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Stable Silica Gel-Bound Crown Ethers. Selective Separation of Metal Ions and a Potential for Separations of Amine Enantiomers*

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Abstract. Silica gel-bound crown ethers and aza macrocycles have been synthesized with the attaching arm connected to the carbon framework of the macrocycles. The interactions of these bound macrocycles with cations are almost identical to those involving the analogous free macrocycles. This has allowed for predictable cation separation, concentration, and removal processes to be performed on a small scale. Quantum mechanical calculations and NMR measurements indicate that similarly bound chiral macrocycles will be capable of use in separating chiral organic amines.

Key words. Macrocyclic compounds, silica gel-bound macrocycles, metal ion separation, chiral macrocycles.

1. Introduction

Selectivity in chemical interactions is the basis for some of the most remarkable phenomena in living and non-living systems. Enzyme catalysis, antibody-antigen interactions, involvement of specific metals in metalloproteins, enantiomeric selectivity, and metal catalysis in industrial reactions provide a partial listing of systems where selectivity is found. The obvious success and efficiency of such systems encourage the identification and investigation of underlying principles which make recognition possible in chemical interactions. Such understanding could lead to the design of new host molecules capable of interacting with guest species in a predetermined, selective manner.

Macrocycles have several features which are desirable in host molecules for an investigation of this type. These molecules are preorganized to allow through synthetic design the fitting of host to guest in a complementary fashion. Donor atoms, aromatic rings, substituent groups and chirality can be designed into these hosts in such a manner as to enhance selectivity for similar chemical guest species.

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Finally, by appropriate synthetic design, particular macrocycles can be attached to a solid support to form a material capable of making quantitative separations of like chemical species in a chromatographic column.

During the past two decades, much attention has been given to the design of marcocycles capable of selective recognition of guest species. Pedersen [1] first reported the crown ether compounds and recognized that they showed selective interaction with alkali metal ions. Lehn and Cram and their coworkers [2, 3] have designed numerous crown ether-type macrocycles and have studied their selective interaction with cations. The significance of the work of these individuals resulted in their receipt of the 1987 Nobel Prize in Chemistry [4]. An extensive compilation of equilibrium constant (K) data is available [5] from which selectivities in a given solvent can be calculated. It is evident from these K data that use of the proper macrocycle can result in selectivity for nearly any metal cation.

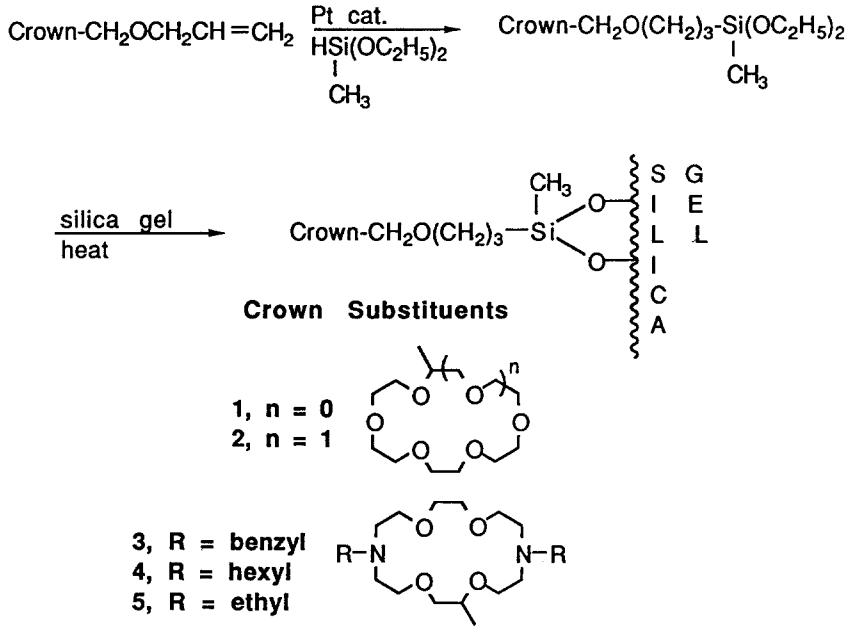
We have made use of the cation-selective properties of macrocycles to design liquid membrane [6], supported liquid membrane [6], and macrocycle-bonded silica gel [7] systems for specific cation separations. The selective transport of Ag^+ [8, 9], Pb^{2+} [8], K^+ [10] and Li^+ [11] was observed in a bulk liquid membrane system using various macrocyclic ligands. In the supported liquid membrane (thin sheet and hollow fiber) systems, selective and predicted separations of Na^+/K^+, Cd^{2+}/Hg^{2+}, and others have been achieved [12, 13],

