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**ONE- AND TWO-STEP METAL ION TEMPLATED SYNTHESSES
OF THE CRYPTANDS**Krzysztof E. Krakowiak^a, Jerald S. Bradshaw^{b*}, Xiaolan Kou^b, and N. Kent Dalley^bIBC Advanced Technologies, Inc., P.O. Box 565, Provo, UT 84603-0565 and Department of Chemistry,
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Abstract. New cryptands [3.2.1], [4.2.1] and [4.2.2] were prepared in good yields by treating the appropriate diazacrown with the ditosylate esters of triethylene, tetraethylene or pentaethylene glycol as required. Treatment of 4,10-diaza-15-crown-5 with α,α' -dibromo-*m*-xylene gave a mixture of the cryptand (1:1 cyclization) and the tricyclic bisdiaz-15-crown-5 connected by two *m*-xylylene units (2:2 cyclization) when K_2CO_3 was used as the base. When Li_2CO_3 was used, the same reaction gave only the 1:1 cyclization. An 1H NMR spectrum of the *m*-xylylene-containing cryptand exhibited a peak at δ 8.85 which suggests that the proton on benzene position 2 is close to the diaza-15-crown-5 cavity. The X-ray crystal structure of that compound showed that to be the case. A metal ion template effect was also observed in the preparation of [3.3.3] from 3,6,9-trioxa-1,11-diiodoundecane and its diamine analog. Only [3.3.3] was observed with K_2CO_3 . When Cs_2CO_3 was used, mainly a bis(aza-12-crown-4) was isolated. When the diiodide was changed to the corresponding ditosylate, both [3.3.3] and the bis(aza-12-crown-4) were isolated.

INTRODUCTION

Cryptands, first discovered by Lehn and coworkers,^{1,2} are superior and selective complexing agents in water for the alkali and alkaline earth cations.^{3,4} The spherands,⁵ calixspherands,⁶ and torands⁷ also have been reported to form strong complexes with these cations but only in chloroform saturated with water. These latter complexing agents are not soluble in water so that no comparative thermodynamic measurements can be carried out in aqueous solutions. Since most of the practical applications of the macrocyclic complexing agents occur in aqueous solution and require ligands with high affinity and selectivity for the metal cations, cryptands are important ligands to study.

These macrocyclic ligands have been attached to solid supports for the removal of cations from aqueous solutions⁸⁻¹⁰ and in clinical chemistry for the determination of lithium, sodium, and potassium in body fluids.¹¹⁻¹⁵

Cryptands are of increasing interest because they now can be prepared in convenient one- and two-step syntheses from inexpensive starting materials.¹⁶⁻²³ Only 4 cryptands can be purchased. In view of the importance

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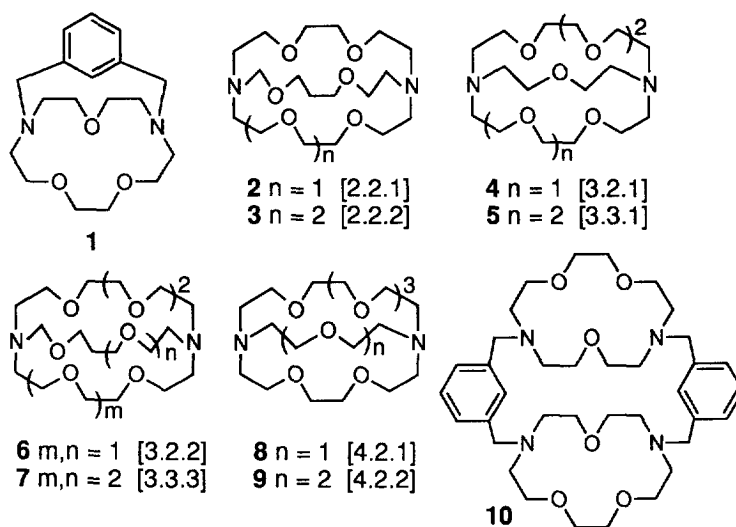
of the cryptands, it is important to publish all simple methods for their preparation.

The simplest one-step method for the synthesis of cryptands containing two identical bridges requires ditosylate or diiodide derivatives of the oligoethylene glycols, the appropriate diamine, and a template cation.^{16,17} Indeed, our one-step process produced four cryptands in good yields from the appropriate oligoethylene glycol ditosylates and diamines.²¹ To make cryptands containing an aromatic subcyclic unit, the appropriate diazacrown, the aromatic-containing ditosylate or dihalide and the template cation are reacted together.^{16,17} Many researchers have stressed that the template cation is very important in these reactions but no real data have been presented. In this paper, we extend our one- and two-step methods²⁰⁻²³ to prepare additional cryptands and to study the effect of metal template cations on the yields of these macrocyclization reactions. A crystal structure of the *m*-xylylene-containing cryptand (**1**) is also included.

