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TWENTY-FIVE YEARS OF "CROWNING" AROUND: SYNTHESIS OF CROWN ETHERS AT BRIGHAM YOUNG UNIVERSITY

JERALD S. BRADSHAW
Department of Chemistry and Biochemistry
Brigham Young University
Provo, UT 84602-5700, U.S.A.

Abstract. A review of the synthesis of crown ethers at Brigham Young University is presented. Topics include: thiacrown ethers, diestercrown ethers, proton-ionizable crown ethers, chiral crown ethers, azacrown ethers, cryptands and other polycyclic ligands, and the Mannich reaction method to prepare azacrown ethers and cryptands.

Key words. Crown ethers, thiacrown ethers, azacrown ethers, diestercrown ethers, cryptands, Mannich reaction.

1. Introduction

Reed Izatt and James Christensen of the Brigham Young University were among the first to realize the potential of the crown ethers, discovered by Pedersen in 1967 [1], to recognize metal ions in solution. Izatt and Christensen used calorimetry to study the log K values for the interaction of various organic ligands with metal ions. They found that K^+ formed the strongest complex with dicyclohexano-18-crown-6 (DC18C6) among the alkali metal ions [2,3]. K^+ fits into the DC18C6 cavity, Li^+ is too small, and Cs^+ too large. These results gave them a desire to study a variety of crown ether macrocycles to determine if the size-fit relationship was applicable to the interactions of macrocyclic ligands with other metal ions.

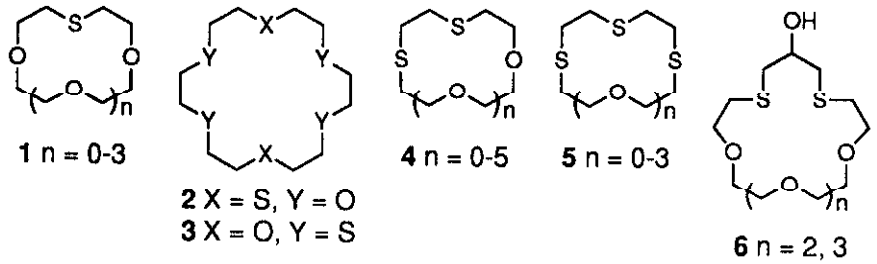
Crown ethers were not available for purchase in 1969, so Izatt and Christensen asked me to help them by synthesizing these macrocycles. Our first collaboration, funded by the National Science Foundation, was for the preparation and metal ion complexation studies of the thiacrown ethers starting in 1970. The present short review outlines the synthesis of crown ethers in my laboratory. Their use in the selective complexation of metal ions is described in numerous publications [4-8]. The

synthetic work will be discussed as follows: thiacrown ethers, diestercrown ethers, proton-ionizable crown ethers, chiral crown ethers, azacrown ethers, cryptands and other polycyclic ligands, and the Mannich reaction as a key strategy in crown ether and cryptand syntheses.

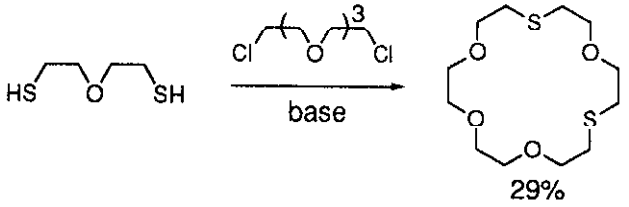
2. Thiacrown Ethers

The thiacrown ethers are similar to the crown ethers except that one or more of the polyether oxygen atoms are replaced by sulfur atoms. Figure 1 shows the variety of the thiacrown ether ligands prepared in our laboratory [9-11]. Barry Haymore, who was working with Reed Izatt, got us started and Joseph Hui and Robert Reeder

Figure 1. Some thiacrown ethers



Scheme 1. Preparation of thiacrown ethers



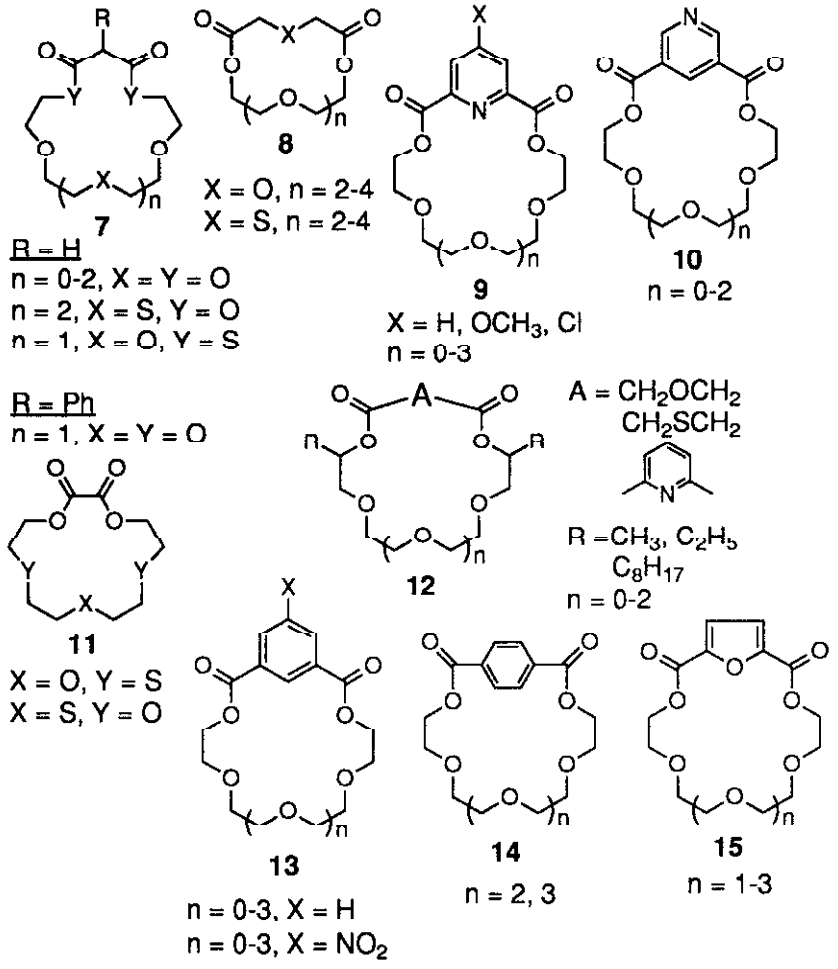
continued the work. As shown in Scheme 1, the thiacrown ethers were prepared by treating an oligoethylene glycol dichloride with the appropriate dimercaptan in base. The sulfur reactant can be sodium sulfide to form a monothiacrown ether [9]. 2-Hydroxy-1,3-propanedithiol reacted with the appropriate dichloride and base to give hydroxy-substituted dithiacrown ethers **6** [11].

3. Diestercrown Ethers

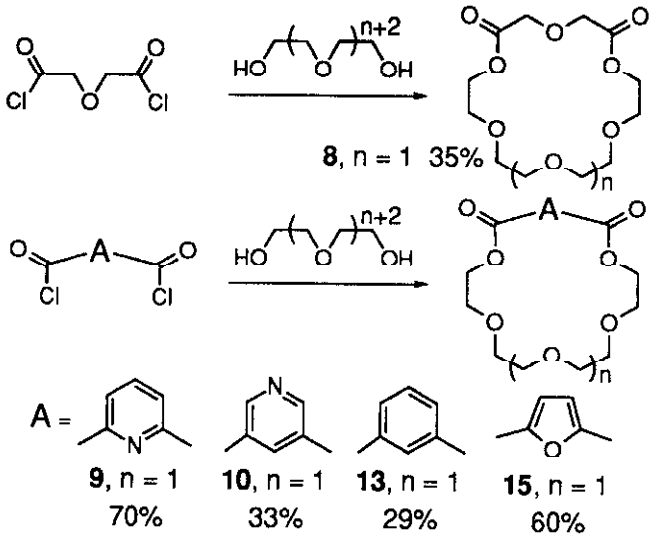
The diestercrown ethers are a logical extension to the crown ethers and are easier to

prepare. Initially, we synthesized the diestercrowns by treating equal amounts of the appropriate oligoethylene glycol with malonyl dichloride in hot benzene. The reaction was continued until HCl was no longer present in the solution [12-14]. The product (**7**, Figure 2) was isolated by extracting the crude reaction mixture with hot hexane. These initial syntheses were started by Michael Thompson with help from some talented undergraduate students. This work was amplified by Garren Maas who prepared a series of diestercrown ethers more closely related to 18-crown-6 (**8**, X = O) and thia-18-crown-6 (**8**, X = S) by treating the appropriate oligoethylene glycol with diglycolyl and thiadiglycolyl dichlorides (Scheme 2) [15,16]. Cram and his coworkers reported the preparation of pyridino-18-crown-6 in 1974 [17]. Garren

Figure 2. Some diestercrown ethers



Scheme 2. Preparation of diestercrown ethers



Maas found that treatment of tetraethylene glycol with 2,6-pyridinedicarbonyl dichloride gave diesterpyridino-18-crown-6 (**9**, X = H, n = 1) (Figure 2, Scheme 2) [18,19]. It is pertinent to note that ligand **9** (X = H, n = 1) formed a strong complex with K^+ in methanol, while the diesterpyridino-18-crown-6 with the pyridine nitrogen atom pointing outside the macroring cavity (**10**, n = 1) did not interact with K^+ [19,20]. Ligands **10** were prepared by Elliott Asay from 3,5-pyridinedicarbonyl dichloride [20].