A major problem with the separation of metal ions using extraction or membrane systems is the slow but steady loss of the expensive macrocyclic compounds from the organic membrane or layer. To circumvent this problem, we have attached various macrocyclic compounds to silica gel using a stable hydrocarbon-ether linkage [7, 14, 15]. Log K values for the interaction of these silica gel-bound macrocycles towards various metal ions were found to be the same ($\pm 10\%$) as those for the analogous unbound macrocycles toward the same cations in water. This paper describes the synthesis of some of these silica gel-bound macrocycles, their metal ion complexation properties, their use in the separation and concentration of certain cations from cation mixtures and the potential use of silica gel-bound chiral macrocycles for the separation of enantiomeric ammonium salts.

2. Synthesis of Silica Gel-Bound Macrocycles

The silica gel-bound macrocycles were prepared as shown in Scheme I. The allyloxymethyl-substituted macrocycle, a catalytic amount of chloroplatinic acid and an excess of diethoxymethysilane were refluxed in benzene for 8 to 24 hours. The benzene and excess diethoxymethysilane were removed under reduced pressure to give the crude silane product. The IR and NMR spectra of these materials were examined to determine the extent of the hydrosilylation reaction. An absence of an IR band at about 2170 cm^{-1} and an NMR peak at about 4.6 δ indicated that there were no free Si—H functions in the mixture. Also loss of the peaks at 4.5–6.0 δ in the NMR indicated a complete reaction of the vinyl-substituted macrocycle due to the absence of peaks indicative of the vinyl group.

The crude macrocycle-containing diethoxysilane was dissolved in chloroform and added to a known amount of 60–200 mesh silica gel so that the macrocycle to silica gel ratio was about 1 : 10 (wt). The solvent was removed on a rotary evaporator to

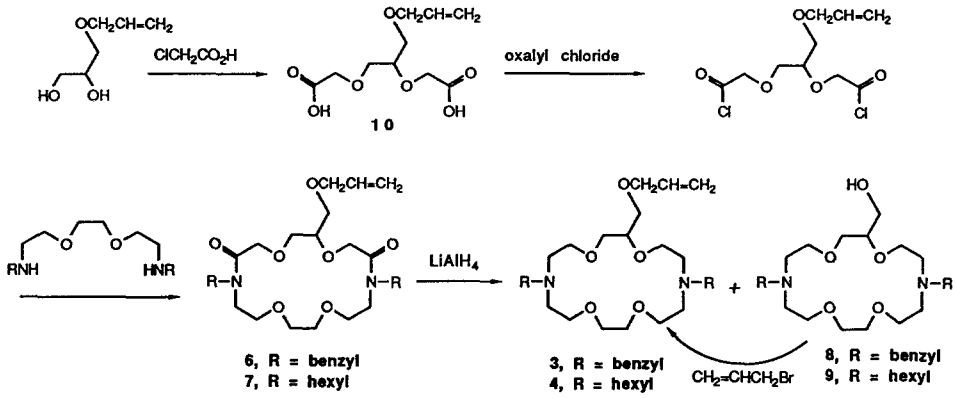


Scheme I. Preparation of silica gel-bound crown compounds.

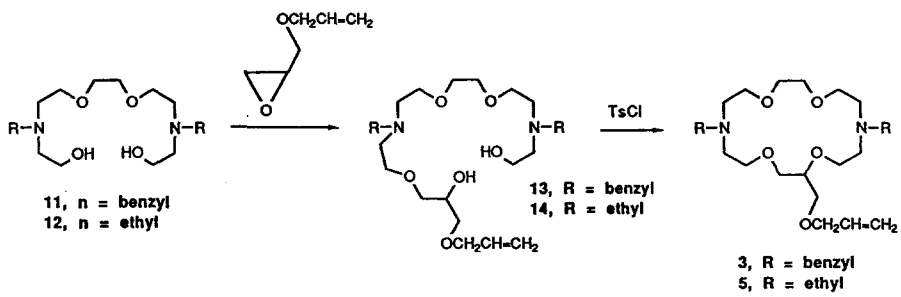
obtain an even coating of the diethoxysilane on the silica gel. The coated silica gel was then heated at 120°C in a Kugel-rohr apparatus for about 24 hours to form the covalent linkage. A chloroform wash of the silica gel-bound macrocycle materials gave little or no residue.

