, -5 °C to rt) of the diacid **2**, which was synthesized from 1,8-dichloroanthraquinone (**1**) by a literature procedure,⁵ gave the desired product **3** as an isomeric mixture. The two isomers **3a-b** were separated by flash column chromatography (R_f in silica gel, hexanes/EtOAc=10:1 (v/v); less polar isomer 0.3 (16% yield), more polar isomer 0.2 (43% yield)). Hydrogenation (5% Pd/C, 50 psi H₂) followed by hydrolysis (KOH/10% aqueous EtOH) of each isomer provided the corresponding 1,8-dicarboxylic acids **5a** and **5b** in a 90% yield. Single crystals of the isomer **5a** from more polar isomer **3a** suitable for investigation by X-ray analysis was obtained in methanol and its geometrical structure was determined unambiguously. As shown below, two carboxylic acids in **5a** are lying in parallel with a *cis* relationship. Each diacid **5a** or **5b** was coupled with 3'-

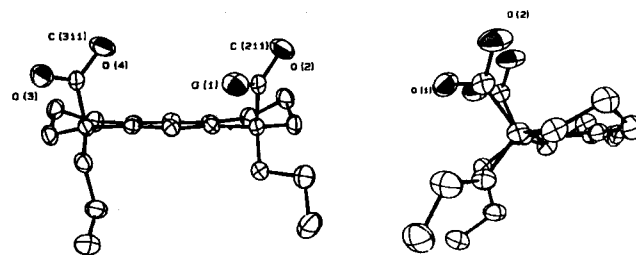
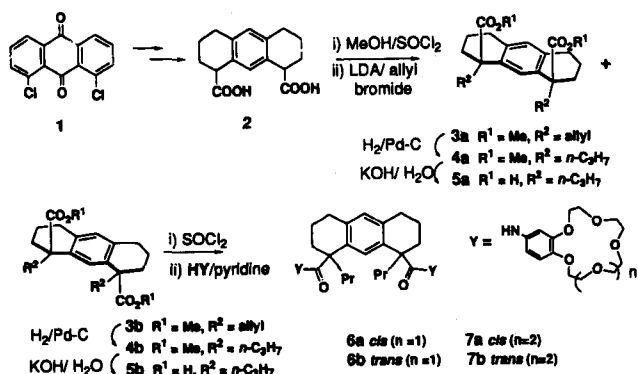


Figure 1. Two side views of the crystal structure of the *cis* diacid **5a**. Hydrogen atoms have been omitted for clarity.

(aminobenzo)crown ethers to give the corresponding bis(benzocrown ether)s **6a-b** and **7a-b** in 30-64% yield.⁶

Since the hosts **6a-b** and **7a-b** are highly lipophilic molecules, their binding abilities were conveniently determined by two phase picrate extractions (CHCl₃, 0.5 mL, 10 mM of host)/(water, 0.5 mL, 10 mM of metal picrates).⁷ The % extractions were determined by measuring changes in absorbances of picrates at 374 nm in aqueous phase. All experiments were triplicated at 24±0.5 °C and the average values (±1.5%) are summarized in Table 1 except for Li⁺ ion due to very low extractions (≤3%) by all hosts.

A number of trends in % extractions are worthy of mention. First, the % extraction order of the *cis*-bis(benzo-15-crown-5) **6a** are K⁺>Rb⁺>Cs⁺>Na⁺ and that of the *cis*-bis(benzo-18-crown-6) **7a** are Cs⁺>K⁺, Rb⁺>Na, while *trans* isomers **6b** and **7b** show the same orders of the corresponding monocrown ethers. Secondly, both *cis* isomers **6a** and **7a** extract alkali metal picrates much more efficiently than do the corresponding *trans* isomers **6b** and **7b**. The largest enhancements of % extractions by the *cis* isomers are observed when alkali metal sizes are a little larger than the crown ether cavities. For example, *cis*-bis(benzo-15-crown-5) **6a** extracts K⁺ and Rb⁺ most efficiently, while *cis*-bis(benzo-18-crown-6) **7a** extracts Cs⁺. Assuming 1:1 complexation, the stability constants⁷ of the *cis* isomers with these cations (K⁺, Rb⁺ for **6a**, and Cs⁺ for **7a**) are ~ three orders of magnitude higher than those of the corresponding *trans* isomers in the extraction conditions. Fi-