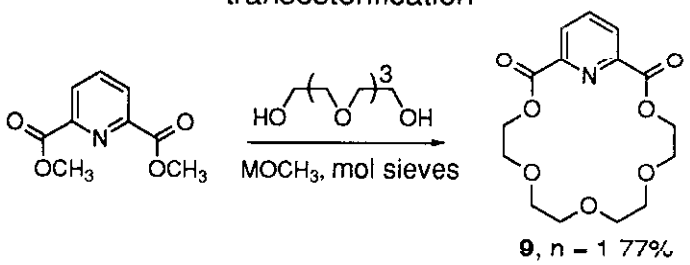
Many other diestercrown ethers have been prepared by treating an oligoethylene glycol with the appropriate diacyl dichloride (Figure 2, Scheme 2). Paul Fore synthesized some oxalate-containing crown and thiacrown ethers (**11**) from oxalyl chloride [21]. Scott Jolley prepared a number of methyl-, ethyl-, and *n*-octyl-substituted diester-18-crown-6 macrocycles (**12**) from the appropriate dialkyl-substituted tetraethylene glycols [22,23]. Diestercrown ethers containing *m*- and *p*-phenylene units (**13** and **14**) were prepared by Michael Thompson [24]. Diesterbenzo-18-crown-5 **13** (n = 1, X = H) does not interact with metal ions [24]. It is interesting that when terephthaloyl dichloride was treated with tetraethylene glycol to form **14** (n = 1), we were able to only isolate the bis-*p*-phenylene-containing 2:2 adduct. Frensch and Vögtle isolated both the 1:1 adduct **14** (n = 1) and the 2:2 adduct [25]. These two macrocycles had very similar physical properties. The ^1H NMR spectrum of **14** (n = 2) has a singlet corresponding to four hydrogen atoms at δ 3.46, a shift from the normal values for **13** (n = 1 or 2) of δ 3.70, for the central hydrogens on the *p*-cyclophane. The signals for these hydrogen atoms are shifted because they are directly below the aromatic ring. The shift for the same protons in

14 (n = 3) was to δ 3.59. Steven Baxter prepared a series of furan-containing diestercrown ethers **15** from 2,5-furandicarbonyl dichloride [26].

These diestercrown ether ligands exhibit some interesting interactive properties with benzylammonium perchlorate [19,26]. Ligand **9** (X = H, n = 1, Figure 2) forms a strong complex with benzylammonium perchlorate in CD_2Cl_2 with a free energy of activation ($\Delta G_c^{\ddagger}$) of 13.0 kcal/mol as determined by a temperature dependent ^{1}H NMR titration technique [19]. This value decreases for **9** (X = Cl, n = 1) and increases for **9** (X = OCH_3, n = 1). These results parallel the basicity for 4-substituted pyridines where basicity is greatest for 4-methoxypyridine and least for 4-chloropyridine. This indicates that the ammonium salt is hydrogen bonded to the pyridine nitrogen atom and two alternate macroring oxygen atoms. This type of hydrogen bond association has been shown by an X-ray crystal stucure determination [27]. While the $\Delta G_c^{\ddagger}$ values for ligands **9** (R = H, Figure 2) greatly diminish as n increases from 1 ($\Delta G_c^{\ddagger}$ = 13.0) to 2 (11.6) to 3 (< 8.6) [19], the values become larger for ligands **13** (R = H) and **15** as n increases from 1 ($\Delta G_c^{\ddagger}$ = <8 for **13** and 9.7 for **15**) to 2 (9.3 for **13** and 10.7 for **15**) to 3 (10.5 for **13** and 10.8 for **15**) [26]. Clearly the benzylammonium perchlorate complexes of 24-crown-8 ligands **13** (n = 3) and **15** (n = 3) are very different from those of **9** (n = 3). In the ^{1}H NMR spectrum for the complex with **15** (n = 3), the peaks for the ether methylene hydrogen atoms fartherest removed from the furan ring are significantly shifted upfield indicating that the benzene ring of the host is over the polyether portion of the macrocycle. Thus, complexation is probably taking place in the polyether portion of the furan-containing macrocycle. Complexation by ligands **9** should involve the pyridine nitrogen atom and the log *K* values would decrease with increasing ring size [26].

Transesterification has also proven to be a good method for the preparation of diestercrown ethers (Scheme 3). Brian Jones and Ralph Nielsen found that treatment of dimethyl 2,6-pyridinedicarboxylate with triethylene glycol in the presence of an alkali metal methoxide in refluxing benzene using molecular sieves to remove the methanol by-product gave **9** (n = 0, Figure 2) in a yield of 25% in comparison to 10%

Scheme 3. Preparation of diestercrown ethers by transesterification

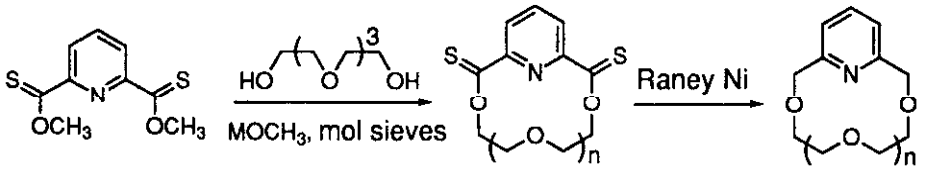


9, n = 1 77%

when the diacid dichloride method was used [28]. Improved yields were also observed for the preparation of **8** (X = O or S) and **11** (X, Y = O) by transesterification. When the method was used to prepare **9** (n = 1), the presumed intermediate, wherein only one alcohol function of the glycol had reacted with one ester group, was observed in the HPLC chromatogram. This intermediate was also observed when **9** (n = 1) was decomposed [28].

The transesterification method allowed the preparation of dithionodiesterpyridino-crown ethers **16** by Brian Jones (Scheme 4) [29]. These macrocycles were synthesized by treating O,O'-dimethyl 2,6-pyridinedicarbothioate with the appropriate oligoethylene glycol and base to form beautiful yellow crystals of **16**. These materials were reductively desulfurized to form the pyridinocrown ethers using Raney nickel.

