EXPLORATIONS WITH POLYCARBOCYCLIC CAGE COMPOUNDS

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A variety of novel cage-functionalized pyridyl containing crown ethers have been prepared for use in selective alkali metal complexation studies. A highly preorganized, cage-functionalized cryptand also has been designed and has been synthesized for use as a selective Li^+ complexant. The alkali metal picrate extraction profiles of these cage-functionalized crown ethers also have been studied.

Novel cage-functionalized diazacrown ethers have been prepared for selective alkali metal complexation studies. Alkali metal picrate extraction experiments have been performed by using this new class of synthetic ionophores to investigate the effects of cage-annulation and the influence of *N*-pivot lariat sidearms upon their resulting complexation properties**.**

Novel pyridyl containing calix[4]arene receptors were prepared. Analysis of their respective ^1H NMR and ^{13}C NMR spectra suggests that calix[4]arene moieties in the ligand occupy the cone conformation. The complexation properties of these host molecules were estimated by performing a series of alkali metal picrate extraction experiments.

An optically active cage-functionalized crown ether which contains a binaphthyl moiety as the chiral unit was prepared. The ability of the resulting optically active crown ether to distinguish between enantiomers of guest ammonium ions (i.e.,

phenylethylamonium and phenylglycinate salts) in transport experiments was investigated.

Hexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5,15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione was prepared from hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$] pentadeca-10,12-diene-2,8-dione**.** Unanticipated but remarkable acid and base promoted rearrangements of this new cage dione to novel polycyclic systems were observed and subsequently were investigated. The structures of the new systems thereby obtained were determined unequivocally by application of X-ray crystallographic methods. It is noteworthy that the reactions reported herein each provide the corresponding rearranged product in high yield in a single synthetic step.

Pi-facial and regioselectivity in the thermal Diels-Alder cycloaddition between hexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5,15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione and ethyl propiolate have been explored. This reaction proceeds via stereospecific approach of the dienophile toward the *syn* face of the diene π-system. However, [4+2]cycloaddition proceeds with only modest proximal/distal regioselectivity. The structure of the minor reaction product was established unequivocally via application of X-ray crystallographic techniques.

ACKNOWLEDGEMENTS

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The author gives special thanks to God for never-ending encouragement and love through the days. The author thanks dear sisters and brothers in Christ for their endless and sincere prayer. The author is sincerely grateful to her family, mother and father, sisters, brothers, sister-in-laws, and brother-in-law for their patience, encourgement, support, and special love through this journey.

Finally, Special thanks to my grandmother who is now in Heaven-----.

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CHAPTER 1

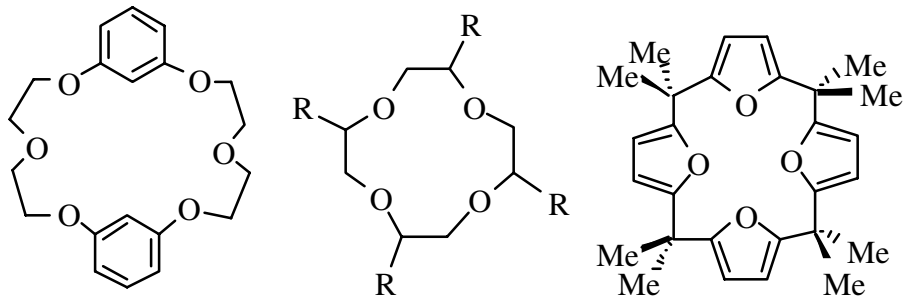
HOST-GUEST CHEMISTRY. SYNTHESIS AND ALKALI METAL PICRATE EXTRACTION CAPABILITIES OF NOVEL CAGE-FUNCTIONALIZED CROWN ETHERS AND CRYPTANDS CONTAINING PYRIDYL UNITS

INTRODUCTION

The chemistry of macrocyclic compounds[1] is one of the most interesting recent developments. In particular, interest has become focused on the ability of these compounds to complex metal cations selectively. Since Pedersen's discovery[2] of crown ethers, scientists have made considerable efforts to prepare these compounds and to investigate their possible applications to various fields. Prominent applications of crown ethers include (i) separation[3] of alkali, alkaline-earth, heavy metal ions, (ii) selective transport[4] of cations across synthetic, lipid, and naturally-occurring biological membranes, (iii) chiral recognition by using optically active crown compounds,[5] (iv) separation of isotopes,[6] (v) the study of organic reaction mechanisms,[7] and (vi) catalysts of organic reactions.[8]

In fact, the synthesis of many macrocyclic polyethers including **1**-**3** (Scheme 1.1)[9] had been reported prior to Pedersen's discovery.

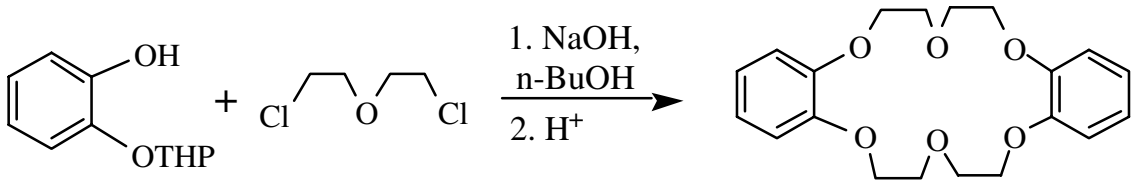
Scheme 1.1



1 **2** **3**

Nonetheless, crown ether chemistry is generally considered to have originated with Pedersen's isolation of benzo-18-crown-6 (**4**) from the reaction of catechol with -β, β'-dichlorodiethyl ether (Scheme 1.2). Indeed, Pedersen obtained the first evidence that crown ethers are able to function as cation hosts by his having isolated and characterized stable complexes between **4** and Na^+.

Scheme 1.2



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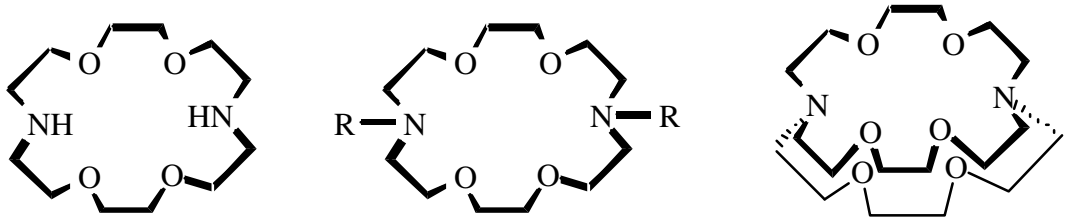
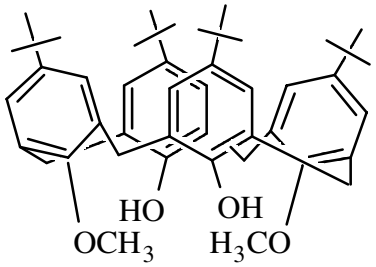
Subsequently, his research[10] on complexation properties and characteristics of crown ethers opened new areas of chemistry, i.e., host-guest chemistry, supramolecular chemistry, and studies of molecular recognition and inclusion phenomena.

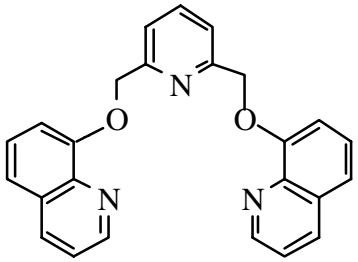
"Host-guest chemistry", a term coined by Cram,[11] is primarily concerned with the noncovalent interactions involved in host-guest binding. Hosts may be acyclic, macrocyclic or oligomeric and may possess cavities or clefts into which the guest fits. Representative host systems are shown in Scheme 1.3.

Scheme 1.3



Crown Ether **Lariat ether** **Cryptand**



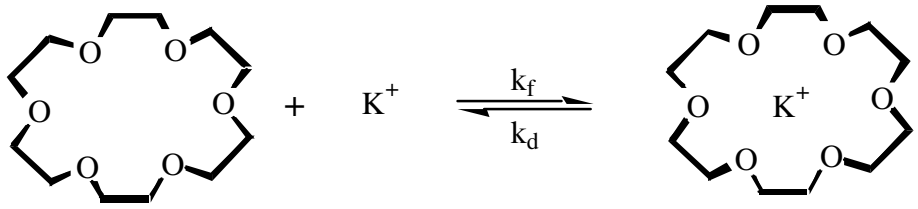


Calixarene **Podand**

Molecules or atoms which may be cationic, anionic or neutral can serve as "guests". Typical guests include cations such as metal ions and ammonium ions, polar neutral species such as acetonitrile, hydrogen-bonding compounds, aromatic substrates, diazonium salts, and anions.

Complexation of hosts with a variety of guests involve equilibrium reactions. As an example, complexation of K^+ by 18-crown-6 (**5**) is shown in Scheme 1.4. Here, k_f and k_d are the rate constants for complexation and dissociation, respectively.

Scheme 1.4



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The stability constant (K_s), which is the equilibrium constant for this reaction, indicates the stability of the resulting complex in the solution and is expressed by the following equation:

$$K_s = k_f / k_d = [\text{18-crown-6} : K^+] / [\text{18-crown-6}]\cdot[K^+]$$

The stability constant (K_s) is related to the free energy of formation (ΔG^o) of a complex by the following equation

$$\Delta G^o = - RT \log K_s$$

K_s values[12] are known for many complexes and reflect the extent to which a given ligand complexes selectively with a particular guest species. For example, selectivity is concerned with the ability of a given host (H) to discriminate among different cations M_1 and M_2.[13] The selectivity can be measured as the ratio of the stability constants of the complexes HM_1 and HM_2.

$$\text{Selectivity} = K_s [HM_1] / K_s [HM_2]$$

To prepare a host which will bind specific guests selectively is the main objective of the synthetic effort in macrocyclic polyether chemistry. The selectivities of crown compounds can be influenced by many factors, including the size-match between the cation and macrocycle cavity dimensions, conformational rigidity and flexibility of macrocycles, shape and topology of macrocycles, and number, type, and arrangement of donor atoms in the ring.

The "size-match principle" states that when the diameter of the metal cation roughly matches the hole diameter of the crown ether, the cation fit is particularly good, and the resulting stability constant (K_s) is generally highest when this occurs. The ionic crystal radii of alkali metal cations and the cavity sizes for crown ethers which have been obtained from X-ray crystallography are shown in Table 1.1[14] and Table 1.2,[15] respectively. As expected from comparison of the data in these two Tables, it has been demonstrated experimentally that K^+ fits snugly inside the cavity of 18-crown-6 (**5**),

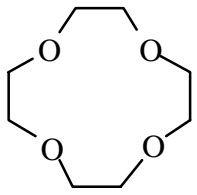
whereas Li^+, and Na^+ fit inside the cavity of 12-crown-4 (**6**) and 15-crown-5 (**7**), respectively. This principle also has been observed to hold for the metal ion complexation behavior exhibited by small preorganized macrocycles,[16] e.g., aza crown ethers, cryptands,[17] calixarenes,[18] etc.

Table 1.1. Cation sizes from X-ray crystallographic data

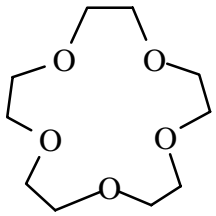
Cation	Li^+	Na^+	K^+	Rb^+	Cs^+
Radius (Å)	0.74	1.02	1.38	1.49	1.70

Table 1.2. X-ray data of cavity radii for several crown ethers

Ligand	12-Crown-4	15-crown-5	18-crown-6
Radius (Å)	0.60 ~ 0.75	0.86 ~ 0.92	1.34 ~ 1.43



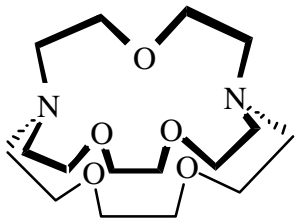
12-Crown-4 (**6**)



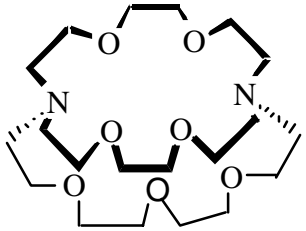
15-Crown-5 (**7**)

Conformational rigidity and flexibility of macrocycles[13,19a] is an another important factor that determines ligand binding selectivity. Rigid macrocycles such as small cryptands and other preorganized macrocycles have relatively fixed coordination cavities, whereas flexible macrocycles such as large polyether crowns and large cryptands behave as conformationally labile ligands and can form cavities of variable dimensions. For example, relatively rigid ligands like [2.2.1]cryptand (**8**) bind selectively to Na^+ and thus discriminate between Na^+ and metal cations that are either smaller or larger than Na^+. Such behavior of rigid ligands is expressed in terms of "peak selectivity".[20]

More highly flexible ligands like [3.2.2]cryptand (**9**) show "plateau selectivity"[17] for K^+, Rb^+, Cs^+, i.e, they display little difference in log K value among these cations. However, they are capable of distinguishing between these cations and smaller metal ions like Na^+, thereby affording significant K^+/Na^+ selectivity in their extraction behavior.[21] The behavior of ligands as a function of their molecular flexibility has been studied in, e.g., many macrocyclic antibiotics[22], and crown ethers[19] that contain incoporated pyridine, benzene, and cyclohexane moieties.



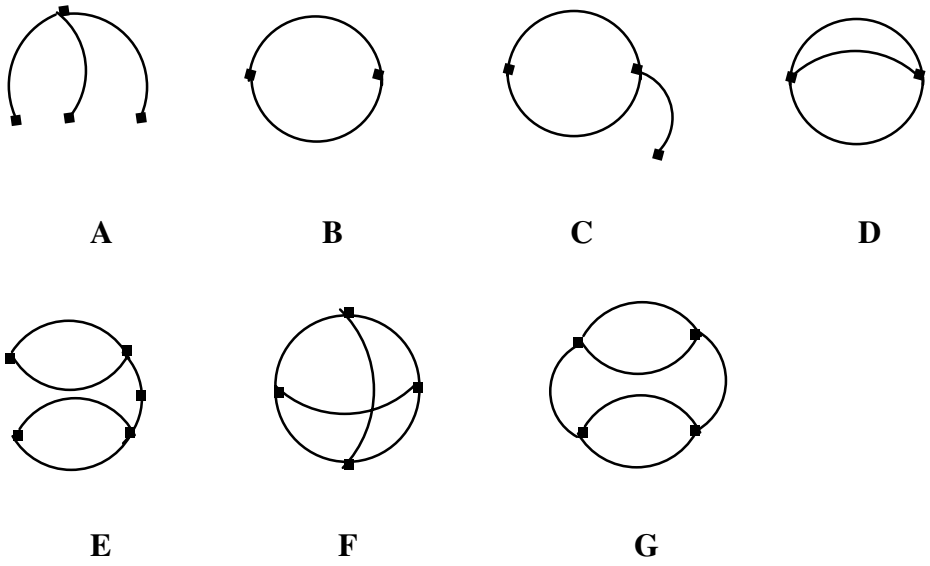
[2.2.1]cryptand (**8**)



[3.2.2]cryptand (**9**)

The shape of macrocyles and the topologies of their binding sites[23,24] can help to determine their selective binding properties. For spherical metal ions, optimum ligands should also possess spherical cavities, as is the case with cryptands. For the rod-like azide ion, the cavities should be somewhat oblate in shape. Significant affinity binding toward tetrahedral NH_4^+ also has been observed in cryptands that possesses a tetrahedral recognition site.[23] Overall ligand topology (connectivity, cyclic order, dimensionality) determines the manner and extent in which ligand and cation interact and also defines the nature of the complex thereby formed (podate, coronate, cryptate). A selection of possible ligand topologies (Figure 1.1) include (i) acyclic ligand **A** (podands), (ii) cyclic ligands **B** and **C** (crown ethers or cornands, lariet ethers), (iii) bicyclic ligands **D** and **E** (cryptands), and (iv) tricyclic ligands **F** and **G** (cylindrical and spherical cryptands).

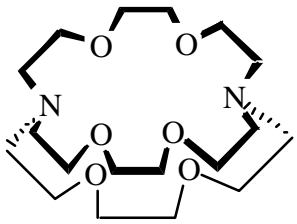
Figure 1.1. Topological representation of various types of hosts[13]



The type, number, and arrangement of donor atoms in the macrocyclic rings also play an important role to determine macrocycle selectivities. **A**-type donors, e.g., oxygen donor atoms in crown ethers, should have the largest affinities for **A**-type metal ions (alkali, alkaline-earth, and lanthanide ions) according to the 'hard and soft acid-base' principle.[25] Thus, complexes of purely oxygen-containing crown ethers with salts of the above cations tend to give high K_s values. However, **B**-type cations (Cu^{2+}, Ag^{+}, Co^{2+}, Ni^{2+}, etc.) interact less strongly with the 'hard' ether oxygens, thereby resulting in lower stabilities of the resulting complexes. Such cations interact favorably with 'soft' **B**-type donors such as nitrogen and sulfur. The results of investigation into the effects of successive substitution of nitrogen or sulphur for oxygen in crown ethers upon host-guest complex formation have been reported.[26]

For selective binding, the number of available donor atoms in the crown ether skeleton should match the coordination number of the particular guest ion. Reference values[27] for the optimum coordination numbers of cations in this regard are provided by

their respective coordination numbers with water molecules. For alkali metal ions, the coordination number is 6, 4 for Be^{2+}, 6 for Mg^{2+}, and 8 for Ca^{2+}, Sr^{2+}, and Ba^{2+}, respectively. The influence of this factor is clearly shown by a comparison[28] of the complexation properties of [2.2.2]cryptand (**10**) and [2.2.C_8] (**11**), which possess similar size cavities. Ligand **10** differs from **11** only by the lack of a pair of O-donor sites in one of the three bridges of the [2.2.2]skeleton in **11**. However, the Ba^{2+}/K^+ selectivity ratio is 10^4 for **10** but, only $<10^{-2}$ for **11**.



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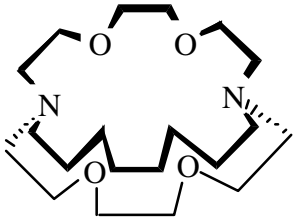


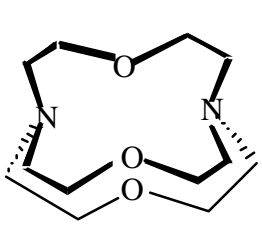
11

The symmetrical arrangement of the donor sites in a crown ether skeleton play an important role in complexation. Every deformation of the inner "charge-shell' that is not in keeping with the geometry of the guest reduces the binding ability of the ligand and the stability of the resulting complex.[29] Thus, the efficiency of K^+ complexation by 18-crown-6 (**5**) falls to *ca*. 50% when a C_2H_4 unit in **5** is replaced by a C_3H_6 unit.[30] A more pronounced effect is noted when an ethyleneloxy unit (-OCH_2CH_2O-) is replaced by an aromatic moiety[31] or by an acetal unit.[32]

The "preorganization principle", together with the results of molecular mechanics calculations, have been utilized to identify host systems that are able to recognize guest species with high selectivity. The design of preorganized host is a important concept: a host is said to be "preorganized" if its bound and unbound conformations closely

resemble one another. The preorganization principle[33] predicts that the log K for host-guest complex formation will be increased significantly if both the host and guest are well-structured for binding and have low solvation prior to complexation. The majority of preorganized macrocycles such as spherands, cryptahemispherands, calixarenes, and small cryptands form very stable complexes with targeted guests and show significant selectivity.[34]

The preorganization effect was first noted by Smith and coworkers,[35] who studied kinetics and thermodynamics of protonation of [1.1.1]macrocyclic cryptand (**12**). The dramatic effect of preorganization upon the protonation constant of [1.1.1]cryptand could be anticipated simply via consideration of the critical dimensions of the cryptand cavity. As an another example, the preorganized aza cryptand, **13**, is known to bind selectively to Li^+, and it also shows a high log K (H_2O) value of 5.5.[36] It was reported that encapsulation of Li^+ by **13** was not influenced by the presence of Na^+ ion.[37] This principle was also demonstrated experimentally via study of preorganized macrotricycle **14**, which appears to display good selectivity toward Cs^+ *vis-å-vis* the smaller alkali metal cations.[12, 38]



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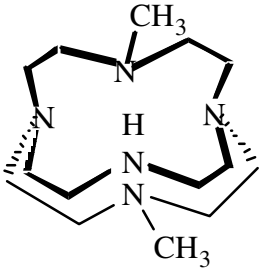
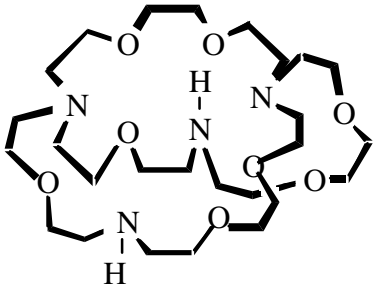


13



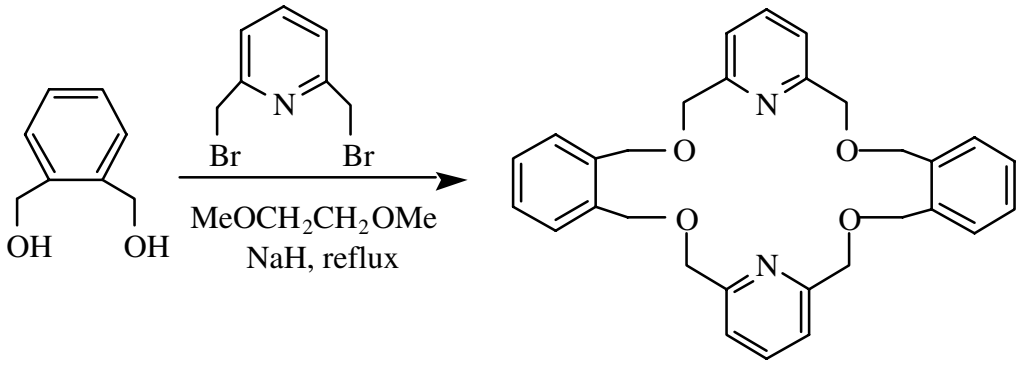
14

Another important approach that has been used to design preorganized macrocycles is based upon molecular mechanics (MM) calculations. This computational method treats molecules or complexes as an assembly of atoms held together by classical forces. Thus, MM calculations can be used to afford insight into the effectiveness of ligand-guest coordination from the steric strain point of view. Good agreement between CPK (space-filled) model estimations and X-ray crystallographic data for cavity sizes in crown ethers has been demonstrated in a variety of examples.[40] Thus, MM calculations can be used to predict ligand cavity sizes and to design preorganized macrocycles for application to complexation of specific guests.

As a way to design preorganized hosts, the introduction of one or more pyridine moieties into macrocyclic rings has been of special interest. It is known that the introduction of pyridine rings rigidifies the skeleton of crown compounds and thereby affects the complexation properties of pyridine-containing crown ethers, cryptands, and podand systems.[41] Such compounds have attracted considerable attention as host systems (i) for complexation of transition metals,[42-44] (ii) in thermodynamic studies on alkylammonium cation complexation[45a,46-49] and (iii) for complexation of some alkali metal cations.[47] Pyridine-containing crown ethers also have been used to prepare chiral crown compounds from natural products,[48,50] and their antibacterial activity[51] has been studied extensively.

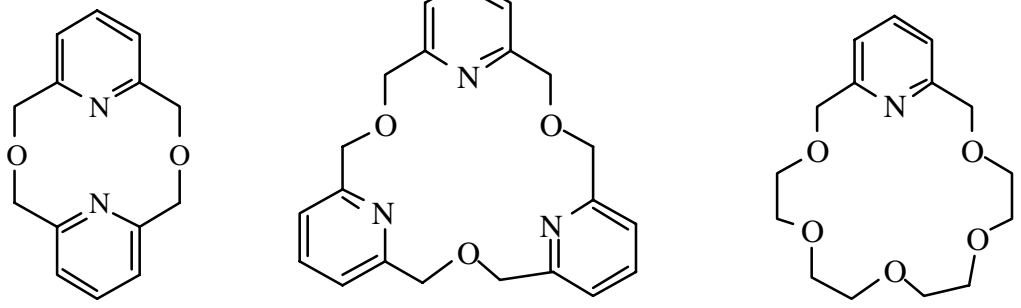
In 1973, Newkome and Robinson[52] prepared **15** by the reaction of 2,6-bis(bromomethyl)pyridine with 1,2-di(hydroxymethyl)benzene in the presence of sodium hydride.

Scheme 1.5



15

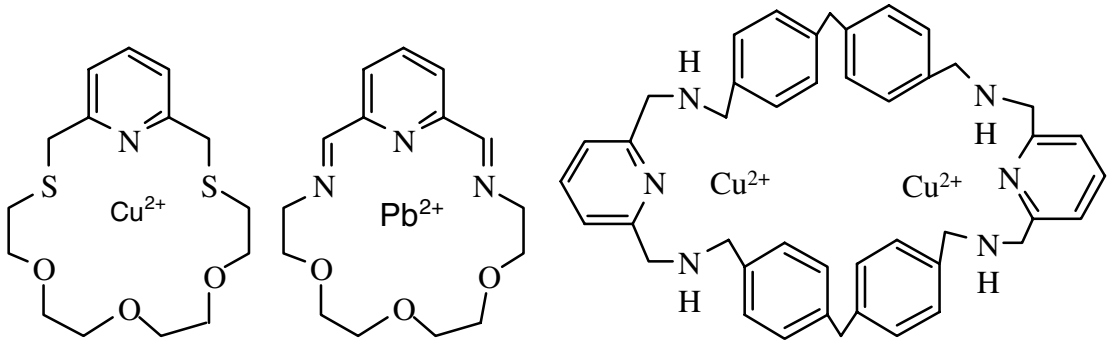
A series of crown compounds, e.g., **16**-**18** have been synthesized similarly via base-promoted reactions by using 2,6-bis(bromomethyl)pyridine as starting material.[45] In particular, thermodynamic studies of alkali metal cation complexation with pyridino-18-crown-6 (**18**) and its derivatives have been reported.[28,49] Some examples of complex formation by **18** with other guests include studies of its 1:1 complex with *t*-butylammonium perchlorate[46] and a complex that **18** forms with water in perchlorate and picric acid environments.[53]



16 **17** **18**

In addition, pyridino crowns that contain nitrogen or sulfur[54] have been prepared for use in complexation studies with transition metal cations. Some reported examples of

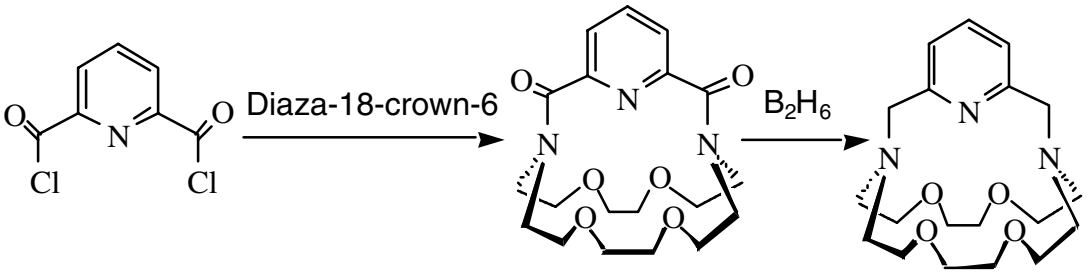
such complexes include a thia-ligand, i.e., **19**-$CuCl_2$ complex[55] and a diaza-ligand, i.e., **20**-PbSCN[42] complex. Meanwhile, ligand **21** was treated with $Cu(NO_3)_2$ to afford a 2:1 complex whose structure was established unequivocally via application of X-ray crystalliographic methods.[43]



19 **20** **21**

The first pyridyl-containing cryptand, **23**, was prepared by Wehner and Vögtle.[56] Cryptand **22** was obtained by reacting 2,6-pyridinedibenzoyl chloride with diaza-18-crown-6 in the presence of base. Subsequent diborane promoted reduction of **22** afforded **23** in 63% yield (Scheme 1.6).

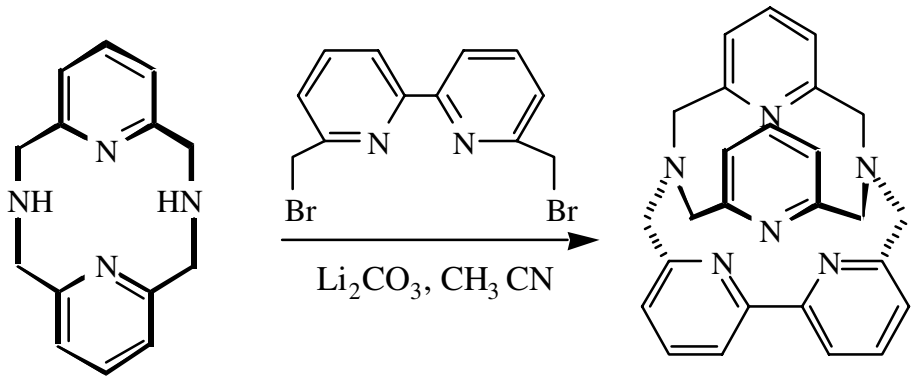
Scheme 1.6



22 **23**

Ligand **24** has been studied extensively.[44] Thus, Lehn and coworkers[57] isolated the LiBr complex of microbicyclic cryptand, **25**, which was prepared in 45% yield via reaction of **24** with 2, 6-bis(bromomethyl)bipyridine (Scheme 1.7).

Scheme 1.7



24 **25**

Numerous crown ethers that contain pyridyl units[45,51,57,58] have been synthesized; however, the results of studies of their corresponding alkali metal extraction properties have been reported only infrequently. When crown compounds containing pyridyl units are to be used as extractants, it is important to increase their lipophilicity. Crown ethers that lack lipophilic groups may not extract metal cations, because they may be too soluble in the aqueous phases of the extraction systems.

Finally, as an extension of our current interest in the chemistry of polycarbocyclic cage compounds, we have synthesized a variety of cage-functionalized crown compounds that contain pyridyl units. Here, the cage moieties serve as lipophilic hydrocarbon groups. Thus, from the standpoint of their liphophilicity, these cage-functionalized crown ethers provide some advantage as host systems.

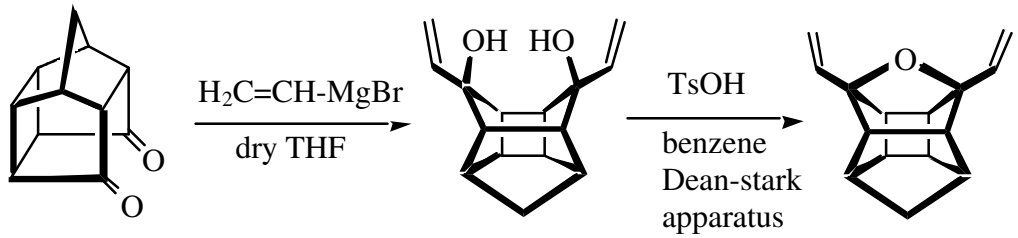
In addition to increasing the solubility of the crown ether in the organic phase of the extracion systems, the incorporation of a cage-moiety confers a measure of rigidity upon the host system and thereby affects its selectivity toward complexation with various guests. We now report the design and synthesis of a variety of novel cage-functionalized crown ethers, i.e., **39**, **40**, and **41**, and cryptands (**43**), each of which contains at least one pyridyl unit. The results of alkali metal picrate extraction experiments that employ these host systems are also described.

RESULTS AND DISCUSSION

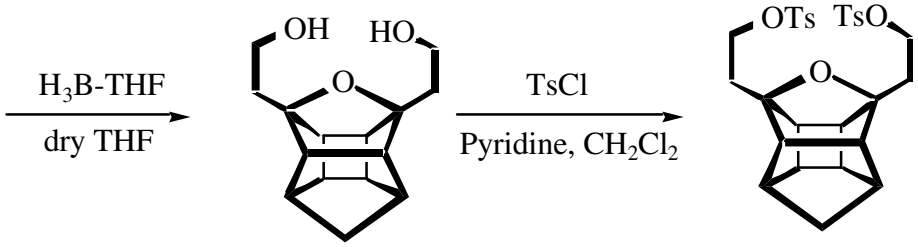
I. Synthesis of New pyridine-Containing Host Systems

The starting materials for the synthesis of crown compounds, i.e., **29** and **30** were prepared by using methods developed in our laboratory. Relevant procedures in this regard are shown in Scheme 1.8. When PCU-8,11-dione (**26**) was reacted with excess vinylmagnesium bromide, the corresponding *endo*-8,*endo*-11 diol, **27**, was obtained in 60% yield. Subsequent dehydration of **27** produced the corresponding hexacyclic ether, **28**. Hydroboration-oxidation of **28** afforded the corresponding cage diol, **29**, in 85% yield. Subsequent base promoted reaction of **29** with TsCl produced the corresponding oxahexacyclic ditosylate (**30**, 47% yield).

Scheme **1.8**



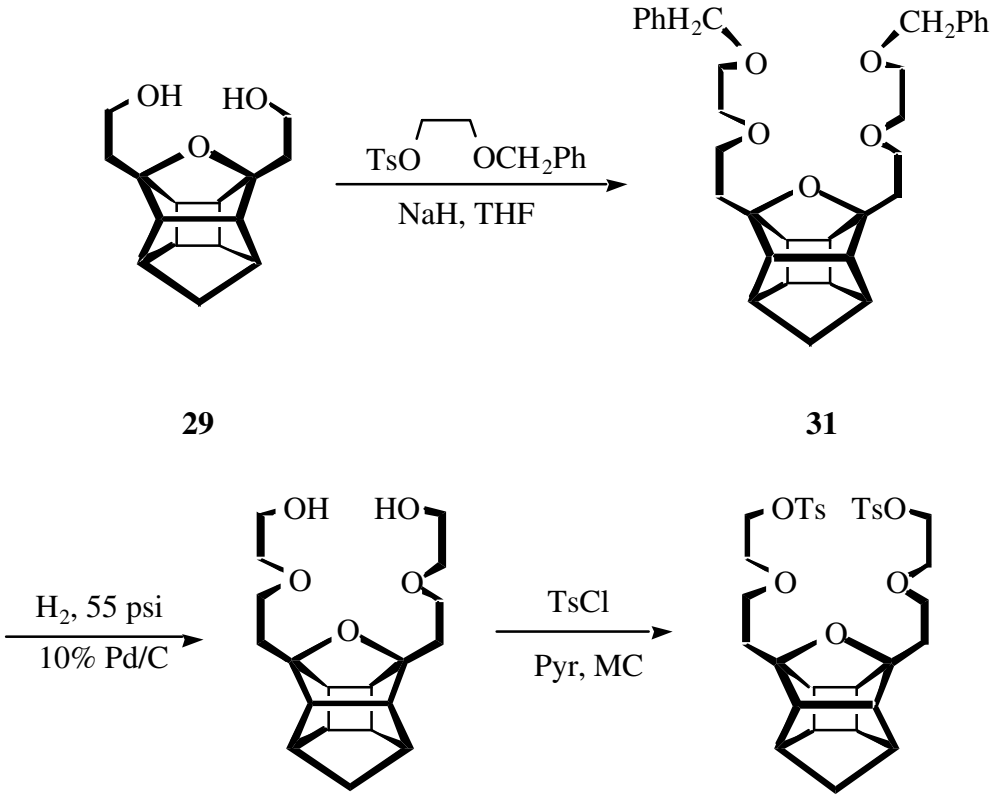
26 **27** **28**



29 **30**

The method employed to prepare **33** is shown in Scheme 1.9. Base promoted reaction of **29** with 1-benzyloxy-2-tosyloxyethane produced benzyl-protected ligand, i.e., **31,** in 44% yield. Subsequent bis(de-*O*-benzylation) of **31** produced **32** in 89% yield. Finally, base promoted reaction of **32** with TsCl afforded the corresponding cage ditosylate, **33**, in 70% yield.

Scheme 1.9

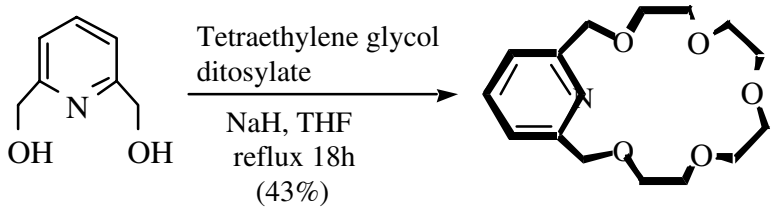


29 **31**

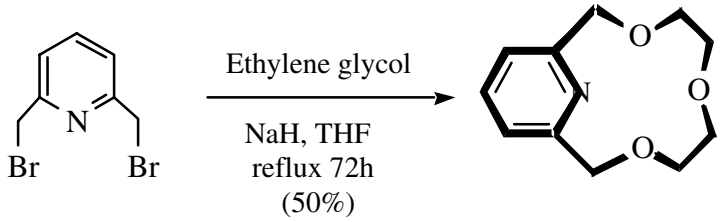
32 **33**

Model crown ethers employed in the extraction studies were prepared as shown in Scheme 1.10. Model crown ether **34**[45b] was prepared by reaction of tetraethylene glycol ditosylate with 2,6-pyridinedimethanol. Model compound **35** was prepared in 50% yield via Na^+ templated reaction of 2,6-bis(bromomethyl)pyridine[59] with diethylene glycol.

Scheme 1.10



34

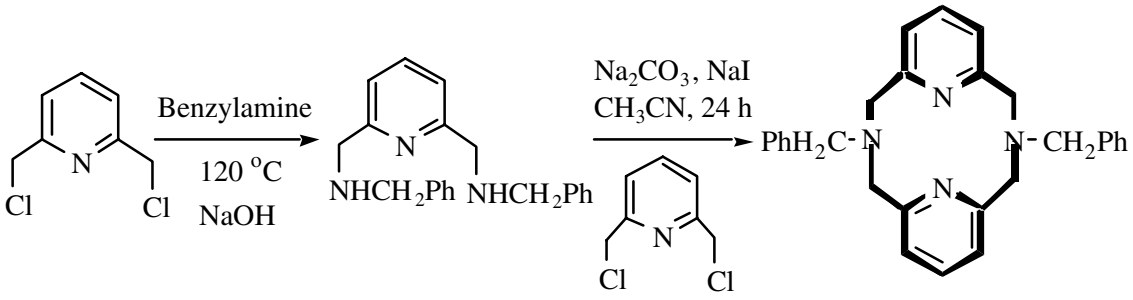


35

Efforts to prepare model compound **24** are shown in Scheme 1.11-13. As the first step to synthesize the corresponding *N*-benzyl-protected compound (**37**), 2,6-chloromethylpyridine was allowed to react with benzylamine during 24 h, thereby affording 2,6-bis[(*N*-benzyl)aminomethyl]pyridine, **36.**[43] Subsequent base promoted reaction of **36** with 2,6-chloromethylpyridine produced **37**[61] in 12% yield. In addition, the structure of **37** was estabilished unequivocally via X-ray crystallographic analysis (Figure 1.2). The X-ray crystal structure of **37** indicates that the four donating nitrogen

atoms are not in symmetrical arrangement in the solid state; this observation is consistent with the results of Monte Carlo calculations. Subsequent attempts to promote bis(***N***-debenzylation) of **37** via catalytic hydrogenolysis were unsuccessful.