Triethoxysilane was also used in many of the hydrosilylation reactions (Scheme I, first reaction). The resulting macrocycle-substituted triethoxysilane could then form a three-bonded linkage to the silica gel. The final bonding of the diethoxy- or triethoxysilane material to silica gel could also be carried out in refluxing toluene.

The starting allyloxymethyl-18-crown-6 and 15-crown-5 compounds needed to prepare **1** and **2** were synthesized as reported [16]. A 3-butenyl substituted 18-crown-6 was prepared in the same manner. The allyloxymethyl-substituted diaza-18-crown-6 compounds needed to prepare **3–5** were prepared by five different synthetic sequences [15]. The most often used procedure to prepare the diazacrowns is through cyclic *bis*-amide compounds like **6** and **7** but without the allyloxymethyl substituents and where R = hydrogen (Scheme II) [17–19]. This sequence to form **6** and **7** requires the preparation of allyloxymethyl-substituted triglycolic acid **10** [19]. In the cyclization step, the diacid chloride and the diamine must be added simultaneously to a large amount of toluene. The reduction of **6** and **7** gave a mixture of desired products **3** and **4** as well as the reduced hydroxymethyl analogs **8** and **9**. Products **8** and **9** can easily be reacted with allyl bromide to give **3** and **4**. In actual practice, the crude reduction product containing both **3** and **8** or **4** and **9** can be treated with allyl bromide to attain the maximum yields of **3** and **4**. Because of the many steps in this reaction leading to an overall yield of 12% [15], a different synthetic route to the allyloxymethyl-substituted diazacrown compounds has been developed.



Scheme II. Allyloxymethyl diaza-18-crown-6 compounds from allyloxymethyl-substituted triglycolic acid.



Scheme III. Allyloxymethyl diaza-18-crown-6 from *N,N'*-dialkyldiazaoligoethylene glycol.

Scheme III shows a convenient three step synthesis of the allyloxymethyl-substituted diazacrowns **3** and **5** [15]. The diazapentaethylene glycols **11** and **12** were prepared in good yields from triethylene glycol dichloride and *N*-benzyl- or *N*-ethylethanolamine [20]. The reaction of **11** or **12** with the allyloxymethyl-substituted epoxide gave a good yield of the allyloxymethyl-substituted diazahexaethylene glycol **13** or **14**. Compound **14** was purified by distillation. The Okahara ring closure reactions of **13** and **14** with tosyl chloride [21] gave excellent yields of **3** and **5**, respectively. The overall yields for this process was 34% for **3** and 35% for **5** [15].

3. Determination of Log *K* Values for the Silica Gel-Bound Macrocycles

Log *K* values for the interaction of the silica gel-bound crown compounds with various cations have been determined [7]. A small amount of the silica gel material was placed in a chromatography column and the column was equilibrated with known concentrations of the cations studied. The cation binding properties of silica gel itself were determined by making blank measurements with plain silica gel. Binding of the cations of interest to the silica gel sites was made negligible by

including excess concentrations of a cation (e.g., Mg^{2+}) which does not complex with the crown but competes effectively with the cations of interest for plain silica gel as measured in plain silica gel measurements. The equilibrium expression for 1:1 cation-macrocycle interaction is given by Equation 1:

$$K = \frac{F(1 + K_1[H^+] + K_1K_2[H^+]^2)}{(1-f)[M^{n+}]} \tag{1}$$

where f = the fraction of ligand sites containing bound cations, K_1 and K_2 are the protonation constants applicable to **3**, and $[M^{n+}]$ and $[H^+]$ are the equilibrium molar free cation and proton concentrations, respectively. The quantities $[M^{n+}]$ and $[H^+]$ are taken to be the effluent M^{n+} and H^+ concentrations as determined by atomic absorption spectroscopy (AA) and pH measurements when these concentrations are equal to the input concentrations. The total number of moles of ligand sites is known from the organic synthesis and was checked by quantitatively loading every macrocycle site with a strongly interacting cation (i.e., for **3**, Ag^+ at concentrations $\geqslant 1 \times 10^{-5}$ M and pH > 8.0 were found to be sufficient to load the column with Ag^+). After equilibrium was reached, the column was stripped using either pure water, a complexing agent such as EDTA or, for **3**, an acidic solution such as an acetic acid-acetate buffer. The resulting solution of known volume was analyzed for cation concentration by AA. The fraction of ligand sites containing the cation can now be calculated as moles of bound cation/mole of ligand. The pK_a values for **3** were determined by repeating the above log K experiments for Ag^+ and Cd^{2+} at several pH values and curve fitting the results according to Equation 1.