Scheme 4. Preparation of dithionoesterpyridino-crown ethers and their reduction



16

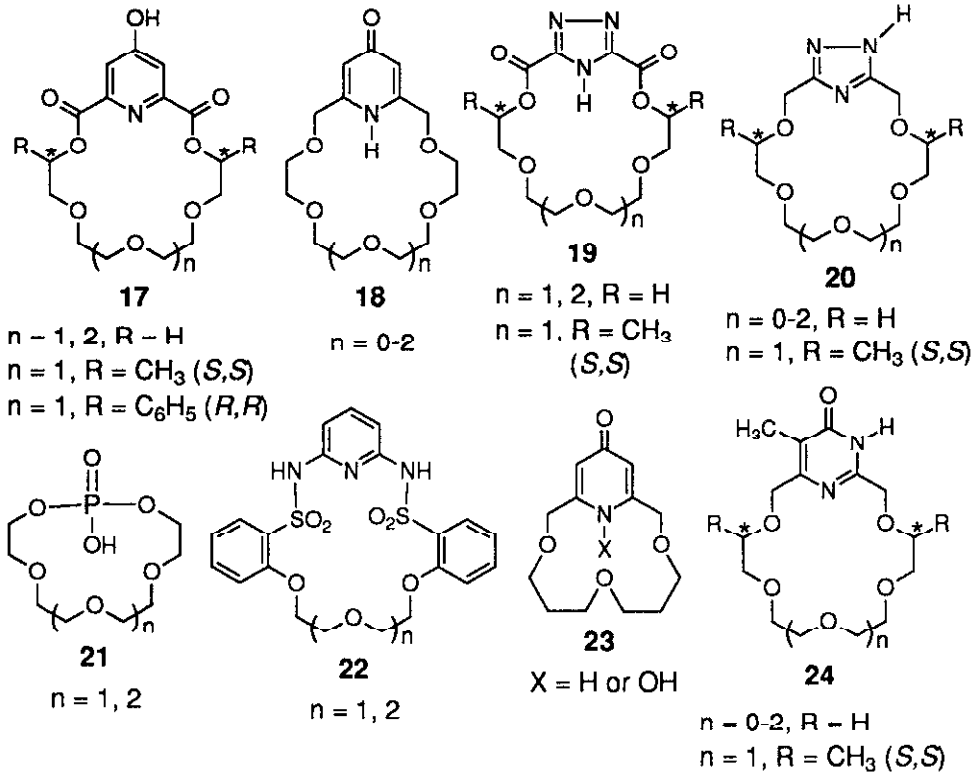
n = 2 71%
n = 3 39%
n = 4 26%
n = 5 10%

n = 2 40%
n = 3 56%
n = 4 76%
n = 5 40%

4. Proton-Ionizable Crown Ethers

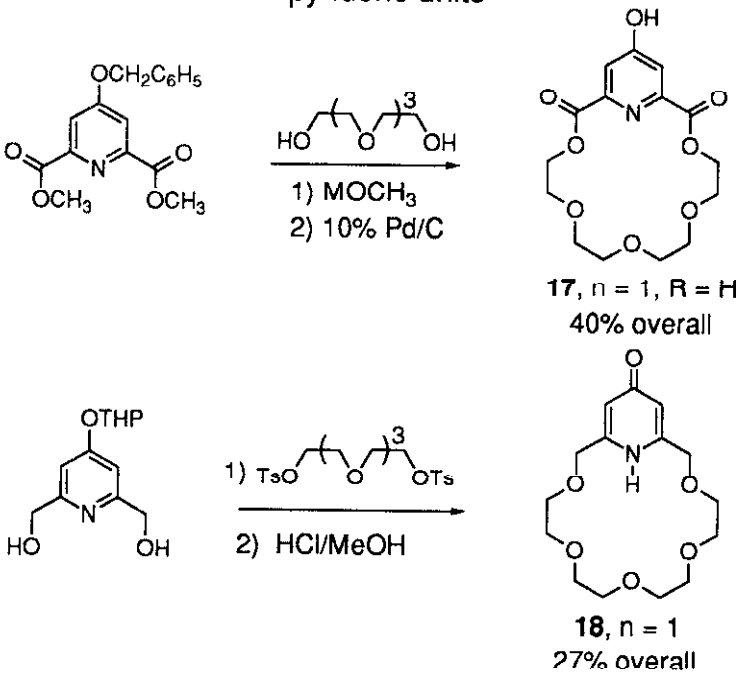
A series of proton-ionizable crown ether compounds (Figure 3) were synthesized to study proton-driven metal ion transport across liquid membranes. Mary Lee Colter prepared diester-4-hydroxypyridino-18-crown-6 **17** (n = 1, R = H) by first treating tetraethylene glycol with dimethyl 4-benzyloxy-2,6-pyridinedicarboxylate in the transesterification process (Scheme 5). The benzyl group was removed by catalytic hydrogenation in the presence of 10% Pd/C [30]. Yohji Nakatsuji used the THP protecting group to prepare diester macrocycle **17** (n = 1, R = H) [30]. Nakatsuji also treated THP-protected 4-hydroxy-2,6-pyridinedimethanol with tetraethylene glycol ditosylate in base followed by acid to give pyridono-18-crown-6 **18** (n = 1) (Scheme 5) [31,32]. Crystal structure determinations showed that **17** (n = 1, R = H) contained the 4-hydroxypyridine subcyclic unit [30] while **18** contained the 4-pyridone unit [32] as shown in Figure 3. Ligand **17** is acidic enough (pK_a = 8.49) to react with primary

Figure 3. Some proton-ionizable crown ethers



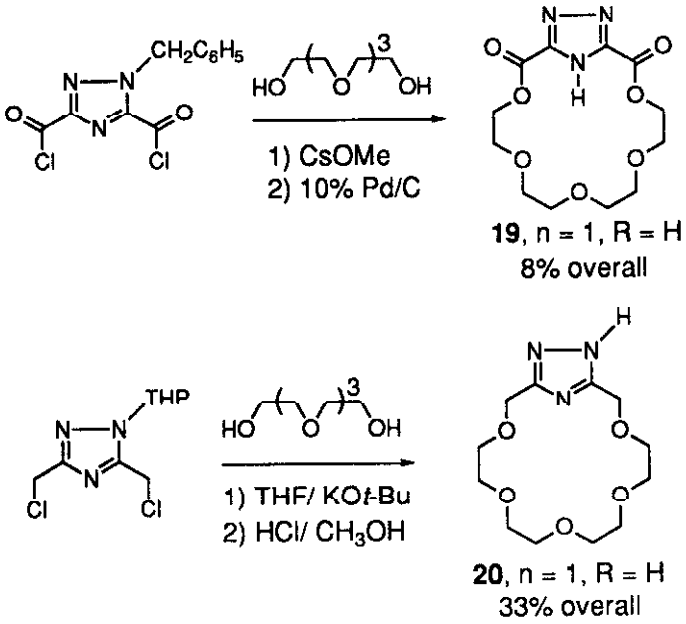
amines. The crystal formed when **17** (n = 1, R = H) was treated with benzylamine was found to contain a benzylammonium ion in the cavity bound to a 4-pyridone nitrogen atom and two alternate oxygen atoms of one macrocycle and the hydroxypyridine part of a separate macrocycle was hydrogen-bonded to the pyridone oxygen [30]. The amine abstracted a proton from the hydroxy group of one macrocycle forming an ammonium cation and the anion became the deprotonated pyridone moiety. Ligand **18** (n = 1) (pK_a = 10.98) [32] did not interact with a primary amine. Ligands **17** (n = 1, R = CH_3 and R = C_6H_5) exhibited excellent recognition for the enantiomers of both α-(1-naphthyl)ethylammonium perchlorate and α-(1-naphthyl)ethylamine, wherein (*S,S*)-**17** (n = 1, R = CH_3) formed stronger complexes with the (*R*)-forms of the salt and amine than with the (*S*)-forms and (*R,R*)-**17** (n = 1, R = C_6H_5) formed stronger complexes with the (*S*)-forms of the salt and amine [30].

Scheme 5. Preparation of proton-ionizable crown ethers containing 4-hydroxypyridine or 4-pyridone units



Proton-ionizable triazolocrown ethers **19** and **20** (Figure 3) were also prepared [33,34]. David Chamberlin prepared diestertriazolo-18-crown-6 (**19**, n = 1, R = H) from dimethyl 1-benzyl-2,5-triazoledicarboxylate with tetraethylene glycol in the transesterification process followed by reduction (Scheme 6) [33]. Crystal structure determinations showed that ligand **19** (n = 1, R = CH_3) contained a water of hydration in the cavity. Macrocycle **19** (n = 1) formed a complex with benzylamine wherein a proton was transfered from the triazole unit to the amine [33]. Indeed, **19** (n = 1, R = H) interacted more strongly with benzylamine than it did with benzylammonium perchlorate. Ralph Nielsen prepared **20** (n =1, R = H) by treating 3,5-bis-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole with tetraethylene glycol in THF using potassium *t*-butoxide as the base (Scheme 6) [34]. The THF protecting group was removed in acidified methanol. **Warning: 2-(chloromethyl)triazole is a severe skin irritant and should be used with caution.** Although **20** (n = 1, R = H) formed a strong complex with Cu(II) (log K = 24.9 in H_2O), it did not interact with benzylamine [34].