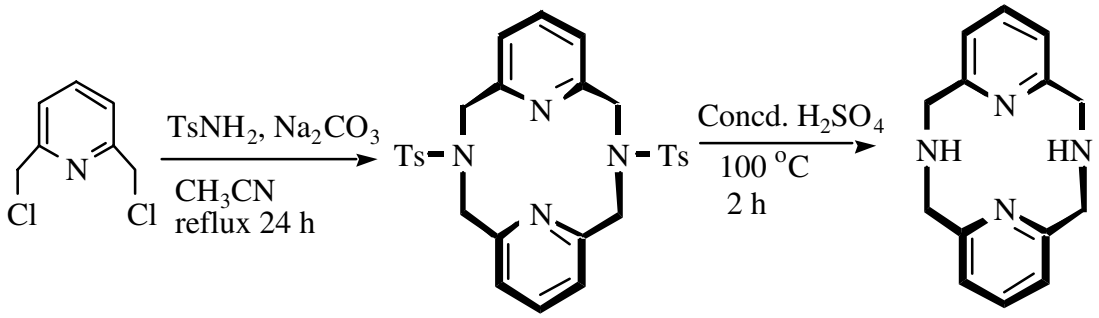
Scheme 1.11



36 **37**

Additionally, **38**[57] was prepared in low yield (16%) via base promoted reaction of 2,6-bis(chloromethyl)pyridine[59] with tosylamine. Acid promoted hydrolysis of the ***N***-tosyl groups in **38** to afford **24** was performed by using a previously reported procedure.[57]

Scheme 1.12



38 **24**

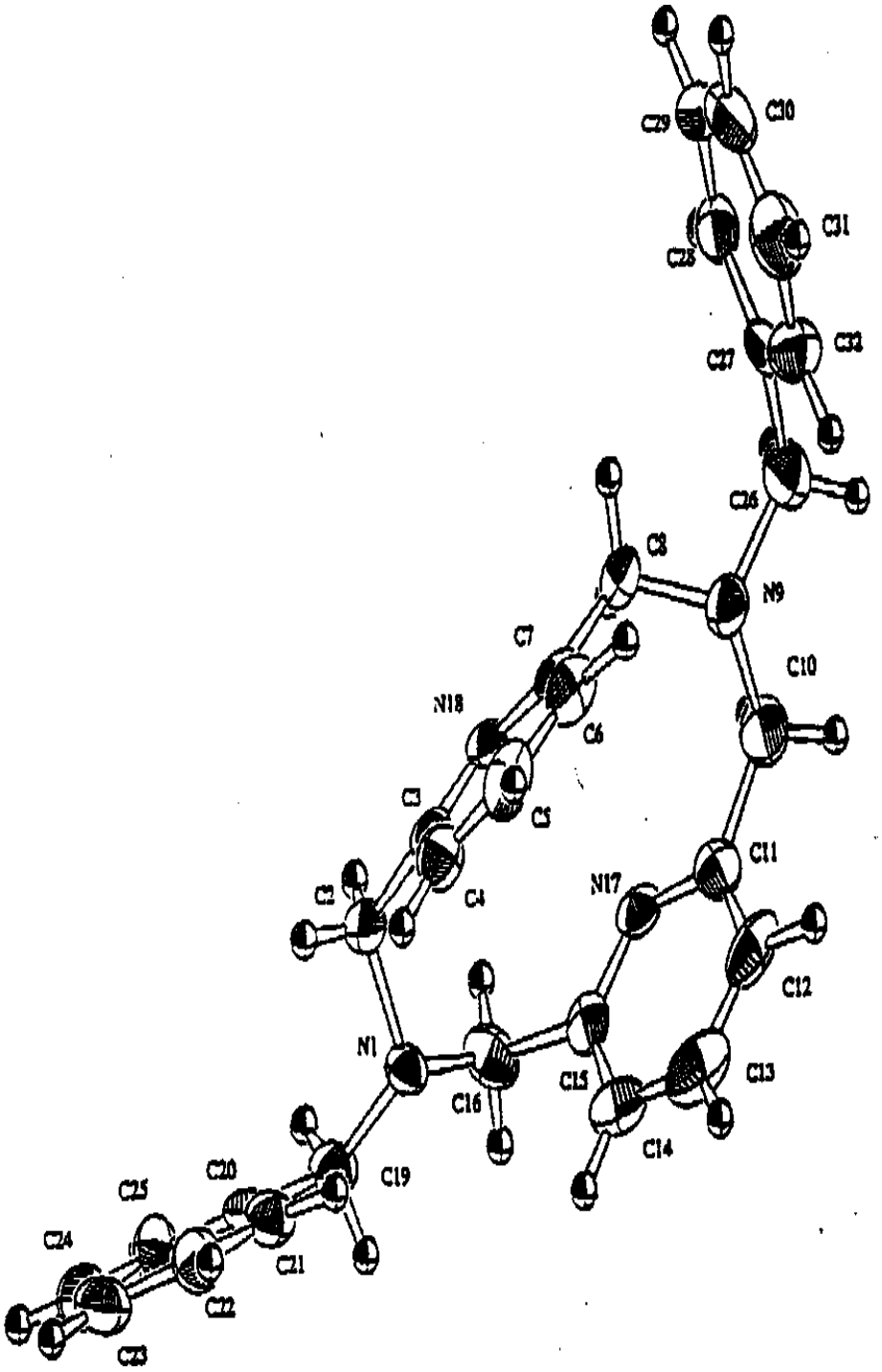
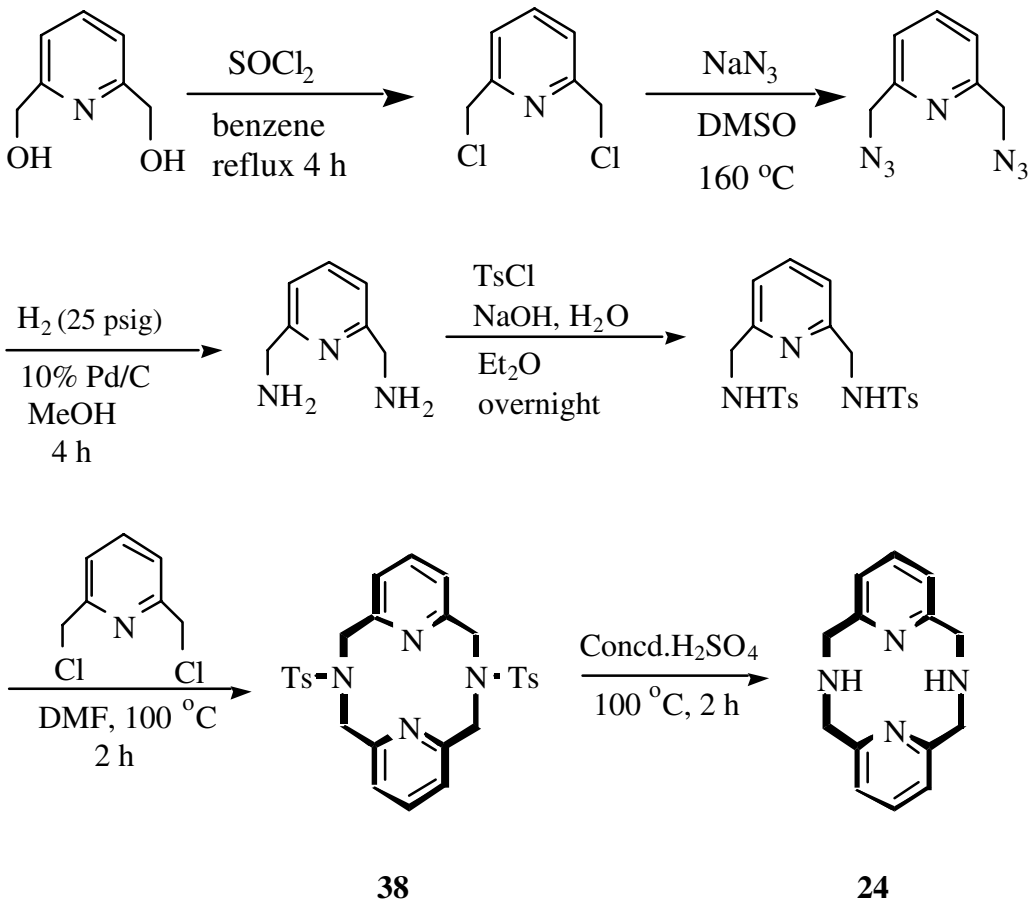


Figure 1.2. X-ray Structure drawing of **37**.

A procedure for large-scale synthesis of **24** is shown in Scheme 1.13. The steps that has been reported previously are employed.[57, 59, 60]

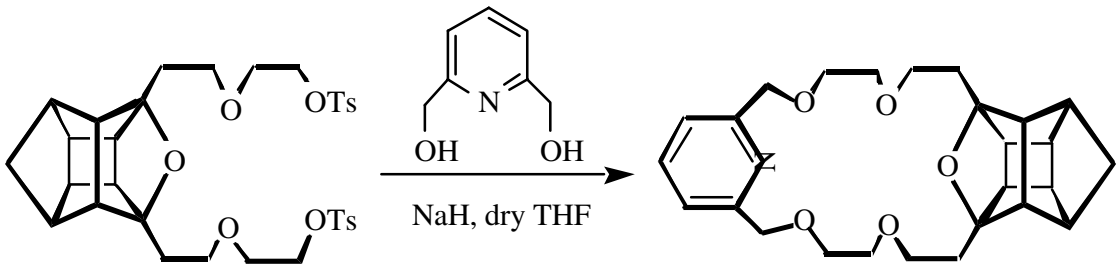
Scheme 1.13



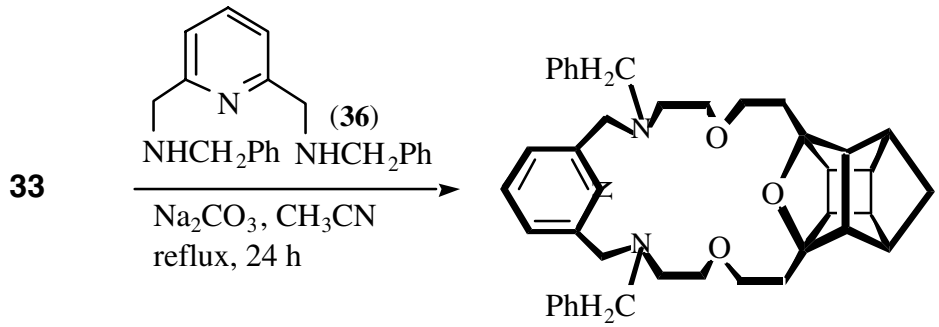
38 **24**

Cage-functionalized crown ethers **39**, **40**, and **41** were prepared by using the method shown in Scheme 1.14. Base promoted reaction of **33** with 2,6-pyridinedimethanol produced the corresponding cage-functionalized crown ether, **39**, in 38% yield. Similar reaction of **33** with 2,6-bis(***N***-benzylaminomethyl)pyridine (**36**)[42] afforded **40**. Crown ether **41** was obtained in 53% yield via the reaction of **29** with 2,6-bis(bromomethyl)pyridine.

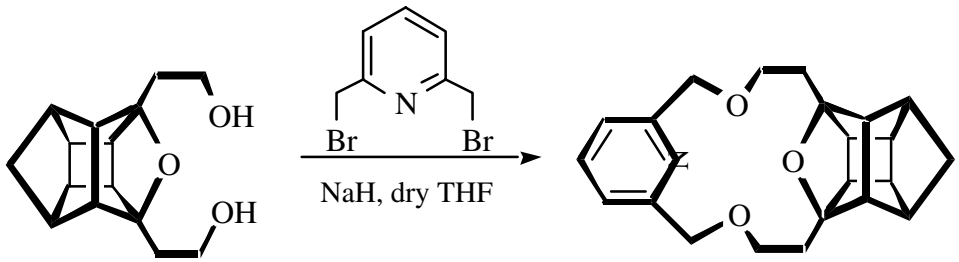
Scheme 1.14



33 **39**



33 **40**

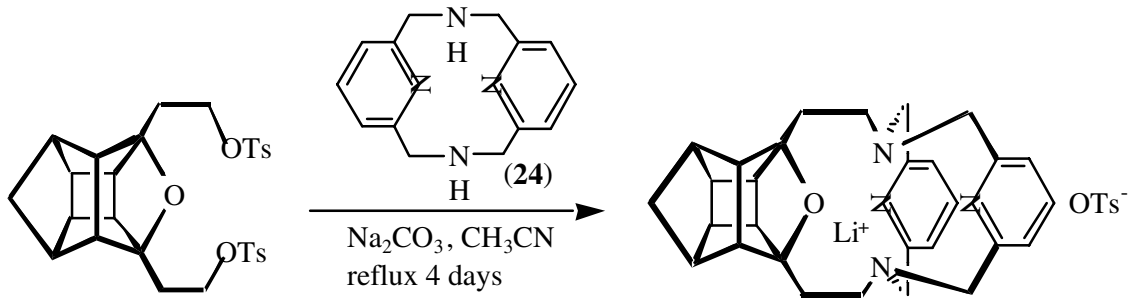


29 **41**

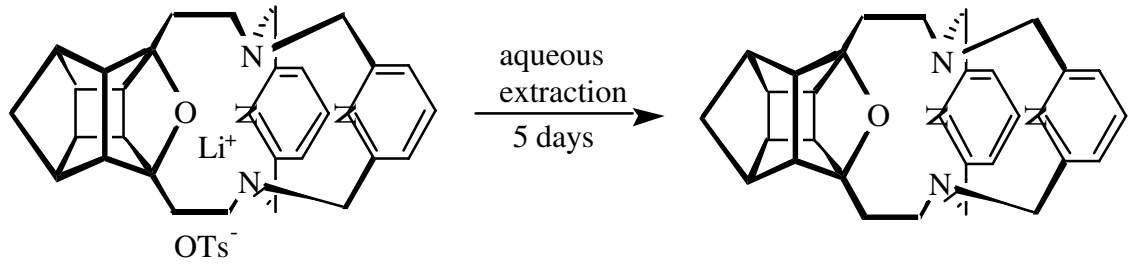
The synthesis of **43** as an example of a highly preorganized host[48] is described in Scheme 1.15 (*vide infra*). The Li^+ templated reaction of **24** with cage ditosylate **30** gave the corresponding Li^+ cryptate, **42,** in 43% yield. Subsequent aqueous extraction of **42** for 5 days, which was monitored by the presence of counter anion (OTs^-), afforded the corresponding non-complexed (i.e., "free") cryptand, **43,** in 62% yield. The structures of

the corresponding Li^+ cryptate (**42**) and the free ligand (**43**) were confirmed via analysis of their ^1H NMR and ^{13}C NMR spectra, and via high-resolution mass spectra (HRMS) analysis (see the Experimental Section).

Scheme 1.15



30 **42**



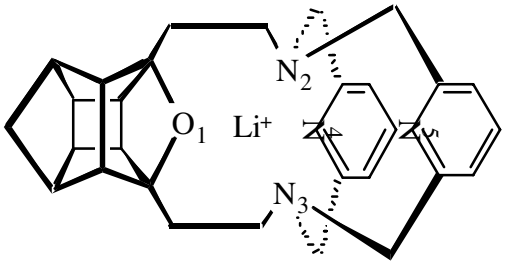
42 **43**

II. Results of molecular modeling studies.

Cryptand **43** was designed as a preorganized ligand that is considered to be likely to bind selectively to Li^+ cation. A Monte Carlo conformational search[70] was performed for **43** by using the Amber force field. The minimized structures of noncomplexed ligand **43** and of the corresponding Li^+/**43** complex are shown in Figures 1.3 and 1.4, respectively. Figure 1.4 shows that the energy-minimized conformer of **43** contains two orthogonal pyridine rings, as was also noted in X-ray structure drawing of **37** (see Figure

1.2). The optimization was intiated by placing Li^+ in a central location within cryptand **43.** It was found that the energy-optimized Li^+/**43** complex contains one short Li^+---O (1) distance of 2.17 Å, and three Li^+---N distances that average 2.41 Å, and one long Li^+---N (5) distance of 2.70 Å (see Scheme 1.16). Examination of Scheme 1.16 reveals that the five ligating atoms do not bind equivalently to Li^+ in the resulting cryptate. In particular, an internal ligating oxygen atom located within the PCU moiety plays an important role in binding, as evidenced by its short Li^+---O bond length (2.17 Å). The binding enthalpy for the complex of **43** with Li^+ is calculated to be -167.1 kcal-mol^{-1}. Inspection of the structural data indicates that **43** provides a suitable cavity for Li^+ complexation.

Scheme 1. 16



Calculated bond distances

O (1)-----Li^+= 2.17 Å	N (4)-----Li^+ = 2.23 Å
N (2)-----LI^+ = 2.50 Å	N (5)-----Li^+ = 2.70 Å
N (3)-----Li^+ = 2.50 Å	

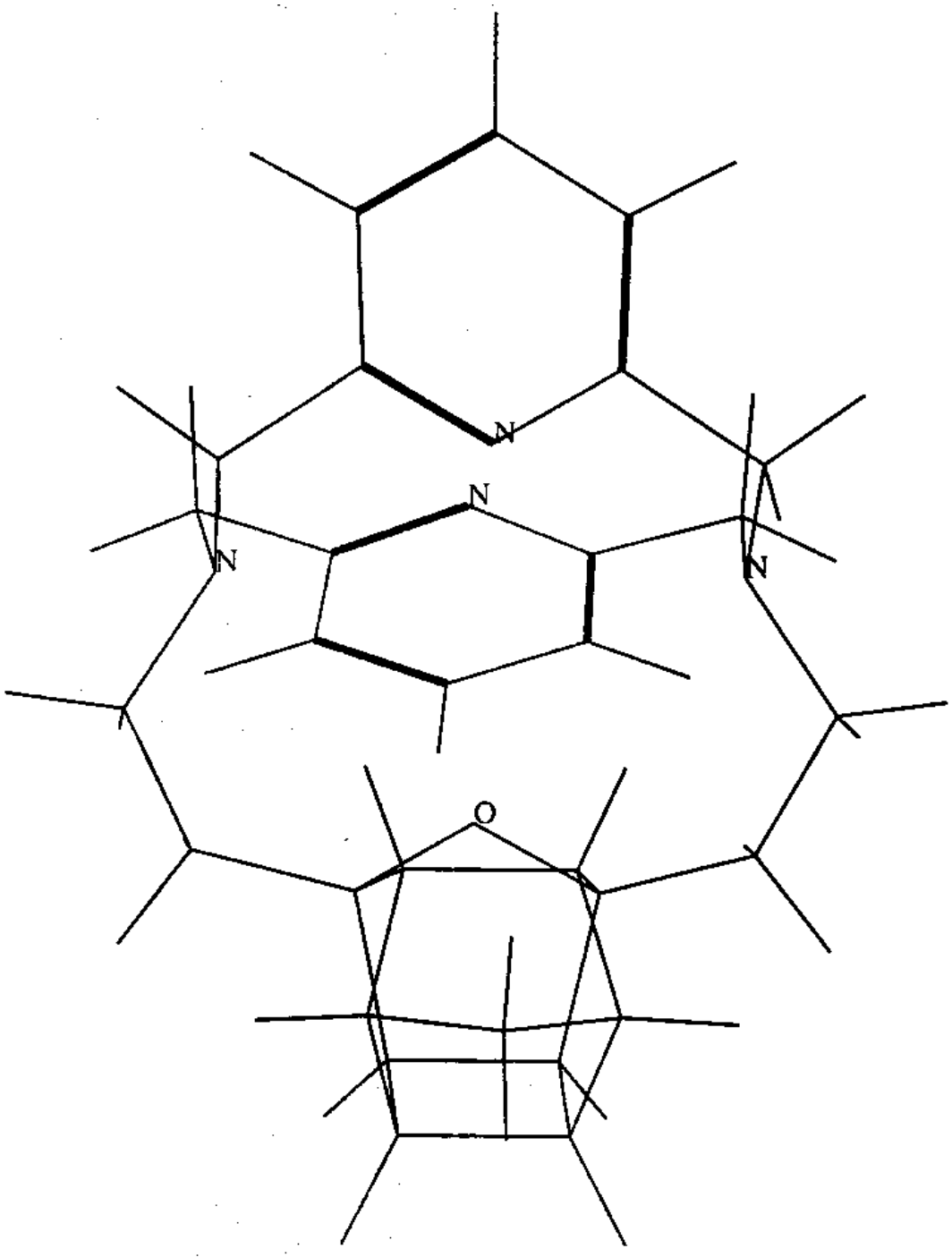


Figure 1.3. Minimum Energy Conformer of Noncomplexed ligand **43**

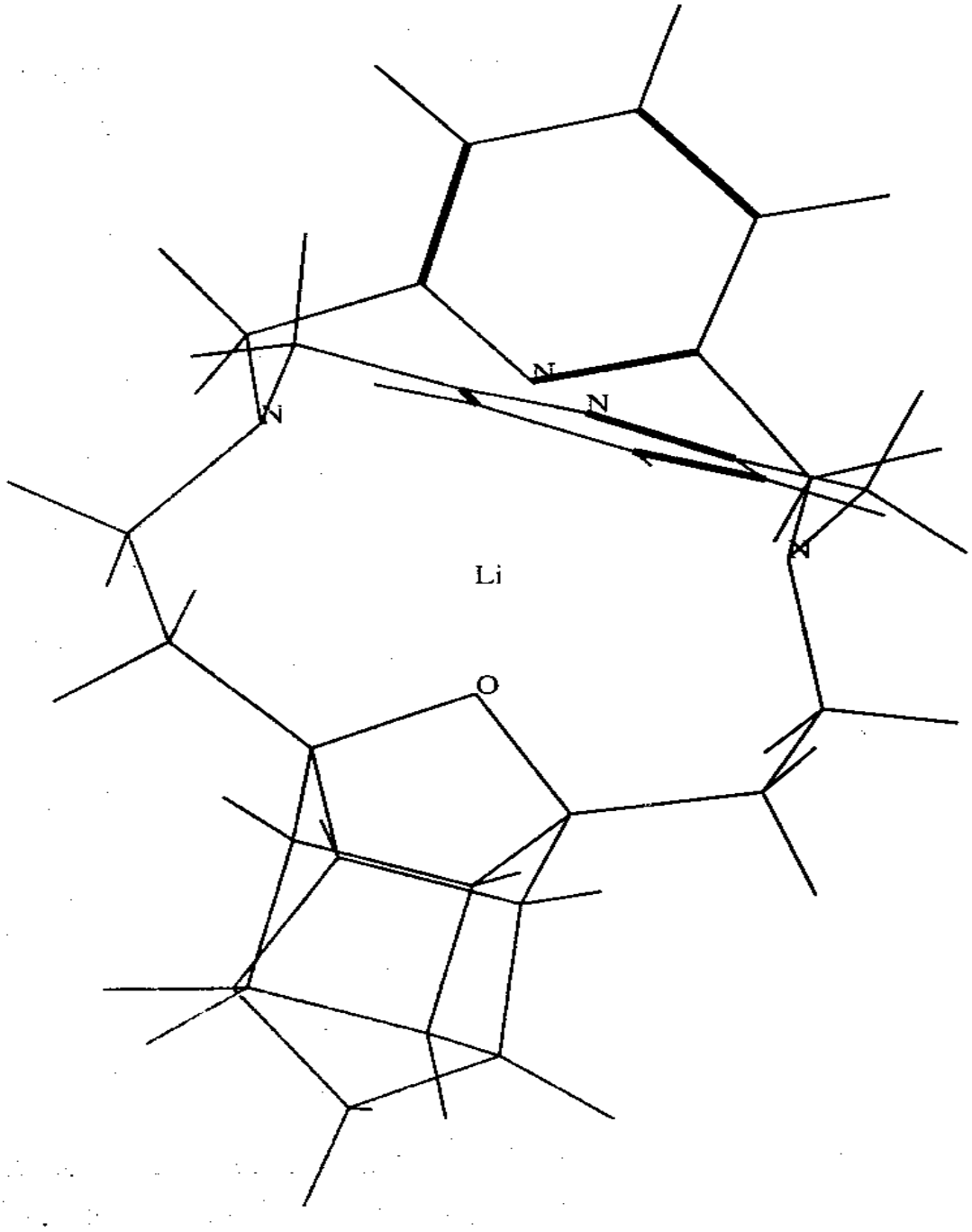


Figure 1.4. Minimum Energy Conformer of Complex of the 1:1 Li^{+}·complex of **43**.

III. Results of Alkali Metal Picrate Extraction Studies.

The thermodynamic aspects of host-guest complex formation have been assessed in a variety of ways. Picrate extractions and determination of the stability constant (K_s) in

homogeneous solution have been employed most frequently. It is important to note that stability constants are determined in very polar solvents like 90% methanol, whereas the corresponding extraction constants reflect the stability of the ligand-cation complex in a less polar solvent like CH_2Cl_2. As a result, equilibrium constants, K_s, and extraction constants can not be equated although they provide similar information.

In particular, the picrate extraction procedure which was developed by Pedersen[62] and Frensdorff[63] is convenient to apply, and the only equipment required is a UV-vis spectrophotometer. The extraction constants are given as the percentage of metal picrate in the aqueous phase that has been extracted into the organic phase. When a solution of metal picrate in the aqueous phase is shaken with a solution of crown ether in organic media such as $CHCl_3$ and CH_2Cl_2, the cation becomes complexed by the crown ether and is transported into the organic phase. The yellow picrate anion accompanies the crown-cation complexes, thereby rendering the organic phase yellow. The method also has the drawback that the extraction equilibrium constant, K_e, as defined by the equation

$$M^+ + Pi^- + (Crown)_{org} \underset{}{\overset{K_e}{\rightleftharpoons}} Pi^-, M^+, (Crown)_{org}$$

is a composite constant, $K_e = K_s P_e P_c$, where P_e and P_c refer to the partition coefficients of the crown ether and its ion pair complex, respectively. Hence, K_e values also depend on partition coefficients, which in turn are dependent on the crown structure. Nevertheless, extraction data can be used to evaluate the complexing ability of crown ligands, at least in a qualitative way. We have studied the binding abilities of a variety of crown compounds by using simple picrate extraction techniques.[64, 65]

The alkali metal picrate extraction of cage-functionalized crown ethers, i.e., **39**, **41**, and **43** have been studied by using a $CHCl_3$-H_2O extraction system. The results thereby obtained have been compared to those obtained by the corresponding of model (non-cage) compounds, i.e., **24, 34,** and **35.**

Relevant extraction data appear in Table 3. Examination of the extraction results reveals the apparent low avidity that is displayed by **39** toward all alkali metal ions studied. This result was disappointing, since we already knew that the relevant model compound (i.e., pyridino-18-crown-6, **34**) displayed a high value of K_s (stability constant) for complexation of alkali metal cations. The comparison of CPK modeling[49b] to 18-crown-6 (**5**) showed that the difference is pyridyl nitrogen slightly tipped out from the cavity. As expected, extracting ability of **34** for alkali metal ions was a little lower than that of 18-crown-6. However, the corresponding cage-functionalized crown ether (**39**) didn't show avidity for any metal ions. Indeed, CPK modeling estimations[66] show the macrocyclic cavity almost always are away from guest due to rigidity which is given by cage moiety. The conformation of the ligand doesn't allow it to interact with any cations favorably. Interestingly, cage-functionalized crown ether **41** was interacted with cations in a more favorable way than its model compound, pyridino-12-crown-4 (**35**), does. In particular, the ligand **41** show six times higher avidity toward extraction of Li^+ cation compared to the model compound, **35**. Furthermore, an our effort to prepare the preorganized host, **43,** that will bind Li^+ cation selectively is proved to be somewhat successful. Table 3 shows that the most effective Li^+ extractor, **43**, extracts 81.9% of the salts of Li^+ into Chloroform, displaying both high avidity and good selectivity for Li^+

cation. The model compound, **24**, extracts only 31% of the salts of Li^+. Its extracting ability toward alkali metal ions is almost the same and doesn't show selectivity for any metal cations.

Table 1.3. Results of Alkali Metal Picrate Extraction Experiments.

	Percent of Picrate Extracted (%) [a]				
Host Molecule	**Li^+**	**Na^+**	**K^+**	**Rb^+**	**Cs^+**
18-crown-6	2.3 ± 0.9	5.7 ± 0.9	68.3 ± 0.7	52.0 ± 0.6	31.0 ± 1.0
35	3.3 ± 0.6	3.0 ± 1.5	1.3 ± 0.4	1.7 ± 0.5	1.3 ± 0.7
41	19.5 ± 1.0	6.3 ± 1.3	5.1 ± 0.7	4.3 ± 1.4	2.6 ± 0.7
34	2.2 ± 0.4	7.5 ± 1.0	51.5 ± 1.0	33.2 ± 1.4	16.1 ± 1.2
39	1.7 ± 0.6	1.9 ± 1.3	3.4 ± 0.4	1.8 ± 0.9	5.2 ± 0.7
24	31.1 ± 0.6	30.9 ± 1.3	30.3 ± 0.5	33.0 ± 0.9	29.8 ± 1.4
43	81.9 ± 0.7	70.7 ± 0.8	40.3 ± 0.5	46.0 ± 0.6	40.9 ± 0.9

[a] Averages and standard deviations calculated for data obtained from three independent extraction experiments.

SUMMARY AND CONCLUSIONS

As a our current interest in the chemistry of polycarbocyclic cage compounds, a variety of novel cage-functionalized crown ethers containing pyridyl unit (**39**, **40**, and **41**) have been prepared for selective alkali metal complexation studies. The preorganized cage-functionalized cryptand (**43**) also has been designed and synthesized as a selective Li^+ binder. The alkali metal picrate extraction of cage-functionalized crown ethers, i.e., **39**, **41**, and **43** has been also studied. The results of the alkali metal picrate extraction of cage-functionalized crown ethers have been compared to that of model crown ethers, i.e., **24**, **34**, and **35**. An examination of extraction results shows that the ligand (**39**) with a large cavity gives much lower avidity toward all alkali metal cations than model compound (**34**) due to rigidity of cage moiety. On the contrary, the ligand (**41**) with a small cavity shows much higher avidity toward all alkali metal cations than the model compound (**35**), specially, for Li^+ cation. We also have proven the importance of the preorganiztion effect in the design of selective extractor via high Li^+ extracting ability of the preorganized cage cryptand (**43**).

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. Absorption intensities of alkali metal picrate solutions were measured at λ = 374 nm by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a

ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

***exo*-8-*exo*-11-Divinylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-*endo*-8-*endo*-11-diol (27).** To a solution of **26** [69] (1.00 g, 5.74 mmol) in dry THF (10 mL) under argon was added with stirring a 1 M solution of vinylmagnesium bromide in dry THF (22.9 ml, 22. 9 mmol). The resulting solution was stirred at ambient temperature for 3 h and then was heated to 50 ^{o}C and was stirred at that temperature for an additional 12 h. The reaction mixture was cooled to 0 ^{o}C via application of an external ice-water bath, and the reaction was quenched via addition of cold saturated aqueous NH_4Cl (10 mL). The resulting aqueous suspension was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed with water (10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on silica gel by eluting with 20% EtOAC-CH_2Cl_2, thereby affording **27** (780 mg, 59%). Recrystallization of this material from CH_2Cl_2-hexane afforded analytically pure **27** as a colorless microcrystalline solid: mp 66-67 ^{o}C; IR (nujol) 3180 (m), 2980 (s), 1610 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 10 Hz, 1 H), 1.52 (d, J = 10 Hz, 1 H), 1.79-2.20 (m, 8 H), 4.90-5.22 (m, 4 H), 5.71-5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 33.9 (t), 40.1 (d), 41.2 (d), 44.4 (d), 51.1 (d), 76.9 (s), 112.8 (t), 142.7 (d). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.21; H, 8.00.

3,5-Divinyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane (28). To a solution of **27** (1.00 g, 4.34 mmol) in dry benzene (30 mL) was added TsOH (81 mg, 0.43

mmol), and the resulting mixture was refluxed in a Dean-Stark apparatus until the distillate became clear (*ca*. 2 h). The layers in the distillate were separated, and the organic layer was washed sequentially with water (10 mL), 10% aqueous Na_2CO_3 (10 mL), and water (10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on neutral alumina by eluting with 1:1 CH_2Cl_2-hexane. Pure **28** (715 mg, 77%) was thereby obtained as an oil; bp 210-213 °C (1 mmHg); IR (neat) 2985 (s), 1150 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.56 (d, *J* = 10 Hz, 1 H), 1.94 (d, *J* = 10 Hz, 1 H), 2.50 (br s, 2H), 2.72 (br s, 6H), 5.08-5.32 (m, 4 H), 6.21-6.33 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 41.8 (d), 43.5 (t), 44.5 (d), 49.2 (d), 58.9 (d), 96.0 (s), 114.5 (t), 136.3 (d). Anal. Calcd for $C_{15}H_{16}O$: C, 72.55; H, 8.12. Found: C, 72.65; H, 8.06.

3,5-[2',2''-Bis(hydroxyethyl)]-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$] dodecane (29). To a solution of **28** (610 mg, 2.87 mmol) in dry THF (20 ml) was added with stirring a 1 M solution of BH_3·THF in dry THF. The mixture was cooled to 0 °C via application of an external ice-water bath. To this cooled mixture was added dropwise with stirring 30% aqueous NaOH (1 ml, 7.5 mmol), followed by 30% aqueous H_2O_2 (1.8 ml, excess). The resulting mixture then was heated to 40 °C and was stirred at that temperature for 1 h. The reaction mixture was cooled and then was extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with water (10 ml), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAC-hexane. Pure **29** (600 mg, 85%) was thereby obtained as a colorless microcrystalline solid: mp

153.0-153.5 ^{o}C; IR (nujol) 3320 (m), 2980 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, *J* = 10 Hz, 1 H), 1.70-2.05 (m, 4 H), 2.28-2.69 (m, 9 H), 3.50-3.86 (m, 6 H); ^{13}C NMR (CDCl3) δ 34.3 (t), 41.4 (d), 43.5 (d), 44.1 (d), 47.7 (d), 58.2 (d), 60.0 (t), 96.4 (s). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.65; H, 8.06.

Tosylation of 29 (**30**). To a solution of **29** in dry CH_2Cl_2 (20 ml) and pyridine (10 ml) at 0 ^{o}C was added Dimethylaminopyridine (122 mg, 1.0 mmol) and p-TsCl (2.87 g, 15.1 mmol) in small portions. After the reaction, ice-bath was removed, and the reaction mixture was stirred at room temperature for 24 h. It was acidified with 5% aqueous Hcl and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (60 ml), water (60 ml), and dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting 50% CH_2Cl_2-hexane. Pure **30** (1.32 g, 47%) was thereby obtained as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.47 (d, *J* = 10 Hz, 1 H), 1.81 (d, *J* = 10 Hz, 1 H), 2.07 (t, *J* = 7 Hz, 4 H), 2.34 (m, 2 H), 2.39 (m, 4 H), 2.43 (s, 6 H), 4.07 (t, *J* = 7 Hz, 4 H), 7.32 (AB, J_{AB} = 8 Hz, 4 H), 7.76 (AB, J_{AB} = 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 31.7 (t), 41.5 (d), 43.3 (t), 44.1 (d), 48.2 (d), 58.7 (d), 67.6 (t), 93.6 (s), 127.9 (d), 129.8 (d), 132.7 (s), 144.4 (s). H), 3.51-3.59 (m, 12 H), 4.55 (s, 4 H), 7.27-7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 32.8 (t), 41.8 (d), 43.4 (t), 44.5 (d), 48.4 (d), 58.8 (d), 68.4 (t), 69.5 (t), 70.2 (t), 73.2 (t), 94.4 (s), 127.6 (d), 127.7 (d), 128.3 (d), 138.3 (s). Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80; Found: C, 76.48; H, 7.70.

3,5-Bis[2-(2'-benzyloxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}] dodecane (31). A suspension of NaH (60% suspension in mineral oil, 660 mg, 16.4

mmol) in dry DMF (10 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of **29** (1.85 g, 7.45 mmol) in DMF (10 mL). The resulting white suspension was stirred at 0 °C for 10 minutes, at which time the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture again was cooled to 0 °C via application of an external ice-water bath, and to the cooled reaction mixture was added dropwise with stirring a solution of 1-(benzyoxy)-2-(*p*-toluensulfonyloxy)ethane (5.02 g, 16.4 mmol) in DMF (10 mL). The resulting suspension was stirred at 0 °C for 10 minutes, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature for 2 days. The reaction mixture was concentrated *in vacuo*, and ice-water (50 mL) was added to the residue. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure **31** (1.7 g, 44%) was thereby obtained as a colorless viscous oil. IR (film) 2951 (s), 2870 (s), 1450 (m), 1111 (vs), 736 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 10 Hz, 1 H), 1.82 (A*B*, J_{AB} = 10 Hz, 1 H), 2.10 (t, J = 7 Hz, 4 H), 2.36 (br s, 2 H), 2.48-2.54 (m, 6 H), 3.51-3.59 (m, 12 H), 4.55 (s, 4 H), 7.27-7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 32.8 (t), 41.8 (d), 43.4 (t), 44.5 (d), 48.4 (d), 58.8 (d), 68.4 (t), 69.5 (t), 70.2 (t), 73.2 (t), 94.4 (s), 127.6 (d), 127.7 (d), 128.3 (d), 138.3 (s). Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80; Found: C, 76.48; H, 7.70.

3,5-Bis[2-(2'-hydroxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$] dodecane (32). To a solution of **31** (1.70 g, 3.29 mmol) in EtOH (50 mL) was added 10% Pd-C (180 mg), and the resulting mixture was hydrogenated by using H_2(g) (58 psi) on a Parr shaker apparatus during 24 h. The reaction mixture was filtered through a bed of Celite to remove spent catalyst. The filtrate was concentrated *in vacuo*, thereby affording **32** (990 mg, 89%), as a colorless viscous oil; IR (film) 3416 (s), 2945 (s), 2864 (s), 1367 (w), 1128 (s), 1066 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.44 (*A*B, J_{AB} = 10 Hz, 1 H), 1.80 (A*B*, J_{AB} = 10 Hz, 1 H), 2.01 (t, *J* = 7 Hz, 4 H), 2.32 (br s, 2 H), 2.40-2.53 (m, 6 H), 3.04 (s, 1 H, peak disappears when NMR sample is shaken with D_2O), 3.40-3.61 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 32.2 (t), 41.5 (d), 43.3 (t), 44.2 (d), 48.1 (d), 58.5 (d), 61.4 (t), 67.8 (t), 71.7 (t), 94.7 (s). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39; Found: C, 67.60; H, 8.23.

3,5-Bis[2-(2'-*p*-toluenesulfonyloxyethoxy)ethyl]-4oxahexacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (33). A solution of *p*-TsCl (0.697 g, 3.66 mmol) in dry pyridine (6 mL) was placed in a round-bottom flask that previously had been thoroughly fluxed with argon. This solution was cooled to 0 °C via application of an external ice-water bath. To the cooled solution was added dropwise with stirring a solution of **32** (410 mg, 1.22 mmol) in dry CH_2Cl_2 (10 mL) during 15 minutes. After the addition of **32** had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring overnight. The reaction mixture was poured into ice-water (150 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (200 mL). The organic layer was washed with ice-cold 5 M HCl (2 x 50 mL), dried ($MgSO_4$), and filtered, and the filtrate was

concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Compound **33** (550 mg, 70%) was thereby obtained as a colorless viscous oil; IR (film) 2958 (s), 2872 (m), 1356 (s), 1178 (vs), 1024 (m), 927 (s), 665 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 10 Hz, 1 H), 1.81 (A*B*, J_{AB} = 10.Hz, 1 H), 1.97 (t, *J* = 7 Hz, 4 H), 2.30 (br s, 2 H), 2.42 (s, 10 H), 2.49-2.58 (m, 2 H), 3.45 (t, *J* = 7 Hz, 4 H), 3.57 (t, *J* = 5 Hz, 4 H), 4.11 (t, *J* = 5 Hz, 4 H), 7.31 (*A*B, J_{AB} = 8 Hz, 2 H), 7.77 (A*B*, J_{AB} = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.6 (q), 32.6 (t), 41.7 (d), 43.4 (t), 44.4 (d), 48.3 (d), 58.7 (d), 68.1 (t), 68.4 (t), 69.2 (t), 94.2 (s), 127.9 (d), 129.8 (d), 133.0 (s), 144.7 (s). Anal. Calcd for $C_{33}H_{40}O_9S_2$: C, 61.47; H, 6.25; Found: C, 61.62; H, 6.08.

Model Crown Ether 34. To a suspension of NaH (obtained as a dispersion of 60% w/w NaH in mineral oil, 77 mg, 2.53 mmol) in dry THF (23 mL) under argon was added with stirring a solution of 2,6-bis(hydroxymethyl)pyridine (140 mg, 1.0 mmol) in dry THF (38 mL). The resulting mixture was refluxed for 0.5 h, at which time a solution of tetraethyleneglycol ditosylate (510 mg, 1.0 mmol) in dry THF (58 mL) was added dropwise with stirring during 20 minutes. The reaction mixture was refluxed for 19 h and then was allowed to cool gradually to ambient temperature. The reaction was quenched via addition of water (20 mL), and the resulting aqueous suspension was extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **34** (116 mg, 39%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR

spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **34**. [24]

Model Crown Ether 35. To a suspension of NaH (obtained as a dispersion of 60% w/w NaH in mineral oil, 520 mg, 2.08 mmol) in dry THF (12 mL) under argon was added with stirring a solution of diethylene glycol (110 mg, 1.04 mmol) in dry THF (35 mL). The resulting mixture was refluxed for 0.5 h, at which time a solution of 2,6-bis(bromomethyl)pyridine (270 mg, 1.04 mmol) in dry THF (60 ml) was added dropwise with stirring during 0.5 h. The reaction mixture was refluxed for 24 h and then was allowed to cool gradually to ambient temperature. The reaction was quenched via addition of water (5 mL), and the resulting aqueous suspension was extracted with $CHCl_3$ (4×45 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **35** (100 mg, 50%) was thereby obtained as a colorless oil: IR (neat) 3449 (s), 2870 (s), 1602 (w), 1452 (w), 1350 (w), 1118 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 3.64-3.71 (m, 8 H), 4.70 (s, 4 H), 7.31 (d, J = 8 Hz, 2 H), 7.42 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 70.2 (t), 70.6 (t), 73.1 (t), 119.7 (d), 137.9 (d), 157.9 (s). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.20; H, 7.19.

2,6-Bis(*N*-benzylaminomethyl)pyridine (36). A solution of benzylamine (23.0 g, 210 mmol, large excess) and 2,6-bis(chloromethyl)pyridine (2.30 g, 13 mmol) was heated with stirring in an external oil bath at 120 °C for 28 h. The reaction mixture was allowed to cool gradually to ambient temperature, crushed NaOH pellets (1.00 g, 25 mmol) then was added, and the resulting mixture was heated with stirring in an external

oil bath at 120 °C for 1 h. The reaction mixture was allowed to cool gradually to ambient temperature, and the resulting mixture was concentrated *in vacuo* (water aspirator) to remove excess benzylamine. The residue was dissolved in $CHCl_3$ (100 mL); the resulting solution was filtered, and the filtrate was washed with water (50 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via bulb-to-bulb distillation (Kügelruhr apparatus), thereby affording **36** (1.80 g, 43%) as a pale yellow oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that have been reported previously for authentic **36**.[43]

Model Crown Ether 37. A solution of **36** (360 mg, 1.13 mmol), Na_2CO_3 (600 mg, 5.65 mmol), NaI (85 mg, 0.65 mmol) in CH_3CN (25 mL) was refluxed with stirring during 0.5 h. To the hot reaction mixture was added portionwise with stirring 2,6-bis(chloromethyl)pyridine (200 mg, 1.13 mmol), and the resulting mixture was refluxed during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, and the residue thereby obtained was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **37** (26 mg, 12%) was thereby obtained as a colorless oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained is essentially identical with the correspond-ing spectral data that has been reported previously for authentic **37**.[61]

Model Crown Ether 38. A solution of bis(chloromethyl)pyridine (200 mg, 1.10 mmol), $TsNH_2$ (753 mg, 4.4 mmol), and Na_2CO_3 (2.20 g, 27.5 mmol) in CH_3CN (10 mL) was refluxed with stirring during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with EtOAc. Pure **38** (96 mg, 16%) was thereby obtained as a colorless oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectral data that has been reported previously for authentic **38**. [57]

Crown Ether 39. To a suspension of NaH (60% suspension in mineral oil, 46 mg, 1.79 mmol) in dry THF (14 mL) under argon was added dropwise with stirring a solution of 2,6-dimethanolpyridine (84 mg, 0.60 mmol) in dry THF (23 mL), and the resulting mixture was refluxed with stirring during 0.5 h. To the reaction mixture was added drop-wise with stirring a solution of **33** (370 mg, 0.60 mmol) in dry THF (35 mL) during 0.5 h. After all of the reagent, **33**, had been added, the resulting mixture was refluxed for 56 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was quenched via addition of water (20 mL). The resulting aqueous suspension was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **39** (120 mg, 38%) was thereby obtained as a colorless oil: IR (film) 3350 (s), 2930 (s), 1730 (m), 1580 (m), 1456 (m), 1223 (s), 732 cm^{-1} (s);^{1}H NMR ($CDCl_3$) δ 1.40 (*A*B, J_{AB} = 10 Hz, 1 H), 1.67 (A*B*, J_{AB} = 10 Hz, 1 H), 1.95 (t, *J* = 7 Hz, 4 H), 2.25 (s, 2 H), 2.35-2.48 (m, 5

H), 3.43-3.82 (m, 12 H), 4.73 (s, 4 H), 7.35 (d, *J* = 7 Hz, 2 H), 7.76 (t, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.3 (t), 41.5 (d), 43.3 (t), 44.1 (d), 47.9 (d), 58.9 (d), 67.6 (t), 69.5 (t), 69.7 (t), 73.8 (t), 94.2 (s), 120.7 (d), 136.9 (d), 157.9 (d). Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57. Found: C, 70.86; H, 7.60.