In Table I, log K values for the association of several cations with the silica gel-bound and analogous free crown compounds are compared. The agreement between the two sets of log K values is generally good. Four of the free crown log K values presented in the table were measured in methanol. Log K values for unbound 18-crown-6 interaction with Cd^{2+} and Ni^{2+} have only been obtained in methanol. Log $K(H_2O)$ values [5] for unbound 15-crown-5-Sr^{2+} (1.95) and unbound 18-crown-6-Ca^{2+} (<0.5) interaction have been measured but are unreliable since the heats of reaction used to make the calorimetric measurements were small. Values for the same reactions in methanol shown in Table I were also measured calorimetrically, but had large heats of reaction. Log K values for cation-macrocycle interactions have been shown to be 2 to 3 log K units higher in methanol than in water [22, 23]. Hence, the degree of interaction for metal ions with the silica gel-bound macrocycles for these four cases also appears to be close to that with the free macrocycles in water.

The similarity of the log K values for the silica gel-bound and unbound crown-cation interactions suggests that both crown entities are effectively solvated by the aqueous solution. Thus, the silica gel-bound macrocycles form complexes in the same manner as do the free crowns in water. On the other hand, the bonding of macrocycles to hydrocarbon polymers, such as polystyrene, causes a considerable modification in metal ion binding properties in both organic solvents and aqueous solutions. In particular, aqueous solutions cannot be treated effectively because the hydrocarbon polymers are not wetted by water [24, 25].

Table I. Log K values at particular ionic strength (I) values for the interaction of M^{n+} with silica gel-bound and the analogous free (in parentheses) crown compounds (**1–3**)[a]

Cation	Log K		
	1	2	3
H^+(**1**)	–	–	8.9 ± 0.2 ($I = 0.5$) ($9.08^b - I = 0.1$)
H^+(**2**)	–	–	7.5 ± 0.2 ($I = 0.5$) ($7.94^b - I = 0.1$)
Sr^{2+}	0.57 ± 0.05 ($I = 3$) (2.63^c)	2.83 ± 0.01 ($I = 3$) (2.72)	2.4 ± 0.2 ($I = 0.5$) ($2.57^b - I = 0.1$)
Ba^{2+}	–	3.56 ± 0.01 ($I = 3$) (3.87)	–
Cd^{2+}	–	0.39 ± 0.13 ($I = 3$) (3.0^c)	5.0 ± 0.2 ($I = 0.5$) ($5.25^b - I = 0.1$)
Ca^{2+}	–	1.03 ± 0.10 ($I = 3$) (3.9^c)	–
Pb^{2+}	–	3.96 ± 0.05 ($I = 3$) (4.27)	–
Tl^+	1.38 ± 0.01 ($I = 3$) (1.23)	2.01 ± 0.06 ($I = 3$) ($2.2 - I = 0.1$)	–
Ni^{2+}	–	<0.2 ($I = 3$) (2.9^c)	–
K^+	–	1.75 ± 0.03 ($I = 1$) 2.10 ± 0.03 ($I = 0$)[d] (2.03)	
Ag^+	0.90 ± 0.15 ($I = 1$) (0.94)	1.61 ± 0.09 ($I = 0.5$) (1.50, 1.60)	8.2 ± 0.2 ($I = 0.5$) ($7.8^b - I = 0.1$)

[a] Ref. [5].
[b] The values are for diaza-18-crown-6 in Ref. [5].
[c] Values valid in methanol. See text for comparison to H_2O values.
[d] Value adjusted to 0 M ionic strength using the 1 M ionic strength activity coefficient for KNO_3 (0.443) from Ref. [23].