Scheme 6. Preparation of proton-ionizable crown ethers containing triazole units



Other proton-ionizable macrocyclic ligands shown in Figure 3 were also prepared. Peter Huszthy synthesized dialkylhydrogenphosphate-containing macrocycle **21** (n = 1) by treating tetraethylene glycol with phosphorus oxychloride followed by hydrolysis in wet dioxane [35]. Visiting professors Jan Biernat, Maria Bochenska and Hiroyuki Koyama prepared a series of sulfonamide-containing macrocyclic ligands depicted by **22** [36,37]. These materials were prepared by treating bis(sulfonyl chloride)s with various diamines. The proton-ionizable macrocyclic ligands have been used to transport metal ions across a liquid membrane [7,8,38,39].

14-Crown-4 ligands containing pyridine, 4-pyridone (**23**, X = H), 4-pyridone *N*-hydroxide (**23**, X = OH) and pyridine *N*-oxide subcyclic groups were prepared by John Guynn and Steven Wood [40,41]. The pyridine- and pyridone-containing ligands were prepared as mentioned previously. The 4-pyridone *N*-hydroxide- and pyridine *N*-oxide-containing ligands were prepared by treating the THP-protected 4-hydroxypyridino- or pyridinocrown ether with a peracid. Ligand **23** (X = OH) has the pyridone *N*-hydroxide structure in CD_3OD as shown by a ^1H NMR signal at δ 6.35 indicating the pyridone ring hydrogen atoms [41]. In the solid state, however, the stucture becomes a 4-hydroxypyridine *N*-oxide. All of these 14-crown-4 ligands are conformationally labile in solution at room temperature. Using a temperature dependent ^1H NMR spectral technique, the $\Delta G_c^{\ddagger}$ values for conformational inversions

were found to be 15.5 kcal/mol for **23** (X = OH) as compared to 12.8 kcal/mol for the corresponding 15-crown-5 and 18-crown-6 analogs [41].

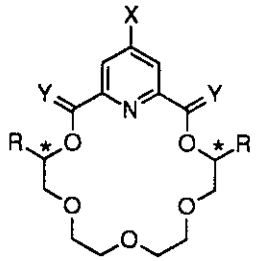
Ty Redd has prepared some pyrimidine- and pyrimidone-containing crown ethers (**24**) by treating the appropriate oligoethylene glycol with 4-methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate and base to form the methoxy-substituted pyrimidinocrown ethers followed by stong base to remove the methoxy protecting group to form the pyrimidonocrown ethers [42,43]. The ditosylate was prepared in a seven-step process from acetamidine and diethyl oxalpropionate [42]. Ligand **24** (n = 1, R = H) interacts readily with both benzylammonium perchlorate and benzylamine [43].

5. Chiral Crown Ethers

A series of pyridino-18-crown-6 ligands containing alkyl or phenyl substituents on two stereogenic centers in the macroring have been prepared (Figure 4). Brian Jones was the first member of our group to synthesize chiral crown ethers when he prepared the (*S,S*)-, (*R,R*)-, and *meso*-forms of **25** (X = H, Y = O, R = CH_3) [44]. Others who prepared the chiral pyridino-18-crown-6 ligands of the **25** type include Pat Thompson [45], Scott Jolley [46], Chris McDaniel [47], Peter Huszthy [47-49], Masatoshi Oue [49], and Tingmin Wang [50]. These ligands were prepared as shown in Schemes 2, 3, and 7 from 2,6-pyridinedicarbonyl dichloride, dimethyl 2,6-pyridinedicarboxylate, or 2,6-pyridinedimethyl ditosylate as appropriate and the chiral disubstituted tetraethylene glycols.

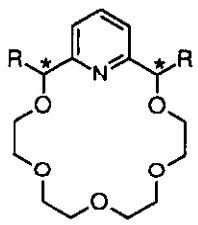
Chiral ligands **25** exhibit considerable recognition toward the enantiomers of various chiral organic ammonium salts as determined by differences in log *K* values for their interactions with the (*R*)- and (*S*)-forms of the organic ammonium salts. The enantiomeric recognition abilities of these ligands have been studied extensively and described in reviews [51-54].

Figure 4. Some chiral crown ethers



25

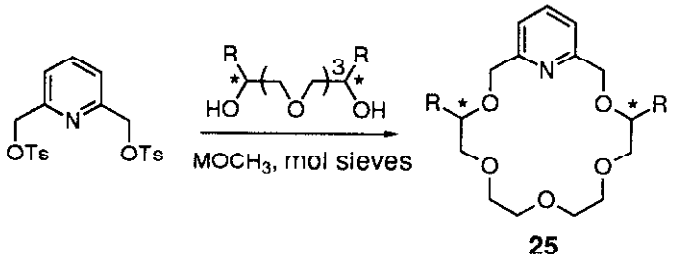
Y = O, R = CH_3
X = H, Cl, OCH_3
Y = O, X = H
R = C_6H_5, t-C_4H_9
Y = H_2, X = H
R = CH_3, C_6H_5, t-C_4H_9, i-C_3H_7, C_2H_5



26

R = CH_3, t-C_4H_9, CH_2=$CHCH_2$

Scheme 7. Preparation of chiral pyridino-18-crown-6 ligands



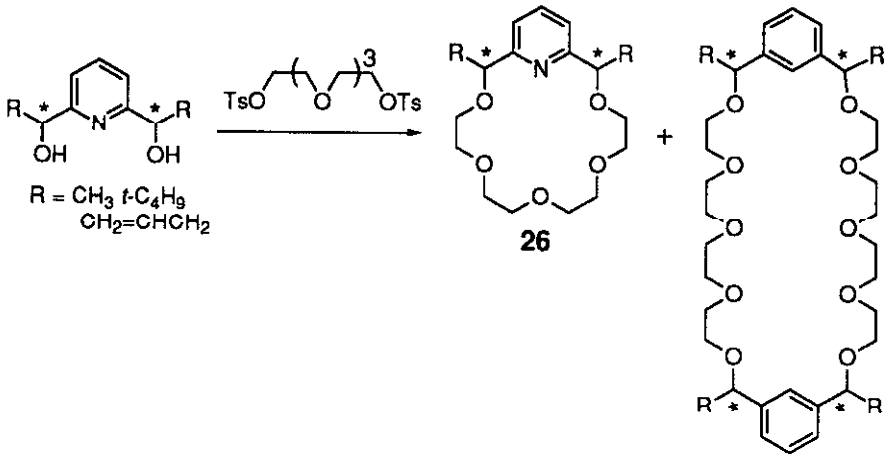
R	Yld (%)
Me	56
iPr	55
iBu	43
secBu	52
tBu	73
Ph	36

New pyridino-18-crown-6 ligands containing two methyl, two *t*-butyl, or two allyl substituents on chiral positions next to the pyridine ring (**26**, Figure 4) have recently been prepared by Yoichi Habata, Jolene Young and undergraduate Steven Castle (Scheme 8) [55]. As shown in Scheme 8, 2:2 macrocyclic adducts, the chiral dipyridino-36-crown-12 ligands, were also isolated in these reactions. The 18 crown 6 ligands **26** exhibited enantiomeric recognition toward chiral ammonium salts. New chiral cleft **27**, prepared by Paul Hellier as shown in Scheme 9, also exhibited considerable enantiomeric recognition for the chiral organic ammonium salts [56].

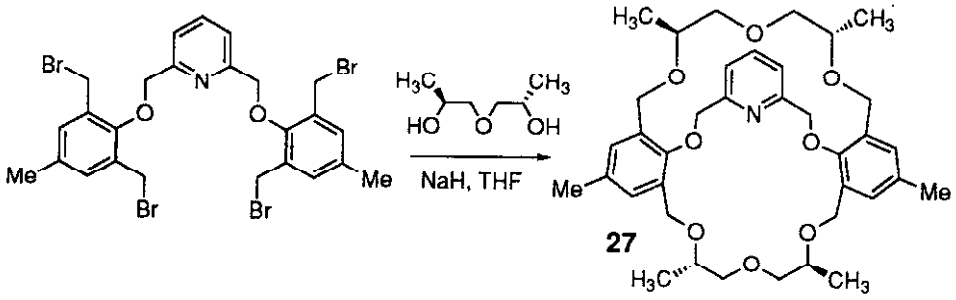
6. Azacrown Ethers

Our initial efforts to prepare the azacrown macrocycles centered on the synthesis of allyloxymethyl-substituted diaza-18-crown-6 (**28**, Figure 5) for attachment to silica

Scheme 8. Preparation of chiral 2,16-disubstituted pyridino-18-crown-6 ligands **26** and the 36-crown-12 by-products