Crown Ether 40. To a mixture of **33** (190 mg, 0.30 mmol) and Na_2CO_3 (160 mg, 1.5 mmol) in CH_3CN (15 mL) was added **36** (98 mg, 0.3 mmol), and the resulting mixture was refluxed for 34 h. The reaction mixture was allowed to cool gradually to ambient temperature; the reaction mixture then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **40** (48 mg, 27%) was thereby obtained as a colorless oil: IR (film) 3408 (br, s), 2950 (s), 1708 (m), 1610 (w), 1438 (m), 1247 (s), 1112 (s), 738 (m), 700 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.51 (d, *J* = 11.0 Hz, 1 H), 1.71-2.03 (m, 5 H), 2.32-2.61 (m, 11 H), 2.74 (t, *J* = 7 Hz, 4 H), 3.45 (t, *J* = 5 Hz, 8 H), 3.70 (s, 2 H), 3.85 (s, 2 H), 7.21-7.53 (m, 14 H), 7.64 (t, *J* = 8 Hz 1 H); ^{13}C NMR ($CDCl_3$) δ 32.3 (t), 42,0 (d), 43.9 (t), 44.5 (d), 48.5 (d), 53.4 (t), 59.4 (t), 60.8 (t), 61.5 (t), 67.9 (t), 69.7 (t), 94.7 (s), 121.3 (d), 127.4 (d), 128.7 (d), 129.3 (d), 137.1 (d). 140.0 (s), 160.1 (s). Anal. Calcd for $C_{40}H_{47}N_3O_3$: C, 77.76; H, 7.67. Found: C, 77.51; H, 7.78.

Crown Ether 41. To a suspension of NaH (60% suspension in mineral oil, 675 mg, 2.7 mmol) in dry THF (15 mL) under argon was added dropwise with stirring a

solution of **29** (200 mg, 1.35 mmol) in dry THF (45 mL), and the resulting mixture was refluxed with stirring during 0.5 h. To the reaction mixture was added drop-wise with stirring a solution of 2,6-bis(bromomethyl)pyridine (350 mg, 1.35 mmol) in dry THF (75 ml) during 0.5 h. After the addition of 2,6-bis(bromomethyl)pyridine had been completed, the resulting mixture was refluxed for 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was quenched via addition of water (5 mL). The resulting aqueous suspension was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chroma-tography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **41** (250 mg, 53%) was thereby obtained as a colorless oil: IR (film) 3408 (br, s), 2987 (s), 1714 (m), 1597 (w), 1454 (m), 1257 (s), 1103 (s), 748 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 11 Hz, 1 H), 1.73-2.72 (m, 10 H), 3.40-3.73 (m, 4 H), 4.71 (m, 8 H), 7.12 (d, J = 8 Hz, 2 H), 7.50 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.3 (t), 41.5 (d), 43.3 (t), 44.1 (d), 49 (d), 58.1 (d), 65.6 (t), 70.8 (t), 94.2 (s), 122.7 (d), 135.9 (d), 157.9 (d). Anal. Calcd for $C_{22}H_{24}NO_3$: C, 75.19; H, 7.17. Found: C, 74.85; H, 7.26. Exact mass (CI HRMS) Calcd for $C_{22}H_{25}NO_3$: $[M_r + H]^+$ 352.19127. Found: $[M_r + H]^+$ 352.19014.

Li^+ Cryptate 42. To a mixture of **30** (494 mg, 0.89 mmol) and Li_2CO_3 (270 mg, 3.65 mmol) in CH_3CN (30 mL) was added **24**[23] (200 mg, 0.83 mmol), and the resulting mixture was refluxed for 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10%

CH_3OH-CH_2Cl_2. Pure Li^+ cryptate **42** (224 mg, 43%) was thereby obtained as a colorless, waxy solid; IR ($CHCl_3$) 3350 (br, s), 2963 (s), 1724 (w), 1585 (m), 1456 (m), 1223 (s), 1354 (w), 1008 (m), 751 (w), 732 (s), 680 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.65 (d, *J* = 12 Hz, 1 H), 2.14-2.25 (m, 4 H), 2.60 (s, 1 H), 2.76-2.90 (m, 4 H), 3.25-3.40 (m, 2 H), 3.70-3.83 (m, 2 H), 4.09-4.28 (m, 3 H), 6.80 (d, *J* = 8 Hz, 4 H), 7.05 (*A*B, J_{AB} = 7 Hz, 2 H), 7.30 (t, *J* = 8 Hz, 2 H); 7.75 (A*B*, J_{AB} = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.9 (q), 29.5 (t), 41.1 (t), 43.4 (t), 43.8 (d), 47.0 (d), 55.8 (t), 57.8 (d), 63.2 (t), 63.6 (t), 96.4 (s), 120.1 (d), 125.8 (d), 127.9 (d), 138.3 (d), 157.1 (s) Exact mass (CI HRMS) Calcd for $C_{29}H_{32}N_4OLi$: $[M_r]^+$ 459.27362. Found: $[M_r]^+$ 459.27432.

Cryptand 43. A solution of **42** (220 mg, 0.35 mmol) in $CHCl_3$ (50 mL) was placed in separatory funnel, placed on a mechanical shaker apparatus, and extracted with H_2O (30 mL). The layers were separated after each 12 h interval, the water layer was replaced at that time with fresh water, and the extraction procedure was continued for a total of 5 days. The presence (or absence) of LiOTs was confirmed by withdrawing aliquots at 24 h intervals; each aliquot was then concentrated *in vacuo*, and the residue was analyzed via careful inspection of its ^1H NMR spectrum. After the lengthy water-extraction procedure had been completed, the layers in the separatory were separated. The organic layer then was filtered, and the filtrate was concentrated *in vacuo*. Pure **43** (98 mg, 62%) was thereby obtained as a colorless oil; IR (film) 3376 (br, s), 2938 (s), 1634 (m), 1603 (m), 1444 (m), 1200 (s), 1030 (m), 749 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, *J* = 12 Hz, 1 H), 1.65-1.80 (m, 5 H), 2.63-2.90 (m, 5 H), 3.21-3.34 (m, 2 H), 3.73 (m, 2 H), 4.12-4.30 (m, 2 H), 6.82 (d, *J* = 7.7 Hz, 4 H), 7.40 (m, 4 H), 7.94 (m, 2 H);^{13}C NMR

($CDCl_3$) δ 30.5 (t), 40.3 (d), 43.3 (t), 43.8 (d), 47.1 (d), 55.0 (t), 58.2 (d), 60.3 (t), 60.6 (t), 95.5 (s), 121.5 (d), 121.6 (d), 140.8 (d), 141.2 (d), 155.6 (s), 157.2 (s). Exact mass (CI HRMS) Calcd for $C_{29}H_{32}N_4O$: $[M_r + H]^+$ 453.26544. Found: M_r^+ 453.26628.

Alkali Metal Picrates. Lithium, sodium, potassium, rubidium, and cesium picrates were prepared from picric acid and the corresponding metal hydroxide according to the reported method.[67]

Alkali Metal Picrate Extraction Experiments. The general procedures employed are similar to the methods reported previously.[68] $CHCl_3$ was washed with deionized H_2O to remove methanol. The extraction experiments were performed by using 5 mM solutions of each compounds in $CHCl_3$. Equal volumes (0.5 ml) of a $CHCl_3$ solution of the respective crown compound (5 mM) and of an aqueous solution of the corresponding metal picrate (5 mM) were introduced into a screw-topped vial and shaken mechanically for 0.5 h at ambient temperature. The mixture was then allowed to stand for at least 2 h at that temperature in order to complete phase separation. Each volume (50 μl) of the organic phase was taken to volumetric flask (25 ml) and diluted with acetonitrile to 25 ml. The picrate concentration in acetonitrile was determined from its absorbance at 375 nm. The percentage of metal picrate (in aqueous phase) extracted into the organic phase was calculated.

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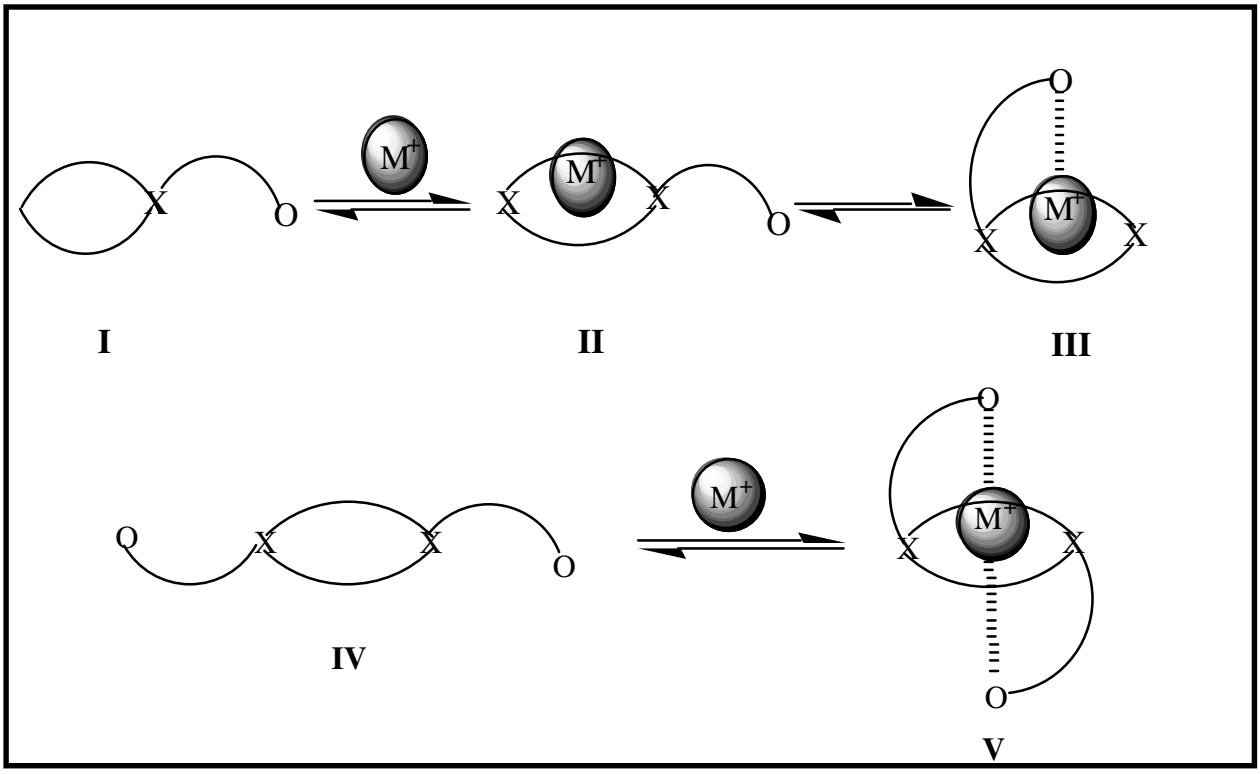
CHAPTER 2

SYNTHESIS OF NOVEL CAGE-FUNCTIONALIZED LARIAT ETHERS AND CRYPTANDS AND STUDIES OF THEIR SELECTIVITY IN ALKALI METAL COMPLEXATION USING PICRATE EXTRACTION TECHNIQUES

INTRODUCTION

Lariat ethers[1-6] and cryptands[7-10] are interesting macrocyclic compounds for the study of host-guest interactions. Numerous reports[11-12] indicate that these hosts display selective complexation properties. In particular, lariat ethers represent a new class of synthetic cation binders, which are characterized by a parent macrocyclic ligand and a cation-ligating functionalized arm. In this class of compounds, the donor group on the flexible side arm can provide further coordination to the cation trapped in the parent macrocycle by wrapping around the guest. In fact, early studies of the complexation properties of lariat crown ethers arose via an attempt to mimic naturally occurring ionophores like valinomycin,[11a] known to be an ideal carrier for K^+. A variety of lariat crown ethers[12] have been shown to be very promising agents for the design of synthetic ion-carrier molecules, i.e., ionophores. In general, dynamic monocyclic crowns display weak binding strength, whereas the less mobile cryptands possess three dimensional binding character. Lariat ethers are expected to give better cation binding than simple monocyclic crowns via three-dimensional binding and to bind more rapidly the cations than cryptands via dynamic binding.

Complexation of lariat ethers which are represented by a strong, selective, and dynamic three-dimensional binding of cations are considered to proceed as shown in Figure 2.1.



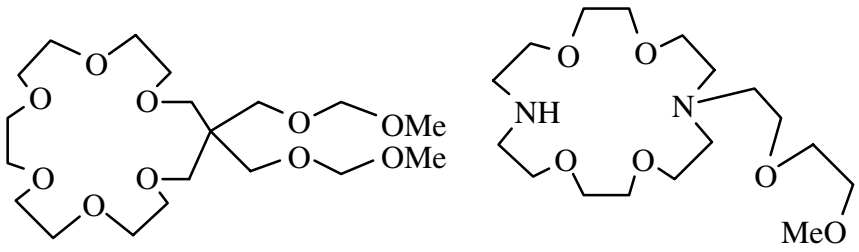
X= pivot atom (C, N), M^+ = Metal cation, O = Ligating atoms (O, N etc.)

Figure 2.1. Complexation of lariat ethers

As implied by the name 'lariat',[13] the lariat ethers bind the cation in the same fashion as a lasso is used to "rope and tie" an animal. Thus, the macrocycle would envelop the cation normally, as in the case of crown ether binding (see **II** in Figure 2.1). In addition, the donor groups attached to the flexible podand arm would further coordinate the bound cation to form a lariat complex (**III**).

Lariat ethers can be divided into two classes: *mono*bracchial lariat ethers (**I**) and *bi*bracchial lariat ethers (**IV**) according to the number of flexible podand arms attached to a crown macrocycle. A further distinction of lariat ethers is made in respect to the nature of the pivot atom (**X**, Figure 2.1) which can be either carbon or nitrogen. *C*-pivot lariat ethers (e.g., **1**[14], Scheme 2.1) have a side arm attached to carbon in the polyoxy ring. *N*-Pivot lariat ethers (e.g., **2**[15]) possess a side arm attached to a ring nitrogen atom.

Scheme 2.1



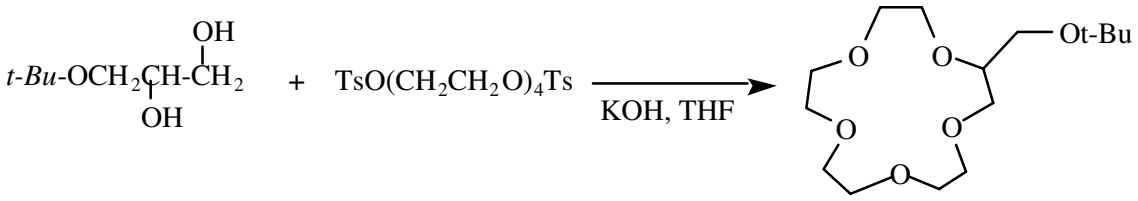
1 **2**

In general, the addition of *N*-alkyl or *C*-alkyl groups to a ligand has two opposing effects. First, both types of alkyl addition lead to an increase in the donor strength of the nitrogen (or other type of) donor atom. The second effect is to increase steric crowding, thereby resulting in unusually high steric strain. The resulting complex stability represents a delicate balance between these two opposing effects. It is often difficult to predict the effects of these seemingly simple alterations in ligand structure with any degree of reliability.

Lariat ethers with suitably functionalized sidearms are known to give significantly enhanced avidity and selectivity *vis-à-vis* the parent crown ether.[11] In general, it is known that when the donor groups on side arm are situated such that a metallic cation complexed in the ring will be within bonding distance of the donor group, cation-binding will be enhanced by means of side-arm involvement. This fact has been demonstrated by several research groups via synthesis of some carbon-and nitrogen-pivot lariat ethers.[11] On the contrary, some lariat ethers[16] don't exhibit enhanced binding abilities compared to the parent crown ethers, thereby indicating that they may not necessarily be the best choice with respect to specific cation selectivity.

As an example of *C*-pivot lariat ethers, **4** was prepared via base-promoted reaction of **3** with tetraethylene glycol ditosylate.[17]

Scheme 2.2



3 **4**

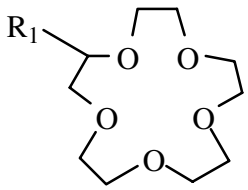
Ouchi and coworkers[18] have investigated the cation binding abilities of *C*-pivot lariat ethers that contain a variety of single or double side arms. The results of the cation binding ability of several lariat ethers as evaluated via extraction studies of aqueous alkali-metal picrates are shown in Table 2.1.

Examination of Table 2.1 indicate that lariat ethers which contain different side arms do not display significantly enhanced avidity toward metal cations when compared to the behavior of the corresponding parent crown ethers, i.e., **5a** and **6a**. In particular, lariat 15-crown-5 ether (**5b)** falls to show enhanced avidity except toward Na^+ when compared to the parent 15-crown-5 ether (**5a**). It seems that the additional side arms do not cooperate with the parent macrocycle in cation binding. It is interesting to note that **6b** displays considerably enhanced avidity toward Na^+ compared to the parent 16-crown-5 ether (**6a**). Here, it seems likely that the terminal oxygen atoms on double-armed lariat ether **6c** are placed at a favorable position to access Na^+ which resides in the crown ether cavity. The double-armed lariat 16-crown-5 (**6d**) displays decreased avidity toward all metal cations studied compared to the correspoding single-armed lariat ether (**6c)**.

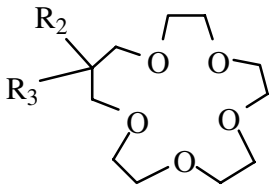
Even though it is not worthwhile to dwell upon the small differences observed in Table 2.1, it seems that the correct placement of lariat that is capable of complexing with a ring-bound cation is important for enhanced binding. Otherwise, the lariat sidearms result only in the steric crowding and thereby reduce binding to the guest cation, as indicated by the results for **6d**.

Table 2.1. Solvent Extraction of Metal Picrate with Some Hosts[18]

Host Molecule	% extractibility			
	Na^+	K^+	Rb^+	Cs^+
5a	13.2	14.3	9.6	3.3
5b	14.9	9.6	7.6	2.6
6a	13.5	3.0	2.1	0.9
6b	9.8	2.7	2.5	2.1
6c	19.2	2.6	1.5	0.9
6d	10.2	1.9	1.3	0.9
6e	18.2	2.3	1.7	1.1



5a: $R_1 = H$
5b: $R_1 = CH_2OCH_2CH_2OCH_3$



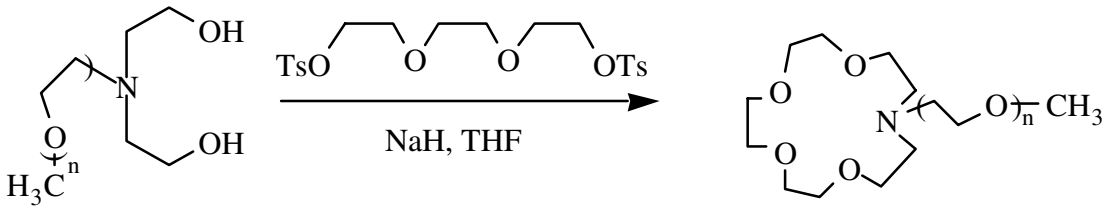
6a: $R_2, R_3 = H$
6b: $R_2, R_3 = CH_2OCH_3$
6c: $R_2, R_3 = CH_2OCH_2CH_2OCH_3$
6d: $R_2 = H, R_3 = CH_2OCH_2CH_2OCH_3$
6e: $R_2 = CH_3, R_3 = CH_2OCH_2CH_2OCH_3$

Whereas *C*-pivot lariat compounds suffer from the inherent disadvantage associated with the fixed geometry of the side-arm, *N*-pivot lariats[19] are more flexible due to inversion at the N atom. This effect reduces steric inhibition of potential cation access, with concomitant manners in the number of collisions between a cation and crown

that lead to complex formation. Increased binding constants of several *N*-pivot lariats *vis-à-vis* simple monocyclic systems have been reported.[19]

As a example of *mono*bracchial *N*-pivot lariat ethers,[20] i.e., side-arm containing monoaza 15-crown-5-ethers, i.e., **8a-d,** were synthesized (Scheme 2.3) and their binding to Na^+ was studied via determination of relevant complex stability constants for complexes (Table 2.2).[21]

Scheme 2.3



7 (**8a-d**) n=1-4

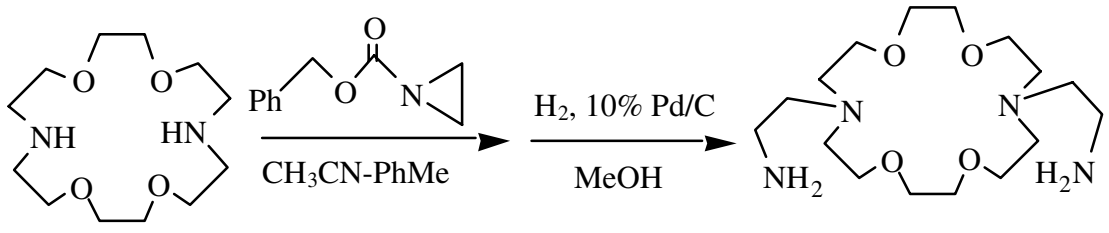
These binding studies reveal that as the number of oxygen in the side-arm increase to two, binding constants reach a maximum value. However, as the number of oxygens increases further, the corresponding binding constants decrease in value. One possible rationale for the reduced binding constants is that when the number of oxygen increase, hydrogen bonding by the medium will increase, thereby reducing the conformational and translational mobility of the side-arm. The result also suggests that when donor groups are situated appropriately on the side arms to promote cooperative binding with the parent crown ring (as, e.g., in **8b**), the cation-binding ability of the lariat ethers will be enhanced.

Ligand	n	side-arm	Log K_s (Na^+)
8a	1	CH_2CH_2OMe	3.88
8b	2	$(CH_2CH_2O)_2Me$	4.54
8c	3	$(CH_2CH_2O)_3Me$	4.32
8d	4	$(CH_2CH_2O)_4Me$	4.15

Table 2.2. Stability constants (log K_S, potentiometric, 25 ^oC) for complexes between *N*- pivot lariat ethers and Na^+.[21]

A variety of *bi*bracchial lariat ethers[19] have been synthesized. Among these, a interesting ligand **10**[22] was prepared via reaction of **9** with *N*-benzyloxycarbonylaziridine followed by hydrogenolysis. It was found the lariat ether **10** interacts more strongly with cations than does its corresponding parent crown ether, i.e., **9**, via intramolecular side-arm participation in **10**.

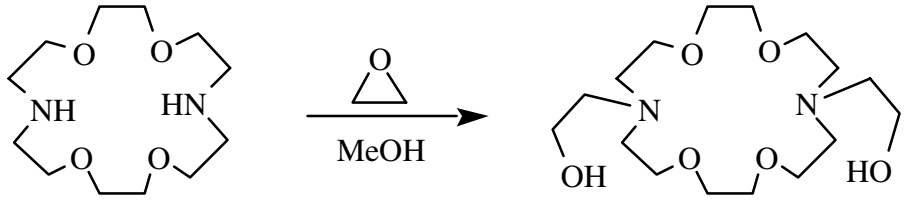
Scheme 2.4



9 **10**

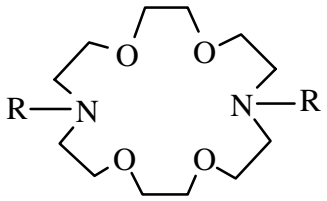
As an another example of a *bi*bracchial lariat ether, i.e., ethylenloxy-armed 18-crown-6 (**9a**), was prepared via the reaction of ethylene oxide with 18-crown-6 (**9**).[23]

Scheme 2.5

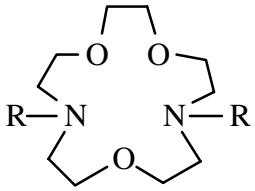


9 **9a**

The results[24] of stability constant determinations that involve several ligands, including **9a,** are shown in Table 2.3. All lariat ethers studied were found to be more efficient extractants than the corresponding parent crown ethers, i.e., **9** and **11**, respectively. When sidearm donors are present in the crown ethers, the binding constants increased. This result suggests that cation binding is furthered via cooperative interactions that involve the macrocycle as well as donor groups on the sidearm.



9: R = H
9a: R = CH_2CH_2OH
9b: R = $CH_2CH_2OCH_3$



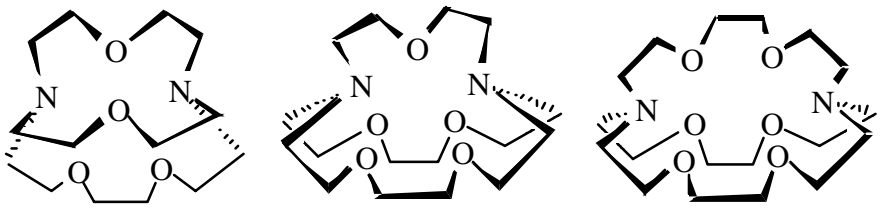
11: R = H
11a: R = $CH_2CH_2OCH_3$

Host Molecule	Log Ks		
	Na^+	K^+	Rb^+
9	1.50	1.80	nd
9a	4.87	5.08	6.02
9b	4.75	5.46	4.48
11	<1.5	<1.5	nd
11a	5.09	4.86	nd

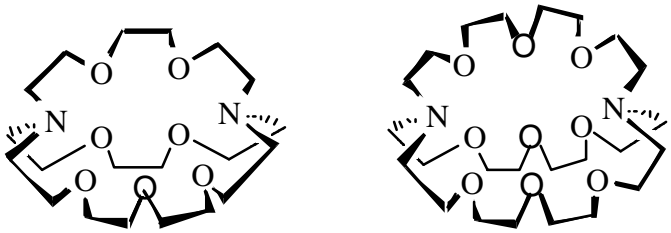
Table 2.3. Stability constants (log K_s, potentiometric, 25 °C) for complexes between *bi*bracchial lariat compounds and metal cations in MeOH.[24]

As an effort of an increase of avidity and selectivity of hosts, many cyclic compounds that contain two rings have been prepared. In particular, it is known that the ability of bicyclic crown compounds to form complexes selectively and the stability of the resulting complexes are much greater *vis-å-vis* those that involve the corresponding monocyclic crown ethers. Such bicyclic crown compounds were termed “cryptands” by Lehn [25] due to their ability not only to complex cations but also to encapsulate or entomb them. Many articles[12c] on cryptand complexation with metal ions have been published.

Figure 2.2[26] shows the results of measurements of complex constants of cryptands [2.1.1] through [3.3.3] with alkali metal ions that range from Li^+ to Cs^+.



[2.1.1] [2.2.1] [2.2.2]



[3.2.2] [3.3.3]

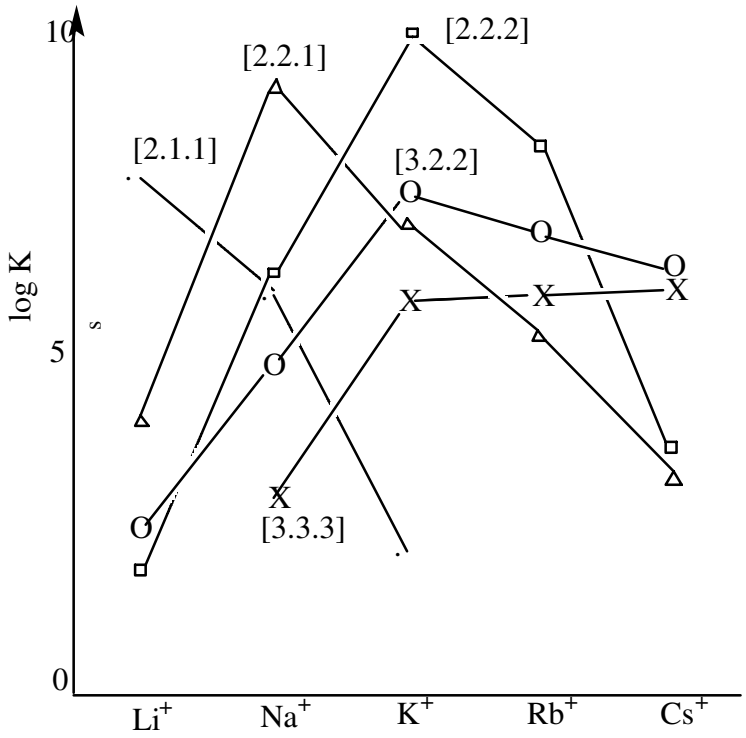
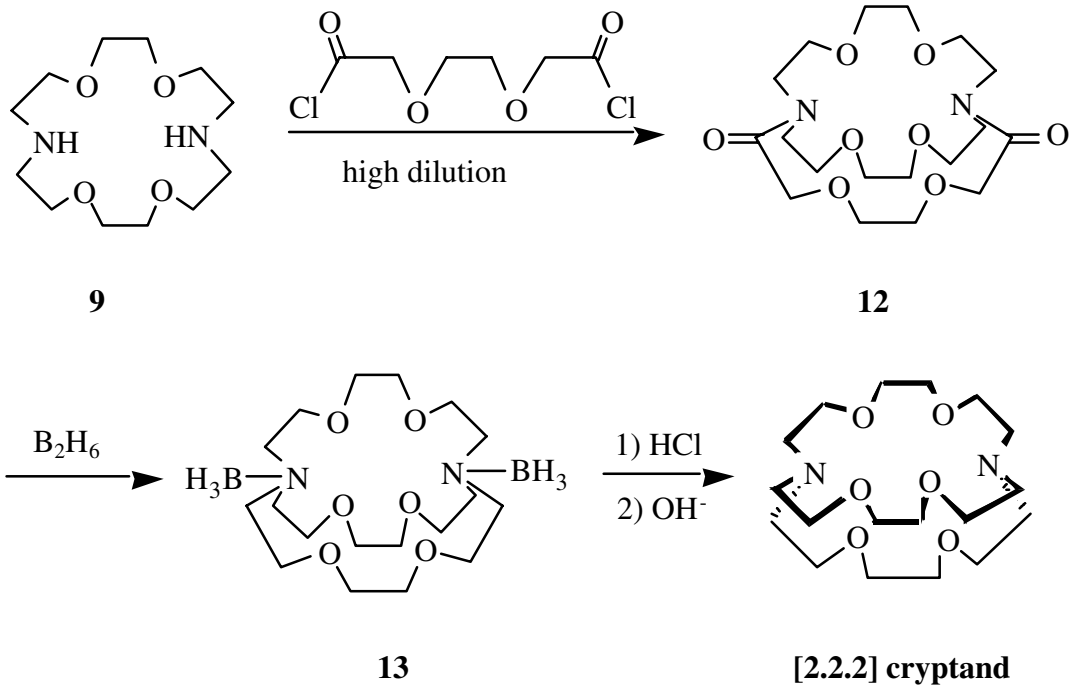


Figure 2.2. Plot of stability constants (log K_s) of various cryptates as a function of the ionic radii of alkali metal cations at 25 ^oC in 95 : 5 methanol/ water or pure methanol or in water.[30]

It is known that the thermodynamic stabilities of these complexes depend upon the quality of the size-match between the cation and cryptand cavity diameters.[27] The close relationship between log K_s for cation-macrocycle interaction and the fit of the cation into the ligand cavity[28] is shown in Figure 2.2. [2.1.1] Cryptand which contains the smallest inner volume possesses the highest K_s value for Li^+, while the [2.2.1] and [2.2.2] cryptands are best suited to complex Na^+ and K^+, respectively. The very large cryptand [3.3.3] combines better with Cs^+ than with other metal cations.[29]

The first cryptand was prepared by Lehn and coworkers in 1969; this host molecule formed a series of well-defined complexes (cryptates) with alkali and alkaline-earth metal cations.[31] Thus, [2.2.2]cryptand was synthesized via reaction of diaza-18-crown-6 (**9**) with the α,ω-oligoethyleneglycol diacid dichloride performed at high dilution .

Scheme 2.6

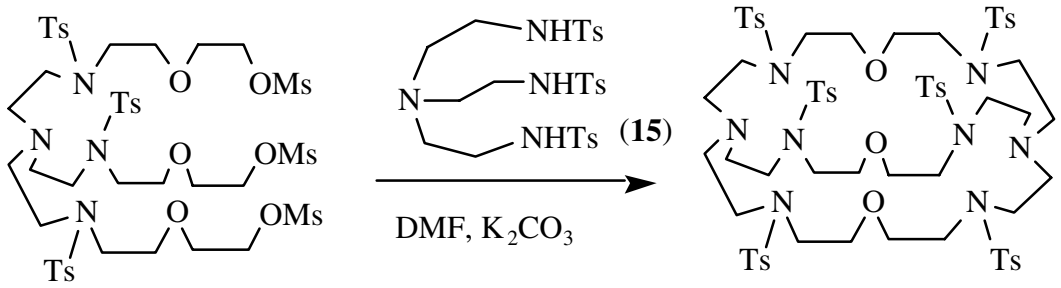


9 **12**

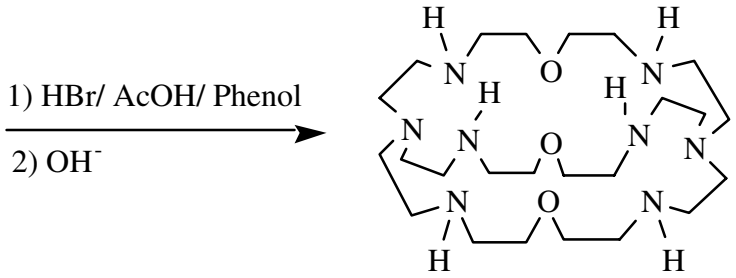
13 **[2.2.2] cryptand**

Another synthetic method used to prepare cryptands involves a tripod-tripod coupling reaction, which may be performed without the need for high-dilution conditions. This method also provide a shorter route to the desired macrocyclic compound than does Lehn's original route.[32] By using this method, a bis-tren ligand, i.e., **17**, was synthesized. Thus, trimesylate **14** was reacted with tri-*N*-tosylated tren (**15**) to afford the corresponding hexatosyl macrobicycle (**16**) in 31% yield. The removal of the tosyl groups with HBr/ AcOH/ phenol[32] afforded **17** as the corresponing bromide salt. The free macrobicyclic ocatamine **17** was obtained by passing **17**·8 HBr over Dowex resin.

Scheme 2.7



14 **16**



17

Pursuant to our interests in the synthesis and chemistry of novel polycarbocyclic cage compounds, members of our research group have prepared a variety of cage

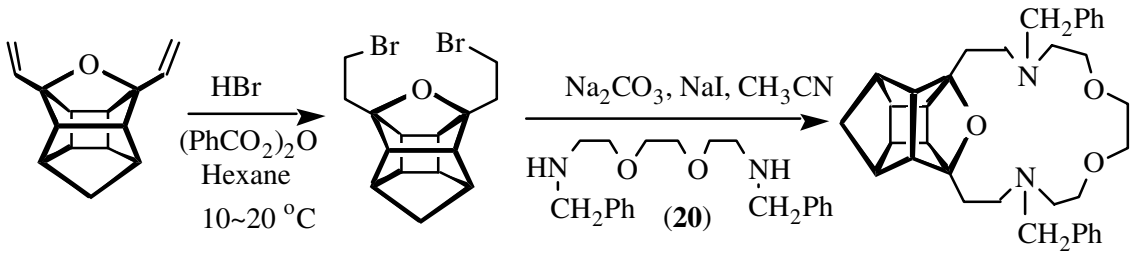
functionalized crown ethers and cryptands as "host" systems for the study of host-guest interactions.[33] As an part of these studies, we have synthesized novel cage-functionalized diaza(17-crown-5) ethers and the corresponding model compounds. The results of the alkali metal picrate extraction of these compounds are described herein. Based on the extraction results of the compounds, we shall assess the extent to which the side arms attached at *N*-pivots and the cage moiety might influence the complexation properties of diazacrown ethers toward alkali metal cations. Finally, a cage-functionalized cryptand (**34**) also was synthesized, and the results of extraction experiments that employ this host were compared to those obtained for extractions that involve the corresponding non-cage model compound.

RESULT AND DISCUSSIONS

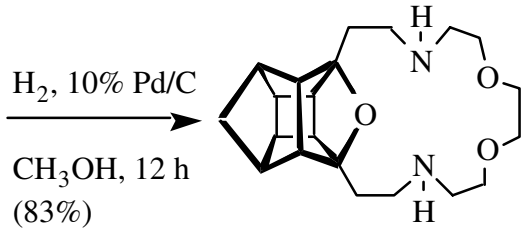
I. Synthesis of New cage-functionalized diaza-crown ethers and cryptands

Our approach to the synthesis of cage-functionalized diaza(17-crown-5) ethers is shown in Scheme 2.8-10. Compound **19**[34] was prepared in 68% yield via reaction of **18** with HBr under free radical conditions. Subsequent base promoted reaction of **19** with **20** afforded the corresponding *N,N′*-dibenzylated diaza(17-crown-5) ether (i.e., **21**, Scheme 3.8). Catalytic hydrogenolysis of **21** produced **22.** (Scheme 2.8)

Scheme 2.8



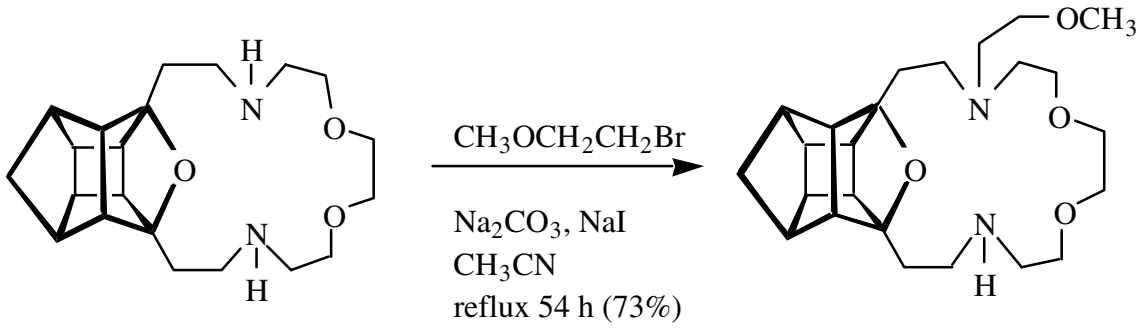
18 **19** **21**



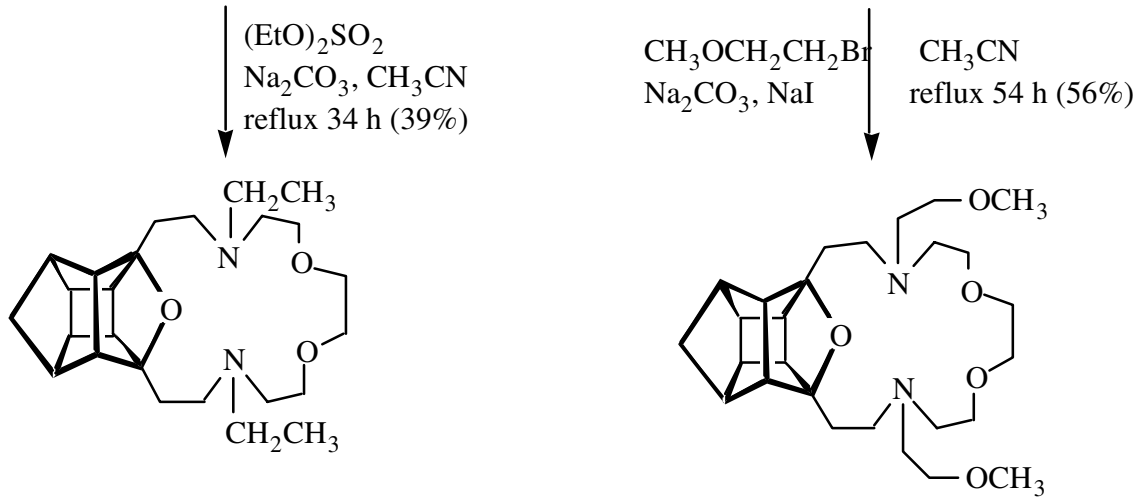
22

Cage-functionalized diaza(17-crown-5) ether **22** was employed for the purpose of preparing novel *mono*brachial and *bi*brachial crown ethers, i.e., **23**-**25**, respectively (Scheme 2.9). Thus, base promoted reaction of **22** with 1-bromo-2-methoxyethane produced the corresponding *mono*braccial lariat ether, i.e., **23**, in 73% yield. Subsequent reaction of **23** with 1-bromo-2-methoxyethane afforded the corresponding *bi*brachial lariat ether, **24**, in 56% yield. Ethyl-armed crown ether **25** was obtained in 39% yield via reaction of **22** with $(EtO)_2SO_2$ (scheme 2.9).

