

Synthesis of a Novel , Tetra-crowned Molecular Cleft and Studies of Its Selectivity in Alkali Metal Ion Complexation

Alan P. Marchand*, G. Madhusudhan Reddy, and Florencio Zaragoza
Department of Chemistry, University of North Texas, Denton, TX 76203-0068

Richard A. Bartsch* and Mark D. Eley
Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061

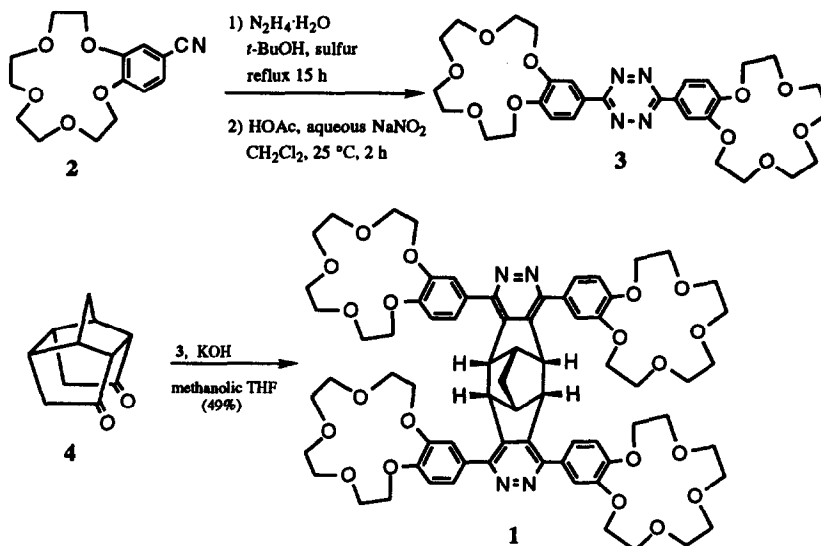
Abstract: A novel tetra-crowned cleft **1** has been synthesized and characterized spectrally, and its ability to extract and to transport alkali metal cations has been studied. Compound **1** generally displays greater affinity toward such cations, particularly K^+ and Rb^+ , than do equivalent concentrations of either benzo-15-crown-5 or 2,3-naphtho-15-crown-5. The results obtained from alkali metal picrate extraction and alkali metal perchlorate transport studies both suggest that the spatially proximate benzo-15-crown-5 moieties in **1** may interact cooperatively with the guest cation, thereby forming a "sandwich" complex.

Introduction: The synthesis and chemistry of rigid heterocyclic *syn*-orthocyclophanes has received considerable attention in recent years.¹⁻³ Of particular interest in this connection is a group of highly organized, polycyclic, polyaza cavity-shaped molecules which constitute a potential new class of molecular clefts.^{1,2} As part of a program that is concerned with the development of new molecular clefts of this type,³ we now report the synthesis of a novel *syn*-orthocyclophane **1** which contains four benzo-15-crown-5 moieties (see Scheme 1). The crown ether units in **1** are arrayed in two "sets", each of which contains two spatially proximate crown ether rings. The adjacent crown ether units are situated in such a manner that they conceivably can interact cooperatively with a "guest" molecule or ion, which then would reside between them in the resulting sandwich-type complex. Thus, it is also of interest to assess the potential capability of **1** to serve as a "host" system by investigating its ability to extract and to transport alkali metal cations.

Synthesis of 1. Our synthesis of tetra-crowned cleft **1** is outlined in Scheme 1. The synthetic approach is based upon the use of an appropriately functionalized 3,6-diaryl-1,2,4,5-tetrazine **3** as an electron-poor diene, which enters into an inverse electron demand Diels-Alder cycloaddition with the electron-rich enolate anion derived from tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,6-dione (**4**).⁴ Tetrazine **3**, mp 157-159 °C, is prepared conveniently in 50% overall yield via hydrazine promoted self-condensation⁵ of two equivalents of 4-cyanobenzo-15-crown-5 (**2**)⁶ followed by aromatization of the resulting dihydrotetrazine.⁷ Subsequent base-promoted reaction of **3** with **4**¹ afforded **1**, mp 301-302 °C, in 49% yield.⁸

Alkali Metal Picrate Extraction into Chloroform. The ability of **1** to extract the different alkali metal picrates was compared with that of benzo-15-crown-5 (**5**) and 2,3-naphtho-15-crown-5 (**6**). Thus, into a 3 mL

Scheme 1



centrifuge tube was placed the alkali metal picrate (0.50 mL of a 5.00 mM aqueous solution) and a solution of the host (5.00 mM in the case of **1**, 20.00 mM in the case of **5** and **6**, respectively) in CHCl_3 (0.50 mL), and the resulting mixture was agitated on a vortex mixer for 4 minutes. The mixture then was centrifuged for 4 minutes to effect phase separation, and the resulting two-phase system was allowed to stand undisturbed for 10 minutes. An aliquot (10 μl) was removed from the aqueous phase and was diluted to a total volume of 5.00 mL with CH_3CN . For comparison purposes, a sample of the original aqueous alkali metal picrate solution was diluted similarly. UV-visible spectra of the two solutions were obtained, and the percent of picrate extracted was calculated from the absorbance measured at 375 nm in each case. For each combination of host and alkali metal picrate, the picrate extraction was conducted on five different samples, and the average value of percent picrate extracted, with standard deviation, was calculated.