RESULTS AND DISCUSSION

Cryptands **2**, **3**, and **5-7** (see Figure 1) were prepared by a one-step method from the appropriate diamine and ditosylate, diiodide, or dimesylate as shown in Scheme I. Cryptand **7** was in one instance accompanied by a bis(aza-12-crown-4) by-product as will be discussed later. The structure of the 7-KI complex was recently published²⁴ without complete details of the template effect for different cations. This template effect will be discussed later. The synthesis of cryptands **2**, **3**, **5**, and **6** have been reported in communication form without complete synthetic details.²¹

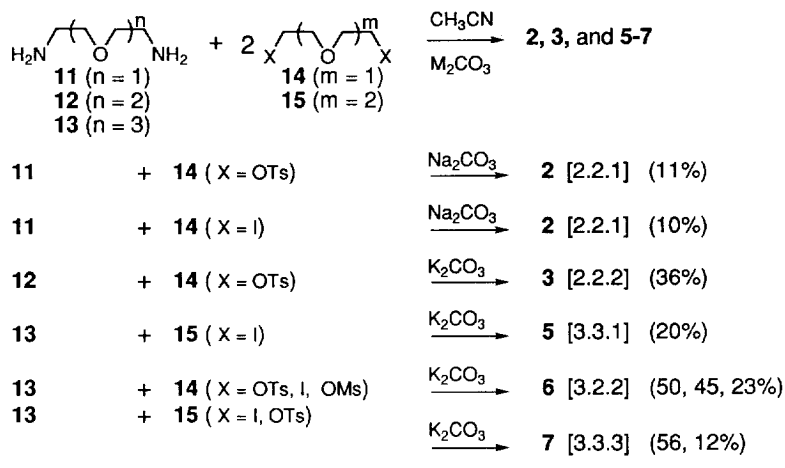
Figure 1. Cryptands mentioned in this study



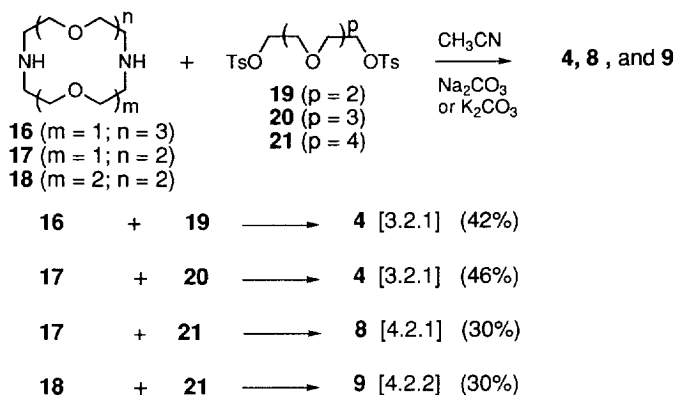
Cryptands **4**, **8**, and **9** were prepared from the appropriate diazacrown and ditosylate as shown in Scheme II. Cryptand **1** and the 2:2 tricyclic adduct **10** were prepared from diaza-15-crown-5, α, α' -dibromo-*m*-xylene and K_2CO_3 in acetonitrile. We observed similar results when diaza-18-crown-6 was treated with α, α' -dibromo-*m*-xylene to give the corresponding cryptand and the 2:2 tricyclic adduct similar to **10**.¹⁶ Other researchers have reported only **10** in a 30% yield in this reaction.^{25,26} In our hands, potassium, rubidium or cesium ion templates gave both **1** and **10**. However with Li_2CO_3 , only **1** was formed. We believe that the metal template must be smaller than the cryptand cavity to effectively catalyze its synthesis. So, Li^+ is smaller than the cavity of **1**.