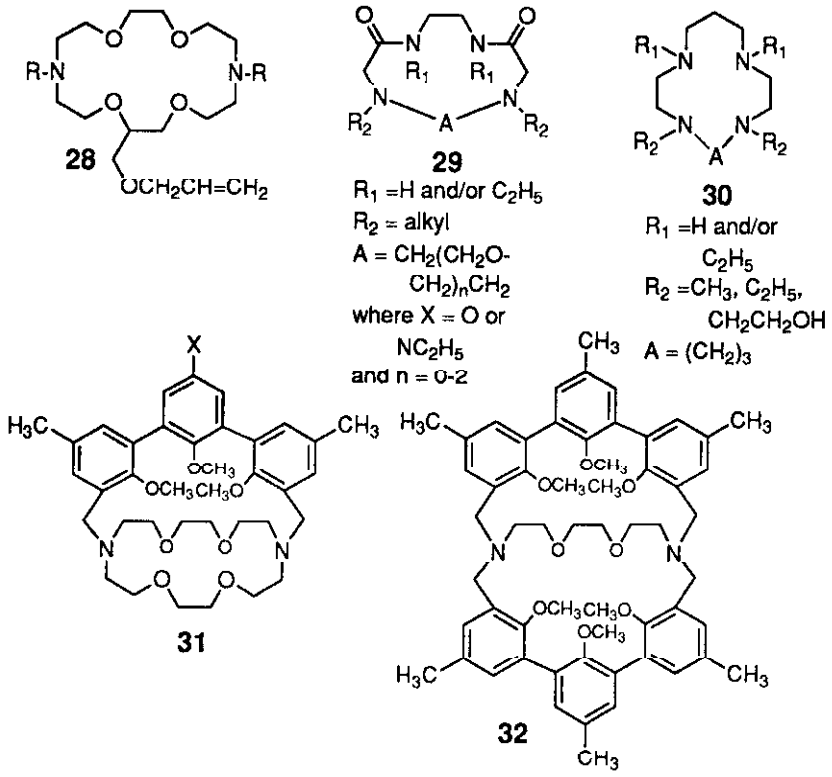


Scheme 9. Preparation of chiral cleft **27**



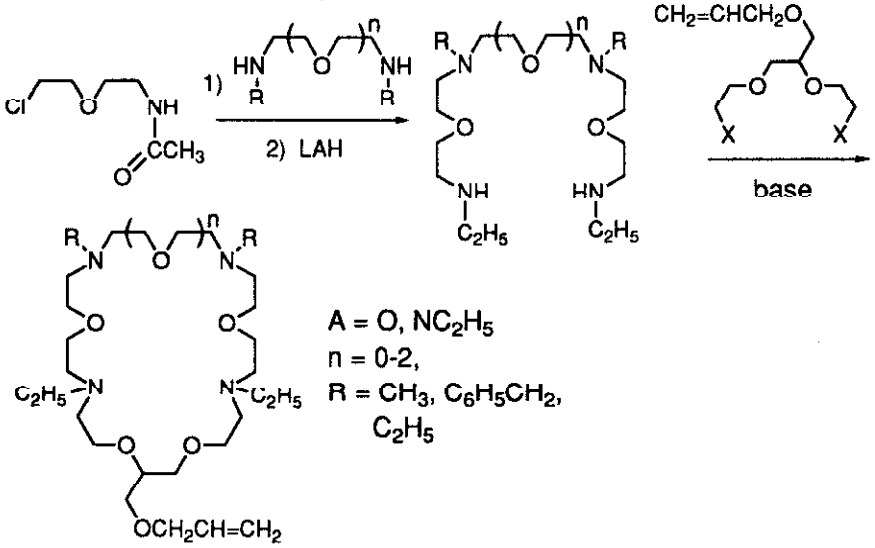
gel [57]. We had prepared 18-crown-6-bound silica gel and found that it could not remove heavy metals from water [58]. The azacrown ethers have strong interactions with the heavy metals. Dr. Krzysztof Krakowiak prepared **28** by treating diazapentaethylene glycol with allyl glycidyl ether to form the allyloxymethyl-substituted hexaethylene glycol. This glycol was treated with tosyl chloride and base to close the ring [57]. The overall yield was 36%.

Figure 5. Azacrown ethers and polycyclic ligands



We realized that azacrown ethers containing more than two nitrogen atoms were needed to form very strong complexes with all types of heavy metal ions. The building block method was devised by Krakowiak to prepare a variety of polyaza macrocycles, such as the ones shown in Scheme 10 [59]. N-[2-(2-Chloroethoxy)-ethyl]acetamide, prepared by treating 2-(2-aminoethoxy)ethanol with acetic anhydride followed by thionyl chloride, was reacted with a bis-primary amine in a 1:2 ratio followed by reduction to form an elongated bis-secondary amine synthon as shown. This synthon was treated with an allyloxymethyl-substituted ditosylate to form

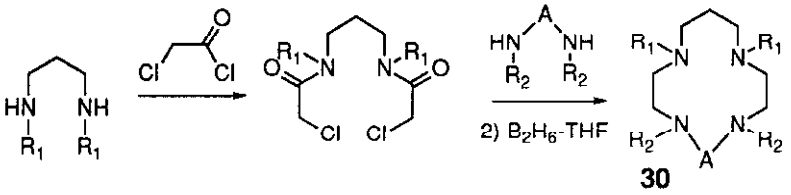
Scheme 10. Preparation of azacrown ethers using the building block method



the macrocycle [59]. A total of 23 polyazacrown ethers was prepared by Krakowiak using this new building block method [59].

A "crab-like" method to form the azacrown macrocycles was next developed by Krakowiak to prepare the polyazacrowns containing one or two secondary amine functions. A secondary amine allows the macrocycle to be attached to a solid support without the need of a vinyl-substituent. As shown in Scheme 11, a "crab-like" bis(α-chloroamide) intermediate can be prepared from any diamine and chloroacetyl chloride. The chloride ions of the bis(α-chloroamide)s are excellent leaving groups and this synthon interacts with any bis-secondary amine to form a macrocyclic diamide, such as **29** or **30** (Figure 5) [60-64]. The macrocyclic diamides were reduced with diborane to form the polyazacrown ethers. It is important to note that the amide nitrogen atoms of the bis(α-chloroamide)s do not act as nucleophiles so that they can contain hydrogen atoms in the amide groups (R_1 = H). Thus, polyazacrown ethers can

Scheme 11. Preparation of azacrown ethers using the crab-like method



30

be prepared with one or two secondary amines without the need for protecting groups.

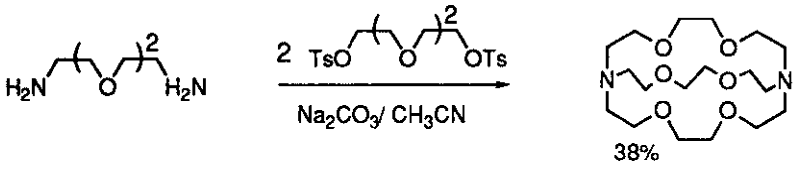
Many other azacrown macrocycles have been prepared in our laboratory. We have written reviews [64,65] and a book [66] which describe these interesting ligating agents.

7. Cryptands and Other Polycyclic Ligands

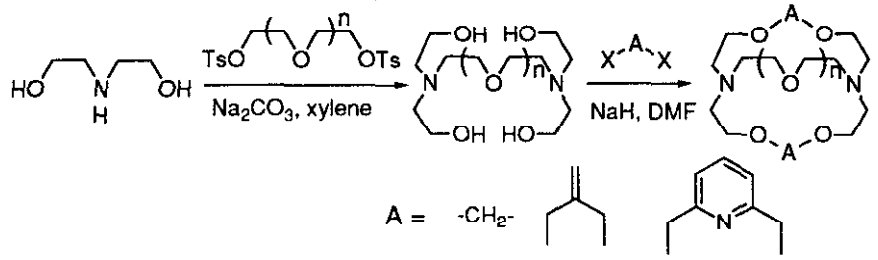
Our main research focus during the early 1990s was to prepare the nitrogen atom-containing macrocyclic and macropolycyclic ligands by new high yield reactions. Cryptands interact very strongly with metal ions [5]. Külstad and Malmsten attempted to prepare cryptands in one-step by treating oligoethylene glycol diiodides with the appropriate diamines, but did not observe the bicyclic products [67]. Krakowiak found that reaction of commercially available 3,6-dioxa-1,8-octanediamine with two equivalents of commercially available triethylene glycol ditosylate gave cryptand [2.2.2] in a 38% yield (Scheme 12) [68]. Other aliphatic cryptands were also prepared in good yields by this one-step process [64,68]. The one-step method was used to synthesize some cryptahemispherands and cryptaspherands (**31, 32**, Figure 5) [69]. Haoyun An and Krakowiak also developed a novel two-step route to some unsymmetrical cryptands (Scheme 13) [70].