The results obtained from the alkali metal picrate extraction experiments are shown in Table 1. These data show that the tetra-crowned cleft **1** provides much higher levels of picrate extraction than do equivalent quantities (based on the number of 15-crown-5 units present) of **5** or of **6**. All three host systems display extraction selectivity toward K^+ which is consistent with the formation of sandwich complexes of two 15-crown-5 units with one K^+ .⁹ In the case of **5** or of **6**, this pattern of complexation requires the involvement of two host molecules in the extraction complex, whereas for **1**, two spatially proximate crown ether moieties within a single host molecule can participate cooperatively to complex the alkali metal cation.

Transport of Alkali Metal Perchlorates across a Bulk Chloroform Membrane. Ion transport studies were performed at 25 °C in a cell which was configured as a "hollow tube within a vial".¹⁰ A hollow glass tube (7 mm I. D.) was placed vertically within a glass vial (23 mm I. D.) such that the bottom of the glass tube extended below the surface of the CHCl_3 membrane. Thus configured, the CHCl_3 membrane separates the aqueous receiving phase (6.5 mL of distilled, deionized water, located outside the hollow glass tube) from the

aqueous source phase (1.00 mL of a 7.00 mM aqueous solution of the alkali metal perchlorate, located inside the hollow glass tube). The liquid membrane consisted of 4.0 mL of a 10.00 mM solution of **1** (or 4.0 mL of a 40.0 mM solution of **5** or **6**) in CHCl_3 . The area of the source phase - CHCl_3 phase interface was 38.5 mm^2 , and the area of the CHCl_3 phase - receiving phase interface was 352 mm^2 . The organic phase was stirred mechanically at 120 rpm. After 24 h, an aliquot was withdrawn from the aqueous receiving phase, and the concentration of transported alkali metal perchlorate was determined by ion chromatography. Triplicate runs were conducted for each combination of host and alkali metal picrate.

Table 1. Results of alkali metal picrate extraction experiments

Host Molecule	Percent of Picrate Extracted (%)				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1	20.1 ± 1.4^a	26.3 ± 1.4	97.0 ± 1.8	55.9 ± 1.6	44.0 ± 1.7
5	BDL ^b	11.8 ± 1.8	19.3 ± 1.9	5.9 ± 1.2	4.1 ± 1.4
6	3.6 ± 1.4	11.7 ± 1.2	27.1 ± 1.2	4.3 ± 1.1	BDL ^b

^a Average and standard deviations obtained from five extraction experiments; ^b BDL = below detection limit.

The results obtained from the transport experiments appear in Table 2. These data show that tetra-crowned cleft **1** is considerably more effective at transporting K^+ and Rb^+ perchlorates than are equivalent quantities (based on the number of 15-crown-5 units present) of either **5** or **6**. As was the case in the picrate extraction experiment (*vide supra*), formation of sandwich complexes that involve cooperative complexation of the metal ion by adjacent 15-crown-5 units is indicated by the alkali metal transport profile of tetra-crowned cleft **1**.⁹

Table 2. Results of alkali metal perchlorate transport experiments

Alkali Metal Cation	Moles of Alkali Metal Perchlorate Transported in 24 Hours by:		
	1	5	6
Na^+	$(5.6 \pm 0.4) \times 10^{-7a}$	$(3.8 \pm 0.4) \times 10^{-7}$	$(2.9 \pm 0.2) \times 10^{-7}$
K^+	$(1.2 \pm 0.2) \times 10^{-5}$	$(4.3 \pm 0.5) \times 10^{-7}$	$(3.9 \pm 0.3) \times 10^{-7}$
Rb^+	$(1.3 \pm 0.2) \times 10^{-5}$	$(1.4 \pm 0.2) \times 10^{-7}$	$(0.7 \pm 0.3) \times 10^{-7}$
Cs^+	$(3.6 \pm 0.4) \times 10^{-6}$	$(1.8 \pm 0.2) \times 10^{-7}$	$(1.0 \pm 0.5) \times 10^{-7}$

^a Average and standard deviations obtained from three transport experiments.