4. Removal, Separation and Concentration of Metal Ions Using the Silica Gel-Bound Macrocycles

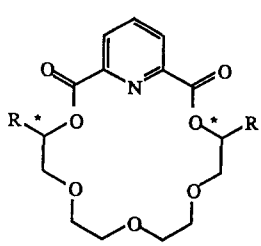
The similarity of the log K values for the bound macrocycles to those involving the unbound macrocycles suggests that prediction of metal separations using silica gel-bound macrocyclic ligands should be possible. Thus, one has a powerful means to predict separations using available data compilations [5]. Such separations have been studied. For example, 18-crown-6 gel material **2** was used to separate 0.001 M concentrations of the alkaline earth cations [14]. The log K values for the association of unbound 18-crown-6 with Sr^{2+} and Ba^{2+} in water are 2.72 and 3.87, respectively [5]. The log K value for 18-crown-6-Ca^{2+} interaction should be between 0.9 and 1.9 as described in Section 3. Magnesium ions do not complex with 18-crown-6. All the heavier alkaline earth cations were separated from Mg^{2+} by their being retained on the gel **2** column. Sr^{2+} and Ba^{2+} were selectively retained on the column over Ca^{2+} by factors of 54 and 339, respectively, and Ba^{2+} was retained

over Sr^{2+} by a factor of 10 [14]. These selectivity numbers are similar to the predicted selectivities based on the relative values of the respective metal ion-unbound macrocycle association constants [14]. All of these separations were performed in 1 M HNO_3 so that alkaline earth cation-blank silica gel interaction would be negligible.

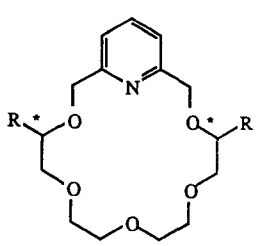
In each of the separation experiments mentioned above, the metal ion that was retained on the column was stripped off the column in a concentrated form by an aqueous EDTA solution. The desired ion can then be recovered. This process can also be used to determine trace amounts of various cations in an aqueous solution. A large volume (i.e. 1 L) of water containing ppb levels of Hg^{2+} and Pb^{2+} and also containing several hundred ppm of Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+} as the nitrate salts was rapidly passed through 2–4 g of gel **3**, **4**, or **5**. The metal ions formed complexes with the diazacrown and were removed quantitatively from solution. A much smaller amount of either 1 M aqueous HCl or EDTA was used to remove the metal ions from the column. Hence, a more concentrated solution of Hg^{2+} and Pb^{2+} was obtained and the solution was easily analyzed for Hg^{2+} and Pb^{2+} content by flame or inductively coupled plasma atomic absorption spectrophotometry.

5. Potential Separations of Enantiomeric Amines Using Silica Gel-Bound Chiral Macrocyclic Ligands

Chiral compounds **15**, **16**, **18**, and **20** shown in Figure 1 have been synthesized and their selective complexation with the enantiomers of organic ammonium salts have been studied using the temperature dependent NMR technique [26–29]. In many instances, excellent chiral recognition by the chiral ligand for one of the enantiomers of a chiral organic ammonium salt was observed. Table II shows the differences in $\Delta G^{\ddagger}$ values as obtained by the temperature dependent NMR technique for the interaction of the chiral ligands with (*R*)- and (*S*)-1-(1-naphthyl)ethyl ammonium perchlorate. Also in Table II are differences of the calculated values of the conformational strain energies of the same (*R*) and (*S*) complexes. The strain energy is the main component of $\Delta G^{\ddagger}$. Furthermore the other components, that are temperature and solvent dependent, are to a large extent the same for the (*R*) and the (*S*) complex, and are therefore mostly canceled out in the difference [30, 31].



15, R = methyl
16, R = phenyl
17, R = t-butyl



18, R = methyl
19, R = t-butyl

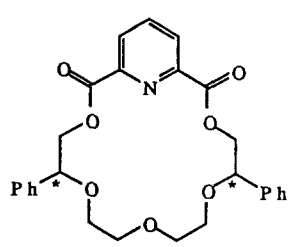


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Fig. 1. Chiral crown compounds.