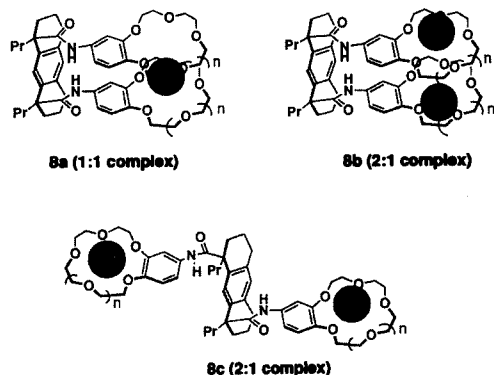


Scheme 1.

Table 1. Extraction Percentages of Alkali Metal Cations by Bis(benzocrown ethers) **6a-b** and **7a-b**

Host	Na ⁺	K ⁺	Rb ⁺	Cs ⁺
bis(15-C-5) <i>cis</i> 6a	29	87	81	52
<i>trans</i> 6b	17	21	7.0	3.5
bis(18-C-6) <i>cis</i> 7a	21	80	77	84
<i>trans</i> 7b	8.3	74	58	39

nally, though enhancements are modest, it is apparent that the *cis* isomers extract higher than do the corresponding *trans* isomers when the metal size are smaller than, or similar to the cavity size.



The *cis* and *trans* isomers have the identical molecular components but their geometries are different from each other. The *cis* isomers **6a** and **7a** can form two types of complexes **8a** and **8b**. If two crown units individually bind metal cations like in **8b**, the extractabilities of the *cis* isomers might be smaller than those of the corresponding *trans* isomers **8c** because electrostatic repulsions between two binding cations might be greater in *cis* than in *trans* isomers. On the other hand, like in **8a**, cooperative binding of two adjacent crown units *via* intramolecular sandwich-type complex will greatly increase extractabilities of the *cis* isomers. All observations in extraction experiments indicate that intramolecular sandwich-type 1:1 complex **8a** could be formed in the *cis* isomers regardless metal cation sizes. When the ratio of the cation size and cavity size is >1 , extraction by the *cis* isomers **6a** and **7a** occurs completely, at least predominantly, *via* the stable 1:1 complex **8a**. When the ratio of the cation size and cavity size is ≤ 1 , both complexes **8a** and **8b** may exist as an equilibrium mixture in solution, but the relative populations presumably depend on the concentrations.

Finally, ^1H NMR studies also support that the *cis* isomers could form sandwich-type 1:1 complex **8a** with any alkali metal cations. The signals for aryl protons of the *cis* isomers **6a** and **7a** were significantly changed in chemical shifts (up to 0.5 ppm) and relative positions and broadened upon in presence (1 equiv) of any metal picrate in CDCl_3 , while those of the *trans* isomers **6b** and **7b** were slightly (≤ 0.2 ppm) changed without changing relative positions and

broadening the peaks. This observation might be attributed to the conformational reorganization and restricted rotation of the single bonds adjacent to the amide bonds upon formation of the stable sandwich-type complex **8a** between the *cis* isomers and the metal cations.

In conclusion, using geometrical isomers of new bis(crown ether)s which are structurally well-defined, we have demonstrated that the biscrown effects can be always present regardless of the size correlation, but the magnitudes are much higher when the the ratio of the cation size and the cavity size is >1 .

Acknowledgment. This work was financially supported in part by the Basic Science Research Institute Program, Ministry of Education (Project No, BSRI-96-3422). We thank Professor Moon-Gun Choi and Dr. Youngmee Kim for X-ray analysis of compound **5a**.

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- The yields were not optimized. All of the bis(benzocrown ether)s prepared here were fully characterized by ^1H NMR, IR and mass spectrometry analyses: **6a** mp 188-190 °C; **6b** mp 98-100 °C; **7a** mp 136-137 °C; **7b** 63-65 °C.
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