Scheme 2.9



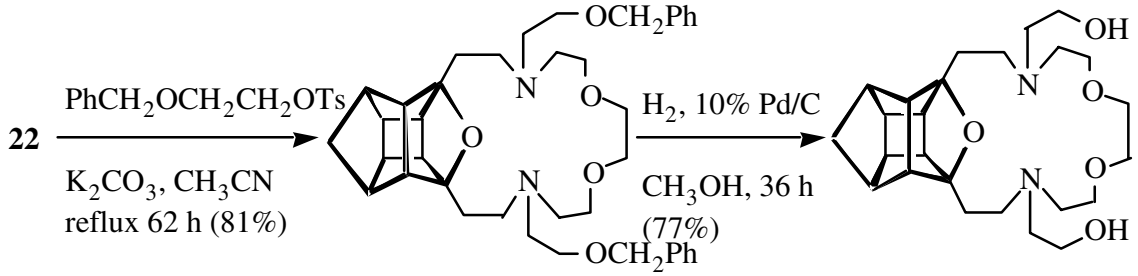
22 **23**



25 **24**

The method employed to prepare **27** is shown in Scheme 2.10. Base promoted reaction of **22** with 1-benzyloxy-2-tosyloxyethane produced the corresponding benzyl-protected crown ether, i.e., **26**, in 81% yield. Subsequent bis(de-*O*-benzylation) of **26** produced **27** in 77% yield.

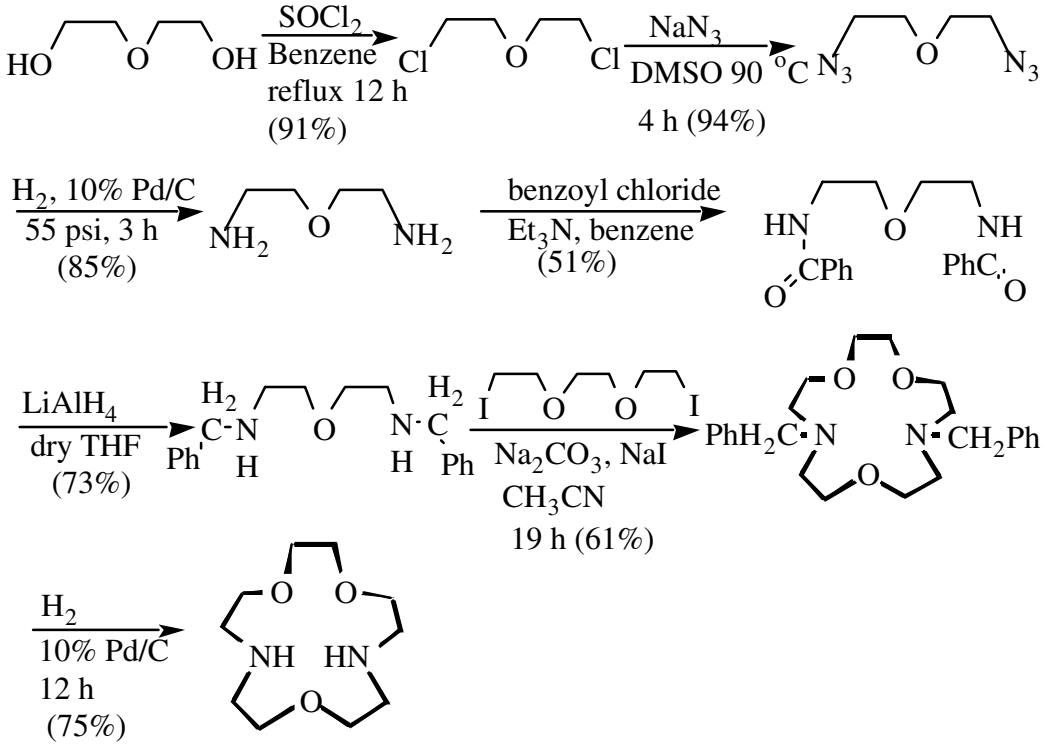
Scheme 2.10



26 **27**

A method to prepare a model compound, i.e., diaza-15-crown-5 (**11**) includes steps that have been reported previously (see Scheme 2.11).[22,35]

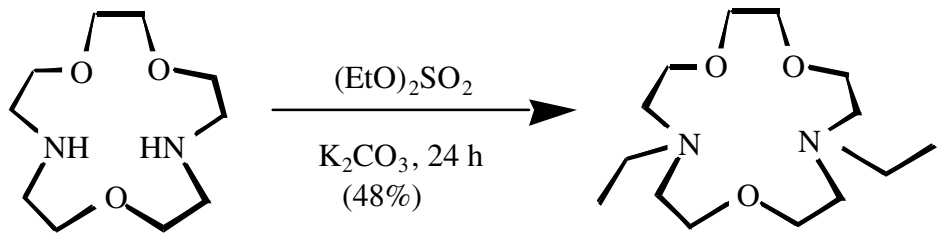
Scheme 2.11



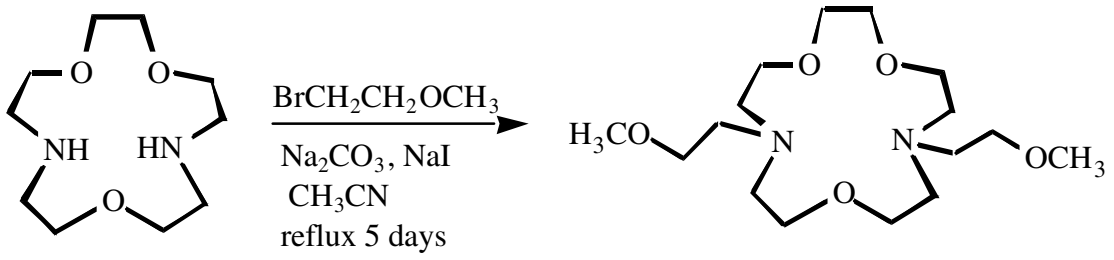
11

Other model crown ethers employed in the extraction studies were prepared as shown in Scheme 2.12. Model crown ether **28** was prepared in 48% yield via reaction of **11** with $(EtO)_2SO_2$. Model compound **29**[36] was prepared in 48% yield via base promoted reaction of **11** with 1-bromo-2-methoxyethane. Model compound **31** was produced in two steps from **11**. Base promoted reaction of **11** with 1-benzyloxy-2-tosyloxyethane produced the corresponding benzyl-protected crown ether, i.e., **30**, in 81% yield. Subsequent bis(de-*O*-benzylation) of **30** afforded **31.**[37]

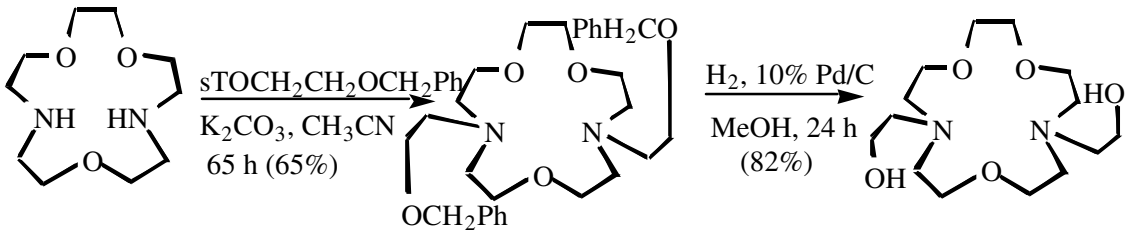
Scheme 2.12



11 **28**



11 **29**

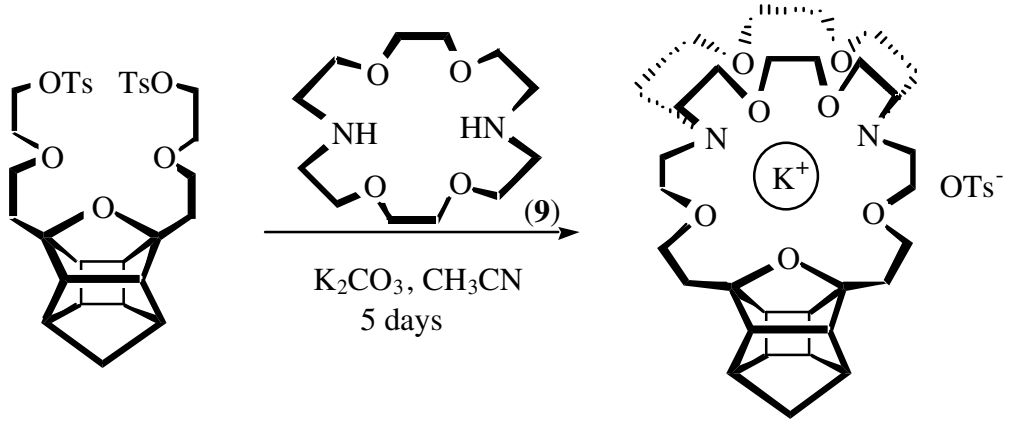


11 **30** **31**

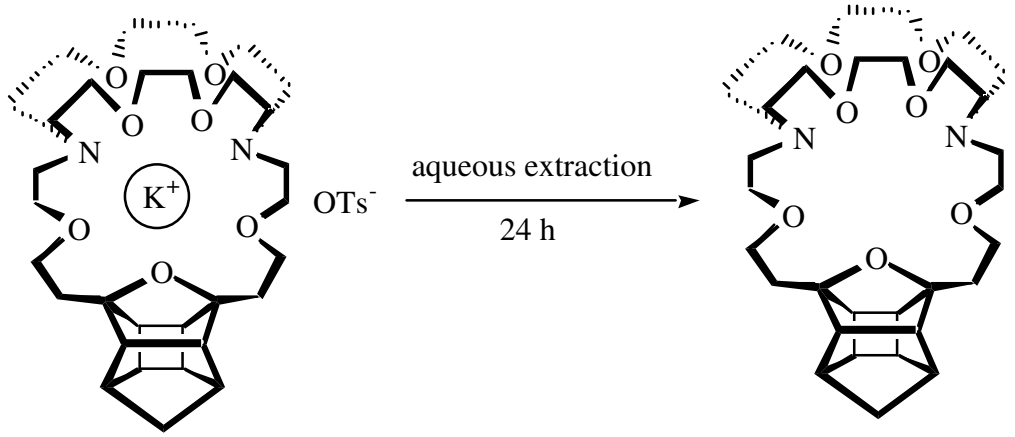
The synthesis of a bicyclic cryptand, i.e., **34** is described in Scheme 2.13. The K^+ templated reaction of 1,10-diaza(18-crown-6) (**9**) with cage ditosylate **32** gave the corresponding K^+ cryptate, **33**, in 43% yield. Subsequent aqueous extraction of **33** during 24 h afforded the corresponding noncomplexed cryptand, **34**, in 75% yield. The structures of the cryptate (**33**), i.e., the K^+ complex, and the free ligand (**34**) were confirmed via

analysis of their respective ^{1}H NMR and ^{13}C NMR spectra, and via HRMS analysis (see the Experimental Section).

Scheme 2.13



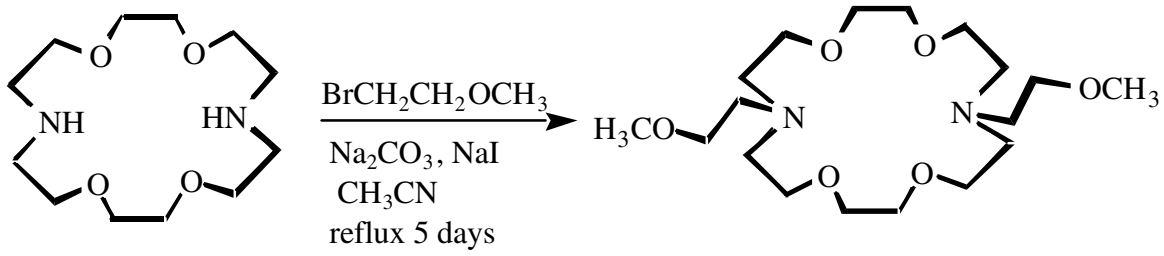
32 **33**



33 **34**

For comparison in extraction studies, model compound **35** was prepared in 48% yield via base promoted reaction of **9** with 1-bromo-2-methoxyethane.

Scheme 2.14



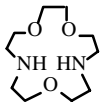
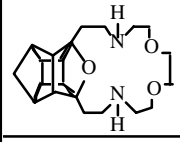
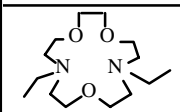
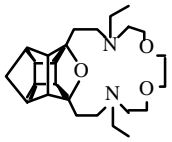
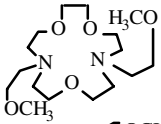
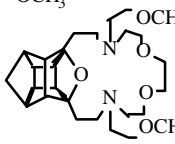
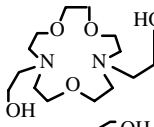
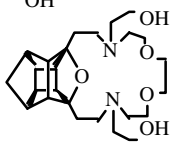
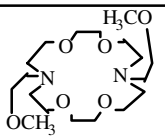
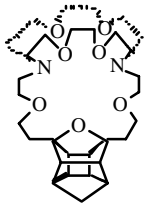
9 **35**

II. Results of Alkali Metal Picrate Extraction Experiments.

In an effort to evaluate the effects of cage-annulation and sidearms located at *N*-pivot positions, a series of alkali metal picrate extraction experiments was performed by using the new host molecules prepared herein. The results thereby obtained are shown in Table 2.4.

Inspection of the data in Table 2.4 indicates that the binding abilities of crown ethers toward alkali metal cations appear to be influenced by the presence of *N*-pivot side arms. As can be seen therein, cage-functionalized lariat ethers, i.e., **24**, **25** and **27,** display greater avidity toward Na^+ picrate than the corresponding parent crown ether (**22**). It is interesting to note that **25**, which bears nondonating ethyl groups, displays higher extracting ability toward Na^+, Rb^+ picrates than **22**. It seems likely that the presence of the *N*-ethyl group in **25** results in a more favorable conformational arrangement of donor atoms for complexation of Na^+, Rb^+ *vis-à-vis* that which exists in the parent crown ether. The reduced ability of **25** to extract other metal cations may be attributed to steric hindrance, which renders the favorable conformations irreversible. Compound **27,** which possesses

Table 2.4. Results of alkali metal picrate extraction experiment

Host Molecule	Percent of Picrate Extracted				
	Li^+	Na^+	K^+	Rb^+	Cs^+
 (**11**)	13.2 ± 0.6	14.1 ± 0.6	12.6 ± 0.4	12.1± 0.4	8.5 ± 0.5
 (**22**)	30.3 ± 0.9	17.4 ± 0.7	39.7 ± 1.1	19.4 ± 0.8	31.5 ± 1.1
 (**28**)	18.8 ± 2.4	25.1 ± 1.0	22.5 ± 1.0	8.3 ± 0.6	14.4 ± 0.8
 (**25**)	21.0 ± 0.8	19.7±1.4	23.6 ± 0.8	24.3 ±0.7	16.2 ±0.7
 (**29**)	28.6 ± 1.2	46.8 ±0.8	37.2 ±0.5	28.5 ± 0.7	26.9 ± 0.7
 (**24**)	16.6 ±0.6	19.1 ± 1.2	22.6± 0.6	16.0 ± 0.4	15.4 ± 0.8
 (**31**)	29.8 ± 0.6	37.4 ± 0.5	33.4 ± 0.7	31.9 ± 0.5	33.0 ± 0.5
 (**27**)	16.5± 1.3	22.7 ± 0.7	34.9 ± 1.6	19.9 ± 0.9	36.1 ± 1.4
 (**35**)	17.5 ±0.5	36.0 ± 0.7	46.3 ± 0.8	34.6± 0.9	21.3 ± 0.5
 (**34**)	36.3 ± 0.6	50.0 ± 0.7	74.4 ± 0.8	68.4 ± 1.0	60.9± 0.8

electron-donating hydroxyl groups on the lariat sidearm, displays higher extraction avidity toward K^+ and Cs^+ picrates *vis-à-vis* **22**. The hydroxyl groups on the sidearms appear to provide additional coordination to the cations that are complexed by the parent crown ring. On the contrary, **24**, which possesses methoxy groups on the lariat sidearm, displays lowered extraction avidity toward all metal cations *vis-à-vis* **22** except toward Na^+ picrate.

The effect of cage-annulation on complexation was demonstrated by comparing the metal ion extraction characteristics of cage-annulated crown ethers with that of their corresponding parent crown ethers. The data in Table 2.4 indicate that cage-annulated crown ether **22** is a much more efficient alkali metal picarate extractor than its corresponding model compound, i.e., **11**, particularly toward Li^+, K^+ and Rb^+ picrates. One possible rationale for this result is that the cage moiety in **22** renders the spatial arrangement and orientation of the crown's donor atoms more favorable than in the corresponding model (non-cage) crown ether, thereby resulting in enhanced binding with metal cations. Cage-annulated crown **25**, which contains nondonating *N*-ethyl groups, also displays increased avidity toward all metal cations studied, except for Na^+. In particular, **25** displays *ca.* three times higher extracting ability toward Rb^+ *vis-à-vis* the corresponding model compound, **28.**

Cage-annulated crown ether **27** displays greater avidity toward K^+ and Cs^+ picrates compared to its corresponding model compound (**31**). In the case of **24**, cage-annulation leads to reduced avidity toward all alkali metal picrates compared to their model compound, i.e., **29**.

It appears that the availability of electron-donating oxygen atoms on the side arms for coordination with M^+ may be significantly constrained by the presence of the cage moiety. Therefore, the sidearms do not contribute efficiently toward complexation of the various alkali metal cation guests studied. The most efficient alkali metal picrate extracting agent among those studied herein is the highly preorganized cage-functionalized cryptand, i.e., **34**. As expected on the basis of the size-match principle, **34** displays higher extraction selectivity toward K^+ and Rb^+ picrates and greater avidity toward all alkali metal picrate than the corresponding model system (**35**).

SUMMARY AND CONCLUSIONS

As our current interest in the chemistry of polycarbocyclic cage compounds, a variety of novel cage-functionalized diaza crown ethers (**21-27**) have been prepared for selective alkali metal complexation studies. The alkali metal picrate extraction experiments have been performed by using this new class of synthetic ionophores to investigate the effects of cage-annulation and the influence of sidearms at *N*-pivot on complexation properties**.** The results of extraction experiments indicate that the extraction ability of crown ethers toward alkali metal cations are evidently influenced by the type of the sidearms introduced at the *N*-pivot and the presence of cage moiety. In particular, the cage-annulated diaza crown ether **22** displays much greater avidity toward all metal picrate than the corresponding model system (**11**). All cage-annulated lariat ethers (**24**, **25,** and **27**) display increased avidity for Na^+ compared to the parent crown ether (**22**). The lariat ethers bearing the different sidearms display different extraction pattern toward alkali metal cations. Finally, a cage-annulated bicyclic cryptand **34** was synthesized and

is proven to be the most efficient extractant among those studied herein. As expected by size-match principle, **34** displays higher extraction ability toward K^+, Rb^+ picrates and greater avidity toward all metal picrate than the corresponding model system (**35**).

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. Absorption intensities of alkali metal picrate solutions were measured at λ = 374 nm by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

Bromination of vinyl ether (19). A mixture of **18** (4.30 g, 11.5 mmol) and benzoyl peroxide (430 mg) in hexane (60 mL) was cooled to 10-20 °C via application of an external ice-water bath. Hydrogen bromide gas, produced by heating a solution of Br_2 (21.5 mL, 41.7 mmol) in tetralin (30 mL, excess) was allowed to bubble through this solution slowly during 6 h. Subsequently, the resulting mixture was stirred at 10-20 °C during 2 h. The reaction mixture was washed sequentially with H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and H_2O (20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column

chromatography on silica gel by eluting with hexane. Pure **19** (6.10 g, 78%) was thereby obtained as a colorless oil: IR (neat) 2970 (s), 1450 (m), 1103 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.52 (*A*B, J_{AB} = 10.7 Hz, 1H), 1.86 (A*B*, J_{AB} = 11 Hz, 1H), 2.26-2.66 (m, 15 H), 3.38 (t, *J* = 9 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.9 (t), 36.9 (t), 42.0 (d), 44.2 (t), 44.7 (d), 48.2 (d), 58.8 (d), 96.7 (s). The IR, ^1H NMR, ^{13}C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectral data that has been reported previously for authentic **19**.[39]

Synthesis of 21. To a solution of **19** (740 mg, 1.98 mmol) and **20** (542 mg, 1.65 mmol) in CH_3CN (44 mL) was added sequentially with stirring Na_2CO_3 (1.84 g, 16.5 mmol) and NaI (130 mg, 0.875 mmol), and the resulting mixture was refluxed with stirring during 24 h. The reaction mixture was allowed to cool to ambient temperature and then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), and the resulting solution was washed with water (3 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **21** (610 mg, 63%) was thereby obtained as a colorless oil: IR (film) 2968 (s), 1630 (m), 1450 (m), 1148 (m), 1358 (w), 730 and 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.50 (d, *J* = 10.0 Hz, 1 H), 1.78-2.04 (m, 5 H), 2.35 (s, 2 H), 2.50-2.70 (m, 10 H), 3.33 (s, 6 H), 3.45 (t, *J* = 6.6 Hz, 4 H), 3.55-3.62 (m, 8 H), 7.18-7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 30.3 (t), 41.9 (d), 44.2 (t), 44.4 (d), 48.6 (d), 51.0 (t), 53.6 (t), 59.2 (d), 59.4 (t), 95.4 (s), 127.3 (d), 128.7 (d), 129.4 (d), 140.4 (s). Anal. Calcd for $C_{35}H_{44}N_2O_3$: C, 77.74; H, 8.20. Found: C, 77.53; H, 7.96.

Hydrogenolysis of the *N*-Benzyl Groups in 21. To a solution of **21** (900 mg, 1.6 mmol) in MeOH (70 mL) was added 10% palladized charcoal (200 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig at ambient temperature during 12 h on a Parr shaker hydrogenation apparatus. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 15% MeOH-EtOAc. Pure **22** (480 mg, 83%) was thereby obtained as a colorless oil; IR (film) 3347 (br, s), 2982 (s), 1468 (m), 1350 (w), 1135 cm^{-1} (m) ; ^1H NMR ($CDCl_3$) δ 1.52 (AB, J_{AB} = 10 Hz, 1 H), 1.75-2.02 (m, 5 H), 2.32 (s, 2 H), 2.41-2.60 (m, 8 H), 2.70-2.83 (m, 8 H), 3.50-3.62 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 31.8 (t), 41.2 (d), 43.4 (t), 43.7 (d), 46.2 (t), 47.6 (d), 49.2 (t), 58.2 (d), 70.0 (t), 71.0 (t), 96.2 (s). Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95. Found: C, 69.79; H, 8.97.

Synthesis of 23. To a solution of **22** (270 mg, 1.98 mmol) in CH_3CN (15 mL) under argon was added sequentially Na_2CO_3 (740 mg, 3.33 mmol) and NaI (110 mg, 2.18 mmol), and the resulting mixture was refluxed for 65 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting at first with 20% EtOAc-hexane, followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Pure **23** (190 mg, 73%) was thereby obtained as a colorless oil; IR (neat)

2969 (s), 1461 (m), 1351 (w), 1116 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46 (AB, J_{AB} = 10 Hz, 1 H), 1.74-2.02 (m, 5 H), 2.28 (s, 2 H), 2.38-3.79 (m, 17 H), 3.26 (s, 3 H), 3.36 (t, *J* = 6 Hz, 2 H), 3.45-3.60 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 29.6 (t), 31.1 (t), 41.3 (d, 2 C), 43.5 (t), 43.78 (d), 43.84 (d), 47.0 (t), 47.5 (d), 47.8 (d), 49.8 (t), 50.2 (t), 53.4 (t, 2 C), 58.1 (d), 58.6 (d), 58.8 (d), 70.1 (t), 70.3 (t), 71.2 (t), 71.3 (t), 95.4 (s), 96.6 (s), Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.87; H, 9.15. Found: C, 68.96; H, 9.09. This material was used as obtained in the next synthetic step.

To a solution of **23** (190 mg, 0.48 mmol) and 1-bromo-2-methoxyethane (200 mg, 1.44 mmol) in CH_3CN (15 mL) under argon was added sequentially with stirring Na_2CO_3 (640 mg, 2.88 mmol) and NaI (430 mg, 2.88 mmol), and the resulting mixture was refluxed for 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (15 mL), and the resulting solution was washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 25% EtOAc-hexane followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Pure **24** (97 mg, 48%) was thereby obtained as a colorless oil; IR (neat) 2962 (s), 1481 (m), 1341 (w), 1122 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.55 (AB, J_{AB} = 10 Hz, 1 H), 1.78-1.97 (m, 5 H), 2.35 (s, 2 H), 2.46-3.66 (m, 20 H), 3.33 (s, 6 H), 3.45 (t, *J* = 5 Hz, 4 H), 3.55-3.65 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 29.2 (t), 41.3 (d), 43.5 (t), 43.8 (d), 47.9 (d), 50.4 (t), 53.6 (t), 53.8 (t), 58.5 (d),

58.7 (d), 70.4 (t), 71.0 (t), 71.2 (t), 94.6 (s). Anal. Calcd for $C_{27}H_{44}N_2O_5$: C, 68.04; H, 9.30. Found: C, 67.87; H, 9.10.

Synthesis of 25. To a mixture of **22** (270 mg, 1.98 mmol) and Na_2CO_3 (250 mg, 2.33 mmol) in CH_3CN (10 ml) was added $(EtO)_2SO_2$ (180 mg, 1.17 mmol), and the resulting mixture was refluxed with stirring during 34 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. Dichloro-methane (10 mL) was added to the residue; the resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **25** (85 mg, 39%) was thereby obtained as a colorless oil; IR (neat) 2969 (s), 1461 (m), 1370 (w), 1122 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7 Hz, 4 H), 1.51 (d, J = 11 Hz, 1H), 1.75-2.05 (m, 5 H), 2.35 (s, 2 H), 2.38-2.62 (m, 10 H), 2.66 (t, J = 5 Hz, 4 H), 2.76 (t, J = 6 Hz, 4 H), 3.55 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.3 (q), 29.0 (t), 41.4 (t), 43.5 (t), 43.8 (d), 47.97 (t), 47.99 (d, 2 C), 49.3 (t), 52.5 (t), 58.6 (d), 70.5 (t), 71.1 (t), 94.8 (s). Exact mass (CI HRMS) Calcd for $C_{25}H_{40}N_2O_3$: M_r^+ 416.303894. Found: M_r^+ 416.303048.

Synthesis of Crown Ether 26. To a solution of **22** (380 mg, 1.05 mmol), 1-benzyloxy-2-tosyloxyethane (700 mg, 2.1 mmol) in CH_3CN (45 mL) was added K_2CO_3 (1.45 g, 10.5 mmol), and the resulting mixture was refluxed for 62 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc, thereby

affording pure **26** (430 mg, 81%) as a colorless oil; IR (film) 3073 (w), 3041 (w), 2962 (s), 1620 (w), 1468 (m), 1116 (m), 730 (m), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.42 (AB, J_{AB} = 8 Hz, 1 H), 1.85-1.92 (m, 5 H), 2.34 (s, 2 H), 2.45-2.53 (m, 6 H), 2.65-2.85 (m, 9 H), 3.42-3.65 (m, 12 H), 4.45-4.52 (m, 4 H), 7.18-7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.3 (t), 41.3 (t), 43.5 (t), 47.9 (d), 50.4 (d), 53.8 (t), 54.0 (t), 58.6 (t), 68.9 (t), 70.5 (t), 71.1 (t), 73.1 (t), 94.7 (s), 127.4 (d), 127.4 (d), 128.2 (d), 138.4 (s). Anal. Calcd for $C_{39}H_{52}N_2O_5$: C, 74.49; H, 8.33. Found: C, 74.28; H 8.40.

Hydrogenolysis of the *O*-Benzyl Groups in 26. To a solution of **26** (350 mg, 0.78 mmol) in MeOH (50 mL) was added 10% palladized charcoal (150 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig at ambient temperature during 36 h on a Parr shaker hydrogenation apparatus. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **27** (200 mg, 77%) was thereby obtained as a colorless oil; IR (neat) 3334 (br), 2982 (s), 1475 (m), 1347 (m), 1113 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.53 (AB, J_{AB} = 10 Hz, 1 H), 1.98-2.02 (m, 5 H), 2.36 (s, 2 H), 2.45-2.79 (m, 16 H), 3.45 (t, J = 5 Hz, 4 H), 3.56-3.64 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 41.4 (d), 43.3 (t), 44.1 (d), 47.9 (d), 52.5 (t), 53.6 (t), 55.7 (t), 56.5 (t), 58.3 (d), 64.7 (t), 70.4 (t). 96.4 (s). Anal. Calcd for $C_{25}H_{40}N_2O_5$: C, 66.94; H, 8.99. Found: C, 66.74; H, 8.70.

Synthesis of 28. To a mixture of **11** (300 mg, 1.37 mmol) and Na_2CO_3 (580 mg, 5.49 mmol) in CH_3CN (10 mL) was added $(EtO)_2SO_2$ (420 mg, 2.75 mmol), and the

resulting mixture was refluxed with stirring during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. Dichloro-methane (10 mL) was added to the residue, and the resulting mixture was heated to the reflux temperature to effect dissolution. The resulting mixture was filtered, and the filtrate was concen-trated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 1% MeOH-EtOAc. Pure **28** (180 mg, 48%) was thereby obtained as a colorless oil; IR (neat) 2957 (s), 1453 (m), 1316 (m), 1115 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 8 Hz, 6 H), 2.48 (q, 4 H), 2.55-2.70 (m, 8 H), 3.42-3.58 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 11.8 (q), 50.3 (t), 53.7 (d), 53.9 (t), 69.7 (t), 70.5 (t), 70.6 (t). Exact mass (CI HRMS) Calcd for $C_{14}H_{30}N_2O_3$: M_r^+ 275.233468. Found: M_r^+ 275.233178.

***N,N'*-Bis(2-methoxyethyl)-4,10-diaza-15-crown-5 (29).** To a solution of **11** (160 mg, 0.73 mmol) and 1-bromo-2-methoxyethane (570 mg, 4.10 mmol) in CH_3CN (25 mL) under argon was added sequentially with stirring Na_2CO_3 (813 mg, 3.65 mmol) and NaI (54 mg, 1.5 mmol), and the resulting mixture was refluxed with stirring during 6 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was extracted with 6 N aqueous HCl (2 × 10 mL). The combined aqueous phases were adjusted to pH 8-10 by careful, gradual addition of solid Na_2CO_3 (100 mg), and the resulting mixture was extracted with $CHCl_3$ (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral

alumina by eluting with EtOAc. Pure **29** (115 mg, 56%) was thereby obtained as a colorless oil. The IR, ^{1}H NMR, ^{13}C NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **29**.[36]

Synthesis of 30. To a solution of **11** (170 mg, 0.78 mmol) and 1-benzyloxy-2-tosyloxyethane (520 mg, 1.71 mmol) in CH_3CN (15 mL) under argon was added K_2CO_3 (1.10 g, 7.78 mmol), and the resulting mixture was refluxed with stirring for 65 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **30** (220 mg, 58%) was thereby obtained as a colorless oil. IR (neat) 3056 (m), 2967 (s), 1615 (w), 1459 (m), 1110 (m), 728 and 709 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.70-2.92 (m, 12 H), 2.56-3.65 (m, 16 H), 4.55 (s, 4 H), 7.32-7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 54.3 (t), 54.6 (t), 55.3 (t), 69.3 (t), 70.0 (t), 70.1 (t), 127.1 (d), 127.9 (d), 138.0 (s). Exact mass (CI HRMS) Calcd for $C_{28}H_{42}N_2O_5$: M_r^+ 487.317198. Found: M_r^+ 487.316896.

Hydrogenolysis of the *O*-Benzyl Groups in 30. To a solution of **30** (200 mg, 0.41 mmol) in MeOH (50 mL) was added 10% palladized charcoal (150 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig at ambient temperature during 24 h on a Parr shaker hydrogenation apparatus. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **31** (100 mg, 79%) was thereby

obtained as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.50-2.82 (m, 12 H) 3.43-3.74 (m, 16 H), 4.50 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 55.4 (t), 55.9 (t), 58.6 (t), 59.6 (t), 69.8 (t), 70.0 (t), 70.3 (t). The IR, ^{1}H NMR, ^{13}C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectral data that has been reported previously for authentic **31**.[36]

K^+ Cryptate 33. To a mixture of **32** (220 mg, 0.34 mmol) and K_2CO_3 (186 mg, 1.34 mmol) in CH_3CN (15 mL) was added **9** (84 mg, 0.32 mmol), and the resulting mixture was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% MeOH-CH_2Cl_2. Pure K^+ cryptate **33** (94.2 mg, 43%) was thereby obtained as a colorless, waxy solid; IR ($CHCl_3$) 3350 (br, s), 2963 (s), 1724 (w), 1585 (m), 1456 (m), 1223 (s), 1354 (w), 1008 (m), 751 (w), 732 (s), 680 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.53 (AB, J_{AB} = 8 Hz, 1 H), 1.70-2.03 (m, 5 H), 2.21-2.70 (m, 6 H), 3.35-3.78 (m, 8 H), 7.10 (*A*B, J_{AB} = 7 Hz, 2 H), 7.85 (A*B*, J_{AB} = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.5 (t), 41,4 (t), 43.4 (t), 43.8 (d), 47.9 (d), 54.3 (t, 2 C), 58.4 (d), 68.2 (t, 2C), 69.5 (d, 2 C), 94.8(s), 126.4 (d), 128.3 (d), 133.8 (s), 139.5 (s). Exact mass (CI HRMS) Calcd for $C_{38}H_{57}KN_2O_{10}S$: M_r^+ 773.339053. Found: M_r^+ 773.341600.

Cryptand 34. A solution of **33** (220 mg, 0.35 mmol) in $CHCl_3$ (20 mL) was placed in separatory funnel, placed on a mechanical shaker apparatus, and extracted with H_2O (15 mL). The layers were separated at 12 h intervals, the water layer was replaced at

that time with fresh water (15 mL), and the extraction procedure was continued during 24 h. The presence (or absence) of KOTs was confirmed by withdrawing aliquots at 12 h intervals. Each aliquot was concentrated *in vacuo*, and the residue was analyzed via careful inspection of its ^{1}H NMR and ^{13}C NMR spectra. After the water-extraction procedure had been completed, the layers were separated; the organic layer was filtered, and the filtrate was concentrated *in vacuo*. Pure **34** (98 mg, 62%) was thereby obtained as a colorless oil; IR (neat) 3376 (br, s), 2938 (s), 1634 (m), 1603 (m), 1444 (m), 1200 (s), 1030 (m), 749 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.54 (AB, J_{AB} = 8 Hz, 1 H), 1.80-2.13 (m, 5 H), 2.76-2.90 (m, 4 H), 2.20-2.90 (m, 8 H), 3.40-3.70 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 41.6 (t), 43.5 (d), 44.0 (t), 48.2 (t), 55.2 (t), 55.3 (t), 59.1 (t), 68.2 (t), 69.7(t), 70.1 (t), 70.8 (t), 94.5(s). Exact mass (CI HRMS) Calcd for $C_{31}H_{50}N_2O_7$: $[M_r + H]^+$ 563.369628. Found: $[M_r + H]^+$563.370430.

***N,N'*-Bis(2-methoxyethyl)-5,12-diaza-18-crown-6 (35).** To a solution of **9** (250 mg, 1.90 mmol) and 1-bromo-2-methoxyethane (396 mg, 5.70 mmol) in CH_3CN (50 mL) under argon was added sequentially with stirring Na_2CO_3 (2.10 g, 9.50 mmol) and NaI (145 mg, 2.1 mmol), and the resulting mixture was refluxed with stirring during 6 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (30 mL), and the resulting solution was extracted with 6 N aqueous HCl (2 × 15 mL). The combined aqueous phases were adjusted to pH 8-10 by careful, gradual addition of Na_2CO_3 (100 mg), and the resulting mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was

concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 25% EtOAc-hexane followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Pure **35** (159 mg, 42%) was thereby obtained as a colorless oil. The IR, ^{1}H NMR, ^{13}C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectral data that has been reported previously for authentic **35**.[37]

Alkali Metal Picrate Extraction Experiments. The general procedures employed have been described previously (see Chapter 1).

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CHAPTER 3

SYNTHESIS AND ALKALI METAL PICRATE EXTRACTION STUDIES OF *P*-TERT-BUTYLCALIX[4]ARENE CROWNS BRIDGED AT THE LOWER RIM WITH PYRIDYL UNITS

INTRODUCTION

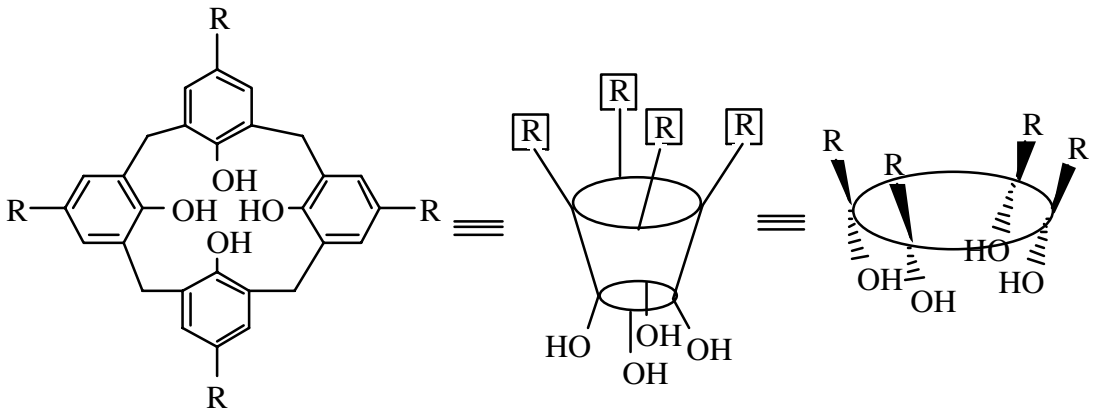
Calixarenes[1] have become an important class of molecules for a variety of structural, conformational, and host-guest studies during the past decade. Gutsche[2] introduced the term "calixarene" to describe a homologous series of macrocycles that are composed up of alternating phenol and methylene units. This term originated from the observation that the tetracyclic members of the series can assume a chalice or cup-like conformation.[2]

In particular, calixarenes offer many interesting possibilities to host-guest chemistry. Compounds of this type can be synthesized readily on a large scale via simple one-pot procedures by using inexpensive starting materials. In addition, calixarenes can be functionalized selectively both at the phenolic groups (lower rim) and at the *p*-positions of the phenol rings (upper rim). In lower rim functionalization, the phenolic OH groups provide the sites for the attachment of ethers, esters, amides, and acids.[4] Since *tert*-butyl groups attached to phenyl rings are easily removed by Lewis acids,[5a] a variety of functional groups can be introduced into *p*-positions at the upper rim.[5] Finally, calixarenes provide a functionalized cavity that might be expected to bind guests, and their cavity shape also can be varied according to the requirements of different guests.

There are many examples[3] of complexation that involves calix[n]arenes which possess novel cavity shapes.

Readily accessible calix[4]arenes[6] are cyclic tetramers that have been used frequently to study host-guest interactions. A variety of representations of conformers of calix[4]arenes in their cone conformation are shown in Scheme 3.1.

Scheme 3.1



1: R = H, **2**: R = *t*-Butyl

Calix[4]arenes are conformationally flexible molecules. Each phenol unit can rotate to adopt any of four different conformations,[7] i.e., "cone", "partial cone", "1,2-alternate", and "1,3-alternate" (Figure 3.1). The cone conformer of calix[4]arene **1** and of *t*-butylcalix[4]arene **2** is the most favored conformation due to the stabilization that results via intramolecular hydrogen-bonding interactions among OH groups.[8,9]

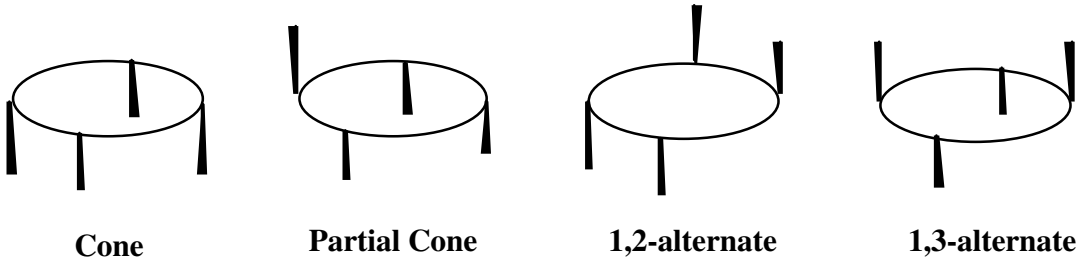
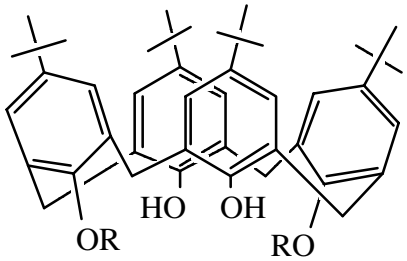


Figure 3.1. Schematic representations of the four possible conformations of calix[4]arenes Filled triangles represent the arene rings; the ellipses represent the best plane containing the methylene bridges.