Cryptand **1** does not form the typical teardrop-shaped spot on silica gel TLC using NH_4OH and methanol as we previously reported for the aliphatic cryptands.^{18,20} Many macrocyclic ligands other than the cryptands, such as 18-crown-6 and 24-crown-8, also form the teardrop-shaped TLC spots. It is important to note that the shape of the spot changes with a water/methanol eluant which indicates that NH_4OH is essential for producing the

Scheme I. One-step Method to Prepare Cryptands 2, 3, and 5-7



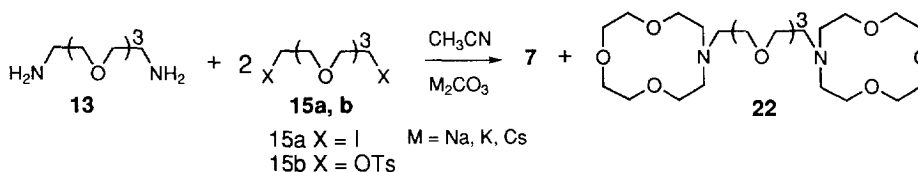
Scheme II. Preparation of Cryptands from Diaza-crowns



distinctive spot, probably a result of an ammonium complex with the macrocyclic ligand. In the case of **1**, the short bridge containing the benzene ring could cause sufficient steric hindrance to prohibit ammonium ion complexation by **1**. Indeed, the ^1H NMR signal attributed to the proton on position 2 of the benzene ring in **1** is shifted downfield to 8.85 δ in comparison to 8.45 for the analogous cryptand prepared from diaza-18-crown-6 and 7.9 δ for the cryptand from 24-crown-8. This result indicates that the proton on position 2 of the benzene ring of **1** is very close to the cavity of the 15-crown-5 moiety. The X-ray study of **1**, discussed below, also shows that the proton is very close to the diaza-15-crown-5 cavity. The ^1H NMR spectrum of biscrown **10** is very different from that of **1**.

Interesting template effects were also observed for the formation of **7** (cryptand [3.3.3]) (see Scheme III). When 3,6,9-trioxa-1,11-diiodoundecane (**15a**) was treated with diamine **13** and K_2CO_3 as the base, only cryptand **7** was isolated in a 40% yield. The same reactants, in the presence of Cs_2CO_3 , gave bis(aza-12-crown-4) (**22**) in a 33% yield and cryptand **7** in only a 13% yield. Using ditosylate **15b** instead of diiodide **15a** resulted in lower yields of the products.

Scheme III. Preparation of Cryptand **7** and Biscrown **22**



The first cryptands were prepared in 1968.^{1,2} Only aliphatic cryptands with cavity sizes from [1.1.1] to [3.3.3] have been reported. Cryptands [3.2.1] (**4**), [3.3.1] (**5**), [4.2.1] (**8**) and [4.2.2] (**9**) are new macrotricycles. It is not possible to use the simple one-step reaction of 1 mole of a diamine with 2 moles of a dihalide (ditosylate) to prepare a cryptand with 3 different bridges between the nitrogen atoms. For those types of cryptands, one needs to condense the appropriate diazacrown with the appropriate dihalide or ditosylate (see Scheme II). Cryptands **4**, **8**, and **9** were prepared by this process as mentioned above, since the starting diaza-15-crown-5 (**17**) and two diaza-18-crown-6 reactants (**16** and **18**) are readily available. Other cryptands could be prepared in the same manner if the diazacrowns were available. Diazacrowns such as **16** can be prepared by a convenient one-step method from the appropriate dihalide (ditosylate) and a diamine as reported.²⁷ Cryptand **4** was prepared from both **16** and **17**, giving about the same yields. Thus, either method could be used, but 4,10-diaza-15-crown-5 is more available than 4,10-diaza-18-crown-6, although the latter compound can easily be prepared.²⁷

An X-ray study of **1** was initiated in order to determine if the hydrogen on the 2-position of the benzene (H18A) is close to the cavity of the crown 15 ring. A computer drawing showing the conformation of **1** and giving

the atom labels is presented in Figure 2.²⁸ The figure shows that H18A is directed into the cavity. Because there is no given point that fixes the location of the cavity, it is difficult to show the relationship of an atom to the cavity of the molecule, but the following indicators are helpful. H18A is 1.46 Å from the least-squares plane

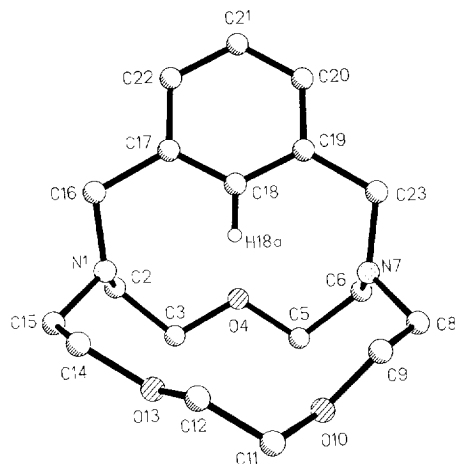


Figure 2. Computer drawing of **1** with O13' and hydrogens, except for H18A, omitted for clarity.