Haoyun An and Krzysztof Krakowiak prepared a series of macrobicyclic polyethers with nitrogen atom bridgeheads (diptychands) in remarkably high yields (Scheme 14) [71]. The diamine portion of the starting N,N′-bis(2-hydroxyethyl)-

Scheme 12. One-step method to prepare cryptand [2.2.2]

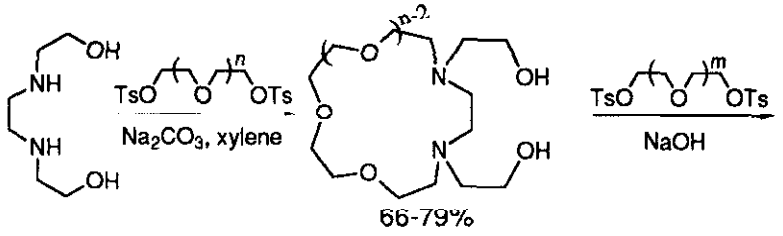


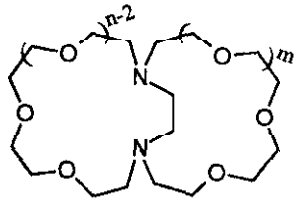
Scheme 13. Two-step method to prepare unsymmetrical cryptands



ethylenediamine reacted with the ditosylate when a carbonate base was employed. The N,N′-bis(2-hydroxyethyl)-substituted diazacrown ether product reacted with a second ditosylate using a stronger base to give the macrobicyclic ligand. As shown in Scheme 14, the yields of this two-step reaction for the preparation of the "butterfly" shaped macrobicyclic ligands were remarkably good. The 15-crown-5/15-crown-5 macrobicycle (n = 3, m = 1) was prepared in an overall yield of 38% [71].

Scheme 14. Preparation of diptychand macrobicycles and suitcase-shaped macrotricycles



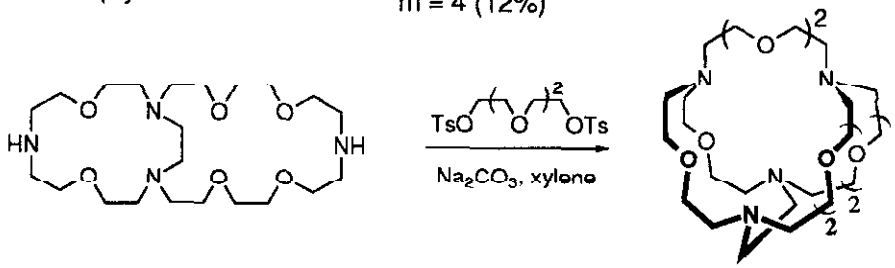


diptychands

n = 2
m = 1 (53%), m = 2 (46%), m = 3 (39%), m = 4 (16%)

n = 3
m = 1 (55%), m = 2 (46%), m = 3 (40%), m = 4 (13%)

n = 4
m = 1 (68%), m = 2 (60%), m = 3 (20%), m = 4 (12%)



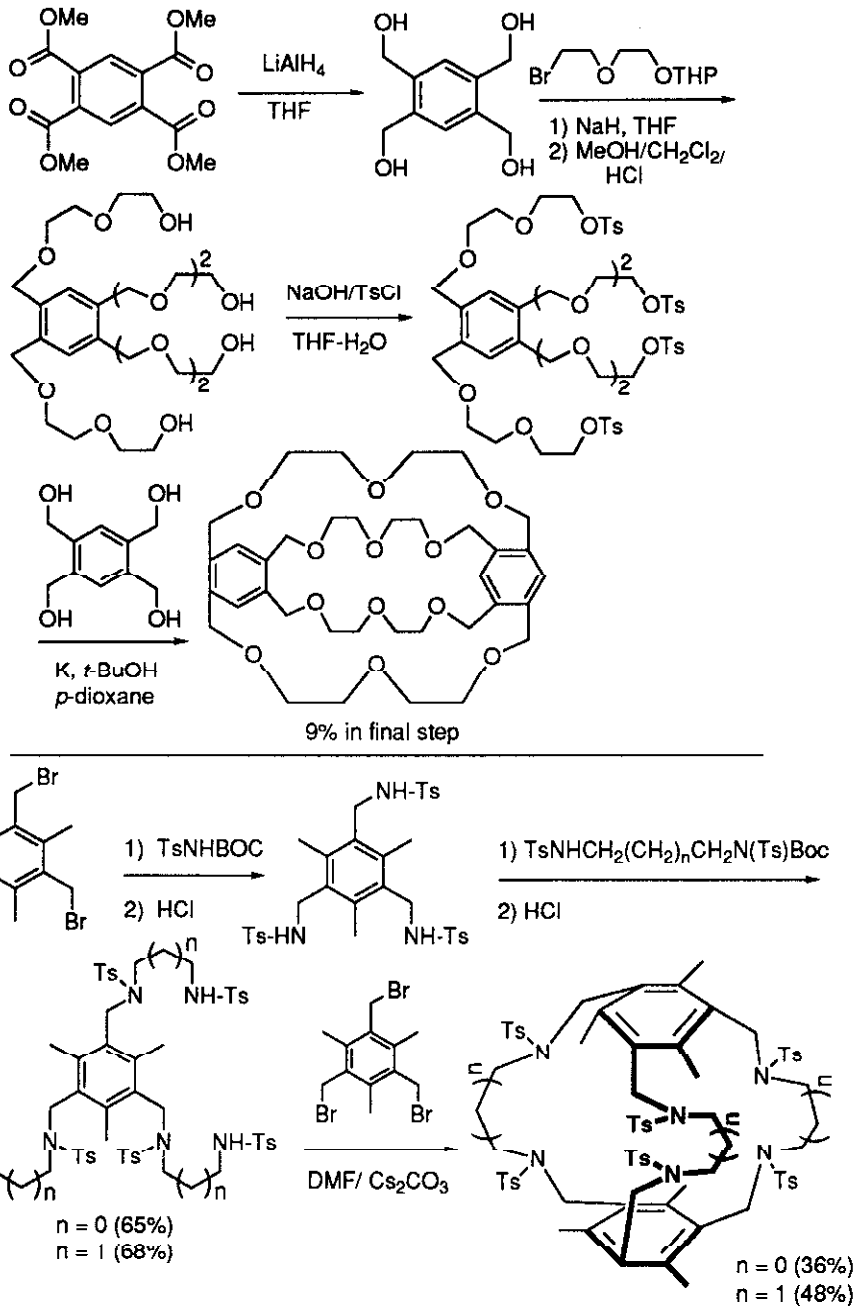
When glycols containing internal N-tosylamino units were used, macrobicyclic polyethers containing two N-tosyl groups were obtained [72]. The tosyl-protecting groups were removed and the internal amine units were connected to form suitcase-shaped macrotricyclic ligands as shown in Scheme 14 [72]. A review covering this research and work done by others on macropolycyclic ethers has been published [73].

Some interesting benzene-bridged macrobicyclic and macrotricyclic ligands have been prepared in our laboratory by Haoyun An and Krzysztof Krakowiak. As shown in Scheme 15, a new benzene-bridged macrotricyclic ligand was synthesized from tetraethyl 1,2,4,5-benzenetetracarboxylate by a five-step process [74]. An analogous macrobicycle was prepared in a similar manner from triethyl 1,3,5-benzenetricarboxylate. A crystal structure of that macrotricycle verified the structure as analogous to that shown in Scheme 15. This ligand has selectivity for Cs^+ over Na^+ and Pb^{2+} [74]. Mesitylene-bridged hexaazamacrobicyclic compounds were prepared by Krakowiak, as shown in Scheme 15 [75].