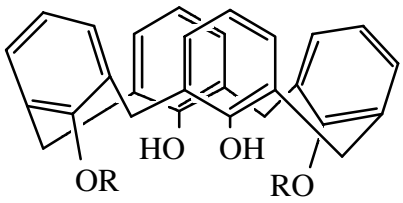
However, when calix[4]arenes are alkylated by ether or ester linkages, the conformational mobility generally is reduced, and the cone conformation no longer is stabilized by intramolecular hydrogen-bonding interactions.[9] Therefore, the introduction of substituents on the phenolic oxygens at the lower rim produces derivatives that have different shapes and conformational mobilities depending on the nature and the number of these substituents. For example, the introduction of four ester,[10] keto,[11] amide,[12] or mixed-type[13] binding sites on the phenolic OH groups fixes these calix[4]arenes in the "cone" conformation.

In particular, selective 1,3-dialkylation[14] of calix[4]arenes (e.g., **3**[15] and **4,**[16] Scheme 3.2) permits the synthesis of a variety of calix[4]arene crowns via introduction of suitable polyether bridges on the two remaining phenolic OH group.

Scheme 3.2



3 (R = CH_3)



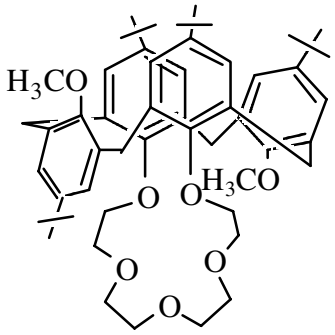
4 (R = CH_3)

The complexation properties of calix[4]arene crowns[17,18] are highly dependent upon the nature and number of donor groups. In addition, their stereochemical arrangement, which is determined by the conformation of the calix (i.e., cone, partial cone, 1,3-alternate, or 1,2-alternate, Figure 3.1) is another important factor in complexation. A variety of calix[4]arene crowns are known to bind alkali and alkaline earth metal cations with an efficiency comparable to that of cryptands.[19]

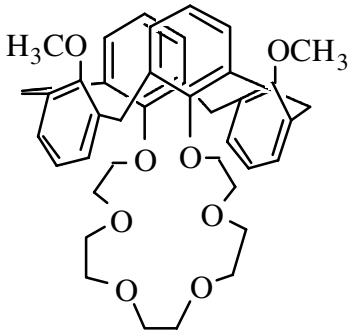
In particular, the 1,3-dimethoxy-*p*-*tert*-butylcalix[4]arene crown-5 (i.e., **5**, Scheme 3.3) displays surprisingly high selectivity for K^+ *vis-à-vis* other alkali metal ions both in extraction experiments and in liquid membrance experiments.[15,20] The preferred conformation for binding in **5** appears to involve a flattened partial cone, i.e., a conformation that lies between a cone and a partial cone. In this conformation, one of the methyl groups is located inside the apolar cavity of the calix[4]arene, while the others reside near the polyether ring.

Ungaro and coworkers[21] observed that a 1,3-dimethoxycalix[4]arenecrown-6 (i.e., **6**, Scheme 3.3) displays a high binding preference for Cs^+ in $CHCl_3$ solution, thereby resulting in high Cs^+/Na^+ selectivity. It is suggested that the preferred conformation that is required for effective binding to Cs^+ is the 1,3-alternate. The less polar 1,3-alternate conformation prefers to bind to Cs^+ *vis-à-vis* Na^+ and allows Cs^+ to interact with the π-electron cloud of the arene rings. This interaction is clearly shown in the X-ray crystal structure of the Cs^+ complexed calix[4]crown. Therefore, the complexation properties of **6** result via the simultaneous operation of several effects, including, e.g., the size of the crown ether ring, the polarity of the calix conformation, and the strength of the cation/π-electron interactions.[22]

Scheme 3.3



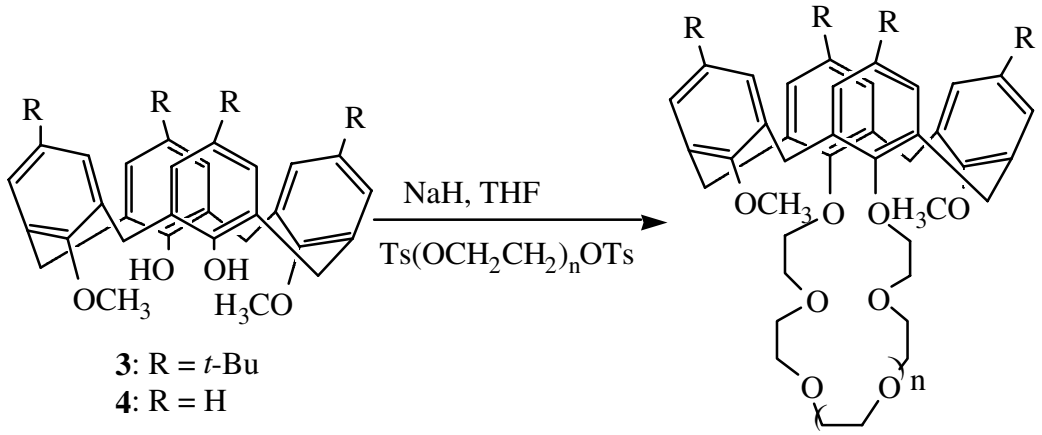
5



6

A method used to prepare *mono*calix[4]arene crowns in a fixed cone conformation[17] is shown in Scheme 3.4. When 1,3-dimethoxycalix[4]arenes (**3** and **4**) were allowed to react with polyethylene glycol ditosylates in the presence of NaH-THF, the corresponding calix[4]arene crowns (**7**-**9**) fixed in their respective cone conformations were obtained in high yields.

Scheme 3.4

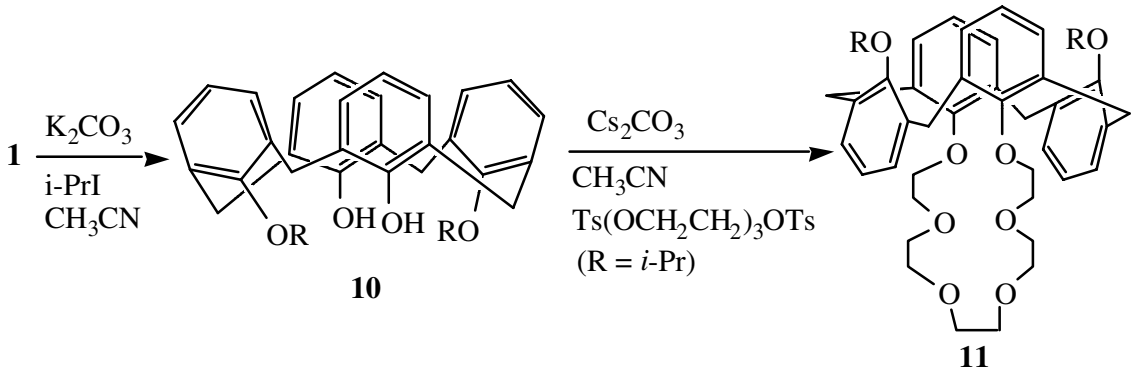


3: R = *t*-Bu
4: R = H

7: n = 0, R = H
8: n = 1, R = H
9: n = 1, R = *t*-Bu

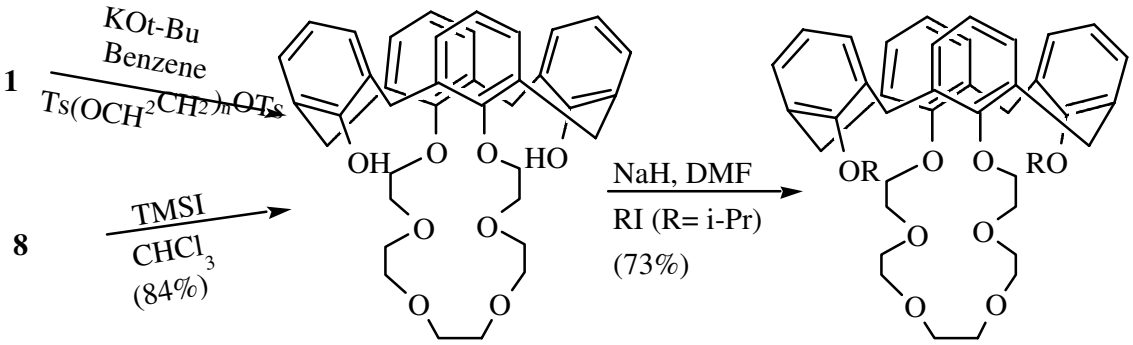
Reinhoudt and coworkers[23] have shown that numerous calix[4]arene crown-6 in a fixed 1,3-alternate conformation can be prepared via reaction of 1,3-dialkoxycalix[4]arenes with polyglycol ditosylate. Thus, 1,3-diisopropylcalix[4]arene **10** was prepared via reaction of calix[4]arene **1** with *i*-PrI. Subsequent Cs^+-templated reaction of **10** with pentaethylene glycol ditosylate afforded calix[4]arene crown-6 **11** fixed in its 1,3-alternate conformation (Scheme 3.5).

Scheme 3.5



In fact, a cone conformer of calix[4]arene crown-6 also can be prepared by using a known procedure[23] (Scheme 3.6). Thus, **13** was prepared in 34% yield via **12** by reacting calix[4]arene **1** with pentaethylene glycol ditosylate. An alternative route (Scheme 3.6) to **13** involves the reaction of 1,3-dimethoxycalix[4]arene-crown-6 (**8**) with trimethylsilyl iodide; application of this method produced **12** in 84% yield. Subsequent NaH promoted reaction of **12** with *i*-PrI afforded **13** in 73% yield.

Scheme 3.6



12 **13**

A few groups of investigators[23-28] have studied the complexation properties of calixcrowns. The results of alkali metal picrate extraction experiments performed by using several calix[4]arene crowns[23] are shown in Table 3.1. Examination of the data presented therein reveals that, among the conformationally mobile 1,3-dimethoxy compounds, the calix[4]crown-5 (**7**) shows slightly higher avidity toward K^+ *vis-à-vis* the other alkali metal cations, whereas the calix[4]crown-6 (**8)** displays high selectivity toward Cs^+. The *tert*-butyl calix[4]crown-6 (**9**) displays high selectivity toward Cs^+ and is a much more efficient alkali metal picrate extractant than its corresponding unsubstituted analog, **8**.

The data in Table 3.1 indicate that 1,3-diisopropylcalix[4]arene crown-6 **11** fixed in the 1,3-alternate conformation display high extraction avidity toward Cs^+ and Rb^+ picrates. Interestingly, ligand **11** does not complex efficiently with small cations such as Li^+ and Na^+, with the result that correspondingly high Cs^+/Na^+ and Cs^+/Li^+ selectivity ratios are observed. On the contrary, the corresponding cone conformer, i.e., **13** shows very low avidity toward all metal cations studied.

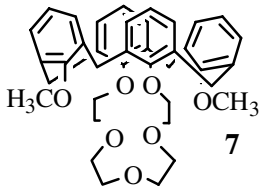
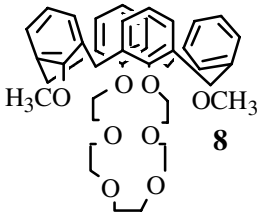
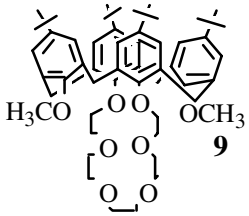
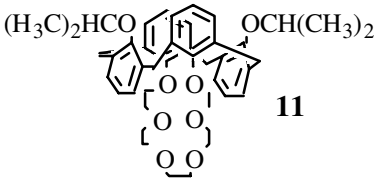
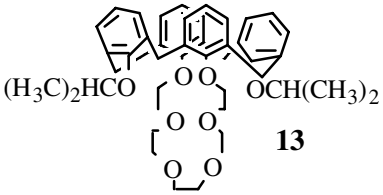
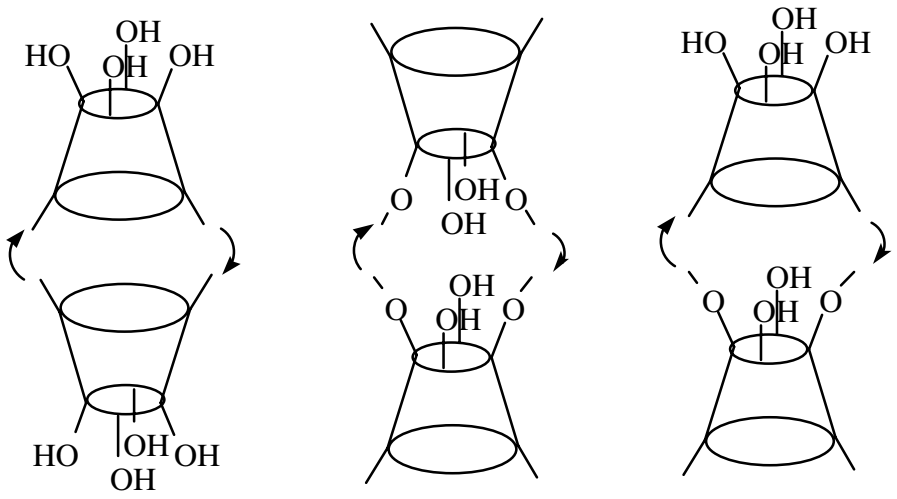
Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+
 **7**	2.0 ± 0.4	1.6 ± 0.3	10.0 ± 1.0	8.9 ± 0.9	2.8 ± 0.3
 **8**	0.4 ± 0.2	0.7 ± 0.1	1.0 ± 0.1	2.3 ± 0.2	6.3 ± 0.2
 **9**	1.4 ± 0.2	1.6 ± 0.4	2.2 ± 0.3	3.1 ± 0.5	19.0 ± 0.7
 **11**	3.0 ± 0.4	2.4 ± 0.1	15.8 ± 0.5	43.8 ± 0.7	64.5 ± 0.7
 **13**	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2

Table 3.1. Extraction percentage of alkali metal picrates by calixcrowns, from water to CH_2Cl_2 at 20 °C.[23]

Recently, calixarenes also have attracted considerable attention as building blocks for the molecular design of higher-order supramolecules. A variety of bis-calixarenes which possess highly organized molecular receptors with well defined cavity dimensions have been designed and prepared by a few groups of investigators.[29-36]

The bis-calix[4]arenes can be arranged into three types depending upon the relative orientations of two reactive centers (the phenolic OH groups and the *para* positions on the phenyl ring): "upper rim-upper rim" (A) in which two calixarenes are linked by the para positions, "lower rim-lower rim" (B) in which two calixarenes are linked by the phenolic oxygens, and "upper rim-lower rim" (C) which is a hybrid of the two preceding arrangements, as shown in Scheme 3.7.

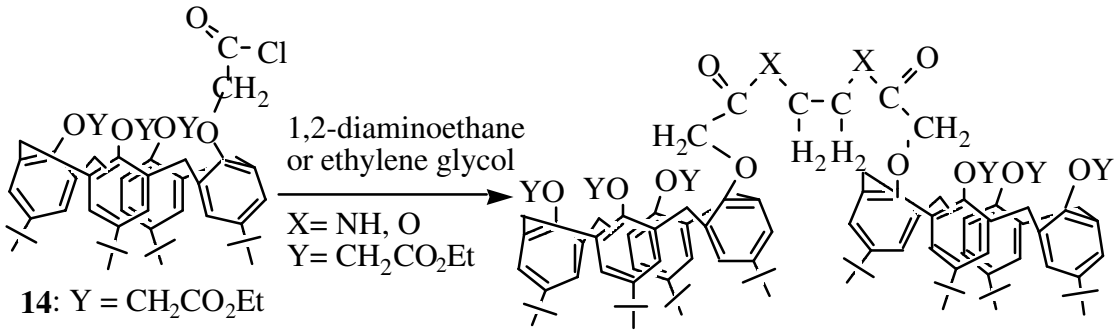
Scheme 3.7



(A) (B) (C)

The first bis-calix[4]arenes of "lower rim-lower rim" type were reported by McKervey and coworkers in 1990.[37] Thus, compound **14** was reacted with 1,2-diaminoethane or with ethylene glycol to afford the respective bis-calix[4]arenes with diamide or diester bridges (i.e., **15** and **16**, respectively, Scheme 3.8).

Scheme 3.8

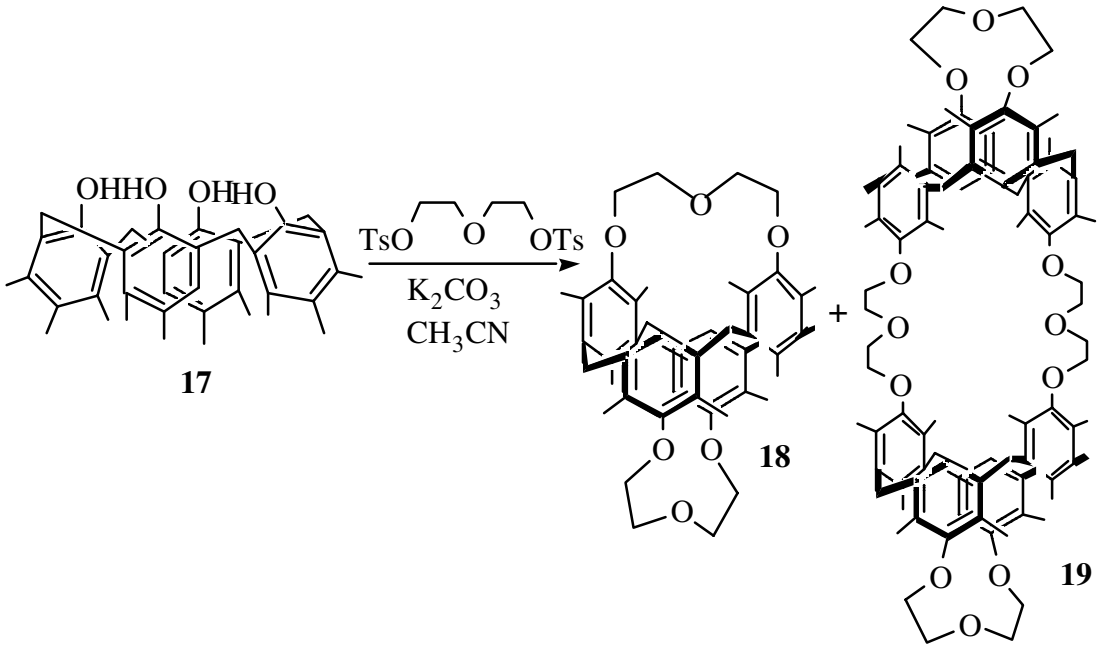


14: Y = CH_2CO_2Et

15: X = NH, Y = CH_2CO_2Et
16: X = O, Y = CH_2CO_2Et

A procedure used to synthesize a bis-calix[4]crown is shown in Scheme 3.9. The base-promoted reaction of mesitol-derived calix[4]arene **17** with diethylene glycol ditosylate produced doubly crowned bis-calix[4]arene **19** in addition to the expected calix[4]arene bis-crown **18**.[38]

Scheme 3.9



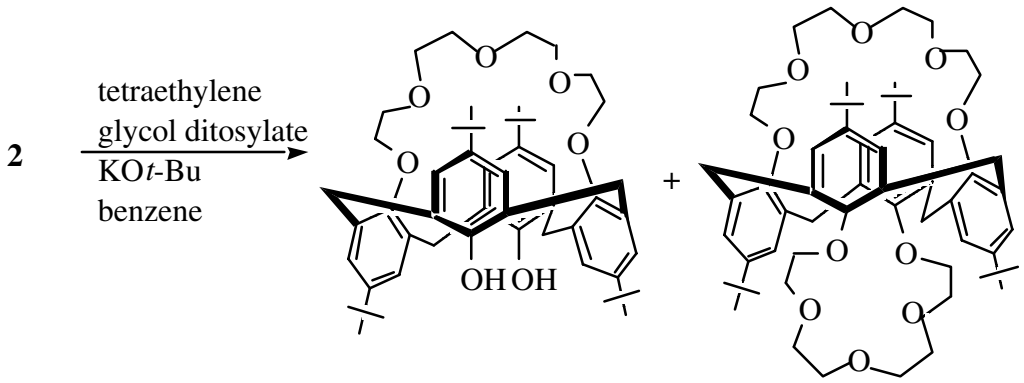
17

18

19

Recently, Reinhoudt and coworkers[27] have prepared a variety of calix[4]arene bis-crowns. Along with 1,3-dihydroxy-*p*-*tert*-butylcalix[4]crown-5 **20**, they also isolated a macrotricyclic *p*-*tert*-butylcalix[4]arene bis-crown-5 (**21**) in which presence of the double 1,3-bridge forces the calix moiety to adopt a 1,3-alternate conformation (Scheme 3.10).

Scheme 3.10



20 **21**

Pyridine-containing crown ethers have been used extensively to form complexes with a variety of guests, e.g., ammonium salts and transition metal cations.[39] However, pyridyl units have been incorporated into calixarenes only relatively recently.[40] Furthermore, the complexation properties of pyridine-bridged calixarenes have not yet been studied extensively.

As a part of our continuing interests in host-guest chemistry, we have synthesized novel bis-calix[4]arene receptors **23**-**24** in which the lower rim of each calix[4]arene moiety is linked covalently with pyridino systems. The complexation properties of the resulting ligands, **23** and **24,** were investigated via alkali metal picrate extraction experiments. The synthesis of a pyridyl-containing calix[4]arene-crown-5 (**30**)

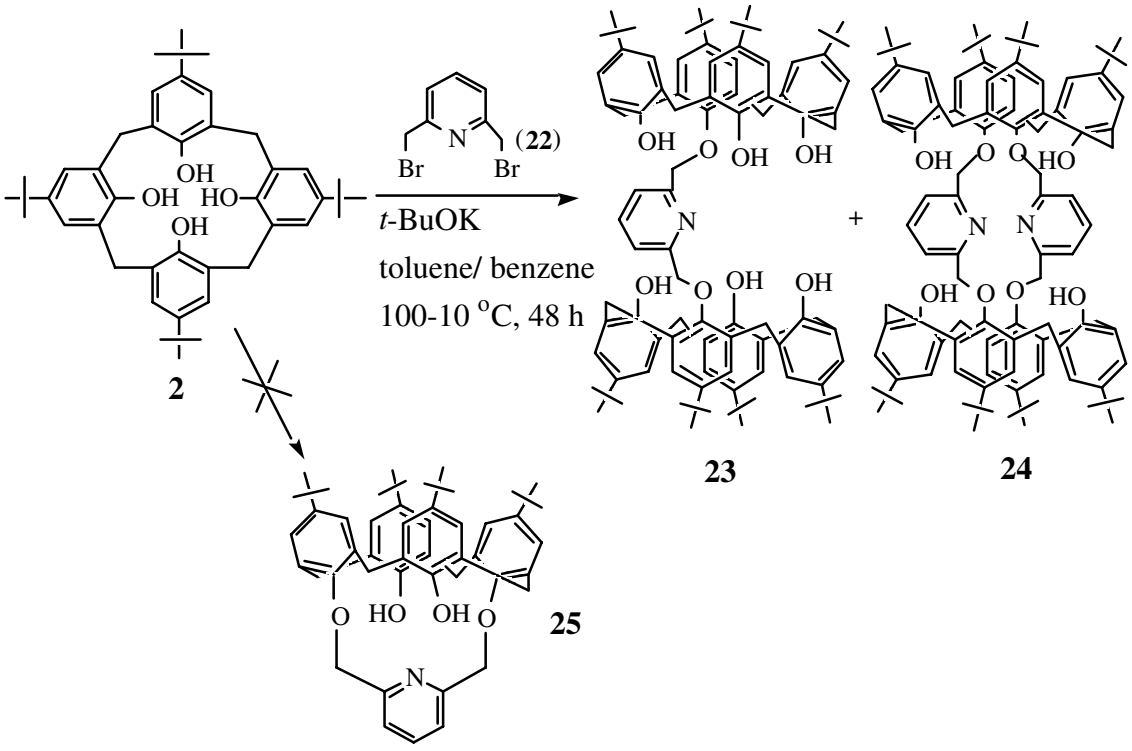
and its alkali metal picrate extraction profile also have been investigated. The objectives of the present study are as follows: i) to investigate whether bis-calix[4]arenes (**23** and **24**) linked by pyridyl units display noteworthy complexation properties toward alkali metal cations, e.g., to seek evidence for cooperative binding of the two calix[4]arene moieties with pyridyl units. ii) whether a pyridyl containing calix[4]crown-5 **30** displays enhanced selectivity brought about via the introduction of a rigid pyridyl unit.

RESULTS AND DISCUSSION

I. Synthesis of *p-tert*-Butylcalix[4]arene Crown Ethers Containing Pyridyl Units.

The syntheses of lower rim pyridyl-linked bis-calix[4]arenes (i.e., **23** and **24**) are shown in Scheme 3.11-12. The base-promoted reaction of *p-tert*-butylcalix[4]arene (**2**) with 2,6-bis(bromomethyl)pyridine (**22**)[41] in toluene/benzene produced both singly-bridged (**23**) and doubly-bridged bis-calix[4]arenes (**24**) in 25% and 6% yield, respectively (Scheme 3.11).

Scheme 3.11

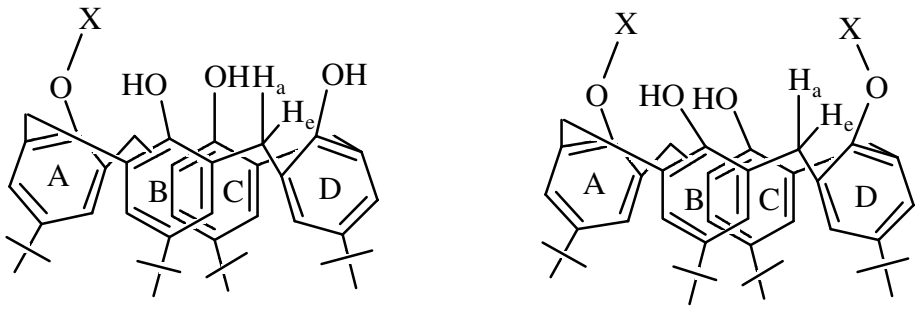


It was anticipated that *mono*calix[4]arene crown-3 **25** might be formed via 1,3-bridging of **22** to **2** (Scheme 3.11). However, in view of the steric strain that would become incorporated into the resulting crown ether (**25**), it seems likely that **22** as a bifunctional reagent prefers intermolecular double-linking rather than intramolecular bridging.

The structures of **23** and **24** were confirmed via analysis of their respective ^{1}H NMR and ^{13}C NMR spectra and via HRMS analysis (see Experimental section). Inspection of their ^{1}H NMR and ^{13}C NMR spectra suggests that the calix[4]arene moieties in **23** and **24** each occupy their respective cone conformation.

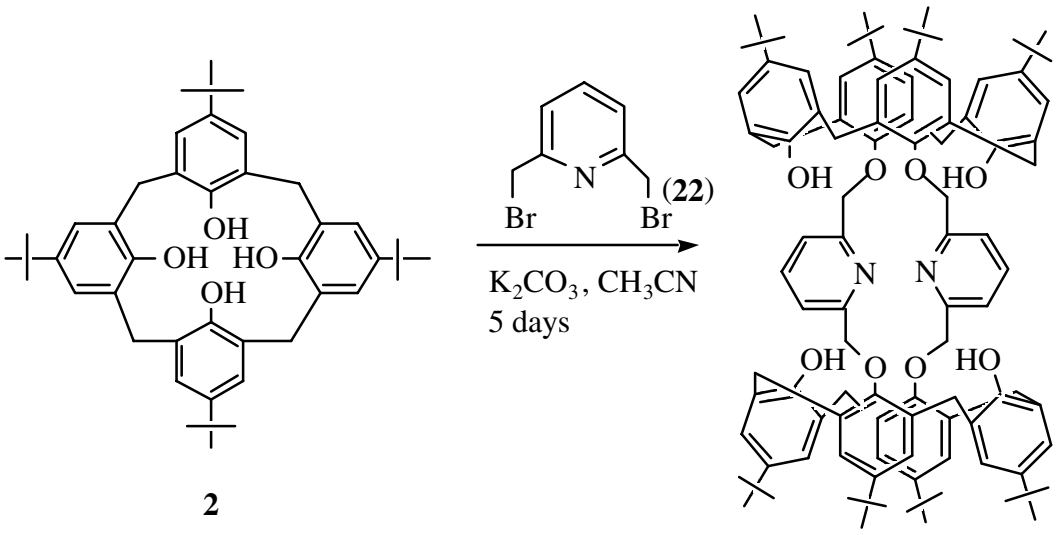
The ^{1}H NMR spectrum of **23** contains overlapping AX-systems that correspond to the two different types of Ar-CH_2-Ar methylene protons at δ 3.45, 4.24 and δ 3.45, 4.52. This observation suggests that the two calix[4]arene moieties remain fixed in the cone conformation.[35] In the ^{1}H NMR spectrum of **23**, a pair of doublets (δ 3.33 and 4.36) that correspond to the respective Ar-CH_2-Ar methylene protons (see Scheme 3.12) are observed. In addition, two singlets that correspond to the *tert*-butyl protons appear at δ 0.93 and 1.24 in 1:1 ratio. These results again suggest that both calix[4]arene moieties occupy cone conformations.[35]

Scheme 3.12



Interestingly, when **2** was reacted with **22** in the presence of K_2CO_3, only **24** was obtained in 30% yield (Scheme 3.13).

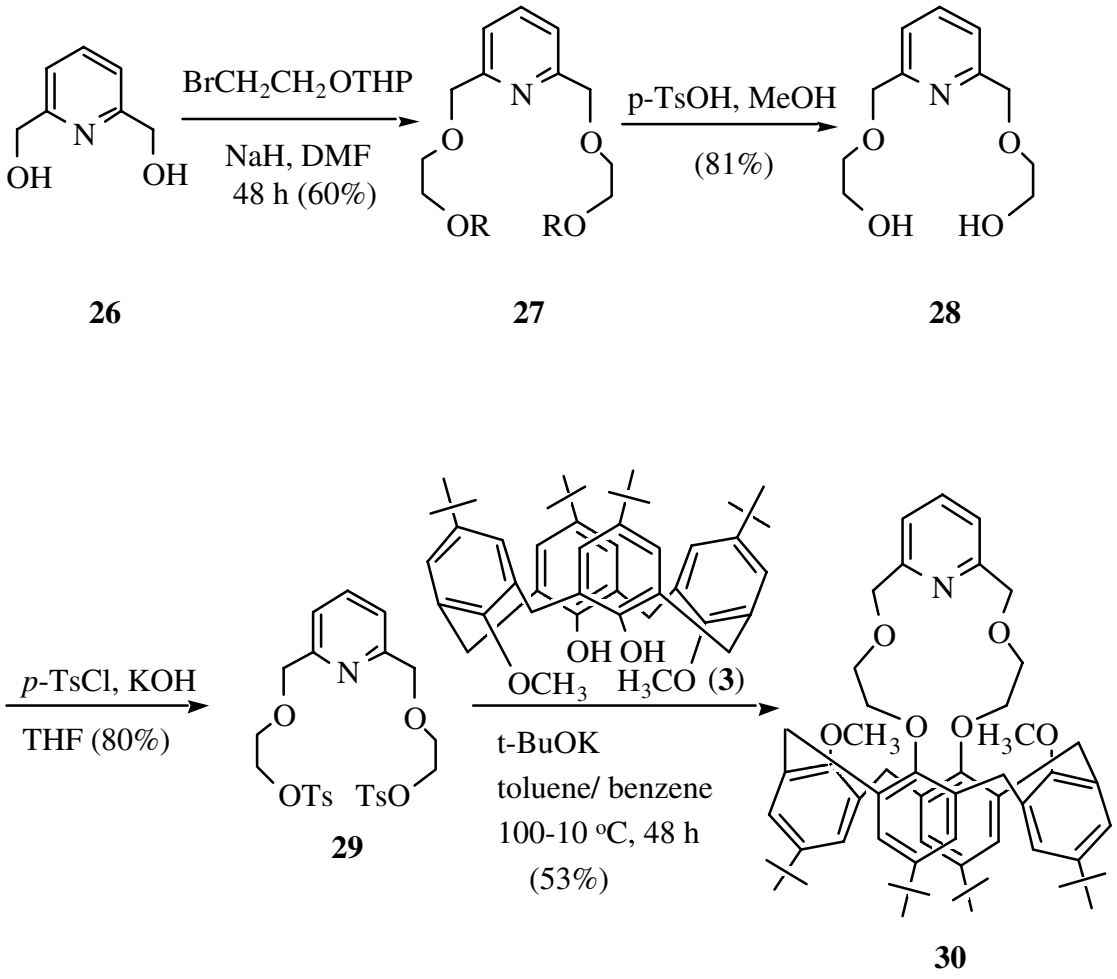
Scheme 3.13



2 **24**

1,3-dimethoxy-*p*-*tert*-butylcalix[4]arene crown-5 **30**, which contains a pyridyl unit, was synthesized in four steps from commercially-available 2,6-bis(hydroxymethyl)pyridine (**26**) (Scheme 3.13). Thus, THP protection of the OH groups in **26** was performed by using NaH and $BrCH_2CH_2OTHP$, thereby affording **27**. Deprotection of the THP moiety was achieved by using *p*-TsOH. This procedure afforded **28**, which subsequently could be converted to the corresponding ditosylate (**29**). Finally, calix[4]crown-5 **30** could be obtained in 53% yield via base-promoted reaction of **29** with tetra-*p*-*tert*-butyl-26,28-dimethoxycalix[4]arene (**3**) by using KO*t*-Bu in toluene/benzene. (Scheme 3.14).

Scheme 3.14



The structure of **30** was confirmed via analysis of its ^{1}H NMR and ^{13}C NMR spectra and via HRMS analysis (see the Experimental section). By referring to previously reported spectral data,[13] we were able to infer the conformation of **30** via analysis of its ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **30** displays an AB pattern for the Ar-CH_2-Ar methylene protons and two distinct singlets for the the *tert*-butyl protons (see Scheme 4.12). The benzylic protons (ArCH_2Ar) appear as an AB system (J_{AB} = 12.3

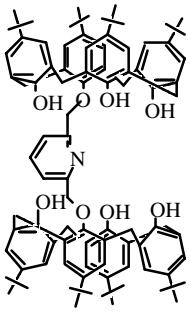
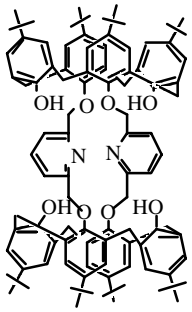
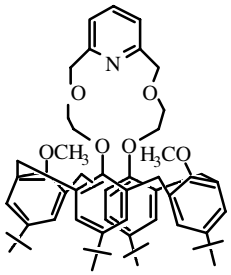
Hz) at δ 3.10 and 4.23. The two singlets for the *tert*-butyl protons appear at δ 0.85 and 1.26 (1:1 ratio). The corresponding ^{13}C NMR spectrum of **30** contains the benzylic methylene carbon as a triplet at δ 34.3, a result which suggests that the *p-tert*-butylcalix[4]arene moiety in **30** exists in its cone conformation.[21]

II. Alkali Metal Picrate Extraction Studies.

In an effort to investigate the complexation properties of ligands **23**, **24**, and **30**, a series of alkali metal picrate extraction experiments was performed. The results thereby obtained are shown in Table 3.2. Inspection of the data in Table 3.2 indicates that the bis-calix[4]arenes (**23** and **24**) are quite inefficient alkali metal picrate extractors. Among the bis-calix[4]arenes studied, the singly-bridged bis-calix[4]arene **23** displays slightly elevated extraction avidity toward K^+ picrate, but **23** is an inefficient extractant toward Li^+ and Cs^+ picrates. The doubly-bridged bis-calix[4]arene **24** displays slightly higher extraction avidity toward all alkali metal picrates studied *vis-à-vis* **23**, with the exception of its behavior toward K^+ picrate. It is interesting to note that **24** displays significantly higher extracting ability toward Rb^+ and Cs^+ picrates *vis-à-vis* **23.** One possible rationale for this result is that the double-linking to pyridyl units results in more favorable conformation for complexation of large metal cations *vis-à-vis* that of **23**.

The data in Table 3.2 indicate that 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-pyrido-crown-5 **30** displays high extraction avidity toward K^+, Rb^+ picrates. However, **30** displays dramatically reduced avidity toward Na^+, Cs^+, and Li^+ picrates; instead, this host displays unusually high selectivities toward K^+ and Rb^+.

Table 3.2. Results of Alkali Metal Extraction experiments

Host molecule	Percent of Picrate Extracted (%)[a]				
	Li^+	Na^+	K^+	Rb^+	Cs^+
 (**22**)	0.8±0.6	6.1±0.6	8.2±0.4	3.1±0.4	1.8±0.6
 (**23**)	1.7±0.5	6.7±0.5	7.2±0.4	13.9±0.5	11.7±0.7
 (**27**)	3.3±0.4	8.6±0.5	40.5±0.6	32.5±0.6	6.6±0.7

[a]Averages and standard deviations calculated for data obtained from three independent extraction experiments

SUMMARY AND CONCLUSTIONS

Novel pyridyl containing calix[4]arene receptors (**23**, **24**, and **30**) were prepared. Inspection of their respective ^{1}H NMR and ^{13}C NMR spectra suggests that calix[4]arene moieties in **23, 24, 30** occupy the cone conformation. The complexation properties of these host molecules were estimated via the results of alkali metal picrate extraction experiments. A pyridyl containing calix[4]arene-crown-5, i.e., **30** displays significantly high extraction avidity toward K^+ and Rb^+ picrates. However, **30** displays dramatically reduced avidity toward Na^+, Cs^+, Li^+ picrates, but, unusually high selectivity for K^+ and Rb^+. The singly-bridged bis-calix[4]arene **23** displays slightly elevated extraction avidity toward K^+ picrate. The doubly-bridged bis-calix[4]arene **24**, which is the most efficient Cs^+ extractor studied herein, displays significantly high extracting abilities toward Rb^+ and Cs^+ picrates *vis-à-vis* **23**. However, it seems likely that the two calix[4]arene moieties and pyridyl units in **23** and **24** do not interact cooperatively as donor ligands with alkali metal cations studied.

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. Absorption intensities of alkali metal picrate solutions were measured at λ = 374 nm by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double

sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode.

Lower Rim Functionalized Bis-calix[4]arenes 23 and 24. A solution of **2** (738 mg, 1 mmol) and KO*t*-Bu (112 mg, 1.00 mmol) in dry $PhCH_3$ (15 mL) under argon was heated to reflux. To this refluxing solution was added dropwise with stirring a solution of 2,6-bis(bromomethyl)pyridine (**22**, 265 mg, 1.00 mmol) in dry benzene (15 mL) during 45 minutes. After all of this reagent had been added, the resulting mixture was refluxed during 24 h, at which time a second portion of KO*t*-Bu (112 mg, 1.00 mmol) was added, and the resulting mixture was refluxed for an additional 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and H_2O (10 mL) then was added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure **23** (350 mg, 25%) was thereby obtained as a colorless microcrystalline solid: mp 249-251 °C; IR (KBr) 3423 (br, s), 2961 (s), 1603 (m), 1489 (m), 1363 (m), 1192 (m), 1092 (m), 1048 (s), 841 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.24 (s, 72 H), 3.45 (d, J = 15 Hz, 8 H), 4.24 (*AB*, J_{AB} = 14 Hz, 4 H), 4.52 (*AB*, J_{AB} = 15 Hz, 4 H), 5.40 (s, 4 H), 6.92-7.16 (m, 16 H), 8.03 (d, J = 8 Hz, 2 H), 8.13 (t, J = 7 Hz, 1 H), 9.43 (s, 4 H), 10.12 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 31.2 (q), 31.5 (t), 32.3 (q), 33.0 (s), 33.8 (s), 34.0 (s), 34.2 (t), 78.7 (t), 122.3 (d), 125.6 (d), 126.5 (d), 127.4 (d), 128.1 (d), 128.3 (d), 133.6 (d), 138.6 (d), 143.0 (s), 143.5 (s), 147.8 (d), 148.1 (d), 148.4 (d), 149.7 (d), 155.8 (s), 158.3 (s). Exact Mass (CI

HRMS) Calcd for $C_{95}H_{117}NO_8$: $[M + H]^+$ *m/z* 1399.87792. Found: $[M + H]^+$ *m/z* 1399.87525.

Continued elution of the chromatography column afforded **24** (90 mg, 6.0%) as a colorless microcrystalline solid: mp 241-244 °C; IR (KBr) 3354 (br, s), 2961 (s), 2870 (m), 1595 (m), 1482 (s), 1352 (m), 1205 (s), 1124 (m), 1012 (m), 879 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.93 (s, 36 H), 1.24 (s, 36 H), 3.33 (d, J_{AB} = 13 Hz, 8 H, $ArCH_2Ar$), 4.36 (d, J_{AB} = 13 Hz, 8 H, $ArCH_2Ar$), 5.18 (s, 8 H), 6.86 (s, 8 H), 7.03 (s, 8 H), 7.21 (s, 4 H), 7.90 (t, *J* = 9 Hz, 2 H), 8.16 (d, *J* = 9 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 31.5 (q), 32.2 (q), 34.3 (t), 34.4 (s), 78.7 (t), 120.5 (d), 125.5 (d), 126.1 (d), 128.0 (d), 128.2 (d), 132.9 (s), 139.2 (d), 142.0 (s), 147.5 (s), 150.5 (d), 151.2 (d), 157.5 (s), 158.3 (s). Exact Mass (CI HRMS) Calcd for $C_{102}H_{122}N_2O_8$: $[M + H]^+$ *m/z* 1503.92795. Found: $[M + H]^+$ *m/z* 1503.93193.