Table II. Differences in free energy of activation values ($\Delta G^{\ddagger}$, kcal mol^{-1}) for the interaction of chiral macrocyclic ligands with (*R*)- and (*S*)-1-(1-naphthyl)ethyl ammonium perchlorate as determined experimentally (NMR) and as calculated from empirical energy functions.[a]

Ligand	$\Delta\Delta G^{\ddagger}$[b]	
	Observed	Calculated[a]
(*S,S*)-**15**	1.1[c]	0.7
(*S,S*)-**16**	0.7[c]	2.5
(*S,S*)-**17**	[d]	2.2
(*S,S*)-**18**	1.6[c]	1.7
(*S,S*)-**19**	[d]	2.2
(*S,S*)-**20**	0[c]	0.1

[a] Calculation method is given in Refs. [30] and [31].
[b] $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_R - \Delta G^{\ddagger}_S$
[c] Reference [28].
[d] Compounds have not yet been prepared.

Consequently, the calculated conformational strain energy difference represents approximately $\Delta\Delta G^{\ddagger}$. The calculated values for these interactions are based on the empirical functions of bond lengths, bond angles, torsional angles and interatomic coulombic and Lennard-Jones interactions. The calculations were performed by the Empirical Force Field method that has been described in detail [30, 31]. The method yields the equilibrium conformations for which the total energy is at a local minimum and determines their energy. In the present macrocyclic molecules, the number of such local low-energy minima is limited because the 'conformational space' is very restricted by the conditions of ring closure. A thorough scan of the conformational space produced all low energy minima of both enantiomers, including the most stable (*R*) and (*S*) conformations, whose energy difference is given in the last column of Table II.

The reliability of this method in making theoretical predictions that were borne out by experiment has been checked and confirmed in many instances [30, 31]. More recently, this method has been used in the discovery of a hydration pattern in enniatin crystals that escaped detection by X-ray diffraction analysis [32] and in the design of biomimetic ferric ion carriers [33].

Three of the compounds listed in Table II [(*S,S*)-**15**, **16**, and **18**] exhibited chiral recognition for the (*R*)-form of 1-(1-naphthyl)ethyl ammonium perchlorate. These compounds also exhibited chiral recognition for the (*S*)-form of the hydrogen perchlorate salt of methyl phenylalaninate [28]. (*R,R*)-**15** exhibited chiral recognition for (*S*)-1-(1-naphthyl)ethyl ammonium perchlorate by nearly the same magnitude ($\Delta\Delta G^{\ddagger} = 0.9$) as (*S,S*)-**15** did for the (*R*)-form ($\Delta\Delta G^{\ddagger} = 1.1$). The difference may be due either to enantiomeric impurities or to the finite accuracy of the measurements. (*S,S*)-**20**, with the phenyl substituents in the more mobile polyether portion of the molecule, did not show chiral recognition for the (*R*)- and (*S*)-forms of the ammonium salt (Table II) [28].

The computer calculations, based on empirical energy functions, gave similar values for the free energy differences for the interaction of either (*S,S*)-**15** or (*S,S*)-**18** (both with methyl substituents) and the (*R*)- and (*S*)-forms of the

ammonium salt (see Table II). The calculated $\Delta\Delta G^{\ddagger}$ values for the interaction of (*S*,*S*)-**16** (with phenyl substituents) and the (*R*)- and (*S*)-forms of the ammonium salt were much higher than those for the observed interactions. Perhaps an estimate of the other contributions to $\Delta\Delta G^{\ddagger}$, or more refinement of the calculation parameters is needed in this case. The calculated value for the interaction of (*S*,*S*)-**20**, with the phenyl substituents in the less rigid polyether portion of the molecule, and the (*R*)- and (*S*)-forms of the ammonium salt also indicated little or no energy differences. The similarity, in most cases, of the calculated and observed $\Delta\Delta G^{\ddagger}$ values has prompted us to calculate the energy differences for the interaction of other chiral bis-alkyl-substituted macrocyclic compounds to determine the chiral ligands which will give the best chiral recognition for the organic amine enantiomers. Two such calculations for the bis-*t*-butyl-substituted macrocycles (**17** and **19**) are shown in Table II. We are presently preparing these compounds to determine the chiral recognition factors experimentally.

We will attach the chiral ligand which displays the best recognition for the enantiomers of the chiral organic amines to silica gel in a manner similar to that given in Scheme I. Although Cram and his coworkers have attached one chiral macrocycle to silica or polystyrene gel [34], few actual separations of chiral organic amines or ammonium salts have been carried out. We expect to demonstrate enantiomeric separations of specific enantiomeric amines.

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