Summary and Conclusions: The synthesis and spectral characterization of **1** is described along with the results of alkali metal extraction and transport studies. Compound **1** generally displays greater affinity toward such cations, particularly toward K^+ and Rb^+ , than do equivalent concentrations of either benzo-15-crown-5 (**5**) or 2,3-naphtho-15-crown-5 (**6**). The data in Table 1 further indicate that the selectivity of **1** in alkali metal picrate extractions differs markedly from that shown by either **5** or **6**. Thus, for **1**, the selectivity order is $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$, whereas for **5** it is $K^+ > Na^+ > Rb^+ \geq Cs^+ > Li^+$, and for **6** it is $K^+ > Na^+ > Rb^+ \geq Li^+ > Cs^+$. The results obtained from alkali metal picrate extraction and alkali metal perchlorate transport studies both suggest that spatially proximate benzo-15-crown-5 moieties in **1** may interact cooperatively with the guest cation, thereby forming a sandwich complex.⁹ Additional studies are underway in our laboratories to determine the ability of **1** to form inclusion complexes with small neutral molecules.¹¹

Acknowledgment: We thank the Robert A. Welch Foundation (Grant No. B-963 to A. P. M., D-775 to R. A. B.) for financial support of this study.

References and Footnotes

- (a) Thummel, R. P.; Lim, J.-L. *Tetrahedron Lett.* **1987**, *28*, 3319. (b) Thummel, R. P.; Hegde, V. *J. Org. Chem.* **1989**, *54*, 1720. (c) Lim, J.-L.; Chirayil, S.; Thummel, R. P. *J. Org. Chem.* **1991**, *56*, 1492. (d) Thummel, R. P.; Chirayil, S.; Hery, C.; Lim, J.-L.; Wang, T.-L. *J. Org. Chem.* **1993**, *58*, 1666.
- For reviews, see: (a) Thummel, R. P. *Tetrahedron* **1991**, *47*, 6851. (b) Marchand, A. P. *SYNLETT* **1991**, 73. (c) Thummel, R. P. *SYNLETT* **1992**, 1.
- (a) Watson, W. H.; Nagl, A.; Marchand, A. P.; Annapurna, P. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988**, *C45*, 856. (b) Marchand, A. P.; Annapurna, P.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *Tetrahedron Lett.* **1988**, *29*, 6681. (c) Marchand, A. P.; Annapurna, P.; Taylor, R. W.; Simmons, D. L.; Watson, W. H.; Nagl, A. *Tetrahedron* **1990**, *46*, 5077.
- For a review of Diels-Alder reactions of heterocyclic azadienes, see: Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
- Abdel-Rahman, M. O.; Kira, M. A.; Tolba, M. N. *Tetrahedron Lett.* **1968**, 3871.
- Synthesis of **2**: (a) Hyde, E. M.; Shaw, B. L.; Shepherd, I. *J. Chem. Soc., Dalton Trans.* **1978**, 1696. (b) Shaw, B. L.; Shepherd, I. *J. Chem. Soc., Dalton Trans.* **1979**, 1634.
- (a) Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318. (b) Lin, C.-H.; Lieber, E.; Horwitz, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 427.
- NMR spectral data for **1**: 1H NMR ($CDCl_3$) δ 2.13 (s, 2 H), 3.50-4.40 (m, 70 H), 6.49 (AB, $J_{AB} = 7.7$ Hz, 4 H), 6.64 (AB, $J_{AB} = 7.7$ Hz, 4 H), 7.27 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 33.96 (t), 49.55 (d), 63.19 (d), 68.66 (t, 2 C), 69.30 (t), 69.44 (t), 70.27 (t, 2 C), 70.90 (t), 71.05 (t), 112.6 (d), 114.1 (d), 121.6 (d), 128.9 (s), 145.1 (s), 149.1 (s), 149.7 (s), 153.7 (s). Anal. Calcd for $C_{71}H_{84}N_4O_{20}$: C, 64.93; H, 6.45. Found: C, 64.86; H, 6.35. Despite numerous attempts performed by using a variety of solvent systems, we were unable to obtain a single crystal of **1** of sufficient quality to permit further elucidation of its structure by X-ray crystallographic methods.
- Kimura, K.; Maeda, T.; Tamura, H.; Shono, T. *J. Electroanal. Chem. Interfacial Electrochem.* **1979**, *95*, 91.
- (a) Izatt, R. M.; Deardon, D. V.; Brown, P. R.; Bradshaw, J. S.; Lamb, J. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1785. (b) Izatt, R. M.; LindH, G. C.; Bruening, R. L.; Huszthy, P.; McDaniel, C. W.; Bradshaw, J. S.; Christensen, J. J. *Anal. Chem.* **1988**, *60*, 1694.
- Weber E. In *Synthesis of Macrocycles: The Design of Selective Complexing Agents*, Izatt, R. M.; Christensen, J. J.; Eds; Wiley-Interscience; New York; 1987; Vol. 3, pp. 337-419 and references cited therein.

(Received in USA 23 April 1993; accepted 21 June 1993)