Doubly-Bridged Bis-calix[4]arene 24. A solution of **2** (738 mg, 1.00 mmol), **22** (265 mg, 1 mmol), and K_2CO_3 (550 mg, 4.00 mmol) in CH_3CN (25 mL) was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure **24** (450 mg, 30%) was thereby obtained as a colorless microcrystalline solid: mp 241-244 °C. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectral data that has been reported above for authentic **24**.

Compound 27. A suspension of NaH (60% suspension in mineral oil, 900 mg, 0.22 mmol) in dry DMF (14 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of 2,6-pyridinedimethanol (**26**, 1.40 g, 10.0 mmol) in DMF (14 mL). The resulting white suspension was stirred at 0 °C for 10 minutes, at which time the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture again was cooled to 0 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring a solution of 1-O-tetrahydropyranyl-2-bromoethane (4.60 g, 22 mmol) in DMF (14 mL). The resulting suspension was stirred at 0 °C for 10 minutes, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature for 72 h. The reaction mixture was concentrated *in vacuo*, and ice-water (50 mL) was added to the residue. The resulting aqueous suspension was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on silica gel by using a 10% EtOAc-hexane gradient elution scheme. Pure **27** (2.67 g, 61%) was thereby obtained as a colorless, viscous oil; IR (film) 3028 (w), 2945 (s), 2873 (s), 1638 (s), 1448 (w), 1337 (w), 1118 (s), 1064 (m), 1027 (w), 782 (w), 639 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.42-1.96 (m, 12 H), 3.42-4.01 (m, 12 H), 4.8 (m, 4 H), 7.3 (d, J = 9 Hz, 2 H), 7.61 (t, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 25.9 (t), 31.0 (t), 62.6 (t), 67.1 (t),

70.3 (t), 74.5 (t), 99.3 (s), 120.3 (d), 137.5 (d), 158.1 (s). Exact mass (CI HRMS) Calcd for $C_{21}H_{33}O_6N$: $[M + H]^+$ *m/z* 396.23861. Found: $[M + H]^+$ *m/z* 396.23917.

Compound 28. To a solution of **27** (320 mg, 0.81 mmol) in MeOH (8 mL) was added *p*-TsOH (50 mg), and the resulting mixture was stirred at ambient temperature during 24 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo.* The residue was purified via column chromatography on basic alumina by eluting with MeOH. Pure **28** (810 mg, 81%) was thereby obtained as a colorless viscous oil; IR (film) 3868 (br, s), 3029 (s), 2878 (s), 1723 (s), 1652 (s), 1591 (m), 1454 (s), 1117 (s), 1068 (s), 766 (w), 632 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 3.51-3.70 (m, 8 H), 4.50 (s, 4 H), 7.16 (d, *J* = 9 Hz, 2 H), 7.54 (t, *J* = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.6 (t), 72.5 (t), 72.7 (t), 120.1 (d), 137.2 (d), 157.5 (s). Exact mass (CI HRMS) Calcd for $C_{11}H_{17}NO_4$: $[M + H]^+$ *m/z* 228.12358. Found: $[M + H]^+$ *m/z* 228.12382.

Synthesis of compound 29. To a solution of **28** (290 mg, 1.29 mmol) in dry THF (2 mL) was added finely pulverized KOH (230 mg, 3.68 mmol). The mixture was stirred and then was cooled to 0 °C via application of an external ice-water bath. To the resulting mixture was added dropwise with stirring a solution of TsCl (freshly recrystallized from hexane, 560 mg, 2.95 mmol) in dry THF (3 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C during 5 h, at which time the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 12 h. The resulting mixture was filtered, and the residue was washed with THF (50 mL). The combined filterates were concentrated in *vacuo*. The residue was purified via column chromatography on silica gel by eluting with 50%

EtOAc-hexane. Pure **29** (480 mg, 80%) was thereby obtained as a colorless oil (480 mg, 80%); IR (film) 3053 (m), 2898 (m), 1625 (w), 1352 (m), 1176 (s), 1029 (m), 1012 (m), 919 (m), 814 (m), 782 (m), 677 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.34 (s, 6 H), 3.80 (t, *J* = 10 Hz, 4 H), 4.21 (t, *J* = 9 Hz, 4 H), 4.54 (s, 4 H), 7.15-7.32 (m, 6 H), 7.51 (t, *J* = 7 Hz, 1 H), 7.73 (d, *J* = 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 20.7 (q), 67.74 (t), 68.6 (t), 73.3 (t), 119.5 (d), 127.4 (d), 129.3 (d), 136.2 (s), 138.3 (d), 142.1 (s), 156.4 (s). This material proved to be unstable; accordingly, it was used immediately as obtained in the next synthetic step.

Monocalix[4]arene (30). A solution of **3** (125 mg, 0.19 mmol) and KO*t*-Bu (11 mg, 0.18 mmol) in dry $PhCH_3$ (15 mL) was heated to reflux. To this refluxing solution was added dropwise with stirring a solution of **29** (89 mg, 0.19 mmol) in dry benzene (5 mL) during 0.5 h. The resulting mixture was refluxed for 24 h, at which time a second portion of KO*t*-Bu (20.7 mg, 0.19 mmol) was added, and the reaction mixture was refluxed for an additional 24 h. The reaction mixture was allowed to cool gradually to ambient temperature, and H_2O (10 mL) then was added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure **30** (85 mg, 53%) was thereby obtained as a colorless microcrystalline solid; mp 263-265 °C; IR (KBr) 3423 (br, s), 2961 (s), 1653 (m), 1603 (m), 1559 (m), 1468 (m), 1363 (m), 1222 (m), 1118 (m), 1032 (s), 882 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.85 (s, 18 H), 1.26 (s, 18 H), 3.10 (*A*B, J_{AB} = 12 Hz), 3.60 (s,

6 H), 3.87-4.08 (m, 8 H), 4.23 (*A*B, J_{AB} = 12 Hz, 4 H), 4.75 (s, 4 H), 6.45 (s, 4 H), 7.13 (s, 4 H), 7.33 (d, *J* = 9 Hz, 2 H), 7.65 (t, *J* = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.5 (q), 31.6 (t), 32.2 (q), 34.5 (s), 61.3 (q), 71.7 (t), 73.9 (t), 76.0 (t), 123.4 (d), 124.8 (d), 125.4 (d), 133.1 (s), 136.24 (s), 137.51 (d), 145.23 (s), 152.60 (s), 156. 32 (s), 157.71 (s, 2 C). Exact mass (CI HRMS) Calcd for $C_{57}H_{73}O_6N$: $[M + H]^+$ *m/z* 868.55162. Found: $[M + H]^+$ *m/z* 868.55249.

Alkali Metal Picrate Extracion Experiments. The general procedures employed herein are described in Chapter 2.

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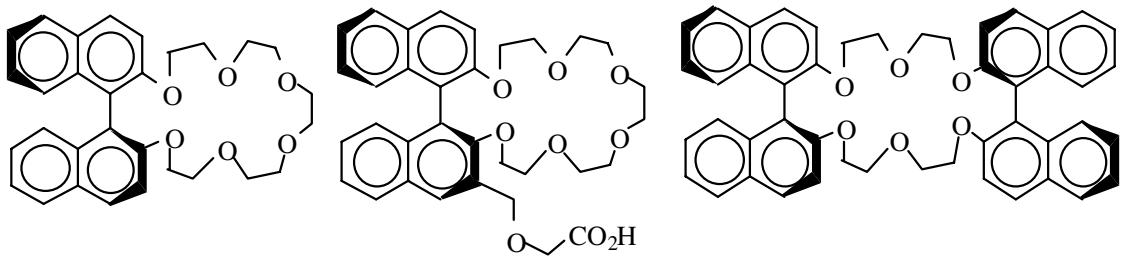
CHAPTER 4

SYNTHESIS AND ENANTIOSELECTIVE RECOGNITION OF AMINO ACIDS BY A NOVEL, CAGE-FUNCTIONALIZED CROWN ETHER THAT CONTAINS A CHIRAL BINAPHTHYL MOIETY

INTRODUCTION

Molecular recognition[1] is the process by which a ligand (molecular receptor) selects and binds to a specific substrate via a structurally well-defined pattern of intermolecular forces. Enantiomeric recognition,[2] as a special case of molecular recognition, involves the discrimination between enantiomers of a guest by a chiral host. A variety of optically active crown compounds[3] capable of differentiating between enantiomeric guest molecules have been prepared via the incorporation of chiral elements into the crown ring skeleton. In particular, optically active crown ethers containing 1,1'-binaphthyl units have received a attention.[4] Several examples[2d] of this type of optically active host system are shown in Scheme 4.1.

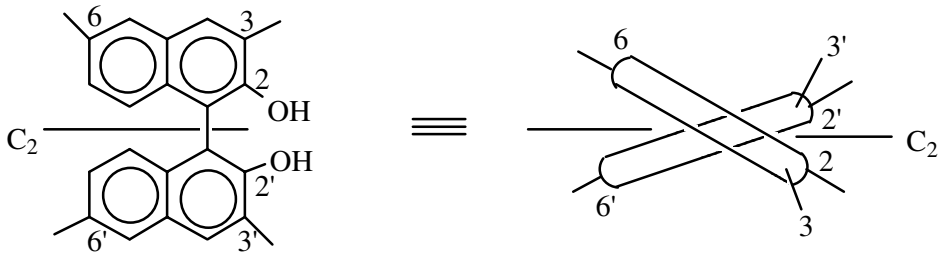
Scheme 4.1



These binaphthyl functionalized crowns are chiral cyclic polyethers that possess C_2 symmetry which form identical complexes by binding to the guest molecules through

either face of the polyether ring. 2,2'-Dihydroxy-1,1'-binaphthyl (**1**, Scheme 4.2), which provides a steric and chiral barrier, is the key starting material that is used to synthesize these compounds.

Scheme 4.2



2,2'-Dihydroxy-1,1'-binaphthyl (**1**)

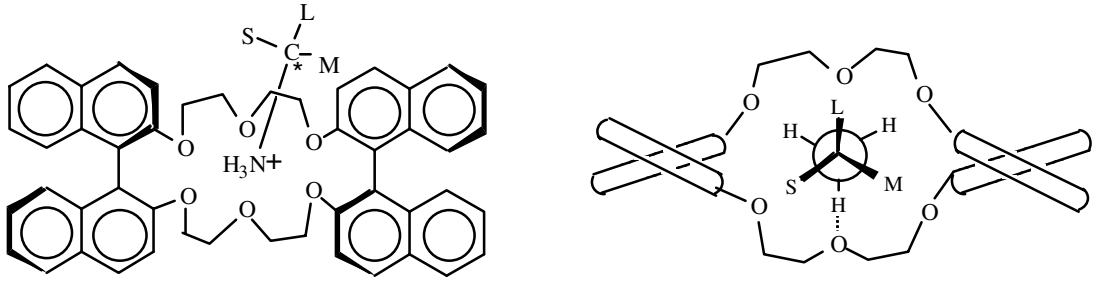
Cross section of **1** viewed along axis of naphthalene-naphthalene bond from under side.

In host systems, two naphthalene rings occupy different planes, each of which is perpendicular to the best plane of the cyclic ether ring. One of the naphthalene rings forms a wall that extends along the side of and outward from one face of the cyclic ether, whereas the other naphthalene ring provides a wall along the side of and outward from the opposite face of the cyclic ether. Thus, enantiomeric discrimination is achieved by the utilization of atropisomerism caused by restricted rotation of the binaphthyl units in the system.

In particular, enantiomeric recognition of primary ammonium salts by using the binaphthyl chiral crowns[5] was first studied by Cram and coworkers. NMR spectroscopy,[6] calorimetric titration,[7] molecular mechanics calculations,[8] liquid-liquid extraction,[9] chromatography,[10] X-ray crystallography,[11] and electrochemical methods[12] all have been used as techniques to evaluate the extent of enantiomeric recognition. Binding between a host and enantiomeric ammonium guests can be affected by hydrogen bonding, van der

Waals forces, short-range repulsions, intermolecular interactions, electronic attractions, etc. It is known that among the various binding types, hydrogen bonding is an important stabilizing force to promote the complexation between the macrocyclic receptor and the substrate. An idealized scheme of a hydrogen bonding association in ammonium complexes of hexa(ethylene oxide) macrocycles is shown in Scheme 4.3.

Scheme 4.3



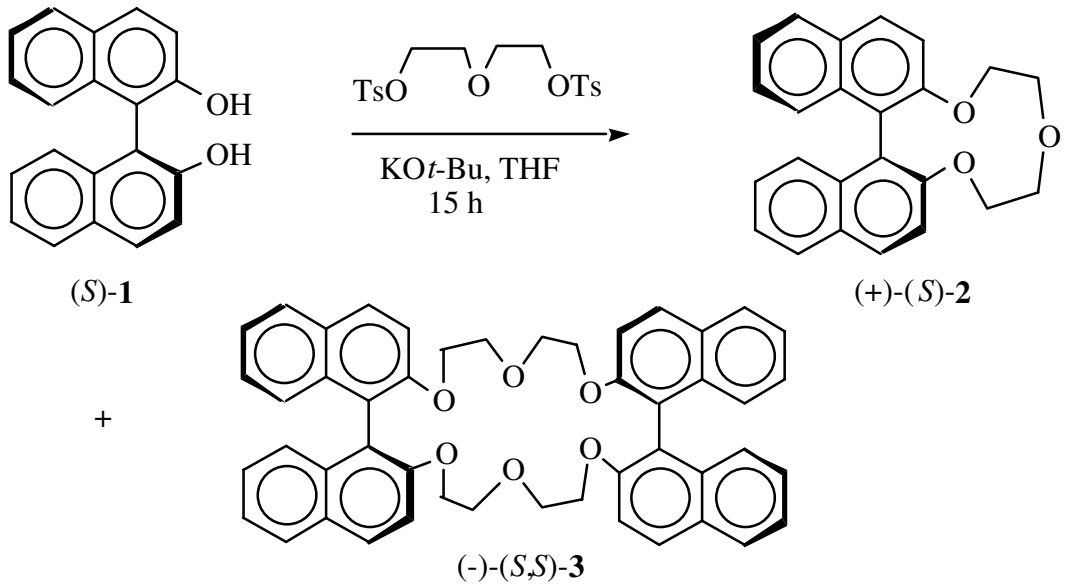
More stable diastereomeric complex

The NH_3^+ group of the alkylammonium salt associates with into the polyether ring and forms three NH----O bonds with the ligating oxygen atoms (three-point model). For optimum binding, the large L group extends over the least hindered portion of the macroring, while the medium M group is located in a space which is less hindered sterically by the chiral barrier of the naphthyl group. In this context, the steric compatibility of a host with a guest is closely related to the relative stability of the two diasteromeric complexes. The stability constant is relatively larger for the complex with the diastereomer that possesses a more fitted configuration, thereby leading to chiral recognition.

Cram and coworkers prepared chiral crown ethers containing binaphthyl units for the first time in 1973. Thus, when optically pure binaphthol (*S*)-**1** was reacted with

diethylene glycol ditosylate in THF in the presence of KO*t*-Bu, two products, i.e., the "1+1" product (**2**) and the "2+2" product (**3**) were obtained in 5% and 31% yield, respectively (Scheme 4.4).[13]

Scheme 4.4



(*S*)-**1**

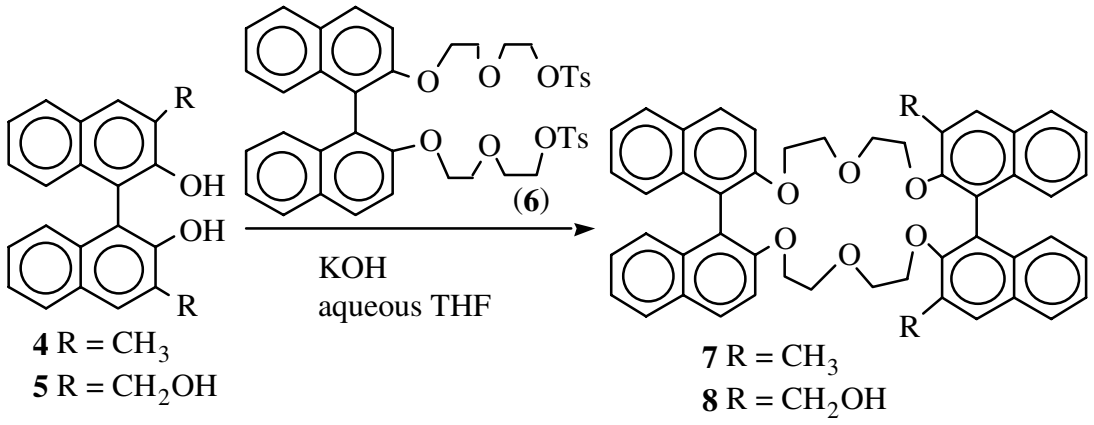
(+)-(*S*)-**2**

+

(-)-(*S*,*S*)-**3**

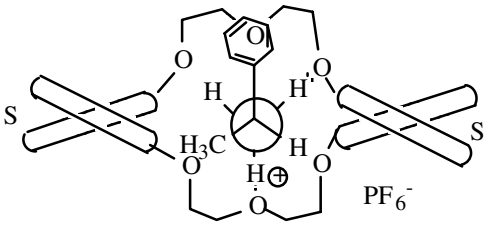
Subsequently, in an attempt to enhance their complexation stability and selectivity, a variety of substituents have been introduced into positions 3, 3′, 6, and 6′. A synthetic procedure[14] that employs these modifications is shown in Scheme 4.5. Thus, when (*S*)-**4** was reacted with (*S*)-**6** in the presence of KOH in aqueous THF during 100 h, the reaction afforded (*S*,*S*)-**7**. Similarly, (*R*,*R*)-**8** was prepared via reaction of (*R*)-**5** with (*R*)-**6**.

Scheme 4.5



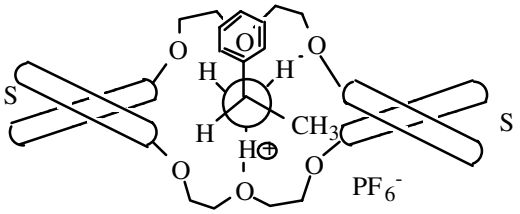
Cram and coworkers carried out the optical resolution of racemic α-phenethylamine (**9**) by using (-)-(*S*,*S*)-bis(binaptho-22-crown-6) (**3**) via simple $CHCl_3$-H_2O extraction for the first time.[15] When **3** and **9** in $CHCl_3$ and H_2O were shaken in the presence of $NaPF_6$, the optical rotation of **9** bound by **3** to form a complex in the $CHCl_3$ layer was [α] +9.41 ($CHCl_3$). The result indicates that the bound stereoisomer was (+)-(*R*)-**9**, with an optical purity of 27%, thereby suggesting that the host, (-)-(*S*,*S*)-**3**, forms a more stable complex with (+)-(*R*)-**9** than with (-)-(*S*)-**9**. The possible conformations of these diastereomeric complexes are shown in Scheme 4.6. In each case, the bulky phenyl group is located in the widest space in the cavity. Examination of CPK molecular models[15] of the various complexes also indicates that the steric relationships between (SS)-**3** and (*R*)-**9** are more compatible than those between (*S*,*S*)-**3** and (*S*)-**9**.

Scheme 4.6



(*S,S*)-**3** (*R*)-**9**

Sterically favorable



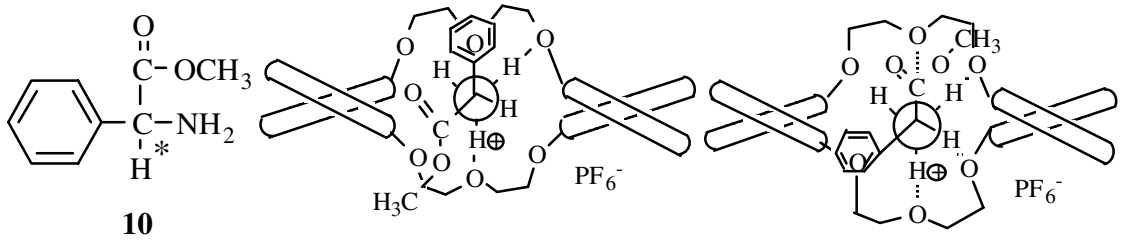
(*S,S*)-**3** (*S*)-**9**

Sterically unfavorable

A thorough enantiomeric separation of racemic phenylglycine methyl ester **10** has been performed using optically pure ligand **3**.[16] The suggested conformations of the complexes are shown in Scheme 4.7. The structure of the complex (*S,S*)-**3**/(*R*)-**10** was determined by X-ray crystallography. Based upon the two diasteromeric complexes that were resolved in solution, this structure corresponds to the less stable isomer.

An idealized four-point binding model was proposed to describe this complex (Scheme 4.7).

Scheme 4.7



10

(*S,S*)-**3** (*S*)-**10**

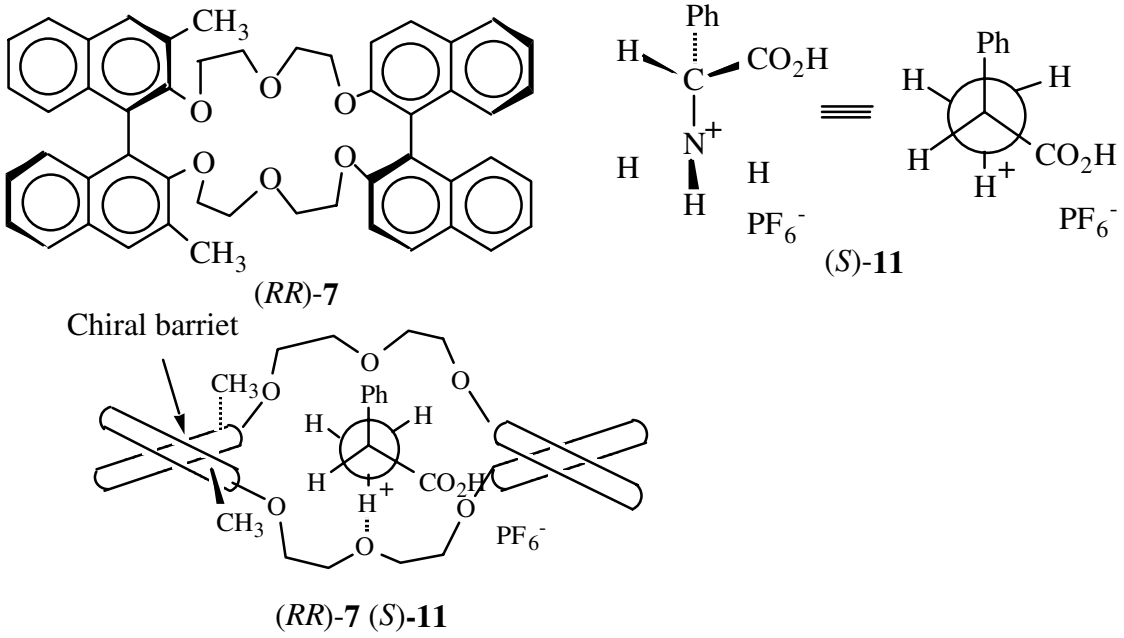
(*S,S*)-**3** (*R*)-**10**

According to the model, three alternate ether oxygen atoms are involved in hydrogen bonds with the ammonium ion, while a fourth oxygen interacts with the ester group of the guest. In addition to hydrogen bonding, the complex appears to be stabilized by a π-acid-

π-base interaction between the CO_2CH_3 group and one naphthalene ring. In the more stable (*S,S*)-(*S*) diastereomer, these substituents are expected to be arranged more favorably with respect to the steric barriers of the ligand via a three-point interaction.

A striking enantioselective recognition towards racemic amino acid **11**[17] was observed when **3** was modified via introduction of two methyl groups in the 3-position of one binaphthyl unit. As predicted by CPK molecular models, the (*S*)-enantiomer of **11** was extracted preferentially into the organic layer. The structure of the energetically preferred complex between chiral host (*R,R*)-**7** and (*S*)-**11** was determined by application of X-ray crystallographic methods (Scheme 4.8).[18] This result was interpreted via host-guest complementarity in the complexes. The methyl substituents in (*R,R*)-**7** apparently increase the steric hindrance between the host and the guest as well as between the naphthalene rings on the noninteracting side of the cavity. Thus, the (*R,R*)(*S*) isomer of the dimethyl complex is more crowded than the unsubstituted compound. The resulting repulsive interactions contribute to further destabilization of the less stable diastereomer of the modified system.[19]

Scheme 4.8



Cram and coworkers resolved racemic amino ester and primary ammonium salts by stereoselective passive transport of their corresponding HCl, HBr, or HPF_6 salts from one aqueous phase to another through a $CHCl_3$ membrane.[20] The apparatus for the investigation of optically selective transport is shown in Figure 4.1.[21]

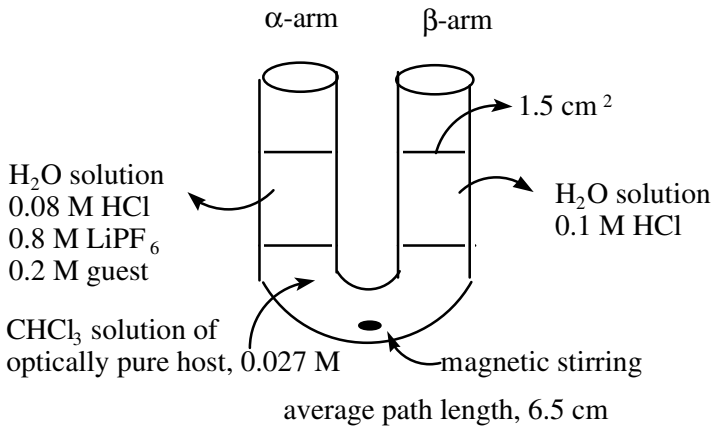
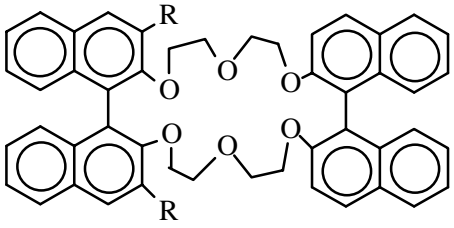


Figure 4.1. Appratus for chiral recognition in transport.

It was suggested that the thermodynamic driving force for transport is (I) entropy of dilution and (ii) changes in solvation energy associated with "salting out" of the organic salt from its original solution.[22] Table 4.1 shows the results of chiral recognition behavior of some hosts obtained via transport experiments.[21] Compounds **3**, **7**, and **12** were employed as chiral hosts with the PF_6^- salt of methyl phenylglycinate (**10**) as guest. These results of these experiments indicate that hosts **7** and **12** which bear side chains at the 3,3'-position of the binaphthyl unit display higher enantiomeric selectivity toward **10** than does host **3** which lacks sidechains. It seems likely that the two methyl groups extend the chiral barrier of the binaphthyl units and thereby increase the level of chiral recognition of the host. The presence of two additional CH_2Cl groups in (*RR*)-**12** produced similar results; have host **12** transported 8% of **10** with 82% optical purity.



R = H, (*S,S*)-**3**
R = CH_3, (*R,R*)-**7**
R = CH_2Cl, (*R,R*)-**12**

		guest				
		initial α phase		final β phase		
time h	host	compd	concn, M	% trans-ferred	configuration of dominant enantiomer	optical purity
45	(*S,S*)-**3**	(*R*)(*S*)-**10**-HCl	0.21 M	17%	*S*	35%
19	(*R,R*)-**7**	(*R*)(*S*)-**10**-HCl	0.28 M	12%	*R*	78%
12	(*R,R*)-**11**	(*R*)(*S*)-**10**-HCl	0.28 M	8%	*R*	82%

Table 4.1. Differential Transport in U-tube of Enantiomers by 0.027 M Hosts in $CHCl_3$

As a part of our continuing interests in host-guest chemistry, we have synthesized an optically active cage-functionalized crown ether, **14**, which incorporates a binapthyl molecular framework as the chiral unit. The chiral recognition which **14** displays toward the enantiomers of guest salts **9** and **10** in transport experiments was studied.

Although a large number of chiral crown ethers derived from 1,1'-binaphthalene-2,2'-diol (**1**) have been prepared, no examples that contains a hydrocarbon cage framework have been reported. We have shown previously via synthesis of cage-functionalized crown ethers that incorporation of a cage moiety into host system can affect its complexation properties. Thus, incorporation of a rigid cage moiety incorporated into cyclic ether **14** is expected to provide useful features for chiral recognition.

It is also interesting to note that the starting material, i.e. cage-ditosylate (**13**) has C_s symmetry, whereas incorporation of a binaphthyl unit into **13** affords **14** with concomitant loss of symmetry. As a result, host molecule **14** will have two different sites of complexation with the incoming guest molecules, i.e., approach of the guest may occur toward either *furano* or *butano* face shown in Figure 4.2.

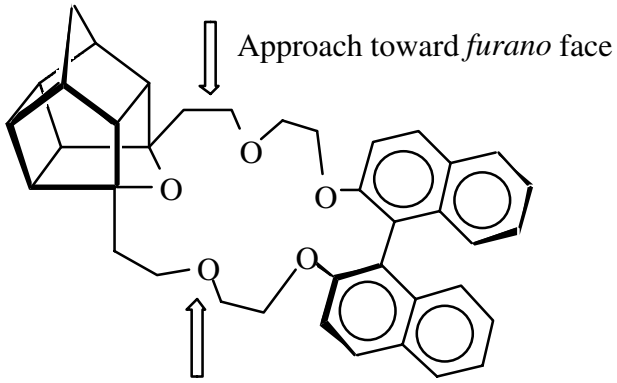


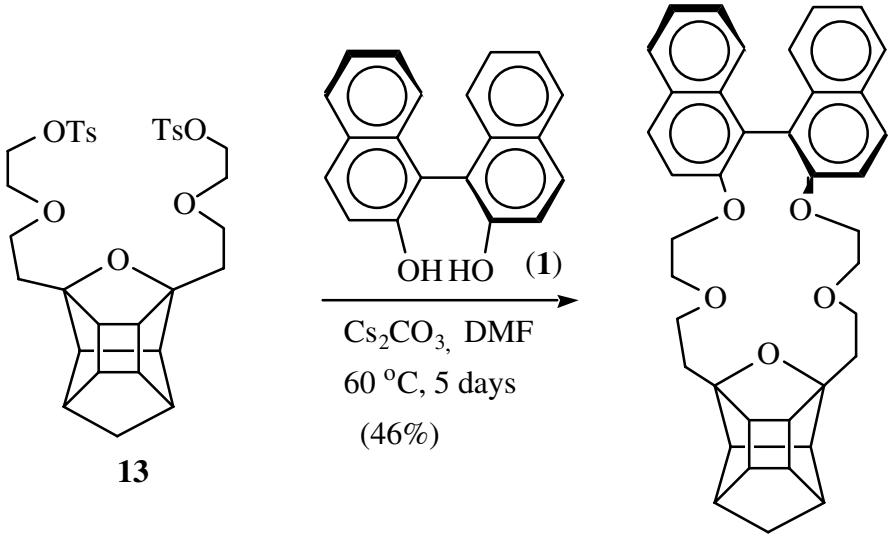
Figure 4.2. Modes of approaches by guest species upon diastereotopically nonequivalent faces in **14**

RESULTS AND DISCUSSION

I. Synthesis of novel cage-functionalized crown ether that contains binaphthyl-derived chiral centers.

Axially dissymmetric 1,1'-binaphthyl-2,2'-diol (*R*)-**1** was used as the chiral component to prepare cage-functionalized chiral crown ether (*R*)-**14**. The synthetic procedure employed this purpose is shown in Scheme 4.9. Thus, the chiral host was obtained in 46% yield via Cs^+-templated reaction of cage ditosylate **13** with (*R*)-**1**.

Scheme 4.9



It seems likely that the use of Cs_2CO_3 as a base is important in synthesis of **14**. In fact, when K_2CO_3 is used as a base, the reaction afforded a mixture of isomers that resulted via 2+2 cyclization, i.e., the formation of dimeric crown ethers was detected by NMR spectra. The structure of (*R*)-**14** was confirmed via analysis of its respective ^1H NMR and ^{13}C NMR spectra and via HRMS analysis (see the Experimental Section). The maximum value of the optical rotation for (R)-**14** was determined by polarimetry to be $[\alpha]_D$ = +54.0 (c=0.2, $CHCl_3$).

II. Transport Experiments in a U-tube.

Table 4.2 contains results that based upon the enantiomeric recognition behavior of (*R*)-**14** toward transport of enantiomers of (±)-1-phenylethylamine (**9**) and (±)-methyl phenylglycinate (**10**). An examination of Table 1 indicates that (*R*)-**14** displays a higher

enantiomer selectivity toward phenylethyl amine **9** *vis-à-vis* methyl phenyl ester **10**. The host molecule transported 8.8% of phenylethyl amine with *ca.* 89% optical purity and complexed preferentially with (S)-**9**. Chiral host **14** displays low chiral recognition toward (±)(*R*)(*S*) **10**, i.e., 18.7%, and 14 displays a slight preference to bind to (*R*)-**10**. In control studies (run 2 and 4), the hosts were absent from the $CHCl_3$ layers, and longer time (24 h) was employed. The results indicate that only 3% of the guest transported in the presence of host was uncomplexed.

Table 4.2. Differential Transport in U-Tube of Enantiomeric molecules by 0.027 M

Run No	time h	host	guest	% trans-ferred	configuration of dominant enantiomer	optical purity
1	4 h	(*R*)-**14**	**9**[a]	8.8%	*S*	89.2%
2	24 h	none	**9**[a]	2.5%		
3	4 h	(*R*)-**14**	**10**[b]	10.7%	*R*	18.7%
4	24 h	none	**10**[b]	2.9%		

[a](±)-1-phenylethylamine hydrochloride. [b](±)–phenylglycinate hydrochloride

Host (**14**) in $CHCl_3$.

These results are compatible with the corresponding results of molecular mechanics calculations. As mentioned above, the host may form different complexes by binding the guest molecules on either the furano or butano face in (*R*)-**14.** Thus, approach

by guests toward either face of the host has been considered in the calculations. The relative binding energies thereby obtained are shown in Table 4.3.

Upon the calculations, the complexes were generated by manual docking of the guests into the cavity of hosts by using Macromodel.[26] The geometries of the resulting complexes were optimized by employing the PRCG algothrim[27] with MM3* force field and the GB/SA solvation model for H_2O.[28] The results of these calculations predict that the furano face of the host is preferred over the butano face for the approach of the enantiomers of both guests. The (*S*)-**9** has been found to be preferred by *ca.* 1.2 kcal/mol, whereas a slight preference for binding to the (*R*)-isomer (0.5 kcal/mol) has been found for guest **10**.

Table 4.3. MM3 Calculated relative complexation energies (kcal/mol) of **14** and guests **9** and **10**.

	Furano face		*Butano* face	
(*R*)-**14** and guest **9**	(*R*)-**14** (*R*)-**9**	(*R*)-**14** (*S*)-**9**	(*R*)-**14** (*R*)-**9**	(*R*)-**14** (*S*)-**9**
	1.2	0.0	1.3	1.2
(*R*)-**14** and guest **10**	(*R*)-**14** (*R*)-**10**	(*R*)-**14** (*S*)-**10**	(*R*)-**14** (*S*)-**10**	(*R*)-**14** (*R*)-**10**
	0.0	0.5	2.4	1.2

SUMMARY AND CONCLUSIONS

Optically active cage-functionalized crown ether **14** which contains a binapthyl molecular framework as the chiral unit was prepared. The ability of **14** to recognize the enantiomers

of guest salts, i.e., **9** and **10** in transport experiments was studied. Host molecule **14** displays a enhanced enantiomeric selectivity toward racemic **9** *vis-à-vis* **10**. The host molecule transported 8.8% of **10** with 89.2% optical purity by complexing preferentially with (*S*)-**10**. Host **14** displays low chiral recognition toward racemic **9** (18.7%) and slightly prefers to bind to (*R*)-**9**. These experimental results are compatible with corresponding results obtained by using molecular mechanics calculations.

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. All UV readings were recorded by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. Optical rotations were taken on a Jasco disital DIP-370 polarimeter. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Host ligand that possessed maximum optical rotation was used unless otherwise noted. Prior to reuse, the host was purified by chromatography to remove small amounts of accured oxidation products. Spectroscopic grade $CHCl_3$ was washed with water to remove EtOH.

Cage-functionalized chiral crown ether 14. A solution of **1** (124 mg, 0.43 mmol) and **13** (273 mg, 0.42 mmol) in DMF (13 mL) was added dropwise to a stirred

suspension of Cs_2CO_3 (291 mg, 0.89 mmol) in DMF (51 mL) at 60 °C during 5 h. The reaction mixture then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and washed sequentially with water (2 x 20 mL) and 2 N NaOH (2 x 20 mL). The organic layer was dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **14** was thereby obtained as a colorless viscous oil (124 mg, 49%): $[\alpha]_D$ = +54.0 (C = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.47 (*A*B, J_{AB} = 10 Hz, 1 H), 1.79-1.93 (m, 5 H), 2.21-2.60 (m, 8 H), 3.23-3.50 (m, 8 H), 3.95-4.18 (m, 4 H), 7.10-7.36 (m, 6 H), 7.46 (d, J = 9 Hz, 2 H), 7.87 (d, J = 8 Hz, 2 H), 7.94 (d, J = 9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 41.8 (d, 2 C), 43.2 (t, 2C), 44.3 (d, 2C), 48.27 (d), 48.33 (d), 58.72 (d), 58.77 (d), 68.11 (t), 68.14 (t), 69.80 (t), 69.84 (t), 69.9 (t, 2C), 94.2 (s, 2 C), 117.00 (d), 117.03 (d), 120.0 (s), 120.3 (s), 123.0 (d), 124.0 (d), 125.8 (d, 2 C), 126.4 (d, 2 C), 129.5 (d), 129.5 (d), 130.1 (s, 2 C), 134.32 (s), 134.35 (s), 154.35 (s), 154.37 (s). Exact mass (CI HRMS) Calcd for $C_{39}H_{38}O_5$: M_r^+ 587.27975. Found: M_r+ 587.27628.

Racemic Methyl Phenylglycinate Hydrochloride.[8b] Racemic phenylglycine (30.2 g, 0.2 mol) was suspended in dry MeOH (500 mL, stored over 3 Å molecular sieves), and dry HCl gas was bubbled into the suspension until complete dissolution had occured. The solution then was refluxed for 5 h, cooled, and evaporated to dryness. The residue was dissolved in water (200 mL), Methylene chloride (500 mL) was added, and sufficient aqueous NH_4OH was added to adjust the pH of the reaction mixture to pH 10. Unreacted amino acid which precipitated from solution at this pH was removed by

filtration and later was recycled. The organic layer that contained the free amino ester was withdrawn, and the aqueous layer extracted with CH_2Cl_2 (500 mL). The combinded organic extracts were dried ($MgSO_4$) and filtered. The dry HCl gas than was bubbled through the filtrate to form the salt. The resulting suspension was concentrated in *vacuo,* and the solid residue was dried in *vacuo*, thereby affording phenylglycinate hydrochloride as a colorless microcrystalline solid (32 g, 80%), mp 223-224 °C (lit. [23] mp 221 °C).

Racemic phenyl ethyl ammonium chloride.[8b] The hydrochloride salt of racemic (*R*)(*S*)-α-phenylethylamine was prepared by bubbling HCl gas into a solution of the amine (20 g,) in dry ether (100 mL). The precipitated salts was isolated by filtration and subsequently was purified via recrystallization.[24]

Preparations of aqueous solutions of 2 M $LiPF_6$-D_2O.[12] To $LiPF_6$ (3.04 g, mmol, weighed in a drybox in a 10 mL graduated cylinder) was added slowly and cautiously D_2O (pre-cooled to 0 °C, 5 mL) in such a way that the temperature never rose above 10 °C. The pH of the solution was adjusted to 4 by addition of a few drops of LiOD in D_2O (saturated).

U-Tube Transport. The procedure used therein has been reported previously.[22] At 24 ± 1 °C in a U-tube of 14 mm i.d was placed a 0.027 M solution of host in $CHCl_3$ (10 mL). 0.8M aqueous $LiPF_6$ and 0.08 M aqueous in HCl (5.0 mL) containing the guest amine hydrochloride was placed in the α-arm. The β-arm contained 5.0 mL of 0.10 M HCl in water. The α and β interfaces were contained 5.0 mL of 0.10 M aqueous HCl. The α and β interfaces were *ca.* 1.5 cm^2 each, and the average $CHCl_3$ path length was *ca.* 6.5

cm. The $CHCl_3$ layer was mixed at a constant rate by a small magnetic stirrer which also mixed the aqueous layers, but less efficiently, by drag. The absorbance of the β phases in the UV spectrum was measured at 256 nm for α-phenylethylamine salt, and at 272 nm for phenyl glycinemethylester salt. The host could not be detected in the UV spectrum of the β phase.

U-tube Experiment Run 1. A solution of 10 mL of $CHCl_3$ containing 158 mg of host (0.027 M) at 24 ± 1 °C was released carefully via syringe into the U-tube with the magnetic stirring bar in place and without wetting the upper part of the arms. Into the α arm was introduced via syringe 5.0 mL of an solution that contained 0.08 M aqueous HCl and 0.8 M aqueous $LiPF_6$ along with 159 mg (0.2M) of racemic guest. The 5.0 mL of aqueous solution in the β arm was 0.10 M in HCl. After 4 h, the aqueous solution was removed with a pipet, the arm was washed with 5 mL of water and the combined aqueous solutions were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filterate was concentrated in *vacuo* to give 14 mg (8.8% transferred) of amine **9** as an oil. This total sample was transferred with CH_2Cl_2 into a 1 mL polarimetry cell, and its optical rotation was determined in a jacketed tube: $[\alpha]_{546}$ - 39.0° (c1.4, CH_2Cl_2) which corresponds to a calculated optical purity of 89.2%. Optically pure (*S*)-(-)-α-phenyl ethyl amine gave $[\alpha]_{546}$ - 43.7° (c 2.6, CH_2Cl_2).[25]

λnm	α_{obsd}	$[\alpha]_\lambda$	% opt. purity
546	-0.546	-39.0	-39.0 x 100 / -43.7 = **89.2%**

Control Experiment run 2. A solution of 10 mL of $CHCl_3$ containing 158 mg of host (0.027 M) at 24 ± 1 °C was released carefully via syringe into the U-tube with the magnetic stirring bar in place and without wetting the upper part of the arms. Into the α arm was introduced via syringe 5.0 mL of an solution that contained 0.08 M aqueous HCl and 0.8 M aqueous $LiPF_6$ along with 159 mg (0.2M) of racemic guest. The 5.0 mL of aqueous solution in the β arm was 0.10 M in HCl. After 24 h, the aqueous solution was removed with a pipet, the arm was washed with 5 mL of water and the combined aqueous solutions were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filterate was concentrated in *vacuo*, thereby affording 4 mg (2.5% transferred) of amine **9** as an oil.