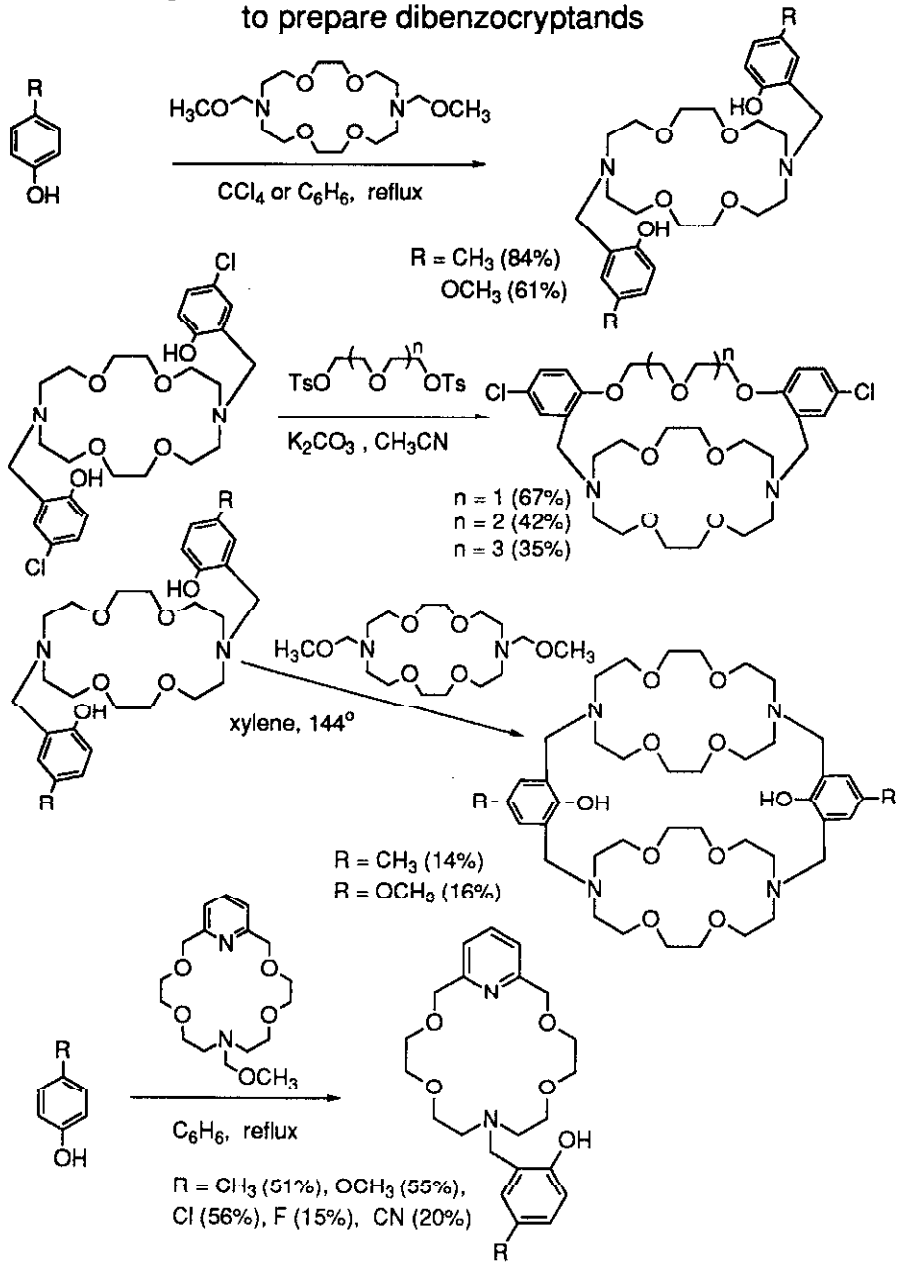
8. The Mannich Reaction in the Synthesis of Azacrown Ethers and Cryptands

We have been interested in the synthesis of proton-ionizable ligating compounds for many years. We first prepared the hydroxypyridine- and triazole-containing crown ethers as mentioned above. Andrei Bordunov from Lukyanenko's Odessa laboratory joined our group in early 1993. Lukyanenko and his coworkers had been using a modified Mannich reaction to introduce phenolic fragments into azacrown ethers and cryptands [76,77]. We realized that we could use the Mannich aminomethylation reaction to attach many types of phenols onto the azacrown ether framework as well as to prepare azacrown ethers containing phenols as part of the macrocyclic ring. Bordunov initially prepared N,N′-bis(2-hydroxy-5-methylbenzyl)- and N,N′-bis(2-hydroxy-5-methoxybenzyl)-substituted diaza-18-crown-6 ligands by treating N,N′-bis(methoxymethyl)diaza-18-crown-6 with the appropriate phenols in refluxing carbon tetrachloride as shown in Scheme 16 [78]. These bis-phenol-substituted diaza-18-crown-6 macrocycles have been used by us to form benzene-containing cryptands by treatment with oligoethylene glycol ditosylates and base, as shown in Scheme 16 [79]. Two bis(diaza-18-crown-6) ligands connected by phenol linkages were prepared in yields of 14% and 16% by treating the bisphenol-substituted diaza-18-crown-6 compounds with another N,N′-bis(methoxymethyl)diaza-18-crown-6 in refluxing xylene (Scheme 16) [78]. A higher reflux temperature was needed to accomplish the second aminomethylation reaction. Bordunov and Paul Hellier also attached various substituted phenol fragments onto azapyridino-18-crown-6 by treating N-(methoxymethyl)azapyridino-18-crown-6 with the phenol in refluxing

Scheme 15. Preparation of benzene-bridged macrotricyclic and mesitylene-bridged hexaazamacrobicyclic ligands



Scheme 16. Preparation of phenol-substituted azacrown ethers using a modified Mannich reaction and their use to prepare dibenzocryptands

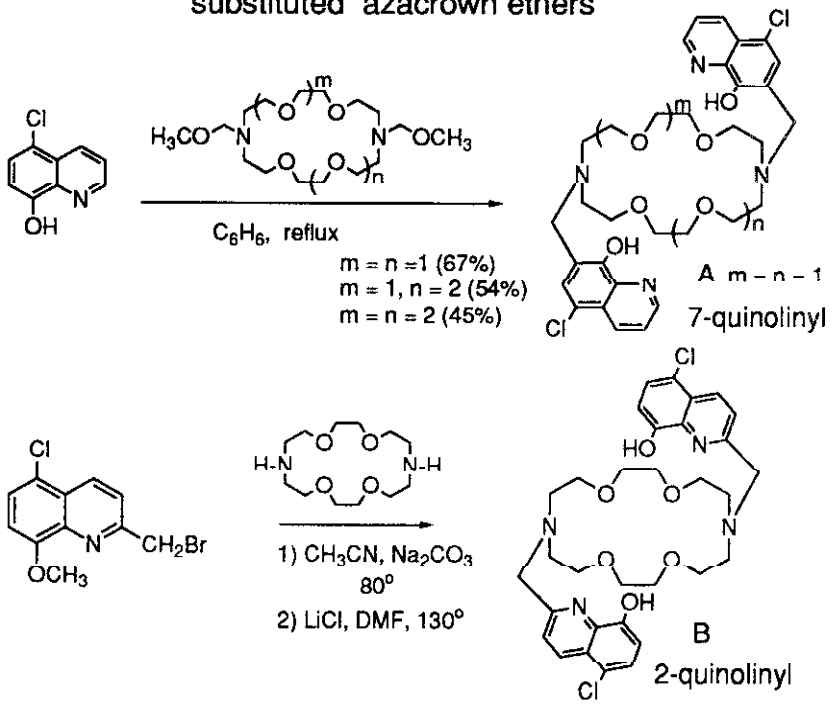


benzene as shown in Scheme 16 [80]. Good yields were obtained for these reactions except when the phenol ring had an electron-withdrawing substituent.

The modified Mannich reaction reaction allows the attachment of all types of phenolic materials to the azacrown ethers. We have a special interest in the synthesis of bis(8-hydroxyquinoline)-containing diaza-18-crown-6 ligands because of the possiblity for 1:2 coordination of cations with two 8-hydroxyquinoline moieties in one molecule. 8-Hydroxyquinoline has been used extensively as an extraction, chromogenic, and precipitation reagent in metal cation analysis [81]. Bordunov prepared the bis((5-chloro-8-hydroxy-7-quinolinyl)methyl)-substituted diaza-18-crown-6 by treating N,N′-bis(methoxymethyl)diaza- 18-crown-6 with 5-chloro-8-hydroxyquinoline (CHQ) as shown in Scheme 17 [82]. We realized that different positioning of the coordination sites could dramatically change the complexing properties of the ligand. Therefore, Bordunov also prepared the bis((5-chloro-8-hydroxy-2-quinolinyl)methyl)-substituted diaza-18-crown-6 from 2-(bromomethyl)-5-chloro-8-methoxyquinoline as shown in Scheme 17 [82,83].