calculated for the hetero atoms of the crown portion of the molecule. The distances of H18A from N1, O4, N7, O10, and O13 are 2.511, 2.652, 2.547, 3.468 and 3.154 Å, respectively, and it is 0.43 Å above the least-squares plane of N1, O4 and N7. By way of comparison, in the diaza-18-crown-6 analogue of **1**,²⁰ the hydrogen in the 2-position of the benzene ring is 1.76 Å from the least-square plane of the hetero atoms. The distances of that hydrogen to the two nitrogens are 2.44 and 2.36 Å but the distances to the four oxygens are 3.656, 3.735, 3.931, and 3.984 Å. Clearly the structural study indicates that H18A more closely approaches the cavity of **1** than does the similar H in the diaza-18-crown-6 analogue.

EXPERIMENTAL

Cryptands **3**,²¹ **5**,²¹ and **7**²⁴ were prepared as reported. Other cryptands, such as **2** and **6**, were obtained in a similar manner and their physical and spectral properties were the same as those reported.²⁹

Preparation of Cryptand 1 and Macropolycycle 10. Diaza-15-crown-5 (0.55 g, 2.52 mmol), 0.67 g (2.53 mmol) of α,α' -dibromo-*m*-xylene and 10.0 g of anhydrous K_2CO_3 were refluxed in 200 mL of CH_3CN for 20 h. After cooling, the mixture was filtered and the solvent was evaporated under reduced pressure. CH_2Cl_2 (30 mL) was added to the residue and the mixture was stirred and filtered. The solvent was evaporated from the filtrate and the residue was purified on an alumina column using CH_2Cl_2/THF : 5/1 as eluant to give 0.36 g (54%)

of **1**, $^1\text{H NMR}$ (δ): 2.5 (m, 2 H), 2.7 (m, 2 H), 2.9 (m, 6 H), 3.35 (m, 2 H), 3.65 (m, 10 H), 4.0 (s, 1 H), 4.08 (s, 1 H), 6.85-7.15 (m, 3 H), 8.85 (s, 1 H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_3$: C, 67.47; H, 8.81. found: C, 67.48; H, 8.79; MS (m/e): 320 (100%), MS (CI): 321.

The above alumina column was further eluted with $\text{CH}_2\text{Cl}_2/\text{THF}$: 3/1 and 1/1 to give 0.20 g (30%) of **10**, $^1\text{H NMR}$ (δ): 2.7-2.9 (m, 16 H), 4.5-4.7 (m, 32 H), 7.1-7.3 (m, 6 H), 7.6 (s, 2 H); *Anal.* Calcd for $\text{C}_{36}\text{H}_{56}\text{N}_4\text{O}_6$: C, 67.47; H, 8.81. Found: C, 67.40; H, 8.63; MS (m/e) 640 (100%); MS (CI) 641.

Preparation of Bis(aza-12-crown-4) (22) (Scheme III). Diamine **13** (0.96 g, 5 mmol), 4.35 g (10.5 mmol) of diiodide **15a** and 10.0 g of Cs_2CO_3 were stirred under reflux in 200 mL of CH_3CN for 24 h. After cooling the reaction mixture was filtered and evaporated under reduced pressure. The residue was stirred in 50 mL of CH_2Cl_2 and filtered. The filtrate was evaporated and the residue was purified on an alumina column using $\text{THF}/\text{C}_8\text{H}_5\text{OH}$: 50:1, 20:1 and 10:1 as eluants and on silica gel using $\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$: 20/1, 10/1, 5/1 and 2/1 as eluants. The appropriate fractions of the second main spot were combined, evaporated, mixed with $\text{C}_6\text{H}_5\text{CH}_3$ and filtered to give 0.75 g (33%) of biscrown **22**; $^1\text{H NMR}$ (δ): 2.75 (m, 12 H), 3.65 (m, 36 H); $^{13}\text{C NMR}$ (δ): 56.21, 56.60, 69.78, 70.23, 70.84, 71.01, 71.21, 71.77. *Anal.* Calcd for $\text{C}_{24}\text{H}_{48}\text{N}_2\text{O}_9$: C, 56.68; H, 9.50. Found: C, 56.81; H, 9.27; MS (M/E) 508; MS (CI) 509.