U-tube Experiment Run 3. A solution of 10 mL of $CHCl_3$ containing 204 mg of host (0.027 M) at 24 ± 1 °C was released carefully via syringe into the U-tube with the magnetic stirring bar in place and without wetting the upper part of the arms. Into the α arm was introduced via syringe 5.0 mL of an solution that contained 0.08 M aqueous HCl and 0.8 M aqueous $LiPF_6$ along with 159 mg (0.2M) of racemic guest. The 5.0 mL of aqueous solution in the β arm was 0.10 M in HCl. After 4 h, the aqueous solution was removed with a pipet, the arm was washed with 5 mL of water and the combined aqueous solutions were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filterate was concentrated in *vacuo* to give 22 mg (10.7%

transferred) of amine ester **10** as an oil. Its rotation was determined in a jacketed tube: $[\alpha]_{546}$–34.7° (C 1.9, CH_2Cl_2), which provided calculated optical purity of 18.7%. Optically pure (*R*)-(-)-α-methyl phenyl glycinate gave $[\alpha]_{546}$ –185.2° (c 1.9, CH_2Cl_2), and our rotations were taken at the same concentration in the same solvent.[19a]

λnm	α obsd	$[\alpha]_\lambda$	% opt purity
546	-0.66	-34.7	-34.7 x 100 / -185.2 = **18.7%**

Control experiment run 4. A solution of 10 mL of $CHCl_3$ containing 204 mg of host (0.027 M) at 24 ± 1 °C was released carefully via syringe into the U-tube with the magnetic stirring bar in place and without wetting the upper part of the arms. Into the α arm was introduced via syringe 5.0 mL of an solution that contained 0.08 M aqueous HCl and 0.8 M aqueous $LiPF_6$ along with 159 mg (0.2M) of racemic guest. The 5.0 mL of aqueous solution in the β arm was 0.10 M in HCl. After 24 h, the aqueous solution was removed with a pipet, the arm was washed with 5 mL of water and the combined aqueous solutions were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filterate was concentrated in *vacuo*, thereby affording 6 mg (2.9% transferred) of amino ester **10** as an oil.

Recovery of the host. The procedure has been reported previously.[12] The various organic layers containing host were combined and washed with 50 mL of 0.1 N HCl to remove traces of amino ester. The organic phase was dried ($MgSO_4$) and filtered, and the

filterate was concentrated in *vacuo*. The residue was purified on alumina chromatography eluting with ethylacetate.

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CHAPTER 5

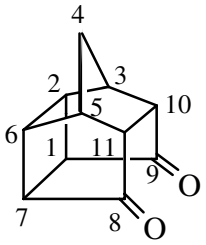
ACID AND BASE PROMOTED REARRANGEMENTS OF HEXACYCLO[[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5.15}$.$0^{10,14}$]HEXADECA-6,8-DIENE-4,11-DIONE

INTRODUCTION

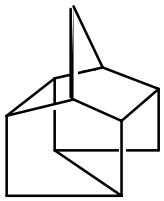
Polycarbocyclic cage compounds[1] have been utilized as substrates for mechanistic studies and as intermediates in organic synthesis. Molecular rearrangements of highly strained cage compounds that lead to the formation of a variety of products are of special interest.[2] In particular, small rings contained within their molecular frameworks have been reported to undergo numerous transformations, which appeal to the intrinsic desire of organic chemists to understand strain-reactivity relationships.

Many factors contribute to the driving force for cage compound rearrangements. In particular, aromatization, relief of steric strain, and/or proximity effects associated with compact cage structures can provide important driving forces. Among the various known types of strained cage compounds, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones (PCU-8,11-dione, **1**) have been studied extensively[3] as substrates for mechanistic studies. Synthetically important rearrangements of the carbon skeleton contained within **1** include C1-C7 to C1-C8 bond reorganizations (i.e., **1** to **2**) and [2 + 2] cycloreversions that occur via C1-C7 and C2-C6 bond cleavage (i.e., **1** to **3**). While the former leads to synthesis of trishomocubane derivatives (**2**),[4] the latter leads to the

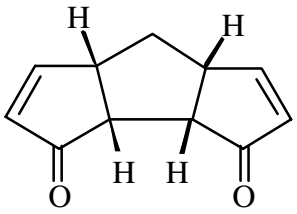
formation of linear triquinanes, **3**, that have been employed as starting materials in several natural product syntheses.[4-5]



1



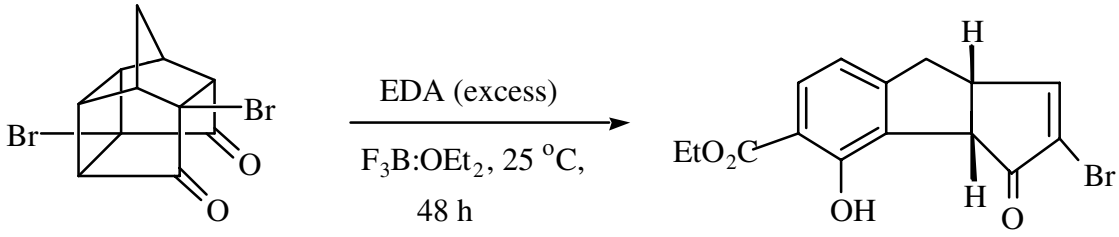
2



3

A unusual example from our laboratory that results in extensive cationic rearrangement[6] of the PCU framework is depicted in Scheme 5.1. Thus, BF_3 mediated reaction of 1,9-dibromo-PCU-8,11-dione **4** with ethyl diazoacetate provides the cyclopent[a]indene ring system (**5**, 42%). Aromatization provides an important driving force for this carbocation-mediated rearrangement.[7]

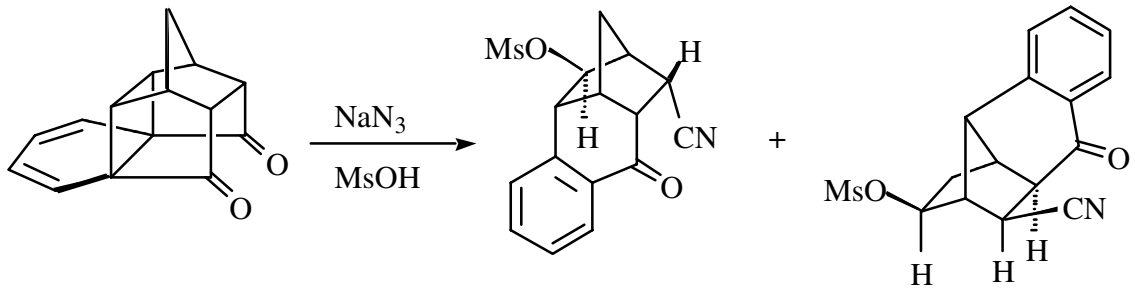
Scheme 5.1



4 **5** (42%)

Another example of interesting rearrangements of the PCU skeleton has been demonstrated by using hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadeca-10,12-diene-2,8-dione (**6,** Scheme 5.2). Dione **6** has been employed as substrate in various studies, e.g., the diene component in studies of π-facial selectivity of Diels-Alder reactions.[8] In addition, **6** has been recognized as a potential source of new polycyclic systems.[9] When treated with NaN_3 in aqueous MsOH (i,e., Schmidt reaction conditions), **6** rearranges to afford two products, i.e., a benzo-annulated tricyclo[5.2.1.$0^{3,8}$]decane (**7**, 15%) and tricyclo[4.4.0.$0^{3,7}$]decane (**8,** 20%) (Scheme 5.2).[10]

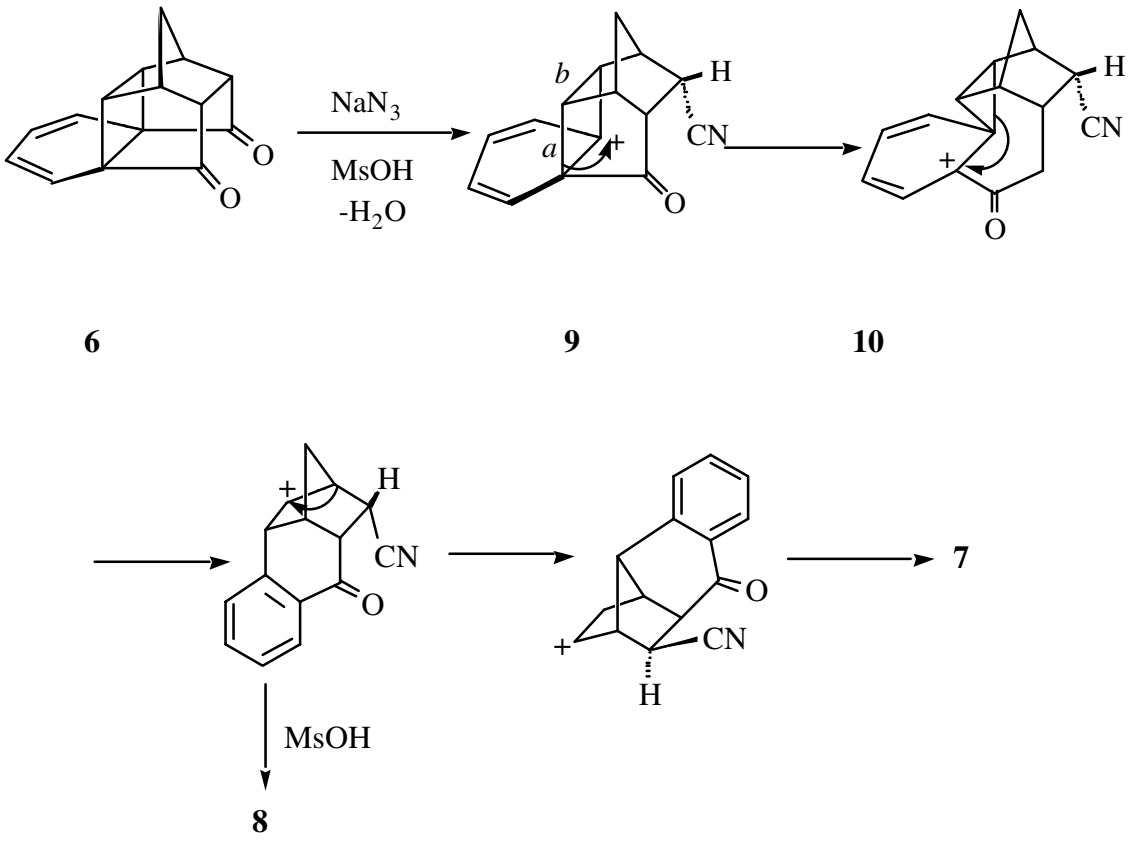
Scheme 5.2



6 **7** (15%) **8** (20%)

A probable mechanistic pathway that accounts for the formation of rearrangement products **7** and **8** that arise from dione **6** is depicted in Scheme 5.3. The initially- formed carbocationic intermediate **9** rearranges to an unusual α-keto-carbocation **10**, which is stabilized through π-delocalization and cyclopropyl conjugation. These stabilization factors are thought to direct the preferential migration of bond '*a*' in the intermediate **9** *vs*. the corresponding migration of bond '*b*'.[10]

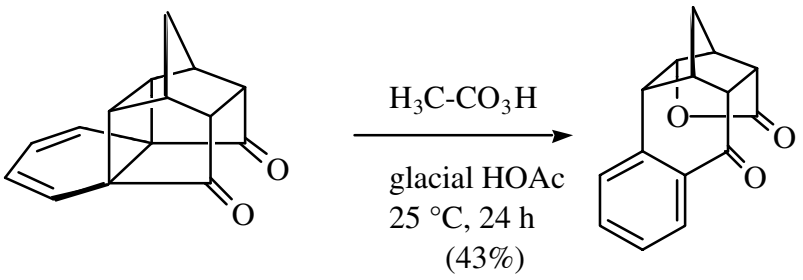
Scheme 5.3



6 **9** **10**

In another study, Pandey and coworkers[11] reported that Baeyer-Villiger (B-V) oxidation of **6** affords an extensively rearranged product (i.e., **11,** Scheme 5.4). When **6** was treated with HCO_3H -NaOAc in glacial HOAc, the reaction furnished a monolactone, **11**, in 43% yield.

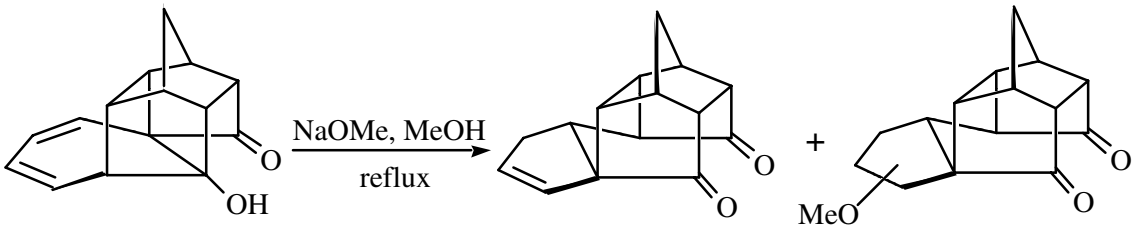
Scheme 5.4



6 **11**

There are also many examples[12] of rearrangements in polycarbocyclic cage compounds that proceed via *carban*ionic intermediates. Thus, reactions of cage compounds with base that result in cleavage of strained cage σ bonds have been studied extensively. A unusual example[13] of such a base-promoted rearrangement is depicted in Scheme 5.5.

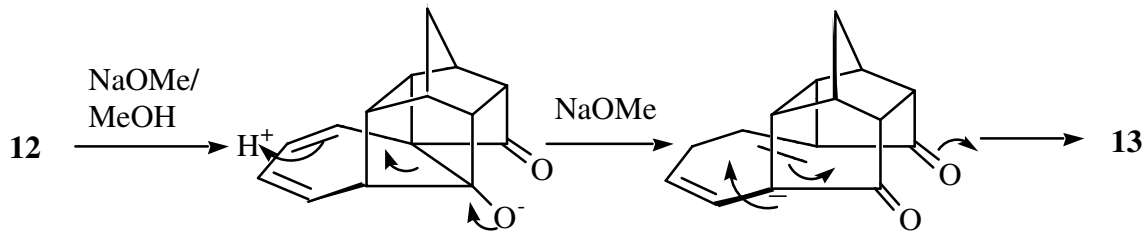
Scheme 5.5



12 **13** **14**

Thus, reaction **12** with refluxing NaOMe-MeOH results in rearrangement to afford a mixture of annulated cages, i.e., **13** (45% yield) and **14** (30% yield). The process by which the anion produced via cleavage of strained cage σ bonds in **12** is captured by solvent is indicated by the mechanism shown in Scheme 5.6.

Scheme 5.6



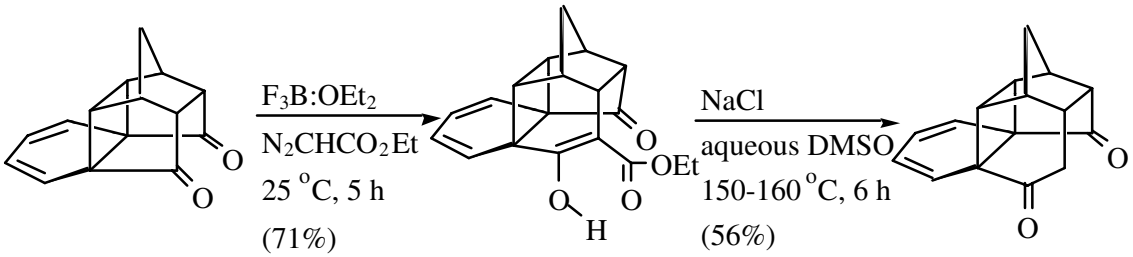
Finally, as an extension of our current interest in the chemistry of polycarbocyclic cage compounds, we synthesized hexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5,15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione **16**, an annulated derivative of **6**,[14] by using the method shown in Scheme 1.7. During the course of investigations of Diels-Alder reactions of **16**, we observed unusual one-step rearrangements of **16** to novel cage systems that occur in the presence of acid or base. We now report our observations concerning acid and base promoted rearrangements of dione **16** to novel cage systems **19** and **22**, respectively.

RESULTS AND DISCUSSION

Hexacyclic cage diketone **16** was readily prepared in good yield via ring expansion of **6** (Scheme 5.7). Since we were interested in studying π-facial selectivity of the Diels-Alder reactions[8] of cage compounds, we planned initially to investigate the

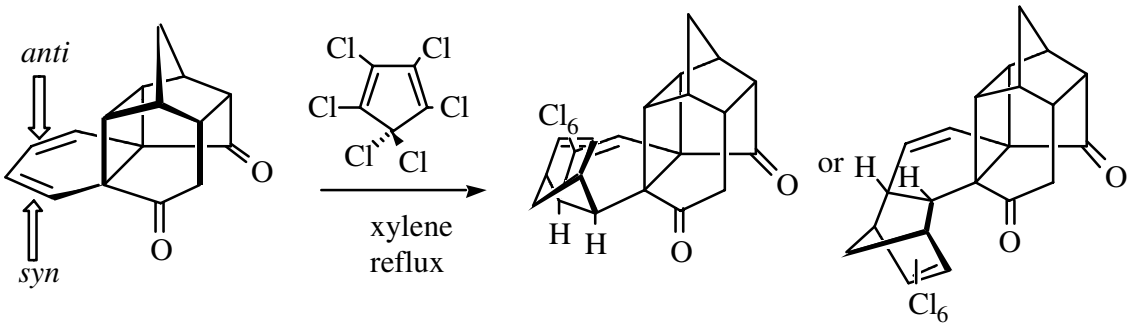
reaction of **16** with hexachlorocyclopentadiene. It was anticipated that products (**17** and/or **18**) might result via *anti* or *syn* [4+2] cycloaddition of hexachlorocyclopentadiene to **16** (Scheme 5.8).

Scheme 5.7



6 **15** **16**

Scheme 5.8

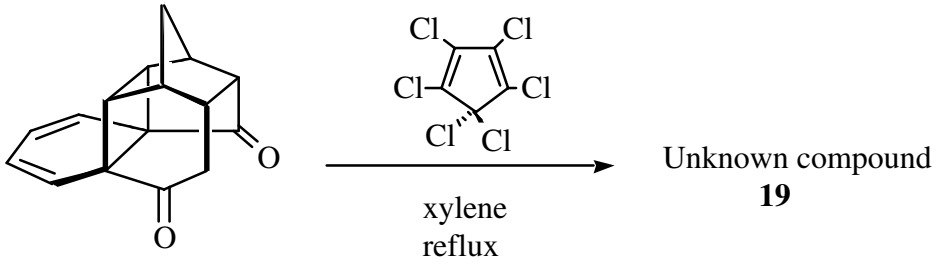


16 **17** **18**

However, when dione **16** was refluxed with hexachlorocyclopentadiene, the reaction unexpectedly produced a single product, **19** (Scheme 5.9). The IR spectrum of the unknown compound **19** exhibited diagnostic bands that can be assigned to C=O (1732 cm^{-1}) and C=C moieties group (1683 cm^{-1}). The ^{13}C NMR spectrum also displays two

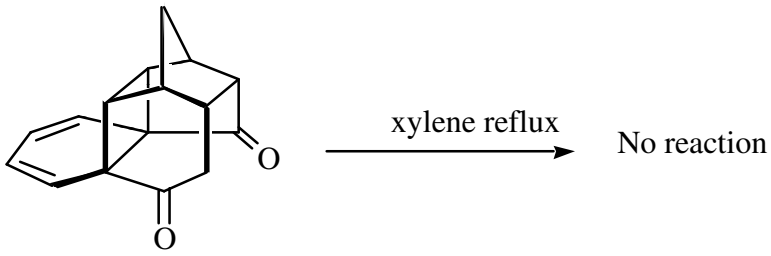
nonequivalent ketone peaks (δ 200.2 and δ 219.2) and vinyl carbon peaks (δ 127.1, 128.3, 130.1, 130.9, 135.0, and 143.1). The spectral data suggest that the reaction of **16** with hexachlorocyclopentadiene proceeds with concomitant extensive skeletal rearrangement.

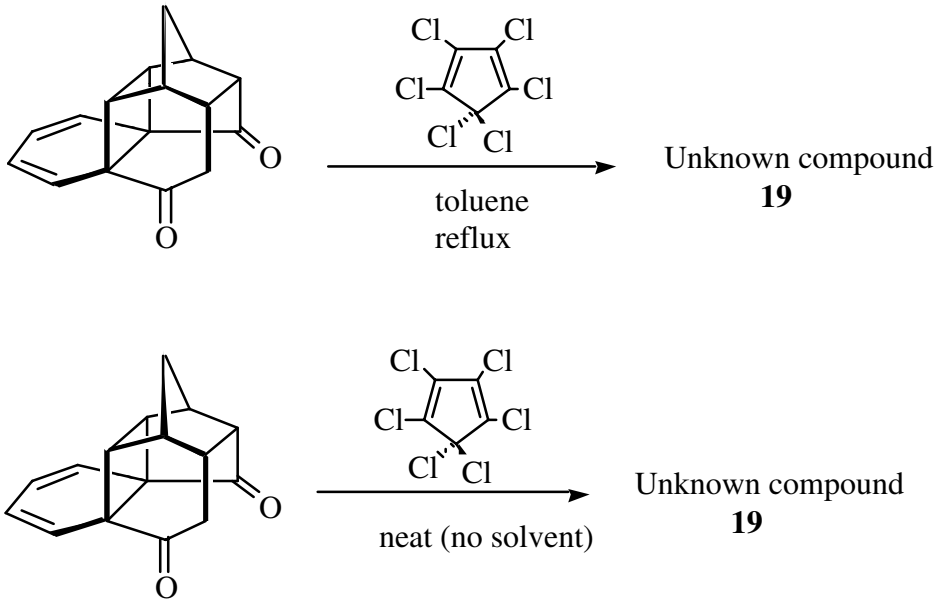
Scheme 5.9



Efforts to characterize unknown compound **19** were furthered by the results of a series of reactions summarized in Scheme 5.10. No reaction occured when **16** was refluxed in xylene solution, thereby indicating the thermal stability of diketone **16**. When **16** was refluxed with hexachlorocyclopentadiene in toluene or in the absence of solvent, the same product, **19**, was obtained.

Scheme 5.10

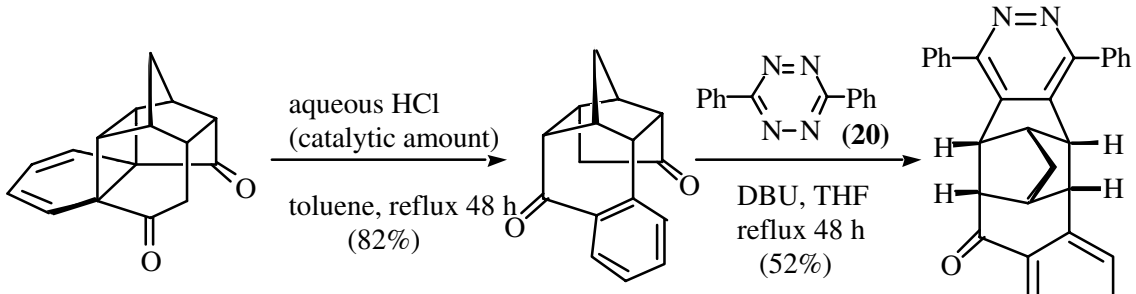




Fortunately, the chemical structure of the unknown compound 19 could be determined via single crystal X-ray structural analysis.[19] Figure 5.1 contains an X-ray structure drawing of **19**.

Based upon the foregoing results, we conclude that rearrangement of **16** is promoted by trace amounts of HCl contained in the hexachloropentadiene. Indeed, when a toluene solution of **16** was refluxed with a catalytic amount of aqueous HCl, compound **19** was produced as the sole reaction product. In addition, **19** was reacted with 3,6-diphenyl-1,2,4,5-tetrazine[15] (**20**) to produce a molecular cleft,[16] **21** (Scheme 5.11). The structure of **19** was established unequivocally via X-ray crystallographic analysis.[19] Figure 5.2 presents an X-ray structure drawing of **21**.

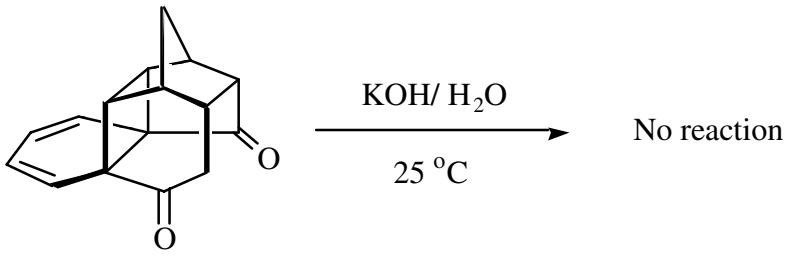
Scheme 5.11

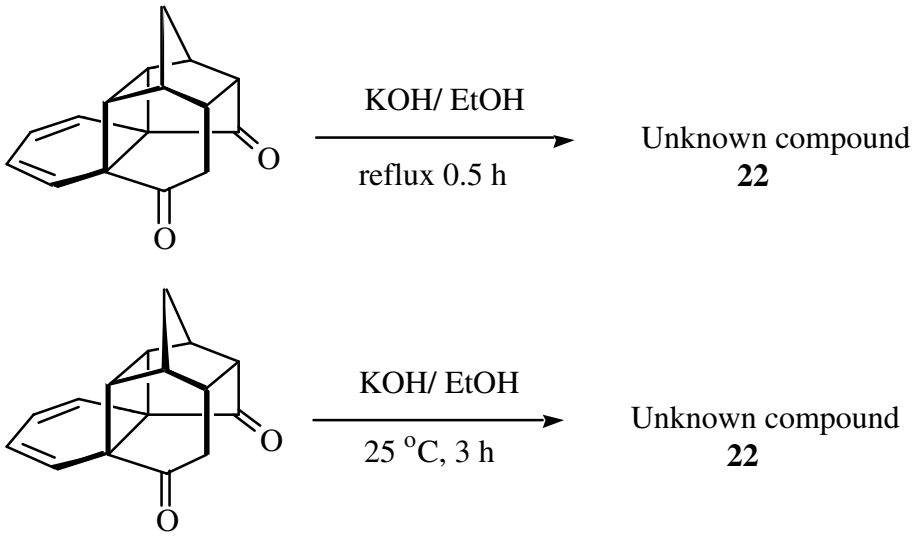


16 **19** **21**

Our observation that an unusual rearrangement occurs when **16** is treated with acid encouraged us to study the corresponding chemical behavior of **16** with base. When **16** was refluxed with aqueous base (KOH), no reaction occured. However, when **16** was reacted with ethanolic KOH at ambient temperature (during 3 h) or at reflux temperature (during 0.5 h), a reaction occured that provided us with another unexpected compound, (i.e., **22**, Scheme 5.12).

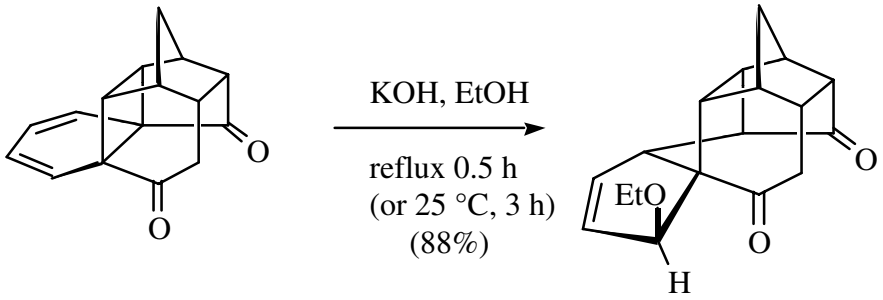
Scheme 5.12





Analysis of the ^{1}H NMR, ^{13}C NMR, and IR spectra of the unknown compound, **22**, indicates the presence of two nonequivalent C=O groups and a C=C group in this compound. In addition, the results of our analysis of the ^{1}H NMR and ^{13}C NMR spectra of **22** suggest that an ethoxy group (-OEt) from solvent had become incorporated into the reaction products. However, it was not possible to deduce the exact structure of **22** simply via analysis of relevant NMR spectral data alone. Fortunately, the chemical structure of **22** could be established via X-ray crystallographic analysis[19] (Figure 5.3). It was found that the strained cage compound **16** had reacted with ethanolic KOH, either at room temperature or at reflux, to afford a rearranged product (i.e., **22,** Scheme 5.13).

Scheme 5.13



16 **22**

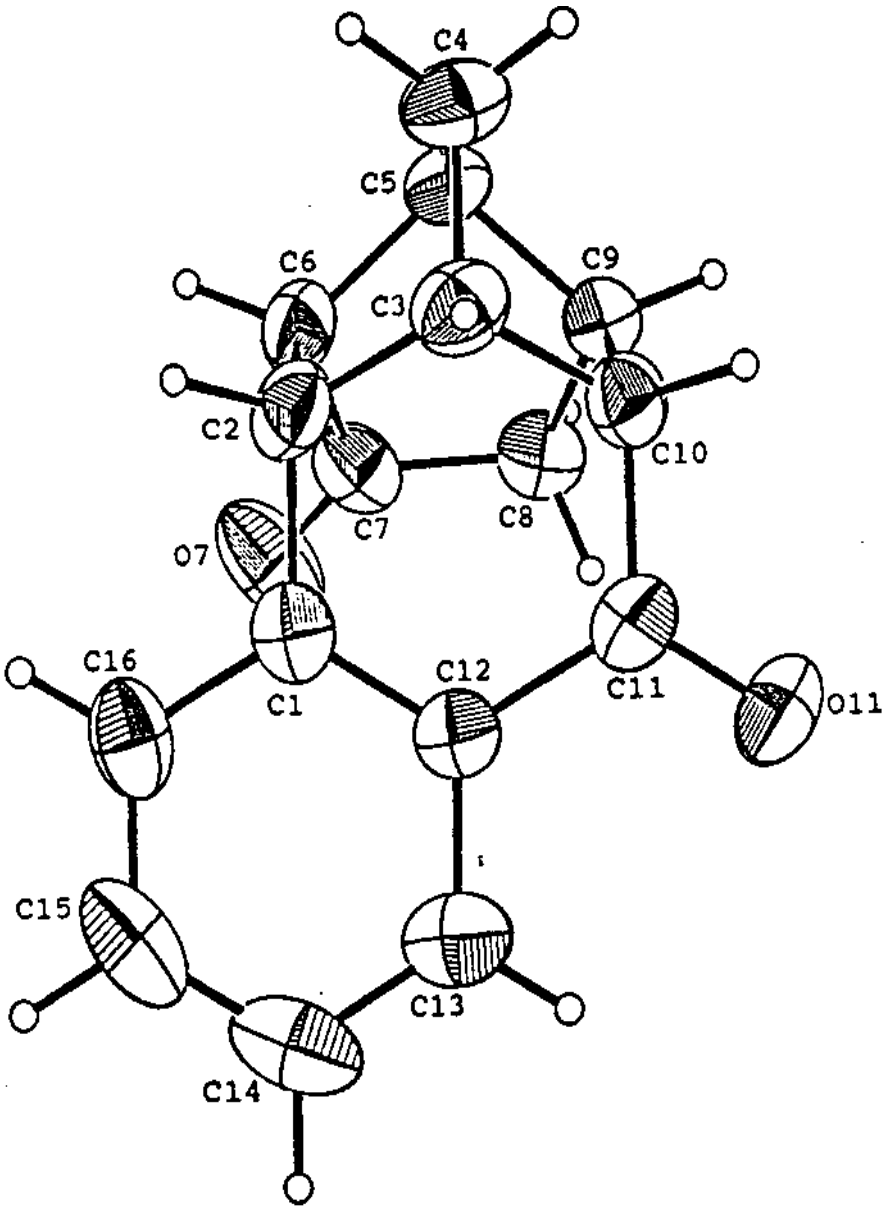


Figure 5.1. X-ray structure drawing of **19**

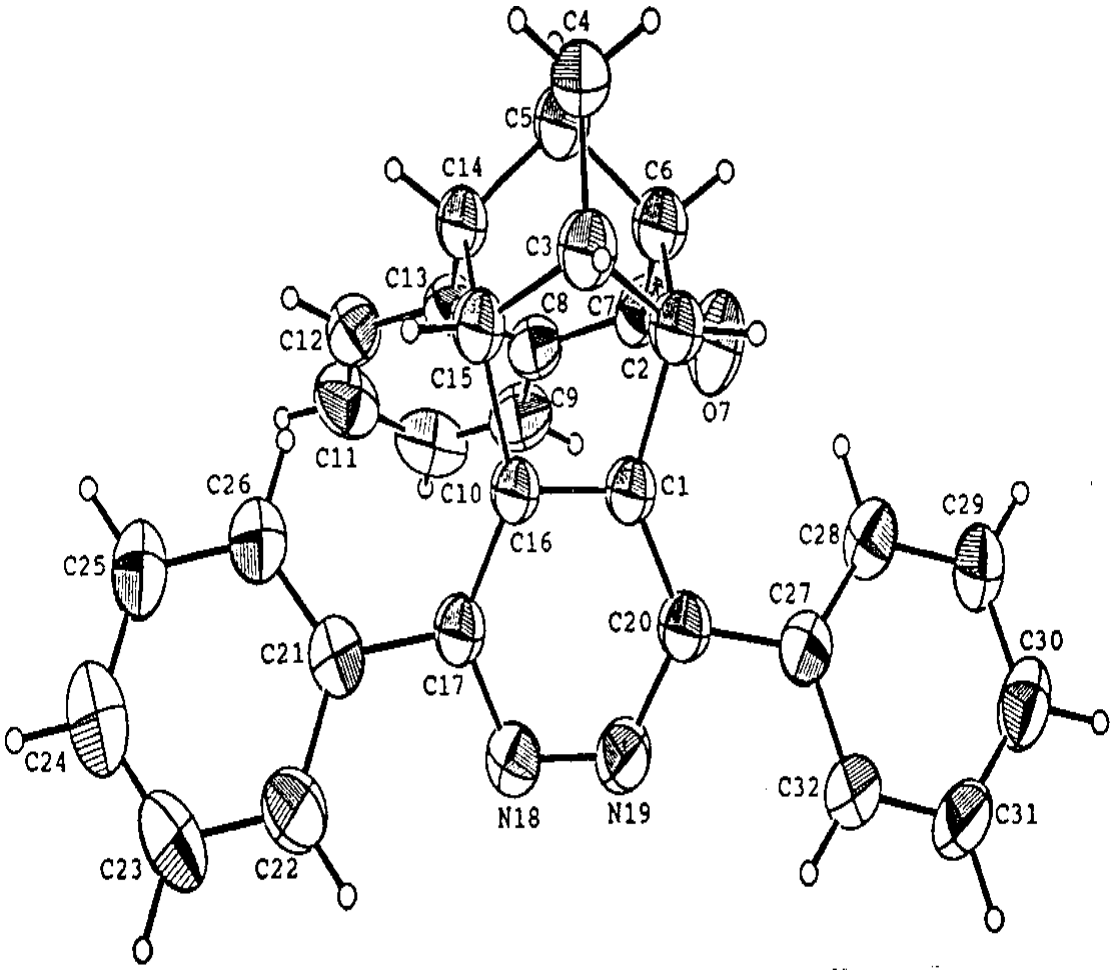


Figure 5.2. X-ray structure drawing of **21.**

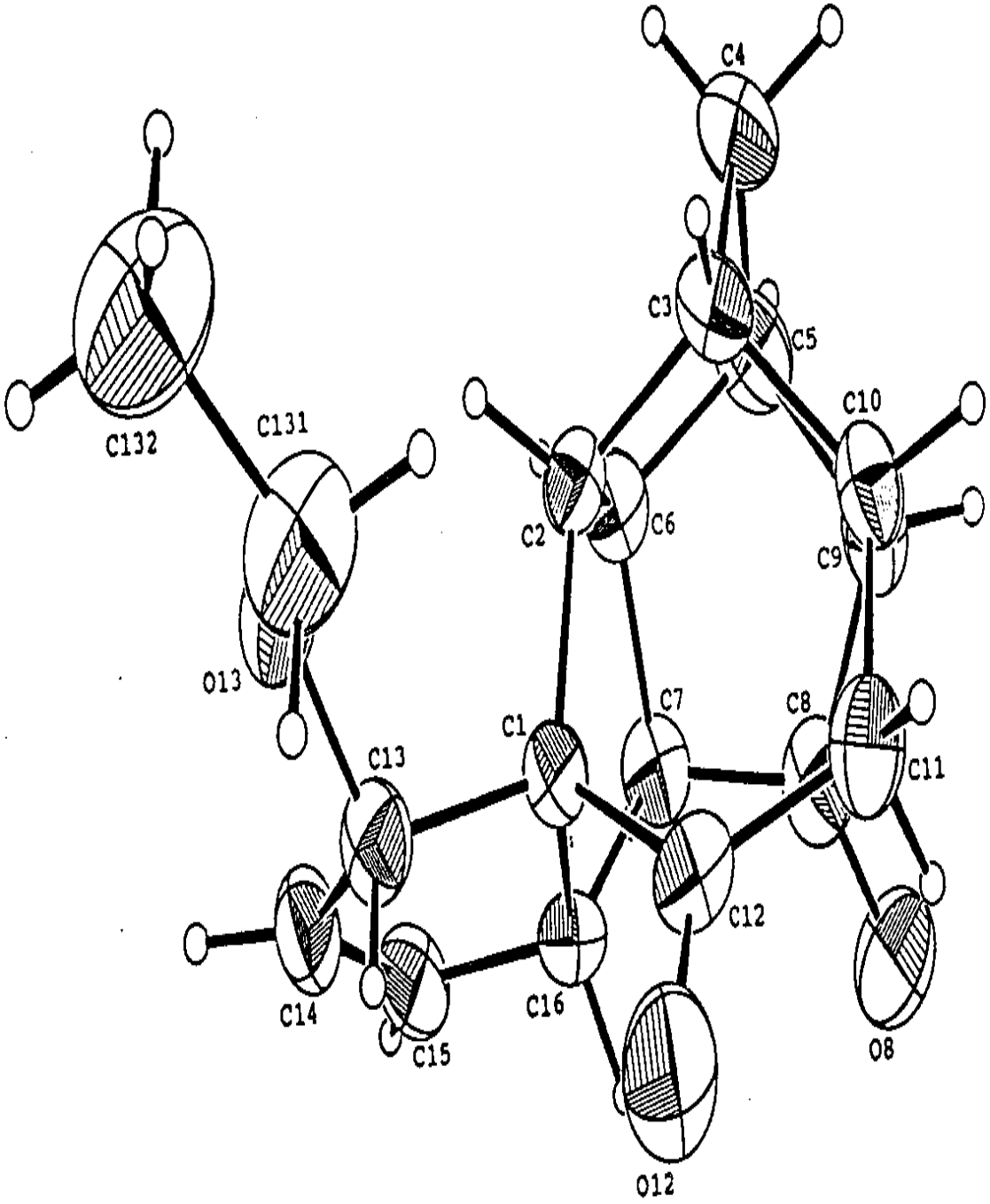
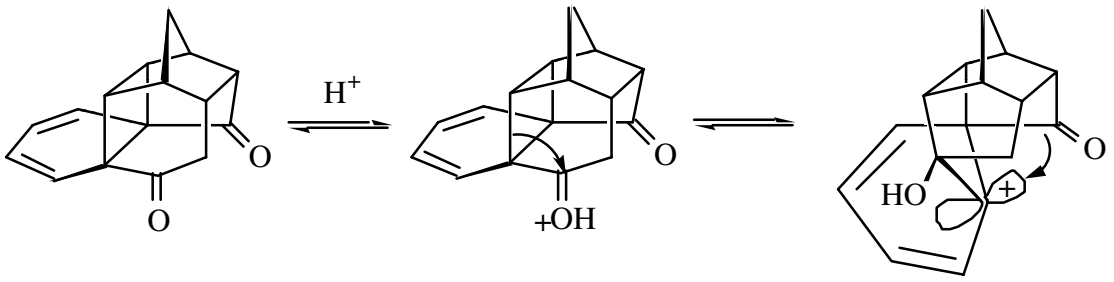


Figure 5.3. X-ray structure drawing of **22**

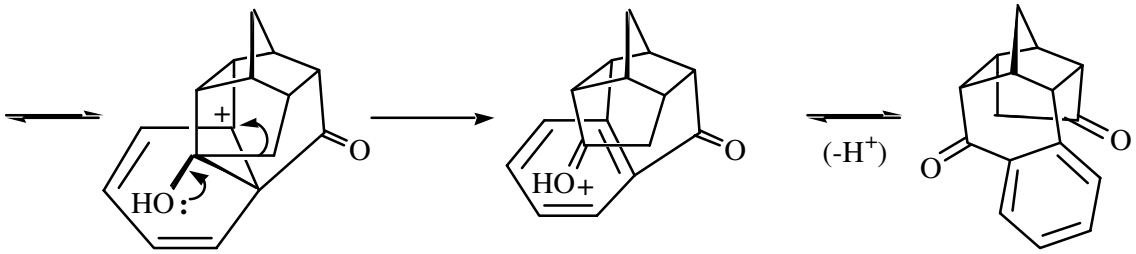
A mechanistic approach toward understanding the acid and base promoted rearrangements reported herein

A possible mechanistic pathway that accounts for the formation of the product of acid-promoted rearrangement of **16** is depicted in Scheme 5.14. In the presence of acid, protonation of the carbonyl group occurs in **16**. This is followed by rearrangement with concomitant participation of an adjacent σ-bond. This rearrangement results in expansion of the cyclobutane ring in **22** and leads to the stabilized benzylic cation, **23**. Then, carbocationic intermediate **23** rearranges to an unusual carbocation, **24**, which is stabilized via pentadienyl π-delocalization. Finally, **24** rearranges to the aromatized intermediate, **25**, which subsequently is deprotonated to afford the rearranged product, **19**. It should be noted that aromatization provides a significant driving force for this rearrangement.