The two bis-CHQ-substituted diazacrown ligands were, indeed, very different complexing agents. The 7-quinolinyl-substituted ligand formed very stable complexes in methanol with Mg^{2+}, Ca^{2+}, Cu^{2+}, and Ni^{2+}, but not with the alkali metal ions. The

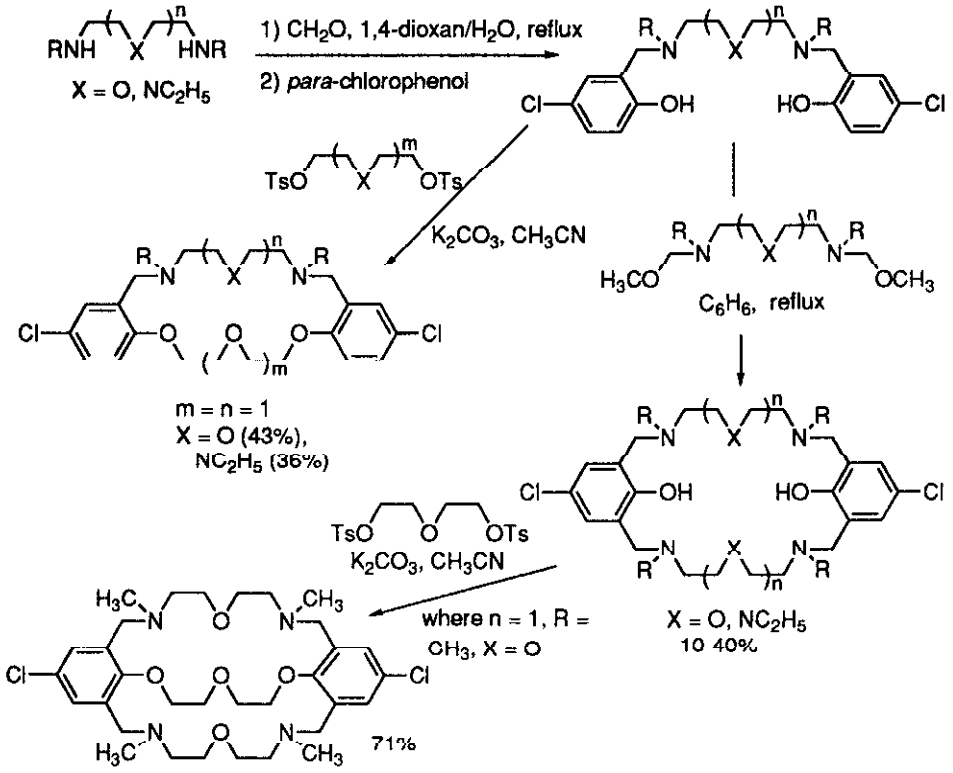
Scheme 17. Preparation of 5-chloro-8-hydroxyquinoline-substituted azacrown ethers



2-quinolinyl-substituted ligand formed very strong complexes in methanol with K^+ and Ba^{2+} ($\log K$ = 6.61 and 12.2, respectively), but not with Mg^{2+} or Cu^{2+}. ^1H NMR and X-ray crystallographic studies indicate that the 2-quinolinyl-substituted ligand forms a cryptate-like structure when coordinated with K^+ or Ba^{2+}. Complete details of these two interesting ligating systems can be found in the published papers [82,83].

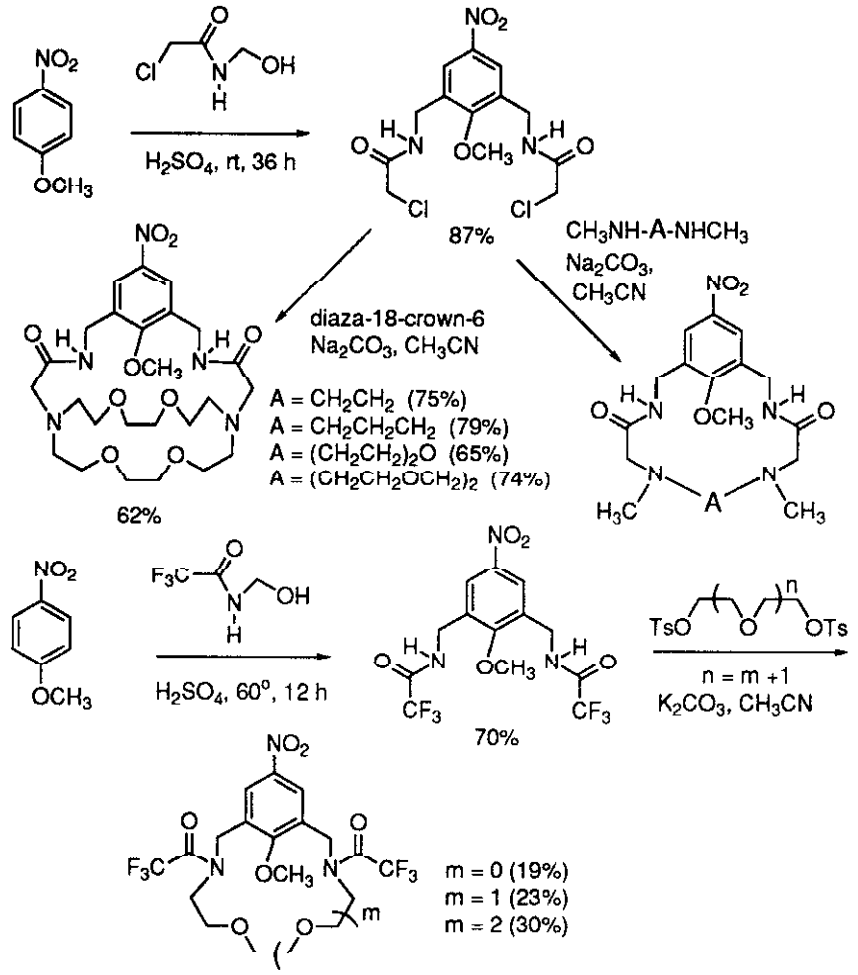
Scheme 18 shows other benzoazacrown ethers and benzocryptands that have been prepared using the modified Mannich reaction [84]. Victor Pastushok and Andrei Bordunov showed that open chain diamines could be treated with formaldehyde in methanol followed by a phenol to give a bisphenol connected by a diamine function. The bisphenol then was reacted with the bis(methoxymethyl)diamine to give the dibenzotetraazacrown ether containing two intraannular hydroxy groups. These two hydroxy moeties were subsequently connected to form a benzocryptand (Scheme 18) [84].

Scheme 18. Preparation of dibenzoazacrown ethers and a benzocryptand using a modified Mannich reaction



The Einhorn amidomethylation reaction is somewhat similar to the Mannich aminomethylation reaction. The Einhorn reaction is a convenient way to prepare aromatic building blocks for macrocyclization [85]. Victor Pastushok and Kejiang Hu prepared nitroanisole-containing tetraazacrown ethers and a cryptand using the intermediate nitroanisole-containing bis(α-chloroamide) prepared by the Einhorn reaction as shown in Scheme 19. Three nitroanisole-containing diazacrown ethers with trifluoroacetyl functions attached to the macroring nitrogen atoms were also synthesized using the Einhorn reaction (Scheme 19) [85].

Scheme 19. Preparation of methoxybenzoazacrown ethers using the Einhorn reaction



9. Conclusion

We have prepared a wide variety of crown ethers in our laboratory since 1970. Our macrocyclic ligands have included: thiacrown ethers; diestercrown ethers; proton-ionizable crown ethers containing the 4-hydroxypyridine, 4-pyridone, triazole, and pyrimidone subcyclic moieties; proton-ionizable crown ethers containing the dialkylhydrogenphosphate and sulfonamide functions; chiral pyridino-18-crown-6 ligands; and a host of azacrown ethers including some with phenolic substitutents. We have discovered new methods to synthesize the azacrown ethers including the "crab-like" synthesis of the polyazacrown ethers, new one-step syntheses of the cryptands, and the use of Mannich and Einhorn reactions in azacrown ether and cryptand syntheses.

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