Preparation of Cryptands 4, 8, and 9 (Scheme II). Diazacrowns **16**, **17** or **18** (0.39 mmol), 4.1 mmole of **19**, **20** or **21** and 10.0 g of Na_2CO_3 were stirred under reflux in 300 mL of CH_3CN for 7 days. The reaction mixtures were cooled and evaporated. Water (40-50 mL) was added and the resulting mixture was extracted 4 times with 150 mL portions of CH_2Cl_2 . The combined CH_2Cl_2 extracts were dried (MgSO_4) and evaporated. The residue was chromatographed on alumina to decompose the complex using $\text{THF}/\text{C}_2\text{H}_5\text{OH}$: 100/1 as the eluant. The solvents were evaporated and the residue was chromatographed on silica gel using $\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$: 40/1, 20/1 and 10/1 as eluants. The residue was dissolved in $\text{C}_6\text{H}_5\text{CH}_3$ and filtered through a glass filter to remove silica gel. The products were obtained as oils follows:

Cryptand 4 (46%), $^1\text{H NMR}$ (δ): 2.7 (m, 12 H), 3.6 (m, 24 H); *Anal.* Calcd for $\text{C}_{18}\text{H}_{36}\text{N}_2\text{O}_6$: C, 57.36; H, 9.63. Found: C, 57.76; H, 9.53; MS (m/e) 376 (82%); MS (CI) 377.

Cryptand 8 (30%), $^1\text{H NMR}$ (δ): 2.75 (m, 12 H), 3.6 (m, 28 H); *Anal.* Calcd for $\text{C}_{20}\text{H}_{40}\text{N}_2\text{O}_7$: C, 57.12; H, 9.58. Found: C, 57.35; H, 9.38; MS (m/e), 420 (86%); MS (CI), 421.

Cryptand 9 (30%), $^1\text{H NMR}$ (δ): 2.8 (m, 12 H), 3.65 (m, 32 H); *Anal.* Calcd for $\text{C}_{22}\text{H}_{44}\text{N}_2\text{O}_8$: C, 56.87; H, 9.54. Found: C, 56.69; H, 9.29; MS (m/e) 464 (96%); MS (CI) 465.

X-ray Crystal Study of 1. Crystallographic and single crystal intensity data for **1** were obtained using a Siemens R3m/V automated diffractometer which utilized graphite monochromated $\text{Mo K}\alpha$ radiation ($\lambda = 0.71073\text{\AA}$). The lattice parameters and orientation matrix were obtained using a least-square procedure involving 32 carefully centered reflections ($8.9 \leq 2\theta \leq 32.7^\circ$). Single crystal data were collected using a variable rate 2θ - ω scanning procedure. The crystal data and a summary of the experimental conditions are contained in Table 1.

The structure was solved using direct methods. It was possible to locate all non-hydrogen atoms in an E-map. A difference map revealed the presence of a small peak near O13 which was a disordered O13'. The ratio of the population parameters for O13:O13' are 0.86:0.14. The approximate ratio was suggested by the peak heights in difference maps and the final values were obtained in the refinement process. The large thermal parameters for C12 and C14 suggested that these atoms were also disordered but the disorder could not be resolved. This resulted in unusual bond angles involving O13'. Positions for all hydrogens were calculated and the hydrogens were assigned isotropic thermal parameters. These H atoms were allowed to ride on their neighboring carbons during the refinement. In the calculations of H positions, O13' was omitted so realistic bond angles could be calculated. It is also omitted from Figure 2 for clarity. In the final stages of refinement all non-hydrogen atoms except O13' were refined anisotropically. O13' was refined isotropically and the hydrogen thermal parameters were not refined. Atomic scattering factors were obtained from the International Tables for X-ray crystallography.³⁰ All computer programs used in the solution, refinement and display of this structure are contained in SHLEXTL-PLUS™.³¹

TABLE 1. Crystal Data and Summary of Experimental Conditions for 1

Formula	C ₁₈ H ₂₈ N ₂ O ₃
Formula weight	320.4
F(000)	696
Crystal size, mm	0.24 x 0.42 x 0.44
μ , mm ⁻¹	0.082
Crystal system	Monoclinic
Space group	P2 ₁ /c
a, Å	12.843(3)
b, Å	15.145(3)
c, Å	9.604(4)
β , deg	108.80(2)
V	1768.4
Z	4
D _x , g/cc	1.203
2 θ range, deg	4.00 to 50.00
Independent data	3129 (R _{int} = 1.64%)
Observed data	1469 (F > 3.5 σ (F))
Data/parameter ratio	6.9:1
R	7.72%
R _w	8.23%
Weighing scheme	w ⁻¹ = σ^2 (F) + 0.0009F ²
Goodness of fit	1.68
Largest peak in difference map e Å ⁻³	0.27
Largest hole in difference map e Å ⁻³	-0.28

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