Scheme 5.14



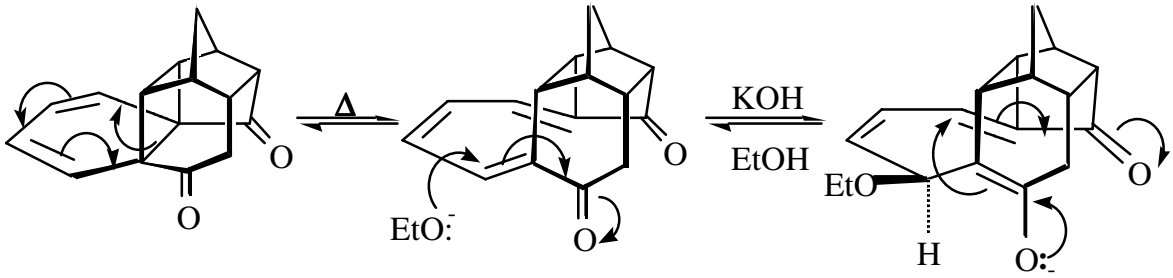
16 **22** **23**



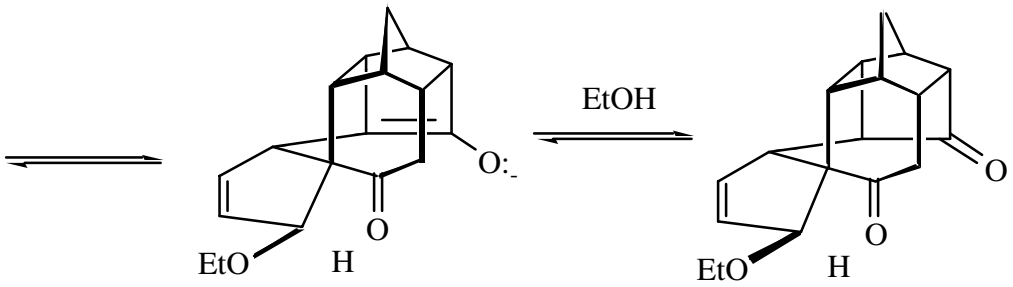
24 **25** **19**

A possible mechanism to account for the observed course of base promoted rearrangement of **16** to **22** is shown in Scheme 5.15. Interestingly, cage diketone **16** first undergoes electrocyclic ring opening followed by nucleophilic Michael addition of ethoxide (OEt^-), which proceeds via attack of the nucleophile toward the *exo* face of the triene system. The resulting anion, **26**, undergoes rearrangement to afford an anionic intermediate, **27**, with concomitant formation of a five-membered ring. The resulting enolate ion, **27**, is protonated to afford the corresponding keto tautomer, thereby affording the ultimate rearrangement product, **22**.

Scheme 5.15



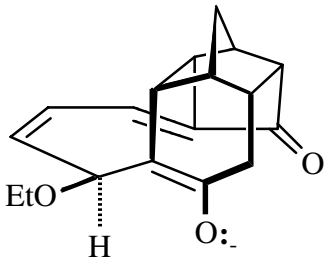
16 **26**



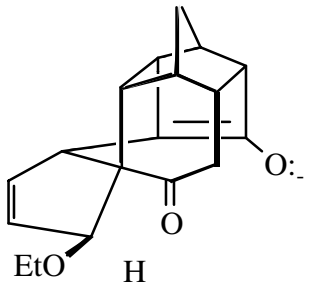
27 **22**

The heats of formation, ΔH°_{f}, of two carbanionic intermediates (**26** and **27**, respectively) and their corresponding conjugate acids (**28** and **22**, respectively) have been calculated (Figure 5.4).[20] It is interesting to note that the results of semi-empirical molecular orbital calculations[11] predict rearrangement of the anion **26** to the anion **27** to be endothermic by *ca*. 6 kcal-mol^{-1}. However, their respective conjugate acids lie in the opposite order of relative stability. Thus, compound **22**, the observed product of base promoted rearrangement of **16**, is favored thermodynamically relative to **28** by *ca*.18 kcal-mol^{-1}.

Calculated Heats of Formation (kcal/mol)

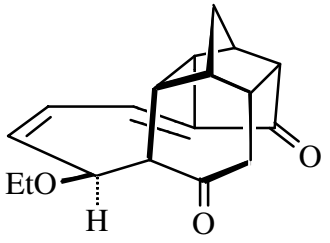


26

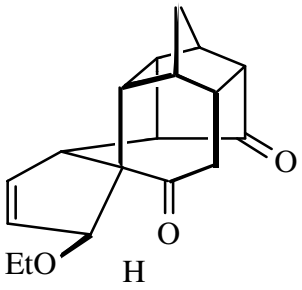


27

$\Delta H°_f$ (AM1, kcal-mol^{-1})	84.07
E_{rel} (kcal-mol^{-1})	(0)



28



22

$\Delta H°_f$ (AM1, kcal-mol^{-1})	-63.91
E_{rel} (kcal-mol^{-1})	(0)

$\Delta H°_f$ (AM1, kcal-mol^{-1})	-77.99
E_{rel} (kcal-mol^{-1})	(+6.07)

$\Delta H°_f$ (AM1, kcal-mol^{-1})	-81.97
E_{rel} (kcal-mol^{-1})	(-18.05)

Figure 5.4. Calculated (AM1)[17] heats of formation of **22**, **26**, **27**, and **28**

SUMMARY AND CONCLUSIONS

Pursuant to our current interests in the synthesis and chemistry of polycarbocyclic cage compounds, we have prepared hexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5,15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione **16**, an annulated derivative of hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$] pentadeca-10,12-diene-2,8-dione **6**. We also have studied the unanticipated but remarkable acid and base promoted rearrangements of dione **16** to new polycyclic systems (**19**, 82%) and (**22**, 88%), whose respective structures were determined unequivocally by X-ray crystallography method. We find good literature precedents for the reactions in similar polycarbocyclic systems which provided structural analogs of **19** and **22**, respectively. However, it is noteworthy that the reactions reported herein provide the corresponding rearranged products in high yield in a single synthetic step.

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

3-Carboethoxyhexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5.15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione (15). A solution of cage diketone **6**[14] (500 mg, 2.23 mmol) in Et_2O (10 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added sequentially with stirring $F_3B{\cdot}OEt_2$ (0.30 mL, 2.5 mmol) and ethyl diazoacetate (EDA, 0.31 mL, 3.0 mmol). After the addition of reagents had been completed, the external cold bath was removed, and the reaction mixture was allowed to warm gradually

to ambient temperature and then was stirred at that temperature for 5 h. Diethyl ether (25 mL) was added, and the resulting mixture was washed sequentially with water (2 x 25 mL), 10% aqueous $NaHCO_3$ (2 x 25 mL), and water (25 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 1:6 EtOAc-ligroin. Pure **15** (490 mg, 71%) was thereby obtained as a colorless microcrystalline solid, mp 145-146 °C; IR ($CHCl_3$) 2906 (s), 1741 (s), 1656 (s), 1429 (w), 1309 (w), 1265 (m), 1091 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 8 Hz, 3 H), 1.42 (*A*B, J_{AB} = 11 Hz, 1 H), 1.80 (A*B*, J_{AB} = 11 Hz, 1 H), 2.26 (br s, 1 H), 2.7-3.1 (m, 4 H), 3.43-3.60 (m, 1 H), 4.08-4.35 (m, 2 H), 5.70 (d, J = 10 Hz, 1 H), 5.75 (d, J = 10 Hz, 1 H), 6.0-6.2 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 36.5 (t), 41.9 (d), 42,3 (d), 44.5 (s), 44.8 (d), 50.9 (d), 51.4 (d), 55.9 (d), 57.2 (s), 61.2 (t), 100.3 (s), 121.8 (d), 123.3 (d), 124.3 (2 C, d), 171.2 (s), 173.7 (s), 216.3 (s). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.71; H, 5.65.

Hexacyclo[11.2.1.$0^{2,12}$.$0^{5,10}$.$0^{5.15}$.$0^{10,14}$]hexadeca-6,8-diene-4,11-dione (16).[18] A mixture of **15** (470 mg, 1.51 mmol), NaCl (300 mg, 5.13 mmol) and water (0.5 mL) in DMSO (10 mL) was heated at 150-160 °C for 6 h. The reaction mixture was cooled to ambient temperature and then was diluted with water (25 mL). The resulting aqueous suspension was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (2 x 25 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 1:5 EtOAc-ligroin. Pure **16** (200 mg, 56%) was thereby obtained as a colorless microcrystalline solid: mp 141-142 °C; IR ($CHCl_3$) 2968 (m), 1732 (vs), 1697

(vs), 1599 (w), 1392 (w), 1263 (w), 1161 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (*A*B, J_{AB} = 10 Hz, 1 H), 2.62 (A*B*, J_{AB} = 10 Hz, 1 H), 2.32-2.80 (m, 6 H), 2.90 (br s, 1 H), 3.04-3.15 (m, 1 H), 5.32 (d, *J* = 10 Hz, 1 H), 5.45 (d, *J* = 10 Hz, 1 H), 5.80-6.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 38.2 (t), 39.2 (t), 40.1 (d), 41.3 (d), 45.2 (d), 48.4 (s), 50.0 (d), 52.4 (d), 53.6 (s), 54.0 (d), 121.5 (d), 123.2 (d), 124.5 (d), 126.1 (d), 208.9 (s), 218.6 (s). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.48; H, 5.77.

Acid Promoted Rearrangement of 16. To a solution of **16** (200 mg, 0.84 mmol) in toluene (20 mL) was added concentrated aqueous HCl (2 drops, catalytic amount), and the resulting mixture was refluxed with stirring for 48 h. The progress of the reaction was monitored by thin layer chromatographic (tlc) analysis; the presence of **16** could no longer by detected by tlc analysis after 48 h. The reaction mixture was cooled to ambient temperature and then was concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL), and the resulting solution was washed successively with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and water (10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **19** (1.72 g, 82%) was thereby obtained as a colorless microcrystalline solid: mp 158-159 °C; IR ($CHCl_3$) 2960 (vs), 2874 (w), 1732 (vs), 1683 (vs), 1601 (s), 1456 (s), 1278 (s), 1147 (s), 833 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.61-2.21 (m, 5 H), 2.73 (*A*B, J_{AB} = 11 Hz, 1 H), 3.00-3.06 (br s, 3 H), 3.45(A*B*, J_{AB} = 11 Hz, 1 H), 7.22 (d, *J* = 8 Hz, 1 H). 7.34 (d, *J* = 8 Hz, 1 H), 7.50 (*A*B, J_{AB} = 7 Hz, 1 H), 8.00 (A*B*, J_{AB} = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 38.8 (t), 40.5 (d). 41.1 (t), 45.6 (d), 46.1 (d), 48.9 (d), 51.5 (d), 55.6 (d), 127.1 (d), 128.3 (d),

130.1 (d), 130.9 (s), 135.0 (d), 143.1 (s), 200.2 (s), 219.2 (s). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.76; H, 5.94. The structure of **19** was established unequivocally via application of X-ray crystallographic methods.[19]

Diels-Alder Cycloaddition of 19 to 3,6-Diphenyl-1,2,4,5-tetrazine (20). To a refluxing solution of **19** (290 mg, 1.26 mmol) and **20**[15] (377 mg, 1.64 mmol) in dry THF (20 mL) was added DBU (0.48 mL, 3.2 mmol), and the resulting mixture was refluxed with stirring for 48 h. The reaction mixture was allowed to cool to ambient temperature and then was concentrated *in vacuo*. Methanol (7 mL) was added to the residue, whereupon a colorless precipitate formed. The precipitate was collected via suction filtration, and the residue was washed with MeOH (2 x 5 mL). The resulting solid was purified via recrystallization from EtOAc-hexane, thereby affording pure **21** (280 mg, 52%) as a colorless microcrystalline solid: mp 205.0-205.5 °C; IR ($CHCl_3$) 2961 (vs), 2881 (w), 1676 (vs), 1606 (m), 1460 (m), 1377 (s), 1298 (m), 1111 (m), 925 (m), 746 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.98 (*A*B, J_{AB} = 11 Hz, 1 H), 2.11 (A*B*, J_{AB} = 11 Hz, 1 H), 3.07-3.15 (m, 2 H), 3.33-3.42 (m, 1 H), 3.66-3.70 (m, 1 H), 3.82-3.87 (dd, *J* = 10, 4 Hz, 1 H), 3.98-4.04 (dd, *J* = 10, 4 Hz, 1 H), 6.54-6.58 (m, 1 H), 7.04-7.11 (m, 2 H), 7.41-7.60 (m, 9 H), 7.89-7.94 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 38.0 (t), 43.9 (d), 48.5 (d), 49.2 (d), 49.4 (d), 51.6 (d), 60.0 (d), 126.8 (d), 127.9 (d), 128.7 (d), 129.0 (d), 129.3 (d), 129.4 (d), 129.5 (d), 129.6 (d), 129.7 (d), 131.4 (s), 134.2 (d), 136.7 (s), 137.1 (s), 142.7 (s), 144.6 (s), 146.5 (s), 155.7 (s), 156.2 (s), 198.3(s). Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20. Found: C, 84.44; H, 5.31. The structure of **21** was established unequivocally via application of X-ray crystallographic methods. [19]

Base Promoted Rearrangement of 16. To a solution of **16** (200 mg, 0.84 mmol) in EtOH (20 mL) under argon was added a solution of KOH (95 mg, 1.68 mmol) in EtOH (5 mL), and the resulting mixture was refluxed for 0.5 h. Thin layer chromatographic (tlc) analysis of the reaction mixture revealed the absence of starting materials and the presence of a single reaction product. The reaction mixture was concentrated *in vacuo*, and Et_2O (20 mL) was added to the residue. The resulting ethereal solution was washed successively with H_2O (10 mL), saturated aqueous NaCl (15 mL), and H_2O (10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained, a yellow solid, was recrystallized from EtOAc. Pure **22** (210 mg, 88%) was thereby obtained as a colorless microcrystalline solid: mp 143-144 °C; IR ($CHCl_3$) 2980 (s), 2881 (m), 1737 (s), 1697 (s), 1352 (w), 1269 (m), 1120 (s), 794 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 8 Hz, 3 H), 1.88 (*A*B, J_{AB} = 11 Hz, 1 H), 2.01 (A*B*, J_{AB} = 11 Hz, 1 H), 2.16 (s, 1 H), 2.49-2.61 (m, 5 H), 2.85 (s, 1 H), 3.01-3.29 (m, 3 H), 3.38 (q, J = 9.8 Hz, 2 H), 5.34-5.40 (m, 2 H), 5.59-5.67 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.8 (q), 37.1 (t), 40.5 (d), 40.7 (d), 42.8 (t), 44.7 (d), 47.9 (d), 50.8 (d), 54.4 (d), 57.6 (d), 65.4 (s), 65.8 (t), 67.1 (d), 86.2 (d), 130.3 (d), 133.2 (d), 212.3 (s), 224.1 (s). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.09; H, 6.88. The structure of **22** was established unequivocally via application of X-ray crystallographic methods.[19]

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19. The author thanks Dr. S. G. Bott for having kindly obtained the X-ray structures of **19**, **21**, and **22**.

20. The author thanks Dr. K. A. Kumar for having kindly performed the semi-empirical molecular orbital calculations of **22**, **26**, **27**, and **28**.

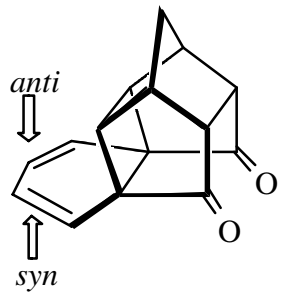
CHAPTER 6

THE STUDY OF p-FACIAL DIASTEREOSELECTIVITY AND REGIOSELECTIVITY IN DIELS-ALDER REACTIONS OF HEXACYCLO[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]PENTADECA-5,7-DIENE-3,10-DIONE AND HEXACYCLO[11.2.1.$0^{2,12}$.$0^{4,9}$.$0^{4,15}$.$0^{9,14}$]HEXADECA-5,7-DIENE-3,10-DIONE WITH ETHYL PROPIOLATE

INTRODUCTION

The regioselectivity and p-facial selectivity in Diels-Alder reactions to a variety of cage-functionalized diene systems have been subjects of considerable interest.[1] Among those diene systems, hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pendeca-5,7-diene-3,10-dione (1, Scheme 6.1)[2] as a p-facial differentiated 1,3-cyclohexadiene component has been employed extensively for studies of p-facial selecitivity.[3] Observed p-facial selectivities in Diels-Alder reactions of 1 with dienophiles have been rationalized via such factors as electrostatic interaction, product stability, σ/π orbital interactions, and/or a combination of torsional and steric effects.[4]

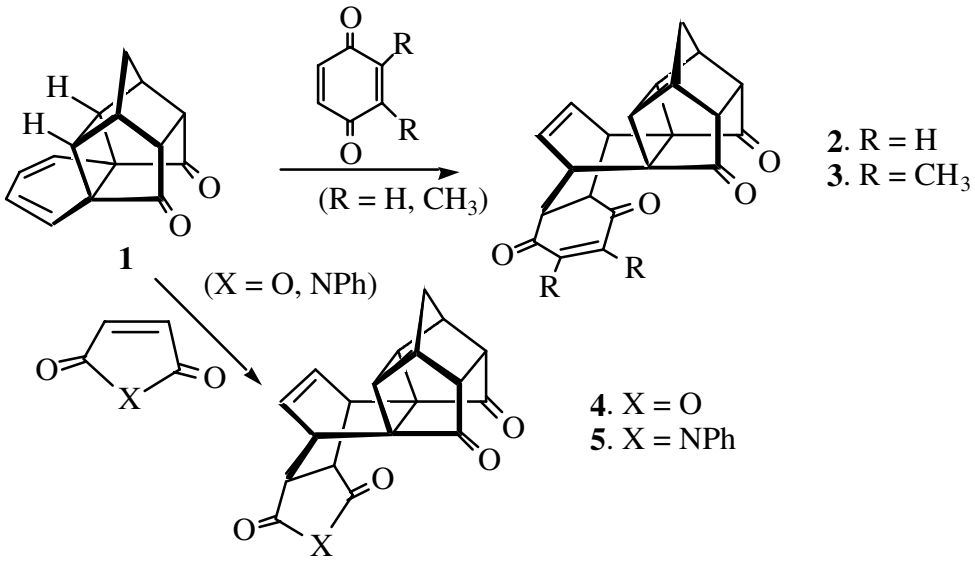
Scheme 6.1



1

In fact, the dienophile might approach from either the *syn* face or *anti* face of the π–system, thereby resulting in formation of two [4+2]cycloadducts. In particular, the influence of carbonyl group has been considered to be a important factor in controlling the approach of dienophile toward the π-face of diene **1**. In this regard, Diels-Alder cycloadditions[3a] of **1** to moderately reactive, p-facially symmetric dienophiles such as *p*-benzoquinone, maleic anhydride, and *N*-phenylmaleimide have been reported to proceed via exclusive approach of the dienophile toward the *syn* p-face of the diene to afford **2**, **3**, **4** and **5** (Scheme 6.2). Observed p-facial discrimination in the cyclohexadiene moiety is manifested through the carbonyl orbital interactions and the steric effects of cyclobutyl hydrogens.

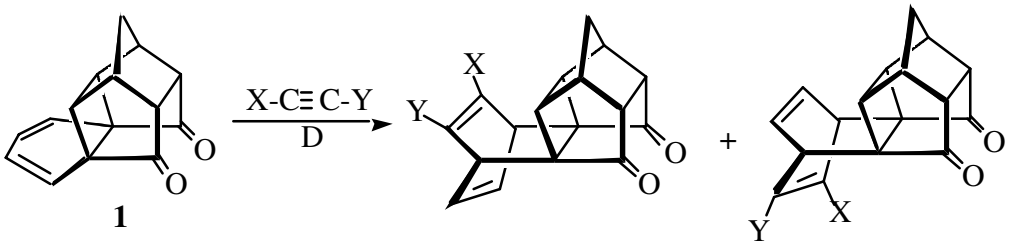
Scheme 6.2



Diels-Alder reactions[3a] of **1** with the electron-deficient acetylenes **6** (X = H, Y = CO_2CH_3) and **7** (X = Y = CO_2CH_3) produced the adducts shown in Scheme 6.3. Thus, methyl propiolate (**6**) reacted stereospecifically to produce single diastereoisomer, i.e., **10**

resulting from *syn* attack on the carbonyl face of the diene, while dimethyl acetylenedicaboxylate (**7**, DMAD) reacted to give a mixture of the two possible isomers (product ratio: **9** : **11** = 45 : 55). These results rule out any significant contribution from steric effects since nonuniform π-facial selectivities were obtained.

Scheme 6.3



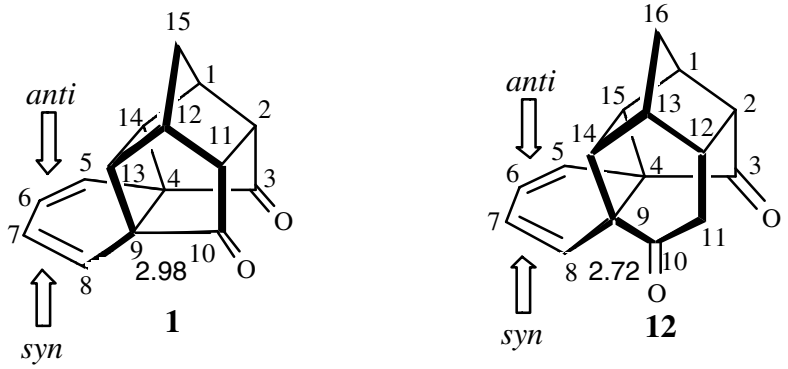
1

8; X = H, Y = CO_2Me
9; X = Y = CO_2Me

10; X = H, Y = CO_2Me
11; X = Y = CO_2Me

As an extension of our interests in diastereofacial selectivities in Diels-Alder cycloadditions, we have synthesized another p-facially differentiated 1,3-cyclohexadiene[5] (i.e., **12**, Scheme 6.4). We now report the regioselectivity in Diels-Alder cycloaddition of hexacyclo[11.2.1.$0^{2,12}$.$0^{4,9}$.$0^{4,15}$.$0^{9,14}$]pendeca-5,7-diene-3,10-dione (**12**) with ethyl propiolate. For purpose of comparison, the corresponding Diels-Alder reaction of diene **1** also has been explored.

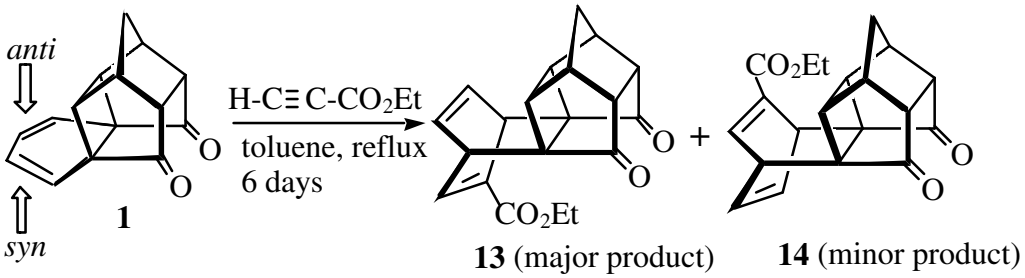
Scheme 6.4



RESULT AND DISCUSSIONS

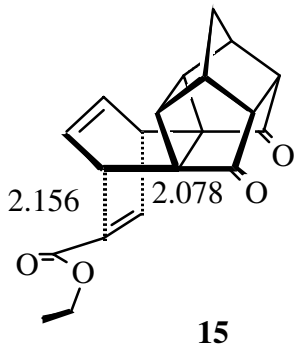
The result of the thermal cycloaddition reaction of diene **1** with ethyl propiolate is shown in Scheme 6.5. Thus, **1** was heated with ethyl propiolate to promote thermal [4+2] cycloaddition. Two cycloadducts (**13** and **14**) were isolated from this reaction (product ratio 80 : 20). The major product (**13**) results via approach the dienophile upon the *syn* face of the diene p-system. This experimental result is closely related to the previously observed p-facial selectivity for Diels-Alder cycloadditions of other dienophile to **1**.[3a]

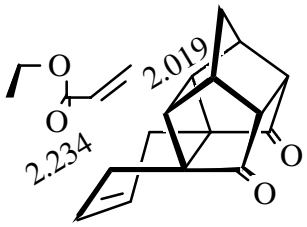
Scheme 6.5



To further support the experimental results, we have performed[6] semi-empirical transition structure MO calculations for [4+2] cycloaddition between diene (**1**) and

ethylpropiolate. The results of theorectical calculations performed at the RHF/3-21G//RHF/AM1 level of theory[7] are shown in Table 6.1. The results of these calculations appear to be consistent with the experimentally observed results, and they confirm the remarkable preference for approach by ethyl propiolate (dienophile) toward the *syn* face of diene **1**.





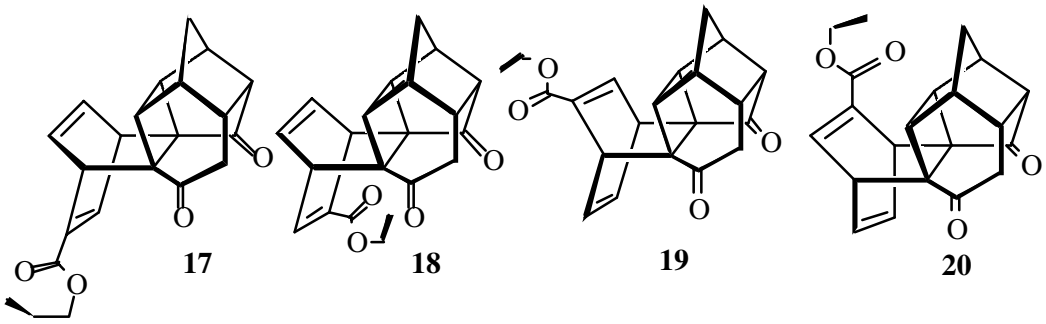
Structure	**15**	**16**
RHF/AM1	0.1	0.0
RHF/3-21G// RHF/AM1	0.0	0.4

Table 6.1. Relative energies (kcal-mol-1) of semiempirical MO transition structure

Subsequently, Diels-Alder reaction of **12** with ethyl propiolate was explored. Compound **12** is expected to provide interesting features in terms of the π-facial selectivity and regioselectivity of its reactivity as a Diels-Alder diene. In particular, the presence of one carbonyl group closer to the diene moiety in **12** may provide an important influence upon the facial approach of dienophile and also upon the regioselectivity of [4+2] cycloaddition. The results of a ground state geometry calculation performed for diene (**12**) at AM1 level suggests that the diene moiety is not planar. The computed torsional angle of C_5-C_6-C_7-C_8 deviates by 4.8° from planarity (Scheme 6.4). In addition, the cyclobutane ring alsois puckered (torsion angle C_4-C_{13}-C_{14}-C_9 = 8.5°,

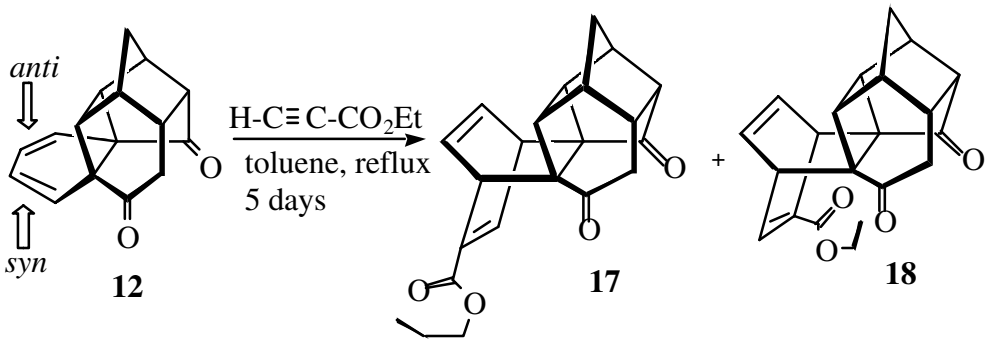
Scheme 6.4). The corresponding torsion angles obtained via X-ray structure analysis of diene **12** are 7.82° and 8.57°.[3a] Therefore, it appears that the geometric perturbation in diene **12** can have significant influence on the approach of incoming dienophile. Four [4+2] cycloadducts can be obtained via the cycloaddition reaction of diene **12** with ethyl propiolate: the structures of these cycloadducts are shown in Scheme 6.6.

Scheme 6.6

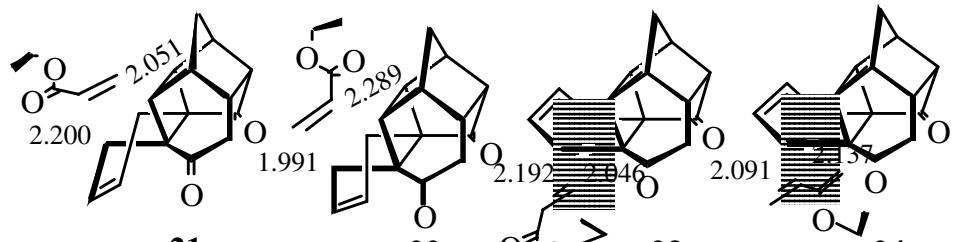


When **12** was heated with ethyl propiolate for 5 days, only two regioisomeric *syn* products of four possible isomers (i.e., **17**-**18**, Scheme 6.7) were obtained (product ratio = 60:40). The structure of the minor product (**17**) was established unequivocally via X-ray crystallographic analysis (Figure 6.1).[8]

Scheme 6.7



Semi-empirical MO transition structure calculations (AM1 Hamiltonian)[7] for four possible Diels-Alder transition state have been performed (Table 6.2). The results of these calculations suggest that ethyl propiolate (dienophile) prefers entirely approach toward the *syn* face of diene **12** rather than via from the corresponding *anti* face. Furthermore, the results indicate that the *syn* transition state for formation of **18** is more stable than that for formation of **17** by *ca*. 0.7-1.3 kcal-mol^{-1}.



Structure	**21**	**22**	**23**	**24**
RHF/AM1	2.4	2.1	1.3	0.0
RHF/3-21G// RHF/AM1	8.4	7.5	0.7	0.0

Table 6.2. The relative energies (kcal-mol^{-1}) of semi-empirical MO transition structure

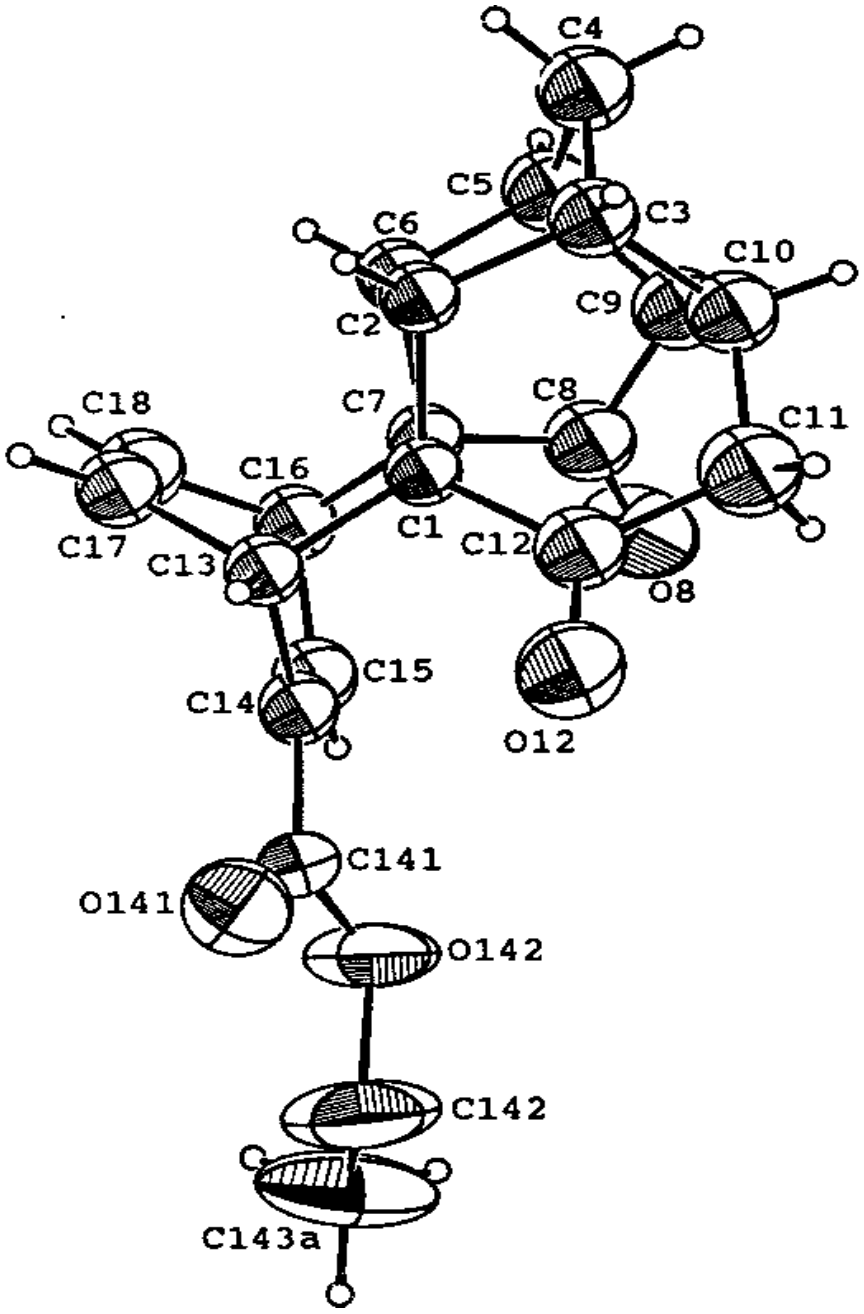


Figure 6.1. X-ray structure drawing of **17**[8]

SUMMARY AND CONCLUSIONS

Pi-facial and regioselctivity in Diels-Alder cycloaddition of hexacyclo[11.2.1.$0^{2,12}$.$0^{4,9}$.$0^{4,15}$.$0^{9,14}$]pentadeca-5,7-diene-3,10-dione **12** with ethyl propiolate have been explored. Diels-Alder cycloaddition of diene (**12**) with ethyl propiolate leads to two *syn* regioisomeric products, i.e, **17** and **18**. The structure of the minor reaction product **17** was estabilished unequivocally via application of X-ray crystallographic techniques. The results of transition state calculations are consistent with the experimentally observed results. The mode of facial approach of dienophile is not influenced by the presence of a carbonyl group proximal to the diene moiety in **12**, whereas the regioselectivity of this reaction can be influenced by the unsymmetrical disposition of carbonyl groups in diene **12.** Diels-Alder reaction of **1** with ethyl propiolate affords the *syn* isomer as a major product. The structure of the major reaction product, **13**, received support confirmed via the results of transition state calculations.

EXPERIMENTAL SECTION

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

Computational Methods. Semiempirical geometry optimizations for all systems were carried out at the AM1[7] level of theory implemented in SPARTAN.[9] Each transition structure gave only one imaginary harmonic vibrational frequency corresponding to the formation of new C-C bonds. The activation energies were

estimated from RHF/3-21G single-point calculations on the AM1-optimized geometries by using Gaussian 94.

Thermal Reaction of 1 with Ethyl Propiolate. To a solution of diketone **1** (250 mg, 1.11 mmol) in $phCH_3$ (20 mL) was added ethyl propiolate (164 mg, 1.67 mmol), and the resulting solution was refluxed for 6 days. The reaction mixture was allowed to cool to the ambient temperature and then was concentrated *in vacuo*. The residue was further purified via flash column chromatography on silica gel by eluting with 20% EtOAc-hexane to afford **13** (50 mg, 15%) as a colorless microcrystalline solid: m.p 139-141 ^oC; IR ($CHCl_3$) 2974 (m), 1741 (s), 1701 (s), 1253 (s), 1082 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7 Hz, 3 H), 1.94 (AB, J_{AB} = 10 Hz, 2 H), 2.42-2.71 (m, 5 H), 2.90 (s, 1 H), 3.61 (t, J = 5 Hz, 1 H), 4.02-4.35 (m, 3 H). 6.52 (t, J = 6 Hz, 1 H), 6.63 (t, J = 6 Hz, 1 H), 7.50 (d, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (q), 37.1 (d), 37.7 (d), 39.9 (d), 40.2 (d), 41.7 (t), 43.9 (d), 44.0 (d), 53.9 (d), 54.3 (d), 60.3 (s), 60.7 (t), 61.2 (s), 132.9 (d), 134.4 (d), 139.9 (s), 144.8 (d), 164.7 (s), 210.6 (s), 210.8 (s). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found C, 74.36; H, 5.70.

Continued elution of the chromatography column gave a second cycloadduct **14** (220 mg, 62%) as a colorless microcrystalline solid: mp 179-180 ^oC; IR ($CHCl_3$) 2980 (s), 1739 (s), 1710 (s), 1261 (s), 1084 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.87 (AB, J_{AB} = 12 Hz,2 H), 2.54 (m, 5 H), 2.80 (s, 1 H), 3.62 (t, J = 5 Hz, 1 H), 4.01-4.22 (m, 3 H). 6.43 (t, J = 6 Hz, 1 H), 6.56 (t, J = 6 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 36.9 (d), 37.9 (d), 39.9 (d), 40.0 (d), 41.7 (t), 43.9 (d), 44.0 (d), 54.2 (d, 2C), 60.3 (s), 61.2 (s), 61.8 (t), 133.7 (d), 135.2 (d), 139.3 (s), 144.1 (d),

164.0 (s), 210.8 (s), 211.0 (s). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52: H, 5.63. Found C, 74.58; H, 5.73.

Thermal Reaction of 12 with Ethyl Propiolate. To a solution of **12** (300 mg, 1.26 mmol) in toluene (20 mL) was added ethyl propiolate (200 mg, 1.89 mmol), and the resulting solution was refluxed for 5 days. The reaction mixture was allowed to cool to ambient temperature and then was concentrated *in vacuo*. The residue, a colorless solid (350 mg), was further purified via column chromatography on silica gel by eluting with 1:7 EtOAc-hexane to afford **17** (200 mg, 47%) as a colorless microcrystalline solid: m.p 202-203 ^oC; IR ($CHCl_3$) 2966 (m), 1712 (s), 1698 (s), 1244 (s), 1234 (m), 1087 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 8 Hz, 3 H), 1.62 (*A*B, J_{AB} = 10 Hz, 1 H), 1.81 (*A*B, J_{AB} = 10 Hz, 1 H), 2.24-2.89 (m, 9 H), 3.94-4.32 (m, 3 H). 6.45 (t, J = 6 Hz, 1 H), 6.84 (t, J = 6 Hz, 1 H), 7.53 (d, J = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 39.1 (d), 39.6 (t), 40.5 (t), 40.6 (d), 41.4 (d), 42.2 (d), 43.3 (d), 43.6 (d), 44.3 (d), 54.6 (d), 60.8 (t), 63.8 (s), 64.2 (s), 131.8 (d), 136.3 (s), 141.5 (d), 149.9 (d), 164.9 (s), 210.8 (s), 216.7 (s). Anal. Calcd for $C_{21}H_{20}O_4$:C, 74.98: H, 5.99. Found C, 74.84; H, 6.25.

Continued elution of the chromatography column gave a second cycloadduct **18** (150 mg, 35.5%) as a colorless microcrystalline solid: mp 198 ^oC; IR ($CHCl_3$) 2988 (m), 2962 (m), 1724 (s), 1707 (s), 1246 (s), 1219 (s), 1087 cm^{-1} (m); ^1H NMR ($CDCl_3$) 1.28 (t, J = 8 Hz, 3 H), 1.59 (*A*B, J_{AB} = 10 Hz, 1 H), 1.78 (*A*B, J_{AB} = 10 Hz, 1 H), 2.23-2.82 (m, 9 H), 4.19-4.37 (m, 3 H), 6.59-6.66 (m, 2 H), 7.17 (d, J = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.8 (q), 39.6 (d), 39.7 (t), 40.5 (t), 40.7 (d), 41.4 (d), 41.7 (d), 42.5 (d), 43.8 (d), 44.7 (d), 54.5 (d), 60.8 (t), 63.4 (s), 64.9 (s), 139.6 (d), 140.2 (d), 140.8 (d), 145.1 (s),

164.9 (s), 210.3 (s), 217.3 (s). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98: H, 5.99. Found C, 75.12; H, 6.16. The structure was established unequivocally via application of X-ray crystallographic methods.

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6. The author thanks Dr. Bishwajit Ganguly for having kindly performed the semiempirical molecular orbital calculations.

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8. The author thanks Dr. Simon. Bott for having kindly obtained the X-ray structure of **17**. 9. SPARTAN, version 5.1; Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.